Prescribing Antiplatelet Medicine and Subsequent Events After Intracerebral Hemorrhage

Robert W.V. Flynn, MSc; Thomas M. MacDonald, MD; Gordon D. Murray, PhD; Ronald S. MacWalter, MD; Alexander S.F. Doney, MD

Background and Purpose—Antiplatelet medicines are commonly perceived as contraindicated after intracerebral hemorrhage (ICH). Many ICH patients have or will have indications for antiplatelet therapy. This observational study describes the level of antiplatelet prescribing and rate of subsequent events after ICH in Tayside, Scotland.

Methods—This study used record-linkage of an existing stroke cohort with antiplatelet prescribing data from 1994 to 2005. Patients were followed-up from discharge after index event. The primary outcome was recurrent ICH. Other outcomes were subsequent ischemic stroke and a composite of ischemic stroke or myocardial infarction. Event rates were calculated as the number of events divided by patient-years of exposure. Univariate hazard ratios associated with antiplatelet exposure were derived from a Cox model using a time-dependent covariate.

Results—There were 417 ICH patients who survived to discharge. Of these, 120 patients were prescribed subsequent antiplatelet medicines (28.8%). The median time from discharge to antiplatelet use was 14.8 months (range, 2 days–7.5 years). Among all survivors, there were 14 recurrent ICH (rate, 9.7 per 1000 patient-years; 95% confidence interval [CI], 5.3–16.4), 29 subsequent ischemic strokes (rate, 20.6; 95% CI, 13.8–29.6), and 40 subsequent ischemic strokes or myocardial infarctions (rate, 28.7; 95% CI, 20.5–39.0). Hazard ratios associated with antiplatelet exposure were 1.07 (95% CI, 0.24–4.84) for recurrent ICH, 0.23 (95% CI, 0.03–1.68) for ischemic stroke, and 0.72 (95% CI, 0.25–2.02) for ischemic strokes or myocardial infarction.

Conclusions—Antiplatelet prescribing was common after ICH. Subsequent ischemic strokes or myocardial infarctions were more common than recurrent ICH. Antiplatelet prescribing did not appear to have a clinically significant impact on outcomes measured. Despite being contraindicated, antiplatelet use was not a major hazard for recurrent ICH. (Stroke. 2010;41:2606-2611.)

Key Words: cardiovascular diseases ■ cerebral hemorrhage cohort study ■ platelet aggregation inhibitors

The use of antiplatelet medication after a primary intracerebral hemorrhage (ICH) is commonly perceived as being contraindicated because of the possibility of increasing the risk of further bleeding. However, there is little evidence to support this position and studies have shown that patients with ICH either may have a history of ischemic events or subsequently will have ischemic pathologies for which such medicines are indicated. This is not surprising because ICH, ischemic stroke, and myocardial infarction (MI) have certain shared risk factors, particularly increasing age and hypertension. This raises the possibility that patients are denied therapy that might be expected to benefit them.

Clinicians therefore are presented with a therapeutic dilemma when managing patients with competing hemorrhagic and ischemic pathologies. Previous systematic reviews have revealed a lack of randomized and observational data addressing this issue. The advanced record-linkage facility available at the University of Dundee in Tayside, Scotland, has previously been used to study prescribing patterns and outcomes in patients with chronic disease through the linkage of hospital inpatient admission data to community-dispensed prescribing data from the medicines monitoring unit. The objectives of this study were to describe the level of antiplatelet prescribing after ICH and to determine the risks of subsequent events associated with antiplatelet use in this patient population.

Subjects and Methods

The record-linkage technology of the University of Dundee is based on the use of a unique patient identifier, the community health number. Every Tayside resident registered with a family doctor is assigned a community health number, and this has, for the past 20 years, been used as the principal identifier for all patient contact with health care services. This means that multiple sources of electronic patient-specific data available in the region can be linked to create a detailed longitudinal clinical record for each of the 400,000 residents.
Data Sources
Community health number master patient index defined the study population from which subjects were identified, providing data on registered Tayside general practitioners, dates registered with general practitioners, date of birth, and date of death.

