European Journal of Neurology 2013, 20: 879–890 doi:10.1111/ene.12060

Prestroke antiplatelet therapy and early prognosis in stroke patients: the Dijon Stroke Registry

Y. Béjot[a], C. Aboa-Eboulé[a], E. de Maistre[b], A. Jacquin[a], O. Troisgros[a,c], M. Hervieu[a], G. V. Osseby[a], O. Rouaud[a] and M. Giroud[a]

[a]*Dijon Stroke Registry, Department of Neurology, University Hospital and Medical School of Dijon, University of Burgundy, Dijon;* [b]*Department of Biological Hematology, University Hospital of Dijon, Dijon; and* [c]*Department of Rehabilitation, University Hospital of Dijon, Dijon, France*

Keywords:
antiplatelet therapy, functional recovery, mortality, outcome, registry, stroke

Received 19 July 2012
Accepted 1 November 2012

Background and purpose: Previous antiplatelet therapy (APT) in cardiovascular prevention is common in patients with first-ever stroke. We aimed to evaluate the prognostic value of APT on early outcome in stroke patients.

Methods: All first-ever strokes from 1985 to 2011 were identified from the population-based Stroke Registry of Dijon, France. Demographic features, risk factors, prestroke treatments and clinical information were recorded. Multivariate analyses were performed to evaluate the associations between pre-admission APT and both severe handicap at discharge, and mortality at 1 month and 1 year.

Results: Among the 4275 patients, 870 (20.4%) were previously treated with APT. Severe handicap at discharge was noted in 233 (26.8%) APT users and in 974 (28.7%) non-users. Prestroke APT use was associated with lower odds of severe handicap at discharge [adjusted odds ratio (OR): 0.79; 95% confidence interval (CI): 063–1.00; $P = 0.046$], non-significant better survival at 1 month [adjusted hazard ratio (HR): 0.87; 95% CI: 0.70–1.09; $P = 0.222$] and no effect on 1-year mortality (HR: 0.94; 95% CI 0.80–1.10; $P = 0.429$). In stratum-specific analyses, APT was associated with a lower risk of 1-month mortality in patients with cardioembolic ischaemic stroke (HR: 0.65; 95% CI: 0.43–0.98; $P = 0.040$).

Conclusions: APT before stroke was associated with less severe handicap at discharge, with no significant protective effect for mortality at 1 month except in patients with cardioembolic stroke. No protective effect of APT was observed for mortality at 1 year. Further studies are needed to understand the mechanisms underlying the distinct effects of prior APT observed across the ischaemic stroke subtypes.

Introduction

For the last three decades, the use of antiplatelet therapy (APT) for the prevention of cardiovascular diseases, including stroke, myocardial infarction and peripheral vascular disease, has been increasing dramatically. As a consequence, APT is common in patients at the time of their first-ever stroke, with a prevalence ranging from 26% to 38% according to data from population-based registries [1–3]. Several previous studies pointed out the fact that prestroke APT, especially aspirin, could affect both the early functional and vital prognosis of stroke patients [4–13]. However, most of these studies were limited either by a small population size, a hospital-based setting, a lack of control for potential confounding factors in multivariate analyses, or no differentiation between stroke subtypes, which probably contributed to the conflicting results.

Therefore, using data from the prospective population-based Stroke Registry of Dijon, France, we aimed to evaluate in this study the prognostic value of APT before stroke on both functional outcome at discharge, and mortality at 1 month and 1 year in stroke patients.

Correspondence: Y. Bejot, Dijon Stroke Registry, Department of Neurology, CHU, 3 Rue du Faubourg Raines, 21000 Dijon, France (tel.: +33 380 293753; fax: +33 380 293672; e-mail: ybejot@yahoo.fr).

Methods

Case collection procedure

All cases of first-ever stroke that occurred within the city of Dijon, France (150 000 inhabitants) from 1985

EUROPEAN JOURNAL OF NEUROLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

to 2011 were identified from the Dijon Stroke Registry, the methodology of which has been described elsewhere [3]. Briefly, the case collection procedure relies on multiple overlapping sources of information to identify fatal and non-fatal, hospitalized and non-hospitalized stroke patients. Data were obtained from: (i) the emergency rooms, and all the clinical and radiological departments of Dijon University Hospital, and the three private hospitals of the city and its suburbs; (ii) the patient's home or nursing homes, with diagnosis assessed by the general practitioners helped by public or private neurologists from outpatient clinics; (iii) the medical records of radiological and Doppler ultrasound centres; (iv) and the death certificates obtained from the local Social Security Bureau that is responsible for the registration of deaths in the community particularly fatal strokes outside hospital.

Definition of stroke

Stroke was defined according to World Health Organization recommendations [14]. The diagnosis of stroke subtype was always made on the clinical examination, cerebral imaging and complementary exams. Only first-ever symptomatic stroke was considered for this study. The classification of the stroke subtypes used since 1985 was as follows: (i) lacunar infarct; (ii) ischaemic stroke from cardiac embolism (CE); (iii) non-lacunar non-cardioembolic ischaemic strokes; (iv) spontaneous intracerebral haemorrhage (ICH); (v) subarachnoid haemorrhage (SAH); and (vi) undetermined stroke.

Baseline characteristics

Vascular risk factors were collected with the same methodology throughout the study period [3]. Hypertension was defined by a history of known hypertension or antihypertensive treatment. Diabetes mellitus was recorded if a glucose level of ≥ 7.8 mmol/l had been reported in the medical record or if the patient was under insulin or oral hypoglycaemic agents. Hypercholesterolaemia was considered if a total cholesterol level ≥ 5.7 mmol/l was reported in the medical history of the patient or if patients were treated with lipid-lowering therapy. We also recorded smoking status, history of atrial fibrillation, previous myocardial infarction, peripheral artery disease (PAD) and previous transient ischaemic attack (TIA). Prestroke treatments were also recorded, including APT (aspirin, clopidogrel, dipyridamole and ticlopidine), anticoagulants (vitamin K antagonists, unfractionated heparin and low-molecular-weight heparin), antihypertensive treatments and statins (only available from 2006 to 2009). Clinical features at stroke onset, treatment centre (public or private hospital, outpatient), and length of stay were also considered. History of retirement home before stroke was assessed as a substitute for level of dependency before stroke. Stroke severity at admission was assessed by three items (impaired consciousness, motor deficit and aphasia) thorough the whole study period, whereas the National Institute Health Stroke Scale (NIHSS) was systematically recorded since 2006 only.

Outcomes

Functional impairment was collected at discharge or at outpatient consultation, and was initially measured with a handicap scale including six grades (1 = walking alone; 2 = walking with support; 3 = walking stick; 4 = wheelchair; 5 = bedridden; 6 = dead). This scale has been in use since the establishment of the registry in 1985 contrary to the modified Rankin score introduced as of 1997. The level of concordance (weighted κ coefficient) between both scales was 0.89 [95% confidence interval (CI): 0.87–0.90] for 2202 patients. In this study, severe handicap was defined by a score $\geq$ 4. The median time lapse between stroke onset and evaluation of functional outcome at discharge was 10 days (IQR: 4–18) and roughly 7 days at the follow-up consultation for outpatients. The second outcome was any-cause mortality at 1 month, which was systematically recorded.

