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Randomized Comparison of Ticlopidine and Clopidogrel After Intracoronary Stent Implantation in a Broad Patient Population

Megumi Taniuchi, MD, PhD; Howard I. Kurz, MD; John M. Lasala, MD, PhD

Background—Although clopidogrel is used to prevent subacute stent thrombosis, its safety and efficacy have not been compared with ticlopidine in a randomized manner in the United States.

Methods and Results—Patients with successful intracoronary stent implantation were randomly assigned to therapy with ticlopidine or clopidogrel. Loading doses were administered immediately after the procedure, and the drugs were prescribed for 2 weeks. One thousand sixteen patients were enrolled: 522 patients were randomly assigned to ticlopidine therapy and 494 to clopidogrel. High-risk characteristics included recent myocardial infarction in 41.4% of the cases, angiographically evident thrombus in 20.9%, and abrupt or threatened closure in 3.64%. An intravenous glycoprotein IIb/IIIa inhibitor was used in 48.2% of the cases, and thrombocytopenia occurred in 1.43% of these patients. Failure to complete 2 weeks of therapy occurred in 3.64% of the patients treated with ticlopidine and in 1.62% of the patients treated with clopidogrel ($P=0.043$). Within 30 days, thrombosis of the stent occurred in 1.92% of the patients in the ticlopidine group and in 2.02% of the clopidogrel group ($P=0.901$). A major adverse cardiac event occurred in 4.60% of patients receiving ticlopidine and in 3.85% of patients receiving clopidogrel ($P=0.551$).

Conclusions—Clopidogrel is better tolerated than ticlopidine during a 2-week regimen after intracoronary stent implantation. Combining either thienopyridine with an intravenous platelet IIb/IIIa inhibitor appears to be safe. When applied to a broad spectrum of patients receiving stent implantation, clopidogrel confers similar protection as ticlopidine against subacute stent thrombosis and major adverse cardiac events. (*Circulation*. 2001;104:539-543.)

Key Words: angioplasty ■ pharmacology ■ platelets ■ stents ■ thrombosis

The clinical utility of intracoronary stent implantation was limited initially by a 3.5% incidence of subacute stent thrombosis.^{1,2} The development of improved stent implantation techniques and use of ticlopidine and aspirin reduced the occurrence of stent thrombosis, with reported rates of 0.6% in the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial³ and 0.5% in the Stent Anticoagulation Restenosis Study (STARS).⁴ In studies in which high-risk patients were included, however, the incidence of major adverse cardiac events remains considerable at 5.6%, even with combined aspirin and ticlopidine therapy.⁵

Clopidogrel is a thienopyridine derivative chemically related to ticlopidine that has been shown to reduce the combined risk of stroke, myocardial infarction, or vascular death when compared with aspirin.⁶ Clopidogrel offers potential advantages compared with ticlopidine with better tolerability, lower cost, reduced risk of neutropenia, and lower incidence of thrombotic thrombocytopenic purpura.⁷ The pharmacokinetics of clopidogrel are also favorable, achieving $\approx 30\%$ to 40% inhibition of platelet aggregation (induced by ADP, collagen, and thrombin receptor agonist peptide) within 2 hours after oral dosing of 200 to 400 mg.⁸ Furthermore, clopidogrel has been shown to act synergisti-

cally with aspirin in inhibiting platelet deposition onto metallic stents in an in vivo model.⁹

In clinical studies, clopidogrel and aspirin treatment for 1 month was comparable to historic results observed with ticlopidine and aspirin treatment for the prevention of stent thrombosis and of major cardiac events.^{10,11} The two thienopyridines have been directly compared in a randomized manner in two published studies. Muller et al¹² showed that clopidogrel (initiated without a loading dose) was better tolerated, with 4.5% failing to complete 4 weeks of treatment, compared with 9.6% with ticlopidine. However, there were more cardiac events in the patients treated with clopidogrel (3.1% versus 1.7%, $P=0.24$), raising the question of clopidogrel efficacy. In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS), clopidogrel had a favorable safety profile at 28 days, with a lower combined incidence of major bleeding, neutropenia, thrombocytopenia, or early discontinuation (4.6% versus 9.1%, $P=0.005$). The 30-day rates of major adverse cardiac events were similar between the two agents, at 0.9% with ticlopidine and 1.3% with clopidogrel ($P\geq 0.555$). In both of these studies, the use of intravenous IIb/IIIa inhibitors was low ($<10\%$) relative to current use in the United States.

