Association Between Previous Use of Antiplatelet Therapy and Intracerebral Hemorrhage Outcomes

Nadeem I. Khan, MD; Fazeel M. Siddiqui, MD; Joshua N. Goldstein, MD, PhD; Margueritte Cox, MS; Ying Xian, MD, PhD; Roland A. Matsouaka, PhD; Paul A. Heidenreich, MD, MS; Eric D. Peterson, MD, MPH; Deepak L. Bhatt, MD, MPH; Gregg C. Fonarow, MD; Lee H. Schwamm, MD; Eric E. Smith, MD, MPH

Background and Purpose—Although the use of antiplatelet therapy (APT) is associated with the risk of intracerebral hemorrhage (ICH), there are limited data on prestroke APT and outcomes, particularly among patients on combination APT (CAPT). We hypothesized that the previous use of antiplatelet agents is associated with increased mortality in ICH.

Methods—We analyzed data of 82 576 patients with ICH who were not on oral anticoagulant therapy from 1574 Get with the Guidelines-Stroke hospitals between October 2012 and March 2016. Patients were categorized as not on APT, on single-APT (SAPT), and CAPT before hospital presentation with ICH. We described baseline characteristics, comorbidities, hospital characteristics and outcomes, overall and stratified by APT use.

Results—Before the diagnosis of ICH, 65.8% patients were not on APT, 29.5% patients were on SAPT, and 4.8% patients were on CAPT. There was an overall modest increased in-hospital mortality in the APT group versus no APT group (24% versus 23%; adjusted odds ratio, 1.05; 95% confidence interval, 1.01–1.10). Although patients on SAPT and CAPT were older and had higher risk profiles in terms of comorbidities, there was no significant difference in the in-hospital mortality among patients on SAPT versus those not on any APT (23% versus 23%; adjusted odds ratio, 1.01; 95% confidence interval, 0.97–1.05). However, in-hospital mortality was higher among those on CAPT versus those not on APT (30% versus 23%; adjusted odds ratio, 1.50; 95% confidence interval, 1.39–1.63).

Conclusions—Our study suggests that among patients with ICH, previous use of CAPT, but not SAPT, was associated with higher risk for in-hospital mortality. **(*Stroke*. 2017;48:1810-1817. DOI: 10.1161/STROKEAHA.117.016290.)**

Key Words: anticoagulant ■ aspirin ■ cerebral hemorrhage ■ prognosis ■ stroke

See related article, p 1717

Platelets are essential to normal hemostasis. They adhere and aggregate at the site of injury and contribute to vessel repair. However, uncontrolled progression of such a process may lead to clot formation, vascular occlusion, and formation and extension of atherosclerosis.[1] Hence, there is an increasing use of antiplatelet therapy (APT) among patients with stroke and heart diseases.[2] The use of newer antiplatelet agents and dual APT (DAPT) in patients with myocardial infarction and stent placement has also increased.[3,4]

Although APT is highly effective in primary or secondary prevention of coronary artery disease and stroke, patients on APT are at increased risk of intracerebral hemorrhage (ICH), which is often fatal.[5,6] Patients presenting with spontaneous ICH are more commonly on APT than anticoagulant therapy.[7] Studies analyzing the association of APT with ICH outcome have conflicting results, possibly reflecting differences in sample size, demographics, methodology, and statistical analysis.[8] A previous comprehensive meta-analysis reported higher in-hospital mortality in patients on APT before ICH.[8] This effect is presumably related to hematoma expansion secondary to platelet dysfunction and subsequent death and disability.[9–11]

We proposed to study the association of prior APT use on patients with ICH in real-world setting, using the Get with the Guidelines (GWTG)-Stroke data set. We also compared the outcomes among patients on single-APT (SAPT) versus combination APT (CAPT) and the trends of starting APT at discharge in all patients with ICH.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received January 24, 2017; final revision received April 24, 2017; accepted May 5, 2017.

From the Department of Neurology, Southern Illinois University School of Medicine, Springfield (N.I.K., F.M.S.); Department of Emergency Medicine (J.N.G.), Department of Neurology (L.H.S.), Massachusetts General Hospital, and Brigham and Women's Hospital Heart and Vascular Center (D.L.B.), Harvard Medical School, Boston; Duke Clinical Research Institute, Durham, NC (M.C., Y.X., R.A.M., E.D.P.); Department of Medicine (E.D.P.), and Department of Neurology (Y.X.), Duke University Medical Center, Durham, NC; Department of Biostatistics and Bioinformatics, Duke University, Durham, NC (R.A.M.); Department of Medicine, Stanford University School of Medicine, CA (P.A.H.); Department of Medicine, Ronald-Reagan UCLA Medical Center (G.C.F.); and Department of Clinical Neurosciences, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Alberta, Canada (E.E.S.).

Guest Editor for this article was Natan Bornstein, MD.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.016290/-/DC1.

Correspondence to Nadeem I. Khan, MD, Department of Neurology, Southern Illinois University School of Medicine, 751 N Rutledge St, Springfield, IL 62702. E-mail nadeem.israr.khan@gmail.com

Methods

Data Source

GWTG-stroke is an ongoing, voluntary, continuous registry, and performance improvement initiative in stroke care. The details of the GWTG-stroke registry data collection and definitions methods have been described earlier.[12,13] Quintiles Company (Cambridge, MA) serves as the Clinical Research Organization and data are analyzed by Duke Clinical Research Institute (Durham, NC). The registry involves deidentification of data at patient collection level by the participating sites, while following local regulations and privacy laws, with local Intitutional Review Board approval obtained as required. The Duke Intitutional Review Board has approved the data analysis by Duke Clinical Research Institute.

