Aspirin for Cardiovascular Disease Prevention: Indications, Contraindications, and the Type of Aspirin to Use

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ABSTRACT: The numerous expert guidelines for the use of aspirin can lead to confusion about prescribing or recommending it for the prevention of cardiovascular disease. This article addresses key questions about aspirin, including which guidelines should be followed; the benefits of and contraindications for aspirin; aspirin resistance, or reduced response; the use of aspirin for cardioprotection in persons with diabetes, and which of the different types of aspirin should be prescribed when.

KEYWORDS: Aspirin, acetylsalicylic acid, atherosclerotic cardiovascular disease, diabetes, prevention, guidelines

Sam is a 61-year-old man with type 2 diabetes that had been diagnosed 4 years ago. His father had had type 2 diabetes and had died at age 60 from a "cardiac event." Sam's past medical history is significant for osteoarthritis of his left hip, and he takes over-the-counter (OTC) ibuprofen as needed for pain.

His physical examination findings are unremarkable except for a body mass index of 34 kg/m^2 and a blood pressure of 135/85 mm Hg. Significant results of laboratory tests are as follows: glycated hemoglobin, 7.5%; total cholesterol, 200 mg/dL; triglycerides, 250 mg/dL; high-density lipoprotein cholesterol, 35 mg/dL; low-density lipoprotein cholesterol, 115 mg/dL; and mean platelet volume (MPV) of 12.5 fL.

His medications include metformin 2000 mg daily, ramipril 2.5 mg once daily, and atorvastatin 40 mg daily.

Should Sam be taking an aspirin, and if so, what dose and how often?

Here are some of the questions that a clinician might ask to help make the decision:

Which guidelines should we follow? How does aspirin (acetylsalicylic acid, or ASA) work? What is the evidence that aspirin has beneficial effects? What are the contraindications? What about aspirin resistance—or reduced response—how do you make that diagnosis? Sam is taking a nonsteroidal anti-inflammatory drug (NSAID)—is that a contraindication to adding aspirin? He has diabetes—how does that influence the decision? Are there different types of aspirin, and which one should I prescribe?

GUIDELINES

The myriad of available guidelines addressing aspirin therapy has led to confusion in prescribing or recommending it. In fact, less than half of physicians (42%-44%) report prescribing an antiplatelet therapy to patients with diabetes and vascular disease, and only 20% recommend treatment to patients with diabetes without known vascular disease.[1] Nearly all major organizations have made guideline recommendations regarding the use of aspirin for atherosclerotic cardiovascular disease (ASCVD) prevention. The American Heart Association/American College of Cardiology Foundation, the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists/American College of Endocrinology, and the US Preventive Services Task Force (USPSTF) are in agreement regarding the benefit of low-dose (75-162 mg) aspirin once daily for the secondary prevention of cardiovascular (CV) events in most high-risk patients. In patients who are at high risk because they already have occlusive ASCVD, it has been well established that long-term antiplatelet therapy (eg, with aspirin) reduces the yearly risk of serious vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death) by approximately 25%.[2]

The use of aspirin therapy for primary prevention is more

controversial and recommended based on a given patient's underlying risk factors. As recently as June 2016, the USPSTF had backed daily low-dose aspirin use for the primary prevention of ASCVD and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year ASCVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.[3] For adults aged 60 to 69 years, the task force recommends that the decision to initiate low-dose aspirin for the primary prevention of ASCVD and CRC should be an individual one. The task force states that the evidence is insufficient to recommend low-dose aspirin to patients younger than 50 or older than 70 years. If they are already taking aspirin, its continuation depends on balance of benefit vs safety.[3]

If a patient has underlying diabetes, the ADA guidelines recommend once-daily low-dose aspirin for individuals with an increased ASCVD risk (10-year risk > 10%) and not at increased bleeding risk. Aspirin is not recommended for ASCVD prevention in adults with diabetes who are at low ASCVD risk (10-year risk < 5%). Clinical judgment is required for those with diabetes and multiple other risk factors (10-year risk 5%-10%), and aspirin is recommended for all persons with known ASCVD.[4]

Sam has a calculated 10-year ASCVD risk of 27.1% (**Table 1**), clearly making him a candidate for aspirin therapy based on USPSTF and ADA guidelines. However, considering his comorbidities, should you give additional thought to his aspirin response or dose? Revisiting the half-life and mechanism of action of aspirin might lend some additional clarity.

Table 1. ASCVD Risk Estimator[a]

Risk Factor	Sam's Results
Gender	Male
Age	61 years
Race	White
Total cholesterol	200 mg/dL
High-density lipoprotein cholesterol	35 mg/dL
Systolic blood pressure	135 mm Hg
Hypertension treatment	Yes
Diabetes mellitus	Yes
Smoker	No
Calculated risk	27.1

[a]Risk estimation determined using the American College of Cardiology's ASCVD Risk Estimator, http://tools.acc.org/ASCVD-Risk-Estimator.

