

Urgent Demand of Network Access for Acute Ischemic Stroke Management in Taiwan

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Abstract

Time is the major determinant in successful reperfusion therapy of acute ischemic stroke. The evolving diagnostic tools and treatment of acute stroke has made a great progress in the past 2 decades and is remodeling current management practices. It demands a timely neurologic evaluation and a neuroimaging study to determine if stroke patients are appropriate candidates for reperfusion demands. Therefore, it is critical for the setting of stroke center accreditation levels and capabilities so that timely and appropriate treatment is initiated for the eligible stroke patients. Optimal acute ischemic stroke treatment requires all levels of stroke center network operating efficiently. In the future, Taiwan should revise the criteria of stroke center accreditation and set up the efficient acute stroke treatment network as soon as possible.

Keywords: stroke, reperfusion, intra-arterial thrombectomy, intravenous recombinant tissue plasminogen activator.

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INTRODUCTION

Increasing evidence proven reperfusion therapy improving the outcome of acute ischemic stroke, inspires the urgent demand of network access for acute ischemic stroke management in Taiwan. A timely neurologic

evaluation and a neuroimaging study is necessary to determine if stroke patients are appropriate candidates for reperfusion demands. Therefore it requires a well-organized stroke management system with involvement of a qualified stroke center to provide optimal treatment.

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The Era of Reperfusion Therapy for Patients with Acute Ischemic Stroke

Acute stroke management is a complex, time-dependent condition to quick recruit a multidisciplinary team working together for emergent treatment. The evolving diagnostic tools and treatment of acute stroke

has made a great progress in the past 2 decades and is remolding current management practices. Alteplase, an intravenous recombinant tissue plasminogen activator (IV rtPA), was the first thrombolytic drug approved for treatment of patients with acute ischemic stroke in 1996 by the U.S. Food and Drug Administration. This