Study Population

All patients with a diagnosis of ICH were identified in the GWTG-stroke registry database. The study period was from October 1, 2012 to March 31, 2016. Pre-ICH APT use was recorded as part of routine care, and defined as any use in the 7 days before hospital arrival. Out of the 154 892 patients identified, 23 896 patients were excluded because they were on anticoagulants before admission, 39 075 patients were excluded because of missing initial computed tomographic scan head, 6004 patients were excluded because of missing admission APT history, and 3340 patients were excluded because of missing discharge status, being transferred out or left against medical advice. For analysis, the final study population was divided into 2 cohorts (Figure). Cohort A included all patients who satisfied the above criteria (82 576 patients from 1574 sites) and was used to analyze the APT-related outcomes. Cohort B included all patients in cohort A except those who had missing discharge APT history (6727 patients) or APT was not started because of contraindication or family or patient refusal (30 738 patients). The specific reasons/contraindications for not starting APT on discharge are described in the (Table I in the online-only Data Supplement). Cohort B was used to examine the trends of prescription of APT in patients with ICH at discharge (45 111 patients from 1431 sites).

Statistical Analysis

We described baseline characteristics, comorbidities, hospital characteristics, and outcomes of the overall population and by APT use, using proportions for categorical variables and means with SD for continuous variables. The differences in these characteristics were compared using standardized mean differences; absolute values >10 indicated an imbalance between groups.

We used logistic regression using generalized estimating equations to assess the relationship between the outcome and prior APT use. Generalized estimating equation allows a given model to account for the clustering of patients within centers. Unadjusted odds ratios (ORs) were first calculated. Thereafter, patient and hospital characteristics (age, sex, race/ethnicity, arrival during off hours, medical history of atrial fibrillation/flutter, previous stroke/transient ischemic attack, coronary artery disease/previous myocardial infarction, carotid stenosis, diabetes mellitus, peripheral vascular disease, hypertension, dyslipidemia, smoking, geographic region, rural location, academic/teaching hospital, number of beds, annual volume of hemorrhagic stroke admission, previous use of antihypertensive, previous use of anticholesterol medications, and the Joint Commission primary stroke center status) were added to the model. In addition, we performed a sensitivity analysis including the National Institute of Health Stroke Scale score as an additional covariate in the model (National Institute of Health Stroke

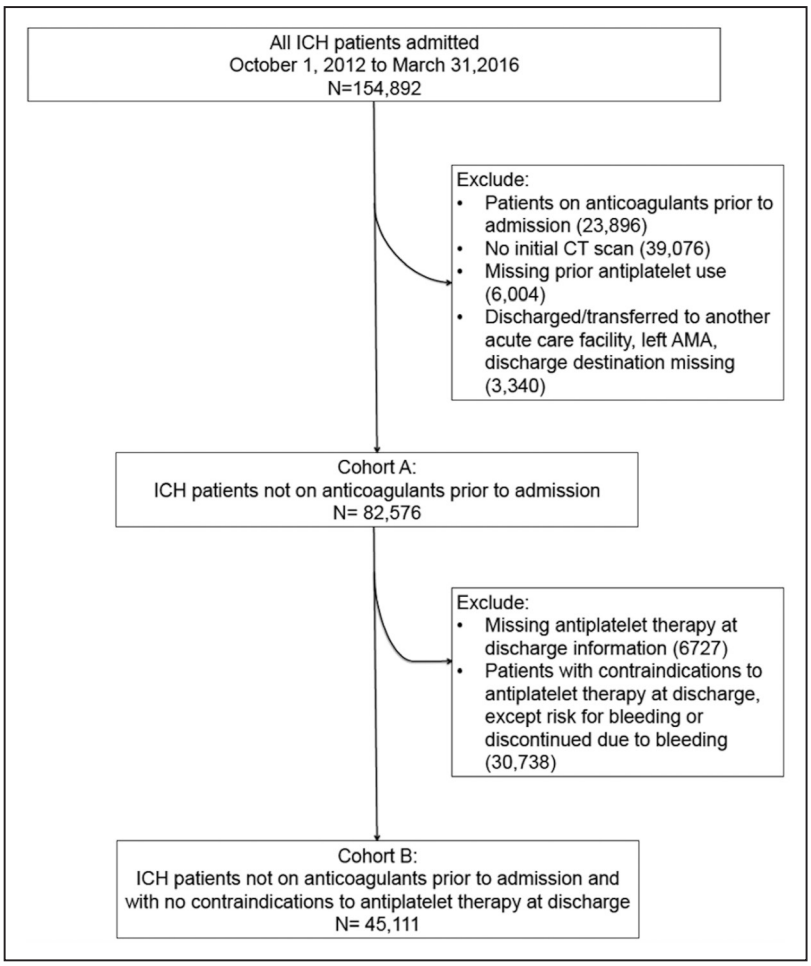

Figure. Selection criteria for the study. CT indicates computed tomography.

Scale score was not included in the initial model because of high missing rates.)

