Relias Media
From Relias

Vol. 40, Issue 3, November 2020
ReliasMedia.com

Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Ketamine for Super-Refractory Status Epilepticus

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Cornell Medical College

Dr. Kandula reports no financial relationships relevant to this field of study.

SYNOPSIS: In this retrospective paper, the authors review the efficacy and safety of ketamine infusion in patients with status epilepticus who have failed benzodiazepine, standard anticonvulsant, and at least one other anesthetic drip.

SOURCE: Alkhachroum A, Der-Nigoghossian CA, Mathews E, et al. Ketamine to treat super-refractory status epilepticus. *Neurology* 2020; Sept. 1. doi: 10.1212/WNL.0000000000010611. [Online ahead of print].

Status epilepticus, defined as an emergent enduring ictal state, has nearly tripled in the last three decades, with an annual mortality of nearly 20%. The treatment of super-refractory status epilepticus (SRSE), or failure of benzodiazepine, one standard anticonvulsant, and anesthetic use, defines a population of patients with potentially increased mortality and morbidity. Despite the increased armamentarium of treatment options, standardized, high-quality data for SRSE are absent in the literature. Predictably, there is great variability across the nation and worldwide regarding management.

Animal models of self-sustaining status epilepticus suggest that drugs with gamma-aminobutyric acid (GABA) mediated inhibition, such as benzodiazepines, may become less effective over time because of receptor trafficking. As status epilepticus continues, $GABA_A$ receptors undergo endocytosis with upregulation of N-methyl-D-aspartate (NMDA) receptors.

This relative GABA pharmacoresistance has led to renewed interest in exploring agents with alternative mechanisms of action. Although ketamine has been in widespread clinical use since the 1970s, secondary to the agent's combined hypnotic, analgesic, and amnestic qualities, recent interest for use in status epilepticus has emerged only over the last two decades as a result of the agent's unique role as an NMDA receptor antagonist. The authors presented a retrospective single-center series of patients treated with adjunctive ketamine infusion for SRSE.

Financial Disclosure: *Neurology Alert*'s Editor in Chief Matthew Fink, MD; Peer Reviewer M. Flint Beal, MD; Editorial Group Manager Leslie Coplin; Editor Jason Schneider; Executive Editor Shelly Morrow Mark; and Accreditations Director Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

[INSIDE]

COVID-19 Infection in MS Patients page 18

IqYmune for CIDP page 20

Tranexamic Acid and Outcomes in Patients with TBI page 21

Stroke Alert: Patients with Asymptomatic Carotid Stenosis page 22

Neurology
[ALERT]

Neurology Alert (ISSN 0741-4234) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-9468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Neurology Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-9468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Questions & Comments:
Please contact Jason Schneider at jschneider@relias.com.

Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

Nearly 261 adult patients were retrospectively identified as meeting SRSE at New York Presbyterian Hospital, Columbia University Medical Center in New York. Nearly one-quarter of patients were treated with adjunctive ketamine. All 68 patients treated with ketamine received prior midazolam anesthetic infusion. Concurrent electroencephalographic (EEG) recording, mean arterial pressure (MAP), arterial blood pressure (ABP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), and cerebral blood flow (CBF) were measured. The main outcome was seizure control (complete seizure cessation or more than 50% reductive burden) within 24 hours of ketamine initiation. Seizure control post-ketamine discontinuation, in-house mortality, discharge status, and modified Rankin and Glasgow outcome scales extended at discharge also were incorporated into the analysis. Practical measures, such as hospital length of stay, withdrawal of life support, resuscitation status, and need for tracheostomy and percutaneous endoscopic gastrostomy, also were recorded. Ketamine was started at the discretion of the treating physician after midazolam failure.

The study cohort was composed of cardiac arrest (27%) and new onset refractory status epilepticus (18%). Seizures were noted as either focal or generalized. Roughly 80% of patients had 50% reduction in seizure burden within 24 hours of ketamine initiation. Nearly 65% of patients had seizure cessation. Forty percent of patients with seizure cessation eventually died. Of those without seizure cessation, nearly 55% of patients died. On average, ketamine was started two days after admission, with an average rate of 1.8 mg/kg/hr to 2.2 mg/kg/hr. MAP and ICP remained stable, along with a decrease in vasodepressor requirements over time, irrespective of dosage or duration of ketamine use.

■ COMMENTARY

Mechanistically, ketamine NMDA antagonism may help offset GABA-mediated pharmacoresistance in refractory status epilepticus. In addition, the lack of profound vasodepressor effect also is appealing in the critically ill population where treatment may carry equal or higher morbidity than the underlying condition.

