Emergency thrombectomy for acute ischaemic stroke: current evidence, international guidelines, and local clinical practice

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ABSTRACT

Acute ischaemic stroke due to large vessel occlusion leads to grave neurological morbidity and mortality. Conventional intravenous thrombolysis is ineffective in achieving timely reperfusion in this group of patients. The publication of five positive randomised controlled trials of emergency thrombectomy for acute ischaemic stroke in 2015 provided strong evidence to support endovascular reperfusion therapy and represented a paradigm shift in acute stroke management. In this article, we review the current evidence and international guidelines, and report on the findings of a survey study of the clinical practice and opinions of local neurologists, neurosurgeons, and interventional radiologists in emergency thrombectomy. We also discuss the controversies around thrombectomy treatment, local experience, and suggestions to incorporate thrombectomy in acute stroke treatment.

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Introduction

Before 2015, the standard of care for emergency ischaemic stroke treatment was intravenous thrombolysis with tissue plasminogen activator (IV-tPA). This stemmed from the National Institute of Neurological Disorders and Stroke trial in 1995, which showed that compared with placebo, patients who were given IV-tPA within 3 hours from symptom onset were 30% more likely to have minimal or no disability at 3 months.[1] The therapeutic window was further extended to 4.5 hours from symptom onset by the European Cooperative Acute Stroke Study III, which demonstrated similar benefits when IV-tPA was administered between 3 and 4.5 hours to selected patients.[2]

Nonetheless, in patients with ischaemia due to occlusion of a major cerebral artery, such as the intracranial internal carotid artery or the first and second segment of middle cerebral artery (M1, M2), the efficacy of intravenous thrombolysis was limited, with a recanalisation rate of only 4% to 30%.[3] This group of patients frequently had a grave neurological prognosis and high mortality owing to the large infarct territory, and could develop malignant cerebral oedema that required decompressive craniectomy.[4]

To improve the recanalisation rate, endovascular mechanical thrombectomy to remove the occluding clot was proposed. Early studies of this technique showed conflicting results and were attributed to poor patient selection and suboptimal endovascular devices that resulted in a low recanalisation rate, thus failing to show the expected benefits of endovascular thrombectomy.[5-7]

With modern improved thrombectomy devices, the publication of five positive randomised trials of acute mechanical thrombectomy for ischaemic stroke resulting from anterior circulation large-vessel occlusion in the *New England Journal of Medicine* in 2015 marked a paradigm shift in stroke treatment.[8-12] Since then, emergency endovascular thrombectomy has been internationally regarded as the new standard of care for acute ischaemic stroke caused by major vessel occlusion, and is recommended by all major stroke guidelines.

Summary of current evidence

The five independent randomised controlled trials that provided strong evidence to support endovascular thrombectomy were MR CLEAN,[8] REVASCAT,[9] ESCAPE,[10] EXTEND-IA,[11] and SWIFT PRIME,[12] conducted in the US, Europe, and Australia from 2010 to 2015. Although there were differences in terms of inclusion and exclusion criteria, all five studies recruited only acute stroke patients with angiogram-proven major vessel occlusion in the anterior circulation, and used newer-generation

血栓移除術治療急性缺血性中風：當前證據，國際指引和本地臨床實踐

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因大血管閉塞引起的急性缺血性中風，會導致嚴重神經性殘障和死亡。傳統的靜脈溶栓對於打通大血管閉塞的療效有限。2015年發表的五項有關急性血栓塞的隨機對照研究，證實經動脈血管的血栓移除術可應用於急性缺血性中風治療，同時亦代表了急性腦中風治理的新標準。本文回顧當前的證據和國際指引，並報告一個以本地神經內科醫生、神經外科醫生和介入放射科醫生為對象的問卷調查，探討他們對於急性血栓移除術的臨床實踐和意見。本文續討論關於血栓移除治療的爭議和本地的經驗，以及在香港急性腦中風治療中普及應用血栓移除術的建議。

thrombectomy devices (mostly stent retrievers) that achieved higher recanalisation rates than earlier devices used in previous trials.