Overall, for each model, multiple imputations were used to handle missing data. For any patient variables with missing rate lower than 20%, multiple imputations with 25 imputed data sets were used. Medical history variables were assumed to be not present because of hypothesized patterns in data collection. National Institute of Health Stroke Scale score and hospital characteristics were not imputed. Missing rates for many variables were 0%, except for race/ethnicity (0.2%), medical history variables (0.2%), academic/teaching hospitals (1.0%), rural location (0.1%), and number of beds (1.1%). We also used variance inflation factors to assess colinearity between all covariates in the model.

All tests were 2-tailed with a level of statistical significance of $P<0.05$. Statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc, Cary, NC).

Results

Characteristics of Study Population

Among 82 576 patients in cohort A, 28 277 patients were on APT and 54 299 were not on APT. Details of different types of APT and various combinations used before admission are described in Table 1. The median age of patients not on APT was 64 years versus 76 years in the SAPT and CAPT groups. There were 48% women in the no APT group versus 50% in the SAPT group and 43% in the CAPT group. Table 2 describes the baseline patient and hospital characteristics, overall and by APT use.

ICH Outcomes With or Without Prior APT Use

In-hospital mortality was 24% in the APT group versus 23% in the no APT group. In the APT group, 41% of patients had more than 5 days of hospital stay versus 48% of patients in the no APT group. Independent ambulation at discharge was achieved by 23% of patients in the APT group versus 28% in the no APT group. Modified Rankin score at the time of discharge was >2 in 83% patients on no APT versus 86% patients on prior APT. After adjustment for covariates, there was a modest increased in mortality in the APT group (OR, 1.05; 95% confidence interval [CI], 1.01–1.10; Table 3). We tested for sex-related differences in outcomes of patients on antiplatelet drugs and found no difference between men and women in the risk of death, death or discharge to hospice, or discharge to home (Table II in the online-only Data Supplement). Differences were seen in disability outcomes, with women having worse outcomes than men (Table II in the online-only Data Supplement).

SAPT Versus CAPT

Out of 28 277 patients on APT, 24 331 (86%) patients were on SAPT and 3946 (14%) were on CAPT. Table 2 describes the baseline patient and hospital characteristics among the 2 groups.

The in-hospital mortality rate for patients in the SAPT group was 23% versus 30% in the CAPT group. In the SAPT group, 42% patients had prolonged length of stay (>5 days) versus 38% patients in CAPT group. Independent ambulation at discharge was achieved by 24% patients in SAPT group versus 21% patients in CAPT group (Table 4).

There was no statistically significant difference in the in-hospital mortality among patients who were not on any APT versus patients on SAPT. However, in-hospital mortality was higher among patients with ICH on CAPT compared with patients not on APT (OR, 1.5; 95% CI, 1.39–1.63). This relationship remained even after including the National Institute of Health Stroke Scale score to the adjusted model (OR, 1.49; 95% CI, 1.33–1.67). There was no significant difference in the length of stay, ambulatory status, and discharge modified

Table 1. Type of Antiplatelet Used Before Admission

APT Groups	Patients, n (%)	Specific APT Combinations	Patients, n (%)
None	54 299 (66)	None	54 299 (66)
One	24 331 (29)	Aspirin	21 778 (26)
		Clopidogrel	2485 (3)
		Ticlopidine	1(0)
		Other antiplatelet	67 (0)
Combination	3946 (5)	Aspirin/Dipyridamole Only	515 (1)
		Aspirin+Aspirin/Dipyridamole	72 (0)
		Aspirin+Clopidogrel	3202 (4)
		Aspirin+Ticlopidine	2 (0)
		Aspirin+Other Antiplatelet	95 (0)
		Aspirin/Dipyridamole+Clopidogrel	32 (0)
		Aspirin/Dipyridamole+Other Antiplatelet	2 (0)
		Clopidogrel+Ticlopidine	1 (0)
		Clopidogrel+Other Antiplatelet	11(0)
		Aspirin+Aspirin/Dipyridamole+Clopidogrel	10 (0)
		Aspirin+Clopidogrel+Other antiplatelet	4 (0)

APT indicates antiplatelet therapy.

Table 2. Baseline Patient and Hospital Characteristics, Overall and by Antiplatelet Use

