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Withdrawal of Antithrombotic Agents and the Risk of Stroke

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Abstract

Background and Purpose—Antithrombotic medications are effective for ischemic stroke prevention, but stoppage of these medications is associated with an increased risk of thromboembolism. The frequency of antithrombotic withdrawal in the general population is unknown.

Methods—We conducted a random phone sample of 2036 households in the Greater Cincinnati metropolitan area, representative of the stroke population by age, sex, and race, to determine the frequency of antithrombotic medication use, and stoppage by physicians for medically indicated procedures.

Results—62% of survey respondents reported that they were on an antithrombotic medication. 10% of participants reported that they had stopped taking their medication within the past 60 days for a medically indicated intervention. Of those that stopped taking the medication, it was more common for persons taking an anticoagulant to stop their medication (20%) than those taking an antiplatelet agent (9%). Colonoscopies and orthopedic surgeries were the most common reasons for withdrawal of antiplatelet agents, whereas orthopedic and vascular surgeries were the most common reason for withdrawal of anticoagulants.

Conclusions—Recommended discontinuation of antithrombotic medication for surgical or diagnostic procedures is common practice for persons in the community representative of a stroke population. Because stoppage of these medications is associated with an increased risk of thromboembolic stroke, further clinical trials are needed to determine best management practices in this setting.

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Keywords

ischemic stroke; thromboembolism; antithrombotic; anticoagulant; antiplatelet; withdrawal; discontinuation; survey

Introduction

Ischemic stroke is the fourth leading cause of death in the United States (US). It is also a major cause of adult disability in the US.¹ Antiplatelet and anticoagulant medications are effective for primary and secondary prevention of ischemic stroke.^{2,3}

Antithrombotic medications are often stopped for several days in preparation for a surgical or diagnostic procedure,^{4–9} the rationale for stoppage being to minimize the risk of hemorrhage associated with the procedure. The exact strategy for stoppage of antithrombotics depends on the procedure to be performed and the risks and benefits of stopping the medication. In general, the international normalized ratio (INR) should be at a subtherapeutic level of 1.3–1.5 before surgery can be performed on a patient taking warfarin,⁴ meaning that warfarin is usually stopped at least four days prior to the procedure to allow clotting factors to increase.⁹ After the procedure, warfarin is restarted, generally within 12–24 hours of the procedure, it takes about three days for the INR to return to therapeutic levels.¹⁰ Platelets have a lifespan of approximately seven days, so antiplatelet agents are generally stopped five to seven days before planned surgery, and then restarted as soon as possible after the procedure.

However, withdrawal of antithrombotic medications also carries a risk of thromboembolism. Perioperative strokes, defined as occurring within 30 days of a surgical procedure, are rare but carry a significantly higher morbidity and mortality than non-perioperative strokes.^{11,12} In addition, several studies have demonstrated that strokes occurring after antithrombotic withdrawal have been associated with a higher morbidity and mortality than strokes in patients who were still taking antithrombotic medication.^{13,14} Kim et al demonstrated that patients with warfarin withdrawal pre-operatively had significantly worse outcomes compared to patients who were still taking warfarin when the stroke occurred. Early neurologic deterioration occurred more frequently, and these patients had a lower frequency of favorable outcomes.¹⁴ Thus, physicians must carefully weigh the risks (increased risk of thromboembolic events) and benefits (decreased risk of bleeding) when deciding if and when to withdraw antithrombotic medications. Yet, frequency of the decision to withdraw antithrombotic medications in the general population is not well characterized.

We report a population-based telephone survey of adults representative of the ischemic stroke population with respect to age, sex, and race that addressed the frequency of discontinuation of antithrombotic medication due to medical intervention.

Methods

In 2011, households with a telephone or cell phone in the Greater Cincinnati metropolitan area were randomly sampled via a phone survey to assess the prevalence of risk factors of

ischemic stroke and knowledge of stroke risk factors. The Greater Cincinnati and Northern Kentucky region includes two counties in southern Ohio and three counties in northern Kentucky that border the Ohio River. This region contains an essentially biracial population of 1.3 million. Survey respondents were contacted by telephone using random-digit selection of telephone numbers. Cell phone numbers were included to account for the growing number of cell-phone-only households. While landline interviews were conducted with a randomly selected household member, cell phone interviews were conducted with the person answering the phone.

By comparison with the 2010 US census, residents of the Greater Cincinnati 5-county area are representative of the US population with regard to median age, percentage of blacks, median household income, educational level, and percentage of population below the poverty level. The survey respondents were quota-matched by demographics: age, sex, and race groups that are at high risk for ischemic stroke. A quota was filled for each of these groups in order to make our respondents representative of the population of stroke patients in this region based on our longstanding stroke epidemiology studies.^{13,15}

In addition to demographic and medical history questions, we asked respondents if they were prescribed antithrombotic medication and if so, if they had stopped the antithrombotic medication by request of their physician for scheduled surgery or other medical procedure during the past 60 days.^{15,16} Respondents were asked which medication they stopped, and for which medical procedure they had stopped the medication. Respondents were not asked if they had stopped medications for reasons of noncompliance. Chi-square and Cochran-Armitage trend test were used, as appropriate, for comparing the proportions. SAS, version 9.3 (SAS Institute, Cary, NC) was used for analysis. A p-value <0.05 was considered statistically significant.

