Approximately 1% to 2% of patients with chronic hypertension at some point develop hypertensive emergency, where blood pressure rises substantially and causes end-organ dysfunction. In ≤16% of these hypertensive emergencies, end-organ dysfunction involves the brain and is termed hypertensive encephalopathy (HE). Current teaching describes HE as a rapidly evolving syndrome of severe hypertension (or sharp relative rise in blood pressure) associated with seizures, focal neurological signs, or symptoms of cerebral edema such as headache, nausea, or depressed consciousness. The mechanisms by which blood pressure elevations result in encephalopathy are uncertain but are postulated to involve arteriolar dilatation beyond autoregulatory capacity, which subsequently disrupts the blood–brain barrier and leads to extravasation of plasma. Because they share similar pathophysiology, HE often manifests as reversible posterior leukoencephalopathy syndrome (RPLS), accounting for 61% of RPLS cases.

Although chronic hypertension is a well-established risk factor for stroke, HE may represent a separate entity that further increases stroke risk. There is a paucity of the literature evaluating the subsequent risk of cerebrovascular events after a diagnosis of RPLS or HE. However, eclampsia, a disease with similar pathophysiology as HE, is associated with increased long-term stroke risk, which raises the question whether episodes of HE may also serve as additive risk factors for stroke. Therefore, we performed a retrospective cohort study to determine the association between a diagnosis of HE and the risk of subsequent stroke.

Materials and Methods

We retrospectively evaluated the risk of stroke after a discharge diagnosis of HE using administrative data from 3 states: the California Office of Statewide Health Planning and Development, the New York State Department of Health, and the Florida Agency for Health Care Planning and Development. We identified all patients discharged from California, New York, and Florida emergency departments and acute care hospitals between 2005 and 2012 with a primary International Classification of Diseases, Ninth Edition, Clinical Modification discharge diagnosis of HE (437.2). Patients discharged with a primary diagnosis of seizure (345.x) served as negative controls, whereas patients with a primary diagnosis of transient ischemic attack (435.x) were positive controls. Our primary outcome was the composite of subsequent ischemic stroke or intracerebral hemorrhage. Kaplan–Meier survival statistics were used to calculate cumulative outcome rates, and Cox proportional hazard analysis was used to examine the association between index disease types and outcomes while adjusting for vascular risk factors.

Results—We identified 8233 patients with HE, 191,091 with seizure, and 308,680 with transient ischemic attack. The 1-year cumulative rate of ischemic stroke or intracerebral hemorrhage after HE was 4.90% (95% confidence interval [CI], 4.45–5.40) when compared with 0.92% (95% CI, 0.88–0.97) after seizure and 4.49% (95% CI, 4.42–4.57) after transient ischemic attack. The risk of intracerebral hemorrhage was significantly elevated in those with HE (hazard ratio, 2.0; 95% CI, 1.7–2.5) but not in those with transient ischemic attack (hazard ratio, 1.0; 95% CI, 0.9–1.1), when compared with seizure patients.

Conclusions—Patients discharged with a diagnosis of HE face a high risk of future cerebrovascular events, particularly intracerebral hemorrhage.
Administration. These organizations collect standardized discharge data from all nonfederal emergency department (ED) visits and hospitalizations within the state, and report these data in a deidentified format to the Agency for Healthcare Research and Quality for its Healthcare Cost and Utilization Project.24 Patients are assigned a deidentified personal linkage number that allows them to be followed across ED encounters and hospitalizations over multiple years.11 Up to 25 discharge diagnoses are coded at each encounter using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) system. The Institutional Review Board at Weill Cornell Medical College approved this study.

