Updates in Stroke Treatment

BRIAN MAC GRORY, MBBC, BAO; SHADI YAGHI, MD

ABSTRACT
In this article, we discuss major advances in the treatment and prevention of ischemic stroke that have taken place in the past 3 years. The most important advance in acute stroke treatment is the validation and widespread adoption of intra-arterial therapies for the treatment of acute ischemic stroke. Five clinical trials spanning multiple continents were published in early 2015 that proved that intra-arterial treatment – both with and without tPA – is beneficial in improving functional recovery after stroke. Emerging literature (including the DAWN trial) also suggests that patients can be treated up to 24 hours after the onset of symptoms based on the size of the infarct core obtained using MRI Perfusion or CT Perfusion imaging. With respect to stroke secondary prevention, widespread adoption of long-term cardiac monitoring has increased the detection rate of atrial fibrillation (as demonstrated in the EMBRACE and CRYSTAL-AF trials). Pioglitazone (an oral hypoglycemic agent of the thiazolidinedione drug class) was shown in the IRIS trial to reduce the risk of recurrent stroke in patients with impaired glucose tolerance who had not developed type 2 diabetes mellitus.

KEYWORDS: Ischemic stroke, transient ischemic attack, mechanical thrombectomy, atrial fibrillation, embolism, pioglitazone

INTRODUCTION
The last 3 years have represented a paradigm shift in the treatment and prevention of ischemic stroke. Overwhelmingly, the most important change has been a comprehensive demonstration of the efficacy of interventional treatment for acute ischemic stroke. In addition to this, there have been advances in medical therapy for the prevention of recurrent stroke, new strategies for the detection of atrial fibrillation and a plethora of new oral anticoagulants for use in the prevention of stroke of embolic origin.

INTERVENTIONAL THERAPY FOR ACUTE ISCHEMIC STROKE
The most important advance in the field of stroke neurology since the discovery of tissue plasminogen activator (tPA) occurred in 2015. Thrombus retrieval using intra-arterial therapies was demonstrated as being both safe and highly effective in the treatment of acute ischemic stroke. This has led to a rapid uptake in its use in the United States and across the world and has galvanized the neurologic community to improve systems of care and rapid access to stroke treatment centers.

The use of mechanical devices to treat acute ischemic stroke was the subject of controversy in the field of stroke neurology for over a decade. Multiple trials1,2 had demonstrated that mechanical clot retrieval devices improved the rate at which arteries were re-canalized after an acute occlusion, but no trials had demonstrated that this necessarily improved functional outcomes. For example, the Merci device3 [Mechanical Embolus Removal in Cerebral Ischemia] used a corkscrew mechanism to penetrate a clot and then retrieve it. [Figure 1] It was effective at achieving the goal of removing clots but was associated with a high rate of complications, specifically arterial dissection.

The Penumbra device5 used a gentle suction mechanism at the proximal end of a clot to attempt to gradually retract it. [Figure 2] It was associated with a lower rate of complications but also never shown to improve functional outcome.

In early 2015, five clinical trials were published in quick succession demonstrating the efficacy of a new generation of devices to treat acute ischemic stroke: MR CLEAN6, ESCAPE7, EXTEND-IA8, SWIFT PRIME9 and REVASCAT10. These trials mostly used a stent retriever device. [Figure 3] This device introduces an undeployed stent directly in to the core of a clot, then expands the stent, leaving it in situ for approximately 5 minutes. This causes a clot to become enmeshed in and adherent to the stent before being extracted.

The results of the trials are depicted in Table 1:

A meta-analysis11 of these trials confirmed that mechanical thrombectomy led to reduced disability at 90 days with an odds ratio of 2.49. The number needed to treat (NNT) was only 2.6 to achieve one favorable outcome. In addition, the risk of death at 90 days and the risk of cerebral hemorrhage were no higher than that of tPA alone. In the last few months, the investigators for the MR CLEAN trial showed that the benefits seen at 90 days persisted after 2 years of follow-up of their original trial subjects.12

