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Article Title: HINTS Outperforms ABCD2 to Screen for Stroke in Acute Continuous Vertigo and Dizziness

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Educational Objectives
After completing this exercise, the reader will be able to compare and contrast two different methods for bedside diagnosis of posterior circulation strokes.

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CME

HINTS Outperforms ABCD2 to Screen for Stroke in Acute Continuous Vertigo and Dizziness

David E. Newman-Toker, MD, PhD, Kevin A. Kerber, MD, MS, Yu-Hsiang Hsieh, PhD, John H. Pula, MD, Rodney Omron, MD, Ali S. Saber Tehrani, MD, Georgios Mantokoudis, MD, Daniel F. Hanley, MD, David S. Zee, MD, and Jorge C. Kattah, MD

Abstract

Objectives: Dizziness and vertigo account for about 4 million emergency department (ED) visits annually in the United States, and some 160,000 to 240,000 (4% to 6%) have cerebrovascular causes. Stroke diagnosis in ED patients with vertigo/dizziness is challenging because the majority have no obvious focal neurologic signs at initial presentation. The authors sought to compare the accuracy of two previously published approaches purported to be useful in bedside screening for possible stroke in dizziness: a clinical decision rule (head impulse, nystagmus type, test of skew [HINTS]) and a risk stratification rule (age, blood pressure, clinical features, duration of symptoms, diabetes [ABCD2]).

Methods: This was a cross-sectional study of high-risk patients (more than one stroke risk factor) with acute vestibular syndrome (AVS; acute, persistent vertigo or dizziness with nystagmus, plus nausea or vomiting, head motion intolerance, and new gait unsteadiness) at a single academic center. All underwent neurootologic examination, neuroimaging (97.4% by magnetic resonance imaging [MRI]), and follow-up. ABCD2 risk scores (0–7 points), using the recommended cutoff of ≥4 for stroke, were compared to a three-component eye movement battery (HINTS). Sensitivity, specificity, and positive and negative likelihood ratios (LR+, LR–) were assessed for stroke and other central causes, and the results were stratified by age. False-negative initial neuroimaging was also assessed.

Results: A total of 190 adult AVS patients were assessed (1999–2012). Median age was 60.5 years (range = 18 to 92 years; interquartile range [IQR] = 52.0 to 70.0 years); 60.5% were men. Final diagnoses were vestibular neuritis (34.7%), posterior fossa stroke (59.5% [105 infarctions, eight hemorrhages]), and other central causes (5.8%). Median ABCD2 was 4.0 (range = 2 to 7; IQR = 3.0 to 4.0). ABCD2 ≥ 4 for stroke had sensitivity of 61.1%, specificity of 62.3%, LR+ of 1.62, and LR– of 0.62; sensitivity was lower for those younger than 60 years old (28.9%). HINTS stroke sensitivity was 96.5%, specificity was 84.4%, LR+ was 6.19, and LR– was 0.04 and did not vary by age. For any central lesion, sensitivity was 96.8%, specificity was 98.5%, LR+ was 63.9, and LR– was 0.03 for HINTS, and sensitivity was 99.2%, specificity was 97.0%, LR+ was 32.7, and LR– was 0.01 for HINTS "plus" (any new hearing loss added to HINTS). Initial MRIs were falsely negative in 15 of 105 (14.3%) infarctions; all but one was obtained before 48 hours after onset, and all were confirmed by delayed MRI.

Conclusions: HINTS substantially outperforms ABCD2 for stroke diagnosis in ED patients with AVS. It also outperforms MRI obtained within the first 2 days after symptom onset. While HINTS testing has traditionally been performed by specialists, methods for empowering emergency physicians (EPs) to leverage this approach for stroke screening in dizziness should be investigated.

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Dizziness and vertigo account for about 4 million emergency department (ED) visits annually in the United States[1] and between 160,000 and 240,000 (4% to 6%) have cerebrovascular causes.[2–6] Rapid, accurate diagnosis of stroke is important to initiate acute treatments and monitor patients to prevent complications.[7] For example, missed cerebellar stroke at the initial ED visit may confer up to an eightfold increased risk of death.[8] Preventable adverse outcomes[9] result from missed opportunities for thrombolysis,[10] early surgical intervention for posterior fossa edema,[7] and averting major vertebrobasilar stroke after initially minor infarction.[11,12] Identifying these posterior circulation stroke patients presents an important clinical challenge for emergency physicians (EPs), because symptoms are frequently isolated,[13] and contrary to conventional wisdom, obvious focal neurologic signs are usually absent.[8]

When vestibular symptoms are of cerebrovascular cause, over 90% are ischemic strokes in the vertebrobasilar (posterior) circulation.[8] Although patients with brainstem or cerebellar (posterior fossa) hemorrhages also present with vertigo or dizziness, these rarely mimic benign dizziness presentations.[14] Brain computed tomography (CT) scans are very sensitive for detecting acute intracranial hemorrhages (93%[15]), but cannot "rule out" ischemic stroke, as CTs detect only about 16%[15] to 42%[16] of early ischemic strokes. Brain magnetic resonance imaging (MRI) scans are costly, not always available, and in the first 24 hours after posterior fossa stroke symptom onset may be falsely negative in up to 20%.[8] So it is not surprising that EPs rate the development of a clinical decision rule for identifying central vertigo a top priority.[17]

Although originally designed to predict future stroke in patients with transient ischemic attacks, a recent retrospective study suggested that a risk stratification approach ('ABCD2' score [Table 1][18–20]) might help identify strokes acutely in ED patients with dizziness.[21] The study showed promising results (86% sensitivity for stroke at a cutoff of ≥4 with nearly 40% specificity; area under the receiver operating characteristic [ROC] curve = 0.79).[21] However, some have questioned these results on methodologic grounds,[22] because dizziness duration was not quantified, MRI brain scans were obtained in only 11% of patients, and investigators did not follow patients to identify missed strokes.[21] Furthermore, risk factor stratification might tend to miss younger stroke patients presenting with dizziness, who often lack traditional vascular risk factors, having vertebral artery dissection rather than atherosclerosis as the cause for posterior fossa infarction.[23,24]

