Low Persistence of Antithrombotic Agents is Associated with Poor Outcomes after First-ever Acute Ischemic Stroke

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Abtract

Objective: This study investigated the time-trend persistence with antithrombotic agents (AT) and assessed the impact of AT persistence on outcome events and adverse events (AE) within two years after first-ever acute ischemic stroke (IS).

Methods: Using Taiwan's National Health Insurance claims dataset, 7,341 IS subjects hospitalized between 2001 and 2005 with AT prescribed at discharge and survived at least 3 months were followed up for 2 years. Time-trends of AT usage were analyzed. Medication persistence was assessed as the proportion of days covered (PDC) for filled prescription, and categorized into low, intermediate and high persistence. Multivariate logistic regression analysis and multivariate Cox proportional hazard regression models were performed to identify factors associated with AT persistence and its impact on vascular outcomes.

Results: AT persistence rates declined sharply from 81% to 52% during the first 6 months. In addition to patient and facility-level characteristics, occurrence of AE (e.g., GI bleeding/ulceration, fractures/major trauma, and iatrogenic/unspecific illness) was inversely related to AT persistence. Compared with patients with low persistence, the composite risk of recurrent stroke, cardiovascular disease, or death from any cause was significantly lower in patients with intermediate (Hazard Ratio [HR] 0.64, 0.57-0.71) or high AT persistence (0.74, 0.66-0.83).

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Conclusion: This study found a suboptimal persistence to AT and associated poor outcomes within two years after IS. Occurrence of AEs was associated with non-persistence, it highlighted the prudent prescription by physicians to optimize patients' medication persistence and hence improve patient's outcomes.

Keywords: Persistence, Antithrombotic Agents, Outcomes, Acute Ischemic Stroke

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INTRODUCTION

Cerebrovascular disease (CVD) is the leading cause of death and disability worldwide[1,2], with ischemic stroke (IS) the most prevalent form of CVD[3-5]. Half of the subjects incurred readmission or death during the first year after stroke in spite of the medical attentions and measures to prevent various adverse events (AE)[5,6].

Antithrombotic agents (AT) including antiplatelet agents and anticoagulants are recommended to be used to prevent recurrent vascular events for patients with prior IS or TIA[7-13]. Use of AT reduced the composite risk of stroke, myocardial infarction or vascular death by 16-30% at a cost of minimal risk of AE including bleeding[14-17].

In spite of the benefits, good compliance and persistence of AT are mandatory to ensure a better outcome[18,22]. Although discontinuation of AT would be avoided, data from well-organized trials or registries with rigorous monitoring schedule reported a high likelihood of non-persistence of secondary preventive medications after stroke[23-29]. Non-persistence might be a crucial factor that hampered the efficacy of AT. However, the impact of AT persistence on long-term AE is not easily available outside clinical trials or registries. Exploration of factors associated with AT persistence in routine practice might be important for healthcare reform to promote persistence and hence improve outcomes with modifiable factors from patient, provider, and system-level explored.

Therefore, by using claims data sampled from a national representative cohort, this study aimed to investigate the time-trend persistence of AT, identify factors associated with AT persistence, and assess the impact of AT persistence on 2-year outcomes and AE under a universal health insurance system.

METHODS

Data Source and Study Subjects

The National Health Insurance Research database (NHIRD), maintained by the National Health Research Institutes (NHRI), is population-based and derived from the claims data of the NHI program. In order to facilitate medical research and inquiry, information from the NHIRD is provided to scientists in Taiwan[30]. This retrospective cohort study utilized the Longitudinal Health Insurance Database 2005 (LHID2005), a subset of NHIRD, as a representative cohort to identify a stroke sample. LHID2005 contains one million individuals randomly sampled from the Registry for Beneficiaries of the NHIRD out of approximately 23.72 million NHI enrollees at year 2005. The distribution of age, sex and health service utilization of the cohort are known to resemble the entire population in Taiwan[31]. Virtually all patients suffering from stroke are hospitalized under NHI program, regardless of severity.

Subjects were selected from the NHI inpatient files with the first 3 discharge diagnoses being acute ischemic stroke (ICD-9-CM codes 433 to 437) between Jan.2001 and Dec.2005. All relevant files from the LHID2005 (including inpatient expenditures/ details of orders by admissions, details of emergency room (ER) prescription, ambulatory care expenditures/ details of orders by visits, prescriptions/ expenditure dispensed at contracted pharmacies, and registry for beneficiaries/ contracted medical facilities) were retrieved and compiled into an analytical file at the patient-level, spanning from 2000 through 2007. The first admission of each patient during the study period was considered as the index stroke. The admission date of the index stroke or any emergency

room stay preceding that event was regarded as the date of onset. To approximate an incident cohort of first-ever stroke, subjects with medical records for late effects of stroke (438) prior to the index stroke were excluded. This resulted in a first-ever IS sample from 2001 to 2005, and followed for a 24-month period up to December 31, 2007. This study protocol has been approved by the Joint Institutional Review Board in Taiwan (JIRB Protocol No.12-S-014).

Characteristics of Subjects

Characteristics of subjects were collected, which included demographics (age, sex), pre-morbid risk factors, clinical characteristics (stroke type, stroke severity proxies, brain imaging, comorbidity, use of inpatient rehabilitation services, initial length of stay), and facility characteristics (admission ward, hospital accreditation level, geographic region). Ischemic stroke types were categorized as: cerebral infarction (CI) (ICD-9-CM codes 433 to 437 except 435); transient ischemic attack (TIA) (ICD-9-CM codes 435); and other unspecified or ill-defined CVD (Unspecified). The presence of pre-morbid risk factors was defined as having diagnosed with diabetes mellitus (DM), hypertension, atrial fibrillation (AF)/ arrhythmia, coronary artery disease (CAD)/ ischemic heart disease, and hyperlipidemia on at least three occasions from ambulatory care records; or one occasion from inpatient records during the previous year throughout the initial hospitalization period for the index stroke. The prescription of brain imaging was explored by retrieving NHI procedure codes for brain computed tomography (CT) or magnetic resonance image (MRI) during the index episode, either at the index hospitalization or during the preceding ER stay.

As no standardized severity scale was routinely collected in this claims dataset, three surrogate measures for stroke severity were constructed from NHI procedure codes and secondary diagnoses[6,32,33], including: 1) Respiratory distress or infections; 2) Neurosurgery; and 3) Charlson Comorbidity Index (CCI)[34] used to quantify preexisting or concurrent comorbidities / complications. However, cerebrovascular disease was excluded as they were reflected in the condition being evaluated[6,32,35]. Higher scores indicated a greater burden of comorbidity.

We used the outpatient department (OPD) follow-up rate to be a proxy for the overall health care services that took place after discharge[32]. The OPD follow-up rate was calculated using the number of OPD visits and divided by the time interval (months) between index stroke discharge and the end of observation; these patients were separated into, low, moderate and high usage groups according to which tertile they were in, namely the ≤ 33th percentile, the 34-66th percentiles and ≥ 67th percentile, respectively. Admission wards were classified into neurology/rehabilitation ward (NW), neurosurgery ward (NS), and general ward/miscellaneous (GW)[5,6]. Hospital accreditation levels were classified into medical center, regional hospital and district hospital based on the number of hospital beds, sophistication of medical services and teaching status. The geographic areas where the hospitals were located were categorized into 6 regions: Taipei, Northern, Central, Southern, Kao-Ping, and Eastern. The methodology to extract subject characteristics has been utilized in our previous studies[5,6,32].

Medication Persistence

Medication persistence was assessed as the proportion of days covered (PDC) for filled AT prescriptions. Use of any antiplatelet or anticoagulant, in mono- or poly-therapy, and any pattern of switching within the AT categories (aspirin, clopidogrel, ticlopidine, dipyridamole, aggrenox, and warfarin) was accepted. For each designated outcome event (OE), PDC was calculated between the date of index stroke discharge and the first occurrence of that OE. Medication persistence was classified into 3 levels: low (< 40%), intermediate (40-79%), and high (≥ 80%)[20].

In addition, since use of analgesics and antipyretics may cause a dose-related gastric ulceration, bleeding, and erosive gastritis which could preclude the continuation of using AT medications. Concomitant use of analgesics and antipyretics, including: NSAIDs, opiate agonists, opiate partial agonists, miscellaneous analgesics and antipyretics, as well as analgesics and antipyretics composite within 2 years after discharge were retrieved and analyzed with PDC calculated.

