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Efficacy and safety of individually tailored antiplatelet therapy in patients with acute coronary syndrome after coronary stenting: a single center, randomized, feasibility study

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Abstract

Background Low responsiveness to clopidogrel (LRC) is associated with increased risk of ischemic events. This study was aimed to explore the feasibility of tailored antiplatelet therapy according to the responsiveness to clopidogrel. **Methods** A total of 305 clopidogrel naïve patients with acute coronary syndromes (ACS) undergoing coronary stenting were randomly assigned to receive standard (n = 151) or tailored (n = 154) antiplatelet therapy. The ADP-induced platelet aggregation tests by light transmission aggregometry were performed to identify LRC patients assigned to the tailored group. The standard antiplatelet regimen was dual antiplatelet therapy with aspirin and clopidogrel. The tailored antiplatelet therapy was standard regimen for non-LRC patients and an additional 6-month cilostazol treatment for LRC patients. The primary efficacy outcome was the composite of cardiovascular death, myocardial infarction or stroke at one year. **Results** LCR was present in 26.6% (41/154) of patients in the tailored group. The percentage platelet aggregation for LCR patients was significantly decreased at three days after adjunctive cilostazol treatment (77.5% ± 12.1% *vs.* 64.5% ± 12.1%, $P < 0.001$). At one year follow-up, a non-significant 37% relative risk reduction of primary events were observed in the tailored group as compared to the standard group (5.8% *vs*. 9.3%, $P = 0.257$). There were no differences in the rates of stent thrombosis and hemorrhagic events between the two groups. **Conclusions** Tailored antiplatelet therapy for ACS patients after coronary stenting according to responsiveness to clopidogrel is feasible. However, its efficacy and safety need further confirmation by clinical trials with larger sample sizes.

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Keywords: Acute coronary syndrome; Antiplatelet therapy; Clopidogrel; Coronary stenting

1 Introduction

Platelet aggregation is a major pathway involving ischemic cardiovascular events.[1,2] Although numerous novel antithrombotic agents and strategies have been developed over the past decades, atherothrombotic events still remain the major problem in patients with cardiovascular disease, especially those patients who have acute coronary syndrome (ACS) and/or are undergoing percutaneous coronary intervention (PCI).[3–7] As reported previously in literature, individual variations of platelet inhibition after antiplatelet therapy may play an important role in ischemic cardiovascular events.[1,2,8–10] Therefore, the concept of individually tailored antiplatelet therapy according to the response of patients to treatment has recently emerged,[11,12] and has been considered an ideal strategy to balance the efficacy and safety of antiplatelet therapy, especially for those patients at high risk for thrombotic or hemorrhagic events. However, many important questions pertaining to this strategy, such as the optimal screening methods of patients and antiplatelet regimens, have not been well elucidated.

We conducted a randomized, controlled study to explore the feasibility of a platelet aggregation function test together with a guided tailored antiplatelet strategy to demonstrate the efficacy and safety of an adjunctive cilostazol

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treatment for patients with low responsiveness to clopidogrel (LRC).

2 Methods

2.1 Study population

Patients were eligible for enrollment if they were aged 35 to 75 years; admitted as non-ST segment elevation ACS [including unstable angina and non-ST elevation myocardial infarction (MI)]; and undergoing successful drug-eluting coronary stent implantation. Exclusion criteria included the following: administration of clopidogrel or ticlopidine within two weeks before randomization; contraindications to antiplatelet therapy; history of intracranial bleeding; known bleeding disorders; severe liver or kidney disease; and pregnancy.

The study complied with the Declaration of Helsinki regarding investigations in humans and was approved by the Ethics Committee at Shenyang Northern Hospital, Shenyang, China. Eligible patients provided written informed consent. The study is registered in the National Institutes of Health website (www.clinicaltrial.gov) as identifier NCT 00404781.

2.2 Randomization and medications

Patients eligible for enrollment were randomly assigned to receive standard (n = 151) or tailored antiplatelet therapy (n = 154) according to a computer-generated randomization list. Patients in the standard group received standard dual antiplatelet therapy (aspirin 300 mg/d for one month followed by 100 mg/d indefinitely and clopidogrel 600 mg loading followed by 75 mg/d for 12 months). Antiplatelet regimens for the patients in the tailored group were dependent upon the results of the platelet function assay: patients with laboratory documentation of LRC received additional cilostazol for 6 months (100 mg, twice daily) on the basis of standard dual antiplatelet therapy, whereas non-LRC patients received standard dual antiplatelet therapy.

