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SPECIAL ISSUE: STROKE

ABSTRACT & COMMENTARY

Idarucizumab: A Promising New Drug that Reverses the Anticoagulant Effects of Dabigatran

By Dana Leifer, MD

Associate Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: A recent study found that idarucizumab rapidly reverses the effects of dabigatran and is likely to have important clinical benefits for patients with intracerebral hemorrhage and other disease processes in which reversal of anticoagulation is important.

SOURCE: Pollack CV Jr, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511-520.

Several new oral anticoagulants are changing the approach to anticoagulation for patients with nonvalvular atrial fibrillation and deep venous thrombosis/pulmonary emboli. These drugs, which include the thrombin inhibitor dabigatran, have been shown to be noninferior both in terms of safety and efficacy to warfarin, which was until recently, the only oral anticoagulant available. In some cases, these drugs also have been shown to be superior to warfarin. In addition, they do not require the intensive monitoring that is needed for warfarin, and they do not have the numerous interactions with other drugs and with diet. Use of these drugs has been limited, however, in part because of fears that they are not rapidly reversible in the event of a hemorrhage or a need for emergency surgery. Several different agents that may rapidly reverse one or more of the new oral anticoagulants are now under development.

In particular, Pollack and colleagues recently reported in the *New England Journal of Medicine* that idarucizumab, a humanized monoclonal antibody that

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binds specifically to dabigatran, reversed its anticoagulant effects within minutes. The study included 51 patients with serious acute bleeding (Group A), including 18 with intracranial hemorrhages, and 39 patients who needed emergency surgery (Group B). The ecarin clotting time (ECT), which is probably the best test for detecting the effects of dabigatran, was normalized in 89% of patients in group A and 88% of patients in group B when tests were done immediately after the first of the two doses of idarucizumab that patients received. The dilute thrombin time (TT), which is more widely available but less sensitive for detecting the effects of dabigatran was normalized in 98% and 93% of patients in groups A and B, respectively. The ECT remained normal at 24 hours in 72% and 54% of patients, respectively. For these analyses, the authors excluded the subsets of patients whose baseline ECT or TT was normal.

It is important to note that correction of laboratory abnormalities does not necessarily mean that there is clinical benefit. The paper presents limited data about clinical outcomes. There were 18 total deaths within the first month, including three from intracranial hemorrhage within 96 hours. Deaths within 96 hours appeared to be related to the index event, while later deaths appeared related to coexisting conditions. These numbers do not seem surprising in view of the serious acute problems that all patients enrolled in the study had. Thrombotic complications (DVT, pulmonary emboli, left atrial clot, myocardial infarction, ischemic stroke) appeared in five patients from 2 to 26 days after treatment; anticoagulation had not been resumed in any of these patients, so again these results are not surprising.

■ COMMENTARY

Unfortunately, the authors report little about clinical outcomes. For patients in group B who underwent surgery, intraoperative hemostasis was described as normal in 92% of patients who underwent surgery emergently, so it is likely that there was at least subjective clinical benefit in Group B patients, though even for these patients, there was no control group.

For patients with intracranial hemorrhage, the authors state that modified Rankin scores were recorded at baseline and at 90 days, but they do not report data about the Rankin scores in this publication. We must hope that this information will be reported in a subsequent paper, but in the absence of a control population, this information will be difficult to interpret.

Despite the lack of data about clinical outcomes in this study, it is likely that the rapid reversal of anticoagulation achieved with idarucizumab will be beneficial.

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For intracranial hemorrhage patients in particular, there is a consensus in the field that rapid reversal of anticoagulation is critically important. Indeed, one of the performance metrics for comprehensive stroke centers is the percent of intracerebral hemorrhage patients with INR > 1.4 who are treated with procoagulant agents. In this background, it is likely that a drug that immediately reverses the effects of dabigatran would have a clinical benefit for dabigatran-associated intracerebral hemorrhage.

In summary, idarucizumab rapidly reverses the effects of dabigatran and is likely to have important clinical benefits for patients with intracerebral hemorrhage and other disease processes in which reversal of anticoagulation is important. The recent paper by Pollack and colleagues, however, reported only limited results about clinical outcomes and lacked a control group that did not receive the study drug. Additional work will therefore be needed to determine if the drug actually improves clinical outcomes. ■

ABSTRACT & COMMENTARY

Incidental Cerebral Microbleeds and Cerebral Blood Flow in Elderly Individuals

By Halina White, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Cerebral microbleeds in non-demented elderly people are associated with a global reduction in cerebral blood flow and a high prevalence of beta-amyloid deposition in the brain.

