Stroke: Vascular and Interventional Neurology

GUIDELINE

Mechanical Thrombectomy in the Late Presentation of Anterior Circulation Large Vessel Occlusion Stroke: A Guideline From the Society of Vascular and Interventional Neurology Guidelines and Practice Standards Committee

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BACKGROUND: Recent clinical trials investigating endovascular therapy in the extended time window have opened new treatment paradigms for patients with late-presenting large vessel occlusion stroke. The aim of this guideline is to provide up-to-date recommendations for the diagnosis, selection, and medical or endovascular treatment of patients with large vessel occlusion presenting in the extended time window.

METHODS: The Society of Vascular and Interventional Neurology Guidelines and Practice Standards committee assembled a writing group and recruited interdisciplinary experts to review and evaluate the current literature. Recommendations were assigned by the writing group using the Society of Vascular and Interventional Neurology Guidelines and Practice Standards Class of Recommendation/Level of Evidence algorithm and Society of Vascular and Interventional Neurology Guidelines and Practice Standards guideline format. The final guideline was approved by all members of the writing group, the Guidelines and Practice Standards committee, and the Society of Vascular and Interventional Neurology board of directors.

RESULTS: Literature review yielded 3 high-quality randomized trials and several observational studies that have been extracted to derive the enclosed summary recommendations. In patients with large vessel occlusion presenting in the 6- to 24-hour window and with clinical–imaging mismatch as defined by the DAWN (Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) studies, endovascular therapy

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is recommended. Noncontrast computed tomography can be used to evaluate infarct size as the sole imaging modality for patient selection, particularly when access to computed tomography perfusion or magnetic resonance imaging is limited or if their performance would incur substantial delay to treatment. In addition, several clinical questions were reviewed based on the available evidence and consensus grading.

CONCLUSIONS: These guidelines provide practical recommendations based on recent evidence on the diagnosis, selection, and treatment of patients with large vessel occlusion stroke presenting in the extended time window.

Key Words: disease management ■ extended window ■ large vessel occlusion ■ late window ■ stroke ■ SVIN scientific statements

The DAWN (Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trials opened a new paradigm of endovascular treatment of large vessel occlusion (LVO) stroke in the extended 6- to 24-hour time window.[1–5] Both trials demonstrated the superiority of endovascular therapy (EVT) and medical therapy compared with medical therapy alone for the treatment of proximal anterior LVO in the late time window.[1–5] Rates of 90-day functional independence between the EVT and control groups in the DAWN and DEFUSE 3 trials were 49% versus 13% and 45% versus 17% ($P<0.001$), respectively. Mortality rates at 90 days were similar between the 2 groups in the DAWN trial (19% and 18%; $P=1.0$); however, the EVT group in the DEFUSE 3 trial had a lower mortality rate compared with the control group (14% versus 26%; $P=0.05$). In light of these late-window trials, the 2019 American Heart Association and European Stroke Organization guidelines provided updated guidance for the management of patients with acute stroke, encompassing patients who present early and late.[6,7] However, these guidelines were written according to the evidence that was available at the time of their issue and did not address other clinical questions that were not answered by the randomized trials.[8]

METHODS

All data and supporting materials have been provided with the published article. The authors declare that all supporting data are available in the article (and its online Supplementary files).

Writing Group

In August 2021, an interdisciplinary, international writing group was assembled and included representatives from the Society of Vascular and Interventional Neurology (SVIN), American Stroke Association, American Academy of Neurology, World Stroke Organization, and European Stroke Organization. The panel was composed of the following: content experts (T.N.N. and A.C.C. writing group co-chairs; R.G.N., G.W.A., T.G.V., S.O.M., M.G.L., S.N., J.E.S., S.A.S., J.P.T., and M.A.), methodology experts (A.C.C. and A.D.), and the Guidelines and Practice Standards committee chair (O.O.Z.). Supplement Table S1 lists the writing authors' disclosures. A population, intervention, comparators, outcomes, timing, and setting table was created (Table 1). Class of Recommendation (COR) and Level of Evidence (LOE) criteria were applied using the SVIN Guidelines and Practice Standards algorithm (Figure).[9] All authors voted on each recommendation using a modified Delphi consensus, except for recommendations with relevance to their industry relations (Supplement Table S1, Table 2).[9,10] The Appraisal of Guidelines for Research and Evaluation reporting checklist for clinical practice guidelines was followed (Supplement Table S3).[11] The guideline was submitted to the SVIN Guidelines and Practice Standards committee and Board of Directors for review and approval.

Summary of Evidence

A PubMed search was performed using the Nested Knowledge platform (AutoLit; Nested Knowledge, St.

Table 1. Mechanical Thrombectomy in the Late Presentation of Large Vessel Occlusion Stroke Guideline Population, Intervention, Comparators, Outcomes, Timing, and Setting Table

Population	Patients with acute ischemic stroke with large vessel occlusion presenting in the 6- to 24-h time window
Intervention	Mechanical thrombectomy
Cointervention	Medical therapy
Outcome	90-d functional independence using modified Rankin Scale score 0 to 2
Time frame	90 to 360 d after stroke onset
Setting	Emergency room and hospital inpatient

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
COR	Class of Recommendation
CS	conscious sedation
CTP	computed tomography perfusion
DUS	daytime unwitnessed stroke
DWI	diffusion-weighted imaging
EVT	endovascular therapy
GA	general anesthesia
GAPS	Guidelines and Practice Standards
LD	limited data
LOE	Level of Evidence
LVO	large vessel occlusion
mRS	modified Rankin Scale
MT	mechanical thrombectomy
NCCT	noncontrast head computed tomography
NIHSS	National Institute of Health Stroke Scale
NR	nonrandomized
SVIN	Society of Vascular and Interventional Neurology
TICI	Thrombolysis in Cerebral Infarction
WUS	wake-up stroke

CLINICAL PERSPECTIVE

- The Society of Vascular and Interventional Neurology Guidelines and Practice Standards committee assembled a writing group to evaluate the current literature for patients with anterior circulation large vessel occlusion presenting in the late window.
- In patients with large vessel occlusion presenting in the 6- to 24-hour window and with clinical–imaging mismatch as defined by the DAWN (Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) studies, endovascular therapy is recommended.
- Noncontrast computed tomography can be used to evaluate infarct size as the sole imaging modality for patient selection, particularly when access to computed tomography perfusion or magnetic resonance imaging is limited or if their performance would incur a delay to treatment.
- The clinical implication of these recommendations is the potential expansion in access to endovascular therapy in centers with limited access to advanced imaging modalities.
- The Society of Vascular and Interventional Neurology developed these recommendations to provide practical focused guidance to inform clinicians in the diagnosis, selection, and treatment of patients with anterior circulation large vessel occlusion presenting in the extended time window.