All patients in the five trials were given IV-tPA as standard treatment when eligible, and were then randomised to receive endovascular thrombectomy or standard care alone. All these trials unanimously showed significant benefit in the thrombectomy group in terms of improved functional outcome at 3 months, as measured by the modified Rankin scale (mRS) [Table 1[8-13]].

Functional outcome benefit

A meta-analysis of the above five trials with a total of 1287 eligible patients showed that 46% of patients treated by endovascular thrombectomy achieved functional independence (mRS score, 0-2) at 90 days, compared with 26.5% of patients in the control group[13] (Table 1). The number needed-to-treat was 2.6 for one patient to improve functionally by at least 1 point on mRS. In terms of safety, there was no significant difference between the intervention group and the control group in symptomatic intracranial haemorrhage (4.4% vs 4.3%; P=0.81) or mortality rate at 90 days (15.3% vs 18.9%; P=0.15).[13]

Moreover, the clinical benefit was maintained whether the patient was eligible to receive IV-tPA in the first place, and across all age-groups including the patients older than 80 years. Patients improved after thrombectomy regardless of the initial severity of stroke, as documented by the National Institutes of Health Stroke Scale (NIHSS) and the initial Alberta Stroke Program Early CT Score.

Therapeutic time frame

Regarding the treatment time frame, thrombectomy within 6 hours from symptom onset was consistently beneficial across all five thrombectomy trials. In the REVASCAT trial that included patients within 8 hours of symptom onset, the median onset-to-reperfusion time was still within 6 hours in the thrombectomy group, although no separate data were provided for those who presented between 6 and 8 hours.[9] Similarly, in the ESCAPE trial, which included patients up to 12 hours from stroke onset, the median time to reperfusion was 4 hours from symptom onset and very few patients beyond 6 hours were recruited.[10] At present, two clinical trials are underway to investigate the benefits of endovascular thrombectomy for anterior circulation stroke beyond 6 hours, and both require computed tomography (CT) perfusion or magnetic resonance imaging (MRI) to assess infarct core and perfusion mismatch to determine eligibility (NCT02586415, NCT02142283). Therefore, the efficacy and risk of anterior circulation thrombectomy beyond 6 hours without advanced imaging selection criteria are uncertain, and should be performed with discretion or in a clinical research setting.

Posterior circulation and the paediatric population

At present, there is no evidence from randomised

TABLE 1. Summary of functional outcome and mortality at 90 days of five thrombectomy for ischaemic stroke trials[8-13]

	No. of patients	mRS score 0-2 at 90 days		Odds ratio (95% CI)	Mortality at 90 days	
		Thrombectomy group (%)	Control group (%)		Thrombectomy group (%)	Control group (%)
MR CLEAN[8]	500	32.6	19.1*	2.05 (1.36-3.09)	13.0	22.1
ESCAPE[10]	316	53.0	29.3*	2.73 (1.71-4.37)	10.3	19.0*
SWIFT PRIME[12]	196	51.0	35.5*	2.75 (1.53-4.94)	9.2	15.5
REVASCAT[9]	205	43.7	28.2*	1.98 (1.11-3.53)	18.4	15.5
EXTEND-IA[11]	70	82.6	40.0*	3.75 (1.38-10.17)	8.6	20.0
HERMES meta-analysis[13]	1287	46.0	26.5*	-	15.3	18.9

Abbreviations: CI = confidence interval; mRS = modified Rankin scale

* P<0.05

trials regarding thrombectomy for posterior circulation large-vessel occlusion or paediatric patients.

Contemporary thrombectomy devices

One major improvement of these five trials[8-12] compared with previous negative thrombectomy trials[5-7] was the exclusive use of newer stent retriever devices and a consequent higher recanalisation rate. Near-complete/complete (TICI 2b/3) recanalisation was achieved in 59% to 88% of patients, compared with only 25% to 41% in early studies that used intra-arterial tPA and first-generation devices.[14]

Another contemporary thrombectomy device was the direct aspiration catheter (ADAPT technique),[15] which applied suction to remove the clot via a large-bore endovascular catheter (Fig 1). This technique was supported by multiple single-centre series that showed comparable and sometimes superior results over stent retrievers, although none of these were head-to-head comparative trials.[16-18] The 2016 THERAPY trial was the only randomised study to compare aspiration thrombectomy versus IV-tPA alone.[19] It was terminated prematurely with a limited sample size after publication of the positive stent retriever trials, and as such failed to demonstrate a statistically significant benefit for aspiration thrombectomy over intravenous thrombolysis alone.