SOURCE: Gregg NM, et al. Incidental cerebral microbleeds and cerebral blood flow in elderly individuals. *JAMA Neurol* doi:10.1001/jamaneurol.2015.1359. Published online July 13, 2015.

Cerebral microbleeds are small, ovoid, hypointense lesions ("black dots") seen on susceptibility-weighted MRI sequences in many older individuals. They are caused by leakage of red blood cells from small cerebral vessels. Cerebral amyloid angiopathy affects cortical and leptomeningeal vessels, leading to microbleeds in the superficial areas of the cerebral hemispheres. Hypertension and cardiovascular risk factors lead to arteriosclerosis and lipohyalinosis, and are associated with microbleeds in the basal ganglia and deep hemispheric white matter. In some studies, patients with cerebral amyloid angiopathy, as evidenced by cortical lobar microbleeds, have been found to have cognitive decline. This study sought to determine possible mechanisms through which this cognitive decline could occur by quantifying how cerebral microbleeds are related to cerebral blood flow and cognition in the very elderly.

Fifty-five cognitively normal elderly individuals (mean age 86.8 years) underwent detailed neuropsychiatric testing and comprehensive MRI brain evaluation, including gradient echo and susceptibility-weighted imaging to detect microbleeds, arterial spin labelling to evaluate cerebral blood flow, and T1 and T2 sequences to evaluate for microvascular disease burden, hippocampal volume, and total cerebral volume. Subjects also underwent FDG-PET, Pittsburgh compound B-PET, apolipoprotein E (ApoE4) genotyping and evaluation for systemic vascular disease burden with carotid ultrasound, Ankle-Brachial Pressure Index, EKG, and serum cystatin C (a measure of renal microvascular resistance). The subject's microbleeds were divided into lobar cortical, lobar subcortical, and deep.

In the study, 38% of participants were found to have cortical microbleeds suggestive of cerebral amyloid angiopathy. Interestingly, the presence of cortical microbleeds was not associated with age, ApoE4 status, the presence of cardiovascular risk factors, or systemic vascular disease burden. Participants with any cerebral microbleeds had a trend toward decreased regional cerebral blood flow in the bilateral frontal and occipital lobes, the right parietal and temporal lobes, and the precuneate cortex. However, this trend was not statistically significant when corrected for age, sex, and global Pittsburgh compound B distribution. Compared to the rest of the cohort, participants with cortical cerebral microbleeds had significantly reduced cerebral blood flow to all lobes and to all deep structures. Cortical microbleeds were not significantly associated with brain metabolism as measured by FDG-PET, with amyloid A-beta as measured by Pittsburgh compound B-PET, nor with cerebral atrophy or hippocampal volume on MRI. Cortical microbleeds were significantly associated with the presence of infarcts, but not with total microvascular disease burden. Cortical microbleeds were also significantly associated with a non-zero score on the clinical dementia rating scale, but not with any other neuropsychiatric testing metric.

In summary, in this cohort of apparently cognitively normal elderly individuals, cerebral cortical microbleeds, likely related to cerebral amyloid angiopathy, were significantly related to globally decreased cerebral blood flow. Moreover, cerebral cortical microbleeds were also significantly associated with the presence of infarcts and subtle decreases in neuropsychiatric testing metrics.

■ COMMENTARY

These findings suggest that elderly individuals with cortical cerebral microbleeds may be exposed to chronic global cerebral hypoperfusion. As this was a cross-sectional cohort study, no assertions as to the causal relationships between these findings can be made. However, it is interesting to hypothesize that perhaps patients with cerebral amyloid angiopathy have chronically poor cerebral blood flow leading to neuronal injury and a greater burden of infarcts, and that these may contribute to their decreased cognitive performance.

In this study ApoE4 status and A-beta amyloid

deposition were not significantly related to the presence of cerebral cortical microbleeds, as one might expect if cerebral cortical microbleeds are simply a biomarker for cerebral amyloid angiopathy. The writers postulate that this may have been caused by the very high prevalence of A-beta amyloid deposition (81%) in this cohort of very elderly patients.

Poor cerebral perfusion associated with the cortical microbleeds also was not correlated with cerebral glucose hypometabolism, suggesting that cerebral hypometabolism is not driving the perfusion deficit. Exactly how cerebral amyloid angiopathy may lead to globally poor cerebral blood flow, however, is unclear.

