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REVIEW ARTICLE

The Role of Clopidogrel in the Management of Patients with Ischemic Heart Disease

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Summary. **Antiplatelet therapy plays a pivotal role in the treatment of patients across the entire spectrum of coronary artery disease. Platelets are believed to be integrally involved in both the development and progression of atherosclerotic heart disease, as well as in its acute thrombotic complications. While aspirin remains the traditional antiplatelet agent in patients with CAD, adverse vascular events continue to occur in patients on aspirin therapy. Clopidogrel is a relatively new antiplatelet agent and is currently one of the most widely prescribed drugs for the treatment of symptomatic coronary artery disease. As a member of the class of drugs known as the thienopyridines, clopidogrel irreversibly prevents platelet activation by blocking one of the three known adenosine 5′-diphosphate (ADP) receptors on its surface. The findings of a number of seminal clinical trials have expanded the indications for the use of clopidogrel in patients with coronary artery disease. When used in conjunction with aspirin, these studies have demonstrated an incremental benefit of clopidogrel above and beyond that of aspirin alone. This article reviews the data supporting the use of clopidogrel in patients with atherosclerotic heart disease, and makes recommendations for its use based on the available evidence.**

Key Words. **atherosclerosis, thrombosis, ischemic heart disease, clopidogrel, aspirin, thienopyridine**

Introduction

Ischemic heart disease (IHD) remains the leading cause of morbidity and mortality in the United States and much of the Western world. The pathophysiologic spectrum of IHD consists of stable angina, unstable angina, non-ST segment elevation MI (NSTEMI), and ST segment elevation MI (STEMI) [1]. Those patients with IHD who become unstable by virtue of developing a change in their usual pattern of angina are classified as having an acute coronary syndrome (ACS), and include patients with unstable angina, NSTEMI and STEMI. While luminal narrowing by an atherosclerotic plaque contributes to some of the clinical manifestations of atherosclerotic arterial disease, there is overwhelming evidence implicating platelet activation and aggregation with subsequent coronary thrombosis as the precipitant for the vast majority of acute ischemic syndromes. These pathophysiologic events occur in response to the disruption of an underlying "unstable and inflamed" atherosclerotic plaque [2–6]. Since platelets and thrombi have been identified as playing central roles in the pathogenesis of ACS, new classes of antiplatelet and anti-thrombotic agents have been introduced and studied for the management of ACS. This article will review the role of clopidogrel, an adenosine diphosphate (ADP) inhibiting antiplatelet agent, in the management of patients with both stable and unstable atherosclerotic heart disease.

The Pathophysiology of Arterial Thrombosis

Platelet activation and aggregation are vital components in the development of ACS. Platelets are integrally involved in the myriad of vascular phenomena that lead to thrombosis with subsequent reduction in vascular flow. Although essentially inert in their circulating form, platelets become activated in a rapid and dramatic fashion once injury to the intima of the vessel has occurred. Following injury, exposure of subendothelial proteins triggers a cascade of events that ultimately leads to the phenomenon of hemostasis. Although classically described as a two-fold process, primary and secondary hemostasis occurs in rapid succession of each other. Primary hemostasis refers to the short-lived (i.e., lasting seconds) response to vessel injury characterized by the immediate attraction of circulating platelets and the subsequent formation of a platelet plug at the site of endothelial damage. The process of secondary hemostasis, which lasts minutes, follows in rapid succession and is marked by the interaction of activated platelets with soluble coagulation factors to form a fibrin-polymer that supports the tenuous platelet-plug. The precise orchestration of these events requires the interaction of multiple agonists and the receptor-mediated release of a variety of chemicals leading to specific changes in platelet morphology and

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conformation. The interruption of primary hemostasis remains the principal mechanism of the anti-platelet agent clopidogrel and is the focus on this brief narrative of *in vivo* platelet activity. There are essentially four sequential steps that platelets must undergo to effect primary hemostasis, as described below:

1. *Platelet Adherence.* Platelet-mediated hemostasis is initiated by injury to the intima and endothelial surface, usually at the site of a ruptured atherosclerotic plaque. The exposed subendothelium at this site 'attracts' circulating, un-activated platelets to bind to fibronectin, vitronectin, von Willebrand factor (vWF) [5], and collagen of the vessel media. vWF in particular is implicated as the major agent responsible for platelet adhesion. This member of the integrin family of proteins allows for the formation of a bridge between exposed collagen fibrils of the vessel wall and the glycoprotein Ib/IX receptor on the platelet. By acting as a specific anchor to platelets, vWF allows for the adhesion of platelets to areas of vessel trauma despite continued shear stress from luminal flow [6]. Once circulating platelets have been attached, platelet degranulation with the release of a variety of mediators follows.

