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Original article

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Abstract

Objective:
To examine healthcare costs among patients hospitalized for transient ischemic attack or ischemic stroke (TIA/stroke) and prescribed aspirin plus extended-release dipyridamole (ASA-ERDP) or clopidogrel (CLOPID) within 30 days post-discharge using a retrospective claims database from a large US managed care organization.

Methods:
Adult patients with ≥1 hospitalizations for TIA/stroke between January 2007–July 2009 and ≥1 claims for an oral anti-platelet (OAP) were observed for 1 year before and after the first TIA/stroke hospitalization or until death, whichever came first. Cohorts were defined by the first claim for ASA-ERDP or CLOPID within 30 days post-discharge. A generalized linear model, adjusting for demographics, baseline comorbidities and costs, compared total follow-up costs (medical + pharmacy) between ASA-ERDP and CLOPID patients.

Results:
Of 6377 patients (2085 ASA-ERDP; 4292 CLOPID) who met the selection criteria, mean (SD) age was 69 (13) years and 50% were male. Unadjusted mean total follow-up costs were lower for ASA-ERDP than CLOPID ($26,201 vs $30,349; $p = 0.002$), of which average unadjusted medical and pharmacy costs were $22,094 vs $26,062 ($p = 0.003$) and $4107 vs $4288 ($p = 0.119$), respectively. Multivariate modeling indicated that the following were associated with higher total costs (all $p < 0.05$): higher baseline Quan-Charlson comorbidity score, history of atrial fibrillation and myocardial infarction, index stroke hospitalization, death post-discharge, and index CLOPID use. Adjusted mean total follow-up costs for CLOPID were 9% higher than ASA-ERDP (cost ratio: 1.09; $p = 0.038$).

Conclusion:
In this study, compared to CLOPID patients, ASA-ERDP patients were observed to have lower total costs 1 year post-discharge TIA/stroke hospitalization, driven primarily by lower medical costs. Further research into the real-world impact of OAP therapies on clinical and economic outcomes of patients with stroke/TIA is warranted. The findings of this study should be considered within the limitations of an administrative claims analysis, as claims data are collected for the purpose of payment.

Introduction

Stroke is a significant cause of morbidity and the fourth leading cause of death in the US[1]. Each year, an estimated 795,000 Americans experience a stroke, of which 610,000 are estimated to be an initial stroke. In addition, ~30% of initial

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stroke patients experience a recurrent stroke in their lifetime[2]. Ischemic strokes, which account for 87% of all strokes, occur when a thrombus or embolus blocks a portion of cerebral circulation. A transient ischemic attack (TIA) is an ischemic stroke with a focal neurological deficit that lasts less than 24 h and leaves no evidence of an acute infarction on imaging tests. Both TIA and ischemic stroke are strong predictors of subsequent ischemic strokes[3,4].

Appropriate medical therapy following a TIA or ischemic stroke is important in order to reduce the risk of subsequent ischemic stroke[5,6]. Anti-coagulation therapy (e.g., warfarin) and anti-platelet agents (e.g., aspirin) are among the anti-thrombotic treatment options available for recurrent stroke prevention. The American College of Chest Physicians (ACCP) recommends anti-platelet therapy for preventing recurrent ischemic stroke of non-cardioembolic origin[7]. Based on accumulated evidence to date, the American Heart Association and American Stroke Association (AHA/ASA) guidelines identify aspirin, the combination of aspirin/dipyridamole, clopidogrel, and ticlopidine as acceptable anti-platelet options to prevent secondary ischemic stroke[6].

According to the Centers for Disease Control (CDC), 3.3 million ambulatory care visits had a stroke diagnosis and 829,000 patients had a hospital discharge with a primary stroke diagnosis in 2006 and 2007[8]. Americans spent an estimated $73.7 billion in 2010 on direct and indirect stroke-related medical costs[9]. By 2050, costs related to ischemic strokes are expected to exceed $2.2 trillion (in 2005 dollars)[10]. Real-world comparisons of healthcare costs following the initiation of an oral anti-platelet agent for secondary stroke prevention are limited. The objective of this study was to examine the 1-year follow-up healthcare costs of patients prescribed one of two common oral anti-platelets (i.e., aspirin plus extended-release dipyridamole or clopidogrel) within 30 days following hospital discharge for a TIA or ischemic stroke.