However, the study is not without several limitations. All data were retrospective, unblinded, and without a control group. Treatment dose and titration schedule also were variable, complicating the independent vs. cumulative effects of concurrent anesthetic agents. The electrographic endpoint also was binary (seizure vs. no seizure), not reflecting the often "gray" zone of ictal equivalents, including periodic discharges. However, despite the aforementioned limitations, the overall rationale for earlier use in status epilepticus is interesting and warrants further prospective investigation. ■

ABSTRACT & COMMENTARY

COVID-19 Infection in MS Patients

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College; Assistant Attending Neurologist, New York-Presbyterian Hospital

Dr. Perumal reports she is a consultant for Biogen and Genzyme.

SYNOPSIS: In a multicenter, retrospective analysis of patients in a multiple sclerosis (MS) registry, the authors described the clinical characteristics and risks associated with severity of complications from COVID-19 infection in patients with MS. The risks were similar to those in the general population, including age, obesity, male sex, and cardiopulmonary comorbidities, but also the level of baseline MS disability. Being on a disease-modifying therapy did not seem to increase the risk of severe COVID-19 disease, but multiple immunosuppressive medications were associated with a higher risk of serious complications.

SOURCE: Louapre C, Collongues N, Stankoff B, et al, for the Covisep investigators. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. *JAMA Neurol* 2020;77:1-10.

This study reviewed data from 347 multiple sclerosis (MS) patients in a nationwide registry in France between March 1 and May 21, 2020. All patients met the diagnostic criteria for MS and were confirmed or highly suspected of having had COVID-19

infection based on at least one of the following: SARS-CoV-2 polymerase chain reaction on nasal swab, typical chest computed tomography findings, acute onset anosmia or ageusia without another explanation, or other typical COVID-19 symptoms, including the triad of cough, fever, and asthenia in an epidemic zone.

The main objective of the study was to assess the association between COVID-19 disease severity based on a seven-point ordinal scale ranging from 1 (not hospitalized and no limitations in activities) to 7 (death). In addition, patient demographics, disability as measured by the Expanded Disability Status Scale (EDSS), comorbidities, and MS disease-modifying therapy (DMT) were collected. The mean age (standard deviation) of the patients was 44.6 years, the mean disease duration was 13.5 years, and the mean EDSS was 2 (range 0 to 9.5). Of the 347 patients, 249 were women and 284 (81.8%) patients were taking DMT. Demographic data were compared between patients with COVID-19 disease severity scales 1 and 2, and patients with COVID-19 disease severity scales 3 or more (indicating hospitalization or death). The DMTs for MS were grouped according to systemic infection risk: 1) no risk (glatiramer acetate and interferon); 2) low risk (teriflunomide, dimethyl fumarate, and natalizumab); and 3) intermediate or high risk (fingolimod, anti-CD20 therapies, cladribine, and alemtuzumab).

Seventy-three (21%) patients had a COVID-19 disease severity of 3 or more. Patients in this more severe disease category were more frequently male, were older (55 years of age vs. 41.9 years of age; $P < 0.001$), had more disability (EDSS 6 vs. 2; $P < 0.001$), and more often had a progressive disease course (36/73 vs. 29/274; $P < 0.001$). Obesity and the presence of cardiopulmonary comorbidities also were associated with an increased rate of hospitalization. In this study, there was a higher proportion of severe disease among patients who were not taking a DMT compared to those who were taking a DMT (26/63 [46%] vs. 44/284 [15.5%]; $P < 0.001$). The authors speculated that differences in baseline demographics of those taking treatment vs. those not taking treatment might be a reason for this finding, but they also noted this has to be explored further. However, among patients on DMT, there was higher rate of severity of COVID-19 disease in patients taking one of the intermediate- to high-risk medications when compared to one of the low- or no-risk medications (24/1,010 [23.8%] in high-risk vs. 17/130 [13.1%] in the low-risk and 3/53 [5.7 %] in the no-risk group; $P = 0.007$). Using multivariate analysis, they found that male sex, obesity, cardiopulmonary comorbidity, and higher EDSS were independent variables associated with severe COVID-19 disease. Twelve (3.5%) patients died from COVID-19, with most having significant baseline MS disability and progressive disease. This percentage is higher than what is reported in the general population. Four patients required mechanical ventilation and three were on anti-CD20 therapies. One had progressive disease and the other two had obesity as a comorbidity. Although their comorbidities would increase their risk of severe disease, immune suppression with these medications could have played a role as well. Since their data did not seem to indicate generally that patients taking a DMT were at significantly higher risk for severe COVID-19 disease, the authors concluded that patients with high inflammatory activity and risk of disability should be started or continued on DMT, but one should exercise caution when using DMTs in patients with significant baseline disability and older age.

