Use of Clopidrogel in Coronary Stenting: What Was the Question?*

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The oral antiplatelet agent clopidrogel has been widely used by interventional cardiologists for the past two years as an adjunct therapy to prevent subacute thrombosis after coronary stenting. Interestingly, the substitution of clopidrogel for ticlopidine occurred even though no conclusive data existed to demonstrate the efficacy and safety of clopidrogel for this indication, and despite two well-performed randomized trials that clearly established ticlopidine as effective. This replacement in clinical practice of a proven agent with an unproved one, prescribed off-label, was justified by the infrequent but severe toxicity of ticlopidine. Clopidrogel and its analogue ticlopidine have similar thienopyridine structures. Both block platelet aggregation induced by adenosine diphosphate and the subsequent transformation of the glycoprotein IIb/IIIa receptor into its high affinity state. Each also inhibits platelet aggregation in response to collagen, thrombin and shear stress. In this issue of JACC, Berger et al. (1) and Mishkel et al. (2) present single-center, observational studies that confirm the clinical impression that this is an appropriate substitution.

Clinical studies using ticlopidine. Ticlopidine has a half-life of ~12 h, requiring it to be given at a dose of 250 mg twice daily to achieve steady state levels. It should ideally be administered for at least three days before elective stenting, although a loading dose of 500 mg twice daily for 48 h may be used in urgent situations. After ticlopidine is stopped, the antiplatelet effect gradually dissipates over one to two weeks. Ticlopidine reduces the risk of myocardial infarction and death in patients with unstable angina (8). In acute coronary syndromes, ticlopidine reduces the risk of nonfatal or fatal infarction at six months by 41%. It also decreases the risk of stroke as compared with the use of aspirin (9).

Unfortunately, ticlopidine has uncommon (0.5% to 3.0%) but very serious adverse effects, including neutropenia (1% to 2.5%), thrombocytopenia, thrombotic thrombocytopenic purpura (10), rash and hepatic cholestasis. In general, these are reversible with discontinuation of the drug. In addition, there are rare cases of aplastic anemia, bone marrow suppression, pancytopenia and agranulocytosis (11). These hematologic side effects almost always occur within several months after the initiation of therapy, and consequently, complete blood counts should be performed every two weeks during the first three months of therapy with this agent (12). However, it is unlikely that this routine surveillance would be useful in detecting thrombotic thrombocytopenic purpura, as the platelet counts can be normal just
two weeks before the onset of this disease (10). The drug also commonly produces nausea, vomiting and diarrhea, which can be ameliorated if taken with meals. An elevation in cholesterol and a decrease in plasma fibrinogen are frequent after long-term administration.

In a randomized trial in which balloon percutaneous transluminal coronary angioplasty was performed, ticlopidine reduced the incidence of ischemic complications more than an aspirin plus dipyridamole combination (2% vs. 5%) (13). In the Intracoronary Stenting And Thrombotic Regimen (ISAR) trial, which compared aspirin plus ticlopidine versus aspirin plus coumadin after stenting, less fever, bleeding and acute ischemic complications were noted at 30 days in the ticlopidine group (6). Among high risk patients, ticlopidine decreased stent thrombosis (0% vs. 11.5%) and major adverse clinical events (MACE) at 30 days (2.0% vs. 12.6%). In the randomized, multicenter Stent Anticoagulation Regimen Study (STARS) (7), ticlopidine plus aspirin was associated with significantly fewer cases of subacute stent thrombosis and MACE than aspirin alone or aspirin plus warfarin. Although therapy with ticlopidine plus aspirin continued for four weeks, patients with coronary stents have often been treated with ticlopidine for shorter durations. The length of therapy was empirically altered from four weeks to three weeks, and frequently to two weeks by many physicians in response to its toxicity and the need for serial blood testing. The duration of the ticlopidine drug regimen was already being altered in Europe at the time the randomized trials were being presented (4,5), and the drug was essentially replaced in practice by the time STARS (7) was published.