A well-studied expert approach relies on differentiating transient from persistent dizziness and then examining eye movements.[8,18,25–27] Most stroke patients present with persistent symptoms. Acute vestibular syndrome (AVS) is a well-defined clinical syndrome[28] of acute, persistent vertigo or dizziness lasting days to several weeks with associated nausea or vomiting, head motion intolerance, gait unsteadiness, and nystagmus.[8] AVS patients (10% to 20% of ED dizziness presentations[8]) are at higher risk for stroke (25%) than average ED dizziness patients (4% to 6%), but the majority of AVS patients (70%) still have benign peripheral causes.[8] A 2-minute, three-item bedside eye movement screen ('HINTS to INFARCT' [Table 1]) assessing vestibulooocular physiology can be used in AVS to localize lesions as central (mostly stroke) or peripheral (mostly vestibular neuritis).[26] Central eye movement findings predict stroke with high accuracy.[8]

Eliciting and interpreting these findings requires special examiner skills not currently available in most EDs, but a new FDA-approved device that can be operated by a technician objectively records these eye movements.[29] Measurement properties of the videooculography device have been validated in laboratory settings[30,31] and, more recently, a small prospective study used the device to accurately distinguish stroke from vestibular neuritis in the ED.[27] This device may make this approach accessible to EPs, obviating the need for subspecialists. Nevertheless, history-based stroke risk factor scoring systems require less technical skill and equipment, so might be easier to implement in the ED. We sought to compare the diagnostic accuracy

Table 1
ABCD2 and H.I.N.T.S. Elements and Stroke Findings

Five-item ABCD2 risk score	Stroke findings: risk score ≥ 4
• Age	• A ≥60 years = 1
• Blood pressure	• B systolic ≥140 or diastolic ≥/90 = 1
• Clinical features	• C unilateral weakness = 2, speech disturbance without weakness = 1, any other symptom = 0
• Duration of symptoms	• D <10 min = 0; 10–59 min = 1; ≥60 min = 2
• Diabetes	• D present = 1
Three-step "H.I.N.T.S." eye examination*	**Stroke findings: "I.N.F.A.R.C.T." (any of these)†**
• Head Impulse (right- and leftward)	• Impulse Normal (bilaterally normal)
• Nystagmus type (gaze testing)	• Fast-phase Alternating (direction-changing)
• Test of Skew (alternate cover test)	• Refixation on Cover Test (skew deviation)

*A fourth step (H.I.N.T.S. "plus") includes assessing the presence of new hearing loss, generally unilateral and on the side of the abnormal head impulse test (the side opposite the fast phase of the nystagmus). Recent evidence suggests that, counter to traditional teaching, the presence of such hearing loss more often indicates a vascular (labyrinthine or lateral pontine infarction) rather than viral (labyrinthitis) cause of the AVS presentation.[8,18,19]

†In the current study, there was only a single peripheral H.I.N.T.S. pattern—unilaterally abnormal head impulse test; *plus* direction-fixed, horizontal or horizontal > torsional nystagmus obeying Alexander's law[20] (i.e., increased intensity in gaze toward the fast phase) with the fast phase beating away from the side of the abnormal impulse; *plus* absent skew deviation by the alternate cover test. Bilaterally abnormal impulses would have been considered peripheral without central nystagmus or skew, but there were no such patients. Any other pattern was considered "central." Central patterns included 1) bilaterally normal head impulse test of vestibuloocular reflex function with any spontaneous or gaze-evoked nystagmus; 2) bilateral, direction-changing, horizontal gaze-evoked nystagmus (or predominantly vertical or torsional nystagmus); 3) skew deviation by alternate cover test; or 4) any combination of these.

of HINTS and ABCD2 in AVS. We hypothesized that the physiologically based eye movement approach (HINTS) would be more accurate than the risk factor approach (ABCD2).

METHODS

Study Design

We analyzed data (1999–2012) from an ongoing, institutional review board–approved, prospective, cross-sectional diagnostic study of AVS patients. The institutional review board at the University of Illinois College of Medicine at Peoria approved this study.

Study Setting and Population

The study is set at a single academic medical center (OSF Saint Francis Medical Center, Peoria, IL) serving as a regional stroke referral center for 25 community hospitals. The center has approximately 86,000 annual ED visits and nearly 900 stroke admissions per year. Blood pressure and diabetes data for ABCD2 calculations were abstracted post hoc from medical charts, making this analysis "ambispective."

Detailed methods have been described previously, and 108 of 190 patients presented here have had oculomotor and radiographic findings reported previously.[25–27] We recruited patients with at least 1 hour of acute, persistent, continuous vertigo or dizziness with spontaneous or gaze-evoked nystagmus, plus nausea or vomiting, head motion intolerance, and new gait unsteadiness (i.e., AVS), presenting within 1 week of symptom onset. Patients would have been excluded if their symptoms abated prior to 24 hours (n = 0), as the technical definition of AVS requires 24 hours of symptoms.[8] We enrolled patients with a shorter duration of symptoms to increase utility and generalizability of the results (because many patients present to the ED less than 24 hours after symptom onset, and most with continuous symptoms lasting more than an hour will continue to be symptomatic at the 24-hour mark). Patients were required to have one or more stroke risk factors (smoking, hypertension, diabetes, hyperlipidemia, atrial fibrillation, eclampsia, hypercoagulable state, recent cervical trauma, prior stroke, or myocardial infarction). This approach was chosen from study inception to enrich the subject pool with stroke patients. Patients were excluded for a history of multiple attacks of recurrent vertigo or dizziness compatible with Menière's disease (n = 17), vestibular migraine (n = 9), idiopathic recurrent vertigo (n = 4), or if they were successfully treated for benign paroxysmal positional vertigo (BPPV) by canalith repositioning (n = 1, horizontal canal variant). Patients were excluded for lethargy sufficient to prevent participation in examination (n = 2) but not for other neurologic findings. As reported previously, focal general neurologic signs are present in fewer than 20% of patients in this study population.[26] Patients were only allowed to enroll in the study once.

