

# Antiplatelet Therapy in Non–ST-Segment Elevation Acute Coronary Syndromes

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## CASE PRESENTATION

A 63-year-old man presented to the emergency department with 8 hours of waxing-and-waning substernal chest pressure. The patient had previously undergone coronary artery bypass graft surgery in 1992, with the left internal mammary anastomosed to the left anterior descending artery and a reverse saphenous vein graft anastomosed to a large circumflex marginal vein. The right coronary artery was nondominant and without disease. Following coronary artery bypass graft surgery, the patient returned to an active lifestyle without symptoms. Relevant medical history also included hypertension and hypercholesterolemia. Medications included aspirin, 325 mg/d, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin), and an angiotensin-converting enzyme inhibitor combined with a low-dose diuretic.

Physical examination results were notable for a blood pressure of 126/70 mm Hg and a heart rate of 70/min. Lung fields were clear. The S<sub>1</sub> and S<sub>2</sub> were normal, but there was an S<sub>4</sub> gallop. Distal pulses were intact. His admission electrocardiogram (FIGURE 1) demonstrated diffuse ischemic changes, including ST-segment elevation in lead aVR. Laboratory evaluation demonstrated the following values: peak troponin I, 5.65 ng/mL (reference range, 0–0.50 ng/mL); creatine kinase, 603 U/L (reference range, 24–170 U/L); and creatine kinase-MB fraction, 14% (reference range, 0%–3%).

See also p 1867.

Acute coronary syndromes are a frequent cause of hospital admission for patients with coronary artery disease. The pathophysiology of acute coronary syndromes often involves plaque rupture or fissure with platelet aggregation. Recognition of the importance of platelet aggregation resulted in several large randomized trials testing 3 types of platelet antagonists, aspirin, glycoprotein IIb/IIIa inhibitors, and adenosine diphosphate inhibitors. A thorough understanding of the data, risks, and benefits of these therapies is important to optimize treatment of the patient with an acute coronary syndrome. Recognition that there is a great deal of interpatient variability in response to these antiplatelet therapies highlights the need for future research in this area.

JAMA. 2004;292:1875-1882

www.jama.com

The patient was admitted to the coronary care unit. He was believed to be at high risk due to the elevated levels of cardiac markers, multiple episodes of ischemic chest pain, current aspirin use, and prior revascularization.<sup>1</sup> The patient's electrocardiogram also contributed to his high risk given the ST-segment depression in multiple leads. The patient's Thrombolysis in Myocardial Infarction (TIMI) risk score based on these features was 5 of 7 (missing age  $\geq$ 65 years and at least 3 risk factors for coronary disease). Based on this risk score, the patient's 14-day risk of death, nonfatal myocardial infarction, or need for urgent revascularization was 26%.<sup>2</sup> Furthermore, the electrocardiogram showed ST-segment elevation in aVR (a reciprocal lead for ischemia in the inferior and lateral distributions), which in patients with non–ST-segment elevation myocardial infarction is an independent risk factor for in-hospital death.<sup>3</sup>

The patient was treated with aspirin, a loading dose of 300 mg of clopidogrel bisulfate, intravenous unfractionated heparin,  $\beta$ -blockers, intravenous nitroglycerin, and the intravenous glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibitor ep-

tifibatide. His chest pain resolved. The results of the cardiac catheterization demonstrated thrombotic occlusion of the left main coronary artery. The vein graft to the circumflex appeared chronically occluded. The entire circulation to the left coronary was dependent on the patent internal mammary graft to the left anterior descending artery. Since the patient had a left dominant circulation, the entire left ventricle was perfused via the internal mammary. There was retrograde filling of the dominant left circumflex artery through a highly diseased proximal left anterior descending artery. The patient underwent successful left main coronary artery angioplasty and stent placement with restoration of flow (TIMI grade III). The remainder of the patient's hospital course

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**Financial Disclosure:** Dr Schulman has received honoraria from Bristol-Myers Squibb and Pfizer.

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was uneventful. During the last 6 months, he has returned to an active lifestyle and has been asymptomatic while undergoing aspirin and clopidogrel therapy.

