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JACC FOCUS SEMINAR: CURRENT BEST PRACTICES AND FUTURE DIRECTIONS IN STROKE

JACC FOCUS SEMINAR

Management of Acute Ischemic Stroke Due to Large-Vessel Occlusion

JACC Focus Seminar

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ABSTRACT

Acute ischemic stroke is a severe and life-threatening disease, particularly when caused by a large-vessel occlusion. The only available 2 treatment options are intravenous alteplase and endovascular therapy (mechanical clot removal), both of which are highly time-dependent. Thus, rapid patient transfer, diagnosis, and treatment are crucial, and time-consuming imaging methods and overly selective treatment selection criteria should be avoided. A combined endovascular therapy approach using stent-retrievers and aspiration is the most effective way to achieve fast first-pass complete reperfusion and should thus be used. To diagnose and treat patients as fast as possible, the organization of existing systems of care, and particularly pre-hospital transfer systems, have to be changed. Several different transport models are currently in use because the optimal patient transfer paradigm is highly dependent on local geography and hospital efficiency. (J Am Coll Cardiol 2020;75:1832–43) © 2020 by the American College of Cardiology Foundation.

Acute ischemic stroke (AIS), particularly if it is caused by a large-vessel occlusion (LVO), is a severe and life-threatening disease. Endovascular therapy (EVT) has rendered safe and effective treatment of AIS due to LVO possible, and new thrombolytic agents and neuroprotectants could soon complement pharmacological AIS therapy. These treatments are highly time dependent. Hence, the overarching goal in the management of patients with AIS is to rapidly and safely transfer, diagnose, and treat patients with AIS.

IMAGING IN AIS: STICK TO THE BASICS

WHY IS IMAGING IMPORTANT IN SUSPECTED AIS?

Imaging is crucial for AIS management, as it confirms the diagnosis and guides treatment, with intravenous tissue plasminogen activator (alteplase) and/or EVT, the 2 evidence-based treatment strategies for AIS (1). Every 30-min delay in recanalization decreases the chance of a good functional outcome by 8% to 14% (2). To initiate appropriate treatment as fast as possible, at the highest level the questions that need to be answered urgently are as follows: Is the patient a candidate for intravenous alteplase? Is the patient a candidate for EVT? This translates into 3 questions that need to be answered by neuroimaging: 1) Is there evidence of intracranial hemorrhage? 2) Is there a vessel occlusion, and if so, where is it located? 3) What is the risk/benefit ratio when treating the patient?

Questions 1 and 3 relate to decision-making for intravenous alteplase treatment, and all questions should be addressed when considering EVT.

Is there evidence of intracranial hemorrhage?

Noncontrast CT (NCCT) is typically used to

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HIGHLIGHTS

- Acute ischemic stroke due to LVO is a severely disabling disease. Intravenous alteplase and endovascular therapy are the only 2 available treatment options.
- Because the treatment effect is highly time-dependent and the natural course of the disease is poor, treatment delays and patient overselection for treatment should be avoided.
- Outcomes are directly related to quality of reperfusion. Treatment techniques and technologies have improved and will continue to improve in the future, thereby allowing for faster and better reperfusion than in the past.
- Current challenges are standardization and simplification of imaging protocols, management of patients who do not meet current guideline recommendations for treatment, and optimization of patient transfer.

differentiate between hemorrhagic and ischemic stroke, which determines further management. In acute hemorrhagic stroke, typical hyperdense hemorrhagic foci can be seen on NCCT, and absence of such foci virtually excludes intracranial hemorrhage. Some centers primarily rely on magnetic resonance imaging (MRI) for acute stroke imaging, but NCCT is the more widely used modality, because it is more time-efficient and widely available, with an acceptable radiation dose of 3 mSv.

Is there a vessel occlusion and if so, where is it located? Visualizing a vessel occlusion confirms the diagnosis of AIS, and its location guides treatment decisions. LVOs (i.e., intracranial carotid artery and M1 occlusions) are less likely to recanalize with alteplase alone and should be considered for EVT. Although distal occlusions have a higher probability to recanalize with alteplase, EVT is increasingly performed in such as well. Accurate clot localization is vital to decide whether a distal occlusion is within the realm of EVT or not.

Most commonly, computed tomography angiography (CTA) is used. In single-phase CTA, a single arch-to-vertex angiography is obtained after iodinated contrast injection, whereas in multiphase CTA, the same contrast bolus is used to obtain 2 additional series during the peak-venous and late-venous phase, which cover only the intracranial vasculature (skull base to vertex). CTA has high accuracy for LVO detection, with high interrater reliability (3). Unlike MRI, the extra- and intracranial vasculature can be covered in 1 sequence. The small risk of contrast-induced nephropathy is considered negligible, and the radiation dose of 5/6 mSv is considered acceptable. With recent advantages in dose reduction through technologies such as automated exposure control, tube voltage reduction, and iterative reconstruction, the radiation dose of a complete CT-based stroke imaging protocol (NCCT, multiphase CTA [mCTA]) ranges at approximately 8.5 mSv. This still exceeds the natural background radiation in North America (3.1 mSv) by almost 200%. Adding computed tomography perfusion (CTP) further substantially increases the radiation dose to 12 to 16 mSv (4).

MRI-based centers perform time-of-flight (TOF) magnetic resonance angiography (MRA) to image the intracranial vessels, which relies on the signal of inflowing spins to visualize the intracranial vasculature. This is advantageous in patients with contrast allergy. However, susceptibility to motion is higher and acquisition times longer, and it cannot be used to image the extracranial vasculature.

What is the risk/benefit ratio when treating the patient? In general, a patient should be treated, unless the potential treatment risks clearly outweigh the benefits.

Intravenous alteplase remains a cornerstone for AIS with and without LVO. It has been proven to be beneficial in patients with AIS when administered within 4.5 h from symptom onset (5), with varying recanalization rates, depending on occlusion site and thrombus characteristics. The greatest risk of intravenous alteplase is treatment-associated intracranial hemorrhage. The risk rapidly increases with increased duration of ischemia, and is also influenced by the extent of early ischemic changes on NCCT, stroke severity, pre-existing coagulopathies/treatment with anticoagulants, recent surgery, and so forth. This translates into numerous clinical, radiological, and laboratory-related contraindications (some of which are controversially discussed among experts) and has resulted in a generally conservative treatment approach with low overall eligibility rates among patients with AIS (1).