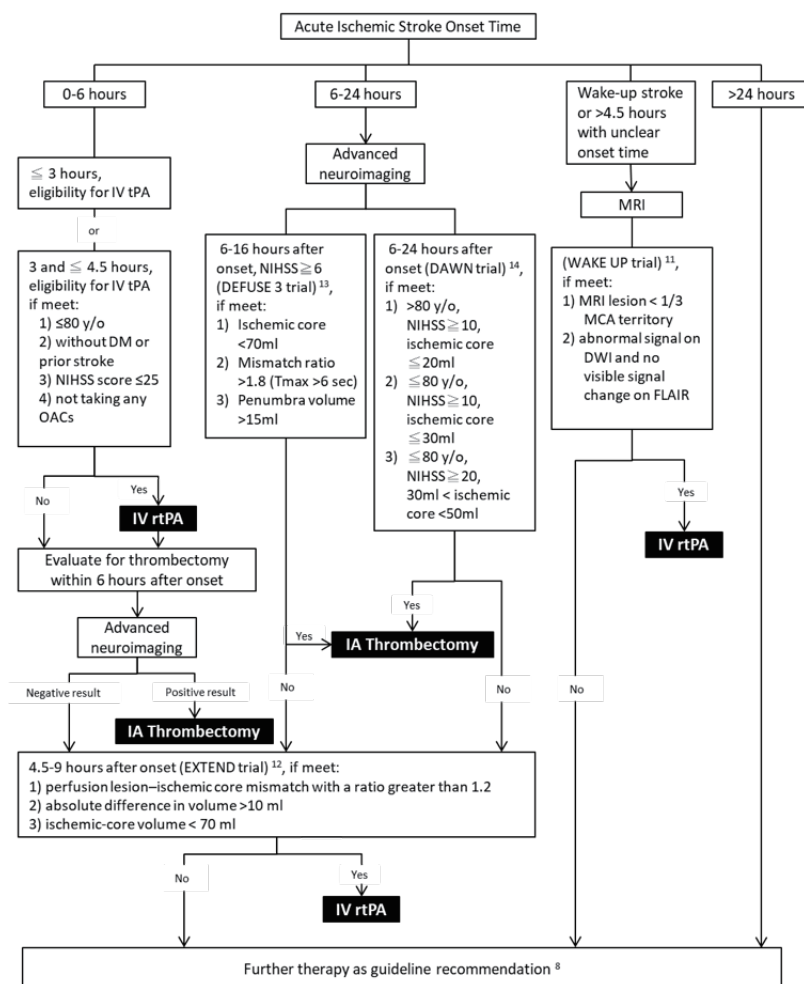


Figure 1. Algorithm of evidence-based reperfusion therapies for patients with acute ischemic stroke. All cases should perform initial neuroimage (usually noncontrast CT) to rule out intracerebral hemorrhage or other pathologic condition. For IA thrombectomy indication, large vessel occlusions of anterior circulation should be verified in advance and meet (1) NIHSS ≥ 6 , (2) Prestroke mRS ≤ 1 , (3) ASPECT ≥ 6 .

Abbreviations: ASPECT, Alberta Stroke Program Early CT Score; DAWN; Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo; DEFUSE; Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution; DM, diabetes mellitus; DWI, diffusion-weighted imaging; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; FLAIR, fluid-attenuated inversion recovery; IV rtPA, intravenous recombinant tissue plasminogen activator; MRI: Magnetic Resonance Imaging; mRS, modified Rankin scale; NIHSS, national institute of health stroke scale; OAC, oral anticoagulant; Tmax, time to maximum of the residue function; WAKE-UP, Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke

treatment is effective in treating strokes due to small vessel occlusions, but much less effective in treating strokes due to large vessel occlusions (LVO)^(1,2). LVO strokes are the most devastating disease causing severe neurological deficits. In the past 10 years, the advent of intra-arterial thrombectomy (IAT) has proved significant clinical benefits for LVO strokes⁽³⁾. Therefore, an update comprehensive guideline (2019)⁽⁴⁾ from American Stroke Association (ASA) recommend IV rtPA be administered to eligible patients as quickly as possible within 3 hours of last known normal with an extended window of 4.5 hours for a selective group of patients. Recent advanced cerebrovascular imaging, including multimodality imaging of magnetic resonance imaging (MRI) and

computed tomography perfusion (CTP) imaging, have been widely used as decision-making diagnostic tools to extend the time window of acute stroke treatment for reperfusion therapies (Table 1). They are used to calculate infarct core, and to estimate potentially salvageable brain tissue.⁽⁵⁾ Accumulative data from the use of advanced cerebrovascular imaging for patient selection have indicated that eligible stroke patients had better outcome even in those with IV rtPA windows presenting up to 9 hours from last known well or upon awakening. By using advanced neuroimaging modalities, IAT is also recommended as early as possible to eligible patients with LVO within 6 to 16 hours of last known normal and is considered reasonable in select patients within 6 to 24

Table 1. Evidence based indication of thrombolytic therapy for acute ischemic stroke

IV rtPA eligibility	
Indication	IV rtPA is recommended for those who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well
Additional concerns	1. IV rtPA treatment in the 3- to 4.5-h time window⁽¹⁰⁾ is recommended for those patients : (1) ≤ 80 y of age, (2) without a history of both diabetes mellitus and prior stroke, (3) NIHSS score ≤ 25, (4) not taking any OACs, and (5) without imaging evidence of ischemic injury involving more than one-third of the MCA territory 2. The treatment may be beneficial in patients with AIS a) who have unknown time of onset >4.5 h from last known well and who have a MRI lesion smaller than one-third of the MCA territory, abnormal signal on DWI and no visible signal change on FLAIR⁽¹¹⁾ b) who have onset of stroke between 4.5 and 9.0 hours or on awakening and who have perfusion lesion–ischemic core mismatch with a ratio greater than 1.2 and an absolute difference in volume greater than 10 ml, and an ischemic-core volume of less than 70 ml⁽¹²⁾ 3. The treatment should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging 4. Patients eligible for IV rtPA should receive IV rtPA even if IAT is being considered
Intra-arterial thrombectomy eligibility	
Indication ⁽⁴⁾	(1) age ≥ 18 years; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) pre-stroke mRS score of 0 to 1; (4) NIHSS score of ≥ 6; (5) ASPECTS of ≥ 6; and (6) treatment can be initiated within 6 hours of symptom onset
Additional concerns	IAT is recommended for selected patients with AIS caused by LVO in the anterior circulation a) within 6 to 16 hours of last known normal and with DEFUSE 3 eligibility criteria⁽¹³⁾ b) within 6 to 24 hours of last known normal and with DAWN eligibility criteria⁽¹⁴⁾

