# Cilostazol for Chinese Patients with Aspirin Intolerance after Coronary Drug-Eluting Stent Implantation

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## Abstract

**Background** Cilostazol-based dual antiplatelet therapy (DAPT) is widely used in patients with aspirin intolerance after coronary drug-eluting stent (DES) implantation in China. However, this empirical strategy is not recommended or even mentioned in Chinese or international guidelines due to a lack of evidence from large-scale studies. We aimed to explore the efficacy and safety of cilostazol-based DAPT in this special population.

**Methods** In this cohort study, patients were grouped according to the DAPT strategy that they received after coronary DES implantation. The primary efficacy endpoint was major adverse cardiovascular and cerebrovascular events (MACCEs). Angiographic follow-up and major bleeding events were also recorded.

**Results** A total of 918 patients receiving cilostazol-based DAPT due to aspirin intolerance were enrolled, matched with 918 patients receiving aspirin-based DAPT. After 15-month prospective follow-up, the cilostazol group had lower risk of MACCE (5.1% vs. 7.6%, propensity score adjusted hazard ratio = 0.671 [95% confidence interval 0.462–0.974], $p = 0.036$) compared with the aspirin group. Lower rate of coronary lesion progression was also found through follow-up angiography in the cilostazol group (17.4% vs. 23.6%, $p = 0.022$), especially in nontarget lesions (12.1% vs. 17.6%, $p = 0.019$). The two groups had the same risk of major bleeding events (0.8% vs. 0.4%, $p = 0.364$).

**Conclusion** In the current study, cilostazol is a good substitute for aspirin in patients who have aspirin intolerance but need DAPT after coronary DES implantation in China. However, large-scale randomized controlled trials were still required to further confirm its efficacy and safety.

**Keywords**
- cilostazol
- aspirin intolerance
- cohort study
- coronary artery disease

## Introduction

Antiplatelet drugs are essential for the management of coronary artery disease. Among them, aspirin is considered the cornerstone and plays an important role.[1] At present, it is recommended that patients be treated with aspirin plus $P2Y_{12}$ receptor antagonist as dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI), which can reduce the incidence of major adverse cardiovascular and cerebrovascular events (MACCEs).[2]

However, some patients cannot tolerate aspirin well due to either contraindications or severe adverse reactions after taking it. To address this problem, guidelines recommended the use of digestive tract protectors like proton-pump inhibitors (PPIs) to reduce gastrointestinal reactions.[3,4] Nevertheless, prolonged use of PPIs may raise the concern of adverse reactions.[5–7] In

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addition, this strategy cannot apply to all conditions of aspirin intolerance, such as severe bleedings outside the digestive tract or aspirin allergy. Thus, there is an urgent need for an alternative when aspirin intolerance occurs, especially when DAPT is required after coronary drug-eluting stent (DES) implantation.

In China, an empirical strategy is to replace aspirin with cilostazol in those suffering from aspirin intolerance. Although it is widely used in clinical practice, it lacks evidence from large-scale studies. Therefore, cilostazol-based DAPT, which means cilostazol plus $P2Y_{12}$ receptor antagonist, is not recommended or even mentioned in Chinese or international guidelines for coronary artery disease.

Hence, we designed this cohort study to explore the efficacy and safety of cilostazol-based DAPT in this special population. Notably, we are not intended to deny other methods of managing aspirin intolerance like PPIs and aspirin desensitization. In contrast, we just display a unique strategy widely used in China.

## Methods

### Study Population and Grouping

The clinical data on patients who underwent DES implantation and received DAPT at Zhongshan Hospital from January 2016 to November 2017 were consecutively collected from an electronic medical record system. The missing data were handled by multiple imputations. The exclusion criteria were as follows: (1) incomplete revascularization without selective retreatment; (2) using percutaneous transluminal coronary angioplasty only or drug-coated balloon; (3) having end-stage diseases like untreatable cancer; and (4) having platelet diseases or severe heart failure.

