SPECIAL ARTICLE

Newer Pharmacotherapy in Patients Undergoing Percutaneous Coronary Interventions: A Guide for Pharmacists and Other Health Care Professionals

Expert Opinion from the American Heart Association's Diagnostic and Interventional Catheterization Committee and Council on Clinical Cardiology, and the American College of Clinical Pharmacy's Cardiology Practice Research Network

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Significant advances in pharmacotherapy for patients undergoing percutaneous coronary intervention (PCI) have occurred during the past decade, including the introduction and approval of new antithrombin and antiplatelet therapies, as well as modifications in dosing, administration, and/or duration of older pharmacotherapy regimens. Also, off-label (i.e., not approved by the United States Food and Drug Administration) use of certain agents has become common. Given the novel nature of these agents and the nuances of therapy, the pharmacist and other health care professionals should play an integral role in collaboration with interventional cardiologists in development of hospital protocols, determination of appropriate agent selection, assessment of patient renal function and hematologic status, dosing, and monitoring for adverse effects. In this guide, the newer antiplatelet and antithrombin drugs that may be used during PCI are reviewed, and recommendations regarding the proper administration of these agents are provided.
Key Words: percutaneous coronary intervention, PCI, antiplatelet drugs, antithrombin drugs, clopidogrel, enoxaparin, bivalirudin, eptifibatide, abciximab, tirofiban, pharmacotherapy utilization guidelines.
(Pharmacotherapy 2006;26(11):1537–1556)

Significant advances in pharmacotherapy for patients undergoing percutaneous coronary intervention (PCI) have occurred during the past decade, including the introduction and approval of new antithrombin and antiplatelet therapies, as well as modifications in dosing, administration, and/or duration of older pharmacotherapy regimens. Also, off-label (i.e., not approved by the United States Food and Drug Administration [FDA]) use of certain agents has become common. The pharmacist is recognized to be an integral member of the patient care team and can serve to ensure that the antithrombin and antiplatelet agents used for patients undergoing PCI are correctly and appropriately prescribed and administered. Therefore, the American Heart Association (AHA), in collaboration with the American College of Clinical Pharmacy (ACCP) Cardiology Practice Research Network, has commissioned the writing of a guide for pharmacists and other health care professionals on newer pharmacotherapy that may be used in patients undergoing PCI. In this guide, the newer antiplatelet and antithrombin drugs that may be used during PCI are reviewed, and recommendations regarding the proper administration of these agents are provided. For a more extensive discussion of pharmacotherapy during

Table 1. American College of Cardiology–American Heart Association Categorization Schema of the Classes of Recommendations and the Weight of Evidence Supporting the Recommendation[1]

Category	Explanation
Class of recommendation	
I	Evidence for and/or general agreement that a given treatment is beneficial, useful, and effective
IIa	Conflicting evidence and/or divergence of opinion; weight of evidence or opinion is in favor of usefulness or efficacy
IIb	Conflicting evidence and/or divergence of opinion; usefulness or efficacy is less well established by evidence or opinion
IIIa	Evidence and/or general agreement that a treatment is not useful or is ineffective and in some cases may be harmful
Evidence level	
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized trial or nonrandomized studies
C	Only consensus of opinion of experts, case studies, or standard of care

PCI, including a discussion of aspirin and unfractionated heparin (UFH) therapy, the reader is referred to the American College of Cardiology (ACC)–AHA–Society for Cardiovascular Angiography and Interventions (SCAI) update to the 2001 guidelines for PCI.[1]

At the end of each section of this article, a brief summary of the current ACC-AHA-SCAI guidelines for the relevant pharmacotherapeutic agent is provided. Recommendations are given both by class of recommendation and level (weight) of evidence supporting the recommendation (Table 1).[1] When referring to these recommendations, note that they are developed to provide guidance on the various therapies used in the PCI setting; they are not a substitute, by themselves, for sound clinical judgment. A summary of the changes between the 2001 PCI guideline revisions[2] and the 2005 PCI guideline update[1] are provided in Table 2.

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This article represents the expert opinion of the Diagnostic and Interventional Catheterization Committee and the Council on Clinical Cardiology of the American Heart Association (AHA) and the Cardiology Practice Research Network of the American College of Clinical Pharmacy (ACCP), and the contents were approved by the AHA Scientific Advisory Coordinating Committee and the ACCP Cardiology Practice Research Network. It does not necessarily represent an official ACCP commentary, guideline, or statement of policy or position.

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Thienopyridines

Pharmacology

Thienopyridines act by directly inhibiting the platelet P2Y12 adenosine 5′-diphosphate (ADP) receptor, reducing ADP-mediated platelet activation and subsequent platelet aggregation. The P2Y12 ADP receptors are located on the platelet surface. Stimulation of this receptor results in increased platelet aggregation, dense granule secretion, increased arachidonic acid production, and likely other processes that contribute to thrombus formation. With both of the currently used thienopyridines, platelet inhibition is irreversible for the life of the platelet (7–10 days). Biotransformation of the prodrug thienopyridines clopidogrel (Plavix; Bristol-Myers Squibb, Princeton, NJ) and ticlopidine (Ticlid; Roche, Nutley, NJ) by the hepatic cytochrome P450 (CYP) enzyme system (CYP2C19 for ticlopidine; CYP3A3, CYP3A4, CYP3A5, and others for clopidogrel) are necessary to inhibit platelet activation.[3] Clopidogrel and ticlopidine are inhibitors of CYP2B6.[4–7]

With administration of ticlopidine 250 mg orally twice/day, the onset of platelet inhibition occurs within 24–48 hours, but maximum platelet inhibition does not occur for 5–7 days. Large loading doses of ticlopidine, administered in an attempt to achieve more rapid maximum inhibition of aggregation, are not well tolerated

Table 2. Summary of Changes in Pharmacotherapy Recommendations from the 2001 Guideline Revisions to the 2005 Guideline Update[1, 2]

Drug	2001 Recommendation	2005 Recommendation
Aspirin	Class I: 80–325 mg at least 2 hrs before PCI	Class I: If taking long-term aspirin therapy, 75–325 mg before PCI. If not taking long-term aspirin therapy, 300–325 mg at least 2 hrs before PCI, preferably 24 hrs. Daily dose of 325 mg for 30 days after bare metal stent placement, 3 mo after sirolimus stent placement, and 6 mo after paclitaxel stent placement, then indefinitely at a daily dose of 75–162 mg.
Thienopyridines	Class I: In conjunction with coronary stent implantation (clopidogrel or ticlopidine) In elective PCI, the drug should be administered 24–48 hrs before procedure (clopidogrel or ticlopidine) Continue 2–4 wks after stent placement (clopidogrel or ticlopidine)	Class I: Initial 300-mg loading dose at least 6 hrs before PCI (clopidogrel). Patients undergoing PCI should receive 75 mg/day for 1 mo after bare metal stent placement, 3 mo after sirolimus stent placement, 6 mo after paclitaxel stent placement, and ideally for up to 12 mo in patients not at high risk for bleeding (clopidogrel). Class IIa: If administered at the time of PCI, supplementation with a GP IIb-IIIa inhibitor can be beneficial to facilitate earlier platelet inhibition. For patients with aspirin allergy, administration of a 300-mg loading dose at least 6 hrs before PCI is a reasonable option, or administered at the time of PCI with supplementation with a GP IIb-IIIa inhibitor (clopidogrel). Larger loading doses (> 300 mg) are reasonable to achieve more rapid antiplatelet activity; however, safety and efficacy are less established (clopidogrel). It is reasonable to consider indefinite use in patients undergoing brachytherapy along with 75–325 mg of aspirin (clopidogrel). Class IIb: For patients in whom subacute thrombosis may be catastrophic (unprotected left main, bifurcating left main, or single patent coronary vessel), it is reasonable to perform platelet aggregation studies, and if < 50% platelet inhibition, consider 150 mg/day (clopidogrel).
GP IIb-IIIa inhibitors	Class I: In patients with unstable angina or other high-risk features undergoing PCI[a] Class II: In patients with class I angina[b] In patients with acute transmural MI[b]	Class I: In patients with unstable angina or NSTEMI undergoing PCI without clopidogrel administration.[a] Class IIa: In patients with unstable angina or NSTEMI undergoing PCI with administration of clopidogrel.[a] In patients with STEMI undergoing PCI, use of abciximab is reasonable as early as possible. In patients undergoing elective PCI with stent placement.[a] Class IIb: In patients with STEMI undergoing PCI, treatment with eptifibatide or tirofiban may be considered.
Low-molecular-weight heparin (enoxaparin)	No recommendation	Class IIa: Alternative to UFH in patients with unstable angina or NSTEMI undergoing PCI. Class IIb: Alternative to UFH in patients with STEMI undergoing PCI.
Direct thrombin inhibitors	No recommendation	Class I: For use in place of UFH in patients with heparin-induced thrombocytopenia (bivalirudin or argatroban). Class IIa: As an alternative to UFH and GP IIb-IIIa inhibitor in low-risk patients undergoing PCI (bivalirudin).