Methods

Study design and data source

This was a retrospective study using an administrative claims database from a large US health plan affiliated with OptumInsight (formerly i3 Innovus) that offers both commercial and Medicare Advantage insurance. The database included medical claims, outpatient pharmacy claims, and enrollment information for 20.6 million individuals enrolled during the study identification period of January 1, 2007 through July 31, 2009. The individuals covered by this health plan were geographically diverse across the US, with the greatest representation in the South and Midwest US census regions. Medical (professional and facility) claims included International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, ICD-9 procedure codes, Current Procedural Terminology, Version 4 (CPT-4) procedure codes, Healthcare Common Procedure Coding System (HCPCS) procedure codes, site-of-service codes, provider specialty codes, and health plan and patient costs. Outpatient pharmacy claims provided National Drug Codes (NDC) for dispensed medications, quantity dispensed, drug strength, days supply, provider specialty code, and health plan and patient costs. All study data were de-identified and accessed with protocols compliant with the Health Insurance Portability and Accountability Act.

Patient identification

The study sample included adults who were aged 18 years or older and had at least one inpatient hospital facility claim with an ICD-9-CM diagnosis code in any position for TIA (362.34, 435.x) or ischemic stroke (433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91) between January 1, 2007 and July 31, 2009 (identification period). The index date was defined as the admission date for the first qualifying inpatient claim. The inpatient hospital stay that started on the index date was referred to as the index hospitalization.

Patients were eligible for study inclusion if they were continuously enrolled with medical and pharmacy benefits for 12 months (365 days) before the index date (baseline period) and until the earliest of death or 12 months after discharge from the index hospitalization (follow-up period). Patients with a diagnosis or procedure code for pregnancy, labor, or delivery any time during the study period were excluded from the analysis. Patient cohorts were determined by the first pharmacy claim for an oral anti-platelet within 30 days after discharge from the index hospitalization. Only patients with a first pharmacy claim for either aspirin plus extended-release dipyridamole (ASA-ERDP) or clopidogrel (CLOPID) were included in the study. Use of aspirin only, an over-the-counter medication, could not be evaluated using administrative claims data and, therefore, was not considered in this study.

Outcome measures

Outcomes were measured in the claims data during the year following discharge from the index hospitalization. All-cause healthcare resource utilization for physician office visits, outpatient hospital visits, emergency department visits, and inpatient admissions (including TIA and stroke hospital readmissions) were assessed during the 1-year follow-up period. All-cause healthcare resource

costs were computed as the sum of health plan and patient paid amounts for all medical and pharmacy claims during the 1-year follow-up period. Costs were adjusted for inflation to 2010 dollars using the medical care component of the Consumer Price Index (CPI). Healthcare costs were calculated for total healthcare services (medical + pharmacy), medical services, pharmaceuticals (including ASA-ERDP and CLOPID), ambulatory services (including physician office and outpatient hospital visits), emergency department services, inpatient hospital services (including index hospitalization and TIA and stroke hospital readmissions), home health services, skilled nursing facility services, and other medical services.

Baseline and index hospitalization characteristics

Age, gender, insurance type, health plan geographic region, and number of follow-up months were captured from the enrollment data. Baseline comorbidities hypothesized to increase the risk of recurrent stroke were identified on medical claims with diagnosis codes in any position for: atrial fibrillation, congestive heart failure (CHF), diabetes mellitus, hyperlipidemia, gastroesophageal reflux disease (GERD), hypertension, pre-cerebral artery disease, stroke, TIA, and valvular heart disease (see Appendix). The Quan-Charlson comorbidity score was computed based on weights assigned for 17 different major comorbidities[11]. The baseline number of unique medications was calculated using the outpatient pharmacy claims, and the total all-cause healthcare costs were calculated using health plan and patient paid amounts (including patient copays) for medical and pharmacy services during the baseline period.

The index event was defined as either TIA or ischemic stroke depending upon the diagnosis codes on medical claims during the index hospitalization. Any vascular-related event during the index hospitalization was determined by the presence of a medical claim with a diagnosis code in any position for myocardial infarction (MI), CHF, gastrointestinal bleeding, intracranial hemorrhage, other vascular events, other hemorrhagic events (e.g., intraocular bleeding), or transfusions for a hemorrhagic event (see Appendix).

Statistical analysis

Descriptive summary statistics were obtained for all study measures. Results were stratified by ASA-ERDP and CLOPID cohorts. Differences between ASA-ERDP and CLOPID patients were compared using the two-sided Student's *t*-test for continuous variables and the Chi-square test for categorical variables.

Total follow-up healthcare costs were estimated using a generalized linear model (GLM) with the gamma distribution and log link. The cost model was adjusted for age, gender, baseline hypertension, baseline atrial fibrillation, baseline Quan-Charlson comorbidity score, total baseline healthcare costs, baseline number of unique medications, number of follow-up months, all-cause death any time during the follow-up period, any vascular-related event during the index hospitalization, index hospitalization event, and treatment cohort. Coefficients in the cost model were exponentiated and reported as cost ratios. All analyses were performed using SAS v9.2 (SAS Institute, Cary, NC) and Stata Version 10.0 (StataCorp LP, College Station, TX). The *a priori* α value of 0.05 was used for all analyses.