Results

Between June 15 and September 7, 2011, 36,951 households (with one person identified per household) were called. 3210 people were identified as demographically eligible to participate in the survey. Of these, 1154 (36.0%) did not complete the interview due to language barriers, illness, or unavailability despite multiple callbacks during the study period, and 20 (0.6%) others refused to complete the survey. The remaining 2036 (66.8%) respondents completed telephone interviews. Demographics of the nonresponders are not known due to the nature of the survey. Of the 2036 households who completed the telephone interview, 1959 self-identified as either black (544) or white (1415) race. The mean ($\pm$ standard deviation) age of the 1959 was 66.3 years $\pm$ 14.7, with 61% being female. 62%, 1207 of the 1959 respondents were on antithrombotic medication; overall, 63 (3%) were taking only an anticoagulant agent, 1073 (55%) were taking only an antiplatelet agent, and 71 (4%) of respondents reported being on both anticoagulant and antiplatelet agents. Antithrombotic usage increased with age ($p < 0.0001$) and was more common in whites than in blacks (64% and 55%, respectively, $p < 0.001$).

The distribution of antithrombotic medication users in the Greater Cincinnati area by age group, sex, and race is shown in Table 1. Antithrombotic usage did not differ significantly

between males and females. Of respondents who had been taking an antithrombotic medication, 10% (120/1207) reported that they had stopped taking their medication within the past 60 days. Of those that reported taking an antithrombotic medication, persons taking an anticoagulant agent were more likely to stop their medication (20%, 27/134) than those taking an antiplatelet agent (9%, 101/1144). Table 2 shows the frequency of medication stoppage in these subjects, and the reason(s) for discontinuation. The most common procedures cited for stoppage of antiplatelet medications were colonoscopies, orthopedic procedures, and heart/vascular surgery, and the most common procedures cited for stoppage of anticoagulants were orthopedic surgery and heart/vascular surgery.

Discussion

Our population survey demonstrates that antithrombotic use is very common in a population representative of the ischemic stroke population. Use of these medications increases with age, and given the medical comorbidities that accumulate with age, medical interventions requiring discontinuation of antithrombotics were also common; 10% of antithrombotic users in our population had discontinued a medication at the instruction of a physician in the preceding 60 days. Discontinuation of antithrombotic medications was more common for subjects on anticoagulants compared to those on antiplatelet medication. The clinical question of how best to balance the risk of an ischemic event off an antithrombotic medication and limit bleeding complications during a procedure is one that physicians and patients must address, but often with incomplete information about risks of both.

Several studies have described discontinuation rates of 18 to 33 percent in various cohorts of subjects, which is higher than the rate of 10% reported here. These previous studies, however, are not population-based and are not restricted to physician instruction for medical intervention; these studies include stoppages due to non-adherence and bleeding complications, and are often over longer periods of time than two months.^{17–20}

Previous studies have described timing of strokes in cohorts of patients who had a thromboembolic strokes after temporarily stopping antithrombotic or anticoagulant medication for various reasons including noncompliance, surgical or diagnostic procedures, and bleeding complications. The timing of the strokes appeared to be clustered in the first one to two weeks after medication stoppage.^{13,20–23} Several other studies have attempted to report the frequency of thromboembolic strokes in cohorts of patients who discontinued antithrombotic therapy temporarily or permanently, most commonly for a surgical or diagnostic procedure.^{19,24–27} One retrospective study found that out of 1892 patients who had thromboembolic events, 73 (3.9%) had recently stopped taking aspirin.²⁸ The average time from aspirin discontinuation to stroke was approximately two weeks.^{28,29}

Several randomized control trials have provided data from their long follow-up period, including the PROFESS³⁰ and the ROCKET AF³¹ trials. There was a significant increase in both stroke and major vascular events within 30 days of medication discontinuation during and after the PROFESS trial. The event rate peaked in the first three to nine days after withdrawal, with events occurring sooner after discontinuation of clopidogrel than events occurring after discontinuation of aspirin plus extended-release dipyridamole.¹⁹ There was

also a significantly higher event rate for rivaroxaban patients who transitioned to warfarin after the ROCKET AF trial was completed compared to those continuously on warfarin. This was not true for patients who had temporary or early permanent discontinuations. Overall, stopping rivaroxaban did not produce a higher ischemic stroke event rate than stopping warfarin, but the difference in patients who discontinued the rivaroxaban at the end of the trial may have been due to the fact that most of them were transitioning, and thus were subtherapeutic, compared to the warfarin patients who just continued taking the warfarin and had no period of undercoverage.²⁶ Some have hypothesized that a prothrombotic rebound phenomenon may account for the significantly higher rate of stroke or systemic embolism for up to a month after the trial drug was stopped.^{22,32–36}

