Editors' Picks: Most Important Papers in Antiplatelet Therapy

The Editors

The following are highlights from the series, Circulation: Cardiovascular Interventions Topic Review. This series summarizes the most important manuscripts, as selected by the editors, that have published in the Circulation portfolio. The studies included in this article represent the most noteworthy research in the area of antiplatelet therapy. (Circ Cardiovasc Interv. 2011;4:e38-e48.)

Clopidogrel and Aspirin

Pharmacodynamic Effects of Concomitant Versus Staggered Clopidogrel and Omeprazole Intake: Results of a Prospective, Randomized, Crossover Study

Summary: A growing body of evidence has shown a broad variability in interindividual pharmacodynamic response profiles to the platelet inhibitor clopidogrel, and patients with reduced platelet inhibition have an increased risk of recurrent atherothrombotic events. Numerous factors may contribute to poor clopidogrel response. Among these, that secondary to a drug interaction with the proton pump inhibitor omeprazole has emerged. The prognostic implications associated with clopidogrel and omeprazole use are not fully elucidated. However, given the high frequency with which both these drugs are prescribed, even a small and limited impairment in clinical outcomes can potentially affect a large number of patients. The Food and Drug Administration and the European Medicines Agency have recently recommended avoidance of this drug combination. Nevertheless, because both clopidogrel and omeprazole are rapidly metabolized, many experts have hypothesized and proposed to stagger clopidogrel and omeprazole intake to minimize or even overcome their interaction. However, this strategy has not been validated yet and represents the rationale for the present study design. The findings of the present investigation demonstrate the presence of a pharmacodynamic interaction between clopidogrel and omeprazole when administered concomitantly as well as staggered. Given the presence of a pharmacodynamic interaction between omeprazole and clopidogrel irrespective of the timing of their administration, use of omeprazole should be avoided in clopidogrel-treated patients.

Conclusions: Omeprazole impairs clopidogrel-induced antiplatelet effects in the maintenance phase of treatment irrespective of timing of their administration.

Editor's Comment: The proton pump inhibitor omeprazole has been shown in pharmacodynamic studies to interfere with the conversion of clopidogrel to its active metabolite by interfering with the P450 (CYP) 2C19 isoenzyme in the liver. Since these agents are frequently given together to reduce gastrointestinal bleeding in patients on dual antiplatelet therapy, understanding this relationship is important. Due to the short half-life of omeprazole, it has been suggested that staggering the dose may overcome this problem. In this study done in normal volunteers, staggering the dosing of both drugs did not affect this interaction. This study continues to raise concerns about coadministration and supports the recommendations to be cautious about using them together. Although one recent randomized clinical trial (COGENT) failed to show any adverse clinical effects of coadministration, it is known that other proton pump inhibitors may not share this same problem and, until this issue is resolved, may be a reasonable alternative to omeprazole.

Pharmacodynamic Evaluation of Pantoprazole Therapy on Clopidogrel Effects: Results of a Prospective, Randomized, Crossover Study

Summary: The prognostic implication of reduced pharmacodynamic efficacy of clopidogrel therapy as a result of a drug-drug interaction with proton-pump inhibitors (PPI) has not been elucidated fully. The regulatory authorities, in particular the Food and Drug Administration and the European Medicines Agency, have recommended avoidance of the combination of clopidogrel and omeprazole, the most commonly prescribed PPI. However, limited information is available on the effects of other PPIs, such as pantoprazole, which has lower potential to inhibit the CYP2C19 enzyme, on the pharmacodynamics of clopidogrel. The results of this prospective, randomized, crossover study demonstrate the absence of any significant impairment in clopidogrel-induced pharmacodynamic efficacy as assessed by several assays when pantoprazole is administered either concomitantly or staggered. Notably, this investigation used a dose of pantoprazole (80 mg) higher than that used in clinical practice to maximize any of its adverse effects on CYP2C19. Therefore, it is unlikely that a pharmacodynamic interaction would be observed with the lower dose used more commonly in clinical practice (eg, 40 mg). These observations are in line with the concept that a PPI-clopidogrel interaction is not a class-specific effect but rather a drug-specific effect affecting PPIs metabolized primarily by CYP2C19 (eg, omeprazole) and support recommendations suggesting that if a PPI is warranted in a patient at increased risk of a gastrointestinal bleed while receiving dual antiplatelet therapy, pantoprazole may be considered as a safe treatment option.

Conclusions: Pantoprazole therapy used at high doses is not associated with modulation of the pharmacodynamic effects of clopidogrel, irrespective of timing of drug administration.

Editor's Comment: Impaired clopidogrel-mediated platelet inhibition is associated with an increased risk of ischemic events. Drug interactions, such as those induced by PPIs, have been implicated in this process, raising serious safety concerns among clinicians given the broad utilization of these drugs. Current evidence suggests that this interaction is drug-specific and not class-specific, as not all PPIs
interfere with the pharmacokinetic and pharmacodynamic effects of clopidogrel. The investigators support this hypothesis by showing the lack of any significant pharmacodynamic interaction using pantoprazole, a PPI that interferes minimally with CYP2C19 activity. These outcomes were obtained using higher than recommended doses of pantoprazole (80 mg) to rule out this interaction, which was not observed regardless of timing of drug administration (concomitant or staggered with clopidogrel). Although clinical data are lacking, this study suggests pantoprazole as a valid treatment option for patients warranting gastric protection while on clopidogrel treatment, in line with expert consensus recommendations.

Clinical Outcomes in Patients With the Concomitant Use of Clopidogrel and Proton Pump Inhibitors After Percutaneous Coronary Intervention: An Analysis From the Guthrie Health Off-Label Stent (GHOST) Investigators

Summary: Some observational studies have demonstrated higher adverse cardiovascular outcomes in patients taking clopidogrel with proton pump inhibitors (PPIs) compared with clopidogrel alone. However, other studies, including a large, randomized placebo-controlled trial, have failed to demonstrate any increase in the risk of adverse clinical events with the combination. In 2651 consecutive patients discharged from the hospital alive after coronary stenting, we found no difference in the 6-month incidence of major adverse cardiovascular events or net adverse clinical events (a composite of major adverse clinical events and thrombolysis in myocardial infarction major or minor bleeding) in patients who received PPI at discharge versus those who did not. Thus, the present study does not suggest a clinically relevant interaction between clopidogrel and PPIs. Gastrointestinal side effects are a common reason for premature discontinuation of antplatelet therapy after percutaneous coronary intervention, which is associated with an increased risk of adverse cardiovascular clinical events. Use of PPIs decreases gastrointestinal side effects related to antplatelet agents. Our findings are reassuring and support the recent endorsement for PPI use in combination with dual antplatelet therapy in high-risk patients.

Conclusions: The use of PPIs with dual antplatelet therapy was not associated with any adverse influence on major adverse cardiovascular events or net adverse clinical events after percutaneous coronary intervention.

Editor’s Comment: While pharmacodynamic studies have shown that PPI, particularly omeprazole, reduce the antplatelet effect of clopidogrel, the clinical significance of this observation has been debated. One randomized trial (COGENT) showed no difference in major adverse events with lower gastrointestinal bleeding on omeprazole, but this trial may not represent real-world patients. This study used a comprehensive database to examine this question. After 6 months of dual antplatelet therapy, the investigators showed no difference in the incidence of major adverse cardiovascular events or net adverse clinical events. Use of PPIs decreases gastrointestinal side effects related to antplatelet agents. Our findings are reassuring and support the recent endorsement for PPI use in combination with dual antplatelet therapy in high-risk patients.

