TREATMENT AND DIAGNOSIS OF CEREBRAL ANEURYSMS IN THE POST-INTERNATIONAL SUBARACHNOID ANEURYSM TRIAL (ISAT) ERA: TRENDS AND OUTCOMES

Evan Luther, David J McCarthy, Marie-Christine Brunet, Samir Sur, Stephanie H Chen, Dallas Sheinberg, David Hasan, Pascal Jabbour, Dileep R Yavagal, Eric C Peterson, and Robert M Starke

ABSTRACT

Background Following publication of the International Subarachnoid Aneurysm Trial (ISAT), treatment paradigms for cerebral aneurysms (CAs) shifted from open surgical clipping to endovascular embolization as primary therapy in a majority of cases. However, comprehensive analyses evaluating more recent CA diagnosis patterns, patient populations and outcomes as a function of treatment modality remain rare.

Methods The National Inpatient Sample from 2004 to 2014 was reviewed. Aneurysmal subarachnoid hemorrhages (aSAHs) and unruptured intracranial aneurysms (UIAs) with a treatment of surgical clipping or endovascular therapy (EVT) were identified. Time trend series plots were created. Linear and logistic regressions were utilized to quantify treatment changes.

Results 114,137 aSAHs and 122,916 UIAs were reviewed. aSAH (+732/year, p=0.014) and UIA (+2,550/year, p<0.0001) discharges increased annually. The annual caseload of surgical clippings for aSAH decreased (~264/year, p=0.0002) while EVT increased (~366/year, p=0.0003). For UIAs, the annual caseload for surgical clipping remained stable but increased for EVT (~615/year, p<0.0001). The rate of incidentally diagnosed UIAs increased annually (~1,987/year, p<0.0001). Inpatient mortality decreased for clipping (p<0.0001) and EVT in aSAH (p<0.0001) (2004 vs 2014—clipping 13% vs 11.7%, EVT 15.8% vs 12.7%). Mortality rates for clipped UIAs decreased over time (p<0.0001) and remained stable for EVT (2004 vs 2014—clipping 1.57% vs 0.40%, EVT 0.59% vs 0.52%).

Conclusion Ruptured and unruptured CAs are increasingly being treated with EVT over clipping. Incidental unruptured aneurysm diagnoses are increasing dramatically. Mortality rates of ruptured aneurysms are improving regardless of treatment modality, whereas mortality in unruptured aneurysms is only improving for surgical clipping.

INTRODUCTION

The cerebrovascular community witnessed a shift in management paradigms for intracranial aneurysms (IAs) following the advent of endovascular treatment (EVT) strategies, with microsurgical clipping now accounting for the minority of IA interventions.1-6 This shift was driven by the results of the International Subarachnoid Aneurysm Trial (ISAT) which demonstrated that functional independence at 1 year and disability-free survival at 10 years was greater in endovascularly coiled aneurysmal subarachnoid hemorrhage (aSAH).7 8 Coupled with new technologies, these results have begun to reshape the treatment of IAs.9 Thus, it is not surprising that many studies in the post-ISAT era have proven that the number of IA interventions, especially EVTs, has dramatically increased.10-15

While these trends have been acknowledged in previous works, there has not been a recent comprehensive longitudinal analysis evaluating unruptured IA (UIA) and aSAH outcomes as a function of treatment modality in the post-ISAT era. We analyzed the Nationwide Inpatient Sample (NIS) from the years 2004–2014 in an effort to quantify the most recent trends in treatment and outcomes for IAs in the decade following ISAT.
Stratified into microsurgical clipping (ICD-9-CM, 39.51) and EVT (ICD-9-CM, 39.52, 39.72, 39.75, 39.76, 38.82). This schema for the identification of IAs in the NIS is similar to previously published works. Non-primary diagnoses indicating a UIA were labeled as incidentally discovered.