The Tayside Stroke Cohort is a region-wide database of stroke patients that has been described in detail elsewhere. In brief, it is derived from Scottish morbidity records hospital discharge codes and death certification data. Cases of ICH were identified from Scottish morbidity records and death certificates using the International Classification of Diseases, ninth (ICD-9) revision or tenth (ICD-10) revision. Pathophysiologically imprecise “stroke” codes were augmented with information derived from computed tomography brain scan reports using natural language processing. Because ICH is a serious event that will almost always be hospitalized, the case ascertainment is good. A validation of the data found an acceptably low error rate (positive predictive value, 93.6%; 95% confidence interval [CI], 86.8–97.0), and comparison of event rates with previously published studies also suggests the case ascertainment is good. Data are currently available from 1994 to 2005.

The medicines monitoring unit prescription dataset is a well-established and routinely validated database that contains subject-specific data on all prescriptions dispensed from all community pharmacies in Tayside since 1993, including drug name, formulation, dosage, frequency, and duration. This provided data on principal exposure of interest, antiplatelet medicines. Other exposures used were prescribing of oral anticoagulants, nitrates, lipid-regulating medicines, and antihypertensive therapy (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β-blockers, calcium channel blockers, and thiazide diuretics).

Scottish morbidity records are data routinely validated and collocated by the Information and Services Division of the National Health Service in Scotland and were available for Tayside from January 1, 1980 onwards. These records contained diagnostic codes relating to all hospital inpatient episodes of care using ICD-9 or ICD-10. As well as having identified strokes in the Tayside Stroke Cohort, these data were used to identify hospital admission attributable to MI (ICD-9, 410; ICD-10, I21) during the study period and secondary causes for ICH.

Death certification data were available in an electronic database from the General Register Office of Scotland. Data used included date and underlying cause of death, which were also coded using ICD-9 or ICD-10. These data were used to identify fatal strokes and fatal MI.

Diabetes audit and research in Tayside, Scotland, data include validated information on all people with type 1 and 2 diabetes in Tayside and provides data on date of diagnosis of diabetes.

Study Population
All residents of Tayside, Scotland, registered with a general practice between January 1, 1994 and December 31, 2005.

Study Subjects
All subjects older than 18 years identified as having had a first ICH during the study period were included. Patients who died within 28 days of discharge with an ICH or a generic “stroke” death code were excluded from the analysis. Thus, only subjects with a radiologically confirmed event were included. Intracranial hemorrhages of nontraumatic origin, such as subarachnoid or subdural, were not included. Patients were excluded if they were identified as having a known cause of ICH, such as trauma, arteriovenous malformation, or hemorrhagic brain tumor.

Exposure
The principal exposure of interest was receipt of antiplatelet medicines (aspirin, clopidogrel, or dipyridamole) after the index event.

Outcomes
Outcomes were identified from the same data sources used to create the cohort, with the same definitions applied. The primary outcome of interest was recurrent ICH. The secondary outcome was subsequent ischemic stroke (radiologically confirmed). Other end points considered were MI, the composite end point of MI and confirmed ischemic stroke, and serious vascular events, a composite end point of MI, all-cause stroke, and vascular death, as used by the Anti-thrombotic Trialists’ Collaboration. When ICH was associated with an initial ischemic stroke (ie, hemorrhagic infarction or hemorrhagic transformation), the event was classified as ischemic stroke. Because of the different rates of recurrent hemorrhage associated with different parts of the brain, we used a subgroup analysis to test whether the location of ICH had an impact on our results. All radiology reports associated with the initial admissions were manually classified when possible by a consultant vascular neurologist as being either “lobar” (restricted to the cerebral cortex and underlying white matter) or “deep” (involving deep brain structures: the striatum, thalamus, cerebellum, and brain stem). The same analysis described herein was used for each group.

