

## Primary Thrombectomy in tPA (Tissue-Type Plasminogen Activator) Eligible Stroke Patients With Proximal Intracranial Occlusions

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### The Case

A 56-year-old diabetic man presented to the emergency room 45 minutes after right-sided hemiplegia and global aphasia. National Institutes of Health Stroke Scale score, 20; ASPECTS score (Alberta Stroke Program Early CT Score), 9, on computed tomographic (CT) scan; and CT angiography showed terminal ICA T occlusion. Both angio suite and interventionalist are available. No contraindication for IV tPA (tissue-type plasminogen activator).

### The Question

Would you consider transferring the patient directly to the angio suite for thrombectomy skipping IV tPA?

### The Controversy

Primary thrombectomy (PT) versus IV tPA followed by thrombectomy in stroke patients with proximal intracranial occlusions.

### PT Should be Considered in tPA-Eligible Stroke Patients With Proximal Intracranial Occlusions

Urs Fischer and Johannes Kaesmacher

*“It seems that perfection is attained, not when there is nothing more to add, but when there is nothing more to take away.”*

Antoine de Saint Exupéry

Do we harm the patient when we take the tPA away? The 2 most important considerations in favor of the bridging approach are preinterventional recanalization obviating the need for thrombectomy and the increased odds for recanalization if the occlusion site is not accessible or reperfusion is not achieved by mechanical thrombectomy (MT). Given the proximal occlusion site, the presumably high thrombus burden and the short tPA-to-groin puncture interval outlined in

the scenario, the odds for all of the latter are negligible ( $\approx 3-4/100$ ).<sup>1</sup> In particular, it seems unlikely that tPA will lyse hard thrombi, which are not retrievable with stent retrievers. A recent meta-analysis has suggested that tPA may promote good angiographic results<sup>2</sup>; however, the interpretation is severely limited by selection and publication bias and not supported by recent post hoc analyses of randomized controlled clinical trials (RCTs) or large prospective cohorts.<sup>3,4</sup> Until now, there is no conclusive evidence: neither that tPA promotes good angiographic results in subsequent MT,<sup>3,4</sup> nor that the effect size of MT is altered by pretreatment with tPA.<sup>5</sup> There are benefits of the bridging approach by all means (eg, Drip and Ship thrombolysis or more distal occlusions), but in the given scenario, they seem to be low.

On the contrary, tPA may harm. It may promote blood-brain-barrier breakdown, potentiate vessel wall damage by stent retrievers, put patients at risk for hemorrhagic transformation and allergic reactions, and induce thrombus fragmentation leading to longer and technically more challenging interventions. The risks for hemorrhagic transformation in patients with acute stroke treated endovascularly are not negligible, especially in diabetic patients with an occlusion pattern involving end-artery territory.

There are a myriad of observational studies reporting on rates of functional outcome (FO) stratified according to IV tPA pretreatment status, and a recent meta-analysis concluded that bridging therapy (BT) is superior to direct MT in terms of clinical outcomes.<sup>2</sup> However, most of these studies compared intravenous thrombolysis (IVT)-eligible and IVT-ineligible patients.<sup>2</sup> IVT-ineligible patients are inherently different from IVT-eligible patients. It is well known that patients treated later and patients with comorbidities, especially patients with anticoagulation treatment, have a genuine poorer outcome than IVT-eligible patients. To the best of our knowledge, there are only 3 observational studies assessing safety and efficacy of direct MT in tPA-eligible patients versus IVT plus MT.<sup>6-8</sup> A pooled analysis of these data suggest that (1) successful reperfusion is actually favored by direct MT

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rather than IVT plus MT, (2) rates of hemorrhagic transformations were lower in the direct MT arm, and (3) skipping the tPA may fasten the workflow and reduce door-to-groin puncture interval. In addition, withholding tPA in the first place may open the door for tailored medical reperfusion strategies if complete reperfusion is not achieved. Such strategies are of rising interest because improving near complete to complete reperfusion has been shown to be associated with a substantial clinical benefit.

In light of recent evidence for direct MT in tPA-eligible patients, we are confident that the 58-year-old man will most likely benefit if we skip the tPA. However, future randomized controlled trials will address this dilemma and will provide firm evidence for this important unanswered question.

No doubt we are far from perfection, but in the given scenario, there is something to take away.