Validation of the HE Diagnosis Code

To our knowledge, the ICD-9-CM code for HE (437.2) has never been validated in the literature. Therefore, we performed a retrospective chart review at our hospital to determine the test properties of the diagnosis code. We identified all admissions to our institution with HE as the primary discharge diagnosis code from 2009 to 2013 (n=22). In addition, we identified 22 discharges with other primary cerebrovascular diagnosis codes (eg, transient ischemic attack [TIA] or ischemic stroke) and no HE code. A board-certified neurologist (M.P.L.) reviewed all available medical records from these 44 encounters and adjudicated a final diagnosis while remaining blinded to the diagnosis code. HE was diagnosed whether systolic blood pressure was ≥180 mm Hg or diastolic blood pressure was ≥120 mm Hg and there were (1) seizures, visual changes, confusion, altered consciousness, or focal neurological deficits that resolved with blood pressure control or (2) brain imaging demonstrating cerebral edema without accompanying hemorrhage or ischemia (any acute infarction on brain imaging resulted in a different cerebrovascular diagnosis such as intracerebral hemorrhage [ICH] or ischemic stroke). We specifically excluded patients with headache as the sole complaint, as there would be no objective clinical findings in these cases, and this would narrow the spectrum of patient presentations in our diagnosis of HE. Using this diagnostic schema as the gold standard, we calculated the sensitivity and specificity of the ICD-9-CM code 437.2 for the diagnosis of HE. Validation of the ICD-9-CM code for HE (437.2) at our institution showed that the code has 93% sensitivity and 71% specificity.

Patients

Using ICD-9-CM code 437.2 in the primary discharge diagnosis position, we identified consecutive patients 18 years or older with the diagnosis of HE between 2005 and 2011 in California, 2006 and 2011 in New York, and 2005 and 2012 in Florida. These observation periods were chosen to have at least 1 year of follow-up data for all study patients. Patients coded as having HE on multiple encounters were identified at the time of their first-ever recorded ED visit or hospital admission with HE. To minimize ascertainment bias, we excluded patients with documented cerebrovascular disease (ICD-9-CM codes 430–438 in any discharge diagnosis position) before, or during, the index hospitalization for HE. We excluded nonresidents of California, New York, or Florida to maximize patient follow-up.

As control groups, we identified all patients discharged from nonfederal California, New York, or Florida EDs or hospitals between 2005 and 2012 with a primary discharge diagnosis of seizure or TIA. We selected seizure (345.x) as a negative control because it is a paroxysmal neurological event that does not considerably increase stroke risk.25 This code has up to a 99% positive predictive value, a 97% negative predictive value, and sensitivities between 70% and 99%.19,20 Conversely, we selected TIA (435.x) as a positive control because it is a well-established risk factor for subsequent stroke.15,21

Measurements

Patients with HE were followed up for at least 1 year from their index visit for a primary composite outcome of ischemic stroke or ICH. Ischemic stroke was defined as a hospitalization with ICD-9-CM codes 433.x1, 434.x1, or 436 in any discharge diagnosis position without a primary discharge code for rehabilitation (V57) or an accompanying diagnosis of trauma (ICD-9-CM 800–804 or 850–854) or ICH (ICD-9-CM 431) or subarachnoid hemorrhage (ICD-9-CM 430) in any diagnostic position.23 ICH was defined using ICD-9-CM code 431 in any discharge position without concomitant codes for rehabilitation (V57) in the primary diagnosis position or trauma (ICD-9-CM 800–804 or 850–854) in any position. These administrative codes for ischemic and hemorrhagic stroke have been previously validated as having a sensitivity and specificity of ≥85%.22 Patients entered observation immediately after discharge from the index encounter with HE diagnosis and were followed up until death, the occurrence of the primary outcome, or the end of follow-up. In secondary analyses, ischemic and hemorrhagic strokes were considered separately.

To account for potential confounding from demographic characteristics and vascular risk factors, we collected data on the following patient variables: age, sex, race, insurance status; and diagnoses of hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, congestive heart failure, peripheral vascular disease, chronic kidney disease, and chronic obstructive pulmonary disease.

Statistical Analysis

Descriptive statistics were used to calculate crude rates and Kaplan–Meier survival statistics were used to evaluate cumulative rates. Patients entered observation at the first visit that resulted in a discharge diagnosis of HE, seizure, TIA, or hypertension and were censored at the time of in-hospital death or last available follow-up data. Multivariable Cox proportional hazard analysis was used to examine the association between index disease type and subsequent stroke while accounting for the potential confounders listed above, using seizure as the reference in our model. We performed sensitivity analyses using inverse probability weighting to account for imbalances in sample size between diagnosis groups. As our goal was to isolate the relationship between our exposures and outcome, all covariates were left in place regardless of statistical significance. Significance was 2 sided and defined using an α of 0.05. All analyses were performed using STATA version 13 (StataCorp, College Station, TX).

