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ASA 4 CVD Prevention: Benefits & Risks

This ***Heartbeat*** will outline a plan of how aspirin should be used in both the primary and secondary prevention of cardiovascular disease (CVD)—keeping in mind that the benefits and risks need to be considered carefully and individually when prescribing aspirin, particularly in primary prevention. Additionally, treatment differences between men and women and a few of the most common difficult clinical treatment decisions will be highlighted.

The support data comes from four very recent reports. The first two studies are post hoc analyses that deal with aspirin use in secondary prevention, a third paper is a review of the current knowledge of the benefits and risks of long-term aspirin therapy for the prevention of CVD, and the fourth is a review of the new recommendations of the **US Preventive Services Task Force** (USPSTF) on the use of aspirin for primary prevention.

What's the Correct Dose of Aspirin?

Evidence is scarce regarding the optimal aspirin dose for preventing CV events. A post hoc analysis of the association between aspirin dose and thrombotic and hemorrhagic outcomes in the randomized, placebo-controlled CHARISMA trial was performed regarding the use of clopidogrel in patients at high risk for atherothrombotic events. [1]

All participants received between 75 and 162 mg of aspirin per day (7180 received <100 mg, 4961 received 100 mg, and 3454 received >100 mg). After a median follow-up of 28 months, aspirin dose was not associated with any differences in incidence of the primary combined endpoint of death, myocardial infarction (MI), or stroke, but a trend toward higher incidence of clinically significant bleeding was exhibited with higher daily doses of aspirin. In patients who were also taking clopidogrel, the incidence of severe or life-threatening bleeding was significantly higher with daily aspirin doses >100 mg than with doses <100 mg.

This analysis suggests that low doses of aspirin (81mg) are better than high doses for prevention of CVD, especially in patients taking clopidogrel –offering the same benefit with lower risk.

Better Data on Women—The Women's Health Initiative (WHI) Observational study provides additional evidence that aspirin may reduce the risk of death in postmenopausal women who have heart disease or who have had a stroke and, in concurrence with the CHARISMA data, show that low-dose aspirin is just as effective as higher doses.[2] This observational study found that *total mortality and cardiovascular mortality were lowered in aspirin users and that the benefit does not seem to be dose-related, whereas the side effects are dose-related*. **Dr Jacques Rossouw** (chief of the WHI branch at the National Heart,

Lung, and Blood Institute, Bethesda, MD), said, *"If you can reduce risk with an intervention as simple as a low-dose aspirin every day, then that's quite something."*

Benefits and Risks of ASA Therapy

A review the current knowledge of the benefits and risks of long-term aspirin therapy for the prevention of CVD was performed via a review of relevant articles.[3] The conclusion was that both the benefits and risks need to be considered carefully when prescribing aspirin, particularly in primary prevention. Patients should be prescribed lower doses rather than higher doses of aspirin. Co-therapy with non-steroidal anti-inflammatory drugs, clopidogrel or warfarin increases the risk of gastrointestinal side effects, while co-therapy with proton pump inhibitors reduces it. Co-prescription of a proton pump inhibitor may be necessary in patients at high risk for upper gastrointestinal complications.

New Primary-Prevention Recommendations

The last guidelines, published in 2002, were based on trials with limited data on women, whereas the new recommendations incorporate the results of the landmark **Women's Health Study** (WHS), which showed no reduction in MI and death with aspirin but a significant reduction in stroke. The new recommendations thus advise use of aspirin in men to reduce MI and in women to reduce stroke.

The following are 10 points to remember about aspirin for the primary prevention of CVD based on the USPSTF Recommendation Statement.[4] These were reproduced from *Cardiosource*.

1. The lifetime risk of CV events in adults older than 40 years is two in three for men and more than one in two for women.

2. These U.S. Preventive Services Task Force recommendations are for men and women without known CAD or stroke, and based on a 32% reduction in risk of myocardial infarction (MI) in men and a 17% reduction in stroke in women with regular aspirin use.

3. Estimated GI bleeds per 1,000 men would be 8 at 45-59 years, 24 at 60-69 years, and 36 at 70-79 years; and for 1,000 women: 4, 12, and 18, respectively. The risks of GI bleeding were developed assuming no use of nonsteroidal anti-inflammatory drugs or other conditions associated with increased risk of GI bleeding.

4. Encourage men ages 45-79 years to use aspirin when the potential benefit of a reduction in MIs outweighs the potential harm of an increase in GI hemorrhage (GI bleeds) (Level A recommendation).

5. The value of aspirin for reducing MI would exceed risk of GI bleeding if 10-year risk is ≥4% in men 45-59 years, ≥9% in men 60-69 years, and ≥12% in men 70-79 years.

6. Encourage women ages 55-79 years to use aspirin when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in GI hemorrhage (Level A recommendation).

7. The value of aspirin for reducing strokes in women would exceed risk of bleeding if the 10-year risk is ≥3% for women 45-59 years, ≥8% for women 60-69 years, and ≥11% for women 70-79 years.

8. The optimal dose of aspirin is not known, but a dose of about 75 mg/d seems as effective as higher doses, which may increase risk of GI bleeding.

9. Evidence is insufficient to assess the balance of benefits and harms of aspirin for CVD prevention in men and women ages 80 years or older. Do not encourage aspirin use for CVD prevention in women younger than 55 years and in men younger than 45 years (Level D recommendation).