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We therefore directly compared ticlopidine and clopidogrel by using a prospective, randomized protocol in a broad range of patients receiving intracoronary stents. Consistent with the common practice in the United States of administering ticlopidine for only 14 days after stent placement,¹³ the primary safety end point was the tolerability of each agent, in conjunction with aspirin therapy, for a 2-week period. Secondary cardiac end points were documented throughout a 30-day period after stent implantation.

Methods

Study Population

Between September 9, 1998, and November 14, 1999, 1367 consecutive patients who had successful implantation (defined as <20% residual stenosis, with TIMI 2 or TIMI 3 flow) of an FDA-approved stent in a native coronary artery or in a coronary bypass graft were screened for enrollment. Exclusion criteria were (1) prior intolerance to aspirin, ticlopidine, or clopidogrel, (2) a comorbidity with expected survival of <6 months, and (3) prior enrollment in a separate research protocol. In particular, patients with acute myocardial infarction and those with cardiogenic shock were not excluded. Informed consent was obtained after the procedure, when the patients had recovered from anxiolytic agents. The study was approved by the Human Studies Committee of the Washington University Medical Center.

Revascularization Procedure and Antiplatelet Therapy

Stent implantation was performed by 1 of 4 operators, using standard techniques. All enrolled patients had received 325 mg of aspirin before the procedure. Patients who were treated with a thienopyridine before catheterization were not enrolled. Preprocedural acute myocardial infarction was defined as an elevation of cardiac enzymes to >2-fold normal values or by the development of new pathological Q waves in the 12-lead ECG, within the 7 days before stent implantation. After a stable stent implantation procedure, the patients were initiated, in a randomized, open-label manner, to therapy with either ticlopidine or clopidogrel. Oral loading doses of ticlopidine (500 mg) or of clopidogrel (300 mg) were administered within 1 hour of stent implantation. Procedural use of intravenous IIb/IIIa inhibitors and postprocedure anticoagulation were left to the discretion of the operator. The primary end point was the failure to complete 2 weeks of the initiated thienopyridine, in conjunction with 325 mg of aspirin. Secondary end points were thrombocytopenia (platelet count <100 000), major bleeding (requiring surgery or transfusion of >2 units of packed red blood cells), cardiac death, Q-wave myocardial infarction (defined by the development of new Q waves in 2 or more ECG leads), stent thrombosis (defined angiographically as a total occlusion of the stented segment), and target vessel revascularization (percutaneous or by bypass grafting).

Statistical Methods

The study size was planned on the basis of an estimated 2-week discontinuation rate of 8% for ticlopidine and 3% for clopidogrel (based on previous clinical experience); a sample size of 458 patients in each group was predicted to show a 50% relative difference, with 95% power. The probability values for the differences between proportions were calculated by means of a 2-tailed Student's *t* test.

Results

Patient and Lesion Characteristics

A total of 1016 patients were randomly assigned (74.3% of the screened population), with 522 patients initiated on ticlopidine therapy and 494 on clopidogrel. Table 1 lists the demographic characteristics of the study population; these were similar between the two treatment groups. The inclusion

TABLE 1. Clinical and Angiographic Characteristics

| | Ticlopidine | Clopidogrel | <i>P</i> |
|---------------------------|-------------|-------------|----------|
| Age, y | 63.1 | 63.6 | |
| Male sex | 60.2% | 61.5% | 0.651 |
| Hypertension | 73.5% | 72.0% | 0.592 |
| Diabetes | 28.3% | 30.0% | 0.482 |
| Prior CABG | 21.0% | 21.4% | 0.881 |
| Prior MI | 28.7% | 32.3% | 0.206 |
| Current MI | 42.1% | 40.6% | 0.637 |
| After thrombolysis | 9.0% | 8.1% | 0.605 |
| Second vessel stented | 8.8% | 9.5% | 0.698 |
| Thrombus | 18.2% | 24.3% | 0.009 |
| Abrupt/threatened closure | 3.1% | 4.3% | 0.315 |
| Residual dissection | 1.2% | 2.0% | 0.266 |
| Vessel stented | | | |
| LAD | 28.9% | 30.9% | 0.477 |
| RCA | 34.7% | 35.2% | 0.855 |
| LCX | 22.2% | 23.6% | 0.580 |
| SVG | 10.9% | 7.9% | 0.098 |