With regard to EVT, 2 distinct treatment risks have to be considered, namely: 1) procedure-related

ABBREVIATIONS AND ACRONYMS

AIS = acute ischemic stroke
CBV = cerebral blood volume
CTA = computed tomography angiography
CTP = computed tomography perfusion
DWI = diffusion-weighted imaging
EVT = endovascular therapy
LVO = large-vessel occlusion
mCTA = multiphase computed tomography angiography
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NCCT = noncontrast computed tomography
TOF = time-of-flight

complications (e.g., vessel perforation); and 2) reperfusion hemorrhage:

1. Procedure-related complications

Prediction of procedure-related complications is generally difficult and there are no imaging markers that reliably predict procedure-related complications, which are also influenced by several other factors, such as operator skills and available equipment. Vascular imaging can theoretically help to reduce procedure-related treatment complications: the first phase of mCTA (arch-to-vertex CTA) provides useful information about extracranial vessel anatomy (tortuosity), whereas the second and third phases depict the vessels immediately distal to the occlusion well and hence allow for accurate determination of clot length. This is important information to select catheters and thrombectomy devices appropriately, thereby minimizing the risk of vessel perforation. Some centers perform MRA for procedural planning (TOF-MRA for intracranial and contrast-enhanced MRA for extracranial vessel visualization). This, however, results in prolonged image acquisition time and the application of gadolinium carries a small risk of adverse reactions and nephrotoxicity.

2. Reperfusion hemorrhage

Patients with large ischemic cores are at an increased risk of reperfusion hemorrhage. However, from the HERMES (Highly Effective Reperfusion Using Multiple Endovascular Devices) meta-analysis and other studies, we know that overall the risk of reperfusion hemorrhage is relatively low (4.4% in the EVT arm vs. 4.3% in the control arm) (6). In addition, in our experience, patients with large infarcts are the ones who have the highest likelihood of developing reperfusion hemorrhage. In this situation, reperfusion hemorrhage does not necessarily affect the patient's final outcome, which would have been equally worse without treatment.

Using NCCT to estimate the ischemic core, which appears hypodense due to the reduced cerebral blood volume, has several advantages including wide availability and whole brain coverage. The Alberta Stroke Program Early CT Score (ASPECTS) can be used to quantify the extent of hypoattenuation in middle cerebral artery (MCA) strokes. The lower the ASPECTS score, the higher the risk of intracranial hemorrhage and poor functional outcome despite treatment with alteplase and/or EVT. However, even patients with ASPECTS <6 on baseline imaging can benefit from EVT (7).

mCTA complements the assessment of ischemic core on NCCT. It allows for a time-resolved depiction of the collaterals, which can be semiquantitatively graded. Collateral circulation is an independent predictor of outcome following treatment with alteplase (8) and patients with good collaterals on baseline mCTA are more likely to benefit from EVT (9). mCTA predicts patient outcome better than single-phase CTA and CTP (4), has a good interrater reliability, covers the whole brain, is robust against patient motion, and requires no post-processing. Extracranial stenoses and poor cardiac output, however, could lead to underestimation of collaterals.

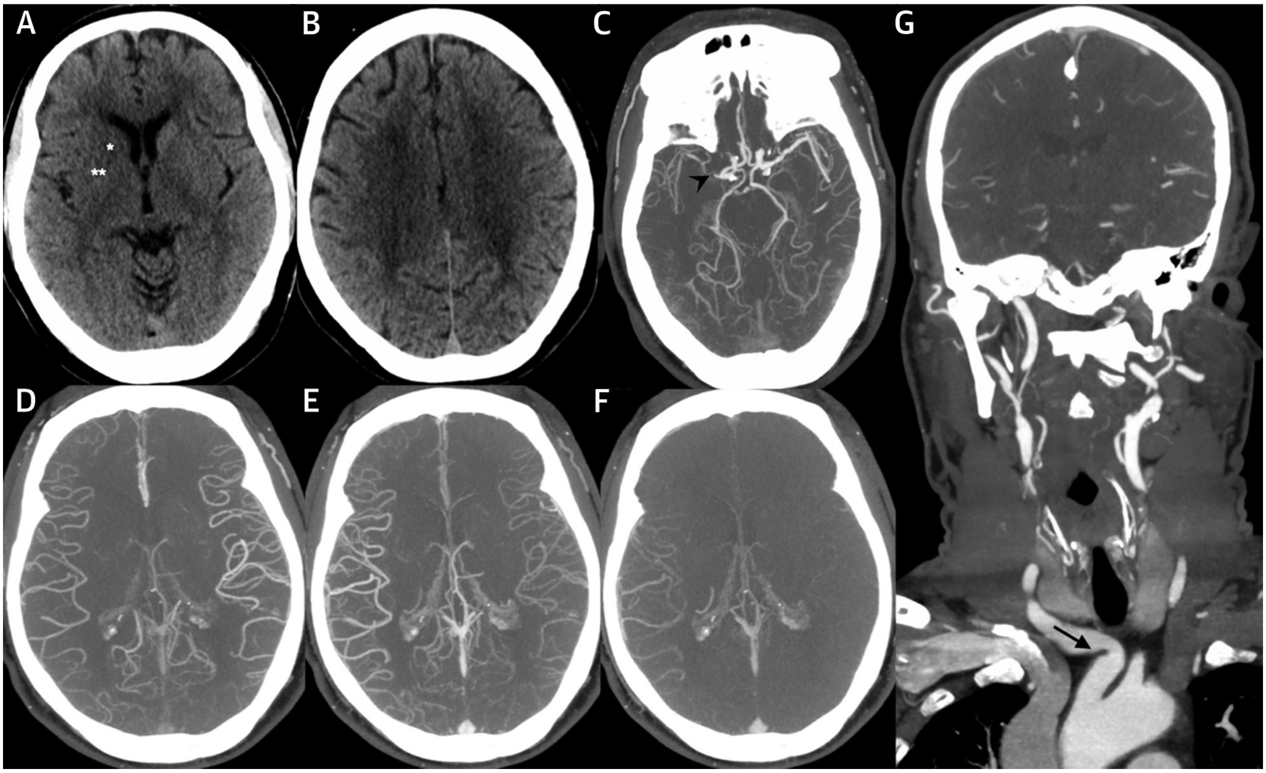
CTP is another technique to assess the risk of ischemic core: a slab of 8 to 16 cm is continuously scanned over 45 to 90 s after injection of a contrast bolus and cerebral blood volume (CBV), cerebral blood flow, mean transit time, and time to peak enhancement are then calculated and displayed as color-coded maps. In theory, ischemic core is characterized by decreased CBV, whereas in the penumbra, CBV is preserved. Quantified CTP maps to estimate the extent of ischemic core were used in several major EVT trials (10), and patients with large core volumes were excluded. CTP is subject to technical failures in up to 30% of patients (11). The quantification of ischemic core and penumbra, which has been neither standardized nor validated, is highly variable among vendors. A subgroup analysis from the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands) trial indicates that CTP did not add value to treatment decision-making (11).