10. Clinicians and policymakers should understand the evidence, but individualize decision making to the specific patient or situation.

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A valuable feature of the new USPSTF recommendations is the emphasis on shared decision making: discussing the benefits and risks of initiating aspirin with the patient and individualizing decisions. There is one group of patients who should absolutely avoid aspirin—those who are at relatively high risk for intracranial bleeding.

Mehta concludes in an accompanying editorial: "The USPSTF has provided us with an important document that is clear and user-friendly for the busy clinician. *Aspirin continues to be underused, and the routine incorporation of the USPSTF's recommendations into the daily practice of clinicians will no doubt increase the use of aspirin and, in turn, prevent many thousands of cardiovascular events every year*."[5]

Is ASA Enough?

Aspirin is the prophylactic anti-platelet drug of choice for all people with CVD (secondary prevention) and for primary prevention of CVD as indicated unless an obvious contraindication exists. However, protection with aspirin anti-platelet therapy in people with a very high risk CVD is unsatisfactory in absolute terms. Adding a second anti-platelet drug to aspirin (clopidogrel) produces additional benefit for those at very high risk (acute coronary syndrome [ACS], percutaneous coronary intervention [PCI])—diabetes may have to be added, but more data is necessary. In patients at high risk of CVD but not presenting acutely or without stent placement, there is only weak evidence of dual therapy benefit, and the hazards of treatment (bleeding) almost match any benefit obtained.[6]

Should patients on long-term warfarin take aspirin for heart disease?

Whether to add aspirin to their treatment or continue it is a common clinical question for patients receiving warfarin therapy. The literature on the topic is limited but suggests the decision to prescribe aspirin should be individualized—again based on CV benefit, which varies with each clinical situation, versus the increased risk of bleeding, which is greater with combination therapy (`1.5x higher).

In patients with stable CAD or those at risk for CAD where primary prevention is considered, warfarin is almost as effective as aspirin in reducing the rate of CV events. The benefit of adding aspirin is not substantial and the risk outweighs the benefit. Continuing warfarin alone would be the preferred strategy.

By contrast, in patients with ACS, PCI with a stent, or a mechanical heart valve, combination therapy is usually recommended.

The addition of aspirin 81mg once daily to therapeutic warfarin is recommended for all patients with mechanical heart valves and those patients with biologic valves who have risk factors including atrial fibrillation, previous thromboembolism, LV dysfunction or hypercoagulable condition.

The optimal anti-thrombotic strategy after PCI—dual aspirin and clopidogrel—for patients receiving warfarin is unclear. The prevalence is increasing and triple drug therapy has proven quite hazardous. In a recent study highlighting the risks of combining dual anti-platelet therapy along with warfarin and an accompanying editorial the authors suggest—and this sounds reasonable—that temporary interruption of warfarin therapy should be considered after stenting, particularly in patients at relatively low risk for thromboembolism (CHAD 2 score $\leq$ 2)—supported even further by the ACTIVE trial showing decreased thromboembolic risk with dual anti-platelet therapy compared to aspirin alone in AF (presented in March at the ACC meeting). Similarly, the duration of dual anti-platelet therapy in stent recipients who require anticoagulation should be minimized; this is an important consideration in the choice between a drug-eluting stent (one year) and a bare-metal stent (one month).[7]

Possible strategies to minimize hemorrhagic risk in patients on triple therapy after PCI are presented in the table below.[8]

1. Vigilant INR monitoring in the first 4 weeks, especially among patients newly starting warfarin or anti-platelet therapy
2. Judicious use of "bridging therapy" with heparin (e.g., highest-risk mechanical prosthetic heart valve, venous thromboembolism within 3 months)
3. Improved risk stratification for warfarin use in patients with AF (CHADS2 score ≥2)—always use warfarin for score ≥ 3
4. Increased awareness of the most potent risk factors for erratic INR control: decompensated heart failure, enteral feeding, erratic dietary vitamin K intake, amiodarone therapy, chemotherapy, protracted new use of high-dose acetaminophen
5. Attention to blood pressure control with goal <130/80 mm Hg
6. Prophylactic proton-pump inhibition for patients with peptic ulcer disease (preferably pantoprazole sodium[protonix])
7. Eradication of *H. pylori* in patients with peptic ulcer disease and uninvestigated dyspepsia
8. Explicit warnings regarding use of over-the-counter NSAIDs and aspirin-containing compounds
9. Physical therapy/safety evaluation before discharge to minimize fall risk
10. There is insufficient evidence to support lower INR target intensities; patients and their caregivers need to be cognizant of the trade-offs inherent to this strategy

Summary/Conclusions:

PRIMARY PREVENTION: The net benefit of aspirin therapy for stroke prevention in women and MI prevention in men depends on the initial risks for stroke and gastrointestinal bleeding. Decisions concerning aspirin therapy should always be individualized to consider the overall risk for stroke or MI and gastrointestinal bleeding.

CHD CALCULATOR

Daily use of aspirin for men over 45 and women over 55 is recommended if the chances of preventing a CV event are greater than precipitating a GI bleed.

Aspirin dosage of 81 mg should do it. There is no evidence that larger aspirin doses decrease CV risk, and there is evidence that larger doses increase GI bleed risk.

Both sexes should stop by age 80, unless their doctors say otherwise.

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