ÇAĞRILI DERLEME
INVITED REVIEW

The Use of Clopidogrel in Patients with Coronary Artery Disease

Koroner Arter Hastalığında Klopidogrel'in Kullanımı

Erdal Çavuşoğlu, MD

Interventional Cardiology SUNY Downstate Medical Center, *Brooklyn, New York, USA*

Abstract

Coronary thrombosis plays a central role in the development, progression, and complications of atherosclerotic heart disease. As a result, pharmacologic manipulation of the hemostatic system has been the mainstay of treatment for coronary artery disease. Since platelets are the most important cellular element in the development of arterial thrombosis, many of the most effective therapies have involved the use of various antiplatelet agents. This article focuses on clopidogrel, an antiplatelet agent belonging to the class of drugs known as the thienopyridines, in the treatment of patients with coronary artery disease. *(Anadolu Kardiyol Derg 2004; 4: 63-72)*
Key words: Coronary artery disease, platelets, clopidogrel

Özet

Aterosklerotik kalp hastalığının gelişiminde, ilerlemesinde ve komplikasyonların oluşumunda koroner trombozisin önemli rolü vardır. Sonuç olarak, koroner arter hastalığı tedavisinin en önemli temelini hemostatik sisteme yönelik pharmakolojik manipülasyonlar olmuşturmaktadırlar. Platelet'ler arteriyel trombozisin gelişiminde önemli hücresel unsur oldukları için, bugünlerde en etkin tedaviler genellikle değişik antiplatelet ajanların kullanımını içermektedirler. Bu makale, tienopiridin sınıfı mensubu olarak bilinen ve bir antiplatelet ajan olan Klopidogrel'in koroner arter hastalığında kullanımı ile ilgili bilgileri toparlamaktadır. *(Anadolu Kardiyol Derg 2004; 4: 63-72)*
Anahtar Kelimeler: Koroner arter hastalığı, plateletler, klopidogrel

Introduction

Coronary artery disease is the leading cause of morbidity and mortality in the Western world. Coronary thrombosis plays a central role in the development, progression, and complications of atherosclerotic heart disease (1-3). As a result, pharmacological manipulation of the hemostatic system has been the mainstay of treatment for coronary artery disease (4). Since platelets are the most important cellular element in the development of arterial thrombosis, many of the most effective therapies have involved the use of various antiplatelet agents. This article focuses on clopidogrel, an antiplatelet agent belonging to the class of drugs known as the thienopyridines, in the treatment of patients with coronary artery disease.

Mechanism of Action and Pharmacology of the Thienopyridines

Clopidogrel and ticlopidine belong to the class of antiplatelet agents known as the thienopyridine ADP receptor antagonists. The thienopyridines prevent platelet aggregation by inhibiting the binding of ADP to one of its three known receptors on the platelet surface named the P2Y12 receptor (5). This in turn prevents ADP-mediated upregulation of the glycoprotein (Gp) IIb/IIIa receptor and subsequent amplification of platelet activation (4,6). In addition to ADP, the thienopyridines also inhibit platelet aggregation ex vivo induced by low concentrations of thrombin, collagen, and shear stress (7). Importantly, the thienopyridines do not have any effect on the cyclooxygenase pathway, indicating a distinct mechanism of action than aspirin. Clopidogrel differs structurally from ticlopidine by the presence of one additional carboxymethyl side group. Both agents are prodrugs and require conversion to an active metabolite by the hepatic cytochrome P450-1A enzyme system in the liver (8-10).

Both ticlopidine and clopidogrel inhibit platelet aggregation in a concentration-dependent manner (11). Following the administration of standard doses of ticlopidine (250 mg twice daily) maximal platelet

Correspondence for address: Erdal Cavusoglu, MD, Interventional Cardiology SUNY Downstate Medical Center, 450 Clarkson Avenue Box 1199, Brooklyn, NY 11203-2098, USA, ECavusoglu@aol.com

inhibition is seen within 4-7 days (12). In the case of clopidogrel, repeated administration of the standard daily dose of 75 mg per day leads to steady-state anti-aggregating activity in 3 to 7 days (13). The fastest responses have been demonstrated with the administration of a loading dose of clopidogrel. When administered as a loading dose of 300 mg, clopidogrel provides 80% platelet inhibition in 5 hours (14). Furthermore, recent data indicate that a 600 mg loading dose of clopidogrel results in a similar level of inhibition but within two hours (14-16).

