Cardiovascular Therapeutics

Aspirin for Primary Cardiovascular Prevention: When Is It Worth the Risks?

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Low-dose aspirin is widely used by individuals to prevent first myocardial infarction and stroke. Although many health care professionals and patients believe that aspirin is safe and effective, the evidence is far from conclusive. As a result, current practice guidelines are inconsistent and leave practitioners with many unanswered questions. Because aspirin is available without prescription, pharmacists may often be the only health care professional positioned to advise and educate the patient.

Many individuals take a low-dose aspirin daily with or without a physician's advice for the primary prevention of myocardial infarction (MI) and stroke. However, it has become increasingly clear that aspirin may not be appropriate for everyone. Recent research has provided some additional information, but many questions are still unanswered. This article will review the current evidence, recommendations, and issues that have yet to be resolved.

STUDIES EVALUATING ASPIRIN'S EFFICACY

In 2002, the United States Preventive Services Task Force (USPSTF) began endorsing the widespread use of low-dose aspirin for primary prevention of cardiovascular disease (CVD).¹ These recommendations were based on findings from 5 clinical trials conducted primarily in White males over 50 years of age. Meta-analyses of pooled data from the 5 trials demonstrated a risk reduction of 28% (95% confidence interval [CI], 0.60-0.87) for coronary heart disease (CHD). No significant benefit was seen for total mortality or stroke. Low-dose aspirin was recommended for primary prevention in patients at increased risk of developing CVD, including men over 40 years of age, postmenopausal women, and younger individuals with established coronary risk factors.

In 2009, acknowledging the limitations of the earlier data and notably the lack of evidence in women, the guidelines were revised.² In addition to subgroup analyses of the 5 earlier trials, data from

the Women's Health Study (WHS) were included.³ The WHS was a double-blind trial of 39,876 female health professionals randomized to aspirin 100 mg every other day or placebo. After 10 years of follow-up, no reduction was seen in the combined cardiovascular events endpoint or the individual endpoints of MI, cardiovascular death, or all-cause mortality. However, aspirin was shown to reduce the risk of stroke (relative risk [RR], 0.83; 95% CI, 0.69-0.99) and more specifically ischemic stroke (RR, 0.76; 95% CI, 0.63-0.93). The risk of hemorrhagic stroke was not increased among women receiving aspirin; however, gastrointestinal (GI) bleeding was more frequent including a 40% increase in serious GI bleeds (RR, 1.40; 95% CI, 1.07-1.83). Based on these findings, the 2009 guidelines supported the use of aspirin in men 45 to 79 years of age for prevention of first MI and women 55 to 79 years of age for prevention of ischemic stroke provided the potential benefit was judged to outweigh the risk of GI bleed. Primary prevention with aspirin was not recommended for younger men or women. For individuals 80 years of age or older, the USPSTF acknowledged that the evidence was insufficient to make any recommendations.

Although the 2009 guidelines were based on the best available evidence at the time, all of the trials had a number of important limitations. These included issues with study design such as lack of blinding and early termination. The majority of studies were limited to White males or health care providers, thus reducing

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the generalizability of the results. In addition, some trials excluded individuals with evidence of adverse events or medication noncompliance during pre-trial run-in periods. The gender-specific effects must be interpreted with some caution, as the majority of women in the analyses were participants in one trial, the WHS, and all were younger than 65 years of age. This is a population in which overall event rates are low and stroke is typically more common than MI.

Inconsistencies in the earlier data along with the failure of more recent studies to support the benefits of aspirin have raised many questions about the wisdom of widespread preventive use.⁴ A major area of uncertainty involves the impact of baseline cardiovascular (CV) risk on the balance between benefit and harm. Even among populations generally considered to be at high risk for coronary events, aspirin's net benefit is uncertain. Among diabetic patients whom many consider to have a coronary equivalent, 2 studies, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial⁵ and the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial,⁶ failed to show a benefit among those without evidence of prior CV events. The Dialysis Outcomes and Practice Patterns Study (DOPPS) was an observational trial in 28,320 patients receiving hemodialysis for chronic renal disease.⁷ Although aspirin therapy was associated with a decreased risk of thrombotic stroke, the risks of MI and cardiac events were increased. Interpretation of this study is complicated, however, by the inclusion of patients both with and without known CVD. The Aspirin for Asymptomatic Atherosclerosis (AAA) trial conducted in Scotland found no benefit and a higher risk of major bleeding and gastric ulcers with aspirin therapy in 3,350 patients aged 50 to 75 years with asymptomatic peripheral vascular disease (PVD).⁸

META-ANALYSES

Many of the individual trials of primary prevention were underpowered to detect a net benefit in low-risk individuals where cardiac event rates are typically low. To address this concern, several recent meta-analyses have been conducted. Unfortunately, the findings of these analyses have also been inconsistent.