The patients were divided into an aspirin group (aspirin 100 mg once daily plus $P2Y_{12}$ receptor antagonist) and a cilostazol group (cilostazol 50 mg twice daily plus $P2Y_{12}$ receptor antagonist) according to the type of DAPT that they received at discharge. The loading dose was 300, 300, and 180 mg for aspirin, clopidogrel, and ticagrelor, respectively. Aspirin intolerance included adverse symptoms like gastrointestinal discomfort, bleedings, allergy, or evidence of contraindications like severe peptic ulcer. It was either self-reported from patients themselves, or verified by abnormal laboratory results, and these patients would take cilostazol instead. This reduced dose of cilostazol is traditionally and empirically used in Chinese patients with aspirin intolerance to reduce drug adverse reaction like palpitation, using a loading dose of 100 mg. In the cilostazol group, all the patients who did not meet the exclusion criteria were enrolled. And they were matched 1:1 with the aspirin group based on the (same) PCI operator, the (adjacent) order of operation, and some important clinical variables (i.e., age, gender, and diagnosis).

This cohort study was in accordance with the Declaration of Helsinki and was approved by the local medical ethics committee. All the patients enrolled provided informed consent.

### Follow-Up

The follow-up time was 15 months (457 days) after discharge. The endpoints were recorded through an electronic medical record system or telephone interview when necessary. The follow-up was completed by a medical practitioner and checked by a specialist.

The primary efficacy endpoint was MACCE, which referred to a combination of cardiogenic death, noncardiogenic death, nonfatal myocardial infarction, repeat revascularization, nonfatal stroke, and stent thrombosis (acute or subacute). Repeat revascularization was clinically driven, including target and nontarget lesion revascularization (TLR and non-TLR). TLR was defined as repeat revascularization in the original stent or lesions within 5 mm from the edge of the stent, while non-TLR referred to other conditions. Stent thrombosis was defined by the Academic Research Consortium criterion.[8] In this study, it mainly referred to the definite and probable ones, and occurred within 1 month after PCI (acute or subacute). Secondary efficacy endpoints included the followings: (1) a combined endpoint consisting of cardiogenic death, noncardiogenic death, nonfatal myocardial infarction, and nonfatal stroke; (2) repeat revascularization, including TLR and non-TLR; and (3) angiographic follow-up at any time after the operation.

Bleeding Academic Research Consortium-defined bleeding events[9] were considered the safety endpoints. Type 1 and 2 bleeding events were defined as minor ones, while type 3 to 5 bleeding events were major ones. Other symptoms associated with the use of antiplatelet drugs were also recorded.

### Statistical Analysis

We assumed cilostazol-based DAPT was superior to aspirin-based DAPT with respect to the occurrence of MACCE after DES implantation based on a previous study.[10] The rate of MACCE was estimated to be 5% in the cilostazol group and 9% in the aspirin group at about 1 year of follow-up. With a sample size of 730 in each group, the study would have 85% power to detect the difference with a two-sided $\alpha$ level of 0.05. Assuming a dropout rate of 5%, a total of 768 patients in each group were required.

Variables with normal distribution are expressed as mean $\pm$ standard deviation and were compared with the Student's *t*-test or *t'*-test, as appropriate; variables with abnormal distribution are expressed as median (interquartile range) and were compared with the Mann–Whitney test. Categorical variables were presented as numbers (percentages) and were compared with the chi-square test or Fisher's exact test, as appropriate. For time-to-event data, the Kaplan–Meier method was used to plot the cumulative incidence curves, and the log-rank test was performed to make comparisons. Landmark analysis was performed for split discussion. The assumption of proportional risk was judged by the Schoenfeld residual test. For proper variables and endpoints, a Cox proportional risk regression model was adopted to make comparisons and calculate hazard ratios (HRs), 95% confidence intervals (CIs), and *p*-values. To further adjust for the confounders after the matching process as mentioned above, we performed a propensity score analysis through a logistic regression model that included all of the variables listed in ►**Supplementary Tables S1** and **S2** (available in the online version). The calculated propensity score was then used as a covariate in the Cox proportional risk regression model to yielded adjusted HRs,

95% CIs, and *p*-values. In subgroup analysis, some variables (i.e., age, gender, diabetes, prior PCI, acute coronary syndrome, severity of lesions, B2/C type target lesions, minimum diameter of stents, total length of stents, duration of DAPT, type of $P2Y_{12}$ receptor antagonist, and ischemic risk) were selected and grouped to calculate *p*-values for interaction.