Side Effects of the Thienopyridines

The most common side effects of the thienopyridines include skin rashes, diarrhea, and nausea. All of these side effects occur less frequently with clopidogrel than with ticlopidine. The most serious side effects of these drugs include thrombotic thrombocytopenic purpura (TTP) and neutropenia. Thrombotic thrombocytopenic purpura, which is fatal in more than one-fifth of cases, occurs at an estimated rate of 1/1600 to 1/5000 patients treated with ticlopidine (17). This side effect is seen much less frequently with clopidogrel, occurring at an estimated rate of 1/360,000 (18). The rate of severe neutropenia (defined as < 0.45/nl) is approximately 0.8% in patients treated with ticlopidine (19,20), compared with only 0.05% in those treated with clopidogrel (21). Given its more rapid onset of action and better safety profile, clopidogrel is now the preferred thienopyridine and has virtually replaced ticlopidine for almost all clinical indications.

Clinical Applications

The Limitations of Aspirin and the Concept of Dual Antiplatelet Therapy

For several decades, antiplatelet therapy has centered on the inhibition of the thromboxane pathway by aspirin. By inhibiting the synthesis of thromboxane, aspirin prevents platelet aggregation in response to agonists such as ADP and collagen. Aspirin is the mainstay of treatment for patients with atherosclerotic heart disease, having documented efficacy in reducing acute ischemic events. Indeed, there is overwhelming evidence supporting the benefit of aspirin in the treatment of patients across the entire spectrum of coronary artery disease (22-24). Furthermore, recent recommendations by the Antithrombotic Trialists, Collaboration have expanded the indica-

tions for the use of aspirin to populations such as those with diabetes, peripheral arterial disease, carotid stenosis, and end-stage renal disease requiring dialysis (25). Despite the wealth of data supporting its use, however, there remains a substantial cohort of patients who continue to have vascular events and thus display clinical "resistance" to aspirin (26). A recent analysis from the Cleveland Clinic Foundation correlated aspirin resistance with adverse clinical outcomes (27). While the precise mechanism(s) of this resistance remains to be elucidated, such patients may, at least in theory, derive particular benefit from dual pathway platelet inhibition. Experimental studies have demonstrated synergy between the thienopyridines and aspirin (28-30). Such experimental observations have laid the groundwork for the subsequent clinical studies examining the role of dual antiplatelet therapy in patients with ischemic heart disease.

The Use of Clopidogrel in Stable and Unstable Coronary Artery Disease

Because of the different and complementary mechanisms of action of aspirin and clopidogrel, important questions emerged regarding the relative efficacy and safety of the two agents, as well as that of their combination, in the treatment of patients with stable and unstable coronary artery disease (31). The first clinical trial to address the issue of the relative efficacy and safety of the two drugs was the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial (21). In this trial, clopidogrel 75 mg/day was compared with aspirin 325 mg/day in 19,185 patients with clinical evidence of atherosclerotic disease (ischemic stroke, , symptomatic peripheral arterial disease). The primary endpoint of the trial was the time to first occurrence of a new ischemic stroke, a new myocardial infarction (MI) (fatal or nonfatal), or other vascular death. At a mean follow-up of 1.9 years, clopidogrel was associated with an overall significant 8.7% reduction in the primary endpoint (9.78% vs. 10.64%; p = 0.045). The benefit of clopidogrel appeared to be greatest in those patients with documented peripheral arterial disease as the qualifying event. In this subgroup of patients, there was a significant 23.8% reduction in the combined primary endpoint. Of note, this reduction was primarily the result of fewer myocardial infarctions and vascular deaths, since the stroke rates were similar. In terms of safety, there was a similar incidence of

gastrointestinal disturbance, intracranial hemorrhage, and abnormal liver function. Patients on clopidogrel were more likely to develop a rash (6.02% vs. 4.61%) than those on aspirin, while they were less likely to have a gastrointestinal hemorrhage (0.49% vs. 0.71%). Although CAPRIE did not demonstrate an overwhelming superiority of clopidogrel over aspirin, its results did lead to the interpretation that clopidogrel is an alternative to aspirin, especially if aspirin is not tolerated or is contraindicated.