Adopted and Modified from reference 4.

hours of last known normal⁽⁴⁾. Here we organize these evidence-based reperfusion therapies into a flow chart (Figure 1).

Accreditation of Stroke Center and Classification

Therefore, it is critical time to revise the criteria of stroke center levels for accreditation and to make a new national network for acute stroke management so that timely and appropriate treatment is initiated for the eligible stroke patients. In Taiwan, the Ministry of Health and Welfare, Executive Yuan, launched the project “Hospital Emergent Capability Accreditation by Level-Stroke (HECAL-Stroke)” to promote the treatment of IV rtPA in eligible patients with acute ischemic stroke (AIS) since 2009. In 2014, 112 hospitals have been qualified as primary stroke centers for performing IV rtPA treatment. The project indicated that certifying authority licensed to issue primary stroke center certificates and significantly improved IV rtPA treatment.⁽⁶⁾ As acute stroke management has evolved into the era of IAT for LVO stroke, further stroke center classification is required to meet both the need for the capabilities of different levels of stroke centers and their corresponding levels of treatment. Waldman A. et al⁽⁷⁾ suggested stroke center classification as four different levels: acute stroke-ready hospital (ASRH), primary stroke centers (PSC), thrombectomy capable stroke centers (TSC), and comprehensive stroke center (CSC). Base on the current project HECAL-Stroke, Taiwan has built up many qualified primary stroke centers (PSC) around the nation. Each of them has a dedicated interdisciplinary stroke team to quickly perform clinical stroke assessment and protocols for administration of rtPA, and an inpatient stroke unit to admit and care for patients with AIS.⁽⁶⁾ However, only some of hospitals designated as “heavy duty (HD),” or “moderate duty (MoD),” lately reach the criteria of highest level of stroke care with a comprehensive team with a stringent protocol to perform acute treatments with IV rtPA or IAT for patients with AIS, advanced cerebrovascular imaging, and other stroke health care facilities. If lack of stroke center accreditation standardization, it would be difficult to set up the optimal prehospital strategy to timely transport stroke patients to the most appropriate stroke certified center. Meanwhile, a good strategic coordinated system to timely transport from lower to higher levels of definitive stroke centers can

markedly shorten IV rtPA and IAT times.

The Time to Set up the Network for Acute Stroke Management

The strategies of drip and ship as well as mothership are currently suggested two care pathways for acute stroke management. Drip and ship strategy is to transport the patients to the nearest stroke center for determining if initiating IV rtPA or further transferring to a IAT available stroke center for intra-arterial thrombectomy. Mothership strategy means to bypass closer IV rtPA available stroke centers to go directly to a IAT available stroke center for possible IAT. The 2018 AHA/ASA guidelines⁽⁸⁾ stated, “It remains unknown whether it would be beneficial for emergency medical services to bypass a closer IV rtPA-capable hospital for a thrombectomy-capable hospital.” The AHA/ASA has proposed that patients with suspected LVO and last known normal within 6 hours should be transported directly to the nearest TSC/CSC if the bypass does not add more than 15 minutes to transport, but not preclude the use of IV rtPA. Facing to the change of acute stroke treatment, Taiwan should upgrade the project HECAL-Stroke from version 1 to version 2, further classified all the primary stroke centers into IV rtPA available, or IAT available centers (Table 2). IAT available stroke centers must be qualified as the highest level of stroke care and be responsible to cooperate with nearby IV rtPA available stroke centers to build up a network for acute stroke treatment. The IV rtPA available stroke centers are responsible to determine if each patient is eligible for IV rtPA treatment or early recognition of LVO stroke for transportation to the IAT available stroke center. Currently, IAT available stroke centers in Taiwan rural region are not enough as a mothership strategy for acute stroke management. Although a previous meta-analysis⁽⁹⁾ indicated that drip-and-ship patients benefit from IAT have no relevant safety concerns, but drip-and-ship patients with a trend to unfavorable outcome compared to mothership patients. However, the drip-and-ship strategy for stroke patients in rural areas now may be suitable before IAT available stroke centers enough in Taiwan.