Study Protocol

Investigators advertised the study to ED personnel and neurology residents, who then contacted study investigators regarding potentially eligible patients. All of the enrolled were ED patients, although some came from regional hospital EDs via direct ED to inpatient transfer. Patients were generally recruited in the ED. Additional active surveillance of neurology admissions, including direct stroke transfers from outside hospital EDs, improved case capture. All patients were followed throughout the duration of hospitalization, and all patients diagnosed with peripheral vestibular disorders were followed for a minimum of 3 months after hospitalization.

All patients underwent structured bedside neurologic and neurootologic exam (including HINTS eye movements [see video demonstration][32]) and then neuroimaging (97.4% by MRI). Stroke protocol MRI images included axial T2, FLAIR, and diffusion-weighted imaging (DWI; twenty 5-mm axial slices; interslice gap 2 mm), performed on a 1.5-T MRI unit (GE Medical Systems, Milwaukee, WI). Repeat delayed MRI was obtained in patients with initially normal imaging if clinical signs suggested a central lesion or new neurologic signs appeared during the inpatient admission. Examinations were conducted by one of two trained neuroophthalmology study examiners (JCK or JHP) who examined patients prior to neuroimaging or were masked to imaging results.

Outcome Measures

Central conditions were usually (96%) diagnosed by radiographic evidence of posterior fossa acute ischemic stroke, acute hemorrhage, or active demyelination with enhancing lesions (clinical neuroradiology interpretation). For cases with multiple MRIs, the presence of an acute, DWI-positive ischemic lesion in the posterior fossa on at least one scan confirmed a stroke diagnosis ("final" MRI). Some central cases (4%) were diagnosed by ancillary laboratory testing (e.g., paraneoplastic antibodies, serum thiamine level) conducted as part of a routine clinical workup. Peripheral lesions (mostly vestibular neuritis in our series) were diagnosed based on compatible clinical findings, normal or nonspecific MRI findings (e.g., atrophy or age-compatible periventricular white matter changes), plus clinical follow-up without indication of a related central event. When a patient had new hearing loss with a peripheral cause of AVS, we diagnosed labyrinthitis,[8] but categorized these with vestibular neuritis for analysis.

"HINTS" was scored as either a "peripheral" or "central" pattern based on the bedside eye movement examination (see Table 1 footnote). We also assessed two prospectively defined HINTS modifications: one with known greater specificity[8] (one-item head impulse test alone[25]), the other with hypothesized greater sensitivity[18] (four–item HINTS "plus," which adds new hearing loss as a predictor of inner ear or cochlear nucleus stroke,[8,19,33,34] rather than labyrinthitis, which is uncommon in AVS[26]). Hearing loss was judged to be present only if bedside examination (finger rubbing) detected a clear right–left asymmetry and the patient confirmed the deficit to be new.

The ABCD2 is a risk prediction score (range 0 to 7) that assigns points based on five elements arranged as a mnemonic acronym (Table 1). We assessed ABCD2 risk scores using the method described by Navi et al.[21]

Age, duration, and clinical features (weakness, speech disturbance) were routinely recorded as part of our structured assessment. Blood pressure and diabetes status were abstracted post hoc from case records by a single unmasked author (JCK) for the purposes of this article. The blood pressure chosen was the first recorded blood pressure in the clinical record, generally one obtained in the ED.

Data Analysis

Because this was a secondary analysis of preexisting data from an ongoing longitudinal study,[25–27] no a priori sample size or power calculations were performed to choose the study sample. It was known from prior work,[26] however, that a sample roughly half that used here produced adequately narrow confidence intervals (CIs) around sensitivity and specificity estimates to inform robust clinical decision-making.

We used descriptive statistics to characterize ABCD2 and HINTS test properties, including sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR–). We calculated test properties for ABCD2 at each of six possible threshold cut points for pursuing a stroke diagnosis (≥2, ≥3, ≥4, ≥5, ≥6, ≥7). For direct comparison of ABCD2 to HINTS, we used ABCD2 ≥ 4 as the threshold, as suggested by Navi et al.[21] We assessed dichotomous HINTS results at three threshold cut points (one item, three item, four item). We compared dichotomous ABCD2 and HINTS results for stroke and for any central lesion and then conducted a subgroup analysis for stroke sensitivity by age group. As part of a ROC curve analysis, we plotted sensitivity (true positive rate) versus 1 – specificity (false positive rate) for central lesions using ABCD2 at each numerical threshold (≥2 through ≥7) and HINTS at the three thresholds. p-values of chi-square (demographic disease analyses), McNemar (primary ABCD2 vs. HINTS outcomes), and Cochran-Armitage trend (age subgroup analysis) tests were calculated using SAS v9.3 (SAS Institute, Cary, NC). ROC analysis and area under the curve calculations were performed using IBM SPSS Statistics v20 (Armonk, NY). The 95% CIs for LRs were calculated using the method described by Simel et al.[35] Two-tailed p-values of <0.05 were considered statistically significant. We conducted 10 hypothesis tests, report them all here, and did not adjust our statistical analyses for multiple comparisons.