Statistical Methods
The proportions of patients subsequently prescribed antiplatelet medicines are expressed as a percentage with 95% CI. Baseline factors potentially associated with subsequent antiplatelet use were compared using χ² tests for categorical variables and unpaired t tests for continuous variables. To investigate whether there was an association between subsequent antiplatelet use and factors occurring after discharge for index event, we calculated the rate of nitrate and lipid-regulating medication use and the rate of first-ever ischemic event between discharge and either first antiplatelet use or end of follow-up. This was only performed for patients who had not received these therapies or had ischemic stroke or MI at baseline. These rates were compared using a z test.

To investigate outcomes after discharge, patients were followed-up from the date of discharge after index event to the outcome of interest or until censored (resulting in different follow-up times for each outcome). Patients were censored on December 31, 2005, if they had not experienced an event. CI were calculated assuming a Poisson distribution. Duration of supply was calculated from the quantity of medicines dispensed and directions provided with the prescription data. When directions were not available (in 30.8% of cases), we assumed aspirin once daily, dipyridamole 100 mg tablets 3 times per day, dipyridamole 200 mg modified release capsules twice daily, and clopidogrel 75 mg once daily. A 28-day carry-over period was allowed after completion of supply, during which time the patients were considered to still be receiving benefit of the therapy, so that a short gap between completion of 1 script and collection of the next were considered to be continuous. Univariate hazard ratios were calculated for all end points using a Cox model with antiplatelet medicine exposure entered as a time-varying covariate to allow for time spent with and without a supply of antiplatelet medicines. Event rates were therefore calculated as the total number of events divided by patient-years of exposure or nonexposure, so individual patients contributed to both exposed and unexposed times. Because the principal end point had insufficient numbers of events, multivariate analyses were not used. All analyses were performed using SAS version 8.

Sensitivity Analysis
The various assumptions made in this analysis were tested in sensitivity analyses. Because aspirin was the predominant antiplatelet drug used in this study, the outcome analyses were repeated using aspirin use only. The 28-day carry-over was also subject to a sensitivity analysis, with carry-over periods of 14 days and 1 day also being used. The Tayside Stroke Cohort also contains a number of events that were coded as ICH but that were not linked to
Table 1. Baseline Characteristics Associated With Subsequent Antiplatelet Use

<table>
<thead>
<tr>
<th>Baseline Status</th>
<th>Patients Supplied Antiplatelet Agents, n (%)</th>
<th>Patients Not Supplied Antiplatelet Agents, n (%)</th>
<th>Significance, ( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>70.3</td>
<td>69.7</td>
<td>0.664</td>
</tr>
<tr>
<td>Female</td>
<td>62 (51.7)</td>
<td>146 (49.2)</td>
<td>0.643</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20 (16.7%)</td>
<td>41 (13.8%)</td>
<td>0.454</td>
</tr>
<tr>
<td>Nitrate use</td>
<td>25 (20.8%)</td>
<td>37 (12.5%)</td>
<td>0.030</td>
</tr>
<tr>
<td>Anti-lipid medications</td>
<td>15 (12.5%)</td>
<td>44 (14.8%)</td>
<td>0.539</td>
</tr>
<tr>
<td>History of MI</td>
<td>6 (5.0%)</td>
<td>18 (6.1%)</td>
<td>0.674</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4 (3.3%)</td>
<td>12 (4.0%)</td>
<td>0.734</td>
</tr>
<tr>
<td>Oral anticoagulation</td>
<td>10 (8.3%)</td>
<td>35 (11.8%)</td>
<td>0.304</td>
</tr>
<tr>
<td>Antiplatelet user</td>
<td>40 (33.3%)</td>
<td>85 (28.6%)</td>
<td>0.342</td>
</tr>
<tr>
<td>Previous ischemic event*</td>
<td>9 (7.5%)</td>
<td>28 (9.4%)</td>
<td>0.531</td>
</tr>
<tr>
<td>History of ischemia†</td>
<td>29 (24.2%)</td>
<td>54 (18.2%)</td>
<td>0.166</td>
</tr>
<tr>
<td>Anti-lipid medication initiated‡</td>
<td>22 (18.3%)</td>
<td>39 (13.1%)</td>
<td>0.174</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>297</td>
<td></td>
</tr>
</tbody>
</table>

- MI indicates myocardial infarction.
- †History of ischemia refers to a history of hospitalization for myocardial infarction or non-hemorrhagic stroke.
- ‡Patient initiating antihypertensive therapy (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, \( \beta \)-blockers, calcium channel blockers, or thiazide diuretics) within 4 weeks of discharge without having had them within 6 months of admission.

