Increased risk of stroke after discontinuation of acetylsalicylic acid

A UK primary care study

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ABSTRACT

Objectives: Discontinuation of low-dose acetylsalicylic acid (ASA) therapy may increase the risk of ischemic events. This study evaluated the risk of ischemic stroke (IS) and TIA after low-dose ASA discontinuation in patients with cardiovascular disease or cerebrovascular disease.

Methods: The Health Improvement Network UK primary care database was used to identify a cohort of individuals aged 50–84 years with a first prescription for low-dose ASA (75–300 mg/day) for the secondary prevention of cardiovascular or cerebrovascular events in 2000–2007 (n = 39,512). Individuals were followed up for a mean of 3.4 years to identify cases of IS/TIA. Nested case-control analyses were used to assess risk factors for IS/TIA, including low-dose ASA discontinuation.

Results: The overall incidence of IS/TIA was 5.0 per 1,000 person-years (95% confidence interval [CI] 4.6–5.4). IS/TIA was significantly more common in patients with a previous diagnosis of cerebrovascular disease (relative risk [RR] 2.79; 95% CI 2.05–3.80) or atrial fibrillation (RR 1.71; 95% CI 1.28–2.29) than in those without these conditions. Compared with current users of low-dose ASA, those who discontinued treatment 31–180 days before the index date had a significantly increased overall risk of IS/TIA (RR 1.40; 95% CI 1.03–1.92). The most common reason for discontinuation was patient nonadherence.

Conclusion: In patients prescribed low-dose ASA for the secondary prevention of cardiovascular or cerebrovascular events, discontinuation of low-dose ASA was associated with a 40% increase in the risk of IS/TIA compared with continuation of therapy.

Classification of evidence: This study provides Class III evidence that discontinuation of low-dose ASA is associated with a 40% increased risk of stroke within 31–180 days of discontinuation.
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GLOSSARY

ASA = acetylsalicylic acid; **BMI** = body mass index; **CI** = confidence interval; **IS** = ischemic stroke; **NSAID** = nonsteroidal anti-inflammatory drug; **PCP** = primary care physician; **RR** = relative risk; **THIN** = The Health Improvement Network.

The antiplatelet agent acetylsalicylic acid (ASA) significantly reduces the incidence of vascular disease, including stroke, in patients with atherosclerotic disease.[1] Evidence-based guidelines therefore recommend long-term use of low-dose ASA in all patients with cardiovascular disease, unless contraindicated.[2] Despite these recommendations, discontinuation of low-dose ASA therapy, due to patient nonadherence or physician concerns regarding safety, remains a problem. The reported rates of ASA discontinuation vary from less than 10% to almost 50%,[3,4] and data on long-term adherence are limited.

The greatest concern among physicians regarding long-term ASA therapy is the increased risk of bleeding and this has previously been the justification for discontinuation of therapy prior to elective surgical procedures. However, there is growing evidence that interrupting ASA therapy increases the risk of cardiovascular events. Several guidelines therefore recommend that

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ASA therapy should only be discontinued prior to surgery in patients who are using it for primary prevention or possibly in those who are at low risk of thrombosis but high risk of intraoperative bleeding.[5-7] Low-dose ASA discontinuation has been reported to increase the risk of mortality[8] and ischemic cerebrovascular and coronary events.[9,10] Pharmacoepidemiologic studies quantifying the increased risk of myocardial infarction and stroke after discontinuation of low-dose ASA are merited but, to date, have been limited.

The aim of the present study was to evaluate the effect of low-dose ASA discontinuation on the risk of ischemic stroke (IS) or TIA in patients with a history of cardiovascular or cerebrovascular disease in UK primary care. The reasons for ASA discontinuation and risk factors for IS/TIA were also investigated.