RESULTS

Demographic and clinical characteristics are shown in Table 2. Men and women with AVS were equally likely to have vestibular neuritis (35.7% vs. 33.3%, chi-square p = 0.74). Men were slightly more likely than women to have stroke (64.3% vs. 52.0%, chi-square p = 0.09), and women were much more likely to have other central causes (0.0% vs. 14.7%, chi-square p < 0.001).

The ABCD2 scores ranged from 2 to 7. Mean (± standard deviation [SD]) ABCD2 was 3.5 (±0.9), and median ABCD2 was 4.0 (interquartile range [IQR] = 3.0 to 4.0). Figure 1 shows the distribution of ABCD2 scores by final diagnosis. Table 3 shows sensitivity, specificity, and LRs of ABCD2 for stroke at different threshold cut-off values. Table 4 compares test properties of ABCD2 ≥ 4 to HINTS at three thresholds for detecting stroke only or any central cause. Figure 2 demonstrates these results as a ROC analysis for detecting any central cause. The area under the curve for ABCD2 was 0.613 (95% CI = 0.531 to 0.695), while the area under the curve for HINTS was 0.995 (95% CI = 0.985 to 1.000).

The HINTS approach was more sensitive and specific than the ABCD2 risk factor approach, regardless of the outcome measure. Overall sensitivity of ABCD2 for stroke at a cutoff threshold ≥ 4 was 61.1% (*n* = 69 of 113), with a specificity of 62.3% (*n* = 48 of 77; LR+ = 1.62, LR– = 0.62). HINTS sensitivity for stroke was 96.5% (*n* = 109 of 113) with a specificity of 84.4% (*n* = 65 of 77; LR+ = 6.19, LR– = 0.04). HINTS correctly identified the 11 central, nonstroke cases, which lowered the test's specificity for stroke, per se, but raised it when considering central causes. False-negative HINTS cases were uncommon (*n* = 4), and all but one was captured by HINTS "plus." There was a single false-positive HINTS (and HINTS "plus") case in a patient with vestibular neuritis who had skew deviation. There was a second HINTS "plus" false positive in a patient with hearing loss who had true labyrinthitis. The head impulse test as a single item had 11 false negatives (nine anterior inferior cerebellar artery territory strokes [five with new hearing loss]; the other two had large posterior inferior cerebellar artery territory strokes with mass effect on the brainstem at the cerebellopontine angle [one with preexisting hearing loss, the other without any hearing loss]).

Figure 3 compares sensitivity of ABCD2 ≥ 4 to HINTS "plus" for stroke diagnosis by age group. ABCD2 sensitivity for stroke differed by age (18 to 49 years, 17.6%; 50 to 59 years, 35.7%; ≥60 years, 82.4%; Cochran-Armitage trend test p < 0.001), but HINTS "plus" did not (Cochran-Armitage trend test p = 0.541). In patients younger than 60 years, the sensitivity of ABCD2 for stroke was dramatically lower than HINTS "plus" (28.9%, 95% CI = 17.1% to 43.3% vs. 97.8%, 95% CI = 89.5% to 99.9%; McNemar p < 0.001); ABCD2 sensitivity was also substantially lower for those ≥ 60 years (82.4%, 95% CI = 71.9% to 90.1% vs. 100%, 95% CI = 95.7% to 100.0%; McNemar p < 0.001).

As in a prior analysis,[25] eye movement approaches (with examinations obtained prior to imaging in almost all patients) matched or outperformed initial MRI-DWI. Initial MRI sensitivity in this series was 86.7% (*n* = 98 of 113, 95% CI = 79.5% to 92.1%). Initial MRI sensitivity was nearly equal to head impulse alone (sensitivity 90.3%, 95% CI = 83.7% to 94.8%; McNemar p = 0.394) but lower than both HINTS (sensitivity 96.5%, 95% CI = 91.7% to 98.9%; McNemar p = 0.008) and HINTS "plus" (sensitivity 99.1%, 95% CI = 95.7% to 100.0%; McNemar p < 0.001). Most MRIs were obtained within 72 hours of AVS onset, and all but one false-negative initial MRI was obtained < 48 hours after onset.

DISCUSSION

The physiologically-based HINTS approach substantially outperforms the risk factor–based ABCD2 approach for detecting stroke and other central causes in AVS

Table 2
Study Population Characteristics

Attribute	Result
Total enrollees (included)	193 (190*)
Admitted	100%
Age range, yr	18–92
Median (IQR) age, yr	61.0 (52.0–70.0)
Sex	60.5% men (n = 115) 39.5% women (n = 75)
Race	90.0% white, non-Hispanic (n = 171) 6.3% black or African American (n = 12) 3.7% other race/culture (n = 7)
Diagnoses	34.7% vestibular neuritis (n = 66)† 59.5% posterior fossa stroke (n = 113) • 92.9% infarction (n = 105) • 7.1% hemorrhage (n = 8) 5.8% other central causes (n = 11)‡
Symptom onset to examination	2 hours–7 days§
ED presentation to examination	<24 hours for all subjects
ED presentation to neuroimaging	<24 hours for all subjects (MRI n = 186; CT n = 4)
Complications of testing	ABCD2, HINTS—none CT—none; MRI—one claustrophobic reaction
False negative initial MRI-DWI	14.3% of ischemic strokes (n = 15/105)‖ • 2–24 hours after onset of symptoms (n = 9) • 24–48 hours after onset of symptoms (n = 5) • >48 hours after onset of symptoms (n = 1)
Thrombolytic therapy for stroke	None
Hospital course for stroke	19.5% of stroke patients deteriorated (n = 22/113)¶ • 7.1% required surgery (n = 8) • 0.9% basilar intravascular stent (n = 1) • 3.5% died acutely (n = 4)

