Direct Transfer to Angiosuite in Acute Stroke
Why, When, and How?

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Abstract

Time to reperfusion is one of the strongest predictors of functional outcome in acute stroke due to a large vessel occlusion (LVO). Direct transfer to angiography suite (DTAS) protocols have shown encouraging results in reducing in-hospital delays. DTAS allows bypassing of conventional imaging in the emergency room by ruling out an intracranial hemorrhage or a large established infarct with imaging performed before transfer to the thrombectomy-capable center in the angiography suite using flat-panel CT (FP-CT). The rate of patients with stroke code primarily admitted to a comprehensive stroke center with a large ischemic established lesion is <10% within 6 hours from onset and remains <20% among patients with LVO or transferred from a primary stroke center. At the same time, stroke severity is an acceptable predictor of LVO. Therefore, ideal DTAS candidates are patients admitted in the early window with severe symptoms. The main difference between protocols adopted in different centers is the inclusion of FP-CT angiography to confirm an LVO before femoral puncture. While some centers advocate for FP-CT angiography, others favor additional time saving by directly assessing the presence of LVO with an angiogram. The latter, however, leads to unnecessary arterial punctures in patients with no LVO (3%–22% depending on selection criteria). Independently of these different imaging protocols, DTAS has been shown to be effective and safe in improving in-hospital workflow, achieving a reduction of door-to-puncture time as low as 16 minutes without safety concerns. The impact of DTAS on long-term functional outcomes varies between published studies, and randomized controlled trials are warranted to examine the benefit of DTAS.

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Glossary

ANGIOCAT = Evaluation of Direct Transfer to Angiography Suite vs. Computed Tomography Suite in Endovascular Treatment: Randomized Clinical Trial; ASPECTS = Alberta Stroke Program Early CT Score; CI = confidence interval; CTA = CT angiography; CTP = CT perfusion; DIRECT-MT = Direct Intra-Arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals; DTAS = direct transfer to angiography suite; DTP = door arrival to femoral puncture; EVT = endovascular treatment; FP-CT = flat-panel CT; HERMES = Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke; LVO = large vessel occlusion; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands; mRS = modified Rankin Scale; MT = mechanical thrombectomy; MVO = medium vessel occlusion; NIHSS = NIH Stroke Scale; OR = odds ratio; OTD = onset to door arrival; RCT = randomized controlled trial; THRACE = Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke; tPA = tissue plasminogen activator.

Bypassing conventional imaging in the emergency room, direct transfer to angiography suite (DTAS) protocols for acute stroke treatment have recently been increasingly implemented in real-world practice. This represents a significant transition from the current treatment guidelines by the American Heart Association/Stroke Association and European Stroke Organization/European Society for Minimally Invasive Neurologic Therapy. Multiple pilot studies have shown encouraging results, and randomized clinical trials are underway to confirm its safety and effectiveness. This review introduces the concept, detailed components, benefits, challenges, and evolving direction of DTAS.

Rationale for DTAS

Endovascular treatment (EVT) has become the standard of care in the management of acute ischemic stroke due to large vessel occlusion (LVO).1 Time from symptoms onset to reperfusion is the main modifiable predictor of functional outcome.2-5 The chances of functional independence decrease by ≈10% to 15% for every 30 minutes of delay4 in achieving reperfusion. Despite that, in most cases, the bulk of the workflow time corresponds to the prehospital phase; in-hospital pathways also need to be continuously reassessed to minimize the time from hospital arrival to recanalization. Door arrival to femoral puncture (DTP) time is a widely used metric in patients undergoing EVT to evaluate in-hospital workflow efficacy. Furthermore, it has been shown to be an independent predictor of good outcome.5

Although multisociety consensus guidelines recommend a DTP time <60 to 62 minutes,5,7 most published center experiences consistently report longer times,8 even if protocols specifically focused on streamlining this workflow9 are used. Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke (HERMES) trial individual patient-level meta-analysis from the 5 pivotal trials that showed the superiority of EVT over medical treatment among patients with LVO reported DTP time ranging between 81 minutes for transferred patients and 116 minutes for direct admissions to the comprehensive stroke center.5

