



# HHS Public Access

Author manuscript

*Stroke*. Author manuscript; available in PMC 2018 June 29.

Published in final edited form as:

*Stroke*. 2017 July ; 48(7): 1802–1809. doi:10.1161/STROKEAHA.117.017327.

## Acute Ischemic Stroke After Moderate to Severe Traumatic Brain Injury:

### Incidence and Impact on Outcome

Robert G. Kowalski, MBBCh, MS, Juliet K. Haarbauer-Krupa, PhD, Jeneita M. Bell, MD, MPH, John D. Corrigan, PhD, Flora M. Hammond, MD, Michel T. Torbey, MD, MPH, Melissa C. Hofmann, PhD, Kristen Dams-O'Connor, PhD, A. Cate Miller, PhD, and Gale G. Whiteneck, PhD

Research Department, Craig Hospital, Englewood, CO (R.G.K., M.C.H., G.G.W.); Division of Unintentional Injury Prevention, Centers for Disease Control and Prevention, Atlanta, GA (J.K.H.-K., J.M.B.); Department of Physical Medicine and Rehabilitation (J.D.C.), and Departments of Neuroscience, Neurology and Neurological Surgery, Division of Cerebrovascular Disease and Neurocritical Care (M.T.T.), Ohio State University Wexner Medical Center, Columbus; Department of Physical Medicine and Rehabilitation, Indiana University School of Medicine, Indianapolis (F.M.H.); Department of Rehabilitation Medicine, Icahn School of Medicine at Mount Sinai, New York, NY (K.D.-O.); and National Institute on Disability, Independent Living, and Rehabilitation Research, Administration for Community Living, U.S. Department of Health and Human Services (A.C.M.)

### Abstract

**Background and Purpose**—Traumatic brain injury (TBI) leads to nearly 300 000 annual US hospitalizations and increased lifetime risk of acute ischemic stroke (AIS). Occurrence of AIS immediately after TBI has not been well characterized. We evaluated AIS acutely after TBI and its impact on outcome.

**Methods**—A prospective database of moderate to severe TBI survivors, admitted to inpatient rehabilitation at 22 Traumatic Brain Injury Model Systems centers and their referring acute-care hospitals, was analyzed. Outcome measures were AIS incidence, duration of posttraumatic amnesia, Functional Independence Measure, and Disability Rating Scale, at rehabilitation discharge.

**Results**—Between October 1, 2007, and March 31, 2015, 6488 patients with TBI were enrolled in the Traumatic Brain Injury Model Systems National Database. One hundred and fifty-nine (2.5%) patients had a concurrent AIS, and among these, median age was 40 years. AIS was associated with intracranial mass effect and carotid or vertebral artery dissection. High-velocity events more commonly caused TBI with dissection. AIS predicted poorer outcome by all

---

Correspondence to Robert G. Kowalski, MBBCh, MS, Craig Hospital, 3425 S Clarkson St, Englewood, CO 80113. rkowalski@craighospital.org.

The online-only Data Supplement is available with this article at <http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.017327/-/DC1>.

**Disclosures**  
None.

measures, accounting for a 13.3-point reduction in Functional Independence Measure total score (95% confidence interval,  $-16.8$  to  $-9.7$ ;  $P<0.001$ ), a 1.9-point increase in Disability Rating Scale (95% confidence interval,  $1.3$ – $2.5$ ;  $P<0.001$ ), and an 18.3-day increase in posttraumatic amnesia duration (95% confidence interval,  $13.1$ – $23.4$ ;  $P<0.001$ ).

**Conclusions**—Ischemic stroke is observed acutely in 2.5% of moderate to severe TBI survivors and predicts worse functional and cognitive outcome. Half of TBI patients with AIS were aged 40 years, and AIS patients more often had cervical dissection. Vigilance for AIS is warranted acutely after TBI, particularly after high-velocity events.

## Keywords

acute ischemic stroke; cognition; outcome; stroke; traumatic brain injury

Traumatic brain injury (TBI) is a major public health concern, leading to an estimated 2.2 million emergency department visits and 300 000 hospitalizations in the United States each year.<sup>1–4</sup> A heterogeneous injury classification, TBI may include multiple mechanisms of brain insult occurring in isolation, in tandem, or sequentially. These include intra-parenchymal, subarachnoid, and intraventricular hemorrhage; contusion; mass effect; diffuse axonal injury, seizures; and disruption of cerebral blood vessel structural integrity.<sup>5</sup> In the rapidly moving environment of acute trauma care, some sequelae of TBI may be occult initially, with signs and symptoms that are subtle or masked by other co-occurring physiological derangements. In this context, specific TBIs that disrupt or lead to occlusion of normal cerebrovascular circulation can produce ischemia in affected cerebral territories. If not treated, this may result in irreversible acute ischemic stroke (AIS).