Statistical analysis

Proportions and mean values of baseline characteristics were compared between groups using Chi-square test and analysis of variance, respectively. Person-days were calculated from the date of admission until death, the last contact date and the end of follow-up at 1 month and 1 year. Survival curves were obtained using Kaplan–Meier analysis, and the log-rank test was used for comparison between groups. Logistic and Cox regression models were used to estimate, respectively, odds ratios (ORs) of severe handicap and their 95% CIs, and hazard ratios (HRs) for mortality at 1 month and 1 year and their 95% CIs. In multivariate models, we introduced APT, anticoagulants, age, gender, retirement home and baseline characteristics with a P-value < 0.20 in unadjusted models. Backward elimination was done using the likelihood ratio test to obtain the final models that included the significant confounders, as well as age, gender, APT, anticoagulants and retirement home. Age, length of stay and stroke subtypes that did not satisfy the propor-

tional hazard assumption were included in the models as stratified variables. Based on prior knowledge, stratum-specific analyses were performed by stroke subtypes, although there were no statistically significant interactions between APT and functional outcome ($P = 0.158$), 1-month mortality ($P = 0.246$) and 1-year mortality ($P = 0.079$). In *post hoc* analyses, we assessed the impact of mono and dual APT on outcomes as a three-level variable: mono APT (single antiplatelet agent including aspirin, clopidogrel, dipyridamole, or ticlopidin); dual APT (aspirin plus another antiplatelet agent); and no APT (reference). *P*-values < 0.05 were considered statistically significant. SAS 9.3 (SAS institute, Cary, North Carolina, USA) was used for statistical analyses.

Ethics

Our registry was approved by the National Ethics Committee (CNIL) and the French Institute for Public Health Surveillance (InVS), and complies with national rules on the informed consent of patients.

Results

Among the 4275 stroke patients (53.8% women, mean age ± SD: 73.9 ± 15.2 years), 3526 (82.5%) had ischaemic stroke, 496 (11.6%) had ICH, 138 (3.2%) had SAH and 115 (2.7) had undetermined strokes. Baseline characteristics of patients are shown in Table 1. Prior to their stroke, 870 (20.4%) patients were on APT. APT users were older, were more likely to have vascular risk factors and to be on antihypertensive treatment and statins, and less likely to be on anticoagulants before stroke than were non-users. Among the 870 patients on APT, 377 (43.3%) used an antiplatelet agent in monotherapy, while 493 (56.7%) were on dual APT. The distribution of stroke subtypes also differed between the two groups, as did the treatment centre and the periods of admission.

A severe handicap at discharge was observed in 1207 (28.3%) stroke patients, including 233 (26.8%) of the APT users and 974 (28.7%) of the non-users. In multivariate analyses, there was a 21% relative odds reduction of severe handicap in APT users as compared with non-users (OR: 0.79; 95% CI: 0.63–1.00; $P = 0.046$; Table 2). Stratum-specific analyses showed that prestroke APT use was associated with lower odds of severe handicap among patients with ICH and CE (Table 3).

At 1 month, 652 (15.3%) patients had died. Kaplan–Meier curves showed non-significant lower survival for APT users than non-users (log-rank $P = 0.073$; Fig. 1). Multivariate analysis confirmed the non-significant protective effect of prestroke APT on 1-month mortality (HR: 0.87; 95% CI: 0.70–1.09; $P = 0.222$; Table 4). In stratum-specific analyses, APT was associated with a lower risk of mortality in patients with cardioembolic ischaemic stroke (HR: 0.65; 95% CI: 0.3843–0.98; $P = 0.040$; Table 3). At 1 year, 1164 (27.2%) patients had died. Kaplan–Meier curves showed no differences in survival between APT users and non-users (log-rank $P = 0.715$; Fig. 2). In multivariate analyses, prior APT was not associated with 1 year mortality in either pooled analyses (HR: 0.94; 95% CI 0.80–1.10; $P = 0.429$; Table 5) or stratum-specific analyses in patients with cardioembolic ischaemic stroke (HR: 0.83; 95% CI 0.63–1.09; $P = 0.181$; Table 3). In sensitivity analysis controlled for NIHSS in 1217 patients (2006–2011), the protective effect of APT use was still observed for severe handicap at discharge (adjusted OR: 0.64; 95% CI: 0.42–0.99; $P = 0.047$), but not for 1-month mortality (adjusted HR: 0.68; 95% CI: 0.43–1.08; $P = 0.104$) and 1-year mortality (adjusted HR: 0.87; 95% CI: 0.65–1.18; $P = 0.379$). In *post hoc* multivariate analyses, mono and dual APT were not significantly associated with severe handicap at discharge (respective adjusted HRs: 0.78; 95% CI: 0.57–1.07; $P = 0.121$; and 0.81; 95% CI: 0.60–1.08; $P = 0.148$; Table 2) and mortality at 1 month (respective adjusted HRs: 0.84; 95% CI: 0.60–1.17; $P = 0.292$; and 0.90, 95% CI: 0.69–1.17; $P = 0.420$; Table 4) as compared with no APT. No association was observed between mono and dual APT and 1-year mortality (respective adjusted HRs: 0.89; 95% CI: 0.71–1.12; $P = 0.321$; and 0.97; 95% CI: 0.80–1.18; $P = 0.792$; Table 5) in comparison with no APT.

Discussion

This large population-based study demonstrated that prestroke APT was associated with the functional prognosis at hospital discharge. Conversely, patients treated with APT before their stroke tended to have a lower though non-significant risk of 1-month mortality. This beneficial effect was significant in those with cardioembolic ischaemic stroke. However, the protective effect of APT use was not observed for 1-year mortality. Functional and mortality outcomes did not differ between users of mono and dual APT and non-users.

The prevalence of prestroke APT in our study significantly rose with time, reaching 24% of patients in the last study period (2005–2011). This increased trend in prevalence was similar to that observed in other population-based stroke registries [1,2], and reflects some changes in medical practices with regard to primary prevention of cardiovascular diseases. But, our

