Expanding the Recognition and Assessment of Bleeding Events Associated With Antiplatelet Therapy in Primary Care

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Antiplatelet therapy is an evidence-based, guideline-recommended, worldwide standard of care for treatment of patients with atherothrombosis. However, clinical implementation of the guidelines is suboptimal, in part because of physician and patient nonadherence. The increased risk of bleeding associated with antiplatelet therapy is often the reason for nonadherence, and several programs have been created to increase adherence to guideline treatment recommendations. Despite the relative success of such initiatives, including Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines, Guidelines Applied in Practice, and the American Heart Association's Get With the Guidelines and a Science Advisory, a current estimate is that less than 50% of atherothrombotic patients are taking antiplatelet therapies as recommended by national guidelines. A PubMed and MEDLINE search of the literature (January 1, 1983-May 15, 2008) was performed to examine the bleeding risks associated with various antiplatelet therapies. Relevant clinical trials, observational registry data, and other studies relevant to treatment and guideline recommendations were selected from articles generated through specific search terms. This comprehensive review contributes to the understanding of the benefit-to-risk ratio of antiplatelet therapy for patients with atherothrombosis.

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ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass grafting; CI = confidence interval; CLARITY = Clopidogrel as Adjunctive Reperfusion Therapy; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial; COX-2 = cyclooxygenase 2; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; DISPERSE-2 = Dose Confirmation Study Assessing Antiplatelet Effects of AZD6140 vs. Clopidogrel in non-ST-segment Elevation Myocardial Infarction; ER = extended release; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; HR = hazard ratio; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; TIMI = Thrombolysis in Myocardial Infarction; TRITON = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel

Substantial evidence exists for the benefit of secondary prevention with antiplatelet therapy for patients who have experienced an acute atherothrombotic event.[1] Long-term antiplatelet therapy significantly reduces the risk of major cardiovascular events across a wide range of atherothrombotic syndromes.[1] Accordingly, the American Heart Association (AHA) and American College of Cardiology (ACC) have published evidence-based guidelines to provide physicians with a framework for secondary prevention in patients at risk of ischemic or cardiovascular events.[2-5] Although these recommendations increase use of risk-reducing medications,[6] physician and patient adherence to the guidelines needs to improve.

Several hospital-based quality initiatives have improved adherence with consensus guideline recommendations. For instance, the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) initiative, the Guidelines Applied in Practice, and the AHA's Get With the Guidelines Program[6-8] have improved adherence to secondary prevention guidelines such that more than 90% (up from approximately 81%) of US patients are discharged with an antiplatelet agent prescription after an acute coronary event.[6,8,9]

However, a prescription at discharge does not necessarily translate into long-term use or therapy adherence by the patient. Findings from an ambulatory care database indicated that only 30% of patients with a history of atherothrombotic events were receiving aspirin as part of their routine care in 2002,[10] and data from the Duke Databank for Cardiovascular Disease in the same year showed that almost 30% of patients who were prescribed aspirin were not consistently taking it.[11] This information is disconcerting because poor adherence with antiplatelet therapy as secondary preventive therapy is associated with a substantially worse outcome.[12-15]

Many factors can influence prescribing practices and patient adherence. One of these factors may be an overestimation of the bleeding risk in relationship to cardiovascular benefit of antiplatelet therapy. A PubMed and MEDLINE search of the literature (January 1, 1983-May 15, 2008) was performed to examine the bleeding risks associated with various antiplatelet therapies. Relevant clinical trials, observational registry data, and other studies relevant to treatment and guideline recommendations were selected from articles generated through specific search terms, including *antiplatelet therapy* (and specific agents), *safety*, *tolerability*, *bleeding classification*, *cardiovascular risk*, *benefit to risk*, and *treatment recommendations*. This article reviews the risk of bleeding with antiplatelet therapy, including classification schemes used to stratify bleeding severity and the

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TABLE 1. **Classification Systems for Evaluating Bleeding Events**[a]

Reference	Most severe	Intermediate	Least severe
TIMI[22]	**Major** Intracranial bleeding Overt bleeding with decrease in Hb ≥5 g/dL Decrease in Hct ≥15%	**Minor** Spontaneous gross hematuria Spontaneous hematemesis Observed bleeding with decrease in Hb ≥3 g/dL but ≤15%	**Insignificant** Blood loss insufficient to meet criteria for major or minor bleeding
GUSTO[23]	**Severe** Deadly bleeding Intracerebral bleeding Substantial hemodynamic compromise requiring treatment	**Moderate** Bleeding requiring transfusion	**Mild** Other bleeding not requiring transfusion or causing hemodynamic compromise
BleedScore[24]	**Alarming** (score, 6 points) Transfusion needed Intracranial bleeding Life-threatening bleeding	**Internal** (score, 3 points) Hematoma Epistaxis Blood loss from mouth or vagina Melena Eye bleed Hematuria Hematemesis	**Superficial** (score, 1 point) Easy bruising Bleeding from small cuts Petechia Ecchymosis

[a] Terms used to describe severity for each classification system are in boldface type. GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; Hb = hemoglobin; Hct = hematocrit; TIMI = Thrombolysis in Myocardial Infarction.

influence of bleeding on adherence. In light of this discussion, strategies for maintaining long-term adherence in primary care are explored.

BLEEDING RISK: QUANTIFICATION, CLASSIFICATION, AND ASSOCIATION WITH OUTCOMES

All antiplatelet agents are associated with an increased risk of bleeding complications; however, no universally accepted definition exists for major bleeding. As shown by a recent analysis of large randomized clinical trials, there is considerable heterogeneity among the measurement scales used to define bleeding complications.[16] This often leads to differences in reporting rates of major bleeding among studies and disparity in the estimated impact of bleeding on clinical outcomes.