Paul, MN) from January 2010 to March 2022 using broad search criteria that included the following terms: acute ischemic stroke (AIS), thrombectomy, and 6- to 24-hour or late-window thrombectomy. A total of 358 studies were identified in the initial search and were screened by 2 authors (T.N.N. and A.C.C). Studies were excluded for the following reasons: no late-window treatment, qualitative review, mixed patient population (early and late window), case study or <5 patients, full-text unavailable, commentary, protocol, secondary analysis, patients not treated between 6 and 24 hours, guidelines, mixed population (thrombectomy and nonthrombectomy patients), in vivo/in vitro, and no LVO (Supplement Figure S1, Table S2).

PATIENT SELECTION IN THE 6- to 24-HOUR TIME WINDOW

Mismatch Criteria

In contrast to early time window MT trials,[12,13] DAWN and DEFUSE 3 used advanced imaging studies (computed tomography perfusion [CTP] or magnetic resonance imaging [MRI]) to assess for both salvageable brain tissue and extent of infarcted tissue.[1,2] Mismatch, defined as having a larger volume of viable brain tissue at risk (penumbra) than volume of existing infarcted brain tissue, was a key enrollment criteria of DAWN and DEFUSE 3 (Table 3). Target mismatch in DEFUSE 3 was defined as having an infarct core volume <70 mL, mismatch volume of ≥15 mL, and a ratio of the volume of ischemia to infarct volume of ≥1.8. In addition, DAWN applied clinical criteria, age, and National Institute of Health Stroke Scale (NIHSS) score cutoffs as part of

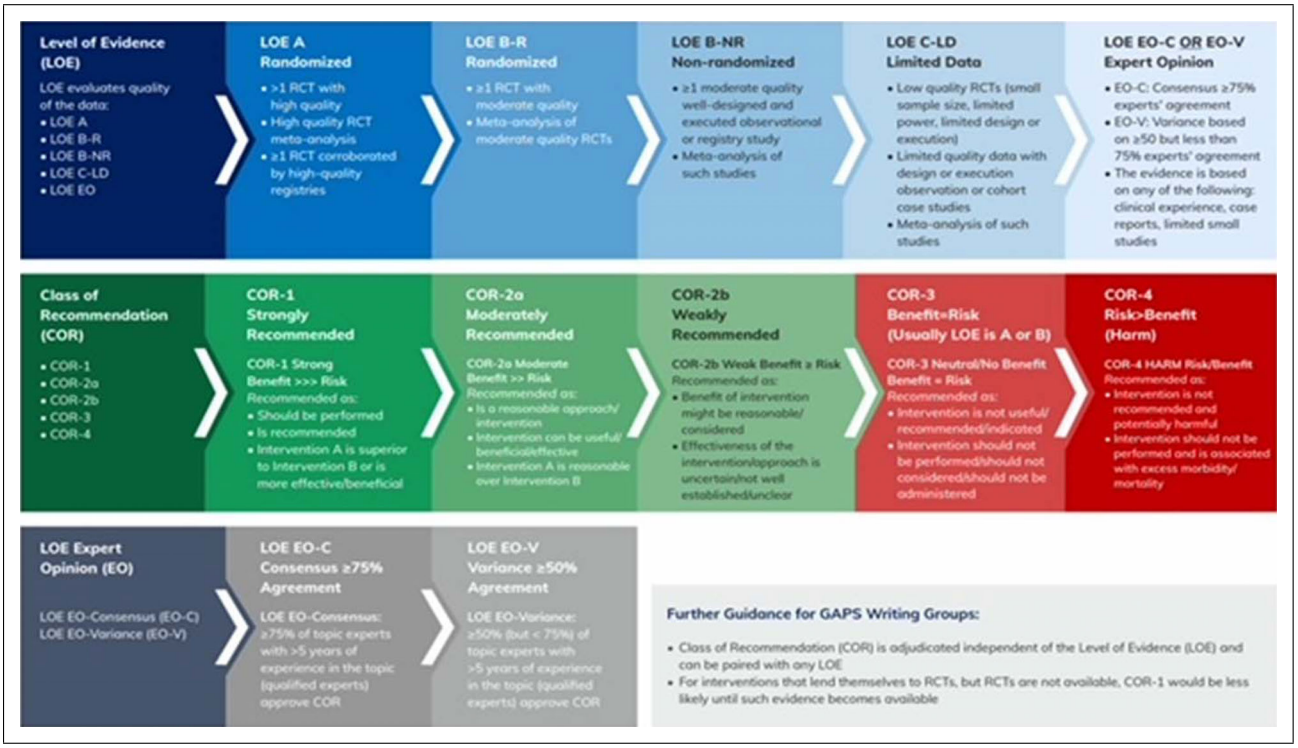

Figure. Society of Vascular and Interventional Neurology GAPS algorithm for applying LOE of COR to intervention, approach, and treatment (adapted from American College of Cardiology/American Heart Association, 2021).
COR indicates Class of Recommendation; EO, Expert Opinion; EO-C, EO-Consensus; EO-V, EO-Variance; GAPS, Guidelines and Practice Standards; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

the mismatch criteria.[14] Given the evidence of superiority, EVT is recommended for patients meeting DAWN and DEFUSE 3 criteria (COR-1, LOE A).

Recommendation	COR	LOE
In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO and with clinical–imaging mismatch as defined in the DAWN or DEFUSE 3 trials, EVT is recommended.	1	A

Advanced Imaging Selection

Computed Tomography Perfusion

CTP scan is a validated tool that can image blood flow abnormalities and estimate the volume and location of the ischemic core and penumbra. It is accessible and efficient, with a limited effective radiation dose, an acquisition time averaging <90 seconds, and automated postprocessing software allowing rapid and convenient point-of-care access to CTP results.[15,16]

Clinical use of CTP requires technically adequate image acquisition and accurate understanding of its interpretation and limitations. Validated optimal CTP parameters, thresholds, and postprocessing algorithms should be used. Unlike diffusion-weighted imaging (DWI), the ischemic core on CTP does not demonstrate dead tissue, but outlines regions with blood flow so low that irreversible injury is highly likely.[15,17] The relative cerebral blood flow reduction identifies the ischemic core with an optimal threshold of <30% to 35% of normal, whereas the time to maximum of the residue function of >6 seconds marks the ischemic penumbra at risk of infarction in the absence of reperfusion.[18–20] As CTP is a probabilistic map of tissue fate based on the hemodynamics at the moment of image acquisition, prolongation or exacerbation of cerebral hypoperfusion may introduce variability in the perceived accuracy of this prediction when compared with the final infarct volume.