Ischemic stroke is a leading neurological emergency and a major cause of death and disability, affecting  $\approx 700$  000 individuals each year in the United States<sup>6</sup> Prompt recognition of AIS is critical for recovery, with a narrow window for therapeutic interventions associated with improved outcomes. The principal emergent treatment available for the past 2 decades, thrombolytic therapy with recombinant tissue-type plasminogen activator, must be administered within 3 to 4.5 hours after AIS symptom onset for optimal efficacy.<sup>7,8</sup> Based on limited available clinical trial evidence, recombinant tissue-type plasminogen activator currently is contraindicated for ischemic stroke after recent, serious head trauma in US stroke guidelines because of potential increased bleeding risk. However, the guidelines provide that physicians with expertise in stroke care may modify the recommendations.<sup>9,10</sup> In 2015, several major randomized clinical trials reported results that demonstrated endovascular thrombectomy is associated with improved functional outcome after AIS, suggesting the possibility of an important new tool for AIS treatment.<sup>11–13</sup> The therapeutic window for these intra-arterial procedures also is limited—to 4.5 to 8 hours after stroke symptom onset. Since the approval of tissue-type plasminogen activator as an AIS treatment in 1996,<sup>14</sup> there have been increasing numbers of designated stroke centers established at larger medical centers. The association between TBI and ischemic stroke, thus, far has received relatively scant research attention, despite what is known about the pathophysiology of brain trauma in precipitating cerebral ischemia. The role of TBI as a risk factor for longer-term ischemic and hemorrhagic stroke onset has been investigated, with increased risk reported in a limited number of recent studies.<sup>15,16</sup> To date, however, there has

been little clinical or research focus on AIS occurring during the hours and days immediately after TBI.

In light of the paucity of clinical evidence on AIS in TBI and the importance of early recognition and treatment, we sought to assess the frequency of AIS acutely after TBI in a large, multi-year, multicenter cohort of TBI patients. Data from 22 acute inpatient brain injury rehabilitation centers and their referring acute-care hospitals in the Traumatic Brain Injury Model Systems (TBIMS) National Database (NDB) were analyzed. Our objective for this study was to characterize the incidence of AIS after moderate to severe TBI among a population that subsequently received inpatient rehabilitation and evaluate its role in short-term outcome.

## Methods

This study was a retrospective analysis of a prospective cohort of patients with acute, moderate to severe TBI enrolled in the TBIMS NDB. The sample included subjects discharged from acute hospitalization between October 1, 2007, and March 31, 2015, a period during which an extended range of concurrent medical conditions were recorded for each patient in the TBIMS NDB by *International Classification of Diseases*, Ninth Revision, Clinical Modification code. The study was approved by the Institutional Review Board at each participating center.

### Study Data

Neuroanatomic data for study patients in the TBIMS NDB were derived from radiology reports of brain computed tomography obtained clinically during acute care. *International Classification of Diseases*, Ninth Revision, Clinical Modification codes designated for AIS in the study analysis were 433.01 to 433.91 and 434.01 to 434.91 (Table I in the online-only Data Supplement). *International Classification of Diseases*, Ninth Revision, Clinical Modification codes designated for cervical artery dissection were 443.21 and 443.24.

### Outcome Measures

Study outcome measures were Functional Independence Measure Total, Motor and Cognitive scores,<sup>17</sup> Disability Rating Scale<sup>18</sup>, duration of posttraumatic amnesia, and emergence of posttraumatic amnesia by rehabilitation discharge (online-only Data Supplement).

### Statistical Analysis

For the main study analyses, patients were dichotomized into those with AIS versus no AIS. Clinical characteristics and outcome measures were treated as continuous or categorical variables, as appropriate, and were dichotomized or categorized into logical or clinically relevant groupings.

Dichotomous variables were analyzed with the Pearson  $\chi^2$  test or Fisher exact test where appropriate. Continuous variables were analyzed with the independent samples Student *t* test (2-tailed) when normally distributed. For categorical variables and those not normally

distributed, nonparametric tests (Mann–Whitney *U* test and Kruskal–Wallis test) were used. Independent associations with AIS onset, and predictors of outcome, were identified with multivariable linear regression for continuous outcome variables and backward stepwise logistic regression for dichotomous outcome variables. Factors with clinical relevance found to be associated with AIS incidence and outcome in univariate analyses were incorporated in multivariable models. Significance was set at  $P<0.05$ . Data were analyzed with SPSS version 22.0 (IBM, Armonk, NY).

### **AIS Data Sensitivity Analysis**

Validity and reliability of AIS diagnoses were assessed by secondary analyses of TBIMS NDB data (online-only Data Supplement).

## **Results**

During the study period, 6488 patients with moderate to severe TBI were enrolled in the TBIMS NDB. Of these patients, 159 (2.5%) were diagnosed with AIS before acute hospital discharge. Among all study patients, 73% were male; median age was 42 years (range 16–99), and 68% were white. The most common causes of TBI were automobile, truck, and bus crashes (31%) followed by falls (31%), motorcycle crashes (12%), and traumatic pedestrian events (7%). At time of initial presentation after injury, 41% of patients did not follow commands (Glasgow Coma Scale motor score  $<6$ ; Table 1).