Results

Baseline population characteristics

The study sample included 6377 patients: 2085 patients in the ASA-ERDP cohort and 4292 patients in the CLOPID cohort. Figure 1 shows the sample selection criteria and attrition. Tables 1 and 2 present the summary statistics for baseline demographic and clinical characteristics by treatment cohort. ASA-ERDP and CLOPID patients were similar in age, with roughly 60% of patients above age 65 and an average ± standard deviation (SD) age of 69 ± 13 years. Distributions of gender, insurance type, and health plan region between cohorts were also similar. In both cohorts, ~7–8% of patients died during the follow-up period, with a mean follow-up of 5 months before death.

In general, ASA-ERDP patients had a lower proportion of baseline comorbidities than CLOPID patients (Table 2). Compared to CLOPID patients, ASA-ERDP patients had a lower proportion of baseline atrial fibrillation, congestive heart failure, dyslipidemia, pre-cerebral artery disease, and valvular heart disease. There were no differences between cohorts in terms of baseline diabetes, hypertension, and prior stroke. CLOPID patients had a higher proportion of patients with a Quan-Charlson score of 5 or more compared to ASA-ERDP patients, and approximately a quarter of patients in both cohorts had a Quan-Charlson score of 0.

During baseline, the ASA-ERDP cohort had lower all-cause healthcare utilization and costs than the CLOPID cohort (Tables 2 and 3). Although the average length of stay for the index hospitalization was ~9 days for each cohort ($p = 0.237$), the average total costs of the index hospitalization were lower for the ASA-ERDP cohort than the CLOPID cohort ($12,796 ± $14,177 vs $15,907 ± $22,600; $p \leq 0.001$) (Table 2).

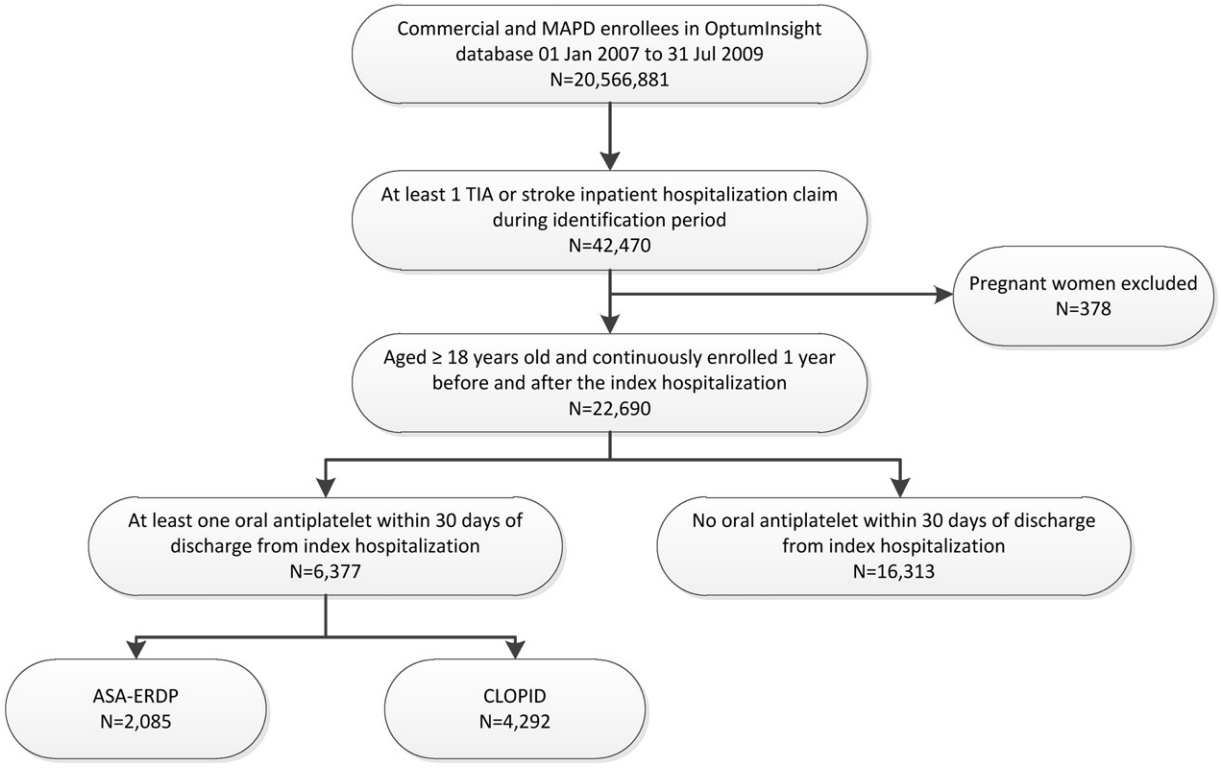

Figure 1. Flow Chart of Patient Selection Criteria.

