Clopidogrel in the Management of Ischemic Heart Disease

Erdal Cavusoglu, MD,†‡ Judy Cheng, PharmD,§ Rajat Bhatt, MD,* Prabhakara B. Kunamneni, MD,* Jonathan D. Marmur, MD,‡ and Calvin Eng, MD*†*

Abstract: Ischemic heart disease (IHD) represents a pathophysiologic continuum consisting of stable angina, unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. Patients who develop a change in their usual stable pattern of ischemia are classified as having an acute coronary syndrome, which includes patients with unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. Such progression from a stable to an unstable state is believed to result from disruption of an atherosclerotic plaque with subsequent platelet aggregation and thrombus formation. This, in turn, leads to the clinical manifestations of unstable angina, MI or death. Because platelets play a central role in the thrombotic complications of atherosclerosis, antiplatelet agents have been the cornerstone of the therapy for IHD. Aspirin has been the traditional antiplatelet agent, and remains the mainstay of treatment for all forms of IHD. However, aspirin is a weak antiplatelet agent and is often poorly tolerated by many patients. Clopidogrel is a new antiplatelet agent of the thienopyridine class. Clopidogrel, when used alone, and especially in combination with aspirin, has been shown to improve outcomes in patients with IHD across a variety of syndromes. However, combination therapy with aspirin and clopidogrel has been associated with an increased risk of bleeding. Therefore, despite improved outcomes, further studies are required to determine the optimal duration and dosage regimen of such combination therapy to maximize its risk-benefit ratio.

From the *Department of Medicine, Bronx VA Medical Center, Bronx, NY; §Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University and Mount Sinai Medical Center, New York, NY; †Department of Medicine, Mount Sinai School of Medicine, New York, NY; ‡Department of Medicine, Division of Cardiology, SUNY Health Science Center at Brooklyn, NY.

Reprints: Erdal Cavusoglu, MD, Division of Cardiology, Bronx VA Medical Center, 130 West Kingsbridge Road, Bronx, NY 10468. ECavusoglu@aol.com.

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Ischemic heart disease (IHD) continues to be the leading cause of morbidity and mortality in the United States.[1–3] IHD represents a pathophysiologic continuum consisting of stable angina, unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction. The subgroup of IHD patients who become unstable by developing a change in their usual pattern of angina (ie, patients with unstable angina, non-ST-segment elevation myocardial infarction and ST-elevation myocardial infarction) are classified as having an acute coronary syndrome (ACS).[2] Although it was traditionally believed that progressive narrowing and subsequent occlusion of the coronary artery at the site of atherosclerotic plaque was the cause of ACS, more recent studies examining the progression of stable atherosclerosis to ACS have focused on the interaction of blood elements with the atherosclerotic plaque itself. Indeed, the severity of pre-existing occlusion of the coronary artery is no longer felt to be the major risk factor for the development of ACS.[4] Acute plaque rupture leading to platelet aggregation and thrombus formation can lead to sudden critical occlusion of the coronary arteries, resulting in myocardial infarction (MI), unstable angina, and sudden death.[5,6] Because of this, many of the recent therapies for ACS have focused on the stabilization of the unstable plaque and prevention of plaque rupture, in addition to the traditional treatments aimed at ameliorating the consequences of coronary artery occlusion. Because platelets and thrombus have been identified as playing central roles in the pathogenesis of ACS, new classes of antiplatelet and antithrombotic agents have been introduced and studied for the management of ACS. This article reviews the role of clopidogrel, an adenosine diphosphate-inhibiting antiplatelet agent, in the management of IHD (Table 1).

PATHOGENESIS OF PLATELET AGGREGATION

Platelets are integrally involved in the thrombotic complications of atherosclerosis. There are 3 processes which platelets must undergo in order for a platelet plug to form at

TABLE 1. Important Clinical Trials of Clopidogrel Used in Management of Ischemic Heart Disease