### **Patients With Ischemic Stroke Onset**

Among patients with AIS, median age was 40 years (range 16–90 years; Table II in the online-only Data Supplement), 71% were male, 66% were white, and the most common cause of injury was motor vehicle crashes (34%) followed by falls (28%). Median duration of acute hospitalization after TBI, during which time AIS was diagnosed, was 25 days (range 4–125 days).

### **Ischemic Stroke Data Consistency and Sensitivity Analysis**

During the 7.5-year study period, AIS was diagnosed in patients at 20 of the 22 centers. The incidence of AIS at centers ranged between 0% and 5.1%, and the incidence of AIS in each calendar year of the study period ranged from 1.9% to 3.3% (Table III in the online-only Data Supplement).

In the sensitivity analysis, with a secondary review of medical records and radiological findings for a sample of study patients at the center with the greatest number of AIS patients, 19 AIS patients (100%) had confirmed new onset of ischemic stroke after the TBI for which they were enrolled in the NDB. Among these patients, one had a previous ischemic stroke, not related to TBI. Seven (37%) of these patients presented initially to a remote healthcare facility after injury and were subsequently transferred emergently to an urban hospital for acute care, while 12 (63%) patients presented initially to an urban emergency department (Table IV in the online-only Data Supplement).

## Univariate Comparison of TBI Patients by Ischemic Stroke Onset

No significant differences were observed between AIS and non-AIS groups in demographic characteristics, including median age, injury cause, severity of initial presentation by Glasgow Coma Scale Motor score or ischemic stroke risk factors, atrial fibrillation, atrial flutter, or hypertension (Table 1). In terms of acute neuroanatomic characteristics after injury, patients who developed AIS were more likely to have radiological evidence of intracranial mass effect, with compression of basal cisterns or midline shift of cerebral structures (50% AIS versus 38% no AIS; odds ratio [OR], 1.515; 95% confidence interval [CI], 1.024–2.241;  $P=0.036$ ). Forty percent of TBI patients had intracranial pressure monitors placed. Among these, patients with AIS were more likely to have elevated intracranial pressure, although this only trended toward significance (63.5% AIS versus 54% no AIS;  $P=0.106$ ; Table 2).

AIS patients were more likely to have subcortical white matter damage (31% AIS versus 20% no AIS; OR, 1.879; 95% CI, 1.332–2.651;  $P<0.001$ ), including injuries in the basal ganglia, brain stem, corpus callosum, and other white matter tracts. AIS patients also were more likely to have either a carotid artery dissection or vertebral artery dissection (9.4% AIS versus 1.5% no AIS; OR, 7.0; 95% CI, 4.0–12.5;  $P<0.001$ ; Table 2). Events involving higher velocity (motorcycle and other motor vehicle collisions) were more often the cause of injury when cervical dissection resulted (64% in patients with dissection versus 42% in patients with no dissection;  $P<0.001$ ; OR, 2.491; 95% CI, 1.671–3.712).

In univariate analyses, presence of AIS was associated with significantly worse outcome by all measures assessed, including lower Functional Independence Measure scores, poorer Disability Rating Scale scores, and longer duration of posttraumatic amnesia (Table V in the online-only Data Supplement).

## Independent Associations With Ischemic Stroke Onset

In a multivariable analysis controlling for age, sex, injury cause, and atrial arrhythmias and hypertension, independent associations with AIS onset were neuroanatomic aspects of the brain injury, including compression of basal cisterns or midline shift (adjusted OR, 1.589; 95% CI, 1.151–2.195;  $P=0.005$ ), damage to subcortical white matter tracts (adjusted OR, 1.853; 95% CI, 1.313–2.615;  $P<0.001$ ), and the presence of atrial flutter (adjusted OR, 3.560; 95% CI, 1.078–11.750;  $P=0.037$ ; Table 3).

## Multivariable Analysis of Ischemic Stroke and Outcome

In multivariable analyses controlling for age, sex, injury type, and acute postinjury neuroanatomic characteristics, AIS predicted worse outcome by all measures considered. At the time of inpatient rehabilitation discharge, AIS accounted for a 13-point reduction in Functional Independence Measure Total score (95% CI, –16.8 to –9.7;  $P<0.001$ ) and a 1.9-point increase in Disability Rating Scale total score (95% CI, 1.3–2.5;  $P<0.001$ ). AIS accounted for an 18.3-day increase in duration of posttraumatic amnesia (95% CI, 13.1–23.4;  $P<0.001$ ; Table 4).

## Discussion

This study of a large, geographically dispersed, multicenter sample of patients with moderate to severe TBI for a 7.5-year period found onset of AIS in  $\approx 2.5\%$  of the cohort. Median age of those who developed AIS was 40 years. Median age of the overall TBI study sample was 42 years. Stroke was identified during acute treatment after TBI and occurred within a median of 25 days after injury in these patients, with exact onset timing unknown. Factors independently associated with AIS included intracranial mass effect, damage to white matter tracts of the brain, and atrial flutter. Outcome in patients who developed AIS was poorer by all measures assessed when compared with patients who did not experience AIS immediately after TBI.