## PT Should Not Be Considered in tPA-Eligible Stroke Patients With Proximal Intracranial Occlusions

Georgios Tsvigoulis and Andrei Alexandrov

*“He will win who knows how to handle both superior and inferior forces.”*

Sun Tzu (The Art of War)

As vascular neurologists treating this acute ischemic stroke (AIS) patient with large-vessel occlusion (LVO), we will (1) mix tPA in the CT scanner as soon as noncontrast CT shows no bleeding; (2) bolus the patient and start tPA in parallel with arming contrast injector for CT angiography; and (3) as soon as we visualize LVO on CT angiography, we will transfer the patient directly to the angio suite for swift initiation of MT. Because the patient is eligible both for IVT and MT, he/she should be offered combined systemic and endovascular reperfusion therapies that currently represent the best standard of care (class I, level of evidence A) according to North American and European recommendations.<sup>9,10</sup> Our therapeutic approach is based on the following facts, evidence, and arguments.

### **Fact 1: IVT Is Effective Across All AIS Subtypes and Severity Subgroups**

The individual patient data meta-analysis of all available randomized controlled clinical trials has confirmed the initial findings of the pivotal NINDS-r-tPA Stroke study and provided unequivocal evidence for the efficacy of IVT in all AIS subtypes, including LVO.<sup>11</sup>

### **Fact 2: Combined IVT and MT Are More Effective Than IVT Monotherapy in LVO**

In all landmark RCTs, ≈80% of patients with AIS randomized to MT were pretreated with tPA, and only 2.6 patients with LVO need to be treated with MT in addition to medical therapy to improve FO.<sup>12</sup>

### **Fact 3: The Efficacy of IVT and MT Is Time Dependent**

The treatment response to both systemic and endovascular reperfusion therapies is determined mainly by the speed of their delivery.<sup>9–12</sup> Consequently, IVT should not delay prompt initiation of MT,<sup>10</sup> and swift pursue of endovascular therapies should not preclude tPA-eligible patients from receiving IVT.

### **Fact 4: PT Is Effective in LVO Patients With Contraindications to IVT**

Current evidence underscore the superiority of MT over standard therapy in patients with LVO independent of pretreatment with IVT.<sup>5,11–13</sup> Thus, PT should be readily offered to LVO patients with contraindications to IVT, but there is no RCT showing that PT should be delivered as monotherapy in tPA-eligible patients.

### **Fact 5: Combined MT and IVT Do Not Increase Periprocedural Complications and Adverse Outcomes Compared With PT**

Different analyses of RCT and cohort data have shown that the risk of symptomatic intracranial hemorrhage and other periprocedural complications is not increased with combination reperfusion therapies.<sup>3</sup> Moreover, a recent systematic review (including 1764 patients with AIS from 7 RCTs) has documented higher rates of death/severe dependency (mRS scores of 5–6) with PT compared with combination therapy (31% versus 19%).<sup>13</sup>

### **Argument 1: Combination Therapy Seems to Be More Effective Than PT in LVO**

A recent meta-analysis including 13 cohorts (12 observational studies and 1 individual patient data meta-analysis of 5 RCTs) and 3553 patients with AIS treated with MT reported that combination therapy was associated with higher rates of successful recanalization (SR) and functional independence in comparison with PT.<sup>2</sup> In addition, BT was related to lower odds of mortality and higher likelihood of SR with fewer (≤2) passes.<sup>2</sup> These preliminary findings based on indirect comparisons of randomized and observational data lend support to the hypothesis that tPA-induced fibrin degradation may lead to easier clot detachment from the vessel wall during endovascular procedures. They also support the argument that the added value of IVT in patients with LVO treated with MT may be attributed to potential augmentation of the collateral circulation because of recanalization of coexisting thrombi located in distal vessels that are not accessible to endovascular devices.<sup>13</sup>

### **Argument 2: Pretreatment With IVT May Reduce the Likelihood of Infarct in a New Previously Unaffected Territory That Can Complicate MT**

A recent subgroup analysis of ESCAPE trial (Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times Trial) has indicated that pretreatment with IVT reduced approximately by two thirds the likelihood of infarct in a new previously unaffected territory complicating MT, whereas infarct in a new previously unaffected territory was in turn associated with substantial reduction in the odds of functional improvement quantified by shift in mRS score.<sup>14</sup> Although the former association has not been reproduced in other RCTs, a pooled analysis of available data may further clarify the potential beneficial effect of IVT in reducing infarct in a new previously unaffected territory risk.

