A Randomized Comparison of Clopidogrel and Aspirin Versus Ticlopidine and Aspirin After the Placement of Coronary-Artery Stents

Christian Müller, Heinz J. Büttner, Jens Petersen and Helmut Roskamm

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Christian Müller, MD; Heinz J. Büttner, MD; Jens Petersen, MD; Helmut Roskamm, MD

Background—The introduction of an effective antiplatelet therapy with aspirin and ticlopidine after the placement of coronary-artery stents has decreased the risk of thrombotic stent occlusions (TSO) and hemorrhagic complications. However, the use of ticlopidine is limited by hematological and gastrointestinal adverse effects. The safety and efficacy of clopidogrel after stenting remains to be established.

Methods and Results—After successful coronary stenting during elective or emergency percutaneous transluminal coronary angioplasty, 700 patients with 899 lesions were randomly assigned to receive a 4-week course of either 500 mg ticlopidine (n=345) or 75 mg clopidogrel (n=355), in addition to 100 mg aspirin. All the following clinical events reflecting TSO were included in the prespecified primary cardiac endpoint: cardiac death, urgent target vessel revascularization, angiographically documented TSO, or nonfatal myocardial infarction within 30 days. The primary noncardiac endpoint was defined as noncardiac death, stroke, severe peripheral vascular or hemorrhagic events, or any adverse event resulting in discontinuation of study medication. Cardiac events occurred in 17 patients [11 (3.1%) with clopidogrel and 6 (1.7%) with ticlopidine ($P=0.24$)]. The primary noncardiac endpoint was observed in 16 patients (4.5%) assigned to receive clopidogrel versus 33 patients (9.6%) assigned to receive ticlopidine ($P=0.01$).

Conclusions—After the placement of coronary-artery stents in unselected patients, antiplatelet therapy with aspirin and clopidogrel seems to be comparably safe and effective as aspirin and ticlopidine. Noncardiac events were significantly reduced with clopidogrel. **(*Circulation*. 2000;101:590-593.)**

Key Words: clopidogrel ■ ticlopidine ■ stents ■ thrombosis ■ prevention

The introduction of an effective antiplatelet therapy with aspirin and ticlopidine after the placement of coronary-artery stents has reduced the risk of thrombotic stent occlusion (TSO), as well as hemorrhagic and vascular complications.[1–3]

However, the use of ticlopidine is limited by hematological and gastrointestinal adverse effects.[4–5] Clopidogrel is a new thienopyridine derivative with an excellent overall safety profile.[6] Experimental studies[7] suggest that clopidogrel has a faster onset of action than ticlopidine. Therefore, a combination of clopidogrel and aspirin might reduce complications even further after stenting.

This trial was designed to evaluate the safety and efficacy of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents in unselected patients.

Methods

Patient Population

Patients in whom primary or provisional stent implantation was successful (<50% residual stenosis without acute complications in the catheter laboratory resulting in death or emergency bypass grafting) were randomly assigned in equal proportions with the use of a prespecified randomization sequence to one of the antiplatelet regimens.

Cardiogenic shock; mechanical ventilation; known allergy to aspirin, ticlopidine, or clopidogrel; long-term treatment with ticlopidine, clopidogrel, or warfarin; and stenting intended primarily as a bridge to coronary bypass grafting were exclusion criteria.

The study was carried out according to the principles of the Declaration of Helsinki and approved by our local hospital investigational review board. Informed consent was obtained from all participating patients.

Stents and Antiplatelet Regimens

Stents were implanted with high-pressure technique as previously described.[3] Patients were assigned to receive ticlopidine (250 mg bid) or clopidogrel (75 mg pd) orally for 4 weeks. The first dose of ticlopidine (500 mg) or clopidogrel (75 mg) was given immediately after the procedure. All patients received aspirin (100 mg pd) for the duration of the study. Treatment was not blinded, but all endpoints were adjudicated by a clinical-events committee whose members were unaware of the patients treatment assignments.

Endpoint Analysis

The primary cardiac endpoint included death from cardiac causes, urgent target vessel revascularization, angiographically evident TSO, or nonfatal myocardial infarction within 30 days.

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From Herz-Zentrum, Bad Krozingen, Germany.
Correspondence to Dr Heinz J. Büttner, Herz-Zentrum, 79189–Bad Krozingen, Germany.