■ COMMENTARY

Given the ongoing COVID-19 pandemic, and the relative dearth of detailed data, the risks associated with immunosuppressive treatment for conditions like MS and the severity of complications from it remain major concerns for patients and the clinicians treating them.

In this study, the authors found that the risks associated with more severe COVID-19 disease were similar to those in the general population, including, among others, age and obesity. Progressive disease and more severe baseline disability also were associated with a higher risk. The lack of association between taking a DMT and severity of COVID-19 disease is likely the result of the baseline demographics of patients taking a DMT, who tend to be younger and have less advanced disease. However, among the DMTs, the more immunosuppressive treatments were associated with more severe COVID-19 disease. In addition, even though the numbers were small, among four patients who required mechanical ventilation, three were on anti-CD20 targeted therapy, which is a significant immune suppressive treatment for MS. It would be prudent to be cautious before starting or continuing this or similar immune suppressive treatment for patients and to assess the need on an individual basis. This study also found that older, progressive, and more disabled patients were at higher risk for severe COVID-19 infections. We also know from published data regarding the efficacy of DMTs that this patient population is least likely to benefit from a DMT. Therefore, even more so during this pandemic, one should be wary of immune suppression for MS in this group.

Overall, the data from this study provide some reassurance in general about MS treatment and COVID-19 disease severity, but it is vital that one assess the risks vs. benefits individually and carefully before starting and/or continuing a DMT. For patients on immune suppressive treatment, we must educate them about COVID-19 infections and emphasize that they follow all measures diligently to decrease the risk of potential exposure to COVID-19. ■

ABSTRACT & COMMENTARY

IqYmune for CIDP

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: IqYmune is a highly purified 10% concentration of human immunoglobulin obtained from healthy volunteers. It appears to have similar efficacy in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) as conventional intravenous immunoglobulin, with 76% of the study patients showing a significant improvement in a standardized disability score.

SOURCE: Nobile-Orazio E, Pujol S, Kasiborski F, et al. An international multicenter efficacy and safety study of IqYmune in initial and maintenance treatment of patients with chronic inflammatory demyelinating polyradiculoneuropathy: PRISM study. *J Peripher Nerv Syst* 2020; Aug. 18. doi.org/10.1111/jns.12408. [Online ahead of print].

Based on several studies, the largest of which is the double-blind, multicenter ICE (Intravenous immunoglobulin [IVIg] in chronic inflammatory demyelinating polyneuropathy [CIDP] Efficacy) trial in 2008, IVIg has become a first-line treatment for CIDP, preferred over steroids because IVIg provides a more rapid onset of clinical improvement and a better adverse effect profile. It also is preferred over plasma exchange because of the ease of use and availability of IVIg.[1] Administered intravenously, IqYmune, a highly purified 10% liquid preparation of normal human immunoglobulin obtained from healthy donors and approved in Europe in 2015 as replacement therapy for primary immunodeficiency syndrome and hypogammaglobulinemia, has been used successfully to treat multifocal motor neuropathy and Guillain-Barré syndrome. Is it beneficial in CIDP?

In this prospective, international, multicenter, single-arm, open-label, Phase III study extending from February 2015 to September 2017, the efficacy and safety of IqYmune in CIDP was examined. Patients with CIDP, 18 years of age or older, diagnosed using the 2010 clinical and neurophysiological criteria of the European Federation of Neurological Societies/Peripheral Nerve Society guidelines, with a disability score of at least 2, were included. Also included were those with pure motor and pure sensory forms, and those with an associated monoclonal gammopathy of unknown significance. Exclusionary criteria comprised immunoglobulin allergy, immunoglobulin A (IgA) deficiency, hepatic disease, or any cardiovascular condition with increased thromboembolic risk. Prior immunomodulatory treatment within 12 months, or plasma exchange, steroids, or blood derivatives in the prior three months also were grounds for exclusion. IqYmune 2 g/kg was administered as an induction dose, followed by seven infusions of 1 g/kg every three weeks.

Inflammatory neuropathy cause and treatment (INCAT) disability score at study end (week 24) was the primary endpoint, with the placebo group of the ICE trial used as a historical control. Secondary endpoints included responder rate at week 12, time to initial response, and grip strength in both hands using the Martin Vigorimeter.