### **Argument 3: Early tPA Delivery May Result in SR of LVO Averting the Need for MT**

The rate of SR in patients with LVO pretreated with IVT who negated the need for additional endovascular procedure ranged between 7% (REVASCAT) and 26% (THRACE) in the recent RCTs of MT. Consequently, a non-negligible proportion of patients with LVO may rapidly recanalize during minutes of tPA infusion preventing further endovascular reperfusion.

In conclusion, stroke physicians now have 2 powerful tools (IVT and MT) to bust clots causing LVO and improve FOs in this emerging era of acute stroke treatment. We strongly believe that IVT and MT are complementary therapies that should be pursued in parallel in a swift and noncompeting fashion, thus not altering existing and often fragile chains of stroke patient survival.

*“When in a fight to the death, one wants to employ all one’s weapons to the utmost.”*

Miyamoto Musashi (The Book of Five Rings)

*“You should not have a favorite weapon. To become overfamiliar with one weapon is as much a fault as not knowing it sufficiently well.”*

Miyamoto Musashi (The Book of Five Rings)

### Rebuttal by Drs Fischer and Kaesmacher

*“People’s minds are changed through observation and not through argument.”*

Will Rogers K

#### Fact 1 and Argument 3

Yes, IVT is an effective therapy across all stroke subtypes and occlusion locations; however, the increase in good FOs compared with placebo is modest ( $\Delta+3\%$ – $4\%$  for National Institutes of Health Stroke Scale score,  $>5$ ), and recanalization before MT is rare.

#### Fact 3

We agree that all efforts should be made not to delay initiation of IVT or MT. Despite all efforts, there may be scenarios where IVT delays initiation of MT and recently published data on patients with direct MT eligible for IVT supports this notion.

#### Fact 5

IVT before MT promotes hemorrhagic transformations, blood–brain barrier breakdown, and aggravates vessel wall damage, thus highlighting that achieving recanalization infrequently is not without risks.

#### Argument 1

The meta-analyses mentioned are confounded by indication for IVT. Patients treated without tPA had higher rates of vascular comorbidities, and the total time of ischemia until MT was longer. Thus, these results should be interpreted with caution, and they are contrasted by observational data without this selection bias.

#### Argument 2

A subanalysis of ESCAPE (intervention and control arm) suggested that patients treated with IVT had fewer infarcts in a new territory. The topic of interest, however, is whether patients treated endovascularly with and without IVT have different rates of infarcts in a new territory. Given the borderline significant result after adjustment for age, sex, treatment type, and type of follow-up imaging, confinement to the endovascular arm probably would have yielded nonsignificant results in the presented data.

IVT followed by MT remains the standard of care until definitive RCT evidence becomes available. However, in some clinical scenarios, direct MT may be a reasonable alternative.

*“The aim of argument, or of discussion, should not be victory, but progress.”*

Joseph Joubert

### Rebuttal by Drs Tsivgoulis and Alexandrov

*“Coming together is a beginning; keeping together is progress; working together is success.”*

Henry Ford

Drs Fischer and Kaesmacher make 3 arguments for direct MT (dMT): (1) IVT does not independently improve MT outcomes, (2) IVT may delay MT and increase intracranial bleeding, and (3) there are only 3 observational studies comparing BT with dMT in tPA-eligible patients. The pooled (unpublished) analysis of these studies shows similar treatment efficacy. We disagree with the following arguments:

#### IVT Pretreatment Independently Improves MT Outcomes

MR-CLEAN and IMS-III investigators developed a new decision tool for the prognostication of individual benefit of MT in LVO (MR-PREDICTS). IVT pretreatment is independently associated with improved FO in MR-PREDICTS.

#### IVT Does Not Delay MT and Does Not Increase Symptomatic Intracranial Hemorrhage Risk

If patients are transferred after tPA bolus directly to the angio suite for immediate initiation of MT, tPA infusion can be delivered in parallel with no delay in endovascular clot retrieval. The theoretical argument that IVT pretreatment increases symptomatic intracranial hemorrhage risk has not been documented in any study comparing dMT and BT. IVT pretreatment may actually increase asymptomatic intracranial bleeding that does not adversely affect FO.