Table 1 Baseline characteristics of stroke patients according to APT

	Total $N = 4275$	APT $N = 870$ (20.4)	No APT $N = 3405$ (79.6)	*P*-value
Age, years (mean ± SD)	73.85 ± 15.15	78.31 ± 11.70	72.71 ± 15.71	**< 0.0001**
<60	674 (15.8)	59 (6.8)	615 (18.1)	**< 0.0001**
60–74	1077 (25.2)	195 (22.4)	882 (25.9)	
≥75	2524 (59.0)	616 (70.8)	1908 (56.0)	
Female gender	2300 (53.8)	463 (53.2)	1837 (54.0)	0.699
Time periods				
1985–1989	612 (14.3)	23 (2.6)	589 (17.3)	**< 0.0001**
1990–1994	667 (15.6)	93 (10.7)	574 (16.9)	
1995–1999	790 (18.5)	218 (25.1)	572 (16.8)	
2000–2004	802 (18.8)	194 (22.3)	608 (17.9)	
2005–2011	1404 (32.8)	342 (39.3)	1062 (31.2)	
Stroke subtype				
Intracerebral haemorrhage	496 (11.6)	86 (9.9)	410 (12.0)	**< 0.0001**
Subarachnoid haemorrhage	138 (3.2)	5 (0.6)	133 (3.9)	
Lacunar infarct	931 (21.8)	197 (22.6)	734 (21.6)	
Cardiac embolism	773 (18.1)	204 (23.4)	569 (16.7)	
Other ischaemic strokes	1822 (42.6)	368 (42.3)	1454 (42.7)	
Undetermined strokes	115 (2.7)	10 (1.2)	105 (3.1)	
Prior vascular risk factors				
Hypertension ($n = 4228$)[a]	2715 (64.2)	703 (81.1)	2012 (59.9)	**< 0.0001**
Diabetes ($n = 4224$)[a]	627 (14.8)	190 (21.9)	437 (13.0)	**< 0.0001**
Hypercholesterolaemia ($n = 4224$)[a]	990 (23.4)	305 (35.2)	685 (20.4)	**< 0.0001**
Smoking status				
Non-smoker	2442 (57.1)	489 (56.2)	1953 (57.4)	0.827
Ever smoker	1267 (29.6)	264 (30.3)	1003 (29.5)	
Unknown	566 (13.2)	117 (13.5)	449 (13.2)	
Myocardial infarction ($n = 4229$)[a]	692 (16.4)	273 (31.4)	419 (12.5)	**< 0.0001**
PAD ($n = 4228$)[a]	377 (8.9)	162 (18.6)	215 (6.4)	**< 0.0001**
Atrial fibrillation ($n = 4224$)[a]	560 (13.3)	149 (17.2)	411 (12.2)	**0.0001**
Prestroke TIA	368 (19.9)	171 (19.7)	467 (13.7)	**< 0.0001**
Prestroke medication				
Anticoagulants	284 (6.6)	33 (3.8)	251 (7.4)	**0.0002**
Antihypertensive drugs	2048 (47.9)	634 (72.9)	1414 (41.5)	**< 0.0001**
Statins from 2006 to 2011 ($n = 1217$)	145 (11.9)	74 (25.9)	71 (7.6)	**< 0.0001**
Clinical features at onset				
Aphasia ($n = 4238$)[a]	1322 (31.2)	291 (33.6)	1031 (30.6)	0.082
Impaired consciousness ($n = 4246$)[a]	959 (22.6)	167 (19.3)	792 (23.4)	**0.010**
Motor deficit ($n = 3801$)[a]	3125 (73.6)	644 (74.4)	2481 (73.4)	0.584
NIHSS from 2006 to 2011 ($n = 1217$)				
Quartile 1, 0–2	386 (31.7)	74 (25.9)	312 (33.5)	0.107
Quartile 2 (median), 3–4	240 (19.7)	59 (20.6)	181 (19.4)	
Quartile 3, 5–12	336 (27.6)	88 (30.8)	248 (26.6)	
Quartile 4, 13–29	255 (21.0)	65 (22.7)	190 (20.4)	
Length of stay				
<10 days	2072 (48.5)	420 (48.3)	1652 (48.5)	0.959
10–30 days	1733 (40.5)	356 (40.9)	1377 (40.4)	
>30 days	470 (11.0)	94 (10.8)	376 (11.0)	
Treatment centres				
Public hospital	3346 (78.3)	672 (77.2)	2674 (78.5)	**0.006**
Private hospital	556 (13.0)	137 (15.7)	419 (12.3)	
Outpatient	373 (8.7)	61 (7.0)	312 (9.2)	
Retirement home before stroke	304 (7.1)	71 (8.2)	233 (6.8)	0.177

Percentages are under brackets.

APT, antiplatelet therapy; NIHSS, National Institute Stroke scale; PAD, peripheral artery disease; TIA, transient ischaemic attack.

[a]Denominator may vary due to missing information.

The significance for bold values is < 0.05.

Table 2 Associations between prior APT and severe handicap at discharge in all patients from 1985 to 2011