Pharmacodynamic Effects of Different Aspirin Dosing Regimens in Type 2 Diabetes Mellitus Patients With Coronary Artery Disease

Summary: The present pilot investigation was designed with the aim of understanding how different aspirin dosing regimens affect platelet response as measured by pharmacodynamic parameters in a cohort of 20 patients with type 2 diabetes mellitus (T2DM) and stable coronary artery disease. The study hypothesis was that an increase in the frequency of aspirin administration may provide more effective platelet inhibition in T2DM patients. The working hypothesis was developed on the basis that patients with T2DM have increased platelet turnover rates resulting in an increased proportion of non-aspirin-inhibited platelets with a once-daily dosing regimen. The present investigations showed that a twice-daily, low-dose aspirin administration results in greater platelet inhibition than a once-daily administration. The clinical implications of such modified aspirin treatment regimen in T2DM patients warrant further investigation.

Conclusions: Aspirin dosing regimens are associated with different pharmacodynamic effects in platelets from T2DM patients and stable coronary artery disease, with a twice-daily, low-dose aspirin administration resulting in greater platelet inhibition than once-daily administration as assessed by aspirin-sensitive assays and a dose-dependent effect on serum thromboxaneB2 levels. The clinical implications of a modified aspirin regimen tailored to T2DM patients warrant further investigation.

The Platelet Activity After Clopidogrel Termination (PACT) Study

Summary: “Rebound” platelet hyperreactivity after discontinuation of clopidogrel has been proposed to lead to increased thrombotic risk, including late stent thrombosis. This putative phenomenon is relevant to the question of when or if clopidogrel treatment after stent placement should be discontinued and whether a tapering regimen of clopidogrel treatment might reduce thrombotic complications. However, the hypothesis that discontinuation of clopidogrel results in platelet hyperreactivity has never been rigorously tested. The authors report a randomized, double-blind, placebo-controlled, crossover study in which platelet reactivity was measured using multiple methods, agonists, and agonist concentrations, before, during, and after exposure of subjects to clopidogrel or placebo. All subjects showed the expected inhibition of platelet reactivity during exposure to clopidogrel. However, at no time point after discontinuation of clopidogrel was platelet reactivity, as determined by any assay end point, significantly greater than after discontinuation of placebo. These results demonstrate that discontinuation of clopidogrel does not result in “rebound” platelet hyperreactivity and suggest that recovery of platelet function to pretreatment levels but not a “rebound” phenomenon accounts for the reported increased incidence of thrombotic events in patients after termination of clopidogrel therapy. Although prolonged clopidogrel treatment would prevent recovery of platelet reactivity to pretreatment levels and perhaps the associated increased incidence of thrombotic events, the optimal duration of dual antiplatelet therapy remains unknown. Large-scale clinical trials, such as the ongoing Dual Antiplatelet Therapy Study (DAPT Study), (http://www.clinicaltrials.gov/ct2/show/NCT00977938), are required to determine the relative risks and benefits of short versus long-term dual antiplatelet therapy.

Conclusions: This randomized, double-blind, placebo-controlled, crossover study demonstrates that discontinuation of clopidogrel does not result in “rebound” platelet hyperreactivity, as determined by multiple time points, assays, agonists, and agonist concentrations.

Editor’s Comment: The increased incidence of ischemic events including stent thrombosis and myocardial infarction has been reported following discontinuation of clopidogrel. A potential explanation for this observation has been a possible platelet hyperactive
“rebound” effect related to clopidogrel discontinuation. This is the first report to address this issue, using multiple different platelet function assays at multiple time points from 1 to 45 days following clopidogrel discontinuation. Platelet hyperactivity was not present at any time point, suggesting a pharmacodynamic rebound effect is not an explanation for the reported increase in ischemic events following discontinuation of clopidogrel.5

Frequency of Allergic or Hematologic Adverse Reactions to Ticlopidine Among Patients With Allergic or Hematologic Adverse Reactions to Clopidogrel

Summary: Clopidogrel and ticlopidine are structurally similar. The authors conducted a retrospective study among patients who had received both drugs and had an allergic or hematologic adverse reaction to one of these drugs to determine the extent and severity of allergic cross-reactivity. Seventy-six patients met the study criteria. Of the 52 patients with an allergic or hematologic adverse reaction to ticlopidine, 14 (27%) were also unable to tolerate ticlopidine. No patient with an allergic reaction to one thienopyridine developed a life-threatening reaction to the other.

Conclusions: In patients with an allergic or hematologic adverse reaction to one thienopyridine, there seems to be an increased frequency of such reactions to the other thienopyridine. However, no patient had a life-threatening reaction after exposure to the alternative thienopyridine.

Editor’s Comment: The frequency and severity of allergic or hematologic cross-reactivity between thienopyridines is not known. A retrospective analysis involving databases from 2 large academic institutions demonstrates that approximately 1 in 4 patients who experienced an allergic or hematologic adverse reaction to ticlopidine or clopidogrel experienced a similar adverse reaction when exposed to the other thienopyridine. The most frequent adverse reaction was a rash. While limited data regarding hematologic cross reactivity are provided in this analysis, the data suggest that switching thienopyridines in patients presenting with an allergic response to one thienopyridine will not be a successful strategy in a significant minority of these patients.6

Increased Risk of Bleeding in Patients on Clopidogrel Therapy After Drug-Eluting Stents Implantation: Insights From the HMO Research Network-Stent Registry (HMORN-Stent)

Summary: Recent studies have suggested that prolonged dual antiplatelet therapy (>6 months) after drug-eluting stent placement may be associated with reduced risk of myocardial infarction and death. As a result, many clinicians have extended treatment with clopidogrel to exceed 12 months and even 18 months. However, clopidogrel use has also been associated with treatment related risks such as bleeding complications. Therefore, to consider the appropriate length of clopidogrel therapy, the risks and benefits must be weighed within a patient population. Accordingly, using the HMO Research Network-Stent Registry, the authors assessed the association between clopidogrel use and risks of major bleeding to the benefit of decreased myocardial infarction or death in 6-month intervals after discharge. Clopidogrel use was determined by pharmacy dispensing data. After adjustment, patients on clopidogrel therapy had an association with increased major bleeding in all time intervals (0–6 months, 7–12 months, and 13–18 months) compared with patients off clopidogrel. In contrast, clopidogrel use was also associated with a decreased risk of myocardial infarction for all time intervals and decreased death in the 7- to 12-month interval. These results illustrate the risks and benefits associated with clopidogrel use in routine clinical practice and highlight the importance of identifying which patient subgroups are most likely to benefit from extended clopidogrel therapy and which are most likely to be harmed.

Conclusions: Clopidogrel use was associated with increased major bleeding and decreased myocardial infarction persisting to 18 months. Bleeding risks on clopidogrel therapy deserve consideration in the ongoing debate regarding optimal clopidogrel duration after percutaneous coronary intervention.

