UPDATES IN CEREBROVASCULAR DISEASE

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Executive Summary *The intent of the article is to review many of the most common but complex challenges in the underwriting of stroke including discriminating TIA from its many mimics, addressing the increasing incidence of stroke in younger individuals, and reviewing basic principles in the evaluation of carotid stenting and cerebral aneurysm.*

Introduction

The underwriting of cerebrovascular disease very often has as its basis an overall assessment of the proposed insured's cardiovascular profile combined with characteristics of the stroke itself, primarily temporal proximity and neurologic residuals. The general belief is that short-term mortality is governed by the characteristics of the stroke, whereas in the longer term, the cardiovascular profile predominates. There are several clinical scenarios which defy simple application of this principle. The purpose of the article is to review the perplexing but common challenges in the underwriting of cerebrovascular disease, highlighting areas in which either clinical advances or trial data have offered guidance.

Transient Ischemic Attack

The label of transient ischemic attack (TIA) is often used loosely in attending physician statements. As radiographic results are often relatively normal or equivocal at the time of the event, it can be exceedingly difficult to determine whether or not an individual has had an actual TIA or one of the common TIA "mimics."

The very definition of TIA has undergone revision as well. The American Heart Association and American Stroke Association (AHA/ASA) published a revision of the definition in 2009.[1] TIA is currently defined as "a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction." There are two key revisions in comparison to the prior definition. The first is the removal of the arbitrary stipulation "lasting less than 24 hours," which was part of the prior definition. Subsequent studies have shown that high proportions of events lasting far less than 24 hours were actually strokes when subjected to magnetic resonance imaging (MRI) examinations. The second revision is the addition of the phrase "without acute infarction," which further emphasizes the importance of MRI in distinguishing TIA from stroke.

A relatively recent study by Amort et al.[2] examines ultimate diagnoses in those who were initially diagnosed with TIA, but subsequently diagnosed with one of the many TIA mimics. Table 1 [next page] illustrates the relative frequency of these alternative diagnoses.

Symptoms that were predictive of mimic rather than true vascular events included headache, isolated memory loss, syncope, and generalized rather than focal symptoms. The distinction was critical as, not surprisingly, there were much higher rates of recurrent TIA, stroke and myocardial infarction (MI) in the TIA group, whereas the mimic group was without complication within a short follow-up period.

Although often lumped in with TIA, both in attending physician statements and underwriting practice, transient global amnesia (TGA) merits special mention given its distinct presentation and more favorable prognosis. TGA refers to a poorly understood but fascinating phenomenon marked by the sudden and isolated inability to formulate new memories, lasting on the order of hours and often following exercise. The results of standard diagnostic testing (MRI of the brain, echocardiogram, carotid Dopplers, electroencephalogram) are most often unremarkable. A study

Table 1. Causes of TIA Mimics

Diagnosis of Mimic	Percent
Seizure	44
Migraine	23
Psychogenic	7
Hypertensive encephalopathy	4
Transient global amnesia	4
Sepsis	4
Hypoglycemia	2
Benign paroxysmal vertigo	2
Cerebral venous thrombosis	2
Brain neoplasm	1
Subarachnoid hemorrhage	1
Peripheral nerve lesion	1

by Pantoni et al.[3] found a low rate of recurrence (6% per year) and, more importantly, significantly lower rates of stroke, MI and death as compared to TIA.

Stroke in the Young

The number of strokes occurring in younger individuals is increasing rapidly. This runs counter to a wider trend supporting both overall decreasing stroke incidence and case fatality rate. According to the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS)[4], by the end of the study period (2005), approximately one in five strokes were occurring in individuals under age 55. The challenge in underwriting these individuals relates to the heterogeneous range of etiologies in these subjects, each with distinctly different prognosis. Diverse causes that are more often found in younger individuals include thrombophilias, cerebral venous thrombosis, genetic syndromes (e.g, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy), vasculitis and dissection[5]. Discussion of each of these entities is beyond the scope of this article but specific discussion will include dissection and cerebral venous thrombosis.