MI indicates myocardial infarction; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; and SVG, saphenous vein graft.

of saphenous vein graft stents resulted in a higher proportion of patients with previous bypass grafting (21% overall) than in prior studies comparing ticlopidine and clopidogrel; stents were placed in vein grafts in 9.5% of the total study population.

The high-risk clinical and angiographic characteristics are also shown in Table 1. Overall, 41.4% of the patients were within 1 week of a myocardial infarction, accounting for the high incidence of angiographically evident thrombus (20.9% overall) and the incidence of threatened or abrupt closure (3.64% overall). The proportion of cases in which a second vessel was stented was similar in the ticlopidine and clopidogrel groups. When multiple vessels were revascularized, stent implantation was performed in all vessels. There were no differences in the two treatment groups in the clinical high-risk features, but there were more lesions with angiographically evident thrombus in the group assigned to clopidogrel therapy (24.3% versus 18.2%; *P*=0.009). Abrupt or threatened closure during the case (before final stent implantation) and residual dissection after final stent implantation were slightly higher in the clopidogrel group, but the differences did not reach statistical significance.

The use of intravenous IIb/IIIa inhibitors is tabulated in Table 2. Overall use was 48.2%, with abciximab used in the vast majority of cases. More patients in the ticlopidine arm

TABLE 2. Use of Intravenous IIb/IIIa Inhibitors

| Agent | Ticlopidine | Clopidogrel | <i>P</i> |
|----------------|-------------|-------------|----------|
| Abciximab | 44.3% | 39.1% | 0.093 |
| Tirofiban | 5.2% | 5.7% | 0.727 |
| Eptifibatide | 0.8% | 1.4% | 0.320 |
| Total IIb/IIIa | 50.2% | 46.1% | 0.198 |

TABLE 3. Adverse Drug Events

| | Ticlopidine | Clopidogrel | P |
|--------------------------------|-------------|-------------|-------|
| Reason for discontinuation | | | |
| Rash | 0.96% | 0.20% | 0.109 |
| Bleeding | 0.38% | 0.40% | 0.956 |
| Gastrointestinal | 0.38% | 0 | 0.156 |
| Neutropenia | 0.38% | 0 | 0.156 |
| Other | 1.53% | 1.01% | 0.458 |
| Total | 3.64% | 1.62% | 0.043 |
| Occurrence of thrombocytopenia | 0.57% | 1.01% | 0.434 |

(44.3%) received abciximab than in the clopidogrel arm (39.1%), but the difference did not reach statistical significance ($P=0.093$). The majority of stents used were Boston Scientific NIR and ACS Duet stents (71% and 11.5%, respectively).

Clinical Outcomes

The primary end point, failure to complete 2 weeks of concurrent therapy with aspirin, was reached in 3.64% of patients treated with ticlopidine and in 1.62% of patients treated with clopidogrel ($P=0.043$), as shown in Table 3. The most common adverse reaction necessitating discontinuation of ticlopidine was the development of a rash, which was confirmed by a physician in all except 2 patients (who self-reported the rash by telephone). In 1.5% of the patients assigned to ticlopidine and in 1.0% of the patients assigned to clopidogrel, the patient stopped the medication without one of the listed major adverse events. There was a single case of major access site bleeding (requiring surgical repair) in each arm (0.2% overall); both of these patients had received abciximab during stent implantation. However, among all the patients receiving an intravenous IIb/IIIa inhibitor, the incidence of major bleeding was low (0.38% with ticlopidine and 0.40% with clopidogrel).