Adverse Events and Outcome Events

Adverse event (AE) is usually defined as any untoward medical occurrence in a subject administered a pharmaceutical product or a medical procedure and which

does not necessarily have a causal relationship with this treatment. In this study, five categories of AEs potentially associated with the prescription or continuation of AT within 2 years after discharge were retrieved and analyzed, including anemia/thrombocytopenia/bleeding of sensory organs, central nervous system hemorrhage (including cerebral hemorrhage, intra-cerebral hemorrhage, subdural hemorrhage, and intracranial hemorrhage), ulceration, bleeding, and erosive lesions of gastrointestinal/ urological/ reproductive systems, fractures or other major traumas, and iatrogenic or other unspecific illness identified by relevant ICD-9-CM codes.

In terms of outcome events (OEs), 4 single OEs: 1) ischemic stroke, 2) hemorrhagic stroke, 3) cardiovascular disease, and 4) all-cause mortality; as well as 4 composite OEs: 1) recurrent stroke (ischemic stroke or hemorrhagic stroke), 2) total vascular events (ischemic stroke, hemorrhagic stroke, or cardiovascular disease), 3) composite of recurrent stroke, cardiovascular disease, or death from any cause, and 4) all-cause readmission or mortality were retrieved by relevant ICD-9-CM codes and analyzed[36].

Statistical Analysis

The Statistical Analysis System (SAS System for Windows, Version 8.2, SAS Institute, Cary, NC, USA) and the Statistical Package for the Social Science (SPSS 19.0 for Windows, SPSS, Chicago, IL, USA) were used for data retrieval, compilation, and statistical analyses. Chi-square tests for categorical variables and one-way ANOVA for continuous variables were conducted to compare the basic characteristics and incidence of AEs among subjects with low, intermediate and high AT persistence. Time-trends of using AT for 3 IS subtypes as well as warfarin use for IS subjects with history of atrial fibrillation/ arrhythmia within 2 years after discharge from index hospitalization were plotted and analyzed by time series autocorrelation function. Multivariate logistic regression analysis was performed to identify factors associated with AT persistence. Multivariate Cox proportional hazard (Cox-PH) regression models with bias-corrected bootstrapping were performed to explore the causal relationship between AT persistence and occurrence of each designated OE. A sensitivity analysis was performed to test the validity and robustness of the findings using hypertension and GI bleeding or ulceration, two diseases positively and reversely related to AT persistence, respectively.

RESULTS

From 2001-2005, 8,946 first-ever acute IS subjects were identified from the LHID2005, with AT prescribed in 80% of the subjects during initial hospitalization for the index stroke. With AT prescribed within 1 month after onset and survived more than 3 months, 7,341 subjects were selected to be the inception cohort and followed-up for 2 years to assess their AT persistence (figure 1). When taking into account whether remaining on the same AT or a switch to another AT among aspirin, clopidogrel, ticlopidine, dipyridamole, aggrenox, and warfarin; the overall PDC of AT during 2-year follow-up period was 53±33% in total, with 56±32% in CI, 46±33% in TIA, and 50±34% in unspecified subjects ($p < 0.001$) (supplemental table 1). Within the first 6 months, a sharp decline of persistence rates was found from 84% to 57%, 74% to 42%, and 77% to 47% in CI, TIA and unspecified, respectively. From 7 to 24 months, there was a slow yet continuous decline of persistence from 55% to 44%, 40% to 36%, and 46% to 40% in CI, TIA and unspecified, respectively (supplemental figure 1).

Among 7,341 subjects, 3,032 subjects (41%) were classified into low persistence (PDC <40%), 2,414 subjects (33%) were intermediate persistence (PDC =40-79%), and 1,895 subjects (26%) were high persistence (PDC ≥ 80%); intermediate and high persistence were combined as "persistent", while low persistence was regarded as "non-persistent". The mean age was 67.8 ± 11.9 years, 56% were male (table 1). Patient- and facility-level variables associated with 24-month AT persistence with stepwise logistic regression were shown in table 2. Subjects who were aged ≥ 80 years, incurred respiratory distress or infections, and admitted to hospitals outside of Taipei region during initial hospitalization tended to have lower AT persistence during 2-year follow-up period. Lower AT persistence was also found in subjects with occurrence of AEs, such as GI bleeding or ulceration, fractures or major traumas, or iatrogenic or unspecific illness. Subjects who had CI, pre-morbid risk factors, brain imaging or rehabilitation during initial hospitalization; initial management in the neurology wards, medical

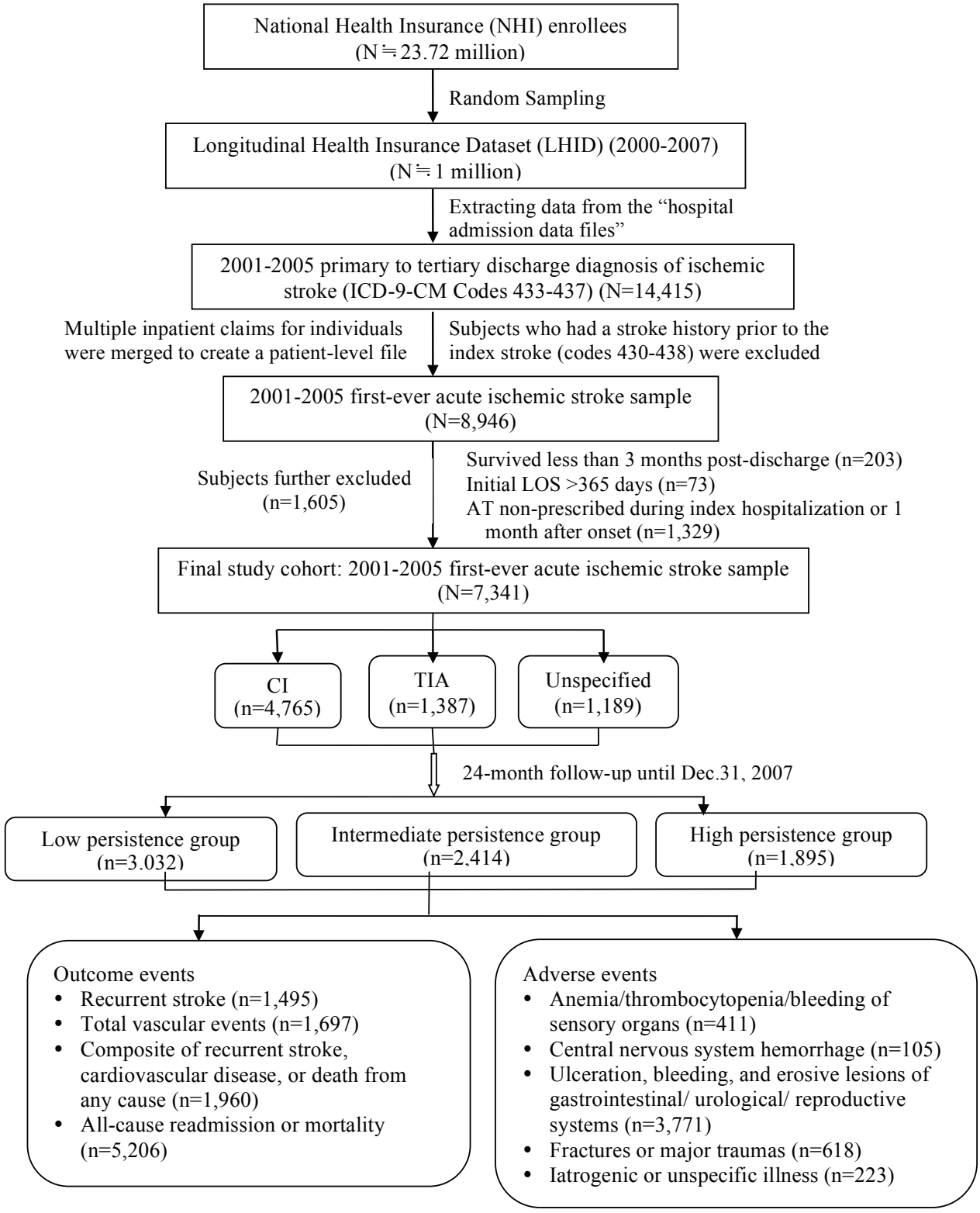

Figure 1. Flow diagram of enrollment for medication persistence after first-ever ischemic stroke subjects