2. *Platelet Activation.* With the effective attachment of platelet GP receptors to the subendothelial collagen stabilized by vWF, there now occurs release of preformed granule contents leading to platelet activation [7]. These vaso-active mediators are released from platelet "alpha granules" and "dense-granules." The principal physiologic mediators of platelet activation within these granules include thrombin, collagen, platelet-derived growth factor (PDGF), adenosine diphosphate (ADP) and thromboxane A2 [8] (which is synthesized from arachidonic acid via the cyclooxygenase enzyme system). These agonists act in the vicinity of vascular injury and produce critical intracellular events within attached platelets. These key events are mediated primarily via activation of the membrane phospholipase C and phospholipase A2 enzyme pathways. These enzyme systems produce the hydrolysis of membrane phospholipids (with subsequent release of arachidonic acid), increased influx of calcium across the platelet membrane, and phosphorylation of key intracellular proteins [9]. The changes in the intra-cellular milieu produced by the activation of the phospholipases lead to specific changes in platelet morphology and function, such as loss of the normal discoid shape, formation of pseudopodia and the continued exocytosis of storage granules. This process is self-sustained and amplified via continued interaction with platelet agonists. For example, TXA2 produces continued release of ADP from platelet alpha-granules that, in turn, further stimulates the arachidonic acid pathway leading to continued production of TXA2. In such fashion, amplification of platelet activation is effected.

3. *Platelet Aggregation.* With the secretion of platelet granule contents into the plasma, changes occur in the platelet IIb/IIIa surface glycoprotein, forming the basis of platelet aggregation. The conformational changes in the GP IIb/IIIa receptors brought about by the release of platelet mediators allows for these receptors to bind fibrinogen [10]. Although the mechanism of this change remains unclear, GP IIb/IIIa differs significantly from GP Ib in that it requires platelet stimulation for its activity. Irrespective of the precise mechanism, however, the binding of this glycoprotein to circulating fibrinogen allows for the formation of a fibrinogen bridge between one platelet and another, thus producing platelet aggregation and formation of the so-called 'platelet plug.' The binding of fibrinogen is further enhanced by a chemical environment that contains thrombin, epinephrine, serotonin and ADP and thromboxane A2 [10], all of which are being actively released from adjacent activated platelets. Fibrinogen, by virtue of its high concentration in plasma, remains the primary protein responsible for platelet aggregation.

4. *Interaction with Coagulation Factors.* As more cross-linking of fibrinogen occurs with activated platelets, changes begin to occur in the platelet phospholipid membranes. These changes allow for non-activated circulating platelets to now become more 'permeable' to circulating coagulating factors. In effect, a scaffold begins to form on which circulating phospholipid-dependent coagulation factors can further attach via the process of cross-linking [11]. Thus, the various vascular elements now join in a uniform crescendo to effect secondary hemostasis.

Pharmacology of Clopidogrel

Clopidogrel is an antiplatelet agent that belongs to the class of antiplatelet agents known as the thienopyridines. Ticlopidine was the first agent developed of this class. However, the use of ticlopidine has decreased dramatically secondary to its significant hematological toxicity, including neutropenia, agranulocytosis and thrombotic thrombocytopenic purpura (TTP). Clopidogrel, on the other hand, has been associated with fewer side effects and is better tolerated than ticlopidine with similar efficacy and benefit. Clopidogrel differs structurally from ticlopidine by the presence of one additional carboxymethyl side group. The mechanism of action of both ticlopidine and clopidogrel is via selective inhibition of ADP-induced platelet aggregation [12]. These drugs directly inhibit the binding of ADP to its receptor on the platelet. The platelet ADP receptor is coupled to a G protein, which upon activation, leads to calcium release from internal cytosolic stores [13,14]. This in turn leads to activation of the GP IIb/IIa receptor with subsequent fibrinogen binding and platelet aggregation. Clopidogrel inhibits the binding of ADP to one of three identified ADP receptors in platelets: the $P2Y_{12}$ receptor [15].

Van Gestel and colleagues were among the first to investigate the effects of *in vivo* blockade of the platelet

ADP receptor $P2Y_{12}$ with regards to thrombus formation and embolization in a rabbit model [16]. These investigators demonstrated that clopidogrel, in a dose of 25 mg/kg administered orally, and the $P2Y_{12}$ antagonist known as AR-C69931 MX significantly reduced both the total duration and amount of embolization following mechanical injury to the vessel wall. Thus, the inhibition of ADP-dependent activation of the GP IIb/IIIa complex leads to the prevention of platelet aggregation and primary hemostasis. In addition to this direct effect, the thienopyridines undergo extensive metabolism and produce pharmacologically active metabolites that further block platelet activation via the inhibition of platelet agonists other than ADP [16]. In short, the modification of the ADP platelet receptor by clopidogrel produces platelets will remain nonfunctional for the remainder of their lifespan.

