

## Controversies in Antiplatelet Therapy for Patients With Cardiovascular Disease

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**C**ase presentation: An asymptomatic man (J.D.) is referred for a cardiovascular evaluation. He has a strong family history of coronary artery disease and has received more than 10 years of treatment for hypertension and dyslipidemia. Past medical history is significant for symptomatic degenerative joint disease. Medications include hydrochlorothiazide, lisinopril, atorvastatin, and celecoxib. How should he be counseled about antiplatelet therapy?

### Aspirin for Primary Prevention

Acetylsalicylic acid (aspirin) has been commercially available as an analgesic and antiinflammatory agent for more than a century. In recent years, the demonstrated ability of aspirin to inhibit platelet aggregation and prevent thrombotic cardiovascular events has made it the most important cardiovascular medication from both risk-benefit and cost-benefit standpoints. Aspirin and other nonsteroidal antiinflammatory agents (NSAIDs) inhibit arachidonic acid metabolism by inactivating the cyclooxygenase (COX) enzyme system.<sup>1</sup> Normally, arachidonic acid gains access to its catalytic site in the platelet through a hydrophobic channel within COX-1 (Figure 1A) and is ultimately converted to thromboxane A<sub>2</sub> (TxA<sub>2</sub>), which

promotes vasoconstriction and platelet aggregation (Figure 2). Aspirin acts by irreversibly acetylating a serine residue at position 530 within the channel, blocking access of arachidonic acid to its catalytic site, and preventing metabolism of arachidonic acid for the lifetime of the platelet (Figure 1B). Other NSAIDs are reversible, competitive inhibitors of the catalytic site, inhibiting platelet aggregation only during part of the dosing interval. No data exist to suggest that NSAIDs, other than aspirin, reduce cardiovascular events.

The use of aspirin for primary prevention remains controversial in low-risk patients because the risk for gastrointestinal bleeding and hemorrhagic stroke may outweigh the benefit of preventing rare cardiovascular events.<sup>2</sup> However, in patients whose estimated risk for an event is >1%/year, as measured by the Framingham Risk Score<sup>3</sup> or a similar risk algorithm, aspirin therapy for cardioprotection is a reasonable recommendation.<sup>2</sup> Risk factors for J.D. include age, gender, family history, hypertension, and dyslipidemia. His risk for a cardiovascular event is increased by any risk algorithm, and he would be a good candidate for aspirin therapy to reduce the risk of a first myocardial infarction (MI).

### COX-2 Inhibitors in Patients at Risk for Cardiovascular Disease

Whereas COX-1 is expressed by many cells and is routinely involved in maintaining cellular functions, COX-2 is expressed only in response to inflammatory stimuli, mediates a significant component of the inflammatory response, and is present in only a small fraction of platelets. COX-2 inhibitors have become a very popular class of drugs for the treatment of arthritis pain because they do not have significant gastric toxicity, a complication associated with inhibition of COX-1. No data exist to suggest that they offer superior pain relief compared with NSAIDs, and like NSAIDs, they can cause salt and water retention, renal insufficiency, and worsening of hypertension. They are convenient, with once- or twice-daily dosing, but they are also expensive, costing \$2 to \$3 per tablet. COX-2 inhibitors are not an acceptable substitute for aspirin in patients who need antiplatelet therapy for cardioprotection because they do not inhibit TxA<sub>2</sub> production. Conversely, their use in patients who require aspirin therapy offers no advantage over less expensive NSAIDs because they do not offer a safety advantage.

By selectively decreasing prostacyclin (PGI<sub>2</sub>) production without inhibit-

