

1 Title: Interruption to antiplatelet therapy early after acute ischaemic stroke: A nested case-  
2 control study

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26

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32 Summary

33 AIMS

34 Antiplatelet drugs are often discontinued early after ischaemic stroke, either because of poor  
35 compliance, complications or withdrawal of care. It is unclear whether this places patients at  
36 increased risk of recurrence. We explored the association between cardiovascular event rate  
37 and persistence with prescribed antiplatelet drugs.

38 METHODS

39 We used a matched case-control design using the Virtual International Stroke Trials Archive  
40 (VISTA). Cases were patients who had an acute coronary syndrome, recurrent stroke or  
41 transient ischaemic attack within 90 days post-stroke and were matched for age  $\pm 10$  years  
42 and sex with up to four controls. Antiplatelet use was categorized as persistent (used for  $> 3$   
43 days and continued up to day 90), early cessation (used antiplatelet  $< 3$  days) or  
44 stopped/interrupted users (used for  $> 3$  days but stopped prior to day 90). These categories  
45 were compared in cases and controls using a conditional logistic regression model that  
46 adjusted for potential confounders.

47 RESULTS

48 A total of 970 patients were included, of whom 194 were cases and 776 were matched  
49 controls. At 90 days, 10 cases (5.2%) and 58 controls (7.5%) stopped/interrupted their  
50 antiplatelet. The risk of cardiovascular event was not different in stopped/interrupted users  
51 (adjusted OR 0.70, 95% CI 0.33, 1.48;  $P=0.352$ ) and early cessations (adjusted OR 1.04,  
52 95% CI 0.62, 1.74;  $P=0.876$ ) when compared to persistent users.

53 CONCLUSION

54 We found no increased risk in patients who stopped and interrupted antiplatelets early after  
55 stroke but the study was limited by a small sample size and further research is needed.

56

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58

59 WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

60 Antiplatelet therapy is recommended for secondary prevention after ischaemic stroke.  
61 Interrupting or stopping antiplatelet therapy increases the risk of cardiovascular events.

62

63 WHAT THIS STUDY ADDS

64 The study did not demonstrate a significantly increased risk with stopping or interrupting  
65 antiplatelet use early after stroke. This may reassure clinicians that, where interruption to  
66 therapy is needed for clinical reasons, there is not a significant increase in short term risk.

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70

71 Introduction

72 There is a risk of recurrence following acute ischaemic stroke [1]. Antiplatelet therapy is  
73 given to reduce this risk and the risk of other vascular outcomes [2, 3]. National Institute for  
74 Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network  
75 (SIGN) guidelines recommend that antiplatelet therapy must be started early and continued  
76 indefinitely for long term secondary stroke prevention [3, 4]. In the UK guidelines favour  
77 aspirin therapy for 2-weeks followed by clopidogrel or the combination of low-dose aspirin  
78 and dipyridamole.

79

80 Persistence with antiplatelet regimens is variable after stroke. Rates of aspirin  
81 discontinuation of less than 10% to almost 50% reported [5, 6]. At one year as many as 50%  
82 of patients who were prescribed aspirin or clopidogrel either discontinued, or failed to adhere  
83 to their regimen [7-9]. This may be for several reasons including patient non-compliance,  
84 bleeding complications, financial pressures, or physician directed withdrawal due to  
85 withdrawal of care, intercurrent illness or planned procedures [10]. Interrupting or stopping

86 antiplatelet therapy may increase the risk of cardiovascular events in patients with a history  
87 of cardiovascular or cerebrovascular disease [11, 12]. One study found that among the 2197  
88 cases of ischaemic stroke, 5.2% cases occurred within 60 days after antithrombotic  
89 withdrawal [10]. In this study, stroke events were clustered mostly in the first 7 days after  
90 stopping medication. Antithrombotic medication was stopped for various reasons including  
91 being stopped by physicians for procedures, patient compliance, bleeding complications and  
92 cost. In another study by García Rodríguez *et al.* [11], among 673 patients who had  
93 diagnosed with ischaemic stroke or TIA, 71.3% patients were taking aspirin on the day of  
94 event and 10% discontinued aspirin within 31-180 days before the event. On the other hand,  
95 a recent prospective observational study found that interruption of antiplatelet therapy due to  
96 surgical necessity was not associated with increased risk of cardiovascular events [13].