In a subsequent secondary analysis of the CAPRIE data, Cannon et al. sought to determine the effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (32). Applying a multivariate model to the CAPRIE data, they were able to demonstrate that acute myocardial infarction can be predicted using baseline characteristics across a wide range of risk, and that clopidogrel significantly reduced this risk by approximately 19% compared with aspirin. Furthermore, in contrast to the effects of intravenous glycoprotein IIb/IIIa inhibitors, this reduction was present in both high- and low-risk patients. This analysis of the CAPRIE data would support the use of clopidogrel across the full spectrum of patients at risk for developing acute myocardial infarction, in contradiction to the glycoprotein IIb/IIIa inhibitors, which can be more appropriately targeted toward high-risk patients (32).

As stated, the overall benefit of clopidogrel compared with aspirin in the CAPRIE trial was very small, with an absolute reduction in the combined end point of only 0.51%. The question remained as to whether the combination of aspirin plus clopidogrel would perform better than aspirin alone (4). The CURE trial was designed to compare the safety and efficacy of short- and long-term use of combination therapy with clopidogrel plus aspirin to that of aspirin alone in patients presenting with unstable angina and non-ST segment elevation MI (33). Patients were enrolled only from centers favoring a conservative approach to managing acute coronary syndromes (i.e., centers with a low rate of angiography and revascularization). A total of 12,562 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 - a composite of death from cardiovascular causes, non-

fatal MI or stroke - was reduced by 20% in the clopidogrel plus aspirin group. This beneficial effect was achieved on top of a broad range of therapies known to improve outcomes in this category of patients (e.g., angiotensin converting enzyme inhibitors, lipid lowering agents, glycoprotein IIb/IIIa inhibitors). Furthermore, the benefit of clopidogrel was consistent and significant in patients with a broad range of risk (as stratified by TIMI risk score into low, intermediate and high), emphasizing the value of its use in all patients with documented non-ST elevation acute coronary syndromes (34). Importantly, the benefits of clopidogrel treatment emerged within 24 hours of initiation of treatment and continued throughout the 12 months (mean 9 months) of the study (35). Even by 24 hours, there was a clear and statistically significant reduction in the risk of the composite endpoint, emphasizing the importance of initiating treatment with clopidogrel as soon as possible (35). 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). 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.

In a subsequent analysis of the CURE data, Peters et al. examined the effects of aspirin dose (on both bleeding risk and efficacy) when used alone or in combination with clopidogrel in the CURE trial (36). In their analysis, patients were divided into the following 3 aspirin dose groups: < 100 mg, 101 through 199 mg, and > 200 mg. This analysis of the CURE data revealed 3 important observations. First, when used in combination with aspirin, the beneficial effects of clopidogrel in reducing major ischemic events were independent of the dose of aspirin used. Second, higher doses of aspirin were not associated with a greater reduction in the primary composite endpoint. Third, whether used alone or in combination with clopidogrel, increasing doses of aspirin were associated with increasing risk of major bleeding.

The CURE trial provides strong support for the addition of clopidogrel to acetylsalicylic acid (ASA) on

admission in the management of patients with uns-table angina and non-ST-elevation MI (NSTEMI). In particular, clopidogrel appears especially useful in hospitals that do not routinely perform invasive pro-cedures and in patients who are not candidates for revascularization. Based on the results of the CURE trial, the ACC and AHA have incorporated the use of clopidogrel into their most recent guidelines for the management of patients with unstable angina and NSTEMI (37). These guidelines recommend that in hospitalized patients in whom an early noninterven-tional approach is planned, clopidogrel be added to ASA as soon as possible on admission and be admi-nistered for at least 1 month and possibly for up to 9 months. Furthermore, they also recommend clopi-dogrel be administered to all hospitalized patients with unstable angina and NSTEMI who are unable to take ASA because of hypersensitivity or major gast-rointestinal upset.