PCI = percutaneous coronary intervention; GP = glycoprotein; MI = myocardial infarction; NSTEMI = non–ST-segment elevation MI; STEMI = ST-segment elevation MI; UFH = unfractionated heparin.

[a]Either abciximab, tirofiban, or eptifibatide may be used.

[b]Every indication may not apply to all individual agents.

as they cause nausea and emesis. In contrast, large loading doses of clopidogrel generally are well tolerated. With administration of clopidogrel 300 mg orally, maximum platelet inhibition as assessed by aggregometry appears to be achieved within 6 hours.[4–6] Clinical studies, however, suggest that the clinical benefit is not fully appreciated until 12–15 hours after administration of a 300-mg loading dose.[8] When a 600-mg oral loading dose is administered, maximum platelet inhibition is achieved after approximately 2 hours.[5, 9, 10] Several recent studies, including Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect (ISAR-CHOICE)[11] and Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation, and Ongoing Necrosis (ALBION)[12] trials, have examined whether administration of clopidogrel 900 mg leads to quicker and/or more complete platelet inhibition than administration of 600 mg (or 300 mg). Results of both studies suggested that a 600-mg loading dose of clopidogrel is approximately as rapid and potent as a 900-mg dose, and these studies demonstrated that both doses were well tolerated.[11, 12] Additional studies are planned.

Ticlopidine and clopidogrel are rapidly absorbed after oral administration; levels of the active metabolites of these drugs are reached within 1–2 hours. Ticlopidine's bioavailability is increased by food and decreased by antacids. Food does not significantly modify the bioavailability of clopidogrel. Results of the ISAR-CHOICE trial suggest that doses above 600 mg are not associated with increased suppression of platelet function, possibly due to limited clopidogrel absorption.[11]

Clopidogrel is extensively metabolized by the liver.[7, 13] Clinically significant drug interactions with the thienopyridines are limited. Although some investigators have contented that atorvastatin and other 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) metabolized by the same CYP system reduce the efficacy of clopidogrel, others contend that there are no clinically significant interactions between statins and clopidogrel.[3, 14–16] In general, studies reporting no significant drug interactions have used lower doses of statins.

Aspirin and Clopidogrel Resistance

The phenomenon of oral antiplatelet resistance, better termed hyporesponsiveness or nonresponsiveness, has become increasingly recognized. The phenomenon of hyporesponsiveness to aspirin, originally denoted as aspirin resistance, began receiving increased attention during this decade with increased use of methods to measure inhibition of platelet aggregation. Numerous methods of measuring the degree of responsiveness to aspirin, as well as numerous definitions of what constitutes resistance, have been used. Some degree of aspirin resistance may affect 5–45% of the aspirin-taking population.[17] The mechanisms of such resistance remain to be fully elucidated but are believed to be a combination of clinical, cellular, genetic, and other factors.[18, 19] The optimal therapeutic approach to patients with aspirin hyporesponsiveness remains to be determined. Although treatment of such patients with clopidogrel has been proposed, such a strategy has never been clinically validated.

More recently, the phenomenon of clopidogrel hyporesponsiveness has received increasing recognition and attention. Dose- and time-dependent variability in clopidogrel response has been demonstrated in numerous studies.[20–22] Clopidogrel hyporesponsiveness, which must always be distinguished from noncompliance, may result from several factors, including impaired absorption of the drug and a reduction in its conversion from the prodrug (i.e., clopidogrel itself) to the active metabolite, as well as genetic polymorphisms involving the P2Y12 receptor.[23, 24] At present, there is no universally accepted definition of hyporesponsiveness, although many studies have defined it as a decrease in platelet aggregability of ranging from 5–35% from baseline. There is also no agreed-on means of determining responsiveness. Most studies have used optical platelet aggregometry, which is labor intensive and both instrument and laboratory dependent. Newer point-of-care devices are now available. At present, however, ex vivo determination of hyporesponsiveness with these methods has not been confirmed to be associated with a worse clinical outcome.

Of note, one recent study of patients undergoing PCI demonstrated correlations between aspirin and clopidogrel resistance.[25] As a group, those found to be aspirin resistant had lower response to clopidogrel, assessed by platelet aggregation and activation markers, than those who were aspirin sensitive. In that study, nine (47%) of 19 patients found to be aspirin resistant were also found to be clopidogrel resistant.

Clinical Studies

Clinical studies evaluating the thienopyridines

can be divided into three broad categories: studies to prevent coronary stent subacute thrombosis, studies of treatment before PCI to prevent PCI-related complications (primarily myocardial infarction), and studies of longer term therapy after PCI aimed at preventing not only stent thrombosis but also thrombotic events unrelated to the PCI procedure.

Several studies compared different antithrombotic regimens after stent deployment for the prevention of subacute stent thrombosis. In the Intracoronary Stenting and Antithrombotic Regimen (ISAR),[26] Stent Anticoagulation Restenosis Study (STARS),[27] Full Anticoagulation versus Aspirin and Ticlopidine (FANTASTIC),[28] and Multicenter Aspirin and Ticlopidine after Intracoronary Stenting (MATTIS) studies,[29] patients undergoing planned coronary stent implantation were randomly assigned at the time of stent placement to treatment for 4 weeks with either the combination of aspirin plus ticlopidine 250 mg orally twice/day or aspirin plus oral anticoagulant therapy (the STARS study also had an aspirin-only group). The rate of major adverse events (included in most subacute stent thrombosis trials) was significantly lower in those treated with aspirin plus ticlopidine compared with those treated with aspirin plus oral anticoagulant therapy or aspirin alone.[26–30]

Due to concerns about the development of neutropenia (occurring in 2–3% of patients) and thrombotic thrombocytopenic purpura (occurring in ~0.1% of patients) with ticlopidine therapy, studies were conducted to compare ticlopidine therapy with clopidogrel therapy. In the first of such trials, the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), 1020 patients undergoing coronary stent implantation, all of whom were treated with aspirin, were randomly assigned to receive 4 weeks of treatment with either ticlopidine 250 mg orally twice/day, clopidogrel 75 mg orally once/day without a loading dose, or clopidogrel 75 mg orally once/day with an initial 300-mg loading dose.[31] The composite end point of major adverse cardiac events or lack of tolerability occurred in 9.1% of ticlopidine-treated patients, compared with 6.3% of those treated with clopidogrel without a loading dose and 2.9% of those treated with a clopidogrel loading dose. Major ischemic events were similar among the three treatment groups. The results of CLASSICS and two other randomized trials, as well as numerous registries, demonstrated generally comparable prevention of major adverse events, including subacute thrombosis, between ticlopidine and clopidogrel.[32, 33] Because clopidogrel is better tolerated, however, and can be administered in a large loading dose leading to a more rapid onset of action, clopidogrel has become the thienopyridine of choice not only to prevent subacute stent thrombosis but also for all other indications for a thienopyridine.