Pharmacokinetically, the use of clopidogrel in doses of 75 mg/d has been shown to produce clinical onset of activity after 12–24 hours of administration, a timespan required for both hepatic microsomal oxidation of the thienopyridines by the cytochrome P450 pathway and ADP receptor inactivation. However, maximal inhibition only occurs after a variable period of 3 to 7 days. The investigators of the PRONTO trial recently evaluated the use of larger loading doses of clopidogrel to determine the optimal loading dose in patients undergoing coronary stenting in an attempt to circumvent this time-delay [17]. These investigators found that pretreatment of patients with a loading dose of 300 mg of clopidogrel three to twenty four hours prior to stent-implantation induced greater inhibitory effects and reduction of platelet activation post-stenting as compared to 75 mg/d [17]. These findings indicate a superior clinical outcome for patients receiving a larger dose of clopidogrel twenty four hours before the onset of stenting.

Clinical Applications of Clopidogrel

The limitations of aspirin

There is overwhelming evidence supporting the role of aspirin in the treatment of patients across a spectrum of coronary artery disease. Aspirin inhibits thromboxane synthesis and thereby platelet aggregation in response to agonists such as ADP and collagen. Although evidence for a survival benefit of aspirin in subjects with preclinical CAD (i.e., primary prevention) is inconclusive, aspirin has been shown in two large studies to reduce the risk of a first non-fatal MI [18]. Furthermore, aspirin has been consistently shown to prevent MI and stroke in patients with established atherosclerotic vascular disease (i.e., secondary prevention) across a variety of clinical syndromes, ranging from chronic stable angina [19] to acute ST-segment elevation MI [20].

Despite its established benefit in patients with IHD, aspirin has numerous limitations. First, it is a relatively weak antiplatelet agent and does not inhibit platelet aggregation induced by thromboxane A2-independent pathways (e.g., via ADP or collagen stimulation). Second, aspirin also has no effect on thrombin, which is believed to play a major role in platelet activation in the acute coronary syndromes. Third, there remain many patients that are allergic to or intolerant of aspirin, most often due to gastrointestinal upset or hypersensitivity. Fourth, despite the widespread use of aspirin, vascular events continue to occur at high rates. Finally, there is now increasing evidence supporting the existence of a population of patients who may be resistant to the antiplatelet effects of aspirin [21]. Such patients appear to be at increased risk for the development of vascular events. At least in theory, such patients may derive particular benefit from dual-pathway platelet inhibition.

Experimental studies have demonstrated synergy between the thienopyridines and aspirin [22–24]. The enhanced and synergetic inhibition produced by this combination is not surprising since these drugs produce platelet blockade via independent mechanisms. By inhibiting both ADP- and thromboxane A2-mediated platelet activation, there is effective blockade of the two different pathways leading to platelet aggregation.

The Use of Clopidogrel in the Secondary Prevention of Vascular Events—The CAPRIE Trial

The CAPRIE trial was a large phase III clinical trial that sought to determine whether the use of clopidogrel was associated with greater efficacy and safety as compared to the use of aspirin alone in patients with established atherosclerosis [25]. The trial enrolled 19,185 patients with clinical evidence of atherosclerotic disease (ischemic stroke, MI, symptomatic peripheral arterial disease) and randomized them to receive either 75 mg of clopidogrel or 325 mg/d of aspirin. The primary endpoint 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. In this study, clopidogrel was associated with an overall risk reduction of 8.7% for this primary outcome (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 this subgroup of patients, there was there was a significant 23.8% reduction in the combined primary endpoint (3.71% per year compared with 4.86% per year; $p = 0.0028$). This reduction was primarily the result of fewer myocardial infarctions and vascular deaths, since the stroke rates were similar. The mechanism(s) for this apparent preferential benefit of clopidogrel in patients with documented PAD remains unknown. 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 two-year period was similar in both the clopidogrel and aspirin groups (5.03% vs. 4.84%, $p = 0.66$). This would suggest that chronic clopidogrel therapy might be a reasonable substitute for aspirin in this subgroup of patients (i.e. patients with MI <35d), who may be unable to take chronic aspirin therapy.

The CAPRIE data led to the FDA approval of clopidogrel for the secondary prevention of vascular events in patients with symptomatic atherosclerosis.