Table 1. Baseline demographics.

	ASA-ERDP ($n=2085$)	CLOPID ($n=4292$)	p-value
Mean age (SD)	70 (12)	69 (13)	0.147
Age (categorical), *n* (%)			
18–44	70 (3)	155 (4)	0.606
45–64	703 (34)	1502 (35)	0.314
65+	1312 (63)	2635 (61)	0.237
Gender, *n* (%)			
Male	1078 (52)	2111 (49)	0.059
Coverage type, *n* (%)			
Commercial	1226 (59)	2461 (57)	0.268
Medicare	859 (41)	1831 (43)	0.268
Geographic region, *n* (%)			
Northeast	194 (9)	450 (10)	0.142
Midwest	627 (30)	1277 (30)	0.794
South	1084 (52)	2167 (50)	0.261
West	180 (9)	398 (9)	0.404

Follow-up all-cause healthcare utilization

The summary statistics for unadjusted healthcare utilization during the 1-year follow-up period are presented in Table 3. ASA-ERDP patients had a significantly lower proportion and average number of inpatient admissions than CLOPID patients (36.1% vs 40.6%; $p \leq 0.001$ and 0.6 vs 0.7; $p < 0.001$). The proportion of other healthcare utilization did not differ between ASA-ERDP and CLOPID patients. Among patients with at least one follow-up inpatient admission, the average number of inpatient admissions was 1.6 for ASA-ERDP patients and 1.7 for CLOPID patients ($p = 0.024$). The average length of an inpatient admission did not differ between cohorts (~7 days for all patients and 20 days for patients with at least one inpatient admission during the 1-year follow-up period). Although the proportion of patients with an outpatient hospital visit did not differ between cohorts, ASA-ERDP patients had a lower average number of outpatient hospital visits than CLOPID patients. Follow-up utilization of home health services and skilled nursing facilities did not differ between cohorts.

Unadjusted all-cause follow-up healthcare costs

The unadjusted average total healthcare costs during follow-up were lower for ASA-ERDP patients than CLOPID patients ($\$26,201 \pm \$47,600$ vs $\$30,349 \pm \$55,023$; $p = 0.002$), as was the unadjusted average medical costs ($\$22,094 \pm \$46,949$ vs $\$26,062 \pm \$54,420$; $p = 0.003$) (Table 4). Follow-up average medical costs accounted for ~85% of average total healthcare costs for ASA-ERDP and CLOPID patients; pharmaceuticals accounted for the remaining costs. Inpatient hospital services accounted for 45%, and outpatient hospital services account for 28% of total medical care costs in both ASA-ERDP and CLOPID cohorts. Compared with CLOPID

Table 2. Baseline and index clinical characteristics.

	ASA-ERDP ($n = 2085$)	CLOPID ($n = 4292$)	p-value
Comorbidities occurring in >5% of patients			
Atrial fibrillation	5.80	8.25	<0.001
Congestive heart failure	11.41	13.63	0.013
Diabetes mellitus	36.02	34.60	0.265
Dyslipidemia	57.70	60.79	0.018
Gastroesophageal reflux disease	16.02	17.22	0.230
Hypertension	75.01	75.68	0.563
Pre-cerebral artery disease	10.07	13.93	<0.001
Stroke, any	21.73	20.60	0.298
Ischemic stroke	15.54	14.75	0.407
Undefined or ill-defined stroke	12.23	11.42	0.343
TIA	15.83	17.52	0.091
Valvular heart disease	10.94	13.91	<0.001
Quan-Charlson comorbidity score, *n* (%)			
0	525 (25)	1,062 (25)	0.706
1–2	911 (44)	1,753 (41)	0.030
3–4	412 (20)	895 (21)	0.311
5+	237 (11)	582 (14)	0.014
Baseline number of unique medications, *M* (SD)	9.1 (6.8)	9.9 (7.0)	<0.001
Number of follow-up months, *M* (SD)	11.5 (1.9)	11.4 (2.1)	0.147
Death during follow-up, *n* (%)	150 (7.2)	342 (8.0)	0.277
Among those who died, number of months followed before death, *M* (SD)	5.2 (3.2)	4.9 (3.3)	0.324
Any vascular-related event during index hospitalization, *n* (%)	207 (9.9)	701 (16.3)	<0.001
Index event			
TIA	656 (31.5)	1,581 (36.8)	<0.001
Ischemic stroke	1429 (68.5)	2,711 (63.2)	<0.001
Total baseline all-cause healthcare costs (USD), *M* (SD), median	14,087 (28,719) 6126	15,982 (30,101) 7374	0.015
Length of index hospitalization (days), *M* (SD), median	9.2 (17.3) 4	9.7 (17.4) 4	0.237
Cost of index hospitalization (USD), *M* (SD), median	12,796 (14,177) 8444	15,907 (22,600) 9088	<0.001

Table 3. Baseline and follow-up all-cause healthcare utilization.