Trial	Patients	Regimen	Primary Endpoints	Primary Outcome, (%)		Total Bleeding, (%)	
				Treatment	Control	Treatment	Control
For medical management							
CAPRIE[22]	19185 patients with ischemic stroke, MI, PVD	Clopidogrel 75 mg daily vs aspirin 325 mg daily for 1 to 3 yr	Time to first new fatal and nonfatal ischemic stroke, MI and other vascular death	9.78*	10.64	0.85	1.19
CURE[23]	12562 patients with ACS	Clopidogrel 300 mg loading dose followed by 75 mg daily vs placebo (all received aspirin) for an average of 9 mo	Death from cardiovascular causes, nonfatal MI or stroke	9.3*	11.4	8.5*	5
For PCI							
Muller et al[28]	700 patients receiving coronary stents	Clopidogrel 75 mg daily or ticlopidine 250 mg twice daily for 4 wk (all received aspirin 100 mg daily)	Death from cardiac causes urgent target vessel revascularization, angiographically evident stent occlusion or nonfatal myocardial infarction within 30 days	3.1	1.7	NA	NA
CLASSICS[29]	1020 patients receiving coronary stents	Clopidogrel 300 mg loading, then 75 mg daily vs Clopidogrel 75 mg daily vs ticlopidine 250 mg twice daily for 1 mo	Major bleeding complications, hematologic side effects or drug discontinuation due to noncardiac adverse effects	2.9* (with loading dose) 6.3* (without loading dose)	9.1	1.5 (with loading dose) 1.2 (without loading dose)	1.2
PCI-CURE[25]	2658 patients from CURE trial	Same as CURE	MI, cardiovascular death and urgent revascularization 30 days after PCI	4.6*	6.4	11	9
WRIST-PLUS[40]	120 patients with in-stent restenosis	Clopidogrel 300 mg loading and 75 mg daily for 6 mo vs 1 mo from historical control (all received aspirin)	Late stent thrombosis rate and the composite clinical events of death, MI, and target lesion revascularization at 6 mo	23.3*	32	NA	NA
WRIST 12[43]	120 patients with in-stent restenosis	Clopidogrel 300 mg loading and 75 mg daily for 12 mo vs 6 mo from historical control(WRIST-PLUS)	Late stent thrombosis rate and the composite clinical events of death, MI, and target lesion revascularization at 15 mo	29*	36	5	5

ACS, acute coronary syndrome; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
* $P < 0.05$ compared to control group.

the site of atherosclerotic plaque disruption: platelet adhesion, activation and aggregation. After atherosclerotic plaque disruption, the subendothelial protein matrix becomes exposed to circulating platelets and other coagulation proteins. The protein matrix contains several platelet adhesive proteins, such as von Willebrand factor, collagen, and thrombospondin, which promote platelet adhesion to the endothelium.[7] After the initial adhesive process, platelets become activated by several mediators, including thromboxane A2, thrombin, epinephrine, collagen, adenosine diphosphate (ADP), and serotonin.[8] Platelet activation is followed by changes in cell shape, induction of platelet coagulant activity, calcium mobilization, and platelet degranulation.[9] The final process of platelet aggregation involves the binding of circulating fibrinogen to the glycoprotein IIb/IIIa receptor on the platelet surface, leading to cross-linking of adjacent platelets.[10] von Willebrand factor may also play a role in cross-linking platelets by binding to the glycoprotein IIb/IIIa receptor under conditions of high-shear stress.[10]

CLINICAL PHARMACOLOGY OF CLOPIDOGREL

Mechanism of Action

Clopidogrel is a thienopyridine antiplatelet agent. Ticlopidine was the first agent developed in this class (Fig. 1). However, the use of ticlopidine has rapidly fallen out of favor because of the high incidence of adverse side effects, including neutropenia, with the subsequent requirement for frequent monitoring. Clopidogrel has been shown to be associated with fewer side effects and is better tolerated than ticlopidine. Both ticlopidine and clopidogrel selectively inhibit ADP-induced platelet aggregation by directly inhibiting the binding of ADP to its receptor on the platelet, thereby affecting ADP-dependent activation of the glycoprotein IIb/IIIa complex.[11] Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation (Fig. 2). Clopidogrel irreversibly modifies the platelet ADP receptor, and platelets which are exposed to clopidogrel are inhibited for the remainder of their lifespan.[11]

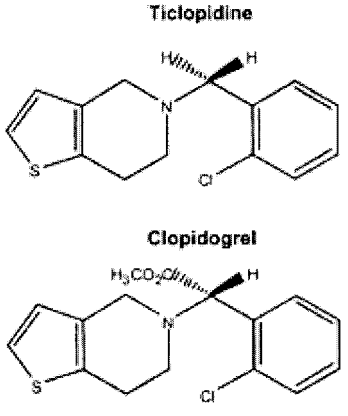

FIGURE 1. Structure of ticlopidine and clopidogrel.