Dissection refers to a tear within the wall of a vessel resulting in a subsequent flap or intramural hematoma. It is an important and frequent (10-25%) cause of stroke in younger individuals. Stroke can occur as a consequence of either embolic showering of the clotted hematoma through a "false lumen" or expansion of the hematoma such that the true lumen closes entirely. Cerebrovascular dissection typically occurs in the carotid or vertebral arteries. Given its thin baseline, a vertebral artery dissection is more frequently complicated by subarachnoid hemorrhage and pseudoaneurysm. The standard of care involves warfarin anticoagulation for a period of 6 months, although there is no convincing or consistent data supporting its usage over aspirin for this indication. Assuming similar degrees of residual deficits, traumatic dissection likely carries the best prognosis, while dissection related to connective tissue disease indicates the worst prognosis, given the increased risk of similar pathology in other vascular beds such as the aorta and renal arteries. It is important to obtain imaging of the entirety of the cerebral vasculature as multiple arteries are involved in approximately 15% of cases, which is strongly indicative of underlying connective tissue disease or vasculopathy. A follow-up magnetic resonance angiogram is typically pursued 3-6 months after the event, as this is the most common time frame for recanalization. This matches well with the time frame during which one can assess the permanency and severity of any comorbid stroke deficit.

Cerebral venous thrombosis (CVT) refers to the development of a clot within the system of venous "gutters" that drain blood away from the brain. If unrecognized, pressure builds which can eventually lead to combinations of venous infarction and often hemorrhage. The condition received much attention in the mainstream press when former Secretary of State Hillary Clinton was hospitalized for cerebral venous thrombosis in 2012. Overall, it is a rare cause of stroke (less than 1%) – but 78% of patients who develop the condition are less than 50 years of age.[6] The peak age of incidence is between 20 and 40, with women outnumbering men 3 to 1.[7] By far the most common presenting symptom is headache, reflecting the rise in intracranial pressure. Focal symptoms as a part of the initial presenting symptoms are troublesome as they imply progression to infarction and hemorrhage (and increase the likelihood of permanent sequela). Risk factors are very similar to other sources of venous thrombosis: cancer, dehydration, inflammatory bowel disease and various thrombophilias (Factor V, protein C and S deficiency, anti-thrombin III deficiency, antiphospholipid antibody syndrome). Not surprisingly, given the female predominance, hormonal risks are also important, including pregnancy and oral contraceptive use. Finally, risk factors more specific to cerebral venous thrombosis include local infections (sinusitis, mastoiditis, dental), lumbar puncture, head trauma and central lines (in the jugular vein)[7]. The condition is detected with MRI–as opposed to computed tomography (CT)–and in particular a magnetic resonance venogram (MRV). As with cerebral arterial dissection, the most common treatment is intravenous heparin bridged to oral anticoagulation (warfarin) for a period of 3-6 months depending on follow-up imaging. Anticoagulation may be continued indefinitely in the context of suspected underlying hypercoagulable state or prior DVT/PE. A recent very small study[8] showed promising results with one of the novel oral anticoagulants, rivaroxaban. The use of more aggressive treatments such as intravenous lysis or mechanical clot extraction implies a more catastrophic presentation.

The long-term prognosis of CVT depends primarily upon the presence or absence of underlying thrombophilia and residual neurologic deficit. The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)[9] is the largest study to date examining the natural history and long-term prognosis of CVT. The overall risk of recurrence is low at 2.2%. Additional factors found to predict a poorer prognosis included:

- Male gender
- Age > 37
- Deep cerebral vein thrombosis
- Comorbid CNS infection

Carotid and Intracranial Stenting

The traditional treatment of carotid stenosis is an open procedure performed by a vascular surgeon through an incision in the neck to remove the atherosclerotic plaque, termed a carotid endarterectomy (CEA). A less invasive alternative, stenting of the internal carotid artery, is being increasingly pursued. Comparison of the two procedures is fraught with controversy. The first question in underwriting an applicant who has undergone stenting of the carotid, however, remains the same: Does the applicant have symptomatic carotid stenosis? Analysis of most outcome studies support this as the primary determinant outcome rather than specific procedure pursued. This is not to say that carotid stenting is without significant caveats. As a relatively new procedure, there is a wide variation in complication rates and skill level among the many subspecialists (vascular surgeons, interventional radiologists, neurosurgeons and cardiologists) who perform the procedure. Some pursue multiyear fellowships in preparation, while others begin with only brief industry-sponsored courses.