Analyses of the Do Tirofiban and Reopro Give Similar Efficacy Trial (TARGET)[34] and Evaluation of Platelet IIb-IIIa Inhibition for Stenting (EPISTENT) trial[35] suggested that patients who had been treated with a thienopyridine before undergoing PCI had a lower rate of ischemic complications (primarily procedural myocardial infarctions) than those who had not been receiving thienopyridine therapy.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study was a trial of 12,562 patients with non–ST-segment elevation acute coronary syndromes (ACS); all patients were treated with aspirin and randomly assigned to treatment with either clopidogrel 300 mg initially then 75 mg once/day or placebo for 3–12 months. A postrandomization subgroup analysis of the 2658 patients in the CURE study who underwent PCI a mean of 10 days after study entry, referred to as the PCI-CURE study, revealed that those who had been randomly assigned to clopidogrel therapy had fewer major adverse ischemic events than those who had been randomized to placebo therapy (4.5% vs 6.4%, p=0.03).[36]

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial was a randomized trial specifically designed in part to identify whether pretreatment with clopidogrel before PCI (as opposed to during or after) would reduce adverse events.[37] As part of the CREDO trial, 2116 patients undergoing PCI were randomly assigned to pretreatment with clopidogrel 300 mg administered 3–24 hours before the procedure or to placebo. Major ischemic events at 28 days after PCI occurred in 6.8% of patients pretreated with clopidogrel and 8.4% of patients pretreated with placebo, a 19% reduction in adverse events that was not statistically significant (p=0.23). However, the results of a prespecified subgroup analysis revealed that in patients who received clopidogrel pretreatment at least 6 hours before PCI there was a 39% relative reduction in ischemic events, a finding that was of borderline statistical significance (p=0.051). A later retrospective analysis of CREDO data revealed that although

only 6 hours were required to achieve the peak platelet inhibition effect of clopidogrel as measured by aggregometry, treatment beginning at least 12–15 hours before the procedure was necessary to produce a reduction in clinical events.[8]

In a more recent study, a group of authors compared rise in troponin I or creatine kinase–MB (CK-MB) fraction in 203 relatively low-risk patients receiving either pretreatment for 3 days with a clopidogrel 300-mg oral loading dose followed by 75 mg orally once/day or no pretreatment.[38] No differences were noted in the rates of those with CK-MB or troponin elevations. In the ISAR–Rapid Early Action for Coronary Treatment (ISAR-REACT) study, 2159 low-risk patients were pretreated with clopidogrel 600 mg orally administered at least 2 hours before PCI and randomly assigned either to treatment with the glycoprotein IIb-IIIa inhibitor abciximab or to placebo therapy.[39] The rates of myocardial infarction and other ischemic complications were similar between the abciximab-treated and placebo-treated patients. Similarly designed studies examining patients undergoing PCI in small vessels (Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries [ISAR-SMART-2])[40] and with diabetes mellitus (ISAR-Is Abciximab a Superior Way to Eliminate Thrombotic Risk in Diabetics [ISAR-SWEET])[41] also found no benefit from abciximab when patients had been pretreated with clopidogrel 600 mg for at least 2 hours. However, different results were found in the ISAR-REACT-2 study, in which 2022 high-risk patients with ACS who were undergoing PCI received pretreatment with clopidogrel 600 mg and were randomly assigned to treatment with either abciximab or placebo.[42] The 30-day composite ischemic triple end point occurred in 8.9% of patients treated with abciximab and 11.9% of patients who received placebo, a 25% risk reduction (p=0.03). No difference was noted in the primary end point in patients who were troponin negative (4.6% in each group), whereas in troponin-positive patients the primary event rates were 13.1% in abciximab-treated patients and 18.3% in placebo-treated patients (p=0.02, p=0.07 for interaction). No significant interaction on the primary results was noted with respect to the presence of diabetes.

In one relatively small study, the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA-2) study, investigators randomly assigned 255 relatively low-risk patients to either a 300-mg or 600-mg loading dose of clopidogrel 4–8 hours before PCI; they reported a lower rate of the primary composite end point (death, myocardial infarction, or target vessel revascularization) with the 600-mg dose than with the 300-mg dose (4% vs 12%, p=0.04).[43] Pharmacists and other health care professionals should be aware that many interventionalists have now adopted the 600-mg loading dose in their practices.

In the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study, patients with ST-segment elevation myocardial infarction who were undergoing fibrinolytic therapy were randomly assigned to treatment with either a clopidogrel 300-mg loading dose then 75 mg once/day or placebo. Of the 3491 patients enrolled in CLARITY, 1863 underwent (in a nonrandomized fashion) PCI in the days following enrollment. In an analysis of these patients (the PCI-CLARITY study), those who had been randomly assigned to clopidogrel therapy at the time of presentation had a lower rate of the composite end point of cardiovascular death, myocardial infarction, or stroke after PCI compared with those who had received placebo (3.6% vs 6.2%, odds ratio 0.54, p=0.008); no significant increase was noted in the rates of Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding.[44]

Several studies have examined the potential of longer term clopidogrel treatment after PCI to decrease future ischemic complications. In the PCI-CURE analysis, event rates from the time of PCI until the end of follow-up (an average of 8 mo) were 18.3% among patients receiving clopidogrel 75 mg once/day and 21.7% among patients receiving placebo (p=0.03). However, no statistically significant reduction in adverse events was observed between 30 days after PCI (the approximate time that clopidogrel therapy would have been continued to prevent subacute stent thrombosis among patients receiving a bare metal stent) and the end of follow-up.[36, 45]

The previously discussed CREDO study was designed in part to assess the impact of longer term (1 yr) therapy with clopidogrel after PCI.[37] Patients who were randomly assigned to pretreatment with clopidogrel before PCI continued to receive clopidogrel 75 mg once/day for 12 months; those randomly assigned to no loading dose were treated with clopidogrel for only 1 month. Analysis of events occurring between 29 days and 1 year after PCI demonstrated a 37.4% reduction in the combined end

point of death, myocardial infarction, or stroke in those receiving clopidogrel compared with those receiving placebo (p=0.04). The extent to which this benefit reflects a continuation of benefit from early pretreatment among the same patient subset is unknown, since patients were not rerandomized to extended therapy in the trial.

Utilization Guidelines

The optimum duration of treatment after stent implantation for the prevention of subacute stent thrombosis has not been definitively determined for patients who receive bare metal (non–drug-eluting) stents or for those who receive drug-eluting stents. Most studies in patients who received bare metal stents tested 2–4 weeks of aspirin plus thienopyridine therapy, and this duration of therapy has been adapted in most patients.[27, 28, 30] Because of concerns that drug-eluting stents delay endothelialization, or that other as-yet-undefined processes occur, some are concerned that the frequency of "late" stent thrombosis (occurring in the months after drug-eluting stent implantation) may be elevated, and occurrence of very late stent thrombus (~1 yr after implantation) after discontinuation of antiplatelet therapy has been reported among drug-eluting stent recipients.[46] Most recent studies of drug-eluting stents have therefore used 2–6 months of dual antiplatelet therapy, and very low rates of stent thrombosis have been reported.[47–50] In most of these studies, an initial loading dose of 300 mg was administered, and this loading dose has become the most frequently used loading dose.

Of importance, clopidogrel should be used with caution in patients at increased risk for bleeding complications; in those with severe liver disease and/or dysfunction, particularly when used for longer term therapy; and in those requiring both aspirin and warfarin.

The ACC-AHA-SCAI guidelines recommend a loading dose of 300 mg, administered at least 6 hours before PCI (class I, evidence level A), although they also note that administration of more than 300 mg is reasonable to achieve higher levels of antiplatelet activity more rapidly, but that the efficacy and safety compared with a 300-mg loading dose are less established (class IIa, evidence level C). The regimen of a 300-mg loading dose at least 6 hours before PCI is also recommended in patients with an absolute contraindication to aspirin (class IIa, evidence level C). These, as well as other recommendations, will be subject to semiannual review, and recommendations may evolve as further data become available. The guidelines also note that in patients in whom subacute thrombosis may be catastrophic or lethal (such as an "unprotected" left main artery), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg/day if less than 50% inhibition of platelet aggregation is demonstrated (class IIb, evidence level C). Note that this recommendation is an evidence level C based on expert opinion, as there are no randomized trials or large registries that have studied this treatment strategy. After stent implantation, the guidelines recommend administration of clopidogrel 75 mg/day orally for at least 1 month after bare metal stent implantation, 3 months after sirolimus stent (Cypher; Cordis Corporation–Johnson and Johnson, Miami Lakes, FL) implantation, 6 months after paclitaxel stent (Taxus; Boston Scientific, Natick, MA) implantation, and ideally up to 12 months in all patients who are not at high risk for bleeding (class I, evidence level B).[1] These recommendations are based primarily on standardized treatment durations selected for use in clinical trials of patients undergoing coronary stent implantation. No recommendations have been made regarding clopidogrel administration in those patients undergoing PCI for acute or recent ST-elevation myocardial infarction. Dosing and precautions for clopidogrel are summarized in Table 3.

