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Prior Antiplatelet Therapy, Platelet Infusion Therapy and Outcome after Intracerebral Hemorrhage

CJ Creutzfeldt, MD[*], **JR Weinstein, MD, PhD**[*], **WT Longstreth Jr, MD, MPH**, **KJ Becker, MD**, **TO McPharlin, RPh**, and **DL Tirschwell, MD, MSc**
Department of Neurology, University of Washington, Seattle, WA

Abstract

Background—Recent studies examining the effect of prior antiplatelet therapy (APT) on outcome in patients with spontaneous intracerebral hemorrhage (ICH) have shown conflicting results. The effect of platelet infusion therapy (PIT) on outcome in APT patients with ICH is unknown.

Methods—We reviewed records of ICH patients admitted to a single hospital, excluding those with INR ≥1.5. Baseline characteristics were compared by APT status in all patients and by PIT status in the subgroup of patients on APT. We used multivariate analyses to generate propensity and prognostic scores for exposures (APT and PIT) and outcomes (favorable outcome and hospital death), respectively. We examined the associations between exposures and outcomes and adjusted these for propensity and/or prognostic scores. We then validated our findings with a sensitivity analysis.

Results—Of 368 patients identified, 121 (31.3%) were on APT, mostly aspirin. Patients on APT were older and more likely to have vascular comorbidities than those not. The APT group also had a higher initial Glasgow Coma Scale score (GCS) at presentation. In analyses adjusted for both propensity and prognostic scores, APT was associated with a higher likelihood of hospital death (OR 2.4; 95% CI 1.1-5.6); PIT did not prevent hospital death (OR 1.2; 95% CI 0.3-5.5) or increase favorable outcome (OR 1.4; 95% CI 0.4-5.4).

Conclusions—In ICH patients, APT is associated with an increased risk of hospital death. In the subgroup of patients on APT, PIT did not prevent death or improve outcome.

Patients presenting with spontaneous intracerebral hemorrhage (ICH) are often on antithrombotic therapy, more commonly antiplatelet therapy (APT) than anticoagulation therapy [1]. Studies examining the effect of APT on ICH outcome have yielded conflicting results [1-11], possibly reflecting differences in sample size, demographics, and statistical analysis. The effect of platelet infusion therapy (PIT) on outcome in ICH patients on APT has not been previously addressed. In this retrospective study at a single tertiary referral center, we examined how APT related to hospital outcome in patients with ICH, and among those using APT, how PIT related to hospital outcome.

Correspondence to: Claire J. Creutzfeldt, Department of Neurology, University of Washington, Harborview Medical Center, Box 359775, 325 Ninth Ave, Seattle, WA 98104-2420; Tel.: +1 206 744-3251; Fax: +1 206 744-8787, clairejc@u.washington.edu.
[*]equal contribution

METHODS

We conducted a single-center retrospective study based on review of medical records. We included 368 consecutive patients with non-traumatic spontaneous ICH and an INR <1.5 between May 2001 and September 2003, who were admitted to Harborview Medical Center, a Joint Commission Primary Stroke Center that serves as a tertiary referral center for patients with severe neurological diseases. Patients with a secondary cause for their hemorrhage, such as ruptured aneurysm, primary ischemic stroke, trauma, AVM or tumor, were excluded. Approximately 20% of all Seattle and surrounding King county residents with ICH are seen at this hospital.

Data collection

Information was abstracted from medical records. Attributes were considered present if specifically mentioned in the medical records; otherwise, they were considered absent. Information collected included the following baseline characteristics: admission year, age, gender, race, pre-hospital functional status, medical conditions and medications prior to hospitalization. Medication use prior to admission was documented as antiplatelet, antihypertensive and cholesterol lowering therapy. Antiplatelet therapy included aspirin, clopidogrel and dipyridamole. Cardiac disease was defined as a previous history of myocardial infarction, coronary artery bypass grafting or cardiac catheterization.