Statistical analysis was done by intent to treat, using IBM SPSS Statistics software version 25.0 (IBM Corp., Armonk, New York, United States) and R software version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). A *p*-value of $< 0.05$ was considered statistically significant.

## Results

### Basic Characteristics of the Cohort

The study flowchart is shown in ►**Fig. 1**. A total of 11,470 patients who received DAPT after PCI were assessed. At discharge, 1,139 (9.9%) patients took cilostazol because of aspirin intolerance. According to the exclusion criteria, 918 patients were enrolled as the cilostazol group and were matched with 918 patients in the aspirin group. There were 1,359 (74.0%) males and 477 (26.0%) females in this cohort. The average age was 64.5 years. During follow-up, 26 patients discontinued or changed cilostazol-based DAPT, while 8 patients discontinued or changed aspirin-based DAPT.

►**Supplementary Fig. S1** (available in the online version) shows the specific causes of taking cilostazol. The main cause was gastrointestinal intolerance (76.9%).

The baseline characteristics were comparable between the two groups after 1:1 matching (see ►**Supplementary Tables S1** and **S2**, available in the online version).

### Primary Efficacy Endpoint

After 15-month follow-up, 117 cases of MACCE occurred, including 47 (5.1%) cases in the cilostazol group and 70 (7.6%) cases in the aspirin group. The cumulative incidence curves of MACCE are shown in ►**Fig. 2**. In the Cox proportional risk regression model, compared with the aspirin group, the cilostazol group was less likely to have MACCE (HR = 0.663 [95% CI 0.458–0.959], $p = 0.029$; propensity score adjusted HR = 0.671 [95% CI 0.462–0.974], $p = 0.036$), as shown in ►**Table 1**.

Notably, there was an intersection between the two cumulative incidence curves (see ►**Fig. 2**). The corresponding time point was approximately 48 days of follow-up. The results of landmark analysis are shown in ►**Table 2**. Within 48 days of follow-up, the cumulative incidence of MACCE was 0.7% versus 0.8%, $p = 0.967$. Between 48 and 150 days of follow-up, it was comparable again (0.3% vs. 0.5%, $p = 0.330$). However, after 150 days of follow-up, the cumulative incidence of MACCE began to be lower in the cilostazol group (4.1% vs. 6.3%, $p = 0.045$). Further analysis revealed that in the early follow-up period (within 48 days of follow-up), two cases of nonfatal stroke and three cases of stent thrombosis occurred in the cilostazol group, compared with none in the aspirin group.

In subgroup analysis (see ►**Fig. 3**), the effect of cilostazol-based DAPT on MACCE was consistent across all subgroups

