Aspirin and Risk of Subarachnoid Hemorrhage
Systematic Review and Meta-Analysis

Kevin Phan, BSc(Adv); Justin M. Moore, MD, DPhil; Christoph J. Griessenauer, MD; Christopher S. Ogilvy, MD; Ajith J. Thomas, MD

Background and Purpose—Recent studies have suggested that the use of low-dose aspirin may reduce the risk of aneurysmal subarachnoid hemorrhage (aSAH). We aimed to evaluate any association between aspirin use and risk of aSAH based on the literature, and whether this is influenced by duration or frequency of aspirin use.

Methods—A search of electronic databases was done from inception to September 2016. For each study, data on risk of aSAH in aspirin versus nonaspirin users were used to generate odds ratios and 95% confidence intervals, and combined using inverse variance–weighted averages of logarithmic odds ratios in a random-effects models.

Results—From 7 included studies, no significant difference was noted between aspirin use of any duration or frequency and nonaspirin users (odds ratio, 1.00; 95% confidence interval, 0.81–1.24; P=0.99). We found a significant association between short-term use of aspirin (<3 months) and the risk of aSAH (odds ratio, 1.61; 95% confidence interval, 1.20–2.18; P=0.002). No significant difference was found in terms of risk of aSAH for 3 to 12 months, 1 to 3 years, and >3 years of durations of use. No significant association was found between infrequent aspirin use (≤2× per week) or frequent use (≥3× per week) with risk of aSAH.

Conclusions—Current evidence suggests that short-term (<3 months) use of aspirin is associated with increased risk of aSAH. Limitations include substantial heterogeneity of the included studies. The role of long-term aspirin in reducing risk of aSAH remains unclear and ideally should be addressed by an appropriately designed randomized controlled trial. (Stroke. 2017;48:1210-1217. DOI: 10.1161/STROKEAHA.116.015674.)

Key Words: aspirin ■ randomized controlled trial ■ stroke ■ subarachnoid hemorrhage ■ thromboembolism
As such, we performed a systematic review and meta-analysis of all the available literature to assess the potential benefits and risks of aspirin use with regard to the risk of aSAH.

Methods

Literature Search Strategy

Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Review of Effectiveness, and Google Scholar from their dates of inception to September 2016. To achieve the maximum sensitivity of the search strategy, we combined the terms: aspirin, acetylsalicylic acid, aneurysm, subarachnoid hemorrhage, SAH as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies using the inclusion and exclusion criteria.

Selection Criteria

Eligible studies for the present systematic review and meta-analysis included those that reported an odds ratio (OR) and confidence interval (CI) for aspirin use with risk of aSAH. The OR was manually derived from studies that reported the proportion of patients who developed aSAH in aspirin users versus nonaspirin users or from the relative risk reported from the included study. When possible, the adjusted OR and CI were used for the present meta-analysis. When institutions published duplicate studies with accumulating numbers of patients or increased length of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects and in the English language. Abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded.

Data Extraction

All data were extracted from article texts, tables, and figures using a standardized form. Information was collected included (1) study characteristics, (2) number of patients in aspirin versus nonaspirin user groups, (3) effect size for relationship between aspirin use versus nonaspirin use and risk of aSAH, (4) factors/confounders adjusted for when the study reported the relationship between aspirin use and risk of aSAH. Because quality scoring is controversial in meta-analyses of observational studies, each article included in our analysis was appraised based on a critical review checklist of the Dutch Cochrane Center proposed by the Meta-Analysis of Observational Studies in Epidemiology group. The key points of this checklist include (1) clear definition of study population; (2) clear definition of outcomes and outcome assessment; (3) independent assessment of outcome parameters; (4) sufficient duration of follow-up; (5) no selective loss during follow-up; and (6) important confounders and prognostic factors identified. The final results were reviewed by senior investigators.