Among 59 patients screened for the study, only 44 met all criteria for enrollment. Of these, 23 were Ig-naïve, and 21 had relapsed following prior Ig treatment. In this latter group, one withdrew consent prior to treatment, and another was not assessed post-baseline. Among 42 patients remaining in the study and included in the efficacy set, having primary efficacy endpoint assessment availability, overall response rate at study end with an improvement of at least one point in the INCAT disability score was 76.2%, with IqYmune demonstrating superiority to historical placebo controls ($P < 0.0001$). Time to response varied from nine to 19 weeks, with a median time of 15 weeks. Adverse effects (AEs) were experienced by 90.7% of patients and believed to be related to IqYmune in 69.8%. Headaches, fever, and myalgias were the most common drug-related AEs, all of which resolved without sequelae, except for worsening of pre-existing anemia in a gastrectomy patient treated with B12. Nine serious AEs were seen in seven patients, five of which were related to IqYmune in three patients, including a transient ischemic attack in one patient (who was withdrawn prematurely); a severe headache leading to hospitalization, an anaphylactic reaction, and an increase in D-dimer, all in a second patient; and an asymptomatic neutropenia in a third patient. IqYmune appears safe and effective for CIDP.

■ COMMENTARY

IVIg also appears safe at higher infusion rates than usual. The standard infusion rate of 10% IVIg is 0.08 mL/kg/min. When incrementally increased to a maximum rate of 0.14 mL/kg/min in patients who tolerated the initial infusion rate, 19 of 25 patients in a prospective, open-label trial at the Ellen and Martin Prosserman Center for Neuromuscular Diseases, University Health Network, Toronto, Ontario, safely tolerated the increased rate. No treatment-related AEs were associated with the higher infusion rate. Increasing the infusion rate will reduce treatment time and reduce healthcare costs.[2] ■

REFERENCES
1. Hughes RAC, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculo neuropathy (ICE study): A randomized placebo-controlled trial. *Lancet Neurol* 2008;7:136-144.
2. Jiang Y, Mendoza M, Sarpong E, et al. Efficacy and safety of high infusion rate IVIG in CIDP. *Muscle Nerve* 2020; Aug. 12. doi: 10.1002/mus.27044. [Online ahead of print].

ABSTRACT & COMMENTARY

Tranexamic Acid and Outcomes in Patients with Moderate or Severe TBI

By Alexander E. Merkler, MD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College, and Assistant Attending Neurologist, New York-Presbyterian Hospital

Dr. Merkler reports he receives grant/research support from the American Heart Association and is a consultant for Medicolegal.

SYNOPSIS: In this randomized, placebo-controlled trial using tranexamic acid to treat patients with moderate or severe traumatic brain injury within two hours of injury, there was no significant difference between treatment groups in either mortality or functional recovery at six months.

SOURCE: Rowell SE, Meier EN, McKnight B, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. *JAMA* 2020;324:961-974.

Traumatic brain injury (TBI) is common. Worldwide, 27 million people sustained a TBI in 2016 and there were 288,000 TBI-related hospitalizations in the United States alone.[1,2] In addition, more than 3 million Americans live with disability related to TBI.[3] Current treatment of acute TBI includes supportive medical management and surgery, yet there are no available medications proven to treat TBI.

Tranexamic acid prevents clot breakdown by inhibiting plasminogen and plasmin. In the randomized clinical trial CRASH-2, tranexamic acid improved survival in patients with severe hemorrhagic shock. Garnering interest from this positive trial, CRASH-3 evaluated the effect of tranexamic acid in more than 12,000 patients with TBI.[4] CRASH-3 found that tranexamic acid did not improve mortality from head injury.[4] Rowell et al, in this current randomized clinical trial, examined whether tranexamic acid administered within two hours of TBI would result in improved neurological outcomes in patients with moderate or severe TBI. Eligible patients were 15 years of age or older with a Glasgow Coma Scale (GCS) of 3 to 12, at least one reactive pupil, and a systolic blood pressure of at least 90 mmHg. Participants were randomly assigned to one of three treatment groups: 1) out-of-hospital tranexamic bolus with in-hospital tranexamic infusion; 2) out-of-hospital tranexamic bolus with placebo infusion; or 3) out-of-hospital placebo bolus with placebo infusion. Because of concerns with study power, the two tranexamic treatment groups were combined in the analyses. The primary outcome was a favorable functional neurological outcome at six months after injury, defined as a Glasgow Outcome Scale-Extended (GOSE) of > 4.