## DISCUSSION

This patient illustrates numerous issues in the pathophysiology and management of non-ST-segment elevation acute coronary syndromes (ACSs). Currently, non-ST-segment elevation ACS refers to previously characterized unstable angina or non-Q-wave myocardial infarction. Central to the pathophysiology of ACSs is endothelial dysfunction and inflammation. Endothelial dysfunction contributes to the progression of atherosclerosis with loss of endothelium-derived nitric oxide, resulting in an increase in adhesion of platelets and inflammatory cells.<sup>4</sup> Patients with coronary endothelial dysfunction have a higher risk of future ACSs than patients with preserved endothelial function.<sup>5</sup> In patients with ACSs, endothelial dysfunction with resultant coronary vasoconstriction participates in the pathophysiology of decreased blood flow in this syndrome.<sup>6</sup> Recent data confirm that in ACS patients the entire coronary tree is involved with endothelial dysfunction and inflammation.<sup>7</sup> Although ACSs gener-

ally result from a plaque rupture or erosion with subsequent thrombosis,<sup>8</sup> intravascular ultrasound studies<sup>9</sup> support the fact that there are often multiple plaque ruptures present throughout the coronary tree.

### Platelet Aggregation and Activation

Platelet activation and aggregation contribute to thrombosis in ACSs.<sup>4,10</sup> Following plaque rupture or erosion, platelets become activated. With platelet activation, the platelet and platelet receptors, including the most abundant receptor on the platelet, the Gp IIb/IIIa receptor, change shape. The activated Gp IIb/IIIa receptor becomes avid to bind fibrinogen. The final common pathway of platelet aggregation is the binding of a fibrinogen molecule with 2 activated Gp IIb/IIIa receptors. The importance of the Gp IIb/IIIa receptor was recognized many years ago in patients with Glanzmann thrombasthenia, who either lack or have a dysfunctional Gp IIb/IIIa receptor and have life-long bleeding diathesis.<sup>11</sup> Although antithrombotic agents are standard therapy for these patients, unlike ST-segment elevation myocardial infarction, where fibrin-rich thrombus predominates, non-ST-segment elevation ACS patients often demonstrate platelet-rich thrombus.<sup>12</sup>

### Antiplatelet Therapy

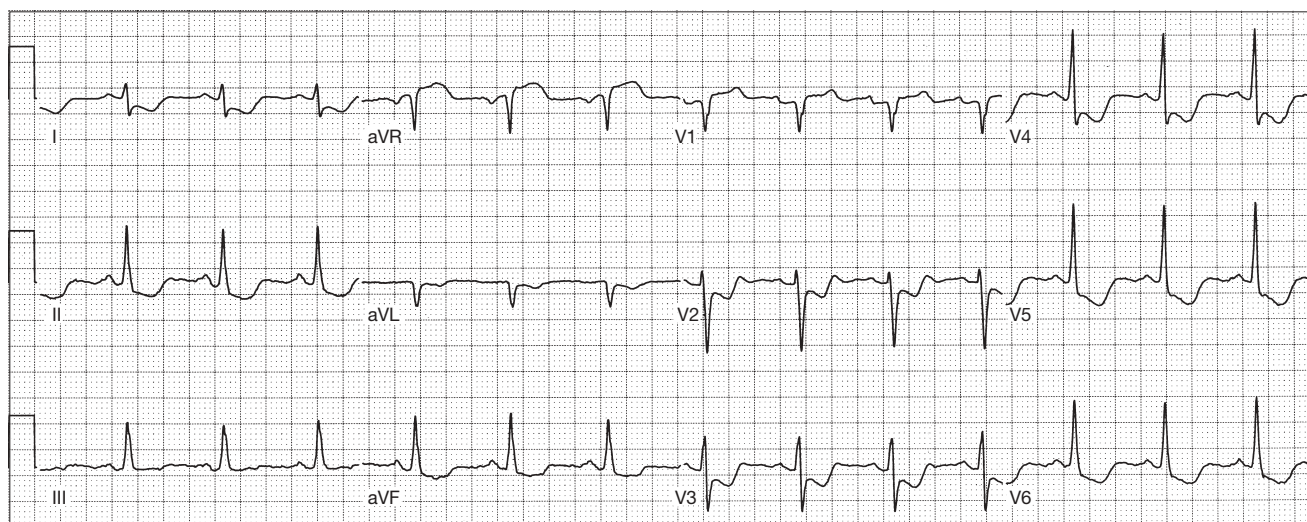
Inhibition of platelet activation and aggregation is central to the therapy of non-ST-segment elevation ACSs. There are 3 approaches to medical therapy, including aspirin, Gp IIb/IIIa inhibitors, and thienopyridenes (TABLE).

