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National Trends in Utilization of Endovascular Treatment in Acute Ischemic Stroke Patients in Post-Stent Retriever Approval and Post-Clinical Trials Completion Era in United States

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Abstract

Introduction— Several recent trials have demonstrated the superiority of endovascular treatment in the treatment of acute ischemic stroke. However, the pattern of utilization and associated outcomes in real world practice have not been studied.

Methods— We obtained data for patients admitted with a primary diagnosis of ischemic stroke in the United States from 2010 to 2017 using the Nationwide Inpatient Sample (NIS). We determined the rate and pattern of utilization and associated in-hospital outcomes in identified patients. Outcomes were classified as either none to minimal disability, moderate to severe disability, and death, and were compared between three time periods: 2010 to 2011, 2013 to 2014 and 2016 to 2017. These time periods represent the pre-stent retriever approval era, the post-stent retriever approval era, and the years immediately following the publication of major clinical trials in United States, respectively.

Results— Of the 3,792,252 patients admitted with ischemic stroke, 45,692 (1.2%) underwent endovascular treatment during the three time periods. There was an almost fourfold increase in patients who underwent endovascular treatment in the span of 8 years (0.75% in 2010 vs. 2.89% in 2017, trend p<0.001). The rate of none to minimal disability consistently improved between the three study intervals (2010-2011 versus 2013-2014: odds ratio (OR) 1.51, 95% confidence interval (CI) 1.18-1.91, p=0.0009) and (2013-2014 versus 2016-2017: OR 1.87, 95% CI 1.49-2.35, p= <0.0001)), respectively. There was significant decrease in inpatient mortality for patients treated during 2013-2014 (OR 0.68, 95% CI 0.55-0.85, p=0.0006) and 2016-2017 (OR 0.52, 95% CI 0.43-0.63, p<0.0001).

Conclusions— There has been a significant increase in the proportion of acute ischemic stroke patients who receive endovascular treatment with improvement of outcomes in real world practice.

Keywords— Ischemic stroke, endovascular treatment; ischemic stroke, national cohort, stent retriever devices.

INTRODUCTION

The Food and Drug Administration (FDA) has approved several devices for endovascular treatment in acute ischemic stroke patients. Subsequently, five landmark randomized clinical trials have conclusively demonstrated the superiority of endovascular treatment over standard medical care in the treatment of acute ischemic stroke.[1-5] There has been a continuous increase in utilization of endovascular treatment for acute ischemic stroke as a result of ease of use, high recanalization rates, and favorable outcomes demonstrated in recent randomized controlled trials.[6-9] Although it is reasonable to assume utilization and outcomes of endovascular treatment have improved in the United States after FDA approval in 2012 and after the publication of major clinical trial results in 2015, there is a paucity of studies focusing on real-world practice. We determined the trend of endovascular treatment utilization in acute ischemic stroke by comparing the rate of utilization between the pre-stent retriever approval era (2010-2011), the post-stent retriever approval era (2013-2014), and post-clinical trial era (2016-2017). Furthermore, we evaluated the outcomes of acute ischemic stroke patients who underwent endovascular treatment during the three study periods.

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MATERIALS AND METHODS

Database

Analysis was performed on data obtained from the NIS between the years of 2010 to 2017. This dataset sample represents an estimated 20% of all patients admitted to national inpatient hospitals which are short-term, non-federal hospitals within the United States.[10] Hospital characteristics documented within the dataset include geographic location, size, teaching status, bed number, and ownership.

Study cohort, patient demographics, and measured outcomes

The International Classification of Diseases (ICD) codes were used to identify patients admitted with ischemic stroke. Between 2010 to the first three-quarters of 2015, ICD-9 codes were used to identify the cohort of patients; ICD-10 codes were used thereafter from the fourth quarter of 2015 to 2017. Ischemic stroke patients were included if they had a primary diagnosis of either 433.x1-434.x1 (ICD-9) or I63 (ICD-10). Patient demographic data was acquired from the database including age, gender, race/ethnicity, and presence of comorbid conditions such as hypertension, diabetes mellitus, chronic renal failure, or congestive heart failure. The presence of comorbid conditions was obtained using the Agency for Healthcare Research and Quality (AHRQ) comorbidity data. Additional hospital and patient features were recorded including in-hospital length of stay and total cost of hospital care. Patient disposition was classified as either routine, requiring home health care, short-term hospitalization, requiring other intermediate care, requiring skilled nursing facilities, or death. Using previous research by Qureshi, et al[11], in which discharge disposition was shown to be suitable surrogate for Modified Rankin Scale (MRS) score clinical outcomes, patients in our analsyis who underwent routine discharge were categorized as having minimal or no disability whereas patients with any other documented discharge disposition were stated to have moderate-to-severe disability.