### Overall Magnitude of Ischemic Stroke in TBI

Although enrollment in the TBIMS NDB includes only people with moderate to severe TBI who received inpatient rehabilitation, the study's findings may help inform preliminary estimates of the overall extent of AIS after TBI. As many as 300 000 individuals are hospitalized in the United States each year with a primary diagnosis of TBI of all severities,<sup>1</sup> and  $\approx 20$  000 receive inpatient rehabilitation for a primary diagnosis of TBI.<sup>19</sup> If a substantial proportion of individuals hospitalized with moderate to severe TBI were also found to have a similar incidence of AIS, this would equate to hundreds or thousands of new ischemic strokes annually in the United States likely attributable to TBI, with a substantially larger number worldwide. Including all hospitalized head-injury patients in this type of extrapolation may overestimate the true incidence of AIS after TBI by incorporating some milder head injuries, although this is not certain. Alternately, underestimation in this extrapolation may occur from failing to include patients who die after TBI and those with TBI who do not receive inpatient rehabilitation, both of which may have AIS episodes. Regardless, the findings from the current study suggest that incidence of ischemic stroke after TBI acutely is an important public health concern.

To our knowledge, no previous recent studies have attempted to quantify the incidence and characterize ischemic stroke that is associated acutely with TBI. Some investigators have explored the role of TBI as a potential risk factor for development of ischemic stroke in longer time frames (months or years) after TBI. For example, a retrospective review of trauma patients in California found a 1.1% incidence of ischemic stroke in TBI patients 14 to 44 months after initial injury.<sup>20</sup> This incidence is comparable to the frequency of ischemic stroke we identified acutely in our TBIMS sample. A separate research group investigated composite incidence of all stroke types (ischemic and hemorrhagic) in adults in Taiwan 3 months, 1 year, and 5 years after TBI and reported stroke incidence of 2.91%, 4.17%, and 8.20%, respectively.<sup>21</sup> Annual incidence of new or recurrent ischemic stroke in the overall US population is 213 per 100 000 individuals (0.2%).<sup>6</sup> The risk is approximately double in current smokers and black or African Americans and elevated with high blood pressure and age  $>55$  years.<sup>6</sup> By contrast, the incidence of ischemic stroke acutely among patients with moderate to severe TBI in this study was the equivalent of 2450 per 100 000 individuals (2.5%).

## Treatment Implications for Early Diagnosis of AIS

Ischemic stroke after TBI can be harmful whether experienced acutely or at a later time. However, ischemic stroke that arises immediately after TBI may warrant particular attention given its robust association with poorer patient outcomes, which may be avoidable with timely intervention. The narrow window of time to treat ischemic stroke and preserve brain function makes better understanding of AIS after TBI critical. As with spontaneous ischemic stroke, AIS after TBI involves disruption or occlusion of normal blood flow to regions of the brain, resulting in ischemia and infarction. Thrombolysis with tissue-type plasminogen activator is contraindicated for severe TBI under 2013 guidelines of the American Heart Association and American Stroke Association.<sup>9</sup> However, those guidelines state that the recommendation is based on sparse clinical evidence and specify that a physician with expertise in treatment of acute stroke may modify the contraindication list. Enactment of acute stroke protocols, with rapid magnetic resonance imaging acquisition and other specialized neuro-imaging, including angiography, to better identify AIS and dissection, may be warranted when clinical manifestations suggest stroke onset acutely after TBI. Similarly, antiplatelet or anticoagulation therapy may be an appropriate consideration if dissection is observed.

In some cases, AIS may have immediately preceded or precipitated TBI in the field, with the exact timing of each condition difficult to ascertain. Implications for treatment of stroke in such scenarios are no less pressing. Accurate diagnosis of TBI and AIS also has implications for prognosis and for care decisions beyond acute treatment, including specific rehabilitation regimen, and secondary prevention, such as lifestyle modification. Furthermore, onset of AIS creates an increased risk for recurrent ischemic stroke, although the frequency of this in TBI has not been well studied. With an average annual rate of future ischemic stroke after incident ischemic stroke or transient ischemic attack of 3% to 4%, evidence-based preventive therapies are recommended for AIS by the American Heart Association and the American Stroke Association.<sup>22</sup> Those preventive measures include smoking cessation, proper nutrition, control of hypertension and hyperlipidemia, and antiplatelet therapy. Secondary prevention could potentially benefit individuals who experience AIS immediately after TBI. Future studies that elucidate the specific mechanisms that may lead to AIS after TBI could help guide secondary prevention efforts in these cases.