The Use of Clopidogrel in the Acute Coronary Syndromes—The CURE Trial

Despite major advances in the pharmacologic treatment of patients with ACS, including aspirin and heparin, there remains the need to further reduce the risk of both short- and long-term ischemic events in these patients. The CURE trial was designed to test the hypothesis that the combination of aspirin plus clopidogrel is superior to that of aspirin alone when initiated early and continued for the long term in the prevention of cardiovascular death, MI, or stroke in patients with unstable angina and non-ST-segment elevation myocardial infarction. Patients were enrolled from centers favoring a conservative approach to the management of the acute coronary syndromes (i.e., centers with a low rate of angiography and revascularization) [26]. This international study enrolled a total of 12,652 patients from 28 countries and randomized them 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. Importantly, patients were allowed to receive other contemporary therapies, such as heparin, beta-blockers, ACE inhibitors, and lipid lowering medications. The primary outcome of the trial was a composite of death from cardiovascular causes, nonfatal MI or stroke (Table 1).

The trial demonstrated that clopidogrel, when used in addition to aspirin, significantly reduced the incidence of this primary outcome by 20% (Figure 1). (9.3% in the clopidogrel group vs. 11.4% in the placebo group). Moreover, the benefit seen with clopidogrel was incremental to, and independent of, other acute and long-term therapies (including coronary interventions). Notably, the 20% relative risk reduction observed with the combination therapy was observed in all components of the primary composite endpoint; however, the greatest effect was in the reduction in MI, particularly

Table 1. *Overview of evidence for the use of clopidogrel: The CURE and PCI-CURE data*

Clinical trial	Study design & population	Endpoint(s)	Results and analysis
CURE trial (Clopidogrel in Unstable angina Recurrent Events)	*Design:* 12,562 patients who developed Acute Coronary Syndromes [Non STEMI/ACS] were enrolled in a double blind RCT to compare the efficacy of Clopidogrel [300 mg loading dose + 75 mg qd + ASA], to Placebo + ASA for an average duration of nine months. *Inclusion criteria:* Patients were eligible if they presented within 24 h of chest pain onset and had objective evidence of ischemia as demonstrated by elevated troponins or (+)ve EKG changes consistent with NQW-MI.	Composite of Death from CV causes, MI or Stroke.	*Early benefit* (<24 hrs): 34% reduction on CV Death, MI, stroke or severe ischemia. *Late benefit* (31 days–1 yr): 18% incremental reduction in the primary outcome. *Specific benefit*: as stratified by TIMI Risk, a consistent benefit was demonstrated through the entire spectrum of risk scores. Significant advantage was also demonstrated in patients with a history of CABG from Clopidogrel treatment with a 19% reduction in the primary end point.
PCI-CURE study (Prospective substudy of the CURE Trial examining the role of Clopidogrel in pt's. undergoing PCI)	*Design:* 2,658 patients who underwent PCI were randomized to two treatment arms—(a) pre-treatment with Clopidogrel + ASA [vs. treatment with ASA alone], and (b), long term therapy post-PCI with Clopidogrel vs. ASA therapy alone. *Inclusion criteria:* pt's from the CURE Trial who underwent PCI at the discretion of the site investigator.	Cardiovascular death, MI, or urgent revascularization post PCI.	*Early benefit* (0–30 d): 30% reduction in the primary end point from the time of PCI to 30 days indicating that pre-treatment with Clopidogrel was beneficial in preventing adverse events in a post-procedure setting. *Late benefit* (30 d onwards): consistent benefit of Clopidogrel over placebo in reduction of the primary endpoint. *Specific benefit:* 38% decrease in RR was demonstrated in patients who underwent PCI within 72 h of admission with Clopidogrel pre-treatment compared with patients who underwent delayed interventions.

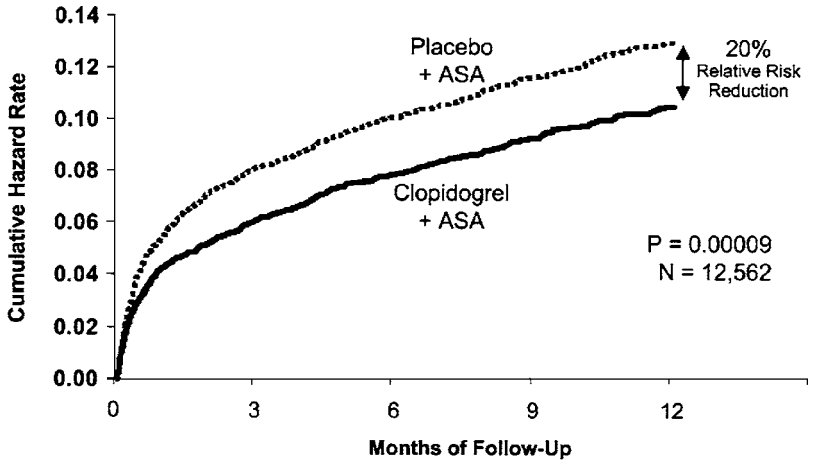

Fig. 1. *First co-primary outcome in CURE: CV death, MI or stroke from randomization to one year of follow-p (mean nine months). ASA = acetylsalicylic acid. Reprinted from Mehta and Yusuf. Short and long-term antiplatelet therapy. J Am Coll Card 41(4):79S–88S. Reproduced with permission 2003. © 2003 American College of Cardiology Foundation.*

