A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after coronary stent implantation

Craig P. Juergens, MBBS, Adelina M. Wong, MClinPrac, Dominic Y. C. Leung, PhD, Harry C. Lowe, PhD, Sidney Lo, MBBS, Clyne Fernandes, MBBS, Elizabeth F. Newland, BHlthSc, and Andrew P. Hopkins, MBBS
Liverpool, Australia

Background The combination of a thienopyridine and aspirin has become the standard of care after intracoronary stenting. Clopidogrel appears to be better tolerated than ticlopidine but may be associated with more adverse cardiac events. We assessed the tolerability and efficacy of 2 weeks of therapy with ticlopidine and aspirin in comparison to clopidogrel and aspirin after coronary stent implantation.

Methods Patients with successful intracoronary stent implantation at our institution were randomly assigned, in addition to aspirin, to receive either ticlopidine or clopidogrel. Loading doses were administered immediately after the procedure, and the drugs were continued for 2 weeks.

Results Three hundred seven patients were randomly assigned: 154 patients to clopidogrel and 153 to the ticlopidine group. The primary end point of early drug discontinuation occurred in 5 patients (3.3%) in the ticlopidine group and 1 patient (0.6%) in the clopidogrel group ($P = .121$). Within 30 days, thrombotic stent occlusion occurred in 1 patient (0.7%) in the ticlopidine group and 3 patients (1.9%) in the clopidogrel group ($P = .623$). A major adverse cardiac event occurred in 3 patients (~1.9%; $P = 1.00$) in each group.

Conclusions There was a nonsignificant trend to improved tolerability of a 2-week regimen of clopidogrel and aspirin when compared with ticlopidine and aspirin in patients undergoing intracoronary stent implantation. The combination of clopidogrel and aspirin results in a comparably low incidence of major adverse cardiac events when compared with ticlopidine and aspirin. (Am Heart J 2004;147:e15.)

Intracoronary stenting is an accepted treatment for vessel closure after percutaneous transluminal coronary angioplasty (PTCA)[1,2] and to reduce restenosis.[3,4] Initially, thrombotic occlusion of the stent, as well as peripheral vascular complications and hemorrhagic events related to the use of aggressive anticoagulation regimes, limited the benefits of coronary stenting. The use of the antiplatelet regime of ticlopidine and aspirin was shown to be superior to anticoagulation therapy, with less stent thrombosis and bleeding events,[5–8] when optimal stent deployment methods are used. As a consequence of these landmark studies, the use of ticlopidine and aspirin after coronary stent placement became standard practice. However, because of concerns of potentially life-threatening neutropenia, which occurs in approximately 1% of patients treated for more than 2 weeks with ticlopidine, a number of centers, including our own, adopted a strategy of discontinuing therapy 2 weeks after stent placement. A subsequent study of more than 800 patients suggested that this could be done relatively safely, with no case of stent thrombosis observed after ticlopidine cessation at 14 days.[9]

Clopidogrel is a thienopyridine derivative closely related to ticlopidine in chemical structure and function. Clopidigrel has been compared with aspirin in more than 19,000 patients with vascular disease in the clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study.[10] In this study, clopidogrel reduced the frequency of adverse cardiovascular events by 8.7% when compared with aspirin therapy. The side effect profile of clopidogrel and aspirin was similar, and, notably, there was no increase in neutropenia. With the widespread availability of clopidogrel and better tolerability, many interventional cardiology centers changed to a regime of clopidogrel and aspirin

From the Department of Cardiology, Liverpool Hospital, Liverpool, Australia.
Submitted June 24, 2003; accepted October 29, 2003.
Reprint requests: Craig Juergens, MBBS, Department of Cardiology, Liverpool Hospital, Locked Bag 7103, Liverpool BC NSW 1871, Australia.
E-mail: C.Juergens@unsw.edu.au
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2003.10.040

in their post–coronary stenting cases. This change of practice occurred largely before the publication of randomized, controlled trials comparing ticlopidine and aspirin with clopidogrel and aspirin in this group of patients. Subsequently, 2 large-scale, randomized, controlled clinical trials[11,12] concluded that 1 month of therapy with clopidogrel and aspirin was better tolerated when compared with 1 month of therapy with ticlopidine and aspirin in patients who had undergone intracoronary stent placement. However, both studies revealed a higher number of major adverse cardiac events in the clopidogrel groups, although the differences were not statistically significant. Our trial evaluated the tolerability and efficacy of 14 days of therapy with ticlopidine in combination with aspirin compared with clopidogrel and aspirin in patients who had undergone successful intracoronary stenting.