During the thrombolytic era, before the widespread use of percutaneous coronary intervention (PCI) or the advent of long-term antithrombotic therapy, including low-molecular-weight heparins, clopidogrel, or dipyridamole, 2 main bleeding scales were developed: Thrombolysis in Myocardial Infarction (TIMI) and Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO)[17-21] (Table 1[22-24]). The TIMI scale uses objective laboratory criteria (eg, hemoglobin levels) in the assessment of major and minor bleeding,[22] whereas the GUSTO scale relies more on clinical assessments (eg, hemodynamic compromise requiring treatment, bleeding requiring transfusion) and is therefore more subjective.[23]

Although bleeding complications are associated with poorer outcomes (death or myocardial infarction [MI]) compared with no bleeding, the effect on outcomes is most important for severe bleeding; both 30-day and 6-month mortality rates increase with increasing severity of bleeding as classified by the GUSTO scale (Figure 1).[21] This trend was also apparent in patients with mild bleeding, although to a lesser extent. At 30 days and at 6 months, mild bleeding was associated with a significant increase in the adjusted hazard ratios (HRs) for death and death or MI in patients with GUSTO-classified mild bleeding.[21] Similarly, in a retrospective analysis of patients undergoing PCI, 1-year mortality rates were also higher in patients with major bleeding according to the TIMI criteria compared with those with minor or no bleeding.[18]

When both scales were used to analyze the association between bleeding and outcomes, there was a stepwise increase in the risk of death or MI at 30 days or at 6 months as bleeding severity increased according to the GUSTO scale, but the risk of death or MI was similar for all grades of TIMI bleeding (Figure 2, A and B).[25] Separate models were constructed for each grade. Adjustments were made for age, sex, weight, site, diabetes mellitus, smoking status, prior angina, peripheral arterial disease, prerandomization therapy, MI at enrollment, systolic and diastolic blood pressure at randomization, heart rate at randomization, Killip class, and assigned treatment. This association remained consistent for each scale when applied in a model incorporating bleed severity as a time-dependent covariate,[25] suggesting that a bleeding measure based on observational factors (GUSTO) may be a better prognostic indicator than a laboratory-based scale (TIMI), hence indirectly emphasizing the importance of

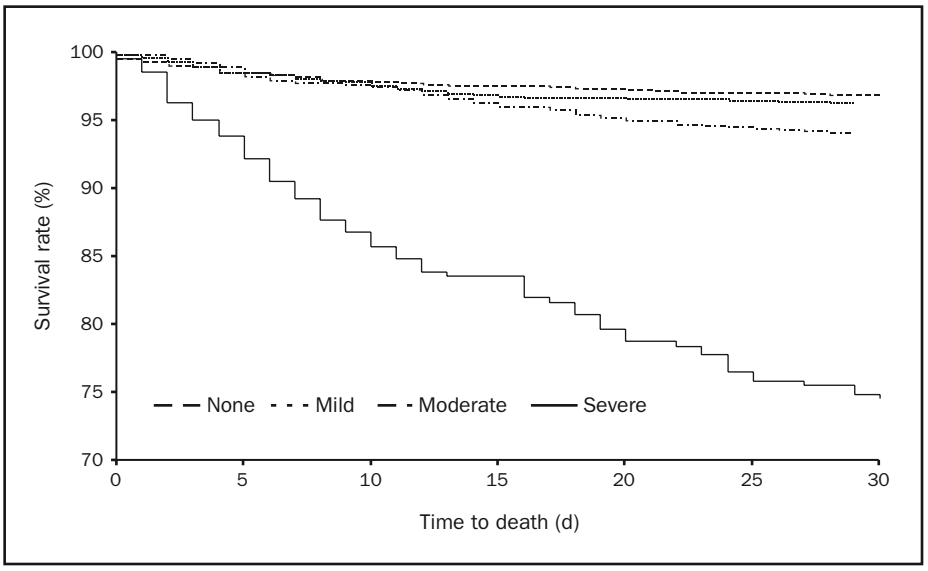

FIGURE 1. Kaplan-Meier survival curves for 30-day mortality by severity of bleeding using Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries criteria in an analysis of data from 26,452 patients with acute coronary syndrome participating in 4 randomized controlled trials.[21] Log rank *P* values are *P*=.20 for mild bleeding vs no bleeding, *P*<.001 for mild vs moderate bleeding, and *P*<.001 for moderate vs severe bleeding. Reprinted from *Am J Cardiol*,[21] with permission from Elsevier, ©2005.

physician involvement in the monitoring of patients with atherothrombosis.

Despite these findings, the TIMI and GUSTO scales are not universally used to assess bleeding complications. Among 13 trials reviewed by Steinhubl et al,[16] 9 used trial-specific bleeding scales. Although there were some similarities among these scales, there were also important differences, namely, the hemoglobin decrease or number of blood transfusion units that qualified a bleed as major and the subcategorization of major bleeding into severe