An Example for IAT in a Patient with LVO Stroke under Drip and Ship Strategy

A 72-year-old female had the history of coronary

Table 2. Accreditation of stroke center and classification

	IV rtPA available,	IAT available,
Clinical rapid stroke assessment	+	+
Interdisciplinary stroke team	+	+
Protocols for safe administration of rtPA.	+	+
Inpatient stroke unit	+	+
Availability of advanced cerebrovascular imaging	+/-	+
A comprehensive neuro-vascular or neuro-interventional team	+/-	+

+, available; +/-, availability option

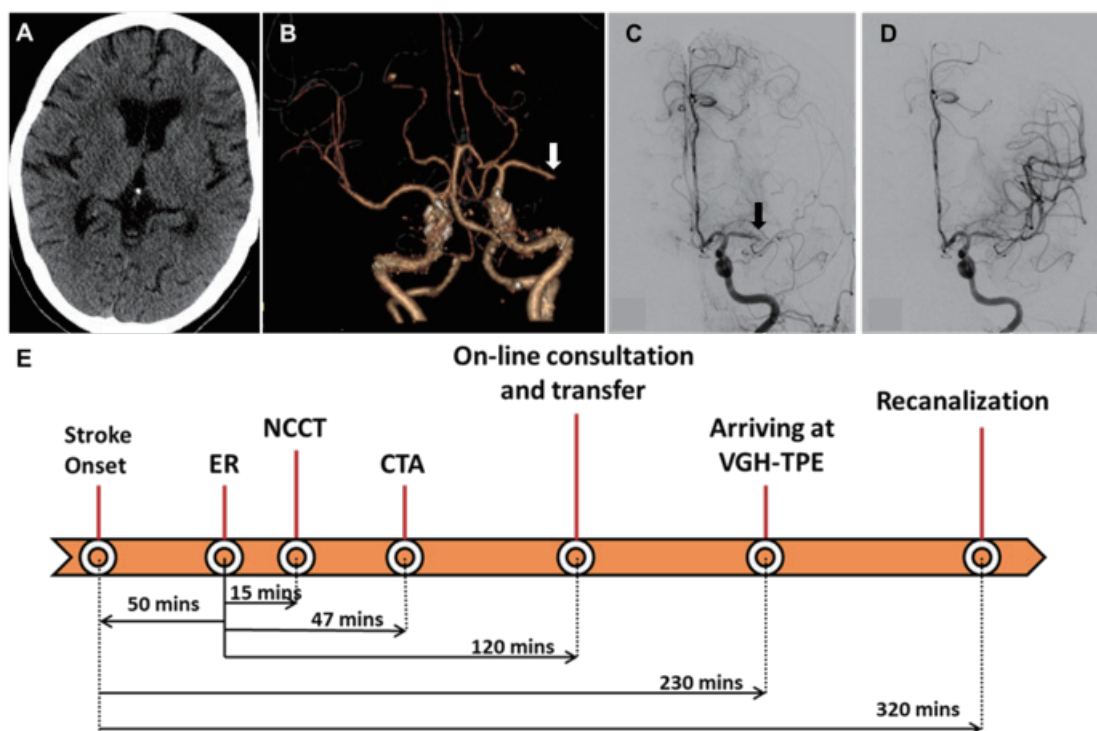


Figure 2. Initial non-contrast brain CT (NCCT) scan (A) disclosed an old hypodense lesion at left anterior horn of lateral ventricle. Reconstruction of head CT angiography (CTA) (B) discovered the total occlusion at distal M1 segment of left middle cerebral artery (MCA, Arrow). Digital subtraction angiography (DSA) image before intra-arterial thrombectomy (IAT) (C) also demonstrated the total occlusion at distal M1 segment of left MCA and after IAT (D) showed a good recanalization of the occluded left MCA. Timeline (E) was listed to demonstrate each time point of acute ischemic stroke management till the completion of IAT.