Variable	Level	Overall (n=82 576)		No APT (n=54 299)		Prior APT (n=28 277)			
						SAPT (n=24 331)		CAPT (n=3946)	
Patient demographics									
Age	Median		69		64	24 331	76	3946	76
	25th		57		53		65		66
	75th		81		77		84		83
Sex	Female	40 111	(48.6%)	26 285	(48.4%)	12 128	(49.8%)	1698	(43.0%)
Race	White	48 557	(58.9%)	29 358	(54.2%)	16 360	(67.3%)	2839	(72.1%)
	Black	16 810	(20.4%)	12 278	(22.6%)	4008	(16.5%)	524	(13.3%)
	Hispanic	8342	(10.1%)	6240	(11.5%)	1806	(7.4%)	296	(7.5%)
	Asian	4675	(5.7%)	3389	(6.2%)	1146	(4.7%)	140	(3.6%)
	Other	4052	(4.9%)	2938	(5.4%)	974	(4.0%)	140	(3.6%)
Patient arrival and admission									
Onset to arrival time, mins	Median	43 785	131	28 219	126	13 454	140	2112	135
	25th		57		56		60		60
	75th		395		392		414		357
NIHSS score	Median	53 588	9	34 831	10	16 163	9	2594	10
	25th		3		3		3		3
	75th		20		20		19		21
Medical history									
Atrial fibrillation/Flutter		6022	(7.3%)	2628	(4.8%)	2941	(12.1%)	453	(11.5%)
Prosthetic heart valve		387	(0.5%)	144	(0.3%)	196	(0.8%)	47	(1.2%)
Previous stroke/TIA		19 518	(23.6%)	9629	(17.8%)	7869	(32.4%)	2020	(51.3%)
CAD/Previous MI		12 640	(15.3%)	4171	(7.7%)	6327	(26%)	2142	(54.4%)
Carotid stenosis		1258	(1.5%)	332	(0.6%)	634	(2.6%)	292	(7.4%)
Diabetes mellitus		20 634	(25%)	11 028	(20.4%)	8001	(32.9%)	1605	(40.7%)
PVD		2062	(2.5%)	717	(1.3%)	982	(4%)	363	(9.2%)
Hypertension		60 536	(73.4%)	37 001	(68.3%)	20 172	(83%)	3363	(85.3%)
Smoker		11 089	(13.4%)	8046	(14.8%)	2567	(10.6%)	476	(12.1%)
Dyslipidemia		26 109	(31.7%)	12 255	(22.6%)	11 561	(47.6%)	2293	(58.2%)
Heart failure		4169	(5.1%)	1804	(3.3%)	1969	(8.1%)	396	(10%)
Medications before admission									
Antihypertensive		39 161	(54.7%)	20 206	(42.5%)	16 057	(77.7%)	2898	(85.1%)
Cholesterol-reducer		26 378	(32%)	10 245	(18.9%)	13 278	(54.7%)	2855	(72.5%)
Diabetic medication		12 019	(17.4%)	5646	(12.2%)	5273	(26.7%)	1100	(33.7%)
Hospital characteristics									
Teaching Hospital		54 346	(66.5%)	36 166	(67.2%)	15 708	(65.3%)	2472	(63.4%)
TJC Primary Stroke Center		26 200	(43.8%)	23 832	(43.9%)	10 680	(43.9%)	1688	(42.8%)

APT indicates antiplatelet therapy; CAD, coronary artery disease; CAPT, combined antiplatelet therapy; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease; SAPT, single-antiplatelet therapy; TIA, transient ischemic attack; and TJC, The Joint Commission.

Rankin score among all groups (Table 5). Sex-related difference in outcome with regards to SAPT versus CAPT is described in Table III in the online-only Data Supplement.

APT Use on Discharge in ICH

Cohort B was used to evaluate the frequency of APT prescription in patients with ICH on discharge. Of 45 111 patients

Table 3. Association Between Previous Antiplatelet Use and Outcome

Outcome	Unadjusted Model			Main Models Adjusted Model (Patient and Hospital Characteristics, Without NIHSS Score)			Sensitivity Analysis Adjusted Model (Patient and Hospital Characteristics, With NIHSS Score Included as a Complete Case Analysis)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
In-hospital mortality	1.06	(1.03–1.10)	0.0007	1.05	(1.01–1.1)	0.012	1.09	(1.02–1.15)	0.007
In-hospital mortality or hospice care	1.18	(1.14–1.22)	<0.0001	1.02	(0.98–1.06)	0.311	1.07	(1.01–1.12)	0.023
Discharge home	0.77	(0.75–0.80)	<0.0001	1.03	(0.99–1.07)	0.1675	1.00	(0.94–1.07)	0.9361
Independent ambulation at discharge	0.80	(0.77–0.83)	<0.0001	1.02	(0.97–1.06)	0.4760	0.99	(0.93–1.05)	0.7684
Modified Rankin score at discharge >2	1.24	(1.16–1.31)	<0.0001	0.95	(0.89–1.03)	0.2068	0.95	(0.87–1.04)	0.2353

NIHSS indicates National Institutes of Health Stroke Scale; CI, confidence interval; and OR, odds ratio.

in this cohort, 15 247 (33.8%) were discharged on APT and 29 864 (66.2%) were not on APT. The baseline patient and hospital characteristics were similar among all groups (APT versus no APT). There were higher odds of resuming APT at the time of discharge in patients who were on APT before the ICH diagnosis versus patients who were not on APT before the ICH diagnosis (30% versus 8%; adjusted OR, 3.64; 95% CI, 3.4–3.91).

Discussion

APT is the mainstay treatment for stroke, heart, and peripheral vascular diseases. Our study addresses several issues. We found that SAPT (most commonly aspirin) had no association with ICH outcomes, including morbidity and mortality. However, CAPT was associated with higher mortality when compared with no therapy. These findings provide important insights into the risks associated with prior APT use among spontaneous patients with ICH and suggest that excess mortality risk associated with APT use is confined to those patients receiving CAPT before ICH.

Extensive research has been done to evaluate the incidence of ICH in patients on APT. Several meta-analyses of primary and secondary prevention trials in aspirin users showed higher incidence of ICH in those patients.[14] The risk of ICH increases with incremental increase in the dose of aspirin.[15] Similar trends of higher incidence of major systemic and intracranial bleeding were observed in patients on DAPT, especially with long-term use.[16,17] A few meta-analyses have studied the incidence of ICH in patients on DAPT for the prevention of transient ischemic attack or minor stroke. Lee et al[18] identified 7 randomized, controlled trials that involved a total of 39 574 patients and found a higher risk for ICH (4 more events per 1000 patients) with prolonged use of DAPT (>1 year) versus clopidogrel monotherapy. Chen et al[19] analyzed 15 trials on stroke prevention that compared DAPT versus monotherapy. Long-term DAPT substantially increased the risk of intracranial bleeding (relative risk, 1.76; 95% CI, 1.22–2.54).[19]