METHODS

Data source. The Health Improvement Network (THIN) is a computerized medical research database that contains systematically recorded and anonymized data on over 3 million patients who are currently registered with participating primary care practices. Patients included in the database are representative of the entire UK population with respect to age, sex, and geographic region.[11] The information collated and organized by THIN includes patient demographics and lifestyle factors (e.g., alcohol use, body mass index [BMI], and smoking status), and details of consultations with primary care physicians (PCPs), referrals, hospitalizations, laboratory test results, diagnoses, and prescriptions ordered by the PCPs. Diagnoses are recorded using Read codes.[12,13] Prescriptions issued by PCPs are recorded automatically in the database; drugs are coded using the Multilex classification.[14] The validity of THIN for pharmacoepidemiologic research has been demonstrated.[15]

Study design. The source population included all individuals who were aged 50–84 years during January 1, 2000, to December 31, 2007, who had been enrolled with their PCP for at least 2 years and who had a computerized prescription history of at least 1 year. Patients who had received at least 1 prescription for low-dose ASA (75–300 mg/day) for the secondary prevention of cardiovascular or cerebrovascular events were then identified for inclusion in the study cohort. Individuals were retained in the study cohort if this was their first ever recorded low-dose ASA prescription and they had no diagnosis of cancer, alcohol abuse, or alcohol-related disease. Individuals aged ≥70 years who had a follow-up longer than 1 year, but less than 2 recorded consultations with a PCP during their entire follow-up (n = 170), were excluded as a proxy for incomplete data recording.

The final study cohort comprised 39,512 patients followed for an average of 3.42 years.

Standard protocol approvals, registrations, and patient consents. Ethical approval for the study was obtained from the Research Ethics Committee (NHS) (REC reference number: 08/H0305/49).

Case ascertainment. All individuals in the study cohort were followed up from 1 day after the start date (defined as the date of first low-dose ASA prescription) until the earliest of the following endpoints: recorded diagnosis of IS/TIA, recorded diagnosis of an exclusion factor, death, reaching the age of 85 years, or the end of the study period (December 31, 2007). Patient profiles were manually reviewed by 2 of the authors (L.A.G.R. and L.C.S.) when there was a computer-recorded entry of IS, TIA, or death due to a cerebrovascular event during the follow-up period. On reviewing these profiles, patients were excluded if they had an IS or TIA but were not admitted to hospital (this includes patients admitted to an emergency department and discharged on the same day); were admitted to hospital for any reason other than cerebrovascular disease in the month before the index date; were admitted to hospital for a non-cerebrovascular disease and developed an episode of IS or TIA during hospitalization; or experienced a hemorrhagic cerebrovascular event. The case definition was restricted to IS/TIAs requiring hospital admission in order to improve the validity of the study. Ischemic cerebrovascular events that do not require hospitalization have lower diagnostic value than those that do require hospitalization, which results in greater misclassification.

During the study period, 6,007 patients had a computer-recorded code of IS/TIA, and death was recorded for 2,663 additional patients (figure 1). The case ascertainment and validation process resulted in a final case group of 673 individuals with IS/TIA (nonfatal IS, n = 417; fatal IS, n = 111; TIA, n = 145).

Selection of controls. A total of 5,000 age-, sex-, and calendar year–matched controls were sampled from the same study cohort of 39,512 patients. This was done by generating at random a date encompassed within the study period for each member of the study population. If the random date for a study member was included in his or her eligible person-time (follow-up period), we marked that person as an eligible control and the random date was used as his or her index date.