## Implications of Patient Age in AIS After TBI

The median age of patients with AIS in this study was 40 years. Thirteen percent of AIS patients were aged 16 to 20 years and one third were <25 years. Patient age may play a role in clinical suspicion and recognition of AIS when it occurs as an acute sequela to TBI. Historically, TBI has been more common in younger individuals, with a median age of onset in the 30s, although the affected population is aging.<sup>23,24</sup> While ischemic stroke historically has affected predominantly older adults, its frequency in a younger population has been increasing.<sup>25-30</sup> This trend is of particular concern because stroke in younger individuals may lead to disability during the most productive years of life. Risk factors for ischemic stroke in young adults include hypertension, smoking, diabetes mellitus, and obesity.<sup>30</sup> Stroke in young adults also has other etiologies that are not fully understood but may differ from those of ischemic stroke in individuals of more advanced age, particularly a greater

association with cervical artery dissection.<sup>31</sup> While our study suggests mass effect and cervical dissection are associated with AIS onset after TBI, future prospective studies may help better characterize specific mechanisms leading to AIS acutely in these types of brain injuries.

## Limitations

The study is based on a database of patients who experienced TBI, received acute hospital care, and subsequently were admitted for care at hospitals providing specialized inpatient rehabilitation for TBI. As such, it may incorporate unintended selection bias from exclusion of TBI patients who did not have access to such rehabilitation geographically, financially, or because of referral patterns. The study includes only survivors of acute hospitalization, thereby, excluding patients who may have had a stroke during that care and died. It is possible that in some cases, ischemic stroke precipitated TBI. Although this is less likely in younger patients, and known risk factors for AIS were assessed, the exact timing of concurrent TBI and AIS relative to each other is not possible to ascertain from our data. The study also was not designed to assess therapeutic intervention for ischemic stroke and cannot evaluate the role that any acute stroke treatment administered may have had for outcome in AIS patients in this TBI sample. The number of patients in the sample with evidence of atrial flutter was small, suggesting caution is warranted in interpreting findings of association between this condition and outcome. The study used a large database, which provided sufficient power to detect AIS prevalence in TBI. However, this analysis was limited in clinical detail regarding the precise mechanisms of injury leading to AIS and resulting deficits. The study was based on medical record coding for billing purposes, which is subject to error. Coding would only be expected to pick up AIS where it was identified and mentioned in the medical record and would not capture undiagnosed instances. For patients with disordered consciousness, AIS may be more likely to go unidentified.

## Conclusions

Ischemic stroke is observed acutely in 2.5% of moderate to severe TBI patients who receive rehabilitation and independently predicts worse functional and cognitive outcome after controlling for age, sex, and injury cause. Half of patients with new-onset AIS after TBI are 40 years. Cervical dissection is observed more frequently in patients who experience AIS after TBI, and higher-velocity events are more commonly the cause of TBI when dissections are observed. These findings may help guide identification and diagnosis of AIS, help initial treatment decisions when AIS is suspected after TBI, and help direct appropriate subsequent rehabilitation and secondary prevention. Vigilance for AIS is warranted when associated signs or symptoms are observed acutely after TBI or polytrauma, particularly in higher-velocity injuries, given the narrow available therapeutic window.

## Acknowledgments

### Sources of Funding

This research was supported by an interagency agreement between the US Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC), and the US Department of Education, National Institute on Disability and Rehabilitation Research (NIDRR) with supplemental funding to the NIDRR-funded



Traumatic Brain Injury Model Systems National Data and Statistical Center (grant no. H133A110006; online-only Data Supplement).

## References

1. Coronado VG, McGuire LC, Sarmiento K, Bell J, Lionbarger MR, Jones CD, et al. Trends in traumatic brain injury in the US and the public health response: 1995–2009. *J Safety Res.* 2012; 43:299–307. DOI: 10.1016/j.jsr.2012.08.011 [PubMed: 23127680]
2. Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. *J Head Trauma Rehabil.* 2010; 25:72–80. DOI: 10.1097/HTR.0b013e3181ccc8b4 [PubMed: 20234226]
3. Centers for Disease Control and Prevention. [Accessed May 12, 2017] TBI: Get the Facts. [http://www.cdc.gov/traumaticbraininjury/get\\_the\\_facts.html](http://www.cdc.gov/traumaticbraininjury/get_the_facts.html)
4. Centers for Disease Control and Prevention. [Accessed May 12, 2017] Traumatic Brain Injury and Concussion. <http://www.cdc.gov/traumaticbraininjury/data/index.html>
5. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth.* 2007; 99:4–9. DOI: 10.1093/bja/aem131 [PubMed: 17573392]
6. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Writing Group Members; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: A report from the American Heart Association. *Circulation.* 2016; 133:e38–360. DOI: 10.1161/CIR.0000000000000350 [PubMed: 26673558]
7. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr. American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke.* 2009; 40:2945–2948. DOI: 10.1161/STROKEAHA.109.192535 [PubMed: 19478221]
8. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008; 359:1317–1329. DOI: 10.1056/NEJMoa0804656 [PubMed: 18815396]
9. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2013; 44:870–947. DOI: 10.1161/STR.0b013e318284056a [PubMed: 23370205]
10. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al. American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke.* 2016; 47:581–641. DOI: 10.1161/STR.0000000000000086 [PubMed: 26696642]
11. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med.* 2015; 372:1009–1018. DOI: 10.1056/NEJMoa1414792 [PubMed: 25671797]
12. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. SWIFT PRIME Investigators. Solitaire™ with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: protocol for a randomized, controlled, multicenter study comparing the Solitaire revascularization device with IV tPA with IV tPA alone in acute ischemic stroke. *Int J Stroke.* 2015; 10:439–448. DOI: 10.1111/ijss.12459 [PubMed: 25777831]
13. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. ESCAPE Trial Investigators. Randomized assessment of rapid endo-vascular treatment of ischemic stroke. *N Engl J Med.* 2015; 372:1019–1030. DOI: 10.1056/NEJMoa1414905 [PubMed: 25671798]
14. Zivin JA. Acute stroke therapy with tissue plasminogen activator (tPA) since it was approved by the U.S. Food and Drug Administration (FDA). *Ann Neurol.* 2009; 66:6–10. DOI: 10.1002/ana.21750 [PubMed: 19681102]