Statistical Analysis

For each study, data on risk of aSAH in aspirin versus nonaspirin users were used to generate OR and 95% CIs. Study-specific estimates were combined using inverse variance–weighted averages of logarithmic ORs in a random-effects models. Between-study heterogeneity was analyzed by means of standard chi-squared tests. We also quantified the degree of heterogeneity using the I² statistic, which represents the percentage of the total variability across studies that is because of heterogeneity. I² values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively. All analyses were conducted using review manager (RevMan version 5.3.5; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen). Publication bias was assessed using funnel plot asymmetry, Trim-and-Fill analysis, and Egger test for publication bias.

Results

Search Strategy

A total of 5978 references were identified through 6 electronic database searches (Figure 1). After exclusion of duplicate or irrelevant references, 5921 potentially relevant articles were retrieved. After a detailed evaluation of these articles via title and abstract screening, 21 studies remained for assessment. After applying the selection criteria, 7 studies6,11,12,14–17 were selected for further analysis. The study characteristics of these trials are summarized in the Table. All included studies were population based with the exception of the study of Gross et al.16 which was a retrospective institutional review over a 7-year period. Risk of bias assessment for included studies is shown in Table I in the online-only Data Supplement. Specific study population details for each included study is outlined in Table II in the in the online-only Data Supplement.

Risk of aSAH in Patients Currently Using Aspirin of Any Duration or Frequency

The risk of aSAH in aspirin users (of any duration and frequency) was compared with that that in nonaspirin users and is summarized in the Forest plot in Figure 2. There was no significant difference noted between aspirin and nonaspirin users (OR, 1.00; 95% CI, 0.81–1.24; P=72%; P=0.99), however, there was significant heterogeneity (P<0.0001). To determine potential sources of heterogeneity, we performed subgroup analyses based on the duration of aspirin use and the frequency of aspirin use per week.

Risk of aSAH With Aspirin Use <3 Months in Duration

The relationship between aspirin use in the short-term (<3 months) and the risk of aSAH was reported in 3 studies11,12,16 (Figure 3A). There was a significant association between short-term use of aspirin and the risk of aSAH (OR, 1.61; 95% CI, 1.20–2.18; P<37%; P=0.002), and no significant heterogeneity was detected (P=0.19).
No significant association was found between aspirin use in the short to medium term and the risk of aSAH (OR, 1.12; 95% CI, 0.79–1.58; $I^2=78\%$; $P=0.53$). Significant heterogeneity was noted ($P=0.53$).

No significant association was found between aspirin use in the long term and the risk of aSAH (OR, 1.01; 95% CI, 0.87–1.17; $F=0\%$; $P=0.86$). No significant heterogeneity was noted ($P=0.95$).

### Risk of aSAH in Aspirin Use of 3- to 12-Month Duration
These subgroups were reported in 3 studies (Figure 3B). No significant association was found between aspirin use in the short to medium term and the risk of aSAH (OR, 1.12; 95% CI, 0.79–1.58; $F=78\%$; $P=0.53$). Significant heterogeneity was noted ($P=0.01$).

### Risk of aSAH in Aspirin Use of 1- to 3-Year Duration
These subgroups were reported in 3 studies (Figure 3C). No significant association was found between aspirin use in the long term and the risk of aSAH (OR, 1.01; 95% CI, 0.87–1.17; $F=0\%$; $P=0.86$). No significant heterogeneity was noted ($P=0.95$).
Risk of aSAH in Aspirin Use >3 Years in Duration

These subgroups were reported in 4 studies\cite{6,11,16,17} (Figure 3D). No significant association was found between aspirin use in the very long term and the risk of aSAH (OR, 0.92; 95% CI, 0.68–1.25; \(I^2=64\%\); \(P=0.60\)). Significant heterogeneity was noted (\(P=0.004\)).

Risk of aSAH in Current Aspirin Use ≤2× Per Week

These subgroups were reported in 2 studies\cite{6,17} (Figure 4A). No significant association was found between infrequent aspirin use (≤2× per week) and the risk of aSAH (OR, 0.85; 95% CI, 0.55–1.33; \(I^2=0\%\); \(P=0.48\)). No significant heterogeneity was noted (\(P=0.79\)).