Table 1. Subjects' Characteristics Stratified by Persistence of Antithrombotic Agents (N =7,341)

	Total (N=7,341)		Low persistence (n=3,032)		Intermediate persistence (n=2,414)		High persistence (n=1,895)		p value
	N	(%)	n	(%)	n	(%)	n	(%)	
Demographic & clinical Characteristics									
Age (years, mean±SD)	67.8	±11.9	67.7	±13.0	67.7	±11.4	68.0	±10.7	0.702
Sex, male	4,110	(56.0)	1,695	(55.9)	1,347	(55.8)	1068	(56.4)	0.928
Diabetes mellitus	2,517	(34.3)	876	(28.9)	866	(35.9)	775	(40.9)	<0.001
Hypertension	5,027	(68.5)	1,874	(61.8)	1,726	(71.5)	1,427	(75.3)	<0.001
Atrial fibrillation/ arrhythmia	887	(12.1)	305	(10.1)	317	(13.1)	265	(14.0)	<0.001
Coronary artery disease/ ischemic heart disease	1,639	(22.3)	562	(18.5)	572	(23.7)	505	(26.6)	<0.001
Hyperlipidemia	1,583	(21.6)	502	(16.6)	608	(25.2)	473	(25.0)	<0.001
CCI (mean±SD)	1.8	±2.1	1.7	±2.1	1.8	±2.0	2.0	±2.1	<0.001
Brain imaging	5,851	(79.7)	2,309	(76.2)	1,978	(81.9)	1,564	(82.5)	<0.001
Respiratory distress or infections	2,027	(27.6)	892	(29.4)	629	(26.1)	506	(26.7)	0.013
Neurosurgery	53	(0.7)	25	(0.8)	19	(0.8)	9	(0.5)	0.333
Inpatient rehabilitation use	2,606	(35.5)	854	(28.2)	923	(38.2)	829	(43.7)	<0.001
Initial LOS (days, mean±SD)	12.4	±18.0	12.2	±20.5	12.4	±16.7	12.7	±14.7	0.656
Facility characteristics									
Admission department									<0.001
NW	4,829	(65.8)	1,793	(59.1)	1,720	(71.3)	1,316	(69.4)	
NS	156	(2.1)	83	(2.7)	37	(1.5)	36	(1.9)	
GW	2,356	(32.1)	1,156	(38.1)	657	(27.2)	543	(28.7)	
Hospital accreditation Level									<0.001
Medical center	2,343	(31.9)	810	(26.7)	922	(38.2)	611	(32.2)	
Regional hospital	3,262	(44.4)	1,332	(43.9)	1,041	(43.1)	889	(46.9)	
District hospital	1,736	(23.7)	890	(29.4)	451	(18.7)	395	(20.8)	
Geographic region									<0.001
Taipei	1,937	(26.4)	683	(22.5)	697	(28.9)	557	(29.4)	
Northern	1,289	(17.6)	550	(18.1)	418	(17.3)	321	(16.9)	
Central	1,404	(19.1)	596	(19.7)	400	(16.6)	408	(21.5)	
Southern	1,177	(16.0)	527	(17.4)	393	(16.3)	257	(13.6)	
Kao-Ping	1,322	(18.0)	579	(19.1)	435	(18.0)	308	(16.3)	
Eastern	212	(2.9)	97	(3.2)	71	(2.9)	44	(2.3)	
Adverse events (AEs) within 2 years									
Anemia or thrombocytopenia	411	(5.6)	202	(6.7)	121	(5.0)	88	(4.6)	0.003
Hemorrhagic stroke	105	(1.4)	48	(1.6)	32	(1.3)	25	(1.3)	0.652
GI bleeding or ulceration	3,771	(51.4)	1593	(52.5)	1231	(51.0)	947	(50.0)	0.194
Fractures or major traumas	618	(8.4)	293	(9.7)	204	(8.5)	121	(6.4)	<0.001
Iatrogenic or unspecific illness	223	(3.0)	116	(3.8)	68	(2.8)	39	(2.1)	0.002

CI: Cerebral infarction; TIA: Transient ischemic attack; Unspecified: Other unspecified or ill-defined cerebrovascular diseases; CCI: Charlson Comorbidity Index; NW: Neurology/ rehabilitation wards; NS: Neurosurgery wards; GW: General wards, including general medicine and other wards

Table 2. Characteristics Associated with Persistence of Antithrombotic Agents (N = 7,341)

	Persistent *(intermediate + high persistence) Vs* ***Non-persistent*** *(low persistence)*				
Variables	*Adjusted OR* (95% CI)		***Variables***	*Adjusted OR* (95% CI)	
Demographic Characteristics			CCI subgroup	NS	
Age			0		
≦ 64	1.00	(Reference)	1 – 2		
65-74	1.07	(0.94- 1.20)	³3		
75-79	1.03	(0.88- 1.21)	***Facility Characteristics***		
≧ 80	0.75*	(0.64- 0.88)	Admission department		
Sex	NS		NW	1.37*	(1.21- 1.56)
Male			NS	0.84	(0.59- 1.19)
Female			GW	1.00	(Reference)
Pre-morbid Risk Factors			Hospital accreditation Level		
Diabetes mellitus			Medical center	1.42*	(1.22- 1.66)
Yes	1.26*	(1.13- 1.40)	Regional hospital	1.19	(1.04- 1.37)
No	1.00	(Reference)	District hospital	1.00	(Reference)
Hypertension			Geographic region		
Yes	1.49*	(1.33- 1.66)	Taipei	1.00	(Reference)
No	1.00	(Reference)	Northern	0.83*	(0.71- 0.97)
Atrial fibrillation/arrhythmia			Central	0.75*	(0.64- 0.87)
Yes	1.46*	(1.24- 1.71)	Southern	0.67*	(0.57- 0.79)
No	1.00	(Reference)	Kao-Ping	0.65*	(0.56- 0.76)
Coronary artery disease / ischemic heart disease			Eastern	0.72*	(0.53- 0.98)
Yes	1.50*	(1.32- 1.71)	OPD follow-up rate		
No	1.00	(Reference)	Low	1.00	(Reference)
Hyperlipidemia			Intermediate	2.31*	(2.04- 2.61)
Yes	1.43*	(1.26- 1.63)	High	2.70*	(2.36- 3.10)
No	1.00	(Reference)	***Use of analgesics & antipyretics***		
Clinical Characteristics			PDC, low	1.00	(Reference)
Ischemic stroke subtype			PDC, intermediate	1.38*	(1.17- 1.62)
CI	1.48*	(1.29- 1.70)	PDC, high	1.68*	(1.25- 2.24)
TIA	1.00	(Reference)	***Adverse Events (AEs)***		
Unspecified	1.09	(0.92- 1.29)	Anemia or thrombocytopenia	NS	
Brain imaging			Yes		
Yes	1.21*	(1.06- 1.38)	No		
No	1.00	(Reference)	Hemorrhagic stroke	NS	
Respiratory distress or infections			Yes		
Yes	0.74*	(0.66- 0.83)	No		
No	1.00	(Reference)	GI bleeding or ulceration		
Neurosurgery	NS		Yes	0.75*	(0.67- 0.83)
Yes			No	1.00	(Reference)
No			Fractures or major traumas		
Inpatient rehabilitation use			Yes	0.76*	(0.64- 0.91)
Yes	1.40*	(1.25- 1.57)	No	1.00	(Reference)
No	1.00	(Reference)	Iatrogenic or unspecific illness		
			Yes	0.56*	(0.42- 0.75)
			No	1.00	(Reference)

NS: Non-significant in the multivariate stepwise logistic regression model; * Statistical significance; CI: Cerebral infarction; TIA: Transient ischemic attack; Unspecified: Other unspecified or ill-defined cerebrovascular diseases; CCI: Charlson Comorbidity Index; NW: Neurology/ rehabilitation wards; NS: Neurosurgery wards; GW: General wards, including general medicine and other wards

Table 3. Association between Persistence of Antithrombotic Agents and Two-year Outcome Events for Ischemic Stroke Patients Based on the Multivariate Cox-PH Regression Analyses (N=7,341)