Statistical analysis
Aggregate national estimates of yearly discharge frequencies were calculated utilizing weighted observations. For the years 2004–2011 and 2012–2014 the adjusted weights and normal weights were utilized, respectively, to adjust for temporal database changes. To adjust for population growth, US per capita estimates were calculated by dividing the weighted yearly frequencies by the US population (https://www.census.gov). Statistical analysis was performed with SAS 9.4 (Cary, NC) utilizing procedures that account for NIS stratified-cluster sampling methodology. NIS sampling is clustered by hospital and stratified by hospital region/division for all years.

Continuous variables with yearly non-parametric and normal distributions were represented as yearly weighted median and mean estimates, respectively, with associated 95% confidence intervals (95% CI). Comparisons of means/distributions of normally continuous variables were carried out using least squared means analysis; non-parametric distributions were compared with a modern extension of the Wilcoxon rank sum test that adjusts for clustering, stratification, and weights. Categorical variables were presented as an estimated weighted frequency and percent. Statistical analyses of categorical variables were carried out using χ² and Fisher’s exact t-tests, as appropriate.

Time trend series plots were created for aSAH, UIAs and treatment trends for each pathology type. To yield a quantitative measurement of yearly distribution trends, yearly means/medians of continuous variables were assessed with linear regression following Shapiro-Wilks normality confirmation. Univariate logarithmic regression was utilized to assess the relationship of time with likelihood of mortality, NIS-SOM, routine and non-routine discharge dispositions. Values of p≤0.05 were considered statistically significant. We performed univariate yearly quantification to portray the longitudinal trends in patient population and treatment climate.

RESULTS
A total of 237,053 aSAHs/UIAs were identified from 2004–2014; 60.8% were associated with an EVT. Figure 1A–C displays the annual number of discharges stratified by treatment modality and rupture status. More than half of the patients had UIAs (51.9%) and the majority was female (71.7%). Average age was 55.3 years and average length of stay (LOS) was 8.2 days. To better evaluate trends over time, a year-to-year linear regression analysis was performed. Table 1 displays the overall treatment comparisons for aSAH and UIAs. Table 2 and the more detailed online supplementary table S1 delineate the treatment trends over time.

Aneurysmal subarachnoid hemorrhage
A total of 114,137 aSAHs were identified from 2004 to 2014: 64,344 (56.3%) had EVT and 49,793 (43.6%) underwent microsurgical clipping. The average age was 54.2 years and surgically clipped patients were younger (p<0.0001). The majority of the patients were female (68.3%) and there was no difference in treatment between sexes (table 1).

EVTs had shorter median LOS when compared with clippings (p<0.0001), yet before 2007 clipped patients were generally healthier (EI 10.4 vs 8.9; p<0.0011) (table 1). Interestingly, this difference was not found starting in 2008 (figure 1D). Before 2010 EVTs had higher median NIS-SSS (p<0.0001) and a greater frequency of NIS-SSS > 7 (p=0.0051) (table 1). Starting in 2011, no difference in NIS-SSS was found between EVTs and clippings (figure 1E).

There was no change in NIS-SOM over time for either group (figure 1F). Inpatient aSAH mortality rates decreased overtime for clippings (p=0.0494) and EVTs (p<0.0001) (figure 1G, table 2). However, EVTs had higher inpatient mortality rates (p=0.0128) when compared with clippings (table 1). In contrast, routine discharges following aSAH decreased over time for clipping (p=0.03) yet remained constant for EVT (figure 1H). Furthermore, non-routine discharges have increased over time.

Figure 1 Treatment trends for cerebral aneurysms and aneurysmal subarachnoid hemorrhage from 2004 to 2014. (A) Overall trends. (B) Aneurysmal subarachnoid hemorrhage treatment trends. (C) Unruptured aneurysm treatment trends. (D) Median Elixhauser index for aneurysmal subarachnoid hemorrhage. (E) NIS-stroke severity scale for aneurysmal subarachnoid hemorrhage. (F) NIS-severity outcome measure for aneurysmal subarachnoid hemorrhage. (G) Inpatient mortality rates for aneurysmal subarachnoid hemorrhage. (H) Routine discharge rates for aneurysmal subarachnoid hemorrhage. NIS, Nationwide Inpatient Sample.
for both treatments (clipping, p<0.0001; EVT, p=0.0499). When compared directly, EVTs exhibited higher routine discharges (p=0.0017) than surgical clipping (table 1).

