

# Investigation of standardized administration of anti-platelet drugs and its effect on the prognosis of patients with coronary heart disease

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**Abstract.** The aim of the present study was to explore the effect of adherence to standardized administration of anti-platelet drugs on the prognosis of patients with coronary heart disease. A total of 144 patients newly diagnosed with coronary heart disease at Lu'an Shili Hospital of Anhui Province (Lu'an, China) between June 2010 and June 2012 were followed up. Kaplan-Meier curves and the Cox regression model were used to evaluate the effects of standardized administration of anti-platelet drugs on primary and secondary end-point events. Of the patients with coronary heart disease, 109 (76%) patients took standard anti-platelet drugs following discharge. Kaplan-Meier curve and Cox regression analysis showed that standardized administration of anti-platelet drugs reduced the risk of primary end-point events (including all-cause mortality, non-lethal myocardial infarction and stroke) of patients with coronary heart disease [hazard ratio (HR)=0.307; 95% confidence interval (CI): 0.099-0.953; P=0.041] and all-cause mortality (HR=0.162; 95% CI: 0.029-0.890; P=0.036); however, standardized administration had no predictive value with regard to secondary end-point events. Standardized administration of anti-platelet drugs obviously reduced the risk of primary end-point events in patients with coronary heart disease, and further analysis showed that only all-cause mortality exhibited a statistically significant reduction.

## Introduction

Coronary heart disease severely threatens the health of individuals worldwide. While it was the seventh-most frequent cause of mortality in China in 1990, it became the second-most frequent cause in 2010 (1). The main pathophysiological mechanism is the reduction of myocardial flow and insufficient oxygen supply of myocardial cells caused by coronary artery stenosis, leading to a series of hypoxic ischemic symptoms (2). Aggravation of atherosclerosis as well as cracking or even rupture of local plaques leads to platelet aggregation to result in an increase in blood viscosity, which causes a sudden reduction of coronary blood flow and induce acute myocardial infarction. As activation and aggregation of platelets is the cause of coronary heart disease (3), it is treated by standardized administration of anti-platelet drugs to reduce the risk of further coronary heart disease-associated events.

Percutaneous coronary intervention (PCI) is a common therapy for coronary heart disease. Stent thrombosis (ST) is one of the most severe complications after PCI. Compared with a bare metal stent, a drug-eluting stent obviously reduces the occurrence rate of in-stent restenosis after PCI but increases the risk of ST. Drug-eluting stents also delay vascular endothelial healing. Incomplete endothelialization and local vascular hypersensitivity may cause late ST, which increases patient mortality by 15-45% (4,5). Thus, anti-platelet therapy should be enhanced in patients with coronary heart disease after PCI, particularly after implantation of a drug-eluting stent. Studies have indicated that dual anti-platelet therapy comprising clopidogrel combined with aspirin after PCI significantly reduced the incidence rate of major adverse cardiac events (6,7). The CURE trial confirmed that compared with aspirin treatment alone, long-term combined therapy with clopidogrel and aspirin significantly reduced the risk of cardiac events in patients presenting with acute coronary syndrome (ACS) after PCI (8). Furthermore, the CREDO trail showed that patients treated with aspirin and clopidogrel for up to 1 year had a significantly lower rate of cardiac events than those without dual anti-platelet therapy within 1 year (9).

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Anti-platelet therapy has an important role in the primary and secondary prevention of cardiovascular diseases and reduces the incidence of cardiac events, which is also a therapeutic basis of vascular diseases (10). Although relevant guidelines have emphasized the important role of anti-platelet therapy in coronary heart disease and recommended the standardized management to all physicians, certain patients with coronary heart disease do not adhere to their prescribed regimens for various reasons. The RESOLUTE China Registry Research (11) registered 1,800 patients with coronary heart disease who were implanted with the resolute zotarolimus-eluting stent at 30 centers in China and analysis suggested that adherence to dual anti-platelet therapy was 94% at 1 year. However, it is difficult to achieve this high proportion of adherence in clinical practice. The present study analyzed the standardized management of anti-platelet therapy in patients with coronary heart disease at Lu'an Shili Hospital of Anhui Province (Lu'an, China) and its impact on patient prognosis and the risk of end-point events through a prospective follow-up study.

## Materials and methods

**Subjects.** A total of 144 patients newly diagnosed with coronary heart disease at Lu'an Shili Hospital of Anhui Province (Lu'an, China) between June 2010 and June 2012 were enrolled in the present study. The cohort comprised 59 females and 85 males, 56 patients with stable angina pectoris and 88 patients with acute coronary syndrome. The present study was performed in accordance with the declaration of Helsinki and approved by the Ethics Committee of Lu'an Shili Hospital (Lu'an, China). Written informed consent was obtained from all participants. Patients who suffered from peripheral vascular disease, thrombotic disease, severe liver and renal dysfunction, thyroid disease, cancer as well as infectious or autoimmune diseases were excluded. Patients who had received surgery <3 months previously, those receiving anti-inflammatory drugs or hormone replacement therapy as well as those with severe peptic ulcers, inflammation and hemorrhage were also excluded.

