The Effect of Treatment with Clopidogrel Prior to Percutaneous Coronary Intervention as Well as Sustained Treatment Afterwards on the Composite Endpoint of Death, Myocardial Infarction and Urgent Target-Vessel Revascularization

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Introduction

Antiplatelet therapy plays an important role in improving outcomes in percutaneous coronary interventions (PCI). During this procedure, enlargement of the luminal dimensions of the diseased coronary vessel causes disruption of the integrity of the vascular endothelium and other vessel components, creating a local environment conducive to thrombosis.[1] Essential steps involved in the formation of a platelet-rich thrombus after plaque disruption include platelet adhesion, activation, secretion and aggregation. Currently available antiplatelet agents act by inhibiting one or more of these steps, and various clinical trials of antiplatelet therapies have led to questions regarding the appropriate selection, timing and duration of these agents when used in PCI.[2]

Clopidogrel is an oral antiplatelet agent of the thienopyridine class. It is an adenosine diphosphate (ADP) receptor antagonist that inhibits platelet activation and ultimately aggregation. This dose dependent inhibition takes effect rapidly and can be seen in as little as two hours.[3]

The purpose of this paper is to review the results of five independent studies which looked at pre-treatment with clopidogrel prior to PCI as well as long-term use following PCI to see if these dosing strategies had any effect on the composite endpoint of death, nonfatal myocardial infarction (MI), and urgent target-vessel revascularization (TVR). A summary of these studies is presented in Table 1.

Evaluation of Studies

The PCI CURE Study

The PCI CURE study [4] was designed to test the hypothesis that, in addition to aspirin, treatment with clopidogrel before PCI was superior to placebo in preventing major ischemic events afterwards, and that long-term treatment with clopidogrel after PCI would result in additional benefit. The PCI CURE study was a prospectively planned study of CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events).[5] CURE was designed to test the hypothesis that clopidogrel plus aspirin was superior to aspirin alone when given early and continued long-term in the prevention of cardiovascular death, MI or stroke in patients with non-ST-segment elevation acute coronary syndrome (NSTE ACS).

In the PCI CURE study, 2658 patients were randomly assigned clopidogrel or placebo. A loading dose of clopidogrel 300mg or matching placebo was given immediately on a double-blind basis. In addition, aspirin (75-325mg) was started or continued simultaneously with the study drug. This combination was continued until PCI, at which time stented patients received an open-label thienopyridine (either clopidogrel or ticlopidine) in combination with aspirin for 2-4 weeks. After this period, the previous randomly assigned study drug was resumed and continued until the end of scheduled follow-up (from 3 to 12 months after randomization).

The primary outcome of the study was the composite of cardiovascular death, MI, or urgent target vessel revascularization (TVR) within 30 days of PCI. Cardiovascular death or MI from the time of PCI to the scheduled end of the trial was also assessed to determine the effects of long-term clopidogrel use. The authors reported a 30% relative risk reduction in the composite outcome of CV death, MI or urgent TVR when pre-treated with clopidogrel prior to PCI, as well as a 31% relative risk reduction with long-term clopidogrel use after PCI.

Limitations of this study include the fact that its study population was limited to acutely ill patients, and that the data was derived from a trial (CURE) that was based on a conservative approach to the management of non-ST-elevation ACS. Other problems include the authors ignored the role of GP IIa/IIIb inhibitor use, as well as one-fourth of the subjects received an open label thienopyridine prior to PCI.

Although PCI CURE was an observational study, it had a large number of subjects and was hoped to be an important starting ground for subsequent, more focused studies.

The CREDO Trial

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial [6] was a randomized, double-blind, placebo controlled trial conducted among 2116 patients who were to undergo elective PCI or deemed highly likely to undergo PCI. The purpose of this study was to evaluate the benefit of a pre-procedure loading dose of clopidogrel as well as long-term (12 month) treatment with clopidogrel after PCI, both in addition to aspirin therapy.

Patients were randomly assigned to receive a 300mg clopidogrel loading dose or placebo 3 to 24 hours prior to PCI. Thereafter, all patients received 75mg of clopidogrel daily through day 28. From day 29 through 12 months, patients in the clopidogrel loading dose group continued to receive clopidogrel 75mg daily, while those in the placebo loading dose group received placebo daily. Both groups received aspirin throughout the study.

The main outcome measures were the 28-day incidence of the composite of death, MI or urgent TVR in the protocol population, which included all randomized patients who underwent PCI, and the one-year incidence of the composite of death, MI, or stroke in the intent to treat population. The intent to treat population was used in the one-year analysis due to the relatively large number of patients who did not continue the clopidogrel or matching placebo for the full year of therapy.