	ASA-ERDP ($n = 2085$)	CLOPID ($n = 4292$)	p-value
Baseline utilization, *n* (%)			
Office visits	1923 (92.2)	4021 (93.7)	0.030
Outpatient hospital visits	1480 (71.0)	3040 (70.8)	0.899
Emergency department visits	926 (44.4)	1955 (45.6)	0.392
Inpatient admissions	436 (20.9)	1053 (24.5)	0.001
Baseline utilization, *M* (SD)			
Office visits	11.6 (11.7)	12.5 (12.1)	0.003
Outpatient hospital visits	4.9 (6.9)	5.5 (8.5)	<0.001
Emergency department visits	0.9 (2.2)	1.0 (2.5)	0.084
Inpatient admissions	0.3 (0.7)	0.4 (0.9)	<0.001
Follow-up utilization, *n* (%)			
Office visits	2025 (97.1)	4144 (96.6)	0.229
Outpatient hospital visits	1859 (89.2)	3832 (89.3)	0.883
Emergency department visits	1770 (84.9)	3606 (84.0)	0.367
Inpatient admissions	753 (36.1)	1744 (40.6)	<0.001
Home health service	831 (39.9)	1762 (41.1)	0.361
Skilled nursing facility	321 (15.4)	685 (16.0)	0.562
Follow-up utilization, *M* (SD)			
Office visits	16.1 (13.1)	16.6 (13.8)	0.134
Outpatient hospital visits	7.9 (10.7)	8.8 (11.0)	0.001
Emergency department visits	2.0 (2.5)	2.2 (3.8)	0.052
Inpatient admissions	0.6 (1.0)	0.7 (1.1)	<0.001
Length of inpatient admissions, days	7.3 (20.0)	7.8 (21.6)	0.324
Conditional inpatient admissions (>1 admission)	1.6 (1.1)	1.7 (1.2)	0.024
Length of conditional inpatient admissions (>1 admission)	20.2 (29.1)	19.2 (30.5)	0.462

Table 4. Follow-up all-cause healthcare cost[a].

	Cost (USD), *M* (SD) median		
	ASA-ERDP ($n=2085$)	CLOPID ($n=4292$)	*p*-value[b]
Total cost	26,201 (47,600) 14007	30,349 (55,023) 15967	0.002
Medical cost	22,094 (46,949) 9560	26,062 (54,420) 11416	0.003
Office visits	2789 (8,087) 1487	2781 (7,378) 1644	0.968
Outpatient visits	6123 (21,294) 1764	7540 (26,944) 2038	0.023
Emergency department	1068 (1,657) 553	1246 (2,446) 620	<0.001
Inpatient	9936 (37,076) 0	11,810 (33,943) 0	0.052
Other medical	2177 (5,856) 410	2685 (9,383) 458	0.008
Home health services[c]	3702 (8180) 1113	3938 (7,340) 1157	0.479
Skilled nursing facility[d]	13,834 (17,496) 6692	13,155 (20,657) 5557	0.589
Pharmacy cost[e]	4247 (4,371) 3284	4412 (4,359) 3458	0.158
Total oral anti-platelet	1150 (704) 1246	1196 (655) 1393	0.014
Index anti-platelet	976 (705) 909	1171 (657) 1371	NA
Other pharmacy	3097 (4,195) 2010	3216 (4,203) 2175	0.287

[a]Cost was adjusted for inflation to 2010 dollars using the medical care component of the Consumer Price Index (CPI).
[b]*p*-values represent differences between means.
[c]Conditional on use: $n=453$ for ASA-ERDP cohort and $n=996$ for CLOPID cohort.
[d]Conditional on use: $n=134$ for ASA-ERDP cohort and $n=310$ for CLOPID cohort.
[e]Pharmacy cost also included cost of pharmacy claims on the day of discharge from the index hospitalization.

Table 5. Follow-up TIA and stroke inpatient hospital readmission characteristics.