Cost-effectiveness of thrombectomy

Cost-utility analyses have been performed in several health care systems around the world and all have shown the cost-effectiveness of endovascular thrombectomy. The cost per quality-adjusted life year (QALY) gained for thrombectomy over standard thrombolysis treatment varies between US$7988 (Sweden), US$9386 (US), US$11 651 (UK), and US$11 990 (Canada).[18,20-22] Using internationally accepted willingness-to-pay per QALY threshold of the gross domestic product per capita, all of the above health care systems found endovascular thrombectomy to be cost-effective.

International guidelines

The overwhelming clinical evidence to support application of thrombectomy in anterior circulation stroke prompted the European Stroke Organisation (ESO) and subsequently the American Heart Association/American Stroke Association (AHA/ASA) to release a focused update of early stroke treatment guidelines in 2015, recommending endovascular thrombectomy with stent retriever device if onset of symptoms was within 6 hours and was due to a major vessel occlusion of the anterior circulation, and when suitable criteria were met (Class I, Level of Evidence A).[23,24] The Box lists the latest AHA/ASA and ESO recommendations regarding endovascular thrombectomy.[23,24]

Emergency thrombectomy in Hong Kong

Endovascular thrombectomy for ischaemic stroke is a relatively new procedure in Hong Kong and is not routinely available. Although it was practised in certain centres prior to 2015 for selected cases,[25] there was no consensus on treatment indications, patient selection criteria, or operative techniques. With acute mechanical thrombectomy now becoming the international standard of care for acute anterior circulation ischaemic stroke, we undertook a survey to identify the availability, clinical practice, and potential obstacles of an acute stroke thrombectomy service in Hong Kong.

Design of the survey

We designed a survey which addressed the availability

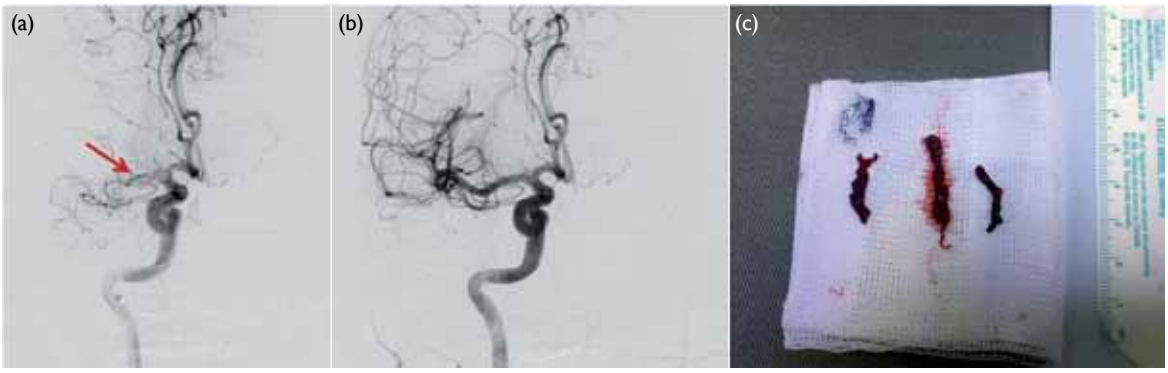

FIG 1. (a) Angiogram showing acute occlusion of the right middle cerebral artery (arrow). (b) Post-thrombectomy angiogram showing revascularisation of the right middle cerebral artery territory. (c) Thrombus removed by endovascular thrombectomy

BOX. New international guidelines for endovascular thrombectomy[23,24]

American Heart Association/American Stroke Association 2015[24]

Patients should receive endovascular therapy with a stent retriever when all of the following are met (Class I, Level of Evidence A):