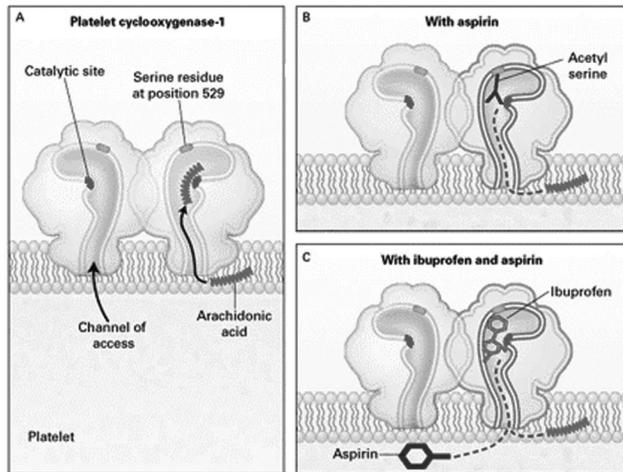
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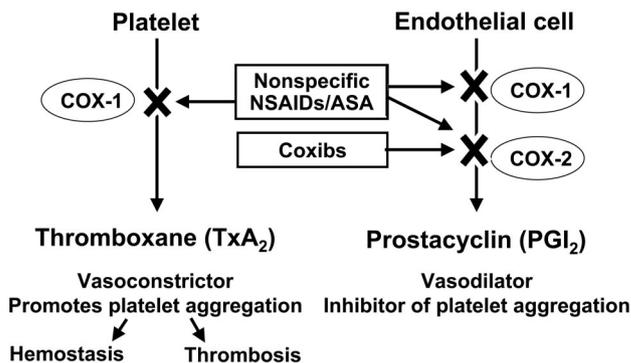
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**Figure 1.** Effect of aspirin alone and ibuprofen plus aspirin on platelet COX-1. A, Arachidonic acid substrate binds to its catalytic site within hydrophobic channel in COX-1 enzyme. B, Aspirin blocks access of arachidonic acid to its catalytic site by irreversibly acetylating serine residue at position 530 (depicted as 529) in COX-1. C, Prior occupancy of catalytic site by ibuprofen prevents aspirin from gaining access to its binding site.<sup>1</sup> Copyright © 2001 Massachusetts Medical Society. All rights reserved.

ing  $TxA_2$  production (Figure 2), COX-2 inhibitors theoretically might decrease the vasodilatory and platelet antiaggregatory effects of  $PGI_2$  without inhibiting the vasoconstrictor and platelet aggregatory effects of  $TxA_2$ . The concern that one COX-2 inhibitor, rofecoxib, could increase the risk of thrombotic cardiovascular events has existed for several years.<sup>4</sup> Rofecoxib was withdrawn from the market after the 25-mg dose was found to double the risk of MI or stroke compared with placebo (3.5% versus 1.9%) after 18 months of therapy in a randomized

trial that tested the utility of rofecoxib in preventing recurrent colorectal polyps in patients with no significant history for cardiovascular disease. The risk could be greater in patients at risk for or with known atherosclerotic vascular disease. Although the other COX-2 drugs on the market, celecoxib and valdecoxib, have not yet been shown to increase cardiovascular events, neither one has been tested long-term in patients with cardiovascular disease. The cardiovascular question about the available drugs in this class is whether their antiinflammatory



**Figure 2.** Effects of NSAIDs on platelets and vascular endothelial cells. Balance between thromboxane and prostacyclin is important in thrombosis. COX-1 inhibitors decrease thromboxane production more effectively than prostacyclin production, tipping the balance away from thrombosis. In contrast, COX-2 inhibitors inhibit only prostacyclin production, decreasing inflammation but tipping the balance toward thrombosis. ASA indicates aspirin; Coxibs, COX inhibitors.

effects balance their potential prothrombotic effects. Their prescription to patients at risk for cardiovascular events probably should be avoided until their safety can be demonstrated.

A better strategy for treating patients with both arthritis and risk for cardiovascular events would be to first try acetaminophen, up to 4 g/d. If acetaminophen is not successful, then naproxen may be prescribed. If the patient is at increased risk for a gastrointestinal event caused by aspirin or naproxen (eg, age >60 years old, history of gastrointestinal or duodenal ulcer, taking coumadin), then a gastroprotective agent (a proton pump inhibitor or misoprostol) can be added. This information was discussed with J.D., and he was advised to stop taking celecoxib.

### The Aspirin-Ibuprofen Drug-Drug Interaction

The omission of ibuprofen as an acceptable substitute for COX-2 inhibitor therapy in patients taking aspirin for cardioprotection should be noted. Aspirin given 2 hours before a daily dose of ibuprofen successfully inhibits platelet aggregation<sup>1</sup>; however, ibuprofen administered 3 times per day competitively prevents aspirin from accessing its target serine and inhibiting platelet aggregation (Figure 1C). Some post hoc analyses<sup>5-7</sup> suggested that patients taking both aspirin and ibuprofen had more cardiovascular events than patients taking either drug alone, although others found no clinical risk.<sup>8,9</sup> J.D. was advised that ibuprofen could be taken episodically after his daily aspirin dose, but that it should not be taken daily in multiple doses to treat arthritis pain because of his need for aspirin cardioprotection.