	Unadjusted $N = 4262$					Multivariate model		
	Severe handicap							
	Yes $N = 1207$ (28.3)	No $N = 3055$ (71.7)	OR	95% CI	P value	OR	95% CI	P-value
APT	233 (19.3)	636 (20.8)	0.91	0.77–1.08	0.269	0.79	0.63–1.00	**0.046**
Mono or dual APT								
No APT	974 (80.7)	2419 (79.2)	1.00	–	–	1.00	–	–
Monotherapy	100 (8.3)	277 (9.1)	0.90	0.71–1.14	0.374	0.78[a]	0.57–1.07	0.121
Dual APT	133 (11.0)	359 (11.8)	0.92	0.74–1.14	0.442	0.81[a]	0.60–1.08	0.148
Covariates								
Age (mean ± SD)	79.17 ± 12.41	71.77 ± 15.62	1.04	1.04–1.05	**< 0.0001**	1.04	1.03–1.04	**< 0.0001**
Female gender	699 (57.9)	1591 (52.1)	1.27	1.11–1.45	**0.0006**	0.78	0.64–0.95	**0.014**
Time periods								
1985–1989	229 (19.0)	379 (12.4)	1.00	–	–	1.00		
1990–1994	211 (17.5)	450 (14.7)	0.78	0.62–0.98	**0.032**	0.81	0.59–1.10	0.175
1995–1999	192 (15.9)	595 (19.5)	0.53	0.42–0.67	**< 0.0001**	0.78	0.57–1.07	0.128
2000–2004	208 (17.2)	594 (19.4)	0.58	0.46–0.73	**< 0.0001**	1.26	0.92–1.73	0.154
2005–2011	367 (30.4)	1037 (33.9)	0.59	0.48–0.72	**< 0.0001**	0.94	0.71–1.24	0.661
Stroke subtype								
Intracerebral haemorrhage	258 (21.4)	234 (7.7)	1.00	–	–	1.00	–	–
Subarachnoid haemorrhage	31 (2.6)	104 (3.4)	0.27	0.17–0.42	**< 0.0001**	0.45	0.26–0.79	**0.005**
Lacunar infarct	58 (4.8)	873 (28.6)	0.06	0.04–0.08	**< 0.0001**	0.14	0.10–0.21	**< 0.0001**
Cardiac embolism	317 (26.3)	455 (14.9)	0.63	0.50–0.79	**< 0.0001**	0.80	0.60–1.08	0.142
Other ischaemic strokes	487 (40.3)	1333 (43.6)	0.33	0.27–0.41	**< 0.0001**	0.61	0.46–0.79	**0.0002**
Undetermined strokes	56 (4.6)	56 (1.8)	0.91	0.60–1.37	0.641	0.91	0.53–1.56	0.730
Hypertension ($n = 4215$)[b]	788 (66.7)	1918 (63.2)	1.17	1.01–1.34	**0.033**	–	–	–
Diabetes ($n = 4211$)[b]	194 (16.4)	432 (14.3)	1.18	0.98–1.42	0.076	1.39	1.09–1.78	**0.009**
Hypercholesterolaemia ($n = 4211$)[b]	196 (16.6)	792 (26.1)	0.56	0.47–0.67	**< 0.0001**	0.62	0.50–0.79	**< 0.0001**
Smoking status								
Non-smoker	721 (59.7)	1711 (56.0)	1.00	–	–	1.00	–	–
Ever smoker	248 (20.6)	1019 (33.4)	0.58	0.49–0.68	**< 0.0001**	0.71	0.56–0.90	**0.004**
Unknown	238 (19.7)	325 (10.6)	1.74	1.44–2.10	**< 0.0001**	1.47	1.13–1.91	**0.005**
Myocardial infarction ($n = 4216$)[b]	235 (19.9)	454 (15.0)	1.41	1.19–1.68	**0.0001**	–	–	–
PAD ($n = 4215$)[b]	137 (11.6)	238 (7.8)	1.54	1.24–1.93	**0.0001**	1.72	1.27–2.34	**0.0005**
Atrial fibrillation ($n = 4212$)[b]	233 (19.7)	325 (10.7)	2.04	1.69–2.45	**< 0.0001**	–	–	–
Prestroke TIA	133 (11.0)	505 (16.5)	0.63	0.51–0.77	**< 0.0001**	–	–	–
Anticoagulants	106 (8.8)	178 (5.8)	1.56	1.21–2.00	**0.0005**	1.10	0.80–1.52	0.561
Antihypertensive drugs	574 (47.6)	1466 (48.0)	0.98	0.86–1.12	0.800	–	–	–
Statins from 2006 to 2011 ($n = 1217$)	24 (7.1)	121 (13.8)	0.48	0.30–0.76	**0.002**	–	–	–
Aphasia ($n = 4226$)[b]	485 (40.6)	835 (27.5)	1.80	1.56–2.07	**< 0.0001**	–	–	–
Impaired consciousness ($n = 4234$)[b]	656 (54.6)	298 (9.8)	11.02	9.35–13.00	**< 0.0001**	8.24	6.74–10.09	**< 0.0001**
Motor deficit ($n = 4232$)[b]	1088 (90.7)	2026 (66.8)	4.87	3.95–6.01	**< 0.0001**	3.73	2.90–4.79	**< 0.0001**
NIHSS from 2006 to 2011 ($n = 1217$)								
Quartile 1, 0–2	20 (5.9)	366 (41.6)	1.00	–	–	–	–	–
Quartile 2 (median), 3–4	22 (6.5)	218 (24.8)	1.85	0.99–3.46	0.056	–	–	–
Quartile 3, 5–12	86 (25.5)	250 (28.4)	6.29	3.77–10.51	**< 0.0001**	–	–	–
Quartile 4, 13–29	209 (62.0)	46 (5.2)	83.13	47.88–144.34	**< 0.0001**	–	–	–
Length of stay								
<10 days	488 (40.4)	1577 (51.6)	1.00	–	–	1.00	–	–
10–30 days	449 (37.2)	1280 (41.9)	1.13	0.98–1.31	0.097	0.84	0.69–1.01	0.067
>30 days	270 (22.4)	198 (6.5)	4.41	3.57–5.43	**< 0.0001**	2.31	1.77–3.01	**< 0.0001**
Treatment centres								
Public hospital	1119 (92.7)	2219 (72.6)	1.00	1.00	–	1.00	–	–
Private hospital	72 (6.0)	479 (15.7)	0.30	0.23–0.39	**< 0.0001**	0.48	0.34–0.66	**< 0.0001**
outpatient	16 (1.3)	357 (11.7)	0.09	0.05–0.15	**< 0.0001**	0.25	0.14–0.43	**< 0.0001**
Retirement home before stroke	123 (10.2)	179 (5.9)	1.82	1.44–2.32	**< 0.0001**	1.04	0.75–1.43	0.822

Percentages are in brackets.

OR, odds-ratio; PAD, peripheral artery disease; TIA, transient ischaemic attack.

[a]Adjusted OR for covariates of aspirin therapy were similar to those for APT and are not presented.

[b]Denominator may vary due to missing information; APT, antiplatelet therapy; CI, confidence interval.

The significance for bold values is < 0.05.

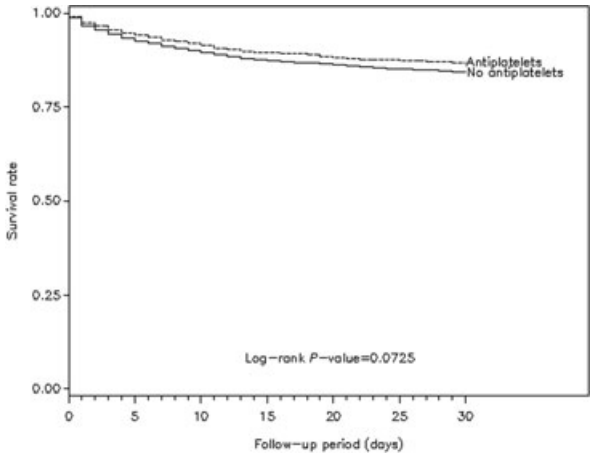

Figure 1 Kaplan–Meier estimation of 1-month survival rates stratified by APT use.

observational data indicated that utilization rates of APT in patients with prior cardiovascular conditions, including myocardial infarction (31%), TIA (19.7%) and PAD (18.6%), were still largely suboptimal despite evidence-based guidelines in secondary prevention.

Our results are consistent with previous reports that focused on aspirin showing significant benefit for APT users compared with non-users for the early functional prognosis, while there was a non-significant protective effect of APT on 1-month mortality [5–7]. Nevertheless, this association was not proved by other studies [4,8,9]. The reasons for discrepancies in the results of studies vary, and include differences in the study design, the length of follow-up, the recruitment of the population or the potential confounding variables included in the analyses. Another important consider-

Table 3 Stratum–specific analyses of the association between APT and outcomes from 1985 to 2011

	Severe handicap at discharge							
	Unadjusted					Multivariate model		
Outcome	*N*	% APT vs. no APT	OR	95% CI	*P* value	OR[a]	95% CI	*P*-value
Stratum								
Stroke subtypes								
Intracerebral haemorrhage	492	46.5 vs. 53.7	0.75	0.47–1.20	0.227	0.47	0.26–0.86	**0.014**
Subarachnoid haemorrhage	135	50.0 vs. 22.1	3.52	0.48–26.06	0.218	1.57	0.09–28.30	0.760
Lacunar infarct	931	7.6 vs. 5.9	1.32	0.72–2.44	0.367	1.46	0.75–2.82	0.265
Cardiac embolism	772	34.3 vs. 43.5	0.68	0.49–0.95	**0.023**	0.66	0.44–1.00	**0.049**
Other ischaemic strokes	1820	27.4 vs. 26.6	1.05	0.81–1.35	0.739	0.87	0.64–1.20	0.394
Undetermined	112	50.0 vs. 50.0	1.00	0.27–3.67	1.000	1.71	0.32–9.08	0.528
Stroke subtypes with cerebral infarcts altogether								
Intracerebral haemorrhage	492	46.5 vs. 53.7	0.98	0.81–1.18	0.227	0.49	0.27–0.90	**0.022**
Subarachnoid haemorrhage	135	50.0 vs. 22.1	0.75	0.47–1.20	0.218	1.68	0.09–31.37	0.728
Cerebral infarct	3523	24.2 vs. 24.5	3.52	0.48–26.06	0.837	0.88	0.70–1.12	0.302
Undetermined	112	50.0 vs. 50.0	1.00	0.27–3.67	1.000	1.79	0.33–9.69	0.498