### Aspirin

Aspirin inhibits platelets by irreversibly acetylating cyclooxygenase 1 and thereby inhibiting thromboxane A<sub>2</sub> production (FIGURE 2).<sup>13</sup> Thromboxane A<sub>2</sub> is a potent mediator of platelet aggregation. In a large meta-analysis,<sup>14</sup> long-term aspirin therapy resulted in a significant reduction in nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality compared with placebo in high-risk patients with pre-existing vascular disease. The absolute risk reduction of vascular events was 16.0% in patients taking placebo but decreased to 12.9% in patients taking aspirin. Although aspirin is impressively beneficial and cost-effective, these data suggest that aspirin fails to prevent a substantial number of cardiovascular events in high-risk patients.

There are some patients who are aspirin resistant. A cohort of 326 patients with stable coronary disease who were treated for at least 1 week with aspirin, 325 mg/d, had in vitro platelet

**Figure 1.** Electrocardiogram on Patient Admission Demonstrating Diffuse Ischemic ST Depression and ST-Segment Elevation in Lead aVR



aggregation studies by light transmission aggregometry.<sup>15</sup> Aspirin resistance in this study was defined as having greater than 70% platelet aggregation to the agonist adenosine diphosphate (ADP) plus greater than 20% aggregation to the agonist arachidonic acid. Seventeen patients (5.2% of this cohort) met aspirin resistance criteria by light transmission aggregometry. The risk of myocardial infarction, death, or stroke during 1.9 years of follow-up was 24% (4/17) in the aspirin-resistant group and 10% (30/309) in those patients demonstrating platelet inhibition by aspirin therapy. Recently, 151 patients undergoing elective percutaneous coronary intervention (PCI) while receiving chronic aspirin therapy had platelet aggregation studies with a point-of-care platelet aggregation assay (*Ultegra* Rapid Platelet Function Assay; Accumetrics, San Diego, Calif).<sup>16</sup> Nineteen percent of patients were aspirin resistant. Postprocedure myonecrosis with serial creatine kinase-MB and troponin I sampling was significantly greater in patients who were aspirin resistant than those who were aspirin sensitive. Future studies that involve a larger number of patients will help identify the prevalence and clinical significance of aspirin resistance.

Our patient was undergoing long-term aspirin therapy following coro-

nary artery bypass graft surgery. Data suggest that those patients admitted to the hospital with an ACS who are already receiving aspirin therapy are at higher risk of an adverse outcome<sup>2</sup> and may require more aggressive antiplatelet therapy or other management strategies. Aspirin use before admission to the hospital was evaluated in The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, a randomized, placebo-controlled study of the Gp IIb/IIIa inhibitor eptifibatide added to aspirin and heparin therapy in patients with non-ST-segment elevation ACSs.<sup>17</sup> Those patients with a history of prior aspirin use were more likely to be admitted with unstable angina than with a non-ST-segment elevation myocardial infarction. Nevertheless, the risk of death or nonfatal myocardial infarction during short-term follow-up was significantly greater in those patients with prior aspirin use compared with patients naïve to aspirin. Furthermore, the benefit of a Gp IIb/IIIa inhibitor added to standard aspirin and heparin therapy was demonstrated in the large subgroup of patients who were admitted to the hospital with an ACS already receiving aspirin therapy (ie, those patients for whom aspirin therapy had failed). Thus, although aspirin is an ex-

tremely cost-effective platelet antagonist, it is often not fully effective in the prevention or treatment of ACS.

### Gp IIb/IIIa Inhibitors

As the integral role of the Gp IIb/IIIa receptor in the common final pathway of platelet aggregation became recognized, inhibitors to the Gp IIb/IIIa receptor were developed and tested in patients with ACSs (Figure 2). Currently available Gp IIb/IIIa inhibitors for non-ST-segment elevation ACS management include abciximab in patients undergoing PCI, eptifibatide, and tirofiban hydrochloride. Abciximab is a Fab fragment that permanently binds to platelet Gp IIb/IIIa receptors, inhibiting aggregation. Eptifibatide and tirofiban are competitive inhibitors of the Gp IIb/IIIa receptor such that platelet aggregation returns to normal approximately 4 hours following drug cessation. All 3 inhibit in vitro platelet aggregation by approximately 80%. The doses of eptifibatide and tirofiban need adjustments for the high-risk patient with renal insufficiency. Both randomized, placebo-controlled trials and a large observational database analysis suggest that high-risk ACS patients, similar to the one described herein, benefit from the early initiation of a Gp IIb/IIIa inhibitor.<sup>18-20</sup> Large, randomized placebo-controlled trials show a mod-

