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 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.

**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 investiga-
tors observed a dose-response relationship, with more frequent aspirin use associated with greater risk.

**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 prespecification 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.

**CLINICAL IMPLICATIONS**

From a purely science-of-medicine perspective, the strength of evidence is not sufficiently robust to be clinically directive. These findings are, at best, hypothesis-generating that should await validation in prospective randomized studies before guiding clinical practice or patient behavior. However, from an art-of-medicine perspective, based on the limited amount of available evidence, there are some courses of action available to the thoughtful clinician. In the absence of definitive evidence regarding whether limiting aspirin exposure mitigates AMD risk, one obvious course of action is to maintain the status quo. This is currently the most prudent approach, especially in secondary prevention settings where the benefits of aspirin are indisputable and greatly exceed the risk. For primary prevention of cardiovascular disease, where the evidence is less certain, the decision to prescribe aspirin should be predicated on the balance of risks (bleeding and possibly AMD) and benefits (cardiovascular disease and possibly cancer). For guideline-eligible patients (the 10-year risk of myocardial infarction in men aged 45-79 years is >4%, and the 10-year risk of stroke in women aged 55-79 years is >3%, and in whom the bleeding risk is low), the presence or absence of strong risk factors for neovascular AMD might tilt treatment decisions in one direction or the other. For patients taking long-term aspirin for other indications (pain control), caution is warranted in light of these observations. In the final analysis, decisions about aspirin use are best made by balancing the risks against the benefits in the context of each individual’s medical history and value judgments.

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