#### There Are Only 3 Studies Comparing BT and dMT in tPA-Eligible LVO Patients

These observational studies are open to selection bias because the selection of dMT over BT was made by interventionalists without any prespecified rationale. Specifically, patients in the Chinese study (Wang et al) received dMT when they refused IVT pretreatment or when interventionalists suspected huge thrombus load. The Swiss study (Fischer et al) reported excessive (48%) 3-month mortality rates in the propensity-matched BT cohort. The German study (Weber et al) included both ineligible and eligible for patients with IV tPA.

Winston Churchill once said, “If we open a quarrel between past and present, we shall find that we have lost the future”. To paraphrase, opening a quarrel between the past (IVT) and the present (MT) reperfusion therapies will result in missing the opportunity for combining them effectively for the maximal benefit of our patients.

### Comments by Drs Molina and Selim

Several years of romantic affairs and 5 randomized controlled trials consummated the reperfusion marriage between the seductive primadonna Mrs tPA and the handsome rising star Mr

MT. The couple matched perfectly, Mrs tPA moves quickly and is widely available, but alone, she is too weak to beat the beast, LVO. On the contrary, Mr MT moves slow and is confined to few centers, but he is highly effective retrieving the beast from his cave. This marriage consistently achieved high rates of SR and good clinical outcome in tPA-eligible stroke patients with LVO, and the union was blessed with the class A recommendation by American and European guidelines. Two years after the honeymoon, however, Mr MT became more popular, faster, and stronger, especially in high volume, well-resourced, and experienced centers. Although, in the drip and ship scenario the marriage works, Mr MT considers that in certain situations, such as early presenting patients with LVO and available angio suite, Mrs tPA may slow down and even complicate the fight against the beast.

### Does IV tPA Delay the Initiation of MT?

Currently, in most academic endovascular capable centers, patients eligible for tPA are delivered directly to the CT suite, and tPA bolus is given during or right after fast-track CT/CT angiography. If an LVO is confirmed, the patient is immediately transferred to the angio table for MT. In this scenario of parallel process of care, tPA administration is not the main cause of delay in the imaging-to-groin time. Logistical barriers leading to transfer delay from CT to angio suite, unavailability of 24/7 angio suite or in-house interventionalist, patient's preparation or less frequently difficult arterial access may account to more delay than the tPA administration itself. In contrast, some experienced endovascular centers have sub-optimal door-to-needle times that markedly affect door-to-groin times. Therefore, optimal and well-polished workflows are needed during the entire process.

Direct transfer of patients to the angio suite dramatically shortens door-to-groin times, but direct transfer does not mean direct thrombectomy. Direct thrombectomy would be particularly attractive in patients at increased bleeding risk, but still tPA-eligible patients, and in those cases with low chances for SR—tandem extracranial and intracranial occlusions—that may require additional stenting and potentially immediate antiplatelet therapy. Low preintervention recanalization rates (7%–8%) because of the short clot exposure to tPA before MT, clot dislocation and distal embolization, and an unnecessary increased risk of intracranial hemorrhage are the main allegations of Mr MT lawyers for skipping tPA. In contrast, Mrs tPA lawyers argue that pretreatment with tPA may soften the thrombus, requiring less passes of the stentriever to achieve SR. Moreover, in cases of incomplete postprocedure recanalization (Thrombolysis in Cerebral Infarction [TICI] 2b), the still on-board tPA—because of extremely efficient workflow—may restore perfusion in distal arterial territories. However, this cross fire of arguments and allegations between Mrs tPA and Mr MT are mainly based either on inappropriate comparisons between tPA-eligible versus ineligible patients from RCTs and PDMA or on observational, retrospective, single-center cohorts of tPA-eligible patients with inherent selection bias.

Unavoidably, Mrs tPA and Mr MT will go to court. Such an RCT trial (SWIFT DIRECT) will compare bringing tPA+MT

versus primary MT in tPA-eligible patients under optimized workflow conditions, including patients directly transferred to the angio suite in both treatment arms. Regardless of this trial results, tPA administration before MT will likely remain the standard of care for the vast majority of tPA-eligible LVO. Drip and ship will save the marriage.

### Disclosures

Dr Fischer receives research grants from Swiss National Science Foundation, is a global PI for SWIFT DIRECT trial, and is a consultant for Medtronic. Dr Alexandrov serves in the Genentech Speaker Bureau. The other authors report no conflicts.

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