2.3 Blood sample collection

In the tailored group, two blood samples were collected at admission (T0) and 24 h after clopidogrel loading (T1), respectively. For patients who received additional cilostazol treatment, the third blood sample was collected three days following the administration of cilostazol (T2).

2.4 Platelet aggregation function assessment

Platelet aggregation function was assessed by light transmission aggregometry (LTA). Blood was centrifuged (200 r/min, 10 min) to obtain platelet-rich plasma (PRP). The platelet count in the PRP was adjusted to the range of 150,000 to 300,000 platelets/L by dilution with autologous plasma when out of range. The remaining specimen was re-centrifuged (1500 r/min, 15 min) to obtain platelet-poor plasma (PPP). Platelets were stimulated with 20 μmol/L adenosine diphosphate (ADP). Aggregation was measured at 37℃ with a PACKS-4 Aggregometer (Helena Laboratories, Beaumont, Texas) and expressed as the maximal percentage change in light transmittance from baseline to 5 min after the addition of the agonist, with PPP as a reference. The percentage of inhibition of platelet aggregation (IPA) was defined as an absolute reduction of platelet aggregation at T1 compared to T0. An IPA < 10% was defined as LRC.[9,13]

2.5 Study end points, definitions and follow-up

The primary outcome was the composite occurrence of cardiovascular death, MI or stroke at one year. Secondary end points were major adverse cardiac and cerebral events [MACCE, defined as the composite of cardiac death, MI, ischemic driven target vessel revascularization (TVR) or stroke], hemorrhagic events and stent thrombosis.

All deaths were considered cardiovascular-related unless non-cardiac causes were clearly identified. MI was diagnosed when creatine kinase and creatine kinase-MB were ≥ 2-fold of the normal upper limit (≥ 3-fold of the normal upper limit within two days after the PCI procedure) accompanied by chest pain for ≥ 30 min or the appearance of new electrocardiographic changes. TVR was defined as clinically driven PCI or bypass surgery of the target lesion or any segment of the epicardial coronary artery containing the target lesion. Stent thrombosis was defined as angiographically documented stent thrombosis, target vessel-related MI without clear evidence of thrombosis, or unexplained sudden death after index procedure. Hemorrhagic events were classified as major (a drop in hemoglobin of > 50 g/L or any intracranial bleeding), minor (a drop in hemoglobin of 30 g/L to 50 g/L) and minimal (a drop in hemoglobin of < 30 g/L) according to thrombolysis in the myocardial infarction (TIMI) definition.[14] All of the end points were measured and judged by two experienced physicians who were blinded to both the objectives and protocol of this study as well as the patient allocations.

Clinical follow-ups were performed at 30, 180 and 360 days after index procedure via the clinic, re-hospitalization, or a telephone call.

2.6 Cost analysis

All costs of major tests, therapies, and hospital stays related to primary and secondary events were recorded. In the tailored group, the additional costs of the platelet aggregation function test and cilostazol were recorded separately. The cost was 45 RMB for a single platelet aggregation function test and 6.5 RMB for each cilostazol tablet (Pletal, Otsuka Pharmaceutical, Japan).

2.7 Statistical analysis

Data were expressed as mean ± SD for continuous variables and frequencies for the categorical variables. Continuous variables were compared by unpaired Student's *t*-test, and the categorical variables were compared by the χ^2 test. Kaplan-Meier analyses were performed to compare the primary end point. Because the LTA results were not normally distributed by the Kolmogorov-Smirnov goodness-of-fit test, the Mann-Whitney test was used to compare platelet aggregation values between experimental groups. A P value of < 0.05 was considered statistically significant. Analysis was performed using SPSS 19.0 (SPSS Inc. Chicago, Illinois).

3 Results

3.1 Patient enrollment and baseline characteristics

A total of 305 consecutive patients were enrolled, which accounted for 43.8% (305/697) of eligible patients. The main cause for exclusion was an inability to obtain baseline platelet aggregation (Figure 1). The demographic and clinical details of the 305 patients are presented in Table 1. There were no significant differences between the baseline characteristics of the two groups. Concomitant medication regimens did not differ significantly between the two groups.

Table 1. Baseline clinical characteristics.