Ethical Approval

Approval was obtained from the Tayside Committee on Medical Research Ethics, and permission to access patient records was granted by the Tayside Caldicott Guardian. All analyses were performed on anonymous datasets.

Results

There were 942 patients with an initial radiologically confirmed ICH in Tayside from 1994 to 2005. Of these, 417 survived to discharge, were older than 18 years, and did not have an identifiable cause for hemorrhage. The mean age at index event was 69.9 years, and the cohort was 49.9% female.

Antiplatelet Prescribing

One hundred twenty of the patients surviving to discharge received subsequent antiplatelet medicines (28.8% of total). Tables 1 and 2 show factors associated with antiplatelet exposure. None of the considered baseline covariates was significantly associated with subsequent antiplatelet exposure, with the exception of nitrate use. Use of nitrates or lipid-modifying medication and ischemic events occurring after discharge for the index event were all significantly associated with subsequent antiplatelet medicine exposure. The median time from discharge to first antiplatelet use was 14.8 months and ranged from 2 days to 7.5 years; 18.3% of patients starting antiplatelet therapy did so within 1 month, 24.2% started within 3 months, and 46.7% started within 1 year of discharge.

Subsequent Events Among ICH Patients

Among the 417 ICH patients, there was a total of 1510 years of patient follow-up. There were 14 radiologically confirmed recurrent ICH during 1437 patient-years of follow-up (rate, 9.7 per 1000 patient-years; 95% CI, 5.3–16.3), 29 subsequent ischemic strokes during 1405 patient-years (rate, 9.0 per 1000 patient-years; 95% CI, 4.8–15.3), 40 subsequent ischemic strokes or MI during 1395 patient-years (rate, 28.7 per 1000 patient-years; 95% CI, 20.5–39.0), and 138 serious vascular events during 1293 patient-years of follow-up (rate, 106.7 per 1000 patient-years; 95% CI, 89.7–126.1). The number of events, event rates, and hazard ratios associated with antiplatelet exposure are shown in Table 3. Use of antiplatelet medicines was not significantly associated with either recurrent ICH or subsequent ischemic stroke. The hazard ratios associated with the other end points considered were also not significant for MI (1.77; 95% CI, 0.49–6.49), for ischemic stroke and MI combined (0.72; 95% CI, 0.25–2.02), and for serious vascular events (0.73; 95% CI, 0.42–1.28).

Deep vs Lobar Hemorrhages

It was possible to classify 374 (89.7%) of the initial 417 ICH as either lobar (n=235; 56.4%) or deep (n=139; 33.3%).

Table 2. Characteristics Associated With Subsequent Antiplatelet Use After Discharge