Diffusion-weighted MR imaging (DWI-MRI) relies on cytotoxic edema to estimate ischemic core. Cytotoxic edema occurs in severely ischemic brain parenchyma and results in decreased diffusivity of water molecules in the extracellular space, which appears bright on DWI sequences. DWI turns positive within minutes, with a high sensitivity and a specificity (3). It is therefore considered the gold standard for ischemic core assessment. However, DWI-MRI is more time-consuming and susceptible to motion than CT.

The validity of the core-penumbra concept has recently been challenged: in some regions that are classified as "ischemic core," selective neuronal loss rather than pan-necrosis is present, and no reliable imaging marker exists so far to differentiate one from the other. Hence, it is questionable whether we should refrain from treating patients due to apparently large ischemic core volumes on baseline imaging, particularly when considering the natural history of AIS.

SUGGESTED IMAGING PROTOCOL IN PATIENTS WITH SUSPECTED AIS. An optimal imaging protocol should be available 24/7, fast, inexpensive, robust

FIGURE 1 **Suggested Imaging Protocol in Patients With Suspected Acute Ischemic Stroke**



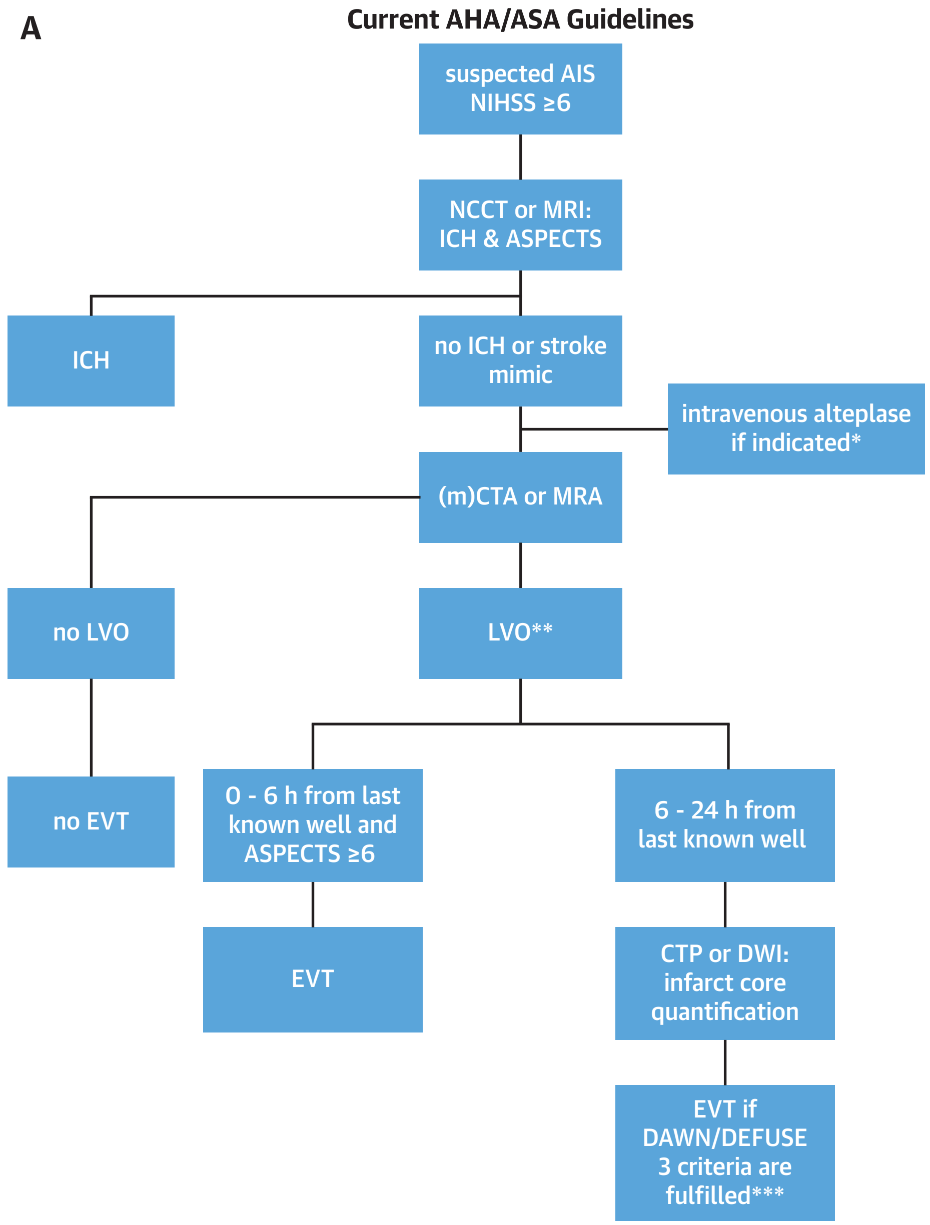
(A, B) The noncontrast head CT (NCCT), which is obtained first to rule out hemorrhage and provide a rough estimate about ischemic core, shows hypodensity of the caudate nucleus **(*)** and lentiform nucleus **(**)**, consistent with a small ischemic core. **(C to G)** Multiphase CT angiography is then obtained. **(C, D)** The first phase shows a right-sided M1 middle cerebral artery segment occlusion **(black arrowhead in C)** and some collateral opacification in the arterial phase **(D)**. **(E, F)** The second **(E)** and third **(F)** phases show good collateral opacification. **(G)** The first phase also covers the extracranial vasculature from skull base to vertex and provides valuable information for procedural planning, such as extracranial vessel tortuosity **(black arrow in G)**.