In this study, clopidogrel pre-treatment did not significantly reduce the combined risk of death, MI or urgent TVR at 28 days (relative risk reduction = 18.5%). However in a subgroup analysis, patients who received a loading dose of clopidogrel at least 6 hours prior to the PCI experienced fewer events than those patients receiving pre-treatment less than 6 hours prior to the procedure. At 1 year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI or stroke.

In this study the researchers were trying to determine the optimal timing for the initiation of clopidogrel as well as optimal duration of treatment after PCI. Unlike the PCI CURE trial, this study was limited to stable patients awaiting a planned PCI. It was an improvement over the PCI CURE trial in that they were specifically looking at patients undergoing PCI in a double-blind, placebo controlled study, however, there were a number of variables that were not controlled. For example, 45% of the per-protocol population received a GP IIb/IIIa antagonist (use was allowed "at the discretion of the physician performing PCI"). In addition, patients were not rerandomized after 28 days of therapy, so one is not able to totally separate pre-treatment dosing from long-term treatment benefits. Finally, a relatively high proportion (39%) of patients discontinued the study drug prior to one year and therefore results may not reflect the total study population.

The TARGET Study

The Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial (TARGET) study [7] was a direct comparison of two glycoprotein IIb/IIIa antagonists (tirofiban and abciximab) during percutaneous coronary revascularization and stent placement. The TARGET study was a randomized, double-blind, head-to-head trial. Although the primary focus of the trial was to evaluate the efficacy of the two GP IIb/IIIa antagonists in patients undergoing PCI, the study also examined if pre-treatment with clopidogrel verses standard post-procedure dosing improved clinical outcomes in this group of patients.[8]

In this study, 4,809 patients were randomized to receive a bolus and infusion of either abciximab or tirofiban. All patients received aspirin within 24 hours before, and continued daily after the procedure. A loading dose of 300mg of clopidogrel at least 2 to 6 hours before PCI (or just before if performed immediately following diagnostic angiography) was recommended. As a result of this recommendation, a greater majority of patients received a loading dose of clopidogrel prior to PCI. The group of patients who received clopidogrel at any time prior to PCI was categorized into the pre-treatment

group. The remaining patients received clopidogrel 300mg as soon as possible after the procedure. Both groups received clopidogrel 75mg daily for 30 days after PCI.

The primary end point of TARGET was the composite of death, MI, or urgent TVR within 30 days of the procedure. Secondary end points included death, MI or any TVR at six months, and mortality at one year.

Of the 4,809 patients enrolled, 4,477 were given clopidogrel before PCI. The primary composite end point occurred in 10.4% of patients without pre-treatment compared to 6.6% of patients with pre-treatment (relative risk reduction = 36.9%). There was no significant difference in the end point event rates between patients who received clopidogrel pre-treatment from 0 to 2 hours and those who received the drug from 2 to 6 hours. However patients who received loading doses greater than 6 hours before PCI had a 29% lowering in 30 day events as compared to those who received a loading dose from 0 to 6 hours. This same outcome extended to the six month composite end point with a 38% reduction in death and MI in the 0 to 6 hour group with an additional 26% reduction in the greater than 6 hour group. Finally, clopidogrel given before PCI was associated with a mortality reduction within the first year (1.7% vs. 3.6%).

The results from this study concurred with the previous studies, i.e., that pre-treatment with clopidogrel greater than six hours prior to PCI, as well as continued long-term treatment improved outcomes, and that this risk reduction was irrespective of whether or not a glycloprotein IIb/IIIa antagonist was used. This study was also important in that it showed that the incidence of major and minor bleeding was not significantly increased with triple antiplatelet therapy.

This study, like PCI CURE, was an observational study which used another "primary" source to extract its data and form conclusions. Clopidogrel pretreatment was not randomized, duration of therapy prior to procedure was variable, and timing of the loading dose was "at the interventional cardiologists' discretion." This subjective decision may have introduced a significant bias, in that the patient's initial condition may have influenced both the decision as to when to dose the clopidogrel and ultimately the study's outcome. Finally, sample sizes were not equivalent with 93% of the patients receiving pre-treatment with clopidogrel.

The "CBRACE" Study

The Clopidogrel Treatment Before Percutaneous Coronary Intervention Reduces Adverse Cardiac Events study [9] (hereafter referred to as "CBRACE") was undertaken to evaluate the effects if a loading dose of clopidogrel given the day before PCI in an unselected, non-randomized population. This population consisted of consecutive patients who where admitted for PCI into one facility.