Pharmacokinetics and Pharmacodynamics

Clopidogrel is converted to its active form via metabolism by the hepatic cytochrome P450-1A and 3A enzyme systems. Its bioavailability is unaffected by food. Clopidogrel is 98% protein bound and has an elimination half-life of approximately 8 hours.[11] The active metabolite of clopidogrel is highly reactive and binds rapidly and irreversibly to platelets. In healthy volunteers and in patients with atherosclerosis, dose-dependent inhibition of platelet aggregation can be seen 2 hours after a single oral dose of up to 400 mg, with maximal inhibition occurring within 5 hours and persisting for 24 hours.[12] After repeated doses of 75 mg/d, steady-state anti-aggregating activity (defined as 40-60% platelet inhibition) and bleeding time prolongation ($\sim$1.5 to 2 times baseline) is achieved in 3 to 7 days.[13] After discontinuation of clopidogrel, recovery of normal platelet function occurs over a period of about 5 days, a rate consistent with platelet turnover.[12,13]

USE OF CLOPIDOGREL IN IHD

The use of aspirin is the most important and most effective therapy in the management of patients with atherosclerotic heart disease. Although evidence for a survival benefit of aspirin in subjects with preclinical coronary artery disease (ie, primary prevention) is inconclusive, aspirin has been shown to reduce the risk of a first nonfatal MI in 2 large studies.[14] Furthermore, aspirin has been consistently shown to prevent MI and stroke in patients with established atherosclerotic vascular disease (ie, secondary prevention) across a variety of clinical syndromes, ranging from chronic stable angina[15] to acute ST-segment elevation MI.[16]

Aspirin inhibits platelet aggregation by inhibiting the activity of cyclooxygenase in cells. Inactivation of the platelet enzyme cyclooxygenase results in decreased production of thromboxane A2, which causes both vasoconstriction as well as platelet aggregation. The importance of platelet inhibition in acute MI was first demonstrated in the Second International Study of Infarct Survival (ISIS-2) trial. In this large trial, aspirin reduced mortality in patients with MI by 23%.[16] This effect was sustained long term at 10-year follow-up.[17] In patients with unstable angina, aspirin has been shown to lead to a reduction in the incidence of death and MI by 31-50%.[18–20] Because aspirin is inexpensive, it has become an extremely cost-effective life-saving therapy. As a result of both cost-effectiveness as well as proven efficacy, aspirin is the mainstay of ACS therapy. The 2002 AHA/ACC guidelines[21] for unstable angina and non-ST segment elevation MI have recommended that aspirin be initiated promptly in patients presenting with ACS. In such patients, aspirin re-

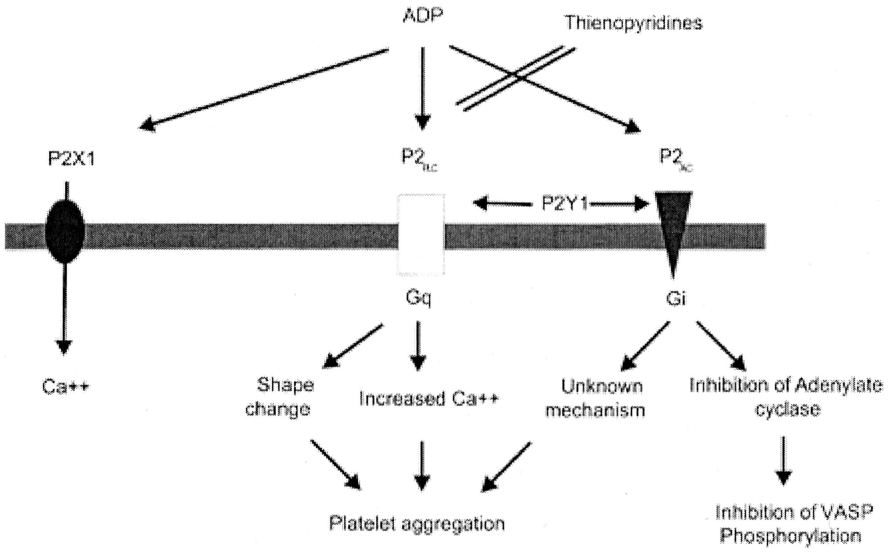

FIGURE 2. Clopidogrel mechanism of action. Three separate platelet ADP receptors have been proposed: a P2X1 ligand-gated ion-channel receptor; a $P2_{PLC}$ linked to phospholipase C, platelet shape change, and aggregation; and a $P2_{AC}$ linked to inhibition of adenylate cyclase and platelet aggregation. Reproduced with permission from Lippincott, Williams & Wilkins.[8]

mains the first-line antiplatelet agent and should be continued indefinitely.