Editor’s Comment: The risks and benefits of prolonged dual antiplatelet therapy have been the subject of intense investigation and discussion over the past decade. Most available data come from large, randomized, clinical trials, often not reflecting a real-world practice population. Using a propensity risk-adjusted analysis of data from 3 large, integrated health care delivery systems, the investigators report an increased risk of major bleeding in patients maintained on dual antiplatelet therapy at measured time intervals 0–6 months, 2–12 months, and 13–8 months. A decreased risk of myocardial infarction during these time periods was also observed. This study supports our current clinical concerns regarding the increased risk of major bleeding in patients maintained on prolonged dual antiplatelet therapy.7

Safety of Short-Term Discontinuation of Antiplatelet Therapy in Patients With Drug-Eluting Stents

Summary: The authors identified 161 cases of late stent thrombosis or very late stent thrombosis from 84 articles in a systematic Medline search. Patients had a mean age of 58.4±13.4 years, and 88% were male. A total of 19 cases occurred in patients who were receiving dual antiplatelet therapy at the time of the event. If patients stopped both a thienopyridine and acetylsalicylic acid simultaneously, the median time to event was 7 days. If patients had previously stopped a thienopyridine with no ill effect and subsequently stopped acetylsalicylic acid, the median time to event was also 7 days. If a thienopyridine was stopped but acetylsalicylic acid was maintained, the median time to event was 122 days. Among the 48 patients who stopped both agents, 36 cases (75%) occurred within 10 days. Among the 94 patients who stopped a thienopyridine but not acetylsalicylic acid, only 6 cases (6%) occurred within 10 days. If acetylsalicylic acid therapy is maintained, short-term discontinuation of a thienopyridine may be relatively safe in patients with drug-eluting stents.

Conclusions: If acetylsalicylic acid therapy is maintained, short-term discontinuation of a thienopyridine may be relatively safe in patients with drug-eluting stents.

Editor’s Comment: The influence of discontinuation of antiplatelet therapy on late stent thrombosis risk is difficult to study. This modified case design takes advantage of available reported drug eluting stent thrombosis events and suggests that brief discontinuation of a thienopyridine (5–7 days) on a background of aspirin therapy carries a low risk. Physicians trying to weigh the options for patients with bleeding or requiring surgical procedures can use this information.8

Background, Incidence, and Predictors of Antiplatelet Therapy Discontinuation During the First Year After Drug-Eluting Stent Implantation

Summary: All guidelines agree on the need for at least 1 year of double-antiplatelet therapy after drug-eluting stent implantation. This study, conducted in 29 hospitals, shows that 14.4% of 1622 patients receiving drug-eluting stents interrupted at least 1 antiplatelet drug for at least 5 consecutive days during the first year after implantation. Although antiplatelet therapy discontinuation (ATD) can be justified by the occurrence of major hemorrhage or surgical procedure, these events occurred in only 25.7% of ATD cases. The most common scenarios for ATD were minor hemorrhages/proce-
dures, medical decisions without any bleeding or bleeding-risk event, and patient initiative. Several patient characteristics predicted higher risk for ATD; some were associated with future bleeding events or the need for invasive procedures, whereas others were associated with ATD due to patient initiative. Although these determinants are not modifiable, they emphasize the need for careful patient selection. Other determinants were related to the process of care. Thus, long-term use of anticoagulants predicted ATD due to medical decision, whereas simple provision of written instructions about the importance of antiplatelet maintenance may avoid some cases of unjustified ATD. These results highlight that medical patterns of care of patients with drug-eluting stents should be better defined, particularly relative to the maintenance of antiplatelet therapy during procedures. In addition, they illustrate a common dilemma in contemporary medicine as a whole, not just in cardiology: Patients who are cared for by their general practitioners may pose formidable dilemmas to such practitioners because of the subtleties of the therapeutic technology used by different specialists.

**Conclusions:** ATD during the first year after drug-eluting stent implantation is based mainly on patient decision or a medical decision not associated with major bleeding events or major surgical procedures. Individual- and hospital-level variables are important to predict ATD.

**Editor’s Comment:** Premature discontinuation of antiplatelet therapy after drug-eluting stent implantation is a strong predictor of stent thrombosis. Knowledge of factors associated with drug discontinuation can assist physicians in selection of appropriate patients for drug-eluting stent and optimizing compliance in these patients. This prospective study highlights the facts that medical, psychosocial, and health care processes are all important variables. Discontinuation in many cases may be appropriate and temporary. Implementation of protocols for assessing bleeding risk and delivering patient education, however, could lower the incidence of drug discontinuation.9

**Antiplatelet Therapy and Stent Thrombosis After Sirolimus-Eluting Stent Implantation**

**Summary:** Randomized data are lacking on the optimal duration of dual-antiplatelet therapy after drug-eluting stent implantation and on the risks associated with discontinuation of dual-antiplatelet therapy. Despite the absence of randomized data, the use of dual-antiplatelet therapy beyond 1 year has become commonplace in clinical practice. In the j-Cypher registry, 10,778 Japanese patients treated exclusively by sirolimus-eluting stents were followed up for up to 2 years with prospective data collection on the status of antiplatelet therapy during follow-up. Incidences of definite stent thrombosis were 0.34% at 30 days, 0.54% at 1 year, and 0.77% at 2 years. Thienopyridine use was maintained in 97%, 62%, and 50% of patients at 30 days, 1 year, and 2 years, respectively. The main findings of the present study were that discontinuation of both aspirin and thienopyridine, but not discontinuation of thienopyridine therapy only, was associated with an increased stent thrombosis risk and that no apparent clinical benefit of thienopyridine use could be seen beyond 6 months after sirolimus-eluting stent implantation, according to the 6-month landmark analysis. Given the increased risk of bleeding and huge economic burden associated with prolonged dual-antiplatelet therapy, the optimal duration of dual-antiplatelet therapy should be defined by prospective, randomized trials evaluating its net clinical benefit after consideration of both ischemic events and bleeding complications.

**Conclusions:** Discontinuation of both thienopyridine and aspirin, but not discontinuation of thienopyridine therapy only, was associated with an increased risk of stent thrombosis. Landmark analysis did not suggest an apparent clinical benefit of thienopyridine use beyond 6 months after sirolimus-eluting stent implantation.

**Editor’s Comment:** In contemporary clinical practice, dual antiplatelet therapy is recommended for 1 year following implantation of a drug-eluting stent to limit stent thrombosis; premature discontinuation of these drugs is a well-recognized predictor of stent thrombosis and associated major adverse cardiovascular events. This large-scale, retrospective analysis confirms that the highest incidence of stent thrombosis occurs in individuals that discontinue both aspirin and thienopyridine early as well as after the recommended 1-year treatment period. In contrast, early discontinuation of the thienopyridine alone did not appear to increase stent thrombosis. While these findings highlight that the risk of stent thrombosis is increased for those patients that must discontinue dual antiplatelet therapy early for other medical or surgical reasons, they also reveal that this risk extends beyond the 1-year time point. They also do not support the safety of early discontinuation of thienopyridines alone and underscore the fact that findings from ongoing randomized clinical trials to determine the optimal duration of dual antiplatelet therapy will be needed before changing current clinical practice.10

**Cardiovascular Death and Nonfatal Myocardial Infarction in Acute Coronary Syndrome Patients Receiving Coronary Stenting Are Predicted by Residual Platelet Reactivity to ADP Detected by a Point-of-Care Assay: A 12-Month Follow-Up**

**Summary:** A growing body of evidence shows that an in vitro residual platelet reactivity (RPR) in patients undergoing dual antiplatelet (aspirin plus clopidogrel) treatment is associated with an increased risk of adverse cardiovascular events in high-risk vascular patients. Light transmittance aggregometry is considered the standard method for assessment of platelet function, but logistic problems make its routine use difficult. In recent years, point-of-care assays of platelet function have become available, including the VerifyNow P2Y12 system, which provides values of RPR after ADP stimulus correlated with those found by light transmittance aggregometry induced by ADP. In 683 patients with acute coronary syndrome treated by percutaneous coronary intervention, we sought to verify whether the VerifyNow P2Y12 assay is able to predict clinical recurrences, and we found that RPR to ADP measured by a point-of-care assay is an independent predictor of cardiovascular death and nonfatal myocardial infarction at 12-month follow-up. The availability of a simple test for assessment of this biological entity (persistent in vitro platelet hyperreactivity with ADP) in the panel of clinical, laboratory, and procedural risk factors may allow for better risk stratification and identification of patients in whom an aggressive blood is likely to play a key role in making the patient a vulnerable patient.