97

98 Data to demonstrate the impact of stopping antiplatelet therapy early after ischaemic stroke,  
99 where recurrence rate is highest are lacking. We aimed to explore the rate of antiplatelet  
100 cessation and interruption in a sample of patients with recent ischaemic stroke and assess  
101 the risk of cardiovascular events associated with cessation and interruption of antiplatelet  
102 drugs.

103

## 104 Methods

### 105 Study design

106 We used a matched case-control study design to examine association between antiplatelet  
107 exposure and risk of a cardiovascular event. We used individual matching to identify up to  
108 four controls for each case, matched by age  $\pm 10$  years and sex. We followed the STROBE  
109 guidance in reporting this case-control study [14].

110

### 111 Data sources

112 We used data from the Virtual International Stroke Trials Archive (VISTA) [15]. VISTA is a  
113 collaborative registry that collates and provides access to anonymised data from completed  
114 clinical trials. VISTA data are stored at the Robertson Centre for Biostatistics, University of  
115 Glasgow, Glasgow, UK. VISTA contains patients' demographic data such as age, sex and  
116 ethnicity; smoking history and co-morbid conditions as well as details on the index stroke,  
117 and functional outcome measures. Adverse events (AE) data, laboratory measurements and  
118 prescribed medications are available from certain trials. All trials lodged in VISTA already  
119 have local institutional review board approved procedures in accordance with the  
120 Declaration of Helsinki. Thus, our analysis does not require a new study approval.  
121 Nevertheless, access to data is subject to approval by the steering committee.

122

#### 123 Study cohort

124 All acute ischaemic stroke patients in the VISTA who took antiplatelet therapy and had  
125 complete information on initiation day of antiplatelet therapy were identified. Patients with  
126 concurrent use of vitamin K antagonist such as warfarin were excluded as it may influence  
127 clinical [16] and safety [17] outcomes in acute ischaemic stroke patients. Patients who had a  
128 cardiovascular event within the first two days after ischaemic stroke were excluded as the  
129 event might not be associated to antiplatelet but due to the specific pattern of ischaemic  
130 changes after acute stroke [18].

131

132 Cases were defined as patients who had at least one cardiovascular event in the first 90  
133 days after acute ischaemic stroke. A cardiovascular event was defined as a acute coronary  
134 syndrome (ACS), recurrent ischaemic stroke or TIA. The event was identified from AE and  
135 SAE reports datasets using these key terms: (a) for ACS - unstable angina, acute coronary  
136 syndrome or myocardial infarction; (b) for recurrent ischaemic stroke - stroke, cerebral  
137 infarction or cerebrovascular accident; and (c) TIA - transient ischaemic attack. Controls  
138 were identified from the same source to minimize the potential of bias [19]. Controls were

139 defined as patients who had no cardiovascular event within 90 days after acute ischaemic  
140 stroke. The flowchart of patient's selection are shown in Figure 1. The sample size was  
141 determined by the number of cases available in the study cohort.

142

#### 143 Antiplatelet drug exposure

144 The information on antiplatelet drugs was obtained from the current medication dataset in  
145 VISTA. Data on start and stop dates of antiplatelet drugs were available on certain trials that  
146 had monitored start and stop dates for all medications. Antiplatelet drugs were identified  
147 using the World Health Organization's Anatomical Therapeutic Chemical (ATC)  
148 classifications i.e. antiplatelet with ATC code: B01AC. The antiplatelet exposure period for  
149 each patient began after the diagnosis of acute ischaemic stroke and ended at the index  
150 date. The index date was the date of the first cardiovascular event recorded after antiplatelet  
151 exposure in cases. In controls it was the same date as the matched case [20, 21]. Exposure  
152 to antiplatelet drugs prior to the index date was classified as persistent use, early cessation,  
153 interruption, or stopped (Figure 2). Persistent use was defined as taking antiplatelet therapy  
154 up to, or within 3 days of the index date. Patients who switching to another antiplatelet  
155 therapy were considered as continuing antiplatelet treatment. Early cessation was defined as  
156 patient who took antiplatelet therapy less than three days post-stroke or prior to the index  
157 date. Interruption was defined as taking antiplatelet therapy up to, or within 3 days of the  
158 index date, but with two days or more interrupted use. Stopped was defined as stopping  
159 antiplatelet therapy at least 5 days before the index date.