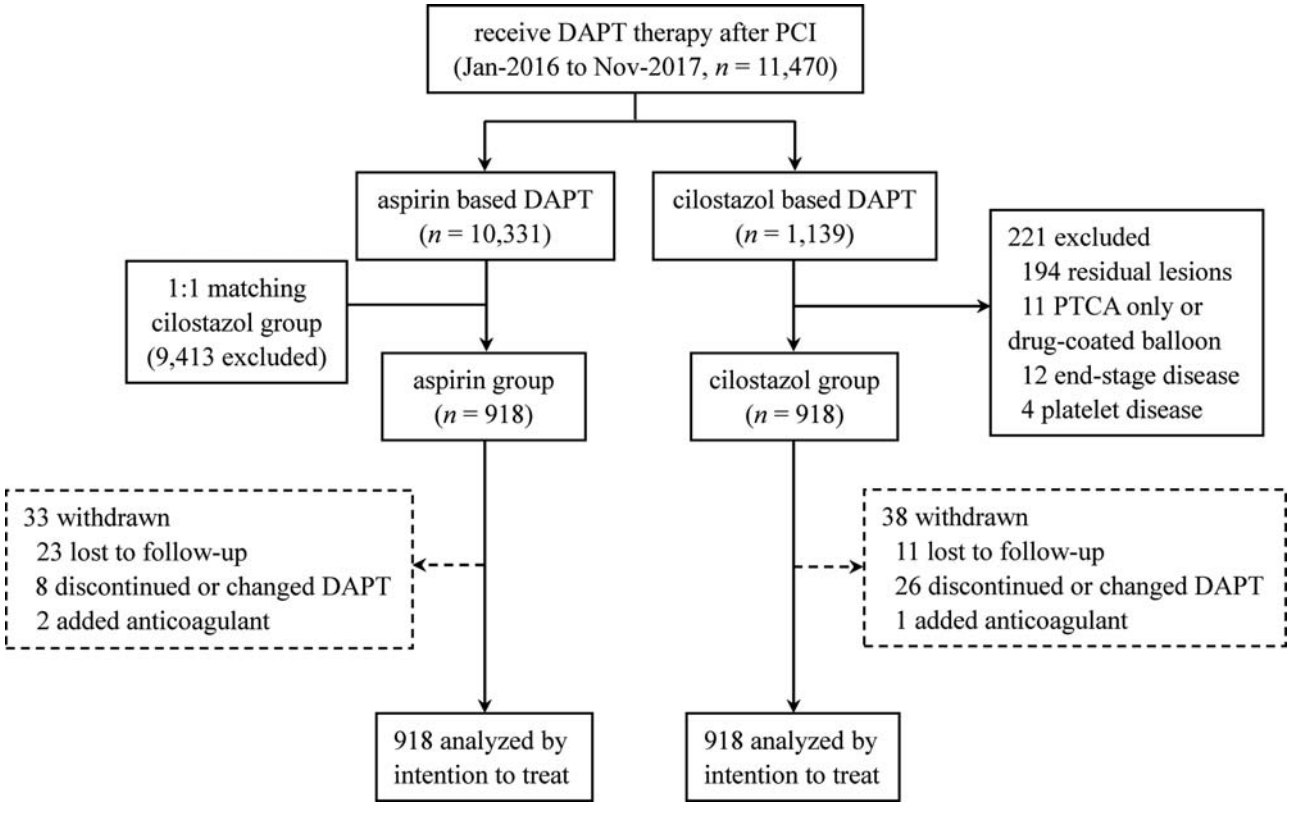


**Fig. 1** Study flowchart. DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

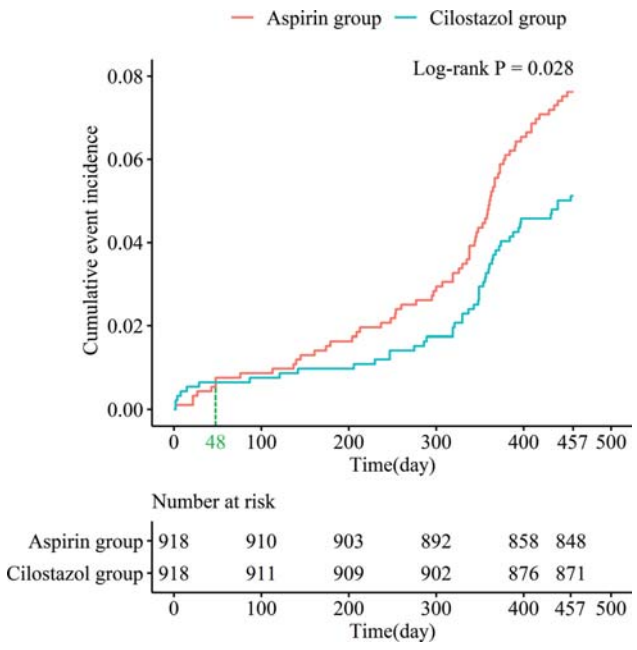


**Fig. 2** Primary efficacy endpoint (MACCE) in both groups. It shows the cumulative incidence of MACCE described by the Kaplan–Meier curves. Log-rank $p = 0.028$. The intersection of the two curves was represented with green dotted line and the time corresponding to the intersection was ~48 days of follow-up. MACCE, major adverse cardiovascular and cerebrovascular events.

except for the followings: acute coronary syndrome, minimum diameter of stents, and total length of stents.

### Secondary Efficacy Endpoints

During follow-up, we observed 31 cases of the combined endpoint consisting of cardiogenic death, noncardiogenic death, nonfatal myocardial infarction, and nonfatal stroke. Specifically, 10 (1.1%) cases were in the cilostazol group, while 21 (2.3%) cases were in the aspirin group (see ►**Table 1**, ►**Fig. 4A**).

As for repeat revascularization (see ►**Table 1**, ►**Fig. 4B** and **C**), the incidence of TLR was 1.9% versus 1.6%, HR = 1.134 (95% CI 0.566–2.270), $p = 0.723$; propensity score adjusted HR = 1.144 (95% CI 0.567–2.308), $p = 0.706$. The incidence of non-TLR was 2.7% versus 4.1%, HR = 0.650 (95% CI 0.392–1.076), $p = 0.094$; propensity score adjusted HR = 0.668 (95% CI 0.401–1.112), $p = 0.121$.