Parameters	Tailored (n = 154)	Standard (n = 151)	P value
Age, yrs	60.2 ± 10.9	60.1 ± 10.9	0.964
Male	103 (66.9)	98 (64.9)	0.715
Risk factors			
Diabetes	27 (17.5)	33 (21.9)	0.342
Hypertension	64 (41.6)	69 (45.7)	0.466
Cigarette smoker	60 (39.0)	49 (32.5)	0.236
Hyperlipidemia	79 (51.3)	86 (57.0)	0.322
Prior MI	15 (9.7)	13 (8.6)	0.732
Laboratory test at entry			
Troponin T positive	31 (20.1)	24 (15.9)	0.336
Platelet count (×109)	192.3 ± 87.3	191.7 ± 82.2	0.951
Procedural results			
Multivessel disease	68 (44.2)	66 (43.7)	0.937
Stent number per patient	1.46 ± 1.02	1.54 ± 1.06	0.544
Drug eluting stent	109 (70.8)	102 (67.5)	0.541
Mean stent length, mm	36.8 ± 24.4	36.4 ± 23.7	0.896
In-hospital medication			
ACE inhibitor	78 (50.6)	80 (53.0)	0.683
β-blocker	94 (61.0)	89 (58.9)	0.708
Statin	72 (46.8)	72 (47.7)	0.871
Heparin/LMWH	131 (85.1)	122 (80.8)	0.321

Data are shown as n (%) for dichotomous variables and mean ± SD for continuous variables. MI: myocardial infarction; ACE: angiotensin-converting enzyme; LMWH: low molecular weight heparin.

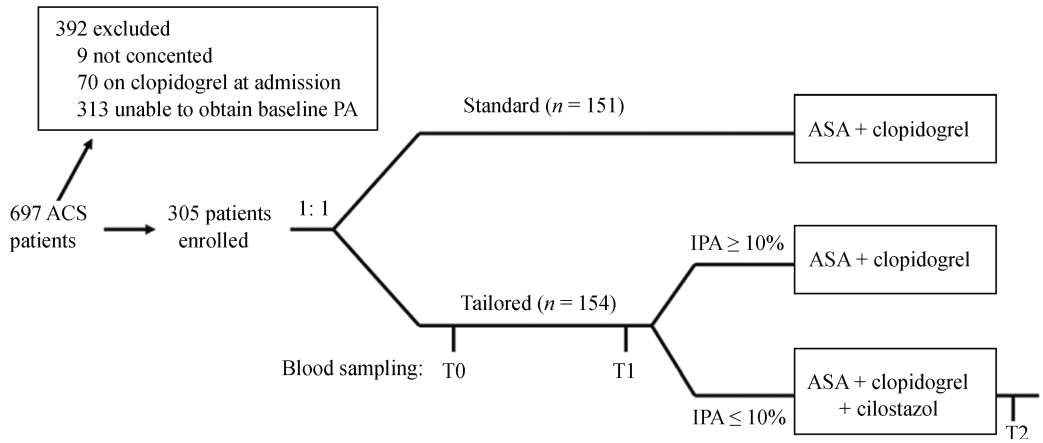

Figure 1. Flow chart of the study. ACS: acute coronary syndromes; ASA: acetylsalicylic acid; PA: platelet aggregation; IPA: inhibition of platelet aggregation; T0: before clopidogrel therapy; T1: 24 h after 600 mg clopidogrel loading; T2: three days after cilostazol treatment.

3.2 Platelet aggregation assay

In the tailored group, the mean platelet aggregation percentages were 79.4% ± 14.9% before treatment and 57.8% ± 18.5% after clopidogrel loading ($P < 0.001$). The results of laboratory tests indicated that 26.6% (41/154) of patients developed LRC. Three days after cilostazol treatment, the mean platelet aggregation percentage for LRC patients was significantly decreased (T1: 77.5% ± 12.1% *vs.* T2: 64.5% ± 12.1%, $P < 0.001$). LRC were turned over in 28 out of 41 patients (68.3%) with the addition of cilostazol (Figure 2).

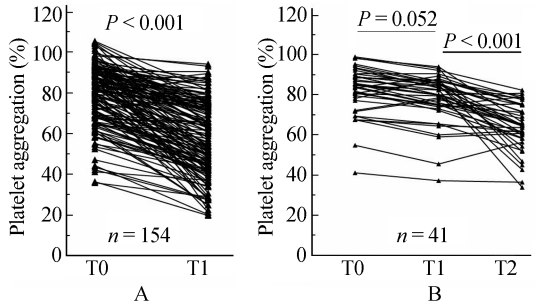

Figure 2. Laboratory platelet aggregation function assessment. (A): patients who received tailored antiplatelet therapy; (B) patients with low responsiveness to clopidogrel in the tailored group. T0: before clopidogrel therapy; T1: 24 h after 600 mg clopidogrel loading; T2: three days after cilostazol treatment.