Despite its established benefit in patients with coronary artery disease, aspirin has numerous limitations. It is a relatively weak antiplatelet agent and does not inhibit platelet aggregation induced by thromboxane A2-independent pathways (eg, via ADP or collagen stimulation). Aspirin also has no effect on thrombin, which is believed to play a major role in platelet activation in the acute coronary syndromes. Furthermore, many patients are allergic to or intolerant of aspirin, most often because of gastrointestinal upset or hypersensitivity. In such patients, the guidelines recommend that clopidogrel replace aspirin as the antiplatelet agent of choice. In addition, in patients with non-ST segment MI in whom an early noninvasive approach is planned, the guidelines recommend that clopidogrel be used together with aspirin for at least 1 month and possibly even up to 9 months.

These recommendations for the use of clopidogrel were made based upon 2 important clinical studies, the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) and the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trials.[22,23] In CAPRIE, clopidogrel 75 mg/d was compared with aspirin 325 mg/d in 19,185 patients with clinical evidence of atherosclerotic disease (ischemic stroke, MI, symptomatic peripheral arterial disease) in a double-blind and randomized fashion.[22] The primary end point of the trial was the time to first occurrence of a new ischemic stroke (fatal or nonfatal), a new MI (fatal or nonfatal), or other vascular death. Clopidogrel was associated with a lower incidence of this primary outcome (Fig. 3). The overall risk reduction was 8.7%, (clopidogrel 9.78% vs. aspirin 10.64%; $P = 0.045$). Although the study was not powered to evaluate the relative benefit of clopidogrel in individual patient subgroups, the benefit appeared to be greatest in those patients with a history of peripheral vascular disease. In addition, approximately one-third of the patients in this trial had experienced MI within the previous 35 days. In this subgroup of previous MI patients, the rate of the primary outcome (ischemic stroke, MI, vascular death) per year over an approximately 2-year period was similar in both

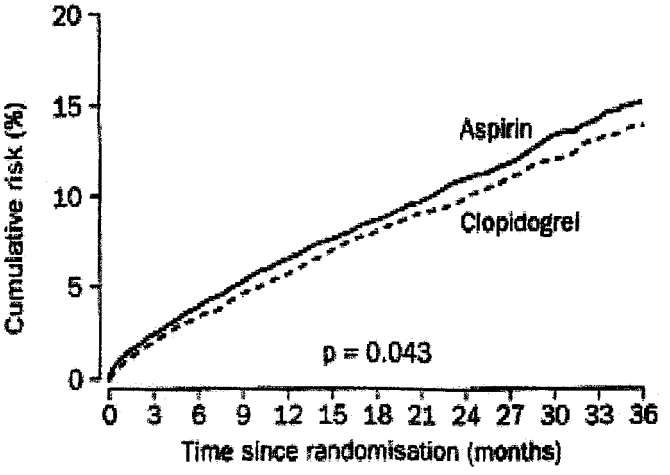

FIGURE 3. The CAPRIE trial. Cumulative risk of ischemic stroke, myocardial infarction, or vascular death. Reproduced with permission from Elsevier Science.[22]

the clopidogrel and aspirin groups (5.03% vs. 4.84%; $P = 0.66$). This would suggest that chronic clopidogrel may be a reasonable substitute for aspirin in this subgroup of patients who may be unable to take chronic aspirin therapy.