Study limitations included the advanced age of the subjects, small sample size, and cross-sectional study design. Strengths included the fact that this was a study of cognitively normal elderly subjects in the presymptomatic stage of dementia.

This study suggests that MRI arterial spin labelling measures of cerebral blood flow may be an early marker for cerebral amyloid angiopathy. This early marker could be useful in diagnosis and in treatment. Further work with repeated evaluation of these subjects is needed to elucidate the temporal relationships between cerebral microbleeds, cerebral hypoperfusion, and cognitive decline. ■

ABSTRACT & COMMENTARY

Blood Pressure Lowering After Acute Stroke: Can It Kill You?

By Dara Jamieson, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is on the stroke adjudication committee for Bayer and is a consultant for Boehringer-Ingelheim.

SYNOPSIS: Although lowering of systolic blood pressure (SBP) in chronically hypertensive individuals decreases the risk of ischemic and hemorrhagic stroke, decreased SBP in the 2 years immediately after a stroke may be associated with an increase in all causes of mortality.

SOURCE: Okin PM, et al. Systolic blood pressure control and mortality after stroke in hypertensive patients *Stroke* 2015;46:2113-2118.

Patients with chronically elevated blood pressure (BP) are at increased risk of all-cause and cardiovascular death, with a particularly increased risk of ischemic and hemorrhagic stroke. Treatment to lower systolic BP (SBP) decreases stroke risk, without an apparent lower threshold down to 120 mmHg. However, lowered SBP (≤ 120 mmHg) in the 5 years after a stroke may be associated with increased mortality. Lower SBP over a shorter period of time after a stroke in chronically hypertensive patients could potentially increase mortality as well.

The authors performed a post-hoc analysis of data from the Losartan Intervention For Endpoint reduction (LIFE) study to determine the relationship between SBP and all-cause and cardiovascular mortality in the 541 out of 9193 hypertensive patients with electrocardiographic left ventricular hypertrophy, a marker of increased vascular risk, who had an incident stroke during the study. Mortality was examined as a function of the average on-treatment SBP, which was measured after strokes that occurred during the follow-up antihypertensive treatment. Blinded treatment was begun with daily losartan 50 mg or atenolol 50 mg and matching placebo of the other agent with a target BP of 140/90 mmHg or lower. Hydrochlorothiazide and other antihypertensive medications were added, if necessary, to achieve the target pressure. Patients with average on-treatment SBP < 144 mmHg (lowest tertile) and average on-treatment SBP > 157 mmHG (highest tertile) were compared to patients with average on-treatment SBP between 144 and 157 mmHg.

Of the 170 patients (31.4%) in the LIFE study who died during the 2.02 ± 1.65 years mean follow-up after their incident stroke, 135 (25.0%) deaths were from cardiovascular causes. Compared with SBP of 144 to 157 mmHg, SBP < 144 mmHg was associated with significantly higher all-cause mortality and SBP > 157 mmHg with significantly higher cardiovascular and all-cause mortality rates. However, in a multivariate Cox analyses, adjusting for other univariate predictors of post-stroke mortality in the population, an average SBP < 144 mmHg was a significant predictor of cardiovascular and all-cause mortality, whereas an average SBP > 157 mmHg was not associated with significantly increased adjusted risk of either all-cause or cardiovascular death compared with an average SBP of 144 to 157 mmHg. In a multivariate analysis restricted to deaths occurring more than 90 days after the initial stroke, average in-treatment SBP < 144 mmHg remained significantly associated with an increased risk of all-cause mortality,

after adjusting for other potential predictors of death. An average SBP > 157 mmHg more than 90 days after the stroke was not associated with a significant increased risk of death. The effect of SBP on mortality did not show any significant interaction with sex, age, history of atrial fibrillation, or randomized anti-hypertensive treatment arm. The authors concluded that lower achieved SBP (< 144 mmHg) is associated with a significantly increased risk of cardiovascular and all-cause mortality after initial stroke in hypertensive patients during short-term (i.e., average 2 years) follow-up.

