Withdrawal of Antithrombotic Agents and Its Impact on Ischemic Stroke Occurrence

Joseph P. Broderick, MD; Jordan B. Bonomo, MD; Brett M. Kissela, MD; Jane C. Khoury, PhD; Charles J. Moomaw, PhD; Kathleen Alwell, BSN; Daniel Woo, MD; Matthew L. Flaherty, MD; Pooja Khatri, MD; Opeolu Adeoye, MD; Simona Ferioli, MD; Dawn O. Kleindorfer, MD

Background and Purpose—Antithrombotic medications (anticoagulants and antiplatelets) are often withheld in the periprocedural period and after bleeding complications to limit the risk of new or recurrent bleeding. These medications are also stopped by patients for various reasons such as cost, side effects, or unwillingness to take medication.

Methods—Patient records from the population-based Greater Cincinnati/Northern Kentucky Stroke Study were reviewed to identify cases of ischemic stroke in 2005 and determine the temporal association of strokes with withdrawal of antithrombotic medication. Ischemic strokes and reasons for medication withdrawal were identified by study nurses for subsequent physician review.

Results—in 2005, 2197 cases of ischemic stroke among residents of the region were identified through hospital discharge records. Of the 2197 ischemic strokes, 114 (5.2%) occurred within 60 days of an antithrombotic medication withdrawal, 61 (53.5%) of these after stoppage of warfarin and the remainder after stoppage of an antiplatelet medication. Of the strokes after withdrawal, 71 (62.3%) were first-ever and 43 (37.7%) were recurrent; 54 (47.4%) occurred after withdrawal of medication by a physician in the periprocedural period.

Conclusions—The withdrawal of antiplatelet and antithrombotic medications in the 60 days preceding an acute ischemic stroke was associated with 5.2% of ischemic strokes in our study population. This finding emphasizes the need for thoughtful decision-making concerning antithrombotic medication use in the periprocedural period and efforts to improve patient compliance. (Stroke. 2011;42:00-00.)

Key Words: anticoagulant therapy  ■ antiplatelet therapy  ■ ischemic stroke

The frequency and burden of ischemic strokes after discontinuation of antithrombotic (AT) medication in the population overall is not defined. The cessation of antiplatelet and anticoagulant medications has been associated with an increased incidence of ischemic stroke and other thrombotic events within several months of medication discontinuation. Experimental studies in humans after discontinuation of aspirin have also demonstrated a stimulating effect on the cyclo-oxygenase activity in human platelets under certain conditions that may last up to 6 weeks.

Reasons for discontinuance of AT medications by physicians and patients include planned procedures, bleeding complications, fall risk, financial burden, and poor compliance. The most common reason in several cohorts is discontinuation in the periprocedural period to limit the risk of bleeding complications.

This project was a retrospective review designed to determine the number of acute ischemic strokes associated with cessation of antiplatelet or anticoagulant medications in an ongoing population-based study. The data regarding stoppage of medication, timing of stoppage, and reasons for stoppage were a priori included in the chart abstraction packet for the epidemiology study for 2005 to address the issue of medication withdrawal.

Methods

The Greater Cincinnati/Northern Kentucky Stroke Study is a population-based study of stroke and transient ischemic events in a region that includes 2 southwestern Ohio counties and 3 contiguous northern Kentucky counties separated by the Ohio River. Only residents of the 5 study counties are considered for case ascertainment. The most recent completed study period was calendar year 2005. In the greater Cincinnati/northern Kentucky region, 17 hospitals were active in 2005. Previous studies have documented that residents of the 5 counties who have a stroke exclusively seek care at these hospitals rather than at hospitals in the outlying region. This study was approved by the Institutional Review Boards at each participating hospital. Details of case ascertainment for 2005 and previous study periods have been previously published. More detailed methodology about case ascertainment, detailed abstraction...
of data from the medical record from all sources in the community, and physician phenotyping of cases can be found in the online supplement (http://stroke.ahajournals.org). Only acute ischemic strokes, both first ever in a lifetime or recurrent, were included in the present analysis.

Each verified case of acute ischemic stroke was reviewed in detail by a study nurse and physician investigators to determine whether there was a proximal withdrawal of anticoagulant or antiplatelet medications before stroke onset. The time interval from withdrawal of medication to stroke event was ascertained, and the record was reviewed to determine the reason for withdrawal of medication. Reasons were broadly categorized into those stopped in accordance with physician direction and those stopped independently by the patient. The reasons for stoppage by physician were specified as periprocedural, bleeding, supratherapeutic anticoagulation, history of falls, or "other"; and reasons why patients discontinued medications were specified as noncompliance, financial, "other," and unknown. Antiplatelet medications included clopidogrel, aspirin, dipryridamole, and ticlopidine; anticoagulant medications included warfarin sodium and unfractionated and low-molecular-weight heparins.

For the analysis, stroke events were classified into 3 groups based on AT status at the time of stroke onset: (1) patient was not on an AT medication within 60 days of stroke onset; (2) patient was on an AT medication at time of onset; and (3) patient stopped taking an AT medication within 60 days of onset. The prospective rationale for the cutoff of 60 days included the following: (1) evidence of increased risk of stroke and thrombotic events for 1 to 2 months in prior observational studies and clinical trials that is consistent with experimental studies showing rebound effects after discontinuation of anticoagulant medication that can last up to 6 weeks; (2) some patients have no bridging therapy and it may be 1 to 2 months before stable anticoagulation with warfarin is reattained; and (3) some patients may have substantial delays in restarting of AT medication after a procedure because of complications or because of failure by the responsible physician to restart medication.

Data were managed and analyzed using SAS, Versions 8.02 and 9.2, respectively (SAS Institute, Cary, NC). Generalized estimating equations were used to examine bivariate differences between groups combined and also between the "on AT" group and "stopped AT" group. This statistical method was used to account for patients with 1 event in the time period. The working correlation structure that gave the best model fit was obtained. A binary or multinomial model was used for the dichotomous outcomes. Appropriate transformations were used when necessary. Data are reported as frequencies and percentages or means with associated SEs, as appropriate.

Results

We identified 2197 ischemic strokes in 2090 adult patients in the Greater Cincinnati/Northern Kentucky Stroke Study population during 2005. The mean (SEM) age of the patients with stroke was 70.6 years (0.32); 55.1% were female, and 21.6% were black. Of the 2197 ischemic strokes, 1991 occurred in patients who had a single stroke during the study period, 91 occurred in patients who had 2 strokes, and 8 in patients who had 3 strokes; 1710 (77.3%) were first-ever-in-a-lifetime ischemic strokes and 487 (22.2%) were recurrent ischemic strokes.

The AT status breakdown of the 2197 strokes is (1) 999 not on AT within 60 days of stroke onset (not on AT group); (2) 1084 on AT at the time of onset (on AT group); and (3) 114 in which AT was stopped within 60 days of onset (stopped AT group). Of the 114 patients in the stopped AT group, 108 had clinical symptoms lasting >24 hours and 6 had clinical symptoms of <24 hours with a diffusion-positive stroke on MRI.