Since 2004, aSAH clippings have decreased by 264 cases annually (p=0.0002) while EVTs have increased (+366, p=0.0003) (figure 1B, table 2). There was no change in LOS for either treatment during the same timeframe (online supplementary figure S1). The mean age of surgically clipped aSAH increased (p=0.0002) but did not change for EVTs (online supplementary figure S2). Surgically clipped aSAHs demonstrated an increase in the median EI from 2004 to 2014 (p=0.0205) while EVTs s exhibited no change (online supplementary figure S2). Surgically clipped aSAHs demonstrated an increase (p=0.0106) but did not change for EVT s (online supplementary figure S1). The mean age of surgically clipped aSAH increased (p<0.0001) during the same timeframe (online supplementary figure S1). The average age was 56.4 years and surgically clipped patients were significantly younger (p<0.0001).

**Unruptured intracranial aneurysms**
A total of 122916 treated UIAs were identified from 2004 to 2014: 79862 (65.0%) underwent EVT and 43054 (35.0%) underwent clipping. The average age was 56.4 years and surgically clipped patients were significantly younger (p<0.0001),...
The rate of incidentally diagnosed UIAs increased annually (+1987/year; p<0.0001) (figure 2D) and only 2.17% underwent treatment during the same hospitalization. The five most common primary diagnoses associated with incidentally diagnosed UIAs were unspecified cerebral artery occlusion, unspecified transient cerebral ischemia, care involving other specified rehabilitation procedure, occlusion and stenosis of the carotid artery, and syncope/collapse.

For treated UIAs, yearly discharges remained stable for surgical clipping and increased for EVT (+630, p<0.0001) (figure 1C, table 2). There was no significant difference in LOS for either treatment modality over time (online supplementary figure S3). The mean age for treated UIAs increased over time for both treatment modalities (p<0.0001) (figure 2B) and EVT demonstrated an increase in the median EI as well (p=0.0010) (figure 2C).

**DISCUSSION**

We present the first comprehensive longitudinal analysis of the NIS evaluating aneurysmal treatment trends as a function of preprocedural comorbidities, inpatient mortality, periprocedural morbidity, aSAH severity, and degree of disability at discharge for aSAH and UIAs in the post-ISAT era.

Several studies have been performed utilizing the NIS to evaluate IA treatment trends in the years leading up to ISAT. Andaluz et al evaluated treatment patterns from 1993 to 2003, observing that the number of UIAs undergoing treatment and total IAs undergoing EVT nearly doubled while aSAH clipping remained stable.

Most strikingly, they observed that in-hospital mortality and morbidity were converging over time for both treatment modalities.² Cowan
et al validated these results, demonstrating increased EVTs with stable clipping rates for aSAH and UIAs before ISAT. The results published by Hoh et al also demonstrated that increasing hospital case volume reduced mortality for all IAs regardless of treatment type during the same timeframe.

Brinjikji et al used the NIS from 2001 to 2008 and identified that the percentage of UIAs treated endovascularly nearly tripled and were associated with less morbidity and mortality than clipping. Second, they demonstrated that centers treating higher proportions of UIAs endovascularly had lower rates of morbidity and mortality when compared with centers with higher percentages of clipping for UIAs. Lastly, they found that more aSAHs were undergoing EVT, especially in elderly patients, and that mortality for aSAH was decreasing overall regardless of treatment. Hoh et al also used the NIS from 2002 to 2006 to evaluate cost and LOS for IAs and found that both variables were increased in IAs treated with clipping.

Although the aforementioned studies did assess treatment trends for IAs pre- and post-ISAT, many utilized a narrow timeframe, exclusively focused on specific outcome measures, or evaluated UIAs or aSAH independently. In order to truly demonstrate how practice patterns have changed in the decade following ISAT, we felt a more inclusive approach needed to be taken in which variables such as mortality, preoperative/perioperative morbidity, NIS-SSS, NIS-SOM, and discharge disposition could be individually evaluated over time and directly compared for both aSAH and UIAs treated surgically or endovascularly.