**Figure 2.** Forest plot of short-term aspirin use (any duration and frequency) and risk of aneurysmal subarachnoid hemorrhage (SAH). CI indicates confidence interval.

**Figure 3.** A, Forest plot of short-term aspirin use (<3 mo) and the risk of aneurysmal subarachnoid hemorrhage (aSAH). B, Forest plot of aspirin use (3–12 mo) and the risk of aSAH. C, Forest plot of aspirin use (1–3 y) and the risk of aSAH. D, Forest plot of aspirin use (>3 y) and the risk of aSAH.
Risk of aSAH in the Current Aspirin Use ≥3× Per Week
These subgroups were reported in 2 studies6,17 (Figure 4B). No significant association was found between infrequent aspirin use (≥3× per week) and the risk of aSAH (OR, 1.00; 95% CI, 0.49–2.05; I²=76%; P=1.00). Significant heterogeneity was noted (P=0.005).

Bias Assessment
Potential publication bias in the present study was tested using several methods. Egger test for publication bias was also nonsignificant (P=0.38, 2 tailed). Publication bias was assessed using funnel plot methodology, shown in Figure 5.

Discussion
As we continue to expand our understanding of aneurysm pathophysiology and their complications, there is increasing importance placed on understanding and potentially
mitigating the risk factors that give rise to aSAH. Given the widespread use of aspirin and antiplatelet agents, establishing the association, if any, and direction of association with regard to the risk of aSAH is of utmost importance from both clinical and public health perspectives. To address this question, we performed a systematic review and meta-analysis of available studies exploring the association between aspirin use and the risk of aSAH. Our analysis included several patient subgroups. We showed that when considered collectively, aspirin use, regardless of frequency and duration, was not associated with a significantly increased risk of aSAH when compared with no therapy. In subgroup analysis, patients on aspirin of <3-month duration had significantly higher risk of aSAH. For patients on aspirin for intermediate-term (3–12 months; 1–3 years) and longer-term (>3 years) duration, no significant difference in the risk of aSAH was found between aspirin users and nonaspirin users. Subgroup analysis according to the frequency of aspirin use per week (<2x per week) or (≥3x per week) demonstrated no significant difference between aspirin and nonaspirin users.

Studies Finding an Association Between Aspirin and a Reduction in aSAH

The possible protective effect of aspirin on risk of aSAH was first reported by Hasan et al., in their nested case-controlled study from the ISUIA study (International Study of Unruptured Intracranial Aneurysms). Fifty-eight patients were retrospectively matched to 4 controls each, all of which had been followed up for 5 years as part of the ISUIA study. Interestingly, they showed that aspirin use at least 3x per week had been followed up for 5 years and as part of the ISUIA study. Interestingly, they showed that aspirin use at least 3x per week was associated with a lower odds of aSAH (OR, 0.27; 95% CI, 0.11–0.67; \( P = 0.03 \)). García-Rodríguez et al.16 also reported a large study of 1340 aSAH cases compared with 10000 controls and demonstrated a significant association between aspirin use for >3-year duration with reduced risk of aSAH (OR, 0.82), whereas no increased risk of intracerebral hemorrhage was identified. Although both studies demonstrated protective effects for aspirin use, it must be noted that this effect was only seen in a subset of patients taking aspirin: patients taking aspirin ≥3x weekly for the ISUIA trial and patients using aspirin for ≥3 years for the study by García-Rodríguez et al.16 Both of these studies are also limited by bias inherent to retrospective data analysis. For the ISUIA trial, no benefit was found with regard to the risk of aSAH when aspirin was used up to twice a week or when used monthly. With regard to the European study, there was no benefit observed for aspirin users in the short and intermediate term (<3 years).