Glycoprotein IIb-IIIa Inhibitors

Pharmacology

Glycoprotein IIb-IIIa receptors are present on the platelet membrane and are the major platelet surface receptor involved in the final common pathway of platelet aggregation. When platelets become activated, the glycoprotein IIb-IIIa receptor undergoes a conformational change and becomes able to crosslink fibrinogen, thereby serving as the final common pathway resulting in platelet aggregation.[51] Three glycoprotein IIb-IIIa inhibitors have been studied and used in PCI: abciximab (Reopro; Eli Lilly, Indianapolis, IN), a monoclonal antibody; eptifibatide (Integrilin; Schering-Plough, Kenilworth, NJ), a hexapeptide; and tirofiban (Aggrastat; Merck, West Point, PA), a nonpeptide. Eptifibatide and tirofiban are primarily renally excreted, and the half-lives of these agents are approximately 2–2.5 hours, with restoration of normal platelet function occurring

Table 3. Newer Pharmacotherapy in Patients Undergoing Percutaneous Coronary Interventions

Class, Agent	Pharmacology	Dosage	Comments, Monitoring, and Precautions
Thienopyridines			
Clopidogrel	Metabolized by liver to active metabolite Irreversibly inhibits P2Y12 ADP-mediated platelet activation Rapidly absorbed (absorption not affected by food)	Pretreatment before PCI: 300 mg p.o. at least 6 hrs (ideally 12–15 hrs) before PCI Prevention of stent thrombosis: 300 mg p.o. before or immediately after PCI, then 75 mg/day p.o. for 2–4 wks if bare metal stent, 3 mo for sirolimus stent, and 6 mo for paclitaxel stent Longer term treatment for prevention of ischemic complications: 75 mg/day p.o. for 1 yr if not at high risk for bleeding	Should be used with caution for longer term therapy in patients with severe kidney disease and those at increased risk for bleeding. A 600-mg oral loading dose administered at least 2 hrs before PCI has also been studied and is used by many practitioners; a regimen of > 300 mg is considered to be reasonable to achieve higher levels of antiplatelet activity more rapidly, although further study is needed to determine its clinical safety and efficacy. Follow clinically for signs or symptoms of bleeding. Obtain a CBC with platelet count at baseline. Thrombotic thrombocytopenia purpura has been reported as a very rare complication of therapy. If possible, CABG should be delayed 5–7 days in patients treated with clopidogrel. In patients who receive long-term dual antiplatelet therapy, lower dose aspirin 75–162 mg/day is recommended after the initial treatment period with aspirin 325 mg/day to prevent stent thrombosis.
GP IIb-IIIa inhibitors			
Abciximab	Clearance is by the reticuloendothelial system	0.25-mg/kg i.v. bolus, then 0.125 µg/kg/min (maximum 10 µg/min) for 12 hrs	No dosage adjustment necessary for patients with renal insufficiency; patients weighing > 80 kg (176 lbs) should receive 0.25-mg/kg i.v. bolus, then 10-µg/min infusion for 12 hrs. Contraindicated in patients at high risk for bleeding or increased risk for catastrophic bleeding and with platelet counts < 100 x 10^3/mm^3. Monitor for signs or symptoms of bleeding. Thrombocytopenia (often profound) can occur with therapy; patients who have been previously treated with abciximab are at increased risk for profound thrombocytopenia. Obtain CBC with platelet count before drug administration, 4 hrs after start of therapy, and then before discharge; discontinue abciximab immediately if platelet count decreases by > 50%. When UFH is used, recommended bolus dose is 50–70 U/kg, with target ACT of of 200–300 sec.
Eptifibatide	Primarily renally cleared Half-life ~2.5 hrs	180-µg/kg i.v. bolus, then 2.0 µg/kg/min for up to 18–24 hrs; a second 180-µg/kg i.v. bolus is administered 10 min after the first bolus	If Cl_{cr} < 50 ml/min, reduce maintenance infusion dosage to 1.0 µg/kg/min (still give both boluses); should not be used in patients receiving hemodialysis. Patients weighing > 121 kg (> 267 lbs) should receive 22.6-mg boluses and infusion of 15 mg/hr. Use with caution, if at all, in patients with thrombocytopenia. Contraindicated in patients at high risk for bleeding or at increased risk for catastrophic bleeding. Monitor for signs or symptoms of bleeding. Obtain CBC with platelet count before drug administration, 4 hrs after start of therapy, and then before hospital discharge. When UFH is used, recommended bolus dose is 50–70 U/kg, with target ACT of 200–300 sec.

Table 3. Newer Pharmacotherapy in Patients Undergoing Percutaneous Coronary Interventions (continued)

Class, Agent	Pharmacology	Dosage	Comments, Monitoring, and Precautions
GP IIb-IIIa inhibitors (continued)			
Tirofiban	Primarily renally cleared Half-life ~2 hrs	RESTORE and TARGET trials: 10-µg/kg bolus then 0.15 µg/kg/min for 18–24 hrs ADVANCE and TENACITY (study discontinued) trials: 25-µg/kg bolus then 0.15-µg/kg/min infusion	Not FDA approved for PCI. Dosages listed are given only to make the reader aware of dosage regimens being used by some practitioners. No specific dosage recommendations for patients with severe renal insufficiency receiving the listed dosage regimens (bolus and maintenance infusion dosages are decreased for ACS therapy); thus, use with caution, if at all, in such patients. Use with caution, if at all, in patients with thrombocytopenia. Contraindicated in patients at high risk for bleeding or at increased risk for catastrophic bleeding. Monitor for signs or symptoms of bleeding. Obtain CBC with platelet count before drug administration, 4 hrs after start of therapy, and then before hospital discharge. A higher bolus dose of 25 µg/kg has been used in some patients and was being evaluated in the United States in the TENACITY trial before the study was discontinued. When UFH is used, recommended bolus dose is 50–70 U/kg, with target ACT of 200–300 sec.
Direct thrombin inhibitors			
Argatroban	Clearance by liver metabolism	For PCI in patients with HIT or HITTS: 350-µg/kg bolus over 3–5 min, then infusion of 25 µg/kg/min	If ACT < 300 sec, give additional i.v. bolus of 150 µg/kg and increase infusion dosage to 30 µg/kg/min. If ACT > 450 sec, decrease infusion rate to 15 µg/kg/min. Should not be used during PCI in patients with significant liver disease (check liver function tests before use).
Bivalirudin	Clearance by renal mechanisms and proteolytic cleavage	Hirulog Angioplasty Study: 1.0-mg/kg bolus, then 2.5 mg/kg/hr for 4 hrs, then 0.2 mg/kg/hr for 14–20 hrs REPLACE trials: 0.75-mg/kg bolus then 1.75 mg/kg/hr for duration of PCI ACUITY trial: Initial ACS regimen was a 0.10-mg/kg bolus, then 0.25 mg/kg/hr; if PCI to be performed, an additional bolus of 0.50 mg/kg was administered and the maintenance infusion was increased to 1.75 mg/kg/hr	REPLACE-2 dosage regimen adjustment for renal insufficiency (adjust the continuous-infusion dosage in patients with severely impaired renal function; bolus dose remains the same): Cl_{cr} 10–29 ml/min: 1.0 mg/kg Dialysis dependent: 0.25 mg/kg REPLACE-2 dosage regimen: If ACT < 225 sec, a 0.3-mg/kg bolus may be administered. ACUITY ACS and PCI dosage regimens not FDA approved. ACUITY ACS and PCI dosage regimens should not necessarily be extrapolated to patients with Cl_{cr} < 30 ml/min.

within 4–6 hours after drug discontinuation. The clearance of abciximab is complex and not completely characterized, although it is known that 12 hours after discontinuation of treatment, approximately 75% of receptors remain occupied, and some pharmacologic effects of abciximab persist for more than 24 hours after drug discontinuation.[13, 52, 53] As eptifibatide and tirofiban are

Table 3. Newer Pharmacotherapy in Patients Undergoing Percutaneous Coronary Interventions (continued)

Class, Agent	Pharmacology	Dosage	Comments, Monitoring, and Precautions
Low-molecular-weight heparin			
Enoxaparin	Significant renal clearance Half-life ~4.5 hrs with s.c. administration	No prior antithrombin therapy and elective PCI: 0.5–1.0 mg/kg i.v. if no GP IIb-IIIa inhibitor 0.5–0.75 mg/kg i.v. if GP IIb-IIIa inhibitor s.c. dosing before PCI: If 0–8 hrs since last s.c. dose, then no additional treatment If 8–12 hrs since last s.c. dose, then 0.3 mg/kg i.v.	No i.v.-only dosage regimen is FDA approved or suggested by the ACC-AHA-SCAI guidelines. Monitor for signs or symptoms of bleeding. Should not be used in patients with history of HIT; HIT can occur with therapy. Check CBC with platelet count at baseline and follow every 1–2 days. No specific recommendations available for dosage adjustment of i.v. administered enoxaparin in patients with severe renal insufficiency (Cl_{cr} < 30 ml/min) and in those receiving dialysis; may be prudent to avoid use in such patients. LMWHs only modestly elevate ACT, thus ACT level should not be used to guide anticoagulant management. In patients without severe renal insufficiency, sheaths may be removed 4 hrs after the last i.v. dose or 6–8 hrs after the last s.c. dose.

