Insights from ESOC: Improving Patient Pathways in Stroke

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Abstract

This symposium focused on emerging pathways for improving patient care in acute and cryptogenic stroke. Optimizing treatment of stroke complications was also discussed. The symposium provided insight into transfer and treatment patterns for acute stroke in Catalonia, Spain, as well as patient evaluation for mechanical thrombectomy. In addition, secondary stroke prevention strategies in the setting of cryptogenic stroke were examined. Topics included: an update on the RACECAT clinical trial, emerging diagnostic tools and care models in acute stroke, the role of long-term cardiac monitoring for cryptogenic stroke, and treatment plans for post-stroke spasticity.

KEYWORDS: ACCIDENTS; ADHD; DIAGNOSIS; DRIVING; STIMULANTS; TREATMENT

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Introduction

The symposium *Improving Patient Pathways* was held at the 5th European Stroke Organisation Conference (ESOC) on May 22-24, 2019 in Milan, Italy. The symposium included presentations on acute stroke assessment and treatment, secondary stroke prevention in the setting of cryptogenic stroke, and treatment of post-stroke spasticity. Presenters provided an update on the Direct Transfer to an Endovascular Center Compared to Transfer to the Closest Stroke Center in Acute Stroke Patients With Suspected Large Vessel Occlusion (RACECAT) trial.[1] This trial is evaluating transfer of patients with a suspected large vessel occlusion (LVO) to comprehensive stroke centers (CSCs) for endovascular therapy (EVT) assessment. Presenters also examined the role of long-term cardiac monitoring to establish the presence of silent atrial fibrillation (AF) and discussed the effect of delivery of baclofen into cerebrospinal fluid (CSF) on post-stroke spasticity, pain, and quality of life (QoL).

Facilitating acute stroke assessment and transfer

Dr. Marc Ribo of Hospital Vall d'Hebron in Barcelona, Spain explored new models and technology for acute stroke assessment and treatment. In Catalonia, the number of stroke activations rose by more than 20% in 2018 from 2016, with a 120% increase for EVT. Approximately 25% of patients received tissue plasminogen activator (tPA), 10% had primary EVT, and about 8% had both IV-tPA and EVT. Most patients

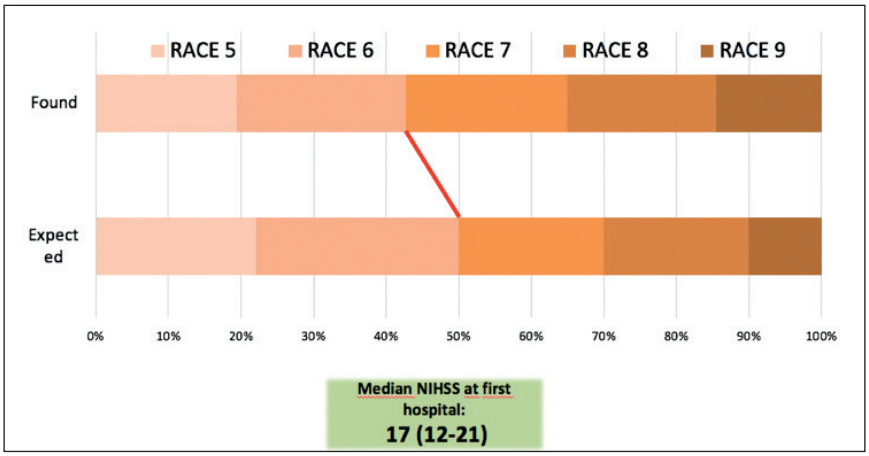
were transferred to the nearest primary stroke center (PSC) where they could be evaluated for tPA. Direct transfer to a CSC with EVT capabilities, instead of a PSC, may be preferable for patients in whom tPA fails to dissolve the clot.