<table>
<thead>
<tr>
<th>After Discharge</th>
<th>Patients Supplied Antiplatelet Agents N (Follow-Up)† Rate</th>
<th>Patients Not Supplied Antiplatelet Agents N (Follow-Up)‡ Rate</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrate use</td>
<td>10 (195.4) 5.1</td>
<td>13 (775.3) 1.7</td>
<td>0.0080</td>
</tr>
<tr>
<td>Anti-lipid medication</td>
<td>38 (216.0) 17.6</td>
<td>60 (767.3) 7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ischemic events*</td>
<td>16 (220.9) 7.2</td>
<td>18 (793.8) 2.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>Ischemia†</td>
<td>20 (185.2) 10.8</td>
<td>23 (722.6) 3.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- †Ischemic events refer to history of hospitalization for myocardial infarction or non-hemorrhagic stroke.
- ‡History of ischemia refers to a history of hospitalization for myocardial infarction or non-hemorrhagic stroke or previous nitrate use.
- †Indicates the number of patients followed-up and the person-years of exposed or unexposed follow-up time.
Among those with an initial lobar hemorrhage, there were 9 recurrent ICH (8 lobar, 1 undetermined) in 801 patient-years of follow-up (recurrence rate, 11.2 per 1000 patient-years; 95% CI, 5.1–21.3), 2 of which occurred while exposed to antiplatelet medication and 7 of which occurred while not exposed. The hazard ratio for ICH associated with antiplatelet use was 1.52 (95% CI, 0.31–7.39). Among those with an initial deep ICH, there were 3 recurrent hemorrhages (2 deep and 1 lobar) in 469 patient-years of follow-up (recurrence rate, 6.4 per 1000 patient-years; 95% CI, 1.32–18.7). All 3 events occurred while not exposed to antiplatelet medicines. For patients with a deep hemorrhage, a relative risk could not be calculated because there were no events among exposed patients. In addition to this subgroup analysis, the other sensitivity analysis had only minor impact on the number of patients exposed and the numbers of events occurring, and none had a significant impact on the rates of events or the hazard ratios associated with antiplatelet use.

### Use of Oral Anticoagulation

Of the 417 initial ICH survivors, 15 received subsequent oral anticoagulants (all warfarin). These patients had a follow-up of 43.2 patient-years. None had a recurrent ICH (rate, 0.0 per 1000 patient-years; 95% CI, 0.0–85.4), and 1 had a subsequent ischemic event (rate, 23.1 per 1000 person-years; 95% CI, 6.6–128.9).

### Discussion

We have used the Tayside Stroke Cohort to investigate the impact of antiplatelet drug prescribing after primary ICH. Although this is the largest such study to date, the numbers available for analysis were still relatively small, mainly because of the low number of patients surviving to discharge and the low recurrence rate. Despite being a perceived contraindication, we found community-dispensed antiplatelet medicines were still prescribed to almost 30% of patients surviving ICH. The overwhelming proportion of prescriptions have originated from general practitioners, although prescribing by both nurses and pharmacists is increasingly common in the United Kingdom, this represented a tiny percentage (<1%) of overall prescribing in the United Kingdom during the period of this study. Overall, the rate of secondary ischemic events after a primary intracerebral bleed was 3-times higher than recurrent ICH. The rate of recurrent ICH during antplatelet exposure and nonantplatelet exposure were found to be similar. Although CI were wide, we found no convincing evidence that subsequent antiplatelet use was a major hazard for recurrent ICH. To test whether the location of the initial ICH had an impact on the findings, we separately analyzed baseline events that were lobar or deep in origin, as has been performed in previous studies. This revealed no reason to think that the impact of antiplatelet was different between hemorrhages originating in different regions of the brain; however, the number of events was insufficient to provide a clear answer to this question, with hazard ratio CI that were wide for recurrent lobar hemorrhages and nonexistent for recurrent deep hemorrhages when there were no events while exposed to antiplatelet agents. The rate of ischemic stroke during antiplatelet exposure was similar to that of recurrent hemorrhage, whereas the event rate during nonexposure to antiplatelet drugs was 3-times higher, although the CI overlapped considerably. The rate of subsequent MI was higher during antiplatelet exposure, which may reflect channeling of medication to patients at high risk, although we found no baseline factors, apart from nitrate use, that were associated with subsequent antiplatelet use. However, postdischarge use of nitrates, lipid-modifying medication, and postdischarge ischemic events were all positively associated with subsequent antiplatelet exposure. This finding suggests some patients were being prescribed antiplatelet agents after the development of cogent indications for their use.