15. Chen GS, Liao KH, Bien MY, Peng GS, Wang JY. Increased Risk of Post-Trauma Stroke after Traumatic Brain Injury-Induced Acute Respiratory Distress Syndrome. *J Neurotrauma*. 2016; 33:1263–1269. DOI: 10.1089/neu.2015.4063 [PubMed: 26426583]
16. Liao CC, Chou YC, Yeh CC, Hu CJ, Chiu WT, Chen TL. Stroke risk and outcomes in patients with traumatic brain injury: 2 nationwide studies. *Mayo Clin Proc*. 2014; 89:163–172. DOI: 10.1016/j.mayocp.2013.09.019 [PubMed: 24485130]
17. Ottenbacher KJ, Hsu Y, Granger CV, Fiedler RC. The reliability of the functional independence measure: a quantitative review. *Arch Phys Med Rehabil*. 1996; 77:1226–1232. [PubMed: 8976303]
18. Gouvier WD, Blanton PD, LaPorte KK, Nepomuceno C. Reliability and validity of the Disability Rating Scale and the Levels of Cognitive Functioning Scale in monitoring recovery from severe head injury. *Arch Phys Med Rehabil*. 1987; 68:94–97. [PubMed: 3813863]
19. Cuthbert JP, Harrison-Felix C, Corrigan JD, Kreider S, Bell JM, Coronado VG, et al. Epidemiology of adults receiving acute inpatient rehabilitation for a primary diagnosis of traumatic brain injury in the United States. *J Head Trauma Rehabil*. 2015; 30:122–135. DOI: 10.1097/HTR.000000000000012 [PubMed: 24495917]
20. Burke JF, Stulc JL, Skolarus LE, Sears ED, Zahuranec DB, Morgenstern LB. Traumatic brain injury may be an independent risk factor for stroke. *Neurology*. 2013; 81:33–39. DOI: 10.1212/WNL.0b013e318297eefc [PubMed: 23803315]
21. Chen YH, Kang JH, Lin HC. Patients with traumatic brain injury: population-based study suggests increased risk of stroke. *Stroke*. 2011; 42:2733–2739. DOI: 10.1161/STROKEAHA.111.620112 [PubMed: 21799162]
22. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014; 45:2160–2236. DOI: 10.1161/STR.0000000000000024 [PubMed: 24788967]
23. Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: A public health perspective. *J Head Trauma Rehabil*. 1999; 14:602–615. [PubMed: 10671706]
24. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*. 2013; 9:231–236. DOI: 10.1038/nrneurol.2013.22 [PubMed: 23443846]
25. Aarnio K, Siegerink B, Pirinen J, Sinisalo J, Lehto M, Haapaniemi E, et al. Cardiovascular events after ischemic stroke in young adults: A prospective follow-up study. *Neurology*. 2016; 86:1872–1879. DOI: 10.1212/WNL.0000000000002689 [PubMed: 27164672]
26. Kwon HS, Kim C, Lee SH, Jung KH, Kim YD, Kwon HM, et al. Protocol of the stroke in Korean young adults study: A multicenter case-control study and prospective cohort study. *J Stroke Cerebrovasc Diseases*. 2016; 25:1503–1508. DOI: 10.1016/j.jstrokecerebrovasdis.2016.02.034 [PubMed: 27038977]
27. Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Hansson PO, Dellborg M. Ischemic stroke in children and young adults with congenital heart disease. *J Am Heart Assoc*. 2016; 5 pii: e003071. doi: 10.1161/JAHA.115.003071
28. Rutten-Jacobs LC, Maaijwee NA, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, van der Vlugt MJ, et al. Long-term risk of recurrent vascular events after young stroke: The FUTURE study. *Ann Neurol*. 2013; 74:592–601. DOI: 10.1002/ana.23953 [PubMed: 23776015]
29. Ramirez L, Kim-Tenser MA, Sanossian N, Cen S, Wen G, He S, et al. Trends in acute ischemic stroke hospitalizations in the United States. *J Am Heart Assoc*. 2016; 5 pii: e003233. doi: 10.1161/JAHA.116.003233
30. Tibaek M, Dehlendorff C, Jorgensen HS, Forchhammer HB, Johnsen SP, Kammergaard LP. Increasing incidence of hospitalization for stroke and transient ischemic attack in young adults: A registry-based study. *J Am Heart Assoc*. 2016; 5 pii: e003158. doi: 10.1161/JAHA.115.003158
31. Smajlovi D. Strokes in young adults: epidemiology and prevention. *Vasc Health Risk Manag*. 2015; 11:157–164. DOI: 10.2147/VHRM.S53203 [PubMed: 25750539]

