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ORIGINAL RESEARCH ARTICLE

Low-Dose Aspirin Discontinuation and Risk of Cardiovascular Events

A Swedish Nationwide, Population-Based Cohort Study

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Abstract

Background: There are increasing concerns about risks associated with aspirin discontinuation in the absence of major surgery or bleeding. We investigated whether long-term low-dose aspirin discontinuation and treatment gaps increase the risk of cardiovascular events.

Methods: We performed a cohort study of 601527 users of low-dose aspirin for primary or secondary prevention in the Swedish prescription register between 2005 and 2009 who were >40 years of age, were free from previous cancer, and had ≥80% adherence during the first observed year of treatment. Cardiovascular events were identified with the Swedish inpatient and cause-of-death registers. The first 3 months after a major bleeding or surgical procedure were excluded from the time at risk.

Results: During a median of 3.0 years of follow-up, 62690 cardiovascular events occurred. Patients who discontinued aspirin had a higher rate of cardiovascular events than those who continued (multivariable-adjusted hazard ratio, 1.37; 95% confidence interval, 1.34–1.41), corresponding to an additional cardiovascular event observed per year in 1 of every 74 patients who discontinue aspirin. The risk increased shortly after discontinuation and did not appear to diminish over time.

Conclusions: In long-term users, discontinuation of low-dose aspirin in the absence of major surgery or bleeding was associated with a >30% increased risk of cardiovascular events. Adherence to low-dose aspirin treatment in the absence of major surgery or bleeding is likely an important treatment goal.

aspirin **cohort studies** **primary prevention** **secondary prevention**

Introduction

Clinical Perspective

What Is New?

- Discontinuing long-term low-dose aspirin treatment in the absence of major surgery or bleeding may be hazardous.
- We investigated that question among 601527 users of low-dose aspirin for primary or secondary prevention identified in the Swedish drug prescription register.
- Patients who discontinued aspirin had a 37% higher rate of cardiovascular events than those who continued, corresponding to an additional cardiovascular event observed per year in 1 of every 74 patients who discontinue aspirin.
- The risk increased shortly after discontinuation and did not appear to diminish over time.

What Are the Clinical Implications?

- Adherence to low-dose aspirin treatment in the absence of major surgery or bleeding is likely an important treatment goal.
- Millions of patients worldwide take aspirin on a daily basis and might consider stopping at some time during their lives.
- This article may help physicians and patients to make an informed decision on whether to stop aspirin use.

Low-dose aspirin has strong evidence for use in the secondary prevention of cardiovascular disease and is uniformly recommended in guidelines.[1–3] Its utility in primary prevention is under investigation.[4–6] In patients with a recent myocardial infarction, 10% to 20% have been reported to discontinue aspirin use during the first 1[7–9] to 3[10] years after the infarction. In broader patient settings, discontinuation rates of up to 30% have been reported, and poor aspirin compliance has been noted in up to 50%.[11] The public health effects of discontinuing long-term aspirin treatment may be substantial but are not well known.

Discontinuation of secondary prevention with aspirin has been associated with higher risk of cardiovascular events in some studies,[12,13] with indications of an increased risk shortly after discontinuation.[14–18] Aspirin is often withdrawn because of surgery[14–17,19] or bleeding,[14,18] factors that per se may stimulate platelet aggregation and increase the risk of cardiovascular events. Effects of discontinuation in settings other than surgery or bleeding are unknown.

Aspirin can be bought over the counter in many countries, and previous studies have typically relied on self-reported use data. Registers with complete coverage in a country where low-dose aspirin is available only by prescription have a unique potential to shed light on the issue.

We hypothesized that patients with aspirin treatment gaps and those who discontinue long-term aspirin treatment in the absence of major surgery or bleeding are at higher risk of cardiovascular events than adherent patients without treatment gaps. We aimed to investigate the associations of aspirin treatment persistence patterns and aspirin discontinuation with risk of cardiovascular events using a large nationwide cohort of patients on long-term low-dose aspirin therapy for primary and secondary prevention.

Methods

Study Sample

Using the unique civil registration number allocated to all Swedish citizens, we linked the mandatory nationwide Swedish prescribed drug register with the mandatory inpatient and cause-of-death registers with the help of the Swedish National Board of Health and Welfare. In Sweden, low-dose aspirin cannot be purchased over the

counter without a prescription.

For this study, we considered all individuals >40 years of age who had collected prescribed aspirin during the study period between July 1, 2005, and December 31, 2009, as identified in the prescribed drug register by the detection of an aspirin dispense of 75 to 160 mg. We also included aspirin 75 to 160 mg dispensed as part of pharmacy-prepacked multidose prescriptions used for patients unable to safely self-administer their medication. Aspirin tablet strengths other than 75 or 160 mg are not available for prevention of cardiovascular events in Sweden; neither is carbasalate calcium (B01AC08). We considered all 889655 aspirin-treated patients who were free from previous cancer (*International Classification of Diseases, 10th Revision* codes C00–C99) at baseline. We were interested in treatment breaks and permanent discontinuation after a stable (1-year) period of continuous aspirin treatment. Therefore, we excluded 207180 patients who had <292 defined daily doses of aspirin dispensed during the first year after their first aspirin prescription (which equals 1 year of aspirin treatment with ≥80% adherence, or medication possession ratio, which is commonly viewed as adequate[20]). We also excluded 80621 patients who had a cardiovascular event (because our research question involved long-term use) or died during this first year of aspirin treatment, as well as 327 patients without any exposure time after the first year, rendering a final study sample of 601527 long-term low-dose aspirin users who entered the follow-up phase.