3.3 Clinical outcomes

A one year clinical follow-up was available for all eligible patients. A total of 23 patients reached the primary end point, including nine patients who received tailored antiplatelet therapy and 14 patients who received standard antiplatelet therapy. A non-significant 37% relative reduction in the risk of primary events was observed in the tailored group as compared to the standard group (5.8% *vs.* 9.3%, respectively, $P = 0.257$). The rates of cardiovascular death, stroke and ischemic driven TVR, as well as the rate of MACCE were not significantly different between the tailored and standard group (Table 2). Kaplan-Meier curves showed a tendency towards a lower probability of primary events for the tailored antiplatelet strategy compared with the standard antiplatelet therapy (log rank $P = 0.238$, Figure 3).

3.4 Clinical outcomes of LRC patients

The incidence of primary events for LRC patients in the tailored group was 19.5% (8/41), which was significantly higher than that of non-LRC patients in the same group (0.9%, 1/113, $P < 0.001$). Patients with improved clopidogrel responses after additional cilostazol medication had a non-significant 54% relative risk reduction of primary events compared with non-responders to cilostazol [14.2% (4/28) *vs.* 30.8% (4/13), respectively, $P = 0.237$].

Table 2. Clinical outcomes at one year follow-up.

Events	Tailored ($n = 154$)	Standard ($n = 151$)	*P* value
Cardiovascular death	3 (1.9)	4 (2.6)	0.489
Non-fatal MI	4 (2.6)	7 (4.6)	0.340
Stroke	2 (1.3)	3 (2.0)	0.491
Ischemic driven TVR	6 (3.9)	9 (6.0)	0.331
Death, MI or stroke	9 (5.8)	14 (9.3)	0.257
MACCE	15 (9.7)	22 (14.6)	0.197

Data are shown as *n* (%). MACCE: major adverse cardiac and cerebral events; MI: myocardial infarction; TVR: target vessel revascularization.

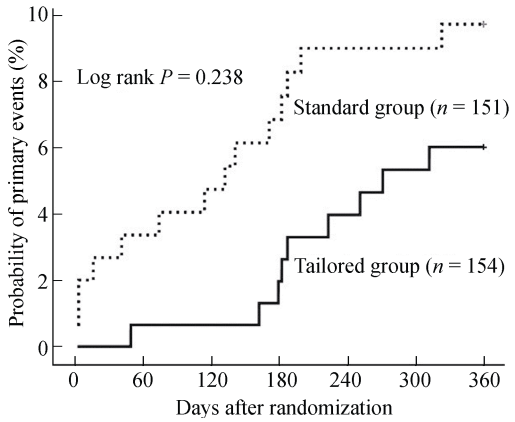

Figure 3. Kaplan-Meier assessment of the probability of a primary event.

3.5 Safety

Stent thromboses were developed in three patients, including one (0.6%) late stent thrombosis in the tailored group and two (1.3%) subacute stent thromboses in the standard group ($P = 0.620$). There were no TIMI major bleeding events in either group. The incidences of TIMI minor bleeding events (0.6% for tailored *vs*. 0% for standard group, $P = 1.0$) and minimal events (3.2% for tailored *vs*. 1.9% for standard group, $P = 0.723$) were not significantly different between the two groups.

3.6 Compliance

There was no discontinuation of aspirin during the follow-up period. Each group had one patient prematurely discontinue the clopidogrel treatment due to bleeding. Three LRC patients (7.3%) in the tailored group prematurely discontinued cilostazol therapy due to bleeding (two patients) or severe headache (one patient). Two patients halved the cilostazol dose due to palpitation.

3.7 Cost outcomes

The mean event-driven medical costs during the follow-up period were 2801 RMB per patient in the standard group and 2261 RMB per patient in the tailored group. For patients in the tailored group, the mean incremental costs of the platelet function test and additional cilostazol treatment were 90 RMB and 1201 RMB, respectively, per patient. The overall incremental cost of the tailored antiplatelet regimen compared with the standard regimen was 751 RMB per patient, which was associated with a non-significant 37% risk reduction of primary events.

4 Discussion

The present study, to our knowledge, is the first study to explore the long-term efficacy and cost effectiveness of tailored antiplatelet therapy with adjunctive cilostazol in patients with LRC. Although the advantages of individually tailored antiplatelet therapy compared with standard antiplatelet therapy were not fully demonstrated in this feasibility study, it provides the rationale for further investigations to evaluate whether optimizing an antiplatelet strategy with adjunctive cilostazol can cost-effectively improve long-term outcomes for patients with ACS undergoing PCI.