160

#### 161 Bleeding events

162 Bleeding events occurring during the study period were divided into two categories  
163 (intracerebral haemorrhage (ICH) and extracranial haemorrhage (ECH)). Intracerebral  
164 haemorrhage included all types of ICH except haemorrhagic transformation 1 and 2 of  
165 cerebral infarction, which were not counted. ECH was defined as all other types of bleeding

166 and was split into gastrointestinal (GI) and non-GI bleeding. These information were  
167 extracted from AE and SAE datasets in VISTA.

168

## 169 Statistical analysis

170 Descriptive statistics were recorded for cases and controls and according to the three types  
171 of antiplatelet exposures. The Chi-square test was used to compare baseline characteristics  
172 between cases and controls. Comparison between antiplatelet exposures group were  
173 conducted using the Kruskal-Wallis test or the chi-square test depending on the distribution  
174 and nature of the data. Categorical variables were summarised using frequencies and  
175 proportions and continuous variables as mean [standard deviation (SD)] or median  
176 [interquartile range (IQR)].

177

178 We used conditional logistic regression to calculate odds ratios (OR) and 95% confidence  
179 intervals (95% CI) for risk of cardiovascular event associated with exposures of antiplatelet  
180 before the index date. We first conducted univariable analyses. In multivariable analysis, we  
181 first included all significant variables (first model). We then consecutively dropped the least  
182 significant variable until all included variables were significant at  $P < 0.05$  (final model). A  
183  $P < 0.05$  was considered significant. Point estimates and 95% CI are presented for all results.  
184 We used a complete-case approach to analysis so there was no imputation of missing data.  
185 All analyses were performed using IBM SPSS Statistics version 21.0 [22].

186

187 A post-hoc power analysis to determine the power of the study and the sample size needed  
188 to detect a desired degree of statistical power was performed using PS (version 3.0 2009) to  
189 address the likelihood of type II error.

190

## 191 Results

### 192 Study population



193 Complete data were available for analysis of antiplatelet exposure in 4050 patients. Of these,  
194 a total of 194 patients who had at least one cardiovascular event (126 ischaemic stroke, 45  
195 ACS and 23 TIA) within 90 days following acute ischaemic stroke. These cases were  
196 matched to 776 controls. Baseline characteristics of patients with cardiovascular event and  
197 their matched controls are shown in Table 1. Compared with the control group, the cases  
198 were more likely to have a history of diabetes, heart failure and previous TIA. Among cases,  
199 there were 136 (70.1%) persistent users, 48 (24.7%) with early cessation and 10 (5.2%)  
200 stopped/interrupted users. Among controls, there were 534 (68.8%) persistent users, 184  
201 (23.7%) early cessation and 58 (7.5%) stopped/interrupted users.

202

203 Patients who interrupted/stopped their antiplatelet therapy had higher baseline NIHSS and  
204 were more likely to have previous ischaemic heart disease and stroke (Table 2) than  
205 persistent users. Aspirin was the most common antiplatelet prescribed followed by  
206 clopidogrel for both cases and controls (Table 3). More than two-third of persistent users,  
207 early cessation and interrupted/stopped users were exposed to aspirin and followed by  
208 clopidogrel (Table 4). The occurrence of bleeding events was highest in interrupted/stopped  
209 users (10.3%) followed by early cessation users (7.6%) (Table 5).

210

211 Antiplatelet exposure and cardiovascular event

212 There was no significant difference in cardiovascular event rate in early cessation and  
213 interrupted/stopped users compared to persistent users on univariable analysis (OR 1.07,  
214 95% CI 0.67, 1.71;  $P=0.784$  and OR 0.67, 95% CI 0.34, 1.36;  $P=0.269$  respectively) (Table  
215 6). Results were similar following adjustment (adjusted OR 1.04, 95% CI 0.62, 1.74;  $P=0.876$   
216 and OR 0.70; 95% CI 0.33, 1.48;  $P=0.352$  respectively) (Table 7).

217

218 Discussion

219 We performed a nested case-control study to explore the relationship between stopping or  
220 interrupting antiplatelet drugs and cardiovascular risk in patients with recent ischaemic  
221 stroke. We found no evidence for an increased risk of cardiovascular among patients who  
222 stopped or had interrupted use of antiplatelets.