To study treatment patterns in aspirin-naïve patients, we also studied a sample of 227135 patients who collected their first low-dose aspirin dispense at least 1 year after the start of the study period. This subsample was not subjected to the 1-year definition of long-term users and was not used in any statistical modeling.

In a second set of analyses, the timing of cardiovascular events in people who discontinued aspirin was investigated. We defined inclusion criteria on the dispense level and defined a timely dispense as one that was collected between 0 and 10 days before the end of the previous timely dispense, and it had to be the last in a chain of 4 consecutive timely dispenses (typically equal to 1 year of treatment, chosen to balance strictness of the inclusion criteria with statistical power). This strict definition, although rendering a small sample of patients with presumed high adherence, was used to determine the time of discontinuation as precisely as possible and to avoid periods of accumulated medication during and after which drug use status is more uncertain. This sample included the 38736 patients who had 4 consecutive timely dispenses.

The construction of the samples is displayed in **Figure 1**.

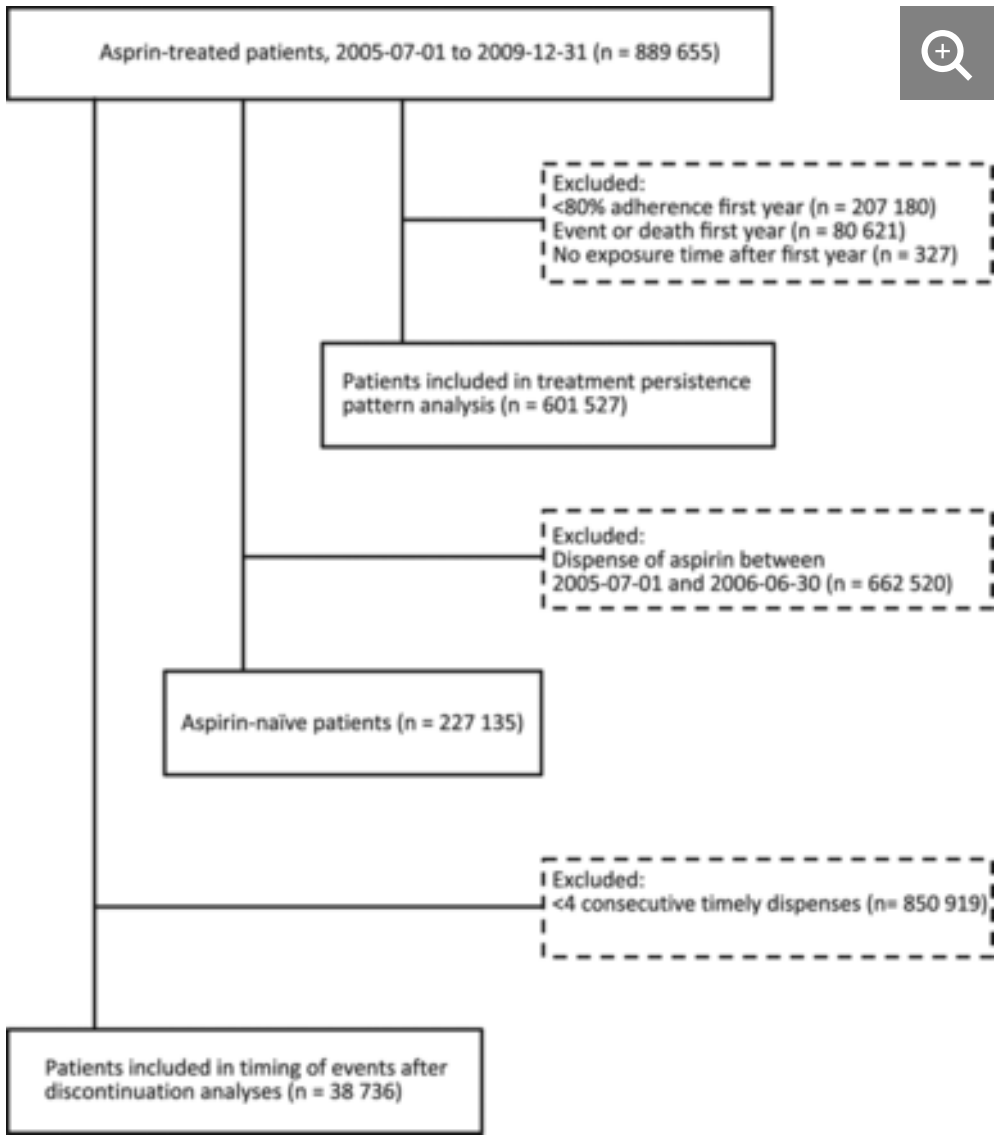

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Figure 1.