The Use of Clopidogrel in the Prevention of Stent Thrombosis

Early on in its development, coronary stenting was associated with a high incidence of subacute stent thrombosis. This dreadful complication is often resulted in myocardial infarction or even death. The initial antithrombotic regimens used to prevent this complication consisted of varying combinations of aspirin, dipyridamole, dextran, heparin and couma-din. Despite the use of these intense regimens, ho-wever, the rates of stent thrombosis remained as high as 20% in some series. Furthermore, these complicated regimens were associated with unac-ceptable rates of bleeding and prolonged hospitali-zations. With the subsequent realization that stent thrombosis was predominantly a platelet-related phenomenon, the focus of treatment shifted to-wards the use of antiplatelet, rather than anticoagu-lant, therapies (38). Early studies of combination the-rapy with ticlopidine (which had been clinically ava-ilable since the early 1980s) and aspirin demonstra-ted significantly lower rates of stent thrombosis and bleeding (39-41). The STARS trial was the first large randomized study, which demonstrated the superi-ority of a ticlopidine-containing regimen over both anticoagulation and aspirin-only regimens (42). Follo-wing the FDA approval of clopidogrel in 1998 (in res-ponse to the publication of the CAPRIE trial), many centers adopted a policy of using clopidogrel instead of ticlopidine following stent implantation given its

better side effect profile. While several randomized and registry studies comparing aspirin and clopidog-rel to aspirin and ticlopidine did report greater safety and tolerability with the former combination, none of these studies were individually powered to assess the comparative efficacy of clopidogrel versus ticlopi-dine. In response to these concerns, Bhatt et al. per-formed a meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. (43). The meta-analysis used the rate of 30-day major adverse cardiac events (MACE), as defined in each trial, 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 adver-se cardiac events was 2.10% in the clopidogrel gro-up and 4.04% in the ticlopidine group. Furthermore, there was a statistically significant 56% reduction in mortality in those patients treated with clopidogrel and aspirin instead of ticlopidine and aspirin (0.48% versus 1.09%). Therefore, based on their meta-analy-sis, the authors concluded that clopidogrel is at least as efficacious as ticlopidine in reducing MACE. The comparable efficacy, coupled with the better tolera-bility and safety, has established the combination of clopidogrel plus aspirin as the standard antiplatelet regimen after stent deployment.

The Optimal Loading Dose of Clopidogrel for Coronary Stenting

Despite limited information on the time depen-dence of platelet inhibition induced by clopidogrel in patients undergoing coronary stenting, it has beco-me common practice to administer a loading dose of clopidogrel before the procedure. To better define the time dependence and degree of platelet inhibiti-on after this therapy, Gurbel and colleagues analy-zed platelet function and membrane receptors after 4 different clopidogrel dosing regimens in patients undergoing elective coronary stenting (44). They fo-und that loading with 300 mg of clopidogrel 3 to 24 hours before stent implantation inhibits platelets be-fore the onset of the procedure and reduces activa-tion induced by stenting more than the administrati-on of 75 mg at the time of the procedure. They also demonstrated that this loading was associated with early increased GP IIb/IIIa expression but a reduction in the expression of other adhesive molecules and a late inhibition of GP IIb/IIIa expression (day 5). They speculated whether even higher periprocedural do-sing may be required to attenuate this phenomenon.

In another study, Muller et al. compared the antiplatelet effects of two different loading doses of clopidogrel (300 mg and 600 mg) in patients undergoing coronary stent placement with each other and to that of the standard load with ticlopidine (2 x 500 mg) (16). Measuring platelet aggregation in response to ADP and TRAP at various time points up to 48 hours with the use of optical platelet aggregometry, they were able to demonstrate that the 600 mg loading dose of clopidogrel was superior to either of the other two regimens in suppressing platelet aggregation after coronary stenting.