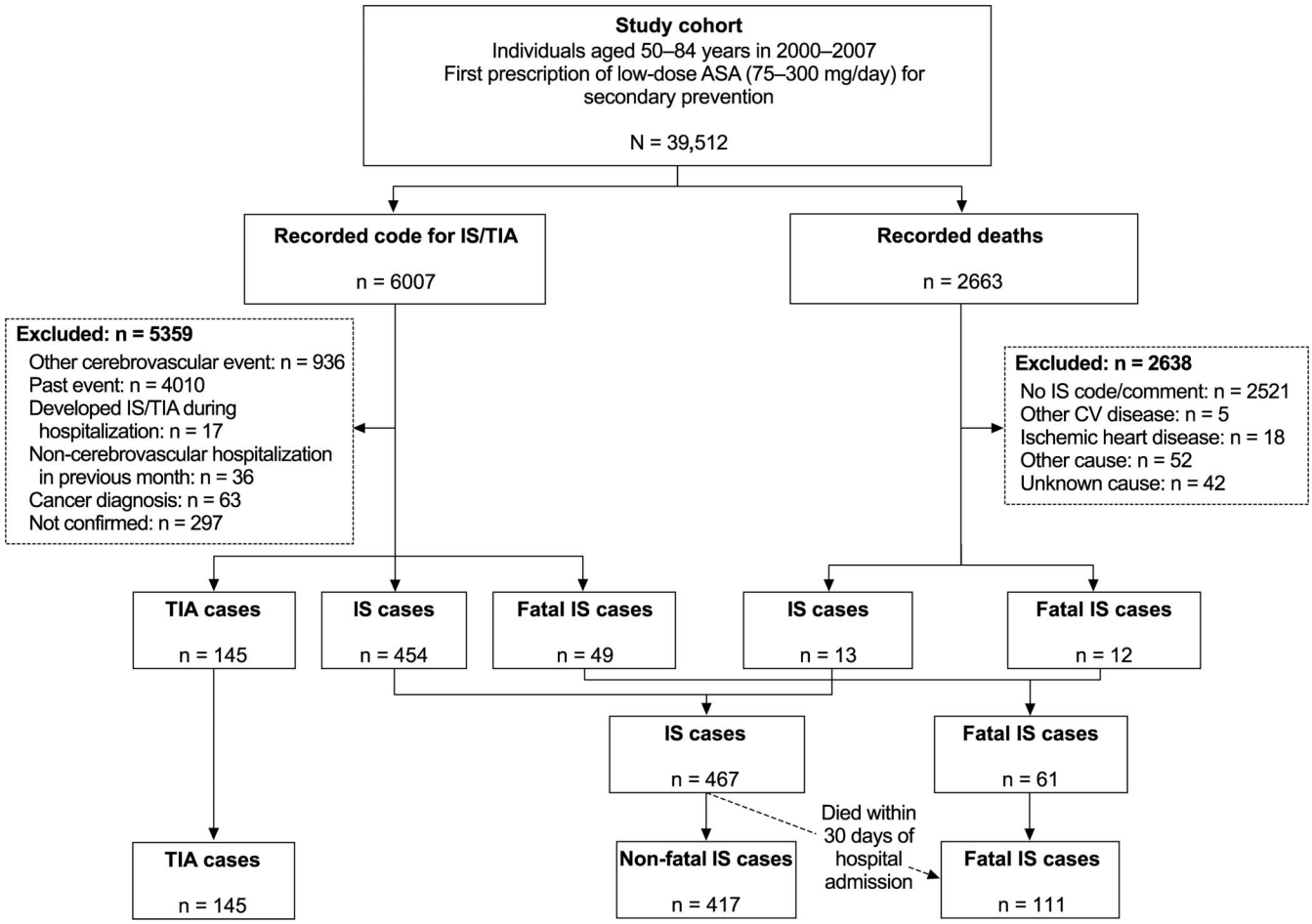
Analysis. The incidence of IS/TIA was calculated and a nested case-control analysis was performed to assess potential risk factors for IS/TIA. Relative risks (RR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis adjusted for known risk factors. All potential confounders were treated as categorical variables and a separate level was created for variables with missing information.

Assessment of risk factors. Data on the number of PCP visits, referrals, and hospitalizations were collected from the database for the year before the index date. Data on comorbidity were collected for any time before the start date and data on lifestyle factors were collected for any time prior to the index date. Data on drug exposure were collected for the period between the start date and the index date.

Drug use was classified into 4 categories: current use when the supply of the most recent prescription lasted until the index date or ended in the 6 days before the index date; recent use when the supply of the most recent prescription ended 7–90 days before the index date; past use when the most recent prescription ended 91–365 days before the index date; and nonuse when there was no recorded prescription of the relevant medication in the 365 days before the index date.

Assessment of low-dose ASA discontinuation. Discontinuation of ASA was defined as follows. Current users were defined as individuals on low-dose ASA treatment at the index date. ASA discontinuers were defined as individuals with a pe-

Figure 1 Study design and case ascertainment



ASA = acetylsalicylic acid; CV = cardiovascular; IS = ischemic stroke.

riod of >30 days after the end of their last low-dose ASA prescription (assuming complete adherence) with no prescription refill during this time. Discontinuers were then categorized into 2 mutually exclusive groups: recent discontinuers whose most recent low-dose ASA prescription ended 31–180 days before the index date and past discontinuers whose supply ended 181–365 days before the index date. To assess the effect of the definition of discontinuation, additional analyses were performed to estimate the risk of IS/TIA in individuals with a period of 1–15 days after the end of their last low-dose ASA prescription (assuming complete adherence) with no prescription refill during this time.