**Conclusions:** RPR to ADP with clopidogrel therapy, measured by the point-of-care assay VerifyNow P2Y12, is able to detect acute coronary syndrome patients at risk of 12-month cardiovascular death and nonfatal myocardial infarction. The optimal cutoff value was identified as being 240 P2Y12 reaction units.

**Editor’s Comment:** There is significant interindividual variability in the response to clopidogrel, owing to the diverse pharmacogenetics of clopidogrel metabolism. In those individuals in whom the drug is not metabolized adequately, platelets retain some reactivity and contribute to acute coronary syndromes and adverse events. This has led investigators to utilize a point-of-care assay system to measure the antiplatelet efficacy of clopidogrel to identify individuals with high residual platelet reactivity that are at risk for adverse events. Here, investigators identified a P2Y12 reaction unit value of ≥240 as the optimal cutoff value to predict adverse events, a finding that is in line with prior studies. Thus, while the point-of-care assay can identify individuals at risk for future adverse cardiovascular events, it remains unclear if modifying this response by either switching P2Y12 antagonists or changing the dosing regimen in selected high-risk patient populations will influence outcomes.11
Aspirin Plus Clopidogrel Versus Aspirin Alone After Coronary Artery Bypass Grafting: The Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) Trial

Summary: Coronary artery bypass grafting (CABG) is an effective treatment for ischemic heart disease, but its long-term results are compromised by the development of saphenous vein graft (SVG) disease. After surgery, a platelet-mediated thickening of the SVG wall occurs, with smooth muscle cell proliferation and extracellular matrix protein synthesis. This process, termed intimal hyperplasia, forms a template for the development of SVG atherosclerosis and eventual occlusion. Clopidogrel has been shown to inhibit intimal hyperplasia in animal studies and therefore may reduce SVG intimal hyperplasia after CABG. In the Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) study, the authors conducted a double-blind, placebo-controlled trial to evaluate whether the addition of clopidogrel to aspirin inhibits the development of SVG disease. A total of 113 patients undergoing CABG with SVGs were randomized to receive either aspirin 162 mg plus clopidogrel 75 mg daily or aspirin 162 mg plus placebo daily for 1 year, followed by SVG intravascular ultrasound and coronary angiography. The primary outcome, SVG intimal area at 1 year, did not differ significantly between the 2 groups (4.1 ± 2.0 versus 4.5 ± 2.1 mm², aspirin-clopidogrel versus aspirin-placebo, P = 0.44). Gaia genotype and freedom from major adverse cardiovascular events also did not significantly differ between the 2 groups. In summary, CASCADE indicated that compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce SVG intimal hyperplasia 1 year after CABG. Newer antiplatelet agents with purported advantages over clopidogrel may constitute important areas for future research to target the inhibition of SVG disease after CABG.

Conclusions: Compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce the process of SVG intimal hyperplasia 1 year after CABG.

Editor’s Comment: Intimal hyperplasia leading to luminal stenosis or occlusion is a recognized mechanism of saphenous vein graft failure after CABG surgery. To date, the etiology of vein graft intimal hyperplasia has not been elucidated; however, preclinical studies have provided evidence to suggest that platelet-derived factors and/or nonplatelet effects of clopidogrel inhibit vein graft neointima formation. This randomized clinical trial of clopidogrel added to standard aspirin therapy found that the addition of clopidogrel had no effect on limiting SVG intimal hyperplasia or clinical outcomes after 1 year. Although the study cannot exclude the possibility that longer-term clopidogrel therapy may improve intimal hyperplasia, these findings indicate that saphenous graft failure is a complex multifactorial process that will likely require multitarget interventions to prevent intimal hyperplasia and subsequent vein graft failure.

Bleeding Complications With Dual Antiplatelet Therapy Among Patients With Stable Vascular Disease or Risk Factors for Vascular Disease: Results From the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) Trial

Summary: Choosing the optimal antiplatelet regimen for a patient requires a thorough understanding of not only the benefits of therapy but the risks as well. This is especially important now that several different antiplatelet agents are available. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial is the largest and longest study of the risks of dual antiplatelet therapy, and this analysis of CHARISMA data provide insights into the frequency of bleeding, risk factors for bleeding, and consequences of bleeding. Clinicians will find the data useful when they try to balance the risks and benefits of dual antiplatelet therapy with aspirin and clopidogrel in stable patients with vascular disease or with risk factors for vascular disease, like those enrolled in the CHARISMA trial.

Conclusions: In CHARISMA, there was an increased risk of bleeding with long-term clopidogrel. The incremental risk of bleeding was greatest in the first year and similar thereafter. Moderate bleeding was strongly associated with mortality.

Editor’s Comment: One hazard associated with prolonged dual antiplatelet therapy is the risk of bleeding that may result in morbidity and mortality. Using data from a large-scale clinical trial, this study found that there was a significant increase in moderate bleeding events that was associated with all-cause mortality and major adverse cardiovascular events in dual antiplatelet therapy patients. While it is known that significant bleeding and anemia are linked to adverse events, this study identifies moderate bleeding events as a risk factor for all-cause mortality. Findings from this study further highlight the fact that bleeding is more likely to occur in individuals with high-risk clinical characteristics or comorbidities that already portend a worse outcome.

Paraoxonase-1 Q192R Polymorphism and Antiplatelet Effects of Clopidogrel in Patients Undergoing Elective Coronary Stent Placement

Summary: There is strong evidence that the variability in antiplatelet response to clopidogrel is associated with an increased risk for ischemic events. A diminished pharmacodynamic response to the inactive produg clopidogrel is related to a decreased in vivo formation of the active metabolite. Several polymorphically expressed CYP, including CYP2C19, contribute to the formation of this metabolite. Carriers of CYP2C19 loss-of-function alleles have a reduced pharmacodynamic response to clopidogrel. Although CYP2C19 polymorphism has been identified as the strongest predictor of antiplatelet response to clopidogrel, only 5–12% of the variability in antiplatelet effect can be attributed to this variable. However, a recently published case-cohort study suggested PON-1 as the key enzyme for bioactivation of clopidogrel. This study reported that the PON-1 QQ192 genotype compared with PON-1 RR192 genotype was associated with a reduced antiplatelet response to clopidogrel and with a more than 12-fold increase in risk of stent thrombosis. By contrast, CYP2C19 loss-of-function polymorphisms were not significantly associated with any of these outcomes in this study. The main finding in this study is that the PON-1 Q192R genotype was not associated with on-clopidogrel platelet reactivity. On the other hand, the authors confirmed the previously shown association of antiplatelet response to clopidogrel with the CYP2C19*2 loss-of-function allele and the CYP2C19*2 gain-of-function allele together as well as baseline clinical and demographic variables. Thus, this study does not provide evidence that PON1 genotyping may be useful in tailoring antiplatelet treatment with clopidogrel.

Conclusions: On-treatment platelet reactivity in patients undergoing percutaneous coronary intervention after loading with clopidogrel 600 mg was not associated with PON1 Q192R genotype.