**Table.** Antiplatelet Therapies Used in Non-ST-Segment Elevation Acute Coronary Syndromes

Agent	Action	Use in ACSs	Patient Variability	Clinical Outcomes in ACSs
Aspirin	Cyclooxygenase 1 inhibition	Start immediately and continue indefinitely	Present; multifactorial, including genetic polymorphisms, drug interactions	Decreases death and myocardial infarction Patients with aspirin resistance at higher risk of events
Gp IIb/IIIa inhibitors	Inhibit the interaction of fibrinogen with the Gp IIb/IIIa receptor	Start on admission or at time of PCI in those patients at high enough risk as needing revascularization	Present; probably multifactorial	Decreases short-term death and nonfatal myocardial infarction Patients with Gp IIb/IIIa inhibitor resistance undergoing PCI have higher risk of short-term ischemic events
ADP inhibitors	ADP receptor blocker, inhibits platelet activation and aggregation	Start immediately and continue for up to 9 mo in medically and PCI managed patients Hold if catheterization immediate and/or CABG possible	Present; multifactorial, including genetic polymorphisms, and patient variability in the hepatic metabolism of the prodrug clopidogrel bisulfate	Reduces cardiovascular death, myocardial infarction, and stroke when added to aspirin Patients with clopidogrel resistance have higher rates of short-term cardiovascular events

Abbreviations: ACS, acute coronary syndrome; ADP, adenosine diphosphate; CABG, coronary artery bypass graft; Gp IIb/IIIa, glycoprotein IIb/IIIa; PCI, percutaneous coronary intervention.

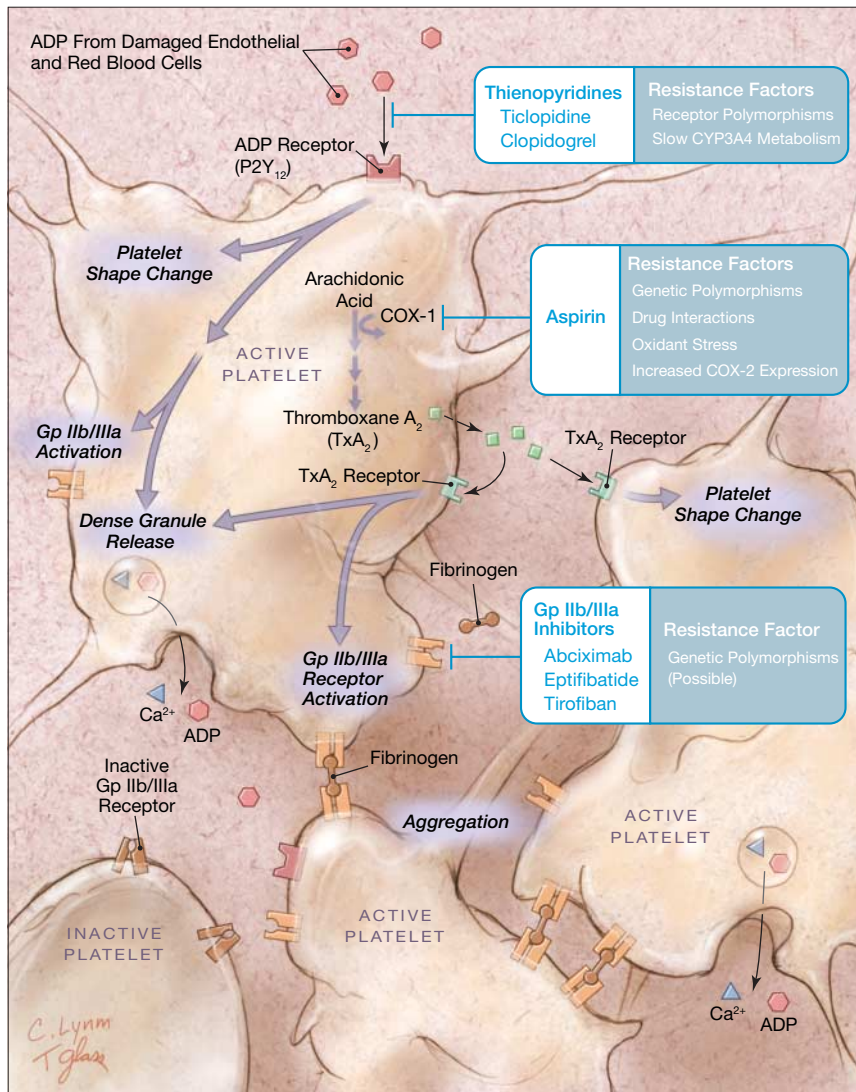
est benefit to adding a Gp IIb/IIIa inhibitor to aspirin and heparin therapy in reducing short-term death or non-fatal myocardial infarction (approximately 9% relative and 1% absolute reduction).<sup>19</sup> Bleeding is increased from 1.4% to 2.5% in Gp IIb/IIIa inhibitor-treated patients compared with placebo.<sup>19</sup> There is no excess intracranial

