

The Platelet in Diabetes

Focus on prevention of ischemic events

JOHN A. COLWELL, MD, PHD¹
RICHARD W. NESTO, MD^{2,3}

Accelerated atherosclerosis and the increased risk of thrombotic vascular events in diabetes may result from dyslipidemia, endothelial dysfunction, platelet hyperreactivity, an impaired fibrinolytic balance, and abnormal blood flow. There is also a correlation between hyperglycemia and cardiovascular (CV) events. The importance of platelets in the atherothrombotic process has led to investigation of using antiplatelet agents to reduce CV risk. A meta-analysis conducted by the Antiplatelet Trialists' Collaboration demonstrated that aspirin reduced the risk of ischemic vascular events as a secondary prevention strategy in numerous high-risk groups, including patients with diabetes. Based on results from placebo-controlled randomized trials, the American Diabetes Association recommends low-dose enteric-coated aspirin as a primary prevention strategy for people with diabetes at high risk for CV events. Clopidogrel is recommended if aspirin allergy is present. There is occasionally a need for an alternative to aspirin or for additive antiplatelet therapy. Aspirin in low doses inhibits thromboxane production by platelets but has little to no effect on other sites of platelet reactivity. Agents such as ticlopidine and clopidogrel inhibit ADP-induced platelet activation, whereas the platelet glycoprotein (Gp) IIb/IIIa complex receptor antagonists block activity at the fibrinogen binding site on the platelet. These agents appear to be useful in acute coronary syndromes (ACSs) in diabetic and nondiabetic patients. A combination of clopidogrel plus aspirin was more effective than placebo plus standard therapy (including aspirin) in reducing a composite CV outcome in patients with unstable angina and non-ST segment elevation myocardial infarction. In a meta-analysis of six trials in diabetic patients with ACSs, intravenous GpIIb-IIIa inhibitors reduced 30-day mortality when compared with control subjects. Results from controlled prospective clinical trials justify the use of enteric-coated low-dose aspirin (81–325 mg) as a primary or secondary prevention strategy in adult diabetic individuals (aged >30 years) at high risk for CV events. Recent studies support the use of clopidogrel in addition to standard therapy, as well as the use of GpIIb-IIIa inhibitors in ACS patients.

Diabetes Care 26:2181–2188, 2003

Cardiovascular disease (CVD) is the leading cause of disability and premature mortality in patients with diabetes (1). Diabetes increases the risk for coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD) from twofold to fourfold (2,3). The increased risk is independent of and addi-

tive to other cardiovascular (CV) risk factors, such as hypertension, albuminuria, obesity, cigarette smoking, and dyslipidemia, relative to nondiabetic patients with these comorbidities (4,5). Type 2 diabetes is associated with insulin resistance and hyperinsulinemia and is often part of a metabolic syndrome called "Syndrome X," which comprises hypertension, dyslipidemia, decreased fibrinolysis, and increased procoagulation factors (6). This metabolic syndrome may also be seen in obese insulin-resistant individuals who do not yet have overt diabetes (7,8).

In addition to heightened risk for CVD, patients with diabetes have a poorer prognosis than nondiabetic patients when they experience a major ischemic vascular event. Diabetic patients who suffer an acute myocardial infarction (MI) have a more complicated hospital course and a higher incidence of recurrent vascular events than nondiabetic patients (9,10). For example, the 7-year incidence of recurrent MI in a large population-based study was 45% in diabetic patients versus 19% in nondiabetic patients (11). Moreover, the prognosis for diabetic patients who undergo coronary revascularization procedures is worse than that for nondiabetic subjects; patients with diabetes experience more postprocedural complications and have decreased infarct-free survival (12,13). PAD is present in 8% of patients at the time of diabetes diagnosis but in 45% of patients who have had diabetes for 20 years (14). The presence of symptomatic PAD is a marker for systemic atherosclerotic disease, including ischemic coronary and cerebrovascular events (8,15).

Both atherosclerosis and thrombosis appear to contribute significantly to the increased CV risk of diabetic patients (7). The majority of ischemic coronary and cerebrovascular events are precipitated by vessel occlusion caused by atherosclerotic plaque disruption, platelet aggregation, platelet adhesion, and resulting intravascular thrombosis. Several systems that maintain the integrity and patency of the vasculature are impaired in diabetes, including platelet and endothelial function,

From the ¹Diabetes Center, Medical University of South Carolina, Charleston, South Carolina; the ²Department of Cardiovascular Medicine, Lahey Clinic Medical Center, Burlington, Massachusetts; and ³Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Richard W. Nesto, MD, Department of Cardiovascular Medicine, Lahey Clinic Medical Center, 41 Mall Rd., Burlington, MA 01805. E-mail: richard.w.nesto@lahey.org.

Received for publication 9 December 2002 and accepted in revised form 2 April 2003.

J.A.C. has served on a clinical trial committee for Pfizer, has served on an advisory board for Takeda Pharmaceuticals America, and has received honoraria for speaking engagements from Bayer and Pfizer.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ACS, acute coronary syndrome; ADA, American Diabetes Association; ATC, Antithrombotic Trialists' Collaboration; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CHD, coronary heart disease; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV, cardiovascular; CVD, cardiovascular disease; ETDRS, Early Treatment of Diabetic Retinopathy Study; Gp, glycoprotein; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment; MI, myocardial infarction; NO, nitric oxide; PAD, peripheral arterial disease; RR, relative risk; TASS, Ticlopidine Aspirin Stroke Study; TTP, thrombotic thrombocytopenic purpura; TXA₂, thromboxane A₂; USPHS, U.S. Physicians' Health Study; vWF, von Willebrand factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

© 2003 by the American Diabetes Association.

coagulation, and fibrinolysis (16,17). Thus, the balance in normal hemostasis is shifted to favor thrombosis, increasing CV risk. This review focuses on the role of platelets in promoting thrombosis and explores how antiplatelet therapies can reduce the risk of ischemic events in diabetic patients.

