Annals of Internal Medicine | PERSPECTIVE

Role of Clopidogrel in Managing Atherothrombotic Cardiovascular Disease

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Aspirin is the most widely used antiplatelet agent for preventing and treating vascular events. The thienopyridine derivatives, ticlopidine and clopidogrel, are a suitable alternative in patients who are intolerant to aspirin, and clopidogrel exhibits better tolerability than ticlopidine. The available evidence from randomized trials indicates that dual therapy with clopidogrel and aspirin is modestly but significantly more effective than aspirin in preventing serious vascular events. It is also associated with a favorable benefit–risk profile in patients at high risk (especially in acute coronary syndromes and after stenting). In patients at low risk (stable cardiovascular disease), however, the bleeding risk of dual therapy exceeds its potential benefit. The dose and duration of pretreatment before stenting, the optimal duration of treatment after drug-eluting stent implantation, concurrent administration of platelet glycoprotein IIb/IIIa inhibitors, and the exact mechanism and clinical relevance of clopidogrel resistance are unclear.

Ann Intern Med. 2007;146:434-441. www.annals.org
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Clopidogrel is a platelet adenosine diphosphate $P2Y_{12}$-receptor antagonist that is widely used to prevent vascular events across a wide spectrum of atherothrombotic cardiovascular disease (1). The purpose of this Perspective is to critically evaluate the evidence from clinical trials in support of its use, to address some of the controversies in its current role, and to summarize key issues of potential importance to the practicing clinician in the management of patients with atherothrombotic cardiovascular disease. The **Appendix** (available at www.annals.org) shows the literature search and selection methods.

Overview of Clinical Trials

Is Monotherapy Superior to Placebo?

To date, there have been no direct comparisons of clopidogrel and placebo in preventing vascular events, presumably because a placebo-controlled trial would be considered unethical because of the proven effectiveness of aspirin (or ticlopidine) in this clinical setting.

Is Monotherapy Superior to Aspirin?

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial demonstrated that clopidogrel was superior to aspirin: A 9% odds reduction (95% CI, 1% to 17%) was produced in the primary composite end point in 19 185 patients with a recent history of stroke, myocardial infarction (MI), or symptomatic peripheral artery disease (2). However, because of the small effect size and the marginal statistical significance ($P = 0.045$) achieved in a large sample, the U.S. Food and Drug Administration (FDA) did not grant a superiority claim over aspirin. However, it did allow a claim of efficacy (relative to placebo) on the basis of an indirect comparison that demonstrated a 30% relative risk reduction (CI, 22% to 36%) in the composite outcomes of stroke, MI, or vascular mortality (3). The overall safety and tolerability profile of clopidogrel was as good as that of medium-dose aspirin; and there was no difference in neutropenia or thrombocytopenia (2).

Is Combined Therapy Superior to Monotherapy?

Clopidogrel plus Aspirin versus Aspirin Alone

Five large randomized trials have evaluated clopidogrel plus aspirin compared with aspirin alone—1 trial each in patients with unstable angina/non–ST-elevation myocardial infarction (UA/NSTEMI) (4), in patients undergoing planned percutaneous coronary intervention (PCI) (5), and in patients at high risk for atherothrombotic vascular disease (6) and 2 trials in patients with ST-elevation myocardial infarction (STEMI) (7, 8). Clopidogrel was administered as a 300-mg loading dose followed by a 75-mg maintenance daily dose in all trials except 2 (6, 8), and the aspirin dose ranged from 75 to 325 mg daily. The primary outcome measure in these trials was a composite efficacy end point (typically death, MI, or stroke). Secondary safety end points included the Thrombolysis In Myocardial Infarction (TIMI) major criteria for bleeding in 3 trials (4, 5, 7); the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criterion for severe bleeding in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial (6); and need for transfusion or fatal hemorrhage in the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) (8). Follow-up ranged from 8 days (7) to 28 months (6). The **Table** summarizes the principal efficacy and safety results.

Figure 1 shows an analysis that focuses on the composite end point of cardiovascular death, MI, or stroke and major bleeding (using the TIMI criterion) at the longest

See also:

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Key Summary Points 435

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Appendix
Conversion of figures and table into slides

Key Summary Points

Monotherapy with clopidogrel compared with aspirin

Clopidogrel is nominally superior to aspirin in reducing ischemic vascular events in high-risk patients.