**Table 1**  
Comparison of TBI Patient and Injury Onset Characteristics by Ischemic Stroke Incidence

Patient and Injury Characteristics	All (n=6488)	No Ischemic Stroke (n=6329)	Ischemic Stroke (n=159)	P Value	OR	95% CI
Age at injury	42 (16-99)	42 (16-99)	40 (16-90)	NS		
Male	4725 (73)	4612 (73)	113 (71)	NS	0.915	0.646-1.294
Race/ethnicity						
White	4386 (68)	4281 (68)	105 (66)			
Black or African American	1022 (16)	992 (16)	30 (19)	NS		
Hispanic or Latino	788 (12)	773 (12)	15 (9)			
Other	81 (1)	79 (1)	2 (1)			
Atrial fibrillation	333 (5)	327 (5)	6 (4)	NS	0.720	0.316-1.640
Atrial flutter	38 (1)	35 (1)	3 (2)	0.065	3.458	1.052-11.365
Hypertension	1683 (26)	1648 (26)	35 (22)	NS	0.802	0.549-1.172
Cause of injury						
MVC	1994 (31)	1940 (31)	54 (34)			
Fall	2038 (31)	1994 (31)	44 (28)			
Sports	137 (2)	131 (2)	6 (4)	0.015		
Falling/flying object	82 (1)	79 (1)	3 (2)			
Gunshot	222 (3)	211 (3)	11 (7)			
ED GCS (initial presentation)						
Total unadjusted (excludes intubated, sedated)	13 (3-15)	13 (3-15)	12.5 (3-15)	NS		
Eye	3 (1-4)	3 (1-4)	2.5 (1-4)	NS		
Verbal	4 (1-5)	4 (1-5)	4 (1-5)	NS		
Motor*	5 (1-6)	5 (1-6)	5 (1-6)	NS		
6. Obeys commands	2250 (35)	2211 (35)	39 (24)			
5. Localizes	788 (12)	773 (12)	15 (9)			
4. Withdraws	555 (9)	544 (9)	11 (7)	NS		
3. Flexion	158 (2)	156 (2)	2 (1)			
2. Extension	116 (2)	111 (2)	5 (3)			

Patient and Injury Characteristics	All (n=6488)	No Ischemic Stroke (n=6329)	Ischemic Stroke (n=159)	P Value	OR	95% CI
1. No response	1021 (16)	995 (16)	26 (16)			
ED GCS Motor<6* (not following commands)	2638 (41)	2579 (41)	59 (37)	NS	0.771	0.512–1.160

Data are N (%), median (range); NS >0.100. CI indicates confidence interval; ED, emergency department; GCS, Glasgow Coma Scale; MVC, motor vehicle crash; NS, nonsignificant; and TBI, traumatic brain injury.

\* Among 4888 patients with available GCS Motor score data.

**Table 2**  
Comparison of TBI Onset\* Neuroanatomic Characteristics by Ischemic Stroke Incidence

Neuroanatomic Characteristic	All (n=6488)	No Ischemic Stroke (n=6329)	Ischemic Stroke (n=159)	P Value	OR	95% CI
Intracranial mass effect						
Basal cistern compression/midline shift						
No intracranial compression	3750 (58)	3676 (58)	74 (46)			
Cisterns present, midline shift 1–5 mm	711 (11)	692 (11)	19 (12)			
Cisterns compressed or absent, shift 0–5 mm	504 (8)	486 (8)	18 (11)	0.034		
Midline shift >5 mm	968 (15)	935 (15)	33 (21)			
Extent shift, cistern compression not specified	306 (5)	297 (5)	9 (6)			
Any cistern compression or midline shift	2489 (38)	2410 (38)	79 (50)	0.003	1.628	1.181–2.245
Midline shift >5 mm (vs > 5 mm or none)	968 (15)	935 (15)	33 (21)	0.036	1.515	1.024–2.241
Intracranial hemorrhage or fluid collection/injury						
Intraventricular hemorrhage	1675 (26)	1637 (26)	38 (24)	NS	0.908	0.626–1.316
Punctate/petechial hemorrhage	1474 (23)	1443 (23)	31 (19)	NS	0.826	0.554–1.231
Cortical injury	4137 (64)	4034 (64)	103 (65)	NS	1.071	0.759–1.512
Noncortical injury	1310 (20)	1260 (20)	50 (31)	<0.001	1.879	1.332–2.651
Extra-axial hemorrhage or fluid collection						
Subarachnoid or subdural fluid collection	5180 (80)	5048 (80)	132 (83)	NS	1.370	0.852–2.203
Epidural hemorrhage or fluid collection	708 (11)	688 (11)	20 (13)	NS	1.190	0.739–1.917
Cervical artery dissection						
Carotid artery dissection	66 (1%)	56 (1)	10 (6)	<0.001	7.518	3.763–15.022
Vertebral artery dissection	46 (1%)	40 (1)	6 (4)	0.001	6.166	2.576–14.760
Carotid or vertebral artery dissection	107 (2)	92 (1)	15 (9)	<0.001	7.062	3.993–12.490