- pre-stroke modified Rankin score 0 to 1
- acute ischaemic stroke receiving IV-tPA within 4.5 hours according to guidelines
- causative occlusion of the internal carotid artery or proximal middle cerebral artery (M1)
- age ≥18 years
- NIHSS score ≥6
- ASPECTS ≥6
- Treatment can be initiated within 6 hours from symptom onset

European Stroke Organisation–KSU 2015[23]

1. Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hours after symptom onset (Grade A, Level 1a, KSU Grade A).
2. Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy (Grade A, Level 1a, KSU Grade A).
3. Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level 1a, KSU Grade A).
4. For mechanical thrombectomy, stent retrievers approved by local health authorities should primarily be considered (Grade A, Level 1a, KSU Grade A).
5. If intravenous thrombolysis is contra-indicated (eg warfarin-treated with therapeutic INR), mechanical thrombectomy is recommended as first-line treatment in large vessel occlusions (Grade A, Level 1a, KSU Grade A).

Abbreviations: ASPECTS = Alberta Stroke Program Early CT Score; INR = international normalised ratio; IV-tPA = intravenous thrombolysis with tissue plasminogen activator; KSU = Karolinska Stroke Update; NIHSS = National Institutes of Health Stroke Scale

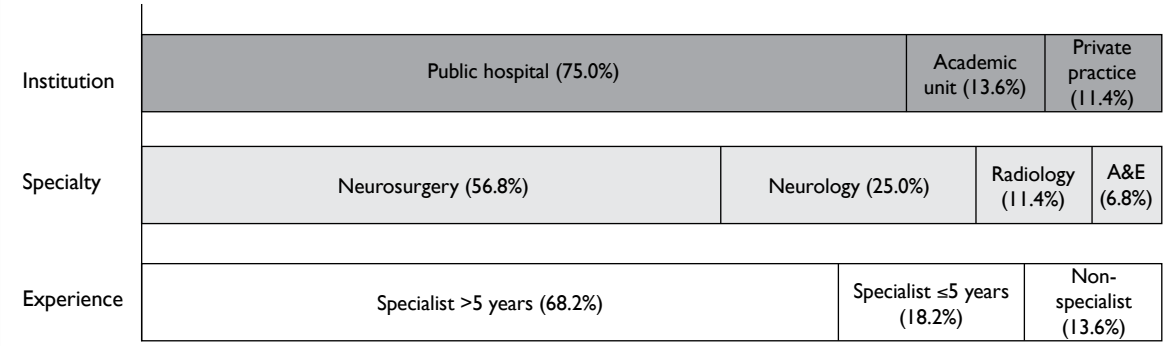

FIG 2. Background characteristics of respondents (n=44)
Abbreviation: A&E = accident and emergency

of expertise, the indications, patient selection for stroke treatment, interventional techniques, and perceived obstacles to timely stroke treatment. This was a web-based survey consisting of 43 questions and was administered from May to August 2016. Respondents were drawn from the Hong Kong Stroke Society, Hong Kong Neurosurgical Society, and Hong Kong Society of Interventional and Therapeutic Neuroradiology. Invitations to participate were sent by email. Participants did not receive any incentive to complete this survey. We received 44 responses from the three societies. Background characteristics of the respondents are shown in Figure 2.

Service availability

Overall, 24 (54.5%) respondents from six public hospitals and five private practices were regularly involved in the decision and provision of mechanical thrombectomy for patients with acute ischaemic stroke. Most were neurosurgeons (75.0%), and the remainder were neurologists and interventional radiologists. In most centres, the interventionist capable of performing thrombectomy was a neurosurgeon or interventional radiologist, whereas in half of the responding centres there were also neurologists who were able to perform this procedure. For the majority of interventionists (62.5%), mechanical thrombectomy was offered only on an 'ad hoc' basis with no official service hours. The mean number of interventionists currently available was 4.3 per centre. The questions and responses of the survey are shown in Table 2.