Information collected from around the time of admission included whether or not patients were referred from an outside hospital and initial findings at Harborview. These included blood pressure, heart rate and rhythm, temperature, Glasgow Coma Scale (GCS) score, serum glucose level, and brain imaging characteristics. Platelet infusion therapy (PIT) for ICH patients on APT was defined as administration of at least six units of platelets while in the emergency room. Based on initial imaging reports, hemorrhage location was classified as supratentorial or infratentorial, and the following findings were documented as present or not: obvious mass effect, midline shift, ventricular extension, hydrocephalus, and herniation. In the subset of patients where all three dimensions of the hemorrhage were specified in the report, volume was calculated with the ABC/2 method [12].

Information collected from after the initial evaluations included: admission to the neurology or neurosurgery service; endotracheal intubation; surgical intervention with ventriculostomy or craniotomy; do-not-attempt-resuscitation (DNAR) status; and withdrawal of life-sustaining treatments. We did not collect information on hematoma expansion. Outcomes were death and functional status at discharge, which was abstracted from the medical chart and translated into the modified Rankin score (mRS). Favorable outcome was defined as moderate disability or better at time of hospital discharge corresponding to a mRS ≤ 3.

This study was approved by the Human Subjects Research committee at the University of Washington.

Statistical analysis

Clinical characteristics described in the previous section were compared between ICH patients based on the exposures of interest, APT status in the entire cohort and PIT status in the subgroup with APT use. Nonparametric and parametric statistics were used as appropriate.

For a variable to confound an association, it must be related to both exposure and outcome. In order to control for possible confounding, we generated multivariate models and calculated propensity scores for exposures (APT status and PIT status) and prognostic scores for outcomes (hospital death and favorable outcome). For the group of interest, logistic regression was used with the dependent variable being one of these two exposures or two outcomes and the

independent variables being all clinical characteristics significantly associated with the dependent variable in bivariate analyses. Only those variables remaining significant ($p < 0.05$) were retained in the logistic regression models and are listed in table 1. The C statistic, reflecting the area under the Receiver Operator Characteristic (ROC) curve, is presented as a summary measure of discriminative performance of the different models [13], with a C statistic of 1.0 indicating perfect performance. The models were used to generate for each patient propensity scores for the two exposures and prognostic scores for the two outcomes. To examine associations between exposures and outcomes, we used logistic regression with the outcome (hospital death or favorable outcome) as the dependent variable and the exposure (APT status or PIT status) as the independent variable. The strength and precision of association were summarized with an odds ratio (OR) and 95% confidence interval (CI), respectively. We examined unadjusted models and models adjusted for propensity score, prognostic score, or both.

In sensitivity analyses, we repeated the logistic regressions using the well-validated ICH Score [14] instead of our prognostic score. The ICH Score could be calculated in 267 of the 368 ICH patients (72%). Of note, our “obvious mass effect” variable agreed with the “> 30 cc” variable from the ICH Score 84% of the time, with a kappa statistic of 0.67, which is interpreted as substantial agreement.

All analyses were performed using Stata (version 10, StataCorp, College Station, TX).

RESULTS

We identified 368 eligible ICH patients of whom 121 (31.3%) were on APT. All but three, who were taking clopidogrel alone, were on aspirin (118/121), either alone (105/121) or in combination with clopidogrel (11/121) or extended release dipyridamole (2/121). Of the 121 patients on APT, 53 received PIT.

The results of the bivariate analyses for APT and PIT are summarized in table 2. Compared to patients not on APT, those on APT were significantly older and had more comorbid conditions but higher initial GCS scores. Compared to patients on APT who did not receive PIT, those who received PIT were significantly more likely to be men, to have been transferred from an outside hospital and to be admitted to the neurology service.

Results of the multivariate analyses are presented in the Figure for APT and PIT. The shifts in point estimates following adjustment for propensity score, prognostic score, or both suggest confounding was present. In the adjusted analyses, APT was not associated with favorable outcome but instead was associated with an increased risk of death. Among patients on APT, PIT was not associated with favorable outcome or hospital death after adjustment for both prognostic and propensity score.

In sensitivity analyses, when we repeated the logistic regressions using the ICH Score [14] instead of our prognostic score, results and conclusions were largely unchanged (data not shown).

A third of all patients died during their hospital stay, and 80% of these had life-sustaining measures withdrawn. Withdrawal did not significantly differ by APT status or by PIT status among those on APT.