Nine hundred sixty-six participants were enrolled and included in the analysis. The median age ranged from 36 to 40 years in the treatment groups; 73% to 85% of the participants were men; the median GCS was 7.6 to 7.8; and 48% to 54% needed an out-of-hospital advanced airway. Intracranial hemorrhage was present on the initial brain imaging in 57% to 59% of participants. There was no difference in the primary outcome; a good functional outcome was present in 65% of participants who received tranexamic acid vs. 62% of those who received placebo. Similarly, there was no statistical difference in mortality (14% in the tranexamic group vs. 17% in the placebo group). In addition, among participants with multiple brain imaging, there was no significant difference in progression of intracranial hemorrhage in participants who received tranexamic vs. placebo.

■ COMMENTARY

There now are two randomized clinical trials showing no benefit of early tranexamic acid for moderate to severe TBI. Both trials found that tranexamic did not improve survival at 28 days in patients with moderate to severe TBI. Although this trial did not examine patients with less severe injuries, in the subgroup of participants with mild and moderate TBI in CRASH-3, there was an improvement in mortality (risk ratio 0.78). This trial underscores the importance of patient selection — 20% of patients had a GCS of 13 or higher on admission, less than 60% had evidence of hemorrhage on initial brain imaging, and 15% of participants were lost to follow-up. These factors may have led to inaccurate findings. Future studies should evaluate alternative therapies aimed at improving neurological outcomes in patients with TBI,

and improved patient selection will be critical. In conclusion, two randomized clinical trials have failed to show a benefit of early tranexamic acid in patients with moderate or severe TBI. ■

REFERENCES

1. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18;459-480.
2. Peterson AB, Xu L, Daugherty J, Breiding MJ. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths, United States, 2014. Centers for Disease Control and Prevention. https://www.cdc.gov/traumaticbraininjury/pdf/TBI-Surveillance-Report-508.pdf
3. Zaloshnja E, Miller T, Langloi JA, Selassie AW. Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. *J Head Trauma Rehabil* 2008;23:394-400.
4. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): A randomized, placebo-controlled trial. *Lancet* 2019;394:1713-1723.

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Carotid Endarterectomy vs. Medical Therapy in Patients with Asymptomatic Carotid Stenosis

SOURCE: Keyhani S, Cheng EM, Hoggatt KJ, et al. Comparative effectiveness of carotid endarterectomy vs initial medical therapy in patients with asymptomatic carotid stenosis. *JAMA Neurol* 2020;77:1-12.

Multiple randomized clinical trials have demonstrated that carotid endarterectomy is beneficial in patients who have symptomatic carotid stenosis, and currently, that is the recommendation for such patients. Several trials from 25 years ago also reported that carotid endarterectomy is beneficial in patients with asymptomatic carotid artery stenosis greater than 60%. However, in the intervening years, advances in medical therapy, including statins and antiplatelet regimens, as well as significant improvement in the management of blood pressure, diabetes, diet, and exercise, have been shown to reduce stroke rate. Therefore, it is currently controversial whether carotid endarterectomy is still beneficial in asymptomatic patients with carotid artery stenosis compared to current medical management.

These investigators analyzed several large databases from the U.S. Department of Veterans Affairs that collected clinical data on veterans of the U.S. Armed Forces age 65 years or older who had carotid imaging performed between 2005 and 2009. Patients who had less than 50% stenosis or had a history of stroke or transient ischemic attack in the six months before imaging was performed were excluded from the analysis. A cohort of patients who were treated with initial medical therapy and a cohort of similar patients who were treated with carotid endarterectomy were collected and followed for up to five years. Kaplan-Meier curves were computed, and estimates of both fatal and nonfatal strokes were determined in each cohort over a five-year period of follow-up.

The study identified and followed 5,221 patients. The mean age was 73.6 years and 98.8% were men. Among the study participants, 2,509 received carotid endarterectomy and 2,479 received initial medical therapy within one year after carotid imaging. In those who underwent carotid endarterectomy, the observed rate of stroke or death as a perioperative complication was 2.5%. The five-year risk of fatal and nonfatal strokes was lower in those who underwent carotid endarterectomy compared to the patients randomized to initial medical therapy (5.6% vs. 7.8%). However, when the perioperative risks of death and perioperative stroke were included, there was no significant difference in the overall risk of stroke or death over a five-year period. The overall five-year risk of fatal and nonfatal strokes was 5.5% in patients undergoing carotid endarterectomy and 7.6% among those randomized to medical therapy. These differences were not statistically significant. Compared to trials performed more than 20 years ago, the risk reduction was less than half in the current study, and supports medical therapy as an acceptable alternative strategy for these patients. ■

Can Anticoagulant Strategies Reduce Covert Brain Infarcts in Patients with Cardiovascular Disease?