Analysis of data from the Catalan Stroke Registry show that individuals living in a major metropolitan area (MMA) in Catalonia were significantly more likely to receive EVT than those who lived one or more hours from an MMA. The EVT rate was 9.6 per 100,000 inhabitants residing in an MMA compared to 1.9 per 100,000 persons located more than one hour from an MMA. The increase in EVTs in the Catalan Stroke Registry was predominantly for individuals who lived in an MMA.

The RACECAT trial is evaluating two options for acute stroke with suspected LVO:

1. Group A: Patient taken to a PSC for tPA assessment and administration with later transfer to a secondary facility for potential EVT or
2. Group B: Patient directly transferred to a CSC for EVT evaluation.

RACECAT uses the pre-hospital stroke assessment scale Rapid Arterial oCclusion Evalation (RACE) to identify individuals who potentially have an LVO,[1-2] and has already enrolled a greater number of patients with severe stroke than originally anticipated. Of the first 700 patients, ~43% had a RACE score of 5 or 6 compared to the 50% envisioned, with a median National Institutes of Health Stroke Scale (NIHSS) score of 17. The presence of LVO was 45.4%, slightly higher than the 43% the researchers had expected.



Source: Marc Ribo, MD.

Figure 1. Distribution of RACE Scores of 700 Patients Enrolled in RACECAT

RACECAT has enrolled nearly 1,000 patients. An interim analysis of 1,200 patients is expected at the end of 2019. Results from RACECAT may help inform protocols for regional stroke transfers, particularly if outcomes show that direct transfer of certain individuals with acute stroke benefit from early EVT evaluation.

However, other emerging tools and concepts could change acute stroke assessment and treatment. For instance, devices using artificial intelligence may help Emergency Medical Services differentiate between stroke and stroke mimics. One such tool is the Lucid Robotic System, a noninvasive, point-of-care diagnostic device that uses doppler ultrasound. It is hypothesized that the system can be trained to identify the presence of an LVO without use of contrast material. A clinical study validating Lucid Robotic System's accuracy in this area is expected in the first quarter of 2020.

In addition, stroke centers that specialize in EVT may change stroke transfer protocols.[3] Having a mechanical thrombectomy-ready CSC is supported by evidence showing that centers which perform a high volume of EVTs have faster times to EVT, a higher percentage of successful reperfusions, and better outcomes compared to lower-volume centers.[4-5] Dr. Ribo foresees an executive body at the regional level that will register, monitor, and coordinate care for patients with acute stroke. Decisions made by the executive body would be binding on all stakeholders and would facilitate the optimal treatment for each patient.

Personalizing treatment in cryptogenic stroke

Prof. Georgios Tsivgoulis of National & Kapodistrian University of Athens in Greece examined whether prolonged cardiac monitoring (PCM) should be used in patients with cryptogenic stroke as well as PCM's role in secondary stroke prevention. Cryptogenic stroke is estimated to account for 30%-46% of ischemic stroke.[6-7]

Embolic stroke of undetermined source (ESUS) is a recently introduced subset of cryptogenic stroke which encompasses a variety of mechanisms for ischemic stroke

(minor cardiac, valvular disease, paradoxical, cancer-associated, etc).[8] Two non-vitamin-K oral anticoagulants (NOACs), rivaroxaban and dabigatran, have been studied for secondary stroke prevention in the setting of ESUS. Compared to aspirin, NAVIGATE-ESUS (rivaroxaban) and RE-SPECT ESUS (dabigatran) showed significantly higher bleeding rates in ICH and major or clinically relevant nonmajor bleeding, respectively.[9-10] As a result, NOACs cannot be given indiscriminately to patients with ESUS or cryptogenic stroke.