	Crude Event Rates			***Multivariate Cox-PH Regression Analyses***	
	No. of affected	No. of followed-up	(%)	Adjusted HRs (95% CI)	
Prespecified OE					
Ischemic stroke	***1,432***	***7,341***	***(19.5)***		
Low persistence	750	3,304	(22.7)	1.00	(Reference)
Intermediate persistence	338	2,235	(15.1)	0.60*	(0.53- 0.67)
High persistence	344	1,802	(19.1)	0.74*	(0.64- 0.84)
Hemorrhagic stroke	***105***	***7,341***	***(1.4)***		
Low persistence	53	3,037	(1.7)	1.00	(Reference)
Intermediate persistence	22	2,404	(0.9)	0.51*	(0.30- 0.80)
High persistence	30	1,900	(1.6)	0.96	(0.59- 1.53)
Cardiovascular disease	***340***	***7,341***	***(4.6)***		
Low persistence	163	3,083	(5.3)	1.00	(Reference)
Intermediate persistence	88	2,367	(3.7)	0.68*	(0.52- 0.88)
High persistence	89	1,891	(4.7)	0.84	(0.63- 1.10)
All-cause mortality	***403***	***7,341***	***(5.5)***		
Low persistence	222	3,044	(7.3)	1.00	(Reference)
Intermediate persistence	128	2,140	(6.0)	0.82	(0.66- 1.04)
High persistence	53	2,157	(2.5)	0.57*	(0.41- 0.75)
Composite OE					
Recurrent stroke (ischemic or hemorrhagic stroke)	1,495	7,341	(20.4)		
Low persistence	781	3,308	(23.6)	1.00	(Reference)
Intermediate persistence	351	2,228	(15.8)	0.59*	(0.52- 0.67)
High persistence	363	1,805	(20.1)	0.75*	(0.66- 0.85)
Total vascular events (recurrent stroke or cardiovascular disease)	***1,697***	***7,341***	***(23.1)***		
Low persistence	871	3,325	(26.2)	1.00	(Reference)
Intermediate persistence	410	2,207	(18.6)	0.63*	(0.56- 0.71)
High persistence	416	1,809	(23.0)	0.76*	(0.68- 0.87)
Composite of recurrent stroke, cardiovascular disease, or death from any cause	**1,960**	**7,341**	**(26.7)**		
Low persistence	1,026	3,329	(30.8)	1.00	(Reference)
Intermediate persistence	485	2,207	(22.0)	0.64*	(0.57- 0.71)
High persistence	449	1,805	(24.9)	0.74*	(0.66- 0.83)
All-cause readmission or mortality	***5,206***	***7,341***	***(70.9)***		
Low persistence	2,466	3,371	(73.2)	1.00	(Reference)
Intermediate persistence	1,332	2,085	(63.9)	0.73*	(0.68- 0.77)
High persistence	1,408	1,885	(74.7)	0.84*	(0.78- 0.89)

Model was adjusted for age, gender, onset year, pre-morbid risk factors (DM, hypertension, AF/arrhythmia, CAD/ischemic heart disease, hyperlipidemia), stroke subtype, CCI; and brain imaging, respiratory disease/infections, neurosurgery, rehabilitation use, admission department, hospital level, geographic region, and use of NSAID)

centers/regional hospitals tended to have higher AT persistence. For use of analgesics and antipyretics, 6,168 subjects (84%) were classified into low persistence, 906 subjects (12%) were intermediate persistence, and 267 subjects (4%) were high persistence and concomitant use of analgesics and antipyretics were associated with higher AT persistence. Additionally, the result of sensitivity analysis found the hypertension group had higher AT persistence (OR, 1.49, $p < 0.05$). In contrast, GI bleeding or ulceration had lower AT persistence (OR, 0.75, $p < 0.05$) (table 2).

Compared with the low persistence, both the intermediate and high persistence decreased the risk for the recurrence of ischemic stroke (HR, 0.60 and 0.74, respectively). Compared with the low persistence, only the intermediate persistence decreased the risk for occurrence of hemorrhagic stroke (HR, 0.51, $p < 0.05$) and incidence of cardiovascular disease (HR, 0.68, $p < 0.05$). In contrast, compared with the low persistence, high persistence decreased the risk for the occurrence of all-cause mortality (HR, 0.57, $p < 0.05$) (table 3) (figure 2).

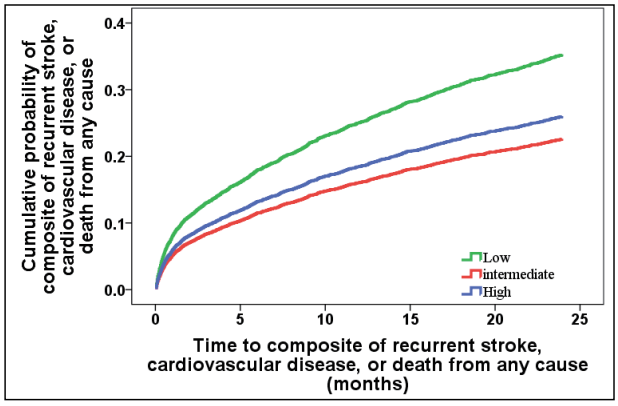

Figure 2-1. Cumulative incidence of composite of recurrent stroke, cardiovascular disease, or death from any cause among 3 persistence levels within 2 years after discharge from index hospitalization for IS subjects (N=7,341)

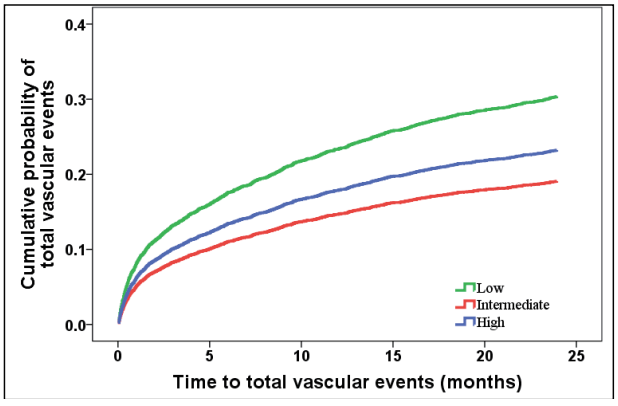

Figure 2-2. Cumulative incidence of total vascular events among 3 persistence levels within 2 years after discharge from index hospitalization for IS subjects (N=7,341)

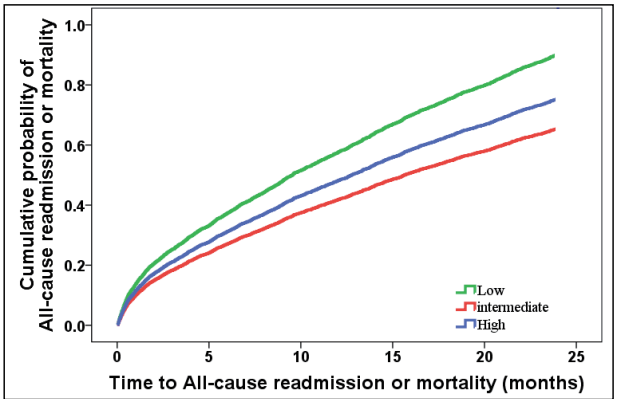

Figure 2-3. Cumulative incidence of all-cause readmission or mortality among 3 persistence levels within 2 years after discharge from index hospitalization for IS subjects (N=7,341)

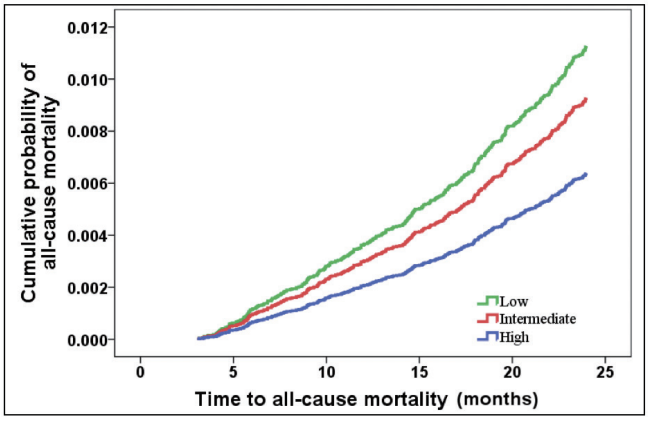

Figure 2-4. Cumulative incidence of all-cause mortality among 3 persistence levels within 2 years after discharge from index hospitalization for IS subjects (N=7,341)

DISCUSSION

This study found a suboptimal persistence of AT associated and the low persistence was associated with poor outcomes within two years after IS. Our data accessing long-term persistence rate in IS which are still limited but important for clinician, health care systems and insurance providers. From our study, the incidence of AEs from ulceration, bleeding and erosive lesions was high. Occurrence of AEs was associated with non-persistence.

