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ASPIRIN FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN

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Introduction

Cardiovascular disease (CVD) accounts for 34% of overall mortality in the United States or an average of 1 death every 38 seconds.[1] While the majority of these events are related to coronary heart disease (CHD), stroke accounts for a sizeable burden of CVD among postmenopausal women.[1, 2] Before 75 years of age, a higher proportion of CVD events due to CHD occur in men than in women, as opposed to a higher proportion of events due to stroke occurring in women.[1] Sex-based disparities in medical care are well documented,[3, 4] and under-treatment of women with aspirin for secondary prevention of CVD is a blatant example of the quality chasm described in the Institute of Medicine report "between the care we have and the care we could have."[5] However, while aspirin appears to be of substantial net benefit in secondary prevention,[6, 7] the balance of its beneficial effects and bleeding hazards in primary prevention remains less certain, especially in women. The current review examines the evidence and provides recommendations for the use of aspirin for primary prevention of CVD in women.

Evidence for the Use of Aspirin in Primary Prevention

Several randomized controlled trials (RCTs) examined the benefits of aspirin in primary prevention for CVD.[8–13] The largest of those, the Women's Health Study[13] (n= 39,876 women), reported a significant benefit from aspirin for the reduction of stroke in women (RR=0.83, 95% CI: 0.69–0.99), specifically ischemic stroke (RR=0.76, 95% CI: 0.63–0.93), but no benefit for the reduction of combined CV events, myocardial infarction (MI), and CVD or all-cause mortality. The Antithrombotic Trialists' (ATT) Collaboration conducted a meta-analysis of 6 primary prevention trials of aspirin using individual participant data on >95,000 individuals.[14] They demonstrated that aspirin was associated with a 12% reduction in serious vascular events due mainly to a reduction of about one-fifth in nonfatal MI. This was, however, associated with an increase in major bleeding risk and no benefit in reducing CVD or all-cause mortality. Although this meta-analysis did not include separate effectiveness data for women and men, it did not find gender differences in the reduction in specific vascular outcomes after adjustment for multiple comparisons.[14]

Earlier, Berger and colleagues performed a sex-specific meta-analysis using aggregate data from the same aforementioned primary prevention trials.[15] Again, they reported significant reductions with aspirin in CVD events and stroke among women, driven predominantly by a reduction in ischemic stroke, but no significant reductions in MI or cardiovascular mortality and an increased risk of bleeding.[15]

Thus, aspirin appears to have a differential benefit in primary prevention of CVD depending on sex: men derive benefit in MI reduction and women in ischemic stroke reduction. However, this differential effect is based predominantly on non pre-specified pooled data analyses and should be interpreted with caution.

Estimating Cardiovascular Risk of Women

The current framework for assessment of CVD risk includes risk equations that assess the absolute risk in the next 10 years based on multivariable equations that include a number of established risk factors. A number of risk scores are currently available. Of these, the 1998 Framingham Risk Score[16] has been broadly validated, has the most years of follow-up, and provides excellent

discrimination of high- (≥20%), intermediate- (10–20%), and low-risk (<10%) individuals. A newer version of this score was published with the added utility of predicting 10-year global CVD risk and specific endpoints, including stroke.[17] The Reynolds Risk Score is another score with good face validity that estimates women's CVD risk, including stroke and revascularization, based on a large panel of traditional and novel risk factors.[18] The U.S. Preventive Services Task Force (USPSTF)[19] report outlined several important risk factors for ischemic stroke based on the Framingham model, which included age, high blood pressure, diabetes, smoking, CVD history, atrial fibrillation, and left ventricular hypertrophy. They also provided the following Web link for a 10-year Framingham stroke risk calculator:[19] www.westernstroke.org/index.php?header_name=stroke_tools.gif&main=stroke_tools.php.