The clinical benefits of EVT for LVO in the late time window were established by the ability of these techniques (CTP and MRI) to identify patients who were likely to have salvageable tissue. Per the DAWN and DEFUSE 3 eligibility criteria, the 2019 American Heart Association/American Stroke Association guidelines recommended the use of CTP as 1 of the imaging modalities for patient selection for EVT (COR-1; LOE A).[6]

Table 2. Summary of Recommendations and Expert Opinion in the Late Window

	Recommendation(s)	Expert opinion
Patient selection	In patients presenting within 6 to 24 h from last known well with proximal anterior circulation LVO and with clinical–imaging mismatch as defined in the DAWN or DEFUSE 3 trials, EVT is recommended. (COR-1; LOE A)	(13/13 votes) There was unanimous consensus among the panel to support this recommendation.
	In patients with proximal anterior circulation LVO 6 to 24 h from last known well, NCCT can be used as the sole imaging modality to evaluate infarct size, particularly when access to CTP or MRI is limited or if their performance would incur substantial delay to treatment. (COR-2a; LOE B-NR)	(10/13 votes) There was majority consensus (>50%) among the panel to support this recommendation.
Systems of care	In patients with a suspected LVO presenting within the 6 to 24 h of last known well, it may be reasonable to transport the patient directly to an EVT-performing center if transport time would not be delayed by >15 min relative to the nearest stroke center. (COR-2b; LOE EO-C)	(11/13 votes) There was majority consensus (>75%, EO-C criteria) among the panel to support this recommendation.
Peri-procedural Considerations	In patients presenting within 6 to 24 h from last known well with a proximal anterior circulation LVO who are candidates for EVT, the use of either conscious sedation or general anesthesia is reasonable. (COR-2a; LOE B-NR)	(6/11 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients with late-window LVO, following successful reperfusion (TICI 2b/3), reduction, and maintenance of systolic BP to a target of ≤140 mm Hg may be reasonable. (COR-2b; LOE B-NR)	(13/13 votes) There was unanimous consensus among the panel to support this recommendation.
	In patients presenting within 6 to 24 h from last known well with a proximal anterior circulation LVO, use of a balloon-guided catheter is reasonable during EVT in the extended window. (COR-2b; LOE B-NR)	(7/11 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients presenting within 6 to 24 h from last known well with a proximal anterior circulation LVO, the use of a stent retriever is recommended. (COR-1; LOE A)	(13/13 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients presenting within 6 to 24 h from last known well with a proximal anterior circulation LVO, first-line contact aspiration or combined aspiration technique can be as effective as the first-line stent retriever technique. (COR-2a; LOE B-R)	(13/13 votes) There was majority consensus (>50%) among the panel to support this recommendation.
Special considerations	In patients presenting within 6 to 24 h from last known well with NIHSS scores <6 and proximal anterior circulation LVO, the effectiveness of EVT compared with medical management is unknown. (COR-2b; LOE C-LD)	(6/11 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients with premorbid disability presenting within 6 to 24 h from last known well with a proximal anterior circulation LVO, EVT may be reasonable if other MT criteria are met. (COR-2b; LOE B-NR)	(8/11 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients aged ≥80 years presenting within 6 to 24 h from last known well with a proximal anterior circulation LVO, EVT is reasonable if other established criteria for MT are met. (COR-2a; LOE B-NR)	(6/11 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients with anterior circulation LVO presenting within 6 to 24 h of last known well, EVT is recommended regardless of the presentation (witnessed, daytime unwitnessed, wake-up unwitnessed stroke). (COR-1; LOE A)	(8/11 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients with anterior circulation LVO presenting within 6 to 24 h of last known well with large core infarct as defined by CT or DWI ASPECTS 2 to 5, enrollment in ongoing clinical trials is recommended. (COR-2b; LOE B-NR)	(12/13 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients with LVO presenting beyond 24 h with target mismatch profiles based on CT perfusion imaging or MRI, EVT may be considered. (COR-2b; LOE C-LD)	(12/13 votes) There was majority consensus (>50%) among the panel to support this recommendation.
	In patients with LVO presenting beyond 24 h, it is unknown whether selection by NCCT to EVT confers benefit. (COR-2b; LOE C-LD)	(11/13 votes) There was majority consensus (>50%) among the panel to support this recommendation.

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; COR, Class of Recommendation; CT, computed tomography; CTP, computed tomography perfusion; DAWN, Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; DWI, diffusion-weighted imaging; EO-C, Expert Opinion-Consensus; EVT, endovascular therapy; LD, limited data; LOE, Level of Evidence; LVO, large vessel occlusion; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; NCCT, noncontrast head computed tomography; NIHSS, National Institute of Health Stroke Scale; NR, nonrandomized; R, randomized; and TICI, Thrombolysis in Cerebral Infarction.

Table 3. Mismatch Criteria in the DAWN and DEFUSE 3 Trials

Trial	Time window	Mismatch criteria
DAWN[1]	6 to 24h	Clinical–imaging mismatch
		Age <80 y, NIHSS score ≥10, and infarct core 0 to 30 mL
		Age <80 y, NIHSS score ≥20, and infarct core 31 to 50 mL
		Age ≥80 y, NIHSS score ≥10, and infarct core 0 to 20 mL
DEFUSE 3[2]	6 to 16 h	Target mismatch profile (CT or MR perfusion)
		Infarct core volume <70 mL and mismatch volume >15 mL (T_{max}>6 s) and mismatch ratio (penumbra/core) ≥1.8

CT indicates computed tomography; DAWN, Diffusion-Weighted Imaging or Computed Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke; MR, magnetic resonance; NIHSS, National Institute of Health Stroke Scale; and T_{max}, time to maximum.

