Direct to Angiography: Shifting Pretreatment Stroke Paradigms

Dr. Tudor G. Jovin outlines the direct to angiography approach for patients with large vessel occlusions, discusses the benefits and challenges to widespread adoption, and breaks down results from the ANGIO-CAT and RACECAT studies.

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To start off, please walk us through the direct to angiography (DTA) approach. How does it work, and what is the primary rationale for it?

The goal of DTA is to improve time to reperfusion in patients with a high likelihood of large vessel occlusion (LVO) by going directly to the angio suite, bypassing conventional imaging that adds additional time. And, this is not a new concept to the endovascular world; cardiologists do it as a matter of routine. In acute stroke interventions, you can diagnose the occlusion via angiography, and depending on the kind of equipment you have, you can even diagnose lack of hemorrhage.

There is also increasing discussion about treating patients with medium vessel occlusions. CTA and MRA have significant limitations in detecting these, so another potential benefit of DTA is the ability to make the occlusion diagnosis when conventional studies fall short.

What else do we know about which patients might benefit the most from a DTA approach, and which patients perhaps not as much?

In patients with poor collaterals and a fast-growing infarct, the time-to-outcome relationship is strong. These so-called "fast progressors" are found with the highest frequency in patients who present early; in the first 6 hours after the time last seen well, about 50% of early patients are intermediate to fast progressors. In patients with severe neurologic deficit and proximal LVO, the more severe the deficit, the more likely it is that the collateral status is not good. Thus, the ideal target population for the DTA approach is patients in the early time window with severe neurologic deficit (ie, National Institutes of Health Stroke Scale [NIHSS] score of 10 within 6 hours). This is where the main advantage for a DTA approach lies and where we pay the steepest price in terms of outcomes when we lose time with additional imaging.

When patients are transferred directly to an endovascular center, we know the average door-to-puncture time is > 60 minutes. A lot of these delays are incurred by imaging, so there are substantial opportunities to save time by cutting down on imaging in patients transferred from smaller hospitals where CTA systems are not as efficient and time delays caused by imaging are even longer. At centers that still perform imaging on arrival from primary to the

endovascular center, there is a double whammy and therefore twice the opportunity to save time by skipping conventional imaging.

ANGIO-CAT and RACECAT are two studies recently presented on this topic. What have these studies demonstrated about door-to-access puncture times and patient outcomes?

ANGIO-CAT and RACECAT have yielded somewhat contradictory results. The ANGIO-CAT study is a single-center, intrahospital workflow, randomized study showing that times are reduced and outcomes improved with the DTA approach. Patients with a high likelihood of LVO went directly to angiography, and the time savings were impressive. The DTA group had approximately 37 minutes faster door-to-reperfusion times than the direct to CT suite group, which translated into better outcomes.[1]

RACECAT is a prehospital workflow study looking at direct transfer to an endovascular center versus the classic transfer pathway, which is the closest center where thrombolytics is available and then a transfer if occlusion is present. The premise was that there would be time savings translating to better outcomes in patients with LVO. The randomized approach was chosen because it was thought that there could be patients who would be hurt by this approach, such as those without an LVO, those with medium vessel occlusion, or occlusions that respond to tissue plasminogen activator (tPA) and by taking the extra time for transport to the endovascular center, tPA administration is delayed. For that reason, although the assumption was that this approach is better for patients who actually have proximal LVO, it wasn't clear that this is a better approach for all-comers with a suspicion of LVO, which, based on the Rapid Arterial Occlusion Evaluation (RACE) scale of > 4 used as cutoff for enrollment in RACECAT, yields a proximal LVO likelihood of about 50%.

In RACECAT, all assumptions that the study was based upon and designed were confirmed, except for the impact of delays to treatment on outcomes. The study identified patients with LVO, with the expected accuracy based on the RACE scale and direct transfer to an endovascular center translating to the expected shorter onset to reperfusion times in patients transferred directly. But as opposed to ANGIO-CAT, faster treatment times did not translate to any differences in outcomes. By the same token, the faster onset-to-treatment times seen in RACECAT when tPA was administered at the primary center did not translate to better outcomes, even among those without proximal LVO. It's almost as though RACECAT challenged this central dogma that time to reperfusion is critically important.

One explanation for the puzzling results of RACECAT is that the trial only enrolled patients who were not already primarily assigned to an endovascular center; in Catalonia, every geographic point is assigned to a stroke center, so it is predetermined where the patient will be transferred. Those already within 30 minutes of an endovascular center were not part of the trial because there was nothing to randomize; they were already determined to go to an endovascular center. Thus, the population studied, which was slightly less than half of the province's population, was the population that would be assigned to a primary nonendovascular center as the first destination of transport. It's possible that RACECAT took part within a time window depleted of fast progressors, which could explain some of these findings.

The other reason why RACECAT may not have shown what we thought it would is that the workflow metrics were incredibly efficient and different than what we see here in the United States. Because of the efficiency even in transfer patients, the time differences between the two groups in terms of onset to reperfusion might not have been long enough to yield a difference. The bottom line is that RACECAT was surprising in that we could not see a big effect of time on outcomes.

What do you see as the barriers to widespread adoption of DTA, and how might they be addressed? For a hospital looking to implement this approach, what additional resources would be required?

The main resource is a 24/7 operational angio suite. I think we need to get out of this concept that neurointerventional procedures are niche procedures and instead operate like interventional cardiologists. At my hospital, there are four or five cath labs, with some being dedicated for emergencies. But many centers just have one neuroangio suite. There should only be large-volume thrombectomy centers, with two angio suites (one for routine cases and one for emergencies) and appropriate staffing as standard. This would require a big mentality change.