hemorrhage risk in appropriately treated patients. Similar to our patient, studies show that patients at higher risk (elevated levels of cardiac markers, ST-segment depression, diabetes, and need for revascularization) derive the greatest benefit from the addition of a Gp IIb/IIIa inhibitor to aspirin and heparin therapy.<sup>19</sup> In the Na-

tional Registry of Myocardial Infarction database of 61 000 patients with non-ST-segment elevation infarction and no contraindication to Gp IIb/IIIa inhibitor therapy, only 25% of patients received a Gp IIb/IIIa inhibitor early in the hospital course.<sup>20</sup> Across all risk groups, in-hospital mortality was significantly lower in patients receiving a Gp IIb/IIIa inhibitor within 24 hours of admission compared with those who did not. Data were also presented relating the frequency of hospital use of Gp IIb/IIIa inhibitors and in-hospital mortality. In hospitals where the use of Gp IIb/IIIa inhibitors was only 1% to 5% of patients with a non-ST-segment elevation infarction, in-hospital mortality was approximately 12%. In contrast, among hospitals in which use of Gp IIb/IIIa inhibitors was 30% to 85%, in-hospital mortality was 50% lower. These observational data highlight the benefit of this therapy and the fact that the frequency of Gp IIb/IIIa inhibitor use is likely an indicator of other good practice for treatment of non-ST-segment elevation myocardial infarction.

In contrast to the benefit that higher-risk ACS patients who commonly undergo PCI receive, medically treated ACS patients are less likely to benefit from a Gp IIb/IIIa inhibitor. In the Global Use of Strategies to Open Occluded Coronary Arteries IV—Acute Coronary Syndrome Trial (GUSTO-IV ACS), 7800 medically treated patients with non-ST-segment elevation ACS were randomized to receive the Gp IIb/IIIa inhibitor abciximab or placebo for 24 or 48 hours in addition to receiving aspirin and heparin.<sup>21</sup> In this study, abciximab- and placebo-treated patients had similar rates of 30-day death or nonfatal myocardial infarction. This study shows that the Gp IIb/IIIa inhibitor abciximab is not indicated in non-ST-segment elevation ACS patients who are treated medically. A recent, large meta-analysis<sup>19</sup> of the randomized, placebo-controlled Gp IIb/IIIa inhibitor trials assessed the relationship between the short-term risk of death or nonfatal myocardial infarction and whether the patient subse-

**Figure 2.** Sites of Action of Antiplatelet Therapy on Mechanisms of Platelet Activation and Aggregation



The final event in the pathway of platelet aggregation is binding of fibrinogen by activated glycoprotein (Gp) IIb/IIIa receptors on adjacent platelets. Thienopyridines—which inhibit stimulation of the adenosine diphosphate (ADP) receptor, P2Y<sub>12</sub>, and aspirin, which inhibits thromboxane A<sub>2</sub> (TxA<sub>2</sub>) production resulting in decreased stimulation of the TxA<sub>2</sub> receptor—interfere with steps leading to activation of Gp IIb/IIIa receptors. Glycoprotein IIb/IIIa inhibitors directly inhibit platelet aggregation at the Gp IIb/IIIa receptor. Factors that may limit the effectiveness of specific antiplatelet therapies are shown in the blue boxes. Ca indicates calcium; COX, cyclooxygenase.

quently underwent PCI or coronary artery bypass graft surgery. The higher-risk subgroup of patients who subsequently underwent coronary revascularization benefited from adding a Gp IIb/IIIa inhibitor to aspirin and heparin. Thirty-day outcomes were similar between the placebo and Gp IIb/IIIa inhibitor groups in the lower-risk patients who did not undergo revascularization. In this meta-analysis, there was no statistical difference among the 3 Gp IIb/IIIa inhibitors. Based on these data, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend Gp IIb/IIIa inhibitor therapy added to aspirin and heparin in non-ST-segment elevation ACS patients whose risk level would warrant their undergoing cardiac catheterization for revascularization.<sup>22</sup>