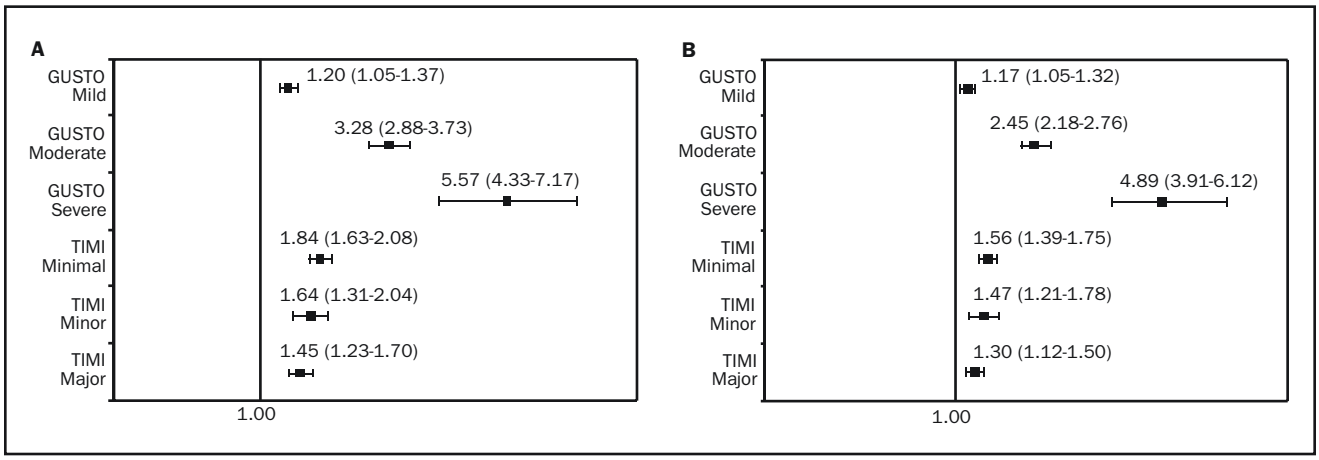

FIGURE 2. Adjusted hazard ratios (95% confidence intervals) of death or myocardial infarction at 30 days (A) and at 6 months (B) by worsening grade of bleeding using the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) and Thrombolysis in Myocardial Infarction (TIMI) criteria for bleeding severity in a pooled analysis of data from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy and the Platelet Glycoprotein IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network studies.[25] Separate models were constructed for each grade. Adjustments were made for age, sex, weight, site, diabetes mellitus, smoking status, prior angina, peripheral vascular disease, prerandomization therapy, myocardial infarction at enrollment, systolic and diastolic blood pressure at randomization, heart rate at randomization, Killip class, and assigned treatment. Reprinted from *J Am Coll Cardiol*,[25] with permission from Elsevier, ©2006.

TABLE 2. **Guidelines for Antiplatelet Therapy for Specific Atherothrombotic Disorders**

Indication	Recommended therapy
Secondary prevention of stroke or transient ischemic attack[30,31]	Aspirin, clopidogrel, aspirin with extended-release dipyridamole
After acute coronary syndrome or percutaneous coronary intervention with stent implantation[a2-5,32]	Clopidogrel with aspirin (up to 12 mo)
Peripheral arterial disease[30]	Clopidogrel (as an alternative to aspirin)

[a] A Science Advisory by several cardiology organizations extended the recommended duration of dual antiplatelet therapy to at least 12 months after drug-eluting stent implantation because of increased risk of late thrombosis if clopidogrel therapy is discontinued within 3 to 6 months of percutaneous coronary intervention.

and life-threatening.[16] Such differences in the definition of bleeding events lead to difficulties in comparing results across various clinical trials, particularly with respect to the efficacy of different therapies and the associated relative risk of complications.[26]

Recently, a single-site, retrospective analysis of 17,901 consecutive patients who underwent PCI showed that major femoral bleeding complications (ie, major hematoma, major femoral bleeding, and retroperitoneal hemorrhage) are strong predictors of 30-day mortality (HR, 9.96; 95% confidence interval [CI], 6.94-14.30; $P<.001$).[27] This study also identified blood transfusion within 7 days of PCI as an independent predictor of 30-day mortality, the risk of which increased with the number of units transfused.

Another type of bleeding event that commonly accompanies antiplatelet therapy is "nuisance bleeding," such as that from shaving cuts or purpura. Although not life-threatening, this type of bleeding is important because it may lead to nonadherence. A rebound platelet activation effect has been documented after cessation of antiplatelet therapy in a nonadherent patient,[28] putting the patient at increased risk of recurrent ischemic events. Because the TIMI and GUSTO scales are not sensitive to such nuisance bleeding events, they may overestimate the benefit-to-risk ratio of antiplatelet therapy.[29] Recently, another bleeding assessment scale, the BleedScore, has been introduced to address the cumulative effect of minor bleeding in patients undergoing long-term antiplatelet therapy (Table 1).[24] Although providing additional tools to quantify bleeding, the new scale has not yet been validated in relationship to clinical outcomes and may complicate comparisons among trials. A recommended standard bleeding scale is needed, particularly taking into account nuisance bleeding effects that may occur with long-term antiplatelet administration.

THE BENEFIT-TO-RISK PROFILE OF ANTIPLATELET THERAPY

A collaborative meta-analysis of randomized trials of antiplatelet therapy showed an almost 25% reduction in the risk of serious vascular events (ie, nonfatal MI, nonfatal stroke, or vascular death) in patients with unstable angina, acute MI, stroke, transient ischemic attack (TIA), coronary artery disease, peripheral arterial disease, and/or high risk of embolism.[1] Although the proportional reduction in serious vascular events varied among different categories of patient risk, the absolute risk of fatal and major nonfatal bleeding with antiplatelet therapy was small, and overall mortality was significantly reduced, suggesting that the cardiovascular benefit of antiplatelet therapy outweighs the risk of major bleeding.[1] Accordingly, current evidence-based guidelines strongly recommend using antiplatelet therapy, particularly aspirin, for patients with atherothrombotic disease.[5,30,31] Furthermore, dual antiplatelet therapy (aspirin plus clopidogrel or aspirin plus extended-release [ER] dipyridamole) is recommended for various atherothrombotic patient groups, unless the patient has a very low risk or cannot tolerate one of the agents (Table 2).