■ COMMENTARY

It is a truth, universally acknowledged, that treatment of chronically elevated BP decreases the risk of acute ischemic and hemorrhagic stroke. So how can there be anything but a beneficial effect of chronically lowered BP in a patient who has had a stroke? Some SBP treatment studies, including this analysis of the LIFE study, indicate an association between lowered SBP and increased cardiovascular and all-cause mortality. Even after factoring out effects of cardiac disease with SBP and early deaths due to low SBP, as well as studying chronically hypertensive patients with increased risk, the authors analyzing the LIFE data still did not explain the conundrum of the risk of decreased stroke, but increased death, with lowered BP. However, the data, which appeared to show mortality benefit from treatment failure, were not adequately analyzed to evaluate cerebrovascular disease. The relationship of SBP levels to recurrent stroke was not assessed and recurrent strokes were not adjudicated. Epidemiological studies frequently lump disparate vascular diseases together, ignoring obvious pathophysiological differences between cerebrovascular disease due to ischemic or hemorrhagic stroke and cardiovascular disease. Further dissection of BP and mortality may help to individualize patient management. In the 541 stroke patients in the LIFE study, incident strokes were characterized as atherothrombotic (74.5%), embolic (15.5%), and hemorrhagic (10.0%). However, mortality and recurrent stroke type were not categorized based on incident stroke type. Patients with hemorrhagic stroke may benefit from stricter blood pressure control, especially with a history suggestive of cerebral amyloid angiopathy. While there was no subgroup effect associated with atrial fibrillation, strict blood pressure control may have less impact on an embolic, rather than on an atherosclerotic, stroke mechanism. More details are needed to interpret these results that appear to show benefit to lack of adherence to the study treatment protocol.

Self-laudatory speculation by a vascular neurologist includes the theory that lower stroke risk related to hypertension treatment, combined with improved patient survival after stroke, has tipped risk of BP lowering to non-cerebrovascular causes of mortality. Distinguishing between cerebrovascular vs cardiovascular death in the BP treatment trials could differentiate the effect of BP lowering on distinctly different vascular systems. The results of the LIFE study emphasize that vascular researchers need to acknowledge the differences between cerebrovascular disease and cardiovascular disease. Clinical trials must abandon their "one-size-fits-all" approach to vascular disease and do a better job of differentiating brain vascular disease from heart vascular disease. ■

ABSTRACT & COMMENTARY

Pattern of Atrial Fibrillation Is Associated with Outcomes After Stroke

By Hooman Kamel, MD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

SYNOPSIS: In a Japanese stroke registry, permanent as opposed to paroxysmal atrial fibrillation was associated with higher in-hospital mortality after stroke.

SOURCE: Deguchi I, et al, for the Japan Standard Stroke Registry. Features of cardioembolic stroke with persistent and paroxysmal atrial fibrillation — a study with the Japan Stroke Registry Study Group. *Eur J Neurol* 2015;22:1215-1219. doi:10.1111/ene.12728

Atrial fibrillation (AF) has long been associated with an increased risk of ischemic stroke. However, identifying the precise degree of stroke risk in any given patient with AF can be challenging. In attempting to use clinical features to understand the risk of stroke in AF, it remains unclear whether determining the burden of AF is helpful. Prior studies have found conflicting evidence on whether more frequent or chronic AF confers greater stroke risk than brief paroxysms of AF. Similarly, AF-related strokes are associated with worse disability and higher mortality than other types of stroke, but it remains unclear whether the pattern of AF is related to stroke

prognosis. Given this uncertainty, investigators in Japan have assessed the relationship between AF pattern and outcomes after ischemic stroke.

In a large prospective registry of patients with stroke, these investigators identified 9293 patients with non-valvular AF and ischemic stroke that was determined to be cardioembolic. Patients with AF episodes lasting ≤ 1 week were classified as having paroxysmal AF, while those with longer episodes were classified as having permanent AF. Compared to the 2771 patients (30%) with paroxysmal AF, the 6522 patients (70%) with permanent AF were older, had more vascular comorbidities, had higher NIH Stroke Scale scores, and were less often treated with recanalization therapy. In unadjusted analyses, permanent (as opposed to paroxysmal) AF was associated with a higher odds of disability on discharge (73% vs 67%), but this association did not hold true after adjustment for other confounding factors. However, permanent AF was associated with a higher odds of in-hospital mortality, even after adjustment for other factors (76% vs 70%; odds ratio, 1.26).

■ COMMENTARY

These results suggest that patients with permanent AF and cardioembolic stroke are likely to fare worse than those with stroke in the setting of paroxysmal AF. Although this was a nicely done study, it still leaves open the question of whether these findings are due to the effect of the AF pattern itself or simply to the greater burden of comorbidities that are associated with permanent AF. Nevertheless, identifying the pre-stroke pattern of AF may provide one more useful piece of information to help guide prognostication in patients with cardioembolic stroke. ■

ABSTRACT & COMMENTARY

Circadian Rhythms Predict Small Vessel Ischemic Disease

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: The presence of white matter infarcts and cerebral microbleeds is associated with disruption of sleep but not total sleep time.