Flowchart for construction of the study samples.

Ethics approval was obtained from the Ethics Review Board in Uppsala, Sweden. No informed consent was required.

Clinical Characteristics

All definitions are described in **Table I in the online-only Data Supplement**. Age, sex, and diabetes mellitus were determined at the inclusion date—that is, the first day of the first stable 1-year period of continuous aspirin treatment. Use of nonsteroidal anti-inflammatory drugs, oral steroids, and antiplatelet (other than aspirin) or oral anticoagulant drugs was defined as the fraction of an aspirin treatment period covered by the respective drug and was time updated during follow-up. Concomitant cardiovascular disease was defined as a prior hospitalization for myocardial infarction (*International Classification of Diseases, 10th Revision* codes I21 and I22) or stroke (*International Classification of Diseases, 10th Revision* codes I63 and I64). Patients with concomitant cardiovascular disease were defined as users of aspirin for secondary prevention. Patients without concomitant cardiovascular were presumed to use their aspirin for primary prevention. Major bleeding was defined as a hospital admission caused by gastrointestinal bleeding, intracranial bleeding, hemopericardium, postoperative bleeding, bleeding from venous varices, bleeding events in the respiratory system, hematuria, and other signs of blood loss. We determined the occurrence of surgery as all surgical procedures except small diagnostic procedures such as gastroscopy and coronary angiography.

Exposures

We investigated 2 sets of exposures. In the first set of comparisons, we constructed groups based on time-updated aspirin treatment persistence patterns. In the second set, we constructed groups that were on aspirin versus those that had just discontinued aspirin treatment. For both exposures, time spent in the hospital for diagnoses other than the outcome was added to the time at risk for the particular exposure group at the time of admission because patients are provided all in-hospital medications free of charge and hence do not use their dispensed prescribed medications during hospitalization. We were well equipped to study persistence (staying on a drug long term or discontinuing) but not adherence (taking the prescribed number of pills).

Aspirin Treatment Persistence Patterns

To record time on aspirin and off aspirin as accurately as possible, accounting for the fact that the exact time of discontinuation is uncertain, we constructed 4 time-updated aspirin persistence groups, between which patients could move freely over time during follow-up:

1. On aspirin: the nominal duration of each aspirin dispense.

2. Accumulated period: the time after the nominal duration of each aspirin dispense when the patient has tablets left over from previous dispenses in a consecutively dispensed period.

3. Grace period: from the end of the accumulated period plus 25% of the total duration on aspirin in the last consecutively dispensed period plus 20 days. This corresponds to 80% adherence with up to a week's gap between dispenses.

4. Off aspirin: from the end of the grace period.

Although the hypothesis is answered with the use of groups 1 and 4, the other 2 groups are included for transparency. Persistence patterns were described for both aspirin-naïve patients and long-term aspirin users.

Timing of Events After Aspirin Discontinuation

For this set of analyses, we sought to determine the risk of cardiovascular events in relation to the time of the aspirin discontinuation among patients who collected their dispenses in a timely manner (as defined above). We compared patients who collected a timely fifth dispense with patients who did not after a series of 4 timely dispenses. A patient could contribute several times at risk to these analyses.

Follow-Up and Outcomes

Outcomes were defined with the Swedish inpatient and cause-of-death registers, which include all hospitalizations and deaths, respectively, classified with the *International Classification of Diseases* (codes in **Table I in the online-only Data Supplement**). The outcome investigated was a first incidence of cardiovascular disease after the start of follow-up, defined as a hospitalization for myocardial infarction, stroke, or cardiovascular death. Only the primary diagnoses in the discharge letter or death certificates were used for classification of the outcome. The accuracy in the Swedish registers is high for the diagnoses examined in this study (positive predictive values, 98%–100% for myocardial infarction and 69%–98% for stroke).[21]

Because there may be a risk of reverse causation (aspirin withdrawn from people about to die), we also investigated a secondary nonfatal cardiovascular events outcome similar to the primary outcome but without cardiovascular death. A similar bias may arise if patients discontinue aspirin because they start using an oral

anticoagulant as a result of change to a higher risk stratum; we therefore also investigated models censoring participants at the time of start of oral anticoagulant treatment.

Follow-up started after 1 year of aspirin treatment with high adherence, as defined above. Patients were followed up until the first instance of the cardiovascular outcome, a new diagnosis of cancer, noncardiovascular death, or the end of follow-up on December 31, 2009. In the timing of events after aspirin discontinuation analyses, patients were also censored after 100 days because that is the maximum duration of the fifth dispense. Patients were followed up from the day after dispense (or start of a gap) until a cardiovascular disease event or censoring, whichever came first.

Major bleeding and surgical procedures may affect thrombogenicity, cause aspirin discontinuation, and be related to cardiovascular disease incidence for an unknown duration of time that we assumed to be less than a few months. Therefore, in this study, a major bleeding or a surgical procedure during the study incurred a 3-month refractory period from the time at risk, during which person-time was not counted and outcomes were not considered.

Statistical Analysis

Baseline characteristics were presented per patient as observed numbers (percentages) for categorical variables and as means (SDs) for continuous variables. Absolute risks of events were illustrated with Nelson-Aalen cumulative incidence plots, which were also used to assess proportionality of hazards.