**Follow-up.** For each of the outpatients, self-administration of drugs was analyzed and follow-up was performed every three months. For this purpose, follow-up tables were designed and telephone interviews were performed by two professional cardiologists with sufficient knowledge regarding the diagnosis and prevention of coronary heart disease and who had been trained in a specific seminar. One further professional cardiologist monitored the follow-up process.

**Definition of standardized administration.** According to guidelines (12), patients were administered anti-platelet drugs as follows: Patients who had stable angina pectoris required continuous oral aspirin, and patients with ACS after PCI (drug-eluting stent implantation) required dual antiplatelet therapy with coadministration of aspirin and clopidogrel, for at least one year, followed by continuous oral aspirin. Continuous oral administration of statins, beta-receptor antagonist and angiotensin-converting-enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) is required.

**Clinical end-points.** Primary end-points, also called major adverse cardiac events, included all-cause mortality, non-lethal myocardial infarction and stroke. Diagnostic evidence of myocardial infarction included clinical symptoms, electrocardiogram and myocardial enzyme, while that of stroke included clinical symptoms and computed tomography. Secondary end-points included grade-IV heart failure according to the New York Heart Association classification (13), hospitalized therapy and revascularization (PCI or coronary artery bypass graft surgery).

**Statistical analysis.** Statistical analysis was performed using SPSS13.0 software (SPSS, Inc., Chicago, IL, USA). Values are expressed as the mean  $\pm$  standard deviation. Student's *t*-test was used to analyze differences in continuous variables between two groups, and the chi-square test was used for classified variables. Furthermore, patients were divided into a standardized and a non-standardized administration group, according to administration of anti-platelet drugs standardly or not, and Kaplan-Meier curves were drawn to compare the incidence of end-point events between the two groups. The COX proportional hazards model was used for multiple factor analysis, providing the hazard ratio (HR) value and 95% confidence interval (CI) in order to determine the risk of end-point events in patients with coronary heart disease treated with standardized therapy.

## Results

**Comparison of general data.** A total of 114 patients with coronary heart disease were enrolled in the present study and the median follow-up time was 360 days. The standardized administration group contained 109 patients (76%) and the non-standardized administration group contained 35 (24%). A total of 70 patients with PCI treatment were included in the present study, and 56 patients (80%) took standard administration of anti-platelet therapy. Table I shows that the non-standardized administration group contained a high proportion of smokers ( $P=0.020$ ), while there were no significant differences between the two group regarding the other indexes, including age, gender, hypertension, diabetes, cardiovascular conditions, multiplicity of diseased vessels, side of main lesion or PCI therapy. However, the proportion of patients taking oral statins, beta receptor antagonists and ACEI/ARB was higher in standardized administration group compared to that in the non-standardized group ( $P<0.01$ ).

**Comparison of end-points between the two groups.** Table II shows that the incidence rate of primary end-point events in the standardized administration group was significantly lower than that in the non-standardized administration group (6 vs. 17%;  $P=0.030$ ). Single event analysis showed that the incidence rate of non-lethal myocardial infarction and stroke was not significantly different, but that the incidence rate of all-cause mortality was significantly lower in the standardized administration group compared to that in the non-standardized administration group (2 vs. 11%;  $P=0.013$ ). In addition, there was no statistical difference in the incidence rate of secondary end-point events between the two groups (Table II).

Table I. Comparisons of indexes between two groups.

Index	Standardized OA-P administration group (n=109)	Non-standardized OA-P administration group (n=35)	P-value
Mean age (years)	63±9	63±9	0.320
Male gender, n (%)	65 (60)	20 (57)	0.794
Smoking, n (%)	9 (8)	8 (23)	0.020
Hypertension, n (%)	62 (57)	17 (49)	0.390
Diabetes, n (%)	10 (9)	3 (9)	0.914
Groups, n (%)			0.206
Stable angina pectoris	38 (35)	18 (51)	
Unstable angina pectoris	45 (41)	10 (29)	
Acute myocardial infarction	26 (24)	7 (20)	
Multiplicity of vessels diseased, n (%)			0.401
One	48 (44)	20 (57)	
Two	33 (30)	8 (23)	
Three	28 (26)	7 (20)	
Left main lesion, n (%)	7 (6)	3 (9)	0.663
PCI therapy, n (%)			0.241
Yes	56 (80)	14 (20)	
No	53 (72)	21 (28)	
Drug treatments, n (%)			
Standardized oral statins	99 (91)	8 (23)	<0.001
Standardized oral β-receptor antagonist	78 (72)	5 (14)	<0.001
Standardized oral ACEI/ARB	87 (80)	8 (23)	<0.001

O-AP, oral anti-platelet; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker.