Methods

Patient population

Patients in whom intracoronary stents were successfully deployed (<30% residual stenosis without acute complications in the catheterization laboratory resulting in death or emergency bypass surgery) at our institution were eligible to participate in this trial. Cardiogenic shock; unsuccessful stent deployment; known allergy to aspirin, ticlopidine, or clopidogrel; recent treatment with clopidogrel or ticlopidine; and need for anticoagulants after the procedure were exclusion criteria. The institutional committee on human research of our hospital approved the study. At the end of a successful procedure, patients were randomly assigned in an open-label manner to receive clopidogrel or ticlopidine by means of a sealed envelope system.

Stents and antiplatelet regimens

Stents were implanted with the use of standard high-pressure techniques. Heparin was administered as boluses to maintain an activated clotting time >250 seconds, and glycoprotein IIb/IIIa inhibitors could be used at the operator's discretion. The sheath was removed after the procedure when the activated clotting time was <180 seconds. Heparin could be restarted after sheath removal at the operator's discretion. Patients were assigned to receive ticlopidine (250 mg bid) or clopidogrel (75 mg pd) orally for 14 days. The first dose of ticlopidine (500 mg) or clopidogrel (150 mg) was given immediately after the procedure. Treatment was not blinded. All patients received at least 300 mg of aspirin in the 24 hours before the procedure and a minimum of 100 mg per day for the duration of the study.

End points

The primary end point was the failure to complete 2 weeks of initiated thienopyridine in combination with aspirin. The reason for discontinuation was noted.

Secondary end points included hemorrhage (defined as bleeding complications requiring surgery or transfusion or bleeding associated with objective evidence of organ dysfunction); vascular end points (false aneurysms, surgical repair of puncture site complications or arteriovenous fistulae), and the combined incidence of major adverse cardiac events including cardiovascular death, nonfatal myocardial infarction (MI), and urgent target vessel revascularization. The diagnosis of MI was made if at least 2 of 3 the following criteria were met: occurrence of typical ischemic chest pain lasting more than 30 minutes, abnormal Q waves not present on the baseline electrocardiogram, or an increase in the creatinine kinase (CK) concentration to twice the upper limit of normal with a concomitant rise in the CK-MB isoenzyme above the upper limit of normal. The diagnosis of recurrent MI was determined if there was an increase of >30% in the CK concentration above baseline. Creatinine kinase (and CK-MB) measurements were performed routinely on all patients the morning after the procedure and more frequently if there was a clinical suspicion of an adverse cardiac event. Occurrences of thrombotic stent occlusion (TSO), defined angiographically as total occlusion of the stented segment, were also noted. Routine full blood count analysis was not performed as part of the trial after hospital discharge, but when incidental blood tests were performed, we endeavored to obtain the result to ascertain any adverse hematologic events.

If a patient reached more than 1 cardiac end point, only the most severe end point was counted as a major adverse cardiac event (MACE) for the final analysis. Patients were contacted by telephone at 2 weeks and 4 weeks to assess the presence of any adverse events. MACE were verified by independent chart review.

Statistical analysis

The study size was planned on the basis of estimated discontinuation rate of 9% for ticlopidine and 3% for clopidogrel; a sample size of 140 patients in each group was predicted to show a 67% relative difference, with 90% power. Proportions were compared between treatment groups by means of χ^2 or Fisher exact test where appropriate. Continuous variables in each group where compared by means of an unpaired Student t test. Statistical significance was defined as a 2-tailed P value of <.05. Statistical analysis was performed with SPSS for Windows (version 10).