Emergency department bypass for patients with ST-segment-elevation myocardial infarction identified with a prehospital ECG interpreted by emergency medical service has been associated with shorter reperfusion time and lower mortality rates.10 Current guidelines recommend that when an ST-segment-elevation myocardial infarction diagnosis is made in the prehospital setting and the patient is eligible for percutaneous coronary intervention, it is indicated to bypass the emergency department and take the patient directly to the cardiac catheterization laboratory.11 DTAS protocols are promising strategies to reduce DTP times in patients who are candidates for EVT. By bypassing sophisticated imaging workup at the emergency department, several comprehensive stroke centers have shown that mean DTP time can be reduced to 16 minutes without safety concerns.12-17

The main aim of DTAS is to shorten DTP time by appropriately selecting patients with acute stroke to bypass complicated and time-consuming imaging evaluation in the emergency department. Reducing time to recanalization, especially during the very early phase of LVO stroke,18 has the potential to maximize the benefit of endovascular thrombectomy. Different strategies for selecting a patient for DTAS have been suggested and used by different groups. The target population is usually limited to patients admitted within 6 hours of symptoms onset.

The odds of following DTAS protocol vary due to the provenance of the patient and mainly the previous neuroimaging. According to the prehospital workflow, DTAS protocols include mainly 2 kinds of patients: those with (transfer patients from a primary stroke center or mobile stroke unit where a noncontrast CT or CT angiography [CTA] was performed) and those without (direct from field or from a primary stroke center without CT) previous neuroimaging. DTAS is mostly accepted for and followed up among drip-and-ship patients with a primary stroke center diagnostic of LVO. On the other hand, some centers have developed DTAS among drip-and-ship patients without previous CTA, and although the effect of DTAS seems to be higher in the very early window, few
comprehensive stroke centers contemplate DTAS among primarily admitted patients, basing the treatment indication on FP-CT and FP-CTA or angiogram. Because primarily admitted patients constitute a substantially different profile, DTAS safety and efficacy will have to be proved separately in each of these groups.

Role of Advanced Imaging for Patient Selection for EVT

The ideal imaging modalities to identify and select patients for endovascular procedures have not been established. The goal of imaging protocols in acute stroke is to assess the parenchyma and to confirm the presence of an LVO suitable for EVT. Current guidelines from the American Heart Association/Stroke Association recommend noncontrast CT and CT/MRI angiography with or without additional advanced multi-parametric MRI/CT imaging, depending on time from onset to admission. This imaging allows confirmation of an LVO and a better understanding of the pathophysiologic status, but it is not recommended for patients within 6 hours from symptom onset on the basis of the results of Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands (MR CLEAN) and Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke (THRACE) trials. However, the benefits of this additional information in decision-making and outcome have not been proved in the early time window. Several issues arise from this protocol. First, sophisticated imaging selection may result in better outcomes among treated patients but at the risk of overselection and treatment denial to patients who may still benefit from EVT. Second, even when a disabling stroke such as that with an NIH Stroke Scale (NIHSS) score ≥9 has a high pretest probability of proximal LVO, in which only ≈14% have absence of LVO, CTA is performed on virtually all potential EVT candidates, which results in at least an ≈20-minute EVT treatment delay in the 86% majority population with LVO. For this population, patients not only have delayed reperfusion but also receive unnecessary large contrast load and significant radiation for CTA/CT perfusion (CTP). Third, with recent advances in endovascular technology, more distal medium vessel occlusions (MVOs), which were previously thought to be less ideal candidates for mechanical thrombectomy (MT) compared to LVOs, are now emerging as the next potential EVT frontier. Different EVT’s such as smaller stent retrievers, more tractable aspiration catheters, and intra-arterial thrombolysis may prove to be useful for MVOs. For current CTA imaging, these MVOs are frequently missed. For this patient group, digital subtraction angiography with the possibility of intra-arterial intervention will be beneficial.

Recently published studies showed growing evidence for EVT benefit among patients with low Alberta Stroke Program Early CT Score (ASPECTS) and the possibility of using ASPECTS-based paradigm for late-window patient selection. Despite the prognostic value, advanced neuroimaging seems to be less necessary to select patients for EVT, supporting a DTAS paradigm.