The results of follow-up angiography are shown in ►**Table 3**. Without intervention, the natural rate of angiographic follow-up was not high: 448 (48.8%) cases in the cilostazol group and 454 (49.5%) cases in the aspirin group. The aspirin group were prone to clinically driven angiographic follow-up (30.6% vs. 22.8%, $p = 0.008$). The cilostazol group had a lower incidence of lesion progression (17.4% vs. 23.6%, $p = 0.022$), which was mainly driven by nontarget lesion progression (12.1% vs. 17.6%, $p = 0.019$).

**Table 1** Primary efficacy endpoint (MACCE) in both groups

| | Aspirin group ($n = 918$) | Cilostazol group ($n = 918$) | $p$-Value |
|---|---|---|---|
| MACCE | | | |
| No. of events (%) | 70 (7.6) | 47 (5.1) | |
| Crude HR (95% CI) | 1 | 0.663 (0.458, 0.959) | 0.029 |
| Adjusted HR (95% CI) | 1 | 0.671 (0.462, 0.974) | 0.036 |
| Cardiogenic death | | | |
| No. of events (%) | 2 (0.2) | 1 (0.1) | |
| Crude HR (95% CI) | / | / | / |
| Adjusted HR (95% CI) | / | / | / |
| Noncardiogenic death | | | |
| No. of events (%) | 5 (0.5) | 2 (0.2) | |
| Crude HR (95% CI) | 1 | 0.399 (0.077, 2.057) | 0.272 |
| Adjusted HR (95% CI) | 1 | 0.307 (0.058, 1.614) | 0.307 |
| Nonfatal myocardial infarction | | | |
| No. of events (%) | 9 (1.0) | 5 (0.5) | |
| Crude HR (95% CI) | 1 | 0.554 (0.186, 1.654) | 0.290 |
| Adjusted HR (95% CI) | 1 | 0.602 (0.200, 1.813) | 0.367 |
| Repeat revascularization | | | |
| No. of events (%) | 53 (5.8) | 42 (4.6) | |
| Crude HR (95% CI) | 1 | 0.786 (0.524, 1.178) | 0.243 |
| Adjusted HR (95% CI) | 1 | 0.803 (0.533, 1.209) | 0.293 |
| TLR | | | |
| No. of events (%) | 15 (1.6) | 17 (1.9) | |