Next, underwriters must ask why the traditional open carotid endarterectomy is not being performed. Very often it is because the applicant is a poor surgical candidate, which of course should give one pause in the consideration of life insurance. Early indications for pursuing carotid stenting over endarterectomy included congestive heart failure, positive cardiac stress test or known need for cardiac revascularization, severe chronic obstructive pulmonary disease, contralateral carotid occlusion, or restenosis after prior CEA. Not surprisingly, the SAPPHIRE trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy)[10] which compared stenting to CEA in this high-risk population, showed high risk of poor outcome (stroke, myocardial infarction or death) regardless of which procedure was undertaken: 24.6% in stenting group vs. 26.9% in CEA group at 3 years.

Indications have slowly liberalized and more often carotid stenting is being performed in lower risk populations. Accordingly, the CREST trial (carotid revascularization endarterectomy vs. stenting trial)[11] which randomized a pool of patients without these significant vascular risk factors, found similar and much lower rates of the same cardiovascular endpoint. As seen in Table 2 (below), the higher risk periprocedural stroke in the carotid stenting group was roughly offset by the higher risk of periprocedural

MI, producing a roughly equivalent 7% risk of stroke, myocardial infarction or death at 2.5 years.

What if significant atherosclerosis is found distally within the intracranial arteries? Two interventions beyond the traditional aspirin therapy have been explored in these patients, both with disappointing outcomes. In the WASID trial (Warfarin-Aspirin Symptomatic Intracranial Disease), warfarin was compared to aspirin in the treatment of intracranial atherosclerosis. The trial was ended early due to a higher vascular complication rate in the warfarin group. In the subsequent SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis)[12] trial, stenting of these distal vessels was attempted, but this trial was also stopped prematurely secondary to significantly elevated stroke outcomes in the stenting group.

Underwriting of Cerebral Aneurysm and Arteriovenous Malformation

The underwriting of cerebral aneurysm is particularly challenging given the stakes: If the risk of rupture is underestimated, the case fatality rate within the first 6 months of rupture is 65%.[13] The background overall prevalence of cerebral aneurysm is 3.2%.[14] The most common locations are the anterior communicating artery (30%), posterior communicating artery (25%) and middle cerebral artery (20%)[15]. Well-established risk factors for cerebral aneurysm include:

- Tobacco
- Hypertension
- Female gender
- Family history
- Polycystic kidney disease (autosomal dominant)
- Age
- Atherosclerosis
- Infections, endocarditis, intravenous drug use
- Connective tissue diseases – Ehlers-Danlos, Marfan syndrome

Several of these risk factors are fairly common, so which patients should be screened for cerebral aneurysm? The Stroke Council of the AHA has actually found a very limited range of patients for which screening has been found beneficial: patients with not one, but two family members with a history of cerebral aneurysm, and those with genetic syndromes predisposing to development of aneurysmal subarachnoid hemorrhage such as Ehlers-Danlos syndrome Type IV and polycystic kidney disease.[16] The "protective tail" of such screening may not be as long as initially estimated. A second study[17] found that in this high-risk population, 20% of individuals had developed aneurysm by 10 years after negative initial screen. CT angiogram (CTA) and magnetic resonance angiogram (MRA) are fairly equivalent at detecting aneurysms above 3 mm.[18]

Studies of the natural history of aneurysm rupture highlight the importance of aneurysm detection at this size. For example the UCAS (unruptured cerebral aneurysms) Japan investigators found a marked increase in rupture rate above 5 mm (Table 3 next page).[19] Location of aneurysm was also found to be important, with anterior communicating artery aneurysms and internal carotid artery aneurysms representing roughly twice and half the rupture risk, respectively. Additional risk factors for rupture are very similar to those for initial development including age, hypertension, tobacco and female gender. In addition, any growth in aneurysm size has been found to be predictive of rupture. For example, a recent study (Villablanca et al. 2013)[20] showed 12 times the rupture rate with growth defined as an increase by just 5% of volume even for small aneurysms.