If we start to adopt this practice, we will need more neurointerventionalist practitioners. But it's important to emphasize that it won't be a sea of patients overwhelming the system. It's 20% more than you would already be treating. Because they'll be selected based on a high NIHSS score and depending on where this NIHSS threshold is set, 80% of patients will have an LVO and will be treated eventually anyway, just later. People don't necessarily grasp that the infrastructure requirements are not that onerous.

How common of an occurrence is it for a patient without an LVO to be sent directly to the angio suite, and how can this be avoided?

An NIHSS score > 10 already predicts LVO with a positive, predictive value of about 70% to 80%, and most of these patients will be treated anyway. You're only unnecessarily

taking about 20% to 30% of the patients. That's not that different from cardiology labs, where not all ST-segment elevation myocardial infarctions end up having a coronary occlusion. Myocardial infarction with nonobstructive coronary arteries (or MINOCA) is a term that characterizes the situation when there are ST-segment elevations on electrocardiography, but the coronaries are open. This happens about 10% to 20% of the time, but cardiologists don't perform CTAs to identify occlusion with 100% accuracy because they know there is a price to be paid for that: delay in perfusion.

The other concern for patients who go directly to angiography is that you're potentially subjecting a patient without an occlusion to the risks of an angiogram. While these risks aren't nonexistent, multiple prospective trials have shown that they are low. And, again, if you are reluctant to perform conventional angiography and have the right equipment, you can diagnose lack of hemorrhage and vessel status on a noninvasive flat-panel CTA.

What it ultimately comes down to is that the risks of subjecting the minority of patients to an unnecessary angiogram must be balanced against the benefits of reperfusing the vast majority of these patients faster. There are also cost considerations, but I am not sure what is more cost-effective: the cost associated with skipping 100% of CTAs and reperfusing 80% of patients faster versus the cost associated with performing the 20% of unnecessary angiograms. To me, the balance is not clearly in favor of the conventional imaging approach.

Beyond DTA, what other prehospital/pretreatment stroke trends are most promising to you?

Ambulance-based LVO detection is promising. There's also a lot of talk about mobile stroke units (MSUs), and some trials have been positive. Although there's a lot of excitement, I'd like to see the decisions regarding angio suite versus no angio suite before the stroke unit is dispatched. This prehospital diagnosis of LVO needs to be made independent of an MSU. Ideally, patients who need thrombectomy should go directly to angio, and only those in whom thrombectomy is not indicated should be treated in the MSU because MSUs take additional time compared to a direct, from the field to angiography approach. When intravenous thrombolysis has limited effectiveness, this time will be detrimental to patient outcomes.

Therefore, in my opinion, if proximal LVO is highly suspected in the field, a direct path to the angio suite is preferred to the MSU approach. Considering the substantial costs associated with their purchase and maintenance, MSUs can be implemented in highly developed countries or regions but are challenging to scale more globally. We need solutions that are applicable in all health care systems across the world.

What role do you think new technology such as artificial intelligence (AI), mobile applications, and machine learning will play in pretreatment over the next decade?

It's going to be more and more important. In the not-so-distant future, I hope we'll have better tools for estimating LVO. For instance, there are AI applications for detecting LVO based on a plain CT in conjunction with the NIHSS score. Or, there are technologies such as transcranial Doppler, electroencephalography somatosensory evoked potentials, impedance, and several other rapidly applied infield technologies, including blood biomarkers, that could increase the diagnostic yield of an LVO.

In all these applications, the detection of blood vessel occlusion is aided by AI, so everything should improve in terms of diagnosis and detection. There are even applications for automatically abstracting the NIHSS score based on a filmed physical exam. Right now, for prehospital evaluations, the RACE scale is mainly used. But several companies or technologies are testing and developing technologies that aim to obtain elements of the neurologic exam based on AI.

I see a great role for AI in identifying the best candidates for DTA based on where patients are geographically and the closest endovascular center versus the closest primary center. As we saw in RACECAT, it is a geographic and distance game. Beyond a certain distance, the difference in delivery between a primary and endovascular center is annulled. Computers and AI will help determine where patients can get reperfused the fastest, with what modalities, and at which hospital.

What potential benefits do you think there are to neuroprotectant strategies?

There's great potential for neuroprotectant treatment at multiple steps in the ischemic cascade. For each physiologic mechanism underlying ischemic process, there are protective strategies that might be helpful in conjunction with reperfusion. The concept of neuroprotectant strategies to transform fast progressors into slow progressors (ie, increasing collateral capacity and slowing down the progression of the ischemic process) is very exciting, especially tying into the DTA concept.

The number one priority is to reperfuse the patient. Because we would have fewer patients with large infarcts, it would be even more of an imperative solution to get the patient as quickly as possible to a place where they can be reperfused, without regard for any imaging requirements. Antiplatelet drugs (eg, glycoprotein IIb/IIIa inhibitors) are adjunctive to thrombectomy or to reperfusion pharmacologic agents. There may be a role for that in the prehospital arena. I think that's less likely to happen, but it is possible. ■

1. Requena M. Evaluation of direct transfer to angiography suite vs. computed tomography suite in endovascular treatment or stroke: ANGIO-CAT a randomized clinical trial. Presented at: International Stroke Conference; March 17-19, 2021; virtual presentation.