Table 2. Clinical Risk Predictors for High Platelet Reactivity[12]

Variable	Odds Ratio
Age > 63 y	2.11
Female gender	1.46
Diabetes mellitus	1.78
Body mass index > 30 kg/m^2	1.86
Reduced left ventricular function	1.54
Reduced renal function	1.48

HOW DOES ASPIRIN WORK?

Low-dose aspirin has been proven to reduce the risk of secondary CV events and mortality in high-risk patients with stable CV disease. This is primarily due to aspirin's ability to inhibit platelet aggregation. Platelet activation and aggregation are the most critical factors in the generation of thrombotic events. At low doses, ASA irreversibly acetylates a serine residue in the cyclooxygenase (COX)-1 enzyme and thereby prevents binding of arachidonic acid to the catalytic site and reduces production of prostacyclin. Reduction of prostacyclin results in lower levels of the thromboxane A_2 (TxA_2) and subsequent TxA_2-induced platelet aggregation. Although ASA inhibits both COX-1 and COX-2, its affinity for COX-1 is 166 times greater than for COX-2; thus, COX-1 inhibition is primarily responsible for ASA-induced reductions in TxA_2.[5]

Due to their original design as antipyretics and pain relievers, both immediate-release and enteric-coated aspirin formulations have a rapid onset of effect but a brief therapeutic window. Standard aspirin formulations are rapidly absorbed by the stomach and/or the upper small intestine and provide peak plasma aspirin concentrations within 40 minutes (immediate release) to 5 hours (enteric coated) after administration; however, the half-life of aspirin is only 15 to 20 minutes,[6] which limits the window of time during which ASA is available to inhibit platelets. In fact, immediate-release and enteric-coated formulations are undetectable in serum 4 to 6 hours after absorption, even though the body is making platelets 24 hours a day. So when prescribing aspirin, clinicians should keep in mind that the efficacy of ASA in the prevention of CV events relies largely on the ratio of platelet exposure to ASA vs platelet generation.

ASPIRIN RESISTANCE OR NONRESPONDERS

Unfortunately, the recommended once-daily low-dose aspirin may not provide adequate protection in many patients. Up to 37% of patients with a history of CV disease and up to 42% of patients with diabetes show a reduced response to aspirin therapy.[7] This reduced response to aspirin is most commonly known as aspirin resistance. The generally accepted definition of aspirin resistance is insufficient inhibition of COX-1 and residual platelet function on doses of aspirin of 75 to 300 mg/d.[8] In some it may be a reflection of nonadherence to

taking aspirin, but in others it can be associated with inflammatory states such as diabetes, smoking, metabolic syndrome, post-coronary artery bypass grafting, and extensive atherosclerosis. The number of newly formed platelets dramatically increases in inflammatory states, up to 20-fold in some cases. High platelet turnover results in increased numbers of newly formed platelets that are larger and more hyperreactive and that have been associated with an increased likelihood of thrombosis formation[9] and increased CV mortality.[10]

So this raises the question: How can the average clinician identify patients who are at increased risk for aspirin resistance?

MPV is standard on most commercial complete blood cell counts and is frequently overlooked as a marker of newly formed hyperreactive platelets. MPV is a machine-calculated measurement of the average size of platelets found in the blood, and it is the most accurate measure of platelet size and functional status. An increased MPV is an indicator of large, more reactive platelets from high platelet turnover. The normal range is 7.5 to 11.5 fL, and the size is inversely related to platelet count. Our patient had an elevated MPV (12.5 fL). MPV has been found to be increased before acute myocardial infarction, upon admission for severe cerebrovascular accident, and predictive of adverse cardiac outcomes.

Low-dose aspirin has been proven to reduce the risk of secondary cardiovascular events and mortality in high-risk patients with stable cardiovascular disease.

Aspirin resistance can also be measured with the following commercially available assays: VerifyNow (Accriva Diagnostics), which measures response to arachidonic acid, and AspirinWorks (Corgenics), which measures urinary thromboxane. Both tests are covered by insurance and are reimbursed at approximately $30. Current guidelines do not advocate routine assessments for aspirin resistance or aspirin nonresponders. However, aspirin-resistant patients are at a greater risk of death, myocardial infarction, or a new cerebrovascular event (hazard ratio, 3.12; 95% confidence interval, 1.10 to 8.90; $P = .03$).[11]

Alternatively, clinical risk factors have been identified that can accurately identify patients at risk for high platelet reactivity (HPR) and subsequent major adverse CV events who are undergoing nonurgent percutaneous coronary intervention. Clinical risk predictors for HPR in this population are listed in **Table 2**. Patients with a high score were significantly more likely to develop adverse cardiac events within 1 year of follow-up.[12] Although he is not undergoing intervention, our patient has several of these variables.