The CURE trial was designed to compare the efficacy and safety of the early and long-term use of clopidogrel plus aspirin to that of aspirin alone in patients presenting with unstable angina and non-ST segment elevation MI.[23] Patients were enrolled only from centers favoring a conservative approach to managing acute coronary syndromes (ie, centers with a low rate of angiography and revascularization). In this study, there were 12,562 patients enrolled. Patients were randomized to clopidogrel or matching placebo with a 300 mg loading dose, followed by a 75 mg daily dose for the duration of follow-up (average 9 months). All patients received aspirin in a dose ranging from 75 mg to 325 mg daily at the discretion of the treating physician. The primary outcome of the trial was a composite of death from cardiovascular causes, nonfatal MI or stroke. This trial demonstrated that clopidogrel, when used in addition to aspirin, reduced the incidence of the primary outcome {relative risk for clopidogrel 0.8 (95% confidence interval [CI], 0.72-0.9; $P < 0.001$)}. Furthermore, the beneficial effect was incremental and independent of other acute or long-term therapies (eg, angiotensin-converting enzyme inhibitors, lipid-lowering agents, glycoprotein IIb/IIIa inhibitors) and coronary interventions. The benefit of clopidogrel was seen early (within a few hours of initiating treatment) and persisted for the duration of follow-up. However, patients receiving clopidogrel and aspirin did have a higher risk of both major bleeding (3.7% vs. 2.7%; $P = 0.001$) and minor bleeding (5.1% vs. 2.4%; $P < 0.001$), although there was no increase in the incidence of life-threatening bleeding or hemorrhagic stroke (2.1% vs. 1.8%; $P = 0.13$). Of note, major bleeding risk appeared to be related to the dose of aspirin used.[24] Major bleeding rates for clopidogrel and aspirin were 2.6% when the aspirin dose was <100 mg daily, 3.5% when the aspirin dose was 100-200 mg daily, and 4.9% when the aspirin dose was >200 mg daily. The major bleeding rates for placebo and aspirin were 2% when the aspirin dose was <100 mg daily, 2.3% when the dose was 100-200 mg daily, and 4% when the dose was >200 mg daily.[24] No such analysis was made with regards to clinical efficacy. With respect to bleeding risk, there was also a concerning trend toward higher postoperative bleeding in patients who received clopidogrel within 5 days of undergoing CABG (9.6% vs. 6.3% in the placebo group; relative risk 1.53; $P = 0.06$). No such trend was seen if clopidogrel was withheld for at least 5 days preoperatively. Thus, based on the CURE trial, it seems that there is a benefit of combination therapy in this patient population, but that this benefit comes at the expense of an increased risk of bleeding, particularly when a full dose of aspirin is used.

In a substudy of the CURE trial, the PCI-CURE study, the benefits of administering clopidogrel prior to percutaneous coronary intervention (PCI) were investigated.[25] A total of 2658 patients who participated in the CURE trial underwent PCI at the discretion of their physician and constituted the patient population for this subanalysis. These patients underwent PCI at a median of 10 days after enrollment. The primary outcome of the study was the composite of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI. In this CURE substudy, the use of clopidogrel was associated with a reduction in this primary outcome (4.5 vs. 6.4%, relative risk 0.70, $P = 0.03$). This benefit was seen as early as 2 days after PCI, with continuing benefit until 30 days. It is important to note that because most patients received open-label thienopyridine after PCI ($>80\%$ in both groups), it is likely that the early postprocedural benefit seen was mainly due to the effects of clopidogrel pretreatment. The benefit seen within the first 30 days was maintained in the months thereafter when double-blind study medication was continued long-term. Fewer patients received glycoprotein IIb/IIIa inhibitor in the clopidogrel group than in the placebo group (20.9% vs. 26.6%, relative risk 0.70, $P = 0.001$). In addition, the need for a second revascularization was also lower in the clopidogrel group than in the placebo group (17.1% vs. 14.2%, $P < 0.05$). These benefits were seen with a nonsignificant excess in major, but not life-threatening, bleeding with clopidogrel compared with placebo.

Despite the encouraging results of CURE, there remain questions regarding the widespread applicability of these findings to all patients with unstable angina and non-ST-segment elevation myocardial infarction. A recent pharmacoeconomic analysis examined the cost-effectiveness of using aspirin, clopidogrel or both for secondary prevention of coronary artery disease.[26] By using a computer simulation model of the U.S. population to estimate the incremental cost effectiveness (in dollars per quality-adjusted years of life gained) in patients over 35 years of age with coronary disease from 2003 to 2027, this analysis found the incremental cost effectiveness of routine clopidogrel use (either alone or in combination with aspirin) to be unattractive unless its use was restricted to patients who are allergic to or intolerant of aspirin.[26] Therefore, based on this analysis, clopidogrel should be reserved for patients who are ineligible for aspirin therapy. Besides pharmacoeconomic considerations, another very important factor limiting the application of the CURE data to the "real world" is the necessity of withholding clopidogrel therapy for a minimum of 5 days prior to surgical revascularization to prevent excessive operative bleeding. In daily practice, when patients present to a hospital with ACS, it is usually not possible to determine the need for subsequent bypass surgery prior to the performance of coronary angiography. If coronary bypass surgery is deemed necessary, the administration of clopidogrel upon presentation to the emer-