Imaging Protocols for DTAS

Current DTAS imaging protocols are based largely on the use of FP-CT with rotational C-arm systems (Figure). FP-CT offers the possibility to perform cross-sectional imaging, although it is still inferior to conventional multislice CT. Noncontrast FP-CT can be used to detect the presence of ICH with a very high sensitivity comparable to that of multislice CT. The latest-generation FP-CT allows detection of a large infarct core with a significant reduction of artifacts.

The main difference between DTAS protocols published by different research groups lies in the use of FP-CTA with IV contrast (Table). Performing an FP-CTA adds the possibility of LVO detection and evaluation of collateral circulation status in the angiography suite before arterial puncture. Last, FP-CTP has been developed even with the possibility of automatic imaging processing. At the moment, it is used only in pilot studies but will likely be available for decision-making in the near future, including in patients in the late window or with unknown onset. The function of FP-CTP will also be useful in the cases of symptomatic patients with no LVO.
detected on the FP-CTA; currently, these patients would be brought back to the emergency department for regular CTP.

Acquisition times of advanced imaging in the angiosuite are rather short. Most relevant delays are linked to the preparation of IV lines and contrast pumps. In scenarios in which DTP times may be as short as 10 minutes, spending an additional 5 to 10 minutes obtaining contrasted FP-CTA imaging may be considered a significant delay, especially if the added value is not clearly established. Protocols avoiding FP-CTA showed a slightly lower DTP time (22 and 16 minutes) compared to protocols with included FP-CTA (29 and 33 minutes). Reported door-to-reperfusion times were also shorter when FP-CTA was not performed (66 and 60 minutes vs 72 and 85 minutes).

Some DTAS centers advocate for the use of digital subtraction angiogram to first diagnose and locate the LVO, while others perform FP-CTA before groin puncture to minimize the number of patients undergoing an angiogram in which LVO will not be confirmed and therefore undergoing an unnecessary arterial puncture. Published rates of no LVO among patients undergoing DTAS vary from 3.6% (DTAS applied only to transferred patients with or without confirmed LVO at primary stroke center) to 26% (DTAS applied to all admissions with NIHSS score ≥7). Although selection algorithms should be improved, false-positive DTAS activation rates remain similar to those observed in patients with suspected myocardial infarction undergoing emergent coronary angiograms.

There are some concerns for the DTAS protocol without CTA (from either FP or regular CTA) from a proceduralist perspective. The CTA before skin puncture can inform procedural planning. The information on aortic arch anatomy and cervical vessel tortuosity obtained from CTA may guide the surgical approach and choice of endovascular device, possibly increasing the procedural success rate and shortening

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<tr>
<th>Table Qualitative Assessment of Between Studies Differences in Population: Imaging Criteria and Results</th>
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<tbody>
<tr>
<td>Studies</td>
</tr>
<tr>
<td>Jadhav et al.12 (2017)</td>
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<tr>
<td>Requena et al.49 (2020)</td>
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<td>Psychogios et al.17 (2019)</td>
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<td>Bouslama et al.16 (2019)</td>
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Abbreviations: CT = CT angiography; DTAS = direct transfer to angiography suite; FP-CT = flat-panel CT; LVO = large vessel occlusion; mRS = modified Rankin Scale; NC = noncontrast; NIHSS = NIH Stroke Scale; RACE = Rapid Arterial Occlusion Evaluation Scale.

‡ Statistical differences.
the procedure time. On the other hand, both conventional CTA and FT-CTA increase contrast exposure and pre-procedure time. This may not be suitable for the patient with kidney disease, commonly seen in the patient with stroke with advanced age.

**Identifying Patients With LVO for DTAS**

On the basis of the positive trials leading to EVT approval and current guidelines, within 6 hours from symptom onset, selection of EVT candidates relies on the identification of those patients with substantial neurologic symptoms (NIHSS score >6), absence of an intracranial hemorrhage or a large ischemic burden (ASPECTS <6), and the presence of an LVO.