DISCUSSION

Having excluded patients with an INR of 1.5 or more, whether on anticoagulants or not, we found that almost a third of patients (31.3%) in this study were on APT with all but three on

aspirin, either alone or in combination with other antiplatelet agents. The results suggest that patients with ICH are more likely to die in hospital if they were taking APT prior to the event. The increased risk of death was evident only after adjusting for 1) factors related to the use of APT and 2) factors related to outcomes. The change in risk with adjustment for these factors indicates that they confounded the relationship between APT and hospital death in this study. Among the patients on APT, PIT was not associated with improved outcomes.

Table 3 places our results in context with recent studies that examine the effect of APT on ICH outcome. Our findings agree with a number of the earlier studies that suggested a worse clinical outcome for ICH patients on prior APT [5-8,10].

Although these studies showed patients on APT to be older and with more premorbid conditions than those not on APT, identification of and adjustment for possible confounders was only done in a few [1,8]. In one study, adjustment for age and premorbid conditions led to a loss of association between APT and outcome [1], while in the other study, mortality was still increased in the APT group after adjusting for age, hypertension and alcohol use [8]. In the other earlier studies [2-7,9-11], it is possible that adjustment for other confounders, factors related to APT use and outcomes, may have yielded different results.

In hemorrhagic stroke, the effect of antiplatelet agents on bleeding time may contribute to worse outcome. Reliable measures of platelet dysfunction would be useful in this setting but are not reported in any of these studies, including ours.

The risk of hematoma expansion is increased with APT [6,7,10], and hematoma expansion is related to a worse outcome [15]. The design of our study did not allow us to determine the effect of APT use on hematoma expansion.

In our study, patients on APT presented with a significantly higher GCS score than those not (tables 2 and 3), and there was a trend in the APT group toward better prognostic scores at time of presentation (data not shown). These findings seem paradoxical in light of the significant association between APT use and hospital death in the fully adjusted analyses (Figure). This discrepancy, which was not described in any of the prior studies (table 3), may indicate that confounding was present in the bivariate analyses. It could also suggest, however, that APT use, despite its association with hospital death, is also independently associated with a less severe clinical presentation. A potential physiological explanation could be that the anti-inflammatory effects of aspirin predominate on initial presentation but are outweighed by the anti-hemostatic properties during the later clinical phases of ICH, possibly contributing to hematoma expansion and, thus, increased hospital death.

If APT is associated with a worse outcome in patients with ICH, treatments such as PIT would be important to evaluate, especially given the large proportion of patients with ICH who are on APT at presentation. Although PIT has been recommended in life-threatening ICH secondary to autoimmune thrombocytopenia (17), we are not aware of prior studies, either with an experimental or observational design, that have examined the efficacy of PIT in ICH patients on APT. This study demonstrates the feasibility of initiating PIT in the emergency room for patients with ICH. After adjusting for potential confounders associated with both outcome and exposure, we did not find a significant relationship between PIT and outcome. Confidence intervals around our risk estimates were broad, reflecting the relatively small number of APT users eligible for these analyses (n = 121). Thus, these findings do not exclude the possibility of PIT causing clinically important benefit or harm in these patients.

This study is limited by its moderate sample size and retrospective design. Misclassification of exposures was possible, care was not standardized and interventions were not randomized (including the use of PIT). Imaging data were also based on record review, and we could not

determine if hematoma expansion occurred. Patients were not followed after discharge from hospital, so their functional status several months after hospitalization is unknown. The ICH onset was often unknown, so the interval to the start of PIT could not be calculated.

We tried to minimize the risk of confounding by determining baseline characteristics of all ICH patients and using multivariate analyses to adjust for differences in the comparison groups. In baseline characteristics, we included several variables of potential relevance (frequency of withdrawal of medical support as well as withdrawal of medical support as a cause of death, DNAR status and hospital referral status) that have not been uniformly included in prior studies (see table 3). In addition, we used two outcome variables, favorable outcome and hospital death, to provide a broader perspective than simply mortality. When using the well validated ICH Score [14] rather than our prognostic score, results were largely unchanged. Finally, in contrast to prior studies, we have attempted here to systematically control for confounding factors related to both exposure and outcome using propensity and prognostic scores, respectively.