### The Aspirin-ACE Inhibitor Drug-Drug Interaction

The inhibition of COX-1 by aspirin in the endothelial cell also inhibits the synthesis of  $PGI_2$  (Figure 2). ACE inhibitors (ACEIs) increase prostaglandin production by inhibiting the breakdown of bradykinin. Coadministration of these agents could reduce the

prostaglandin-mediated decrease in arterial pressure associated with ACEIs and potentiate depression of renal function by decreasing synthesis of renal vasodilatory prostaglandins. Although some retrospective analyses have suggested that coadministration of these drugs decreases the mortality benefit associated with ACEI therapy in patients with heart failure or ischemic heart disease, other studies have suggested that a decrease in mortality does not occur.<sup>10</sup> Because aspirin 81 mg/d has the same efficacy as 325 mg/d, with half the bleeding risk,<sup>11</sup> J.D. was advised to take the lower aspirin dose with the additional theoretical possibility that any interaction with his ACEI would be decreased.

*Case presentation, continued:* Unfortunately, J.D. presented 6 months after initial evaluation to his community hospital with an anterior ST-elevation MI and was successfully treated with fibrinolytic therapy 2.5 hours after symptom onset. He had no complications, and a submaximal exercise treadmill test was negative for ischemia; he was discharged from the hospital and referred to a cardiac rehabilitation program.

### Aspirin “Resistance”

One definition of the term “aspirin resistance” is the occurrence of cardiovascular events despite aspirin therapy. This term is imprecise, because 75% of cardiovascular events are not prevented by aspirin,<sup>12</sup> and no pharmacological intervention is perfect in preventing adverse outcomes. These events might better be characterized as treatment failures rather than drug resistance due to failure of the drug to hit its pharmacological target or alter the target.<sup>13</sup> However, measurements of bleeding time, platelet activation, platelet aggregation, and urinary thromboxane B<sub>2</sub> metabolites confirm variability in patient responses to aspirin, and some patients are nonresponders. Moreover, small observational studies suggest that nonresponders have increased cardiovascular events compared with responders,<sup>14–17</sup> and the occurrence

of a cardiovascular event while taking aspirin is designated as a risk point in the TIMI (Thrombolysis In Myocardial Infarction) risk score for unstable angina/non-ST-elevation MI or ST-elevation MI.<sup>19,20</sup> Until a biochemical mechanism for aspirin resistance can be defined and measured with a laboratory test that can be linked to clinical outcomes in randomized clinical trials, the concept of aspirin resistance will remain controversial and of unknown clinical significance. Because of the epidemiological evidence supporting the benefit of aspirin cardioprotection and the absence of data on the benefit of thienopyridines after ST-elevation MI, J.D. was instructed to continue taking low-dose aspirin. A  $\beta$ -blocker was added to his medications, his atorvastatin dose was increased to 80 mg/d, and his lisinopril dose was also increased.

*Case presentation, continued:* J.D. developed reproducible exertional chest discomfort during cardiac rehabilitation. A nuclear imaging study demonstrated a large anterior perfusion defect with significant redistribution. Cardiac catheterization was performed, single-vessel disease with a high-grade stenosis in the proximal left anterior descending artery was demonstrated, and the stenosis was successfully treated with implantation of a coronary stent.