As opposed to the myocardial infarction scenario in which a preadmission ECG is used to make the EVT decision, in patients with stroke, symptom severity is the only currently available prehospital indicator that can be used to select candidates for EVT. The main predictor of LVO among acute ischemic stroke is clinical severity measured by the NIHSS. Although the NIHSS has a proven predictive value, clinical assessment requires sophisticated training and certification. Other prehospital stroke scales may have a weaker but still acceptable LVO prediction power and are more easily used by emergency medical system and widely implemented in some regions. The generalized adoption of prehospital scales is essential to allow DTAS protocols because the arrival prenotification of a patient with a potential LVO stroke allows efficient preparation at the receiving center.

A repeated fast neurologic assessment performed by a qualified physician is recommended to confirm initial prehospital findings or to identify clinical fluctuations on hospital arrival. Different cutoffs for the NIHSS have been applied, ranging from 7 to 10 as best predictors of LVO. A screening protocol combining symptom severity (NIHSS score >10) and exclusion of ICH, ensured by the FP-CT, identified EVT candidates with a sensitivity and specificity >75%. Several technologic solutions ranging from mobile videoconference to artificial intelligence algorithms are under development to assist in prehospital patient management. For the patient with an NIHSS score <10, a regular protocol other than DTAS is recommended at this point. In the future, if ongoing clinical trials (Endovascular Therapy for Low NIHSS Ischemic Strokes [NCT04167527], Minor Stroke Therapy Evaluation [NCT03796468]) show that this population benefits from EVT, then the population with lower NIHSS scores should be included in the DTAS protocol if LVO is suspected.

Many prehospital stroke scales have been described in previous years and have proved to be useful tools to identify, grade, and alert providers about the arrival of a DTAS candidate. However, training emergency staff to use these scales is necessary and often constitutes a bottleneck. Sensitivity and specificity were also expected to improve further. A faster and easier predictive instrument incorporating additional rapid assessments (such as head CT findings) readily available in the primary stroke center or even the ambulance other than symptom severity has been developed with better sensitivity, specificity, and accuracy than the NIHSS and other predicating scales. Several techniques have been tested for determining LVO in the prehospital setting such as EEG or transcranial Doppler, which could improve the accuracy of diagnosis without actual clinical performance nowadays. The mobile stroke unit, which has been implemented in several cities, includes in prehospital attention the possibility of performing a noncontrast CT or CTA that can rule out ICH and increases the accuracy of prehospital scales. DTAS protocols could be applied in these patients without repeating parenchyma imaging.

Patients arriving at the comprehensive stroke center after transfer from a primary stroke center constitute a group with some important differences. First, these patients are admitted on an average 2 hours later from symptoms onset than primary admissions to the comprehensive stroke center. Therefore, patients transferred from a primary stroke center may benefit to a lesser degree from DTAS compared to those with primary admissions. However, the transfer population is more likely to have undergone additional imaging (CT of the head, CTA, CTP) and thereby is prescreened for EVT eligibility. This additional preselection may lead to more accurate patient identification and longer prealert time, resulting in short DTP time. Previous studies demonstrated that, even after a median transfer time >2 hours, only 12% to 20% of transferred patients present an ASPECTS <6 at the comprehensive stroke center. This low probability of finding low ASPECTS supports the DTAS approach for transfer patients.

In conclusion, although the selection of patients for DTAS with different predictors is not 100% perfect, there is significant benefit for a majority of the patients, who may be harmed by current standard protocol recommended by the guidelines. In contrast, a small number of patients may be subjected to unnecessary invasive angiograms from DTAS yet may benefit from DTAS given that many of them eventually need digital subtraction angiography for further workup of their presenting problems.

**Evidence Supporting DTAS**

While the evidence supporting DTAS is mostly positive, it is based on few retrospective studies, and its efficacy and safety should be confirmed by prospective registries and randomized clinical trials.

The different published series (Table) showed that after DTAS, median DTP time had been reduced to as low as 16 to 22 minutes, which translates to a 30- to 50-minute reduction compared with the conventional pathway. Time from arrival
to reperfusion was also improved from 106 to 125 minutes to as low as 60 to 85 minutes.\textsuperscript{12-17} The effectiveness of DTAS protocols in shortening in-hospital workflow is similar to or even greater than the time reduction observed in ST-segment–elevation myocardial infarction code.