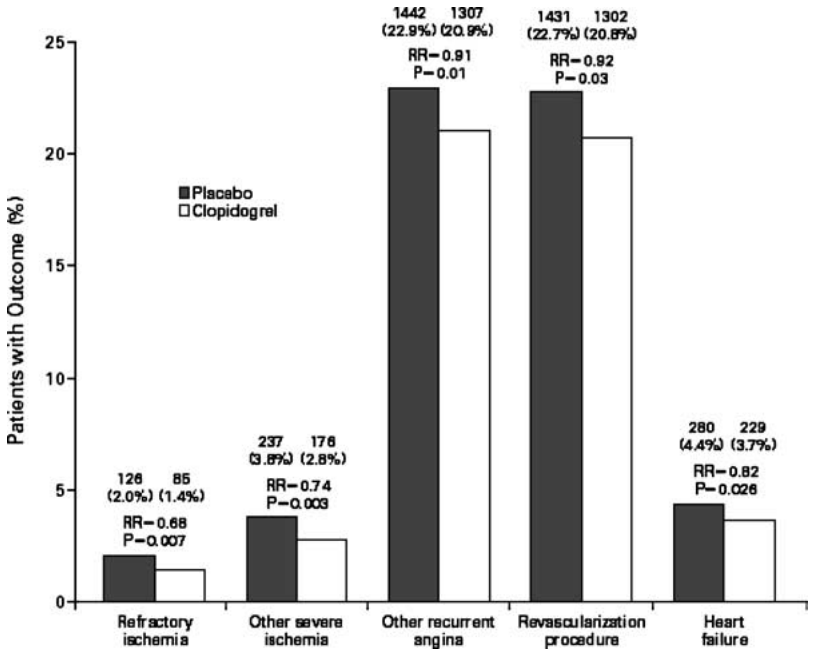

Fig. 2. *Proportion of patients who had events other than those included in the First Primary Outcome. RR Denotes Relative Risk. Reprinted from The clopidogrel in unstable angina to prevent recurrent events trial investigators: Effects of clopidogrel in addition to Aspirin in patients with acute coronary syndromes without ST-Elevation. NEJM 2001;345:494–502. Reproduced with Permission 2003. © New England Journal of Medicine.*

large MIs, which were reduced by 40%. Consistent with the decrease in large MIs was a reduction in new-onset congestive heart failure (Figure 2).

In a subsequent analysis of the CURE data, Yusuf et al. explored the rapidity with which treatment was effective and its sustainability over 1 year [27]. The treatment benefit observed with the use of clopidogrel was observed as early as four hours after randomization. By 24 hours, there was a clear and statistically significant reduction in the risk of the composite outcome of cardiovascular death, stroke, MI, or refractory or severe ischemia. This benefit was sustained both at 30 days and in the later stages of the trial. At 30 days, the relative risk reduction of the primary outcome was 21%. Importantly, this long-term benefit was in addition to the rapid early benefit observed within the first

Table 2. *Risk and ramifications of bleeding associated with the use of clopidogrel*

Variable	Clopidogrel group ($N = 6259$)	Placebo group ($N = 6303$)	Relative risk (95% Cl)	P value
	no. (%)			
Major bleeding	231 (3.7)	169 (2.7)	1.38 (1.13–1.67)	0.001
Necessitating transfusion of ≥2 units of blood	177 (2.8)	137 (2.2)	1.30 (1.04–1.62)	0.02
Life-threatening	135 (2.2)	112 (1.8)	1.21 (0.95–1.56)	0.13
Fatal	11 (0.2)	15 (0.2)		
Causing 5 g/dl drop in hemoglobin level	58 (0.9)	57 (0.9)		
Requiring surgical intervention	45 (0.7)	43 (0.7)		
Causing hemorrhagic stroke	7 (0.1)	5 (0.1)		
Requiring inotropic agents	34 (0.5)	34 (0.5)		
Necessitating transfusion of ≥4 units of blood	74 (1.2)	60 (1.0)		
Non-life-threatening	96 (1.5)	57 (0.9)	1.70 (1.22–2.35)	0.002
Site of major bleeding				
Gastrointestinal	83 (1.3)	47 (0.7)		
Retroperitoneal	8 (0.1)	5 (0.1)		
Urinary (hematuria)	4 (0.1)	5 (0.1)		
Arterial puncture site	36 (0.6)	22 (0.3)		
Surgical site	56 (0.9)	53 (0.8)		
Minor bleeding	322 (5.1)	153 (2.4)	2.12 (1.75–2.56)	<0.001
Total with bleeding complications	533 (8.5)	317 (5.0)	1.69 (1.48–1.94)	<0.001

Rates of bleeding complications associated with the use of Clopidogrel. Reprinted from The clopidogrel in unstable angina to prevent recurrent events trial investigators: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-elevation. *NEJM* 2001;345:494–502. Reproduced with Permission 2003. © New England Journal of Medicine.