Results

We identified 8233 patients with a diagnosis of HE, 19109 patients with seizure, and 308680 patients with TIA. When compared with the other diagnostic cohorts, those with HE were more likely to be women, black, and have more vascular risk factors (Table 1). Within the HE cohort, patients were mostly white women with a high proportion of traditional vascular risk factors. Most patients (89.7%) diagnosed with HE were hospitalized from the ED.

There were 27642 strokes over the course of follow-up, of which 24780 (89.6%) were ischemic and 2862 (10.4%) were hemorrhagic (Table 2). The 1-year cumulative rate of our combined primary end point of ischemic stroke or ICH was 4.90% (95% confidence interval [CI], 4.45–5.40) after a diagnosis of HE when compared with 4.49% (95% CI, 4.42–4.57) after TIA and 0.92% (95% CI, 0.88–0.97) after seizure. Similar findings were observed when considering only ischemic strokes: the 1-year cumulative rate of ischemic stroke was 4.12% (95% CI, 3.70–4.59), 4.15% (95% CI, 4.08–4.22), and 0.75% (95% CI, 0.71–0.79) for HE, TIA, and seizure diagnoses, respectively. In contrast, first-year rates of ICH were substantially higher in patients diagnosed with HE (0.81%; 95% CI, 0.63–1.04) than in patients with TIA (0.36%; 95% CI, 0.34–0.38) and seizure patients (0.18%; 95% CI, 0.16–0.20).

After adjusting for patient demographics and vascular risk factors, ischemic stroke risk was elevated in patients with diagnoses of HE (hazard ratio, 1.9; 95% CI, 1.7–2.0) and TIA (hazard ratio, 2.2; 95% CI, 2.1–2.3) when compared with those with seizures. ICH risk was significantly increased in...
patients with HE (hazard ratio, 2.0; 95% CI, 1.7–2.5) but not in those with TIA (hazard ratio, 1.0; 95% CI, 0.9–1.1). Our findings were unchanged in sensitivity analyses weighted to account for imbalances in sample size between groups.

### Discussion
Using administrative claims data from a large, multistate cohort, we found that patients diagnosed with HE are at high risk for stroke over the ensuing year. Specifically, patients diagnosed with HE have comparable annual rates of ischemic stroke and significantly higher rates of ICH than patients diagnosed with TIA. Few data exist on the risk of stroke after a HE diagnosis, as most reports focused on the increased risk of stroke at presentation with HE. We found that stroke risk remains increased long after the resolution of an episode of HE. This evidence suggests that patients with uncontrolled hypertension, particularly when their disease results in neurological manifestations, may need improved long-term observation and blood pressure management.

Our study has several notable limitations. First, by relying on administrative claims and diagnosis codes, we have no means to confirm the assigned diagnoses through review of imaging studies, and some of these cases of HE may have represented diagnoses of stroke. Because the rate of misdiagnosis is bidirectional (ie, strokes are misclassified as HE, and HE is misclassified as stroke), such misclassification would have

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HE (n=8233)</th>
<th>TIA (n=308 680)</th>
<th>Seizure (n=191 091)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>3026 (36.8)</td>
<td>130 527 (42.3)</td>
<td>99 011 (51.8)</td>
</tr>
<tr>
<td>Race†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3998 (49.8)</td>
<td>211 758 (70.3)</td>
<td>107 376 (57.7)</td>
</tr>
<tr>
<td>Black</td>
<td>2312 (28.8)</td>
<td>34 110 (11.3)</td>
<td>37 046 (19.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1092 (13.6)</td>
<td>39 144 (13)</td>
<td>30 386 (16.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>361 (4.5)</td>
<td>8252 (2.7)</td>
<td>3580 (1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>269 (3.4)</td>
<td>7804 (2.6)</td>
<td>7787 (4.2)</td>
</tr>
<tr>
<td>Payment source†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>4584 (55.7)</td>
<td>198 760 (64.4)</td>
<td>56 249 (29.5)</td>
</tr>
<tr>
<td>Medicaid</td>
<td>985 (12)</td>
<td>17 827 (5.8)</td>
<td>42 427 (22.2)</td>
</tr>
<tr>
<td>Private</td>
<td>1729 (21)</td>
<td>71 814 (23.3)</td>
<td>50 274 (26.3)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>635 (7.7)</td>
<td>11 577 (3.8)</td>
<td>30 425 (15.9)</td>
</tr>
<tr>
<td>Other</td>
<td>300 (3.6)</td>
<td>8631 (2.8)</td>
<td>11 637 (6.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8233 (100)</td>
<td>206 207 (66.8)</td>
<td>44 719 (23.4)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2822 (34.3)</td>
<td>78 515 (25.4)</td>
<td>20 124 (10.5)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1740 (21.3)</td>
<td>68 262 (22.1)</td>
<td>10 624 (5.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>899 (10.9)</td>
<td>19 686 (6.4)</td>
<td>42 44 (2.2)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>527 (6.4)</td>
<td>13 690 (4.4)</td>
<td>18 75 (1.0)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>657 (8.0)</td>
<td>24 138 (7.8)</td>
<td>68 39 (3.6)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1979 (24)</td>
<td>17 776 (5.8)</td>
<td>54 37 (2.9)</td>
</tr>
</tbody>
</table>