Importantly, the risk of major bleeding events or ischemic stroke when antithrombotic medications are continued or discontinued, respectively, in the perioperative period often depends on the procedure being performed. For example, several authors have found that continuing aspirin during the perioperative period significantly increases the frequency of bleeding complications, but not the severity.^{37–39} One study found that continuing aspirin therapy in patients undergoing transurethral resection of the prostate does not lead to a significant increase in blood loss after the procedure, compared to a control group.³⁷ A recent review also found that although bleeding complications are more frequent when aspirin is continued perioperatively, the clinical significance was minimal. The authors described only one study that reported an increased perioperative blood loss that was associated with increased long-term mortality. Many procedures have been shown to be safe to perform while aspirin is continued, including dermatologic, dental, ophthalmologic, and peripheral vascular procedures, neuraxial anesthesia, and endoscopies. Similarly, continuing warfarin seems to be safe during cataract and cutaneous surgeries, limited dental procedures, and endoscopy. For some patients, the risk of increased morbidity and mortality from stroke and other thromboembolic events may outweigh the risk of bleeding.^{38,39} The POISE 2 trial, on the other hand, showed that bleeding was a major adverse event of continuing antiplatelet agents in the perioperative period of low-to-moderate bleed risk surgery.⁴⁰

Both the American Academy of Neurology (AAN) and American College of Chest Physicians (ACCP) have recently published evidence-based guidelines recommending that anticoagulants or antiplatelet agents should be continued perioperatively for dental, dermatologic, and some ocular procedures due to their low bleeding risk.^{9,41} Our survey demonstrates that several patients in our survey population discontinued their antithrombotic medication for dental or dermatologic procedures. The current guidelines were published after our survey was completed, however, given that much of the source documentation was already available,⁹ our survey demonstrates that there is room for improvement in how physicians in our survey area manage these medications in the perioperative period. This warrants follow-up in a future survey to examine any change in practice.

The major limitation of our data is that the use of anti-thrombotic medication is self-reported, and there is the potential bias associated with subject recall of antithrombotic use in the prior months. Additionally, our survey did not assess medication stoppage for reasons of noncompliance or whether any strokes resulted from discontinuing the medication.

Indication for anticoagulation and the use of bridging agents was also not addressed in our survey.

In summary, discontinuation of antithrombotic medications as recommended by physicians is common in a population representative of the stroke population with respect to age, sex, and race. Prior reports have demonstrated the associated risks of discontinuation, particularly in the first weeks after stoppage. The increased use of newer anti-thrombotic medications with shorter half-lives than warfarin will likely further impact physician decision-making for these patients. Randomized trials of bridging therapies or randomized trials of stopping versus not stopping antithrombotic medications for various procedures are needed to determine the best approach for patients in different clinical settings who undergo various medical procedures.

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Table 1

Number of survey participants on antithrombotic medication (n=1278) by age, sex and race. AC = anticoagulant. AP = antiplatelet.

Age	Men (n = 763)		Women (n = 1196)		White (n = 1415)		Black (n = 544)		All	
	AP	AC	AP	AC	AP	AC	AP	AC	AP	AC
0–34 (n = 90)	16	1	15	0	21	0	10	1	31	1
35–44 (n = 63)	11	0	12	2	17	0	6	2	23	2
45–54 (n = 194)	38	3	48	6	54	4	32	5	86	9
55–64 (n = 356)	101	1	95	9	144	8	52	2	196	10
65–74 (n = 702)	185	27	256	19	338	33	103	13	441	46
75+ (n = 554)	111	23	256	43	286	51	81	15	367	66
Overall	462	55	682	79	860	96	284	38	1144	134

Table 2

Medical reasons for stoppage of medication in survey participants. Refused = declined to provide reason for stoppage.

Reason	Antiplatelet (n = 101/1144)	Anticoagulant (n = 27/134)
Colonoscopy	16	1
Knee/hip/foot/shoulder/arm surgery	12	4
Eye surgery	9	
Epidural or spine surgery	8	2
Heart or vascular surgery*	8	4
Colorectal surgery	5	1
Dental surgery	4	1
Cancer surgery	3	
Skin surgery	3	
Plastic surgery	1	
Other surgeries or indications*	24**	10***
Refused	9	4

* One subject was taken off antiplatelet medication for both leg and heart surgery.

** Most common "other" reasons include: cyst removal (4), biopsy (2), carpal tunnel surgery (2), throat surgery (2)

*** Most common "other" reasons include: leg surgery (3), carpal tunnel surgery (2)