	Mortality at 1 month							
	Unadjusted					Multivariate model		
Outcome	*N*	Death rates[b] APT vs. no APT	HR	95% CI	*P* value	HR[c]	95% CI	*P*-value
Stratum								
Stroke subtypes								
Intracerebral haemorrhage	496	15.98 vs. 16.00	1.01	0.68–1.50	0.975	0.96	0.63–1.47	0.860
Subarachnoid haemorrhage	138	16.00 vs. 7.01	2.22	0.53–9.41	0.277	0.57	0.13–2.49	0.456
Lacunar infarct	931	0.86 vs. 0.93	0.93	0.35–2.47	0.882	0.91	0.34–2.44	0.856
Cardiac embolism	773	5.50 vs. 9.02	0.62	0.42–0.93	**0.020**	0.65	0.43–0.98	**0.040**
Other ischaemic strokes	1822	4.39 vs. 4.49	0.97	0.70–1.35	0.872	1.01	0.72–1.41	0.977

Table 3 (*Continued*)

Outcome	Severe handicap at discharge							
	Unadjusted					Multivariate model		
	N	% APT vs. no APT	OR	95% CI	*P* value	OR[a]	95% CI	*P*-value
Undetermined	115	30.86 vs. 19.51	1.56	0.62–3.95	0.348	1.94	0.75–5.05	0.173
Stroke subtypes with cerebral infarcts altogether								
Intracerebral haemorrhage	496	15.98 vs. 16.00	1.01	0.68–1.50	0.975	0.99	0.65–1.51	0.969
Subarachnoid haemorrhage	138	16.00 vs. 7.01	2.22	0.53–9.41	0.278	0.57	0.13–2.48	0.451
Cerebral infarct	3526	3.72 vs. 4.34	0.86	0.67–1.10	0.221	0.87	0.67–1.12	0.278
Undetermined	115	30.86 vs. 19.51	1.56	0.62–3.95	0.347	2.13	0.82–5.53	0.121

Outcome	Mortality at 1 year							
	Unadjusted					Multivariate model		
	N	Death rates[c] APT vs. no APT	HR*	95% CI	*P* value	HR[d]	95% CI	*P*-value
Stratum								
Strokes subtypes								
Intracerebral haemorrhage	496	71.34 vs. 66.54	1.07	0.77–1.50	0.684	0.97	0.68–1.37	0.846
Subarachnoid haemorrhage	138	53.84 vs. 23.11	2.11	0.50–0.86	0.307	0.79	0.18–3.36	0.746
Lacunar infarct	931	13.92 vs. 8.83	1.57	1.03–2.41	**0.038**	1.55	1.00–2.38	**0.048**
Cardiac embolism	773	39.01 vs. 53.59	0.77	0.59–1.01	0.058	0.83	0.63–1.09	0.181
Other ischaemic strokes	1822	24.57 vs. 25.76	0.96	0.76–1.21	0.741	0.89	0.70–1.14	0.360
Undetermined	115	114.20 vs. 80.95	1.42	0.61–3.31	0.414	1.50	0.59–3.82	0.395
Stroke subtypes and cerebral infarcts								
Intracerebral haemorrhage	496	71.34 vs. 66.54	1.07	0.77–1.50	0.683	0.99	0.69–1.40	0.932
Subarachnoid haemorrhage	138	53.84 vs. 23.11	2.11	0.50–8.85	0.308	0.81	0.19–3.46	0.774
Cerebral infarct	3526	24.96 vs. 25.18	1.00	0.85–1.18	0.988	0.97	0.81–1.15	0.682
Undetermined	115	114.20 vs. 80.95	1.42	0.61–3.31	0.413	1.60	0.63–4.07	0.324

CI, confidence interval; HR, hazard ratio; OR, odds-ratio.

[a]Adjusted for anticoagulants, age, gender, retirement home, time periods, diabetes, hypercholesterolaemia, smoking status, peripheral artery disease, impaired consciousness, motor deficit, length of stay, and treatment centres.

[b]Death rates for APT users versus non–users expressed per 1000 person-days.

[c]Death rates for APT users versus non-users expressed per 1000 person-months.

[d]Adjusted for anticoagulants, age, gender, retirement home, time periods, hypercholesterolaemia, smoking status, myocardial infarction; peripheral artery disease, impaired consciousness, motor deficit, length of stay, and treatment centres.

The significance for bold values is $P < 0.05$.

ation for the interpretation of the results is the stroke subtype. In our work, a significant beneficial effect of prestroke APT was found in patients with cardioembolic ischaemic stroke for both early outcomes, whereas the treatment appeared to be effective in those with ICH for early functional outcome. In their study, Kalra *et al*. [5] also observed lower 4-week mortality in APT users with either cardioembolic or large-vessel atherosclerotic strokes. Of note, our results were adjusted for prestroke anticoagulant therapy, which has been demonstrated to be associated with a better prognosis in patients with stroke from atrial fibrillation [15,16].

Prior APT was associated with a non-significant protective effect on early outcomes, but this effect disappeared at later outcomes such as 1-year mortality. The lack of any association at 1 year may be partly explained by mixed effects due to APT during the hospital stay and after discharge. Our negative findings regarding the possible superiority of dual APT over

Table 4 Associations between prior APT and 1-month mortality in 4275 patients from 1985 to 2011