**Diagnosis and treatment trends**

For both aSAH and UIAs, our results are contiguous with Andaluz et al and demonstrate that an increasing proportion of IAs are undergoing EVT each year. In aSAH, the increase in EVT was mirrored by a decrease in surgical clippings. The same proportion-numeric mirroring pattern is not observed in UIAs, where surgical clipping has remained stable despite exhibiting a decrease in the proportion of overall treatments. This finding is due to the overall increase in UIAs undergoing EVT.

This increase in EVT for UIAs is likely to be multifactorial. While the International Study of Unruptured Intracranial Aneurysms (ISUIA) found that anterior circulation UIAs <7 mm had a 0% 5 year rupture risk, 90% of aSAHs from anterior circulation aneurysms in the ISAT were <10 mm. This discrepancy has led many to rely on clinical discretion, rather than solely aneurysmal size, for treatment decisions. This fact, paired with the continual technological advancements in EVT and the favorable outcomes presented in ISAT, have provided many with a justification to decrease the EVT threshold for aneurysms. Additionally, we observed that the number of incidentally diagnosed UIAs has increased dramatically post-ISAT. Together, the decreased treatment threshold coupled with the increased diagnosis of UIAs can certainly explain the substantial numerical increase in EVTs for UIAs.

To that end, this is the first study to analyze national trends of incidentally diagnosed UIAs from the NIS. Our “incidental” labeling method was supported by the low inpatient treatment rate of these aneurysms. The most common primary diagnoses associated with incidentally diagnosed UIAs were syncope or stenosis/occlusion of a cerebral artery—clinical situations that often require vascular imaging. This indicates that a correlation exists between UIA diagnoses and the use of non-invasive angiography. Thus, as imaging modalities continue to improve, the rates of incidentally diagnosed UIAs are likely to climb.

**Patient age and baseline health**

Studies following ISUIA suggested that EVT might be more beneficial for older patients harboring IAs. However, the results of ISAT only showed a benefit in outcome from ages 50–69 in EVT with no discernible benefit observed in patients >70. We were interested in how these conclusions affected the patient population for each treatment modality over time and our findings appear to be in accordance with these results, showing a longitudinal shift towards older and worse baseline health status for aSAH undergoing clipping and UIAs undergoing EVT.

For aSAH, EVTs had more preprocedural comorbidities as evidenced by a higher EI; however, this trend was not temporally constant. Instead, after 2007 the median EIs for aSAH treatment populations converged. This was due to the significant increase over time of the median EI for the aSAH population undergoing clipping, with a stable median EI in the aSAH EVTs. Not surprisingly, this increase in preprocedural comorbidities for aSAH undergoing clipping was accompanied by an older mean treatment age. For endovascularly treated aSAH, age and EI remained stable over time. We hypothesize that the discordant age results in ISAT may be responsible for the observed changes in aSAH clippings.

Interestingly, UIA patient trends were much different. Aggregate counts revealed that compared with endovascularly treated UIAs, clipped UIAs were younger with higher median EIs. Over time, UIAs mean age increased for both treatment modalities, although median EI only increased for EVTs. This suggests that following ISUIA, physicians have become increasingly more confident in the EVT of UIAs and have begun utilizing it in an older population with increasing comorbidities.

**Outcomes**

Non-routine discharges (NRDs) have previously been used as a surrogate for perioperative morbidity in the NIS. Although EVT had lower overall NRDs, from 2004 to 2014 rates of NRD in aSAH increased for both surgical clipping and EVTs. Washington et al developed the NIS-SOM, a superior proxy for the discharge mRS. We observed that, although the NIS-SOM for aSAH did not change over time for either treatment modality, mortality rates for all treated aSAHs improved. These findings suggest a change in nationwide discharge protocols likely secondary to several studies that have advocated for early rehabilitation as a means to improve long-term outcome in aSAH.