	ASA-ERDP ($n=2085$)	CLOPID ($n=4292$)	*p*-value
Any TIA or stroke hospital readmission, *n* (%)	189 (9)	387 (9)	0.950
Number of TIA and stroke hospital readmissions, *M* (SD)	1.1 (0.4)	1.2 (0.5)	0.417
Length of TIA and stroke hospital readmission, days, *M* (SD)	16.7 (21.2)	14.2 (25.9)	0.227
Cost of TIA and stroke hospital readmissions (USD), *M* (SD), median	20,674 (27,042) 11,533	21,702 (40,669) 10,156	0.719

patients, ASA-ERDP patients had lower average costs during follow-up for outpatient hospital visits ($6123 ± $21,294 vs $7540 ± $26,943; $p=0.023$), inpatient hospital visits ($9936 ± $37,067 vs $11,810 ± $33,943; $p=0.052$), emergency department services ($1068 ± $1657 vs $1246 ± $2446.34; $p<0.001$), and other medical services ($2177 ± $5856 vs $2685 ± $9383; $p=0.008$). There was no significant difference in pharmacy costs ($4247 ± $4371 vs $4412 ± $4359; $p=0.158$) and physician office visit costs ($2789 ± $8087 vs $2781 ± $7378; $p=0.968$) between the two cohorts. Total oral anti-platelet costs accounted for 27% of total pharmacy costs in both cohorts. The average costs of the index medication in each cohort were similar: aspirin plus extended-release dipyridamole cost $976 on average for patients in the ASA-ERDP cohort and clopidogrel cost $1171 on average for patients in the CLOPID cohort. Follow-up costs for home health services and skilled nursing facilities were also similar between cohorts.

Follow-up hospital readmissions for TIA and stroke

Table 5 presents the summary statistics of hospital readmissions for TIA and stroke during the 1-year follow-up period. The proportion of ASA-ERDP and CLOPID patients with at least one hospital readmission for TIA or stroke of any kind during the follow-up period was 9% ($p=0.950$). Both cohorts averaged approximately one TIA or stroke hospital readmission during the 1-year follow-up period ($p=0.417$), with an average length of 2 weeks per hospitalization ($p=0.227$). Average costs per TIA and stroke hospital readmission were also similar between the two cohorts (ASA-ERDP: $20,674 ± $27,042; CLOPID $21,702 ± $40,669; $p=0.719$).

Multivariate analysis

After adjustment for baseline demographic and clinical characteristics, the CLOPID cohort had significantly higher total healthcare costs than the ASA-ERDP cohort (cost ratio: 1.09; 95% CI: 1.004–1.178; $p=0.038$) (Table 6). Covariates associated with higher total all-cause healthcare costs included: higher baseline Quan-Charlson comorbidity score, higher total baseline healthcare costs, higher baseline number of unique medications, longer follow-up, any vascular-related event during the index hospitalization, and death during follow-up (all $p<0.05$). Covariates associated with lower total all-cause healthcare costs included: older age, female, baseline hypertension,

Table 6. Factors associated with total all-cause healthcare cost during 1-year follow-up period from generalized linear model.

Variable	Cost ratio	95% CI	*p*-value	Predicted average cost
Treatment cohort				
ASA-ERDP (reference group)				$32,828
CLOPID	1.09	1.004–1.178	0.038	$35,713
Age				
18–44 (reference group)				
45–64	0.98	0.797–1.206	0.851	
65+	0.80	0.655–0.987	0.037	
Gender				
Male (reference group)				
Female	0.90	0.838–0.974	0.008	
Baseline comorbidities				
Hypertension	0.88	0.794–0.966	0.008	
Atrial fibrillation	1.01	0.872–1.165	0.914	
Baseline Quan-Charlson comorbidity score				
0 (reference group)				
1–2	1.05	0.953–1.164	0.310	
3–4	1.21	1.071–1.371	0.002	
5+	1.24	1.061–1.451	0.007	
Baseline number of unique medications	1.02	1.010–1.024	<0.001	
Number of follow-up months	1.17	1.114–1.226	<0.001	
Any vascular event during index hospitalization	1.74	1.390–2.188	<0.001	
Death during follow-up	4.27	2.982–6.129	<0.001	
Total baseline healthcare cost/10,000 (USD)	1.09	1.071–1.109	<0.001	
Index hospitalization event				
Stroke (reference group)				
TIA	0.76	0.706–0.827	<0.001	

and an index hospitalization for TIA (all $p < 0.05$). During the 1-year follow-up period, the predicted average total healthcare costs for ASA-ERDP and CLOPID cohorts were $32,828 and $35,713, respectively.