against patient motion, easy to perform and interpret for readers with limited expertise, and have no or few contraindications. Thus, most centers, including our own, rely on CT-based acute stroke imaging. In our opinion, the optimal imaging protocol consists of (Figure 1) the following:

1. NCCT to rule out hemorrhage and roughly estimate the ischemic core using ASPECTS
2. followed immediately by multiphase CTA to detect and localize the occlusion, estimate treatment risks and benefits, and allow for procedural planning.

For patients presenting within the 6-h timeframe, we feel that CTP is *not* necessary for clinical decision-making. Current guidelines recommend CTP in patients with unknown onset and those presenting >6 h from onset because the only 2 late-window EVT trials, DAWN (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 3), relied either on DWI or CTP to determine ischemic core (12,13), and only included patients with small ischemic core volumes. These trials used 1 distinct imaging protocol and highly selective inclusion criteria to evaluate the benefit from EVT, and these trial eligibility criteria translated into guideline recommendations. Of note, they did not compare the performance of different imaging modalities. Many late-window patients with unknown symptom onset (wake-up strokes) might actually be within the 6-h time window, and will be denied treatment because of the more stringent late-window inclusion criteria. We believe that the advantages of 1 single robust AIS imaging protocol justifies the use of mCTA in all patients with AIS, including late-window patients, and avoids overly selective treatment criteria.

CENTRAL ILLUSTRATION Management of Acute Ischemic Stroke



Ospel, J.M. et al. J Am Coll Cardiol. 2020;75(15):1832-43.

(A) Current American Heart Association (AHA)/American Stroke Association (ASA) guidelines (1). *For intravenous eligibility criteria, see current AHA/ASA guidelines. **Intracranial internal carotid artery or M1 occlusion. ***For DAWN (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 3) criteria, see Supplemental Table 1. **(B)** Alternative practical approach for endovascular management. *For intravenous eligibility criteria, see current AHA/ASA guidelines. **M2, A2, major M3 occlusions and posterior circulation occlusions (basilar artery, P1, P2) should be considered for endovascular therapy (EVT) as well, depending on symptom severity and patient factors, operator skill set, and so forth. ***Age, time from last known well, baseline functional status, patient wishes, operator skill set, and so forth. Differences to current guideline recommendations are highlighted in **red.** AIS = acute ischemic stroke; ASPECTS = Alberta Stroke Program Early CT Score; CTP = computed tomography perfusion; DWI = diffusion-weighted imaging; ICH = intracranial hemorrhage; LVO = large-vessel occlusion; mCTA = multiphase computed tomography angiography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; NCCT = noncontrast computed tomography; NIHSS = National Institutes of Health Stroke Score.

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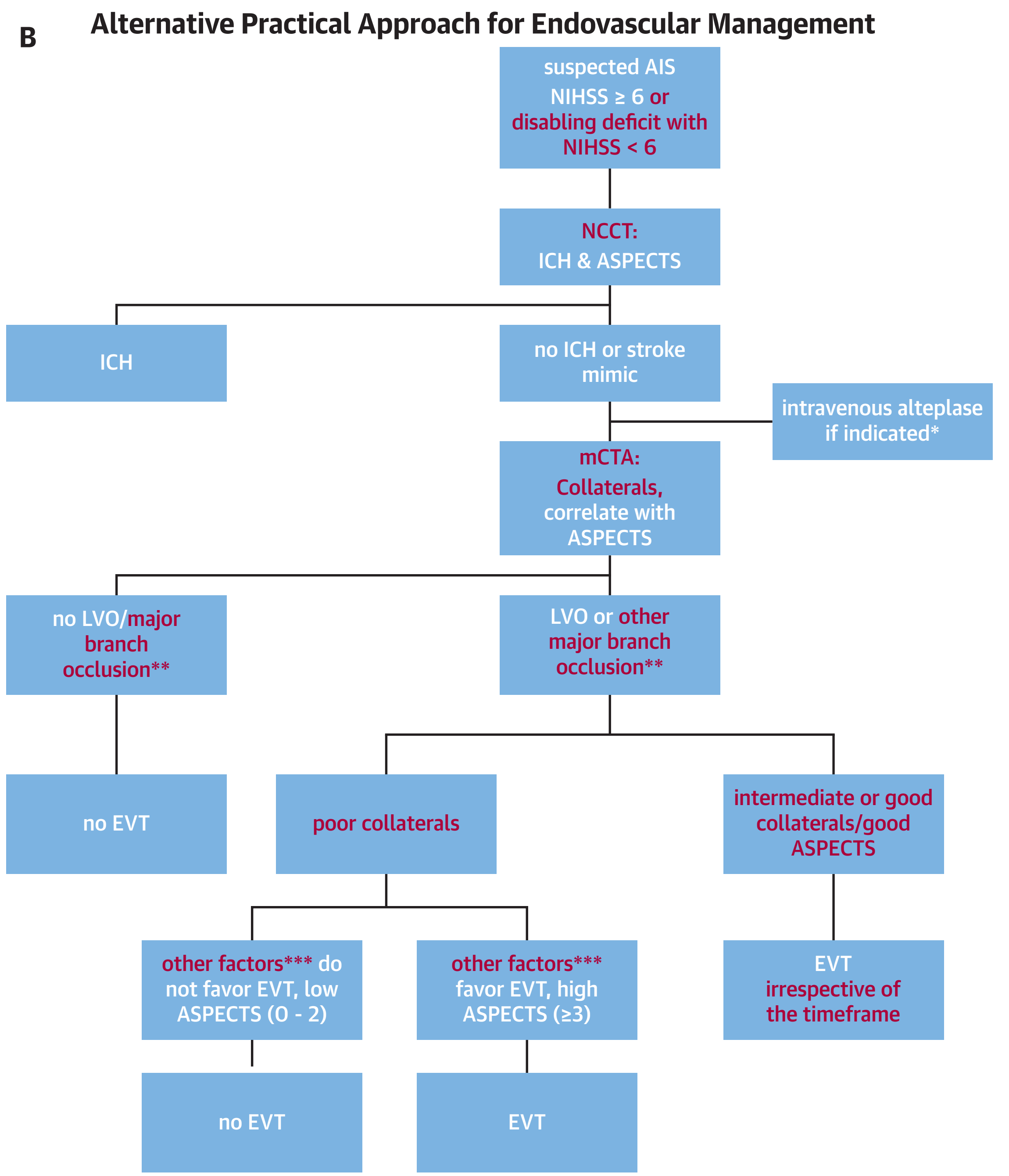
CENTRAL ILLUSTRATION Continued