In a larger clinical study, Pache et al. assessed the value of a 600 mg loading dose of clopidogrel initiated prior to stent placement (45). They compared a consecutive series of 864 patients treated with a high loading clopidogrel regimen (600 mg given 2-4 hours prior to intervention) to 870 patients treated with conventional ticlopidine therapy. Sixty-two percent of the patients received periprocedural abciximab. Clopidogrel therapy was associated with a 35% reduction in the composite endpoint of death, myocardial infarction, or urgent revascularization. The authors concluded that a high-loading dose clopidogrel regimen in patients undergoing stenting was associated with a more favorable outcome than conventional therapy with ticlopidine whether or not concomitant abciximab therapy was used.

Based in part on these findings, as well as on earlier observations suggesting that the incremental benefit provided by the GP IIb/IIIa receptor antagonists may not be as great in patients who are adequately pretreated and/or loaded with thienopyridines (46), Kastrati et al. sought to determine whether abciximab was beneficial in patients undergoing elective percutaneous coronary intervention after pretreatment with a high loading dose of clopidogrel (47). They randomized 2159 patients scheduled to undergo a percutaneous coronary intervention and who were pretreated with 600 mg of clopidogrel at least two hours before the procedure to either abciximab or placebo. The primary endpoint of the trial - a composite of death, myocardial infarction, and urgent target-vessel revascularization within 30 days after randomization - did not differ between the two groups. They concluded that in low-to-intermediate risk patients undergoing elective PCI who are pretreated with a high loading dose of clopidogrel, there is no clinically measurable benefit of abciximab use. It is anticipated that these studies will lead to the adoption of 600 mg as the new optimal loading dose for clopidogrel during stent implantation.

The Rationale for Long-term Therapy Post Coronary Intervention

In patients who have undergone percutaneous coronary intervention (PCI), there is often an ongoing thrombotic stimulus, characterized by persistent platelet activation and thrombin generation. Indeed, patients who have undergone PCI remain at continued heightened risk for thrombotic events throughout the vasculature (48). While the strategy of 4 weeks of dual antiplatelet therapy post-stenting is adequate for preventing most cases of stent thrombosis, this duration of treatment is not necessarily optimal for protection against the ongoing thrombotic risk. The PCI-CURE study was the first study to provide data supporting the benefit of prolonged dual antiplatelet therapy beyond 4 weeks following PCI (49). The PCI-CURE was a subanalysis of the 2658 patients in the CURE trial who had undergone PCI at the discretion of the treating physician. These patients underwent PCI at a median of 10 days after enrollment, and dual antiplatelet therapy was continued for a mean of 9 months. There was a 30% risk reduction in the primary composite outcome of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of the PCI. This benefit was sustained long-term when the medication was continued beyond 30 days.

The CREDO (Clopidogrel for the Reduction of Events During Observation) trial was another study designed to evaluate the benefit of long-term treatment with clopidogrel after PCI in a randomized fashion (50). This study randomized 2116 patients undergoing PCI between short- and long-term clopidogrel (28 days vs. 1 year, respectively) in addition to aspirin therapy. Long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI, or stroke at 1 year. This reduction was associated with a nonsignificant increase in the risk of major bleeding in the clopidogrel group.

The results of PCI-CURE and CREDO have led to a change in the duration of the postprocedural dual antiplatelet regimen to 1 year in patients undergoing PCI in many laboratories in the United States.

