It may be that the landscape of stroke care is changing, as more attention is being drawn to the benefits of intravenous (IV) tenecteplase for acute stroke reperfusion therapy, particularly given the ease of administration and affordability highlighted by the COVID-19 pandemic. The latest ANA Investigates podcast asks Professor Bruce Campbell important questions about the body of evidence surrounding tenecteplase, including whether it is superior to IV alteplase, the current drug used as an acute stroke thrombolytic. Dr Campbell provides his expertise as a researcher in this area and co–principal investigator for the EXTEND-IA and EXTEND-IA TNK (tenecteplase) multicenter randomized clinical trials.

Since the 1995 National Institute of Neurological Disorders and Stroke trial cited a 30% chance of minimal disability at 90 days and a symptomatic intracerebral hemorrhage (sICH) rate of 6.4%, IV alteplase has been routinely administered to eligible acute stroke patients. Tenecteplase has important differences when compared to alteplase. Dr Campbell discusses that alteplase is naturally occurring in our blood and, when administered to stroke patients, helps activate plasminogen, which turns into plasmin, which then acts to break down the clot. Tenecteplase is a genetically modified form of alteplase, with only 3 amino acids distinguishing the two molecules. This modification increases the half-life to 22 minutes, compared to that of alteplase, which is approximately 3 minutes. As a result, tenecteplase does not have to be given as a drip infusion over an hour as is the case with IV alteplase; rather, tenecteplase can be administered as a bolus in about 5 seconds. These changes to its structure also make it more specific to the clot and more resistant to breakdown in the bloodstream.

From an economic perspective, the cost savings of the drug could be substantial. Dr Campbell points out that, outside the United States, patients weighing more than 55kg require 2 vials of alteplase, so switching to tenecteplase could represent a 50% cost savings. In the United States, he estimates replacing IV alteplase save about $3,000 per treatment.

When considering the risks of the medication, the sICH risk and rate of angioedema appear to be similar to those of alteplase; however, the data are more limited, as medication use is not widespread. Dr Campbell highlights that use of tenecteplase for acute stroke treatment is currently off label. As a result, it is important not to follow the package insert dosing instructions, which relate to the on-label indication of myocardial infarction. The dose used in stroke is approximately half that used for myocardial infarction, and no adjunctive heparin or antiplatelet agents are used.

Dr Johansen and Dr Campbell then turn to the practice and practicality of administration of tenecteplase. The trials have incorporated different doses, with the 3 most discussed being 0.1mg/kg, 0.25mg/kg, and 0.4mg/kg. Dr Campbell summarizes the most important literature, including the Australian trial that suggested superiority of the 0.25mg/kg dose compared to alteplase and 0.1mg/kg tenecteplase in patients with large vessel occlusion (who were treated prior to the availability of endovascular thrombectomy). There did
not appear to be a benefit of increasing from 0.25mg/kg to 0.40mg/kg tenecteplase in his own EXTEND-IA TNK part 2 trial,7 with earlier data suggesting an increased sICH risk,5 although later trials have not always supported this concern.8 Dr Campbell summarizes his research demonstrating that among those who received 0.25mg/kg IV tenecteplase, they saw a doubling from approximately 10% to 20% in the rate of reperfusion of large vessel occlusion, as well as a shift in the functional benefit to those patients.7,9 Registry data for basilar artery occlusion, potentially one of the most deadly types of large vessel occlusion, also suggest benefit of IV tenecteplase.10

Dr Campbell describes his experience in Australia, where IV tenecteplase is now recommended in guidelines as an alternative to alteplase, particularly in patients with large vessel occlusion. Some systems such as the stroke telemedicine service in his state of Victoria have switched entirely to the use of tenecteplase. He emphasizes the importance of a protocol, and that the rationale used by some institutions for switching entirely to tenecteplase was that maintaining two thrombolytic drug options at different doses created substantial clinical risk.

Beyond the 4.5-hour window, the experience with tenecteplase is limited. Prior tenecteplase trials did enroll some patients beyond 4.5 hours, but did not test patients in this time window specifically.6 The data that support thrombolysis beyond 4.5 hours are based on alteplase.11,12 Similar trials using tenecteplase are ongoing. Dr Campbell states that the Australian13 and European Stroke Guidelines14 now include recommendations for thrombolysis in patients in the 4.5- to 9-hour window and with wake-up stroke who have computed tomography or magnetic resonance imaging (MRI) perfusion mismatch, similar to the imaging selection recommended in guidelines for endovascular thrombectomy 6 to 24 hours after onset. The American Heart Association (AHA) guidelines have not assessed these data as yet, but there are recommendations in AHA, European, and Australian guidelines that MRI fluid-attenuated inversion recovery–diffusion mismatch may be used to select patients with unknown stroke onset for thrombolysis with alteplase.

Upon being asked whether there are sufficient data to suggest that IV tenecteplase is actually superior to IV alteplase, Dr Campbell highlights that there are more data available now for tenecteplase than there were for alteplase when it was implemented as a treatment for stroke. However, he emphasizes the importance of completing the ongoing clinical trials using tenecteplase. These include the TASTE, ATTEST-2, AcT, and NORTEST-2 trials in patients 0 to 4.5 hours after onset, predominantly without large vessel occlusion; the TIMELESS and ETERNAL-LVO trials in patients with large vessel occlusion predominantly at 4.5 to 24 hours; and the TEMPO-2 trial utilizing IV tenecteplase in patients with nondisabling stroke symptoms but vessel occlusion or perfusion lesion, particularly considering the results of the PRISMS trial for alteplase, which did not show a benefit.15 Dr Campbell anticipates that IV tenecteplase will continue to play an important role in the treatment of acute ischemic stroke patients and may in the future be combined with other medications that address other components of thrombus.

Link: https://traffic.libsyn.com/secure/myana/S2_Ep5_ANA_Investigates_Tenecteplase_in_Stroke.mp3

Author Contributions
M.C.J. conceptualized the podcast episode, crafted the questions, conducted the podcast interview, and drafted the summary manuscript. B.C.V.C. reviewed the podcast interview content, provided the subject area expertise, and assisted in manuscript editing.

Potential Conflicts of Interest
Nothing to report.

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