WHAT IS THE BEST DOSE OR FORMULATION?

So, what is the best antiplatelet regimen for Sam? Current guidelines recommend low-dose aspirin once a day. However, we know the half-life of OTC aspirin is approximately 20 minutes, that it is undetectable in 4 to 6 hours, and that Sam has risk factors for high platelet turnover. So should we increase the dose, increase the frequency, or consider a different formulation?

Studies have clearly demonstrated that doses of aspirin greater than 200 mg/d have the highest risk of gastrointestinal (GI) tract bleeding.[13] Many patients continue to purchase enteric-coated preparations of aspirin with the belief that enteric-coated aspirin offers GI tract protection. While the enteric coating on aspirin might offer relief from immediate GI tract irritation, it has not been found to reduce ulceration or bleeding. It is aspirin's systemic effect on the reduction of prostaglandins (which protect the stomach lining) that is associated with GI tract bleeding. Additionally, the enteric coating has been shown to reduce the bioavailability of aspirin and to potentially decrease aspirin's effectiveness.

What about dosing twice a day? Twice-daily dosing of ASA provides an additional window of time for inhibition of platelet activation in patients with high platelet turnover, which may improve response. In patients with diabetes and coronary artery disease, twice-daily dosing of aspirin 100 mg (total dose, 200 mg/d) or 75 mg (total dose, 150 mg/d) has been shown to improve platelet aggregation and slow recovery of thromboxane B_2 concentrations compared with once-daily administration of aspirin 100 mg/d or 75 mg/d. Interestingly, there was no improvement observed with twice-daily dosing of higher doses (ie, 162 mg once daily vs 162 mg twice daily [324 mg/d total dose], or 200 mg once daily vs 200 mg twice daily (400 mg/d total dose]), suggesting that this effect may plateau at certain daily dosages.[14] Adherence to twice-daily dosing would need to be taken into consideration. Patient nonadherence to coronary artery disease preventive regimens tends to be high (approximately 35% of patients),[15] and nonadherence tends to increase with increasing dosing frequency among patients with diabetes.

Two prescription formulations of aspirin are being introduced to address some of the shortcomings of the available OTC preparations. Durlaza (New Haven Pharmaceuticals), a microencapsulated extended-release aspirin formulation, was approved by the US Food and Drug Administration (FDA) in September 2015. The once-daily dosing is designed to provide 24-hour aspirin exposure. Durlaza was approved based on immediate-release aspirin's efficacy and safety data. No comparator or outcome trials have been completed to date. Yosprala

(Aralez Pharmaceuticals), a fixed-dose coordinated-delivery tablet combining immediate-release omeprazole 40 mg layered around a pH-sensitive enteric-coated aspirin (81 mg or 325 mg) core, was given approval by the FDA in September 2016 for the secondary prevention of CV and cerebrovascular events in patients who are at risk of developing aspirin-associated gastric ulcers.

ADDITIONAL CONSIDERATIONS BEFORE PRESCRIBING

Contraindications. Aspirin formulations have been around since antiquity, and most providers are well versed in the prescribing guidelines. The most common adverse effects are stomach pain, nausea, vomiting, and occult GI tract blood loss. Dangerous GI tract complications (bleeding, perforated ulcers) are relatively rare. The uncommon, so-called aspirin intolerance with potentially life-threatening bronchospasms occurs more frequently in persons with asthma, nasal polyps, or urticaria. Aspirin rarely causes hepatitis (if so, then especially in persons with systemic lupus erythematosus). The role of the salicylate in analgesic nephropathy (combination of analgesics) is not clear. High doses cause tinnitus and hearing loss. Doses of less than 100 mg/d very rarely cause complications. Newer microencapsulated formulations should not be taken 2 hours before or 1 hour after consuming alcohol, as it may interfere with the microencapsulation properties.

Use of ASA and NSAIDs together. Our patient has osteoarthritis and takes ibuprofen as needed for pain. Concerns about this drug combination include the increased risk of GI tract distress and bleeding and the increased risk of CV complications. In fact, in 2015 the FDA strengthened an existing warning in prescription drug labels and OTC Drug Facts labels to indicate that NSAIDs can increase the chance of a heart attack or stroke, either of which can lead to death. Additionally, people with established CV disease are at the greatest risk for CV adverse events associated with NSAIDs, and no period of use has been shown to be without risk.[16]

So is there a safer alternative?

