The Future of Minor Stroke and Transient Ischemic Attack: The RAVEN Approach Is Promising but Not Ready for Prime Time

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In this issue of *Annals*, Chang et al[1] present experience with a rapid outpatient approach for transient ischemic attack and minor stroke, the Rapid Access Vascular Evaluation–Neurology (RAVEN). The authors performed a retrospective analysis of 162 patients at a single center who had minor stroke or transient ischemic attack. They describe the design and implementation of a protocol that allowed discharge of select patients from the emergency department (ED) with outpatient neurology follow-up within 24 hours. The 90-day follow-up rate was approximately 90%, and of patients who were followed to 90 days, 19% returned to the ED or hospital, 3.7% had recurrent symptoms, and 0.7% had a recurrent stroke. Overall, implementation of this strategy is laudable, and is indeed needed in this era of ED crowding. However, more work is necessary before translation to the bedside to achieve optimal success in variable patient populations, and to identify optimal diagnostic testing strategies. Key questions include the timing of vascular imaging (ie, computed tomography [CT] angiography), tissue imaging (by magnetic resonance imaging [MRI]), optimal management for the large proportion of patients with mimics, the need to incorporate dual antiplatelet therapy for high-risk patients, and risk-stratification strategies to identify patients at risk for cardiac emboli (ie, abnormal atrial electrical activity on ECG).[2] Thus, widespread use of the RAVEN approach for patients with transient ischemic attack or small stroke isn't ready for prime-time implementation, but the authors' efforts advance finding the ideal population and system resources necessary for such short-term follow-up.

The RAVEN authors are to be commended for setting up a rapid comprehensive clinical evaluation for their population of patients, which can serve as a model for other settings and even different disease states. Furthermore, similar protocols have been successfully implemented outside the United States,[3] although other non–US-based transient ischemic attack clinics have evaluated patients referred from outpatient physicians' offices rather than EDs and have variably included minor strokes. By selecting patients who are safe for discharge from the ED, the RAVEN protocol has the potential to reduce ED length of stay, prevent hospital admissions, and increase ED throughput. Prevention of admissions could lead to an overall reduction in the cost of care for patients with minor stroke, transient ischemic attack, or both. Previous data have shown a link between ED crowding, time to treatment for certain conditions, and rates of leaving without being seen,[4] so strategies such as RAVEN that could facilitate discharge and reduce ED crowding have the potential to also improve care and clinical outcomes for the broader ED population. For transient ischemic attack alone, the annual incidence rate ranges from 102 to 182 per 100,000, depending on sex and time period.[5] Costs for hospital admissions for transient ischemic attack are substantial as well; administrative data suggest that the majority of hospital admissions for transient ischemic attack last from 2 to 6 days, with mean billed hospital charges greater than $17,000.[6] Other studies of actual cost estimate approximately $3,000 per hospital day, although this estimate is based on a decision-tree analysis of simulated data.[7] As a result, the potential influence of rapid outpatient management on overall cost and resource use for these patients is substantial. In addition, if outpatient minor stroke and transient ischemic attack management proves to be successful, similar outpatient protocols could be set up for other disease entities such as pneumonia, cellulitis, and low-risk chest pain.

Despite the potential for the outpatient management of minor stroke and transient ischemic attack to lead to increased efficiency, more data are needed before consideration of the widespread implementation of the RAVEN approach. First, in the era of advanced imaging and mechanical thrombectomy, more evidence is needed to

inform the role of immediate vessel imaging as part of the management of patients with transient ischemic attack and minor stroke. Specifically, in which subset of patients can CT angiography be safely deferred? Many EDs have rapid access to vascular imaging through CT angiography. Although the RAVEN group's methodology likely excluded a portion of large vessel occlusion patients by excluding those with fluctuating symptoms, a disabling deficit, or both, the existing literature in regard to the sensitivity of these criteria is not well defined. The rates of large vessel occlusion in patients with low National Institutes of Health Stroke Scale score and management of these patients have become of great interest to stroke researchers, given that rates of large vessel occlusion in patients with minor symptoms are not inconsequential. Among patients with suspected stroke, a National Institutes of Health Stroke Scale score cutoff of 6, not taking into account other variables, will miss 20% of large vessel occlusions.[8] For patients with transient ischemic attack, critical vascular lesions can occur in up to 13%.[9] The presence of large vessel occlusion in combination with minor symptoms may be a critical marker of early disease escalation. One study of patients with mild stroke (National Institutes of Health Stroke Scale score <6) with large vessel occlusion had an 11.3% clinical decompensation rate, with the median time to emergency rescue thrombectomy being 6.8 hours.[10] Incorporating CT angiography more routinely into the protocol would also be an optimal approach to screening for high-grade symptomatic carotid stenosis because such patients are at high risk of impending stroke and thus can benefit from early inpatient carotid interventions. The safety of discharging patients with minor stroke, and without vascular imaging, remains to be seen. Several ongoing trials (Mild and Rapidly Improving Stroke Study [MARISS] and Endovascular therapy for low NIHSS ischemic stroke [ENDO-LOW]) are expected to offer insights into this population of patients. One potential solution to reducing the risk of missed critical stenosis, large vessel occlusion, or both would be to perform routine vessel imaging during the initial ED visit, before discharge for outpatient follow-up. In RAVEN, only 13.5% of patients had CT angiography performed before discharge, which seems low, given the widespread availability of CT angiography and lack of well-defined, sensitive criteria to identify large vessel occlusion.