Clopidogrel has improved gastrointestinal tolerance but causes an excess of rash, diarrhea, and adverse hematologic outcomes.

Combined therapy (clopidogrel plus aspirin) compared with monotherapy

Clopidogrel plus aspirin versus aspirin

Beneficial in high-risk patients, such as those with unstable angina/non–ST-elevation myocardial infarction (UA/NSTEMI), ST-elevation myocardial infarction (STEMI), and stenting.

Long-term benefit is driven by reductions in nonfatal myocardial infarction, but there is little or no impact on death or stroke.

Major bleeding complications are increased.

Clopidogrel plus aspirin versus clopidogrel

No benefit in reducing ischemic stroke.

Major bleeding complications are increased.

Clopidogrel versus ticlopidine

No major difference in efficacy and safety has been reported in randomized trials; increased adverse hematologic events with ticlopidine have been reported in nonrandomized studies.

Ticlopidine is less expensive; clopidogrel has better tolerability and convenience (once-daily dosing).

Key issues regarding clopidogrel use in clinical practice

Duration of treatment

No long-term benefit but excess moderate bleeding risk in patients with stable cardiovascular disease; therefore, it is not recommended in such patients.

At least 1 month and up to 9 months in high-risk patients with UA/NSTEMI who are at low-risk for bleeding.

At least 1 month with fibrinolytic treatment in patients with STEMI; there are no direct studies in patients with primary percutaneous coronary intervention (PCI).

Up to 1 month with bare metal stents, longer treatment (>6 mo and perhaps longer) with drug-eluting stents in patients with PCI.

Not recommended as first-line therapy for patients with cerebrovascular accidents unless a clear indication, such as acute coronary syndromes or stent placement, also are present.

Key Summary Points—Continued

Pretreatment

No definite benefit but increased bleeding risk is associated with coronary artery bypass grafting.

Timing of elective coronary artery bypass grafting and other surgical procedures

Stop therapy at least 5 days, preferably 7 days, before surgery.

Adjunctive use with glycoprotein IIb/IIIa inhibitors

Effective and safe at 600-mg dose in high-risk patients with acute coronary syndromes.

Clopidogrel resistance

Unclear entity; definition, prevalence, diagnosis, mechanism, and clinical relevance are not precisely known.

follow-up times available for these studies. The results suggest a relationship between treatment benefit and underlying cardiovascular risk in the control group (greater benefit in higher-risk patients). In high-risk patients with acute coronary syndromes (4, 7, 8) or in those undergoing PCI (4, 5, 7) (conditions characterized by platelet hyperreactivity), the efficacy benefit outweighs the bleeding risk. In contrast, bleeding risk exceeds benefit in low-risk patients who are not undergoing PCI (6). The very low bleeding risk observed in the 2 STEMI trials, in which clopidogrel was used adjunctively during thrombolytic therapy, is probably due to careful exclusion of patients at high risk for bleeding (7, 8). It should be emphasized, based on the analysis of the individual component end points (**Figure 2**), that the measurable impact of combined therapy is largely restricted to nonfatal MI except in COMMIT, in which a small but statistically significant reduction in death was observed (primarily because of the large sample size).

The **Table** also shows the results of a Bayesian analysis that quantifies the posterior probabilities of benefit and harm for these trials. A major advantage of this approach over the conventional frequentist approach is that the probability of any difference can be estimated (9). In each case, the posterior probability for any outcome decreases as the threshold for clinically important difference increases. For example, for a benefit greater than 0%, the posterior probability exceeded 95% in all trials except 1 (6), which is concordant with the frequentist results; for a benefit greater than 10%, only 2 trials achieved the threshold probability of greater than 95% (4, 7); and for a benefit greater than 20%, only 1 trial achieved the threshold probability (7). The probability for greater than 0% harm exceeded 95% in 3 trials (4–6), for greater than 10% harm in 2 trials (4, 6), and for greater than 20% harm in 1 trial (6). Thus, the probability of important clinical benefits (typically ranging from 10% to 20% risk reduction for vascular events) is far less than that implied by conventional frequentist analysis.