The AURORA (Analysis of Pooled Data From Randomized Studies of Thrombectomy More Than 6 Hours After Last Known Well) collaboration pooled data from 505 patients across 6 clinical trials and further supported the benefit of thrombectomy as related to independent function (modified Rankin Scale [mRS] score 0–2) at 90 days, with an unadjusted common odds ratio (OR) of 2.42.[4] In 372 patients for whom clinical mismatch or perfusion mismatch imaging profiles were available, the presence of a target mismatch on CTP was a predictor of improved functional outcome (OR, 3.13; P=0.001).[5] This effect strengthened over time and was greatest between 12 and 24 hours (OR, 5.01; P<0.001). In contrast, patients without definite target mismatch on CTP derived no significant clinical benefit from EVT.[5]

Magnetic Resonance Imaging

Although CT-based imaging remains the most accessible method of evaluating patients with AIS with LVO and determining eligibility for EVT, some centers prefer MRI-based protocols because of their superiority in determining ischemic core volume on DWI.[21,22] However, computed tomography (CT) angiography is more accurate than magnetic resonance angiography for the identification of LVO given the higher likelihood that time-of-flight magnetic resonance angiography overcalls severe stenosis as occlusion.[23,24] In addition, the hypothesis that DWI reflects an irreversibly injured ischemic core remains vigorously debated. For example, DWI reversibility in the early hours of stroke can be seen in up to 25% of patients with AIS,[25,26] but DWI remains superior to CT-based infarct core measurement in the 24 hours after stroke onset.

In both the DEFUSE 3 and DAWN trials, MRI evaluation of the ischemic core volume was permitted, and in DEFUSE 3 MRI perfusion with a dynamic susceptibility contrast sequence was permitted for evaluation of the hypoperfused volume (ischemic penumbra+ischemic core).[1,2] In DEFUSE 3 and DAWN, 26.9% (49/182) and 36.4% (75/206) of participants were evaluated by MRI, respectively. Although DAWN did not report an interaction between imaging modality and EVT treatment in the primary analysis, in DEFUSE 3 the interaction lacked significance (P=0.41), suggesting that patients enrolled by CTP or MRI did not change the efficacy of EVT. As a result, the 2019 American Heart Association guideline acknowledged MRI as equivalent to CTP-based evaluation when identifying randomized controlled trial–concordant eligibility for EVT in the late window. However, the trials were not powered to address this comparison.[6]

There are several drawbacks for the MRI-based evaluation of patients with AIS compared with CT-based imaging. Ferromagnetic materials in the patient's body can present a safety concern and necessitates either the ability to exclude them through a reliable patient or surrogate history, which can be challenging in the setting of AIS, or screening through x-ray or CT imaging.[27] In addition, if applying the DEFUSE 3 criteria, then gadolinium contrast would be administered for the perfusion component of the MRI, although the presence of DWI fluid-attenuated inversion recovery mismatch may be used as a surrogate for early onset or salvageable brain tissue in patients with unknown symptom onset of stroke.[28] Although exceedingly rare and almost exclusively in patients with end-stage renal disease, gadolinium contrast has been associated with the systemic and potentially fatal complication of nephrogenic systemic fibrosis.[29] Finally, MRI-based evaluation may take longer than CT-based evaluation because of the duration of MRI sequences and complexity of maintaining an environment free of ferromagnetic material.[30] Using a cohort of >2000 patients, the BEYOND-SWIFT and Swiss Stroke Registry investigators observed better outcomes in patients selected using MRI over CT; however, this came at the cost of an average delay to thrombectomy of 30 minutes with MRI use in BEYOND-SWIFT but no delay in door to puncture in the Swiss Stroke Registry.[31,32] Whether MRI overselects patients who might be eligible for thrombectomy remains controversial.

Noncontrast Head CT Selection

There is growing interest in simplifying the screening criteria for EVT and limiting the barriers to treatment. In particular, the need for advanced imaging with CTP

or MRI to screen patients presenting in the late time window has been questioned. There are several reasons motivating a screening approach that relies on noncontrast head CT (NCCT) alone. First, CTP imaging is not widely available. In a statewide cohort using Medicare claims data, only 17% of hospitals caring for patients with AIS were CTP performing, and nearly 70% of patients with AIS presented to hospitals that were not CTP performing.[33] On the other hand, these hospitals were NCCT performing. This limited access to MRI and lack of CTP access is even more pronounced outside the United States.[34] Because the transfer of all patients with late-window LVO to CTP-performing centers is not feasible, a screening strategy that uses available imaging modalities would improve stroke systems of care. In addition, there are practical limitations with CTP, including substantial head motion limiting interpretation in up to 25% of patients with AIS, slower treatment times, inaccuracies in infarct core and penumbra prediction, the high cost associated with postprocessing packages, and limited contrast supply amidst a breach in the supply chain.[35] Routine use of CTP has also been shown to lead to a reduced likelihood of offering EVT, fueling concerns of overselection and undertreatment.[36] Finally, it is highly likely that the accuracy of NCCT to detect ischemic changes increases in later time windows as the infarct evolves. Thus, an approach that uses NCCT as the sole evaluation for infarct in late-window LVO AIS may have numerous benefits.

The largest study to date on NCCT versus CTP selection for patients with late-window AIS LVO was the CLEAR collaboration, a multicenter cohort study of consecutive patients treated with EVT.[37] The study included 1604 patients from 15 sites in Europe and North America. Of those, 534 underwent EVT selection with NCCT, 752 with CTP and 318 with MRI. Rates of symptomatic intracranial hemorrhage were not significantly different between patients treated by different imaging selection modalities (8.1% in the NCCT group, 5.8% in the CTP group, and 4.7% in the MRI group), even in patients who were successfully reperfused.[38] Rates of 90-day functional independence were comparable between NCCT and CTP; unadjusted values were 41% and 44% for NCCT and CTP, which were comparable with the DAWN and DEFUSE 3 endovascular arms (49% and 45%, respectively). In multivariable analysis, there was no difference in 90-day disability outcomes between the NCCT and CTP groups (adjusted OR, 0.90 [95% CI, 0.7–1.2]). Notably, door-to-groin times were faster in the NCCT group (76 versus 93 minutes, NCCT versus CTP).[37]