The rate of stroke mimics (34%) in this study is notable; these diagnoses included peripheral neuropathy, migraine, and seizure or recrudescence. Although the authors note that this proportion of mimics did not put any undue burden on the RAVEN clinic, the high proportion of mimics could make the RAVEN protocol underestimate longer-term adverse outcomes in patients with pure neurovascular syndromes.

Additionally, the use of MRI for transient ischemic attack and minor stroke requires further investigation in the context of safely deferring or not acquiring it. An area of restricted diffusion on MRI indicates permanent brain damage (stroke), is a strong predictor of recurrent stroke,[11,12] and can offer critical information suggesting the cause of a stroke (eg, cardioembolic, artery to artery, watershed, hypertensive). Although MRI may not change management in all patients, identifying potentially cardioembolic causes by MRI could lead to initiation of anticoagulation for some patients, rather than the standard antiplatelet regimen. In addition, negative MRI results may help to identify patients with nonvascular diagnoses, and they could then be given follow-up recommendations specific to their nonstroke diagnosis (ie, headache clinic, primary care, or psychiatry). Finally, delayed imaging with MRI may lead to testing degradation by which abnormal signals indicating a stroke on early imaging (<24 hours) may not be present on imaging conducted later.[13] In the RAVEN study, 1.2% of patients had an MRI before discharge, and 3.2% had MRIs performed in the emergency clinic setting, suggesting that the acquisition of an MRI in their system was challenging both in the ED and in acute follow-up clinical settings. One patient in the follow-up clinic had a capsular infarct and was admitted. This action suggests the treatment team was alarmed by this finding and believed the patient required further testing, interventions, or both. To ensure that such a strategy of deferring MRI to facilitate ED discharge is safe, more investigation in regard to MRI use and timing is necessary. A strategy for selection of patients who would benefit from echocardiogram for evaluation of possible atrial cardiopathies, as well as screening stroke laboratory tests, including a lipid panel for all patients, should be considered in future versions of RAVEN.

Adding prompt initiation of dual antiplatelet therapy is also needed for future versions of RAVEN or similar outpatient protocols. Both the Platelet-Oriented Inhibition in New/TIA and Minor Ischemic Stroke (POINT) and Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trials demonstrated significant decreases in 90-day stroke risk among patients who were randomized to both clopidogrel and aspirin compared with aspirin alone among patients with high-risk transient ischemic attack (defined with the ABCD2 score) or minor strokes, with the POINT trial initiating dual antiplatelet therapy within 12 hours of onset. In the future, implementation of outpatient protocols such as RAVEN needs to include a strategy for identifying this high-risk group of patients

(using either advanced imaging [ie, MRI] or clinical risk scores such as the ABCD2) or initiating dual antiplatelet therapy for all patients with suspected transient ischemic attack at ED discharge, before the 24-hour follow-up visit, based on the timing of dual antiplatelet therapy initiation in the POINT and CHANCE trials.

It is also unknown whether the RAVEN group's strategy or a similar protocol would be equally successful in other populations of ED patients. RAVEN was piloted in 162 patients, and 95.1% attended the 24-hour clinic visit, an impressive follow-up rate. One of the exclusion criteria was the inability to follow up within 24 hours, which may introduce a component of selection bias, especially if factors related to the ability to follow up (eg, factors linked to socioeconomic status) are also related to outcomes after stroke. This raises the concern that similar outpatient strategies may be variably successful in populations in whom factors such as access to transportation or ability to miss work are a barrier. Prospective validation in other study populations is needed.

In summary, the RAVEN study describes a novel approach to the management and disposition of patients with minor stroke and transient ischemic attack, with the potential for significant cost savings and more effective use of precious ED resources. This is promising in this setting of increasing ED volumes and challenges related to crowding. Next steps include investigating the RAVEN strategy in combination with other available risk-stratification tools, including, perhaps, clinical risk scores (eg, ABCD2), a more widespread use of vascular imaging, and the use of tissue imaging (MRI). Theoretically, incorporating the use of ED CT angiography of the head and neck in outpatient protocols in a more widespread and standardized way would identify an important subset of patients at risk for short-term clinical deterioration. Additionally, a formal cost-effectiveness analysis comparing outpatient management strategies with costs incurred for similar patients admitted to the hospital or to ED observation units merits consideration for further investigation. A trial following up on the RAVEN group's work in identifying a safe and efficacious way to discharge patients and arrange rapid neurovascular clinic follow-up for those with transient ischemic attack, small stroke, or both could improve emergency medicine and stroke systems, with the potential to result in a change in current clinical practice and practice guidelines.

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