**Table 1** (*Continued*)

| | Aspirin group ($n = 918$) | Cilostazol group ($n = 918$) | *p*-Value |
|---|---|---|---|
| Crude HR (95% CI) | 1 | 1.134 (0.566, 2.270) | 0.723 |
| Adjusted HR (95% CI) | 1 | 1.144 (0.567, 2.308) | 0.706 |
| Non-TLR | | | |
| No. of events (%) | 38 (4.1) | 25 (2.7) | |
| Crude HR (95% CI) | 1 | 0.650 (0.392, 1.076) | 0.094 |
| Adjusted HR (95% CI) | 1 | 0.668 (0.401, 1.112) | 0.121 |
| Nonfatal stroke | | | |
| No. of events (%) | 5 (0.5) | 2 (0.2) | |
| Crude HR (95% CI) | / | / | / |
| Adjusted HR (95% CI) | / | / | / |
| Stent thrombosis (acute or subacute) | | | |
| No. of events (%) | 0 (0.0) | 3 (0.3) | |
| Crude HR (95% CI) | / | / | / |
| Adjusted HR (95% CI) | / | / | / |

Abbreviations: CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; TLR, target lesion revascularization.
Note: HRs and *p*-values were calculated by Cox proportional hazard regression model and were subsequently adjusted by propensity scores.

### Safety Endpoints

As presented in ►**Table 4**, the incidence of bleeding events in the cilostazol group was significantly lower than that in the aspirin group (2.9% vs. 6.5%, $p < 0.001$). Further, the incidence of minor bleeding events was 2.2% versus 6.1%, $p < 0.001$, while that of major bleeding events was 0.8% versus 0.4%, $p = 0.364$. In terms of other symptoms related to the use of antiplatelet drugs, severe gastric discomfort was more common in the aspirin group (2.0% vs. 3.7%, $p = 0.024$), while palpitation was more frequent in the cilostazol group (0.7% vs. 0.0%, $p = 0.041$).

**Table 2** Landmark analysis of MACCE in both groups

| | ≤ 48 days of follow-up | | | 48∼150 days of follow-up | | | > 150 days of follow-up | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of events (%) | | *p*-Value | No. of events (%) | | *p*-Value | No. of events (%) | | *p*-Value |
| | Cilostazol group ($n = 918$) | Aspirin group ($n = 918$) | | Cilostazol group ($n = 918$) | Aspirin group ($n = 918$) | | Cilostazol group ($n = 918$) | Aspirin group ($n = 918$) | |
| MACCE | 6 (0.7) | 7 (0.8) | 0.967 | 3 (0.3) | 5 (0.5) | 0.330 | 38 (4.1) | 58 (6.3) | 0.045 |
| Cardiogenic death | 1 (0.1) | 1 (0.1) | 1.000[a] | 0 (0.0) | 1 (0.1) | 1.000[a] | 0 (0.0) | 0 (0.0) | 1.000[a] |
| Noncardiogenic death | 0 (0.0) | 1 (0.1) | 1.000[a] | 0 (0.0) | 1 (0.1) | 1.000[a] | 2 (0.2) | 3 (0.3) | 0.453 |
| Nonfatal myocardial infarction | 3 (0.3) | 4 (0.4) | 0.843 | 1 (0.1) | 0 (0.0) | 1.000[a] | 1 (0.1) | 5 (0.5) | 0.144 |
| Revascularization | 3 (0.3) | 1 (0.1) | 0.292 | 3 (0.3) | 3 (0.3) | 0.868 | 36 (3.9) | 49 (5.3) | 0.192 |
| Target lesion | 3 (0.3) | 0 (0.0) | 0.250[a] | 1 (0.1) | 1 (0.1) | 0.819 | 13 (1.4) | 14 (1.5) | 0.883 |
| Nontarget lesion | 0 (0.0) | 1 (0.1) | 1.000[a] | 2 (0.2) | 2 (0.2) | 0.961 | 23 (2.5) | 35 (3.8) | 0.144 |
| Nonfatal stroke | 2 (0.2) | 0 (0.0) | 0.500[a] | 0 (0.0) | 1 (0.1) | 1.000[a] | 0 (0.0) | 4 (0.4) | 0.125[a] |
| Stent thrombosis (acute or subacute) | 3 (0.3) | 0 (0.0) | 0.250[a] | 0 (0.0) | 0 (0.0) | 1.000[a] | 0 (0.0) | 0 (0.0) | 1.000[a] |