	Unadjusted							Multivariate model		
	No. patients	No. deaths	At risk	Death rate[a]	HR	95% CI	*P* value	HR	95% CI	*P*-value
APT	870	116	23 612	4.91	0.83	0.68–1.02	0.073	0.87	0.70–1.09	0.222
Mono or dual APT										
No APT	3405	536	90 352	5.93	1.00	–	–	1.00	–	–
Monotherapy	377	41	10 422	3.93	0.67	0.49–0.92	**0.013**	0.84[b]	0.60–1.17	0.292
Dual APT	493	75	13 190	5.69	0.96	0.75–1.22	0.742	0.90[b]	0.69–1.17	0.420
Covariates										
Age, years	–	–	–	–	1.04	1.04–1.05	**< 0.0001**	–	–	–
<60	674	46	19 075	2.41	1.00	–	–	–	–	–
60–74	1077	90	30 063	2.99	1.24	0.87–1.77	0.241	–	–	–
≥75	2524	516	64 826	7.96	3.20	2.36–4.32	**< 0.0001**	–	–	–
Female gender	2300	380	60 691	6.26	1.22	1.04–1.42	**0.013**	0.90	0.75–1.09	0.271
Time periods										
1985–1989	612	123	15 326	8.03	1.00	–	–	1.00	–	–
1990–1994	667	147	16 680	8.81	1.10	0.87–1.40	0.428	0.96	0.74–1.25	0.771
1995–1999	790	122	21 231	5.75	0.73	0.57–0.94	**0.013**	0.66	0.50–0.87	**0.004**
2000–2004	802	98	22 020	4.45	0.57	0.44–0.74	**< 0.0001**	0.88	0.66–1.18	0.392
2005–2011	1404	162	38 707	4.19	0.54	0.42–0.68	**< 0.0001**	0.71	0.55–0.92	**0.009**
Stroke subtype										
Intracerebral haemorrhage	496	171	10 690	16.0	1.00	–	–	–	–	–
Subarachnoid haemorrhage	138	26	3548	7.33	0.48	0.32–0.75	**0.0004**	–	–	–
Lacunar infarct	931	25	27 348	0.91	0.06	0.04–0.09	**< 0.0001**	–	–	–
Cardiac embolism	773	160	19 858	8.06	0.52	0.42–0.64	**< 0.0001**	–	–	–
Other ischaemic strokes	1822	225	50 308	4.47	0.29	0.24–0.36	**< 0.0001**	–	–	–
Undetermined strokes	115	45	2212	20.34	1.26	0.91–1.76	0.163	–	–	–
Hypertension (n = 4228)[c]	2715	427	72 007	5.93	1.18	1.00–1.39	0.058	–	–	–
Diabetes (n = 4224)[c]	627	86	16 944	5.08	0.89	0.71–1.12	0.329	–	–	–
Hypercholesterolaemia (n = 4224)[c]	990	89	27 834	3.20	0.51	0.41–0.64	**< 0.0001**	0.76	0.60–0.96	**0.024**
Smoking status										
Non-smoker	2442	370	65 144	5.68	1.00	–	–	1.00	–	–
Ever smoker	1267	119	35 321	3.37	0.60	0.49–0.74	**< 0.0001**	0.81	0.63–1.03	0.080
Unknown	566	163	13 499	12.07	2.05	1.71–2.47	**< 0.0001**	1.34	1.08–1.67	**0.008**
Myocardial infarction (n = 4229)[c]	692	135	18 025	7.49	1.41	1.17–1.71	**0.0004**	–	–	–
PAD (n = 4228)[c]	377	73	9883	7.39	1.35	1.06–1.72	**0.016**	1.48	1.14–1.93	**0.004**
Atrial fibrillation (n = 4224)[c]	560	126	14 252	8.84	1.69	1.39–2.05	**< 0.0001**	–	–	–
Prestroke TIA	638	68	17 662	3.85	0.64	0.50–0.83	**0.0006**	–	–	–
Anticoagulants	284	75	6936	10.81	1.97	1.55–2.50	**< 0.0001**	1.77	1.37–2.29	**< 0.0001**
Antihypertensive drugs	2048	315	54 635	5.77	1.01	0.87–1.18	0.875	–	–	–
Statins from 2006 to 2011 (n = 1217)[c]	145	10	4141	2.41	0.51	0.27–0.97		–	–	–
Aphasia (n = 4238)[c]	1322	274	33 909	8.08	1.70	1.45–1.98	**< 0.0001**	–	–	–
Impaired consciousness (n = 4246)[c]	959	418	19 214	21.75	8.13	6.92–9.55	**< 0.0001**	5.37	4.49–6.44	**< 0.0001**
Motor deficit (n = 4244)[c]	3125	571	81 330	7.02	2.94	2.31–3.75	**< 0.0001**	2.10	1.60–2.75	**< 0.0001**
NIHSS from 2006 to 2011 (n = 1217)										
Quartile 1, 0–2	386	13	11 259	1.15	1.00	–	–	–	–	–
Quartile 2 (median), 3–4	240	10	7032	1.42	1.23	0.54–2.80	0.625	–	–	–
Quartile 3, 5–12	336	31	9468	3.27	2.80	1.47–5.35	**0.002**	–	–	–
Quartile 4, 13–29	255	95	5577	17.03	13.65	7.65–24.38	**< 0.0001**	–	–	–
Length of stay										
<10 days	2072	430	50 774	8.47	1.00	–	–	–	–	–
10–30 days	1733	220	49 135	4.48	0.54	0.46–0.63	**< 0.0001**	–	–	–
>30 days	470	2	14 055	0.14	0.02	0.00–0.07	**< 0.0001**	–	–	–

Table 4 (*Continued*)

	Unadjusted							Multivariate model		
	No. patients	No. deaths	At risk	Death rate[a]	HR	95% CI	*P* value	HR	95% CI	*P*-value
Treatment centres										
Public hospital	3346	618	87 095	7.10	1.00	–	–	1.00	–	–
Private hospital	556	25	16 061	1.56	0.23	0.15–0.34	**< 0.0001**	0.31	0.20–0.48	**< 0.0001**
Ambulatory	373	9	10 808	0.83	0.12	0.06–0.24	**< 0.0001**	0.22	0.11–0.42	**< 0.0001**
Retirement home before stroke	304	65	7828	8.30	1.48	1.14–1.91	**0.003**	0.86	0.66–1.13	0.276

Percentages are in brackets.
APT, antiplatelet therapy; CI, confidence interval; HR, hazard ratio; PAD, peripheral artery disease; TIA, transient ischaemic attack.
[a]Expressed per 1000 person-days.
[b]Adjusted OR for covariates of aspirin therapy were similar to those for APT and are not reported.
[c]Denominator may vary due to missing information.
The significance for bold values is < 0.05.

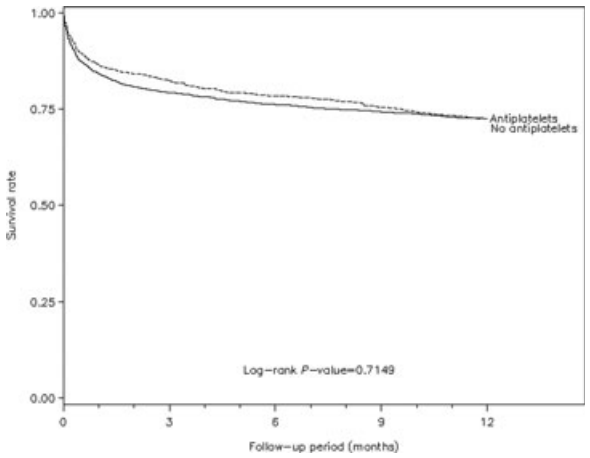

Figure 2 Kaplan–Meier estimation of 1-year survival rates stratified by APT.

mono APT on mortality and functional outcomes were consistent with those of a recent systematic review and meta-analysis of 12 randomized controlled trials. In comparison with mono APT, dual APT significantly reduced stroke recurrence, and composite vascular events including stroke, myocardial infarction and vascular deaths, although it had no impact on all-cause mortality and other secondary outcomes such as fatal strokes and vascular death [17]. As also observed in the meta-analysis, we cannot rule out a possible lack of statistical power to detect significant associations owing to the relatively small number of events for mono and dual APT.