SOURCE: Sharma M, Hart RG, Smith EE, et al. Rivaroxiban for prevention of covert brain infarcts and cognitive decline: The COMPASS MRI substudy. *Stroke* 2020;51:2901-2909.

Covert brain infarcts are detected on magnetic resonance imaging (MRI) studies in the aging brain in about 10% of people at age 65 years, increasing to 25% at age 80 years. They are more common than symptomatic ischemic stroke and are associated with the long-term development of cognitive decline, gait impairments, and behavioral disorders. Covert vascular lesions include white matter hyperintensities and cerebral microbleeds. They accumulate over time and are additive to changes

that occur with amyloid deposition in Alzheimer's disease. Most patients who develop dementia have a combination of multiple small infarcts, plus amyloid deposition. Prevention of covert infarcts is a strategy to mitigate the frequency and severity of late-life dementia.

Sharma et al evaluated a subset of patients who underwent brain MRIs in the COMPASS study. This study included patients who had stable coronary or peripheral artery disease, including carotid artery stenosis, who were randomized to aspirin 100 mg daily, or rivaroxiban 5 mg twice daily or 2.5 mg twice daily plus aspirin. The study showed a significant benefit for the combination of rivaroxiban and aspirin for the composite endpoint of stroke, myocardial infarction, or vascular death.[1] Patients who underwent serial brain MRIs were evaluated for changes in covert infarcts during the course of the study. Baseline and follow-up imaging of the brain was completed in 1,445 participants over an interval of two years. Participants also had measurements of cognition and function. The primary endpoint was a proportion of participants with incident covert infarcts. Secondary endpoints were a composite of clinical stroke, covert infarcts, cerebral microbleeds, and white matter hyperintensities. At baseline, 493 (34.1%) participants had infarcts on imaging. Incident covert infarcts occurred in 55 (3.8%) participants. In the overall trial, rivaroxiban plus aspirin reduced clinical ischemic stroke by 49%. In the substudy looking at covert infarcts, the effects of rivaroxiban plus aspirin vs. aspirin alone were 2.4% vs. 3.5% respectively, a non-statistically significant difference. Incident microbleeds occurred in 6.6% of participants, and 65.7% of the participants had an increase in white matter hyperintensities over time with no effect of treatment for any endpoint. There was no effect on cognitive testing as well. In conclusion, treatment with rivaroxiban and aspirin did not reduce the development of covert infarcts but did have a beneficial effect in reducing the risk of clinical ischemic stroke. ■