ER: emergency room, VGH-TPE: Veterans General Hospital-Taipei,

artery disease s/p stent implantation and atrial fibrillation with regular new oral anticoagulant (Rivaroxaban) therapy. She was found to have sudden onset of consciousness disturbance and palsy of right limbs 50 minutes later. She was sent to Taipei Veteran General Hospital, Hsin-

Chu branch. It is a local hospital with IV rtPA available stroke center in Hsinchu County. Quick neurological examinations showed drowsy consciousness; global aphasia; eyeball conjugate deviation to left side and right hemiplegia with Gr. 2 muscle power. National institute

of health stroke scale (NIHSS) estimated 17 points. The emergent non-contrast brain computed tomography (CT) scan revealed an old hypodense lesion located in periventricular region of left anterior horn of lateral ventricle and the Alberta Stroke Program Early CT Score (ASPECT) estimated 9 points (Fig. 2A). IV rtPA therapy was contraindicated because of the current anticoagulant therapy. Head CT angiography was performed and it revealed occlusion of distal M1 segment of left middle cerebral artery (Fig. 2B). After discussion with a vascular neurologist in the mother hospital, Veterans General Hospital-Taipei, she was soon transferred to our mother hospital with a distance about 90 km due to IAT available. IAT was undergone with a good recanalization at 5 hours 20 minutes after stroke onset (Fig. 2C & D). Timeline (Fig. 2E) listed each time point of acute ischemic stroke management. Her NIHSS recovered to 5 points at discharge (13 days after stroke onset) and 2 points at 3-month follow-up. It may be not a perfect example for IAT because of waste so much time to wait ambulance and to prepare the performance of IAT. However, it would like to point out an urgent demand of stroke care network in Taiwan rural regions.

CONCLUSION

Optimal acute ischemic stroke treatment requires all levels of stroke center network operating efficiently. It includes pre-hospital contact by EMS to quick stroke assessment and management upon hospital arrival. The transfer to different level of reperfusion therapy available hospital also should be involved in the important process. In the future, Taiwan should revise the criteria of stroke center accreditation and set up the efficient acute stroke treatment network.

REFERENCES

1. Mokin M, Kass-Hout T, Kass-Hout O, Dumont TM, Kan P, Snyder KV, et al. Intravenous thrombolysis and endovascular therapy for acute ischemic stroke with internal carotid artery occlusion: a systematic review of clinical outcomes. *Stroke* 2012;43:2362-8.
2. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke* 2007;38:967-73.
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016;387:1723-31.
4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2019;50:e344-e418.
5. Albers GW. Use of Imaging to Select Patients for Late Window Endovascular Therapy. *Stroke* 2018;49:2256-60.
6. Cheng TJ, Peng GS, Jhao WS, Lee JT, Wang TH. Nationwide "Hospital Emergent Capability Accreditation by Level-Stroke" Improves Stroke Treatment in Taiwan. *J Stroke* 2017;19:205-12.
7. Waldman A, Tadi P, Rawal AR. Stroke Center Certification. StatPearls. Treasure Island (FL)2020.
8. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46-e110.
9. Ismail M, Armoiry X, Tau N, Zhu F, Sadeh-Gonik U, Piotin M, et al. Mothership versus drip and ship for thrombectomy in patients who had an acute stroke: a systematic review and meta-analysis. *Journal of NeuroInterventional Surgery* 2019;11:14-9.
10. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.
11. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *N Engl J Med* 2018;379:611-22.
12. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, et al. Thrombolysis Guided by Perfusion

- Imaging up to 9 Hours after Onset of Stroke. *N Engl J Med* 2019;380:1795-803.
13. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med* 2018;378:708-18.
14. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N Engl J Med* 2018;378:11-21.