Table 1 compares the demographics and clinical characteristics of the 3 groups. As compared with the on AT group, the stopped AT group was more likely to have atrial fibrillation (41.2% versus 22.9%), to be male (59.7% versus 44.9%), and tended toward a higher baseline National Institutes of Health Stroke Scale score (5.7 versus 5.0). Of the 114 patients in the stopped AT group, 42.1% had died within 1 year as compared with 29.2% of the on AT group. The percentage of strokes in the stopped AT group with a modified Rankin Scale score of 0 to 2 or a return to prestroke modified Rankin Scale score at discharge (33.3%) was significantly lower than those in the on AT group (43.9%, P=0.03). In multivariate logistic regression models of mortality at 3 months and 1 year that controlled for atrial fibrillation, diabetes, black race, age, prior infarct, and baseline modified Rankin Scale score, being on an AT medication at the time of stroke onset remained significantly associated with lower mortality, compared with stopping an AT medication before onset (3-month mortality OR, 0.55; 95% CI, 0.34 to 0.90; 1-year mortality OR, 0.56; 95% CI, 0.36 to 0.87).

Table 2 shows the distribution of the 114 withdrawals of medication by type of drug and time interval; 61 patients (53.5%) had strokes after stoppage of warfarin, which include 10 patients who had stoppage of both warfarin and an antiplatelet agent. The remainder had strokes after stoppage of an antiplatelet agent.

Table 3 shows the timing of ischemic strokes after discontinuation of AT medication and the reasons why the medications were stopped. Nearly half of the patients had medications stopped by physicians for procedures, and over half of these patients’ strokes occurred within 7 days of medication stoppage. Nineteen (35.2%) of the 54 patients who had medication stopped for a procedure had recurrent strokes. Patient compliance, bleeding complications, and financial pressures were the next largest reasons for stoppage of medication. Stroke events were clustered mostly in the first 2 weeks after stoppage of medications, which was particularly the case for medications stopped for procedures or for supratherapeutic anticoagulation. Strokes for other categories of medication withdrawal also occurred more frequently in the first several weeks after stoppage of medication, but strokes continued to occur up to 60 days after stoppage. The number of ischemic strokes overall after discontinuation of AT medication was 59 in Week 1, 21 in Week 2, 22 in Weeks 3 to 4, and 12 in Weeks 5 to 8.

Supplemental Table I shows the specific procedures for which AT medication was discontinued. The most common surgeries and procedures were cardiac surgeries and procedures (11), hip and knee surgeries (9), carotid artery surgeries and procedures (8), epidural steroid injections (5), and endoscopic procedures (5). Of these 38 most common procedures, only 5 (13.2%) patients had bridging heparin/low-molecular-weight heparin, of which 2 were cardiac valve replacement surgeries.

Discussion

Antithrombotic medications, which include both antiplatelet agents and anticoagulants, have had a large impact in the reduction of first-ever and recurrent ischemic stroke in
patients with atrial fibrillation, prior ischemic stroke or transient ischemic attack, prior myocardial infarction, and other subpopulations at higher risk for ischemic events, yet the effectiveness and safety of AT medications depend on patient compliance as well as their appropriately prescribed use in various clinical situations in which bleeding risks of these medications may be temporarily or chronically increased. Decisions regarding perioperative management of AT medication are among the most common and complex treatment decisions that physicians face.

Our population-based study indicates that approximately 5% of ischemic strokes are associated with withdrawal of AT

### Table 1. Characteristics of 3 Groups of Ischemic Stroke Events: Not on AT Within 60 Days of Onset, on AT at the Time of Onset, and Stopped AT Within 60 Days of Onset

<table>
<thead>
<tr>
<th></th>
<th>Not on AT ≥60 D (N=999)</th>
<th>On AT at the Time of Stroke ≥60 D (N=1084)</th>
<th>Stopped AT ≥60 D (N=114)</th>
<th>P, Not on AT vs on AT/Stopped AT*</th>
<th>P, on AT vs Stopped AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SEM)</td>
<td>67.3±0.49</td>
<td>73.1±0.40</td>
<td>72.4±1.03</td>
<td>&lt;0.0001</td>
<td>.59</td>
</tr>
<tr>
<td>Female, %</td>
<td>55.6</td>
<td>56.1</td>
<td>40.3</td>
<td>.68</td>
<td>.001</td>
</tr>
<tr>
<td>Black, %</td>
<td>24.9</td>
<td>19.3</td>
<td>14.0</td>
<td>.0005</td>
<td>.17</td>
</tr>
<tr>
<td>Prior ischemic stroke, %</td>
<td>10.5</td>
<td>31.3</td>
<td>37.7</td>
<td>&lt;0.0001</td>
<td>.16</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>8.2</td>
<td>22.9</td>
<td>41.2</td>
<td>&lt;0.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>71.4</td>
<td>86.3</td>
<td>86.0</td>
<td>&lt;0.0001</td>
<td>.92</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29.2</td>
<td>37.9</td>
<td>42.5</td>
<td>&lt;0.0001</td>
<td>.34</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>32.5</td>
<td>19.4</td>
<td>22.9</td>
<td>&lt;0.0001</td>
<td>.38</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>6.2</td>
<td>18.4</td>
<td>20.2</td>
<td>&lt;0.0001</td>
<td>.64</td>
</tr>
<tr>
<td>Baseline NIHSS, geometric mean (95% CI)</td>
<td>4.8 (4.5–5.0)</td>
<td>5.0 (4.8–5.3)</td>
<td>5.7 (4.9–6.7)</td>
<td>.07</td>
<td>.09</td>
</tr>
<tr>
<td>Prestroke mRS, median (25th/75th percentile)</td>
<td>1 (0, 2)</td>
<td>2 (1, 3)</td>
<td>2 (1, 3)</td>
<td>&lt;0.0001</td>
<td>.85</td>
</tr>
<tr>
<td>No medical insurance, %</td>
<td>7.8</td>
<td>2.5</td>
<td>2.8</td>
<td>&lt;0.0001</td>
<td>.85</td>
</tr>
<tr>
<td>Discharge mRS 0–2 or return to baseline, %</td>
<td>41.3</td>
<td>43.9</td>
<td>33.3</td>
<td>.46</td>
<td>.03</td>
</tr>
<tr>
<td>90-d mortality, %</td>
<td>16.0</td>
<td>18.7</td>
<td>28.1</td>
<td>.03</td>
<td>.02</td>
</tr>
<tr>
<td>1-y mortality, %</td>
<td>24.9</td>
<td>29.2</td>
<td>42.1</td>
<td>.004</td>
<td>.005</td>
</tr>
</tbody>
</table>

AT indicates antithrombotic; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

*For this comparison, “on AT” and “stopped AT” were combined into a single group.