Reasons for discontinuation of ASA therapy were examined and classified into one of the following 4 groups: treatment change, defined as physician-initiated switching from low-dose ASA to another antiplatelet drug or to an oral anticoagulant with no evidence to suggest an adverse event; safety concerns, defined as evidence of adverse events related to low-dose ASA (such as upper gastrointestinal disorders and upper gastrointestinal bleeding), evidence of intolerance to low-dose ASA (allergy/urticaria), initiation of gastroprotective medication use, or planned surgery; use of over-the-counter ASA, reported when the PCP specified that patients were receiving low-dose ASA but that there was no recorded prescription, or when the PCP noted that patients were receiving over-the-counter ASA; or nonadherence, defined as discontinuation in the absence of any of the above factors.

RESULTS

Incidence of IS/TIA. The overall incidence of IS/TIA was 5.0 per 1,000 person-years (95% CI 4.6–5.4). Among women, the incidence was 5.5 per 1,000 person-years (95% CI 4.9–6.1), while in men the incidence was 4.6 per 1,000 person-years (95% CI 4.2–5.1). Among patients taking low-dose ASA for the secondary prevention of cerebrovascular disease, the incidence of recurrent IS/TIA was 8.6 (95% CI 7.7–9.6).

Risk factors for IS/TIA. Lifestyle risk factors for IS/TIA in patients receiving low-dose ASA for secondary prevention of cardiovascular or cerebrovascular disease are presented in table 1.

A diagnosis of IS/TIA was significantly more common in patients with a prior diagnosis of cerebrovascular disease, atrial fibrillation, heart failure, or complicated peptic ulcer disease than in individuals without the respective diagnosis (table 2). The presence of myocardial infarction, angina, ischemic heart disease, hypertension, chronic obstructive pulmonary disease, diabetes, or uncomplicated peptic ulcer disease at the start date was

Table 1 Prevalence of lifestyle characteristics in individuals with IS/TIA and controls with no IS/TIA and their association with a diagnosis of IS/TIA in a cohort of low-dose ASA users

	Controls with no IS/TIA (n = 5,000), n (%)	IS/TIA cases (n = 673), n (%)	RR[a] (95% CI)
Smoking			
Never	2,236 (44.7)	291 (43.2)	1.00 (—)
Current	610 (12.2)	124 (18.4)	1.51 (1.18–1.95)
Former	2,016 (40.3)	236 (35.1)	1.00 (0.82–1.22)
Unknown	138 (2.8)	22 (3.3)	0.84 (0.51–1.38)
BMI, kg/m^2			
15–19	158 (3.2)	38 (5.6)	1.61 (1.06–2.46)
20–24	1,225 (24.5)	157 (23.3)	1.00 (—)
25–29	1,943 (38.9)	251 (37.3)	1.04 (0.83–1.30)
30–59	1,192 (23.8)	131 (19.5)	0.94 (0.72–1.23)
Unknown	482 (9.6)	96 (14.3)	1.37 (1.00–1.86)
PCP visits[b]			
≤4	432 (8.6)	46 (6.8)	1.00 (—)
5–9	1,325 (26.5)	143 (21.2)	1.14 (0.79–1.64)
10–19	2,136 (42.7)	285 (42.3)	1.46 (1.03–2.08)
≥20	1,107 (22.1)	199 (29.6)	2.03 (1.39–2.96)
Referrals[b]			
0–1	2,350 (47.0)	213 (31.6)	1.00 (—)
2–4	1,555 (31.1)	228 (33.9)	1.64 (1.33–2.02)
5–9	795 (15.9)	157 (23.3)	2.21 (1.73–2.82)
≥10	300 (6.0)	75 (11.1)	2.54 (1.84–3.51)
Hospitalizations[b]			
0	4,059 (81.2)	434 (64.5)	1.00 (—)
1–2	795 (15.9)	188 (27.9)	2.00 (1.63–2.45)
≥3	146 (2.9)	51 (7.6)	2.79 (1.93–4.03)

Abbreviations: ASA = acetylsalicylic acid; BMI = body mass index; CI = confidence interval; IS = ischemic stroke; PCP = primary care physician; RR = relative risk.
[a] Adjusted for age, sex, calendar year, time to event, smoking, ischemic heart disease (at start date), cardiovascular disease (at start date), diabetes (at start date), chronic obstructive pulmonary disease (at start date), atrial fibrillation (at start date), and use of clopidogrel, statins, anticoagulants, nitrates, antihypertensives, oral steroids, nonsteroidal anti-inflammatory drugs, and ASA.
[b] In the year prior to the index date.

not significantly associated with the risk of IS/TIA.