Table. **Randomized Clinical Trials of Clopidogrel plus Aspirin versus Aspirin Alone***

Study, Year (Reference)	Patients, *n*	Clinical Setting	Primary End Point (Follow-up)	Primary End Point Rate, %		Odds Ratio (95% CI)	Probability of Benefit, %†			Bleeding Rate, %	
				New	Control		$\delta > 0$	$\delta > 10$	$\delta > 20$	New	Control
CURE, 2001 (4)	12 562	UA/NSTEMI	CV death, MI, or stroke (12 mo)	9.3	11.4	0.80 (0.72–0.90)	1.000	0.970	0.358	3.7	2.7
CREDO, 2002 (5)	2116	Planned PCI	Death, MI, or stroke (12 mo)‡	8.4	11.5	0.77 (0.56–0.96)	0.990	0.936	0.734	8.8	6.7
CHARISMA, 2006 (6)	15 603	CVD or risk factors	CV death, MI, or stroke (28 mo)	6.8	7.3	0.93 (0.83–1.05)	0.888	0.273	0.004	1.7§ (2.1)‖	1.3§ (1.3)‖
CLARITY, 2005 (7)	3491	Fibrinolysis in STEMI	Death, MI, or occluded artery (8 d)	14.9	21.7	0.64 (0.53–0.76)	1.000	1.000	0.982	1.3	1.1
COMMIT, 2005 (8)	45 852	Fibrinolysis in STEMI	Death, MI, or stroke (28 d)	9.2	10.1	0.91 (0.86–0.97)	0.999	0.275	0.000	0.58	0.55

* CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLARITY = Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction (TIMI); 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 ischemic Events; CV = cardiovascular; CVD = cardiovascular disease; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UA= unstable angina.
† Posterior probabilities of benefit or harm that the percentage relative risk difference is greater than the putative threshold value for clinical importance (δ >0%, >10%, or >20%) are derived from a Bayesian analysis using an uninformative prior probability (log odds mean, $\mu = 0$ [SD, $\sigma = 10$]) and the empirical trial data (9). Threshold probability of significant benefit or harm is ≥0.950.
‡ CREDO was powered for death, MI, or revascularization, but the primary reported efficacy outcome was for death, MI, or stroke.
§ TIMI criterion for major bleeding (intracranial hemorrhage or bleeding associated with a decrease in hemoglobin level of >5 g/dL or a decrease in hematocrit of at least 15%) was used as the primary safety outcome in all trials except CHARISMA, in which serious bleeding criterion based on the Global Use of Strategies to Open Occluded Coronary Arteries classification was used, and the COMMIT trial, which defined major bleeding as need for transfusion or any fatal hemorrhage.
‖ Data for TIMI major bleeding in the CHARISMA trial are shown in parenthesis.

Clopidogrel plus Aspirin versus Clopidogrel

A single trial of high-risk patients with a history of transient ischemic attack or ischemic stroke showed that the combination of aspirin and clopidogrel does not lower the incidence of recurrent vascular events (odds ratio, 0.93 [95% CI, 0.82 to 1.05]) but doubles the risk for life-threatening bleeding (odds ratio, 2.0 [95% CI, 1.41 to 2.82]) (10).

Is Clopidogrel Superior to Ticlopidine?

Whether clopidogrel offers any advantage over ticlopidine has been the subject of 5 nonrandomized trials and 3 randomized trials (11–15). Meta-analysis of these trials showed that the aspirin-clopidogrel combination was just as efficacious as the aspirin-ticlopidine combination. There were fewer adverse drug reactions, primarily skin rashes and gastrointestinal side effects (14, 15). A recent randomized trial comparing ticlopidine with clopidogrel in patients with drug-eluting stents revealed similar safety and effectiveness (16). In contrast to these findings, a randomized study by Müller and colleagues (11) reported a nonsignificant increase in cardiac events at 30 days (3.1% vs. 1.7% [$P = 0.240$]) and a significant increase in all-cause mortality at longer follow-up (8.2% vs. 2.6% [$P = 0.002$]) (17) with the aspirin-clopidogrel combination. Two recent retrospective studies have corroborated these findings (18, 19).

Taken together, these data suggest few differences between ticlopidine and clopidogrel in terms of efficacy and safety. Although ticlopidine is less expensive, clopidogrel is more tolerable and convenient to use (once-daily dosing). Both agents can be used interchangeably except there is no approved indication for ticlopidine in patients with acute MI.