Our previous systematic review found just a single study that has addressed the issue of long-term antiplatelet medicines after ICH. Using a different methodology from ours, this study by Viswanathan et al found the overall rate of recurrent ICH was higher and the rate of recurrent ischemia was lower than those observed here (Table 4). Despite these differences, the hazard ratios for the hemorrhagic and ischemic events associated with antiplatelet use were similar. Although previous studies have found similar rates of recurrent ICH to those found by Viswanathan et al, more recent studies have produced findings similar to our own. This difference in recurrent ICH rate may be explained by our cohort of patients being defined by hospital admissions and therefore is only able to detect symptomatic ICH, whereas the study by Viswanathan et al included follow-up imaging and therefore also included asymptomatic microbleeds. This difference may also be attributable to the different background population, with ours being a truly population-based study and others have been based on secondary care referral centers. Alternatively, there may be a difference in the rates

### Table 3. Events, Event Rates, and Hazard Ratios After Intracerebral Hemorrhage Analyzed by Subsequent Antiplatelet Exposure

<table>
<thead>
<tr>
<th></th>
<th>Intracerebral Hemorrhage</th>
<th></th>
<th>Ischemic Stroke</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (Follow-Up Years)</td>
<td>Rate 1000 Patient-Years (95% CI)</td>
<td>N (Follow-Up Years)</td>
<td>Rate/1000 Patient-Years (95% CI)</td>
</tr>
<tr>
<td>AP exposure</td>
<td>2 (212)*</td>
<td>9.4 (1.1–34.0)</td>
<td>1 (195)</td>
<td>5.1 (0.1–28.5)</td>
</tr>
<tr>
<td>No AP exposure</td>
<td>12 (1225)</td>
<td>9.8 (5.1–17.1)</td>
<td>28 (1210)</td>
<td>23.1 (15.4–33.4)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.07 (0.24–4.84)</td>
<td>0.23 (0.03–1.68)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AP indicates antiplatelet. 194 patients-years were accounted for by aspirin exposure. The rest were attributable to clopidogrel and dipyridamole.
of recurrent ICH in different populations and different localities.

Our inability to identify baseline characteristics associated with subsequent prescribing of antiplatelet drugs is intriguing, and the long duration between discharge and first antiplatelet use also raises the possibility that these medicines are being used without prescriber awareness of the full medical history of the patient. These issues that warrant further investigation cannot be fully addressed using our methodology.

Our study has a number of strengths. Because the data are drawn from a complete and representative population base, our study has high external validity, and this is in contrast to previous studies in the region of Tayside have shown this to be attributed to an ascertainment bias; however, in light of the study had been better-powered to allow multivariate analysis, the possibility of confounding by indication or channeling bias would remain a possibility.

Several lessons can be learned from this study and previous studies. The low survival rate to discharge and the low rate of subsequent events mean that future studies will need to be of an even larger scale. Our study used a population with 5 million person-years of follow-up, and yet there were few secondary events for us to analyze. Future studies should come from multiple locations, with further exploration of the differing rates of recurrent ICH between localities. Additionally, the decision processes and mechanisms behind the prescribing of antiplatelet medicines after ICH should be understood better.

**Conclusion**

In conclusion, we found the prescribing of antiplatelet agents after ICH was common. In patients with ICH, the rate of subsequent ischemic events was higher than that of recurrent hemorrhages. No significant differences in risks associated with antiplatelet use were noted for recurrent ICH or subsequent ischemic events. There remains insufficient evidence to guide prescribers when treating ICH patients with cogent indication for antiplatelet therapy. However, from a clinical perspective, we found no evidence that antiplatelet agents were harmful in patients who had previously experienced ICH.

**Sources of Funding**

Robert Flynn is funded by Chief Scientist Office, Scottish Executive Health Department (fellowship grant CZF/1/41).

**Disclosures**

None.