SOURCE: Zuurbier LA, et al. Cerebral small vessel disease is related to disturbed 24-h activity rhythms: A population-based study. *Eur J Neurol* 2015; July 24. doi:10.1111/ene.12775 [Epub ahead of print].

As the brain ages, its ability to generate deep, slow-wave sleep declines. Chronic illness may accelerate this process. Equally important is our circadian rhythm, which drives multiple endocrine axes and acts as a counterbalance to sleep. The circadian process allows us to stay awake into the evening (when sleep propensity is increasing) and to sleep into the morning hours (when sleep propensity is waning). Because of these factors, it is possible that it is the timing of our sleep, rather than its quantity or quality, that defines the physiological benefits of our slumber.

In the present study, the authors used an actigraph, a movement sensor with an accelerometer not unlike a "Fitbit," to measure patients' activity. Worn on the wrist, an actigraph produces an imperfect characterization of sleep, since the sedentary awake state would decrease actigraphic output and a state of active movement during sleep would augment actigraphy. Subjects (n = 970) were middle-aged and drawn from a large cohort of patients in the Rotterdam Community Study. Each subject underwent an MRI to evaluate white matter lesion (WML) volume and the presence of cerebral microbleeds (CMBs) and lacunar infarcts.

It was shown that disruption of overall daily actigraphy correlated with WML volume and CMBs but not lacunar infarcts. Importantly, sleep itself did not affect these imaging parameters. Sleep duration, wake after sleep onset, and subjective ratings of sleep quality did not show any consistent effects. Although it is thought to be important that bed and wake times be consistent, actigraphy only correlated with "intraday" 24-hour readings, not day-to-day changes. Erratic, fragmented sleep habits were deleterious, whether they were the same each day or randomly changed for every 24-hour period.

As the authors note, it is not clear if changes in the brain are producing these circadian changes or whether disorders of circadian rhythms affect the brain. Damage to subcortical fibers, including periventricular tracts, may affect coordination between the cortex and hypothalamus (supraoptic and suprachiasmatic nuclei).

■ COMMENTARY

Actigraphy is not an accurate reflector of sleep and neither is it as precise a marker of circadian rhythms as body temperature or melatonin levels. There is little doubt, however, that a robust circadian rhythm is a

marker of health. Robust circadian rhythms have been shown to be predictive of other important endpoints such as overall mortality, heart disease, and mood disorders.

The difficulty, however, is accurately discerning the directionality of these effects. Circadian rhythms wane as we age and deteriorate with dementia and chronic disease. It is not known, however, whether circadian rhythms protect against damage to the nervous system or rather if they are an early sensitive marker of neurodegenerative disease. Further study is needed to clarify this "chicken or egg" problem. ■

ABSTRACT & COMMENTARY

Rate and Predictors of Futile Hospital Transfers for Acute Stroke Endovascular Therapy

By Babak Navi, MD, MS

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

SYNOPSIS: A large number of futile transfers take place for consideration of endovascular therapy, and better selection criteria need to be developed.

SOURCE: Fuentes B, et al. Futile interhospital transfer for endovascular treatment in acute ischemic stroke. The Madrid Stroke Network experience. *Stroke* 2015;46:2156-2161.

Stroke is the fifth leading cause of death in the United States and the leading cause of adult disability. Until recently, the only proven treatment for acute ischemic stroke was intravenous thrombolysis, which increases the odds of excellent neurological outcome by 30%. However, in the past year, five landmark trials have demonstrated that endovascular therapy, primarily with stent-retriever devices for acute stroke from large vessel occlusions, dramatically improve functional outcomes with a number-needed-to-treat of four patients in some studies. Therefore, many community hospitals without endovascular capability are now implementing collaborative systems to transfer acute stroke patients with suspected or confirmed large vessel occlusions to larger hospitals with endovascular capability. Given the strong correlation between time to recanalization and outcomes, the emphasis of these acute stroke transfers is on timely recognition and transport, and thus some patients transferred to comprehensive stroke centers ultimately may not receive endovascular therapy because of absence of proximal occlusion or other contraindications. As hospital transfers are expensive and resources are limited, the authors of this study sought to investigate the frequency and predictors of futile hospital transfers for acute stroke endovascular therapy.