APT use is also an independent predictor of cerebral microbleeds which, in turn, are independent predictors of future ICH.[20]

The association of prior use of APT on ICH outcomes has been studied extensively with conflicting results. The variations in the outcomes of different studies could be unreliable history or nondisclosure of drugs like nonsteroidal anti-inflammatory agents that reduce platelet activity but not often reported on admission.[21] Overall, the findings of these previous studies have suggested increasing odds for death in patients on APT before ICH.[8] However, these studies had limited data on the APT type, dosing, and combination therapy, and many were not performed in a contemporary era where there is increasing use of DAPT. In contrast, our study suggests that the increased mortality risk is confined to patients with ICH on CAPT.

The findings of our study are unique and interesting as we studied the largest cohort of ICH patients with available data

Table 4. Outcomes for Patients With ICH, Overall and by Antiplatelet Use (Single Versus Combination Use)

Variable	Level	Overall (n=28 277)		SAPT (n=24 331)		CAPT (n=3946)	
In-hospital mortality		6848	(24.2%)	5645	(23.2%)	1203	(30.5%)
In-hospital mortality or hospice care		9854	(34.9%)	8251	(33.9%)	1603	(40.6%)
Discharged home		6276	(22.2%)	5481	(22.5%)	795	(20.2%)
Length of stay, d	Median	27 336	5	23 563	5	3773	4
	25th		2		3		2
	75th		8		8		8
Independent ambulation at discharge		5878	(23.1%)	5145	(23.5%)	733	(20.6%)
Modified Rankin score at discharge >2		14 725	(85.8%)	12 565	(85.5%)	2160	(87.5%)

ICH indicates intracerebral hemorrhage; CAPT, combination antiplatelet therapy; and SAPT, single-antiplatelet therapy.

Table 5. Association Between Previous Antiplatelet Use (Single Versus Combination Use) and Outcomes (Reference=No Antiplatelet)

	Unadjusted Model			Main Models Adjusted Model (Patient and Hospital Characteristics, Without NIHSS Score)			Sensitivity Analyis Adjusted Model (Patient and Hospital Characteristics, With NIHSS Score Included as a Complete Case Analysis)		
Outcome	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
In-hospital mortality									
SAPT	1.00	(0.97–1.04)	0.83	1.01	(0.97–1.05)	0.7339	1.04	(0.98–1.11)	0.1746
CAPT	1.48	(1.37–1.58)	<0.0001	1.50	(1.39–1.63)	<0.0001	1.49	(1.33–1.67)	<0.0001
In-hospital mortality or discharge hospice									
SAPT	1.13	(1.10–1.17)	<0.0001	0.99	(0.95–1.03)	0.5046	1.04	(0.98–1.10)	0.2041
CAPT	1.51	(1.41–1.62)	<0.0001	1.32	(1.23–1.42)	<0.0001	1.33	(1.19–1.49)	<0.0001
Discharge home									
SAPT	0.79	(0.76–0.82)	<0.0001	1.04	(1.00–1.09)	0.0523	1.01	(0.95–1.08)	0.6687
CAPT	0.68	(0.63–0.74)	<0.0001	0.92	(0.84–1.01)	0.0674	0.90	(0.78–1.04)	0.1514
Independent ambulation at discharge									
SAPT	0.82	(0.79–0.85)	<0.0001	1.03	(0.98–1.08)	0.2244	1.00	(0.94–1.06)	0.9071
CAPT	0.70	(0.64–0.76)	<0.0001	0.91	(0.83–1.00)	0.0397	0.94	(0.82–1.08)	0.3707
Modified Rankin score at discharge >2									
SAPT	1.21	(1.14–1.29)	<0.0001	0.95	(0.88–1.02)	0.1467	0.95	(0.87–1.04)	0.2560
CAPT	1.40	(1.22–1.59)	<0.0001	1.03	(0.89–1.18)	0.7214	0.94	(0.77–1.14)	0.5109

CAPT, combination antiplatelet therapy; CI, confidence interval; NIHSS indicates National Institutes of Health Stroke Scale; OR, odds ratio; and SAPT, single-antiplatelet therapy.

on combination versus SAPT use. These findings also suggest that there is a threshold effect, where the reduction in platelet activity has to be substantial enough (such as with CAPT rather than SAPT) to influence outcome. Naidech et al[22–25] demonstrated that increased platelet inhibition for aspirin and clopidogrel correlated with increased ICH volume growth, volume of intraventricular hemorrhage, increased chance of death at 14 days, increased chances of undergoing a craniotomy for ICH, and poor outcome at 3 months. Future trials may be better served either using platelet activity to guide therapy or restricting enrollment to those on CAPT.

Resumption of APT After ICH

There is some evidence that stopping of APT in patients with ICH may put them at risk of disabling stroke and heart diseases due to preexisting vascular comorbidities.[26] This issue is further complicated in patients on DAPT for recent coronary stent placement with the risk of in-stent thrombosis and resultant coronary ischemia.[27,28] There is growing evidence that patients who are prescribed APT after ICH have decreased vascular events when compared with those not prescribed on APT, without any significant increase in the risk of recurrent ICH except in patients with a history of cerebral microbleeds.[20,29–32] Findings of our study suggest a 30% restart rate of APT in ICH (although it remained significantly higher than patients who were not on any APT before ICH). However, this data cannot be generalized as a high percentage of patients were excluded from the analysis because of missing data, family or patient refusal, or contradications to APT (Table I in the online-only Data Supplement).