Clinical practice

Direct aspiration technique (ADAPT[15]) was the most popular first-line thrombectomy technique,

TABLE 2. Questions and responses on endovascular thrombectomy for acute ischaemic stroke (n=24)

Question	Choices	% Of respondents
1. What is the availability of emergency mechanical thrombectomy service for acute ischaemic stroke at your centre?	- On ad-hoc basis, no official available time - Available during specific office hours (eg 9 am to 5 pm) - Always available, 24 hours/7 days	- 62.5 - 33.3 - 4.2
2. If acute ischaemic stroke treatment (IV-tPA thrombolysis and/or endovascular treatment) is not available at your centre, or when it is outside the available hours, is there a formal acute stroke referral/diversion pathway?	- Yes - No	- 10.0 - 90.0
3. In your centre, who is capable of performing mechanical thrombectomy?	- Neurosurgeon - Interventional radiologist - Neurologist - Other	- 100 - 100 - 50.0 - 4.2
4. In the past 12 months, how many patients were treated with mechanical thrombectomy at your centre?	- ≤5 - 6-10 - 11-20 - 21-30 - >30	- 0 - 62.5 - 33.3 - 4.2 - 0
5. What is the maximum time window from stroke onset for performing mechanical thrombectomy in patients with anterior circulation stroke?	- ≤4.5 Hours - ≤6 Hours - ≤8 Hours - ≤12 Hours - Other	- 0 - 62.5 - 33.3 - 4.2 - 0
6. What is the maximum time window from stroke onset for performing mechanical thrombectomy in patients with posterior circulation stroke?	- No specific time window - ≤4.5 Hours - ≤6 Hours - ≤8 Hours - ≤12 Hours - ≤24 Hours - Other	- 37.5 - 0 - 12.5 - 12.5 - 8.3 - 25.0 - 4.2
7. What is the imaging modality used to decide whether the patient can proceed with mechanical thrombectomy? (can choose more than 1 answer)	- CT angiogram - Digital subtraction angiogram - MR angiogram - DWI MRI - T1-/T2-weighted MRI - PWI/FLAIR MRI - CT perfusion scan - Other	- 87.5 - 25.0 - 20.8 - 16.7 - 12.5 - 12.5 - 8.3 - 4.2
8. What are the patient selection criteria for mechanical thrombectomy in your practice? (can choose more than 1 answer)	- M1/M2 occlusion - Intracranial internal carotid artery occlusion - Basilar artery occlusion - NIHSS score >5 - Contra-indications to IV-tPA thrombolysis - Pre-stroke mRS score ≤2 - Failed IV-tPA thrombolysis - NIHSS score <21 - Evidence of MRI diffusion-perfusion mismatch - CT perfusion assessment - PCA occlusion - ACA occlusion - Age <80 years - Other	- 91.7 - 87.5 - 87.5 - 75.0 - 75.0 - 70.8 - 54.2 - 33.3 - 25.0 - 16.7 - 20.8 - 37.5 - 37.5 - 4.2
9. In your practice, what are the imaging parameters that contra-indicate mechanical thrombectomy? (can choose more than 1 answer)	- Evidence of midline shift/mass effect - ASPECTS ≤6 on non-contrast CT/DWI MRI - Ischaemic region >1/2 MCA territory - M2 segment of MCA occlusion - Tandem ICA+MCA occlusion - Evidence of microbleeds on presentation - Evidence of poor collateral circulation - Ischaemic regions involving both anterior and posterior circulation territory - Ischaemic core lesion volume >70 mL - Other	- 79.2 - 58.3 - 45.8 - 12.5 - 0 - 29.2 - 20.8 - 25.0 - 25.0 - 0
10. What is the preferred mode of anaesthesia for endovascular thrombectomy?	- Local anaesthesia - Monitored anaesthetic care - General anaesthesia	- 54.2 - 33.3 - 12.5

Abbreviations: ACA = anterior cerebral artery; ASPECTS = Alberta Stroke Program Early CT Score; CT = computed tomography; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuation inversion recovery; ICA = internal carotid artery; IV-tPA = intravenous thrombolysis with tissue plasminogen activator; MCA = middle cerebral artery; MR = magnetic resonance; MRI = magnetic resonance imaging; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; PCA = posterior cerebral artery; PWI = perfusion-weighted imaging