There were several strengths to this study. First, the NHIRD we used was a comprehensive and national database captured a population of patients with diagnosis of IS. It avoided selection bias, recall bias and fragmental care information allowing systematically observing the relationships between medication persistence and OE in a population-based cohort of stroke patients. Second, we defined the research variables rigorously and sophisticatedly analyzed date with bootstrap approach to improve construction and internal validation. Third, this research simultaneously explored the antecedents and outcomes of AT persistence to provide a whole picture that is still limited in the study field. Finally, exploration of incidence and factors related to the persistence in daily practice might be important at the health care reform and the drug reimbursement policies to demonstrate efforts of providing adequate quality of care of patients after stroke[19,21,37-39]. Data from insurance claim dataset might describe the practice pattern of prescription utilization and the outcome events in a natural way without purified and artificial manipulation[37,40].

In this nationwide follow-up study, among those who had AT prescribed during index hospitalization or 1 month after stroke, 36% to 44% of subjects had regular prescription of AT in the study period. AT persistence rates declined sharply from 81% to 52% during the first 6 months and a slow yet continuous drop from 51% to 42% during 7 to 24 months. The sharp decline during the first 6 months and suboptimal persistence rates were compatible to previous studies. From study period of 12 months to 2 years after stroke, from 45% to 73% reported, AT persistence had the considerable variation, but all the results pointed out AT persistence needed to be improved in daily practice[25,27,38,41]. Recently, though with promising efficacy and minimal AE, even with the Hawthorne effects existed, real world data from new oral anticoagulants post marketing studies confronted unsatisfactory persistence rates attributed to a variety of factors at multi-level aspects, including patient-related, socioeconomic, stroke-related, therapy-related, and health system or caregiver-related factors[18,37,40,42].

Our study showed age > 80 years, existence of pre-morbid factors, and CI subgroup were associated with higher persistence. Existence of pre-morbid factors (e.g., hypertension, diabetes, hyperlipidemia) at patient level improved medication persistence that was similar with past research[23,26,27,39,42]. Patients treated at department of neurology and medical center who had high OPD follow up rates were associated with AT persistence. Our results supported the processes and outcomes of IS care influenced by the hospital level of care. The AT persistence rate IS in our study was considered modest and even lower than literature which might be due to unexpected high occurrence of AE, such as 51.4% of subjects incurred ulceration, bleeding, or erosive lesions of gastrointestinal/ urological/ reproductive systems within the study period. Bleeding complications might be an inevitable cause of discontinuing AT therapy[43]. Additionally, our supplemental analysis found concomitant use of analgesics and antipyretics was positively associated with AT persistence as well as the occurrence of GI bleeding and ulceration. The results indicated use of analgesics and antipyretics may increase the risk of GI bleeding and ulceration, but it may also improve AT persistence to indirectly prevent vascular diseases.

This study found that compared to low persistence, the risk of the occurrences of stroke, cardiovascular disease, and death from any cause were significantly lower in patients with intermediate and high persistence[26]. Except all-cause mortality, there was no difference of the occurrences of OEs between intermediate and high persistence. Fewer incidence of hemorrhagic stroke was found in intermediate persistence. This finding might be suggestive of an optimal range of AT persistence such as 40%-79% existed on IS patient for OE prevention with the same efficacy but less AE.

There were several limitations of this study. First, despite the AT prescribing in Taiwan being conducted through NHIRD, the real taking-drug behavior was not examined directly and PDC might be over-estimated.

Second, NHIRD is a secondary dataset that was collected by NHI claims else for our purpose. A few factors associated with AT persistence and OEs were not to be recorded in the database, such as patient concerns and belief about medication[21,44] and patient and their supporter socioeconomic factors[23,26,27]. Third, the relationship between low adherence and adverse event may be due to health use bias[45]. The relationships among AEs, medication persistence, and OEs contributed some insights into the daily practice; however, the causal relationships have not yet been verified and leading to a bias to estimate the true risk attributed to antiplatelet drug discontinuation[21]. Finally, the medication adherence (compliance) is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen. And, medication persistence is described as the duration of time from initiation to discontinuation of therapy. From literature review, with the same study design, some studies used adherence while some used persistence (https://www.pharmacist.com/adherence-vs-persistence).

CONCLUSION

AT persistence after IS was lower than expected with rapid decline in the first six months and slow decline in the subsequent 18 months. Not only patient characteristics but also facility characteristics were associated with AT long-term persistence. In addition, this study found a suboptimal persistence to AT persistence and the persistence and OE by stroke survivors was inversely related within two years after IS. Occurrence of AEs was associated with non-persistence. These results highlighted the importance of conducting strategies to improve AT persistence and the risk-benefit profile of medication treatment must be considered and monitored for optimizing prescription.

ACKNOWLEDGEMENTS

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Supplemental Table 1. Use of antithrombotic agents (AT) within 2 years after discharge from index hospitalization among 3 ischemic stroke Subtypes (N=7,341)

	Total (N=7,341)		***CI (n=4,765)***		***TIA (n=1,387)***		***Unspecified (n=1,189)***		*p value*
	N	(%)	N	(%)	N	(%)	N	(%)	
Use of AT									
Aspirin	5,280	(71.9)	3,482	(73.1)	964	(69.5)	834	(70.1)	0.011†§
Clopidogrel/Ticlopidine	1,955	(26.6)	1,407	(29.5)	298	(21.5)	250	(21.0)	<0.001†§
Dipyridamole	1,792	(24.4)	1,068	(22.4)	398	(28.7)	326	(27.4)	<0.001†§
Warfarin	530	(7.2)	400	(8.4)	75	(5.4)	55	(4.6)	<0.001†§
A or C/T or D	6,651	(90.6)	4,381	(91.9)	1,220	(88.0)	1,050	(88.3)	<0.001†§
A or C/T or D or W	6,852	(93.3)	4,530	(95.1)	1,248	(90.0)	1,074	(90.3)	<0.001†§
A and D (A+D or aggrenox)	1,522	(20.7)	1,034	(21.7)	235	(16.9)	253	(21.3)	<0.001†‡
PDC* (%, mean±SD)									
Aspirin	39	±31	40	±31	34	±31	39	±31	<0.001†‡
Clopidogrel/Ticlopidine	33	±29	34	±29	28	±25	32	±30	0.004†
Dipyridamole	16	±23	15	±22	16	±23	17	±25	0.386
Warfarin	42	±33	43	±33	38	±32	39	±33	0.416
A or C/T or D	51	±33	53	±32	44	±33	49	±34	<0.001†‡§
A or C/T or D or W	53	±33	56	±32	46	±33	50	±34	<0.001†‡§
A and D (A+D or aggrenox)	23	±27	23	±27	24	±28	21	±25	0.449
PDC category*, AT (A, C/T, D, or W)									0<0.001
0 – 39%	3,032	(41.3)	1,750	(36.7)	709	(51.1)	573	(48.2)	
40% – 79%	2,414	(32.9)	1,675	(35.2)	414	(29.9)	325	(27.3)	
80% – 100%	1,895	(25.8)	1,340	(28.1)	264	(19.0)	291	(24.5)	