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FUTURE DIRECTIONS: SIMPLIFYING AND AUTOMATIZING THE IMAGING WORKFLOW. Because of the variety of AIS imaging modalities, study interpretation and decision-making is highly variable. As CTP will temporarily remain part of the AIS imaging workflow in many centers, CTP thresholds need to be harmonized throughout different vendors and software packages.

Parts of the imaging workflow can be accelerated through automatization: automated ASPECTS algorithms are reasonably reliable (14); once further refined, they will most likely find their way into

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clinical routine. Automated color-coding of mCTA will soon facilitate collateral assessment and vessel occlusion detection, and mCTA-derived CTP-like maps could replace actual CTP maps.

CLINICAL DECISION-MAKING AND PATIENT SELECTION CRITERIA: THINKING OUTSIDE THE BOX. The natural history of AIS due to LVO is poor, and treatment is effective and safe. Thus, treatment should be offered to all such patients except when treatment futility can be expected due to a combination of poor prognostic factors. Besides imaging findings, age, baseline functional status, and time since symptom onset are important determinants of outcome after treatment with alteplase and/or EVT. They strongly influence the treatment decision and reduce the relative importance of imaging findings (Bayesian approach to decision-making [15]). For instance, uncertainty regarding the extent of ischemic core is reduced in this Bayesian framework: if all other variables favor EVT, one will decide to treat the patient regardless of the estimated core volume. Hence, the impact of time-consuming advanced imaging techniques such as CTP on clinical decision-making is limited.

The **Central Illustration** provides an overview of the current best practice of endovascular AIS management; however, current guideline recommendations, including ischemic core thresholds, were derived from highly selective clinical trial inclusion criteria. These trials aimed to maximize treatment benefit to generate a significant effect size and hence only included patients in which the treatment effect of EVT is certain and large. There is evidence from nonrandomized studies that many of the excluded patients (e.g., those with large core on baseline imaging [7] and M2 occlusions [16]) are also likely to benefit from EVT. We must decide whether to "stay in the box" and confine ourselves to current guideline recommendations (and, at best, slowly expand these by adding evidence for different patient subgroups), or if we want to think outside the box, and treat patients with EVT and/or alteplase even if they do not exactly fulfill all eligibility criteria if the overall Bayesian framework speaks in favor of treatment. This becomes particularly important for patients "on the fringes" of current guidelines (**Table 1**). Indeed, attempts have been made to establish prediction models to support physicians in EVT decision-making, particularly in those "borderline patients." However, because of the relatively small derivation cohort and the complex interplay of variables that affect patient outcome, these models achieve only moderate performance (17).

Given the futile natural course of AIS and the high treatment efficacy, undertreatment of patients probably causes more harm than overtreatment. We believe that we should think outside the box and, instead of asking ourselves "which patients should be treated?," we should rather ask "which patients should *not* be treated?" This is consistent with patients' demands for more aggressive treatment approaches (18), and physicians' beliefs, who already offer treatment routinely beyond guideline recommendations (19).

OPTIMIZING TREATMENT TECHNIQUE IN AIS

Intravenous alteplase and EVT are the only evidence-based treatment options that are currently available for AIS, and extensive work is being done to further develop them.

OPTIMIZING INTRAVENOUS THROMBOLYSIS IN AIS: WORKFLOW MODIFICATIONS AND IMAGING-BASED TREATMENT SELECTION IN WAKE-UP STROKES. Alteplase has long been the mainstay of AIS therapy. Increasing treatment speed yields the greatest potential for improving alteplase treatment because its efficacy is highly time dependent. Administering alteplase in the CT room directly after excluding hemorrhagic stroke and keeping the patient on the emergency stretcher instead of relocating to a hospital bed can significantly reduce door-to-needle times. Many AIS patients with unknown symptom onset ("wake-up strokes") have traditionally been considered ineligible for alteplase, but it has recently been shown that patients with unknown symptom onset may benefit from alteplase, if a DWI/fluid-attenuated inversion recovery mismatch is present on MRI (20). Hence, some centers now offer alteplase treatment to patients with wake-up strokes and a favorable imaging profile on MRI.

OPTIMIZING ENDOVASCULAR THERAPY IN AIS: COMBINING STENT-RETRIEVERS AND ASPIRATION. Because the benefit of EVT is reduced with increasing onset-to-treatment times and incomplete recanalization, fast first-pass complete reperfusion should be achieved whenever EVT is performed. In the major positive EVT trials, stent-retrievers were used in most patients. A stent-retriever is a self-expandable stent that can be navigated to the site of occlusion via a microcatheter and microwire and is deployed within the clot. A delivery wire is attached to the stent, and once fully deployed, the stent-retriever with the captured clot is removed by pulling the delivery wire back to restore blood flow.

First-line aspiration, an alternative approach, entails clot removal through aspiration. Ideally, a combined technique is used because it synergizes the benefits of primary aspiration and stent-retrievers (Figure 2). Stent-retriever placement in the inferior rather than the superior M2 division is safer because its caliber is larger and its course more straight. The stent-retriever should be placed distally, with two-thirds of the stent beyond the thrombus to capture distal clot fragments that might shear off. Aspiration should be applied through a balloon guide catheter and a distal access catheter ("dual aspiration") during the clot retrieval to prevent distal embolization (so-called BAlloon guide with large bore Distal access catheter with Dual Aspiration with Stent-retriever as Standard Approach [BADDASS]).