Studies Finding an Association Between Aspirin and an Increase in aSAH

Any potential benefits of aspirin need to be carefully considered and balanced with the possible risk of increased bleeding events or more severe hemorrhage in the event of rupture. Indeed, there have been conflict reports on the influence of aspirin on patients and their subsequent risk of aSAH. Pottegard et al.17 performed a large study of Danish neurosurgery units, matching 5834 patients presenting with their first aSAH diagnosis with 40 age-, sex-, and period-matched population controls. The authors reported no reduction in aSAH risk with the long-term aspirin use (OR, 1.11). However, they reported that short-term aspirin use <3 months was significantly associated with an increased risk of aSAH. Similar conclusions were attained by Schmidt et al.12 in patients with new use of aspirin. The results of our own meta-analysis demonstrated a significant association between aspirin use of <3 months and an increased risk of aSAH, with OR of 1.61. As such, the prophylactic use of aspirin for aSAH, particularly with known unruptured aneurysms, is not without its own inherent bleeding risks, particularly in the short term.

Aspirin and aSAH: Systematic Review and Meta-Analysis

In the present meta-analysis, we performed a subgroup analyses on the literature based on the duration of aspirin use, as well as the frequency of aspirin use per week. For long-term aspirin use, defined as ≥3-year duration, pooled data from 4 cohorts did not demonstrate any significant decrease or increase of aSAH risk with the aspirin use (OR, 0.92). This was similarly the case for the intermediate duration use of aspirin for 3 to 12 months (OR, 0.96) and 1 to 3 years (OR, 1.01). As such, based on the limited evidence published to date on this topic, there is no clear consistent evidence linking long-term aspirin use to either a decreased or increased risk of aSAH. What the current data suggest is that if aspirin does provide any beneficial effect in the context of aSAH risk, this effect will be dependent on the duration of aspirin use, and further studies are required to elucidate the optimal patient population who are likely to benefit from such recommendations. The optimal way to address the question whether aspirin can protect against aSAH would be a large, multicenter, randomized trial. Such a trial may be challenging as to what duration and frequency of aspirin to choose.

Pathophysiology

It has been previously proposed that aspirin may exert a protective effect on aSAH risk via its antiplatelet activity, which can impede thrombus formation, endothelial injury, irritation, and inflammation of the aneurysm wall. However, Pottegard et al.17 in a Danish study did not demonstrate any benefit for either aspirin or clopidogrel in terms of the risk of aSAH, which brings into question this hypothesis. Another theory suggests that aspirin may have an inhibitory effect on the inflammatory cascade that is implicated in intracranial aneurysm formation and rupture.8,18–21 Numerous cells and molecular pathways have been implicated in this inflammatory cascade including macrophages, vascular smooth muscle cells, nuclear factor-κB, interleukin-1β, matrix metalloproteinases, and tumor necrosis factor-α.6,18–22 Hasan et al.19 demonstrated, in a small randomized sample of patients with unruptured aneurysm who underwent microsurgical clipping after 3 months of aspirin treatment, a decreased expression of inflammatory cells and markers such as cyclooxygenase-2. Ferumoxytol-enhanced magnetic resonance imaging, a marker of macrophage activity, showed a reduction in signal intensity after aspirin treatment.21 Certainly, such findings, in addition to the current lack of affordable and noninvasive options for patients at risk
of aSAH, make aspirin a promising candidate. Our results, however, demonstrate a distinct lack of evidence to strongly recommend aspirin as a potential medical therapy to reduce aSAH in the presence of unruptured aneurysms.