There are several limitations to our study. Patients without initial computed tomographic scan head at the time of admission (39 076) were excluded from the study. It is a retrospective analysis of prospectively collected data. Residual measured and unmeasured confounding may influence these findings. The data are drawn from hospitals participating in GWTG-Stroke and may not apply to patients and hospitals that have different characteristics. The accuracy of the data is dependent on accurate reporting by participating sites, although good validity of same has been shown in a previous study by Xian et al.[33] Our study was also dependent on the subjective history of APT use, data on when last doses were taken before the onset of ICH are not available, and platelet function assays were lacking to demonstrate reliable platelet inhibition. Also, data on the use of other medications such as nonsteroidal anti-inflammatory drugs, serotonin–norepinephrine reuptake inhibitors, and serotonin-specific reuptake inhibitors, which may affect the risk of bleeding and potentially affect the results, are not available. The GWTG database does not contain information about hematoma size, type, location, or growth, and therefore, we were unable to determine whether the above-mentioned factors led to increased mortality in CAPT users potentially influencing the outcomes. We also do not have the comorbidity score, which may have a confounding effect on the results; but all the major risk factors for ICH in our study we included as individual variables in the analysis.

Conclusions

The findings of our study suggest that patients on CAPT, but not on SAPT, have higher mortality rates after ICH compared with patients on no APT. These findings suggest that greater platelet function inhibition may be related to worsening outcomes in ICH. Future interventional trials should be considered to test whether patients with ICH on CAPT would benefit from restoring platelet function. Concentrated efforts are also needed to study the effect and timing of resumption of APT in ICH patients with significant vascular comorbidities.

Sources of Funding

This study was financially supported by American Heart Association. Data were provided by Get With the Guidelines (GWTG) registry

Disclosures

Dr Khan, Research Grant: AHA Young Investigator Database Seed Grant. Dr Goldstein, Research funding: NIH, Boehringer Ingelheim, Portola, and Pfizer. Advisory Board: CSL Behring. Dr Peterson, Research Grant: Janssen, Genetech, AHA Get With The Guidelines (GWTG)-Stroke Analytic. Consultant/Advisory Board: Janssen, Boehringer Ingelhiem, Sanofi, Bayer, Merck, Astra Zeneca, Signal Path, and Venable. Dr Bhatt, Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (Continuing Medical Education steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), Veterans Affairs Clinical Assessment Reporting and Tracking Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda. Dr Fonarow, Member of GWTG Steering Committee; Grant funding from Patient Centered Outcome Research Institute; Employee of the University of California which has a patent on an endovascular therapy device, Consultant: Janssen. Dr Schwamm: Chair, GWTG-Stroke Clinical Workgroup.