We have reviewed a number of studies examining the effect of APT on ICH outcome (table 3); the heterogeneity in the design of these studies is striking. Differences were seen in inclusion/exclusion criteria, statistical analyses and outcome measures. All studies, including ours, were observational and subject to a large number of potential confounding factors and biases. Given the known limitations of meta-analyses, particularly with respect to observational studies [16], we have chosen here to present an overview of these studies in this comparative table.

CONCLUSIONS

This study adds to the evidence that ICH patients on APT are more likely to die than those not on APT. Whether PIT could improve outcomes in ICH patients on APT is not answered by this study, but to our knowledge, this is the only study that has addressed the effect of PIT on outcome in patients with ICH. A randomized trial in which platelets are given by a standard protocol and within a specific time interval from ICH symptom onset will ultimately be required to determine if PIT improves outcome.

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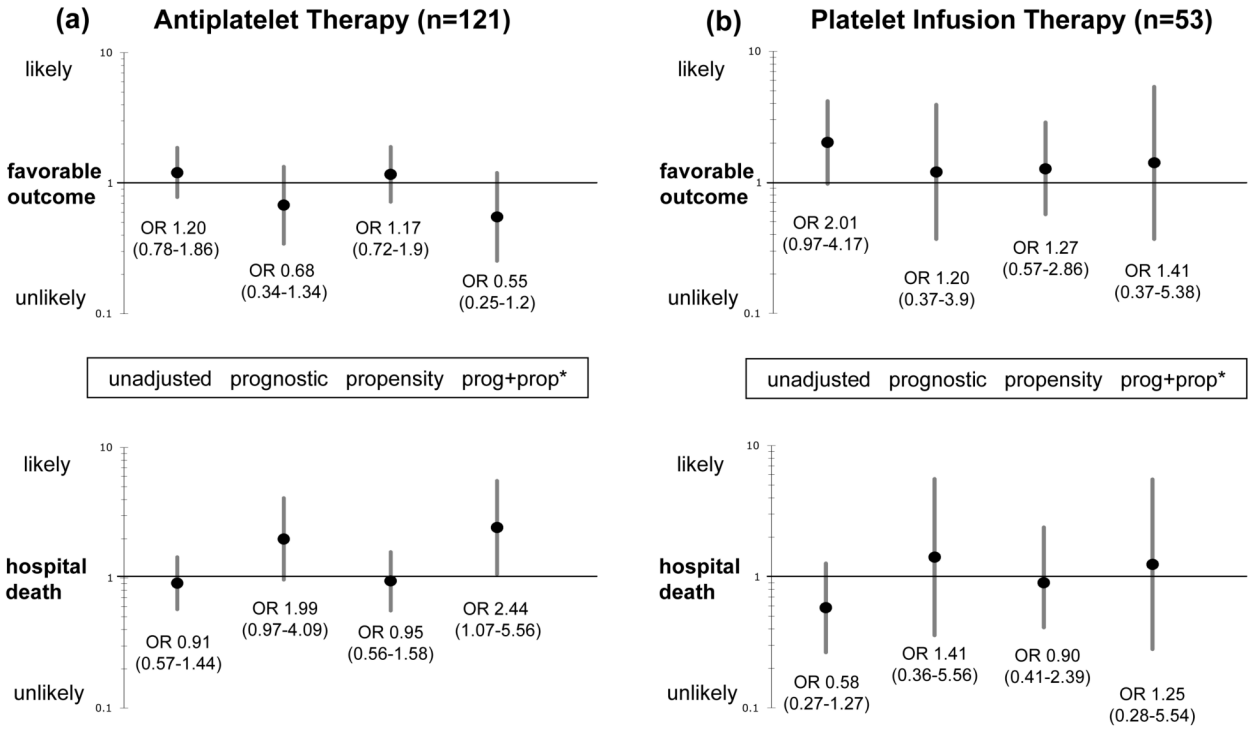

Figure.

Associations between exposures and outcomes (favorable outcomes and hospital death). odds ratios (OR) and 95% confidence intervals (CI) derived from unadjusted and adjusted logistic regression models. See text for details.