The way by which APT before ischaemic stroke could improve the patients' prognosis remains to be elucidated. Several authors argued that aspirin could lessen stroke severity [18,19], but this hypothesis was refuted by others [20,21]. This hypothesis may be possible for early outcomes as in our study, further control for NIHSS in multivariate analyses restricted from 2006 to 2011 yielded similar protective estimates of APT use compared with those obtained after statistical adjustment for items of stroke severity (impaired consciousness, motor deficit).

Finally, it was assumed that the beneficial effect of aspirin on stroke mortality could be related to potential neuroprotective properties through its anti-excitotoxic and anti-inflammatory effects [22].

In the present study, APT was not an independent predictor of poor outcome in patients with spontaneous ICH. Surprisingly, it was associated with a better early functional outcome. This spurious beneficial effect may be explained either by chance or by sicker patients dying before having been assessed for functional outcome at discharge leading to an overestimation of APT benefit in ICH (survivor selection bias). Several studies on this topic drew conflicting conclusions [10–12,23], a recent meta-analysis indicated a weak but significant association between prior APT and early mortality in haemorrhagic stroke [24].

The major strengths of this study include its exhaustive, continuous and prospective ascertainment in a well-defined population without any selection of patients, and with clinically meaningful outcome measures. Active monitoring allowed survival analysis with almost complete follow-up at 1 month (loss to follow-up 0.4%). In addition, our analyses were adjusted for the most important prognostic variables.

However, several limitations must be acknowledged. Indeed, we were not able to analyse either the class of APT, duration of the APT, the dose or the compliance of the patients to their treatment, which could have been relevant, all the more so as it has been suggested that the effect of aspirin on mortality after stroke could be different according to the dose [7]. Assessing stroke severity with clinical data at admission may be an imperfect measure

Table 5 Associations between APT and 1-year mortality in 4275 patients from 1985 to 2011

	Unadjusted							Multivariate model		
	No. patients	No. deaths	At risk	Death rate[a]	HR	95% CI	*P* value	HR	95% CI	*P* value
APT	870	237	8196	28.92	0.97	0.84–1.12	0.713	0.94	0.80–1.10	0.429
Mono or dual APT										
No APT	3405	927	30 851	30.05	1.00	–	–	1.00	–	–
Monotherapy	377	91	3611	25.20	0.85	0.68–1.05	0.136	0.89	0.71–1.12	0.321
Dual APT	493	146	4585	31.84	1.07	0.90–1.28	0.438	0.97	0.80–1.18	0.792
Covariates										
Age, years	–	–	–	–	1.05	1.05–1.06	**<0.0001**	–	–	–
<60	674	64	7163	8.93	1.00	–	–	–	–	–
60–74	1077	176	10 928	16.11	1.77	1.33–2.35	**<0.0001**	–	–	–
≥75	2524	924	20 956	44.09	4.46	3.46–5.74	**<0.0001**	–	–	–
Female gender	2300	669	20 603	32.47	1.19	1.06–1.34	**0.003**	0.87	0.76–1.00	0.050
Time periods										
1985–1989	612	233	4913	47.43	1.00	–	–	1.00	–	–
1990–1994	667	239	5604	42.64	0.93	0.78–1.11	0.415	0.98	0.81–1.19	0.839
1995–1999	790	204	7478	27.28	0.62	0.51–0.74	**<0.0001**	0.72	0.58–0.88	**0.002**
2000–2004	802	168	7968	21.09	0.49	0.40–0.59	**<0.0001**	0.77	0.62–0.95	**0.017**
2005–2011	1404	320	13 084	24.46	0.54	0.46–0.64	**<0.0001**	0.75	0.62–0.91	**0.003**
Stroke subtype										
Intracerebral haemorrhage	496	229	3400	67.35	1.00	–	–	–	–	–
Subarachnoid haemorrhage	138	30	1249	24.03	0.39	0.26–0.57	**<0.0001**	–	–	–
Lacunar infarct	931	101	10 200	9.90	0.17	0.13–0.21	**<0.0001**	–	–	–
Cardiac embolism	773	303	6142	49.33	0.73	0.62–0.87	**0.0004**	–	–	–
Other ischaemic strokes	1822	443	17 360	25.52	0.41	0.35–0.48	**<0.0001**	–	–	–
Undetermined strokes	115	58	695	83.47	1.23	0.92–1.63	0.167	–	–	–
Hypertension (n = 4228)[b]	2715	777	24 505	31.71	1.23	1.09–1.40	**0.001**	–	–	–
Diabetes (n = 4224)[b]	627	163	5900	27.63	0.94	0.80–1.11	0.472	–	–	–
Hypercholesterolemia (n = 4224)[b]	990	169	10 020	16.87	0.52	0.44–0.62	**<0.0001**	0.67	0.56–0.79	**<0.0001**
Smoking status										
Non–smoker	2442	689	22 025	31.28	1.00	–	–	1.00	–	–
Ever smoker	1267	246	12 639	19.46	0.65	0.56–0.75	**<0.0001**	0.84	0.70–0.99	**0.040**
Unknown	566	229	4383	52.25	1.61	1.38–1.87	**<0.0001**	1.27	1.07–1.51	**0.007**
Myocardial infarction (n = 4229)[b]	692	260	5765	45.10	1.60	1.40–1.84	**<0.0001**	1.30	1.11–1.51	**0.0009**
PAD (n = 4228)[b]	377	137	3178	43.12	1.46	1.22–1.75	**<0.0001**	1.33	1.09–1.62	**0.004**
Atrial fibrillation (n = 4224)[b]	560	240	4305	55.75	1.94	1.68–2.23	**<0.0001**	–	–	–
Prestroke TIA	638	137	6258	21.89	0.72	0.60–0.86	**0.0003**	–	–	–
Anticoagulants	284	122	21 25	57.40	1.88	1.56–2.27	**<0.0001**	1.67	1.37–2.04	**<0.0001**
Antihypertensive drugs	2048	593	18 473	32.10	1.14	1.01–1.28	**0.029**	–	–	–
Statins from 2006 to 2011 (n = 1217)[b]	145	21	1395	15.06	0.56	0.36–0.87	**0.010**	–	–	–
Aphasia (n = 4238)[b]	1322	449	11 086	40.50	1.52	1.35–1.71	**<0.0001**	–	–	–
Impaired consciousness (n = 4246)[b]	959	575	5196	110.66	5.20	4.63–5.84	**<0.0001**	3.34	2.93–3.80	**<0.0001**
Motor deficit (n = 4244)[b]	3125	1007	27 088	37.17	2.74	2.30–3.25	**<0.0001**	1.90	1.58–2.29	**<0.0001**
NIHSS from 2006 to 2011 (n = 1217)										
Quartile 1, 0–2	386	29	4127	7.03	1.00	–	–	–	–	–
Quartile 2 (median), 3–4	240	28	2420	11.57	1.59	0.94–2.67	0.082	–	–	–
Quartile 3, 5–12	336	74	3168	23.36	3.15	2.05–4.84	**<0.0001**	–	–	–
Quartile 4, 13–29	255	155	1391	111.41	12.35	8.30–18.38	**<0.0001**	–	–	–
Length of stay										
<10 days	2072	558	18 484	30.19	1.00	–	–	–	–	–
10–30 days	1733	414	16 561	25.00	0.80	0.71–0.91	**0.0006**	–	–	–
>30 days	470	192	4002	47.98	1.40	1.19–1.65	**<0.0001**	–	–	–