Cox proportional hazards models were used to investigate associations of the 4 aspirin persistence groups with risk of cardiovascular events. Models for minimizing bias were identified with directed acyclic graphs (**Figure I in the online-only Data Supplement**).[22] All models were adjusted for age, sex, previous cardiovascular disease, diabetes mellitus, antiplatelet or oral anticoagulant drugs, nonsteroidal anti-inflammatory drugs, and oral steroids. Interactions in the form of deviation from multiplicativity were investigated between the aspirin persistence groups and age, sex, prior cardiovascular disease, diabetes mellitus, nonsteroidal anti-inflammatory drugs, oral steroids, other antiplatelet or oral anticoagulant drugs, aspirin-naïve/non-naïve, previous major bleeding, and pharmacy-prepacked multidose dispenses. Because of potential interaction signals, the main analyses were also performed in subgroups with and without prior cardiovascular disease.

For the timing of events after aspirin discontinuation analysis to which patients could contribute >1 observation period, a model with shared frailty for participant identity was used. Because we assumed a priori that the hazard function associated with aspirin discontinuation may initially be nonmonotonic and because we wanted to compute time quantiles, we investigated parametric regression models with exponential, Gompertz, Weibull, log logistic, and log normal parameterizations. The log normal distribution had the highest log likelihood and lowest Akaike information criterion and was used, with results displayed graphically and presented in the accelerated failure time metric. This analysis was adjusted for the same covariates as the Cox models, and the same set of covariates was time updated at each dispense.

Because this study used only official registers mandatory for all citizens, we assumed that no data were missing. The data were managed and analyzed at both an independent statistical contract company (Statisticon) and Uppsala University, and all authors had full access to the data. The statistical packages R version 3.0.1 and Stata version 14 were used.

Results

Clinical characteristics of the aspirin treatment persistence groups are displayed in **Table 1**. Notably, half of the sample were female, the mean age was 73 years, 16% had diabetes mellitus, and half of the sample were on long-term aspirin treatment without having had a prior hospitalization for cardiovascular disease. During a median of 3.0 years of follow-up (range, 0.002–3.5 years), corresponding to 1491369 person-years at risk, 62690 cardiovascular events occurred (incidence rate, 42.0 per 1000 person-years at risk; separate outcomes presented in **Table II in the online-only Data Supplement**). A total of 73636 people died during this time; 19978 person-years were excluded from the analyses because of surgical procedures and major bleeding events as defined above.

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Table 1.

Clinical Characteristics by Aspirin Persistence Patterns

Treatment patterns are displayed in **Figure 2** and **Figure II in the online-only Data Supplement**. Among the long-term low-dose aspirin users (**Figure 2**), persistence gradually but slowly tapered off; 3 years after inclusion, 3 of 4 patients collected their aspirin dispenses before the expiration of the previous dispense, and 4 of 5 had access to accumulated aspirin. Approximately 15% were off long-term aspirin treatment after 3 years. Among the 227135 aspirin-naïve patients, ≈20% did not collect a second aspirin prescription (**Figure II in the online-only Data Supplement**). After the first year of inconsistent prescription collections, those who remained on treatment had approximately the same persistence pattern as those treated with long-term aspirin.