FUTURE DIRECTIONS OF AIS TREATMENT: NEW DRUGS, REFINED DEVICES, AND SIMULATION. Because the recanalization rates for proximal occlusions are low with alteplase, other thrombolytic agents, such as intravenous tenecteplase, have been investigated. Tenecteplase has improved fibrin-specificity, a longer half-life, and can be administered as a single bolus injection. It leads to better functional outcomes compared with alteplase in patients with AIS treated with EVT (21). Several ongoing trials are comparing alteplase and tenecteplase, and it is likely that tenecteplase will soon complement, if not replace, alteplase in AIS treatment.

Neurointerventional devices will continue to evolve. Given the growing evidence for safety and efficacy of EVT in M2 occlusions, there is an increasing demand for development of smaller stent-retrievers in particular.

The increasing availability of simulator-based training will allow us to standardize neurointerventional training programs and accelerate trainees' learning curves. Simulator training is also beneficial to streamline the stroke treatment workflow outside the angiography suite and can substantially reduce door-to-needle times (22).

Last, the recent establishment of EVT as standard of care has opened the field for neuroprotection trials. Neuroprotectants allow brain cells to tolerate ischemia longer. Past neuroprotection trials have failed, most likely because reperfusion, which is crucial for neuroprotectants to be effective, was achieved in only a minority of patients. EVT allows us for the first time to evaluate neuroprotectants in an ischemia-reperfusion model. Drugs like NA-1, which can easily be administered in the pre-hospital setting, are currently being evaluated (NCT02930018) and could potentially boost the treatment effect of EVT.

TABLE 1 Common Scenarios of Patients Who Are Considered EVT-Ineligible Based on Current Guidelines But Frequently Treated in Clinical Practice

Scenario	Explanation
Proximal vessel occlusion with low NIHSS	Current guidelines suggest an NIHSS cutoff of 6 for EVT. Although the initial NIHSS might be low, early neurologic deterioration in these patients is common. Patients with "low" NIHSS also can have varying clinical syndromes, some of which are clearly disabling.
Distal (M2/3, A2/3, P2/3) occlusions	Although recent data have shown safety and efficacy of EVT in distal occlusions, current guidelines confine level 1A recommendations for EVT to proximal occlusions.
Last seen normal >6 h with significant symptoms and "good scan" and LVO but not meeting DAWN/DEFUSE3 criteria	Although current guidelines confine their EVT recommendation to late-window patients meeting the DAWN/DEFUSE 3 criteria, other patients can benefit from EVT as well.

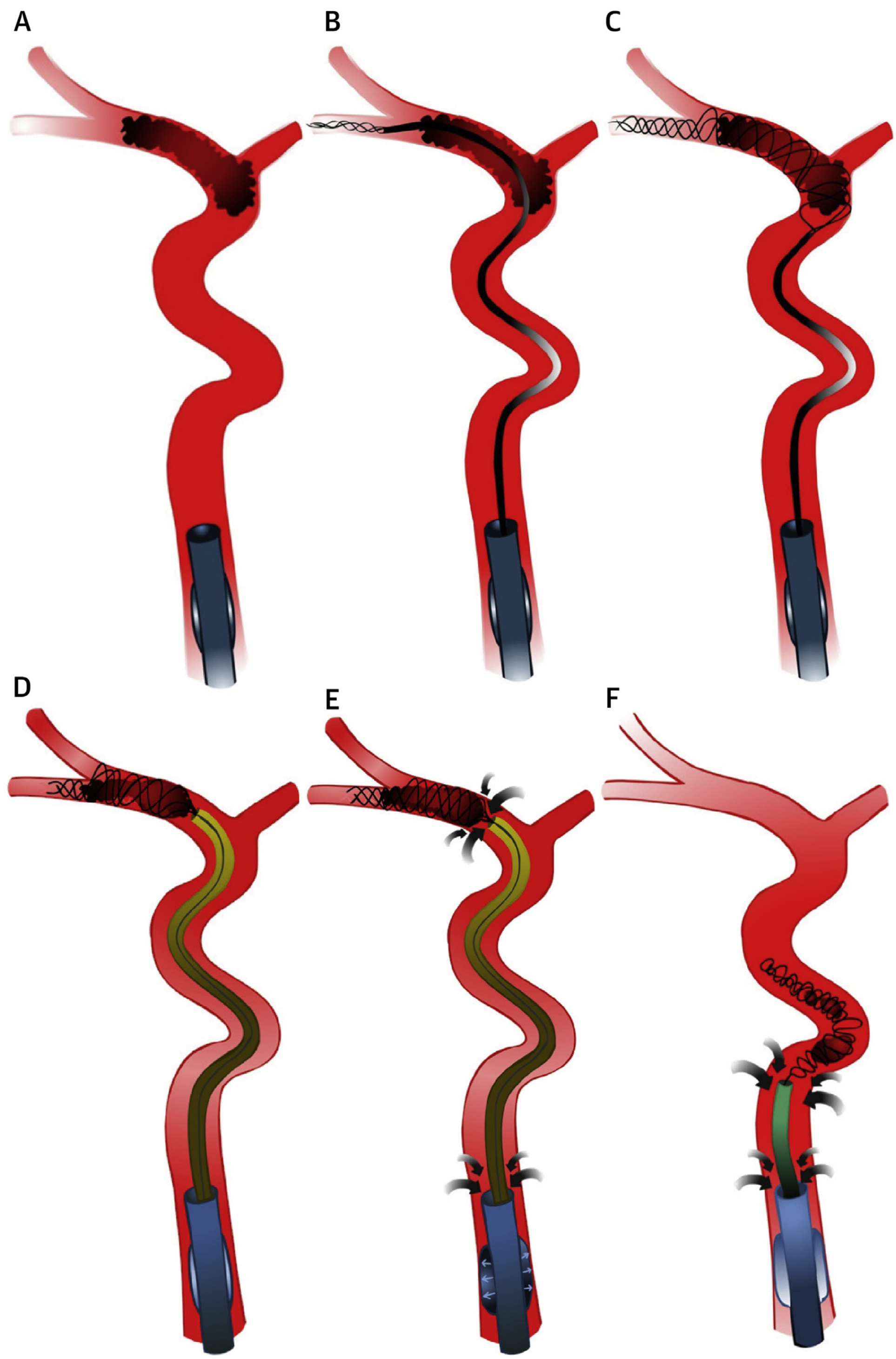
DAWN = Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo; DEFUSE-3 = Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; EVT = endovascular therapy; LVO = large-vessel occlusion; NIHSS = National Institutes of Health Stroke Score.