Identification of endovascular treatment

ICD-9 procedure codes of 39.74 and ICD-10 codes of 03CG3ZZ were used to identify patients treated with endovascular treatment for acute ischemic stroke.

Statistical Analysis

SAS statistical software (version 9.1, SAS Institute, Cary, NC) was used for analysis per the HCUP-NIS recommendations. Overview of these recommendations is publicly available at: http:// www.hcup-us.ahrq.gov/nisoverview.jsp. With regard to the current study, "x2" was used for analysis of variance for continuous data. We determined the rate and pattern of utilization and associated in-hospital outcomes of endovascular treatment among ischemic stroke patients. Outcomes were compared between three time periods: the pre-stent retriever era (2010-2011) to post-stent retriever era (2013-2014) and post major clinal trials era (2016-2017) in the United States. SAS procedures SURVEYMEANS, SURVEYFREQ, or SURVEYLOGISTIC was used for descriptive and modeling operations, and logistic regression was used for analysis of effect of time periods on rates of none to minimal, moderate to severe, or death. To examine the trends of utilization over time, endovascular treatment utilization, minimal disability, moderate to severe disability, and in-hospital mortality were examined in 2010. The rates observed within this year served as a reference for all subsequent years.

RESULTS

Baseline demographic and clinical characteristics

We identified 3,792,252 patients admitted with ischemic stroke from 2010 to 2017, of whom 271,785 (7.17%) received intravenous thrombolytic treatment and 60,802 (1.6%) underwent endovascular treatment. Of all patients admitted with ischemic stroke, 45,692 (1.2%) underwent endovascular treatment during the three time periods: 6,867 in 2010-2011, 12,070 in 2013-2014, and 26,755 in 2016-2017. In the 8-year span from 2010 to 2017, there was an almost fourfold increase in patients who underwent endovascular treatment (0.75% in 2010 versus 2.89% in 2017, trend $p<0.001$). The mean age of patients within the pre-stent retriever approval era was lower compared to the post-stent retriever approval era ($p<.0001$). No significant differences were observed in terms of gender or race/ethnicity between the three eras. Significant differences in utilization rates were observed based on geographical location and the teaching status of the hospital. When medical complications and in-hospital procedures were examined, the rate of urinary tract infection, pneumonia, and mechanical ventilation decreased significantly. However, the rate of sepsis, pulmonary embolism, and deep venous thrombosis increased (see Table 1).

Analysis of clinical outcomes

Significant improvement in disposition was observed from a shorter length of hospital stay and a decrease in hospital deaths. The rates of moderate to severe disability were also significantly decreased between the three study intervals. Compared with pre-stent retriever approval era (2010-2011), there was a significant reduction in-hospital mortality among patients treated during post-stent retriever approval era (2013-2014) (OR 0.68, 95% CI 0.55-0.85, $p=0.0006$) and the post-clinical trials era (2016-2017) (OR 0.52, 95% CI 0.43-0.63, $p<0.0001$). Compared with the pre-stent retriever approval era, there was a significant reduction in moderate to severe disability among patients treated during post-stent retriever approval era (OR 0.68, 95% CI 0.55-0.85, $p=0.0006$) and the post-clinical trials era (OR 0.52, 95% CI 0.43-0.63, $p<0.0001$). There was no statistical difference in the rate of intracerebral hemorrhage between the three study periods. Results are summarized in Table 2. A linear comparison of minimal disability compared to mortality is illustrated in Figure 1. In the figure, the rate of minimal disability in inversely correlated with mortality.

Trends analysis

In terms of endovascular treatment utilization, we observed a significant increase in utilization (see Table 3 for summary). For clinical outcomes, we observed a significant improvement in rates of none to minimal disability with a concomitant decline in moderate to severe disability and in-hospital mortality for

TABLE 1: Baseline demographics, characteristics, and outcomes between time periods.