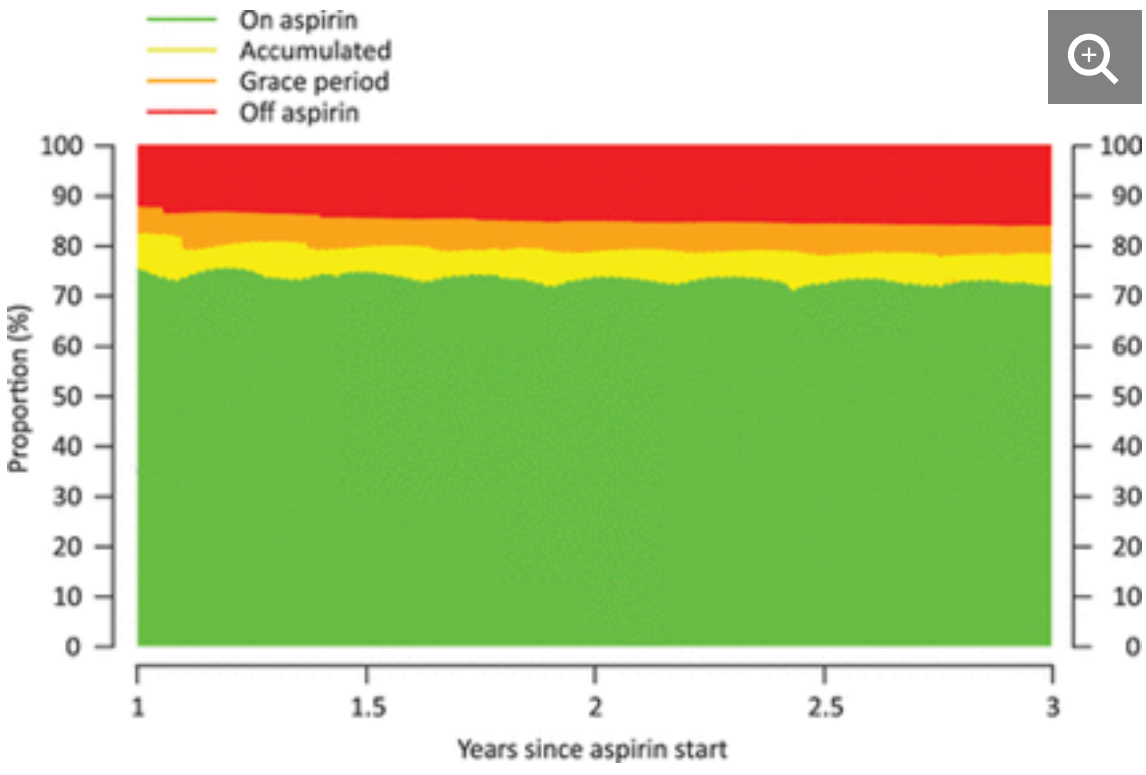

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Figure 2.

Persistence patterns in patients on stable long-term aspirin treatment (n=601527). *On aspirin* is the nominal duration of each aspirin dispense. *Accumulated* is the time after the nominal duration of each aspirin dispense when the patient has tablets left over from previous dispenses in a consecutively dispensed period. *Grace period* is from the end of the accumulated period plus 25% of the total duration on aspirin in the last consecutively dispensed period plus 20 days. This corresponds to 80% adherence with up to a week's gap between dispenses. *Off aspirin* is from the end of the grace period.

Adjusted cumulative incidence of cardiovascular events according to aspirin treatment persistence groups is presented in **Figure 3**. Patients on persistent aspirin treatment had the lowest incidence of cardiovascular events. Patients who had discontinued aspirin had a 37% higher rate of cardiovascular events (**Table 2**), corresponding to an absolute risk increase of 13.5 events per 1000 person-years at risk. Put another way, on average, 1 of every 74 patients who discontinued aspirin had an additional cardiovascular event in 1 year.

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Table 2.

Risk of Cardiovascular Events by Aspirin Persistence Patterns

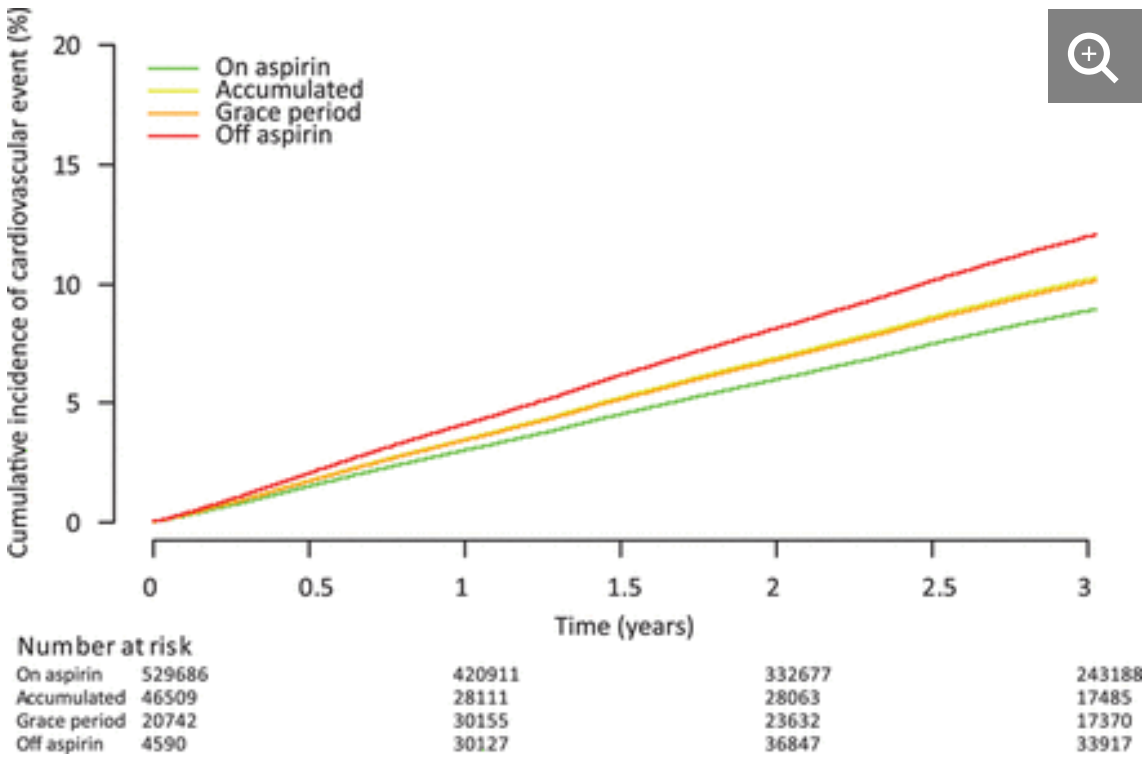

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Figure 3.