Thrombocytopenia was rare with either ticlopidine or clopidogrel (Table 3). When the subgroup of patients receiving the combination of either thienopyridine and an intravenous IIb/IIIa inhibitor was analyzed, thrombocytopenia developed overall in 1.42%. Among the 262 patients who received ticlopidine and a IIb/IIIa inhibitor, thrombocytopenia developed in 1.15%, and among the 228 patients treated with clopidogrel and a IIb/IIIa inhibitor, thrombocytopenia developed in 1.75% ($P=0.576$). Thus, the occurrence of thrombocytopenia was similar between the two thienopyridine agents, whether or not they were combined with an intravenous IIb/IIIa inhibitor. There was no occurrence of thrombotic thrombocytopenic purpura in either treatment arm.

The cardiac outcomes are presented in Table 4. No events occurred between the end of the stenting procedure and the administration of the loading dose of thienopyridine. Acute stent thrombosis (within 24 hours of implantation) or subacute stent thrombosis (occurring from day 1 through day 30 after stent implantation) occurred in 2.02% of patients in the clopidogrel arm and in 1.92% in the ticlopidine arm ($P=0.901$). The timing of stent thrombosis is shown in the Figure. Stent thrombosis occurred predominantly during the

TABLE 4. Cardiac End Points

| | Ticlopidine | Clopidogrel | P |
|---------------|-------------|-------------|-------|
| Acute closure | 0.57% | 0.61% | 0.946 |
| SAT | 1.34% | 1.42% | 0.917 |
| 30-d Closure | 1.92% | 2.02% | 0.901 |
| TVR | 2.30% | 2.43% | 0.891 |
| Cardiac death | 1.53% | 0.61% | 0.149 |
| MACE | 4.60% | 3.85% | 0.551 |

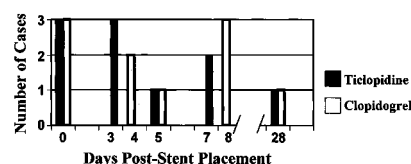
SAT indicates subacute thrombosis; TVR, target vessel revascularization; MACE, major adverse cardiac events.

first 8 days for both agents, with only a single case in each treatment group falling outside of the 2-week treatment period. Cardiac death occurred more frequently in the ticlopidine group (1.53% versus 0.61%), resulting in a higher overall rate of major adverse cardiac events (4.60% versus 3.85%), but neither difference reached statistical significance.

Discussion

In a randomized manner, we compared the safety and efficacy of ticlopidine and clopidogrel treatment after stent implantation in a broad, unrestricted population of patients. By including cases with acute myocardial infarction, cases that used adjunctive therapy with an intravenous IIb/IIIa inhibitor, and those involving stent implantation in bypass grafts, we extend the findings of Muller et al¹² and CLASSICS to a population more representative of patients receiving intracoronary stents in the United States. Furthermore, diabetics constituted 29% of the current study population, compared with 21% to 23% in the Muller study¹² and 10% to 12% in CLASSICS.¹⁴ Randomization allowed concurrent comparison of ticlopidine and clopidogrel in well-matched populations undergoing contemporaneous stenting, thus minimizing the confounding effects of comparing the thienopyridines in populations receiving different stents and adjunctive therapies during separate time periods.^{10,11}

In concordance with the prior studies, we found that drug intolerance was greater with ticlopidine, even during a truncated 2-week treatment period. However, there was a low incidence of major adverse drug-related reactions. In particular, despite the use of an intravenous IIb/IIIa inhibitor in almost half of the cases, the incidence of major bleeding was very low (0.39% overall), comparable to that reported with the use of abciximab and weight-adjusted heparin.^{15,16} When ticlopidine or clopidogrel was combined with a IIb/IIIa inhibitor, the incidence of thrombocytopenia remained low, with no significant difference between the two agents in the



Time of stent thrombosis: Number of cases with stent thrombosis is shown on ordinate; day after implantation that thrombosis occurred is shown on abscissa. Ticlopidine cases are displayed as solid bars; clopidogrel cases as open bars.