Ischemic Stroke Patients Treated with Endovascular Treatment

	Study period 2010-2011	Study period 2013-2014	Study period 2016-2017	p-value
Overall Number (n)	6867	12070	26755	
Demographic and Social Characteristics				
Age, mean y (95% CI))	66.17 (65.18-67.16)	67.37 (66.72-68.02)	69.02 (68.59-69.50)	<.0001
% Female	50.9	50.2	51.3	0.8134
Race/Ethnicity				
White	72.4	71.1	69.9	0.3186
Blacks	11.7	12.8	15.2	
Hispanic	8.9	8.5	7.6	
Other	6.9	7.5	7.1	
Comorbid Conditions				
Hypertension	73.1	75.8	59.4	<.0001
Diabetes mellitus	21.8	25.3	26.6	0.0009
Congestive heart failure	17.2	21.5	21.8	0.0004
Renal failure	7.5	8.4	12.9	<.0001
Geographic region				
Northeast	18.1	18.8	17.7	0.0447
Northcentral	27.1	23.3	21.1	
South	24.3	36.1	40.4	
West	30.5	21.7	20.6	
Hospital Location and Teaching Status				
Rural	0.5	0.3	0.1	0.0003
Urban nonteaching	16.7	13.3	10.3	
Urban teaching	82.7	86.4	89.6	
Medical complications and in hospital procedures				
Subarachnoid or Intracerebral hemorrhage	20.6	21.5	21.3	0.8781
Pneumonia	7.6	5.1	6.5	0.0089
Urinary tract infection	19.1	16.2	11.7	<.0001
Sepsis	3.1	4.2	4.3	0.1419
Pulmonary embolism	1.3	1.9	1.5	0.2323
Deep venous thrombosis	2.1	2	4.1	<.0001
Mechanical ventilation	28.5	23.2	18	<.0001
Discharge Status				
Length of hospital stay (Days±SD)	9.22 (8.48-9.96)	9.24 (8.83-9.64)	8.33 (8.03-8.63)	0.0042
Hospital charges (USD±SD)	169758 (147193 -192322)	183731 (173873 -193589)	183731 (178401 -193565)	<.0001
Died in hospital	20.4	14.9	12.1	<.0001
Analysis limited to alive patient at discharge				
Minimal disability	21.5	28.3	31.8	<.0001
Moderate to severe disability	78.1	71.6	68.1	
Missing/not reported	0.3	0.1	0.1	

TABLE 2: Clinical outcome comparison between time periods.

	Minimal disability	Died in hospital	Intracerebral hemorrhage
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Study period 2010-2011	1 (Reference)	1 (Reference)	1 (Reference)
Study period 2013-2014	1.51 (1.18-1.91)	0.68 (0.55-0.85)	1.18 (0.93-1.51)
Study period 2016-2017	1.87 (1.49-2.35)	0.52 (0.43-0.63)	1.18 (0.94-1.49)

Abbreviations: OR - Odd's ratio; 95% CI - 95% confidence interval.

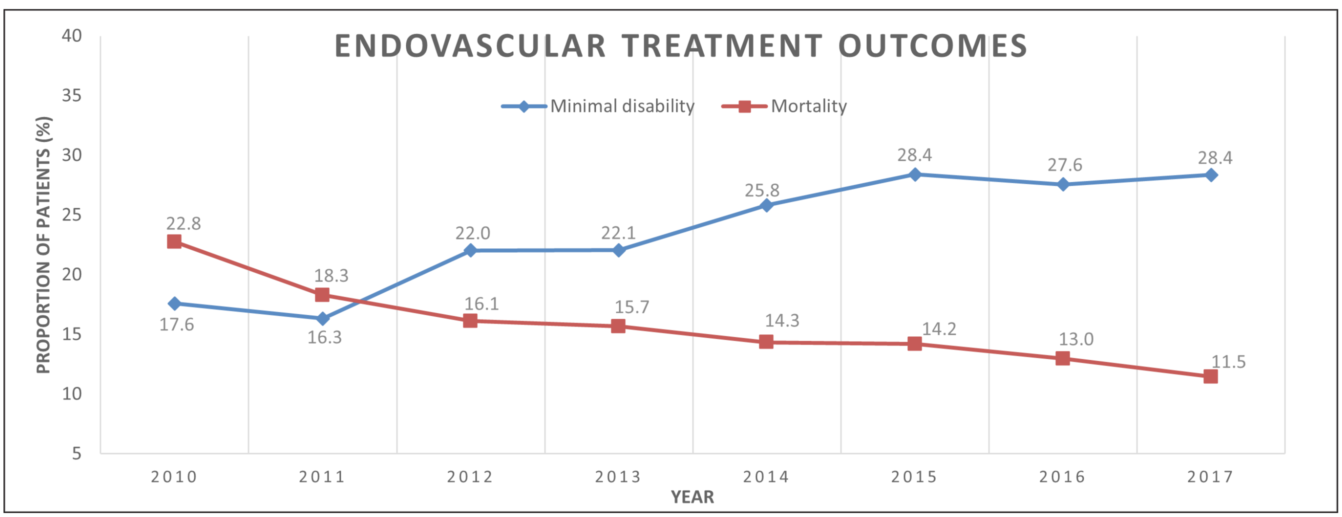
TABLE 3: Endovascular utilization and associated rate of disability over time.