Although the risk of bleeding increases when a combination of antiplatelet agents is used, for most patients, the benefit-to-risk ratio still favors combination therapy[32] (Table 3[33-41]). In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the combination of clopidogrel plus aspirin significantly reduced the risk of death from cardiovascular causes, nonfatal MI, or stroke in patients with acute coronary syndrome (relative risk of 0.80 compared with patients receiving aspirin alone; $P<.001$).[33] Although significantly more bleeding events were reported in the clopidogrel group than in the placebo group (3.7% vs 2.7%; $P=.001$), the occurrence of life-threatening bleeding was not increased (2.2% vs 1.8%; $P=.13$), suggesting a favorable benefit-to-risk profile.[33] In contrast to CURE, results from the CLopidogrel as Adjunctive ReperfusIon TherapY (CLARITY) trial[36] and ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)[35] showed no statistically significant increases in the risk of major bleeding among patients who received clopidogrel and aspirin compared with aspirin alone. Similar to CURE, the combination significantly improved outcomes (in CLARITY, the composite of an occluded infarct-related artery on angiography or death or recurrent MI before angiography; in COMMIT, the composite of in-hospital death, reinfarction, and stroke and in-hospital all-cause death). Similarly, in the European/Australasian Stroke Prevention in Reversible Ischaemia Trial, ischemic events were less frequent in patients with cerebral ischemia of arterial origin receiving aspirin plus dipyridamole than in patients

TABLE 3. **Summary of Clinical Benefits and Bleeding Risks of the 2 Main Dual Antiplatelet Therapy Regimens: Aspirin Plus Clopidogrel or Aspirin Plus Dipyridamole**[a]

Reference	Patient group	Primary end point	Effects on		Effect of dual therapy on primary end point	Comments
			Major bleeding	Minor bleeding		
Aspirin plus clopidogrel						
CURE[33]	NSTEMI (N=12,562)	Cardiovascular death, nonfatal MI, or stroke during 3- to 12-mo follow-up	Significant increase from 2.7% to 3.7% (*P*=.001)	Significant increase from 2.4% to 5.1% (*P*<.001)	Significant decrease from 11.4% to 9.3% (*P*<.001)	For every 1000 patients taking clopidogrel, 6 may require transfusion
CREDO[34]	PCI (N=2116)	Death, MI, or stroke at 12 mo	Not significant	Not significant	Significant decrease from 11.5% to 8.5% (*P*=.02)	
COMMIT[35]	Acute MI (N=45,852)	Death, reinfarction, or stroke	Not significant	Significant increase from 3.1% to 3.6% (*P*=.005)	Significant decrease from 10.1% to 9.2% (*P*=.002)	4.7±1.7 more minor bleeds per 1000 patients
CLARITY[36]	STEMI (N=3491)	Occluded artery on angiography, death or MI before angiography, OR death or MI before day 8 or discharge for patients not undergoing angiography	Not significant	Not significant	Significant decrease from 21.7% to 15.0% (*P*<.001)	Composite end point at 30 d significantly decreased from 14.1% to 11.6% (*P*=.003)
Aspirin plus dipyridamole						
AICLA[37]	Ischemic stroke or TIA (N=604)	Fatal or nonfatal cerebral infarction	1/198 (aspirin) vs 2/202 (aspirin plus dipyridamole)	4/198 (aspirin) vs 5/198 (aspirin plus dipyridamole)	Not significant	Major bleeding was hematemesis; minor bleeding was all other hemorrhages
ESPS[38]	Prior stroke, TIA, or reversible ischemic neurologic deficit (N=2500)	Stroke or death from any cause	Not applicable	Not applicable	Significant decrease from 22.6% to 15.2% (*P*<.001)	Comparison was to placebo (no aspirin); bleeding was not monitored
EPSP2[39]	Prior stroke or TIA (N=6602)	Stroke, death, and stroke or death together	Not significant	Not significant	Stroke: significant decrease from 12.6% to 9.5% (*P*=.006); stroke or death: decrease from 20.0% to 17.3% (*P*=.056); death: not significant	
ESPRIT[40]	Prior stroke or TIA (N=2739)	Vascular death, nonfatal stroke or MI, nonfatal major bleeding	Not significant	Not significant	Decrease from 16% to 13%, significance not reported	Fewer major bleeds with dual therapy but not significant
PRoFESS[41]	Prior stroke (N=20,332)	Recurrent stroke	Increase in major hemorrhagic events associated with dipyridamole compared with clopidogrel	Not applicable	No difference in rate of recurrent stroke: 9.0% with aspirin plus ER-dipyridamole vs 8.8% with clopidogrel (*P*=.78)	Combination therapy with aspirin plus ER-dipyridamole compared with clopidogrel
Antithrombotic Trialists' Collaboration[1]	Patients at high risk of an occlusive vascular event (N=135,000)	Nonfatal MI, nonfatal stroke, or vascular death	Not applicable	Not applicable	Not significant	Bleeding was not monitored; meta-analysis