gency room would lead to an unnecessary and potentially hazardous delay of this procedure. Finally, the utilization of the glycoprotein IIb/IIIa inhibitors in the CURE trial was low (5.9% in the clopidogrel group and 7.2% in the placebo group) compared with contemporary U.S. practice. Thus, it is unknown if the same benefit with the use of clopidogrel would have been seen if a greater proportion of patients had been on glycoprotein IIb/IIIa inhibitors.

USE OF CLOPIDOGREL IN PERCUTANEOUS CORONARY INTERVENTIONS

Intracoronary stenting is performed in the majority of PCIs today, including those associated with acute MI. Antiplatelet therapy plays a central role in PCI, because it has been shown to decrease the incidence of subacute stent thrombosis.[27] The initial studies of antiplatelet therapy in this setting were done using ticlopidine and aspirin. However, given its requirement for hematological monitoring and adverse side-effect profile, ticlopidine has been replaced by clopidogrel at many institutions in patients receiving intracoronary stents. This change occurred even before the results of the controlled trials on the use of clopidogrel after stenting became available. The latest AHA/ACC guidelines recommend that, for patients in whom a stent has been placed, aspirin plus clopidogrel therapy be used in combination for 1 month after the procedure and possibly even up to 9 months in those who are not at high risk of bleeding.[21]

The first prospective, randomized trial comparing ticlopidine and clopidogrel in patients undergoing intracoronary stent implantation was performed by Muller et al.[28] Four weeks of clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily were administered to 700 patients receiving intracoronary stents. All patients received concurrent daily aspirin at a dose of 100 mg. In this study, clopidogrel reduced the frequency of adverse effects leading to drug discontinuation (2.0% vs. 5.8%; $P = 0.01$) and was associated with a nonsignificant trend toward an increase in thrombotic stent occlusion (2.0% vs. 0.6%; $P = 1.0$). Leukopenia or thrombocytopenia occurred in 3 patients (0.9%) taking ticlopidine and in no patients taking clopidogrel.

The largest randomized comparative trial of clopidogrel and ticlopidine to date, CLASSICS (the Clopidogrel Aspirin Stent International Cooperative Study),[29] compared 2 regimens of clopidogrel, 75 mg once daily or a 300-mg loading dose followed by 75 mg once daily, to ticlopidine 250 mg twice daily for one month in 1020 patients. The use of glycoprotein IIb/IIIa receptor inhibitors was not permitted in this trial. The primary end point—a composite of bleeding, hematologic adverse effects, or drug discontinuation caused by noncardiac adverse effects—occurred in 50% fewer patients receiving clopidogrel (4.6% vs. 9.1%; $P = 0.005$) and was lowest in the group randomized to receive the clopidogrel loading dose (2.9% with loading dose vs. 6.3% but with no loading dose; $P = 0.043$). There were no occurrences of neutropenia in clopidogrel-treated patients, but one case (0.3%) in a patient receiving ticlopidine. Four patients (0.6%) receiving clopidogrel experienced thrombocytopenia compared with none in those receiving ticlopidine. The rates of major adverse cardiac events were similar between the 2 groups (0.9% with ticlopidine, 1.5% with clopidogrel 75 mg/d, 1.2% with clopidogrel loading dose; P = NS), a finding that was not unexpected because the study was not powered to detect a difference in efficacy.

A recent meta-analysis was performed to determine whether clopidogrel is at least as efficacious as ticlopidine when used after stenting.[30] All published data from trials and registries that compared clopidogrel with ticlopidine in patients receiving coronary stents were pooled and analyzed. The rate of 30-day major adverse cardiac events, as defined in each trial, was used as the primary end point. Data from a total of 13,955 patients were available from these trials and registries. The pooled rate of major adverse cardiac events was 2.10% in the clopidogrel group and 4.04% in the ticlopidine group ($P = 0.001$) After adjustment for heterogeneity, the odds ratio of having an ischemic event with clopidogrel, as compared with ticlopidine, was 0.72 (95% CI, 0.59 to 0.89; $P = 0.002$). Mortality was also found to be lower in the clopidogrel group compared with the ticlopidine group—0.48% versus 1.09% (odds ratio 0.55; 95% CI, 0.37 to 0.82; $P = 0.003$). These findings may be caused by the more rapid onset of an antiplatelet effect seen with the loading dose of clopidogrel used in most of these studies. Therefore, based on all available evidence from randomized clinical trials and registries, and in view of its better side effect profile, clopidogrel plus aspirin has replaced ticlopidine plus aspirin as the standard antiplatelet regimen after stent deployment.