Perhaps the more common scenario in the underwriting of cerebral aneurysm is the evaluation of an applicant who has already undergone aneurysm treatment. Originally, the primary method of treating aneurysms entailed an open craniotomy, exposing and then clipping the aneurysm. In the early '90s an alternative procedure, endovascular coiling, was developed. Endovascular coiling entails accessing the aneurysm intra-arterially, and

Table 2. CREST Trial Outcomes

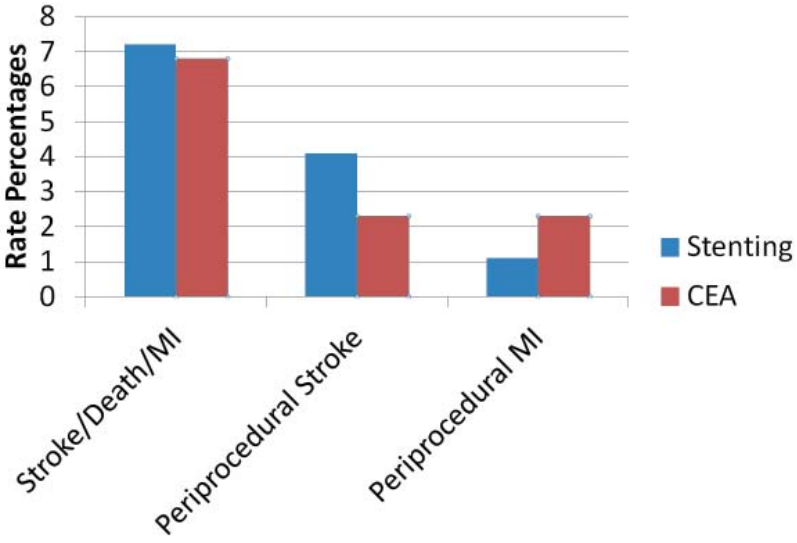

Table 3. Risk of Aneurysm Rupture According to Size

Size	Hazard Ratio
3-4 mm	Reference
5-6 mm	1.13
7-9 mm	3.35
10-24 mm	9.09
>25 mm	76.26

then sealing off blood flow to the aneurysm by placing a coil within the aneurysm itself. As with carotid stenting, comparison between the two therapies remains controversial. Longest term data available for larger scale trial comparing clipping with coiling is from extension of ISAT (International Subarachnoid Hemorrhage Trial).[21] This trial reported somewhat paradoxical results: the risk of re-bleeding was higher in the coiling group. However, the risk of death was ultimately lower in the coiling group (relative risk 0.77). Perhaps more important from an underwriting standpoint is that regardless of which therapy was pursued, the overall risk of re-bleed at 5 years was quite low after 1 year (24 rebleeds out of 2143 patients, 1.1%).

A similar controversy reigns over the management, and thus the underwriting, of unruptured arteriovenous malformation (AVM). Options for treatment include medical management (essentially blood pressure control) and a variety of interventional therapies (any combination of neurosurgery, embolization or radiosurgery), as discussed in the recently published ARUBA trial (unruptured brain arteriovenous malformations).[22] This was a multicenter (39) trial where patients with unruptured AVM were randomized to interventional surgery or medical management.The primary endpoint was death or stroke. Quite surprisingly, the trial was stopped by the National Institute of Neurological Disorders and Stroke after only 223 patients had enrolled. At the time that trial was stopped, 30% had reached primary endpoint of stroke or death in surgical group vs. 10% in the medical management group. A cohort study from Scotland[23] with 12 years of follow-up published in 2014 also supported better outcomes with conservative management.

Finally, the recently published MARS (Multicenter AVM Research Study)[24] trial offers the largest cohort for analysis of the natural history of AVM to date. The overall risk of rupture was 2.3% for all AVMs, 1.3% for unruptured AVMs and 4.8% for ruptured AVMs. Accordingly, the most significant risk factor for rupture was hemorrhage at presentation. Additional risk factors for hemorrhage included female gender, associated arterial aneurysm and exclusively deep venous drainage.

Conclusion

While overall stroke incidence and case fatality rates are decreasing, cerebrovascular disease remains an exceedingly important but rapidly changing cause of mortality and an even more important cause of disability. While the trials discussed above offer guidance, future highly anticipated research includes long-term data relating to the use of the novel oral anticoagulants in preventing stroke, further elucidating the reasons behind the increase in stroke incidence in younger individuals, and the ever-elusive goal of utilizing stem cells to enhance stroke recovery.

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