PLATELET ACTIVATION AND THE ATHEROTHROMBOTIC EVENT

Platelet activation is initiated by the binding of thrombogenic substances, such as collagen, thrombin, or components of atheromatous plaque, to receptors located on the platelet surface. Receptor binding triggers a series of events that include hydrolysis of membrane phospholipids, mobilization of intracellular calcium, and phosphorylation of important intracellular proteins (18). Notably, arachidonic acid is released from membrane phospholipids and is converted into thromboxane A₂ (TXA₂), which produces vasoconstriction and further augments the platelet activation process.

Calcium release and phosphorylation are critical for regulating the secretion of ADP and several proteins—including von Willebrand factor (vWF), fibronectin, plasminogen activator inhibitor 1, thrombospondin, platelet-derived growth factor, β -thromboglobulin, and platelet factor 4—from platelet granules. ADP, in turn, binds to platelet purinergic receptors and triggers a conformational change in glycoproteins IIb and IIIa on the platelet surface (19). This causes platelets to form a functional heterodimeric platelet glycoprotein (Gp) IIb-IIIa receptor complex that binds to fibrinogen and links adjacent platelets as part of the platelet aggregation process.

Prostacyclin and nitric oxide (NO), produced by normal endothelium, inhibit platelet activation and relax vascular smooth muscle to promote normal blood flow. People with diabetes have reduced release of prostacyclin and NO (20). At sites of tissue injury, platelets adhere to the subendothelium (21). In regions of low blood flow, subendothelial collagen fibrils bind to the platelet collagen GpIIa receptor. This interaction is stabilized in regions of higher blood flow by vWF, which links the collagen fibril to the platelet GpIb-IX receptor. These endothelium-platelet interactions are resistant to the

shear stress imposed by blood flow and enable the platelet to remain attached to the vascular surface at the tissue injury site. Furthermore, these interactions cause activated platelets to degranulate and release ADP and TXA₂. Once released, ADP and TXA₂ bind to other specific receptors, and those functions amplify the platelet aggregation process. In patients with diabetes, platelet function is altered in several ways, including an increased release of TXA₂ (22), accelerated platelet turnover (23,24), and an increase in platelet aggregation (25). Platelet activation and aggregation can be interrupted at several of the steps detailed above (21).

The formation of a platelet thrombus is accompanied by activation of the plasma coagulation cascade, leading to production of thrombin. Thrombin stimulates platelet aggregation, but more importantly, it mediates the conversion of fibrinogen into fibrin, which polymerizes into an insoluble cross-linked gel that forms the matrix for the thrombus, resulting in a stable clot. (The processes of platelet activation, secretion, and aggregation leading to intravascular thrombus formation occur as a result of atherosclerotic plaque rupture.)

After plaque rupture, blood from the lumen of the vessel comes into contact with the lipid-rich core of the plaque, where it interacts with the highly prothrombotic substances collagen and tissue factor (26). Thrombus formation leads to vessel obstruction. The thrombus may expand and result in total vessel occlusion, depending on the balance between factors that promote and those that oppose thrombosis. Factors that enhance thrombus progression include large plaque ruptures, lipid extrusion from the core, high-grade stenosis, low blood flow, high levels of fibrinogen, high levels of plasminogen activator inhibitor 1 (the major inhibitor of factors that promote fibrinolysis, such as tissue plasminogen activator), and reactive platelets. Factors that limit thrombus progression include high local blood flow, small and rapidly healing plaque ruptures, and high levels of fibrinolysis.

ALTERED PLATELET FUNCTIONS IN DIABETES

Diabetic thrombocytopeny refers to differences in platelet function between diabetic and nondiabetic individuals. Among diabetic individuals, increased

platelet aggregability and adhesiveness (16,22,27–33) are due to the following:

- Reduced membrane fluidity
- Altered Ca²⁺ and Mg²⁺ homeostasis (increased intracellular Ca²⁺ mobilization and decreased intracellular Mg²⁺)
- Increased arachidonic acid metabolism
- Increased TXA₂ synthesis
- Decreased prostacyclin production
- Decreased NO production
- Decreased antioxidant levels
- Increased expression of activation-dependent adhesion molecules (e.g., GpIIb-IIIa, P-selectin)

Platelets from patients with type 1 and type 2 diabetes exhibit enhanced platelet aggregation activity early in the disease course that may precede the development of CVD (22,25,34). Numerous biochemical abnormalities have been found that correlate with platelet hyperactivity. Platelets from diabetic patients exhibit reduced membrane fluidity, which may reflect changes in the lipid composition of the membrane or glycation of membrane proteins (16). Arachidonic acid metabolism is increased in platelets from diabetic patients; this leads to enhanced TXA₂ production and may contribute to increased platelet sensitivity (22,27).

An increase in calcium mobilization from intracellular storage pools, resulting in increased intracellular calcium levels, has been correlated with the reduction in membrane fluidity (28). In addition to alterations in platelet calcium homeostasis, intracellular magnesium concentrations are reduced, consistent with an increase in platelet hyperaggregability and adhesiveness (35). Magnesium supplementation can reduce these abnormal platelet functions in people with diabetes (35).

Platelets from diabetic subjects produce less NO and prostacyclin, which normally inhibit platelet-endothelium interactions and promote endothelium-mediated vasodilation. The concentration of NO synthase in platelets from patients with type 1 and type 2 diabetes is less than half that measured in platelets from nondiabetic individuals (29); however, insulin will stimulate NO synthesis in platelets (30). Moreover, platelets from diabetic subjects contain reduced antioxidant levels, which tend to be associated with increased aggregability and low platelet vitamin C levels (31). Platelet dysfunction

Table 1—Aspirin as a primary prevention strategy in diabetes: evidence from collaborative trials

Trial	Number of diabetic subjects	Years of study	CV end points	Aspirin dose (mg)	Patients with events			
					Aspirin	Placebo	RR	P
USPHS (42)	533	5	MI	325 q.o.d.	4.0%	10.1%	0.39	NR
ETDRS (43)	3,711	5	MI	650 q.o.d.	9.1%	12.3%	0.72	0.038
HOT (44)	1,501	3.8	MI	75 q.d.	2.3*	3.6*	0.64	0.002
			Major CV events		8.9*	10.5*	0.85	0.03

*Events per 1,000 patient-years. NR, not reported.

can be reversed by the addition of vitamin E (36–38).