223

224 We found that the rates of early cessation of antiplatelet therapy were higher in our study  
225 compared to others [23, 24]. We defined early cessation as taking an antiplatelet for fewer  
226 than 3 days post-stroke or before a cardiovascular event. We used this definition because  
227 most patients took aspirin and fewer than 3 days of aspirin use is unlikely to lead to full  
228 inhibition of platelets [25].

229

230 Withdrawal of antiplatelets is associated with an increase in thromboxane A2 activity [26]  
231 which could increase the risk of ischaemic stroke [10, 11, 27]. These studies found that  
232 discontinuation of antiplatelet therapy within one to six months is associated with increased  
233 risk of ischaemic stroke or TIA. We did not see an increase and several factors could explain  
234 the difference between our findings and previous studies. First, our sample size was small  
235 compared to the studies by García Rodríguez, *et al.* [11] and Broderick, *et al.* [10] so there is  
236 a risk of type 2 error. Further, previous studies have assessed different time periods and  
237 clinical scenarios. The study cohort in García Rodríguez *et al.* was followed up for  
238 approximately 3.4 years. The STRATAGEM trial assessed the interruption of antiplatelets in  
239 patients undergoing surgery [28] and found no increased risk. This suggests the risk of  
240 stopping or interrupting antiplatelet drugs may be acceptable in the short term and we  
241 wished to assess whether this was the case after stroke.

242

243 After stroke, there are several reasons why clinicians may be faced with decisions regarding  
244 continuing or stopping anti-platelets. These include bleeding complications and other  
245 adverse events such as worsening stroke symptoms or changes in haematological

246 measures. At present, little data exist to inform these decisions in terms of risk of recurrence  
247 following cessation. Our study should reassure that, if clinically indicated, the short term risk  
248 of stopping anti-platelets does not appear to be significantly increased.

249

250 In the present study, comorbidity was more common in cases and stroke severity was higher  
251 in patients who were interrupted or stopped users. We also found stroke severity, age,  
252 hypertension, diabetes and quality of life were related to the pattern of anti-platelet use.

253 Patients with higher stroke severity, previous stroke and lower life quality were more likely to  
254 stop. Although we cannot be sure, this likely reflects the underlying reasons for stopping

255 treatment, such as change in clinical condition or withdrawal of care. Early cessation users  
256 had a higher rate of atrial fibrillation which may be explained by decisions to start

257 anticoagulation therapy. On the other hand, interrupted/stopped users had a higher rate of  
258 bleeding suggesting this also influenced the reason to interrupt or stop antiplatelet therapy.

259

260 Strengths and limitations

261 Despite their known problems of bias and confounding, case-control designs are efficient in

262 examining the association between outcomes and exposures. VISTA database sample

263 provided data that were prospectively collected during clinical trials in patients with

264 confirmed ischaemic stroke. We minimized selection bias by including all cases of

265 cardiovascular event within the selected time period (day 3 up to 90 days) and matched

266 controls, free of the outcome of interest and independent of the exposure of interest.

267 Matching for age and sex increased the precision of our results compared with those of

268 previous unmatched case-control studies. Information on exposures was recorded in the

269 database, eliminating recall bias.

270

271 An important limitation of this study is the lack of information on the underlying reasons for

272 interruption/stopping of antiplatelets. This limits the generalizability of our findings to clinical

273 practice. Generalizability is further limited by the fact that data come from a clinical trial  
274 registry and because most patients took aspirin and few received the combination of aspirin-  
275 dipyridamole or clopidogrel as recommended in national and international guidelines. The  
276 main limitation is study power. Although there is a large number of cases and controls, the  
277 number of patients with the different antiplatelet exposures was limited. Post hoc analysis  
278 revealed that this study, at alpha <0.05, with 194 cases and matched with four controls has  
279 insufficient power (0.239). Thus, to obtain 80% power, with the level of alpha 0.05, 801  
280 cases with 4 matched controls per case are needed.

281

## 282 Conclusion

283 We found no significant association between interrupted or stopped use of antiplatelets and  
284 risk of cardiovascular events. This might reassure clinicians who need to stop antiplatelets  
285 for clinical reasons. However, our study had limited power and a clinically important risk  
286 cannot be excluded. Further research is needed.