(a) Association with antiplatelet therapy (APT) status

(b) Association with platelet infusion therapy (PIT) status

*prognostic and propensity score

Table 1

Factors significantly and independently associated with different exposures and outcomes and used to create the propensity score for antiplatelet therapy (APT) and platelet infusion therapy (PIT) and the prognostic score for favorable outcome and hospital death.

	Outcome	Independently Associated Factors	C statistic
Propensity score	**All Patients (n = 368)**		
	APT	older age, history of antihypertensive and/or cholesterol lowering medication on admission, history of CAD, stroke, TIA and transfer from an outside hospital	0.77
	APT Patients only (n = 121)		
	PIT	male gender, transfer from an outside hospital, more recent admission year, and admission to the Neurology (vs. Neurosurgery) service	0.74
Prognostic score	**All Patients (n = 368)**		
	Favorable Outcome	lower age, premorbid functional independence, higher initial GCS score, lower initial heart rate and lack of obvious ICH mass effect	0.93
	Hospital Death	older age, lower initial GCS score, obvious ICH mass effect, higher initial heart rate and herniation	0.92
	APT Patients only (n = 121)		
	Favorable Outcome	younger age and higher initial GCS score	0.94
	Hospital Death	lower initial GCS, ventricular extension and hydrocephalus	0.95

Table 2

Clinical characteristics of 368 patients with spontaneous intracerebral hemorrhage based on use prior to the hemorrhage of antiplatelet therapy (APT) and, among those on APT, receiving platelet infusion therapy (PIT).

	APT (−) n = 247	APT (+) n = 121	p-Value*	PIT (−) n = 68	PIT (+) n = 53	p-value*
BASELINE CHARACTERISTICS						
Age, years (SD)	62 (17)	70 (12)	<0.001	71 (12)	70 (13)	0.65
Women	121 (49%)	62 (51%)	0.69	42 (62%)	20 (38%)	0.01
Premorbid mRS ≤ 3	229 (93%)	107 (88%)	0.17	57 (84%)	50 (94%)	0.07
Cardiac disease	11 (5%)	24 (20%)	<0.001	11 (17%)	13 (25%)	0.25
Ischemic stroke	8 (3%)	22 (18%)	<0.001	14 (21%)	8 (15%)	0.44
TIA	5 (2%)	16 (13%)	<0.001	9 (13%)	7 (13%)	1.00
Diabetes mellitus	38 (15%)	34 (28%)	0.00	18 (26%)	16 (30%)	0.65
Hypertension	154 (62%)	90 (74%)	0.02	53 (78%)	37 (70%)	0.31
Previous ICH	22 (19%)	8 (7%)	0.45	4 (6%)	4 (8%)	0.72
Hypercholesterolemia	24 (10%)	28 (23%)	<0.001	14 (21%)	14 (26%)	0.45
Medication:antihypertensive	107 (43%)	80 (66%)	<0.001	49 (72%)	31 (58%)	0.12
lipid-lowering	19 (8%)	28 (23%)	<0.001	13 (19%)	15 (28%)	0.24
ADMISSION FINDINGS - Physiologic status						
SBP (SD)	172 (39)	167 (32)	0.20	170 (33)	163 (31)	0.21
DBP (SD)	100 (25)	91 (19)	<0.001	92 (19)	90 (18)	0.56
Heart Rate (SD)	88 (22)	80 (20)	0.00	81 (22)	79 (16)	0.65
Temperature °C (SD)	36.3 (1.2)	36.4 (0.8)	0.25	36.3(0.83)	36.5 (0.73)	0.19
Median first GCS (IQR)	9 (6-14)	12 (7-14)	0.02	11 (6.5-14)	13 (9-15)	0.10
Median Glucose (SD)	161 (55)	159 (62)	0.78	167 (70)	150 (48)	0.15
- Imaging						
Obvious mass effect	148 (60%)	64 (53%)	0.20	37 (54%)	27 (51%)	0.71
Ventricular extension	125 (51%)	61 (50%)	0.97	36 (53%)	25 (47%)	0.53
Hydrocephalus	72 (29%)	24 (20%)	0.06	16 (24%)	8 (15%)	0.25