Patients with type 1 and type 2 diabetes have increased populations of platelets that express activation-dependent adhesion molecules, such as activated GpIIb-IIIa, lysosomal Gp53, thrombospondin, and P-selectin (32). The increased expression of GpIIb-IIIa is consistent with the enhanced fibrinogen binding and aggregability seen in platelets from diabetic subjects (33). Further, serum fibrinogen levels are also elevated in many patients with type 1 or type 2 diabetes. In addition to reflecting increased aggregability, the enhanced surface expression of these adhesion molecules suggests that platelets can also communicate with leukocytes and possibly play a role in inflammation-mediated tissue damage in the vasculature. Finally, platelets may interact with plasma constituents, such as glycosylated LDLs, immune complexes, or vWF, to increase platelet aggregability or adhesion (16,17).

Although antiplatelet agents, including aspirin and clopidogrel, irreversibly inactivate platelet function (39) for the 7- to 10-day average life span of the platelet in normal subjects, diabetic patients with vascular disease may have a greater rate of platelet turnover.

ASPIRIN AS A PRIMARY PREVENTION STRATEGY IN DIABETES

Based on collaborative trial data, the American Diabetes Association (ADA) recommends that enteric-coated aspirin be used as a primary prevention strategy in patients with diabetes who are classified as being at high risk for CV events on the basis of the following risk factors (39–40):

- Family history of CHD
- Cigarette smoking
- Hypertension
- Weight >120% of ideal body weight

- Microalbuminuria or macroalbuminuria
- Total cholesterol >200 mg/dl (LDL cholesterol >100, HDL cholesterol <55 in women and <45 in men, and triglycerides >200)

This body of evidence is further supported by the results of the recently completed Primary Prevention Project in which low-dose aspirin (100 mg/day) was evaluated for the prevention of CV events in individuals with one or more of the following: hypertension, hypercholesterolemia, diabetes, obesity, family history of premature MI, or being elderly ($n = 4,495$). After a mean follow-up of 3.6 years, aspirin was found to significantly lower the frequency of CV death (from 1.4 to 0.8%; relative risk [RR] 0.56 [CI 0.31–0.99]) and total CV events (from 8.2 to 6.3%; RR 0.77 [0.62–0.95]) (41).

In addition to the Primary Prevention Project, there are three pertinent large-scale trials: the U.S. Physicians' Health Study (USPHS) (42), the Early Treatment of Diabetic Retinopathy Study (ETDRS) (43), and the Hypertension Optimal Treatment (HOT) study (44) (Table 1). The USPHS was a 5-year primary prevention trial in 22,701 healthy men that included 533 men with diabetes. Among diabetic men, 4.0% of those treated with 325 mg aspirin every other day had an MI versus 10.1% of those who received placebo (RR 0.39). In the ETDRS, although aspirin did not prevent progression of retinopathy, it did produce a significant reduction in risk for MI (28%) over 5 years ($P = 0.038$) without an excess of retinal or vitreous hemorrhage. This study may be viewed as a mixed primary and secondary prevention trial because 6% of those enrolled had a history of MI and <50% had elevated blood pressure or a history of CVD.

The HOT trial studied antihypertensive treatment in 18,790 hypertensive

individuals, 1,501 of whom had diabetes (44). Subjects were randomized to either low-dose aspirin (75 mg/day) or placebo therapy. Less than 10% of the participants had clinical evidence for previous MI, stroke, or other CHD. The aspirin study, therefore, may be viewed as a primary prevention trial in high-risk individuals. Aspirin therapy resulted in an additional 15% reduction in the risk for CV events over that seen with antihypertensive therapy ($P = 0.03$). Fatal bleeding, including cerebral, was equally common in the aspirin and placebo groups, whereas nonfatal bleeding was more common with aspirin therapy. Thus, the USPHS, the ETDRS, and the HOT trial support the ADA's position that low-dose aspirin therapy is indicated in diabetic individuals who are at high risk for CV events.

Aspirin dosage in the primary prevention strategy

The ADA recommends that a dosage of 81–325 mg of enteric-coated aspirin be used as a preventive strategy in high-risk diabetic individuals. The American Heart Association has recently issued similar guidelines (45). The American Heart Association recommends 75–160 mg/day of aspirin as a primary prevention strategy in high-risk individuals, defined as those with a 10-year risk of CHD $\geq 10\%$. A similar view has been put forth by the U.S. Preventive Services Task Force (46).

ASPIRIN AS A SECONDARY PREVENTION STRATEGY IN DIABETES

The ADA recommends the use of aspirin (81–325 mg/day) as a secondary prevention measure in diabetic patients with large vessel disease (history of MI, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina) (40). Two large meta-analyses of major secondary prevention trials by the Antithrombotic Trialists' Collaboration

(ATC) have concluded that aspirin (or another oral antiplatelet drug) is protective in most patients who are at high risk for CVD, including those with diabetes (47,48).

The ATC meta-analysis of 287 secondary prevention trials involved 212,000 high-risk patients who had acute or previous vascular disease or another condition that increased the risk of vascular occlusion (48). Aspirin was the most frequently used agent, with doses ranging from 75 to 325 mg/day. A low dose of aspirin (75–150 mg/day) was found to be at least as effective as higher daily doses, although it was noted that an initial higher loading dose of at least 150 mg might be needed in acute settings. In the main high-risk groups—acute MI, past history of MI, past history of stroke or transient ischemic attack, acute stroke, and other relevant history of vascular disease—antiplatelet therapy significantly reduced the incidence of vascular events by 23%. In an earlier meta-analysis, the ATC reported that vascular event reductions remained significant in subgroup analyses of middle- and older-aged, male and female, hypertensive and nonhypertensive, and diabetic and nondiabetic patients (47). Low doses of aspirin were as effective as high doses, but bleeding complications were reduced at the lower dosage levels (47).