References

1. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med*. 2007;357:2482–2494. doi: 10.1056/NEJMra071014.
2. Karve S, Levine D, Seiber E, Nahata M, Balkrishnan R. Trends in ambulatory prescribing of antiplatelet therapy among US ischemic stroke patients: 2000-2007. *Adv Pharmacol Sci*. 2012;2012:846163. doi: 10.1155/2012/846163.
3. Green A, Pottegård A, Broe A, Diness TG, Emneus M, Hasvold P, et al. Initiation and persistence with dual antiplatelet therapy after acute myocardial infarction: a Danish nationwide population-based cohort study. *BMJ Open*. 2016;6:e010880. doi: 10.1136/bmjopen-2015-010880.
4. Sherwood MW, Wiviott SD, Peng SA, Roe MT, Delemos J, Peterson ED, et al. Early clopidogrel versus prasugrel use among contemporary STEMI and NSTEMI patients in the US: insights from the national cardiovascular data registry. *J Am Heart Assoc*. 2014;3:e000849
5. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. *JAMA*. 1998;280:1930–1935.
6. Ducrocq G, Amarenco P, Labreuche J, Alberts MJ, Mas JL, Ohman EM, et al. A history of stroke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. *Circulation*. 2013;127:730–738. doi: 10.1161/CIRCULATIONAHA.112.141572.
7. Foerch C, Sitzer M, Steinmetz H, Neumann-Haefelin T. Pretreatment with antiplatelet agents is not independently associated with unfavorable outcome in intracerebral hemorrhage. *Stroke*. 2006;37:2165–2167. doi: 10.1161/01.STR.0000231842.32153.74.
8. Thompson BB, Béjot Y, Caso V, Castillo J, Christensen H, Flaherty ML, et al. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology*. 2010;75:1333–1342. doi: 10.1212/WNL.0b013e3181f735e5.
9. Toyoda K, Okada Y, Minematsu K, Kamouchi M, Fujimoto S, Ibayashi S, et al. Antiplatelet therapy contributes to acute deterioration of intracerebral hemorrhage. *Neurology*. 2005;65:1000–1004. doi: 10.1212/01.wnl.0000179178.37713.69.
10. Toyoda K, Yasaka M, Nagata K, Nagao T, Gotoh J, Sakamoto T, et al. Antithrombotic therapy influences location, enlargement, and mortality from intracerebral hemorrhage. The bleeding with antithrombotic therapy (bat) retrospective study. *Cerebrovasc Dis*. 2009;27:151–159.
11. Saloheimo P, Ahonen M, Juvela S, Pyhtinen J, Savolainen ER, Hillbom M. Regular aspirin-use preceding the onset of primary intracerebral hemorrhage is an independent predictor for death. *Stroke*. 2006;37:129–133. doi: 10.1161/01.STR.0000196991.03618.31.
12. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, et al. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107–115. doi: 10.1161/CIRCULATIONAHA.108.783688.
13. Smaha LA; American Heart Association. The American Heart Association Get With The Guidelines Program. *Am Heart J*. 2004;148:S46–S48.
14. Gorelick PB, Weisman SM. Risk of hemorrhagic stroke with aspirin use: an update. *Stroke*. 2005;36:1801–1807. doi: 10.1161/01.STR.0000174189.81153.85.
15. Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. *Am J Hematol*. 2004;75:40–47.
16. Serebruany VL, Malinin AI, Ferguson JJ, Vahabi J, Atar D, Hennekens CH. Bleeding risks of combination vs. single antiplatelet therapy: a meta-analysis of 18 randomized trials comprising 129,314 patients. *Fundam Clin Pharmacol*. 2008;22:315–321. doi: 10.1111/j.1472-8206.2008.00582.x.
17. Savarese G, Savonitto S, Lund LH, Paolillo S, Marciano C, Dellegrottaglie S, et al. Efficacy and safety of prolonged dual antiplatelet therapy: a meta-analysis of 15 randomized trials enrolling 85 265 patients. *Eur Heart J Cardiovasc Pharmacother*. 2016;2:218–228. doi: 10.1093/ehjcvp/pvw011.
18. Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbiagele B. Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159:463–470. doi: 10.7326/0003-4819-159-7-201310010-00006.
19. Chen S, Shen Q, Tang Y, He L, Li Y, Li H, et al. Efficacy and safety of adding clopidogrel to aspirin on stroke prevention among high vascular risk patients: a meta-analysis of randomized controlled trials. *PLoS One*. 2014;9:e104402. doi: 10.1371/journal.pone.0104402.
20. Wang DN, Hou XW, Yang BW, Lin Y, Shi JP, Wang N. Quantity of cerebral microbleeds, antiplatelet therapy, and intracerebral hemorrhage outcomes: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2015;24:2728–2737. doi: 10.1016/j.jstrokecerebrovasdis.2015.08.003.
21. Naidech AM, Bassin SL, Bernstein RA, Batjer HH, Alberts MJ, Lindholm PF, et al. Reduced platelet activity is more common than reported antiplatelet medication use in patients with intracerebral hemorrhage. *Neurocrit Care*. 2009;11:307–310. doi: 10.1007/s12028-009-9219-7.

22. Naidech AM, Jovanovic B, Liebling S, Garg RK, Bassin SL, Bendok BR, et al. Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. *Stroke*. 2009;40:2398–2401. doi: 10.1161/STROKEAHA.109.550939.
23. Naidech AM, Rosenberg NF, Bernstein RA, Batjer HH. Aspirin use or reduced platelet activity predicts craniotomy after intracerebral hemorrhage. *Neurocrit Care*. 2011;15:442–446. doi: 10.1007/s12028-011-9557-0.
24. Naidech AM, Bernstein RA, Levasseur K, Bassin SL, Bendok BR, Batjer HH, et al. Platelet activity and outcome after intracerebral hemorrhage. *Ann Neurol*. 2009;65:352–356. doi: 10.1002/ana.21618.
25. Naidech AM, Bendok BR, Garg RK, Bernstein RA, Alberts MJ, Bleck TP, et al. Reduced platelet activity is associated with more intraventricular hemorrhage. *Neurosurgery*. 2009;65:684–8; discussion 688. doi: 10.1227/01.NEU.0000351769.39990.16.
26. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation*. 2004;110:2361–2367. doi: 10.1161/01.CIR.0000145171.89690.B4.
27. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. *J Am Coll Cardiol*. 2005;45:456–459. doi: 10.1016/j.jacc.2004.11.041.
28. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126–2130. doi: 10.1001/jama.293.17.2126.
29. Flynn RW, MacDonald TM, Murray GD, MacWalter RS, Doney AS. Prescribing antiplatelet medicine and subsequent events after intracerebral hemorrhage. *Stroke*. 2010;41:2606–2611. doi: 10.1161/STROKEAHA.110.589143.
30. Chong BH, Chan KH, Pong V, Lau KK, Chan YH, Zuo ML, et al. Use of aspirin in Chinese after recovery from primary intracranial haemorrhage. *Thromb Haemost*. 2012;107:241–247. doi: 10.1160/TH11-06-0439.
31. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. *Neurology*. 2010;75:693–698. doi: 10.1212/WNL.0b013e3181eee40f.
32. Ottosen TP, Grijota M, Hansen ML, Brandes A, Damgaard D, Husted SE, et al. Use of antithrombotic therapy and long-term clinical outcome among patients surviving intracerebral hemorrhage. *Stroke*. 2016;47:1837–1843. doi: 10.1161/STROKEAHA.116.012945.
33. Xian Y, Fonarow GC, Reeves MJ, Webb LE, Blevins J, Demyanenko VS, et al. Data quality in the American Heart Association Get With The Guidelines-Stroke (GWTG-stroke): Results from a National data validation audit. *Am Heart J*. 2012;163:392–398.