The Antithrombotic Trialists' Collaboration (ATT) conducted a pooled analyses of 95,000 individuals from the 6 primary prevention trials that formed the basis of the 2009 guidelines.⁹ Aspirin therapy resulted in a small 0.07% annual absolute reduction in the risk of major vascular events (0.51% vs 0.57% per year; $P = .0001$). This corresponded to

a proportional reduction of 12% (RR, 0.88; 95% CI, 0.82-0.94; $P = .0001$). The decrease was due primarily to a reduction in nonfatal MI. This benefit however came at the expense of an increased risk for GI and extracranial bleeds (0.10% vs 0.07%; RR, 1.54; 95% CI, 1.30-1.82; $P < .0001$). There was no impact on vascular mortality. Aspirin therapy resulted in a slight increase in hemorrhagic stroke ($P = .05$) offset by a slight decrease in ischemic stroke ($P = .05$), resulting in no net difference. Surprisingly, age and gender did not appear to impact the effect of aspirin on vascular events. In addition, the proportional reduction appeared to be similar regardless of baseline 5-year risk for CHD, although the authors noted that the number of individuals in the high-risk group may have been too small to yield reliable results.

A later meta-analysis included the same 95,000 patients from the 6 trials plus an additional 7,105 patients from 3 more recent trials. In addition, this analysis took a unique approach to analyzing the data.¹⁰ Because aspirin may have varying effects on different endpoints, combined endpoints can be misleading. In this analysis, separate meta-analyses were conducted for each of the following 6 endpoints: total CHD, nonfatal MI, total CV events, stroke, CV mortality, and all-cause mortality. Primary prevention with aspirin decreased the risk for total CV events (odds ratio [OR], 0.865; 95% CI, 0.804-0.930; $P = .001$) and nonfatal MI (OR, 0.813; 95% CI, 0.667-0.992; $P = .042$). Conversely, there were no significant differences in the incidences of total CHD, stroke, CV mortality, or all-cause mortality. Unfortunately, these analyses did not take into account bleeding events so net benefit could not be assessed. The findings are consistent with those of one additional meta-analysis of the same population from the 9 available studies conducted by different investigators. The analysis found a reduction in nonfatal MI (OR, 0.80; 95% CI, 0.67-0.96) but no effect on vascular mortality or stroke.¹¹ There was a significant increase in total bleeding (OR, 1.70; 95% CI, 1.17-2.46) and serious bleeding (OR, 1.31; 95% CI, 1.14-1.50). These findings translated into a number needed to treat (NTT) to prevent one nonfatal MI of 162 versus a NTT to induce nonminor bleeding of 73.

Due to the lack of consistent evidence supporting the net benefit of aspirin, the Renal Drugs Advisory Committee of the US Food and Drug Administration (FDA) has rejected requests from Bayer Healthcare to change the product labeling to include use for primary prevention of MI.¹² When explaining their decision, the committee cited uncertainty of the

overall benefit-risk ratio, inadequate data in certain populations such as women and non-Whites, lack of an overall effect on mortality, and a trend toward excess strokes in some populations. Due to concerns about the widespread unlabeled use of nonprescription aspirin by consumers for cardioprotection, the FDA has also provided a consumer brochure that is available online.¹³