In the >4,500 patients with diabetes studied in the ATC, the incidence of vascular events was reduced from 23.5% with control treatment to 19.3% with antiplatelet therapy ($P < 0.01$) (47). By comparison, the lower incidence of vascular events among nearly 42,000 nondiabetic patients was reduced from 17.2 to 13.7% with antiplatelet therapy ($P < 0.00001$). Although the overall incidence of vascular events is much higher in patients with diabetes (consistent with their higher risk), the benefit of antiplatelet therapy in diabetic and nondiabetic patients was comparable: 42 vascular events were prevented for every 1,000 diabetic patients and 35 events for every 1,000 nondiabetic patients.

Aspirin irreversibly inhibits the cyclooxygenase pathway of arachidonic acid metabolism; it blocks platelet thromboxane synthesis, resulting in inhibition of platelet aggregation (19,22,39) (Fig. 1.). However, aspirin has a paradoxical effect—particularly at doses >325 mg/day—because it also inhibits prostacyclin

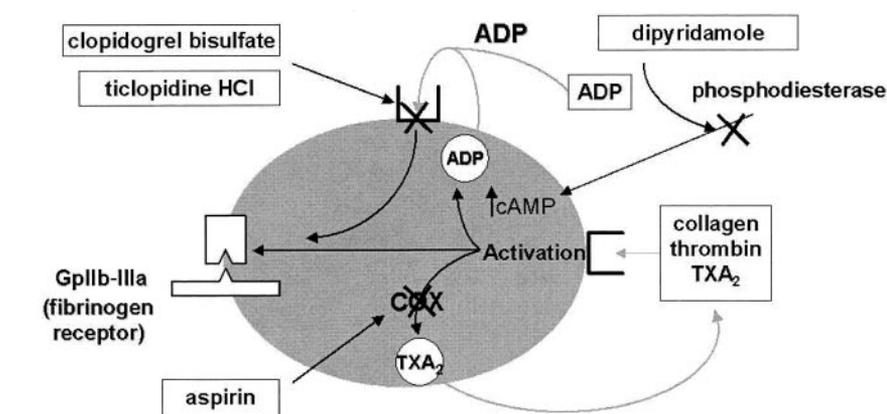


Figure 1—Mechanism of action of antiplatelet agents. COX, cyclo-oxygenase. From Schafer (19).

synthesis by endothelial cells and platelets, which might be expected to favor thrombus formation. For this reason, low-dose aspirin is favored for cardioprotection. This may be important in patients with diabetes, whose levels of prostacyclin are already reduced. Further, during treatment with low-dose aspirin, platelets from diabetic patients released greater amounts of TXA₂ than platelets from nondiabetic individuals (24). The physiological importance of this is unknown, and many prospective clinical trials support the use of aspirin in people with diabetes (14,24,39,41–48).

An important consideration affecting the use of aspirin in patients with diabetes is the interaction of aspirin with ACE inhibitors. In the wake of the Heart Outcomes Prevention Evaluation (HOPE) study, ACE inhibitors are emerging as a standard of care for many patients with atherosclerosis and diabetes. In the 3,577 patients with diabetes in the HOPE study, treatment with ramipril (10 mg/day) lowered the risk of MI, stroke, or CV death by 25% ($P = 0.0004$)—an effect that persisted after adjustments were made for changes in systolic and diastolic blood pressures (49). By blocking prostaglandin synthesis, aspirin has been hypothesized to blunt the bradykinin-related vasodilatory effects of ACE inhibitors (50). Clinical data on the interaction of aspirin with ACE inhibitors have been mixed; retrospective analyses of two large heart failure trials suggested that aspirin blunted the benefit achieved with ACE inhibitor treatment (50). On the other hand, in a retrospective analysis of 11,575 patients with coronary artery disease in the Bezafibrate Infarction Prevention Trial, patients who were treated with 250 mg/day aspirin and

ACE inhibitor therapy had a lower mortality rate than those who were not treated with aspirin (51). To date, all these analyses are observational. Prospective randomized trials are needed for definitive evidence. The current consensus is that low doses of aspirin can safely be used along with ACE inhibitors in patients with CHD, even in the presence of coronary heart failure.

ADP receptor antagonists

Ticlopidine and clopidogrel are thienopyridine antiplatelet agents that inhibit the binding of ADP to the platelet type 2 purinergic receptor (Fig. 1), an effect that lasts for the lifetime of the platelet (7–10 days). By blocking the purinergic receptor, these agents prevent the activation of the GpIIb-IIIa receptor and the subsequent binding of fibrinogen. Clopidogrel and ticlopidine inhibit ADP-induced platelet aggregation and amplification of aggregation induced by other agonists. The mechanism of action of clopidogrel and ticlopidine differs from that of aspirin.

Ticlopidine was evaluated for its effects on microvascular disease in diabetic patients in the Ticlopidine in Microangiopathy of Diabetes study (52). A total of 435 patients with nonproliferative diabetic retinopathy were randomized to receive ticlopidine, 250 mg b.i.d., or placebo and were followed for up to 3 years. Ticlopidine significantly reduced annual microaneurysm progression by 67% based on fluorescein angiograms ($P = 0.03$), and among insulin-treated diabetic patients, it reduced annual microaneurysm progression by 85% ($P = 0.03$). Moreover, the insulin-treated diabetic patients had a trend for developing fewer new vessels. Overall progression of

retinopathy was significantly less severe with ticlopidine ($P = 0.04$). This study supports the postulate that platelets are involved in the pathogenesis of microvascular disease in patients with diabetes. It was not designed to evaluate the effect of ticlopidine on CV events. A similar study with aspirin in diabetic individuals, the ETDRS, showed no effect on progression of retinopathy (43).