ABCD2 = age, blood pressure, clinical features, duration of symptoms, diabetes; DWI = diffusion-weighted imaging; HINTS = head impulse, nystagmus type, test of skew; MRI = magnetic resonance imaging.
*Three patients were excluded: two stroke suspects were not imaged because of contraindications; one confirmed stroke patient was excluded for missing blood pressure data.
†One patient with a peripheral final diagnosis had bedside evidence of new hearing loss (i.e., "labyrinthitis"; 1.5%, n = 1/66). This patient is counted here with vestibular neuritis. One neuritis patient with a negative delayed MRI was lost to follow-up.
‡Eleven other central causes were as follows: six multiple sclerosis, two paraneoplastic syndrome (initial manifestation of ovarian carcinoma, small cell carcinoma of the lung), one Wernicke's syndrome, one cerebellar metastasis from breast carcinoma, and one carbamazepine intoxication.
§Most of the patients were examined within 24 hours of symptom onset and almost all within 72 hours.
‖In the 14 with early false-negative MRI (<48 hours), follow-up ("final") MRI-DWI an average of about 3 days after symptom onset (range = 2–10 days) revealed infarctions located in the lateral medulla (11, one extending to the pons and one associated with a cerebellar infarction), middle cerebellar peduncle (2), and pontomesencephalic junction (1). Two of these false-negative initial MRI patients deteriorated substantially and one died. The one delayed false negative (5 days post–symptom onset) occurred in a patient with clinically diagnosed labyrinthine infarction (AVS plus sudden deafness) who developed multiple cerebellar strokes within 2 weeks due to intravascular lymphoma.
¶Of 22 deteriorating patients, eight required surgery (decompressive craniotomy or ventriculoperitoneal shunt) for posterior fossa mass effect or obstructive hydrocephalus (six ischemic stroke; two hemorrhage from cavernoma). Four ischemic stroke patients died (3.5%), one despite two posterior fossa decompression surgeries and shunt placement.

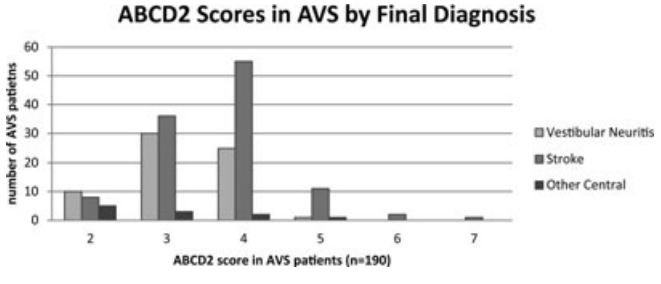

Figure 1. Histogram of ABCD2 scores in AVS by final diagnosis. Patients received ABCD2 points for age (n = 104), blood pressure (n = 126), clinical features (weakness n = 9, speech disturbance n = 2), duration (n = 190), and diabetes (n = 35). AVS = acute vestibular syndrome; ABCD2 = age, blood pressure, clinical features, duration of symptoms, diabetes.

patients. It also detects stroke with greater sensitivity than initial MRI-DWI. The HINTS rule can be tuned for greater specificity (head impulse test alone) or greater sensitivity (HINTS "plus" hearing loss). HINTS diagnostic properties make it ideally suited to guide downstream imaging choices in AVS (Figure 4). Although the specificity of HINTS might turn out to be lower in a population with a lower stroke prevalence, sensitivity estimates are generally unaffected by studies using high-prevalence populations.[36] HINTS sensitivity appears higher than any other published diagnostic strategy at initial ED assessment, suggesting that it can be appropriately used to screen for stroke in AVS. Other strategies risk high rates of diagnostic error (58% to 84% missed by CT,[15,16] 13.3% [n = 15/113] missed by MRI) and low cost-effectiveness.[37]

Table 3
Test Properties of ABCD2 for Diagnosing Stroke in AVS at Different Thresholds

ABCD2 Score Cutoff Value	Sensitivity for Stroke,* % (95% CI)	Specificity for Stroke, % (95% CI)	LR+ Stroke, (95% CI)	LR– Stroke, (95% CI)
2 or above	100.0 (97–100)	0.0 (0–5)	1.00 (1.00–1.00)	NC
3 or above	92.9 (87–96)	19.5 (12–30)	1.15 (1.02–1.30)	0.36 (0.16–0.82)
4 or above	61.1 (52–70)	62.3 (51–72)	1.62 (1.17–2.24)	0.62 (0.47–0.83)
5 or above	12.4 (8–20)	97.4 (91–99)	4.77 (1.12–20.40)	0.90 (0.83–0.97)
6 or above	2.7 (1–8)	100.0 (95–100)	>2.65† (NC)	0.97 (0.94–1.00)
7	0.9 (0–5)	100.0 (95–100)	>0.88† (NC)	0.99 (0.97–1.01)

ABCD2 = age, blood pressure, clinical features, duration of symptoms, diabetes; AVS = acute vestibular syndrome; DWI = diffusion weighted imaging; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; MRI = magnetic resonance imaging; NC = not calculable.
*Includes ischemic strokes (n = 105) and hemorrhages (n = 8). Stroke diagnoses were based on MRI-DWI showing acute stroke in 97.4% and CT showing a clear infarction or hemorrhage in the remaining patients (n = 4, one of whom died of their stroke and three of whom required surgical decompression).
†The LR+ for ABCD2 $\geq$ 6 and ABCD2 $\geq$ 7 were calculated using a specificity of 99.0% and listed as ">" since the LR+ associated with 100% specificity (measured in this sample) is infinite.