Key Issues in Clinical Practice

Based on the available evidence, several key issues emerge regarding the use of clopidogrel, which may be important to the practicing clinician in the management of patients with atherothrombotic vascular disease.

How Long Should Clopidogrel Be Given for Optimal Benefit?

The optimal duration of clopidogrel therapy varies with the clinical setting. In patients with stable cardiovascular disease, the unfavorable benefit–risk–cost profile observed in CHARISMA (6) argues against use of long-term aspirin and clopidogrel for antiplatelet therapy.

In patients undergoing PCI, the guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend clopidogrel therapy for at least 1 month after bare-metal stent implantation and, because of delayed endothelialization and healing, for a minimum of 3 or 6 months after sirolimus- and paclitaxel-eluting stents, respectively (20). Increasing concerns regarding late thrombosis after drug-eluting stent implantation (21) have motivated clinicians to empirically prescribe dual antiplatelet therapy well beyond the 3 to 6 months indicated for drug-eluting stents. However, the optimal duration of clopidogrel therapy beyond 3 to 6 months has not been established and ideally should depend on the risk–benefit ratio for the individual patient. According to a recent science advisory endorsed by 5 major professional societies, longer treatment may be warranted to prevent late stent thrombosis, especially in patients who are not at high risk for bleeding, similar to patients undergoing

Table—**Continued**

Odds Ratio (95% CI)	Probability of Harm, %†		
	δ > 0	δ > 10	δ > 20
1.39 (1.14–1.70)	0.999	0.988	0.914
1.35 (0.98–1.87)	0.967	0.886	0.735
1.25 (0.97–1.63) (1.64 [1.27–2.10])‖	0.956 (1.000)‖	0.834 (0.999)‖	0.620 (0.992)‖
1.20 (0.65–2.22)	0.635	0.485	0.349
1.07 (0.84–1.37)	0.704	0.407	0.174

brachytherapy, for whom a minimum of 6 months (and up to 1 year) of treatment is recommended (22). To reduce the incidence of bleeding complications associated with dual antiplatelet therapy, lower-dose aspirin (75 to 162 mg daily) may be considered for long-term therapy (4, 20). The prolonged antiplatelet regimen is expensive (approximately $1000 to $1400/y) and has attendant bleeding risk (6). In addition, it also poses a major dilemma if noncardiac surgery or procedures become necessary. This would probably obviate the quality-of-life advantage afforded by drug-eluting stents over bare-metal stents (that is, reduction in repeated revascularization for restenosis).

It is not clear whether long-term use of clopidogrel will abrogate the 0.2% to 0.6% per year increase in late stent thrombosis (up to 3-year follow-up) recently reported for drug-eluting stents compared with bare-metal stents (23, 24). Although premature discontinuation of clopidogrel therapy has been identified as a major correlate of stent thrombosis (25, 26) leading to an increased risk for death (25–27), the wide window of thrombotic risk (the median time to late stent thrombosis of 55 [26] to 116 days [21] after withdrawal of clopidogrel and 1 meta-analysis reporting median times of 16 to 18 months [28]) argues against the critical role of adherence to clopidogrel therapy and suggests that additional mechanisms may be operative. Indeed, most cases (68% to 85%) of late stent thrombosis are not related to nonadherence to clopidogrel therapy (29). Because of our limited understanding of the exact mechanism and incidence of stent thrombosis, inability to accurately identify at-risk patients, and lack of effective and safe therapies to mitigate this risk at this time, the most prudent strategy to limit this rare but potentially life-threatening complication is a selective, thoughtful, and evidence-based application of drug-eluting stents in clinical practice.