Other smaller studies have also suggested that screening patients with clinical–imaging mismatch as used in the DAWN trial, but with the NCCT Alberta Stroke Program Early Computed Tomography Score (ASPECTS) rather than CTP or DWI, may be sufficient. In a cohort that included Trevo Registry and DAWN trial patients, 67 patients with AIS LVO in the late time window were treated with EVT after screening with NCCT alone, and 180 also had CTP. No differences in 90-day mRS score were observed between patients screened with these 2 approaches (adjusted OR, 0.98 [95% CI, 0.8–1.7]). In a study from Germany, in patients who met standard early time window criteria but presented in the late time window, NCCT ASPECTS scoring was effective at predicting good functional outcomes, whereas screening with MRI or CTP was not.[39]

Recommendation	COR	LOE
In patients with a proximal anterior circulation LVO 6 to 24 hours from last known well, NCCT can be used as the sole imaging modality to evaluate infarct size, particularly when access to CTP or MRI is limited or if their performance would incur substantial delay to treatment.	2a	B-NR

Systems of Care

Transfers Versus Mothership Paradigms

EVT can only be performed at select hospitals that have the necessary infrastructure and medical expertise available to perform this procedure. Approximately one-third of stroke centers in the United States are equipped to perform EVT, and only one-fifth of people in the United States live within 15 minutes from 1 of these EVT-capable centers.[40,41] This raises the question if patients who are suspected to have suffered an acute stroke should be transported by first responders directly to an EVT center (mothership paradigm) or if they should be transported to the nearest hospital for triage and subsequently transferred to an EVT center if they meet the criteria for EVT (transfer paradigm).

The potential benefit of the mothership paradigm is that it can reduce the time from symptom onset to start of the endovascular procedure by eliminating time spent on organizing and executing interfacility transfers. A potential benefit of the transfer paradigm, where patients are transported to the nearest hospital by emergency responders, is that it can reduce door-to-needle time in patients who are eligible for thrombolysis. This is relevant in the <4.5-hour time window when shorter door-to-needle times are associated with a greater benefit of thrombolysis. This association has not been established in the late time window, when only patients with evidence of salvageable tissue benefit from thrombolysis. However, even in the late time

window, reducing stroke-onset-to-treatment times can biologically only benefit patients.

Studies comparing the mothership and transfer paradigms are mostly of low quality, as they include prospective and retrospective observational studies with no randomized trial conducted in the late window. A systematic review and meta-analysis of these studies showed shorter symptom-onset-to-EVT times and better functional outcomes among patients who were directly transported to the mothership.[42] A key limitation of these observational studies is that shorter stroke-onset-to-EVT times observed with the mothership paradigm are likely attributed to a bias where patients who live in close proximity to an EVT center are directly transported to EVT centers, whereas patients who live far from EVT centers follow the interfacility transfer paradigm. Thus, the shorter times observed with the mothership paradigm are likely in large part the result of geographical differences in the patient populations rather than efficiencies of the mothership paradigm. Another limitation of these studies is that they mostly included patients treated in the earlier time window. Subanalyses of the DEFUSE 3 and DAWN late-window EVT trials showed no effect of time on treatment effect and no difference in outcomes between the mothership and transfer paradigms. However, these subanalyses were biased in that the trials only included patients with evidence of salvageable tissue on brain imaging. Thus, patients whose ischemic core expanded during transfer and who no longer had salvageable tissue on arrival at the EVT center were excluded.

RACECAT was a randomized trial in Catalonia evaluating whether direct transport to a thrombectomy-capable center was better than transport to the closest local stroke center in patients presenting in the early window (up to 7 hours from last known well). The study found no difference in 90-day outcomes between either transportation strategy.[43] Altogether, in light of the data from the RACECAT study, in patients with suspected LVO presenting within the 6- to 24-hour time of last known well, it may be reasonable to transport the patient directly to an EVT-performing center if transport time would not be delayed by >15 minutes relative to the nearest stroke center. The rationale of patients presenting to a non-EVT hospital are 2-fold. First, not every patient with suspected stroke is a candidate for EVT (ie, stroke mimic, lacunar stroke, patient with completed infarct, an occlusion too distal to treat, and hemorrhagic stroke), and it would be advantageous for some of these patients to receive medical care at the earliest possible time. Second, an EVT hospital may become overburdened by an influx of all incoming patients with suspected stroke.

Recommendation	COR	LOE
In patients with a suspected LVO presenting within the 6 to 24 hours of last known well, it may be reasonable to transport the patient directly to an EVT-performing center if transport time would not be delayed by >15 minutes relative to the nearest stroke center.	2b	LOE EO-C*

*There was majority consensus (>75%) among the experts panel to support this recommendation (11/13 votes).

Periprocedural Considerations

There are limited data regarding the procedural and periprocedural medical management of patients undergoing EVT,[44] particularly in the extended window.

Procedural Sedation

Regarding the method of procedural sedation in the early window, 3 single-center randomized clinical trials (SIESTA, GOLIATH, and AnStroke)[45–47] demonstrated no superiority of general anesthesia (GA) over conscious sedation (CS) for each trial's primary endpoint. Several exploratory and secondary endpoints favored the use of GA. In the extended window, the DEFUSE 3 trial investigators reported patients treated with GA were at a lower odds of achieving functional independence (mRS score 0–2) at 90 days when compared with patients treated under CS (adjusted common OR, 0.27 [95% CI, 0.09–0.75]; P=0.01).[48] In a subgroup analysis including sites that exclusively used 1 modality of sedation, a significantly higher proportion of patients treated with CS achieved functional independence at 90 days when compared with GA (58% versus 21%; P=0.03). This may have been in part attributed to a longer duration from arrival to arterial puncture in the GA versus CS cohorts (median 18 versus 14 minutes; P=0.05) and longer time from groin puncture to recanalization (median 42 versus 35 minutes; P=0.03). These outcome differences were not observed in the DAWN trial.[49]

Recommendation	COR	LOE
In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO who are candidates for EVT, the use of either CS or GA is reasonable.	2a	LOE B-NR