In Northern Madrid, there is a tiered hospital stroke system, whereby three comprehensive stroke centers provide 24-7 endovascular capability for multiple community hospitals serving nearly 3 million inhabitants. A consensus protocol is used to determine which stroke patients should be emergently transferred to the comprehensive stroke centers for possible endovascular therapy. This protocol is primarily based on last-known well time and stroke severity; assessment of large vessel occlusion with noninvasive imaging is recommended but not required. Upon arrival at the receiving endovascular-capable hospital, neurologists use clinical and radiographic criteria to make the final decision about endovascular therapy. From February 2012 to May 2013, 120 patients were transferred to comprehensive stroke centers in Northern Madrid for acute stroke endovascular therapy, 50 (41%) of whom did not receive an intervention and were deemed futile transfers. No clinical characteristics were associated with futile transfer; this included age, baseline NIH Stroke Scale and ASPECTS scores at the transferring hospital, and use of intravenous thrombolysis. The main reasons for ineligibility were clinical improvement or arterial recanalization (48%) and findings on the second neuroimaging test performed at the receiving hospital (32%), which usually was a low ASPECTS score. Interestingly, transport delays were a rare (2%) cause of futile transfer and median transfer times were only 56 minutes. The main limitation of the study was the relatively small sample size and the poor external validity since the patient population and stroke network of Madrid may not generalize to other populations and stroke systems.

■ COMMENTARY

Fuentes et al have shown that about two in five hyperacute stroke transfers for possible endovascular therapy in Northern Madrid are futile, and the most

common reasons for futility are clinical improvement, arterial recanalization, or neuroimaging findings on repeat brain imaging. These findings raise the question of where advanced neuroimaging should be performed and whether it is necessary to repeat neuroimaging at the receiving hospital. This is especially germane since the first positive endovascular trial[1] did not exclude patients based on ASPECTS score, although the median ASPECTS score was 9 and very few patients had scores < 5. Furthermore, less than 5% of all ischemic stroke patients receive endovascular therapy, so better systems are needed to increase treatment rates while keeping treatment times low. Future studies will be needed to determine the best hospital system and patient selection criteria for acute stroke patients being considered for endovascular therapy. ■

REFERENCE

1. Berhemer OA, et al; MR CLEAN investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11-20.

CME QUESTIONS

1. **Idaruczumab has been shown to:**
   a. reverse the effects of all novel oral anti-coagulants.
   b. specifically block the anticoagulant effects of dabigatran.
   c. improve outcomes in patients with dabigatran-associated intracerebral hemorrhages.
   d. be free of all thromboembolic complications.

2. **Which of the following statements is true about cerebral microbleeds?**
   a. The presence of cerebral microbleeds predicts a future intracerebral hemorrhage.
   b. Cerebral microbleeds are common in the elderly.
   c. Cerebral microbleeds are only seen in hypertensive people.
   d. Cerebral microbleeds indicate the presence of a bleeding disorder.
   e. Cerebral microbleeds are more common in women than men.

3. **According to the LIFE study, which of the following best describes the effect of systolic blood pressure (SBP) lowering in hypertensive patients who have had a stroke?**
   a. Blood pressure lowering preferentially decreased cardiac mortality in patients with known heart disease.
   b. The specific medication used to lower blood pressure affects vascular mortality.
   c. The mortality effect of SBP lowering was not seen 3 months after the incident stroke.
   d. Systolic BP below 144 mmHg was associated with increased cardiovascular and all-cause mortality.

4. **Which of the following statements regarding atrial fibrillation and stroke is false?**
   a. Atrial fibrillation is associated with an increased risk of cardioembolic ischemic stroke.
   b. Permanent atrial fibrillation is associated with other comorbidities and older age.
   c. Paroxysmal atrial fibrillation does not confer an increased risk of stroke.
   d. Permanent atrial fibrillation is associated with a higher rate of stroke mortality.
   e. Antithrombotic therapy is the best treatment to prevent stroke for patients with atrial fibrillation.

5. **Which of the following statements regarding small vessel disease is false?**
   a. Small vessel disease is often associated with strokes and dementia in late life.
   b. Cerebral microbleeds are a marker for small vessel disease of the brain.
   c. Small vessel disease appears to disrupt normal circadian rhythms.
   d. Small vessel disease has no pathological consequences.
   e. Lacunar infarcts are associated with chronic hypertension.

6. **What is the most common reason that acute ischemic stroke patients transferred to another hospital for possible endovascular therapy do not receive treatment?**
   a. Transfer delay
   b. Hemorrhagic transformation
   c. Clinical improvement or arterial recanalization
   d. Completed infarction
   e. Internal carotid artery occlusion

[IN FUTURE ISSUES]

Update on Epilepsy