Intravenous tPA and intra-arterial clot retrieval can only be delivered if a person presents within the “therapeutic
window” – 4.5 hours for tPA and 6–12 hours for intra-arterial therapy. Therefore, an enormous challenge in the field of stroke neurology is the treatment of strokes that present late (after 12 hours) or from sleep [so-called “wake-up strokes”]. The DAWN trial [13] (Clinical Mis-mash in the Triage of Wake Up and Late Presenting Stroke Undergoing Neuro-intervention with Trevo) was recently completed. This was a randomized, controlled trial of thrombectomy vs. best medical therapy in patients who had a stroke beginning between 6 and 24 hours prior to presentation and who would not have not strictly been eligible for treatment with intra-arterial therapy. However, in this trial the investigators performed an assessment of the size of the “core infarct” [the area of dead tissue that is felt not to be salvageable] using magnetic resonance imaging (MRI) or computed tomography perfusion (CTP) imaging. They enrolled patients with a core infarct volume of <50 cc and a large stroke syndrome (NIHSS >20) meaning that the person’s stroke syndrome was worse than their imaging demonstrated, suggesting that there was a large volume of brain tissue that was salvageable. Using this protocol, they enrolled people presenting late in their “stroke window” and perform intra-arterial clot retrieval safely. Of 206 subjects, those treated with intra-arterial clot retrieval, achieved a favorable functional outcome in 48.6%, in comparison to 13.1% of patients in the control arm.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Intervention</th>
<th>Outcome measure</th>
<th>Enrollment criteria</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR-CLEAN(6)</td>
<td>500 (233 in intra-arterial treatment group vs. 267 in control group)</td>
<td>Stentriever</td>
<td>mRS at 90 days</td>
<td>Within 6 hours of symptom onset</td>
<td>OR of 1.67 for functional independence</td>
</tr>
<tr>
<td>ESCAPE(7)</td>
<td>316 (165 in intra-arterial group vs. 150 in control group)</td>
<td>Any thrombectomy device</td>
<td>mRS at 90 days</td>
<td>Within 12 hours of symptom onset</td>
<td>OR of 2.6 for functional independence</td>
</tr>
<tr>
<td>EXTEND-IA(8)</td>
<td>70 (35 patients in each group)</td>
<td>Stentriever</td>
<td>mRS at 90 days</td>
<td>Ischemic core of &lt;70ml on CT Perfusion</td>
<td>71% functional independence in treatment group vs. 40% in control group</td>
</tr>
<tr>
<td>SWIFT PRIME(9)</td>
<td>196 (98 patients in each group)</td>
<td>Stentriever</td>
<td>mRS at 90 days</td>
<td>Within 6 hours of symptom onset</td>
<td>60% functional independence in treatment group vs. 35% in control group</td>
</tr>
<tr>
<td>REVASCAT(10)</td>
<td>206 (103 patients in each group)</td>
<td>Stentriever</td>
<td>mRS at 90 days</td>
<td>Within 8 hours of symptom onset</td>
<td>OR of 2.1 for functional independence</td>
</tr>
</tbody>
</table>
DETECTION OF ATRIAL FIBRILLATION AFTER ISCHEMIC STROKE

Approximately one-third of all strokes are labelled as cryptogenic i.e., there is no cause identified despite a comprehensive workup. There is, however, growing recognition that paroxysmal atrial fibrillation is challenging to diagnose and can easily be missed with only short-term cardiac telemetry. So, a large proportion of patients with “cryptogenic stroke” may have atrial fibrillation that has simply not been diagnosed. Since strokes due to atrial fibrillation are eminently preventable – anticoagulation with inexpensive, widely available medications such as coumadin reduce the risk of stroke due to atrial fibrillation by approximately two-thirds it is important to evaluate. Even brief bouts of atrial fibrillation substantially increase the risk of stroke. The fact that strokes due to atrial fibrillation are so severe – and so treatable – lends an urgency to its detection.

Two recent trials are informative in this regard:

1) EMBRACE: The EMBRACE trial was a study of patients aged 55 years and above who had suffered a cryptogenic stroke or cryptogenic TIA in the 6 months preceding screening and who had no evidence of atrial fibrillation after 24 hours of cardiac telemetry. The investigators randomized them to either a further 24 hours of telemetry or 30-days of continuous ambulatory cardiac rhythm monitoring. The primary outcome measure was the detection of 30 seconds of continuous atrial fibrillation. In the intervention group, 16.1% of patients were found to have new paroxysmal atrial fibrillation in contrast to a 3.2% of patients in the control group. They also demonstrated a very clear, incremental yield with an increased length of monitoring time. [Figure 4]

2) CRYSTAL-AF: The CRYSTAL-AF trial examined the use of an insertable cardiac monitor (ICM) for the purpose of detecting paroxysmal atrial fibrillation. An ICM is a small device that is placed under the skin of the chest through a very minor outpatient procedure with no need for sutures or anesthesia. It has the ability to continuously monitor heart rate and remotely transmit data. The device is left in place for up to 3 years at a time and is well tolerated. The CRYSTAL-AF investigators enrolled patients aged 40 or older who had a stroke or TIA within the preceding 90 days and labelled as cryptogenic after a work-up which included 24 hours of EKG monitoring. 441 were successfully randomized to either the intervention group (ICM insertion) or the control group (with no specific protocol for heart rhythm monitoring specified). They also used the primary outcome of 30 seconds of continuous atrial fibrillation. In the patients assigned to the control group, the rate of atrial fibrillation diagnosis was only 1.4% at 6 months of follow-up whereas in the intervention group it was 8.9%. Only 2.4% of ICMs had to be removed in this study – the most common reason being local infection, pain or irritation.