	Endovascular Utilization		Minimal Disability	Moderate to Severe Disability	In-Hospital Mortality
Year	Utilization % (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
2010	0.75 (0.70 - 0.81)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
2011	0.78 (0.73 - 0.84)	1.04 (0.93 - 1.15)	0.79 (0.58 - 1.07)	1.35 (0.99 - 1.81)	0.89 (0.67 - 1.17)
2012	1.08 (1.02 – 1.15)	1.44 (1.31 - 1.59)	1.26 (0.96 - 1.66)	0.84 (0.64 - 1.10)	0.69 (0.53 – 0.91)
2013	1.22 (1.15 - 1.29)	1.62 (1.48 – 1.79)	1.20 (0.92 – 1.57)	0.88 (0.67 – 1.14)	0.71 (0.54 - 0.91)
2014	1.36 (1.28 - 1.43)	1.81 (1.65 – 1.98)	1.52 (1.17 – 1.96)	0.69 (0.54 - 0.90)	0.64 (0.49 - 0.82)
2015	2.07 (1.98 – 2.16)	2.77 (2.54 - 3.03)	1.71 (1.33 - 2.19)	0.62 (0.48 - 0.79)	0.61 (0.47 - 0.77)
2016	2.28 (2.19 - 2.37)	3.07 (2.82 – 3.35)	1.68 (1.32 – 2.14)	0.63 (0.49 - 0.79)	0.57 (0.46 - 0.73)
2017	2.89 (2.79 – 2.99)	3.91 (3.60 - 4.26)	1.84 (1.45 - 2.32)	0.58 (0.46 - 0.73)	0.46 (0.36 - 0.57)

Abbreviations: OR - Odd's ratio; 95% CI - 95% confidence interval.

Model adjusted for age, gender, intracerebral hemorrhage and APDRG severity scale.

FIGURE 1: National trends of mortality and minimal disability with endovascular utilization.