The Rationale for Clopidogrel Preadministration During Coronary Intervention

In addition to studying the benefits of prolonged administration of clopidogrel post-PCI, both the

PCI-CURE and the CREDO trials also examined the effects of clopidogrel administration prior to the performance of coronary intervention. In the PCI-CURE trial, patients underwent PCI at a median of 10 days after enrollment. Thus, the duration of pretreatment was quite long. As stated above, there was a 30% reduction in the primary outcome at 30 days. Importantly, this benefit was seen as early as 2 days after PCI. Since most patients received open-label thienopyridine after PCI (>80% in both groups), it is likely that the early postprocedural benefit seen was due in large part to the effects of clopidogrel pretreatment. Like the PCI-CURE trial, the CREDO trial also sought to determine the benefit of a 300 mg pre-procedural loading dose of clopidogrel (between 3 and 24 hours prior to PCI). In a prespecified subgroup analysis, patients who received 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. These two studies strongly support a benefit for clopidogrel pretreatment prior to the performance of PCI.

The Use of Clopidogrel Post-Brachytherapy

Restenosis following the placement of intracoronary stents continues to be a significant problem in interventional cardiology (51). While the use of drug-eluting stents is expected to decrease the incidence of this problem in the future, instent restenosis remains a significant problem at the present time. To date, vascular brachytherapy has become the standard of care based upon several randomized studies (52-55). However, the early experience with brachytherapy was associated with a high incidence of early adverse events, believed to be the result of late stent thrombosis (defined as occurring > 30 days after intervention and radiation) (55-58). Subsequently, it was realized that the incidence of this serious problem could be significantly reduced with the use of prolonged dual antiplatelet therapy coupled with the avoidance of new stent implantation at the time of brachytherapy (59, 60). Based on the results of the WRIST 12 study, the most recent recommendations call for at least 12 months of clopidogrel therapy in patients undergoing radiation treatment for instent restenosis (60).

The Phenomenon of Clopidogrel Resistance

Recently, there has been much interest in the variability among individuals in their platelet inhibitory response to standard doses of clopidogrel. Jaremo and colleagues were among the first to investigate individual variations of platelet inhibition after clopidogrel loading. They studied 18 patients undergoing coronary stenting who received a 300 mg loading dose of clopidogrel immediately after stenting (day 1) followed by an additional 75 mg 24 hours later (day 2) (61). Platelet reactivity was estimated immediately before angiography and on day 2 by analyzing ADP-evoked platelet fibrinogen binding using a flow cytometry technique. Soluble P-selectin was also used as a marker of platelet activity. Using two different ADP solutions (final concentrations of 0.6 and 1.7 mmol L-1), these investigators demonstrated that clopidogrel-evoked platelet inhibition exhibited considerable individual heterogeneity. They concluded by speculating that subjects with weak platelet responses to clopidogrel might have an increased risk for thrombotic events in conjunction with coronary stenting while those with strong reactions might be predisposed to an increased bleeding tendency.

In another study involving a larger number of patients, Gurbel et al. examined platelet aggregation and activation in 96 patients undergoing elective coronary stenting (62). All patients received aspirin, and clopidogrel was administered as a loading dose of 300 mg followed by 75 mg daily. Platelet aggregation and activation were assessed at baseline and at 2 hours, 24 hours, 5 days, and 30 days after stenting. The investigators found that the platelet inhibitory response to the standard dosing regimen of clopidogrel for coronary stenting demonstrated marked interindividual variability, followed a normal distribution, and appeared stable for 30 days. Using an empirical definition of clopidogrel resistance, defined as baseline aggregation (%) minus post-treatment aggregation (%) < or = 10% by 5 mmol/L ADP, they found that 31% and 15% of the patients were resistant at 5 and 30 days, respectively. They also noted that patients with the highest pretreatment platelet reactivity remained the most reactive at 24 hours after treatment, and thus had the least antithrombotic protection. The obvious implication of the study is the potential correlation between level of platelet reactivity and adverse clinical events. Larger clinical stu-

dies will be required to determine the relationship between levels of response to clopidogrel and adverse ischemic events.