Inpatient mortality rates have decreased for all aSAH and clipped UIAs. Surprisingly, before 2010 endovascularly treated aSAH had higher rates of inpatient mortality when compared with clipping. This can be explained by the fact that during the same timeframe the NIS-SSS for endovascularly treated aSAH had a higher proportion of NIS-SSS >7. Interestingly, from 2010 to 2014, the proportion of NIS-SSS >7 and mortality rates for both treatment modalities converged. Moreover, from 2004 to 2014, all aSAHs demonstrated an increase in the proportion of discharges with an NIS-SSS >7. These results suggest that
over time physicians have become more comfortable treating higher grade aSAHs with either treatment modality, thus indicating a shift in the dogma that these aneurysms should be secured in a delayed fashion or not treated at all.\textsuperscript{29} Additionally, in the years immediately following ISAT, poorer grade aSAHs were more frequently being treated with EVT, although eventually this difference dissipated.

Strengths and limitations
Our study draws strength from its utilization of a large nationwide database intended to accurately represent the annual US inpatient population. However, the hospital sampling is not biased on available subspecialties within each institution. Therefore, if a high volume center for either treatment modality were excluded, their rates would ultimately be underrepresented.\textsuperscript{9} The NIS also remains retrospective and provides no information regarding post-discharge course or readmissions, making analysis of long-term outcomes or re-hemorrhage rates impossible.\textsuperscript{4,13,20,21} Furthermore, because of the NIS sampling, any patient admitted for retreatment of a recurrent/partially obliterated aneurysm or transferred from another facility would be analyzed as a new patient. This inherent bias prevents analysis of patients undergoing multiple treatments or crossing over from one treatment to another on separate admissions, and likely leads to an overestimation of the rates of EVT and an inability to account for the additive effects of repeat treatments on morbidity and mortality.\textsuperscript{11,30} It also provides no characteristics of aneurysm morphology or location, which are both variables known to significantly affect clinical decision-making. There is also no ICD-9-CM code for intraoperative aneurysm rupture or incomplete aneurysm occlusion, yet both can ultimately affect treatment efficacy and patient outcomes.\textsuperscript{4,13,20,21} Moreover, the NIS provides no information on the type of endovascular treatment or medical therapies administered, therefore the effects of improving technologies and neurocritical care cannot be evaluated.\textsuperscript{21} Additionally, a large dataset like NIS can identify very small statistically significant trends that may be difficult to interpret clinically. Also, any analyses performed on NIS data rely on accurate ICD-9-CM coding which is inherently error-prone. With that in mind, our evaluation of incidental UIAs could overestimate their incidence because we included all patients with a non-primary diagnosis code of cerebral aneurysm, which may include patients who merely have a history of an aneurysm rather than a newly discovered aneurysm on that admission.

CONCLUSIONS
In the post-ISAT era, increasingly larger proportions of patients with IAs continue to be treated with endovascular occlusion while rates of aSAH clipping have decreased. Although perioperative morbidity has increased for clipping, inpatient mortality has decreased. Furthermore, poorer grade aSAHs are being treated more frequently and incidentally discovered UIAs are being increasingly identified every year.

Twitter Pascal Jabbour @PascalalabourMD and Robert M Starke @Starke_neurosurgery

Contributors
EL: conception of the work, acquisition, analysis, or interpretation of data, drafting the work. DMcC: conception of the work, acquisition, analysis, or interpretation of data, drafting the work, final approval. M-CB: drafting the work, interpretation of data, final approval. SS: drafting the work, interpretation of data, final approval. CS: drafting the work, interpretation of data, final approval. DS: drafting the work, interpretation of data, final approval. DHi: drafting the work, interpretation of data, final approval. P: drafting the work, interpretation of data, final approval. D: drafting the work, interpretation of data, final approval. EP: drafting the work, interpretation of data, final approval. RS: conception of the work, interpretation of data, drafting the work, final approval.

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ORCID iDs
David J McCarthy http://orcid.org/0000-0002-8734-9795
Dallas Steinberg http://orcid.org/0000-0002-1480-9500
Pascal Jabbour http://orcid.org/0000-0002-8965-2413
Eric C Peterson http://orcid.org/0000-0002-0625-8438

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