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial examined the effects of 75 mg clopidogrel once daily versus 325 mg aspirin once daily in a large secondary prevention population consisting of 19,185 patients with recent ischemic stroke, recent MI, or established PAD. Approximately 20% of these patients were known to have diabetes. More than 6,300 patients in each subgroup were randomized to receive 75 mg clopidogrel once daily or 325 mg aspirin once daily (53). The primary end point was the combined incidence of ischemic stroke, MI, or vascular death. Patients were followed up for a mean of 1.9 years. The annual incidence of the primary end point was 5.32% with clopidogrel and 5.83% with aspirin, representing an 8.7% RR reduction with clopidogrel above aspirin ($P = 0.043$) (Fig. 2A). Clopidogrel was more effective than aspirin in preventing fatal and nonfatal MI (incidence: 5.2 vs. 7.6%; risk reduction: 19.2%; $P = 0.008$) (54,55). Clopidogrel provided an RR reduction of 5.2% for stroke and 7.6% for vascular death.

In a recent report, Bhatt et al. (56) retrospectively analyzed results in the diabetic subgroup in the CAPRIE study. Of 1,914 diabetic patients randomized to clopidogrel, 15.6% had the composite vascular primary end point versus 17.7% of 1,952 diabetic patients randomized to aspirin therapy ($P = 0.042$). Thus, clopidogrel appears to be an effective antiplatelet agent for secondary prevention in diabetic subjects, whereas aspirin is more cost-effective (57).

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study examined CV outcomes with clopidogrel plus aspirin versus aspirin alone in patients with acute ischemic heart disease (58). In the CURE study, 12,562 patients with unstable angina or non-Q-wave MI who were being treated with aspirin, β -blockers, and other conventional therapies were randomized to receive either clopidogrel (300 mg loading dose and 75

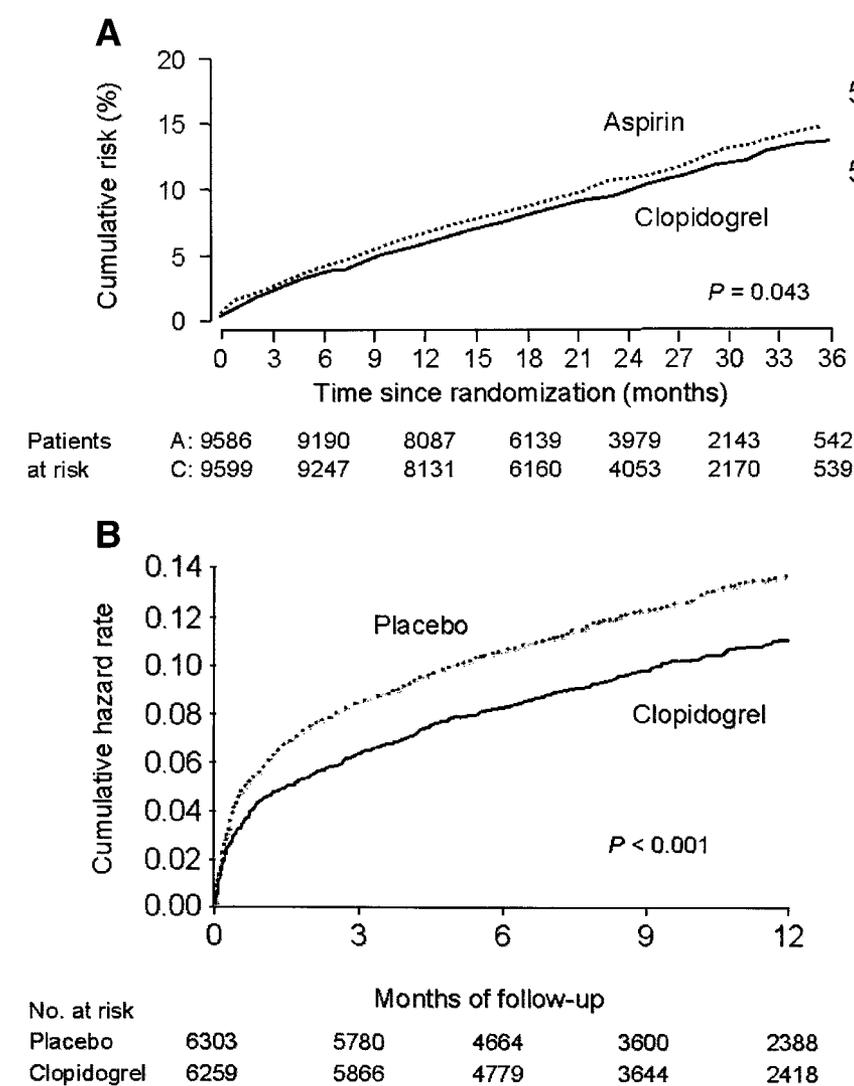


Figure 2—Kaplan-Meier analysis of the cumulative risk of primary end-point events in the CAPRIE (A) and CURE (B) studies. The primary end point in CAPRIE was the combined incidence of ischemic stroke, MI, or vascular death; CAPRIE included patients with more severe macrovascular disease (recent stroke or MI or symptomatic PAD). The CURE study included patients with unstable angina and non-Q-wave MI and who had a primary first outcome of CV death, nonfatal MI, or stroke. Modified with permission from CAPRIE (53) and CURE (58).

mg thereafter) or placebo in addition to aspirin for up to 1 year.

After the mean follow-up period of 9 months, patients on clopidogrel and aspirin experienced a significant 20% reduction in the first primary outcome, a composite of CV death, nonfatal MI, or stroke, compared with patients receiving aspirin and placebo (RR 0.80; 95% CI 0.72–0.90; $P < 0.001$) (58) (Fig. 2B). An analysis of subgroups showed consistency of effect on the primary outcome in patients with diabetes or those with no diabetes. The trend favoring the addition of clopidogrel was consistent across all

subgroups analyzed and was incremental to the standard therapy, including GpIIb/IIIa inhibitors. The second primary outcome consisting of the first primary outcome or refractory ischemia was also significantly reduced (RR 0.84; $P < 0.001$) (58). Significantly more patients in the clopidogrel and aspirin group had major bleeding (3.7 vs. 2.7%), but there was no increase in life-threatening bleeds.