Table 4
ABCD2 $\geq$ 4 Versus HIT, HINTS, and HINTS "plus" for Stroke or Central Cause in AVS

Test Properties	ABCD2 $\geq$ 4 (Five-item Rule*)	HIT (One-step Rule*)	HINTS (Three-step Rule*)	HINTS "Plus" (Four-step Rule*)
Stroke only (n = 113 stroke, n = 77 nonstroke)				
Sensitivity for stroke	61.1 (51.8–69.7)	90.3 (83.7–94.8)	96.5 (91.7–98.9)	99.1 (95.7–100.0)
Specificity for stroke	62.3 (51.2–72.6)	87.0 (78.1–93.2)	84.4 (75.0–91.3)	83.1 (73.5–90.3)
LR+ stroke	1.62 (1.17–2.24)	6.95 (3.89–12.43)	6.19 (3.68–10.42)	5.87 (3.58–9.64)
LR– stroke	0.62 (0.47–0.83)	0.11 (0.06–0.20)	0.04 (0.02–0.11)	0.01 (0.00–0.08)
Reduction missed stroke†	Reference case	75.0	90.9	97.7
Any central cause (n = 124 central, n = 66 peripheral)				
Sensitivity for central	58.1 (49.2–66.5)	91.1 (85.1–95.3)	96.8 (92.4–99.0)	99.2 (96.1–100.0)
Specificity for central	60.6 (48.5–71.8)	100.0 (95.6–100.0)	98.5 (92.8–99.9)	97.0 (90.4–99.5)
LR+ any central cause	1.47 (1.05–2.06)	>91.1‡ (NC)	63.9 (9.13–446.85)	32.7 (8.36–128.16)
LR– any central cause	0.69 (0.52–0.92)	0.09 (0.05–0.16)	0.03 (0.01–0.09)	0.01 (0.00–0.06)
Reduction missed central†	Reference Case	78.8	92.3	98.1

Data are reported as percentages, except LRs, with (95% CI)
ABCD2 = age, blood pressure, clinical features, duration of symptoms, diabetes; AVS = acute vestibular syndrome; LR+ = positive likelihood ratio; LR– = negative likelihood ratio; HINTS = head impulse, nystagmus type, test of skew; HINTS "plus" = HINTS plus new hearing loss detected by finger rubbing; HIT = head impulse test.
*The ABCD2 rule requires five historical elements. The standard HINTS approach has three physical examination elements, the most predictive of which is the HIT. HINTS "plus" adds the presence of new hearing loss by bedside finger rub as a predictor of a stroke syndrome.
†These values represent the reduction in missed stroke or central causes relative to ABCD2 that would be projected if HIT, HINTS, or HINTS "plus" were used to determine the diagnosis instead of ABCD2.
‡The LR+ for HIT alone was calculated using a specificity of 99.0% and listed as ">" since the LR+ associated with 100% specificity (measured in this sample) is infinite.

The HINTS rule and its variations outperform ABCD2 on both sensitivity and specificity, regardless of the endpoint considered—stroke, any central cause, or diagnostic final MRI scan. ABCD2 was not intended to detect nonstroke central lesions but, from an EP perspective, this is a "bug" rather than a "feature." The HINTS rule is based on differentiating central from peripheral causes, not etiology per se, making it well suited to the ED diagnostic environment that values prompt disposition decisions over exact etiologic diagnoses. As expected, HINTS performs best in predicting central causes (as opposed to specifically predicting stroke or gauging the presence of a structural lesion by MRI).

While ABCD2 might be easier to implement in clinical practice than HINTS, doing so in this patient population would not yield high-quality patient care. At acceptable sensitivity levels, ABCD2 would result in enormous overuse of neuroimaging, while at acceptable specificity levels, it would result in unacceptable missed stroke rates. The consequences of implementing ABCD2 $\geq$ 4 to pursue a stroke diagnosis throughout U.S. EDs would be 40,000 to 80,000 missed strokes and 110,000 to 220,000 nondiagnostic MRIs, at a cost of $135 to $270 million annually. HINTS "plus" would yield 98% fewer missed strokes at 87% lower cost (Table 4 and Data Supplement S1, available as supporting information in the online version of this paper).

Although most ED clinicians do not formally use ABCD2 to identify stroke in dizziness or vertigo, many do use risk factor–based clinical reasoning to assess the

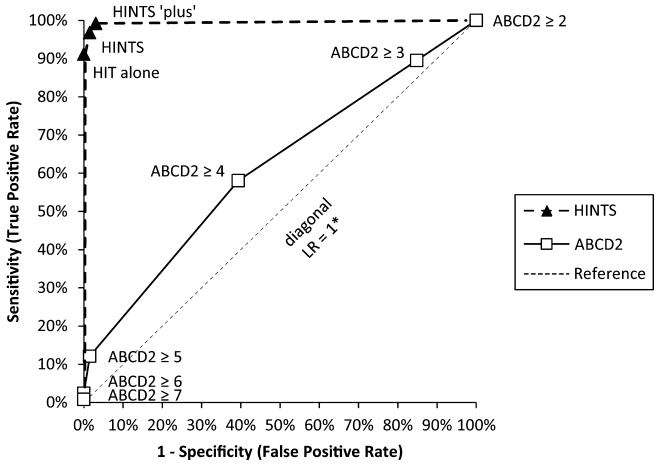

Figure 2. ROC analysis for central causes of AVS: HINTS versus ABCD2. *The reference diagonal line indicates a hypothetical useless diagnostic test with a LR of 1 at all threshold cutoffs. Such a test provides no additional information about the underlying diagnosis. A perfect test or decision rule has threshold cutoffs in the upper left corner (100% sensitivity, 100% specificity). ABCD2 = age, blood pressure, clinical features, duration of symptoms, diabetes; AVS = acute vestibular syndrome; HINTS = head impulse, nystagmus type, test of skew; HINTS "plus" = HINTS plus new hearing loss detected by finger rubbing; HIT = head impulse test; LR = likelihood ratio; ROC = receiver operating characteristic.