### Clopidogrel “Resistance”

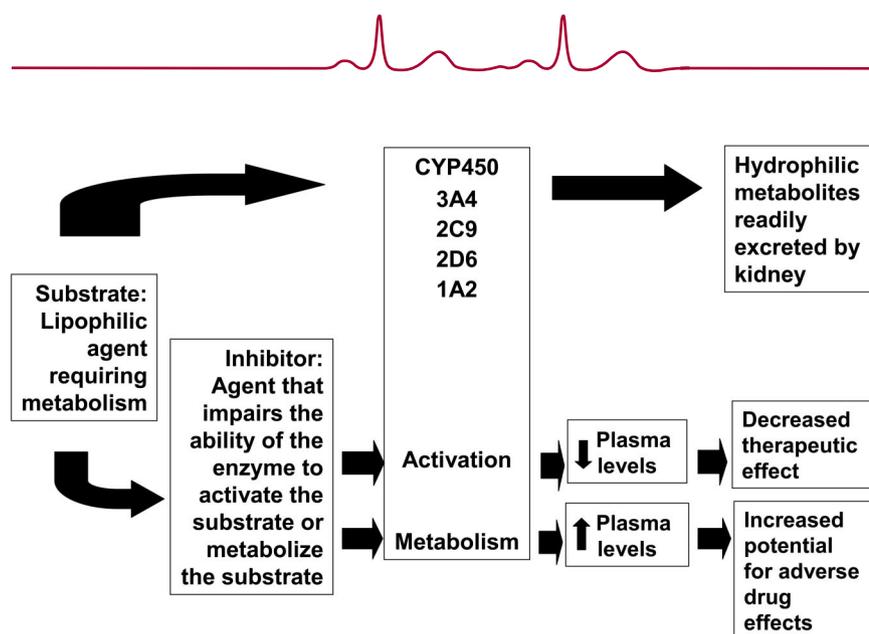
The combination of clopidogrel and aspirin therapy (dual-antiplatelet therapy) has been shown to decrease both subacute stent thrombosis and recurrent ischemic events after acute coronary syndromes<sup>21</sup> and elective percutaneous coronary intervention.<sup>22</sup> As with aspirin, variable platelet aggregation inhibition after clopidogrel occurs among individuals; nonresponders to clopidogrel have been identified.<sup>23,24</sup> One major mechanism may be the failure of clopidogrel, a prodrug, to be metabolized to its active metabolite by hepatic cytochrome P450 (CYP) 3A4.<sup>24</sup> Multiple other possible mechanisms include underdosing, impaired gastric absorption, ADP receptor P<sub>2</sub>Y<sub>12</sub>

polymorphisms, and intracellular signaling variability.<sup>25</sup>

Increased rates of subacute stent thrombosis<sup>23</sup> and recurrent ischemic events after primary PCI<sup>26</sup> have been noted in clopidogrel nonresponders. However, further work is needed in defining clopidogrel “resistance,” measuring it, and correlating it with adverse clinical events before it becomes clinically relevant. J.D. was advised to take clopidogrel 75 mg/d for 6 to 12 months to decrease his risk for subacute stent thrombosis and subsequent ischemic events.

### The Clopidogrel-Atorvastatin Drug-Drug Interaction

Clopidogrel and atorvastatin are competitive substrates for the CYP3A4 enzyme system.<sup>27,28</sup> Because clopidogrel has low bioavailability and a lower affinity than atorvastatin for the substrate binding site, and because atorvastatin has a long half-life, atorvastatin competitively inhibits the ability of clopidogrel to be metabolized to its active metabolite in a dose-dependent manner (Figure 3).<sup>28</sup> A loading dose of clopidogrel 600 mg overcomes this drug-drug interaction,<sup>29</sup> but neither a 300-mg loading dose nor the 75-mg maintenance dose prevents higher doses of atorvastatin from decreasing the ability of clopidogrel to inhibit platelet aggregation.<sup>27</sup> The reports suggesting an association between clinical events and aspirin resistance, aspirin drug-drug interactions, and clopidogrel resistance have been controversial. One report also has suggested that the clopidogrel-atorvastatin drug-drug interaction increases the occurrence of adverse events,<sup>30</sup> although others have contested the clinical significance.<sup>31,32</sup> Until a therapeutic mechanism other than inhibition of platelet aggregation can be proven to be important for antiplatelet agents, however, it appears logical to expect more clinical events in patients with less platelet inhibition. J.D. was advised to stop his high-dose atorvastatin and was given a prescription for pravastatin, because it is not



**Figure 3.** Competition for cytochrome P450 (CYP) pathways increases potential for drug-drug interactions. Most common mechanism for drug-drug interaction is when 2 or more drugs (“substrates”) using same CYP pathway are coadministered, which results in competition for elimination. This results in higher plasma levels of less-competitive agent, which increases potential for adverse drug reaction. With prodrug clopidogrel, failure to be activated because of competition for CYP 3A4 pathway with atorvastatin decreases plasma levels of active metabolite and inhibition of platelet aggregation.

metabolized by the liver and does not interfere with clopidogrel metabolism. Failure to reach his target LDL levels with pravastatin could be treated by the addition of ezetimibe or extended-release niacin, the substitution of rosuvastatin for pravastatin, or resumption of atorvastatin after clopidogrel is discontinued.

### Conclusions

The variable response of platelet aggregation to antiplatelet drugs appears to be a clinically important phenomenon. Clinically, it appears reasonable to avoid drug-drug interactions that might interfere with antiplatelet therapy cardioprotection. Eventually, it is likely that platelet function will be measured before and after the institution of antiplatelet therapy to prove efficacy, as is done with anticoagulation therapy with unfractionated heparin or warfarin, and that optional strategies will be developed for those with inadequate inhibition of platelet aggregation.

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