### Table 2. AT Medication Use in the 2197 Acute Ischemic Strokes Identified by GCNKSS 2005 Hospital Ascertainment

<table>
<thead>
<tr>
<th>Medication</th>
<th>On AT at the Time of Onset</th>
<th>Off AT 1–7 D</th>
<th>Off AT 8–14 D</th>
<th>Off AT 15–30 D</th>
<th>Off AT 31–60 D</th>
<th>Total Off AT ≥60 D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>181 (8.2)</td>
<td>34 (1.5)</td>
<td>12 (0.5)</td>
<td>9 (0.4)</td>
<td>6 (0.3)</td>
<td>61 (2.8)</td>
</tr>
<tr>
<td>LMWH</td>
<td>28 (1.3)</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
<td></td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Aspirin ≥81 mg</td>
<td>857 (39.0)</td>
<td>28 (1.3)</td>
<td>8 (0.4)</td>
<td>10 (0.4)</td>
<td>4 (0.2)</td>
<td>50 (2.3)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>223 (10.2)</td>
<td>10 (0.4)</td>
<td>4 (0.2)</td>
<td>3 (0.1)</td>
<td>4 (0.2)</td>
<td>21 (1.0)</td>
</tr>
<tr>
<td>Aspirin and extended-release dipyridamole</td>
<td>33 (1.5)</td>
<td>1 (0.05)</td>
<td>. . .</td>
<td>1 (0.05)</td>
<td>. . .</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Dipyridamole alone</td>
<td>4 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>1 (0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anticoagulant or antiplatelet</td>
<td>1105 (49.3)</td>
<td>59 (2.7)</td>
<td>21 (1.0)</td>
<td>22 (1.0)</td>
<td>12 (0.5)</td>
<td>114 (5.2)</td>
</tr>
</tbody>
</table>

Results are presented as no. (% of 2197). Some patients were on >1 drug within 60 d of onset. Thus, the sum of the individual medication counts is greater than the total count shown for “any anticoagulant or antiplatelet.” Ten patients had stoppage of both warfarin and an antiplatelet agent. There were 21 patients who discontinued 1 drug but remained on a different drug within 60 d of onset. Of patients who stopped warfarin, 9 remained on aspirin, 2 remained on clopidogrel, 1 remained on aspirin and clopidogrel, and 3 were bridged with LMWH; 3 patients who stopped clopidogrel had continuation of aspirin; 1 patient who stopped clopidogrel (noncompliance) remained on aspirin and LMWH; 1 patient who stopped LMWH remained on aspirin and clopidogrel; 1 patient who stopped aspirin/extended-release dipyridamole remained on aspirin ≥81 mg.

AT indicates antithrombotic; GCNKSS, Greater Cincinnati/Northern Kentucky Stroke Study; LMWH, low-molecular-weight heparin.
medications within 60 days of onset. In our study, strokes associated with discontinuation of AT medication had significantly greater mortality and morbidity than strokes occurring at the time of being on AT medication, even after controlling for higher rates of atrial fibrillation and other variables associated with poorer outcome. This observation is consistent with a Kaiser Permanente study of patients with atrial fibrillation in which patients with stroke who had an international normalized ratio of <2.0 at admission had significantly more severe strokes and higher mortality as compared with patients with an international normalized ratio of ≥2.0.14

Patients with acute stroke are often aphasic or cognitively impaired and ascertainment of medication history may be incomplete, particularly in those patients on medications that are purchased over-the-counter and may not be listed in pharmacy records. Thus, our estimated percent of strokes (5.2%) after stopping AT may be an underestimate. In a prospective survey of discontinuation of antiplatelet medication in patients with stroke, Sibon and colleagues reported that 5% of 289 patients with ischemic stroke at a single university hospital in Bordeaux, France, had stopped an antiplatelet agent within 30 days of stroke onset.1 All of the strokes occurred within 6 to 10 days after stoppage of medication, and 54% of patients had medication held by a physician for surgical procedures (6) or another cause (1). Maulaz and colleagues reported a case–control study from Centre Hospitalier Universitaire Vaudois in Lausanne in which 4.2% of patients with ischemic stroke had discontinued aspirin within the prior month; all strokes occurred within 25 days of discontinuation.3 Neither of these studies included anticoagulant medications.

Our data suggest that the risk of AT medication withdrawal is related to time since withdrawal as well as to reinstitution of an effective AT medication. Stroke events were clustered mostly in the first 2 weeks after stoppage of medications, which was particularly the case for medications stopped for procedures or for supratherapeutic anticoagulation. Strokes for other categories of medication withdrawal also occurred more frequently in the first several weeks after stoppage of medication, but strokes continued to occur up to 60 days after stoppage. This is illustrated by events associated with medication stoppage due to bleeding complications in which AT medications would be less likely to be restarted quickly, if at all. Our data are potentially susceptible to recall and documentation biases given our methodology. However, given that the time period before stroke was only 60 days, recall bias is probably small.

Our data also suggest that withdrawal of warfarin is associated with a greater risk of ischemic stroke than withdrawal of antiplatelet agents, which likely reflects in part the higher risk of ischemic events in subjects on warfarin. In a 2005 telephone survey of a random population sample from the same greater Cincinnati study region, 40% of whites (mean age, 62 years) and 36% of blacks (mean age, 59 years) reported regular aspirin use.15 Questions regarding use of warfarin and other antiplatelet agents were not part of the 2005 survey. Other recent population studies provide useful comparison of relative use of AT agents. The REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study includes 30,166 community-dwelling adults aged ≥45 years who were enrolled throughout the United States during 2003 to 2006. Of this cohort (mean age, 66.1 years; SD 9.0 years), 47.5% were on aspirin, 5.0% were on a thienopyridine or dipyridamole, and 3.6% were on warfarin (Suzanne Judd, George Howard, personal written communication, August 9, 2010). Using the United Kingdom General Practice Research Database from 2000 through 2005, Delaney and colleagues reported a case–control study of gastrointestinal bleeding that included matched 40,171 control subjects (mean age, 69.1 years; SD 17.7); 3.2% of these control subjects were on warfarin and 1.8% were on a thienopyridine.16 In contrast to the much greater use of antiplatelet agents than warfarin in the general population, over half of ischemic strokes in our study population occurred in patients who had withdrawal of warfarin. The majority of these patients are on warfarin for atrial fibrillation, which represents a group at higher risk of thromboembolic event, particularly those with prior strokes or high CHAD2 scores.2,17

To calculate an accurate risk of thrombotic events associated with stoppage of AT medication, one would need to know the prevalence of AT medication in the general population, the frequency and duration of medication stoppage, the number of ischemic and hemorrhagic events on and off AT medication, and the use of bridging therapy during the same time period. Such data are currently not available in our population nor in any larger population of which we are aware. In addition, determination of the risk of ischemic events after stoppage of AT medication can be confounded in part by the reason for stoppage (eg, cardiac surgery, which has a known risk of ischemic stroke). Several smaller cohort

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Procedure</th>
<th>Bleeding</th>
<th>Supratherapeutic</th>
<th>Falls</th>
<th>Other</th>
<th>Noncompliance</th>
<th>Financial</th>
<th>Other</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–7 d</td>
<td>30</td>
<td>5</td>
<td>7</td>
<td>...</td>
<td>...</td>
<td>9</td>
<td>6</td>
<td>...</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>8–14 d</td>
<td>14</td>
<td>2</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>2</td>
<td>2</td>
<td>...</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>15–30 d</td>
<td>8</td>
<td>5</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>31–60 d</td>
<td>2</td>
<td>3</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>15</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>19</td>
<td>10</td>
<td>1</td>
<td>5</td>
<td>114</td>
</tr>
</tbody>
</table>

Percent 47.4% 13.2% 6.1% 0.9% 1.8% 16.7% 8.8% 0.9% 4.4%
studies of subjects who had interruption of AT therapy indicate the absolute risk of thrombotic events associated with interruption of warfarin for procedures is approximately 1% but is higher in those subjects with atrial fibrillation and prior stroke. The effect of bridging therapy on reduction of thromboembolic events in these cohort studies is unclear because subjects who receive bridging therapies are at higher baseline risk of thromboembolic events. The ongoing BRIDGE Study, a randomized trial funded by the National Heart, Lung and Blood Institute, and the PERIOP 2 Study, a randomized trial sponsored by the Lawson Health Research Institute, will hopefully provide more clarity about the role of bridging therapy in patients with atrial fibrillation and/or mechanical valves with a higher risk of thromboembolic events. Nonetheless, our data support current guidelines recommending minimization of the time off AT medication, particularly in those patients with prior stroke, mechanical heart valves, or atrial fibrillation with higher CHAD2 scores, and continuation of antiplatelet medication in those patients undergoing cardiac and carotid artery procedures. In addition, the specific properties of new oral AT medications like dabigatran (half-life, measurement of biological effect, etc) will need to be considered in these ongoing studies and in clinical practice.