Discussion

This retrospective analysis of hospitalized TIA and ischemic stroke patients was conducted with administrative claims data from one of the largest health plans in the US. The association of post-discharge oral anti-platelet use on economic outcomes was evaluated. The results showed that, after adjusting for differences in baseline characteristics, patients first treated with CLOPID post-discharge had significantly higher all-cause healthcare costs 1 year after a TIA or ischemic stroke hospitalization than patients first treated with ASA-ERDP post-discharge. However, the costs for TIA and stroke hospital readmissions were similar, possibly due to the patients' similar length of stay. With no difference in pharmacy costs, the cost difference between ASA-ERDP and CLOPID cohorts was primarily driven by differences in medical services.

Although the study designs differ, our findings of the 1-year total follow-up costs are consistent with previous stroke observational and randomized studies. In one systematic review of 48 published studies with 1-year follow-up costs of stroke patients, the average healthcare cost of stroke patients across all studies was $28,525 [10], which is similar to the unadjusted average total healthcare costs identified for ASA-ERDP and CLOPID patients in our study ($26,201 and $30,349, respectively). The median cost across all 48 review studies was $19,635, while the median costs for our ASA-ERPD and CLOPID patients were $14,007 and $15,967, respectively. However, the cost methodologies used in published stroke cost studies varies widely. They often involve different populations, time frames, cost components, diseases, and treatments, which complicates their direct comparison and interpretation. For example, while the average 1-year follow-up healthcare costs in the systematic review studies ranged from $7342–$146,149, the studies with higher average costs were more likely to report charges rather than amounts paid and included additional categories of costs as compared to studies with lower average costs. In addition, all costs in the reviewed studies were adjusted to 2006 US dollars using the healthcare component of the consumer price index and wage inflation indices for direct costs[10].

Stroke is common and consequential, both clinically and financially. Moreover, stroke patients usually present with more than one health condition. As demonstrated in our study, the comorbidity burden in both treatment cohorts was high. CLOPID patients appeared sicker than ASA-ERDP patients during baseline and follow-up, which may have contributed to the higher costs in CLOPID patients. However, a 9% cost difference remained after multivariate adjustment. A limitation of our study is that, while our study adjusted for many confounding factors observed in the dataset, many unobservable factors

such as disease severity and physicians' prescribing behavior were not included in the model, which could have attenuated the cost difference found between these two cohorts.

Limitations

The interpretation of our results comparing ASA-ERDP and CLOPID patients requires additional caution. While administrative claims data offer large and diverse samples of patients treated in a real-world setting away from the highly controlled environment of clinical trials, they nonetheless have some intrinsic limitations. One limitation is that claims data are collected for the purpose of payment and not research. Due to the observational nature of claims data, a pharmacy claim for a filled prescription does not guarantee that a patient adhered to the regimen as prescribed. Patients could have received medication samples from physicians, purchased over-the-counter medication (e.g., aspirin), or filled a pharmacy prescription outside the healthcare pharmacy system, all of which is not captured in the claims data. Additionally, patients were assigned to treatment cohorts without regard to treatment compliance or persistence, which may have misattributed the treatment effects on study outcomes. Similarly, administrative claims data may not accurately capture and represent a patient's medical history and a diagnosis code on a medical claim does not confirm the presence of actual disease. For example, patients may have had medical claims for an illness that was later ruled-out after diagnostic testing. As a result, patients may have been incorrectly assigned to co-morbid categories. In addition, hospital readmissions were based on medical claims with inpatient site-of-service codes, which may have overestimated the TIA and stroke readmissions results if codes for acute rehabilitation hospitals were also included.

Another limitation is that study results from observational data only demonstrate correlations and do not imply a causal relationship. Therefore, the baseline demographic and clinical characteristics were associated with the observed cost difference, and the index treatment did not cause one group to have higher healthcare costs than the other in this study. In fact, there were a number of observed and unobservable factors not included in the cost model such as the patient's treatment history and disease severity that may have explained the observed cost difference between the ASA-ERDP and CLOPID cohorts. For example, the incomplete ascertainment of disease severity may have led to residual confounding in the observed treatment effect on costs.

Finally, although AHA/ASA also recommends the use of aspirin and ticlopidine, this database does not capture over-the-counter drug use such as aspirin and no patients in the database had a ticlopidine claim within 30 days post-discharge. Thus, our study results are primarily applicable to TIA and stroke patients treated post-discharge with ASA-ERDP or CLOPID in stable managed care settings within the US.

Conclusion

This study found that patients first treated with ASA-ERDP within 30 days post-discharge a TIA or ischemic stroke hospitalization had significantly lower average healthcare costs than patients treated with CLOPID during the 1-year follow-up period, driven primarily by lower average medical costs. Given the significant economic burden associated with strokes, prevention and effective disease management offer an opportunity to improve patient outcomes and reduce healthcare costs. Further research into the real-world impact of oral antiplatelet therapies on clinical and economic outcomes of patients with TIA or ischemic stroke is warranted.