Intracoronary stenting has dramatically improved upon the procedural success and restenosis rates seen with balloon angioplasty alone.[31] Despite these improvements, however, restenosis after intracoronary stenting still occurs and continues to be a significant problem in interventional cardiology.[32] Treatment of in-stent restenosis with vascular brachytherapy has become the standard of care based upon several well conducted and randomized studies of intracoronary radiation therapy. These trials used both γ- and β-emitters and demonstrated a reduction in restenosis as well as the need for both target-lesion revascularization and target-vessel revascularization compared with control.[33–36] However, early on in the brachytherapy experience, it was observed that the overall rate of major cardiovascular events at 6-9 months remained >20%. These events included late total occlusion (defined as occurring >30 days after intervention and radiation) and repeat target vascular revascularization. The reported rates of these events ranged from 6% to 15% and from 20% to 30%, respectively.[37–39] It became apparent that prolonged dual antiplatelet therapy and the avoidance of new stents at the

time of brachytherapy were associated with a reduction in the incidence of these adverse events, which were believed to be caused by late stent thrombosis. The Washington Radiation for In-Stent Restenosis Trial (WRIST) PLUS study, which involved using 6 months of treatment with clopidogrel and aspirin (instead of the usual one month in most other studies), was designed to examine the efficacy and safety of prolonged antiplatelet therapy for the prevention of late thrombosis.[40] A total of 120 consecutive patients with diffuse in-stent restenosis in native coronary arteries and vein grafts with lesions <80 mm who underwent PCI were enrolled. Additional stents were placed in 34 patients (28.3%). After the intervention, brachytherapy was performed using 192-iridium. Patients were discharged with clopidogrel and aspirin for 6 months and followed both angiographically and clinically. The late occlusion and thrombosis rates were compared with the γ-radiation-treated ($n = 125$) and the placebo-treated ($n = 126$) patients from the WRIST[41] and LONG WRIST[42] studies (which involved only 1 month of antiplatelet therapy). At 6 months, the group receiving prolonged antiplatelet therapy had total occlusion and late thrombosis rates of 5.8% and 2.5%, respectively. These rates were lower than those in the active γ-radiation group and similar to those in the placebo historical control group. There was also a trend towards a reduction in the incidence of major adverse coronary events compared with patients from the WRIST and LONG WRIST studies (23.3% in 6-month therapy group vs. 32.0% in the historic 1-month therapy group; $P = 0.13$). Therefore, in this trial, 6 months of clopidogrel and aspirin in patients with in-stent restenosis who were treated with γ-radiation was well tolerated and was associated with a reduction in the late thrombosis rate, compared with a similar cohort treated with only 1 month of clopidogrel and aspirin.

An even more recent study extended the time course of treatment with aspirin and clopidogrel postbrachytherapy to 12 months. The WRIST 12 study studied 120 patients with extensive in-stent restenosis who had been treated with ^{192}Ir brachytherapy, followed by 12 months of aspirin and clopidogrel after intervention.[43] The follow-up period for these patients was 15 months. The late occlusion and thrombosis rates were compared with patients from the WRIST-PLUS study. Major cardiac events at 15 months occurred in 25 patients (21%) in WRIST 12 compared with 43 patients (36%, $P = 0.01$) in WRIST PLUS. Furthermore, there was a reduction in target lesion revascularization (20% vs. 35%, $P = 0.009$) and target vessel revascularization (23% vs. 39%, $P = 0.005$) with 12 months of clopidogrel therapy. Despite the prolonged antiplatelet therapy, WRIST 12 patients had equivalent rates of transfusion (2.5% vs. 3.3%, $P = 0.70$) and femoral artery hematomas that required treatment (2.5% vs. 1.7%, $P = 0.65$) compared with WRIST PLUS patients during hospitalization. Based on this study, it seems that 12 months of clopidogrel is superior to 6 months in reducing overall major cardiac events and revascularization rates at 15 months for patients with in-stent restenosis treated with γ-radiation. Based on these findings, the authors of the WRIST 12 study have recommended at least 12 months of clopidogrel therapy for patients undergoing radiation therapy for in-stent restenosis. Larger prospective randomized controlled studies are needed to confirm these results and to define the most optimal duration of antiplatelet therapy.