The American College of Chest Physicians Guidelines for perioperative management of AT therapy provide a stratification of risk as well as recommendations for continuation or bridging of AT therapy based on the underlying indication for AT medication and the risk of bleeding for a given surgery. For example, for minor dental, ophthalmic, and dermatologic procedures, maintenance of anticoagulation or antiplatelet therapy throughout the perioperative period is recommended by the American College of Chest Physicians. However, the American College of Chest Physicians Guidelines do not address all minor procedures such as lumbar punctures. Lumbar punctures have a very low risk of epidural hematoma in the setting of antiplatelet agents, yet national guidelines recommend stoppage of thienopyridines for 7 days before performance of a lumbar puncture, 1 of the most common procedures in neurological practice, without stratification of risk. Local institutions or physicians may be even more rigid and require stoppage of any antiplatelet agents, including aspirin, for minor procedures, even in those patients with higher risk of thromboembolic events.

The financial burden of medication also impacts patient compliance. We found that 8.4% of infarcts that occurred within 60 days of medication withdrawal were associated with patient-directed cessation of medication as a result of financial burden. This may underestimate the true burden represented by financial constraints in that 16.7% of patients with infarcts within 60 days of medication withdrawal were categorized as noncompliant with medications, yet the reasons for their noncompliance were not always available.

Conclusions

The withdrawal of anticoagulant and antiplatelet medications is associated with a substantial number of acute first-ever and recurrent ischemic strokes. This finding emphasizes the need for thoughtful decision-making concerning antithrombotic medication use in the periprocedural period and for recruitment in ongoing trials addressing this issue.

Acknowledgments

We express our appreciation to the following hospitals for their participation in the Greater Cincinnati/Northern Kentucky Stroke Study: University Hospital; Good Samaritan Hospital; Bethesda North Hospital; Christ Hospital; St Elizabeth Edgewood, Covington, Florence, and Ft Thomas Hospitals; Mercy Anderson, Clermont, Fairfield, Mt Airy, and Western Hills Hospitals; the Jewish Hospital; Deaconess Hospital; Cincinnati Children’s Hospital Medical Center; and the Cincinnati Veteran Affairs Medical Center. The contents of this manuscript do not represent the view of the Department of Veterans Affairs or US Government or the other hospital systems. We also thank George Howard, DPH, and Suzanne Judd, PhD, for the use of REGARDS data.

Source of Funding

This study was supported by National Institutes of Health Grant R01 NS30678.

Disclosures

M.L.F. and D.O.K. have acted as consultants for Boehringer Ingelheim and P.K. has acted as consultant for Otsuka Pharmaceuticals. Both companies produce antithrombotic medications.

References


Withdrawal of Antithrombotic Agents and Its Impact on Ischemic Stroke Occurrence

Joseph P. Broderick, Jordan B. Bonomo, Brett M. Kissela, Jane C. Khoury, Charles J. Moomaw, Kathleen Alwell, Daniel Woo, Matthew L. Flaherty, Pooja Khatri, Opeolu Adeoye, Simona Ferioli and Dawn O. Kleindorfer

Stroke. published online June 30, 2011;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/early/2011/06/30/STROKEAHA.110.611905

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/07/06/STROKEAHA.110.611905.DC1
http://stroke.ahajournals.org/content/suppl/2013/10/08/STROKEAHA.110.611905.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/
Online Supplemental Methods:

To qualify as a GCNKSS case, an event must have met the criteria for one of the stroke categories adapted from the Classification for Cerebrovascular Diseases III\(^8\) and from epidemiological studies of stroke in Rochester, MN:\(^9\) cerebral ischemia, intracerebral hemorrhage, subarachnoid hemorrhage, or stroke of uncertain cause. To identify potential cases, study research nurses reviewed the medical records of all inpatients with primary or secondary stroke-related ICD-9 discharge diagnoses (430-436) at all 17 acute-care hospitals in the study region. They also reviewed discharge records of all 17 hospital emergency departments with ICD-9 discharge diagnoses 430-436.

Once potential cases were identified, a study research nurse abstracted information from the medical record, including self-reported race/ethnicity, stroke symptoms, physical exam findings, past medical/surgical history, medication use prior to stroke, social history/habits, neurological evaluation, diagnostic test results (including laboratory testing, cardiac testing, and neuroimaging), treatments, outcome, type of insurance, and county of residence. Stroke severity was estimated via a validated method of retrospective NIH Stroke Scale Score (rNIHSSS)\(^10\) obtained from review of the physician exam as documented in the emergency department and hospital records. Baseline and discharge modified Rankin Scale scores (mRS, a measure of functional independence) were estimated from hospital charts. Death certificate records from the Ohio and Kentucky Departments of Vital Statistics and the Social Security Death Index were screened to ascertain 1-year mortality. A study physician made the final clinical
judgment about whether or not a stroke had occurred, after taking into account all available information, including imaging results, and assigned a stroke category and mechanism to each verified case.
### Supplemental Online Table 1: Scheduled procedures for which AT medication was discontinued

<table>
<thead>
<tr>
<th>AT Medication(s) Withdrawn</th>
<th>Procedure (N)</th>
<th>Bridging Therapy (if blank, none used)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Hip fracture surgery (4)</td>
<td>IV heparin (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epidural steroids (3)</td>
<td>LMWH (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colonoscopy (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trans-urethral prostate resection (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac stent (1)</td>
<td></td>
<td>Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Cataract surgery (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate biopsy (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lung biopsy (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AICD replacement (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacemaker insertion (1)</td>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Cerebral angiography (1)</td>
<td></td>
<td>Clopidogrel</td>
</tr>
<tr>
<td></td>
<td>Cardiac angiography (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Anticoagulant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac valve replacement (1)</td>
<td>LMWH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orchiectomy (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debridement for below the knee amputation (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left foot surgery for gangrene (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental procedure (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined surgery (1)</td>
<td>LMWH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker insertion (1)</td>
<td>Aspirin, Clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystectomy (1)</td>
<td>IV heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip replacement (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total knee replacement (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid endarterectomy (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CABG and single valve replacement (1)
Coronary angioplasty and stenting (1)
Cranial bone flap replacement (1)
Cataract (1)
Bronchoscopy (1)
Prostate biopsy (1)
Epidural steroid (1)

Clopidogrel

Epidural steroid (1)

Total knee replacement (1)
Below the knee amputation (1)