ORGANIZATION OF ACUTE STROKE SERVICES TO ENSURE RAPID ACCESS TO TREATMENT

THE IMPACT OF EVT ON THE ORGANIZATION OF ACUTE STROKE SERVICES. EVT has revolutionized the care and outcomes of patients with AIS; however, most of the developed world's health systems (e.g., those in North America and Europe) have been organized such that the equipment and expertise needed to provide EVT are centralized at large urban tertiary centers, which limits its availability. This has created a new transport dilemma for patients with suspected AIS: those with potential LVO need to be quickly identified and transported to a center that provides EVT because interhospital transfer leads to time delays and worse outcomes (23). However, the efficacy of alteplase, although lower than that of EVT, cannot be discounted in these patients. Thus, universal bypass to an EVT-equipped center, especially when rapid alteplase is available, may not be appropriate. The question becomes: when is delaying access to alteplase in favor of earlier access to EVT in the best interest of the patient? There are 2 different transportation frameworks to be evaluated (Figure 3): 1) transporting the patient to the nearest stroke center for alteplase treatment followed by transfer to an EVT-capable center (drip-and-ship); or 2) direct transport, potentially bypassing a closer stroke center, to an EVT-capable center for alteplase and EVT (mothership).

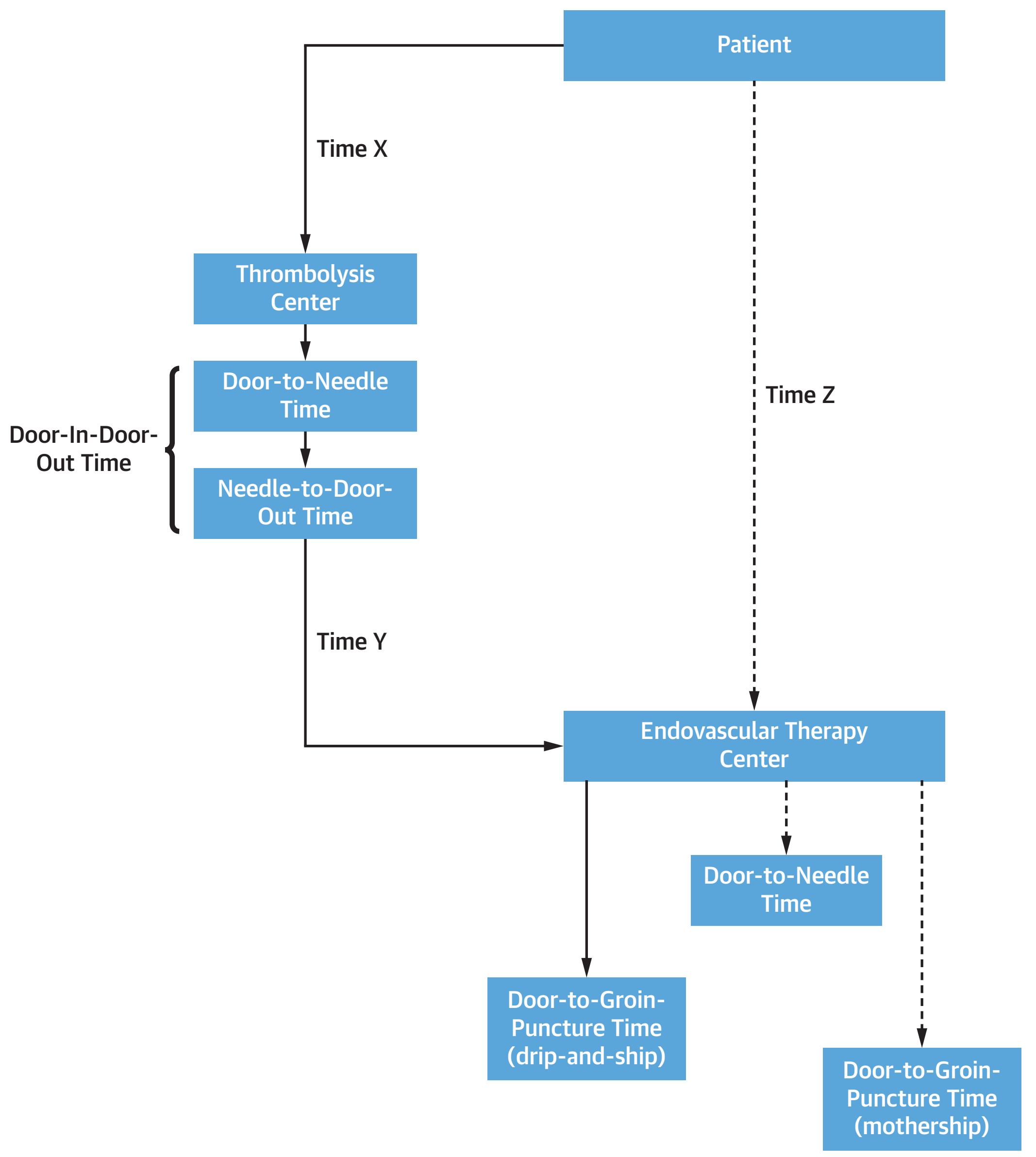
There have been several different studies approaching this complex problem from a

FIGURE 2 Balloon Guide With Large Bore Distal Access Catheter With Dual Aspiration With Stent-Retriever as Standard Approach (BADDASS)



A balloon guide catheter is placed in the cervical internal carotid artery **(A)**. A microwire and microcatheter loaded with a stent-retriever is then advanced past the thrombus in the inferior M2 division **(B)**. The stent-retriever is deployed distally **(C)**. A distal access catheter is advanced to the proximal clot interface **(D)**. Immediately before clot retrieval, the balloon is inflated, and aspiration is applied to the distal access catheter and the balloon guide catheter ("double aspiration" **[E])**. The distal access catheter, stent-retriever, and the entrapped clot are then retrieved in the balloon guide catheter bore and removed from the patient under maintained double aspiration **(F)**.