Based in part on the CURE data, the American College of Cardiology and the American Heart Association (ACC/AHA) task force on practice guidelines recently issued an updated version of their guide-

lines for the management of unstable angina and non-Q-wave MI and the prevention of secondary CV events (59). Because clopidogrel is now recognized as efficacious in both the early phase and during long-term treatment of unstable angina and non-Q-wave MI, the guidelines recommend promptly adding clopidogrel to aspirin in patients presenting with unstable angina and non-Q-wave MI. The guidelines recommend that clopidogrel be administered to patients who are hypersensitive or intolerant to aspirin. Further, clopidogrel should be used both in patients being treated with medical therapy or percutaneous coronary intervention for up to 9 months (59).

Although there were instances of major bleeds beyond 30 days, no cases of life-threatening bleeds were reported. Thus, the data suggest that the benefits of taking clopidogrel plus aspirin for up to 9 months outweigh the risks (58). However, in patients taking clopidogrel in whom coronary artery bypass graft is planned, the drug should be withheld for at least 5 days and preferably for 7 days.

GP IIb-IIIa receptor antagonists

Recent data from a meta-analysis of six trials of intravenous GpIIb-IIIa inhibitors in acute coronary syndrome (ACS) patients with diabetes have reinforced the concept that treatment targeting the platelet can play a major role in reducing CV events in diabetic individuals (60,61). These inhibitors act at the fibrinogen binding site (Fig. 1). The meta-analysis included 6,458 diabetic patients in the following trials: Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM), Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), Platelet IIb/IIIa Antagonist for Reduction of Acute Coronary Events in a Global Organization Network (PARAGON) A and B, Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Arteries (GUSTO) IV. GpIIb-IIIa blockers significantly reduced mortality at 30 days from 6.2 to 4.6% ($P = 0.007$) in the diabetic patients. Among the more than 22,000 patients in these trials who did not have diabetes, GpIIb-IIIa inhibitors did not improve survival. The effect of GpIIb-IIIa inhibitors

in diabetic individuals was even greater in the 1,279 patients who underwent percutaneous coronary intervention during the index hospitalization; in these individuals, GpIIb-IIIa inhibitors reduced 30-day mortality from 4 to 1.2% ($P = 0.002$). The large number of patients and events (339 deaths) in this meta-analysis provide strong evidence in support of the concept of platelet inhibition for diabetic patients with ACS.

SAFETY OF ANTIPLATELET DRUGS

Aspirin, like other nonsteroidal anti-inflammatory drugs, has the potential to cause gastrointestinal adverse effects, such as gastric mucosal injury or bleeding. These effects are dose related and may be minimized with enteric-coated low-dose aspirin. However, gastrointestinal toxicity may occur even at low doses of aspirin (51). Although quite rare, the adverse effect of most concern is intracerebral hemorrhage. It is important to recognize that there is no increase in the risk for retinal or vitreous bleeding with aspirin therapy (43). Additionally, if blood pressure is controlled in hypertensive patients, there is no increased risk of intracerebral bleeding (44).

A limitation to the use of ticlopidine is its potential to cause bone marrow suppression. Severe neutropenia and/or agranulocytosis have been observed in ~1% of 2,048 stroke patients in clinical trials (62). In the Ticlopidine Aspirin Stroke Study (TASS), 2.4% of patients receiving ticlopidine had neutropenia (absolute neutrophil count $<1,200$ cells/ mm^2) and 0.9% had severe neutropenia (absolute neutrophil count <450 cells/ mm^2). Thrombotic thrombocytopenic purpura (TTP) has also been reported and may be fatal if untreated. During clinical trials of ticlopidine, one case was reported, but based on postmarketing data, U.S. physicians reported ~100 cases between 1992 and 1997. The estimated incidence of ticlopidine-associated TTP may be as high as one case in every 2,000–4,000 patients exposed. This result necessitates hematological monitoring for the first 3 months of treatment with ticlopidine (61).

Clopidogrel did not produce bone marrow toxicity in either tissue cultures or animal models during preclinical studies. The incidence of neutropenia with clopidogrel in the CAPRIE trial (0.10%) was comparable to that associated with

aspirin (0.17%) (53). Additionally, there was no difference between aspirin and clopidogrel in the incidence of thrombocytopenia (53). Among the many millions of individuals worldwide who have received clopidogrel, there have been 11 cases of possible TTP (62). Reportedly, however, clopidogrel was implicated as a causative factor in only 5 of the 11 cases (63). In these patients, TTP occurred within the first 2 weeks of therapy. Of the 11 patients, 10 recovered after receiving plasma exchange. This rate is essentially the same as the background rate in the population at large. Physicians should be aware of the possibility of this syndrome during the first 2 weeks after initiation of clopidogrel therapy. However, blood monitoring is not required.

In the CURE study, clopidogrel plus aspirin had a greater incidence of major bleeding than aspirin alone (3.7 vs. 2.7%; RR 1.38; $P = 0.001$) (58). Bleeding was most common at puncture sites and in the gastrointestinal system (64). There was no increase in fatal hemorrhages or intracranial hemorrhages.

In the meta-analysis of GpIIb-IIIa studies (48), there was an absolute excess of 23 major extracranial bleeding episodes per 1,000 patients treated. Fatal bleeding was rare. Intracranial hemorrhages were few in number (GpIIb-IIIa plus aspirin, 0.2% vs. aspirin alone, 0.1% [NS]).