PCM is used to assess whether individuals with cryptogenic stroke have undiagnosed AF, which would inform secondary stroke prevention strategies. While studies have shown that PCM detects paroxysmal AF in a minority of patients with cryptogenic stroke,[11-12] the yield of AF detection generally increases with the duration of PCM. A meta-analysis showed an AF detection rate of 4% when an implantable cardiac monitor (ICM) was used for <6 months. The AF yield increased to 34% when an ICM was used for >24 months. Interestingly, the timing of ICM implantation, ≤1 month or > 1 month from stroke or transient ischemic attack, did not affect AF yield.[13]

Detection and confirmation of AF can change treatment and affect outcomes. Analysis of FIND-AF found that long-term PCM lowered the recurrent stroke rate and number of deaths compared to conservative cardiac monitoring. The number needed to treat to prevent a recurrent stroke or death was 28.[14] In RE-SPECT ESUS, 7.7% of individuals treated with dabigatran and 7.2% of those in the aspirin arm were found to have AF. Recurrent stroke after AF confirmation was lower in the dabigatran-treated patients at 5.8% versus 10.8% in control.[15] Furthermore, a meta-analysis showed PCM to be associated with increased likelihood of AF detection. Subsequent OAC initiation reduced recurrent stroke by 55%.[16]

The HAVOC risk scoring system was developed to assess the likelihood of individuals with cryptogenic stroke developing AF, which may help clinicians to decide whether to use PCM. Of note, HAVOC has demonstrated greater specificity and accuracy than the CHA2DS2-VASc stroke risk scoring tool.[17] In the REVEAL-AF trial, 42% of patients with a HAVOC score of 5-9 and 50% of those with a HAVOC score of 10-14 were found to have AF.[18] A secondary analysis of NAVIGATE-ESUS showed that AF detection rose with higher HAVOC scores. A greater number of atrial premature beats and increased left atrial diameter were also associated with increased AF detection.[19]

Table 1. HAVOC Risk Scoring System for Likelihood of AF in Cryptogenic Stroke[17]

Predictor	Score
Hypertension	2
Age >75 years	2
Valvular heart disease	2
Vascular disease (peripheral)	1
Obesity (BMI >30)	1
Congestive heart faiure	4
Coronary artery disease	2

BMI – Body mass index.

Guidelines from both the European Society of Cardiology and American College of Cardiology/American Heart Association recommend that long-term cardiac monitoring or ICMs should be considered to assess the presence of silent AF in patients with cryptogenic stroke.[20-21]

Filling an unmet need: treating post-stroke spasticity

Professor Geoffrey Cloud, consultant stroke physician at Alfred Hospital, Melbourne, Australia, discussed post-stroke spasticity, which affects 17%-43% of individuals with stroke.[22] Post-stroke spasticity causes muscles to tighten and reduces both functional ability and Quality of Life.

Oral medication and physical therapy are cornerstones of post-stroke spasticity treatment plans. More advanced treatments include injectable therapies, which are used when spasticity is confined to one limb; intrathecal baclofen (ITB) therapy; and orthopedic and neurosurgical procedures.

Successful treatment plans have goals that are specific, realistic, and reflective of spasticity's impact on daily living activities. It is also important for clinicians to individualize the treatment plan in collaboration with the patient and caregivers. A step-ladder approach, moving from physical therapy to oral medication to focal intervention to ITB, may be difficult to implement with post-stroke spasticity. Clinicians may find it useful to match the treatment with the type of spasticity that the patient is experiencing (Table 2).

Table 2. Applicable Treatments by Spasticity Location23

Spasticity Location		Applicable Treatments
Focal		Botulinum toxins, phenol/alcohol neurolysis
Multifocal		Botulinum toxins, phenol/alcohol neurolysis, oral medications
Regional		ITB, botulinum toxins*, phenol/alcohol neurolysis*
Generalized		ITB, oral medications

*Can be used concurrently for muscles in different regions.