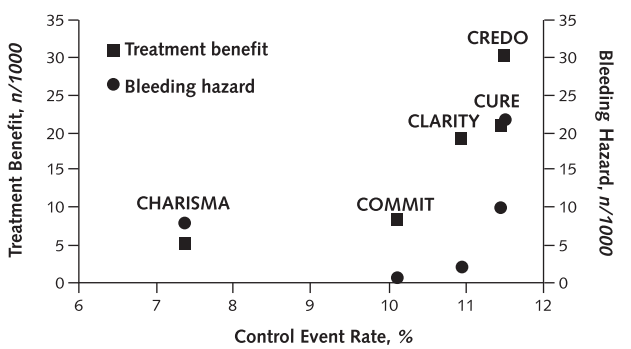
The optimum duration of treatment with clopidogrel in patients with UA/NSTEMI is not clear. The data from Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial suggested that a substantial part of the benefit derived from clopidogrel is achieved by 3 months, and a further small benefit remains over 9 months of long-term treatment (4). The current ACC/AHA guidelines recommend continuation of clopidogrel therapy for at least 1 month and up to 9 months in patients at low risk for bleeding (30). Of note, these recommendations apply only to the use of bare-metal stents for UA/NSTEMI. For drug-eluting stents, long-term use of clopidogrel should be considered to prevent late stent thrombosis.

The ACC/AHA guidelines recommend treatment with clopidogrel for a minimum of 1 month in patients with STEMI who are intolerant to aspirin (31). Adjunctive use of clopidogrel plus aspirin during fibrinolytic therapy for STEMI was recently approved (32). Although the role of combined therapy for catheter-based reperfusion (the preferred strategy in most centers in the United States) has not been directly explored, a nonrandomized subgroup analysis of the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial suggested that over half of the benefit observed with clopidogrel at 30 days occurred in patients undergoing PCI (absolute risk difference, 1.5% of 2.5%) (33, 34).

Is Pretreatment with Clopidogrel Necessary?

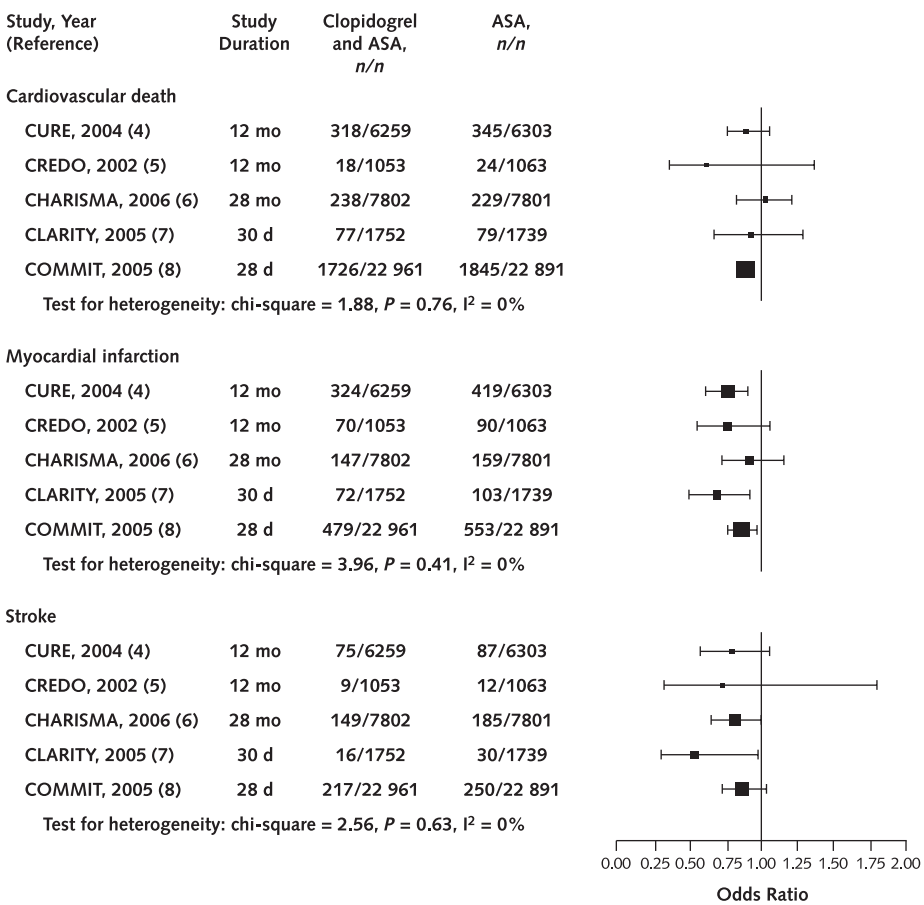
Few concrete data exist about the optimal timing and dose of clopidogrel pretreatment before PCI. Although pretreatment was associated with favorable outcomes in a nonrandomized subgroup analysis of CURE, the duration of pretreatment (range, 3 to 120 d; median, 10 d) (35) was