Editor’s Comment: A number of polymorphisms primarily the CYP2C19 alleles have been associated with both reduced function and increased function of the key liver enzymes responsible for conversion of clopidogrel to its active derivative. One recent study suggested that polymorphisms of the paraoxonase-1esterase, which is responsible for HDL metabolism, also can result in loss of function and worse outcomes in patients treated with clopidogrel. This study refuted this finding in a secondary analysis of the EXCELCIOR trial. It also confirms the findings of a number of other recent trials. The search for additional polymorphisms is important since the commonly recognized one only explains a small fraction of the variabili-
ity in the response to clopidogrel. If genetic testing is to become a useful tool in choosing therapy then it will need to have a much greater predictive value to be valuable to the clinician.14

New Antiplatelet Agents

Novel Antiplatelet Drug Revacept (Dimeric Glycoprotein VI-Fc) Specifically and Efficiently Inhibited Collagen-Induced Platelet Aggregation Without Affecting General Hemostasis in Humans

Summary: Treating atherothrombosis with Revacept in patients with acute cerebral arterial syndromes or acute coronary syndromes is a novel concept. This study drug is a soluble form of the platelet glycoprotein VI receptor and binds specifically to collagen structures of ruptured plaques. Therefore, the first steps of platelet adhesion and the consecutive platelet aggregation are prevented without affecting the general platelet function and hemostasis. Revacept would be the first drug to potently block platelet function without increasing bleeding complications in patients. Preclinical and phase I studies in healthy volunteers have proved the mode of action and safety of this study drug. Despite tremendous progress in the treatment of patients with acute coronary or cerebral syndromes, decreased thrombus formation and reduction of ischemic complications are often achieved at the expense of increased bleeding. Therefore, a potent drug that inhibits platelet activation but would not affect general hemostasis would pose a significant improvement for the treatment of patients with acute arterial syndromes. The problem of increased bleeding has often hampered therapeutic benefits in the prevention or reduction of ischemia by antiplatelet or other antithrombotic drugs, especially in patients with ischemic strokes. Efficacy studies in patients must prove that the expectations will hold true in the future to develop a safe and potent platelet inhibitory drug.

Conclusions: This phase I study demonstrated that Revacept is a safe and well-tolerated new antiplatelet compound with a clear dose-dependent pharmacokinetic profile with specific, dose-related inhibition of platelet aggregation despite completely unaltered general hemostasis.

Editor’s Comment: Revacept is a novel antiplatelet agent that targets collagen-induced platelet activation by binding with collagen and fibronectin in atherosclerotic plaques and occupying ligands critical for platelet activation. Compared with antiplatelet agents currently in use, Revacept has the potential to reduce platelet activation and risk of bleeding. This first in man study in healthy volunteers showed promise with dose-dependent specific inhibition of collagen-induced platelet aggregation and was well tolerated. Onset of inhibition occurred by 2 hours and was long acting. Further studies will need to define the role of this drug with respect to currently used agents.15

Cytochrome 2C19 Polymorphism and Response to Adjunctive Cilostazol Versus High Maintenance-Dose Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention

Summary: Recent data have shown that increased platelet reactivity despite clopidogrel therapy is associated with a higher risk of ischemic events in patients who undergo percutaneous coronary intervention (PCI). Although clinical factors and drug-drug interactions reduce the antiplatelet response to clopidogrel, the hepatic cytochrome P450 (CYP) mutant alleles, especially the CYP2C19 isoenzyme, have shown a strong association with increased platelet reactivity and the risk of major adverse cardiovascular events. Therefore, antiplatelet regimens that retain antiplatelet efficacy in the presence of the CYP2C19 polymorphism would benefit high-risk PCI-treated patients. Adjunctive cilostazol to dual antiplatelet therapy (or "triple antiplatelet therapy") can be an attractive option for this genotypic risk profile. Accumulating data have verified the antiplatelet effects of cilostazol. Furthermore, cilostazol is converted into active metabolites by the CYP3A system and therefore should not lose efficacy in the presence of CYP2C19 isoenzyme mutations. The present study enrolled high-risk patients undergoing elective PCI to evaluate platelet reactivity reductions between preprocedure and 30-day follow-up. Additive platelet inhibition by double-dose clopidogrel was diminished in carriers of the CYP2C19 variant allele. However, adjunctive cilostazol therapy resulted in consistent platelet inhibition irrespective of CYP2C19 genotyping. These results support the hypothesis that triple antiplatelet therapy may be an optimal antiplatelet regimen for PCI-treated patients in high-risk clinical, lesion, or genotyping subsets, which requires further testing in global scaled, large, prospective studies to verify the efficacy and safety of this antiplatelet regimen.

Conclusions: Among high-risk patients undergoing elective PCI, adjunctive cilostazol can achieve consistently intensified platelet inhibition and reduce the risk of high posttreatment platelet reactivity irrespective of CYP2C19 genotyping.

Editor’s Comment: The presence of polymorphisms to the P450 (CYP)C19 isoenzyme as well as others has been shown to result in reduced effectiveness of clopidogrel to inhibit platelet aggregation and is a predictor of a greater risk of adverse events. Higher doses of clopidogrel have been used with some success. This study examined whether use of cilostazol in addition to high dose clopidogrel would increase platelet inhibition in patients with polymorphisms of this allele. The study showed that cilostazol was effective regardless of the presence of the polymorphisms and provides further evidence that triple therapy may be useful in such patients. To further establish the clinical utility of this approach, trials examining clinical outcomes including stent thrombosis need to be conducted.16

Adding Cilostazol to Dual Antiplatelet Therapy Achieves Greater Platelet Inhibition than High Maintenance-Dose Clopidogrel in Patients With Acute Myocardial Infarction: Results of the Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With AMI (ACCEL-AMI) Study

Summary: Because patients with acute myocardial infarction (AMI) have shown enhanced platelet reactivity during the early phase, the standard doses of clopidogrel and aspirin might not achieve adequate platelet inhibition. Furthermore, recent studies have identified that high-postclopidogrel platelet reactivity in these patients has been associated with ischemic clinical events. Based on the premise that intensified antiplatelet therapy in patients with AMI may lead to better ADP-stimulated platelet inhibition and a reduced risk for adverse cardiovascular events, adjunctive cilostazol to dual antiplatelet therapy (or “triple antiplatelet therapy”) can be an attractive alternative in patients with AMI. Triple antiplatelet therapy has shown more beneficial effects on platelet inhibition and endothelial senescence than has dual antiplatelet therapy in selected subsets. In this study, the authors assessed the degree of platelet inhibition by adjunctive cilostazol in patients with AMI. They enrolled patients with AMI treated with drug-eluting stents only and assessed platelet reactivity at predischarge and 30-day follow-up. Among these patients, triple antiplatelet therapy resulted in a greater antiplatelet effect than high maintenance-dose clopidogrel of 150 mg daily, as demonstrated by various parameters of conventional aggregometry and the VerifyNow P2Y12 assay. Because a common polymorphism of cytochrome P450 (CYP) 2C19 gene is more prominent among East Asians than whites (~60% versus 30%), high maintenance-dose clopidogrel can exhibit much diminished platelet inhibition in East Asians than in whites. Furthermore, cilostazol is mainly converted into active metabolites by CYP3A system, and adjunctive cilostazol can inhibit platelet aggregation consistently irrespective of the carriage of CYP2C19 mutant allele.
Conclusions: Among patients with AMI undergoing coronary stenting, triple antiplatelet therapy results in a greater antiplatelet effect at 30 days as compared with a high maintenance dose of clopidogrel or standard dual antiplatelet therapy.