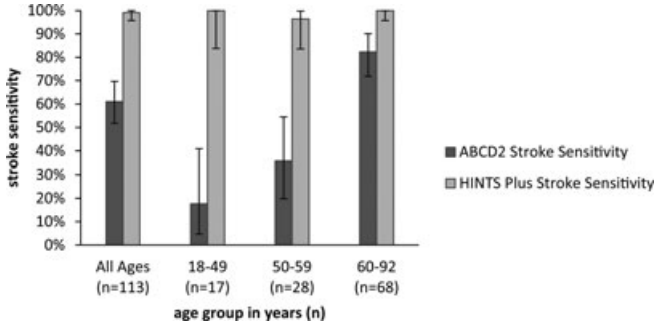

Figure 3. Stroke sensitivity of ABCD2 versus HINTS "plus" in AVS by age group. Includes ischemic strokes (n = 105) and hemorrhages (n = 8). Stroke diagnoses were based on MRI-DWI showing acute stroke in 97.4% and CT showing a clear infarction or hemorrhage in the remaining patients (n = 4, one of whom died and three of whom required surgical decompression). Error bars represent 95% CIs around the proportions; all differences are statistically significant. AVS = acute vestibular syndrome; ABCD2 = age, blood pressure, clinical features, duration of symptoms, diabetes; HINTS = head impulse, nystagmus type, test of skew; HINTS "plus" = HINTS plus new hearing loss detected by finger rubbing.

likelihood of stroke or need for neuroimaging in these patients.[38] This accords with recent studies suggesting that, although (or because) stroke prevalence rises with age, younger age is a risk factor for missed posterior circulation strokes presenting with dizziness.[9,10,39] In current clinical practice, it is possible that up to 35% of strokes may be missed in ED patients presenting with acute dizziness or vertigo.[2] This estimate is close to the 39% of strokes that would have been missed using a

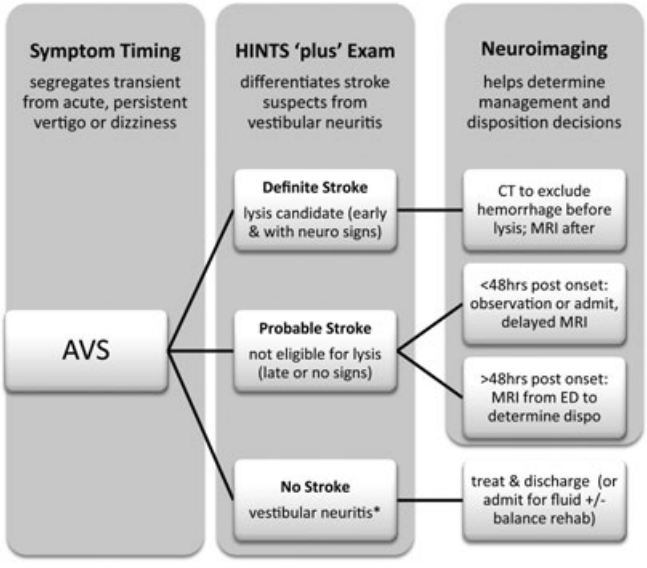

Figure 4. Possible diagnostic strategy in AVS based on HINTS results. *An adaptation of a recently published[18] mnemonic for diagnosing neuritis in AVS using HINTS "plus" and a normal otologic and limited neurologic examination is 'S.E.N.D. H.I.M. O.N. H.O.M.E. S.A.F.E.' (Straight Eyes [no skew]; No Deafness [no new hearing loss]; Head Impulse Misses [unilaterally abnormal]; One-way Nystagmus [predominantly horizontal, direction-fixed in all gaze positions]; Healthy Otic and Mastoid Exam [pearly tympanic membranes; no pimples, pus, perforation, or pain on palpation of mastoid]; Stands Alone [able to stand without holding on to another person or object]; Face Even [no facial palsy or weakness]). AVS = acute vestibular syndrome; HINTS = head impulse, nystagmus type, test of skew; HINTS "plus" = HINTS plus new hearing loss.

formal ABCD2 ≥ 4 approach for our patients (sensitivity for stroke 61% in our AVS population). As with actual clinical practice, the sensitivity of ABCD2 for stroke in our population was lower in younger patients and, had it been used to determine the need for imaging, would have missed 71% of the strokes in AVS patients younger than 60 years (40% of all strokes in our series). A shift to HINTS-based physiologic reasoning might substantially improve current practice. The HINTS approach is grounded in well-established anatomic and physiologic neuroscience. Head impulses assess the integrity of primary vestibular pathways from the labyrinth to the lateral pons.[40] Tests for gaze-evoked nystagmus assess gaze-holding circuits in the brainstem and cerebellum.[41] Tests for vertical ocular alignment primarily assess central otolithic pathways in the brainstem.[42] Not surprisingly, the HINTS rule performs as expected when tested empirically. It is nearly perfect with the more common strokes affecting the lateral medulla or inferior cerebellum (posterior inferior cerebellar artery territory) that do not directly affect the labyrinth or eighth cranial nerve inputs.[8] With rare inner ear strokes (anterior inferior cerebellar artery territory), which are peripherally located but of cerebrovascular cause, HINTS eye movements are indistinguishable from vestibular neuritis.[8] In these latter cases, comorbid sudden hearing loss (HINTS "plus") may be the only clue to

stroke.[8] This last point runs counter to traditional teaching, which generally ascribes combined audiovestibular symptoms to benign peripheral causes.[38] While not yet extensively studied,[43] there is mounting evidence that new hearing loss in patients with AVS favors a stroke syndrome.[8,19,44]