Comedications, including antihypertensives, clopidogrel, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), and warfarin, were not significantly associated with the risk of IS/TIA. For example, the RR of IS/TIA associated with NSAIDs was 1.27 (95% CI 0.95–1.71) and the RR of IS/TIA was 0.65 (95% CI 0.39–1.10) with warfarin use. When cases and controls were stratified by the presence of atrial fibrillation, current warfarin use was associated with a nonsignificant decrease in the risk of IS/TIA in those with atrial fibrillation (RR 0.62; 95% CI 0.28–1.39) but with a nonsignificant increase in the risk of IS/TIA in those without atrial fibrillation (RR 1.68; 95% CI 0.80–3.56).

The risk factors for IS/TIA were similar in the subgroup of patients receiving low-dose ASA therapy for the secondary prevention of cerebrovascular disease. Among these patients, a prior diagnosis of atrial fibrillation was associated with a significantly increased risk of IS/TIA (RR 2.37; 95% CI 1.49–3.75). In addition, the incidence of IS/TIA was significantly higher in current users of cyclooxygenase-2-specific NSAIDs (coxibs) compared with those not receiving these drugs (RR 3.35; 95% CI 1.04–10.87). There was no significant association between the use of traditional NSAIDs and the risk of IS/TIA (RR 0.99; 95% CI 0.59–1.65). In patients receiving low-dose ASA for cerebrovascular disease, current use of warfarin was associated with a significant decrease in the risk of IS/TIA (RR 0.18; 95% CI 0.06–0.50). Due to the small size of this subgroup, it was not possible to stratify this analysis by the presence of atrial fibrillation.

Discontinuation of low-dose ASA. Of the 673 patients who had a diagnosis of IS/TIA, 480 (71.3%) were receiving low-dose ASA on the day of the event, 67 (10.0%) were recent discontinuers, and 29 (4.3%) were past discontinuers (figure 2). In the control group, 76.0% of patients were current low-dose ASA users, 7.5% were recent discontinuers, and 3.7% were past discontinuers.

Risk of IS/TIA after discontinuation of ASA therapy. Recent discontinuers had a significantly increased risk of IS/TIA compared with current low-dose ASA users (RR 1.40; 95% CI 1.03–1.92). The increase in the risk of IS/TIA was higher when discontinuation was defined as a period of 1–15 days after the end of the last low-dose ASA prescription with no prescription refill during this time (RR 1.97; 95% CI 1.24–3.12). However, this risk estimate is less precise because of the smaller sample size. There was a trend toward an increased risk of IS/TIA in patients who were past discontinuers compared with patients who continued ASA therapy, but this did not reach significance (RR 1.25; 95% CI 0.81–1.93).

The RR for IS/TIA in recent discontinuers was similar in the subgroups of patients receiving different doses of ASA and those receiving ASA therapy for different treatment durations (table 3).

Patient nonadherence was the most common reason for discontinuation of ASA therapy (table 3), followed by physician-initiated treatment change. When recent discontinuers were stratified according to their reason for discontinuation, the increased risk of IS/TIA was only significant in those classified as nonadherent (RR 1.46; 95% CI 1.03–2.07). Patients

Table 2 Prevalence of comorbidities in individuals with IS/TIA and controls with no IS/TIA and their association with a diagnosis of IS/TIA in a cohort of low-dose ASA users