Adjusted cumulative incidence of cardiovascular events. Adjusted for the baseline variables of age, sex, and diabetes mellitus and the time-updated variables of previous cardiovascular disease, antiplatelet or oral anticoagulant drugs, nonsteroidal anti-inflammatory drugs, and oral steroids. *On aspirin* is the nominal duration of each aspirin dispense. *Accumulated* is the time after the nominal duration of each aspirin dispense when the patient has tablets left over from previous dispenses in a consecutively dispensed period.

Grace period is from the end of accumulated period plus 25% of the total duration on aspirin in the last consecutively dispensed period plus 20 days. This corresponds to 80% adherence with up to a week's gap between dispenses. *Off aspirin* is from the end of the grace period.

Subgroup analyses further revealed that patients with higher age and prior cardiovascular disease were at higher risk increase for cardiovascular events when off aspirin, whereas treatment with oral anticoagulant or other antiplatelet drugs was associated with lower risk increase for cardiovascular events when off aspirin (**Figure 4**). The majority (54%) of the study sample used aspirin for secondary prevention. Among those, discontinuing aspirin was associated with a 46% higher rate of cardiovascular events than continuing on aspirin (**Table 2**), corresponding to an absolute risk increase of 28.0 per 1000 person-years at risk or an additional cardiovascular event per year in 1 of every 36 patients who discontinued aspirin. Among the 46% who probably used aspirin as part of primary prevention, discontinuing aspirin was associated with a 28% higher rate of cardiovascular events than continuing on aspirin (**Table 2**), an absolute risk increase of 6.9 per 1000 person-years at risk or an additional cardiovascular event per year in 1 of every 146 patients who discontinued aspirin.

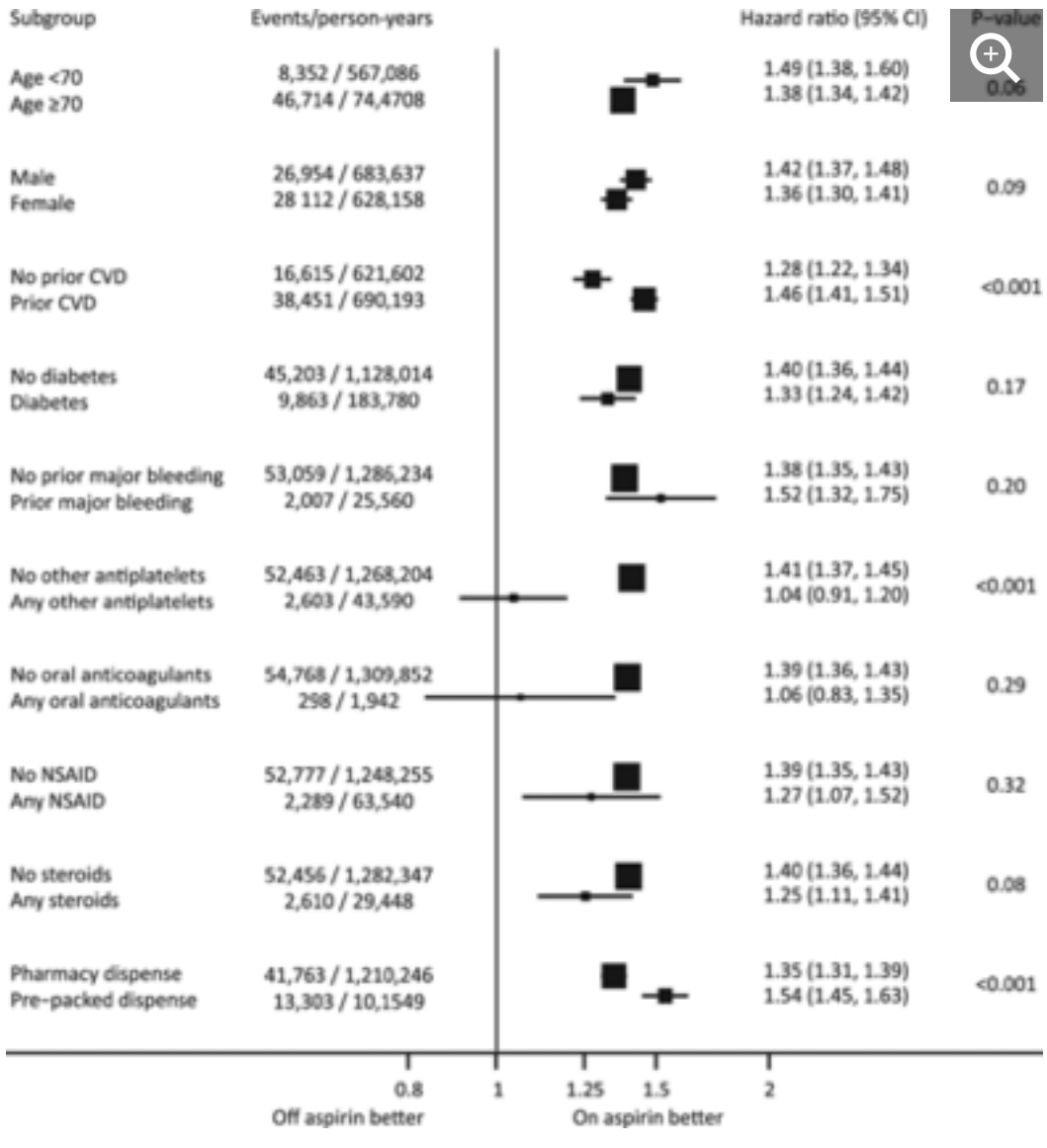

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Figure 4.