INCONSISTENCIES AMONG CURRENT CLINICAL PRACTICE GUIDELINES

Since the release of the 2009 USPSTF guidelines, several more recent practice guidelines have been released by other professional organizations. Although the Antithrombotic Therapy and Prevention of Thrombosis Guidelines (AT9) published by the American College of Chest Physicians in 2012 are somewhat similar to those of the USPSTF, they do not make distinctions based on gender.¹⁴ For primary prevention, aspirin, 75-100 mg daily, is recommended for all adults over 50 years of age regardless of CV risk. However, in their supporting remarks, the panel acknowledges that aspirin must be taken for a prolonged period of time to derive a relatively small benefit that may not be justified in those at low risk. In contrast, based on their interpretation of the ATT meta-analyses described previously, the 2012 European guidelines do not recommend aspirin for primary prevention in individuals with no overt CV disease.¹⁵ Likewise, the 2011 Canadian guidelines do not recommend aspirin for primary prevention due to the relatively small risk reduction shown in the trials coupled with the increase in bleeding.¹⁶ It will be interesting to see if future updates of the USPSTF guidelines follow this trend. In the meantime, these inconsistencies leave practitioners who are attempting to advise patients with many unanswered questions.

VARIATIONS IN INDIVIDUAL RESPONSE TO ASPIRIN

The potential benefits of aspirin are primarily due to irreversible inhibition of the cyclooxygenase (COX)-1 enzyme, thus preventing platelets from clumping together. These platelet aggregates often trigger the clotting cascade leading to thrombus formation and vessel occlusion as occurs in MI or thrombotic stroke. It has longed been recognized, however, that not all individuals derive the same antiplatelet effect from a similar dose of aspirin. Studies using various platelet aggregation tests suggest that anywhere from 2% to 50% of patients may have some degree of aspirin resistance.¹⁷ The concept of resistance is further supported by the fact that many

individuals experience a cardiac event while on treatment. The underlying mechanisms for this aspirin resistance are not fully understood but are likely multifactorial. Numerous factors may play a role including malabsorption, upregulation of alternative aggregation pathways, overexpression of COX-2 with induction of thromboxane A2 synthesis, patient noncompliance, and coadministration of other nonsteroidal anti-inflammatory drugs (NSAIDs) that compete for the COX-1 binding site.

Various genetic polymorphisms have been studied relative to aspirin resistance with mixed results.¹⁸ Recently Voora and colleagues shed some new light on the influence of genetic factors using a novel approach.¹⁹ Whereas the DNA sequence remains relatively fixed for each cell, messenger ribonucleic acid (mRNA) coded proteins reflect genetic activity that is responsive to environmental changes, disease states, and drugs. Measurement of mRNA is rapid, specific, and sensitive and has been used to do gene expression profiling that may indicate how patients respond to various interventions. The Voora study included 3 patient groups taking low-dose aspirin, a study cohort of healthy volunteers ($n = 50$), a validation cohort of healthy volunteers ($n = 53$), and a second validation cohort of outpatient cardiology patients ($n = 25$). After 1 month, platelet function was assessed using a platelet function score derived from a composite of 4 platelet function assays and the *VerifyNow* aspirin assay (Accumetrics Inc., San Diego, CA). RNA profiles were developed for platelet-specific genes. The study identified a set of 60 genes, coined the aspirin response signature (ARS), that correlated with an individual's response to aspirin whether or not the patient had CVD. Moreover, this RNA signature was associated with the likelihood of MI or death (OR, 1.2; $P = .01$), independent of other CV risk factors. As compared to traditional risk factors, the inclusion of the ARS improved reclassification of CV risk ($P < .0002$). The investigators concluded that RNA profiles of platelet specific genes are novel biomarkers that may be useful in identifying patients who will not respond adequately to aspirin therapy and who are therefore at increased risk for MI or death. The next step will be to develop a simple blood test that can be used in clinical practice.

IMPLICATIONS FOR PRACTICE

For patients with pre-existing CVD, the potential benefits of aspirin are indisputable. Long-term therapy for secondary prevention reduces the annual risk of serious vascular events such as nonfatal MI, stroke, or vascular death by approximately 25%.^{20,21}

Conversely, for those with risk factors but no overt disease, the evidence for primary prevention is much less clear.

When recommending any drug or lifestyle change, the potential benefits must be carefully weighed against the potential for harm. Platelet inhibition may increase the risk of bleeding, including serious vascular events such as hemorrhagic stroke. In addition, aspirin inhibition of the COX enzymes blocks the synthesis of prostaglandins that are essential to protect the delicate mucosal lining of the GI tract, thus increasing the risk of major GI bleeds.