TABLE 5. Combined Results of Randomized Comparisons of Ticlopidine and Clopidogrel

| | Ticlopidine | Clopidogrel | <i>P</i> |
|--------------------|-----------------|-----------------|----------|
| 30-d Stent closure | 14/1207 (1.16%) | 24/1529 (1.77%) | 0.355 |
| 30-d MACE | 33/1207 (2.73%) | 40/1529 (2.62%) | 0.850 |

MACE indicates major adverse cardiac events.

rates of thrombocytopenia. Combining IIb/IIIa inhibition with a 300-mg "loading" dose of clopidogrel was not associated with an increased incidence of thrombocytopenia, contrary to results reported in an analysis of 174 patients receiving clopidogrel or ticlopidine in a nonrandomized manner.¹⁷

Prior studies, in particular that of Muller et al,¹² showed a higher incidence of stent thrombosis with clopidogrel than with ticlopidine, although the differences failed to reach statistical significance. In our study population, the occurrence of both acute closure (within 24 hours of implantation) and subacute stent thrombosis (day 1 to day 30) were essentially equal for the two treatment arms. Despite the presumed earlier platelet inhibition achieved with clopidogrel compared with ticlopidine after loading doses, there were equal numbers of acute closure in the two arms. However, because the clopidogrel group had a greater proportion of high-risk characteristics defined by angiography, such as the presence of thrombus, any benefit of earlier platelet inhibition may have been blunted by a greater tendency toward early thrombosis. Subacute stent thrombosis occurred after the 2-week treatment period in only 1 patient in each group, suggesting that a 14-day regimen of thienopyridine and aspirin is effective in the majority of patients receiving intracoronary stents.

The 30-day rates of stent closure in this study (1.92% for ticlopidine and 2.02% for clopidogrel) are similar to the 2.0% rate reported by Muller et al¹² for clopidogrel and aspirin and slightly higher than the range of 0.9% (for ticlopidine) to 1.5% (for clopidogrel) reported in CLASSICS.¹⁴ This probably is due to the inclusion of more patients in higher-risk subsets than in the previous studies, in particular patients with acute myocardial infarction, patients in cardiogenic shock, lesions with thrombus, and cases in which multiple stents were placed. In fact, the 30-day rate of major adverse cardiac events in patients treated with a thienopyridine and aspirin in this study (4.23% overall) lies between those rates reported by Muller et al and by CLASSICS (0.9% to 3.1%) and the rate of 5.6% reported in the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting,⁵ which enrolled patients at high risk for recurrent cardiac events.

The results of randomized treatment are now published for a total of 1207 patients receiving ticlopidine and 1529 patients receiving clopidogrel after intracoronary stent implantation. When the occurrence of 30-day stent thrombosis in the studies of Muller et al, CLASSICS, and TOPPS are combined, the rate associated with ticlopidine treatment is 1.16%, whereas that associated with clopidogrel treatment is 1.77% ($P=0.355$), as shown in Table 5. The combined 30-day major adverse cardiac event rate is 2.73% for ticlopidine treatment and 2.62%, for clopidogrel treatment ($P=0.850$), strongly suggesting that the two thienopyridine

agents confer similar protection against subacute stent thrombosis when combined with aspirin.

Study Limitations

This study was conducted at a single site, comprising the cases of 4 operators, and therefore the results reflect a relatively homogenous practice pattern of stent implantation. There was open-label administration of drugs, with twice-daily dosing of ticlopidine and single dosing of clopidogrel, making bias possible. However, only 2 patients stopped medication without an identified clinical reason; one was from each arm of treatment. Two patients receiving ticlopidine stopped the agent because of a reported rash, which was not confirmed by a physical examination. Nevertheless, the difference in the primary end point would remain statistically significant even if these two patients were excluded from the analysis. Finally, the specified treatment period was 2 weeks, which is shorter than in the two other studies. However, as shown in the Figure, there was only a single case of subacute stent thrombosis in each treatment arm after completion of the prescribed course of therapy, and both occurred very late, at 28 days.

Conclusions

Even during a 2-week treatment regimen after stent implantation, ticlopidine is less well tolerated than is clopidogrel. Both agents can be administered safely with "loading doses," even to patients who have been treated with intravenous IIb/IIIa inhibitors. When administered to a broad spectrum of patients, including those with high-risk clinical and angiographic characteristics, both agents have similar efficacy in preventing subacute stent thrombosis. Combining our results with those of two other randomized studies comparing ticlopidine and clopidogrel reveals no significant difference between the agents in preventing stent thrombosis or major adverse cardiac events. However, as all three randomized studies have shown greater intolerance of ticlopidine, the use of clopidogrel, in combination with aspirin, should be the preferred regimen after intracoronary stent implantation.

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