Blood Pressure Management

Many early window trials enrolled patients concomitantly treated with intravenous thrombolysis; therefore, postprocedural blood pressure (BP) goals of ≤180/105 mm Hg are recommended in this period.[6] In the extended window, the DAWN trial protocol recommended a systolic goal of <140 mm Hg following successful reperfusion, whereas there was no BP target

in DEFUSE 3.[1,2] The BP target study was a randomized controlled trial of patients with EVT who achieved successful (Thrombolysis in Cerebral Infarction [TICI] 2b/3) reperfusion comparing a postprocedure BP target of 100 to 129 mm Hg versus standard care 130 to 185 mm Hg at 4 centers in France.[50] The majority of patients in this study were in the early window. There was no difference in the primary outcome of radiographic parenchymal intracranial hemorrhage between the 2 groups. These findings are in contrast to several multicenter observational cohort studies and a recent meta-analysis demonstrating a higher risk of symptomatic intracerebral hemorrhage and poorer functional outcomes in patients who received a thrombectomy whose postprocedural systolic and diastolic BP remained elevated.[51,52] Other potential predictors of poor functional outcomes from exploratory analyses include severely low mean arterial pressure (<70 mm Hg) during thrombectomy[53] and highly variable BP following thrombectomy.[51,54] Ongoing trials are assessing optimal BP targets after successful reperfusion, including the BEST-II (Blood Pressure After Endovascular Stroke Therapy) randomized clinical trial.[55]

Recommendation	COR	LOE
In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, following successful reperfusion (TICI 2b/3), reduction and maintenance of systolic BP to a target of ≤140 mm Hg may be reasonable.	2b	LOE B-NR

Balloon-Guide Catheter Use

No randomized controlled trials have evaluated outcomes following balloon-guide versus non–balloon-guide catheter use in the extended window. The NASA,[56] TRACK (Trevo Stent-Retriever Acute Stroke),[57] and a meta-analysis of 16 observational cohort studies demonstrated greater odds of first-pass effect[58] (OR, 1.92 [95% CI, 1.34–2.76]; $P<0.01$), successful reperfusion (OR, 1.85 [95% CI, 1.42–2.40]; $P< 0.01$), and good functional outcome (mRS score 0–2 at 90 days; OR, 1.48 [95% CI, 1.27–1.73]; $P<0.01$) with balloon-guide catheter use. This meta-analysis reported a moderate risk of bias.[59]

Recommendation	COR	LOE
In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, the use of a balloon-guided catheter is reasonable during EVT in the extended window.	2b	LOE B-NR

Intracranial Device Use

Stent retrievers were used for thrombectomy in the DAWN trial, with reperfusion (TICI 2b/3) achieved in 84% of patients. Recovery by endovascular salvage for cerebral embolism reperfusion therapy with other devices or pharmacological agents was not permitted in DAWN.[1] The DEFUSE 3 trial and RESCUE-Japan LIMIT (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial) permitted investigators to use devices at their discretion, including combinations of devices. In DEFUSE 3, of 92 patients in the EVT arm, most had a stent retriever (n=74), and aspiration alone was used in 25 patients with an overall result of complete recanalization in 78% of patients.[2] In the RESCUE-Japan LIMIT trial, which included patients in the early and late windows (58/203 in the 6- to 24-hour window), the combined stent retriever and aspiration technique was used in 78 patients in the endovascular arm, followed by aspiration (n=11) and stent retriever (n=9) only. TICI≥2b reperfusion was achieved in 86% of patients.[60]

The ASTER (Contact Aspiration Versus Stent Retriever for Successful Revascularization) trial randomly assigned patients in the 6-hour window to first-line stent retriever or first-line contact aspiration. There was no difference in revascularization rates, which were 85.4% for contact aspiration compared with 83.1% for the stent retriever.[61] ASTER 2 was the follow-up randomized trial of patients presenting in the 8-hour window comparing first-line combination stent retriever and contact aspiration versus first-line stent retriever technique, also not finding a difference in final reperfusion between the 2 techniques.[62] The aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for LVO (COMPASS) trial was a noninferiority randomized clinical trial comparing direct aspiration first pass or stent retriever first-line thrombectomy for patients with LVO presenting in the first 6-hour window. This study also found noninferior functional outcome at 90 days between the 2 groups.[63]

Recommendation	COR	LOE
In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, the use of a stent retriever is recommended.	1	LOE A
In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, first-line contact aspiration or a combined aspiration technique can be as effective as the first-line stent retriever technique.	2a	LOE B-R

SPECIAL CONSIDERATIONS IN THE LATE TIME WINDOW

Low NIHSS Score

There is a paucity of data on the endovascular treatment of patients presenting with mild ischemic stroke and LVO in the 6- to 24-hour time window. Both late-window EVT trials, DAWN and DEFUSE 3,[1,2] excluded patients who presented with a low baseline NIHSS score. DEFUSE 3 excluded patients with baseline NIHSS scores <6, whereas DAWN excluded patients with either baseline NIHSS scores <10 or <20 based on age and infarct core volume (Table 3). As patients presenting with mild stroke often have collaterals, careful consideration must be given as collateral collapse may occur, resulting in early neurologic deterioration. It is estimated that ≈18% to 35% of patients presenting with low NIHSS score and LVO will progress to early neurologic deterioration,[64] and patients with M1 and internal carotid artery occlusions carry a higher likelihood of developing early neurologic deterioration.[65] Furthermore, several studies demonstrated that delaying MT until worsening clinical symptoms in patients with LVO with low NIHSS scores resulted in poorer outcomes and a higher risk of complications.[66–69] In a pooled analysis of patients with NIHSS scores <6 and proximal anterior LVO, EVT was associated with functional independence in patients who had target mismatch profiles on perfusion imaging.[70] Currently, there is 1 ongoing clinical trial that is investigating patients with low NIHSS scores and LVO in the late time window. The MOSTE (European Minor Stroke Therapy Evaluation) trial (NCT03796468) includes patients presenting within 24 hours and NIHSS scores <6 randomly assigned 1:1 to EVT or medical therapy and will hopefully provide further insight into the treatment of patients with low NIHSS scores in the late window.