TABLE 2. (cont'd)

Question	Choices	% Of respondents
11. In your centre, what is the mean door-to-groin puncture time?	- ≤30 Mins - 31-60 Mins - 61-90 Mins - 91-120 Mins - 121-180 Mins - >180 Mins	- 0 - 25.0 - 45.8 - 12.5 - 16.7 - 0
12. Do you give combined IV-tPA to mechanical thrombectomy–indicated patients?*	- No - Yes, as standard treatment if within therapeutic window of intravenous thrombolysis - Yes, with reduced dose before endovascular treatment as a bridging therapy - Yes, after endovascular treatment for incomplete recanalisation or distal emboli	- 12.5 - 70.8 - 0 - 4.2
13. What is the dosage of tissue plasminogen activator if the patient receives both treatments?	- Unchanged, as the standard dosage recommended IV-tPA dosage - ¾ Dose of standard IV-tPA - ½ Dose of standard IV-tPA - ¼ Dose of standard IV-tPA - I do not give concomitant IV-tPA	- 88.8 - 0 - 5.6 - 5.6 - 0
14. What do you use as the first-line device for mechanical thrombectomy?	- Penumbra ACE64/Penumbra System MAX (Penumbra, Inc, Alameda [CA], US) - Solitaire FR (Medtronic, Minneapolis [MN], US) - Trevo (Stryker, Fremont [CA], US) - Merci (Concentric Medical; Stryker, Fremont, [CA], US) - Other	- 83.3 - 8.3 - 4.2 - 0 - 4.2
15. What do you use as a second-line device for mechanical thrombectomy if the first-line failed?	- Solitaire FR (Medtronic, Minneapolis [MN], US) - Trevo (Stryker, Fremont [CA],US) - Merci (Concentric Medical; Stryker, Fremont [CA],US) - Penumbra ACE64/Penumbra System MAX (Penumbra, Inc, Alameda [CA], US) - Other	- 45.8 - 41.7 - 0 - 8.3 - 4.2
16. Do you use systemic heparin or other anticoagulants during the endovascular procedure?	- Yes - No	- 29.2 - 70.8
17. Do you give any antiplatelets or anticoagulants to patients soon after the thrombectomy?	- Yes - No - Other	- 29.2 - 58.3 - 12.5

* The percentages do not total 100 because of missing data

adopted by 83.3% of respondents. A stent retriever was chosen as a second-line thrombectomy device by 91.7% of interventionists. The majority of local practitioners used 6 hours as the time limit for anterior circulation thrombectomy in accordance with current guidelines, but a significant number of respondents (37.5%) adopted a more liberal limit of 8 hours or beyond. Most practitioners would prescribe intravenous thrombolysis using the standard dosage in patients who fulfilled thrombolysis indications, regardless of thrombectomy decision, and in line with current guidelines.

For patient selection, most local interventionists used CT angiography as the predominant imaging modality. This finding is unsurprising considering CT perfusion and MRI scanners were not routinely available in an emergency setting in many public hospitals where most acute stroke patients were treated. Apart from angiographic evidence of major vessel occlusion (intracranial internal carotid artery, M1/M2 segment of middle cerebral artery and basilar artery), stroke symptom severity of NIHSS score of >5 and pre-stroke functional status (mRS score ≤2) were regarded as important selection criteria by over 70% of respondents.

Up to 87.5% of respondents performed thrombectomy without general anaesthesia. This practice has been recommended after a recent meta-analysis that confirmed better outcome in patients treated under conscious sedation than in those under general anaesthesia.[26] A more recent randomised trial, however, showed no difference in outcome whether general anaesthesia or conscious sedation was used.[27]

Incorporating emergency thrombectomy in acute stroke care in Hong Kong

Locally, an acute ischaemic stroke service is heavily dependent on a public health system that handles over 80% of emergency hospital admissions in Hong

Kong.[28] Our neurologists and stroke physicians in public hospitals have made major contributions over the past two decades in implementing intravenous thrombolysis and spearheading 24-hour acute stroke care. As a result of much effort, currently seven of 17 emergency hospitals in the public hospital system provide 24-hour IV-tPA thrombolysis service.[29] Future enhancement of an acute stroke service should aim to provide timely and universal access for patients with acute ischaemic stroke, and divert potentially eligible thrombectomy patients to centres that can provide such service (Fig 3).