PCI = percutaneous coronary intervention; ADP = adenosine 5′-diphosphate; CBC = complete blood count; CABG = coronary artery bypass graft; UFH = unfractionated heparin; ACT = activated clotting time; Cl_{cr} = creatinine clearance; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; TARGET = Do Tirofiban and Reopro Give Similar Efficacy Trial; ADVANCE = Additive Value of Tirofiban Administered with the High-Dose Bolus in the Prevention of Ischemic Complications During High-Risk Coronary Angioplasty; TENACITY = Tirofiban Evaluation of Novel Dosing versus Abciximab with Clopidogrel and Inhibition of Thrombin Study; FDA = U.S. Food and Drug Administration; ACS = acute coronary syndromes; HIT = heparin-induced thrombocytopenia; HITTS = heparin-induced thrombocytopenia with thrombosis syndrome; REPLACE = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; s.c. = subcutaneous; GP = glycoprotein; ACC-AHA-SCAI = American College of Cardiology–American Heart Association–Society for Cardiovascular Angiography and Interventions.

primarily renally excreted, dosage reductions in patients with renal insufficiency are indicated.

Clinical Studies

Numerous randomized, placebo-controlled studies of patients undergoing PCI have demonstrated a reduction in ischemic complications, particularly enzymatically defined myocardial infarction, with glycoprotein IIb-IIIa treatment.[54] In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, the first major trial of glycoprotein IIb-IIIa inhibition in patients undergoing balloon angioplasty, treatment with an abciximab 0.25-mg/kg bolus and subsequent 12-hour infusion of 10 µg/minute was associated with a statistically significant reduction in adverse events compared with placebo (8.3% vs 12.8%), whereas treatment with the bolus alone (without subsequent infusion) was not, establishing that treatment with a glycoprotein IIb-IIIa inhibitor during PCI would consist of both an initial bolus and a subsequent infusion.[55]

In the EPISTENT study, the primary composite ischemic end point occurred in 5.3% of patients randomly assigned to treatment with an abciximab 0.25-mg/kg bolus then 0.125 µg/kg/minute plus coronary stent implantation and in 10.8% of patients randomly assigned to placebo plus coronary stent implantation ($p<0.001$), establishing the benefit of glyco-protein IIb-IIIa inhibition in patients undergoing coronary stent implantation.[56] In 2064 patients undergoing coronary stent implantation, the Enhanced Suppression of the Platelet IIb-IIIa Receptor with Integrilin Therapy (ESPRIT) trial evaluated the potential benefit of a higher dose regimen of eptifibatide, two 180-µg/kg boluses administered 10 minutes apart and a 2-µg/kg/minute continuous infusion, than had been previously studied.[57–59] The second bolus, administered 10 minutes after the initial bolus, was designed to maintain greater than 80% inhibition of platelet aggregation during the PCI procedure. The primary composite ischemic end point occurred in 6.6% of eptifibatide-treated patients and 10.5% of placebo-treated patients ($p=0.0015$).[59]

The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) compared treatment with a tirofiban 10-µg/kg bolus administered over 3 minutes then 0.15 µg/kg/minute, with placebo in patients undergoing coronary angioplasty.[60] The broad composite end point occurred in 10.3% of tirofiban-treated patients and 12.2% of placebo-treated patients (p=0.160). The TARGET trial, a head-to-head study in 2398 patients undergoing coronary stent implantation that compared abciximab (same dosage regimen as EPISTENT) and tirofiban (same dosage regimen as RESTORE), demonstrated significantly fewer adverse events at 30 days with abciximab therapy than with tirofiban therapy (6.0% vs 7.6%, p=0.038).[34] At 6-month follow-up, however, a statistically significant difference was no longer noted between the rates of adverse events with each therapy.[61]

A recent study, the Additive Value of Tirofiban Administered with the High-Dose Bolus in the Prevention of Ischemic Complications During High-Risk Coronary Angioplasty (ADVANCE) trial, of higher bolus dose tirofiban 25 µg/kg intravenously in relatively high-risk patients demonstrated a reduction in a broad composite end point from 35% in patients who did not receive pretreatment to 20% in tirofiban-treated patients (p=0.01).[62] A large trial, the Tirofiban Evaluation of Novel Dosing versus Abciximab with Clopidogrel and Inhibition of Thrombin Study (TENACITY), was designed to compare this higher tirofiban bolus dose regimen of a 25-µg/kg bolus then 0.15 µg/kg/minute, with abciximab, but was discontinued for financial reasons. Data from those patients who were randomized in the trial before its discontinuation are forthcoming.

Primary angioplasty refers to the process by which patients with ST-segment elevation myocardial infarction are taken directly to the cardiac catheterization laboratory, without treatment with thrombolytic therapy, and undergo mechanical reperfusion with use of PCI. Five randomized trials compared abciximab therapy with placebo or no therapy during primary PCI. These trials produced variable results. Pooled data from these five trials demonstrate a 46% reduction in composite ischemic events with abciximab therapy.[63] Pooled results from six studies comparing earlier (such as in the emergency department) versus later (immediately before PCI) administration of abciximab demonstrate that earlier administration was associated with improved coronary artery reperfusion and resolution of ST-segment changes.[64] Few data are available on the utilization of either eptifibatide or tirofiban in patients undergoing primary angioplasty.

The most common adverse effects associated with the glycoprotein IIb-IIIa inhibitors are bleeding and thrombocytopenia. The rates of major bleeding (~1%) with glycoprotein IIb-IIIa inhibitor therapy in most placebo-controlled trials of glycoprotein IIb-IIIa inhibitors (in which carefully selected patients were enrolled and lower dose heparin was used) have either been similar to or modestly higher than those of placebo-treated patients.[56, 59, 60, 65] The observed rate of thrombocytopenia in studies of glycoprotein IIb-IIIa inhibitors is variable, depending on the study design, definitions, and agent used, but occurs in 1–4% of patients.[66] Thrombocytopenia may be profound (especially with use of abciximab) but is generally rapidly reversible with discontinuation of therapy.

Utilization Guidelines

Dosing, monitoring, and precautions regarding glycoprotein IIb-IIIa inhibitor therapy are provided in Table 3. Glycoprotein IIb-IIIa inhibitor therapy, when used, should be started before mechanical intervention whenever possible. The possible benefit of administering a glycoprotein IIb-IIIa inhibitor only after a thrombotic complication has occurred (referred to as "bailout" therapy) remains poorly studied and unproven. The glycoprotein IIb-IIIa inhibitors should be administered as a bolus (or double bolus in the case of eptifibatide) followed by a maintenance infusion for 12–24 hours after the procedure, depending on the agent used. Aspirin and antithrombin therapy should be used at the time of intervention along with glycoprotein IIb-IIIa inhibitor therapy. Patients who arrive at the catheterization laboratory who have been receiving glycoprotein IIb-IIIa inhibitors for the initial medical treatment of non–ST-segment elevation ACS and are to undergo PCI should have their glycoprotein IIb-IIIa inhibitor therapy continued during the PCI and for 12–24 hours after the procedure (depending on the agent used; Table 1). There are no data to support discontinuing one glycoprotein IIb-IIIa inhibitor that had been administered before a PCI procedure ("upstream therapy" for the initial treatment of non–ST-segment elevation ACS) and then starting another glycoprotein IIb-IIIa

inhibitor for the PCI procedure, and we recommend that such a strategy not be used.