	APT (−) n = 247	APT (+) n = 121	p-Value*	PIT (−) n = 68	PIT (+) n = 53	p-value*
Subfalcine herniation	40 (16%)	17 (14%)	0.59	9 (13%)	8 (15%)	0.77
Midline shift	71 (29%)	32 (27%)	0.64	16 (24%)	16 (30%)	0.41
Location - supratentorial	201 (81%)	110 (91%)	p=0.032	61 (89%)	49 (92.5%)	p=0.61
HOSPITAL COURSE, INTERVENTIONS AND OUTCOME						
Neurology Service admit	156 (63%)	93 (77%)	0.01	46 (68%)	47 (89%)	0.01
Transfer from OSH	169 (68%)	100 (83%)	0.00	52 (76%)	48 (90%)	0.04
Intubation	147 (60%)	53 (44%)	0.00	35 (51%)	18 (34%)	0.05
Craniotomy	39 (16%)	8 (7%)	0.01	7 (10%)	1 (2%)	0.07
Ventriculostomy	47 (19%)	14 (12%)	0.07	10 (15%)	4 (8%)	0.22
DNAR	92 (37%)	38 (40%)	0.65	30 (44%)	18 (34%)	0.26
Died in hospital	87 (35%)	40 (33%)	0.68	26 (38%)	14 (26%)	0.17
Cause of death withdrawal of life-sustaining treatment	68 (78%)	34 (85%)	0.81	20 (77%)	14 (100%)	0.15
mRS on discharge ≤ 3	109 (44%)	59 (49%)	0.40	28 (41%)	31 (58%)	0.06

APT, Antiplatelet therapy; DNAR do-not-attempt-resuscitaton; GCS, Glasgow Coma Scale; IQR, interquartile range; mRS, modified Rankin Scale; OSH, outside hospital; PIT, Platelet Infusion Therapy; SBP, systolic blood pressure; SD, standard deviation.

*Nonparametric statistics were used; Wilcoxon rank sum statistics for continuous variables and chisquare statistics for categorical variables.

Table 3

Comparison of 7 recent studies* exploring the effect of Antiplatelet therapy (APT) on primary intracerebral hemorrhage (ICH)**.