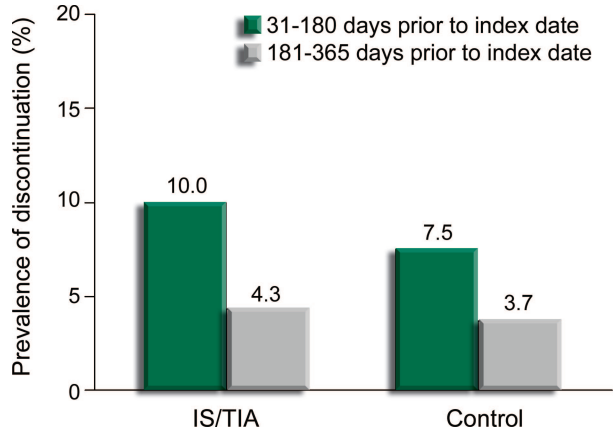
	Controls with no IS/TIA (n = 5,000), n (%)	IS/TIA cases (n = 673), n (%)	RR[a] (95% CI)
Cerebrovascular disease	1,178 (23.6)	365 (54.2)	2.79 (2.05–3.80)
Atrial fibrillation	422 (8.4)	92 (13.7)	1.71 (1.28–2.29)
Heart failure	448 (9.0)	72 (10.7)	1.41 (1.05–1.89)
Hypercholesterolemia	1,081 (21.6)	106 (15.8)	0.80 (0.63–1.01)
Hypertension	2,615 (52.3)	364 (54.1)	1.01 (0.84–1.22)
Myocardial infarction	1,336 (26.7)	137 (20.4)	1.08 (0.85–1.37)
Angina	2,140 (42.8)	166 (24.7)	0.75 (0.60–0.94)
Ischemic heart disease	4,054 (81.1)	367 (54.5)	0.73 (0.53–1.01)
COPD	278 (5.6)	40 (5.9)	0.94 (0.65–1.37)
Diabetes	652 (13.0)	89 (13.2)	1.05 (0.82–1.36)
Anemia	315 (6.3)	58 (8.6)	1.37 (1.00–1.88)
Dyspepsia/gastritis	1,145 (22.9)	138 (20.5)	0.91 (0.74–1.13)
Uncomplicated peptic ulcer disease	216 (4.3)	32 (4.8)	1.15 (0.76–1.72)
Complicated peptic ulcer disease	99 (2.0)	27 (4.0)	1.89 (1.18–3.04)

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; COPD = chronic obstructive pulmonary disease; IS = ischemic stroke; RR = relative risk.
[a] Adjusted for age, sex, calendar year, time to event, smoking, ischemic heart disease (at start date), cardiovascular disease (at start date), diabetes (at start date), COPD (at start date), atrial fibrillation (at start date), and use of clopidogrel, statins, anticoagulants, nitrates, antihypertensives, oral steroids, nonsteroidal anti-inflammatory drugs, and ASA.

who were classified as discontinuers but who were actually taking over-the-counter low-dose ASA were not at increased risk of IS/TIA (RR 0.96; 95% CI 0.28–3.22).

In the subgroup of patients prescribed ASA therapy for cerebrovascular diseases, there was a trend toward an increased risk of IS/TIA in recent discontinuers compared with patients who continued ASA therapy (RR 1.37; 95% CI 0.82–2.31).

Figure 2 Prevalence of low-dose ASA discontinuation in patients diagnosed with IS/TIA and the control group



IS = ischemic stroke.

DISCUSSION This large primary care study showed that among patients prescribed low-dose ASA therapy for the secondary prevention of cardiovascular events, recent discontinuation of the ASA therapy was associated with a significant, 40% increase in the risk of IS/TIA. This is consistent with the reported timing of rebound platelet activity in experimental studies.[16]

The rate of discontinuation of ASA therapy was approximately 14% in patients diagnosed with IS/TIA and approximately 11% in the control group. These rates of ASA discontinuation are similar to those documented in the literature, although not as high as reported in some studies.[3]

The most frequently recorded reason for discontinuing ASA therapy was patient nonadherence. This is in contrast to a previous hospital-based study that reported physicians' safety concerns prior to surgery as the most common reason for discontinuation of ASA therapy,[17] but in agreement with the findings from a more recent systematic review.[18] Patient nonadherence may be due to adverse effects (not discussed with PCP and therefore not recorded as safety concerns), forgetfulness, or lack of perceived therapeutic benefit.

Other risk factors for IS/TIA were smoking, as expected from the wealth of published data on the adverse cardiovascular effects of smoking,[19] and a low BMI. Previous studies have found an inconsistent relationship between BMI and the risk of stroke. In a recent prospective observational study of patients with, or at risk of, atherothrombotic disease, individuals with a low BMI had a higher frequency of adverse cardiovascular outcomes and bleeding complications than those with a high BMI.[20] However, other studies have found that a high BMI is associated with an increased risk of stroke[21] and a greater risk of all-cause and cardiovascular death after stroke[22] compared with a normal BMI.