Jadhav et al.\textsuperscript{12} showed comparable rates of functional independence between patients receiving DTAS and controls at 90 days (43\% vs 44\%; \textit{p} = 0.89). Similar results were shown by Bousslama et al.\textsuperscript{16} (44.9\% vs 40.8\%; \textit{p} = 0.68). On the other hand, Mendez et al.\textsuperscript{15} showed that the DTAS protocol was independently associated with 3-month favorable outcome (DTAS 41\% vs controls 28\%; odds ratio [OR] 2.5, 95\% confidence interval [CI] 1.2–5.3; \textit{p} = 0.01). Similarly, the Psychogios et al. study favors patients receiving DTAS (58\% vs 33\%; \textit{p} = 0.03).\textsuperscript{17} The first 2 studies included transferred patients from a primary stroke center with an onset to door arrival (OTD) time \approx 300 minutes; in contrast, the second set of studies included both transferred and primary admissions to the comprehensive stroke center with shorter OTD times (120–200 minutes).

This observation is in line with a recently published study that suggests a higher “treatment effect” of DTAS in patients admitted within 3 hours from symptom onset.\textsuperscript{49} The impact of DTAS seems to be associated with OTD time. In this study, the beneficial effect of DTAS progressively decreased with a longer time from onset to admission. DTAS protocol was associated with better outcomes in patients admitted in the 0- to 3-hour time window (OR 2.63, 95\% CI 1.31–5.28; \textit{p} < 0.01) but not in the 3- to 6-hour time window (OR 1.37, 95\% CI 0.72–2.60; \textit{p} = 0.2).

These differences in the positive effect of DTAS are likely attributable to the relative reduction of onset-to-reperfusion time: shortening the workflow time by 30 to 40 minutes will have a higher relative impact on a total workflow of 180 minutes than 360 minutes. Moreover, infarct growth usually follows a nonlinear evolution over time\textsuperscript{16} in which some patients show faster lesion growth rates during the ultraearly window after stroke onset.\textsuperscript{50} The so-called fast progressors would benefit from DTAS only if admitted very early but not if admitted once the irreversible lesion is set.

In this scenario, DTAS with FP-CT will be reinforced as an ideal screening tool. To date, all published experiences point to DTAS as an effective and safe method to improve in-hospital workflow; however, future large clinical trials should confirm its effect on long-term outcomes.

Will IV Thrombolysis Be Needed for Patients Receiving DTAS?

There is increasing debate about the benefit of IV tissue plasminogen activator (tPA) in EVT candidates in whom the procedure can be initiated immediately. This issue becomes more relevant given that EVT can be started much earlier in patients receiving DTAS than patients receiving the regular protocol. Some earlier studies pointed out that bridging therapy (IV-tPA + EVT) may be associated with delays, higher rates of hemorrhagic complications, or clot fragmentation with distal embolization during EVT.\textsuperscript{51} On the other hand, other publications indicate that the combined therapy may advance in time and increase the rate of successful reperfusion and outcome.\textsuperscript{52} The combined IV tPA + EVT showed better recanalization than EVT only, probably due to the tPA effect on the clot.\textsuperscript{53} Many retrospective studies comparing combined IV tPA and EVT with EVT only showed no statistically clinical benefits for IV tPA given before EVT treatment. The recently published Direct Intra-Arterial Thrombectomy in Order to Revascularize AIS Patients With Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals (DIRECT-MT) trial, which is the first large randomized controlled trial (RCT) on this topic, demonstrated that EVT alone was noninferior to EVT preceded by IV tPA regarding the functional outcome in patients with acute LVO.\textsuperscript{53} An unpublished matched-control study from a large national registry of acute stroke EVT treatment in China with a large sample (1,026 patients) confirmed the findings of the DIRECT-MT trial in a real-world practice setting, suggesting that EVT may have an effectiveness similar to that of combined IVT + EVT for patients with acute LVO. As workflow continues to be streamlined and devices advance in efficacy, the additional benefit of the IV tPA may diminish at a population level. If more studies, including RCTs, confirm that IV tPA does not yield additional beneficial to the EVT population, the DTAS approach may gain further traction. Current data suggest that IV tPA among patients receiving DTAS is safe without a higher rate of symptomatic ICH or administration delay.