Table 5 (*Continued*)

	Unadjusted							Multivariate model		
	No. patients	No. deaths	At risk	Death rate[a]	HR	95% CI	*P* value	HR	95% CI	*P* value
Treatment centres										
Public hospital	3346	1054	29 010	36.33	1.00	–	–	1.00	–	–
Private hospital	556	75	5945	12.62	0.37	0.30–0.47	**<0.0001**	0.53	0.42–0.69	**<0.0001**
Ambulatory	373	35	4092	8.55	0.26	0.18–0.36	**<0.0001**	0.45	0.32–0.65	**<0.0001**
Retirement home before stroke	304	136	2399	56.68	1.86	1.56–2.23	**<0.0001**	1.08	0.89–1.30	0.428

Percentages are in brackets.
APT, antiplatelet therapy; CI, confidence interval; HR, hazard ratio; PAD, peripheral artery disease; TIA, transient ischaemic attack.
[a]Expressed per 1000 person–months.
[b]Adjusted OR for covariates of aspirin therapy were similar to those for APT and are not presented.
[c]Denominator may vary due to missing information.
The significance for bold values is <0.05.

of NIHSS that could lead to some residual confounding bias. Nevertheless, multivariate analyses controlled for clinical data or for NIHSS yielded similar results reinforcing the validity of our results. Patients were not evaluated at the same time for functional outcome at discharge. To avoid confounding effect of stay duration on functional outcome, multivariate analyses were controlled for length of stay.

To conclude, a beneficial effect of prestroke APT even though statistically modest or borderline was observed for early outcomes but not for later outcome such as 1-year mortality. Because the period of highest mortality is the first 30 days after stroke, these results are somewhat reassuring with regard to the considerable number of at-risk patients on this regimen. Further studies are needed to understand the mechanisms underlying the distinct effects observed across the different ischaemic stroke subtypes.

Acknowledgements

We thank Mr Philip Bastable for reviewing the English.

The Dijon Stroke Registry is supported by the French Institute for Public Health Surveillance (InVS) and Inserm. Y.B. received a grant from the Journées Neurologiques de Langue Francaise and the Regional Council of Burgundy.

Disclosure of conflict of interest:

The authors declare they have no conflict of interest.

References

1. Rothwell PM, Coull AJ, Giles MF, *et al.* Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004; **363:** 1925–1933.
2. Islam MS, Anderson CS, Hankey GJ, *et al.* Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. *Stroke* 2008; **39:** 776–782.
3. Bejot Y, Osseby GV, Gremeaux V, *et al.* Changes in risk factors and preventive treatments by stroke subtypes over 20 years: a population-based study. *J Neurol Sci* 2009; **287:** 84–88.
4. De Keyser J, Herroelen L, De Klippel N. Early outcome in acute ischemic stroke is not influenced by the prophylactic use of low-dose aspirin. *J Neurol Sci* 1997; **145:** 93–96.
5. Kalra L, Perez I, Smithard DG, Sulch D. Does prior use of aspirin affect outcome in ischemic stroke? *Am J Med* 2000; **108:** 205–209.
6. Karlikaya G, Varlbas F, Demirkaya M, Orken C, Tireli H. Does prior aspirin use reduce stroke mortality? *Neurologist* 2006; **12:** 263–267.
7. Lampl Y, Boaz M, Sadeh M. The significance of prestroke aspirin dosage in fatal outcome of acute stroke. *Clin Neuropharmacol* 2005; **28:** 55–59.
8. Carter AM, Catto AJ, Mansfield MW, Bamford JM, Grant PJ. Predictive variables for mortality after acute ischemic stroke. *Stroke* 2007; **38:** 1873–1880.
9. Paciaroni M, Agnelli G, Caso V, *et al.* Prior use of antithrombotic agents and neurological functional outcome at discharge in patients with ischemic stroke. *J Thromb Haemost* 2006; **4:** 1957–1961.
10. Toyoda K, Okada Y, Minematsu K, *et al.* Antiplatelet therapy contributes to acute deterioration of intracerebral hemorrhage. *Neurology* 2005; **65:** 1000–1004.
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.
12. 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.
13. Caso V, Paciaroni M, Venti M, *et al.* Effect of on-admission antiplatelet treatment on patients with cerebral hemorrhage. *Cerebrovasc Dis* 2007; **24:** 215–218.

14. WHO. *The World Health Report Health Systems Improving Performance*. Geneva: WHO, 2000.
15. Hylek EM, Go AS, Chang Y, *et al*. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003; **349:** 1019–1026.
16. O'Donnell M, Oczkowski W, Fang J, *et al*. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. *Lancet Neurol* 2006; **5:** 749–754.
17. Geeganage CM, Diener HC, Algra A, *et al*. Dual or mono antiplatelet therapy for patients with acute ischemic stroke or transient ischemic attack: systematic review and meta-analysis of randomized controlled trials. *Stroke* 2012; **43:** 1058–1066.
18. Sanossian N, Saver JL, Rajajee V, *et al*. Premorbid antiplatelet use and ischemic stroke outcomes. *Neurology* 2006; **66:** 319–323.
19. Wilterdink JL, Bendixen B, Adams HP Jr, Woolson RF, Clarke WR, Hansen MD. Effect of prior aspirin use on stroke severity in the trial of Org 10172 in acute stroke treatment (TOAST). *Stroke* 2001; **32:** 2836–2840.
20. Ricci S, Lewis S, Sandercock P. CN -ICG. Previous use of aspirin and baseline stroke severity: an analysis of 17,850 patients in the International Stroke Trial. *Stroke* 2006; **37:** 1737–1740.
21. Sivenius J, Cunha L, Diener HC, *et al*. Antiplatelet treatment does not reduce the severity of subsequent stroke. European stroke prevention study 2 working group. *Neurology* 1999; **53:** 825–829.
22. Castillo J, Leira R, Moro MA, Lizasoain I, Serena J, Davalos A. Neuroprotective effects of aspirin in patients with acute cerebral infarction. *Neurosci Lett* 2003; **339:** 248–250.
23. Roquer J, Rodriguez Campello A, Gomis M, Ois A, Puente V, Munteis E. Previous antiplatelet therapy is an independent predictor of 30-day mortality after spontaneous supratentorial intracerebral hemorrhage. *J Neurol* 2005; **252:** 412–416.
24. Thompson BB, Bejot Y, Caso V, *et al*. Prior antiplatelet therapy and outcome following intracerebral hemorrhage: a systematic review. *Neurology* 2010; **75:** 1333–1342.