HINTS outperforms initial MRI-DWI for ischemic stroke detection when patients are assessed in the first 48 hours. One in seven ischemic strokes had initially false-negative MRI-DWI scans. This presumably occurs because the structural anatomic changes from brain ischemia generally lag physiologic dysfunction that is already present when symptoms begin. Several patients with false-negative imaging deteriorated clinically, indicating that these were not merely small, benign stroke syndromes requiring no treatment or admission. Prior literature indicates a nearly 20% false-negative rate in the first 24 hours after posterior fossa infarction.[45,46] A high rate of initially false-negative MRIs in the first 48 hours complicates decisions about when to consider neuroimaging in AVS (Figure 4), but there is little doubt that early negative MRIs in AVS patients cannot be considered definitive diagnostically ($LR- = 0.21$[8]). For an older AVS patient with vascular risk factors and an estimated 50% expected probability of stroke before further assessment, a negative MRI-DWI within the first 24 hours would lower the probability of stroke to 17%. By comparison, an abnormal head impulse test would lower the probability of stroke or other central cause to 8%, a benign HINTS result would lower the probability to 3%, and a benign HINTS "plus" (i.e., no hearing loss) result would lower the probability to 1%.

Our recent systematic review found use of the HINTS approach by adequately trained providers to be supported by a "strong" GRADE[47] of evidence, based on a large effect size for diagnosis and homogeneous results across studies from multiple research groups.[8] Some EPs already teach the head impulse test and HINTS, discussing best practices and technique via the Internet.[48–51] A partial task trainer to simulate the head impulse test[52] has been used to help train emergency medicine residents.[53] Most importantly, a commercially available device that can measure these eye movements holds promise as a future stroke diagnostic tool.[27] The device, which is generally operated by nonphysician technicians, is currently used in Europe and is and now available in the United States following recent Food and Drug Administration approval. Using such a device to diagnose stroke in AVS is conceptually similar to diagnosing ST-elevation myocardial infarction by electrocardiography in patients with high-risk chest pain.[27]

Effective education programs or greater availability of quantitative recording devices may be needed before this approach can be widely disseminated, because not all EPs are comfortable with bedside eye movement assessments,[54–56] and the HINTS rule has so far been studied only in the hands of specialists. Device-based quantification could facilitate dissemination by providing immediate feedback confirming accuracy of ED provider clinical interpretation and offering a record that could be reviewed for quality assurance.[27] It could also be coupled to a decision support engine that offers a stroke risk stratification score. Education will probably also be needed to ensure appropriate case selection (i.e., AVS), given that normal physiologic responses are a "bad" sign suggesting stroke, and indiscriminate use in patients with transient or purely positional dizziness would result in substantial overuse of MRI neuroimaging.

Future studies should seek to assess HINTS performance when applied by EPs, establish the added diagnostic value and cost-effectiveness of HINTS over current practice, and determine the most effective methods for education, implementation, and dissemination.

LIMITATIONS

Limitations of our observational methods have been described previously.[26] Some patients were enrolled and examined after admission from the ED, so clinical findings might have evolved, although the accuracy of HINTS appeared to be uniformly high despite intersubject variability in time to examination. Masking of examiners to stroke status was likely imperfect (e.g., if hemiparesis was present or results of imaging were inadvertently disclosed); although we did not explicitly monitor the effectiveness of our masking procedures, the eye examinations were always performed prior to detailed neurologic examinations and typically prior to imaging. Follow-up MRI scans in those with initial negative scans were obtained only if clinical findings did not match a peripheral vestibular pattern; this could have led to some misclassification among "peripheral" patients, although those with vestibular neuritis diagnoses developed no neurological deficits or strokes in the 3-month or longer follow-up period.

The highly selected population, with at least one stroke risk factor, limits generalizability. The recruited, high-risk population was skewed toward a greater fraction with stroke, so high stroke prevalence could have influenced our estimates of test characteristics, particularly specificity.[36] This population is not representative of non-AVS dizziness, to whom HINTS does not apply. Although it was recently repurposed to these ends,[21] the ABCD2 score was not originally designed to diagnose stroke, nor to focus on posterior circulation events.

The chart abstractor (JCK) was not masked to HINTS results or outcome status, although first measured blood pressure and diabetes status are not particularly subjective endpoints. Recruiting patients with at least one stroke risk factor may have reduced the resolving power of ABCD2 relative to a completely unselected population of patients with AVS. Excluding presentations compatible with Menière's disease or other benign vestibular causes may have artificially inflated the specificity of the HINTS approach. Using the HINTS approach requires correct identification of AVS patients, and not all clinicians are familiar with this clinical syndrome; incorrectly relying on HINTS in non-AVS patients will lower the specificity of the approach, resulting in overuse of MRI neuroimaging. Use of HINTS has not been studied with EPs, and it remains unknown whether nonspecialist clinicians can accurately identify the relevant eye movement findings. There are no data on interrater reliability of HINTS between specialists and EPs, but novice and experienced specialists interpret head impulse test results

similarly most of the time.[57] National extrapolations are rough approximations based on best, but limited, available evidence. We did not conduct a formal cost-utility analysis using current data, although our prior analysis suggested implementing the HINTS approach would save lives and prove highly cost-effective.[37]

CONCLUSIONS

The HINTS rule substantially outperforms ABCD2 for efficiently detecting stroke and other central causes in acute vestibular syndrome. The HINTS approach is more sensitive for stroke than magnetic resonance imaging–diffusion-weighted imaging in the first 48 hours after symptom onset. Use of HINTS in this patient population should be strongly considered when adequate expertise or technology is available, although caution should be exercised when examiners lack relevant training in eye examination skills. For acute vestibular syndrome patients with negative early magnetic resonance imaging but HINTS signs suggestive of stroke, close follow-up (or admission) and repeat, delayed magnetic resonance imaging 3 to 7 days after symptom onset are probably warranted.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Projected national cost analysis.