Overall, a careful and individualized assessment of the risk of ischemic stroke, the primary target for aspirin cardioprophylaxis among women, should be undertaken. The ACCF/AHA report on Performance Measures for Primary Prevention of Cardiovascular Disease recommended that women receive identical advice for most CVD risk factors as men and global risk screening to be undertaken for all women ≥45 yrs.[20]

Aspirin Safety and Bleeding Risk

Low-dose aspirin for cardioprophylaxis is associated with a 2- to 4-fold increase in upper gastrointestinal bleeding (GIB) risk.[21] The GIB risk, which accounts for the majority of aspirin-related bleeding, fluctuates with the varying gastrointestinal risk. A notable finding of the ATT meta-analysis is the recognition that the main risk factors for coronary events were the same associated with hemorrhagic events (e.g., age, sex, tobacco, diabetes, BMI, mean blood pressure, cholesterol).[14] While a history of peptic ulcer appears to be the most important risk factor, age is another important risk factor; the relative increase in risk starts at 60 years of age and rises progressively in a nonlinear fashion. In a multicenter study from Europe, over 60% of aspirin users are > 60 years of age, with 4–6% having a recent history of peptic ulcer disease and >13% using other NSAIDs.[22] The average excess risk of upper gastrointestinal complications attributable to aspirin was around 5 cases/1,000 aspirin users-years, but was over 10 cases/1,000 person-years in 10% of aspirin users at increased risk.[22] Bhatt and colleagues cautioned against the synergism between aspirin and NSAID or anticoagulant co-therapy, which substantially increases the risk of ulcer complications, and advocated the use of proton pump inhibitors (PPIs) and testing and eradication of H. pylori when needed.[21] The use of enteric-coated and buffered formulations does not reduce the GIB complications, as these are largely related to aspirin's systemic effects.[23] Substitution of clopidogrel for aspirin is also not recommended and is inferior to aspirin and PPI combination.[24]

Clinicians should assess and discuss the GIB risk of aspirin and its manifestations because they might be mitigated by a patient's early recognition of its signs and symptoms (hematochezia, hematemesis, melena, syncope, and lightheadedness) and the patient's preference.

Aspirin Dose

A meta-analysis of antiplatelet therapy in patients at high-risk for occlusive vascular events demonstrated that aspirin at 75–150 mg daily doses are as effective as higher doses.[6] The effects of doses <75 mg daily were less certain.[6] The AHA Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy[21] advocated use of the 81 mg aspirin dose for the chronic phase of CVD therapy. The 2009 USPSTF report conceded that the optimum aspirin dose for preventing CVD is not definitively established but concluded that a dose of 75 mg/day appears as effective and safer than higher dosages.[19]

Overall, the saturability of the antiplatelet effect of aspirin at low doses, the lack of dose-response relationship in studies evaluating its clinical efficacy, and the dose-dependence response of its side effects all support the use of a low dose of aspirin (such as the 81 mg dosage form available in the United States).

The U.S. Preventive Services Task Force Recommendations

In 2009, the USPSTF revised and updated their prior recommendations[25] on the use of aspirin for the primary prevention of CVD.[19] The USPSTF examined the new evidence published since 2002, synthesized it according to sex, and provided an algorithm for clinicians to assess the potential benefits and risks of aspirin therapy (Figure 1). Overall, the USPSTF found good evidence that aspirin decreases the incidence of MI in men and ischemic strokes in women, but it increases the incidence of GIB and hemorrhagic strokes.

Based on the overall data, the USPSTF encouraged the use of aspirin among women 55–79 years of age when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastro-

<table>
<tr><th>Population</th><th>Men
Age 45–79 Years</th><th>Women
Age 55–79 Years</th><th>Men
Age <45 Years</th><th>Women
Age <55 Years</th><th>Men & Women
Age ≥80 Years</th></tr>
<tr><td></td><td>Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage.</td><td>Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage.</td><td>Do not encourage aspirin use for MI prevention.</td><td>Do not encourage aspirin use for stroke prevention.</td><td>No recommendation</td></tr>
<tr><td></td><td colspan="2">Grade: A</td><td colspan="2">Grade: D</td><td>Grade: I
(Insufficient Evidence)</td></tr>
<tr><td>How to Use This Recommendation</td><td colspan="5">Shared decision making is strongly encouraged with individuals whose risk is close to (either above or below) the estimates of 10-year risk levels indicated below. As the potential CVD benefit increases above harms, the recommendation to take aspirin should become stronger.