HE indicates hypertensive encephalopathy; and TIA, transient ischemic attack.

*Data are presented as number (%) unless otherwise specified.
†Percentages reflect all patients for whom racial and insurance data were available.

### Table 2. First-Year Stroke Risk in Patients Diagnosed With HE, TIA, and Seizure, Stratified by Stroke Subtype

<table>
<thead>
<tr>
<th>Outcome by Stroke Subtype</th>
<th>HE (n=8233)</th>
<th>TIA (n=308 680)</th>
<th>Seizure (n=191 091)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative stroke rate*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>4.12% (3.70–4.59)</td>
<td>4.15% (4.08–4.22)</td>
<td>0.75% (0.71–0.79)</td>
</tr>
<tr>
<td>ICH</td>
<td>0.81% (0.63–1.04)</td>
<td>0.36% (0.34–0.38)</td>
<td>0.18% (0.16–0.20)</td>
</tr>
<tr>
<td>Combined stroke†</td>
<td>4.9% (4.45–5.40)</td>
<td>4.49% (4.42–4.57)</td>
<td>0.92% (0.88–0.97)</td>
</tr>
<tr>
<td>Hazard ratio*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>1.9 (1.7–2.0)</td>
<td>2.2 (2.1–2.3)</td>
<td>Ref</td>
</tr>
<tr>
<td>ICH</td>
<td>2 (1.7–2.5)</td>
<td>1 (0.9–1.1)</td>
<td>Ref</td>
</tr>
<tr>
<td>Combined stroke*</td>
<td>1.9 (1.7–2.0)</td>
<td>2 (1.9–2.1)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

HE indicates hypertensive encephalopathy; ICH, intracerebral hemorrhage; Ref, reference; and TIA, transient ischemic attack.

*Data are presented as outcome measure followed by 95% confidence intervals in parentheses.
†Primary outcome of combined ischemic and hemorrhagic events.
unknown effects on our findings. However, the rate of misdiagnosis of hypertensive emergency for ischemic stroke has been notably small (8%) in a previous report. Furthermore, review of medical records indicated that the diagnosis code for HE faithfully captures the clinical diagnosis at the time of care. This suggests that regardless of any misclassification in regards to the true diagnosis, the current clinical label of HE represents a vulnerable population of adults who face a high risk of subsequent cerebrovascular events. However, we lacked data on the specialty of the providers who cared for these patients and, therefore, could not account for potential differences in diagnosis depending on the physician’s specialty. Second, we were unable to differentiate between patients who did or did not have signs of visible cerebral edema on magnetic resonance imaging studies, as we did not have access to these imaging records and there is no specific ICD-9-CM code for RPLS (ie, those patients who would have positive imaging for cerebral edema). This distinction may be clinically significant as patients with RPLS often present with ICH and, therefore, may have higher rates of recurrent hemorrhage. Additional studies using the ICD-10-CM classification system, which does have a diagnosis code for RPLS, may be helpful to further differentiate HE and RPLS, which are likely 2 disease entities with overlapping features on the same spectrum.

Conclusions

We found that patients discharged from acute care hospitals with the diagnosis of HE face an increased risk of stroke, particularly ICH, long after their index event has resolved. These findings suggest that patients with HE may benefit from improved risk factor modification and closer follow-up.

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Disclosures

None.

References

Risk of Stroke After the *International Classification of Diseases*-Ninth Revision Discharge Code Diagnosis of Hypertensive Encephalopathy
Michael P. Lerario, Alexander E. Merkler, Gino Gialdini, Neal S. Parikh, Babak B. Navi and Hooman Kamel

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