Recommendation	COR	LOE
In patients presenting within 6 to 24 hours from last known well with NIHSS scores <6 and proximal anterior circulation LVO, the effectiveness of EVT compared with medical management is unknown.	2b	LOE C-LD

Premorbid mRS Score

Limited data exist on the treatment of patients with LVO with premorbid disability in the 6- to 24-hour time window. Historically, these patients (premorbid mRS score ≥2) have been excluded from randomized trials of MT in the early window and were also excluded from the late-window trials, DAWN and DEFUSE 3. A study from the TRACK registry showed that 37.7% (20/53) of patients with prestroke disability (mRS score ≥2) and LVO achieved no accumulated disability when treated with EVT.[71] The RESCUE–Japan Registry demonstrated higher rates of favorable outcome in patients with anterior circulation LVO with baseline mRS scores 2 to 4 presenting within 24 hours of last known well when treated with EVT versus medical management (28% versus 10.9%; $P<0.01$).[72]

Recommendation	COR	LOE
In patients with premorbid disability presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, EVT may be reasonable if other MT criteria are met.	2b	LOE B-NR

Advanced Age

Although the pivotal late-window trials included patients aged ≥80 years, there were only 54 patients aged ≥80 years in the DAWN trial (25/107 EVT group, 29/99 control). In the DEFUSE 3 trial, the median age of patients was 70 years (interquartile range, 59–79 years) in the EVT arm and 71 years (interquartile range, 59–80 years) in the medical management arm.[1,2] In a prespecified subgroup analysis from the AURORA analysis, treatment effect (favoring EVT) was shown across all age groups, including ages 70 to 79 years (adjusted OR, 3.03 [95% CI, 1.57–5.84]; $P=0.0011$, n=139) and ≥80 years (adjusted OR, 2.60 [95% CI, 1.23–5.51]; $P=0.013$, n=120).[4]

Recommendation	COR	LOE
In patients aged ≥80 years presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, EVT is reasonable if other criteria for MT are met.	2a	LOE B-R

Witnessed Versus Unwitnessed Presentation

It is important to differentiate between known and unknown onset of symptoms. A common situation occurs in a patient who wakes up with stroke symptoms, described as wake-up stroke (WUS). Importantly, a third of patients have a daytime unwitnessed stroke (DUS) or WUS. In both the DAWN (88%) and DEFUSE 3 (64%) studies, these patients represented the majority of enrolled patients.[1,2] The established term to define the time window for these patients is "time from last seen well," which has been defined as 6 to 24 hours for clinical routine, according to the inclusion criteria for the DAWN trial (in DEFUSE 3, time from last seen well was 6 to 16 hours). Yet, patients with WUS or DUS (according to the aforementioned last seen well time criteria) may have true windows <6 hours if the time from

symptom recognition and presentation is <6 hours, which is regularly the case. Patients with late-presenting stroke with LVO and a suitable imaging profile for EVT are also called "slow progressors," especially if the onset was witnessed (true time window beyond 6 hours). Rocha and Jovin established this pragmatic clinical definition in 2017, and in contrast to a rapid progressor, slow progressors maintain good collaterals and experience slow infarct growth over time.[73]

Patients with WUS and DUS differ in some regards. The interval between time from last seen well and presentation may be shorter in patients with DUS compared with WUS.[74] Patients with DUS may be more likely to be severely affected at presentation and present with altered mental status or aphasia.[75] Yet, outcome is not necessarily different between patients with DUS and WUS,[76] and a post hoc analysis of the DAWN trial showed that the benefit of EVT compared with best medical therapy was maintained across all 3 onset modes (rates of 90-day mRS scores of 0–2 in patients allocated to thrombectomy versus control): WUS (49.3% versus 10.6%), DUS (41.4% versus 13.2%), and witnessed onset (63.6% versus 21.4%).[77]

Recommendation	COR	LOE
In patients with anterior circulation LVO presenting within 6 to 24 hours of last known well, EVT is recommended regardless of the presentation (witnessed stroke, DUS, or unwitnessed WUS).	1	LOE A

Large Core Infarct

The RESCUE-Japan LIMIT was the first study to compare endovascular to medical management in patients with large core infarct as defined by ASPECTS 3 to 5, with most patients (86%) selected by ASPECTS on diffusion-weighted MRI.[60] In contrast to most anterior circulation EVT trials, the primary outcome was 90-day mRS score of 0 to 3. In the 6- to 24-hour window from last seen well, patients were included if there were no fluid-attenuated inversion recovery changes on MRI, indicative of recent infarct.[28] Subgroup analysis of 58 patients in the late window demonstrated a trend toward favorable treatment effect with EVT (relative risk [RR], 2.49 [95% CI, 0.73–8.45]); however, this analysis was underpowered. Several large core infarct trials (TESLA [Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke; NCT 03805308], SELECT2 [A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in AIS; NCT03876457], TENSION [Efficacy and Safety of Thrombectomy in Stroke with Extended Lesion and Extended Time Window; NCT03094715], ANGEL-ASPECT [Endovascular Therapy in Acute Anterior Circulation Large VeSsel Occlusive Patients with a LargE Infarct Core NCT04551664]) continue enrollment in light of these findings and will provide more insight into the optimal selection of patients with large core infarct.[78]

Recommendation	COR	LOE
In patients with anterior circulation LVO presenting within 6 to 24 hours of last known well with large core infarct as defined by CT or DWI ASPECTS 2 to 5, enrollment in ongoing clinical trials is recommended.	2b	LOE B-NR

Beyond 24 Hours

Beyond 24 hours from symptom onset of stroke, 4 nonrandomized studies showed clinical benefit in patients selected with target mismatch profiles[79,80] or per local site protocol[81] with outcomes similar to patients treated in the early window.[82] In a propensity score–matched analysis of a Korean single-center study, EVT was associated with better odds of good outcome compared with medical management (90-day mRS score 0–2, adjusted OR, 11.1 [95% CI, 1.9–108] or 90-day mRS score shift, COR, 5.16 [95% CI, 1.8–15]).[79,80]

Recommendation	COR	LOE
In patients with anterior circulation LVO presenting beyond 24 hours with target mismatch profiles based on CTP imaging or MRI, EVT may be considered.	2b	LOE C-LD
In patients with anterior circulation LVO presenting beyond 24 hours, it is unknown whether selection by NCCT to EVT confers benefit.	2b	LOE C-LD

Posterior Circulation

Basilar artery occlusion is known to have poor outcomes with medical management.[83,84] In the extended window, the BEST trial, a randomized trial of patients with basilar artery occlusion, included patients up to the 8-hour time window.[85] However, most patients in this trial were randomly assigned within 6 hours, as reflected by the upper boundary of the interquartile range (360 minutes intervention arm, 387 minutes control arm). The BAOCHE trial is a randomized trial for basilar artery occlusion patients in the 6- to 24-hour time window, and the ATTENTION trial evaluated patients with basilar artery occlusion in the 12-hour time window.[86,87] The BATMAN study was a retrospective study of patients with basilar artery occlusion. In this study of 64 patients treated in the 6- to 24-hour time window, reperfused patients had good outcome with less thrombus burden and higher collateral score.[88] Consensus on the optimal selection and management of patients with basilar artery occlusion remains variable.[89] The Guidelines and Practice

Standards committee will be discussing posterior circulation LVO MT in early and late window recommendations in a subsequent statement.