	Toyoda et al., Neurology 2005	**Saloheimo et al., Stroke 2006**	**Foerch et al., Stroke 2006**	**Lacut et al., Fund Clin Pharmacol 2007**	**Caso et al., Cerebrovasc Dis 2007**	**Hanger et al., J Neurol 2008**	**Creutzfeldt, Weinstein et al., 2008**
Study type	Retrospective One medical center	Retrospective Population based	Subanalysis of nationwide registry	Subanalysis of ICH trial One medical center	Part of stroke registry 2 medical centers	Retrospective One medical center	Retrospective One medical center
Study period	First 2 hospital days 01/99 – 02/05	Up to 3 months 01/93 – 09/95	Hospital stay 01/03 – 12/04	Up to 3 months 02/02 – 12/03	Hospital stay 01/00 – 12/03	Up to 28 days 01/96 – 12/98	Hospital stay 05/01 – 09/03
No. of patients	251 32.4% APT users	208 33.7% APT users	1691 26% APT users	138 21.7% APT users	457 20.5% APT users	223 40.8% APT users	368 31.3% APT users
Age (yrs)	≥ 70: 60 vs 35% (p < 0.01)	71.6 vs 65.6 (p < 0.01)	75 vs 70 (p < 0.001)	70.5 vs 61.5 (p < 0.01)	78.9 vs 73.8 (p = 0.02)	75.7 vs 69.9 (p < 0.001)	70 vs 62 (p < 0.01)
Pre-hospital status	mRS ≥ 3: 4 vs 6% (ns)	ND%	mRS > 1: 38 vs 18% (p < 0.001)	mRS > 3: 37 vs 32% (ns)	ND	ND	mRS ≤ 3: 88 vs 93% (ns)
Hypertension	86 vs 83% (ns)	66 vs 57%	89 vs 75% (p < 0.001)	57 vs 35% (p = 0.06)	77 vs 66% (p = 0.08)	71 vs 42% (p , 0.001)	74 vs 62% (p = 0.02)
Heart disease	32 vs 8% (p < 0.01)	59 vs 32% (p <0.01)	more freq. (p < 0.01)	ND	collected, not stated	41 vs 12% (p < 0.001)	20 vs 5% (p < 0.01)
Prior IS	54 vs 7 % (p < 0.01)	43 vs 9% (p < 0.01)	ND	ND	Excluded	60 vs 16% (p < 0.001)	22 vs 8 % (p < 0.01)
Admission score	NIHSS < 6: 39 vs 37% (ns) >16: 39 vs 29% (ns)	ICH score 0: 33 vs 29%, (ns) >2: 21 vs 19% (ns)	mRS > 2 88 vs 83% (p = 0.02)	GCS > 8 or mRS > 3 (ns)	collected, but not stated	ND	Median GCS 12 vs 9 p = (0.02)
DNAR order	ND	ND	ND	Excluded	ND	ND	40% DNAR orders (ns)
Withdrawal of care	ND	ND	ND	ND	ND	ND	80% who died (ns)
Hematoma growth (HG)	HG > 140%: 27 vs 8% (p < 0.01)	Any HG increased (p <0.01) HG >133%: 19 vs 8% (ns)	ND	ND	ND	ND	ND
PIT	ND	ND	ND	ND	ND	ND	44% APT users. No association with outcome
Mortality	2-day: 7 vs 5% (ns)	3-month: 43 vs 22% (p=0.005)	In-hospital: 27 vs 21% (p = 0.01)	3-month: 47 vs 19% (p= 0.002)	In-hospital: 23.4 vs 23.1% (ns)	7-day: 33 vs 33% (ns) 28-day: 43 vs 39% (ns)	In-hospital: 35 vs 33% (ns)
Outcome OR [95% CI]	58% vs. 30% either died, had HG or required surgical evacuation (p < 0.005)	3 month mortality RR 2.5 [1.3-4.6] (p < 0.01)	OR after adjustment for age & prehosp status: - for hospital death 1.12 (ns)	OR after adjustment for age, HTN, alcohol use: - for 8day mortality: 4.9	No sign. difference for in-hospital mortality or poor outcome	7day-mortality RR 1.3 [0.6-3.2] 28day-mortality RR 1.2 [0.5-2.7]	OR after adjustment for propensity & prognostic score -for hospital death 2.4 [1.1-5.6]

	Toyoda et al., Neurology 2005	Saloheimo et al., Stroke 2006	Foerch et al., Stroke 2006	Lacut et al., Fund Clin Pharmacol 2007	Caso et al., Cere-brovasc Dis 2007	Hanger et al., J Neurol 2008	Creutzfeldt, Weinstein et al., 2008
			- for unfavorable outcome 0.97 (ns)	[1.2-20.1] - for 3month mortality: 3.4 [1.3-8.7]			-for favorable outcome 0.5 [0.25-1.2]
Conclusions	APT contributes to acute clinical deterioration	APT use is an independent predictor for death within 3 months	APT use is not assoc. with worse outcome after adjusting for age & pre-hospital status,	APT significantly increases mortality	APT is not associated with increased death on hospital discharge	Aspirin use does not independently increase early mortality	APT use is associated with significantly increased risk of hospital death

DNAR, Do-not-attempt-resuscitation; GCS, Glasgow Coma Scale; IS, ischemic stroke; mRS, modified Rankin Scale; PIT, Platelet Infusion Therapy; ND, not documented in paper; NIHSS, National Institute of Health Stroke Scale.

* Choice of studies was based on a Medline search for the terms “Antiplatelet [or Aspirin] AND intracerebral [or intraparenchymal] hemorrhage”. We included those studies that directly addressed the outcome (either functional outcome or imaging) of patients who had been taking APT prior to their spontaneous intracerebral hemorrhage.) Five additional studies that are cited in the text are not included in this table; these are also observational studies regarding outcome and outcome predictors in ICH, but the influence of APT was not their primary focus (2-5, 10).

** Primary ICH is ICH not caused by tumor, trauma, anticoagulation, hemorrhagic conversion of ischemic stroke, aneurysm or arteriovenous malformation (1,6-9,11 and this study). Effects are listed as x versus y with x=APT use and y=no APT use.