Risk of cardiovascular events by aspirin persistence patterns in subgroups. *P* values are for multiplicative interactions of the subgroup factor with aspirin persistence pattern. CI indicates confidence interval; CVD, cardiovascular disease; and NSAID, nonsteroidal anti-inflammatory drug.

Aspirin discontinuation was also associated with nonfatal cardiovascular events, with a 10% higher risk of nonfatal cardiovascular events among people off versus on aspirin (**Table III in the online-only Data Supplement**). Censoring participants at the start of oral anticoagulant therapy produced results very similar to those of the main models, with a 43% higher risk of cardiovascular events if discontinuing rather than continuing on aspirin (**Table IV in the online-only Data Supplement**).

The timing of events after aspirin discontinuation analyses included 38736 patients with 40355 times at risk during which 216 cardiovascular events occurred. Patients who stopped taking aspirin after a period of 4 timely dispenses had an early risk increase for cardiovascular events compared with those who collected their fifth timely dispense (**Figure 5**). The median time to the first cardiovascular event in those who did not collect their fifth dispense on schedule was one-third the time of those who collected their dispense on schedule (time ratio, 0.31; 95% confidence interval, 0.22–0.43).

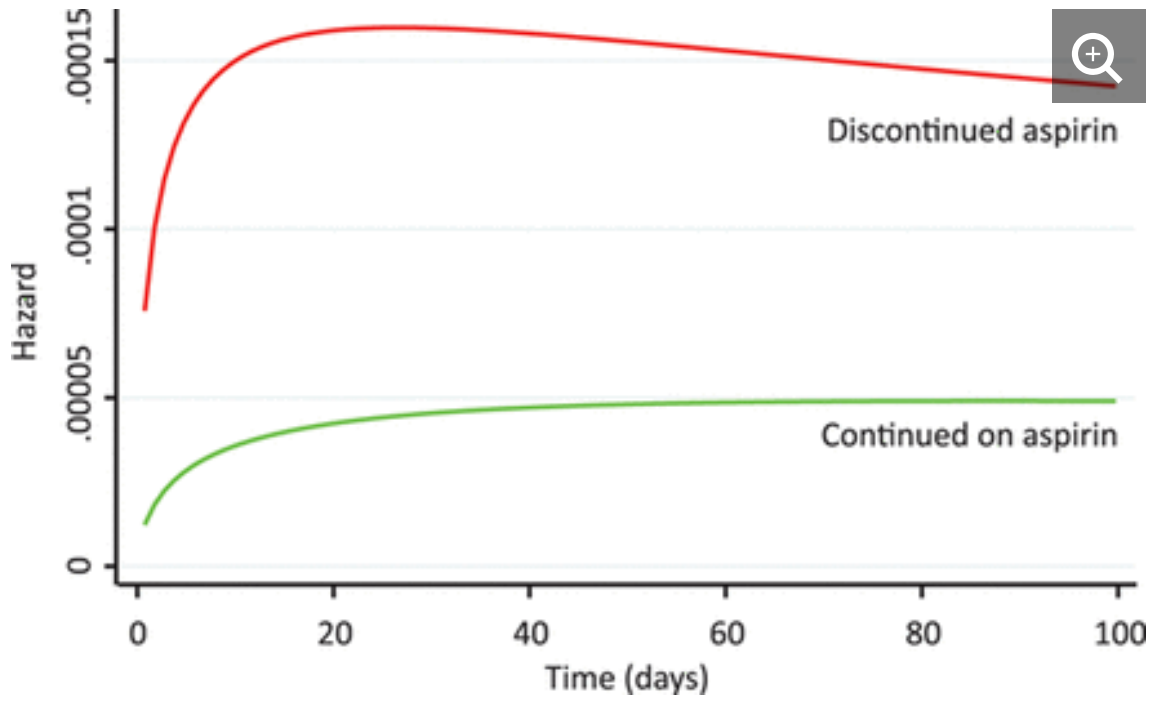

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Figure 5.

Timing of cardiovascular events after aspirin discontinuation in patients who stopped (red line) vs continued (green line) taking aspirin after 4 timely aspirin dispenses. Parametric regression models with log normal parameterization and shared frailty on the patient level. Models adjusted for the baseline variables of age, sex, and diabetes mellitus and the time-updated variables of previous cardiovascular disease, antiplatelet or oral anticoagulant drugs, nonsteroidal anti-inflammatory drugs, and oral steroids.