Figure 1. **Absolute benefit and bleeding hazard of combined treatment with clopidogrel plus aspirin.**



Data for the composite efficacy end point of cardiovascular death, nonfatal myocardial infarction, or stroke (treatment benefit) for the 5 major trials at maximum follow-up is plotted on the left ordinate axis as the number of events prevented by treating 1000 patients with clopidogrel plus aspirin. The bleeding hazard is plotted on the right ordinate axis as the number of major bleeding complications (defined by Thrombolysis In Myocardial Infarction criteria) caused by treating 1000 patients. The incidence of cardiovascular risk at maximum follow-up in control participants (treated with aspirin alone) is plotted on the abscissa. CURE = Clopidogrel in Unstable angina to prevent Recurrent ischemic Events; CREDO = Clopidogrel for the Reduction of Events During Observation; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLARITY = Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial.

Figure 2. **Comparison of clopidogrel plus aspirin (*ASA*) versus ASA alone in high-risk patients with cardiovascular disease.**



Data for cardiovascular death, nonfatal myocardial infarction, and stroke at maximum follow-up for the 5 major trials are shown as point estimate and 95% CIs. Because of major differences in trial demographic characteristics (acute coronary syndrome, stable cardiovascular disease, and low-risk or high-risk patients), concomitant therapies (medical therapy, percutaneous coronary intervention, and thrombolysis), and duration of follow-up (28 d to 28 mo), a formal meta-analysis was not conducted. However, the results of heterogeneity analysis using the Cochran Q-test (chi-square statistics) and I^2 statistic are reported. CURE = Clopidogrel in Unstable angina to prevent Recurrent ischemic Events; CREDO = Clopidogrel for the Reduction of Events During Observation; CHARISMA = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; CLARITY = Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction; COMMIT = Clopidogrel and Metoprolol in Myocardial Infarction Trial.

much longer than that typically encountered in the United States (<48 h). The pretreatment (within 3 to 24 h) hypothesis failed to be validated in a prospective randomized assessment in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial (5). Other studies did not show the benefits of clopidogrel pretreatment in preventing periprocedural biomarker elevations or clinical events (36, 37). Some studies have suggested that doses higher than the 300-mg loading dose used in Percutaneous Coronary Intervention–Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (PCI-CURE) and CREDO may be more effective. However, in the Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT) trial, no treatment differences were observed in patients receiving a 600-mg loading dose 2 to 3 hours before PCI versus those receiving the same loading dose 12 hours before PCI (36). Despite these inconsistent data, the ACC/AHA guidelines recommend that 300 mg of clopidogrel be administered at least 6 hours before elective PCI (20), whereas the European Society of Cardiology (ESC) guidelines recommend 600 mg clopidogrel administered at least 2 to 6 hours before PCI (38). Clearly, further clinical data regarding dose, time course of pretreatment, and associated benefit are warranted to clear the uncertainties.

When Should Clopidogrel Therapy Be Stopped before Coronary Artery Bypass Grafting?

A post hoc subgroup analysis of 2072 patients undergoing coronary artery bypass grafting showed a significant increase in bleeding (9.6% vs. 4.4% [$P = 0.003$]) and reoperation for bleeding (4.1% vs. 1.5% [$P = 0.020$]) in

patients in whom clopidogrel treatment was withheld fewer than 5 days compared with patients in whom is was withheld for more than 5 days before coronary artery bypass grafting (39). Similar observations were reported in recent studies (40, 41).

Thus, in the absence of definitive evidence supporting clopidogrel pretreatment, the potential risk for increased bleeding associated with coronary artery bypass grafting and the poor ability to predict surgical coronary artery disease, a prudent strategy would be to withhold clopidogrel treatment until the coronary anatomy is defined and the need for surgical revascularization is clarified. These data are consistent with the ACC/AHA guideline class 1 recommendations for stopping clopidogrel therapy at least 5 days (preferably 7 d) before coronary artery bypass grafting (30).

Is Adjunctive Use with Glycoprotein IIb/IIIa Inhibitors Effective and Safe?