FIGURE 3 Drip-and-Ship Versus Mothership Models



This figure displays the 2 different transport options, including transport and treatment times. The **solid line** represents the drip-and-ship transport method, and the **dashed line** represents the mothership transport method. Time from onset to leaving the scene is not shown; however, this does not vary with transport strategy.

mathematical modeling perspective (24,25), all of which concluded that there is no one-size-fits-all transport protocol for suspected stroke. Transport decision-making is highly context-specific and sensitive to the following: 1) the likely final diagnosis of the patient (Which LVO screening tool was used in the field? What is the positive predictive value of this tool?); 2) system geography (Where are the different hospitals relative to each other and the patient?); and 3) the treatment efficiency at the hospitals (What are the current door-to-needle, door-in-door-out, and/or door-to-groin-puncture times?). In optimally performing systems, small geographies (short transport/transfer times) and when using an LVO screening tool, the drip-and-ship and mothership transport methods predict nearly identical outcomes. However, in larger geographies where the transfer time between thrombolysis and EVT centers is long, the utilization of the drip-and-ship model predicts best outcomes in many scenarios. This is, however, dependent on treatment times, and increasing door-to-needle/door-in-door-out times at the thrombolysis center increase the utilization of the mothership transport method. Thus, when generating a transport protocol, local geography and hospital efficiencies need to be considered. An ongoing clinical trial compares the drip-and-ship and mothership transport methods (RACECAT [Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion]; NCT02795962), but due to the context of specific factors discussed, its results may not be generalizable. However, the data obtained may be used in future modeling studies for validation and to increase robustness of the models.

Besides drip-and-ship and mothership, several other strategies have been proposed for transporting patients with suspected stroke. The most common alternative is the use of the Mobile Stroke Unit (MSU), a CT-equipped specialized ambulance, which is dispatched to the site of the stroke for diagnosis and thrombolytic treatment if appropriate. Several studies have shown that MSU utilization leads to shorter onset to decision/treatment times (26). Data on long-term outcomes of patients treated by an MSU will be available from the ongoing BEST-MSU study (BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit; NCT02190500). The modeling methods described previously have been applied to the MSU scenario as well. Again, they show that the best transport strategy is highly context-specific and sensitive to transport and treatment times as well as accuracy in dispatching the unit to an appropriate patient (27). A study of MSU versus drip-and-ship versus mothership has yet to be performed. Another alternative to the drip-and-ship transport is the "drip-and-drive" or mobile interventional stroke team (MIST). In these methods, rather than transporting the patient from the thrombolysis center to the EVT center, an interventional team is mobilized from the EVT center and sent to the thrombolysis center. This has been shown to decrease onset-to-treatment times, but long-term outcomes are not available yet (28). In addition, this transport method is appropriate only in systems that contain hospitals with the appropriate facilities to offer EVT but lack neurointerventionalists to perform the procedure; this set of circumstances is currently uncommon. All the previously mentioned transport options are predicated on the assumption that the stroke system at hand contains some centralized EVT centers in addition to centers that cannot provide EVT (only providing alteplase). These transport decisions would not apply to a system that does not have any EVT facilities, such as those in the developing world. In those countries, one would not need to make these transport decisions and would be concerned solely with providing alteplase in the fastest possible time.

Once a patient has arrived at the comprehensive stroke center, door-to-needle/door-to-reperfusion times should be kept as short as possible. In our opinion, pre-notification, parallel processing, teamwork, and standardized workflows are key to avoid unnecessary delays: the stroke team should be pre-notified and receive the patient at his or her arrival. A quick examination is performed by the stroke team to assess the National Institutes of Health Stroke Scale and the history from family members is obtained, while the CT scanner and neuro-interventional team are activated in parallel. Both teams meet at the CT scanner, and after standardized imaging is obtained, the treatment decision is made collectively. Ideally, intravenous alteplase should be administered directly after a hemorrhage has been ruled out on NCCT, before mCTA is obtained. A standardized angiography tray for AIS (Brisk Recanalization Ischemic Stroke Kit) always should be readily available in the angiography suite. Peri- and post-procedural care as well as complications should, again, be managed collectively.

HOW WILL FUTURE INNOVATIONS IN STROKE CARE AFFECT SYSTEM ORGANIZATION AND TRANSPORT? To fully integrate EVT into clinical practice, the system organization will have to be changed. The ease of administration and increased efficacy in LVO of tenecteplase over alteplase may result in an increased utilization of the drip-and-ship method, especially in small geographies with short transfer times and efficient thrombolysis centers. Should neuroprotective agents be proven effective, there may be an increase of mothership transport with neuroprotectants on board. Given the increased time window for alteplase administration with advanced imaging selection, patients with onset-to-treatment time >4.5 h should be directed to a center with advanced imaging capabilities so they can be evaluated for potential late-window alteplase.

In conclusion, recent advancements in endovascular therapy have revolutionized treatment of AIS. As more data on efficacy of EVT becomes available, it gets increasingly difficult to find a subgroup of patients with AIS that does not benefit from EVT. Hence, we should not confine our treatment practice to current guideline recommendations. Rather than asking ourselves "which patients should be treated?," we should now ask "which patients should *not* be treated?," A multifactorial, Bayesian approach is most suitable to answer this question. In such a framework, the relative importance of imaging findings is reduced by the prior clinical information. Thus, time-consuming advanced imaging methods should be avoided. Continuing efforts are made to improve thrombolytic agents and thrombectomy techniques. With regard to EVT, fast first-pass complete reperfusion should be the ultimate goal, and a combined technique (BADDASS) should be used. The biggest challenge we are currently facing is not related to imaging protocols or treatment technique, but to the organization of stroke care: how to get the right patient to the right hospital as fast as possible.

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APPENDIX For a supplemental table, please see the online version of this paper.