One of the more fascinating features of the Gp IIb/IIIa inhibitors is the degree of interpatient variability to the antiplatelet response. Five hundred patients undergoing PCI and treated with a Gp IIb/IIIa inhibitor had serial in vitro determinations of platelet aggregation.<sup>23</sup> At 10 minutes following the Gp IIb/IIIa inhibitor loading dose, one fourth of the patients did not achieve complete in vitro platelet inhibition. The 30-day event rate (death, myocardial infarction, or need for urgent target vessel revascularization) was 14.4% in the patients who did not have complete platelet inhibition compared with 6.4% in those who did. Platelet aggregation was also determined at 8 hours following initiation of Gp IIb/IIIa inhibitor therapy. Seven percent of patients had less than 70% platelet inhibition; their 30-day event rate was 25%, significantly greater than most patients, who achieved 70% or greater platelet inhibition. These data suggest that interpatient variability in response to Gp IIb/IIIa inhibitors exists and that this variability may affect outcomes.

### Antiplatelet Therapy: Thienopyridines

The thienopyridines clopidogrel and ticlopidine are the third group of antiplatelet agents commonly used in non-

ST-segment elevation ACS. Clopidogrel and ticlopidine inhibit ADP stimulation of the platelet P2Y<sub>12</sub> receptor, thereby inhibiting platelet activation, aggregation, and Gp IIb/IIIa receptor activation (Figure 2). When either clopidogrel or ticlopidine is added to aspirin therapy, acute thrombosis following coronary stent placement and long-term ischemic events are reduced.<sup>24</sup> The benefit of clopidogrel therapy added to aspirin for the treatment of non-ST-segment elevation ACS was demonstrated in the more than 12000 patients randomized in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. In this study, the addition of clopidogrel to aspirin in patients with unstable angina or non-ST-segment elevation infarction reduced 9-month cardiovascular mortality, nonfatal myocardial infarction, and stroke by 20% compared with placebo.<sup>25</sup> Benefits of clopidogrel therapy started in the first 24 hours of use.<sup>26</sup> Major bleeding was increased an absolute 1% with the addition of clopidogrel to aspirin therapy. The risk of bleeding was lowest in patients treated with long-term, low-dose aspirin (<100 mg/d),<sup>27</sup> with no difference in efficacy compared with high-dose aspirin therapy (>200 mg/d). On the basis of the CURE trial, the ACC/AHA guidelines recommend clopidogrel therapy in ACS patients with true aspirin intolerance and medically and PCI-treated non-ST-segment elevation ACS patients for a minimum of 1 month and up to 9 months.<sup>22</sup>

An important group of patients with an elevated risk of bleeding due to clopidogrel are those who undergo coronary artery bypass graft surgery within 5 to 7 days of receiving the drug.<sup>22</sup> High-risk ACS patients with an increased likelihood of requiring coronary artery bypass graft surgery should receive aspirin and a Gp IIb/IIIa inhibitor and only receive an ADP antagonist once the coronary anatomy is known and bypass graft surgery is not needed.

Unlike our patient, Gp IIb/IIIa inhibitors were not used in the CURE trial. Therefore, the clinical benefits of com-

bination therapy with all 3 platelet inhibitors compared with 2 are unknown in non-ST-segment elevation ACS. Recent data in a group of stable coronary artery disease patients undergoing PCI suggest that a Gp IIb/IIIa inhibitor has no clinical benefit when added to aspirin, a loading dose of clopidogrel (600 mg), and heparin. Excluded from enrollment were patients with ACS; insulin-requiring diabetes; a total occlusion, thrombus in vessel, or saphenous vein graft disease; and ejection fractions of less than 30%. In this study of 2159 stable patients, the 30-day outcome of death, myocardial infarction, or need for urgent target vessel revascularization was no different in patients randomized to receive abciximab or placebo.<sup>28</sup> Because this study was underpowered due to a very low event rate, more data are needed before routinely withholding Gp IIb/IIIa inhibitor therapy in stable coronary disease patients undergoing PCI. In contrast, recent in vitro platelet studies in patients with ACS show that there is stepwise inhibition of activated platelets following the addition of clopidogrel to aspirin and then a Gp IIb/IIIa inhibitor to the first 2 agents.<sup>29</sup> Although these in vitro data suggest that additive inhibition of platelet activation can be achieved with all 3 antiplatelet agents, clinical trial outcome and safety data are needed before the routine use of all 3 antiplatelet agents in ACS patients.