Editor’s Comment: A significant proportion of patients on dual antiplatelet therapy do not achieve adequate platelet inhibition due to polymorphisms of the CYP2C19 isoenzyme that convert clopidogrel to its active compound. It has been suggested that higher loading and maintenance doses may overcome this problem. The CURRENT OASIS 7 trial demonstrated lower adverse events including stent thrombosis with the higher doses in patients undergoing percutaneous coronary intervention. This study examined the effect of higher-dose clopidogrel as well as triple therapy with the addition of cilostazol versus standard dose clopidogrel and aspirin in patients with an acute myocardial infarction treated with stenting. The study showed that triple therapy was more effective in reducing platelet aggregation. Whether this regimen results in a significant reduction in adverse events, including stent thrombosis, remains to be demonstrated. With the availability of more potent antiplatelet agents, including prasugrel and ticagrelor, it is also not clear if there would be any advantages of triple therapy over use of these newer, more potent agents.17

Triple Versus Dual Antiplatelet Therapy in Patients With Acute ST-Segment Elevation–Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

Summary: Drug-eluting stent implantation in acute myocardial infarction is associated with an increased risk for acute and subacute in-stent thrombosis. Increased platelet activity also has been observed in acute myocardial infarction. Therefore, more aggressive antiplatelet therapy rather than conventional dual antiplatelet therapy may offer extra benefits for acute myocardial infarction patients undergoing primary percutaneous coronary intervention with drug-eluting stents. This article retrospectively evaluates the safety and efficacy of triple antiplatelet therapy (aspirin plus clopidogrel plus cilostazol; n=1634) and dual antiplatelet therapy (aspirin plus clopidogrel; n=2569) in 4203 ST-segment elevation–myocardial infarction patients who underwent primary percutaneous coronary intervention with drug-eluting stents. Selection of patients for treatment with triple antiplatelet therapy was left to the physician's discretion. Compared with dual antiplatelet therapy, triple antiplatelet therapy had a similar incidence of major bleeding events but a significantly lower incidence of in-hospital mortality. After adjustment for known confounders, triple antiplatelet therapy had significantly lower incidences of cardiac death (adjusted odds ratio, 0.52; 95% confidence interval, 0.32–0.84; \( P=0.007 \)), total death (adjusted odds ratio, 0.60; 95% confidence interval, 0.41–0.89; \( P=0.010 \)), and total major adverse cardiac events (adjusted odds ratio, 0.74; 95% confidence interval, 0.58–0.95; \( P=0.019 \)) at 8 months than dual antiplatelet therapy. In this large, real-world clinical study in patients with ST-segment elevation–myocardial infarction who underwent primary percutaneous coronary intervention with drug-eluting stents, triple antiplatelet therapy not only had a good safety profile but also improved midterm clinical outcomes. Randomized trials are needed to compare the safety and efficacy of the triple and dual antiplatelet therapies in these patients.

Conclusions: Triple antiplatelet therapy seems to be superior to dual antiplatelet therapy in patients with ST-segment elevation–myocardial infarction undergoing primary percutaneous coronary intervention with drug-eluting stents. These results may provide the rationale for the use of triple antiplatelet therapy in these patients.

Editor’s Comment: The optimal antiplatelet regimen for ST-segment elevation–myocardial infarction patients treated with drug-eluting stents remains uncertain. This nonrandomized study of dual versus triple antiplatelet therapy with cilostazol in Korean patients suggests that more potent platelet inhibitor results in a lower risk of adverse events. How triple antiplatelet therapy compares with dual antiplatelet therapy with more potent P2Y12 inhibitors and whether these findings are translatable to different genetic populations requires further investigation.18

Randomized, Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Patients With Stable Coronary Artery Disease: The ONSET/OFFSET Study

Summary: In the present study, ticagrelor compared with high loading-dose clopidogrel achieved more rapid and greater platelet inhibition in patients with stable coronary artery disease. Greater inhibition was also sustained during the maintenance phase, and the offset of action was faster with ticagrelor than with clopidogrel. These pharmacodynamic effects may explain why ticagrelor treatment was associated with a lower occurrence of the primary end point (myocardial infarction, stroke, or cardiovascular death), similar coronary artery bypass graft–related bleeding, and no overall difference in major bleeding compared with clopidogrel therapy in the PLATO (PLATelet inhibition and patient Outcomes) trial.

Conclusions: Ticagrelor achieved more rapid and greater platelet inhibition than high loading-dose clopidogrel; this was sustained during the maintenance phase and was faster in offset after drug discontinuation.

Editor’s Comment: Clopidogrel is an irreversible inhibitor of the platelet P2Y12 receptor that requires metabolism to its active metabolite for its antiplatelet effects. It has a relatively slow onset of action, and requires that a 600 mg loading dose must be given at least 6 hours prior to PCI to achieve ~50% platelet inhibition. Furthermore, the drug has a relatively long half-life that can contribute to adverse bleeding events or prolong waiting periods prior to surgeries with a high risk of bleeding complications. By contrast, head-to-head ex vivo platelet reactivity assays performed on the background of aspirin in this study demonstrate that ticagrelor, an orally available reversible P2Y12 receptor antagonist, is a more potent inhibitor of platelet aggregation than clopidogrel with a faster onset of its antiplatelet effects. There was also an earlier offset of ticagrelor’s antiplatelet effects as compared with clopidogrel; however, by 24 hours, the response was similar between ticagrelor and clopidogrel. These antiplatelet properties of ticagrelor indicate that the drug would be advantageous in clinical scenarios where rapid inhibition of platelet aggregation or an early antiplatelet effect is required.19

Apixaban, an Oral, Direct, Selective Factor Xa Inhibitor, in Combination With Antiplatelet Therapy After Acute Coronary Syndrome: Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) Trial

Summary: Patients with acute coronary syndromes continue to have recurrent ischemic events despite revascularization and current antiplatelet therapy. Several novel oral anticoagulants that may reduce recurrent ischemic events are being developed but come with an increased risk of bleeding. Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) is the first phase 2 trial exploring several doses of the oral factor Xa inhibitor apixaban in patients with a recent acute coronary syndrome who received, in many cases, both aspirin and clopidogrel. With the addition of apixaban, there was an increase in bleeding but also promising reductions in clinically important ischemic events, including cardiovascular death, myocardial infarction, stroke, and recurrent ischemia requiring hospitalization or revascularization. The results of APPRAISE set the stage for adequately powered phase 3 trials of apixaban in patients with recent acute coronary syndromes,
which, depending on their results, may establish oral anticoagulation as a new standard approach for preventing recurrent ischemic events in patients with acute coronary syndromes.

Conclusions: The authors observed a dose-related increase in bleeding and a trend toward a reduction in ischemic events with the addition of apixaban to antiplatelet therapy in patients with recent acute coronary syndrome. The safety and efficacy of apixaban may vary, depending on background antiplatelet therapy. Further testing of apixaban in patients at risk of recurrent ischemic events is warranted.

Editor's Comment: Antiplatelet agents have proven therapeutic efficacy for patients with acute coronary syndromes. By contrast, the benefits of oral add-on anticoagulant agents have not been well studied owing to the increased risk of bleeding. This phase 2 clinical trial found that on the background of aspirin and, in the majority of cases, clopidogrel, the lowest doses of the novel oral Factor Xa inhibitor apixaban were associated with a reduction in ischemic events; however, this occurred at the expense of an increase in bleeding events. These observations indicate that the oral Factor Xa inhibitor may be beneficial in a broader patient population with bleeding events; however, this occurred at the expense of an increase in bleeding events. These observations indicate that the oral Factor Xa inhibitor may be beneficial in a broader patient population with symptomatic cardiovascular disease; however, the drug appears to have a narrow therapeutic window. Early results from large-scale clinical studies are becoming available to help determine the optimal dosing regimen and patient populations that will benefit from this agent.

Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies: The RESPOND Study

Summary: The Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) study is the first to demonstrate that ticagrelor therapy overcomes nonresponsiveness to and high platelet reactivity during clopidogrel therapy. The antiplatelet effect of ticagrelor is essentially uniform and high in both clopidogrel responders and nonresponders. Moreover, platelet inhibition in patients responsive and nonresponsive to clopidogrel is enhanced by switching to ticagrelor therapy. These data suggest that ticagrelor may be an important therapeutic alternative in patients who have experienced thrombotic events during clopidogrel therapy. The extremely low prevalence of high platelet reactivity associated with ticagrelor therapy as defined by cut-points associated with ischemic event occurrence with the use of 3 different methods in the RESPOND study provides a mechanism for the clinical benefit demonstrated in the Platelet Inhibition and Patient Outcomes (PLATO) trial. All of these findings support the particular utility of ticagrelor in clinical settings associated with high platelet reactivity, such as acute coronary syndromes, percutaneous coronary intervention, and stent thrombosis.

Conclusions: Ticagrelor therapy overcomes nonresponsiveness to clopidogrel, and its antiplatelet effect is the same in responders and nonresponders. Nearly all clopidogrel nonresponders and responders treated with ticagrelor will have platelet reactivity below the cut-points associated with ischemic risk.

Editor's Comment: Nonresponders to clopidogrel defined as high on treatment platelet aggregation is recognized to occur in 30%–50% of patients, often due to polymorphisms to the CYP2C19 allele. Newer, more potent antiplatelet drugs such as ticagrelor do not share this problem. It has been unclear if switching to ticagrelor in nonresponders will achieve adequate inhibition and whether switching patients who do respond will achieve greater inhibition. In this study, both nonresponders and responders to clopidogrel achieved greater inhibition to ticagrelor and switching back to clopidogrel resulted in reduced inhibition. This study provides evidence that ticagrelor should be considered in patients who are nonresponders or in patients in whom greater platelet inhibition is desired.

Ticagrelor versus Clopidogrel in Acute Coronary Syndromes in Relation to Renal Function: Results From the Platelet Inhibition and Patient Outcomes (PLATO) Trial

Summary: Among patients with acute coronary syndromes, any degree of impairment of renal function is associated with a worse prognosis but also an increased bleeding risk, which may alter the risk-benefit ratio with antiplatelet therapies. The Platelet Inhibition and Patient Outcomes (PLATO) trial investigated the effects of ticagrelor compared with clopidogrel in a broad population of patients with non–ST-segment elevation–acute coronary syndromes, regardless of the intended management strategy. Patients with chronic kidney disease, defined as a baseline creatinine clearance <60 mL/min, constituted 21% of those with baseline creatinine measurements (n=15,203). The numeric absolute (and relative) risk reductions of the primary composite end point and total mortality by ticagrelor versus clopidogrel were 4.7% (23%) and 4.0% (28%) in patients with chronic kidney disease and 1% (10%) and 0.5% (11%) in patients with normal renal function. The incidence of major bleeding did not differ significantly between the ticagrelor and clopidogrel groups in patients with normal renal function or in patients with chronic kidney disease. Thus, ticagrelor is a more effective antiplatelet agent than clopidogrel in acute coronary syndrome patients regardless of renal function, and the benefits are larger in those with poor renal function without any need for dose reduction to prevent major bleeding. Given the high prevalence of renal dysfunction among patients with atherosclerotic disease and the associated elevated risk of ischemic and bleeding complications, ticagrelor provides an important opportunity to substantially improve outcome in patients with acute coronary syndromes and impaired renal function.

Conclusions: In acute coronary syndrome patients with chronic kidney disease, ticagrelor compared with clopidogrel significantly reduces ischemic end points and mortality without a significant increase in major bleeding but with numerically more nonprocedure-related bleeding.

Editor's Comment: Chronic kidney disease is well recognized to be associated with increased cardiovascular events and bleeding. This study of the PLATO trial examined whether the results of the Pla trial were similar in this high-risk group; findings confirm that they were similar. This is encouraging and supports the use of ticagrelor in this group of patients. It is most reassuring that major bleeding was not increased and that the benefit was seen over a wide range of renal function.

First Analysis of the Relation Between CYP2C19 Genotype and Pharmacodynamics in Patients Treated With Ticagrelor Versus Clopidogrel: The ONSET/OFFSET and RESPOND Genetic Studies

Summary: In contrast to clopidogrel, the antiplatelet effect of ticagrelor is not influenced by cytochrome P450 2C19 genotype. Ticagrelor therapy was associated with significantly greater platelet inhibition than clopidogrel irrespective of genotype. Further studies with larger numbers of patients are required to examine the relative influences of *2 and *17 carrier on the antiplatelet effects of ticagrelor during the maintenance phase of therapy. The results of the current study are consistent with the results of the Platelet Inhibition and Patient Outcomes Genetics substudy, demonstrating that ticagrelor is a more-effective treatment for acute coronary syndromes than clopidogrel irrespective of cytochrome P450 2C19 polymorphisms.

Conclusions: This report is the first to demonstrate the superior pharmacodynamic effect of ticagrelor compared with clopidogrel irrespective of CYP2C19 genotype. Whereas CYP2C19 genotype...
influenced the antiplatelet effect of clopidogrel, there was no effect of CYP2C19 genotype during ticagrelor therapy.

**Editor’s Comment:** Polymorphisms of the P450 (CYP) C19 alleles are associated with reduced metabolism of clopidogrel, decreased inhibition of platelet function, and worse clinical outcomes. Newer, more potent agents do not share this problem. In this study, ticagrelor regardless of genotype was more effective in inhibiting platelet function than clopidogrel. The study supports the use of ticagrelor over clopidogrel and suggests that genotyping is not needed when using this agent.23

**GP IIb/IIa Agents**

**Primary Percutaneous Coronary Angioplasty With and Without Eptifibatide in ST-Segment Elevation—Myocardial Infarction: A Safety and Efficacy Study of Integrilin-Facilitated Versus Primary Percutaneous Coronary Intervention in ST-Segment Elevation—Myocardial Infarction (ASSIST)**

**Summary:** The evidence supporting the use of small-molecule glycoprotein IIb/IIIa inhibitors, such as eptifibatide, in patients with ST-segment elevation—myocardial infarction undergoing percutaneous coronary intervention is limited. To determine whether eptifibatide improves clinical outcomes in patients referred for primary percutaneous coronary intervention, the authors randomly assigned 400 patients to treatment, initiated before cardiac catheterization, with either heparin plus eptifibatide (201 patients) or heparin alone (199 patients), in addition to oral aspirin (160 mg) and high-dose clopidogrel (600 mg). At 30 days, there was no significant difference in the primary end point (death from any cause, recurrent myocardial infarction, or recurrent severe ischemia): 6.5% in the heparin plus eptifibatide group and 5.5% in the heparin-alone group. However, the rates of major or minor bleeding were higher in patients assigned to heparin plus eptifibatide than in those patients assigned to heparin alone (22.4% versus 14.6%). These results will likely be of interest to physicians caring for patients with ST-segment elevation—myocardial infarction.

**Conclusions:** In patients pretreated with high-dose clopidogrel who were referred for primary percutaneous coronary intervention, treatment with heparin plus eptifibatide, when compared with heparin alone, did not improve clinical outcomes and was associated with more bleeding complications.