Table II. Comparison of the occurrence of primary and secondary end-point events between the two groups.

Events	Standardized OA-P administration group (n=109)	Non-standardized O-AP administration group (n=35)	P-value
Primary end-point events, n (%)			
Total	6 (6)	6 (17)	0.030
All-cause mortality	2 (2)	4 (11)	0.013
Non-lethal stroke	4 (4)	2 (6)	0.598
Non-lethal myocardial infarction	-	-	-
Secondary end-point events, n (%)			
Total	13 (12)	3 (9)	0.613
Grade-IV heart failure	4 (4)	2 (6)	0.735
Revascularization	9 (8)	1 (3)	0.378

O-AP, oral anti-platelet.

*Effect of standardized administration of dual anti-platelet agents on the end-points.* Age, gender, hypertension, diabetes, smoking, standardized administration of dual anti-platelet agents, standardized administration of statins, standardized administration of beta receptor antagonists and standardized administration of ACEI/ARB were used as co-variants in the

Cox regression analysis, which revealed that standardized administration of dual anti-platelet agents significantly reduced the incidence rate of primary end-point events (HR=0.307; 95% CI: 0.099-0.953; P=0.041), including all-cause mortality (HR=0.162; 95% CI: 0.029-0.890; P=0.036) (Table III). The Kaplan-Meier curves also indicated that in patients who

Table III. Cox regression analysis of standardized administration of dual anti-platelet agents for end-points events.

Event	HR value	95% CI	P-value
Primary end-point events, n (%)			
Total	0.307	0.099-0.953	0.041
All-cause mortality	0.162	0.029-0.890	0.036
Non-lethal stroke	0.685	0.125-3.740	0.662
Non-lethal myocardial infarction	-	-	-
Secondary end-point events, n (%)			
Total	0.836	0.298-2.350	0.735
Grade-IV heart failure	0.990	0.911-1.075	0.812
Revascularization	3.633	0.469-28.162	0.217

HR, hazard ratio; CI, confidence interval.

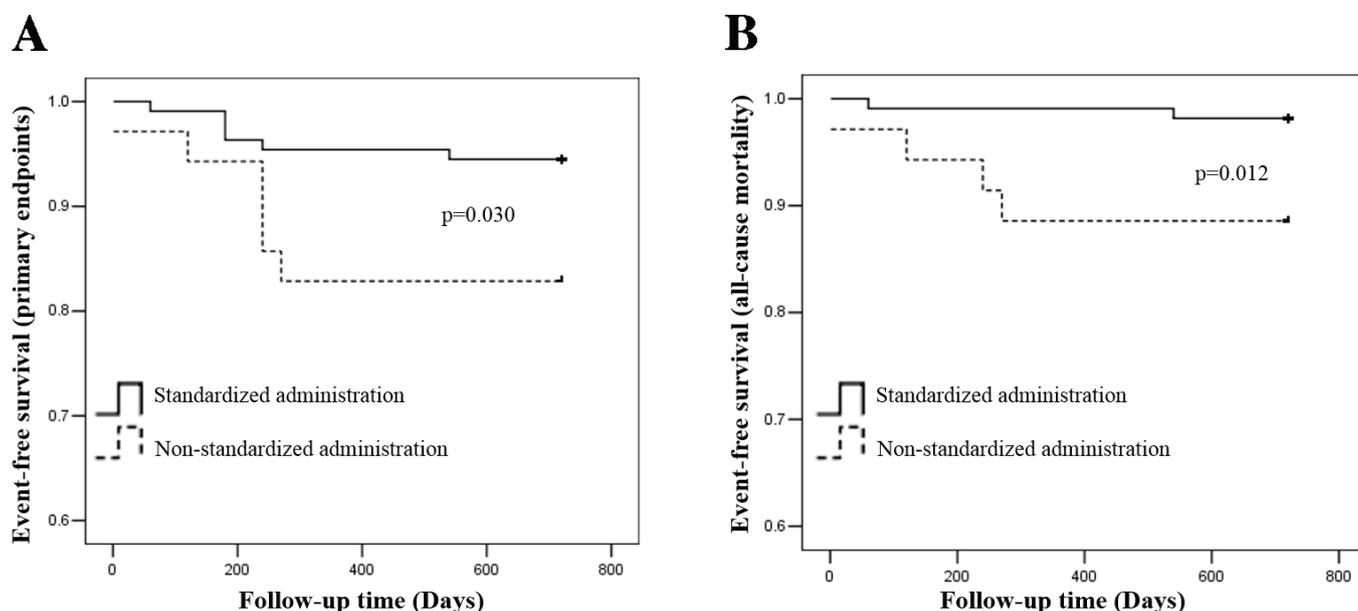


Figure 1. Kaplan-Meier curves of (A) primary endpoint event-free survival and (B) all-cause mortality event-free survival associated with standardized and non-standardized anti-platelet administration.

received standardized administration of dual anti-platelet agents, the risk of primary end-point events ( $P=0.030$ ) and all-cause mortality ( $P=0.001$ ) was significantly decreased (Fig. 1).