Three randomized trials have evaluated the adjunctive use of clopidogrel and glycoprotein IIb/IIIa inhibitors. In 1 trial, no differences were observed in efficacy and safety outcomes (except for an increase in need for transfusion) with abciximab compared with placebo in patients at low- to intermediate-risk who were pretreated with 600 mg of clopidogrel 2 hours before undergoing PCI (42). Similar findings were observed in diabetic patients undergoing PCI (43). Both of these studies, however, had limited power because of the lower-than-expected event rates. In a recent trial in high-risk patients with UA/NSTEMI undergoing PCI, treatment with abciximab reduced adverse events when administered in addition to pretreatment with 600 mg of clopidogrel, especially in patients with elevated troponin levels, and was not associated with increased bleeding complications (44). Thus, the adjunctive use of clopidogrel and glycoprotein IIb/IIIa inhibitor is effective and safe in high-risk patients with acute coronary syndromes. These data also suggest that pretreatment with a higher loading dose (600 mg) of clopidogrel might be an acceptable alternative to glycoprotein IIb/IIIa inhibitor therapy for low-risk patients.

What Is the Clinical Relevance of Clopidogrel Resistance?

The concept of clopidogrel and aspirin resistance has been the subject of much recent attention (45–48). Numerous potential mechanisms have been proposed, including general pharmacokinetic and pharmacodynamic variability, variability in compliance, underdosing, drug–drug interactions, genetic polymorphisms, and upregulation of other platelet activation pathways (45–48). The reported prevalence ranges from 4% to 30%, depending on the clinical indication, dose of clopidogrel, timing of assessment, and the type of agonist or platelet function test that is used (45). Although there have been no prospective studies directly linking the degree of platelet inhibition to clinical outcomes, a few observational reports have shown an association between variability in platelet responsiveness to clopidogrel and thrombotic events in patients undergoing primary PCI for STEMI (46) or elective PCI (47, 48). Large clinical studies that carefully correlate baseline platelet activity with the degree of inhibition by aspirin or clopidogrel and with clinical events are needed to further clarify the clinical relevance of these phenomena. Until these issues are resolved, calls for routine testing remain premature.

CONCLUSIONS

Aspirin is a highly cost-effective antiplatelet agent available for preventing and treating atherothrombotic cardiovascular disease. Monotherapy with clopidogrel offers an attractive alternative for persons who are intolerant to aspirin. Dual therapy with aspirin and clopidogrel is clearly beneficial in preventing stent thrombosis and provides a favorable benefit–risk ratio in the acute coronary syndrome, especially during the early phase, in which the efficacy benefit may outweigh the bleeding risk. The benefit is, however, primarily driven by reduction in nonfatal MI and has little or no impact on death or stroke. In patients with stable cardiovascular disease, dual antiplatelet therapy provides marginal benefit against ischemic events, which is mitigated by increased frequency of major bleeding. The exact dose and duration of pretreatment before PCI, the optimal duration of treatment after drug-eluting stent implantation, and the need for concurrent administration of glycoprotein IIb/IIIa inhibitor are uncertain. Current evidence supports the use of aspirin or clopidogrel—but not both—as first-line agents for cerebrovascular disease. Finally, the role of $P2Y_{12}$-receptor antagonists will continue to evolve as novel third-generation inhibitors, such as prasugrel (CS-747, LY640315), AZD6140, and cangrelor (AR-C69931MX), which offer the potential of lower nonresponse rate, more potent and uniform platelet inhibition, and improved clinical efficacy, become available.

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Grant Support: None.

Potential Financial Conflicts of Interest: None disclosed.

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Appendix: Search Strategy and Selection Criteria

We searched EMBASE, MEDLINE, and the Cochrane Library to 21 November 2006. We used the following terms: *aspirin*, *adenosine diphosphate antagonists*, *clopidogrel*, *atherothrombosis*, *acute coronary syndrome*, *myocardial infarction*, *peripheral artery disease*, *stroke*, *percutaneous coronary intervention*, *clopidogrel pretreatment*, *stent thrombosis*, *guidelines*, and *resistance*. We focused on the randomized, controlled trials; nonrandomized evaluations; pharmacodynamic studies; editorials; and reviews to explore key issues relating to adenosine diphosphate antagonists.