30 days. With respect to adverse effects (particularly bleeding), patients receiving clopidogrel and aspirin did have a higher risk of both major bleeding (3.7% vs., 2.7%; $p < 0.05$) and minor bleeding (5.1% vs. 2.4%; $p < 0.05$), although there was no increase in the incidence of life-threatening bleeding or hemorrhagic stroke (2.1% vs. 1.8%; $p =$ ns) (Table 2). Bleeding risk, however, was directly related to aspirin dose, such that the highest bleeding risk was seen at the highest dose of aspirin (i.e., >200 mg), and the lowest bleeding risk was seen at the lowest doses of aspirin (i.e., <100 mg). Furthermore, the higher doses of aspirin were not associated with further reductions of the primary composite endpoint. Another important finding with regards to bleeding was the fact that there was no evidence of increased bleeding risk among the 823 patients who received GP 2b/3a inhibitors subsequent to receiving clopidogrel. Finally, with regard to bleeding risk, there was a trend toward higher postoperative bleeding in patients who had received clopidogrel within 5 days of undergoing coronary bypass surgery 9.6% vs. 6.3%, $p =$ ns).

In yet another subsequent analysis of the CURE data, Budaj and colleagues examined the safety and efficacy of clopidogrel plus aspirin therapy in patients with ACS, stratified by their cardiovascular events risk [28]. Using the Thrombolysis in Myocardial Infarction (TIMI) risk score criteria [29], these investigators stratified patients in the CURE trial into the following categories: low risk (TIMI score, 0–2), intermediate risk (TIMI score, 3–4), or high risk (TIMI score, 5–7). Compared with placebo, the immediate and long-term administration of clopidogrel was associated with a reduction of the composite endpoint of cardiovascular death, myocardial infarction, and stroke across all levels of cardiovascular risk, as defined by the TIMI risk score. Furthermore, while both the risk and the absolute risk reduction did increase according to TIMI risk level, the relative risk reduction with clopidogrel was consistent across all groups. These findings are very important, since most other therapies (such as invasive procedures, the GP 2b/3a inhibitors, low molecular weight heparins) have not been demonstrated to have a similar consistent benefit across all risk groups (especially in the low risk group).

The Use of Clopidogrel in the Prevention of Stent Thrombosis

Early experience with coronary stenting was hindered by high rates of subacute stent thrombosis, a serious complication that frequently results in myocardial infarction or even death. The early antithrombin regimens consisted of several agents, including aspirin, dipyridamole, dextran, heparin, and warfarin. These regimens were associated with stent thrombosis rates of 5–20%, and were accompanied by unacceptably high bleeding complications and prolonged hospital stays. New data suggested that stent thrombosis was a platelet-dependent event [30]. This led to efforts at

examining the role of ticlopidine, which had been in clinical use since the early 1980s. The initial studies of antiplatelet therapy in this setting were done using ticlopidine and aspirin, and when used in combination with high pressure balloon inflation, were associated with much lower stent thrombosis rates and bleeding [31–33]. The initial small studies ultimately led to a large randomized trial known as the STARS trial, which confirmed a clear and convincing benefit of a ticlopidine-containing regimen over both anticoagulation and aspirin-only regimens [34]. Following the publication of the CAPRIE trial results and the subsequent FDA approval of clopidogrel, many centers began using clopidogrel instead of ticlopidine after stent implantation given its better side effect profile. Indeed, several centers reported their favorable experience with this off-label approved use of clopidogrel. These initial reports were followed by two randomized published studies which both demonstrated the greater safety and tolerability of the combination of aspirin and clopidogrel compared with aspirin and ticlopidine [35,36]. Importantly, however, none of these randomized clinical trials or single-center registries comparing clopidogrel plus aspirin versus ticlopidine plus aspirin were individually powered to assess the comparative efficacy of clopidogrel versus ticlopidine. In an attempt to determine whether clopidogrel plus aspirin is as effective as ticlopidine plus aspirin in reducing ischemic events in patients receiving coronary stents, Bhatt et al. performed a meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting [37]. 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 adverse cardiac events was 2.10% in the clopidogrel group 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 this meta-analysis, clopidogrel is at least as efficacious as ticlopidine in reducing MACE. The comparable efficacy, coupled with the better tolerability and safety, has established the combination of clopidogrel plus aspirin as the standard antiplatelet regimen after stent deployment.