Aspirin/extended release dipyridamole

Carotid endarterectomy (1)

Aspirin

Warfarin and aspirin

CABG (2)
IV heparin (1)
Carotid endarterectomy (1)

Cardiac valve replacement (1)  IV heparin

Cystoscopy (1)

Lung resection (1)

Aspirin and clopidogrel

Carotid endarterectomy (2)

Carotid angioplasty and stenting (1)

Aspirin/extended release dipyridamole and aspirin ≥81 mg

Colonoscopy (1)

LMWH – low molecular weight heparin, AICD – automatic implantable cardiac debrillator, CAGB – coronary artery bypass graft
항혈전제의 중단과 그것이 허혈뇌졸중 발생에 미치는 영향

Withdrawal of Antithrombotic Agents and Its Impact on Ischemic Stroke Occurrence

Joseph P. Broderick, MD; Jordan B. Bonomo, MD; Brett M. Kissela, MD; Jane C. Khoury, PhD; Charles J. Moomaw, PhD; Kathleen Alwell, BSN; Daniel Woo, MD; Matthew L. Flaherty, MD; Pooja Khatri, MD; Opeolu Adeoye, MD; Simona Ferioli, MD; Dawn O. Kleindorfer, MD

(Stroke. 2011;42:2509-2514.)

Key Words: anticoagulant therapy ■ antiplatelet therapy ■ ischemic stroke

배경과 목적: 항혈전제(antithrombotic medication)와 항혈소판제(antiplatelet)는 심장 전후 또는 출혈성 혈관질이 발생한 이후에 새로 출혈이 생기거나 재발하는 것을 방지하기 위해 종종 중단된다. 또한 경제적 문제나 부작용, 또는 약을 복용하기 싫다는 이유 등으로 환자 스스로 중단하기도 한다.

방법: 허혈뇌졸중(ischemic stroke) 증례를 확인하고 뇌졸중과 항혈전제 중단의 시간적 연관 관계를 규명하기 위해 지역사회 기반 Greater Cincinnati/Northern Kentucky Stroke Study의 2005년도 환자 보고서를 검토하였다. 허혈뇌졸중과 약물 중단의 이유는 연구 간호사가 확인하였고, 이어서 임상의가 검토하였다.

결과: 2005년, 지역 주민 중 2,197례의 허혈뇌졸중이 병원 퇴원 기록을 통해 확인되었다. 2,197례의 허혈뇌졸중 중 114례(5.2%)가 항혈전제를 중단한 후 60일 이내에 발생하였으며, 61례(53.5%)는 항혈소판제를 중단한 후 발생하였다. 환자 중단 후에 발생한 뇌졸중 중 71례(62.3%)는 처음 발생한 뇌졸중이었고, 43례(37.7%)는 재발성 뇌졸중이었다. 중단기간 전후 환자 간에 경제의 차이는 약물을 중단시기 이후에 발생하였다.

결론: 급성 허혈뇌졸중 발생 이후 60일 이내의 항혈소판제와 항혈전제의 중단은 본 연구 모집단의 5.2%의 허혈뇌졸중과 연관이 있었다. 이러한 결과는 심장 전후 기간의 항혈전제 사용에 대한 신중한 결정과 환자의 순응도를 높이기 위한 노력이 필요하다는 것을 강조한다.

전 인구에서 항혈전제(antithrombotic, AT)의 중단 이후에 발생하는 허혈뇌졸중(ischemic stroke)의 반도 및 비중은 알려지지 않았다. 항혈소판제(antiplatelet)와 항혈소판제(anticoagulant)의 중단은 약물 중단 수술의 이외의 허혈뇌졸중과 그 외 혈전성 질환의 발생률 증가와 연관되어 있다. 사람을 대상으로 한 실험 연구에서, 아스피린을 끊고 난 후 혈소판의 싱글러알시레아제(cyclo-oxygenase) 작용이 증진되는 효과가 6주 이상 지속되는 것으로 관찰되었다. 의지나 환자가 AT를 중단하는 이유들에는 시간 계획, 출혈성 합병증 발생, 낙상 위험, 경제적 부담, 난은 순응도가 있다. 여러 연구에서의 가장 흔한 이유는 시간 전후 출혈성 혈관질의 위험을 줄이기 위한 것이다. 본 연구는 현재 진행 중인 지역사회 기반 연구에서 항혈소판제나 항혈소판제를 중단한 것과 관련된 급성 허혈뇌졸중의 수를 확인하기 위하여 설계된 후향적 연구이다. 약물 중단, 중단된 시기, 중단된 이유 등의 자료는 약물 중단의 패턴을 확인하기 위해 2005년에 시행된 혈전 연구의 차트 수출 패킷(chart abstraction packet)에 미리 포함된 자료를 이용하였다.
방법
Greater Cincinnati/Northern Kentucky Stroke Study는 미국 오하이오(Ohio) 남서부의 2개 카운티와 오하이오강(Ohio River)에 의해 나뉘어진 인접 북부 헨터키(Kentucky)의 3개 카운티에서 뇌졸중과 일시적혈혈액관절(transient ischemic attack)에 대한 연구에서 선정된 지역이다. 증례 확인에는 5개 연구 대상 카운티의 주민만을 고려하였다. 가장 최근에 완료된 연구 기간은 2005년이다. Greater Cincinnati/ northern Kentucky 지역에서는 2005년 당시 17개소의 병원이 있었다. 이전 연구에서, 뇌졸중은 6개 이상의 주민은 거의 모든 이 5개소의 병원에서 치료를 받게 되었던 것으로 보고되었다. 본 연구는 각 병원의 임상 연구 운영 위원회(Institutional Review Board)의 승인을 받았다. 2005년 및 이전 연구 기간의 증례 확인에 대한 세부 내용은 이전에 발표되었다. 증례 확인 및 지역사회 모든 자료원의 의료 기록에서 데이터를 추출하는 것이, 임상의 증례 분류에 대한 자세한 방법론은 online supplement에서 확인할 수 있다(http://stroke.ahajournals.org).

결과
2005년의 Greater Cincinnati/Northern Kentucky Stroke Study 모집단에서, 2,090명의 성인 환자 중 2,197례의 혈뇌혈증이 확인되었다. 뇌졸중 환자의 평균 연령(SEM)은 70.6세 (0.32)였으며, 55.1%가 여성이고 21.6%가 흙인이었다. 2,197례의 혈뇌혈증 중 1,991례는 연구 기간 중 한 번의 뇌졸중을 겪은 환자의 뇌증으로, 91례는 2번의 뇌졸중을 겪은 환자, 8례는 3번의 뇌졸중을 겪은 환자의 증례였다. 1,710례(77.3%)는 생전 처음 혈뇌혈증을 얻은 경우였고, 487례(22.2%)는 재발성 혈뇌혈증이었다.

2,197례의 뇌졸중의 AT 복용 상태는 (1) 999례는 뇌졸중이 발생하기 전 60일보다 더 이전부터 환자가 AT를 복용하지 않은 경우(AT를 복용하지 않은 군); (2) 1,084례는 뇌졸중 발생 당시 AT를 복용하고 있는 경우(AT를 복용한 군); (3) 114례는 뇌졸중이 발생하기 전 60일 이내에 AT를 복용한 경우(AT를 재복용한 군). AT를 중단한 군의 114명 중 108명은 24시간 이상 지속되는 임상적 증상을 보였고, 6명은 임상 증상은 24시간 이내에 회복되었으나 MRI 화학활영상에서 뇌졸중이 확인된 경우였다.

