Caught between blindness and a heart attack?

Or how research reporting can keep an informed patient awake at night
Daily aspirin may increase risk for age-related blindness

Many people take aspirin to prevent heart attacks, but new research suggests the added benefits may be coming at the expense of pill-takers' eyesight.
Taking aspirin doubles the risk of blindness in elderly people

- Popping the pill more than once a week increased risk
- Particular warning for those with AMD in one eye
- Link could not be explained by a history of heart disease or smoking, both risk factors for the disease

By Jenny Hope Medical Correspondent

Aspirin can triple risk of blindness-causing disease in regular users, researchers warn

Stephen Adams, The Daily Telegraph, National Post Wire Services | January 22, 2013 | Last Updated: Jun 19 3:03 PM ET
More from National Post Wire Services
Aspirin 'triples chance of blindness disease'

Regular use of aspirin can almost triple the chance of developing a condition that causes more older people in Britain to lose their sight than any other, researchers are warning.
An aspirin a day... causes blindness?

Tuesday, February 05, 2013 by: David Gutierrez, staff writer
Tags: aspirin, blindness, risks

(NaturalNews) People who take aspirin regularly to reduce their risk of heart attacks and strokes are significantly more likely to suffer from age-related macular degeneration (AMD), the primary cause of blindness in the elderly. These are the findings of a study conducted by researchers from the University of Sydney and published in the journal JAMA Internal Medicine.
The Association of Aspirin Use With Age-Related Macular Degeneration

Gerald Liew, PhD; Paul Mitchell, PhD; Tien Yin Wong, PhD; Elena Roehchchina, MAppStat; Jie Jin Wang, PhD

Objective: To determine whether regular aspirin use is associated with a higher risk for developing age-related macular degeneration (AMD) by using analyzed data from a 15-year prospective cohort.

Methods: A prospective analysis was conducted of data from an Australian population-based cohort with 4 examinations during a 15-year period (1992-1994 to 2007-2009). Participants completed a detailed questionnaire at baseline assessing aspirin use, cardiovascular disease status, and AMD risk factors. Age-related macular degeneration was graded side-by-side from retinal photographs taken at each study visit to assess the incidence of neovascular (wet) AMD and geographic atrophy (dry AMD) according to the international AMD classification.

Results: Of 2389 baseline participants with follow-up data available, 257 individuals (10.8%) were regular aspirin users and 63 of the 2389 developed neovascular AMD. Persons who were regular aspirin users were more likely to have incident neovascular AMD: the 15-year cumulative incidence was 9.3% in users and 3.7% in non-users. After adjustment for age, sex, smoking, history of cardiovascular disease, systolic blood pressure, and body mass index, persons who were regular aspirin users had a higher risk of developing neovascular AMD (odds ratio [OR], 2.46; 95% CI, 1.25-4.83). The association showed a dose-response effect (multivariate-adjusted P=.01 for trend). Aspirin use was not associated with the incidence of geographic atrophy (multivariate-adjusted OR, 0.99; 95% CI, 0.59-1.65).

Conclusion: Regular aspirin use is associated with increased risk of incident neovascular AMD, independent of a history of cardiovascular disease and smoking.

ASSESSMENT OF ASPIRIN USE

We determined the use of aspirin and other medications during a structured interview using a standard questionnaire.\textsuperscript{16,19,25} We defined regular use of aspirin as frequency of once or more per week in the past year and confirmed this with a current medication list where participants listed all the medications they had taken for at least 1 month before the study examination. This list was then checked against the medication bottles that participants were asked to bring to the examination. Occasional use was defined as a frequency of less than once per week in the past year. Nonregular aspirin users included nonusers and occasional users. Although we did not collect information on aspirin dosage, most aspirin use in Australia is prescribed at 150 mg daily.
Relationship of Aspirin Use With Age-Related Macular Degeneration

Association or Causation?

In their prospective population-based cohort study of 2389 patients in the Blue Mountains region in Australia, Liew and colleagues\(^1\) report on the association of long-term use of low-dose aspirin and age-related macular degeneration (AMD), the leading cause of blindness in Western countries. The principal finding is that regular aspirin use is associated with an approximately 2.5-fold greater risk of incident AMD. This relationship is specific for late neovascular (wet) AMD but not geographic atrophy (dry AMD) and is independent of potential confounders, such as cardiovascular disease, smoking, age, sex, systolic blood pressure, and body mass index.

STRENGTH OF EVIDENCE

This study has important strengths and limitations. It provides evidence from the largest prospective cohort with more than 5 years of longitudinal evaluation reported to date using objective and standardized ascertainment of AMD. Additional strengths include the use of standardized protocols for determining medication use, the recording of detailed demographic and clinical information for risk adjustment, and appropriate methodologic approaches, such as multivariate logistic regression and propensity score adjustment, to minimize the impact of confounding.