[a] All comparisons are dual therapy vs aspirin monotherapy unless otherwise indicated in the "Comments" column. AICLA = Accidents, Ischemiques Cerebraux Lies a l'Atherosclerose; CLARITY = CLopidogrel as Adjunctive ReperfusIon TherapY; COMMIT = ClOpidogrel and Metoprolol in Myocardial Infarction Trial; CREDO = Clopidogrel for the Reduction of Events During Observation; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; ER = extended release; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischemia Trial; ESPS = European Stroke Prevention Study; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PRoFESS = Prevention Regimen For Effectively Avoiding Second Strokes; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

receiving aspirin alone, with an absolute risk reduction of 1% per year.[40] In addition, patients receiving combination aspirin-dipyridamole therapy had fewer major bleeding complications and an equal number of minor bleeding complications compared with patients taking aspirin alone.[40]

However, this favorable benefit-to-risk ratio does not span all patient populations or all antiplatelet therapy combinations. Recent results of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myo-

cardial Infarction 38 (TRITON–TIMI 38) highlight the difficulties of balancing the benefit with risk in patients.[42] Although there was an overall decrease in cardiovascular death, nonfatal MI, and nonfatal stroke (HR, 0.81; 95% CI, 0.73-0.90; *P*<.001) in patients who received prasugrel plus aspirin, overall there was also a statistically significant increase in bleeding compared with clopidogrel plus aspirin (HR, 1.32; 95% CI, 1.03-1.68; *P*=.03) in patients undergoing PCI.[42] In the subset of patients who underwent coronary artery bypass grafting (CABG), the risk of bleeding increased substantially (HR, 4.73; 95% CI, 1.90-11.82; *P*<.001). The risk of bleeding associated with prasugrel is most likely underestimated because patients in TRITON were only randomized after performance of coronary angiography, thus decreasing the chance a patient would require CABG. Bleeding events correlated with approximately 1 additional episode of fatal bleeding per prevention of 1 cardiovascular death in patients taking prasugrel compared with clopidogrel.[43]

Although the risk of major bleeding was increased in the overall TRITON patient population, the risk seems even greater for older patients with multiple coexisting conditions and other patient subpopulations.[43] Subgroup analyses in TRITON showed lower net clinical benefit with prasugrel compared with clopidogrel in patients 75 years or older or weighing less than 60 kg (HR, 0.99; 95% CI, 0.81-1.21; *P*=.89; and HR, 1.03; 95% CI, 0.69-1.53; *P*=.89; respectively) because of a reduction in clinical efficacy and greater absolute levels of bleeding.[42] Patients with previous stroke or TIA who received prasugrel exhibited a greater rate of TIMI major bleeding (*P*=.06) and intracranial hemorrhage (*P*=.02) than those with prior cerebrovascular events who received clopidogrel.[42] In addition, the statistically significant increase in death from any cause, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal major bleeding observed in patients with prior cerebrovascular events who received prasugrel (HR, 1.54; 95% CI, 1.02-2.32; *P*=.04) shows that prasugrel should be avoided in these patients.[42] Conversely, prasugrel was not associated with excess bleeding among patients with diabetes in TRITON (N=3100), suggesting that this particular group of high-risk patients may benefit from the use of this drug. In general, however, although the use of prasugrel was associated with a greater degree of platelet inhibition and greater suppression of clinical ischemic events, the threat of major, life-threatening bleeding was also elevated in most patient populations.

In the Prevention Regimen for Effectively Avoiding Second Strokes trial, a randomized head-to-head comparison, ER-dipyridamole failed to demonstrate noninferiority compared with clopidogrel in preventing recurrent strokes for a median of 2.4 years, and clopidogrel was better tolerated. The rate of recurrent stroke with twice-daily aspirin, 25 mg, plus ER-dipyridamole, 200 mg, was 9.0% compared with 8.8% with once-daily clopidogrel, 75 mg (*P*=.78). Major hemorrhagic events, including intracranial hemorrhage, were increased with ER-dipyridamole compared with clopidogrel. Furthermore, headaches leading to permanent discontinuation of treatment were more frequent in the ER-dipyridamole group (5.9%) compared with the clopidogrel cohort (0.9%).[41]

More recently, a reversible adenosine diphosphate receptor antagonist, AZD6140, has been evaluated for use in patients with atherosclerosis and acute coronary syndrome.[44-46] In a study that compared clopidogrel (75 mg/d) to AZD6140 (50, 100, or 200 mg twice daily or 400 mg/d) in patients taking aspirin (75-100 mg/d), Husted et al[45] found an increase in platelet inhibition and bleeding times in patients receiving AZD6140 compared with those receiving clopidogrel. The most common adverse events were minor bleeding and dyspnea, both of which occurred more frequently with the higher doses of AZD6140 than with either clopidogrel or AZD6140 at 50 mg.[45]

The Dose confIrmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogRel in non-ST-segment Elevation myocardial infarction (DISPERSE-2) trial compared AZD6140, given twice daily at 90 mg or 180 mg, with clopidogrel, administered as a 300-mg loading dose followed by 75 mg/d, in combination with aspirin.[44,46] ADZ6140 produced statistically significantly greater platelet inhibition in a dose-dependent fashion (79%±22% for 90 mg twice daily; 95%±8% for 180 mg twice daily) compared with clopidogrel (64%±22%; *P*<.02), with no difference observed in the rate of protocol-defined major bleeding.[46] However, an increase in minor bleeding was observed in patients receiving AZD6140, and discontinuation of use of the study drug due to bleeding episodes was more common than in patients receiving clopidogrel.[44] Patients receiving AZD6140 also reported higher incidences of dyspnea, hypotension, and nausea,[44] which could contribute to patient nonadherence and affect the overall benefit-to-risk profile. The experiences with prasugrel and AZD6140 highlight the need for caution in using new, relatively untested antiplatelet agents.