Platelet inhibition by standard clopidogrel dose reveals response variability when monitored by *in vitro* platelet function assays. According to previous studies, laboratory results indicated that LRC is associated with increased risks of ischemic cardiovascular events in patients with ACS or undergoing PCI, which strongly imply the rationality of an individually tailored antiplatelet strategy according to treatment response.[2,9,10,15] In recent years, genetic factors, such as cytochrome P450 (CYP) 2C19*2 variant, are considered relevant to impaired platelet inhibition by clopidogrel. However, studies reported that genetic factors attribute only 10%–20% of reduced clopidogrel response.[16] In the present study, the LRC rate (26.6%) was lower than the frequency of CYP2C19*2 polymorphisms in Asian patients (40%–50%),[17] which is in consist with another study, did not suggest that genotyping alone can replace phenotyping of platelet function.[16]

Over the past years, diverse devices and methods have been developed to determine whether patients had responded well to antiplatelet therapy. In the present study, LTA was used to assess platelet aggregation. Although this classic method was cost saving and well correlated to clinical events, it was time consuming and inconvenient for large scale population screening. As shown in the present study, about half of the eligible patients were excluded from this procedure because of an inability to obtain baseline platelet aggregation test results, mainly due to prior chronic clopidogrel treatment or logistic problems, such as admission at an off-duty time. Therefore, an immediately available platelet reactivity assay by LTA or other point-of-care devices, such as VerifyNow, may be promising alternatives in the daily practice for screening LRC patients.[18,19]

For clopidogrel low or non-responders, both enhancing clopidogrel dosage and adding a non-thienopyridine antiplatelet agent (e.g., GPⅡb/Ⅲa receptor inhibitors or cilostazol) have been proven effective in reducing the risk of ischemic events.[10,18–26] However, most of those clinical studies were limited by relatively small sample size and were focused on short-term outcomes, typically 30-day clinical or laboratory results. Recently published randomized trials with large sample sizes, including GRAVITAS and ARCTIC trials, also failed to test the efficacy of tailored antiplatelet therapy with double dose clopidogrel or new P2Y12 receptor inhibitors (prasugrel and ticagrelor).[27,28] Cilostazol, a selective phosphodiesterase 3 inhibitor, was previously reported to attenuate clopidogrel resistance since its antiplatelet mechanism is quite different.[23] In the randomized ACCEL-RESISTANCE trial, adjunctive cilostazol was shown to be more potent in reducing the rate of high post-treatment platelet reactivity than a high maintenance dose of clopidogrel at 150 mg/d.[29] In the present study, adjunctive cilostazol therapy for LRC patients induced significant decreases in platelet aggregation by the third day and a non-significant 37% relative risk reduction of primary events at one year. These results coincided with our previous study, which suggest a potential role of cilostazol in personalized antiplatelet therapy.[30] The CILON-T trial, including about 40% of stable patients, had demonstrated that the additional cilostazol treatment in real world patient populations can significantly lower platelet reactivity compared with standard dual antiplate-let therapy. However, the improvements of laboratorial results did not bring any clinical benefits, which may be due to the different composition of patients between the present study and CILON-T study.[31]

Although additional agents or dosage on the basis of routine antiplatelet therapy have proven more effective in attenuating LRC, unselected use of such regimens was not cost effective. According to the subgroup analysis of

our previous study, clinically assessed or angiographically determined high risk patients have benefited the most from the triple antiplatelet therapy of cilostazol, clopidogrel and aspirin.[30] An individually tailored antiplatelet strategy seems more cost saving than unselected use of intensive antiplatelet therapy in overall cohorts, but the incremental cost of the laboratory tests makes this uncertain, especially if the screening tests are expensive or have a high false-positive rate. Unfortunately, these aspects were ignored by most of the optimizing antiplatelet trials. In the present study, we roughly checked the cost outcomes of LTA screening based optimizing antiplatelet strategy. The results showed that, even with six months cilostazol treatment, the overall incremental costs of tailored antiplatelet therapy were acceptable, which provided more evidence for further investigation.

A few limitations of the present study must be addressed. Firstly, although the study was a prospective randomized trial, the randomization was open-labeled, and the study was performed at a single center. A multicenter double-blind randomization protocol may provide a more scientific assessment of the efficacy and safety of the tailored antiplatelet strategy. Secondly, because it was a feasibility study, the sample size of the present study was too small to detect the differences of primary endpoint between two strategies. The results of this study therefore need confirmation through clinical trials with larger sample sizes. Thirdly, the lack of stratifying patients based on the high on-treatment platelet reactivity may overestimate the risk of LRC.

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