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TABLE 1. Clinical, Angiographic and Procedural Baseline Characteristics

No. (%) if not defined otherwise	Clopidogrel (n=355)	Ticlopidine (n=345)	*P*
Age, y	65±11	64±10	0.11
Female sex	93 (26)	91 (26)	0.98
Diabetes mellitus	80 (23)	72 (21)	0.52
Previous coronary artery bypass graft	53 (15)	42 (12)	0.25
Previous myocardial infarction	170 (48)	153 (44)	0.29
Acute myocardial infarction	40 (11)	38 (11)	0.91
Unstable angina	141 (40)	131 (38)	0.59
Three vessel disease	162 (46)	138 (40)	0.11
Left ventricular function			
Moderately or severely impaired	110 (31)	84 (24)	0.09
Lesions	459	440	
Lesions per patient	1.29±0.54	1.28±0.55	0.66
Lesion type* B2 or C	197 (55)	176 (51)	0.24
Restenotic lesion	46 (13)	34 (10)	0.21
Bifurcation lesion	13 (4)	17 (5)	0.52
Occluded vessel	77 (22)	80 (23)	0.75
Max. balloon size, mm	3.31±0.47	3.30±0.44	0.87
Max. inflation pressure, atm	13.1±2.7	13.0±2.7	0.30
Stent length, mm	18±9	18±12	0.48
Type of stents used:			
NIR Primo®	180 (51)	169 (49)	0.60
ACS Multilink®	66 (19)	72 (21)	0.51
Others	109 (30)	104 (30)	0.76
Glycoprotein IIb/IIIa receptor antagonist	40 (11)	25 (7)	0.07
Duration of procedure, min	56±25	56±26	1.00

Plus-minus values are means±SD.

*American Heart Association/American College of Cardiology classification is given for the first treated lesion in every patient.

Death from any noncardiac cause, stroke, a severe peripheral vascular event (false aneurysms requiring surgery or prolonged ultrasound-guided compression and femoral artery dissection or occlusion requiring urgent percutaneous or surgical treatment), a hemorrhagic event requiring transfusion, or any adverse event resulting in the discontinuation of study medication were included in the primary noncardiac endpoint. For quantitative coronary angiography analysis, the CAAS II system (Pie Medical, The Netherlands) was used.

Statistical Analysis

The primary analysis consisted of a comparison of major noncardiac events within 30 days. Study size was calculated on the assumption that clopidogrel reduces noncardiac events by 50%. If a patient reached more than 1 endpoint, only the most severe endpoint was counted for the final analysis.

Discrete variables were expressed as counts, continuous variables as means±SD. Comparisons were made among continuos variables using ANOVA for independent samples. Comparison of discrete variables were made by χ^2 test. All hypothesis testing was 2-tailed.

Results

Baseline Patient Characteristics and Procedural Details

Among 793 consecutive patients who underwent stent implantation from September 1998 through April 1999, 700 patients with 899 lesions were randomly assigned to receive either ticlopidine (n=345) or clopidogrel (n=355). As shown in Table 1, baseline clinical, angiographical, and procedural characteristics were similar in both groups. Approximately 50% of cases were performed in acute coronary syndromes. Half of all lesions were type B2 or C lesions.

Cardiac and Noncardiac Endpoints

Clinical follow-up was complete for 699 patients (99.9%). A primary cardiac event occurred in 17 patients [11 (3.1%) with clopidogrel and 6 (1.7%) with ticlopidine (P=0.24, Tables 2 to 3)]. TSO developed in 7 patients (2.0%) with clopidogrel but in only 2 patients (0.6%) with ticlopidine (P=0.10). In 5 of these patients (4 and 1, respectively), TSO resulted in nonfatal myocardial infarction. Altogether, 7 patients (2.0%) with clopidogrel and 4 patients (1.2%, P=NS) with ticlopidine suffered a nonfatal myocardial infarction.

A primary noncardiac endpoint was observed in 16 patients (4.5%) assigned to receive clopidogrel versus 33 patients (9.6%) assigned to receive ticlopidine (P=0.01). Hemorrhagic and vascular complications were not significantly different between clopidogrel and ticlopidine. However, intolerance resulting in the discontinuation of study medication

TABLE 2. Cardiac and Noncardiac Events Within 30 Days

No., %	Clopidogrel n=355	Ticlopidine n=345	*P*
Cardiac events*	11 (3.1)	6 (1.7)	0.24
Cardiac death	1 (0.3)	1 (0.3)	0.98
Thrombotic stent occlusion	7 (2.0)	2 (0.6)	0.10
TVR†	6 (1.7)	2 (0.6)	0.17
Nonfatal myocardial infarction	7 (2.0)	4 (1.2)	0.39
Noncardiac events	16 (4.5)	33 (9.6)	0.01
Noncardiac death	0	1 (0.3)	0.31
Hemorrhagic complication	2 (0.6)	3 (0.9)	0.65
Vascular complication	7 (2.0)	6 (1.7)	0.82
Stroke	0	0	1.00
Leukopenia or thrombocytopenia	0	3 (0.9)	0.07
Intolerance‡	7 (2.0)	20 (5.8)	0.01
Allergic exanthema	5 (1.4)	13 (3.7)	0.06
Diarrhea	1 (0.3)	5 (1.4)	0.09
Nausea	4 (1.1)	6 (1.7)	0.50
Liver enzyme elevation	0	1 (0.3)	0.31

*Only the most severe event was counted for any specific patient.