To determine whether the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage, both 10-year CVD risk and age must be considered.
Risk level at which CVD events prevented (benefit) exceeds GI harms
<table>
<tr><th colspan="2">Men</th><th colspan="2">Women</th></tr>
<tr><th colspan="2">10-year CHD risk</th><th colspan="2">10-year stroke risk</th></tr>
<tr><td>Age 45–59 years</td><td>≥4%</td><td>Age 55–59 years</td><td>≥3%</td></tr>
<tr><td>Age 60–69 years</td><td>≥9%</td><td>Age 60–69 years</td><td>≥8%</td></tr>
<tr><td>Age 70–79 years</td><td>≥12%</td><td>Age 70–79 years</td><td>≥11%</td></tr>
</table>
The table above applies to adults who are not taking NSAIDs and who do not have upper GI pain or a history of GI ulcers.
NSAID use and history of GI ulcers raise the risk of serious GI bleeding considerably and should be considered in determining the balance of benefits and harms. NSAID use combined with aspirin use approximately quadruples the risk of serious GI bleeding compared to the risk with aspirin use alone. The rate of serious bleeding in aspirin users is approximately 2–3 times higher in patients with a history of GI ulcers.</td></tr>
<tr><td>Risk Assessment</td><td colspan="5">For men: Risk factors for CHD include age, diabetes, total cholesterol level, HDL level, blood pressure, and smoking.
CHD risk estimation tool: http://hp2010.nhlbihin.net/atpiii/calculator.asp

For women: Risk factors for ischemic stroke include age, high blood pressure, diabetes, smoking, history of CVD, atrial fibrillation, and left ventricular hypertrophy.
Stroke risk estimation tool: http://www.westernstroke.org/index.php?header_name=stroke_tools.gif&main=stroke_tools.php</td></tr>
<tr><td>Relevant Recommendations from the USPSTF</td><td colspan="5">The USPSTF has made recommendations on screening for abdominal aortic aneurysm, carotid artery stenosis, coronary heart disease, high blood pressure, lipid disorders, and peripheral arterial disease. These recommendations are available at http://www.preventiveservices.ahrq.gov.</td></tr>
</table>

Figure 1. Clinical summary of the 2009 U.S. Preventive Services Task Force (USPSTF) Recommendations on aspirin for the prevention of cardiovascular disease. Abbreviations: CHD = coronary heart disease, CVD = cardiovascular disease, GI = gastrointestinal, HDL = high-density lipoprotein, MI = myocardial infarction, NSAIDs = nonsteroidal anti-inflammatory drugs.

intestinal hemorrhage (class A recommendation).[19] The USPSTF noted that the benefit-risk balance favors the use of aspirin with increasing age but that there is insufficient evidence to assess the balance of benefits and harms in women ≥80 years of age. It also discouraged the use of aspirin for primary prevention in women <55 years of age.[19]

Conclusions

Among women with no prior history of CVD, a careful and individualized assessment of the risks of ischemic stroke and bleeding should be undertaken before administering aspirin for cardioprophylaxis. In general, women between 55 and 79 years of age appear to benefit from aspirin use for the primary prevention of ischemic stroke, provided they are not at increased risk for gastrointestinal bleeding or hemorrhagic strokes. Low-dose aspirin (81–100 mg) is an effective and safer regimen than higher doses. Avoiding concomitant therapy with anticoagulants and NSAIDs is advised, and the use of PPIs and H. pylori testing and eradication appear reasonable gastroprotective strategies when needed.

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