Table 1에 새 군의 인구학적 특성과 임상적 특성을 비교하였다. AT를 복용한 군과 비교하여 AT를 중단한 군에서 심방세동(atrial fibrillation)이 더 많았고(41.2% vs. 22.9%), 남성 이 더 많았으며(59.7% vs. 44.9%), 초기 National Institutes of Health Stroke Scale (NIHSS) 점수가 더 높은 경향을 보였다(5.7 vs. 5.0). AT를 중단한 환자 114명의 42.1%가 1년 이내에 사망하였으며, AT를 복용 중인 군에서는 29.2%가 사
Table 1. Characteristics of 3 Groups of Ischemic Stroke Events: Not on AT Within 60 Days of Onset, on AT at the Time of Onset, and Stopped AT Within 60 Days of Onset

<table>
<thead>
<tr>
<th></th>
<th>Not on AT</th>
<th>On AT at the Time of Stroke</th>
<th>Stopped AT</th>
<th>P. Not on AT vs AT at Time of Stroke</th>
<th>P. on AT vs Stopped AT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤60 D</td>
<td>(N=999)</td>
<td></td>
<td>(N=1084)</td>
<td>(N=114)</td>
</tr>
<tr>
<td></td>
<td>(45.5%)</td>
<td>(49.3%)</td>
<td></td>
<td>(5.2%)</td>
<td></td>
</tr>
<tr>
<td>Age, y (mean±SEM)</td>
<td>67.3±0.49</td>
<td>73.1±0.40</td>
<td>72.4±1.03</td>
<td>&lt;0.0001</td>
<td>0.59</td>
</tr>
<tr>
<td>Female, %</td>
<td>55.6</td>
<td>56.1</td>
<td>40.3</td>
<td>.68</td>
<td>.001</td>
</tr>
<tr>
<td>Black, %</td>
<td>24.9</td>
<td>19.3</td>
<td>14.0</td>
<td>.0005</td>
<td>.17</td>
</tr>
<tr>
<td>Prior ischemic stroke, %</td>
<td>10.5</td>
<td>31.3</td>
<td>37.7</td>
<td>&lt;0.0001</td>
<td>.16</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>8.2</td>
<td>22.9</td>
<td>41.2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>71.4</td>
<td>86.3</td>
<td>86.0</td>
<td>&lt;0.0001</td>
<td>.92</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29.2</td>
<td>37.9</td>
<td>42.5</td>
<td>&lt;0.0001</td>
<td>.34</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>32.5</td>
<td>19.4</td>
<td>22.9</td>
<td>&lt;0.0001</td>
<td>.38</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>6.2</td>
<td>18.4</td>
<td>20.2</td>
<td>&lt;0.0001</td>
<td>.64</td>
</tr>
<tr>
<td>Baseline NIHSS, geometric mean (95% CI)</td>
<td>4.8 (4.5–5.0)</td>
<td>5.0 (4.8–5.3)</td>
<td>5.7 (4.9–6.7)</td>
<td>.07</td>
<td>.09</td>
</tr>
<tr>
<td>Prestroke mRS, median (25th/75th percentile)</td>
<td>1 (0.2)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>&lt;0.0001</td>
<td>.85</td>
</tr>
<tr>
<td>No medical insurance, %</td>
<td>7.8</td>
<td>2.5</td>
<td>2.8</td>
<td>&lt;0.0001</td>
<td>.85</td>
</tr>
<tr>
<td>Discharge mRS 0–2 or return to baseline, %</td>
<td>41.3</td>
<td>43.9</td>
<td>33.3</td>
<td>.46</td>
<td>.03</td>
</tr>
<tr>
<td>90-d mortality, %</td>
<td>16.0</td>
<td>18.7</td>
<td>28.1</td>
<td>.03</td>
<td>.02</td>
</tr>
<tr>
<td>1-y mortality, %</td>
<td>24.9</td>
<td>29.2</td>
<td>42.1</td>
<td>.004</td>
<td>.005</td>
</tr>
</tbody>
</table>

AT indicates antithrombotic; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

*For this comparison, "on AT" and "stopped AT" were combined into a single group.

망하였다. 수정행간적(modified Rankin Scale, mRS) 점수가 0~2점이거나 뇌졸중 발생 이전 상태로 완전한 경우가 AT를 중단한 군에서는 33.3%로 AT 복용군에서보다 유의하게 낮았다 (43.9%, P=0.03). 3개월과 1년째 사망률에 대한 다변량 로지스틱 회귀 모델에서 심방세동, 당뇨병, 협력 여부, 나이, 이전의 뇌경색, 초기 mRS 점수를 보정한 후에도 뇌졸중 발생 당시에 AT를 복용한 경우가 뇌졸중 발생 이전에 AT를 중단한 경우와 비교하여 유의하게 낮은 사망률을 나타냈다 (3개월 사망률 OR, 0.55: 95% CI, 0.34~0.90; 1년째 사망률 OR, 0.56: 95% CI, 0.36~0.87).

AT를 중단한 군(114명)의 약물 종류와 중단 기간 분포를 Table 2에 표시하였다. 61명(53.5%)의 환자에서 와파린을 중단한 이후에 뇌졸중 발생하였으며, 이 중 10명은 와파린과 항혈소판제를 모두 중단하였다. 나머지 환자들은 항혈소판제를 중단한 이후에 뇌졸중 발생한 경우였다.

AT 중단 이후 혈전뇌졸중이 발생하기까지의 시간과 AT 중단 이유를 Table 3에 표시하였다. 환자의 거의 절반 가량이 시술로 인하여 의사가 약을 중단시킨 경우에 해당되었으며, 이 들 중 반 이상에서 약물 중단 7일 이내에 뇌졸중이 발생하였 다. 시술로 인하여 약물을 중단한 환자 54명 중 19명(35.2%) 에서 재발성 뇌졸중이 발생하였다. 환자의 약물 순응도, 출혈 성 합병증, 경제적 부담은 약물과 같은 이유 중 그 다음으로 많 은 부분을 차지하였다. 뇌졸중의 발생은 약물과 중단한 이후 첫 2주 동안에 대부분 옳혀 있었는데, 특히 시술 때문에 중단 하였거나 치료 범위를 초과하는 항응고 상태 때문에 중단한 경 우에 더욱 그러하였다. 다른 이유로 인하여 약물중단한 경우 의 뇌졸중도 대부분 중단한 것에 비해 3주 이내에 발생하였다. 중단 이후 60일까지도 발생이 이어졌다. AT 복용을 중단한 이후 혈전뇌졸중이 발생한 수는 1주 이내에 59례, 2주 이내에 21례, 3~4주에 22례, 5~8주에 12례였다.

Supplemental Table 1에 AT를 중단하게 된 시술에 대하여 표기하였다. 가장 혼란 수술, 시술은 심장 수술 또는 시술 (11), 고관절이나 무릎 수술흥, 경동맥 수술이나 시술(8), 경막 외 스테로이드 주사(5), 내시경적 시술(5)이었다. 38례의 가장 혼란 시술 중에서 단 5명(13.3%)만이 언제 치료로 혈판/저 분자량혈판을 투여받았으며, 이 중 2명은 심장판막환수술 을 받은 경우였다.