Large clinical trials have confirmed that COX-2 inhibitors are associated with less GI tract toxicity than nonselective nonaspirin NSAIDs. However, these trials have also raised concerns about the CV safety of this class of drugs. COX-2 inhibitors not only lack the antiplatelet effects of aspirin, but also, by inhibiting the production of prostacyclin, they disable one of the primary defenses of the endothelium against platelet aggregation, hypertension, and atherosclerosis. COX-2 inhibitors also promote an imbalance in favor of vasoconstriction. These biologic actions, known since 1998, suggest that COX-2 inhibitors may increase the risk of CV events, including myocardial infarction, stroke, hypertension, and heart failure.[17]

So what should clinicians do at this time if they decide to prescribe a nonaspirin NSAID?

Although much recent attention has been given to the CV toxicity of COX-2 inhibitors, serious and occasionally life-threatening GI tract toxicity does occur with both nonselective nonaspirin NSAIDs and COX-2 inhibitors, although less so with the COX-2 class. In light of the current uncertainty about whether cardiotoxicity is a class effect of nonaspirin NSAIDs, we suggest using either a very short course of a nonselective nonaspirin NSAID with a concomitant gastroprotective agent or celecoxib for patients at high risk for GI tract toxicity, and, if possible, avoiding NSAIDs 8 hours before or 1 hour after taking aspirin.[17]

Table 3. Risk Factors Impacting Dose and Formulation of Aspirin

Age >63 years
Female gender
Diabetes mellitus
Body mass index >30 kg/m^2
Reduced left ventricular function
Reduced renal function
Mean platelet volume >11.5 fL
Known aspirin resistance
Smoking
Post-coronary artery bypass grafting
Extensive atherosclerotic cardiovascular disease
Inflammatory states

COST OF THERAPY

OTC aspirin can be purchased for pennies a day, so in the era of value-driven health care, can we justify prescribing a different formulation? Consider that thus far, ASA has had a long history of use with little change in delivery formulation, while residual risk in the form of both diabetes and obesity has continued to grow. CV disease remains the No. 1 killer in the United States. So, can we afford *not* to consider alternative treatment regimens? The average wholesale price of extended-release aspirin ($180) is considerably more than OTC aspirin and generic clopidogrel but is less than the cost of other antiplatelet agents or a recurrent event. Undoubtedly, until budget impact models become available to address coverage with managed markets, manufacturers will continue to subsidize consumers' out-of-pocket costs via drug coupons and copay cards, making alternative formulations a viable alternative for some.

WHAT ABOUT ALTERNATIVE ANTIPLATELETS?

Aspirin is the single most commonly prescribed medication worldwide and has been the gold standard for antiplatelet therapy with class 1, level of evidence A in most guidelines. Alternative antiplatelets can be considered if the patient is intolerant

of or allergic to aspirin. If the cost between aspirin and other antiplatelets equalize, and new data emerge favoring alternative antiplatelets, especially in certain disease states (eg, peripheral arterial disease, stroke), we can anticipate that the guidelines will change accordingly.

DISCUSSION

We have established that our patient is at high risk for ASCVD and aspirin resistance. Sam has diabetes, additional uncontrolled risk factors, and an elevated MPV of 12.5 fL. Based on the data presented, we would be concerned that he could be one of the nearly 28% of patients with similar comorbidities who are not protected by their low-dose aspirin.[18]

Given the new insights into the pathophysiology underlying aspirin nonresponse, it is becoming easier to identify patients at high risk for aspirin resistance based on clinical characteristics and common laboratory findings (eg, MPV). This additional information can guide the decision to consider alternative aspirin formulations or dosing regimens to address the residual risk of inadequate antiplatelet coverage. We would not need to consider a higher dose of ASA, because this has not been found to convey an additional benefit and can come at an increased risk of bleeding.

Overall, low-dose aspirin therapy is safe and well tolerated. Our patient has no absolute contraindications for aspirin usage, but his ibuprofen use should be taken in consideration before prescribing aspirin.

CONCLUSION

In addition to improved control of his diabetes and lipid levels, our patient should be placed on daily aspirin therapy. We would recommend 81 mg of uncoated ASA twice daily based on his comorbidities and his MPV of 12.5 fL, which suggests that he has high platelet turnover and is at increased risk of aspirin resistance. This dosage is unlikely to cause dyspepsia and removes the concern regarding decreased bioavailability from enteric-coated ASA preparations.

Prescription therapy could be considered if we are concerned about medication adherence and if cost is not a consideration.

Lastly, given the FDA's more stringent warnings about the CV risks associated with NSAIDs, we would ask Sam to avoid their use and try nonpharmacologic techniques (eg, patient education, alternating heat/cold, weight loss, physical or occupational therapy). **Table 3** summarizes the risk factors that we recommend taking into consideration when evaluating whether your patient should have an alternative dose or formulation of aspirin.

As clinicians, we are being asked to rethink an age-old therapy, now that new aspirin formulations are available and more is known about the underlying pathology of aspirin resistance. Until now, these factors were rarely taken into consideration when prescribing aspirin. ■

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