Data are N (%). NS >0.100. CI indicates confidence interval; NS, nonsignificant; OR, odds ratio; and TBI, traumatic brain injury.

\* Findings from brain computed tomography obtained within 7 days of injury.

**Table 3**

Multivariate Analysis of Associations With Ischemic Stroke Onset (All Study TBI Patients, n=6223)

Factor*	AOR	P Value	95% Confidence Interval
Older age, y		NS	
Sex (male)		NS	
Injury type (MVC or motorcycle)		NS	
Midline shift or compression	1.589	0.005	1.151–2.195
Subcortical injury	1.853	<0.001	1.313–2.615
Cortical injury		NS	
Atrial fibrillation		NS	
Atrial flutter	3.560	0.037	1.078–11.750
Hypertension		NS	

NS>0.100. AOR indicates adjusted odds ratio; MVC, motor vehicle crash; and NS, nonsignificant.

\* Multivariate logistic regression.

**Table 4**

**Predictors of Inpatient Rehabilitation Outcome in TBI**

Outcome and Predictors*	Unstandardized $\beta$	SE	P Value	95% CI for $\beta$	Adjusted $R^2$
Rehab discharge FIM total score (n=6119)					0.095
Constant	103.492	1.548	<0.001	100.456 to 106.527	
Older age	-0.221	0.015	<0.001	-0.250 to -0.191	-
Sex (male)	1.060	0.635	0.095	-0.185 to 2.306	
Injury type (MVC or motorcycle)	-4.049	0.620	<0.001	-5.264 to -2.835	
Ischemic stroke	-13.273	1.820	<0.001	-16.840 to -9.705	
Intraventricular hemorrhage	-7.596	0.644	<0.001	-8.859 to -6.333	
Midline shift or cistern compression	-5.679	0.592	<0.001	-6.838 to -4.519	
Noncortical injury	-6.709	0.706	<0.001	-8.092 to -5.325	
Cortical injury	-1.121	0.616	0.069	-2.327 to 0.086	
Rehab discharge DRS (n=6133)					0.073
Constant	4.199	0.253	<0.001	3.703 to 4.694	
Older age	0.016	0.002	<0.001	0.011 to 0.021	-
Sex (male)	0.176	0.104	0.091	-0.028 to 0.380	
Injury type (MVC or motorcycle)	0.316	0.101	<0.001	0.118 to 0.515	
Ischemic stroke	1.875	0.297	<0.001	1.293 to 2.456	
Intraventricular hemorrhage	1.302	0.105	<0.001	1.095 to 1.508	
Midline shift or cistern compression	0.982	0.097	<0.001	0.793 to 1.172	
Noncortical injury	0.862	0.116	<0.001	0.635 to 1.088	
Cortical injury	0.314	0.101	0.002	0.116 to 0.511	
Duration of PTA (n=6074)					0.099
Constant	14.469	2.259	<0.001	10.041 to 18.897	
Older age	-0.154	0.022	<0.001	-0.198 to -0.111	
Sex (male)	3.958	0.927	<0.001	2.140 to 5.776	
Injury type (MVC or motorcycle)	5.562	0.905	<0.001	3.788 to 7.337	
Ischemic stroke	18.272	2.623	<0.001	13.131 to 23.414	

Outcome and Predictors*	Unstandardized $\beta$	SE	P Value	95% CI for $\beta$	Adjusted $R^2$
Intraventricular hemorrhage	12.523	0.944	<0.001	10.672 to 14.374	
Midline shift or cistern compression	8.920	0.863	<0.001	7.228 to 10.612	
Noncortical injury	9.666	1.033	<0.001	7.842 to 11.691	
Cortical injury	6.364	0.898	<0.001	4.604 to 8.125	

CI indicates confidence interval; DRS, Disability Rating Scale; FIM, Functional Independence Measure; MVC, motor vehicle crash; PTA, posttraumatic amnesia; and TBI, traumatic brain injury.

\* Multivariate linear regression.