THE BENEFIT-TO-RISK BALANCE IN PATIENT SUBGROUPS

The risk of bleeding is not homogeneous across all patient groups, and some subgroup populations may have increased risk factors for major bleeding (Table 4), such as older age, diabetes mellitus, renal dysfunction, female sex, or a history of hypertension.[17-21,27]

The increased risk associated with age, female sex, and renal dysfunction may be because each of these patient

TABLE 4. **Risk Factors for Major Bleeding in Patients With Acute Coronary Syndrome**[a]

Risk factor	Eikelboom et al,[17] 2006 (N=34,126)[b]	Kinnaird et al,[18] 2003 (N=10,974)[c]	Moscucci et al,[19] 2003 (N=24,045)[d]	Rao et al,[21] 2005 (N=26,452)[e]	Manoukian et al,[20] 2007 (N=13,819)[f]
Older age	√	√	√	√	√
Diabetes mellitus	√	√	√	√	√
Renal dysfunction	√	√	√	√	√
Female sex		√	√	√	√
History of hypertension		√	√	√	√
SBP or MAP	√		√		
History of stroke	√			√	
ST-segment deviation ≥1 mm	√				√
Anemia					√
History of bleeding			√		
Prior PCI				√	
Cardiac biomarker elevation					√

[a] Checkmarks indicate factors shown to be significantly associated with major bleeding on multivariate regression analysis.
[b] Patients in the Organization to Assess Ischemic Syndromes (OASIS) Registry, OASIS-2 study, and Clopidogrel in Unstable Angina to Prevent Recurrent Events study.
[c] Database of patients undergoing PCI between 1991 and 2000.
[d] Patients in the Global Registry of Acute Coronary Events.
[e] Participants in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries IIb, Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network A and B, and Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy trials.
[f] Patients in the Acute Catheterization and Urgent Intervention Triage strategy trial.
MAP = mean arterial pressure; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

subgroups appears to metabolize drugs differently than the general population.[2,5] For women and elderly individuals, careful monitoring of antithrombotic therapy has been shown to maintain a positive benefit-to-risk ratio.[2,5] The poor benefit-to-risk ratio with use of antiplatelet therapeutics for patients with renal dysfunction prompted the AHA to release a Science Advisory that all cardiovascular patients be screened for kidney disease.[47] Bleeding complications due to platelet dysfunction and dosing errors can negate benefits from antithrombotic therapy in patients with renal dysfunction; these patients often receive insufficient doses of antiplatelet agents, probably because of concerns of bleeding.[48] A further complication is that patients with renal dysfunction are at greater risk of restenosis after PCI.[2,48] Creatinine clearance should be estimated and renally metabolized drugs adjusted accordingly in these patients.[2]

Procedural and therapeutic factors may also contribute to an increased risk of bleeding. In-hospital treatment with highly active anticoagulant or antiplatelet therapeutics (such as glycoprotein IIb/IIIa inhibitors, hirudin, thrombolytics, or bivalirudin) or performance of invasive procedures (including coronary angiography, intra-aortic balloon angioplasty, PCI, or CABG) also increases the incidence of bleeding.[17-20,27]

ANTIPLATELET EFFECTS AND BLEEDING RISK OF OTHER COMMONLY USED AGENTS

Some supplements or over-the-counter remedies that may affect platelet activity or interact with antiplatelets are occasionally recommended by physicians. Omega-3 fatty acids (fish oil) have shown benefit in reducing cardiovascular events, possibly by enhancing the stability of atherosclerotic plaques,[49] and the Food and Drug Administration has announced the availability of a qualified health claim for the cardiovascular benefits of omega-3 fatty acids.[50] A review of 3 large controlled trials (N=32,000) showed that docosahexaenoic acid and eicosapentaenoic acid omega-3 fatty acid supplements are associated with 19% to 45% reductions in cardiovascular events, suggesting that patients at risk might benefit from these supplements.[51] Other widely used supplements, including ginkgo biloba, ginseng, green tea, papaya, St John's wort, coenzyme Q, and ginger, also affect antiplatelet activity and may interfere with antithrombotic activity.[52]

Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitors are analgesics widely used to treat arthritis pain but have also been shown to increase the risk of gastrointestinal bleeding and cardiovascular events.[53,54] To minimize the risk of gastrointestinal bleeding, physicians should consider use of a proton pump inhibitor for patients who must take antiplatelets for cardioprotection and NSAIDs or COX-2 inhibitors for arthritis pain.[55] Physicians may also consider using the "tweener" NSAIDs, which inhibit only COX-2 at low doses and are considered safer anti-inflammatory drugs with regard to bleeding.[56] However, given the limited utility of COX-2 inhibitors because of cardiovascular events, cotherapy of NSAIDs with a gastroprotective agent may be the preferred option for patients who need cardioprotection and analgesic pain relief for arthritis.[54]

PATIENT ADHERENCE AND OUTCOME

Although considerable research has been done regarding the association between major bleeding and outcome, less attention has focused on the impact of bleeding on patient adherence. Recently, a case report was published of a patient who developed angina symptoms within 30 days of discharge after stent implantation and who admitted to stopping antiplatelet therapy (prasugrel and aspirin) because of repeated bleeding from cuts incurred while shaving.[28] The platelet activation biomarkers in this patient were found to be higher than those previously observed on presentation with an acute vascular event,[28] introducing the potential for hypercoagulation and related complications. In the CURE trial, a total of 21.1% of patients receiving clopidogrel plus aspirin permanently discontinued use of the study medication compared with 18.8% of patients receiving aspirin alone[33]; although this trial did not track patients' reasons for premature discontinuation of treatment, other studies[29] have shown that adverse events are the most common reason patients stop taking their medication. There is increasing awareness that even nuisance bleeding complications are enough for some patients to stop therapy, especially since the benefits of antiplatelet therapy may not be readily apparent.[28,57]