The lower detection rate of atrial fibrillation in the CRYSTAL-AF study compared with the EMBRACE study may reflect the younger population that was studied in that trial. Alternatively, it could represent technical differences between the ability of and ICM and an ambulatory Holter monitor to detect atrial fibrillation. Both of these trials used 30 seconds of atrial fibrillation as a cutoff and so they may still underestimate the true prevalence of atrial fibrillation.

The growing recognition of embolism as a major cause of stroke – especially in those people diagnosed with a cryptogenic stroke – has led to the creation of a new clinical construct: embolic stroke of undetermined source (ESUS). This refers to a stroke that appears embolic (i.e. it is multifocal, based in the watershed zone or cortically-based) and is too large to simply represent a lacunar infarct (i.e., is greater than 1.5cm in maximal diameter) but for which no cause can be found. The potential causes include atrial fibrillation, sub-stenotic or aortic arch atherosclerosis, and cardiac shunt. Recently, atrial dysfunction or cardiopathy in the absence of atrial fibrillation has been proposed as a mechanism in patients with ESUS. This is based on the fact that serum, ECG, and echocardiographic biomarkers of atrial cardiopathy have been shown to be associated with embolic risk in the absence of atrial fibrillation. In addition, recent studies showed no temporal relationship between subclinical atrial fibrillation and embolic events, arguing that atrial fibrillation is a biomarker of atrial cardiopathy which in turn is the direct cause of stroke in most patients with this arrhythmia.

This increased rate of diagnosis of atrial fibrillation resulted in an increased rate of anticoagulant therapy: 18.6% of the intervention group vs. 11.1% of the control group. This trial highlights the fact there is a significant proportion of people who have been historically diagnosed with “cryptogenic” stroke who have probably had occult atrial fibrillation.
**INSULIN RESISTANCE AND THE SECONDARY PREVENTION OF STROKE**

Insulin resistance is a phenomenon observed in those with type 2 diabetes but also in approximately half of all people without diabetes who have had a stroke or TIA. There is a rich basic science literature on the interaction between insulin resistance and atherosclerosis, inflammation and thrombosis. This generated interest in whether not treating insulin resistance itself would aid in the secondary prevention of ischemic stroke. The IRIS trial [Insulin Resistance Intervention after Stroke](https://clinicaltrials.gov/ct2/show/study/NCT02142283) was designed to test whether administration of pioglitazone (a member of the thiazolidinedione drug class of oral hypoglycemic agents) would reduce the risk of recurrent stroke. In this trial, Kernan et al. (2016) studied patients 40 and older who had suffered an ischemic stroke or TIA in the 6 months prior to enrollment. Specifically, within that population they studied patients with evidence of insulin resistance but not frank type 2 diabetes. Patients were randomized to either pioglitazone (at a dose of 15mg which was ramped up to 45mg if well-tolerated) or placebo. Follow-up took place over 5 years and the primary outcome was the occurrence of stroke or myocardial infarction. 3876 patients were randomized to either pioglitazone or placebo – 1939 in the pioglitazone group and 1937 in the placebo group. This trial had a positive outcome: 11.8% of patients administered placebo reached the primary outcome over the 5 year follow-up period whereas only 9.0% of the patients administered pioglitazone did. The p-value for this result was significant at 0.007. Among secondary analyses, it was also noteworthy that the rate of progression to type 2 diabetes was lower in the pioglitazone group.

The results of this trial are impressive but there are a number of important caveats:

The risk of bone fractures was high in the group treated with pioglitazone: 5.1% of patient suffered a bone fracture in the treatment group compared with only 3.2% in the control group [p<0.003].

All patients with stroke or TIA were included in the trial irrespective of the cause of their stroke/TIA. Stroke is the endpoint of multiple, diverse disease states and not a disease itself per se. For instance, approximately 7% of patients in this trial had atrial fibrillation. A stroke due to atrial fibrillation would not be expected to be prevented by a medication that addressed insulin resistance. This point serves to caution against prescribing pioglitazone to a patient who has suffered a stroke, prior to first carefully evaluating the mechanism of the stroke.

**References**


**Authors**

Brian Mac Grory, MBCh, BAO, Department of Neurology, Division of Vascular Neurology, Rhode Island Hospital. Shadi Yaghjii, MD, Department of Neurology, Division of Vascular Neurology, Rhode Island Hospital; Department of Neurology, Warren Alpert Medical School of Brown University.

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**Correspondence**

Dr. Brian Mac Grory
RI Hospital, 593 Eddy Street, APC #758, Providence RI 02903. 401-606-8394, Fax 401-444-8781

brian.macgrory@lifespan.org