ITB involves a catheter and a programmable pump, which is implanted in the anterior abdominal wall. This allows baclofen to be delivered directly to CSF in the intrathecal space. Because of the targeted delivery, there are no issues related to penetrating the blood brain barrier, and doses that are 100x-1,000x smaller than those used in oral baclofen can be administered. As a result, ITB may have a lower risk of intolerable side effects compared to oral baclofen (Figure 2). Drug-related side effects include muscular weakness, hypotonia, urinary retention, falls risk, dizziness, and drowsiness.

Oral baclofen	Intrathecal baclofen
■ Reaches spinal cord via BBB ● Low penetration through BBB ● Low CNS absorption (only 2-3% absorbed by CSF) ● High systemic absorption ● Lack of preferential distribution to spinal cord	■ Delivered directly to CSF in intrathecal space ● High CNS absorption (100% absorbed by CSF) ● Low systemic absorption ● Direct distribution to spinal cord
■ High doses required ● For example*, 60 mg/day oral dose (results in 0.024 µg/ml intrathecal lumbar concentration) ● Half-life 3-4 hours	■ Low doses required ● For example*, 600 µ/day ITB dose (results in 1.24 µg/ml intrathecal lumbar concentration) ● Half-life 4-5 hours ● 4:1 lumbar:cervical concentration
■ High potential for intolerable and unacceptable side effects (e.g. drowsiness, dizziness, nausea)	■ Lower potential for intolerable and unacceptable side effects (e.g. drowsiness, dizziness, nausea)

CNS – Central nervous system.
Source: Geoffrey Cloud, MD.

Figure 2. Comparison of Oral Baclofen and ITB

Patients considering ITB should be aware of procedural-related risks, such as intracranial hypotension, spinal fluid leak, implant site infection, and headache. In addition, the pump needs to be refilled every three to six months; this can be accomplished by inserting a needle through the port on the front of the pump. The pump's battery lasts for four to seven years. The pump beeps when the remaining battery life approximates 90 days. Patients need to be aware that battery replacement is crucial to avoid baclofen withdrawal, which can have serious consequences.

The Spasticity in Stroke Study—Randomized Study (SISTERS) trial enrolled individuals with post-stroke spasticity in ≥2 more extremities, with an Ashworth Scale (AS) of ≥3 in two or more muscle groups in the lower limbs.[24] Patients were randomized to either ITB (N=31) or conventional medical management (CMM, N=29). The primary outcome was the average change in AS score for the affected lower extremity at six months compared to baseline. Prior to implantation of the pump, patients randomized to the ITB arm were given a lumbar injection of baclofen to assess treatment response. Those who failed to respond to treatment were crossed over to the CMM group but were included in the intention-to-treat analysis of the ITB arm.[24]

ITB demonstrated a significantly greater improvement in average AS score than CMM at -0.99 and -0.43, respectively ($P<.05$). ITB also had a significant improvement in average AS score for the upper limbs compared to CMM.[24] ITB lowered pain on a numerical rating scale by -1.17 compared to 0.00 for CMM ($P<.05$) at six months. There was also a significant improvement in least pain recorded for ITB versus CMM. On EuroQol-5 dimensional (EQ-5D) assessment, ITB improved scores from baseline by an average of 0.09, higher than that recorded for CMM (+0.01; $P<.05$). ITB was associated with a greater, but not significant, improvement on a stroke-specific QoL scale. More patients in the ITB arm reported treatment satisfaction than those in CMM at 73% and 48%, respectively.[25]

Conclusion

There are several emerging pathways focused on improving patient care in stroke. The RACECAT trial is evaluating whether patients with suspected LVO should be treated with tPA at a PSC or transferred to a CSC for EVT evaluation. New diagnostic technologies and mechanical thrombectomy-ready CSCs may aid in assessment and early EVT evaluation of patients with possible LVO. Scientific evidence is accumulating with regard to patient selection for ICM and other long-term cardiac monitoring in the setting of cryptogenic stroke/ESUS, which could facilitate clinical decision-making for secondary stroke prevention. In addition, research has demonstrated that ITB is more effective than medical management in patients with severe post-stroke spasticity.

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