For clinicians, it is often useful to evaluate benefit and risk in terms of the numbers needed to treat or harm. Using the findings of the ATT meta-analyses, the authors of the AT9 guidelines calculated that aspirin use in patients at low risk without prior CV events would be associated with 6 fewer MIs and 4 additional major bleeds with no net effect on nonfatal stroke for every 1,000 patients treated over a 10-year period.¹⁴ For those at moderate or high risk, aspirin would be expected to reduce nonfatal MIs (19 fewer and 31 fewer, respectively) and increase major bleeds (16 more and 22 more, respectively) per 1,000 patients treated.

A number of tools are available to assist practitioners in determining a patient's baseline risk. The most commonly used tool is the Framingham risk calculator, which is available online.^{22,23} This tool considers age, gender, systolic blood pressure, high-density lipoprotein (HDL) and total cholesterol, smoking status, and medications for hypertension to calculate an estimated 10-year risk of CVD. Individuals are characterized as low risk (<10%), moderate (10%-20%), or high risk (>20%). Most experts agree that aspirin is beneficial for high-risk patients, but it is likely not worth the risks for low-risk patients. For those in the moderate category, both clinical judgment and patient preference should be considered.

A recent study suggests that long-held beliefs about aspirin's ability to prevent heart disease may be hard to change. Data were collected from 33 primary care practices across 6 states.²⁴ Aspirin use was recorded across 4 time periods. The most notable finding was that between 2007 and 2011, despite studies disputing the efficacy of aspirin and changing practice guidelines derived from this evidence, the initiation of aspirin therapy for primary prevention steadily increased.

Despite the gaps in evidence and the inconsistencies among the practice guidelines, pharmacists can still provide much needed counseling and education to patients. It should be kept in mind that large

numbers of individuals take aspirin without medical advice and the product labeling offers no guidance for this use. Even among individuals taking aspirin at their doctor's direction, many may not receive adequate counseling. Many patients and some practitioners believe that enteric coated or buffered aspirin reduces the risk of adverse GI effects and bleeding. However studies do not support this. Based on 51,869 questionnaires, a Dutch study found that self-reported GI symptoms were similar between plain and buffered aspirin.²⁵ Similarly, no studies have proven that enteric coated aspirin results in fewer GI complications. In a study of patients with upper GI bleeding or perforation, 2,105 cases were compared to 11,500 controls.²⁶ Among these patients, 13.6% of cases and 7.3% of controls were exposed to aspirin (RR, 2.0; 95% CI, 1.7-2.3). No potential dose effect was seen within the range of 75 and 300 mg daily. Moreover, the risk with enteric coated aspirin was similar to that of plain aspirin. It is also important to remind patients that in the event of a sudden onset of chest pain and possible MI, a regular aspirin is preferred in order to facilitate faster absorption.

Patients should be cautioned that aspirin is a potent drug that should be taken daily only if recommended by their physician. Patients should report aspirin use along with their other medications to all health care providers and ask whether their aspirin should be temporarily stopped prior to interventional procedures. Patients should be cautioned that the effects of aspirin may be diminished by concomitant administration of NSAIDs such as ibuprofen due to competitive binding with the COX-1 enzyme. This can be minimized by taking the ibuprofen at least 30 minutes after the aspirin. Additionally, concomitant use of NSAIDs increases the risk of serious bleeding. Gastroprotective agents such as H2 antagonists or proton pump inhibitors should be considered to prevent GI bleeding. Concomitant use of other antiplatelet or anticoagulant drugs may also significantly increase the risk of hemorrhage.

SUMMARY

Studies suggest that approximately 40% of persons in the United States take aspirin regularly for cardiovascular prevention, with the majority using it for primary prevention.²⁷ An estimated 20% of these individuals do so without medical advice. Unfortunately the current evidence has not provided definitive proof of aspirin's effectiveness for primary prevention among those with low baseline risk. In addition, many of the clinical trials were conducted prior to the widespread use of other

preventive therapies such as statins. Whether aspirin's benefit is maintained in contemporary patients on these drugs requires further study. Given the potential for harm with aspirin and the difficulty of changing long-held beliefs, additional studies are urgently needed. In the interim, pharmacists can assist patients by helping them assess their overall risk, urging them to talk with their physicians before self-medicating, and screening medication histories for aspirin use and potential interactions. For those who are taking aspirin, pharmacists can also provide important counseling and education on proper administration, potential risks, and strategies to reduce adverse events.

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