†Urgent target vessel revascularization.

‡Discontinuation of study drug due to other adverse events. Some patients had more than 1 symptom.

(2.0% versus 5.8%, $P<0.01$) and hematological abnormalities (0% versus 0.9%, $P=0.07$) were reduced with clopidogrel.

Discussion

This randomized trial showed that after the placement of coronary-artery stents in unselected patients, antiplatelet therapy with aspirin and clopidogrel seems to be comparably safe and effective as aspirin and ticlopidine. Noncardiac events were significantly reduced with clopidogrel. The reduced incidence of allergic exanthema, diarrhea, and hematological abnormalities accounted for most of the difference. This confirms the findings of an observational study in 1689 consecutive patients.[8]

Our data showed more cardiac events with clopidogrel, exclusively due to a higher incidence of TSO. Although the difference failed to reach statistical significance and the incidence of TSO was low with either clopidogrel or ticlopidine, this finding raises concern. The finding that 6 of the 9 TSOs occurred on or before day 2 may support the role of pretreatment or loading for both regimens.

The aim of this trial was to compare clopidogrel and ticlopidine in "real world stenting" to make the results easily transferable to everyday practice. Therefore, no target lesion exclusion criteria was used. Multivessel interventions, vessels <3 mm, vessels with additional inflow or outflow obstructions, and suboptimal stent results with residual dissections all were included. Thus it is not surprising to find several of these high-risk features in those patients developing TSO (Table 3).

However, given the high percentage of acute coronary syndromes and complex lesion anatomy, as well as the restricted use of glycoprotein IIb/IIIa antagonists, the low rate of major adverse cardiac events demonstrates the effectiveness of both antiplatelet regimens.

It is important to note that ticlopidine and clopidogrel were used without a loading dose. However, a loading dose (especially a loading dose of clopidogrel) may enhance its antithrombotic efficacy without necessarily increasing its side effects.

Study Limitations

This study was not performed to show a statistical significant difference in cardiac events. However, the finding of a higher TSO incidence in patients assigned to receive clopidogrel raises concern and should soon be examined in a large scale randomized trial.

Conclusions

The present study demonstrates that after the placement of coronary artery stents, antiplatelet therapy with aspirin and

TABLE 3. Patients with Thrombotic Stent Occlusion

No	C/T	Day	MI†	TVR‡	Lesion Type‖	Vessel	Vessel Size (mm)	MLD§ Pre (mm)	MLD Post (mm)	% Stenosis Post	Stent Length (mm)	Diss**	TIMI Flow
1	C	0	Yes	Yes	C	RCA	3.63	0.63	3.07	16	32	No	3
2	T	2	Yes	Yes	B2	LAD	2.96	0.97	2.18	26	23	No	3
3	C	4	No	No	C	SVG	2.93	0.00	2.21	25	16	No	2
4*	C	6	No	Yes	C	RCA	3.10	0.00	2.94	5	57	Yes	3
5	C	0	Yes	Yes	B2	LAD	3.02	0.64	2.62	13	17	Yes	3
6	C	1	Yes	Yes	C	SVG	2.78	0.25	2.70	3	48	Yes	3
7	C	8	Yes	Yes	B1	LAD	2.59	0.19	2.11	18	12	No	3
8	T	1	No	Yes	B2	RCX	2.54	0.18	2.32	9	32	No	3
9*	C	1	No	Yes	B1	RCX	3.11	0.50	3.21	−3	17	No	3

*Primary PTCA for acute myocardial infarction.

C indicates clopidogrel; T, ticlopidine; RCA, right coronary artery; LAD, left anterior descending; SVG, saphenous vein graft; RCX, ramus circumflexus; and TIMI, thrombolysis in myocardial infarction.

†Myocardial infarction; ‡Urgent target vessel revascularization; ‖American Heart Association/American College of Cardiology classification; §Minimal lumen diameter; **Residual dissection.

clopidogrel seems to be comparably safe and effective as aspirin and ticlopidine. Noncardiac events were significantly reduced with clopidogrel. However, the more favorable safety profile of clopidogrel might have to be balanced against a slightly lower antithrombotic efficacy if used without a loading dose.

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