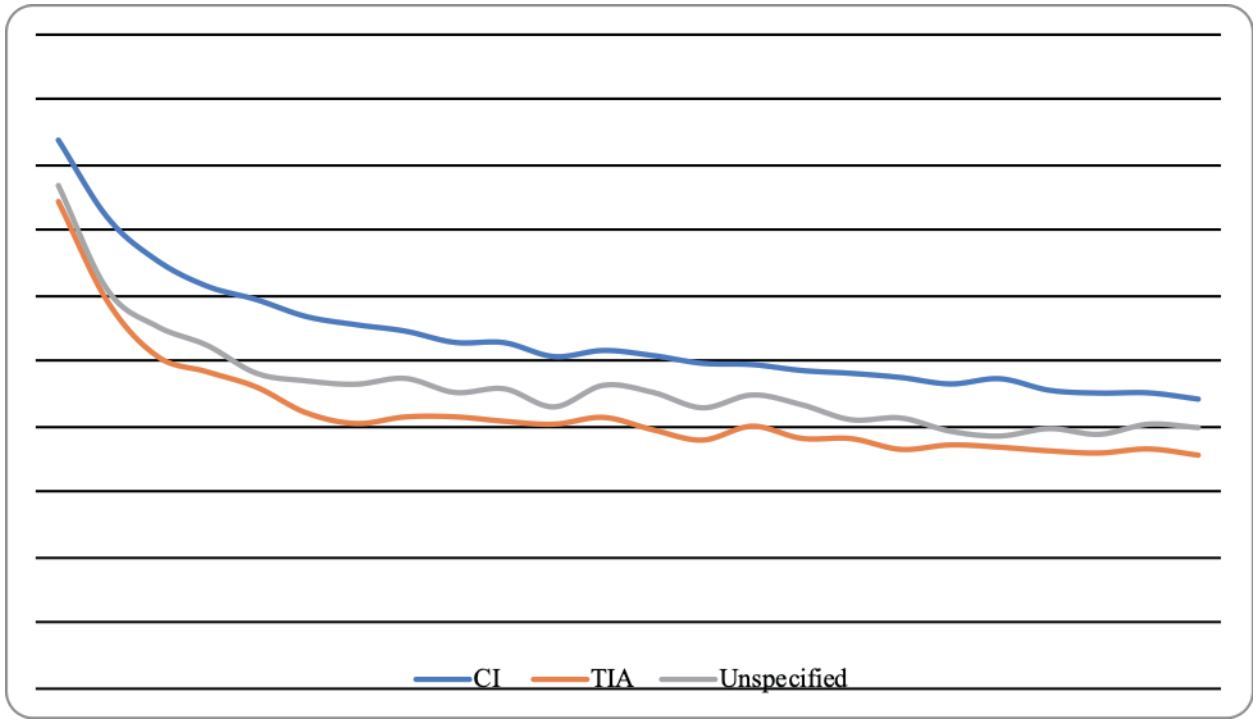
PDC: Proportion of days covered

*The numbers were calculated upon users for each drug or drug class within 2 years after discharge.

†Significant difference between CI and TIA (P<.05)

‡Significant difference between TIA and Unspecified (P<.05)

§Significant difference between CI and Unspecified (P<.05)



	1 Month	3 Months	6 Months	12 Months	18 Months	24 Months	Time-trend P value§
CI	83.7%	65.3%	56.8%	51.6%	47.4%	44.1%	<0.001
TIA	74.3%	50.7%	42.1%	41.4%	36.5%	35.6%	<0.001
Unspecified	76.6%	55.2%	46.9%	46.2%	41.3%	39.8%	<0.001
Total	80.8%	60.9%	52.4%	48.8%	44.3%	41.8%	<0.001
P value	<0.001*‡	<0.001*†‡	<0.001*†‡	<0.001*†‡	<0.001*†‡	<0.001*‡	

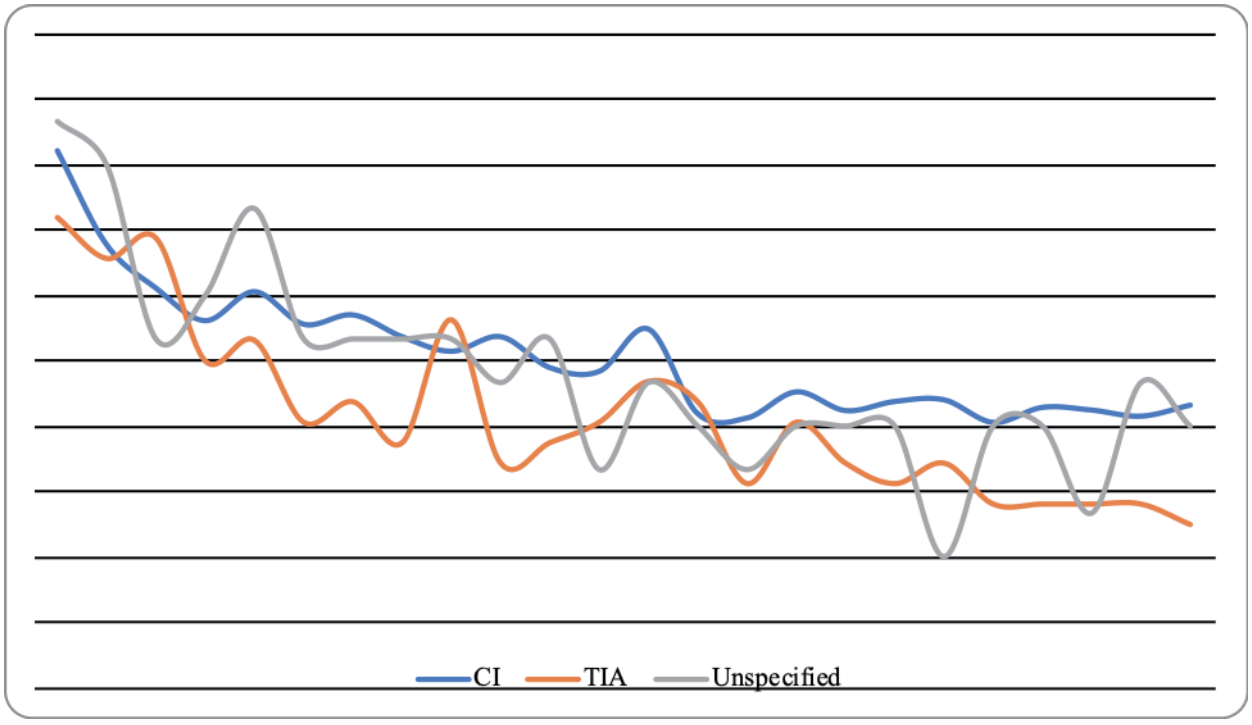
* Significant difference between CI and Unspecified (P<.05).

† Significant difference between Unspecified and TIA (P<.05).

‡ Significant difference between CI and TIA (P<.05).

§ P-value using time series autocorrelation function (AR(1)) among 24 months

Supplemental Figure 1-1. Time-trends of using AT including: aspirin, clopidogrel, ticlopidine, dipyridamole, aggrenox, and warfarin within 2 years after discharge from index hospitalization (N = 7,341)



	1 Month	3 Months	6 Months	12 Months	18 Months	24 Months	Time-trend p value§
CI	82.2%	61.1%	55.6%	48.3%	43.7%	43.1%	<0.001
TIA	71.9%	68.8%	40.6%	40.6%	31.3%	25.0%	<0.001
Unspecified	86.7%	53.3%	53.3%	33.3%	40.0%	40.0%	<0.001
Total	81.1%	61.7%	53.3%	46.2%	41.6%	40.2%	<0.001
P value	0.329	0.565	0.296	0.457	0.507	0.269	

Supplemental Figure 1-2. Time-trends of using warfarin within 2 years after discharge from index hospitalization for IS subjects with atrial fibrillation/ arrhythmia (N = 887)

Supplemental file: ICD-9-CM Coding Lists for Defined Outcome Events and Adverse Events

ICD-9-CM Codes for Defined Outcome Events	
Ischemic stroke	ICD-9-CM 433-437
Hemorrhagic stroke	ICD 430-432, plus Intracranial arteriovenous malformation (AVM)/ Congenital cerebral aneurysm (ICD-9-CM 747.81)
Cardiovascular disease	ICD-9-CM 410.xx, 411.xx, 413.xx, 440.xx, 441.xx

ICD-9-CM Codes for Defined Adverse Events	
I. Anemia/Thrombocytopenia/Bleeding of Sensory Organs	
246.3	Hemorrhage and infarction of thyroid
280.0	Iron deficiency anemias, secondary to blood loss
280.1	Iron deficiency anemias, secondary to inadequate dietary iron intake
280.8	Other specified iron deficiency anemias
280.9	Iron deficiency anemia, unspecified
283	Acquired hemolytic anemias
283.0	Autoimmune hemolytic anemias
283.1	Non-autoimmune hemolytic anemias
283.10	Non-autoimmune hemolytic anemias, unspecified
283.11	Non-autoimmune hemolytic anemias, Hemolytic-uremic syndrome
283.19	Other non-autoimmune hemolytic anemias, unspecified
283.2	Hemoglobinuria due to hemolysis from external causes
283.9	Acquired hemolytic anemia, unspecified
285	Other and unspecified anemias
285.0	Sideroblastic anemia
285.1	Acute posthemorrhagic anemia
285.2	Anemia in chronic illness
285.21	Anemia in end-stage renal disease
285.22	Anemia in neoplastic disease
285.29	Anemia of other chronic illness
285.8	Other specified anemias
285.9	Anemia, unspecified
286.5	Hemorrhagic disorder due to circulating anticoagulants
286.7	Acquired coagulation factor deficiency
286.9	Other and unspecified coagulation defects
287	Purpura and other hemorrhagic conditions
287.0	Allergic purpura
287.1	Qualitative platelet defects
287.2	Other nonthrombocytopenic purpuras
287.3	Primary thrombocytopenia

