

# The Optimal Management for People with Acute Stroke and Minor Deficits: Intravenous Thrombolysis or Medical Management?

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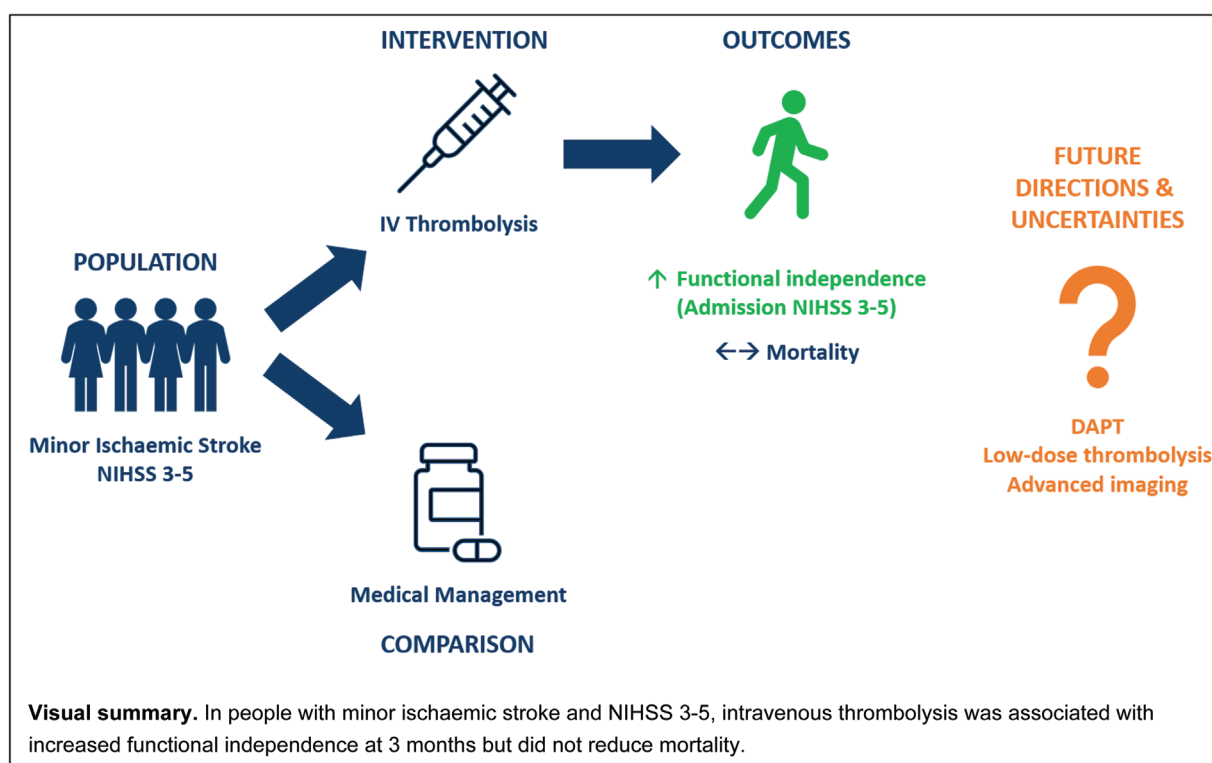
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Stroke remains a global health care problem, associated with a high mortality and morbidity in the poststroke period. Much evidence is accumulated on ischemic strokes (and its acute management) and its associated risk factors,<sup>1,2</sup> as well as the initiation of antithrombotic therapy.<sup>3</sup>

The high risks associated with hemorrhagic stroke are also increasingly recognized,<sup>4</sup> with focus over how and when antithrombotic therapy is started in such patients.<sup>5</sup> In addition, a more holistic and integrated care approach to stroke management has been advocated, given the high risk

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of subsequent cardiovascular events following the initial stroke.<sup>6</sup>

In the acute stage, how best to manage those who present acutely with minor ischemic strokes has posed a therapeutic dilemma for stroke clinicians.<sup>7</sup> We wish to restore, on the one hand, any impairment in cerebral blood flow, prevent subsequent ischemia, and improve functional recovery, while on the other hand, avoiding neurological deterioration or symptomatic intracranial hemorrhage (sICH), which is one of the most feared complications in the early period after stroke. The efficacy of intravenous thrombolysis is generally well established in the context of acute ischemic stroke.<sup>8</sup> However, the relative efficacy and safety of intravenous thrombolysis in people who present with minor symptoms is less clear and often presents a challenge when faced with someone presenting with acute minor focal neurological symptoms in the emergency department.<sup>7</sup> More than half of people with acute ischemic stroke have minor symptoms only,<sup>9,10</sup> yet up to a third of these people have functional disability at 90 days after stroke.<sup>10,11</sup> The optimal management of people presenting with acute minor stroke is therefore of exceptional clinical importance.

In the current issue of the Journal, Tu and colleagues<sup>12</sup> help address uncertainties surrounding the role of intravenous thrombolysis in this context. In a retrospective analysis of more than 26,000 people presenting with acute ischemic stroke in China who were managed with intravenous thrombolysis or medical management, the authors demonstrate that intravenous thrombolysis is associated with an increased probability of functional independence at 3 months although no effect was observed on mortality between the two groups. The benefits in functional independence among people managed with intravenous thrombolysis were observed across the National Institutes of Health Stroke Scale (NIHSS) scores 3–5, but not in people with NIHSS scores 0–2. The authors conclude that intravenous thrombolysis appears an effective treatment to improve functional outcomes among people with acute minor ischemic stroke and NIHSS scores 3–5.