Association Between Previous Use of Antiplatelet Therapy and Intracerebral Hemorrhage Outcomes

Nadeem I. Khan, Fazeel M. Siddiqui, Joshua N. Goldstein, Margueritte Cox, Ying Xian, Roland A. Matsouaka, Paul A. Heidenreich, Eric D. Peterson, Deepak L. Bhatt, Gregg C. Fonarow, Lee H. Schwamm and Eric E. Smith

Stroke. 2017;48:1810-1817; originally published online June 8, 2017;
doi: 10.1161/STROKEAHA.117.016290
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

SUPPLEMENTAL MATERIAL

"The Association between Prior Use of Antiplatelet Therapy and Intracerebral Hemorrhage Outcomes"

Supplemental Table I: Contraindications for Continuing/Starting APT at Discharge

Reasons*	Number of Patients
Patient/family refused	41
Terminal illness/comfort measures only	2267
Allergy to or complication related to APT	95
Risk of systemic/extra-cranial bleeding	654
Serious side effects to medication	235
Other	305
APT was contraindicated but details were missing	27812

*Total number of patients who were not started on APT at discharge due to certain contraindication was 30,738. Patients could have multiple reasons for not continuing/starting APT.

APT indicates antiplatelet therapy.

Supplemental Table II. Sex-related differences in outcomes of patients on antiplatelet drugs

Outcome	Unadjusted Model			MAIN MODELS Adjusted Model (Patient and Hospital Characteristics, Without NIHSS Score)			SENSITIVITY ANALYSIS Adjusted Model (Patient and Hospital Characteristics, With NIHSS Score Included as a Complete Case Analysis)		
	OR	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
In-hospital Mortality	Non-significant Interaction		0.5526	Non-significant Interaction		0.1612	Non-significant Interaction		0.8661
In-hospital Mortality or Hospice Care	Non-significant Interaction		0.6570	Non-significant Interaction		0.2504	Non-significant Interaction		0.4297
Discharge Home	Non-significant Interaction		0.6041	Non-significant Interaction		0.0557	Non-significant Interaction		0.4819
Independent Ambulation at Discharge			0.0258			0.0011			0.0352
Male	0.83	(0.79, 0.87)	<.0001	1.08	(1.01, 1.14)	0.0118	1.05	(0.96, 1.13)	0.2547
Female	0.76	(0.73, 0.81)	<.0001	0.95	(0.90, 1.01)	0.0980	0.93	(0.85, 1.01)	0.0831
Modified Rankin Score at Discharge > 2			0.0112			0.0005			0.0456
Male	1.17	(1.08, 1.26)	0.0001	0.87	(0.79, 0.95)	0.0025	0.88	(0.79, 0.98)	0.0303
Female	1.35	(1.23, 1.48)	<.0001	1.07	(0.97, 1.17)	0.1764	1.03	(0.91, 1.16)	0.5907

NIHSS indicates National Institutes of Health Stroke scale; OR, Odd's ratio; CI, confidence interval

Supplemental Table. III Sex related difference in outcome with regards to SAPT versus CAPT

Outcome	Unadjusted Model			MAIN MODELS Adjusted Model (Patient and Hospital Characteristics, Without NIHSS Score)			SENSITIVITY ANALYIS Adjusted Model (Patient and Hospital Characteristics, With NIHSS Score Included as a Complete Case Analysis)		
	OR	95% CI	P-Value	OR	95% CI	P-value	OR	95% CI	P-value
In-hospital Mortality									
SAPT	Non-significant Interaction		0.4431	Non-significant Interaction		0.1682	Non-significant Interaction		0.7390
CAPT	Non-significant Interaction		0.3488	Non-significant Interaction		0.1829	Non-significant Interaction		0.8496
In-hospital Mortality or Discharge Hospice									
SAPT	Non-significant Interaction		0.6846	Non-significant Interaction		0.0955	Non-significant Interaction		0.8912
CAPT	Non-significant Interaction		0.1602	Non-significant Interaction		0.7221	Non-significant Interaction		0.0864
Discharge Home									
SAPT	Non-significant Interaction		0.3456			0.0450	Non-significant Interaction		0.2578
Male				1.08	(1.02, 1.14)	0.0045			
Female				1.00	(0.94, 1.06)	0.9417			
CAPT	Non-significant Interaction		0.4882	Non-significant Interaction		0.6668	Non-significant Interaction		0.2905
Independent Ambulation at Discharge									
SAPT			0.0166			0.0022	Non-significant Interaction		0.0647
Male	0.85	(0.81, 0.90)	<.0001	1.09	(1.02, 1.15)	0.0044			
Female	0.78	(0.74, 0.82)	<.0001	0.97	(0.91, 1.02)	0.2564			
CAPT	Non-significant Interaction		0.4713	Non-significant Interaction		0.0716	Non-significant Interaction		0.1021
Modified Rankin Score at Discharge > 2									
SAPT			0.0233			0.0030	Non-significant Interaction		0.0813
Male	1.14	(1.06, 1.24)	0.0009	0.87	(0.79, 0.95)	0.0028			
Female	1.31	(1.19, 1.44)	<.0001	1.05	(0.94, 1.16)	0.3687			
CAPT	Non-significant Interaction		0.0777			0.0103	Non-significant Interaction		0.1706
Male				0.89	(0.74, 1.04)	0.1830			
Female				1.28	(0.98, 1.57)	0.0404			

NIHSS indicates National Institutes of Health Stroke scale; OR, Odd's ratio; CI, confidence interval;

SAPT, single antiplatelet therapy; and CAPT, combination antiplatelet therapy.