In patients treated with abciximab, a regimen of a 0.25-µg/kg intravenous bolus followed by a continuous intravenous infusion of 0.125 µg/kg/minute (maximum 10 µg/min) for 12 hours should be used. In those treated with eptifibatide, an initial 180-µg/kg intravenous bolus should be administered, followed by a continuous infusion of 2 µg/kg/minute for 18–24 hours, with a second 180-µg/kg intravenous bolus administered 10 minutes after the first bolus dose. For patients weighing more than 121 kg (> 267 lbs) and treated with eptifibatide, the maximum bolus dose is 22.6 mg and the maximum infusion rate is 15 mg/hour. No recommendations can be made at this time regarding the use (or dosing) of tirofiban for PCI in patients who have not previously started to receive such therapy for the initial medical treatment of non–ST-segment elevation ACS (although tirofiban has been continued for 12–24 hrs after PCI in different trials).

Patients with a creatinine clearance less than 50 ml/minute who are to be treated with eptifibatide should still receive both bolus doses, but should receive only half of the continuous infusion dosage (i.e., 1.0 µg/kg/min). No specific dosage recommendations are available for tirofiban use during PCI in patients with severe renal insufficiency; bolus and maintenance doses are decreased for acute coronary therapy, and thus this drug should be used with caution, if at all, in such patients.

Contraindications to glycoprotein IIb-IIIa inhibitors include a high risk for bleeding and/or an increased risk for catastrophic bleeding, including active internal bleeding or recent major bleeding; recent major surgical procedures or trauma; bleeding diathesis; recent stroke or history of any hemorrhagic stroke; intracranial neoplasm, arteriovenous malformation, or aneurysm; suspected aortic dissection; uncontrolled marked hypertension; and thrombocytopenia. Patients treated with glycoprotein IIb-IIIa inhibitors (particularly abciximab) should have platelet counts checked 4–6 hours after the start of glycoprotein IIb-IIIa therapy and again the following morning in order to detect thrombocytopenia. If a decrease in platelet count of 50% or more is detected, or if the platelet count decreases below approximately 100 x 10^3/mm^3, the agent should be discontinued. Patients should be monitored clinically for signs of bleeding.

The 2005 AHA-ACC-SCAI guidelines recommend administration of a glycoprotein IIb-IIIa inhibitor in patients with unstable angina or non-ST-segment elevation myocardial infarction who have not received pretreatment with clopidogrel and are undergoing PCI (class I, evidence level A) and state that it is reasonable to administer a glycoprotein IIb-IIIa inhibitor in patients with unstable angina or non-ST-segment elevation myocardial infarction who have received pretreatment with clopidogrel (class IIa, evidence level B).[1] The guidelines also state that it is reasonable to administer abciximab as early as possible in patients with ST-segment elevation myocardial infarction (class IIa, evidence level B), and that in patients with ST-segment elevation myocardial infarction who are to undergo PCI, treatment with eptifibatide or tirofiban may be considered (class IIb, evidence level C).[1]

Direct Thrombin Inhibitors

Pharmacology

Direct thrombin inhibitors bind directly to circulating and clot-bound thrombin. Hirudin is a naturally occurring 65-amino-acid polypeptide. Bivalirudin (Angiomax; The Medicines Company, Parsippany, NJ) is a synthetic 20-amino-acid derivative of hirudin. Both hirudin and bivalirudin bind to the catalytic and substrate recognition sites, but bivalirudin undergoes cleavage, with one part of the compound remaining bound reversibly to the active site. Therefore, the duration of thrombin inhibition is much shorter with bivalirudin than with hirudin. Besides proteolytic clearance, bivalirudin is also cleared from the body renally. The half-life of bivalirudin in patients with normal renal function is approximately 25 minutes and is prolonged in patients with moderately (34 min) or severely (57 min) impaired renal function, as well as those undergoing hemodialysis (3.5 hrs).[67]

Argatroban (Argatroban; GlaxoSmithKline, Research Triangle Park, NC) is a synthetic direct thrombin inhibitor derived from L-arginine. The primary route of argatroban metabolism is hydroxylation and aromatization. Formation of the metabolites of argatroban is catalyzed by the enzymes CYP3A4 and CYP3A5. The half-life of argatroban is 30–51 minutes.[68, 69]

Clinical Studies

Of the direct thrombin inhibitors, bivalirudin has undergone the most study in PCI. Four randomized trials have evaluated bivalirudin in

PCI. The results of the Hirulog Angioplasty Study were originally published in 1995.[70] In that study, 4098 patients undergoing predominantly balloon angioplasty for unstable or postinfarction angina were randomly assigned to treatment with either bivalirudin or UFH. The bivalirudin regimen consisted of a bolus dose of 1.0 mg/kg, followed by a 4-hour infusion of 2.5 mg/kg/hour and then a 14–20-hour infusion of 0.2 mg/kg/hour. A very broad primary composite end point was used in the study and occurred in 11.4% of bivalirudin-treated patients and 12.2% of heparin-treated patients during initial hospitalization (p=0.44). Major hemorrhage was significantly less frequent with bivalirudin than with heparin (3.8% vs 9.8%, p<0.001).

In 2001, the results of the study (now renamed the Bivalirudin Angioplasty Study) were reanalyzed, allowing all patients included in the study to be included in this analysis (complete data on all patients were not included in the initial article), and allowing the use of more contemporary definitions of procedural infarction and other adverse events.[71] In this reanalysis, the composite end point of death, myocardial infarction, or urgent revascularization at 7 days was found to have occurred in 6.2% of bivalirudin-treated patients and 7.9% of heparin-treated patients (p=0.039).

In the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-1) pilot trial, 1056 patients were randomly assigned to treatment with a lower dose and shorter duration regimen of bivalirudin 0.75-mg/kg bolus then a 1.75-mg/kg/hour infusion during PCI or UFH.[72] Overall, 72% of patients were treated with a glycoprotein IIb-IIIa inhibitor at the physician's discretion. The primary composite ischemic end point occurred in 5.6% of bivalirudin-treated patients and 6.9% of heparin-treated patients (p=0.40). Major bleeding occurred in 2.1% and 2.7% of patients, respectively (p=0.52).

In the REPLACE-2 trial, 6010 patients (> 80% of whom underwent stent implantation) were randomly assigned to treatment with either bivalirudin and provisional (bailout) glycoprotein IIb-IIIa inhibitor therapy or to UFH plus obligate glycoprotein IIb-IIIa inhibitor therapy.[73] The bivalirudin bolus doses and continuous infusion dosages were the same as in REPLACE-1. If a measured activated clotting time (ACT) was less than 225 seconds, an additional 0.3-mg/kg bolus dose of bivalirudin was administered. The primary end point was a quadruple composite that included the ischemic end points of death, myocardial infarction, or urgent revascularization, as well as major bleeding. The quadruple composite end point occurred in 9.2% of bivalirudin-treated patients and 10.0% of the patients treated with UFH plus glycoprotein IIb-IIIa inhibitor (p=0.32). The rate of myocardial infarction tended to be slightly higher in the bivalirudin-treated patients (7.0% vs 6.2%, p=0.23), whereas major bleeding was lower in the bivalirudin-treated patients (2.4% vs 4.1%, p<0.001). Twelve-month follow-up revealed no difference in mortality between the two treatment strategies,[74] including in patients with diabetes.[75] Thus, it has been concluded that bivalirudin is a reasonable alternative to UFH and glycoprotein IIb-IIIa inhibitors in non–high-risk patients.[76]

Recently, the Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia (PROTECT-TIMI-30) trial compared bivalirudin and provisional eptifibatide therapy to treatment with heparin (either low-dose UFH 50 U/kg or low-dose intravenously administered enoxaparin 0.5 mg/kg) plus eptifibatide therapy in 857 higher risk patients with unstable angina or non–ST-segment elevation ACS who were to undergo PCI.[77] The primary end point of coronary flow reserve was 1.43 in patients treated with bivalirudin and 1.33 in patients treated with heparin plus glycoprotein IIb-IIIa inhibitor (a greater coronary flow reserve is better). Numerous secondary end points were analyzed. Among them, death or myocardial infarction occurred in 8.8% of bivalirudin-treated patients and 6.3% of patients treated with UFH plus glycoprotein IIb-IIIa inhibitor, but the difference was not statistically significant. Major bleeding was 0% in bivalirudin-treated patients and 0.7% in the UFH plus glycoprotein IIb-IIIa inhibitor group (0% in those treated with UFH and 1.5% in those treated with enoxaparin).