**References**


Prescribing Antiplatelet Medicine and Subsequent Events After Intracerebral Hemorrhage

Robert W.V. Flynn, Thomas M. MacDonald, Gordon D. Murray, Ronald S. MacWalter and Alexander S.F. Doney

Stroke. 2010;41:2606-2611; originally published online October 14, 2010;
doi: 10.1161/STROKEAHA.110.589143

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/11/2606

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/03/12/STROKEAHA.110.589143.DC1
http://stroke.ahajournals.org/content/suppl/2013/10/02/STROKEAHA.110.589143.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
향혈소판제 처방과 뇌내출혈 후 혈관 질환 발생 현황

Prescribing Antiplatelet Medicine and Subsequent Events After Intracerebral Hemorrhage

Robert W. V. Flynn, MSc; Thomas M. MacDonald, MD; Gordon D. Murray, PhD; Ronald S. MacWalter, MD; Alexander S. F. Doney, MD

(Stroke; 2010;41:2606-2611.)

Key Words: cardiovascular diseases ■ cerebral hemorrhage cohort study ■ platelet aggregation inhibitors

배경과 목적
항혈소판제(antiplatelet medicine)는 혈관 뇌내출혈(intracerebral hemorrhage, ICH) 후 사용 금지 약물로 인식되고 있다. 그럼에도 불구하고 많은 ICH 환자들은 항혈소판제 치료의 작용중을 가지고 있거나 향후 가장이 될 가능성이 높다. 스코틀랜드 테이사이드(Tayside) 주에서 시행된 본 연구는 항혈소판제 처방 수준과 ICH 후 혈관 질환의 발생률을 기술한다.

방법
본 연구에서는 뇌출혈 환자 코호트와 1994~2005년의 항혈소판제 처방 자료를 결합하여 분석하였다. 환자들은 뇌출혈 발생 후 1년이 끝난 후 정기적으로 추적 관찰되었다. 일부 임상 결과는 ICH의 재발이 었고, 다른 임상 결과는 이차적인 허혈뇌출혈(ischemic stroke)과 허혈뇌출혈 또는 심근경색(myocardial infarction)의 종합을 포함하였다. 사전 발생은 사전 수집 항혈소판제 사용 인턴(patient-years)에 의해 나눈 값으로 계산되었다. 항혈소판제 사용과 연관된 단변량 위험도비는 시간 의존 변량을 사용한 Cox 모델을 통해 계산되었다.

결과
퇴원까지 생존한 417명의 ICH 환자를 대상으로 분석하였다. 이들 중에서 120명(28.8%)이 향후 항혈소판제 처방에 노출되었다. 퇴원 후 항혈소판제 처방까지 걸린 시간의 중앙값은 14.8개월(범위, 2일~7.5년)이었다. 모든 생존자들 중에서 14회의 ICH의 재발(발생률, 연 1,000명당 9.7회; 95% 신뢰구간 [CI], 5.3~16.4)과 29회의 허혈뇌출혈(발생률, 연 1,000명당 20.6회; 95% CI, 13.8~29.6)과 49회의 허혈뇌출혈 혹은 심근경색의 종합 사건(발생률, 연 1,000명당 28.7회; 95% CI, 20.5~39.0)이 있었다. 항혈소판제 처방과 연관된 ICH의 재발 위험도비는 1.07 (95% CI, 0.24~4.84), 허혈뇌출혈은 0.23 (95% CI, 0.03~1.68), 허혈뇌출혈 혹은 심근경색의 종합 사건은 0.72 (95% CI, 0.25~2.02)였다.

결론
항혈소판제 처방이 ICH 이후에도 존재한다. 이차 허혈뇌출혈 혹은 심근경색의 발생은 ICH 재발보다도 높았다. 항혈소판제 처방은 본 연구에서 측정된 임상 결과에 유의한 영향을 가지고 있었다. ICH 후 항혈소판제 처방은 사용 금지 사유로 인식되고 있음에도 불구하고 ICH 재발에 중요한 위험인자는 아니었다.