고찰
항혈소판제와 항응고제를 포함하는 AT는 심장체질, 이전의 혈전뇌졸중이나 간절성혈전발작이 있었던 경우, 이전에 심근 경색이 있었던 경우, 그 외 혈전성 절환의 고위험군 집단에서 혈전뇌졸중의 첫 발생 또는 재발을 줄이는 데 커다란 영향을 준다.23~26 그러나, AT의 효과나 안전성은 환자의 순응도나 약물의 출혈 위험이 일시적, 또는 반성적으로 증가할 수 있는 여러
Table 2. AT Medication Use in the 2197 Acute Ischemic Strokes Identified by GCNKSS 2005 Hospital Ascertainment

<table>
<thead>
<tr>
<th>Medication</th>
<th>On AT at the Time of Onset</th>
<th>Off AT 1–7 D</th>
<th>Off AT 8–14 D</th>
<th>Off AT 15–30 D</th>
<th>Off AT 31–60 D</th>
<th>Off AT ≥60 D</th>
<th>Total Off AT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>181 (8.2)</td>
<td>34 (1.5)</td>
<td>12 (0.5)</td>
<td>9 (0.4)</td>
<td>6 (0.3)</td>
<td>61 (2.8)</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>LMWH</td>
<td>28 (1.3)</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin 81 mg</td>
<td>857 (39.0)</td>
<td>28 (1.3)</td>
<td>8 (0.4)</td>
<td>10 (0.4)</td>
<td>4 (0.2)</td>
<td>50 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>223 (10.2)</td>
<td>10 (0.4)</td>
<td>4 (0.2)</td>
<td>3 (0.1)</td>
<td>4 (0.2)</td>
<td>21 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Aspirin and extended-release dipyridamole</td>
<td>33 (1.5)</td>
<td>1 (0.05)</td>
<td>...</td>
<td>1 (0.05)</td>
<td>...</td>
<td>2 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Dipryidamole alone</td>
<td>4 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>1 (0.05)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any anticoagulant or antiplatelet</td>
<td>1105 (49.3)</td>
<td>59 (2.7)</td>
<td>21 (1.0)</td>
<td>22 (1.0)</td>
<td>12 (0.5)</td>
<td>114 (5.2)</td>
<td></td>
</tr>
</tbody>
</table>

Results are presented as no. (% of 2197). Some patients were >1 drug within 60 d of onset. Thus, the sum of the individual medication counts is greater than the total count shown for "any anticoagulant or antiplatelet." Ten patients had stoppage of both warfarin and an antiplatelet agent. There were 21 patients who discontinued 1 drug but remained on a different drug within 60 d of onset. Of patients who stopped warfarin, 9 remained on aspirin, 2 remained on clopidogrel, 1 remained on aspirin and clopidogrel, and 3 were bridged with LMWH. 3 patients who stopped clopidogrel had continuation of aspirin; 1 patient who stopped clopidogrel (noncompliance) remained on aspirin and LMWH; 1 patient who stopped LMWH remained on aspirin and clopidogrel; 1 patient who stopped aspirin/extended-release dipyridamole remained on aspirin ≥81 mg.

AT indicates antithrombotic; GCNKSS, Greater Cincinnati/Northern Kentucky Stroke Study; LMWH, low-molecular-weight heparin.

임상적 상황에서의 적절한 치료에 의존한다. 수술 전후 AT 사용에 대한 결정은 임상의가에게 되는 가장 흔하고 복잡한 치료 결정 중 하나이다.

본 지역사회 기반 연구는 헬레르뇌졸의 5% 가량이 발생 60일 이내의 AT 중단과 관련이 있다는 것을 보여주었다. 본 연구에서, AT 중단과 관련된 뇌졸중은 약물 복용을 중단한 후 발생한 뇌졸중에 비하여 사망률과 희생률이 높았으며, 이는 심방세동이나 나 타는 예후와 관련된 다른 인자들을 보정한 이후에도 같았다. 이러한 결과는 심방세동 환자에서 입원 당시 국제표준화 비율(interational normalized ratio, INR)이 2.0보다 낮았던 경우의 뇌졸중이 2.0보다 높았던 환자보다 뇌졸중에 비하여 더 높았으며, 더 높은 사망률을 보였던 Kaiser Permanente study의 결과에 부합한다.11

급성 뇌졸중 환자는 종종 실어증 증세를 보이거나 인지기능 장애를 나타내며 약물 복용력의 확인이 불완전하며, 특히 치료 받지 않은 약을 사용해 복용했던 경우, 약물 기록이 남아 있지 않은 경우에는 확인이 더욱 어렵다. 그러므로, 본 연구의 AT 중단 이후에 발생한 뇌졸중 비율은 아마도 실제보다 낮게 측정되었을 것이다. 뇌졸중 환자에서 항혈소판제의 중단을 전향적으로 조사한 실존 연구에서, Sibon과 그 동료들은 프랑스 보르도(Bordeaux)의 한 대학병원에서 헬레르뇌졸증 환자 289명의 5%가 뇌졸중 발생 30일 이내에 항혈소판제를 중단한다고 보고하였다.1 발생한 모든 뇌졸증은 약물 중단 이후 6~10일 이내에 일어났고, 54%의 환자에서 수술적 시술(6)이나 다른 이유 (1)로 인하여 의사가 약물을 중단시켰다. Maulaz와 그 동료들은 로잔(Lausanne)의 Centre Hospitalier Universitaires Vaudois에서 시행한 환자 대조군 연구를 보고하였는데, 헬레르 뇌졸중 환자의 4.2%가 뇌졸중 발생 이전 1달 내에 야스프린을 중단하였으며, 약물 중단 이후 25일 이내에 모든 뇌졸중이 발생하였다. 이들 연구 모두 항응고제는 포함하지 않았다.

본 연구 결과는 AT의 중단으로 인한 위험이 중단 이후 기간 뿐만 아니라 다시 적절한 AT 사용이 이루어지기까지의 시간과 연관이 있음을 시사한다. 뇌졸중은 약물 중단한 후 2주 이내에 대부분 몸이 생한다. 특히 시술 전후에 끊겼거나 치료 범위를 초과하는 항응고 상태로 인하여 많은 경우에서 더욱 고려하였다. 다른 이유로 약물은 끊긴 경우의 뇌졸중 또한 약을 끊은 후 1주 이내에 발생하였으나, 이후 60일 가까운 뇌졸중이 발생하는 경향을 보였다. 이러한 사실은 AT의 재사용이 가능한 한 빠르게 이루어지는, 출혈성 혈중성으로 인하여 AT를 중단한 경우에 발생한 뇌졸중에 의하여도 설명된다. 이번 연구 결과는 연구 방법에 의하여 최상 오류나 기록 오류에 의한 것일 수 있다. 그러나, 뇌졸중 발생 이전 기간 60일만을 대상으로 하였기 때문에 최상 오류는 아마도 작을 것이다.