Similar to the Gp IIb/IIIa inhibitors, interpatient variability exists in the platelet inhibitory response to clopidogrel. Serial in vitro platelet aggregation studies were performed on 92 patients after undergoing coronary stent placement<sup>30</sup> but before clopidogrel initiation and then 2 hours, 24 hours, 5 days, and 30 days following initiation of therapy. At each of these points, but particularly at the 2- and 24-hour points, a significant (approximately 40% and 20%, respectively) proportion of patients showed a greater degree of platelet aggregation than before initiation of clopidogrel therapy. A recent study<sup>31</sup> of clopidogrel resistance was completed in 60 patients with acute myocardial infarction.

tion. Platelet aggregation studies were performed at baseline while the patient was taking aspirin and then daily for 6 days following loading and maintenance clopidogrel dosing. Approximately 25% of patients experienced the minimal effect of clopidogrel on ADP-induced platelet aggregation. These patients had a significantly higher risk of recurrent ischemic events for 6 months than did clopidogrel-sensitive patients. Clopidogrel resistance was a significant predictor of recurrent ischemic events during follow-up.

### Origins to the Patient Variability in Platelet Inhibitory Response to Antiplatelet Therapy

There are likely multiple origins that help explain why one patient has significant platelet inhibition to a particular agent, whereas another patient has minimal antiplatelet response. The studies described herein do not identify any demographic that predicts resistance or responsiveness to a particular antiplatelet agent. Two important mechanisms that likely contribute to variability include genetics and drug-drug interactions. In 2400 healthy family members from the Framingham Study,<sup>32</sup> light transmission aggregometry for platelet aggregation was performed to determine the genetic contribution to platelet aggregability. Family members, such as siblings, had a much higher correlation of the degree of platelet aggregation than spouses did. Based on these data, it was estimated that 21% to 30% of the variance in platelet aggregation was due to heritable factors compared with an only 4% to 7% variance measured from such covariates as age and risk factors.

Genetic polymorphisms of several platelet receptors have been identified that may influence platelet aggregation and predict coronary events. It is likely that many more genetic polymorphisms will be identified during the next several years that may influence platelet aggregation and the response to antiplatelet therapies. One of the first studies that identified a platelet receptor polymorphism as a possible risk fac-

tor for ACSs was written by Weiss and colleagues.<sup>33</sup> They studied a polymorphism of the IIIa integrin that constitutes the Gp IIb/IIIa receptor. These investigators showed in a small cohort of patients that the P1<sup>A2</sup> polymorphism of the IIIa integrin was a significant independent predictor of ACSs. Subsequent studies<sup>34</sup> suggest that patients who have P1<sup>A2</sup> have less platelet inhibition to aspirin therapy compared with patients with P1<sup>A1</sup>. In contrast, larger trials have failed to demonstrate a relationship between this platelet receptor polymorphism and future ischemic events.<sup>35</sup> Other platelet receptor polymorphisms currently under evaluation include Gp<sup>IIb/IIIa</sup> and Gp<sup>IIb/IIIa</sup> receptor polymorphisms. These and other polymorphisms may contribute to our understanding of aspirin resistance and variability in response to Gp IIb/IIIa inhibitors.

There are many other potential causes of aspirin resistance in ACS patients, including failure to prescribe it, noncompliance, increased oxidant stress with resultant arachidonic acid lipid peroxidation, inadequate aspirin dose, impaired interaction between aspirin and cyclooxygenase 1, and overexpression of cyclooxygenase 2.<sup>36-39</sup>

There are several reasons for thienopyridene resistance. A genetic polymorphism that may contribute to the variability in the antiplatelet response to clopidogrel is an ADP P2Y<sub>12</sub> receptor polymorphism. This is the platelet receptor target of the thienopyridines ticlopidine and clopidogrel. An H1/H2 polymorphism of the ADP P2Y<sub>12</sub> receptor was identified, which showed different degrees of platelet aggregation to ADP.<sup>40</sup> It is possible this polymorphism may predict future cardiovascular disease and contribute to our understanding of the variability in response to thienopyridines.