The Use of Clopidogrel in Patients Undergoing Intra-Coronary Brachytherapy

Despite the fact that intracoronary stenting has dramatically improved upon the procedural success and restenosis rates seen with balloon angioplasty alone [38], restenosis after intracoronary stenting still occurs and continues to be a significant problem in interventional cardiology [39]. Based upon a number of well-conducted and randomized studies, vascular brachytherapy has become the treatment of choice for in-stent restenosis. These trials used both gamma and beta emitters and demonstrated a reduction in angiographic restenosis as well as the need for both target-lesion revascularization and target-vessel revascularization compared with control [40–42]. However, it became apparent early on in the brachytherapy experience that brachytherapy was associated with the unique phenomenon of late stent thrombosis (defined as occurring >30 days after intervention and radiation) [43–46]. This phenomenon is believed to be related to a number of potential triggers, such as delayed re-endothelialization after injury, inadequate anti-platelet therapy, and the use of additional stents. Accordingly, prolonged dual antiplatelet therapy and the avoidance of new stents at the time of brachytherapy have been associated with a reduction in the incidence of these adverse events. The WRIST PLUS study, a 120-patient registry using^{192} Ir and 6 months of clopidogrel for in-stent restenosis, demonstrated the superiority of 6 months of dual antiplatelet therapy compared with only 1 month of such therapy [47]. More recently, the WRIST 12 extended the time course of treatment with aspirin and clopidogrel post-brachytherapy to 12 months [48]. Compared to the outcomes of those patients in the WRIST PLUS study, there was an even further reduction in late occlusion and thrombosis rates, as well as both target-lesion and target-vessel revascularization procedures. This was accomplished without an increased risk of bleeding. Based upon the results of the WRIST 12 study, it appears that at least 12 months of dual antiplatelet therapy should be recommended in all patients who have received radiation therapy for the treatment of 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 [49]. In preliminary studies, 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 [50–52]. However, because of the suppression of neointimal hyperplasia, there exists considerable concern 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 [51,52]. Fortunately, either as a result of this prolonged regimen or presumable because some re-endothelialization does occur, there has not been an increase in the incidence of stent thrombosis.

The Timing and Optimal Duration of Clopidogrel Use in Patients Undergoing PCI

The PCI-CURE study was a sub study of the CURE trial which sought to determine the benefits of administering clopidogrel prior to percutaneous coronary intervention (PCI) [53]. The patient population for this sub analysis consisted of 2658 patients who participated in the CURE trial and who had undergone PCI at the discretion of their physician. These patients underwent PCI at a median of 10 days after enrollment. The primary outcome of this study—the composite of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI—was reduced by 30% with the use of clopidogrel (4.5% vs. 6.4%, $p = 0.03$) (Figure 3). The benefit associated with the use of clopidogrel was seen as early as 2 days after PCI, and continued until 30 days. Importantly, since most patients in both groups received open-label thienopyridine after PCI, it is likely that the early post procedural benefit seen was mainly due to the effects of clopidogrel pretreatment. The benefit observed within the first 30 days was maintained in the ensuing months when double blind study medication was continued long-term. Of note, however, this benefit was driven by the rehospitalization component of the composite endpoint, with no difference in the 'hard' endpoints of death or MI. There were fewer patients in the clopidogrel group who received a glycoprotein IIb/IIIa inhibitor compared with placebo group (20.9% vs. 26.6%, $p = 0.001$). 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 obtained at the expense of nonsignificant excess in major, but not life-threatening, bleeding with clopidogrel compared with placebo.

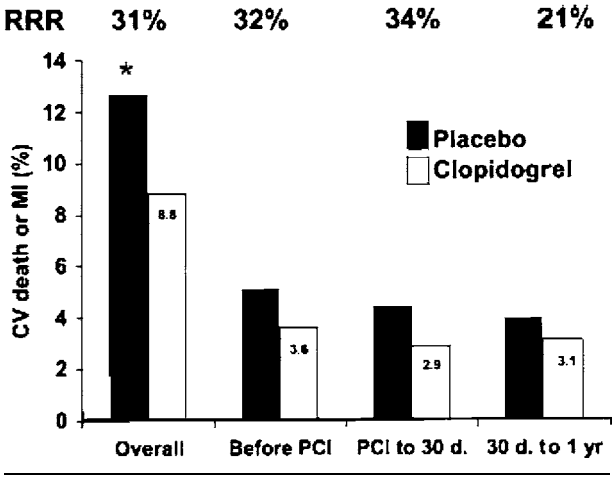

Fig. 3. *Cardiovascular death or MI in Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent recurrent ischemic Events [PCI-CURE]: Consistent benefits of clopidogrel at all non-overlapping time points. MI = myocardial infarction; RRR = relative risk ratio. Reprinted from Mehta and Yusuf. Short and long-term antiplatelet therapy. J Am Coll Card 19:79S–88S. Reproduced with permission 2003. © 2003 American College of Cardiology Foundation.*