Limitations

The present study is constrained by several limitations. Firstly, none of the included studies were randomized trials and as such, all included studies were susceptible to risk of selection bias and study population heterogeneity. We made every effort to include adjusted odds in our pooled analyses although each study adjusted for a different set of confounders. There was only 1 study we included where the odds were derived from the data provided in the published report and were thus unadjusted. Second, a major limitation in pooling available results is the heterogeneity in patient population, the duration of use of aspirin, and the frequency of aspirin use. One of the main limitations of using OR in studies with long-term follow-up is that time is not taken into account. Differences in short- and long-term findings may be because of selection bias. In some cases, patients who were followed up for long term and who were benefited or did not show harm may be in fact because of their underlying baseline characteristics—such as being younger and healthier. The population size and thus statistical power for each studied varied and is a limitation of the present analysis. We attempted to mitigate the above heterogeneity by performing subgroup analysis according to duration and frequency of aspirin use, as well as using adjusted OR whenever reported. We also used a random-effects model to incorporate heterogeneity into the study. However, we do acknowledge that the current results still have substantial heterogeneity and thus should be interpreted with caution. Future studies should ensure that their study design accounts for such factors.

Conclusions

Based on the limited quality evidence in the literature, we found that patients on aspirin for <3 months had a significantly higher risk of aSAH (OR 1.6). For patients on aspirin in the intermediate and long term (3–12 months, 1–3 years, and >3 years), no significant difference in the risk of aSAH was found when compared with nonaspirin users. Subgroup analysis according to the frequency of aspirin use per week (<2x per week or ≥2x per week) demonstrated no significant difference between aspirin and nonaspirin users. Ideally, a well-designed, statistically powered, randomized controlled trial is required to determine whether long-term aspirin use can provide any benefit in terms of risk of aSAH.

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Disclosures

None.

References


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## Supplementary Table I. Assessment of the quality of included studies

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* Lack of blinding during outcome assessment, not independently assessed by multiple investigators

** Diagnoses in this study were based on diagnostic/treatment codes. It is not clear whether codes for each patient for verified...
## Supplementary Table II. Description of population for each study

<table>
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<th>Population description</th>
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| Pottegard 2015     | - Designed as nationwide case-control study  
                      - Retrospective analysis based on Danish registry  
                      - Cases were persons with incident SAH, first-time diagnosis  
                      - Registry codes used to identify patients, and their covariate including drug use and medical history  
                      - Controls selected at random from Danish source population |
| Gross 2014         | - Retrospective review of consecutive patients with at least 1 cerebral aneurysm at a single center over 7 years  
                      - Patients were stratified according to whether aspirin was used or not |
| Garbe 2013         | - Nested case-control study from members of the German Pharmacoepidemiological Research Database  
                      - Database includes data from 4 German health insurances, covering all regions of Germany  
                      - Represents 20% of the German population  
                      - Data from 2004-2006 analysed  
                      - All diagnoses coded according to ICD-10GM  
                      - Database included linkage to a separate pharmaceutical reference data with details on drug use, dose, frequency, brand names |
| Garcia-Rodriguez 2013 | - Patients from UK medical research database THIN from 2000-2008  
                          - Individuals in the THIN study cohort was followed from start date until an endpoint – hemorrhagic stroke, or 90 years of age, or patient death, or end of study period  
                          - A nested case-control study was performed based on this study cohort, by identifying patients who had SAH  
                          - Group of 10,000 controls from THIN randomly selected and frequency-matched to all SAH cases based on sex, age, calendar year of diagnosis |
| Hasan 2011         | - Nested case-control study performed based on subjects enrolled in ISUIA prospective cohort study  
                      - ISUIA is an epidemiological cohort study that involved long-term follow-up of untreated versus treated SAH patients. The initial untreated patients are analysed in this study  
                      - Cases were patients who had proven SAH during 5-year follow-up period  
                      - 4 control subjects matched to each case by site/size of aneurysm  
                      - Aspirin use details determined at baseline interview |
| Schmidt 2010       | - Population based case-control study in northern Denmark, using data from 1997-2008  
                      - 10 population controls were selected for each case, matched by age and sex  
                      - Data on prescriptions for antiplatelet drugs determined from medical databases |
| Iso 1999           | - Data obtained from Nurses’ Health Study Cohort  
                      - This was a study where female registered nurses completed questionnaires with items about lifestyle and medical history  
                      - Every 2 years, follow-up questionnaires were sent |