Lastly, there are many drug-drug interactions that may influence the antiplatelet effects of aspirin and clopidogrel therapy. A drug interaction with aspirin has been described with certain nonsteroidal anti-inflammatory agents.<sup>41</sup> Platelet aggregation studies were per-

formed in healthy volunteers who initially took a single dose of aspirin either 2 hours before or after a single dose of the nonsteroidal anti-inflammatory agent ibuprofen. The latter agent is a competitive inhibitor of platelet cyclooxygenase 1. Aspirin therapy inhibited platelet aggregation when taken before the ibuprofen. However, if the ibuprofen was given 2 hours before the aspirin dose or given in the long term, aspirin had no effect on platelet aggregation. Rofecoxib, a cyclooxygenase 2 inhibitor, had no effect on the degree of platelet inhibition with aspirin therapy.

The likely mechanism of the interaction of nonsteroidal anti-inflammatory agents with aspirin is the former agent serving as a competitive inhibitor of cyclooxygenase 1 and thereby preventing aspirin from reaching its serine-binding site on the enzyme. The clinical relevance of this interaction has been argued in the literature and unanswered by lack of prospective, randomized data. Two recent analyses suggest that the protective effect of aspirin in preventing a first myocardial infarction is lost in patients who are taking nonsteroidal anti-inflammatories in a dose-dependent fashion.<sup>42,43</sup> The nonsteroidal ibuprofen appears to have the greatest impact on preventing platelet inhibition by aspirin.

Some of the variability in platelet inhibition by clopidogrel is likely due to the fact that clopidogrel is an inactive prodrug and is activated by the hepatic cytochrome P-450 3A4 system. The rapidity in which the CYP3A4 system metabolizes drugs relates to the antiplatelet effect of clopidogrel following a loading dose.<sup>44</sup> Patients who rapidly metabolize drugs via the CYP3A4 system have rapid platelet inhibition following an oral loading dose of clopidogrel. Slow metabolizers have a much less antiplatelet effect from a loading dose of clopidogrel. Certain HMG-CoA reductase inhibitors, including atorvastatin, lovastatin, and simvastatin, are also metabolized by the cytochrome P-450 3A4 system. A provocative study<sup>45</sup> of 44 patients who were treated with clopidogrel following placement of a stent sug-

gested that atorvastatin might limit the platelet inhibition induced by clopidogrel therapy in a dose-dependent fashion. This study involved limited patient numbers, and platelet aggregation studies were determined by a point-of-care aggregometer. A subsequent platelet aggregation study<sup>46</sup> showed no interaction of lovastatin, atorvastatin, simvastatin, or fluvastatin with clopidogrel's antiplatelet effects.

Furthermore, there does not appear to be any clinical impact between the type of HMG-CoA reductase inhibitor used and recurrent ischemic events in clopidogrel-treated patients following PCI. Retrospective analyses<sup>47</sup> of clinical trials of clopidogrel show no higher cardiovascular event rates in patients treated with HMG-CoA reductase inhibitors that are metabolized by the cytochrome P-450 system. A recent study<sup>48</sup> of ACS patients, most of whom were treated with PCI with a stent and clopidogrel or ticlopidine therapy (72%), showed that high-dose atorvastatin (metabolized by CYP3A4) reduced recurrent ischemic events compared with moderate-dose pravastatin sodium (not metabolized by CYP3A4).

## CONCLUSION

The data from clinical trials suggest that our patient benefited from aggressive antiplatelet therapy. This therapy affords optimal platelet inhibition in the high-risk patient with non-ST-segment elevation ACS. Furthermore, given the great amount of variability in response to antiplatelet agents, dual or triple antiplatelet therapy may decrease the likelihood that a particular patient with ACS is resistant to therapy. The Table summarizes the actions and uses of these antiplatelet therapies in ACS patients. To advance the study of antiplatelet therapy resistance, a uniform definition (ie, in vitro, clinical) is needed. Larger studies are needed to determine the frequency and clinical relevance of resistance to antiplatelet therapies. It is possible that patients identified as resistant to antiplatelet agents, such as aspirin, are resistant to all antiplatelet therapies. These drug-resistant pa-

tients may have a higher risk of events due to worse endothelial dysfunction and/or greater degrees of inflammation, resulting in greater platelet activation. Clinicians need to prescribe appropriate antiplatelet therapies according to potential benefit in reducing death, myocardial infarction, and refractory ischemia in the ACS patient vs the bleeding risks these agents cause. We need to remain cognizant of potential drug interactions that may limit the effectiveness of potentially life-saving therapies. Finally, a clinically easy-to-use and accurate bedside platelet aggregometer may help deliver optimal antiplatelet therapy to our patients.

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Education is what survives when what has been learned  
has been forgotten.  
—B. F. Skinner (1904-1990)