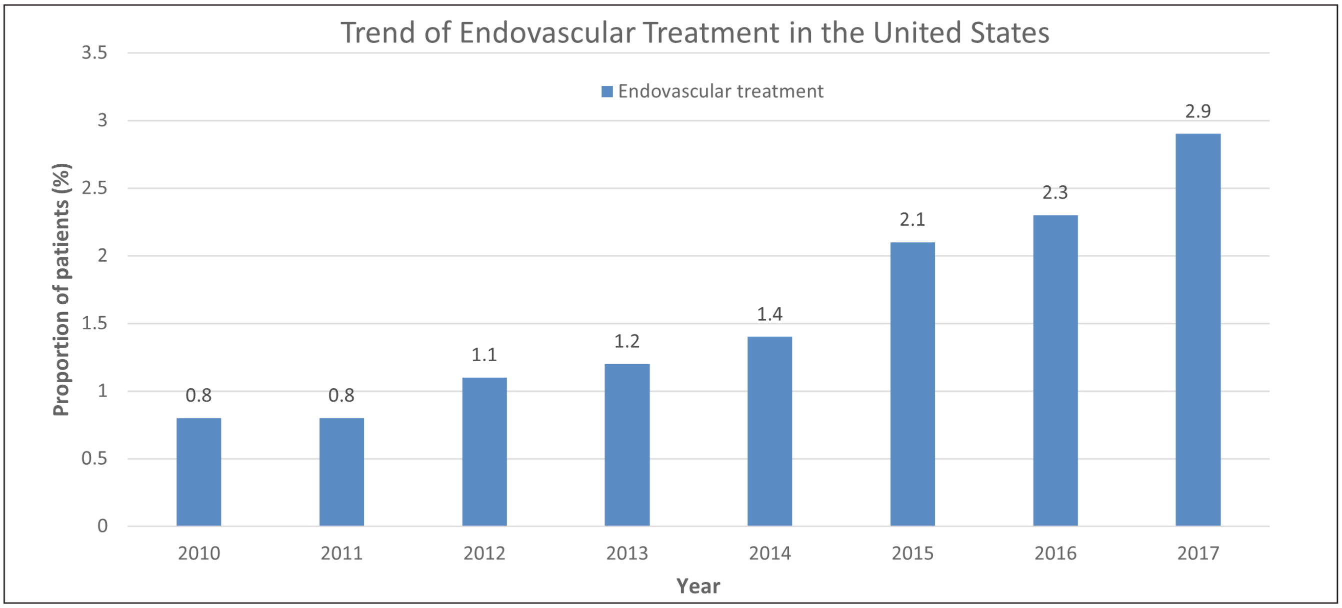


FIGURE 2: National trends in endovascular utilization.

every study period thereafter. A graphical representation of rate of utilization for endovascular treatment is shown in Figure 2. Herein, it is observed that endovascular treatment utlization rates for acute ischemic stroke have increased over the study period.

DISCUSSION

In this study, we examined the relative impact of FDA approval of stent retrievers and the results of major clinical trials on the adoption of endovascular treatment in acute ischemic stroke patients in the United States. In our analysis, we found that endovascular treatment increased 1.7-fold after FDA approval of thrombectomy devices in 2012 and 3.4-fold after the results of major clinical trials were published in 2015. In a previous study, Hassan et al[6] demonstrated a gradual increase in intra-arterial thrombolysis even before the FDA approval of stent retrievers. Another explanation for the increased utilization of endovascular treatment is the increasing number of hospitals that provide it as a treatment option, particularly among comprehensive stroke centers.[12,13,14,15]

We observed a reduction in in-hospital mortality and an increase in the rate of none to mild disability. These findings suggest that current adoption patterns are resulting in improved outcomes for acute ischemic stroke patients. Together, our findings of a decreasing trend in in-hospital mortality, an increased shift from moderate-severe disability to minimal disability, and persistent increase in yearly trends of endovascular treatment utilization agree with those results of a previous study by Behera et al.[16] These authors had specifically focused on comparing utilization and clinical outcomes between two-time intervals corresponding with the FDA approval of stent retrievers in 2012: the pre-stent retriever approval interval (2010-2012) and post-stent retriever approval interval (2013-2014). Rates in utilization nearly doubled from 2010 to 2014 with a steady yearly increase starting from 0.75% in 2010 increasing to 2.89% in 2017.[16] The rates of endovascular treatment utilization is between 4-14% in previous studies[17], confirming our observation that despite increases in implementation, endovascular treatment is still largely underutilized. Regarding outcome, Behera et al[16] similarly found decreases in in-hospital mortality from 18.7% in the pre-stent retriever approval period to 14.8% in the post-stent retriever approval period, similar to rates of 20.4% in 2010 to 12.1% in 2017 in our analysis. Rates of moderate-severe disability decreased in both studies, while rates of none to minimal disability increased. Both analyses found that there was no statistically significant difference in peri-procedural complications such as intraparenchymal hemorrhage in any time period.[16] Our study notably expands on these statistically significant results by extending our analysis to a third time interval of 2016-2017, further validating the value of landmark clinical trials. The reason for the reduction in rates of in-hospital mortality and moderate to severe disability may be multifactorial. There may be improved patient selection as the clinical and neuroimaging criteria become better defined. There may also be more rapid triage and interhospital transfer in the later eras leading to improved outcomes. Furthermore, high rates of recanalization observed with the recent generation of stent retrievers may be a contributing factor.

Our study is an observational study without sufficient evidence to support that improved outcomes are a direct result of increase in utilization of endovascular treatment. We have limited information regarding the use of advanced imaging and other medication. Our study is further limited by the accuracy of ICD-9 and ICD-10 diagnosis codes. In the current study, we used multivariate logistic regression for potential confounders between three study groups, yet the database lacks the standard severity scales such as the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS). In previous analyses done by Qureshi, et al[11], the discharge disposition was correlated with functional outcome by Modified Rankin Scale at 3 months and a high degree of concordance was observed.

CONCLUSION

There has been a significant increase in the proportion of acute ischemic stroke patients receiving endovascular treatment with an improvement of outcomes in real world practice. Our analysis supports generalizability of the successful results observed in clinical trials of endovascular treatment in acute ischemic stroke patients in the United States.

DISCLOSURE

The authors have no financial disclosures and/or conflicts of interest.

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