Our survey identified the most common reported obstacles in implementing prompt stroke interventions as poor inter- and in-hospital logistics of patient transfer and triage, delayed presentation, and insufficient interventionists, as well as difficulty in obtaining emergency CT angiogram in an urgent setting.

The two-tier primary and comprehensive stroke centre model that aims to give priority access to patients with suspected acute stroke may be seen as a framework for acute stroke service.[30-32] The first-tier stroke centre should be capable of providing 24-hour urgent CT and CT angiogram with round-the-clock IV-tPA service. All patients with suspicious stroke symptoms, such as acute hemiplegia or dysphasia, should be directly transferred to one of these first-tier stroke centres, bypassing other non-stroke centres in emergency hospitals to avoid unnecessary delay in diagnosis. When major vessel occlusion is suspected, immediate CT angiography should be performed in the same setting to determine thrombectomy eligibility. Second-tier stroke centres should additionally be capable of 24-hour endovascular thrombectomy, and be equipped with full-time neurosurgery, neurocritical care, and advanced radiological imaging support.[31] Among the local stroke specialists, a median number of four second-tier comprehensive stroke centres is believed to be appropriate in Hong Kong. Support from the health administration, structured training for endovascular techniques, and efficient use of existing resources are required to effectively incorporate emergency thrombectomy into routine clinical service locally.

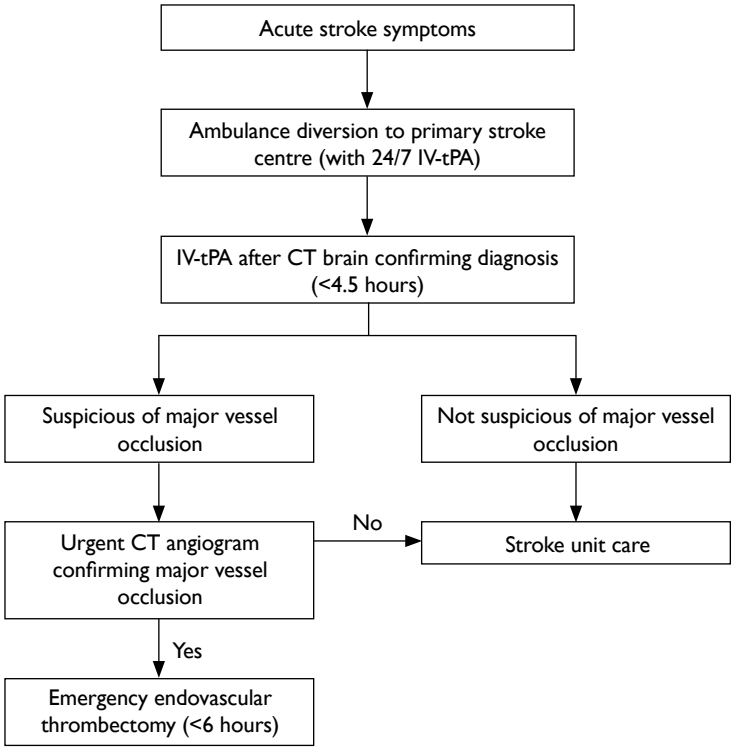

FIG 3. Treatment algorithm for patients with acute ischaemic stroke
Abbreviations: CT = computed tomography; IV-tPA = intravenous thrombolysis with tissue plasminogen activator

Conclusion

There is a strong body of clinical evidence and international guidelines to support emergency endovascular thrombectomy for acute ischaemic stroke due to anterior circulation major vessel occlusion. As the local stroke community embraces this new treatment modality, efforts should be directed towards providing universal and timely access to emergency ischaemic stroke therapy for the Hong Kong population.

Declaration

All authors have disclosed no conflicts of interest.

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