Clinical studies using clopidrogel. Clopidrogel is administered once per day and has a more favorable side-effect profile as compared with ticlopidine. The overall tolerability is similar to aspirin and its hematologic effects are minimal. Its general clinical efficacy was tested in the Clopidrogel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial (14), which was a 304-center trial of 19,185 patients randomized to either 75 mg/day of clopidrogel or 325 mg/day aspirin, treated for an average of 1.6 years. Efficacy for the secondary prevention of adverse cardiovascular events in patients with previous stroke, myocardial infarction or peripheral vascular disease was shown by the relative risk reduction of 8.7% for clopidrogel versus aspirin (p = 0.45), which is itself an active agent in reducing cardiovascular events. No increased incidence of leukopenia, thrombocytopenia or gastrointestinal side effects were observed. Clopidrogel has not been compared with aspirin or anticoagulant agents in acute coronary syndromes or coronary stenting in randomized trials.

Current studies. Berger et al. (1) used an historical control design to study the clinical outcomes of coronary stenting in 500 consecutive patients who received a combination of clopidrogel and aspirin, and 827 consecutive patients from an earlier time frame who had received a combination of ticlopidine and aspirin for a total of 14 days after oral loading just before stent implantation. The baseline characteristics were similar between the two groups, other than the fact that the majority of patients who received clopidrogel had different kinds of stents implanted than the patients who received ticlopidine (an important treatment bias), reflecting the disparate dates at which stenting was performed. In this study, the combination of clopidrogel and aspirin was found to be safe and effective and associated with a very low incidence of MACE (0.8% vs. 1.3%) and subacute stent thrombosis (0.2% vs. 0.7%) as compared with the combination of ticlopidine and aspirin at 30 days.

Mishkel et al. (2) studied a total of 875 patients treated concurrently over a five-month period; 514 received clopidrogel plus aspirin and 361 received ticlopidine plus aspirin for two to four weeks. Only 66% were pretreated, none with a loading dose, and the agents were selected according to operator discretion. At 30 days, a similar incidence of MACE (2.1% vs. 1.4%) and subacute thrombosis (0.2% vs. 0.7%) was observed. It is remarkable that all three patients with acute stent thrombosis were in the clopidrogel group, none of whom had received their first dose. This is a complex issue, as “intention-to-treat” analysis is meaningless when there is no formal protocol and when the agent selected is a function of operator discretion instead of randomization. Although two of these patients had received abciximab, it is unclear why operators would place a stent without pretreatment with one of these antiplatelet agents and aspirin. Two subacute stent thrombosis cases occurred at days 12 and 20, events Berger et al. (1) state are “very rare.” Finally, four of the five serious thrombotic events, five of the seven deaths, five of the seven nonfatal myocardial infarctions and three of the four urgent repeat revascularizations occurred in the clopidrogel group. Although this is statistically insignificant, these are disturbing trends.

The biggest problem with both studies is that neither proves equivalence. It should be recognized that although both studies showed no statistically significant difference in 30-day outcome, this does not demonstrate that the two drugs are equivalent. Efficacy trials are not usually powered to assess relative adverse events rates, often resulting in large confidence intervals bounding the relative risk of an adverse event, as is evident in Table 3 of Mishkel et al. (2). Consequently, the lack of a statistically significant difference is not proof of equivalence, just that no difference is discernable, especially when the 30-day clinical event rates are so infrequent (16 of 875 patients in Mishkel’s study [2] and 17 of 1,327 patients in Berger’s study [1]). As the discussions in both studies note, a much larger series would be required to meet this standard.