Despite the efficacy of intracoronary radiation for the treatment of in-stent restenosis, the use of this technology for the treatment of de novo lesions has not had similar success. One new advance in this regard has been the development of drug-eluting stents.[44] In preliminary studies, such drug-eluting stents have been shown to substantially decrease the incidence of in-stent restenosis by virtue of their ability to decrease the development of neointimal hyperplasia.[44–47] Because of the suppression of neointimal hyperplasia, however, there have been concerns about the development of acute, subacute, or late thrombosis. As a result, most human studies have extended the use of dual antiplatelet therapy to at least 2 months.[46,47] Fortunately, either as a result of this prolonged regimen or because some reendothelialization presumably does occur, there has not been an increase in the incidence of stent thrombosis. It is expected that the first generation of drug-eluting stents will receive FDA approval shortly, and the final recommendations regarding the optimal dose and duration of antiplatelet therapy will be made at that time.

The WRIST-PLUS, WRIST 12 and the PCI-CURE studies have all suggested that aspirin and clopidogrel therapy may provide additional benefit in preventing late in-stent restenosis and cardiovascular events when used beyond one month. With ongoing technological advances in stent design, improved adjunctive pharmacological therapy, and greater use of brachytherapy, the ideal duration and dosage regimen of aspirin and clopidogrel after PCI continues to be defined. The recently published Clopidogrel for the Reduction of Events During Observation (CREDO) trial was designed to evaluate the benefit of long-term treatment with clopidogrel after PCI.[48] In addition, the study also sought to determine the benefit of a pre-procedural loading dose of clopidogrel. All patients received therapy with aspirin. The study randomized 2116 patients undergoing PCI between short- and long-term treatment with clopidogrel (28 days vs. 1 year, respectively) in addition to aspirin therapy. At 1 year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke. There was a nonsignificant increase in the risk of major bleeding in the clopidogrel group. In addition, clopidogrel pretreatment with a 300-mg loading dose between 3 and 24 hours prior to PCI did not significantly reduce the combined risk of death, MI or urgent target-vessel revascularization at 28 days. However, in a prespecified subgroup analysis, patients who re-

ceived clopidogrel at least 6 hours before PCI experienced a relative risk reduction of 38.6% for this end point, compared with no reduction with treatment less than 6 hours before PCI. It is anticipated that the results of the CREDO trial will lead to a change in the duration of the postprocedural antiplatelet regimen in patients undergoing PCI.

CONCLUSIONS

The pharmacological treatment of IHD is both complex and dynamic, and it continues to evolve. In addition to traditional anti-ischemic therapy, early treatment of ACS is increasingly focused on the appropriate management of the ruptured atheromatous coronary plaque, both pharmacologically as well as by means of a variety of revascularization techniques. New antiplatelet drugs and anticoagulants that are effective as either stand-alone therapy or as adjuncts to PCI are currently being investigated in different combinations with the goal of optimizing the risk-benefit ratio of these agents. For most patients with IHD, aspirin remains the antiplatelet agent of choice for secondary prevention. In this setting, clopidogrel has also been demonstrated to be at least as effective as aspirin. However, given its high cost, its use in secondary prevention should be restricted to those patients who cannot tolerate aspirin. When used in combination with aspirin in ACS patients not undergoing PCI, clopidogrel has also been shown to improve cardiovascular outcomes more significantly than aspirin alone. However, the risk of bleeding also remains higher with such combination therapy. The same combination, when used for 1 month after coronary stent placement, has also been demonstrated to reduce unfavorable cardiovascular outcomes. However, the recently published CREDO trial strongly supports the use of prolonged dual antiplatelet therapy in patients undergoing elective PCI, with improved outcomes at 1 year. Although rare, patients treated with clopidogrel need to be monitored carefully for the development of thrombocytopenia and thrombotic thrombocytopenic purpura (TTP). When clopidogrel is used in conjunction with aspirin, particularly full-dose aspirin, there is an increased incidence of bleeding. Thus, the risk-benefit ratio for such dual antiplatelet therapy must be carefully weighed in each individual patient.

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