287.4	Secondary thrombocytopenia
287.5	Thrombocytopenia, unspecified
287.8	Other specified hemorrhagic conditions
287.9	Unspecified hemorrhagic conditions
362.43	Hemorrhagic detachment of retinal pigment epithelium
362.81	Retinal hemorrhage
363.6	Choroidal hemorrhage and rupture
363.61	Choroidal hemorrhage, unspecified
363.62	Expulsive choroidal hemorrhage
363.72	Hemorrhagic choroidal detachment
364.41	Hyphema
372.72	Conjunctival hemorrhage
374.81	Hemorrhage of eyelid
376.32	Orbital hemorrhage
377.42	Hemorrhage in optic nerve sheaths
379.23	Vitreous hemorrhage
381.03	Acute sanguinous otitis media
381.06	Acute allergic sanguinous otitis media
II. Central Nervous System Hemorrhage	
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432	Other and unspecified intracranial hemorrhage
432.0	Nontraumatic extradural hemorrhage
432.1	Subdural hemorrhage
432.9	Unspecified intracranial hemorrhage
III. Ulceration, Bleeding, and Erosive Lesions of Gastrointestinal/Uurological/Reproductive Systems	
440-448	Diseases Of Arteries, Arterioles, And Capillaries
441	Aortic aneurysm and dissection
454.1	Varicose veins of lower extremities with inflammation
454.2	Varicose veins of lower extremities with ulcer and inflammation
454.9	Varicose veins of lower extremities without mention of ulcer or inflammation
455.1	Internal thrombosed hemorrhoids
455.4	External thrombosed hemorrhoids
455.7	Unspecified thrombosed hemorrhoids
456.0	Esophageal varices with bleeding
456.20	Esophageal varices with bleeding
459.0	Hemorrhage, unspecified
530-537	Diseases Of Esophagus, Stomach, And Duodenum

530.1	Esophagitis
530.10	Esophagitis, unspecified
530.11	Reflux esophagitis
530.19	Other esophagitis
530.2	Ulcer of esophagus
530.4	Perforation of esophagus
530.7	Gastroesophageal laceration-hemorrhage syndrome
530.8	Other specified disorders of esophagus
530.81	Esophageal reflux
530.82	Esophageal hemorrhage
530.83	Esophageal leukoplakia
531	Gastric ulcer
531.0	Gastric ulcer, acute with hemorrhage
531.00	Gastric ulcer, acute with hemorrhage, without mention of obstruction
531.01	Gastric ulcer, acute with hemorrhage, with obstruction
531.1	Gastric ulcer, acute with perforation
531.10	Gastric ulcer, acute with perforation, without mention of obstruction
531.11	Gastric ulcer, acute with perforation, with obstruction
531.2	Gastric ulcer, acute with hemorrhage and perforation
531.20	Gastric ulcer, acute with hemorrhage and perforation, without mention of obstruction
531.21	Gastric ulcer, acute with hemorrhage and perforation, with obstruction
531.3	Gastric ulcer, acute without mention of hemorrhage or perforation
531.30	Gastric ulcer, acute without mention of hemorrhage or perforation, without mention of obstruction
531.31	Gastric ulcer, acute without mention of hemorrhage or perforation, with obstruction
531.4	Gastric ulcer, chronic or unspecified with hemorrhage
531.40	Gastric ulcer, chronic or unspecified with hemorrhage, without mention of obstruction
531.41	Gastric ulcer, chronic or unspecified with hemorrhage, with obstruction
531.5	Gastric ulcer, chronic or unspecified with perforation
531.50	Gastric ulcer, chronic or unspecified with perforation, without mention of obstruction
531.51	Gastric ulcer, chronic or unspecified with perforation, with obstruction
531.6	Gastric ulcer, chronic or unspecified with hemorrhage and perforation
531.60	Gastric ulcer, chronic or unspecified with hemorrhage and perforation, without mention of obstruction
531.61	Gastric ulcer, chronic or unspecified with hemorrhage and perforation, with obstruction
531.7	Gastric ulcer, chronic without mention of hemorrhage or perforation
531.70	Gastric ulcer, chronic without mention of hemorrhage or perforation, without mention of obstruction
531.71	Gastric ulcer, chronic without mention of hemorrhage or perforation, with obstruction
531.9	Gastric ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation
531.90	Gastric ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, without mention of obstruction

531.91	Gastric ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, with obstruction
532	Duodenal ulcer
532.0	Duodenal ulcer, acute with hemorrhage
532.00	Duodenal ulcer, acute with hemorrhage, without mention of obstruction
532.01	Duodenal ulcer, acute with hemorrhage, with obstruction
532.1	Duodenal ulcer, acute with perforation
532.10	Duodenal ulcer, acute with perforation, without mention of obstruction
532.11	Duodenal ulcer, acute with perforation, with obstruction
532.2	Duodenal ulcer, acute with hemorrhage and perforation
532.20	Duodenal ulcer, acute with hemorrhage and perforation, without mention of obstruction
532.21	Duodenal ulcer, acute with hemorrhage and perfortion, with obstruction
532.3	Duodenal ulcer, acute without mention of hemorrhage or perforation
532.30	Duodenal ulcer, acute without mention of hemorrhage or perforation, without mention of obstruction
532.31	Duodenal ulcer, acute without mention of hemorrhage or perforstion, with obstruction
532.4	Duodenal ulcer, chronic or unspecified with hemorrhage
532.40	Duodenal ulcer, chronic or unspecified with hemorrhage, without mention of obstruction
532.41	Duodenal ulcer, chronic or unspecified with hemorrhage, with obstruction
532.5	Duodenal ulcer, chronic or unspecified with perforation
532.50	Duodenal ulcer, chronic or unspecified with perforation, without mention of obstruction
532.51	Duodenal ulcer, chronic or unspecified with perforation, with obstruction
532.6	Duodenal ulcer, chronic or unspecified with hemorrhage and perforation
532.60	Duodenal ulcer, chronic or unspecified with hemorrhage and perforation, without mention of obstruction
532.61	Duodenal ulcer, chronic or unspecified with hemorrhage and perforation, with obstruction
532.7	Duodenal ulcer, chronic without mention of hemorrhage or perforation
532.70	Duodenal ulcer, chronic without mention of hemorrhage or perforation, without mention of obstruction
532.71	Duodenal ulcer, chronic without mention of hemorrhage or perforation,with obstruction
532.9	Duodenal ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation
532.90	Duodenal ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, without mention of obstruction
532.91	Duodenal ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, with obstruction
533	Peptic ulcer, site unspecified
533.0	Peptic ulcer, site unspecified, acute with hemorrhage
533.00	Peptic ulcer, site unspecified, acute with hemorrhage, without mention of obstruction
533.01	Peptic ulcer, site unspecified, acute with hemorrhage, with obstruction
533.1	Peptic ulcer, site unspecified, acute with perforation
533.10	Peptic ulcer, site unspecified, acute with perforation, without mention of obstruction
533.11	Peptic ulcer, site unspecified, acute with perforation, with obstruction
533.2	Peptic ulcer, site unspecified, acute with hemorrhage and perforation
533.20	Peptic ulcer, site unspecified, acute with hemorrhage and perforation, without mention of obstruction