CONCLUSIONS AND CLINICAL RECOMMENDATIONS

Macrovascular complications are the leading causes of death in patients with diabetes and are responsible for a significant amount of morbidity in this population. Moreover, patients with diabetes and established atherosclerotic disease are at especially high risk for additional ischemic vascular events, including MI, stroke, and vascular death. Diabetes and prediabetic conditions are associated with platelet and coagulation derangements. Because platelet aggregation plays an integral role in thrombus formation, treatment strategies have focused on using antiplatelet agents to prevent subsequent ischemic events. The efficacy of aspirin relative to placebo as a secondary prevention strategy was established by a meta-analysis of clinical trials in the ATC that included a subgroup analysis of diabetic patients. Three primary prevention trials have sup-

ported the use of aspirin as a primary prevention strategy in patients with diabetes who are at high risk for CV events. The ADP-receptor blocker clopidogrel has been shown to produce additional risk reduction relative to aspirin in two secondary prevention trials (CAPRIE and CURE).

Clinical practice recommendations from the ADA indicate that a secondary prevention strategy including antiplatelet agents should be adopted for patients with diabetes and evidence of macrovascular disease (40). This includes patients with a history of MI, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, or angina. In addition, low-dose (81–325 mg/day) enteric-coated aspirin therapy is recommended by the ADA as a primary prevention strategy for people with diabetes who are at high risk for CV events (40).

References

- Nathan DM: Long-term complications of diabetes mellitus. *N Engl J Med* 328: 1676–1685, 1993
- Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
- Brand FN, Abbott RD, Kannel WB: Diabetes, intermittent claudication, and risk of cardiovascular events. *Diabetes* 38: 504–509, 1989
- Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
- Pahor M, Psaty BM, Furberg CD: New evidence on the prevention of cardiovascular events in hypertensive patients with type 2 diabetes. *J Cardiovasc Pharmacol* 32 (Suppl. 2):S18–S23, 1998
- Serrano Rios M: Relationship between obesity and the increased risk of major complications in non-insulin-dependent diabetes mellitus. *Eur J Clin Invest* 28 (Suppl. 2):14–18, 1998
- Colwell JA: Multifactorial aspects of the treatment of the type II diabetic patient. *Metabolism* 46 (Suppl. 1):1–4, 1997
- Brand FN, Kannel WB, Evans J, Larson MG, Wolf PA: Glucose intolerance, physical signs of peripheral artery disease, and risk of cardiovascular events: the Framingham Study. *Am Heart J* 136:919–927, 1998
- Cantrill JA, D'Emanuele A, Dornan TL, Garcia S: A survey of drug treatment and outcomes in diabetic patients with acute myocardial infarcts. *J Clin Pharm Ther* 20: 207–213, 1995
- MacDonald TM, Butler R, Newton RW, Morris AD, for the DARTS/MEMO Collaboration: Which drugs benefit diabetic patients for secondary prevention of myocardial infarction? *Diabet Med* 15:282–289, 1998
- Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
- Kip KE, Faxon DP, Detre KM, Yeh W, Kelsey SF, Currier JW: Coronary angioplasty in diabetic patients: the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *Circulation* 94:1818–1825, 1996
- Stein B, Weintraub WS, Gebhart SP, Cohen-Bernstein CL, Grosswald R, Liberman HA, Douglas JS Jr, Morris DC, King SB 3rd: Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 91:979–989, 1995
- Colwell JA: Clinical trials of antiplatelet agents in diabetes mellitus: rationale and results. *Semin Thromb Hemost* 17:439–444, 1991
- Aronow WS, Ahn C: Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women ≥ 62 years of age. *Am J Cardiol* 74:64–65, 1994
- Jokl R, Colwell JA: Arterial thrombosis and atherosclerosis in diabetes. *Diabetes Metab Rev* 5:1–15, 1997
- Jokl R, Colwell JA: Clotting disorders in diabetes. In *International Textbook of Diabetes Mellitus*. 2nd ed. Alberti KGMM, Zimmet P, DeFronzo RA, Keen H, Eds. Chichester, U.K., Wiley, 1997, p. 1543–1557
- Handin RI: Bleeding and thrombosis. In *Harrison's Principles of Internal Medicine*. 14th ed. Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, Hauser SL, Longo DL, Eds. New York, McGraw-Hill, 1998, p. 339–345
- Schafer AI: Antiplatelet therapy. *Am J Med* 101:199–209, 1996
- Klein RL, Colwell JA: Altered endothelial function in diabetes mellitus: an overview. In *Contemporary Endocrinology: Endocrinology of the Vasculature*. Conn PM, Sowers JR, Eds. Totowa, NJ, Humana, 1996, p. 125–134
- Boon GD: An overview of hemostasis. *Toxicol Pathol* 21:170–179, 1993
- Halushka PV, Rogers RC, Loadholt CB, Colwell JA: Increased platelet thromboxane synthesis in diabetes mellitus. *J Lab Clin Med* 97:87–96, 1981
- Winocour PD, Laimins M, Colwell JA: Platelet survival in streptozotocin-induced diabetic rats. *Thromb Haemost* 51:307–312, 1984
- DiMinno G, Silver MJ, Cerbone AM, Murphy S: Trial of repeated low-dose aspirin in diabetic angiopathy. *Blood* 68: 886–891, 1986
- Sagel J, Colwell JA, Crook L, Laimins M: Increased platelet aggregation in early diabetes mellitus. *Ann Intern Med* 82:733–738, 1975
- Davies MJ: Stability and instability: two faces of coronary atherosclerosis: the Paul Dudley White Lecture 1995. *Circulation* 94:2013–2020, 1996
- Mayfield RK, Halushka PV, Wohltmann HJ, Lopes-Virella M, Chambers JK: Platelet function during continuous insulin infusion treatment in insulin-dependent diabetic patients. *Diabetes* 34:1127–1133, 1985
- Watala C, Boncer M, Golanski J, Koziolkiewicz W, Trojanowski Z, Walkowiak B: Platelet membrane lipid fluidity and intraplatelet calcium mobilization in type 2 diabetes. *Eur J Haematol* 61:319–326, 1998
- Martina V, Bruno GA, Trucco F, Zumpano E, Tagliabue M, Di Bisceglie C: Platelet cNOS activity is reduced in patients with IDDM and NIDDM. *Thromb Haemost* 79:520–522, 1998
- Trovati M, Anfossi G, Massucco P, Mattiello L, Costamagna C, Piretto V, Mularoni E, Cavalot F, Bosia A, Ghigo D: Insulin stimulates nitric oxide synthesis in human platelets and, through nitric oxide, increases platelet concentrations of both guanosine-3', 5'-cyclic monophosphate and adenosine-3', 5'-cyclic monophosphate. *Diabetes* 46:742–749, 1997
- Sarji KE, Kleinfelder J, Brewington P, Gonzalez J, Hempling H, Colwell JA: Decreased platelet vitamin C in diabetes mellitus: possible role in hyperaggregation. *Thromb Res* 15:639–650, 1979
- Tschoepe D, Rauch U, Schwippert B: Platelet-leukocyte-cross-talk in diabetes mellitus. *Horm Metab Res* 29:631–635, 1997
- Leet H, Paton RC, Passa P, Caen JP: Fibrinogen binding and ADP-induced aggregation in platelets from diabetic subjects. *Thromb Res* 24:143–150, 1981
- Mandal S, Sarode R, Dash S, Dash RJ: Hyperaggregation of platelets detected by whole blood platelet aggregometry in newly diagnosed noninsulin-dependent diabetes mellitus. *Am J Clin Pathol* 100: 103–107, 1993
- Gawaz M, Ott I, Reiningger AJ, Neumann FJ: Effects of magnesium on platelet aggregation and adhesion: magnesium modulates surface expression of glycoproteins on platelets in vitro and ex vivo. *Thromb Haemost* 72:912–918, 1994