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial compared multiple pharmacologic strategies in patients with non–ST-segment elevation ACS who were to undergo cardiac catheterization within 48–72 hours, followed by revascularization if appropriate.[78] A total of 13,819 patients were randomly assigned to one of three regimens: heparin (UFH or enoxaparin) plus glycoprotein IIb-IIIa inhibitor, bivalirudin plus glycoprotein IIb-IIIa inhibitor, or bivalirudin only. Patients who were to receive a glycoprotein IIb-IIIa inhibitor were further randomized to receive the glycoprotein IIb-IIIa inhibitor at the time of

randomization ("upstream" therapy) or at the time of PCI if they were to undergo PCI (deferred therapy). Patients with a creatinine clearance less than 30 ml/minute were excluded from the study. The primary 30-day end point consisted of the ischemic triple end point of death, myocardial infarction, or unplanned revascularization, plus a broadly defined end point of major bleeding, thus a quadruple end point. Patients assigned to bivalirudin therapy were initially treated with a regimen of a 0.10-mg/kg bolus and a 0.25-mg/kg/hour continuous infusion. If at the time of catheterization it was determined that they were to undergo PCI, they were treated with an additional bolus dose of 0.50 mg/kg and the continuous infusion dosage was increased to 1.75 mg/kg/hour. Preliminary results of the trial are that the quadruple end point occurred in 11.7% of the heparin plus glycoprotein IIb-IIIa inhibitor group, 11.8% of the bivalirudin plus glycoprotein IIb-IIIa inhibitor group, and 10.1% of the bivalirudin only group. Upstream and deferred use of a glycoprotein IIb-IIIa inhibitor both resulted in the occurrence of the quadruple end point in 11.7% of patients.

No major studies examining the use of bivalirudin in patients with ST-segment elevation myocardial infarction who are to undergo primary PCI have been completed, although this is being evaluated as part of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS) trial.

One group of authors reported on 51 patients with a new or previous diagnosis of heparin-induced thrombocytopenia (HIT) or HIT with thrombotic syndrome (HITTS) who were undergoing PCI and were treated with bivalirudin.[79] A clinically successful procedure was achieved in 96% of patients. Major bleeding occurred in one patient who underwent coronary artery bypass graft (CABG) surgery. No patient had significant thrombocytopenia. Bivalirudin was recently approved by the FDA for use in patients with a new or prior diagnosis of HIT.

Argatroban was studied in 91 patients with a current or previous clinical diagnosis of HIT or HITTS who underwent a total of 112 interventions.[80] What was deemed a satisfactory procedural outcome occurred in 94.5% of procedures. Argatroban is approved for use in PCI in patients with HIT or HITTS.

Utilization Guidelines

The bivalirudin dosage regimen currently used by most practitioners (and recently approved by the FDA) is the dosage regimen that was used in the REPLACE-2 trial. Treatment usually consists of administering a 0.75-mg/kg bolus dose and then starting the continuous infusion dosage of 1.75 mg/kg, with termination of the continuous infusion at the end of the procedure. The continuous infusion dosage (but not the bolus dose) should be adjusted in patients with moderate to severely impaired renal function (Table 3). Although ACT levels with bivalirudin therapy are usually in the higher range, if the ACT is less than 225 seconds, an additional bolus dose of 0.3 mg/kg may be administered. However, it must be acknowledged that there are no data about whether, let alone how, to use ACT guidance to optimize outcomes with bivalirudin. Bivalirudin, along with argatroban (discussed below), are recommended for use instead of heparin during angioplasty in patients with a history of HIT or HITTS (class I, evidence level B).[1, 81] As of this writing, the ACS dosage regimen used in ACUITY is not FDA approved. If practitioners do decide to use this regimen, then it seems reasonable that patients treated with the ACS dosage regimen who are to undergo PCI receive an additional 0.5-mg/kg bolus and have the infusion rate increased to 1.75 mg/kg/hour. Patients with a creatinine clearance less than 30 ml/minute were excluded from ACUITY, and thus the bivalirudin dosage regimens for ACS and PCI that were used in the ACUITY trial should not necessarily be extrapolated to this patient population.

Argatroban is FDA approved for use in patients with HIT or HITTS who are undergoing PCI. The approved dosage regimen for argatroban for PCI in patients with HIT or HITTS is a 350-µg/kg bolus dose, administered over 3–5 minutes, and an initial infusion rate of 25 µg/kg/minute. If the ACT, measured 5–10 minutes after bolus administration, is less than 300 seconds, an additional intravenous bolus of 150 µg/kg should be administered and the infusion rate increased to 30 µg/kg/minute. If the ACT is greater than 450 seconds, the infusion rate should be decreased to 15 µg/kg/minute. Argatroban should not be used during PCI in patients with significant liver disease.

The current ACC-AHA-SCAI guidelines on PCI state that it is reasonable to use bivalirudin as an alternative to UFH and glycoprotein IIb-IIIa inhibitors in low-risk patients undergoing elective PCI (class IIa, evidence level B). For patients with HIT, it is recommended that

bivalirudin or argatroban be used to replace UFH (class I, evidence level B).[1]

Low-Molecular-Weight Heparin

Pharmacology

The low-molecular-weight heparins (LMWHs) are heterogeneous mixtures of polysaccharide chains with a mean molecular weight of approximately 5000 daltons. The LMWHs are derived by enzymatic or chemical depolymerization of the larger polysaccharide chains found in UFH. A LMWH binds to antithrombin, accelerating its interaction with thrombin (factor IIa) and factor Xa. Compared with UFH, which has an antifactor Xa:antifactor IIa activity ratio of 1:1, LMWH confers greater inhibition of factor Xa (antifactor Xa:antifactor IIa ratios ranging from 2.6:1 to 3.7:1), thus exerting its principal anticoagulant effects "higher up" in the coagulation cascade.[13, 82]

When administered subcutaneously, LMWH is almost completely absorbed. The half-life of LMWH is 2–4 hours after intravenous injection and 3–6 hours after subcutaneous injection.[82] Renal excretion plays a greater role in the clearance of LMWH compared with UFH, and increased anticoagulant activity is observed in patients with severe renal impairment (creatinine clearance < 30–40 ml/min) who are treated with LMWH, particularly after multiple subcutaneously administered doses.[83, 84]

Clinical Studies

Most studies of LMWH during PCI have been performed with enoxaparin (Lovenox; sanofi-aventis, Bridgewater, NJ). Studies of enoxaparin in patients undergoing PCI can be categorized into those studies that focused on enoxaparin administered intravenously at the time of PCI, and those that focused on patients who had previously received subcutaneously administered enoxaparin for non–ST-segment elevation ACS and were then transitioned to PCI.

Intravenous Enoxaparin Administered at Time of Procedure

Three moderately sized observational studies were performed in which patients received intravenous enoxaparin 0.5–1.0 mg/kg at the time of PCI. In the National Investigators Collaborating on Enoxaparin (NICE-1) study, 828 patients were treated with enoxaparin 1.0 mg/kg intravenously; in the NICE-4 study, 818 patients were treated with enoxaparin 0.75 mg/kg intravenously and the glycoprotein IIb-IIIa inhibitor abciximab.[85] In another study, 242 patients were treated with enoxaparin 0.5 mg/kg intravenously; 26% of patients also received the glycoprotein IIb-IIIa inhibitor eptifibatide.[86] In the latter study, 97.5% of patients achieved a peak antifactor Xa level greater than 0.5 IU/ml. In all three studies, the rates of major ischemic complications (2.5–7.9%) and major bleeding (0.4–1.1%) were relatively low.[85, 86]

In the Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin (CRUISE) trial, 261 patients undergoing PCI were treated with the glycoprotein IIb-IIIa inhibitor eptifibatide and then randomly assigned to receive enoxaparin 0.75 mg/kg intravenously or UFH.[87] Major ischemic and bleeding compli-cations with the two antithrombin therapies were similar. In the more recent Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients (STEEPLE) study, 3528 patients undergoing elective PCI were randomly assigned to treatment with enoxaparin 0.5 mg intravenously or 0.75 mg intravenously, or intravenous UFH.[88] The 0.5-mg/kg arm was halted shortly before the end of the study due to a slight increase in mortality. Preliminary results of the study found comparable rates of ischemic compli-cations but lower bleeding rates with both enoxaparin regimens, and no significant differ-ence was noted in mortality rates among the three study arms. The results of the PROTECT-TIMI-30 study,[77] in which patients were randomly assigned to treatment with heparin (UFH or enoxaparin 0.5 mg/kg) plus glycoprotein IIb-IIIa inhibitor therapy, or to bivalirudin and provisional glycoprotein IIb-IIIa inhibitor therapy, have been described previously in this article.