Other studies of clopidrogel in coronary stenting. Moussa et al. (15) reported the outcomes in 283 consecutive patients who received the clopidrogel/aspirin combination as compared with 1,406 consecutive patients, also from
another period, who received ticlopidine plus aspirin. Clopidrogel was administered as a 300-mg loading dose followed by 75 mg/day for four weeks. At one-month follow-up, data were available for 269 patients who received clopidrogel and for 1,313 patients who received ticlopidine, or ~95% of the patient cohort. Event rates at one month were not different between the two patient groups, including the incidence of subacute stent thrombosis (1.4% vs. 1.5%, p = NS) and MACE (2.4% vs. 3.1%, p = NS). In addition, there was a lower incidence (5.3% vs. 10.6%, p = 0.006) of rash and diarrhea and no reports of bone marrow suppression with clopidrogel, whereas there were four reported cases (0.3%) of neutropenia with ticlopidine. Jauhar et al. (16) presented a prospective registry of 240 consecutive patients who underwent coronary stent procedures treated with clopidrogel/aspirin. In this patient cohort, in-hospital complications and clinical outcomes at 30 days were excellent, as only two patients had any adverse event. One patient experienced late acute myocardial infarction and death; however, angiography before death identified that the stent site was patent. The second patient had a subacute thrombosis of the stent in the left main coronary artery; the patient was treated interventionally and was ultimately discharged. The 30-day follow-up was obtained in 96% of the patient cohort. Two additional patients experienced subacute thrombosis. None of the patients had any further target vessel revascularization or late MACE. There were no significant adverse bleeding events or vascular complications. Rash occurred in 4% of the patients, but neutropenia was not observed.

Ongoing clinical trials. Current prospective, randomized trials using clopidrogel in stenting are designed to show improved safety rather than efficacy with the use of ticlopidine. The Clopidrogel/Aspirin Stent International Cooperative Study (CLASICS) was a randomized, double-blind, three-armed study of 1,020 patients conducted in 48 European centers that was completed in December 1998 and presented at the March 1999 meeting of the American College of Cardiology. The aim of the study was to assess the safety of two dosages of clopidrogel plus aspirin as compared with the standard ticlopidine plus aspirin regimen at 28 days. The clopidrogel groups included a high dose cohort that received 300 mg intravenously followed by oral therapy, and a standard dose group with no load. There was no difference in MACE between the groups, but the study was not powered to find one. Both clopidrogel groups had fewer major adverse side effects than the ticlopidine group (4.6% vs. 9.1%). Further, the standard low dose clopidrogel group had a higher event rate than the group given the loading dose (6.3% vs. 2.9%). Thus, the study concluded that clopidrogel plus aspirin is safer than ticlopidine plus aspirin and that intravenous loading is safe in the catheterization laboratory setting. Another randomized trial, CREDO, is in the start-up phase and is designed to determine whether clopidrogel loading should be recommended and to establish the appropriate length of therapy (one month vs. one year).

Is a randomized study necessary? Because most interventional cardiologists in the U.S. currently use clopidrogel rather than ticlopidine, do the studies by Berger et al. (1) and Mishkel et al. (2) offer sufficient data to constitute definitive evidence supporting the use of clopidrogel in stent recipients, even though the randomized, controlled studies proving efficacy were performed with ticlopidine? Both studies reflect data applicable to any “real world” clinical interventional practice. Together with the study by Moussa et al. (15), they strongly suggest that clopidrogel and ticlopidine have equivalent clinical efficacy, but that the advantage of clopidrogel is its diminished toxicity. These conclusions match the widespread clinical experience, but the level of evidence is still only modest (level 3), and thus lacks precision and is subject to change.

With the publication of the studies by Berger et al. (1) and Mishkel et al. (2), as well as the presentation of CLASICS, interventionists can feel assured that their choice to use clopidrogel is reasonable. However, the questions of when and by which route loading should be initiated and how long therapy should be continued, remain unanswered. More importantly, if another agent of the same class with a perceived benefit were introduced now, should it be accepted after preliminary data are obtained, or is a randomized trial required first? This issue has important regulatory and legal ramifications that seem disconnected from clinical practice, where the precedent is clear. The cardiology community must set and follow high standards of proof for new therapy and support efforts that do provide this level of evidence, even when such a “stodgy” approach may temporarily delay the introduction of better therapy in a rapidly changing therapeutic environment. As yet, there is no substitute for the appropriately designed, randomized trial.


REFERENCES