Results

Among 307 patients who underwent successful stent implantation from July 1999 until January 2001, 153 were randomly assigned to receive ticlopidine and 154 to receive clopidogrel. Baseline characteristics of the patient population are shown in Tables I whilst II gives details on stent and angiographic data. There were no significant differences between treatment groups with respect to demographic or lesion subset characteristics. The patient cohort was a relatively high-risk one, with a high percentage of patients presenting with acute coronary syndromes and the majority of lesions either type B2 or C. Intravenous glycoprotein IIb/IIIa antagonists were used in 23% of the patients receiving ticlopidine and 25% of patients in the clopidogrel group. Abciximab, administered in the cardiac catheterization laboratory, was the most fre-

Table I. Baseline characteristics of the patient population

Characteristics	Ticlopidine (n = 153)	Clopidogrel (n = 154)
Mean age (y ± SD)	60 ± 10	60 ± 12
Male/female (%)	123 (80)/30 (20)	110 (71)/44 (29)
Hypertension (%)	90 (58)	87 (56)
Diabetes mellitus (%)	35 (23)	30 (19)
Current smoker (%)	27 (17)	33 (21)
Hypercholesterolaemia (%)	110 (72)	122 (79)
Previous CABG (%)	18 (12)	10 (7)
Recent MI (%)	15 (10)	22 (14)
Unstable angina (%)	72 (47)	67 (44)
Glycoprotein IIb/IIIa receptor antagonist (%)	36 (23)	38 (25)

CABG, Coronary artery bypass grafting.

Table II. Stent and angiographic data

Characteristics	Ticlopidine (n = 153)	Clopidogrel (n = 154)
Stented lesions	175	170
Lesion type B2 or C (%)*	98 (56)	85 (50)
Occluded vessel (%)	22 (14)	15 (9)
Maximum stent size (mm)	3.02 ± 0.53	3.00 ± 0.45
Maximum inflation pressure (atm)	15.4 ± 2.1	15.1 ± 1.9
Stented length (mm)	17.3 ± 8.7	16.2 ± 6.6

*American Heart Association/American College of Cardiology classification.

Table III. Noncardiac events at 30 days

	Ticlopidine (n = 153)	Clopidogrel (n = 154)
Drug discontinuation (%)*	5 (3.3)	1 (0.6)
Gastrointestinal	2 (1.3)	0 (0.0)
Dermatological	2 (1.3)	0 (0.0)
Bleeding	1 (0.7)	1 (0.6)
Haemorrhagic complications (%)	0 (0.0)	1 (0.6)
Vascular complication (%)	2 (1.3)	2 (1.3)
Any noncardiac event (%)†	6 (3.9)	3 (1.9)

Any noncardiac event = composite of drug discontinuation, haemorrhagic and vascular complications. One patient in each group had 2 noncardiac events and therefore are only counted once.
*P = 0.121 by Fisher's exact test.
†P = 0.336 by Fisher's exact test.

Table IV. Cardiac events at day 30

	Ticlopidine (n = 153)	Clopidogrel (n = 154)
Cardiovascular death (%)	1 (0.7)	0 (0.0)
Nonfatal MI (%)	2 (1.3)	2 (1.3)
Q wave	0 (0.0)	2 (1.3)
Non Q ≥2 × CK	2 (1.3)	0 (0.0)
Urgent TVR (%)	1 (0.7)	3 (1.9)
MACE (%)*	3 (2.0)	3 (1.9)
Thrombotic stent occlusion (%)	1 (0.7)	3 (1.9)

TVR, Target vessel revascularization.
*P = 1.00 by Fisher's exact test.

quently administered glycoprotein IIb/IIIa antagonist in both groups (33 of 36 in the ticlopidine group and 36 of 38 in the clopidogrel group). Clinical follow-up was complete in all 307 patients.

Primary end point

Table III summarizes data on the primary end point and other noncardiac events at 30 days. The primary end point, failure to complete 2 weeks of concurrent therapy with aspirin, occurred in 5 patients (3.3%) assigned to receive ticlopidine and in 1 (0.6%) patient assigned to receive clopidogrel (P = .121). The reported reasons for termination of therapy included bleeding, which occurred in 1 patient in each group. Neither patient required transfusion or surgical intervention, although in each case antiplatelet therapy was discontinued. Rash and gastrointestinal side effects occurred in 4 ticlopidine-treated patients (2 cases of each) but in no patients in the clopidogrel group.