Subcutaneous Enoxaparin Administered Before Procedure

Several prospective observational studies examined outcomes in patients who received subcutaneous enoxaparin therapy, with or without glycoprotein IIb-IIIa inhibitors, for the treatment of non–ST-segment elevation ACS, and then underwent PCI. In these studies, by protocol, patients were to receive their scheduled enoxaparin dose before PCI (i.e., the dose before going to the catheterization laboratory was not held). The rates of death or myocardial

infarction (3.0–5.1%) and of non–CABG-related major bleeding (0.8–1.9%) at 30 days in these studies were relatively low.[89, 90] In the Pharmacokinetic Study of Enoxaparin in Patients Undergoing Percutaneous Coronary Intervention (PEPCI) study, the authors demonstrated that in patients who had received previous subcutaneous enoxaparin treatment and then were to undergo PCI 8–12 hours after the last dose, the administration of a 0.3-mg/kg intravenous "booster dose" immediately before PCI resulted in what were considered to be therapeutic range antifactor Xa levels in 96% of patients.[91] Thereafter, in most subsequent trials evaluating subcutaneous enoxaparin in patients undergoing PCI, if the last subcutaneous dose of enoxaparin was administered 8–12 hours before PCI, a supplemental dose of 0.3 mg/kg of intravenous enoxaparin was administered.

In the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb-IIIa Inhibitors (SYNERGY) trial, 10,027 patients with non–ST-segment elevation ACS were randomly assigned to treatment with subcutaneously administered enoxaparin or UFH.[92] In the 47% of study patients who underwent PCI for clinical indications, untoward outcomes (unsuccessful PCI, abrupt vessel closure, emergency CABG) occurred at similar rates between those treated with enoxaparin and those treated with UFH. Major bleeding appeared to be increased in patients who were assigned to and treated with enoxaparin but who then crossed over to receive UFH at the time of randomization or later in the study. Thus, it appears prudent that patients who are treated with subcutaneously administered enoxaparin should not be administered supplemental UFH within 12 hours of the last subcutaneous enoxaparin dose. Outcomes at 6-month and 1-year follow-up in the SYNERGY trial demonstrated comparable rates of major ischemic events between those assigned to UFH and those assigned to enoxaparin.[93]

No major studies have examined the use of intravenously administered enoxaparin in patients with ST-segment elevation myocardial infarction who are to undergo primary PCI.

Utilization Guidelines

Currently, no intravenous dosage regimen for enoxaparin has been approved by the FDA. However, it is recognized that some practitioners do choose to use intravenous enoxaparin during PCI. If intravenous enoxaparin is to be used during PCI for patients who are not receiving antithrombin therapy, it may be reasonable to treat those not receiving glycoprotein IIb-IIIa therapy with an intravenous dose of 0.5–1.0 mg/kg and those receiving glycoprotein IIb-IIIa therapy with an intravenous dose of 0.5–0.75 mg/kg. Note, however, that these intravenous dosing guidelines are not made or recommended in the ACC-AHA-SCAI guidelines but are merely provided as a reference point for pharmacists and health care professionals in case interventional cardiologists at their institution choose to use intravenously administered enoxaparin during PCI.

In patients who have received at least two doses of subcutaneous enoxaparin therapy for non–ST-segment elevation ACS, no additional antithrombin therapy should be administered if the last subcutaneous enoxaparin dose was administered 0–8 hours before PCI. In those undergoing PCI 8–12 hours after the last subcutaneous dose was administered, an additional 0.3 mg/kg should be administered intravenously before PCI (whether or not the patient is to be treated with a glycoprotein IIb-IIIa inhibitor).[94–96] As LMWHs have only modest effect on the ACT, the ACT should not be used to guide anticoagulation management. As with UFH therapy during PCI, no further LMWH should generally be administered after PCI. In patients with a history of HIT, LMWH therapy should not be used because of the potential of cross-reactivity between LMWH preparations and UFH.[97]

In patients with severe renal insufficiency (creatinine clearance 10–30 ml/min) who are receiving multiple subcutaneous doses of enoxaparin, the dosage should be adjusted. The FDA-approved regimen is 1 mg subcutaneously every 24 hours. A different dosage regimen has been proposed but has not been clinically tested.[98] Intravenously administered enoxaparin has not been adequately studied in patients with severe or end-stage renal disease who are receiving renal replacement therapy and are to undergo PCI. No recommendations can be made as to whether the dosage should be adjusted, or enoxaparin therapy avoided, in such patients.

The ACC-AHA-SCAI guidelines state that LMWH is a reasonable alternative to UFH in patients with unstable angina or non–ST-segment elevation myocardial infarction who are undergoing PCI (class IIa, evidence level B) and may be considered as an alternative to UFH in patients with ST-segment elevation myocardial

infarction who are undergoing PCI (class IIb, evidence level B),[1] although, as noted above, specific recommendations regarding intravenously administered enoxaparin are not made.

Conclusion

Newer antiplatelet and antithrombin therapies have expanded the pharmacotherapeutic options available for the treatment of patients undergoing PCI. Studies conducted during the past decade have increased our understanding of how to most appropriately administer and use these agents. Given the novel nature of these agents and the nuances of therapy, the pharmacist and other health care professionals should play an integral role in collaboration with interventional cardiologists in hospital protocol development, determination of appropriate agent selection, assessment of patient renal function and hematologic status, dosing, and monitoring for adverse effects. The ACC-AHA-SCAI guidelines for PCI may be used to help guide antiplatelet and antithrombin therapeutic decisions; refinements of these guidelines may be expected as new data emerge.

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Appendix 1. Author Disclosures

Writing Group Member	Employment	Research Grants	Other Research Support
Glenn N. Levine, M.D.	Baylor College of Medicine	None	None
Peter B. Berger, M.D.	Geisinger Clinic	sanofi-aventis, Lilly, Sankyo, Datascope, Cordis/Johnson & Johnson, The Medicines Company, Boston Scientific, Medtronic	Boehringer Ingelheim, Conor, Cardiokinetix, Guilford
David J. Cohen, M.D.	Mid-America Heart Institute, Saint-Luke's Hospital	sanofi-aventis,[a] The Medicines Company,[a] Schering-Plough, Inc.,[a] Eli Lilly	None
Andrew O. Maree, M.B., B.Ch.	Harvard Medical School, Massachusetts General Hospital	Boehringer Ingelheim,[a] The Medicines Company,[a] Accumetrics[a]	None
Kenneth Rosenfield, M.D.	Massachusetts General Hospital	None	None
Sarah A. Spinler, Pharm.D., FCCP	University of the Sciences in Philadelphia	None	None
Barbara S. Wiggins, Pharm.D.	University of Virginia Health System	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the disclosure questionnaire that all members of the writing group are required to complete and submit. A relationship is considered to be significant if the person receives $10,000 or more during any 12-month period, or 5% or more of the person's gross income; or the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be modest if it is less than significant (using the above definition).
[a]Significant.
[b]Modest.

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Appendix 1. (continued)

Speakers Bureau	Honoraria	Ownership Interest	Consultant/Advisory Board
sanofi-aventis, Millenium/Schering-Plough, The Medicines Company	None	None	sanofi-aventis, Millenium/Schering-Plough, The Medicines Company
BMS, sanofi-aventis, Arginox, Schering-Plough	None	Lumen, Inc	Cordis/Johnson & Johnson, Boston Scientific, Genentech and Guilford
None	None	None	None
None	None	None	None
None	None	None	The Medicines Company,[b] Schering-Plough[b]
Schering, sanofi-aventis Bristol-Myers Squibb	None	None	sanofi-aventis
None	None	None	None

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