본 연구 결과에서는 또한 항혈소판제의 중단보다 와파린의 중단에서 헬레르뇌졸증 위험이 더 높을 것을 나타내었으며, 이는 혈관 질환의 고위험군 환자에 와파린 사용의 대상임을 범위하는 결과일 수 있다. 2005년, 같은 greater Cincinnati 연구 지역에서 시행한 지역사회 기반, 무작위 선정 전화 설문 조사 연구에서, 백인의 40% (평균 연령 62세)와 흑인 36% (평균 연령 59세)가 규칙적으로 야스프린을 복용하고 있다고 보고하였다.16 와파린과 다른 항혈소판제의 사용에 대한 질문은 2005년 설문 조사에는 없었다. 다른 최근의 지역사회 기반 연구에서 AT의 상대적 사용의 비교에 대한 결과를 보고하였다. REasons for
Geographic And Racial Differences in Stroke (REGARDS) 코호트 연구에서, 2003~2006년의 기간 동안, 미국 전 지역의 30,166명의 45세 이상 지역사회 거주 성인을 연구 대상으로 포함시켰다. 이 코호트(평균 연령 66.1±SD 9.0개월)에서 47.5%가 아스피린을 복용하는 것과 같으며, 5.0%는 티에노피리딘 (thienopyridine)이나 디기타드, 3.6%는 와파린을 복용하
는 것으로제시되었다(Suzanne Judd, George Howard, personal written communication, August 9, 2010). 2000~2005년 기간 동안의 United Kingdom General Practice Research Database에서는, 조사를 맞춘 40,171명의 대조군(평균 연령 69.1±SD 17.7개월)을 포함하여 위장출혈의 환자 대조군 연구를 보고하였는데, 대조군의 3.2%에서 와파린을 복용하는 것이 있고, 1.8%가 티에노피리딘을 복용하는 것이고 Delaney 등은 보고하였다. 16 일반인 연구에서 와파린보다 항혈소판제의 사용이 훨씬 많은 것과 달리, 이번 연구 대상의 혈관외출중
의 반 이상이 와파린을 중단한 환자에서 발생하였다. 이들 환
자의 대부분은 혈전성질환의 고위험군을 대표하는 심장
스캔으로 인하여 와파린을 복용하는 것이었고, 특히 이전에
뇌졸중을 앓았거나 CHAD2점수가 높은 환자들이었다. 17

AT의 중단과 연관된 혈전성질환의 정확한 위험도를 계산하
기 위해서는, 일반인에서의 AT 사용이 비율, 약물 중단의 병도
와 기간, AT를 복용할 때와 복용하지 않을 때의 혈관외출중과
출혈성 질환의 발생 수, 해당 기간 동안의 연속적 위험의 시험 어
부를 알아야 할 필요가 있다. 이 자료들은 현재로서는 이번 연
구 대상이나 조사 가능한 다른 대규모 모집단 모두에서 얻을
수가 없다. 또한, AT를 중단한 이후 발생하는 혈관내 혈
행량의 결정은 약물 중단 이유에 부분적으로 영향을 받을 수
있다. 예를 들어, 심장 수술은 혈관외출중의 알려진 위험 요인
중 하나이다. AT 치료를 중단한 사람들 대상으로 했던 여러
소규모 코호트 연구에서, 수술으로 인한 혈관외출중과 연관된
혈전성 질환의 절대 위험도는 거의 1%였으나, 이는 이전에 뇌
졸중이 있었던 심장질환 환자에서는 더 높았다. 18,19 이들 코
호트 연구에서 혈전성질환을 줄이기 위한 연계 치료의 효
과는 분명하지 않았는데, 이를 연계 치료를 시행받은 환자가
혈전성질환의 위험이 더 높은 군이었기 때문이다. 19

National Heart, Lung and Blood Institute의 지원하에
진행 중인 BRIDGE Study와 Lawson Health Research
Institute에 의하여 지원 중인 무작위 선행 임상 연구인 PERI-
OP 2 Study는 심장질환이나 임신과 관련된 환자에
항혈소판제의 위험도에 대해
조직에 적합한 정보를 제공해 줄 것이다. 어떤 이번 연구 결
과는, 특히 이전에 뇌졸중이 있거나 금속심장판을 받고 있
거나, CHAD2점수가 높은 심방세동 환자인 경우 AT 복용 중
단 기간을 최소화하도록 하며, 그러한 환자들의 경우에는 심장이나
경동맥 수술을 받는 환자에게 항혈소판제 복용 유지를 권고하는 현
재의 가이드라인을 뒷받침한다. 20 또한, 다비가트란(dabiga-
tran)과 같은 새로운 경구 AT의 특성(반감기, 생물학적 효과
의 측정 등)이 진행 중인 연구나 실제 임상에서 고려될 필요가
있을 것이다. 21

AT 치료의 수술 전후 치료에 대한 American College of Chest Physicians Guidelines는 위험도의 증가 및 AT 복용의
적응증과 예정된 수술의 종류 위험에 기초한 AT 치료의 연계
치료나 지속에 대한 권고 사항을 제시한다. 22 예를 들어, American College of Chest Physicians에서는 위험도가 낮은 치과, 안
과, 피부과 수술의 경우, 항응고제나 항혈소판제 치료를 시행
전후 기간 동안 유지한 것을 권고하고 있다. 그러나 American
College of Chest Physicians Guidelines에서는 요추침대 등
위험이 낮은 수술 모두에 대하여 언급하고 있는 않는다. 요추
침대는 항혈소판제를 복용하는 중에는 아주 낮은 정도의 경막의
혈종 위험이 있다. 그러나, 국가 가이드라인(national guide-
line)에서는 신경과 임상 영역에서 가장 혼합히 시행되는 수술
중 하나인 요추치자에 대하여 위험도에 대한 단계별 증가도 없
이, 티에노피리딘은 수술 7일 전에 중단할 것을 권고하고 있
다. 21 지역 의료 기관이나 임상의의 아마도 조금 더 엄격해서,
혈전성질환 위험이 높은 환자에서도 위험이 낮은 수술에 대해
아스피린을 포함한 그 외 다른 항혈소판제의 중단을 요구하는
것 같다. 22

약물 복용으로 인한 경색적 부담도 환자의 순응도에 영향을
준다. 약물을 중단한 후 60일 이내에 발생한 뇌졸중 경우 8.4
가, 환자가 경제적 부담으로 인하여 의료 중단한 경우와 연
Acknowledgments

We express our appreciation to the following hospitals for their participation in the Greater Cincinnati/Northern Kentucky Stroke Study: University Hospital; Good Samaritan Hospital; Bethesda North Hospital; Christ Hospital; St Elizabeth Edgewood, Covington, Florence, and Ft Thomas Hospitals; Mercy Anderson, Clermont, Fairfield, Mt Airy, and West Ridge Hospitals; the Jewish Hospital; Deaconess Hospital; Cincinnati Children’s Hospital Medical Center; and the Cincinnati Veteran Affairs Medical Center. The contents of this manuscript do not represent the view of the Department of Veterans Affairs or US Government or the other hospital systems. We also thank George Howard, DPH, and Suzanne Judd, PhD, for the use of REGARDS data.

Source of Funding

This study was supported by National Institutes of Health Grant R01 NS30678.

Disclosures

M.L.F. and D.O.K. have acted as consultants for Boehringer Ingelheim and P.K. has acted as consultant for Otsuka Pharmaceuticals. Both companies produce antithrombotic medications.

References