<table>
<thead>
<tr>
<th>Table 3. Events, Event Rates, and Hazard Ratios After Intracerebral Hemorrhage Analysed by Subsequent Antiplatelet Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral Hemorrhage</td>
</tr>
<tr>
<td>N (Follow-Up Years)</td>
</tr>
<tr>
<td>AP exposure</td>
</tr>
<tr>
<td>No AP exposure</td>
</tr>
<tr>
<td>Hazard ratio</td>
</tr>
</tbody>
</table>

*AP indicates antiplatelet.
*194 patients-years were calculated for aspirin exposure. The rest were attributable to clopidogrel and dipridamole.
脳内出血後の抗血小板薬処方とその後のイベント発生
Prescribing Antiplatelet Medicine and Subsequent Events After Intracerebral Hemorrhage

Robert W.V. Flynn, MSc1; Thomas M. MacDonald, MD1; Gordon D. Murray, PhD2; Ronald S. MacWalter, MD1; Alexander S.F. Doney, MD1

1 University of Dundee, Ninewells Hospital and Medical School, Dundee, UK; 2 University of Edinburgh, Division of Community Health Sciences, Edinburgh, UK.

Abstract

脳内出血（ICH）後の抗血小板薬投与は禁忌とみなされているが、多くのICH患者は抗血小板療法の適応があり、また将来的な適応となることもある。本研究は、スコットランドの7側病院におけるICH後の抗血小板薬処方の程度と、その後のイベント発生率について記述する。

方法：本研究では記録照合システムを用い、1994～2005年の間に抗血小板薬の処方データを現存の脳卒中のコホートのデータに集計した。ICH初発後に退院した患者の経過調査を行った。主な評価項目はICH再発であった。他の評価項目は、その後の虚血性脳卒中、虚血性脳卒中と心筋梗塞の複合評価項目であった。イベント件数を抗血小板薬服用者・年で除し、イベント発生率を算出した。時間依存性共変量を用いたCoxモデルを用い、単変量解析によって抗血小板薬服用に伴うハザード比を算出した。

結果：退院したICH生存患者は417例であった。このうち120例に対して、退院後に抗血小板薬が処方されていた（28.8%）。退院から抗血小板薬処方まで期間の中央値は14.8か月であった（範囲：2日～7.5年）。全生存例のうち、14例がICHを再発（発生率=9.7/1,000患者・年、95%CI：5.3～16.4）、29例がその後虚血性脳卒中を発症（発生率=20.6、95%CI：13.8～29.6）、40例がその後虚血性脳卒中または心筋梗塞を発症した（発生率=28.7、95%CI：20.5～39.0）。抗血小板薬投与に伴うハザード比は、ICH再発が1.07（95%CI：0.24～4.84）、虚血性脳卒中が0.23（95%CI：0.03～1.68）、虚血性脳卒中または心筋梗塞が0.72（95%CI：0.25～2.02）であった。

結論：ICH後の抗血小板薬処方は一般的に行われていた。その後の虚血性脳卒中または心筋梗塞の発生率はICH再発よりも高く、本研究で検討した転帰に対する抗血小板薬処方の影響は臨床的に有意なものではないように思われた。ICH後の抗血小板薬投与は禁忌とされているが、抗血小板薬投与はICH再発の重要因子ではないかった。

Stroke 2010; 41: 2606-2611

表3 脳内出血後の抗血小板薬投与の有無別に解析したイベント、イベント発生率、ハザード比

<table>
<thead>
<tr>
<th></th>
<th>脳内出血</th>
<th>虚血性脳卒中</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>件数（追跡調査年数）</td>
<td>1,000患者・年あたりの発生率（95%CI）</td>
</tr>
<tr>
<td>AP投与</td>
<td>2（212）*</td>
<td>9.4（1.1～34.0）</td>
</tr>
<tr>
<td>AP非投与</td>
<td>12（1225）</td>
<td>9.8（5.1～17.1）</td>
</tr>
<tr>
<td>ハザード比</td>
<td>1.07（0.24～4.84）</td>
<td></td>
</tr>
</tbody>
</table>

AP：抗血小板薬。
* 194患者・年はアスピリン投与、残りはクロピドグレルおよびジブリダモール投与。