533.21	Peptic ulcer, site unspecified, acute with hemorrhage and perforation, with obstruction
533.3	Peptic ulcer, site unspecified, acute without mention of hemorrhage and perforation
533.30	Peptic ulcer, site unspecified, acute without mention of hemorrhage and perforation, without mention of obstruction
533.31	Peptic ulcer, site unspecifide, acute without mention of hemorrhage and perforation, with obstruction
533.4	Peptic ulcer, site unspecified, chronic or unspecified with hemorrhage
533.40	Peptic ulcer, site unspecified, chronic or unspecified with hemorrhage, without mention of obstruction
533.41	Peptic ulcer, site unspecified, chronic or unspecified with hemorrhage, with obstruction
533.5	Peptic ulcer, site unspecified, chronic or unspecified with perforation
533.50	Peptic ulcer, site unspecified, chronic or unspecified with perforation, without mention of obstruction
533.51	Peptic ulcer, site unspecified, chronic or unspecigied with perforation, with obstruction
533.6	Peptic ulcer, site unspecified, chronic or unspecified with hemorrhage and perforation
533.60	Peptic ulcer, site unspecified, chronic or unspecified with hemorrhage and perforation, without mention of obstruction
533.61	Peptic ulcer, site unspecified, chronic or unspecified with hemorrhage and perforation, with obstruction
533.7	Peptic ulcer, site unspecified, chronic without mention of hemorrhage or perforation
533.70	Peptic ulcer, site unspecified, chronic without mention of hemorrhage or perforation, without mention of obstruction
533.71	Peptic ulcer, site unspecified, chronic without mention of hemorrhage or perforation, with obstruction
533.9	Peptic ulcer, site unspecified, unspecified as acute or chronic, without mention of hemorrhage or perforation
533.90	Peptic ulcer, site unspecified, unspecified as acute or chronic, without mention of hemorrhage or perforation, without mention of obstruction
533.91	Peptic ulcer, site unspecified, unspecified as acute or chronic, without mention of hemorrhage or perforation, with obstruction
534	Gastrojejunal ulcer
534.0	Gastrojejunal ulcer, acute with hemorrhage
534.00	Gastrojejunal ulcer, acute with hemorrhage, without mention of obstruction
534.01	Gastrojejunal ulcer, acute with hemorrhage, with obstruction
534.1	Gastrojejunal ulcer, acute with perforation
534.10	Gastrojejunal ulcer, acute with perforation, without mention of obstruction
534.11	Gastrojejunal ulcer, acute with perforation, with obstruction
534.2	Gastrojejunal ulcer, acute with hemorrhage and perforation
534.20	Gastrojejunal ulcer, acute with hemorrhage and perforation, without mention of obstruction
534.21	Gastrojejunal ulcer, acute with hemorrhage and pergoration, with obstruction
534.3	Gastrojejunal ulcer, acute without mention of hemorrhage or perforation
534.30	Gastrojejunal ulcer, acute without mention of hemorrhage or perforation, without mention of obstruction
534.31	Gastrojejunal ulcer, acute without mention of hemorrhage or perforation, with obstruction
534.4	Gastrojejunal ulcer, chronic or unspecified with hemorrhage
534.40	Gastrojejunal ulcer, chronic or unspecified with hemorrhage, without mention of obstruction
534.41	Gastrojejunal ulcer, chronic or unspecified with hemorrhage, with obstruction
534.5	Gastrojejunal ulcer, chronic or unspecified with perforation

534.50	Gastrojejunal ulcer, chronic or unspecified with perforation, without mention of obstruction
534.51	Gastrojejunal ulcer, chronic or unspecified with perforation, with obstruction
534.6	Gastrojejunal ulcer, chronic or unspecified with hemorrhage and perforation
534.60	Gastrojejunal ulcer, chronic or unspecified with hemorrhage and perforation, without mention of obstruction
534.61	Gastrojejunal ulcer, chronic or unspecified with hemorrhage and perforation, with obstruction
534.7	Gastrojejunal ulcer, chronic without mention of hemorrhage or perforation
534.70	Gastrojejunal ulcer, chronic without mention of hemorrhage or perforation, without mention of obstruction
534.71	Gastrojejunal ulcer, chronic without mention of hemorrhage or perforation, with obstruction
534.9	Gastrojejunal ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation
534.90	Gastrojejunal ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, without mention of obstruction
534.91	Gastrojejunal ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, with obstruction
535	Gastritis and duodenitis
535.0	Acute gastritis
535.00	Acute gastritis, without mention of hemorrhage
535.01	Acute gastritis, with hemorrhage
535.11	Atrophic gastritis, with hemorrhage
535.21	Gastric mucosal hypertrophy, with hemorrhage
535.31	Alcoholic gastritis, with hemorrhage
535.41	Other specified gastritis, with hemorrhage
535.5	Unspecified gastritis and gastroduodenitis
535.51	Unspecified gastritis and gastroduodenitis, with hemorrhage
535.61	Duodenitis, with hemorrhage
562.02	Diverticulosis of small intestine with hemorrhage
562.03	Diverticulitis of small intestine with hemorrhage
562.12	Diverticulosis of colon with hemorrhage
562.13	Diverticulitis of colon with hemorrhage
569.3	Hemorrhage of rectum and anus
569.82	Ulceration of intestine
569.83	Perforation of intestine
570-579	Other Diseases Of Digestive System
571.40	Chronic hepatitis, unspecified
571.5	Cirrhosis of liver without mention of alcohol
572.0	Abscess of liver
575.1	Other cholecystitis
578.0	Hematemesis
578.1	Blood in stool
578.9	Hemorrhage of gastrointestinal tract, unspecified
596.7	Hemorrhage into bladder wall

599.7	Hematuria
602.1	Congestion or hemorrhage of prostate
614-616	Inflammatory Disease Of Female Pelvic Organs
623.6	Vaginal hematoma
624.5	Hematoma of vulva
626	*Disorders of menstruation and other abnormal bleeding from female genital tract
VI. Fractures or other Major Traumas	
800-804	Fracture Of Skull
805-809	Fracture Of Spine And Trunk
810-819	Fracture Of Upper Limb
820-829	Fracture Of Lower Limb
830-839	Dislocation
840-848	Other and ill-defined sprains and strains
850-854	Intracranial Injury, Excluding Those With Skull Fracture
860-869	Internal Injury Of Chest, Abdomen, And Pelvis
870-879	Open Wound Of Head, Neck, And Trunk
880-887	Open Wound Of Upper Limb
890-897	Open Wound Of Lower Limb
900-904	Injury To Blood Vessels
905-909	Late Effects Of Injuries, Poisonings, Toxic Effects, And Other External Causes
910-919	Superficial Injury
920-924	Contusion With Intact Skin Surface
925-929	Crushing Injury
930-939	Effects Of Foreign Body Entering Through Orifice
940-949	Burns
950-957	Injury to other and unspecified nerves
958-959	Certain Traumatic Complications And Unspecified Injuries
959	Injury, other and unspecified
959.01	Head injury, unspecified
959.09	Injury of face and neck
959.1	Injury of trunk
959.2	Injury of shoulder and upper arm
959.3	Injury of elbow, forearm and wrist
959.4	Injury of hand, except finger
959.5	Injury of finger
959.6	Injury of hip and thigh
959.7	Injury of knee, leg, ankle and foot
959.8	Injury to other specified sites, including multiple

959.9	Injury, unspecified site
V. Iatrogenic or other Unspecific Illness	
797-799	Ill-Defined And Unknown Causes Of Morbidity And Mortality
960-979	Poisoning By Drugs, Medicinals And Biological Substances
964.2	Poisoning by anticoagulants
994.6	Motion sickness
995.1	Angioneurotic edema
995.2	Unspecified adverse effect of drug, medicinal and biological substance
995.3	Allergy, unspecified
996-999	Complications Of Surgical And Medical Care, Not Elsewhere Classified
996.31	Mechanical complication due to urethral (indwelling) catheter
996.56	Mechanical complication due to peritoneal dialysis catheter
996.64	Infection and inflammatory reaction due to indwelling urinary catheter
997	Complications affecting specified body systems, not elsewhere classified
997.0	Central nervous system complications
997.00	Nervous system complication, unspecified
997.01	Central nervous system complication
997.02	Iatrogenic cerebrovascular infarction or hemorrhage
997.09	Other nervous system complications
997.1	Cardiac complications
997.2	Peripheral vascular complications
997.3	Respiratory complications
997.5	Urinary complications
998.1	Hemorrhage or hematoma or seroma complicating a procedure
998.11	Hemorrhage complicating a procedure
998.12	Hematoma complicating a procedure
998.13	Seroma complicating a procedure
999.1	Complication of medical care, air embolism
999.2	Complication of medical care, other vascular complications
999.3	Complication of medical care, other infection