The key limitation is the nonrandomized design of the study with its potential for residual (unmeasured or unobserved) confounding that cannot be mitigated by multivariate logistic regression or propensity score analysis. Limitations, such as the potential of recall and ascertainment bias, are addressed transparently, and reasonable arguments are offered to counter the effect of these biases on study results. Additional limitations that deserve attention include the modest strength of association (odds ratio, 2.0-2.5); incomplete data on other morbidities, such as arthritis, for which aspirin may be indicated; the potential for “overfitting” resulting in biased estimates because of the limited number of incident cases of AMD (n=63) and 10 or more candidate predictor variables; and the issue of missing data (only 56% of the cohort eligible for follow-up at >15 years were assessed). All of these limitations can potentially undermine the interpretation and threaten the validity of trial results.
IS THE ASSOCIATION CAUSAL?

The Hill criteria are useful and time-tested considerations for determining whether an association is causal. Application of these considerations to the current study yields instructive insights.

Strength of Association

A strong association is more likely to have a causal component than is a modest association. The association between regular aspirin exposure and the risk of AMD is modest, as reflected in the unadjusted odds ratio of 2.5 (P = .01) and the adjusted odds ratios of 2.05 (P = .06) to 2.31 (P = .03). Based on the data provided, we estimate the discriminant ability as measured by the area under the curve to be correspondingly low (c index of 0.66) and the positive predictive value to be only 6% given the very low prevalence of 2.6%.

Consistency

Relationships that are repeatedly observed by different investigators, in different places, circumstances, and times, are more likely to be causal. Previous nonrandomized studies linking aspirin use to AMD have yielded inconsistent results, ranging from a protective effect on geographic atrophy in 1 study to no association in 2 studies and a positive (harmful) association with early and late wet AMD in 1 study.

Two prospective randomized trials reported a nonsignificant protective effect of aspirin use on AMD. Several factors could potentially account for the conflicting results. These include differences in the patient population and their underlying risk of AMD (prevalence of AMD was 10 to 25 times lower in the randomized compared with the nonrandomized studies), methods of ascertainment and adjudication of AMD (self-reported and visually significant criterion used in randomized studies compared with the objective criterion used in the current study), duration of aspirin exposure, and the potential for bias in different study designs (case-control vs prospective cohort vs randomized studies). Thus, studies to date do not clearly demonstrate either a beneficial or harmful effect of low-dose aspirin use on the development or progression of AMD.

Temporal

The factor must precede the outcome it is assumed to affect. This is self-evident in a prospective cohort study.

Biological Plausibility

Associations that are consistent with the scientific understanding of the biology of the disease are more likely to be causal. Potential mechanisms by which aspirin can affect AMD include suppression of prostacyclin synthesis, leading to hypoxia and neovascularization; increased lipid oxidation; subretinal hemorrhages; and involvement of the complement pathway as evidenced by a potential pharmacogenetic interaction with aspirin and Y402H polymorphism reported in this study. Thus, the relationship appears to be biologically plausible, although pre specification of these mechanisms would have provided additional support.

Specificity

A factor influences specifically a particular outcome or population. Given the multifactorial causes of AMD and the multiple effects exerted by aspirin, this is difficult to establish.

Coherence

A causal conclusion should not fundamentally contradict present substantive knowledge. It is difficult to establish coherence given the current state of the knowledge regarding AMD and lack of supportive laboratory evidence.

Experiment

Causation is more likely if evidence is based on randomized experiments. The randomized studies yield directionally opposite results from the current observations, although differences in patient populations and ascertainment of AMD could potentially account for the discordant results.

Analogy

For analogous exposures and outcomes, an effect has already been shown. It is unclear whether other antiplatelet agents or nonsteroidal anti-inflammatory drugs exhibit a similar association with AMD.

Of these 9 criteria, only 3 less critical ones (temporality, dose-response, and plausibility) are fulfilled in the current study. Therefore, based on the totality of data, the evidence is insufficient to adjudicate the relationship between aspirin and AMD, thereby challenging causal inferences.
Temporality

The factor must precede the outcome it is assumed to affect. This is self-evident in a prospective cohort study. Further proof is provided by the observation that the association became evident only after 10 to 15 years of exposure.

Biological Gradient or Dose-Response Relationship

Responses that increase in frequency as exposure increases are more convincingly supportive of causality than are those that do not show this pattern. Although information regarding the exact aspirin dose is missing, the investigators observed a dose-response relationship, with more frequent aspirin use associated with greater risk.

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Conflict of Interest Disclosures: None reported.