Discussion

In this large nationwide patient cohort, discontinuation of long-term low-dose aspirin was associated with a >30% higher risk of cardiovascular events, corresponding to an additional cardiovascular event observed per year in 1 of every 74 patients who discontinue aspirin. The risk appeared to increase as soon as the patients discontinued aspirin, with no safe interval. In this sample, only half of the low-dose aspirin users had been hospitalized for cardiovascular disease before baseline; most of the remaining half were presumably treated, for example, for angina pectoris or stroke prevention in atrial fibrillation or treated as part of primary prevention. Aspirin

discontinuation appeared especially perilous among patients with previous cardiovascular disease, with an additional cardiovascular event per year in 1 of every 36 secondary prevention patients who discontinued aspirin compared with an additional cardiovascular event per year in 1 of every 146 primary prevention patients who discontinued aspirin.

We confirm a high initial discontinuation rate, as seen in prior studies[7–11]: 1 of 5 aspirin-naïve patients did not collect the second aspirin dispense, and the main persistence drop was during the first year after aspirin initiation. In contrast, those who picked up their second prescription had a modest discontinuation rate over time.

Our observations of the risks associated with low-dose aspirin discontinuation are of a magnitude very similar to those of previous randomized trials of aspirin initiation.[1,5] However, the timing of cardiovascular events after aspirin discontinuation remains uncertain. Although those analyses were based on a small number of events, the risk in this study appeared to increase shortly after discontinuation. An acutely increased risk of cerebrovascular events,[14,15] ischemic events,[15–17] and mortality[16] has been observed in case-control studies,[14,16] in perioperative studies,[15,17] and in individuals with bleeding ulcers.[18] In those studies, the main reasons for aspirin withdrawal were surgery[14–17] or bleeding,[14,18] which per se may stimulate platelet aggregation. No increase in cardiovascular events was observed in a recent perioperative aspirin discontinuation trial,[19] although aspirin was stopped within 24 hours before the surgery in that study. Notably, the present study investigated aspirin discontinuation that was unrelated to surgery or bleeding events.

Experimental studies have suggested a rebound effect after aspirin discontinuation, involving increased thromboxane levels[23,24] possibly resulting from the prothrombotic effects of residual very low levels of aspirin.[25] The clinical importance of a rebound effect may be substantial because of the large number of aspirin patients and the high discontinuation rates. For patients undergoing planned surgery or other procedures, it is unknown whether treatment gaps >7 days or <24 hours before the procedure are safe.[19] For patients discontinuing aspirin therapy, it is unknown whether or when the rebound effect happens. In addition, for patients with poor adherence, any rebound effects may be in play more or less continuously. The possibility of such mechanisms is supported by the observation in this study that aspirin discontinuation was not associated with cardiovascular events in patients protected by other antiplatelet or oral anticoagulant drugs (**Figure 4**), although those patients were likely at higher absolute risk of such events.

Some limitations of this study are worth mentioning. Most important, there is a risk of confounding, as in all observational studies. We did not have access to data on socioeconomic status; physical examinations, including blood pressures and lipids; or lifestyle measures such as smoking. However, we used directed acyclic graphs to identify bias-minimized models and included only people who had qualified as long-term users of aspirin. Furthermore, any confounding by indication would bias toward a null result, assuming that people with the highest risk of cardiovascular events would be the ones least likely to discontinue aspirin treatment. There is also a risk of reverse causation—that is, patients about to die stop taking aspirin and then die anyway. Associations of aspirin discontinuation with the secondary nonfatal cardiovascular events outcome were similar but weaker, which may signify some reverse causation, a protective effect of aspirin against fatal events, or lower statistical power in those analyses. Models censoring at the time of start of oral anticoagulant treatment produced results similar to the main results, indicating low risk of reverse causation by patients discontinuing aspirin treatment because of moving to a higher risk stratum and switching to oral anticoagulant therapy. An important limitation is the imprecision in determining the exposure status, which also would bias the results toward the null hypothesis. This is confirmed by the results among people with prepacked dispenses, for which we have good precision in the exposure. These patients appear to be at clearly higher risk of aspirin discontinuation than those who collect dispenses themselves. Thus, the true effect is likely higher than the main observed effect. Another limitation is the end of follow-up in 2009, which implies lack of information on more recent treatment patterns but, on the other hand, avoids cohort effect bias because aspirin guidelines were stable during the study period.

Strengths include the large contemporary sample rendering >60000 cardiovascular events, universal coverage of the prescription register and hence inclusion of all long-term low-dose aspirin users nationwide, the universal coverage of the high-precision[21] registers for determining the outcomes, and minimal loss to follow-up.

Conclusions

Among long-term users of low-dose aspirin, discontinuation of aspirin in the absence of major surgery or bleeding was associated with a >30% increased risk of cardiovascular events. The risk increased shortly after discontinuation. These findings can help policymakers focus on simple measures to ensure treatment persistence with a cheap medication like aspirin with substantial public health gains.

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Disclosures

Drs Sundström, Hedberg, and Oldgren have served on an advisory board for AstraZeneca. P. Aarskog is a current employee and K.M. Johannesen is a former employee of AstraZeneca. Dr Thuresson is employed by Statisticon, of which AstraZeneca is a client. Dr Sundström is on an advisory board for Itrim. Dr Oldgren has received consultancy and lecture fees from Bayer, Boehringer-Ingelheim, BristolMyers Squibb and Pfizer, outside the submitted work.

Footnotes

The online-only Data Supplement is available with this article at **http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.028321/-/DC1**.

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