The majority of randomized controlled trials that provide the evidence base for intravenous thrombolysis in acute stroke did not include people without disabling symptoms.<sup>7</sup> The Potential of r-tPA for Ischemic Strokes with Mild Symptoms (PRISMS) trial assessed the safety and efficacy of thrombolysis with alteplase in people presenting acutely with minor ischemic stroke and NIHSS 0–5.<sup>9</sup> The trial only recruited 313 participants, which is one-third of the planned sample size, and was terminated early. Notwithstanding these limitations, alteplase did not improve functional outcomes at 3 months and increased the rate of sICH compared with aspirin.<sup>9</sup> The population in the PRISMS study had comparable deficits and stroke severity compared with people with minor stroke not treated with alteplase in the prospective Mild and Rapidly Improving Stroke Study (MaRISS).<sup>13</sup>

The 2021 European Stroke Organization (ESO) guideline on intravenous thrombolysis for acute ischemic stroke distinguishes recommendations on intravenous thrombolysis

for people with minor stroke based on the presence or absence of disabling symptoms.<sup>14</sup> Intravenous thrombolysis is recommended for people with minor ischemic stroke and *disabling* syndromes but is not recommended for minor nondisabling syndromes in the absence of large-vessel occlusion. Determining whether symptoms are disabling is therefore an important factor in the management of people with acute minor ischemic stroke. The PRISMS trial operationally defined a clearly disabling deficit as that which, if unchanged, would prevent the patient's basic activities of daily living (for example, bathing, ambulating, toileting, hygiene, and eating) or returning to work.<sup>7,9</sup> Of course, judging if, and to what extent, a deficit may be disabling in the future is challenging in the hyperacute setting.<sup>7</sup>

Using a dichotomous NIHSS cut-off to determine stroke syndromes that are likely to be disabling and which should be treated with intravenous thrombolysis has important limitations. The NIHSS is strongly weighted toward dominant hemisphere anterior circulation deficits and underestimates clinical severity in people with nondominant or posterior circulation strokes.<sup>15,16</sup> Clinicians should therefore exercise caution when applying dichotomous NIHSS thresholds, especially when features are present that could represent a nondominant or posterior circulation stroke.<sup>15</sup>

Increased availability of advanced imaging for people presenting with acute stroke may allow more “personalized” decisions around treatment with intravenous thrombolysis for acute minor stroke. Advanced multimodal imaging which includes angiography and perfusion scan could help to identify people with vessel occlusions or a substantial penumbra who may be most likely to benefit from intravenous thrombolysis. The 2021 ESO guideline includes an expert consensus statement which suggests treatment with intravenous thrombolysis for people with acute minor, nondisabling ischemic stroke within 4.5 hours from symptom onset and large vessel occlusion, although there was insufficient evidence for an evidence-based recommendation.<sup>14</sup> The TNK-tPA Versus Standard of Care for Minor Ischemic Stroke with Proven Occlusion (TEMPO-2) trial (NCT02398656) is an ongoing randomized controlled trial of low-dose tenecteplase compared with standard care in people with minor ischemic stroke and symptomatic vessel occlusion. The findings will help to understand whether advanced imaging can identify people with minor stroke syndromes due to vessel occlusions who could benefit from low-dose tenecteplase.<sup>7,14</sup>

The role of dual antiplatelet therapy (DAPT) to prevent recurrent events in people with minor stroke has emerged following publication of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)<sup>17</sup> and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT)<sup>18</sup> trials, which demonstrate that DAPT with aspirin and clopidogrel reduces the risk of early stroke recurrence for people with minor ischemic stroke (NIHSS  $\leq 3$ ) or high-risk transient ischemic attack (ABCD2  $\geq 4$ ). The benefit is mainly observed in the first 21 days and DAPT is now recommended in this context.<sup>19</sup> The emergence of DAPT as an effective treatment for acute

minor ischemic stroke may change the landscape with respect to the relative benefits of thrombolysis in this group of patients as most previous comparisons were with single antiplatelet. Preliminary findings from the Antiplatelet Versus Alteplase in Acute Mild Ischemic Stroke (ARAMIS) trial, which was a multicenter noninferiority randomized controlled trial that compared DAPT with aspirin and clopidogrel to intravenous thrombolysis in people with acute minor ischemic stroke within 4.5 hours of symptom onset, were presented at the 2023 International Stroke Conference.<sup>20</sup> The findings demonstrate that DAPT is non-inferior to intravenous thrombolysis for the primary outcome of excellent functional recovery (modified Rankin Scale: 0–1: 93.8% with DAPT vs. 91.4% with intravenous thrombolysis). The full publication of ARAMIS results is eagerly awaited.

In summary, Tu and colleagues help answer the clinical conundrum of how to treat people presenting with acute minor stroke. Intravenous thrombolysis appears best reserved for people with disabling deficits or NIHSS  $\geq 3$ . People with less severe or nondisabling stroke syndromes appear better treated with DAPT. The role of advanced neuroimaging to guide personalized approaches to management continues to emerge. The ongoing TEMPO-2 study (NCT02398656) is evaluating the role of low-dose tenecteplase in this context which may change the landscape in time.

#### Conflict of Interest

None declared.

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