36. Gerster H: Prevention of platelet dysfunction by vitamin E in diabetic atherosclerosis. *Z Ernahrungswiss* 32:243–261, 1993
37. Gisinger C, Watanabe J, Colwell JA: Vitamin E and platelet eicosanoids in diabetes mellitus. *Prostaglandins Leukot Essent Fatty Acids* 40:169–176, 1990
38. Jain SK, Krueger KS, McVie R, Jaramillo JJ, Palmer M, Smith T: Relationship of blood thromboxane-B2 (TxB2) with lipid peroxides and effect of vitamin E and placebo supplementation on TxB2 and lipid peroxide levels in type 1 diabetic patients. *Diabetes Care* 21:1511–1516, 1998
39. Colwell JA: Aspirin therapy in diabetes. *Diabetes Care* 20:1767–1771, 1997
40. American Diabetes Association: Aspirin therapy in diabetes (Position Statement). *Diabetes Care* 26 (Suppl. 1):S87–S88, 2003
41. Collaborative Group of the Primary Prevention Project: Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet* 357:89–95, 2001
42. Steering Committee of the Physicians' Health Study Research Group: Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 321:129–135, 1989
43. ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus. *JAMA* 268:1292–1300, 1992
44. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S, for the HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 351:1755–1762, 1998
45. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco RL, Sallis JF Jr, Smith SC Jr, Stone NJ, Taubert KA: AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases (AHA Scientific Statement). *Circulation* 106:388–391, 2002
46. U.S. Preventive Services Task Force: Aspirin for the primary prevention of cardiovascular events: recommendations and rationale. *Ann Intern Med* 136:157–160, 2001
47. Antiplatelet Trialists' Collaboration: Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 308:81–106, 1994
48. Antithrombotic Trialists' Collaboration: Collaboration meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 324:71–86, 2002
49. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253–259, 2000
50. Stys T, Lawson WE, Smaldone G, Stys A: Does aspirin attenuate the beneficial effects of angiotensin converting enzyme inhibition in heart failure? *Arch Intern Med* 160:1409–1413, 2000
51. Leor J, Reicher-Reiss H, Goldbourt U, Boyko V, Gottlieb S, Battler A, Behar S: Aspirin and mortality in patients treated with angiotensin-converting enzyme inhibitors: a cohort study of 11,575 patients with coronary artery disease. *J Am Coll Cardiol* 33:1920–1925, 1999
52. TIMAD Study Group: Ticlopidine treatment reduces the progression of non-proliferative diabetic retinopathy. *Arch Ophthalmol* 108:1577–1583, 1990
53. CAPRIE Steering Committee: A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 348:1329–1339, 1996
54. Gent M: Benefit of clopidogrel in patients with coronary disease (Abstract). *Circulation* 96 (Suppl. 1):467, 1997
55. Easton JD: Benefit of clopidogrel in patients with evidence of cerebrovascular disease (Abstract). *Neurology* 51:332, 1998
56. Bhatt D, Marso S, Hirsch A, Ringleb P, Hacke W, Topol E: Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 90:625–628, 2002
57. Gaspoz JM, Coxson PG, Goldman PA, Williams LW, Duntz KM, Hunink MG, Goldman L: Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 346:1819–1821, 2002
58. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 345:494–502, 2001
59. American College of Cardiology website: ACC/AHA Guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: unstable angina/non-ST elevation myocardial infarction. Available at www.acc.org. Accessed 29 September 2002
60. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, Hamm CW, Moliterno DJ, Califf RM, White HD, Kleiman NS, Theroux P, Topol EJ: Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation* 104:2767–2771, 2001
61. Ticlid (package insert). Nutley, NJ, Roche Laboratories, 1995
62. Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, McCarthy LJ, Sarode R, Hatfield AJ, Feldman MD, Davidson CJ, Tsai HM: Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 342:1773–1777, 2000
63. Paradiso-Hardy FL, Papastergiou J, Lancot KL, Cohen EA: Thrombotic thrombocytopenic purpura associated with clopidogrel: further evaluation. *Can J Cardiol* 18:771–773, 2002
64. Plavix (package insert). New York, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, 2002