Transparency

Declaration of funding

Funding for this study was provided by Boehringer Ingelheim Pharmaceuticals, Inc.

Declaration of financial/other relationships

T.B., M.L., and F.L. have disclosed that they are employed by OptumInsight, a company funded by Boehringer Ingelheim to conduct this study. M.L.M. disclosed that she was employed by PharmaNet/i3, a company that provided medical consultation for this study, which was paid for by the sponsor. K.L. disclosed that she was employed by Boston Health Economics, Inc., the company that provided statistical consultation for this study, and also paind for by the sponsor. Y.Y and S.S. have disclosed that they are employed by Boehringer Ingelheim Pharmaceuticals, Inc., the company that funded this study.

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Appendix: Codes for selected comorbid conditions

Conditions	Code type	Codes
Atrial fibrillation	ICD-9 dx	427.31
Congestive heart failure	ICD-9 dx	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx
Diabetes mellitus	ICD-9 dx	249.xx, 250.xx, 357.2, 362.0 x, 366.41, 648.0 x, 775.0, 996.57, V45.85, V53.91, V58.67, E932.3
	HCPCS	A9274, G8385, G8386, G8390, S3000, S9140, S9141, S9145, S9455, S9460, S9465
Gastroesophageal reflux disease	ICD-9 dx	530.1 x, 530.81
Gastrointestinal bleeding	ICD-9 dx	456.0, 456.20, 530.21, 530.7, 530.82, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 569.86, 578.0, 578.1, 578.9
Hyperlipidemia	ICD-9 dx	272.0, 272.1, 272.2, 272.3, 272.4
Hypertension	ICD-9 dx	362.11, 401.x, 402.xx, 403.xx, 404.xx, 405.xx, 642.xx
Precerebral artery disease	ICD-9 dx	433.10, 433.20, 433.30, 433.80, 433.90, 442.81, 443.21, 443.24
	ICD-9 proc	00.63
	CPT	35005, 35390, 35501, 35508, 35509, 35601, 35642, 35691, 37215, 37216, 61613, 0075T, 0076T, 3101F
	HCPCS	G8240, G8241, G8348, S2211
Stroke, any (hemorrhagic, ischemic, undefined or ill-defined)	ICD-9 dx	431, 432.9, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436, 997.2
- Intracranial hemorrhage	ICD-9 dx	430, 431, 432.x, 997.02
- Ischemic stroke	ICD-9 dx	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91
Transient ischemic stroke	ICD-9 dx	362.34, 435.x
Transfusions for hemorrhagic events (IP, OPH, or ER facility only)	ICD-9 dx	790.01, V58.2
	ICD-9 proc	99.03, 99.04
	Revenue	381, 382
	HCPCS	C1010, C1016, C1018, C1020, C1021, C9504, C9505, P9010, P9011, P9016, P9021, P9022, P9038, P9039, P9040, P9051, P9054, P9056, P9057, P9058, S3906, S9526, S9538, S9546
Valvular heart disease	CPT	33415, 33417, 33460, 33463–33465, 33468, 33470–33472, 33474, 33475, 33496, 33600, 33602, 33660, 33665, 33670, 33676, 33684, 92990
	ICD-9 dx	036.42, 074.22, 112.81, 115.04, 115.14, 115.94, 391.1, 397.x, 424.xx, 746.0-746.2, 746.7, V42.2 V43.3
Other hemorrhagic events	ICD-9 dx	246.3, 362.81, 363.61, 363.62, 376.32, 377.42, 379.23, 446.21, 459.0, 516.1, 596.7, 599.70, 599.71, 599.72, 602.1, 620.7, 621.4, 623.6, 639.1, 719.10, 719.11, 719.12, 719.13, 719.14, 719.15, 719.16, 719.17, 719.18, 719.19, 784.7, 784.8, 786.3
Other vascular events	ICD-9 dx	325, 415.11, 415.12, 415.19, 416.2, 434.10, 437.6, 444.0, 444.1, 444.21, 444.22, 444.81, 444.89, 444.9, 445.01, 445.02, 445.81, 445.89, 449, 451.0, 451.11, 451.19, 451.2, 451.81, 451.82, 451.83, 451.84, 451.89, 451.9, 452, 453.1, 453.2, 453.3, 453.40, 453.41, 453.42, 453.50, 453.51, 453.52, 453.6, 453.71, 453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79, 453.81, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9, 459.10, 459.11, 459.12, 459.13, 459.19