Secondary end points

There were 2 cases of major access site complications in each group. There were 2 femoral artery pseudoaneursyms in the ticlopidine group and 1 in the clopidogrel group. All 3 either closed spontaneously or were managed noninvasively with successful ultrasound-guided compression. In addition, there was a single case of major hemorrhage at the vascular access site in a patient randomly assigned to receive clopidogrel. This patient also received abciximab during her procedure, and after a blood transfusion she completed a 2-week course of ticlopidine. Cardiac events occurring up until day 30 are summarized in Table IV. A MACE occurred in 3 (~1.9%; P = 1.00) patients in each group. TSO occurred in 3 patients (1.9%) in the clopidogrel arm and in 1 patient (0.7%) in the ticlopidine arm (P = .623). The patient who had a TSO in the ticlopidine group subsequently had a cardiac death. This patient's stent thrombosis occurred on day 13, and, notably, their ticlopidine had been stopped on day 8 because of a large groin hematoma. Her stent could not be reopened because of problems with vascular access, and the patient subsequently died 2 days later. In the clopidogrel group, 2 patients (1.2%) had TSO within 24 hours of implantation and 1 patient had a TSO on day 26. There were 2 nonfatal MIs (1.3%) in both groups. There were no documented cases of neutropenia or thrombocytopenia.

Discussion

This single-center study provides further evidence that clopidogrel and aspirin is at least as well tolerated as combination therapy with ticlopidine and aspirin. In addition, we found no significant increase in cardiac events in the patients receiving clopidogrel and aspirin when compared with the group receiving ticlopidine and aspirin. The need to discontinue study drug was lower in our study than in the larger Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)[11] and Muller et al[12] studies. Only 3.3% of patients in our study stopped taking ticlopidine before the prescribed 14 days of this study compared with 8.2% and 5.8%, respectively, in the aforementioned studies. Similarly, only 0.6% of our patients stopped taking clopidogrel when compared with 2% to 5.1% in the CLASSICS study and 2.0% in the Muller study. This is not surprising, given the fact that our patients were asked to take study drug for 14 days in our study compared with 28 days in the larger studies. Although not statistically significant in our study, the trend to more discontinuations of ticlopidine is consistent across all studies. A study by Taniuchi,[13]which was similar in design to our own, compared 2 weeks of therapy with ticlopidine or clopidogrel in combination with aspirin in a broad subset of patients undergoing intracoronary stent implantation. Their reported incidence of drug discontinuation, 3.6% with ticlopidine and 1.6% with clopidogrel, was similar to our study, probably reflecting the shorter duration of therapy.

The incidence of TSO was low in our study, at $<$2.0% in both groups, which is consistent with that reported in other studies of antiplatelet agents.[5–8,12,13] There were 3 (1.9%) TSOs in the clopidogrel group versus 1 (0.7%) in the ticlopidine group. Although not statistically significant in our underpowered study, the higher rate of stent thrombosis in the clopidogrel group observed in our study is consistent with other randomized, controlled trials.[12,13] Stent thrombosis occurred within in 24 hours in 2 patients in the clopidogrel group. This may reflect an inadequate loading dose of clopidogrel, as our protocol mandated a loading dose of 150 mg and not 300 mg, which is more commonly used currently. This loading dose was chosen so that both groups received the same number of doses of their respective thienopyridine, and more than 2 doses of ticlopidine are not well tolerated. It should be noted, however, that 2 trials similar to our own mandated no loading dose of clopidogrel or ticlopidine.[11,12] The overall rate of stent thrombosis is low in all studies, and no individual study has been large enough to specifically address this question. If appropriately sized randomized trails were to be performed in the future to specifically address this question, the absolute difference is likely to be quite small and may not be clinically relevant, given the better tolerability of clopidogrel and the higher incidence of life-threatening hematologic disorders with ticlopidine. There was no statistically significant difference in the combined incidence of adverse cardiac events in our study with 3 events (~1.9%) in both the ticlopidine and clopidogrel groups (P = 1.00). Two large-scale studies[11,12] of 4 weeks of thienopyridine therapy have shown nonsignificant trends to more adverse cardiac events in patients receiving clopidogrel when compared with those receiving ticlopidine. However, in the Taniuchi study,[13] in which therapy was discontinued after 14 days, the 30-day adverse cardiac event rates where nonsignificantly higher in the ticlopidine group when compared with the clopidogrel group (4.60% vs 3.85%; P = .551).