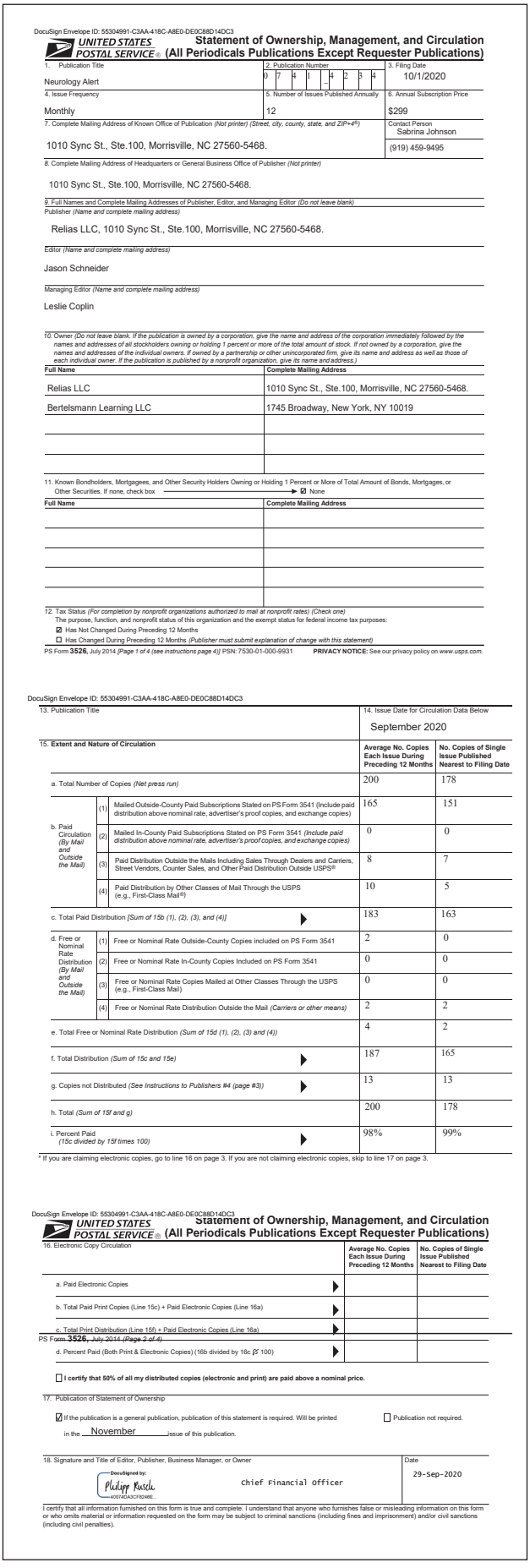
REFERENCE

1. Eikelboom JW, Connolly, SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319-1330.

Recurrent Stroke After Embolic Stroke of Undetermined Source

SOURCE: Veltcamp R, Pearce LA, Korompoki E, et al. Characteristics of recurrent ischemic stroke after embolic stroke of undetermined source: Secondary analysis of the randomized clinical trial. *JAMA Neurol* 2020;77:1233-1240.

Twenty percent to 40% of ischemic strokes are classified as cryptogenic, meaning a specific cause cannot be identified. A subset of those have been classified by some investigators as embolic stroke of undetermined source (ESUS). However, this remains a controversial



DocuSign Envelope ID: 55304991-C3AA-418C-A8E0-DE0C88D14DC3

UNITED STATES POSTAL SERVICE® **Statement of Ownership, Management, and Circulation (All Periodicals Publications Except Requester Publications)**

1. Publication Title	2. Publication Number	3. Filing Date
Neurology Alert	0 7 4 1 - 4 2 5 4	10/1/2020
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$299

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4®)*: 1010 Sync St., Ste.100, Morrisville, NC 27560-5468. Contact Person: Sabrina Johnson, (919) 459-9495

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*: 1010 Sync St., Ste.100, Morrisville, NC 27560-5468.

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*: Relias LLC, 1010 Sync St., Ste.100, Morrisville, NC 27560-5468.

Editor *(Name and complete mailing address)*: Jason Schneider

Managing Editor *(Name and complete mailing address)*: Leslie Coplin

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Relias LLC	1010 Sync St., Ste.100, Morrisville, NC 27560-5468.
Bertelsmann Learning LLC	1745 Broadway, New York, NY 10019

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☑ None

Full Name	Complete Mailing Address

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526,** July 2014 *[Page 1 of 4 (see instructions page 4)]* PSN: 7530-01-000-9931 **PRIVACY NOTICE:** See our privacy policy on *www.usps.com.*

DocuSign Envelope ID: 55304991-C3AA-418C-A8E0-DE0C88D14DC3

13. Publication Title

14. Issue Date for Circulation Data Below: September 2020

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies *(Net press run)*			200	178
b. Paid Circulation *(By Mail and Outside the Mail)*	(1)	Mailed Outside-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)	165	151
	(2)	Mailed In-County Paid Subscriptions Stated on PS Form 3541 *(Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)*	0	0
	(3)	Paid Distribution Outside the Mails Including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid Distribution Outside USPS®	8	7
	(4)	Paid Distribution by Other Classes of Mail Through the USPS (e.g., First-Class Mail®)	10	5
c. Total Paid Distribution *[Sum of 15b (1), (2), (3), and (4)]*			183	163
d. Free or Nominal Rate Distribution *(By Mail and Outside the Mail)*	(1)	Free or Nominal Rate Outside-County Copies included on PS Form 3541	2	0
	(2)	Free or Nominal Rate In-County Copies Included on PS Form 3541	0	0
	(3)	Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (e.g., First-Class Mail)	0	0
	(4)	Free or Nominal Rate Distribution Outside the Mail *(Carriers or other means)*	2	2
e. Total Free or Nominal Rate Distribution *(Sum of 15d (1), (2), (3) and (4))*			4	2
f. Total Distribution *(Sum of 15c and 15e)*			187	165
g. Copies not Distributed *(See Instructions to Publishers #4 (page #3))*			13	13
h. Total *(Sum of 15f and g)*			200	178
i. Percent Paid *(15c divided by 15f times 100)*			98%	99%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.