Clopidogrel-Statin Interaction

Clopidogrel is an inactive prodrug that requires liver metabolism and activation by cytochrome P-450 (8-10). Certain statins are also metabolized by cytochrome P-450 (63), and are frequently co-administered with clopidogrel in patients with established CAD who are undergoing coronary stenting. Recently, a number of experimental studies have suggested that certain statins might inhibit the antiplatelet activity of clopidogrel (64). The concern has been that such potential drug interactions could have significant clinical implications since a substantial number of patients are on both classes of medications. Lau et al (65). reported that clopidogrel given in a loading dose of 300 mg was less effective in inhibiting platelet aggregation when administered with atorvastatin, another substrate of cytochrome P-450-3A4 (CYP3A4). In contrast, use of a statin not metabolized by CYP3A4 (e.g., pravastatin) did not alter the degree of platelet inhibition after clopidogrel administration. However, in another study, Muller et al. found no affect of statin co-administration with clopidogrel on platelet aggregation when using a higher (600 mg) loading dose of clopidogrel (65).

To better understand the clinical significance of this potential interaction, Saw et al. performed a post hoc analysis of the CREDO trial to evaluate the clinical efficacy of concomitant clopidogrel and statin administration, categorizing baseline statin use to those predominantly CYP3A4-metabolized (atorvastatin, lovastatin, simvastatin, and cerivastatin) (CYP3A4-MET) or others (pravastatin and fluvastatin) (non-CYP3A4-MET) (66). Of the 2116 patients enrolled in the CREDO trial, 1001 received a statin metabolized by CYP3A4, while 158 received a statin not metabolized by this enzyme system. As already discussed, clopidogrel use in this study was associated with a 26.9% reduction in the primary end point at 1 year. This analysis revealed that the benefit seen with clopidogrel in this study was the same whether or not a statin was used and whether or not the statin used was metabolized by the CYP3A4 enzyme system. Furthermore, concomitant therapy with statins had no impact on either major or minor bleeding rates. Thus, the authors concluded that despite the suggestions of a potential negative in vitro interaction between clopidogrel and those statins metabolized by the CYP3A4 enzyme system, there appeared to be no clinical significance of this laboratory observation in this post-hoc analysis of a large placebo-controlled study.

Conclusion

Antiplatelet therapy is the mainstay of treatment for patients with coronary artery disease. For the majority of patients with stable ischemic heart disease, aspirin remains the antiplatelet of choice for secondary prevention. While clopidogrel has been demonstrated to be at least as effective as aspirin in this setting, given its high cost, its use for secondary prevention in this subset of patients should be restricted to those who are intolerant of aspirin (67). For those patients presenting and/or recovering from an acute coronary syndrome, the combination of aspirin and clopidogrel has been demonstrated to be superior to that of aspirin alone - at least when used for one year after the acute episode. However, the risk of bleeding with this combination also appears to be higher - particularly if low dose aspirin is not used in the combination. In patients undergoing PCI, the same combination has been shown to reduce the incidence of subacute stent thrombosis when used for one month post-procedure. However, more recently, data from the CREDO trial has shown improved cardiovascular outcomes when the combination therapy is continued for one year. Thus, particularly in patients with acute coronary syndromes and/or those undergoing PCI, the evidence would support long-term (i.e., 1 year) dual antiplatelet therapy. There are several planned and ongoing trials of clopidogrel, which will examine its role in certain heretofore unstudied patient populations (6). Two trials - the COMMIT and CLARITY trials - will compare dual antiplatelet therapy with clopidogrel and aspirin to that of aspirin alone in patients presenting with ST-segment elevation MI. Such patients were excluded from the CAPRIE and CURE trials. The WATCH trial will study the role of clopidogrel in patients with heart failure, and compare it to treatment with aspirin and with warfarin. The CASPAR trial will compare combination therapy with aspirin and clopidogrel to aspirin alone in patients undergoing peripheral artery bypass surgery, while the CAMPER trial will do the same in those undergoing percutaneous peripheral intervention. The CHARISMA trial, a multicenter and randomized international trial planning to enroll mo-

re than 15,000 patients, will compare dual antiplatelet therapy with clopidogrel and aspirin to treatment with aspirin alone in secondary prevention and high-risk primary prevention populations. The goal of this study will be to establish long-term treatment with clopidogrel as a mainstay of therapy in patients with atherosclerotic heart disease, much in the same way as statins, aspirin and ACE inhibitors.

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