## Discussion

In the present study, 76% of the patients with coronary heart disease regularly took standard anti-platelet medication; furthermore, 80% received dual anti-platelet drug therapy in 70 out of 144 patients who received PCI therapy. Furthermore, the incidence rate of primary end-point events was low in patients with standardized administration of anti-platelet drugs compared to that in those without standardized administration. In addition, Kaplan-Meier curves and Cox regression analysis showed that standardized administration of anti-platelet drugs markedly reduced the incidence of primary end-point events; further analysis showed that only all-cause mortality was significantly reduced.

Activation and aggravation of platelets has a critical role in coronary plaque rupture and thrombosis. Anti-platelet therapy with drugs such as aspirin and clopidogrel provides a benefit for patients with coronary heart disease. According to the European Society of Cardiology guidelines (12,14), patients with coronary heart disease require treatment with aspirin and patients with ACS after PCI should be treated with aspirin and clopidogrel for at least 12 months if no contraindications are present. Aspirin is the most common anti-platelet drug used in clinical practice and numerous large-scale, randomized and controlled studies have confirmed that the benefits outweigh the risks. A meta-analysis showed that daily oral aspirin (75-150 mg) leads to a decrease in cardiac events by 33% in patients with steady coronary heart disease and by 53% in patients after PCI (15). Clopidogrel blocks the ADP receptor on the platelet membrane so as to inhibit platelet aggregation. The CURE trial (16), the CURRENT-OASIS study (17) and the TYCOON study (6) demonstrated that combined clopidogrel and aspirin

significantly reduces the incidence rate of major adverse cardiac events in patients with coronary heart disease with after PCI.

The importance of anti-platelet drugs use has been recognized by numerous physicians, while numerous patients in China still do not receive standardized management, particularly in basic hospitals. A total of 144 patients with coronary heart disease were enrolled in the present follow-up study and the results showed that the ratio of patients who received standardized administration of anti-platelet therapy was only 76%. Furthermore, 80% of patients underwent dual anti-platelet therapy in 70 cases with PCI therapy.

Premature discontinuation of dual anti-platelet therapy was a predictive factor of ST after PCI and increased the risk of major adverse cardiac events (18,19). Rossini *et al* (20) performed a 3-year follow-up study and found that patients with early discontinuation of anti-platelet agents within the first 12 months experienced a greater incidence of major adverse cardiac events (28.6 vs. 13.7%;  $P < 0.01$ ) and ST (7.6 vs. 3.4%;  $P = 0.038$ ). Eisenstein *et al* (21) performed a 2-year follow-up study and showed that the risk of mortality and incidence of myocardial infarction was obviously increased in patients treated with anti-platelet agents for  $< 12$  months. A retrospective study showed that the ST rate of patients with the first-generation drug-eluting stent who discontinued clopidogrel within the first year was obviously increased, whereas no definite ST events occurred in the cohort with the second-generation drug-eluting stent (22). Furthermore, the rates of mortality and major adverse cardiac events were increased in the first- as well as in the second-generation drug-eluting stent cohort. Therefore, standardized administration of anti-platelet agents is important for improving the prognosis and reducing the incidence of adverse cardiac events in patients with coronary heart disease. However, numerous studies have shown that compliance of anti-platelet therapy was low, particularly for the dual anti-platelet therapy. The PARIS study assessed 5,018 PCI patients, of which 49.2% discontinued dual anti-platelet therapy within 1 year (23). The APTOR trial, which assessed 4,184 ACS patients from 14 European countries, revealed that only 43% received optimal secondary prevention therapy after PCI and a diet or exercise, and after 1 year, the percentage of patients taking dual anti-platelet medication was 99% in the optimal cohort and 49% in non-optimal cohort (24). In addition, a survey on of 3,080 Taiwanese ACS patients showed that use of dual anti-platelet therapy fell from 74.8% at discharge to 24.9% at 1-year follow-up (25).

In conclusion, the present study revealed that standardized administration of anti-platelet agents markedly reduced primary end-point events in patients with coronary heart disease. Further analysis demonstrated that all-cause mortality was significantly reduced. However, there was low compliance. Therefore, in future clinical practice, communication between physicians and patients should be enhanced and patient management should be focused on in order to enhance the benefit of patients from standardized dual anti-platelet therapy.

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