287

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## 292 Appendix

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304

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310

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424



425 Figures

426

427 Figure 1. Flowchart of patients' selection.

428

429 Figure 2. Determination of persistent user (a), early cessation user (b), interrupted user (c)

430 and stopped user (d) of antiplatelet exposure. AP, antiplatelet; CV, cardiovascular event.

431 Table 1. Characteristics of patients with cardiovascular event and their matched controls

Characteristics	No. (%)			p-value
	Overall <i>n</i> =970	Cases <i>n</i> =194	Controls <i>n</i> =776	
Age, years*	70.9(10.8)	70.9(11.3)	70.9(10.7)	NA <sup>‡</sup>
Male sex	510(52.6)	102(52.6)	408(52.6)	NA <sup>‡</sup>
Caucasian	808/934(86.5)	161/187(86.1)	647/747(86.6)	0.905
Current Smoker	267/936(28.5)	60/187(32.1)	207/749(27.6)	0.240
Baseline NIHSS <sup>†</sup>	12(8-17)	11.5(8-17)	12(8-17)	0.886
Medical history				
Hypertension	692/947(73.1)	147/194(75.8)	545/753(72.4)	0.365
Diabetes	228/970(23.5)	61/194(31.4)	167/776(21.5)	0.004
Atrial fibrillation	159/947(16.8)	37/194(19.1)	122/753(16.2)	0.389
Heart failure	65/859(7.6)	20/184(10.9)	45/675(6.7)	0.060
Ischaemic heart disease	243/915(26.6)	57/187(30.5)	186/728(25.5)	0.194
Previous TIA	69/901(7.7)	19/176(10.8)	50/725(6.9)	0.084
Previous stroke	177/886(20.0)	40/186(21.5)	137/700(19.6)	0.606
rt-PA	318(32.8)	70(36.1)	248(32.0)	0.305
Antiplatelet exposures				
Early cessation	232(23.9)	48(24.7)	184(23.7)	0.520
Stopped/Interrupted	68(7.0)	10(5.2)	58(7.5)	
Persistent	670(69.1)	136(70.1)	534(68.8)	

432 \*Values are reported as mean (SD); <sup>†</sup>median (IQR); <sup>‡</sup>Variables that were matched and  
433 hence not applicable. CI, confidence interval; IQR, interquartile range; NIHSS, National  
434 Institute Health Stroke Scale; TIA, transient ischaemic attack; rt-PA, recombinant tissue  
435 plasminogen activator; SD, standard deviation.

436 Table 2. Distribution of risk factors for cardiovascular event by antiplatelet exposure

Characteristics	No. (%)			p-value
	Persistent user <i>n</i> =670	Early cessation user <i>n</i> =232	Interrupted/ Stopped user <i>n</i> =68	
Age, years*	70.2(10.9)	73.6(10.0)	69.1(11.3)	
Male sex	351(52.4)	122(52.6)	37(54.4)	0.951
Ethnicity, Caucasian	556/646 (86.1)	197/222 (88.7)	55/66 (83.3)	0.444
Current Smoker	185/643 (28.8)	57/226 (25.2)	25/67 (37.3)	0.152
Baseline NIHSS <sup>†</sup>	11(8-16)	13(9-17)	17(12-20)	<0.001
Medical history				
Hypertension	473/654 (72.3)	169/225 (75.1)	50/68 (73.5)	0.716
Diabetes	164/670 (24.5)	51/232 (22.0)	13/68 (19.1)	0.502
Atrial fibrillation	91/654 (13.9)	56/225 (24.9)	12/68 (17.6)	0.001
Heart failure	38/601 (6.3)	21/196 (10.7)	6/62 (9.7)	0.105
Ischaemic heart disease	146/628 (23.2)	74/220 (33.6)	23/67 (34.3)	0.004
Previous TIA	48/623 (7.7)	16/212 (7.5)	5/66 (7.6)	0.997
Previous stroke	111/617 (18.0)	48/207 (23.2)	18/62 (29.0)	0.049
rt-PA	224(33.4)	74(31.9)	20(29.4)	0.755

437 \*Values are reported as mean (SD); <sup>†</sup>median (IQR). CI, confidence interval; IQR,  
438 interquartile range; NIHSS, National Institute Health Stroke Scale; TIA, transient ischaemic  
439 attack; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation.