**Randomized Clinical Trials for DTAS**

Several RCTs are at different stages and aim to address the benefit of DTAS with slightly different selection criteria and designs.

Evaluation of Direct Transfer to Angiography Suite vs. Computed Tomography Suite in Endovascular Treatment: Randomized Clinical Trial (ANGIOCAT [NCT04001738]) is a single-center study that started recruiting patients in August 2018. Patients with suspected acute stroke with LVO (determined by prehospital Rapid Arterial Occlusion Evaluation Scale score >4 and confirmed NIHSS score >9 on admission) within 6 hours from symptom onset are randomized to DTAS vs the conventional imaging pathway. The study is planning to recruit 300 patients, and the primary endpoint is based on 90-day modified Rankin Scale (mRS) score shift analysis among those patients in whom LVO is confirmed.

Effect of Direct Transfer to Angiosuite on Functional Outcome in Severe Acute Stroke (NCT03969511) is a multicenter national...
trial conducted in France that includes young adults (18–60 years old) with acute hemiparesis/hemiplegia with at least 1 symptom of cortical impairment within 3 hours from symptom onset. The study plans to recruit 200 patients.

Workflow Optimization to Reduce Time to Endovascular Reperfusion for Ultra-fast Stroke Treatment (NCT04701684) is a multicenter international trial that will be running in 16 sites to enroll >500 patients globally. This trial will include patients with NIHSS score ≥10 and no significant prestroke functional disability (mRS score 0–2) within 6 hours from symptom onset. As in ANGIOCAT, primary endpoint is based on 90-day mRS score among patients with confirmed LVO. Given that acute stroke treatment is an evolving process, new clinical evidence will lead to new treatment guidelines. DTAS protocol will also be further optimized by new findings of ongoing RCTs on different acute stroke treatment participants.

Bridging Thrombolysis Versus Direct Mechanical Thrombectomy in Acute Ischemic Stroke (NCT03192332) and the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) NO IV (ISRCTN80619088) are RCTs on whether bridging therapy in patients with LVO eligible for both treatments will be beneficial. These RCTs, combined with the already published DIRECT-MT trial and Endovascular Treatment Key Technique and Emergency Work Flow Improvement of Acute Ischemic Stroke registry results, will guide the current DTAS protocol modification. FT-CT may not really be needed to rule out ICH if the bridging therapy is not beneficial, and IV tPA is not recommended for patients who will have immediate EVT treatment.

A review of the indications for EVT therapy for acute stroke showed current evidence suggesting that EVT might be a reasonable treatment option for individuals with low ASPECTS. Several current RCTs (A Randomized Controlled Trial to Optimize Patient’s Selection for Endovascular Treatment in Acute Ischemic Stroke [NCT03876457], Large Stroke Therapy Evaluation [NCT03811769], Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke [NCT03805308], Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window [NCT03094715]) are ongoing. If these RCTs confirm the positive result from retrospective studies, the number of unnecessary procedures will be greatly decreased, and FP-CT may not be needed to identify infarct core size.

Other RCTs on the expansion of EVT indications such as minor stroke with NIHSS score <6 and posterior circulation stroke will also support DTAS. Widened inclusion criteria will greatly decrease the number of unnecessary procedures from DTAS.

**Conclusion**

The current standard stroke treatment protocol involves a sophisticated vascular imaging process, which causes a delay in reperfusion. It may be harmful to patients who have a high clinical suspicion of LVO on presentation. Accumulating evidence suggests that DTAS is a safer and faster option for selected patients with strong clinical suspicion for ELVO. Further RCTs are warranted to examine the risks and benefits of this approach.

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<tr>
<th>Name</th>
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<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://n.neurology.org/content/97/20_Supplement_2/S34.full">http://n.neurology.org/content/97/20_Supplement_2/S34.full</a></th>
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<tbody>
<tr>
<td>References</td>
<td>This article cites 54 articles, 19 of which you can access for free at: <a href="http://n.neurology.org/content/97/20_Supplement_2/S34.full#ref-list-1">http://n.neurology.org/content/97/20_Supplement_2/S34.full#ref-list-1</a></td>
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