DocuSign Envelope ID: 55304991-C3AA-418C-A8E0-DE0C88D14DC3

UNITED STATES POSTAL SERVICE® **Statement of Ownership, Management, and Circulation (All Periodicals Publications Except Requester Publications)**

16. Electronic Copy Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Paid Electronic Copies		
b. Total Paid Print Copies (Line 15c) + Paid Electronic Copies (Line 16a)		
c. Total Print Distribution (Line 15f) + Paid Electronic Copies (Line 16a)		
d. Percent Paid (Both Print & Electronic Copies) (16b divided by 16c ⨯ 100)		

PS Form ~~3526,~~ ~~July 2014 *(Page 2 of 4)*~~

☐ **I certify that 50% of all my distributed copies (electronic and print) are paid above a nominal price.**

17. Publication of Statement of Ownership

☑ If the publication is a general publication, publication of this statement is required. Will be printed in the November issue of this publication. ☐ Publication not required.

18. Signature and Title of Editor, Publisher, Business Manager, or Owner: DocuSigned by: Philipp Ruschi 4007ADA3CF8246E... Chief Financial Officer — Date: 29-Sep-2020

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

category and classification. ESUS is defined by specific neuroimaging features, other diagnostic tests, and exclusion of certain causes. The annual stroke recurrence rate is about 5%, and these investigators undertook this study to try to learn more about the etiology of recurrent stroke.

The investigators performed a secondary analysis of the randomized trial that was conducted from 2014 to 2017 comparing the efficacy and safety of rivaroxiban and aspirin in patients with recent ESUS. During the period of follow up, recurrent ischemic stroke was validated in 309 of 7,213 patients. The recurrent strokes were classified into categories of ESUS or other categories, including cardioembolic, atherosclerotic, lacunar, other determined cause, or insufficient testing. As part of the overall trial, patients had been randomly assigned to receive rivaroxaban 15 mg per day or aspirin 100 mg per day. Diagnostic testing was insufficient to classify 39 patients. Of the 240 that could be classified, 58% were identified as ESUS and 42% were other causes, 32% cardioembolic, 23% atherosclerotic, 31% lacunar, and 14% of other determined cause. Atrial fibrillation was found the 9% of the patients with recurrent ischemic stroke and this was associated with worse morbidity and mortality. The risk of recurrence did not differ significantly by subtype between the two treatment groups. For all groups, infarct location was more often in the left hemisphere, 54% vs. 46%, or in the brainstem or cerebellum, 14% vs. 9%. In conclusion, most recurrent strokes are once again categorized as ESUS. No additional information was found regarding specific etiologies in this group of ischemic stroke patients of uncertain cause. ■

CME QUESTIONS

1. **Super-refractory status epilepticus is defined as which of the following?**
   a. Seizure lasting > 5 minutes
   b. Continued seizure activity despite benzodiazepine use
   c. Continued seizure activity after failure of appropriately dosed anticonvulsants
   d. Continued seizure activity despite anesthetic agents
2. **Which of the following statements about IqYmune is true?**
   a. IqYmune is an alternative immunoglobulin that may be used for treatment of chronic inflammatory demyelinating polyneuropathy.
   b. IqYmune is associated with an increased risk of severe chemical meningitis.
   c. IqYmune is a low concentration 1% intravenous immunoglobulin.
   d. IqYmune must be infused slowly to reduce the adverse effect profile.
3. **Which of the following categories of multiple sclerosis patients has an increased risk of severe COVID-19 infection?**
   a. Young women on treatment with disease-modifying therapy (DMT)
   b. Older and obese patients on DMT
   c. Older patients not on any DMT
   d. Younger patients with disability
4. **A 37-year-old man is brought to the emergency department after falling off a ladder and hitting his head. He is lethargic, with a Glasgow Coma Scale of 12. His systolic blood pressure is 100 mmHg and his oxygenation is stable. Which of the following statements is accurate regarding the use of out-of-hospital tranexamic acid?**
   a. Tranexamic acid should be given because it leads to improved functional neurological outcomes and improved survival.
   b. Tranexamic acid should be given because it leads to improved survival but no improvement in functional neurological outcomes.
   c. Tranexamic acid should not be given because it leads to neither improved survival nor improved functional outcomes.
   d. Tranexamic acid should not be given because, although tranexamic acid improves survival, it does not improve functional neurological outcomes.
5. **Compared to medical therapy, carotid endarterectomy results in better long-term reduction of stroke recurrence in patients with asymptomatic carotid artery stenosis.**
   a. True
   b. False
6. **The use of anticoagulant medication with aspirin reduces the risk of dementia in patients with cardiovascular disease.**
   a. True
   b. False
7. **The classification of embolic stroke of undetermined source is a category that helps to define the course and natural history of cardiovascular disease.**
   a. True
   b. False