This study included a total of 1,430 patients admitted to one study site. The only reason for exclusion in both groups was PCI in the setting of acute myocardial infarction.

The study group consisted of 706 consecutive patients who underwent PCI during a 10 month period. All patients in this group received 375mg of clopidogrel the day before their scheduled PCI or planned coronary angioplasty. If a stent was implanted, clopidogrel was continued at 75mg daily for one month. No further clopidogrel was given if no stent was implanted.

The control group consisted of 724 consecutive procedures from the preceding 14 month period. This group did not receive any clopidogrel pre-treatment, but if a stent was implanted, a loading dose was given directly following the procedure which was then followed by either clopidogrel 75mg daily or ticlopidine 250mg twice daily for one month. All patients in both groups received 75mg of aspirin daily throughout the study period.

The major finding of this study is that the patients pre-treated with clopidogrel had a lower incidence of in-hospital adverse cardiac events, including a 41% relative risk reduction in the composite end point of death, MI or urgent revascularization (4.8% vs. 8.2%).

The main limitation of this study is its non-randomized design. In addition the control and study group procedures were not performed concurrently, possibly giving the study group an advantage of procedural advances and additional operator experience. Finally the study results were limited to in-hospital events.

The "LEC" Study

The Lack of Efficacy of Clopidogrel Pre-Treatment in the Prevention of Myocardial Damage After Elective Stent Implantation study [10] (hereafter referred to as "LEC") was undertaken to determine if pre-treatment with clopidogrel decreased myocardial damage in stable patients undergoing elective stent implantation.

This was a randomized trial involving 203 patients scheduled to undergo elective PCI with stent implantation. In the control group, a loading dose of 300mg of clopidogrel was given immediately after coronary stent implantation whereas the study group received pre-treatment with 300mg of clopidogrel three days before PCI. Both groups received 75mg of clopidogrel daily after the initial dose and continued on this dosage for 4 weeks. Both the study and control groups received aspirin 100mg daily for at least six months.

The primary endpoint in this study was the rise in troponin I and creatine kinase-MB fraction (CK-MB) levels at 6 to 8 hours and 16 to 24 hours after PCI. Secondary endpoints were death, stroke, MI, CABG, repeat PCI, and subacute stent thrombosis at 1 and 6 months after PCI, and the composite of these at six months.

This study found no significant difference between pretreated and non-pretreated patients in the post-procedural elevations of troponin I and CK-MP. And, unlike the

previous studies, found no significant difference at 1 and 6 months in the composite end point.

Limitations of this study were its small sample size and restriction of subjects to stable patients undergoing elective stent implantation. In addition, the timing of the clopidogrel loading dose three days prior to PCI may have been too far in advance, especially in view of the results of previous studies. It is conceivable that there may be a narrow "therapeutic window of time" when loading dose efficacy is optimized.

Summary

The five trials examined here give some insights into the optimal timing and duration of clopidogrel treatment with respect to PCI, however they did not result in clear-cut definitive recommendations.

Both the PCI-CURE and TARGET subset studies were offshoots of primary studies and therefore many variables were not as well controlled as one would like. The CREDO study was a randomized, double-blind, placebo-controlled study which resulted in conflicting results, but brought attention to the probability that pre-treatment with clopidogrel at least 6 hours prior to PCI was more effective in improving outcomes than a shorter period of pre-treatment before PCI. The "CBRACE" study was limited to in-hospital adverse events, but the results of this "real world" study were in agreement with both the PCI-CURE and TARGET studies.

Although the most recent "LEC" study did not show a beneficial effect of pre-treatment with clopidogrel on outcomes, it was a small trial and should not be used to negate the results of the previous studies.

Recommendations

New guidelines regarding antithrombotic therapy during percutaneous coronary intervention have recently been published.[11] These include the recommendation that a loading dose of 300mg of clopidogrel be given at least 6 hours prior to planned PCI and that after PCI, clopidogrel 75mg daily be continued for at least 9 to 12 months. These recommendations are in accordance with the basic conclusions of the studies reviewed; that pre-treatment with clopidogrel at least 6 hours prior to PCI, followed by long-term clopidogrel use, is associated with improved outcomes in patients undergoing percutaneous coronary intervention. Although these studies were less than optimal, in view of the fact that all of these studies showed no significant increase in major bleeding with clopidogrel use in this setting, I feel it would be prudent to follow these guidelines until further results are obtained from additional large, randomized clinical trials.

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