440

441 Table 3. Characteristics of antiplatelet regimen prescribed

Antiplatelet regimen	No. (%)		Unadjusted OR (95% CI)	p-value
	Cases <i>n</i> =194	Controls <i>n</i> =776		
Aspirin	139(71.6)	566(72.9)	1.00	-
Clopidogrel	28(14.4)	105(13.5)	1.10 (0.69-1.74)	0.674
Aspirin+Clopidogrel	10(5.2)	25(3.2)	1.63 (0.75-3.52)	0.215
Aspirin+Dipyridamole	10(5.2)	50(6.4)	0.82 (0.40-1.68)	0.585
Ticlopidine	4(2.1)	16(2.1)	1.01 (0.34-3.05)	0.980
Aspirin+Ticlopidine	1(0.5)	1(0.1)	4.44 (0.28-71.29)	0.293
Carbasalate	1(0.5)	5(0.6)	0.76 (0.09-6.73)	0.825
Dipyridamole	1(0.5)	5(0.6)	0.79 (0.09-6.73)	0.825
Ozagrel	0(0.0)	1(0.1)	-	-
Triflusal	0(0.0)	2(0.3)	-	-

442 CI, confidence interval; OR, odds ratio.

443

444 Table 4. Frequency of antiplatelet regimen according to types of antiplatelet exposure

Antiplatelet regimen	No. (%)			p-value*
	Persistent user <i>n</i> =670	Early cessation user <i>n</i> =232	Interrupted/ Stopped user <i>n</i> =68	
Aspirin	492(73.4)	160(69.0)	53(77.9)	-
Clopidogrel	88(13.1)	38(16.4)	7(10.3)	0.267
Aspirin+Clopidogrel	20(3.0)	12(5.2)	3(4.4)	0.238
Aspirin+Dipyridamole	43(6.4)	13(5.6)	4(5.9)	0.948
Ticlopidine	13(1.9)	7(3.0)	0(0.0)	0.291
Aspirin+Ticlopidine	2(0.3)	0(0.0)	0(0.0)	1.000
Carbasalate	6(0.9)	0(0.0)	0(0.0)	0.467
Dipyridamole	4(0.6)	2(0.9)	0(0.0)	0.774
Ozagrel	0(0.0)	0(0.0)	1(1.5)	0.076
Triflusal	2(0.3)	0(0.0)	0(0.0)	1.000

445 \*Compared with aspirin.

446 Table 5. Frequency of bleeding events following antiplatelet exposure

Bleeding	No. (%)			Overall <i>n</i> =970
	Persistent user <i>n</i> =670	Early cessation user <i>n</i> =232	Interrupted/ Stopped user <i>n</i> =68	
ICH	7(1.1)	6(2.7)	5(7.5)	18(1.9)
ECH	21(3.2)	12(5.4)	2(2.9)	35(3.7)
Total bleeding	28(4.2)	18(7.6)	7(10.3)	53(5.5)

447 ICH, intracranial haemorrhage; ECH, extracranial haemorrhage.

448 Table 6. Univariate analyses (conditional logistic regression) of selected variables against  
 449 outcome of being “case”