The impact of nuisance bleeding is also evident in clinical trial settings. Analysis of COMMIT revealed that bleeding and other adverse events and elective PCI were the most common reasons for discontinuation of antiplatelet therapy.[35] Similarly, patients receiving AZD6140 in the DISPERSE-2 trial were more likely to discontinue study treatment because of bleeding than patients receiving clopidogrel (2.4% in the 90-mg group, 1.5% in the 180-mg group, and 0.9% in the clopidogrel group).[44] In the TRITON-TIMI 38 trial, the increase in the number of patients discontinuing prasugrel treatment because of bleeding compared with patients receiving clopidogrel was statistically significant (2.5% vs 1.4%; $P<.001$).[42]

Premature discontinuation of antiplatelet therapy is a concern because nonadherent patients face a substantially increased risk of an adverse outcome, ranging from a 1.5-fold increase for rehospitalization to a 9-fold increase in the risk of death.[13,14,58] Furthermore, evidence shows that, after discontinuing antiplatelet therapy, platelet function rebounds to a level of activation higher than during the initial acute event.[28] In fact, the phenomenon termed *antiplatelet resistance* (in which patients develop a second ischemic event despite use of antiplatelet therapy) is more likely to result from nonadherence than drug inefficacy because the incidence of resistance often mirrors the incidence of nonadherence.[28,57,59,60] Factors identified as major predictors of nonadherence in patients with cardiovascular disease include having depression,[61,62] having posttraumatic stress disorder,[58] being unmarried,[62] having low levels of educational achievement,[14,62] and taking a large number of medications.[62]

Although bleeding is by far the most common adverse event with antiplatelet therapy, other less common adverse events may also affect adherence, including rash, headache, cramps, joint pain, nausea and vomiting, and constipation. Headache, which is particularly common with use of aspirin plus ER-dipyridamole in the secondary prevention of stroke or TIA, occurs in up to 39% of patients[40,63,64] and is a common cause of treatment discontinuation.[40] Headaches tend to peak 2 to 3 hours after administration, coincident with peak levels of dipyridamole when taken orally.[65] However, the frequency of headache with this combination tends to diminish over time,[63,65] so patients should be encouraged to continue use of their medication through this early period of high headache occurrence.

THE EFFECT OF PHYSICIAN PERCEPTIONS

Patient nonadherence is a major concern when assessing risks, but physician misconceptions of bleeding risks may contribute to patients discontinuing therapy. For example, patients may be erroneously advised to stop antiplatelet therapy before dental procedures. There may be slightly prolonged bleeding during dental procedures in patients undergoing antiplatelet therapy, but local hemostatic measures are sufficient to control it, and uncontrollable intraoperative or postoperative bleeding is unlikely.[66,67] In fact, the AHA and American Dental Association recommend that patients taking clopidogrel and aspirin continue the dual regimen while undergoing dental procedures.[68]

Other procedures for which physicians often withdraw antiplatelet therapy include colonoscopy, endoscopy, intraocular lens implantation, prostate biopsy, and vascular surgery.[69] A meta-analysis has shown that continuation of low-dose aspirin therapy does not increase risk in these patients, except for transurethral prostatectomy,[69] and recommends that patients continue to take aspirin. After PCI, the benefits of dual clopidogrel-aspirin therapy are such that it is strongly recommended that elective surgery be postponed rather than discontinue dual therapy.[70] Table 5 proposes a management scheme for cardiovascular patients requiring surgery while taking antiplatelet agents.

RECOMMENDATIONS FOR MAINTAINING PATIENT ADHERENCE

Studies indicate that use of antiplatelet therapy is lower in patients in primary care compared with those in specialist

TABLE 5. **Management of Antiplatelet Therapies and Cardiovascular Patients Requiring Surgery**[a]

Surgical hemorrhagic risk	Cerebrovascular and cardiovascular risk		
	Low >6 mo after MI, PCI, BMS, CABG, or stroke; >12 mo if complications	Intermediate 6-24 wk after MI, PCI plus BMS, CABG, or stroke (without complication); >12 mo after DES; high-risk stents (long, proximal, multiple, overlapping, small vessels, bifurcation); low EF, diabetes mellitus	High <6 wk after MI, PCI, BMS, CABG; <6 mo after, same if complications; <12 mo after high-risk DES; <2 wk after stroke
Low risk (transfusion normally not required; peripheral, plastic, and general surgery; biopsies; minor orthopedic, ENT, and general surgery; endoscopy; eye anterior chamber; dental extraction and surgery)	Elective surgery: OK; maintain aspirin	Elective surgery: OK; maintain aspirin and clopidogrel therapy (if prescribed)	Elective surgery: postpone; vital or emergency surgery: OK; maintain aspirin and clopidogrel therapy
Intermediate risk (transfusions frequently required; visceral surgery; cardiovascular surgery; major orthopedic, ENT, reconstructive surgery; endoscopic urology)	Elective surgery: OK; maintain aspirin	Elective surgery: postpone; surgery absolutely required: OK; maintain aspirin and clopidogrel therapy (if prescribed)	Elective surgery: postpone; vital or emergency surgery: OK; maintain aspirin and clopidogrel therapy
High risk (possible bleeding in a closed space; intracranial neurosurgery; spinal canal surgery; eye posterior chamber surgery)	Elective surgery: OK; maintain statin; withdraw aspirin (maximum 7 d)	Elective surgery: postpone; surgery absolutely required: OK; maintain aspirin therapy or replace aspirin with ibuprofen; stop clopidogrel therapy	OK only for vital or emergency surgery; maintain aspirin; bridge with tirofiban/eptifibatide and heparin

[a] BMS = bare-metal stent; CABG = coronary artery bypass graft; DES = drug-eluting stent; EF = ejection fraction; ENT = ear, nose, and throat; MI = myocardial infarction; PCI = percutaneous coronary intervention.