There is some evidence showing that coxibs increase the risk of stroke.[23] Some studies have also found use of traditional NSAIDs to be associated with an increased risk of stroke.[24] Overall, we found a nonsignificant increase in the risk of IS/TIA among users of traditional NSAIDs or coxibs. However, in the subgroup of patients who were receiving low-dose ASA for cerebrovascular disease, we observed a significantly increased risk of IS/TIA with coxibs but not with traditional NSAIDs.

The considerable reduction in the risk of IS/TIA associated with concomitant warfarin treatment among those prescribed ASA for cerebrovascular dis-

Table 3 Risk of IS/TIA in recent discontinuers of low-dose ASA therapy compared with current users of ASA according to treatment duration, dose, and reason for ASA discontinuation

	Controls with no IS/TIA (n = 5,000), n (%)	IS/TIA cases (n = 673), n (%)	RR[a] (95% CI)
Current users	3,799 (76.0)	480 (71.3)	1.00 (—)
Recent discontinuers	373 (7.5)	67 (10.0)	1.40 (1.03–1.92)
Treatment duration			
≤1 y	320 (6.4)	56 (8.3)	1.34 (0.96–1.87)
≤30 d	68 (1.4)	15 (2.2)	1.36 (0.73–2.52)
31–365 d	252 (5.0)	41 (6.1)	1.34 (0.92–1.96)
>1 y	53 (1.1)	11 (1.6)	1.84 (0.91–3.70)
Daily dose, mg			
75	332 (6.6)	59 (8.8)	1.39 (1.00–1.92)
>75	41 (0.8)	8 (1.2)	1.47 (0.63–3.43)
Reasons for discontinuation			
Nonadherence	270 (5.4)	52 (7.7)	1.46 (1.03–2.07)
Treatment change	42 (0.8)	10 (1.5)	2.15 (0.95–4.85)
Safety concerns	27 (0.5)	2 (0.3)	0.49 (0.10–2.27)
OTC low-dose ASA use	34 (0.7)	3 (0.4)	0.96 (0.28–3.22)

Abbreviations: ASA = acetylsalicylic acid; CI = confidence interval; IS = ischemic stroke; OTC = over the counter; RR = relative risk.
[a] Adjusted for age, sex, calendar year, time to event, smoking, ischemic heart disease (at start date), diabetes (at start date), chronic obstructive pulmonary disease (at start date), atrial fibrillation (at start date), and use of clopidogrel, statins, anticoagulants, nitrates, antihypertensives, oral steroids, nonsteroidal anti-inflammatory drugs, and ASA.

ease was expected given the proven efficacy of oral anticoagulants in preventing stroke,[25,26] particularly in those with atrial fibrillation.[25,27]

A potential limitation of this study is the use of prescribed therapy to define exposure and the lack of systematic recording of over-the-counter ASA, although most use of ASA in elderly patients in the United Kingdom is prescription-based.[28] In addition, there may have been incomplete recording of the reasons for discontinuation of therapy by the physician. However, the finding that the risk of IS/TIA in patients who were considered to be recent ASA discontinuers but who in fact were taking over-the-counter ASA was similar to the risk in those who continued to be prescribed low-dose ASA therapy (RR 0.96; CI 0.28–3.22) supports the validity of our definition of discontinuation. Also, this study offers the important advantages of a large sample size, a long follow-up period, and a study cohort taken from THIN, which is known to be representative of the entire UK population and therefore increases the external validity of the results.[11,15]

This study highlights the need for greater awareness of the increased risk of cardiovascular events, such as stroke, associated with interruption of ASA therapy and the need for improved adherence to the relevant clinical practice guidelines.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Luis A. García Rodríguez and Lucía Cea Soriano.

DISCLOSURE

Dr. García Rodríguez works for CEIFE, which has received research funding from AstraZeneca R&D, Mölndal, and has received honoraria from serving on a scientific advisory board for AstraZeneca. L. Cea Soriano works for CEIFE, which has received research funding from AstraZeneca R&D, Mölndal. Dr. Hill is an employee of Oxford PharmaGenesis™ Ltd., which has received project funding from AstraZeneca R&D, Mölndal. Dr. Johansson is an employee of and holds stock/stock options in AstraZeneca R&D, Mölndal.

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