**Editor’s Comment:** Clinical benefit resulting from the addition of precathesterization eptifibatide to a pharmacological regimen of heparin, aspirin, and clopidogrel (600 mg) in the setting of primary percutaneous coronary intervention is unproven. This 400-patient, randomized, clinical trial found no benefit using an adjunctive eptifibatide treatment strategy resulting in no significant decrease in the 30-day composite primary end point of death, recurrent myocardial infarction, or recurrent severe ischemia. Notably, the use of eptifibatide did result in an increase in major and minor bleeding. A larger clinical trial would be necessary to more definitively address possible clinical benefits resulting from this treatment strategy; however, the concerning increased bleeding safety signal reported in this study discoures the routine use of precathesterization eptifibatide in the setting of primary percutaneous coronary intervention.24

**A Comparison of Abciximab and Small-Molecule Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Primary Percutaneous Coronary Intervention: A Meta-Analysis of Contemporary Randomized Controlled Trials**

**Summary:** Although current guidelines support the use of abciximab in patients undergoing primary percutaneous coronary intervention, small-molecule glycoprotein IIb/IIIa inhibitors are more commonly used in contemporary clinical practice. Small, randomized trials evaluating predominantly angiographic end points have demonstrated no difference between small-molecule glycoprotein IIb/IIIa inhibitors and abciximab in patients undergoing primary percutaneous coronary intervention, although none of these trials were powered for clinical end points. The authors report a systematic evaluation of clinical outcomes of studies comparing small-molecule glycoprotein IIb/IIIa inhibitors with abciximab in patients undergoing primary percutaneous coronary intervention. Their meta-analysis included 2138 patients from 5 randomized, controlled trials. There were no differences in 30-day mortality (odds ratio, 0.84; P=0.58), reinfarction (odds ratio, 1.22; P=0.69), or major bleeding (odds ratio, 1.21; P=0.61) between the 2 adjunctive strategies. Similarly, there was no significant difference in the incidence of death (odds ratio, 0.77; P=0.43) or reinfarction on intermediate-term follow-up. The authors’ findings provide further support for the widespread current use of small-molecule glycoprotein IIb/IIIa inhibitors in patients undergoing primary percutaneous coronary intervention.

**Conclusions:** In patients undergoing primary percutaneous coronary intervention for ST-segment elevation—myocardial infarction, no difference in outcome could be identified in patients treated with small-molecule glycoprotein IIb/IIIa inhibitor or abciximab.

**Editor’s Comment:** In the era of dual oral antplatelet therapy, there remains a role for glycoprotein IIb/IIIa inhibitors in the high-risk subset of patients undergoing primary percutaneous coronary intervention for ST-segment elevation—myocardial infarction. While the bulk of data supporting their use was derived from studies with the monoclonal antibody abciximab, the small-molecule agents adequately dosed can achieve similar levels of platelet inhibition and therefore may result in similar benefits, but this has not been proven. Studies comparing the types of glycoprotein IIb/IIIa inhibitors to this point have been limited by small sample size or observational design. The meta-analysis reported here evaluated 30-day end points including death, reinfarction, and major bleeding from 5 randomized trials and found no differences between abciximab and the small-molecule agents tirofiban and eptifibatide. This study supports current clinical practice and is unlikely to be refuted by additional randomized trials.25

**Role of the Paclitaxel-Eluting Stent and Tirofiban in Patients With ST-Elevation—Myocardial Infarction Undergoing Postfibrinolysis Angioplasty: The GRACIA-3 Randomized Clinical Trial**

**Summary:** Fibrinolysis is still administered in a high percentage of patients with acute ST-elevation—myocardial infarction in whom primary percutaneous coronary intervention (PCI) cannot be performed in a timely fashion. Routine adjunctive or early postfibrinolytic angiography is often done in these patients to improve outcome. This study was performed to explore the usefulness of administering a IIb/IIIa glycoprotein inhibitor (tirofiban) in patients with acute ST-elevation—myocardial infarction treated with postfibrinolytic angioplasty. In this study, tirofiban did not improve any perfusion parameter and was associated with an increase in overall bleeding. Thus, after full-dose tenecteplase, enoxaparin and aspirin are a good antithrombotic combination for a postfibrinolysis PCI reperfusion strategy. In this study, clopidogrel was given after PCI and not on admission, as currently recommended. The authors further explored the efficacy of the paclitaxel-eluting stent with this regimen. The use of paclitaxel-eluting stents was not associated with an increase in stent thrombosis. Compared with bare-metal stents, paclitaxel-eluting stents significantly reduced late loss but appeared not to reduce in-segment binary restenosis as the rate of binary restenosis with bare-metal stents (11% and not 22%) was unexpectedly low. Implantation of bare-metal stents in postfibrinolysis PCI patients appeared to be a cost-effective approach compared with paclitaxel-eluting stents.
Conclusions: This trial does not provide evidence to support the use of tirofiban after fibrinolysis to improve epicardial and myocardial perfusion. Compared with bare-metal stent, paclitaxel-eluting stent significantly reduced late loss but appeared not to reduce in-segment binary restenosis.

Editor's Comments: In studies examining routine early percutaneous coronary intervention after fibrinolysis, glycoprotein IIb/IIIa receptor antagonists were recommended and commonly used, but allocation was not randomized. The relative benefits and potential harm of these agents in combination with fibrinolysis therefore is unclear. This investigation is the first randomized trial of the small-molecule glycoprotein IIb/IIIa receptor antagonist tirofiban in patients treated with a pharmacoinvasive strategy for ST-segment elevation–myocardial infarction. Using a 2×2 factorial design, patients were also randomized to the paclitaxel-eluting stent or comparable bare metal stent. Although no definitive conclusions can be drawn from the stent stratum of the trial, the lack of benefit and increased bleeding observed in patients randomized to tirofiban suggests that caution should be exercised when using potent intravenous platelet inhibitors as an adjunct to fibrinolysis.26

Intensifying Platelet Inhibition With Tirofiban in Poor Responders to Aspirin, Clopidogrel, or Both Agents Undergoing Elective Coronary Intervention: Results From the Double-Blind, Prospective, Randomized Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel Study

Summary: Previous studies have shown that individual response to aspirin or clopidogrel intake may vary significantly among patients, and those who respond less have been reported to be at higher risk for worse cardiovascular outcomes, especially if treated with percutaneous coronary intervention. It is unknown whether this worse cardiovascular outcome directly reflects suboptimal platelet inhibition per se, which might benefit from more potent antiplatelet agents. Alternatively, this may simply represent a “marker” of worse prognosis without clear therapeutic implications. In this study, the authors have shown that intensifying platelet inhibition through the use of tirofiban, a potent intravenous antiplatelet agent, in patients undergoing percutaneous coronary intervention who have previously been selected to be poor responders to aspirin, clopidogrel, or both agents leads to lower incidence of periprocedural myocardial infarction compared with standard care consisting of aspirin and clopidogrel. Thus, data are provided for the first time showing that implementing alternative treatment strategies in this patient population may result in an improved outcome compared with standard care. These results may suggest a causal relationship between suboptimal platelet inhibition and worse outcomes in this selected patient population.

Conclusions: In low-risk patients according to clinical presentation who had poor responsiveness to standard oral platelet inhibitors via a point-of-care assay, intensified platelet inhibition with tirofiban lowers the incidence of myocardial infarction after elective coronary intervention.

Editor's Comment: Poor response to antiplatelet therapy is common and has been associated with an increase in thrombotic events after angioplasty such as myocardial infarction. More potent antiplatelet therapy with use of GP IIb/IIIa agents is one method to overcome this problem. In this study, the authors randomized patients with a poor antiplatelet response to tirofiban or placebo. Periprocedural myocardial infarction and 30-day major adverse events were significantly less, and bleeding was not increased. This study suggests that use of GP IIb/IIIa agents is an alternative to use of more potent antiplatelet agents such as prasugrel or ticagrelor. The study, however, only examined 30-day outcomes in stable patients and the results cannot be extrapolated to high-risk patients, and long-term outcomes may be different.27

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