The Incremental Nature of Clinical Research

The eloquent Invited Commentary by Kaul and Diamond illustrates the great care that must be taken before concluding that an association described in an observational study truly represents a cause-effect relationship. In our discussion of the article by Liew and colleagues, the editors believed that it provided useful incremental data about an important condition. However, as with many good studies, the data are not definitive enough to suggest changes in clinical practice. Rather, we hope the study galvanizes more research on the relationship between aspirin and macular degeneration. For example, ASPREE (Aspirin in Reducing Events in the Elderly), a large international, randomized controlled trial on the effect of aspirin on cardiovascular outcomes and dementia in elderly persons, hopefully will consider rigorously assessing for macular degeneration.

After the editors decided to accept this article, we discussed the risk that press reports would fall into the trap of reporting this study as definitive. This study provides an opportunity to educate the public about the subtleties and incremental nature of medical research. Our understanding of disease etiology advances as evidence accumulates from multiple good studies.

Kenneth E. Covinsky, MD, MPH
Is 81-mg Aspirin Associated With Age-Related Macular Degeneration Risk?

To the Editor It is unfortunate that the study by Liew and colleagues did not quantify the actual milligram dose of aspirin that was taken by each subject, but rather only the amount of time each subject took aspirin at any dose. The authors stated that aspirin is usually prescribed at a dose of 150 mg/d in Australia, which is an odd dose in that it is probably too small for effective analgesia in most patients, but larger than the minimum dose required for steady-state inhibition of platelet aggregation to reduce cardiovascular thrombosis. The “dose-response effect” that the authors found refers to the “time dose” or cumulative amount of time the patient took aspirin (at any milligram dose). It would be useful to know in addition whether there is a milligram dose-response effect for risks associated with daily aspirin use. Such an effect might be continuous or a “threshold effect,” such that aspirin below a certain dose, taken daily, might have no adverse effect. Most aspirin prescriptions in the United States are written for the lowest dose available, 81 mg, and are prescribed for the purpose of platelet inhibition, not analgesia. The physicians who write these prescriptions would be more interested in knowing whether an aspirin dose of 81 mg/d is associated with increased risk of age-related macular degeneration, rather than the less-commonly prescribed dose of 150 mg.

David L. Keller, MD

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In Reply We completely agree with Dr Keller about the importance of having aspirin intake dose information and his comment about what we reported was “time dose” or use duration-dose pattern but not quantitative dose of aspirin intake. If an intake dose-response pattern were found with the aspirin dose data, this would strengthen the evidence supporting an association between aspirin use and age-related macular degeneration (AMD) and inform clinical practice. However, we do not have precise dosage data collected from our study sample.

In the Blue Mountains Eye Study surveys, we administered a face-to-face interview using a questionnaire covering nearly 500 questions (790 variables), in which the few questions about aspirin intake were very simple. For example, at the baseline survey, we asked the following questions:

1. Over the past year, how often have you taken an aspirin tablet?
2. How many aspirin tablets do you usually take each week?
3. For how many years have you been taking this number?
4. Is that more than/the same/less than the number of aspirin you were taking 10 years ago?

Some participants with a positive response to the question about aspirin use did not answer the questions about intake quantity. The information on number of tablets taken per week provided by participants who answered the questions reflected their intake during the year prior to the study. Questions to interrogate history of aspirin use were insufficiently detailed, and therefore we could not generate precise use dosage data. In population-based surveys, a trade-off for a comprehensive questionnaire is insufficient detailed information on each question.

In relation to our comment regarding a 150-mg dose, this was derived from statements by patients who remarked that their physician advised to take half an aspirin per day. In fact, the majority of participants at this time reported taking approximately 100 mg/d. This was our error in reporting 150 mg/d.

Let us take one step back from the prospective application of these findings to clinical practice. We strongly believe that this reported association has not yet been proven as being causal and needs further confirmation from experimental studies, despite there being relatively consistent evidence from observational studies. Reasons for this caution are well covered in the editorials by Kaul and Diamond and Covinsky.

Jie Jin Wang, MMed, PhD
Gerald Liew, MBBS, PhD
Paul Mitchell, MD, PhD
<table>
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<th>Item No</th>
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| **Title and abstract** | *(a)* Indicate the study’s design with a commonly used term in the title or the abstract  
*(b)* Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** |  
*Background/rationale*  | Explain the scientific background and rationale for the investigation being reported |
|  | *Objectives*  | State specific objectives, including any prespecified hypotheses |
| **Methods** |  
*Study design*  | Present key elements of study design early in the paper |
|  | *Setting*  | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
|  | *Participants*  | *(a)* Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
*(b)* For matched studies, give matching criteria and number of exposed and unexposed |
|  | *Variables*  | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
|  | *Data sources/measurement*  | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
|  | *Bias*  | Describe any efforts to address potential sources of bias |
|  | *Study size*  | Explain how the study size was arrived at |
|  | *Quantitative variables*  | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
|  | *Statistical methods*  | *(a)* Describe all statistical methods, including those used to control for confounding  
*(b)* Describe any methods used to examine subgroups and interactions  
*(c)* Explain how missing data were addressed |
How can patients add value?