A previous study has suggested that the cessation of ticlopidine after 2 weeks may be safe in terms of adverse cardiac events to avoid the risks of profound life-threatening neutropenia.[9] Clopidogrel is not without adverse hematologic sequelae, however, with a small incidence of thrombotic thrombocytopenic purpura occurring within 14 days of initiation of therapy,[14] and there are also the important issues of cost and compliance with the use of expensive antiplatelet agents for longer than 2 weeks. Although we have data on only 307 patients, the occurrence of only 1 TSO between day 14 and day 30 in patients receiving clopidogrel or ticlopidine is reassuring. In more than 1000 patients randomly assigned, in the only other prospective study of 2 weeks of thienopyridine therapy after intracoronary stent implantation,[13] there was only a single case of stent thrombosis in each group occurring outside of the 2-week treatment period.

Since our study was conceived and completed, important information has emerged from 2 large multicenter trials addressing the issue of long-term clopidogrel therapy in patients who have undergone successful intracoronary stenting. In both the Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE)[15] and Clopidogrel for the Reduction of Events During Observation (CREDO)[16] trials, patients who continued to receive clopidogrel long-term therapy had a significant reduction in major cardiovascular events when compared with long-term placebo therapy. These data suggest that there may be sustained cardiovascular benefits beyond reducing the risk of stent thrombosis in the first month after intracoronary stenting. In the context of this evidence, the relevance of our study could be questioned; however, we believe that our results may be of assistance when treating patients who may be intolerant of long-term therapy with thienopyridines.

Study limitations

This study has a number of limitations, including those inherent in single-center studies, the nonblinding of medication use, and the small sample size. The observed incidence of drug discontinuation in the ticlopidine group was 3.3%, which was substantially less than the anticipated incidence of 9%. We based our power calculations on previous studies of 4 weeks of therapy, as the Taniuchi study[13] was not available to us at the time of commencement of our study. Consequently, the study is underpowered to assess the primary end point. Despite this, the results are consistent with other larger-scale multicenter trials showing that combination therapy with clopidogrel and aspirin is better tolerated, with efficacy similar to ticlopidine and aspirin. The available data from this study do not allow us to assess the risk of hematologic side effects, as routine blood counts were not performed after hospital discharge. We did not observe any severe thienopyridine-induced neutropenia or thrombocytopenia during the hospital stay, and it is likely that severe episodes would have come to our attention, but we cannot say with absolute certainty that these events did not occur.

Conclusions

In conclusion, these data demonstrate that after 2 weeks of combination antiplatelet therapy with aspirin, there is a trend toward improved patient tolerability of clopidogrel compared with ticlopidine, with a similarly low incidence of adverse cardiac events. These data may be of assistance in the treatment of patients intolerant of long-term therapy with thienopyridines or where costs of such treatment are prohibitive.

We thank the nurses and scientific officers from the Cardiac Catheterization laboratories at Liverpool hospital for their assistance in performing this research.

References

1. Sigwart U, Puel J, Mirkovitch V, et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701–6.
2. George BS, Voorhees WD III, Roubin GS, et al. Multicenter investigation of coronary stenting to treat acute or threatened closure after percutaneous transluminal coronary angioplasty: clinical and angiographic outcomes. J Am Coll Cardiol 1993;22:135–43.
3. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331: 489–95.
4. Fischman DL, Leon MB, Baim DS, et al. A randomised comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496–501.
5. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation 1995;91:1676–88.
6. Schomig A, Neumann F-J, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary artery stents. N Engl J Med 1996;334:1084–9.
7. Bertrand ME, Legrand V, Boland J, et al. Randomized multicentre comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. Circulation 1998;98:1597–603.
8. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic drug regimens after coronary artery stenting. N Engl J Med 1998;339:1665–71.
9. Berger PB, Bell MR, Hasdai D, et al. Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. Circulation 1999;99:248–53.
10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329–39.
11. Bertrand ME, Rupprecht H-J, Urban P, et al. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102: 624–9.
12. Muller C, Buttner HJ, Petersen J, et al. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary artery stents. Circulation 2000;101:590–3.
13. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. Circulation 2001;104:539–43.
14. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. N Engl J Med 2000; 342:1773–7.
15. Mehta SR, Yusuf S, Peters RJG, et al. Effects of pretreatment with clopidogrel and aspirin followed by long term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
16. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288: 2411–20.