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care.[10] This suggests that primary care physicians should take a more active role in monitoring and treating their patients after hospital discharge. The following is a list of recommendations for primary care physicians with regard to monitoring and managing their patients receiving antiplatelet therapy after an acute event (Table 6[28,57,60-63,65,68,71-75]):

1. Ensure that patients understand the need to take their medication and the type and severity of adverse events that they may encounter, including minor bleeding (gingival, minor cuts) and bruising. At each follow-up visit, always ask patients about adverse events they might be experiencing, including minor bleeding or bruising. Encourage patients to maintain adherence even if they encounter nuisance bleeding and to seek help promptly for bleeding or symptoms of greater concern (eg, prolonged epistaxis, melena, hematuria).[28,57]

2. Engage patients and their families in treatment, including lifestyle changes and therapeutic adherence. Encourage patients to learn more about their condition and to use any Internet-based tools for maintaining adherence. More knowledgeable patients can engage in more informed discussions with their physicians and are more likely to make rational decisions about their future health.[71]

3. Pay close attention to patients at risk of discontinuing treatment, including men, single individuals, those with a psychiatric comorbidity such as depression or posttraumatic stress disorder, those with low levels of education, and those taking multiple medications.[61,62] Invest more time and effort in health education and promotion for these patients. Offer suggestions on how to maintain adherence with multiple medications, such as dosage boxes, which are readily available at pharmacies. If necessary, refer patients with depression or posttraumatic stress disorder to a psychiatrist or counselor.

4. Regularly question patients about nuisance bleeding and other adverse events (eg, headaches) and their effect on adherence. Encourage patients to continue with therapy despite these nuisance events; for example, headache occurrence with ER-dipyridamole is likely to decrease with persistent treatment.[63,65]

5. When nonadherence is suspected, consider performing a platelet function test. Although some physicians may use these assays to assess antiplatelet efficacy, objective assessment of platelet function can also be a good

TABLE 6. **Recommendations for Maintaining Patient Adherence**

1. Communicate and reiterate at follow-ups the importance of adherence, consequences of discontinuation, and expected adverse events[28,57]
2. Engage patients and their families in treatment through education, support groups, and individual online research[71]
3. Target for particular attention those patients at risk of discontinuing treatment (men, single individuals, those with depression or posttraumatic stress disorder, those with low levels of education, and those taking multiple medications)[61,62]
4. Regularly question patients about nuisance bleeding and other adverse events (eg, headaches) and encourage them to continue with therapy[63,65]
5. When nonadherence is suspected, consider performing a platelet function test[60,72]
6. Advise patients to maintain their antiplatelet therapy when undergoing dental procedures or other minor invasive surgical procedures[68]
7. For patients who develop bleeding during dual antiplatelet therapy, consider reducing the aspirin dose rather than discontinuing use of either agent[73]
8. Engage other health care professionals, including nurse-led clinics and collaborative programs with pharmacists, in the treatment of patients[74,75]

indicator of adherence and may be necessary in patients who are not completely honest about adherence during verbal questioning.[60,72]

6. Advise patients to maintain their antiplatelet therapy even when undergoing dental procedures.[68] If in doubt about the risks of bleeding during oral surgery or other elective surgical procedures, consult with the patient's cardiologist before advising discontinuation of antiplatelet therapy. If antiplatelet therapy is discontinued, it should be resumed as soon as possible after the procedure.[68]

7. For patients who develop bleeding during dual antiplatelet therapy, consider reducing the aspirin dose rather than discontinuing use of either agent. Observational studies show that the incidence of bleeding during dual antiplatelet therapy is directly related to the aspirin dose and that a lower aspirin dose has a lower risk of bleeding but has similar efficacy.[73]

8. Engage other health care professionals in the management of patients. Nurse-led clinics and collaborative programs with pharmacists have been shown to enhance patient adherence with secondary prevention medications.[74,75]

CONCLUSION

Adherence with secondary preventive therapy by both patients and physicians is a key determinant of patient outcome. There are many reasons for nonadherence, although adverse effects appear to be the main factors that affect patient adherence. With regard to antiplatelet therapy, perhaps the most important adverse event to address is the increased risk of bleeding. Although risk of bleeding is reported in clinical trials of antiplatelet therapy, the true clinical impact of bleeding is difficult to assess and compare between trials because of the use of various bleeding scales that differ in the criteria used to define bleeding and the categorizations used. In addition to patient concerns about bleeding, physician perceptions of bleeding risks and unfamiliarity with guidelines may contribute to nonadherence. Nuisance effects, such as minor bleeding, may be an underrecognized cause of nonadherence.

Nonadherence can be easily overcome through attention from physicians, patients, and families. Primary care physicians are often the ones who forge the closest relationships with patients through ongoing care and are therefore in a unique situation to identify not only the adverse events that may undermine adherence but also the socioeconomic and psychological factors that affect adherence. As Joseph B. Kirsner wrote in the *Journal of the American Medical Association*, "The patient-physician relationship is, in fact, a powerful therapeutic force, synergistic with medication."[76]

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