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. The recently published CREDO trial was designed to (1) evaluate the benefit of long-term (12-month) treatment with clopidogrel after PCI, and to (2) determine the benefit of initiating clopidogrel with a pre-procedure loading dose, both in addition to aspirin therapy [54]. A total of 2116 patients undergoing PCI were randomized between short- and long-term treatment with clopidogrel (define as 28 days vs. 1 year, respectively) in addition to aspirin therapy. Patients who received long-term clopidogrel therapy had a 26.9% relative reduction in the combined risk of death, MI, or stroke at 1 year compared with those receiving only 28 days of clopidogrel treatment. This benefit was associated with a nonsignificant increase in the risk of major bleeding in the long-term clopidogrel group. In addition, a loading dose of clopidogrel given at least 3 hours before the procedure did not reduce the combined risk of death, MI, or urgent target-vessel revascularization at 28 days. However, subgroup analyses did demonstrate that longer intervals between the loading dose and PCI (i.e., at least 6 hours before PCI) was associated with a 38.6% relative risk reduction for this endpoint. The results of the CREDO trial has already led to a change in the duration of the post procedural antiplatelet regimen duration in patients undergoing PCI at many centers.

Potential Pitfalls Associated with the Use of Clopidogrel

Despite the encouraging results of the CURE trial, there remain questions regarding the widespread applicability of these findings to all patients with unstable angina and NSTEMI. For example, a recent pharmacoeconomic analysis examined the cost-effectiveness of using aspirin, clopidogrel or both for secondary prevention of coronary artery disease [55]. 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 [54]. Therefore, based on this cost-benefit analysis, clopidogrel should essentially be reserved for patients who are ineligible for aspirin therapy.

Besides pharmaco-economic considerations, however, another very important factor limiting the application of the CURE data to the "real world" is the risk of post-operative bleeding associated with clopidogrel should urgent surgical revascularization be required. The necessity of withholding clopidogrel therapy for a minimum of 5 days prior to surgical revascularization to nullify bleeding risk arguably makes it's upfront and universal use debatable in the ACS setting where it is usually not possible to determine the need for subsequent bypass surgery prior to the performance of coronary angiography at the time a patient presents with an ACS. If coronary bypass surgery is ultimately deemed necessary, the administration of clopidogrel upon presentation to the emergency room could lead to an unnecessary and potentially hazardous delay of this procedure.

Another criticism of the CURE Trial remains the relative underutilization of the GP IIb/IIIa inhibitors (5.9% in the clopidogrel group and 7.2% in the placebo group) when compared to contemporary U.S. practice. Thus, it remains unknown if the same benefit with the use of clopidogrel would have been seen if a greater proportion of patients had been on GP IIb/IIIa inhibitors.

Lastly, an area of relative uncertainty remains the unknown interactions of clopidogrel with other agents that form the mainstay of treatment of coronary heart disease. These interactions largely arise from the common metabolism of a variety of drugs (including clopidogrel) by the human hepatic CYP enzyme system. Lau et al. recently described reduced *in vitro* and *in vivo* clinical activity of clopidogrel when co-administered with atorvastatin, an HMG-CoA reductase inhibitor [56]. The authors demonstrated that this novel clinical interaction results from a common CYP3A4 metabolic pathway shared by these two agents. The use of atorvastatin in doses routinely administered to patients produced CYP3A4 inhibition in a dose-dependent manner leading to decreases in the metabolic conversion of clopidogrel to its active form. In contrast, when clopidogrel was administered with pravastatin [a drug not metabolized by the CYP system], no effect on platelet aggregation inhibition was noted [56]. A variety of agents use the CYP3A4 pathway, the most abundant cytochrome P450 enzyme of humans, raising the potential of other clopidogrel-drug interactions.

Conclusion

The pharmacological treatment of ischemic heart disease 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 via 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. Clopidogrel, when used in combination with aspirin in ACS patients not undergoing PCI, 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 one year. Therefore, the data would suggest that both aspirin and clopidogrel be initiated early and continued long term in order to obtain the greatest benefit in the largest number of patients. Although rare, patients treated with clopidogrel need to be monitored carefully for the development of thrombocytopenia and 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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