- Engage physicians, patients from the onset
  - What we seek to answer with the study
  - What we want to ask
  - Discuss results, how to report them
  - Proactive knowledge transfer
  - Standard procedure
  - Built into calls for proposals, funding
How can academics add value?

- Improve quality of conduct (e.g. questionnaires)
- Address communication implications from the get-go.
  - Study limitations
  - Causality, associations
  - Interpretation (expert vs. expert, lay vs. expert)
  - Contradictory evidence
- Assess results in the context of existing knowledge.
- Reporting does not end with publication
Low-Fat Diet Does Not Cut Health Risks, Study Finds

By GINA KOLATA
Published: February 8, 2006

Correction Appended

The largest study ever to ask whether a low-fat diet reduces the risk of getting cancer or heart disease has found that the diet has no effect.

The $415 million federal study involved nearly 49,000 women ages 50 to 79 who were followed for eight years. In the end, those assigned to a low-fat diet had the same rates of breast cancer, colon cancer, heart attacks and strokes as those who ate whatever they pleased, researchers are reporting today.
Mediations: key target

- Take into account all reporting mediations
  - Health professionals
  - Public health communicators
  - Patient groups, fora, bloggers
  - Social media
  - Engage in constructive dialogue
REPORTING

Patients

Interested lay audiences

Health professionals

Editors

Peer reviewers

Journalists, portals, bloggers
Context: patient-centred?

- Patient centred vs. health system/provider/researcher centred
- Patient input built into research
- Read user comments on news articles, blogs, online fora
- Educate the user? Educate the researcher?
- Learn to live with user needs, logic, and use of evidence
Snail Revival Raises Peer Review Debate

Rediscovery of a snail thought to be extinct has raised questions about the peer-review process that approved the publication of the extinction report.

By Jyoti Madhusoodanan | October 15, 2014

One of the first species reported extinct as a result of climate change—a tiny, colorful land snail endemic to Aldabra atoll in the Seychelles Islands—was rediscovered by an expedition led by the Seychelles Island Foundation in August this year.

Prior to this, the last specimens of deep purple, pink-striped Aldabra banded snails (Rhachistia alababrae) were sighted in 1996. Searches for the snail conducted in 2005 and 2006 were unsuccessful, and it was declared extinct in 2007, when a Biology Letters study by Justin Gerlach of the Nature Protection Trust of Seychelles in the U.K. correlated the organism’s disappearance with a decrease in rainfall as a result of short-term climate change. The snail’s extinction was cited as an example of a species whose loss was directly caused by climate change, rather than other factors such as habitat loss or invasive species, earning the tiny creatures a mention in the 2014 report of the Intergovernmental Panel on Climate Change (IPCC).
While good news for snail lovers and conservationists, the animal’s rediscovery reignited a debate about the validity of Gerlach’s study. As early as 2007, when Gerlach published his report linking the snail’s extinction with climate change, biologist Clive Hambler of the University of Oxford and his colleagues submitted a comment to *Biology Letters* pointing to data collection and analysis errors and requesting that the study be retracted. Hambler’s comment was rejected for publication at the time; now, in statements to media outlets, Hambler has once again voiced his concerns about the study and called for a retraction. And in an e-mail to *The Scientist*, his frustration is clear, as he cites the “catastrophic failure of the peer review and editorial process.”

Specifically, Hambler and his colleagues argue that the Gerlach study provided few details of the survey method used, missed some recorded observations of the species, and used climate change data that amplified the trend of lower rainfall. In addition, because the surveys only sampled a small portion of the largely inaccessible islands, said Hambler, who argued with his coauthors in 2007 that more extensive searches would find the species—as proved to be the case this August. “I argue any one of [these errors] should be grounds for retraction,” Hambler told *The Scientist*.

*Biology Letters* has declined to retract, however, according to an editorial penned by the journal’s editor-in-chief Rick Battarbee. Although the paper’s conclusion of extinction was incorrect, “neither misconduct nor honest error have been the cause [of the invalid conclusion],” wrote Battarbee, a palaeoecologist at University College London.

“There are lots of papers that have been published in the past and subsequently were found to be inaccurate,” Battarbee told *The Scientist*. “The fact that someone wanted to contest these analyses, the data, or the interpretation is just standard [scientific process].”