Characteristics	No. (%)		Unadjusted OR (95% CI)	p-value
	Cases <i>n</i> =194	Controls <i>n</i> =776		
Ethnicity				
Caucasian	161/187 (86.1)	647/747 (86.6)	0.94 (0.58-1.51)	0.782
Others	26/187 (13.9)	100/747 (13.4)	1.00	
Smoking history				
Current Smoker	60/187 (32.1)	207/749 (27.6)	1.25 (0.87-1.79)	0.219
Non/Former Smoker	127/187 (67.9)	542/749 (72.4)	1.00	
Baseline NIHSS*	11.5 (8-17)	12 (8-17)	0.99 (0.97-1.02)	0.886
Medical history				
Hypertension				
Yes	147/194 (75.8)	545/753 (72.4)	1.19 (0.82-1.72)	0.356
No	47/194 (24.2)	208/753 (27.6)	1.00	
Diabetes				
Yes	61/194 (31.4)	167/776 (21.5)	1.71 (1.20-2.46)	0.003
No	133/194 (68.6)	609/776 (78.5)	1.00	
Atrial fibrillation				
Yes	37/194 (19.1)	122/753 (16.2)	1.27 (0.82-1.95)	0.285
No	157/194 (80.9)	631/753 (83.8)	1.00	
Heart failure				
Yes	20/184 (10.9)	45/675 (6.7)	1.80 (1.01-3.20)	0.046
No	164/184 (89.1)	630 (93.3)	1.00	
IHD				
Yes	57/187 (30.5)	186/728 (25.5)	1.26 (0.89-1.80)	0.208
No	130/187 (69.5)	542/728 (74.5)	1.00	
Previous TIA				
Yes	19/176 (10.8)	50/725 (6.9)	1.78 (1.01-3.15)	0.049
No	157/176 (89.2)	675/725 (93.1)	1.00	
Previous stroke				
Yes	40/186 (21.5)	137/700 (19.6)	1.08 (0.72-1.62)	0.700
No	146/186 (78.5)	563/700 (80.4)	1.00	
rt-PA				
Yes	70 (36.1)	248 (32.0)	1.20 (0.87-1.66)	0.267
No	124 (63.9)	528 (68.0)	1.00	
Antiplatelet exposures				
Early cessation	48 (24.7)	184 (23.7)	1.07 (0.67-1.71)	0.784
Stopped/Interrupted	10 (5.2)	58 (7.5)	0.67 (0.34-1.36)	0.269
Persistent	136 (70.1)	534 (68.8)	1.00	

450 All values are reported as no. (%) unless otherwise noted. †Values are reported as median  
 451 (IQR). CI, confidence interval; IHD, ischaemic heart disease; IQR, interquartile range;  
 452 NIHSS, National Institute Health Stroke Scale; OR, odds ratio; TIA, transient ischaemic  
 453 attack; rt-PA, recombinant tissue plasminogen activator.

454 Table 7. Multivariable conditional logistic regression of explanatory variables against  
 455 outcome of being “case”

Characteristics	Adjusted OR (95% CI)	p-value*
First model, all variables		
Caucasian	0.89 (0.52-1.54)	0.684
Current Smoker	1.18 (0.77-1.81)	0.442
Baseline NIHSS	0.98 (0.95-1.02)	0.331
Hypertension	1.04 (0.65-1.67)	0.862
Diabetes	1.60 (1.03-2.49)	0.036
Atrial fibrillation	1.32 (0.76-2.29)	0.318
Heart failure	1.33 (0.69-2.55)	0.398
Ischemic heart disease	0.99 (0.65-1.50)	0.964
Previous TIA	2.15 (1.15-4.01)	0.016
Previous stroke	0.97 (0.59-1.59)	0.896
rt-PA	1.05 (0.72-1.54)	0.787
Early cessation†	1.09 (0.60-1.96)	0.779
Stopped/Interrupted†	0.72 (0.32-1.65)	0.441
Final model		
Diabetes	1.72 (1.170-2.52)	0.006
Previous TIA	1.90 (1.06-3.40)	0.031
Early cessation AP†	1.04 (0.62-1.74)	0.876
Stopped/Interrupted AP†	0.70 (0.33-1.480)	0.352

456 \*Adjusted for other variables in model. †Compared to Persistent users. AP, antiplatelet; CI,  
 457 confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; rt-PA,  
 458 recombinant tissue plasminogen activator; TIA, transient ischaemic attack.

459 Tables of Links

LIGANDS		460
<a href="#">aspirin</a>	<a href="#">dipyridamole</a>	
<a href="#">clopidogrel</a>	<a href="#">ticlopidine</a>	461

TARGETS		462
G protein-coupled receptors [30]		463
<a href="#">P2Y<sub>1</sub> receptor</a>	<a href="#">P2Y<sub>12</sub> receptor</a>	
Enzymes [31]		464
<a href="#">COX-2</a>	<a href="#">CYP2B6</a>	
<a href="#">Phosphodiesterases, 3',5'-cyclic nucleotide</a>		465
Ion channels [32]		466
<a href="#">ASICs</a>		
Transporter [33]		467
<a href="#">SLC29 family</a>		
Other Protein Targets [34]		468
<a href="#">regulator of G-protein signaling 18</a>		469

470 These Tables of Links list key protein targets and ligands in this article that are hyperlinked\*  
 471 to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data  
 472 from the IUPHAR/BPS Guide to PHARMACOLOGY [29], and are permanently archived in  
 473 the Concise Guide to PHARMACOLOGY 2015/16 [30-34].