FUTURE DIRECTIONS

Ongoing Trials

Strict adherence to imaging inclusion criteria in the DAWN and DEFUSE 3 trials may exclude patients who can benefit from EVT,[90] and advanced imaging modalities are not widely available at hospitals receiving patients with stroke. To address these concerns, there are 2 ongoing trials. MR-CLEAN LATE was a Dutch multicenter trial (ISRCTN19922220) that enrolled 502 patients with stroke to investigate the efficacy of EVT in the 6- to 24-hour window for AIS attributed to proximal anterior circulation LVO. The study used collateral interpretation on CT angiography as a surrogate for advanced penumbral imaging. Collateral flow rating on single-phase CT angiography (poor, moderate, or good) was included. Preliminary data presented at the October 2022 World Stroke Congress showed better functional outcomes by 90-day mRS in the EVT compared to medical management group (aOR 1.68 (95% CI 1.21–2.33)).[91] NO-CTP (A Randomized Trial of Imaging Selection Modalities for Stroke Thrombectomy) is a randomized non inferiority trial (NCT05230914) in China that will evaluate whether NCCT is non inferior to CTP in patients with anterior large vessel occlusion stroke presenting in the late window.

Similarly, the multicenter RESILIENT Extend^2 (NCT02216643) was designed to examine the safety and efficacy of thrombectomy for large vessel anterior circulation ischemic stroke, compared with medical therapy, within 8 to 24 hours from last known well. The study will use age-adjusted imaging inclusion criteria based on core infarct, as demonstrated by modified clinical ASPECTS mismatch, defined as ASPECTS 5 to 10 with varying criteria based on the percent involvement of cortex (M1-6). Eligible patients must have intracranial internal carotid artery or middle cerebral artery trunk occlusions, be clinically refractory or ineligible for intravenous thrombolysis, and have at least moderate neurologic deficits (NIHSS score $\geq$8). A sample size of 376 patients was estimated, and the primary study was reportedly completed February 1, 2022.

CONCLUSIONS

The DAWN and DEFUSE 3 studies have transformed the care of acute stroke patients in the extended time window. While advanced imaging with CTP or MRI is recommended in the selection of anterior circulation LVO patients presenting between 6 and 24 hours from last known well, selection of patients based on NCCT or CT angiography collaterals may be a reasonable alternative, particularly in cases where access to advanced imaging is not available or could incur significant delay.[92] Recruitment in ongoing trials comparing medical management versus NCCT and NCCT versus CTP is important to answer these questions definitively. This guideline will be updated when significant trial results become available which necessitates a revision.

SUMMARY OF RECOMMENDATIONS

Patient Selection

1. In patients presenting within 6 to 24 hours from last known well with proximal anterior circulation LVO and with clinical–imaging mismatch as defined in the DAWN or DEFUSE 3 trials, EVT is recommended (COR-1; LOE A).
2. In patients with proximal anterior circulation LVO 6 to 24 hours from last known well, NCCT can be used as the sole imaging modality to evaluate infarct size, particularly when access to CTP or MRI is limited or if their performance would incur substantial delay to treatment (COR-2a; LOE B-NR).

Systems of Care

3. In patients with a suspected LVO presenting within the 6 to 24 hours of last known well, it may be reasonable to transport the patient directly to an EVT-performing center if transport time would not be delayed by >15 minutes relative to the nearest stroke center (COR-2b; LOE expert opinion consensus).

Periprocedural Considerations

4. In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO who are candidate for EVT, the use of either CS or GA is reasonable (COR-2a; LOE B-NR).
5. In patients with late-window LVO following successful reperfusion (TICI 2b/3), reduction and maintenance of systolic BP to a target of $\leq$140 mm Hg may be reasonable (COR-2b; LOE B-NR).
6. In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, the use of a balloon-guided catheter is reasonable during EVT in the extended window (COR-2b; LOE B-NR).
7. In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, the use of a stent retriever is recommended (COR-1; LOE A).

8. In patients presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, first-line contact aspiration or combined aspiration and stent retriever technique can be as effective as first-line stent retriever technique (COR-2a; LOE B-R).

Special Considerations

9. In patients presenting within 6 to 24 hours from last known well with NIHSS scores <6 and proximal anterior circulation LVO, the effectiveness of EVT compared with medical management is unknown (COR-2b; LOE C-LD).
10. In patients with premorbid disability presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, EVT may be reasonable if other MT criteria are met (COR-2b; LOE B-NR).
11. In patients aged ≥80 years presenting within 6 to 24 hours from last known well with a proximal anterior circulation LVO, EVT is reasonable if other established criteria for MT are met (COR-2a; LOE B-NR).
12. In patients with anterior circulation LVO presenting within 6 to 24 hours of last known well, EVT is recommended regardless of the presentation (witnessed stroke, DUS, unwitnessed WUS) (COR-1; LOE A).
13. In patients with anterior circulation LVO presenting within 6 to 24 hours of last known well with large core infarct as defined by CT or DWI ASPECTS 2 to 5, enrollment in ongoing clinical trials is recommended (COR-2b; LOE B-NR).
14. In patients with LVO presenting beyond 24 hours with target mismatch profiles based on CTP imaging or MRI, EVT may be considered (COR-2b; LOE C-LD).
15. In patients with LVO presenting beyond 24 hours, it is unknown whether selection by NCCT to EVT confers benefit (COR-2b; LOE C-LD).

ARTICLE INFORMATION

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The Society of Vascular and Interventional Neurology endorses guideline recommendations based on the critical review of available evidence at the time of publication. This guideline provides general guidance on emerging topics and is subject to revision, as current practice evolves in response to results from current and future clinical studies and developments in the field of practice. Recommendations may not be applicable to individual patient-specific scenarios encountered in clinical practice.

APPENDIX

Guidelines and Practice Standards Committee Members

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Supplemental Materials

Supporting Information

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