Abbreviation: MACCE, major adverse cardiovascular and cerebrovascular events.
Note: The landmark (48 and 150 days of follow-up) was determined by the intersection and trend of Kaplan–Meier curves for MACCE (see ►**Fig. 3**). *p*-Values were all calculated by Cox proportional hazard regression model and were subsequently adjusted by propensity scores, except for those marked with "a".
[a]The comparisons were accomplished by the Fisher's exact test.

| Subgroup | Cilostazol group | Aspirin group | Adjusted HR (95% CI) | *P*-value for interaction |
|---|---|---|---|---|
| **All patients** | **47/918** | **70/918** | **0.671 (0.462, 0.974)** | |
| **Age** | | | | **0.280** |
| ≤ 60 | 14/289 | 16/309 | 0.966 (0.470, 1.983) | |
| > 60 | 33/629 | 54/609 | 0.580 (0.374, 0.899) | |
| **Gender** | | | | **0.285** |
| Male | 34/682 | 56/677 | 0.602 (0.392, 0.925) | |
| Female | 13/236 | 14/241 | 0.951 (0.441, 2.051) | |
| **Diabetes** | | | | **0.845** |
| Yes | 14/231 | 21/247 | 0.763 (0.385, 1.510) | |
| No | 33/687 | 49/671 | 0.633 (0.405, 0.989) | |
| **Prior PCI** | | | | **0.099** |
| Yes | 19/260 | 17/241 | 1.032 (0.531, 2.005) | |
| No | 28/658 | 53/667 | 0.548 (0.345, 0.869) | |
| **ACS** | | | | **0.047** |
| Yes | 13/332 | 31/321 | 0.368 (0.191, 0.710) | |
| No | 34/586 | 39/597 | 0.923 (0.581, 1.467) | |
| **Severity of lesions*** | | | | **0.930** |
| Mild | 19/439 | 26/414 | 0.682 (0.375, 1.241) | |
| Severe | 28/479 | 44/504 | 0.663 (0.411, 1.070) | |
| **B2/C type target lesions** | | | | **0.126** |
| Yes | 38/577 | 49/596 | 0.793 (0.516, 1.217) | |
| No | 9/341 | 21/322 | 0.402 (0.183, 0.882) | |
| **Minimum diameter of stents** | | | | **0.043** |
| ≤ 2.8mm | 37/510 | 42/499 | 0.911 (0.583, 1.424) | |
| > 2.8mm | 10/408 | 28/419 | 0.330 (0.159, 0.684) | |
| **Total length of stents** | | | | **0.008** |
| ≤ 38mm | 14/483 | 38/482 | 0.366 (0.197, 0.680) | |
| > 38mm | 33/435 | 32/436 | 1.038 (0.635, 1.697) | |
| **Duration of DAPT** | | | | **0.659** |
| < 12 months | 12/173 | 17/188 | 0.806 (0.384, 1.694) | |
| 12-15 months | 35/745 | 53/730 | 0.626 (0.406, 0.964) | |
| **$P2Y_{12}$ receptor antagonist** | | | | **0.265** |
| Clopidogrel | 38/821 | 61/813 | 0.618 (0.410, 0.931) | |
| Ticagrelor | 9/97 | 9/105 | 1.071 (0.424, 2.708) | |
| **Ischemic risk†** | | | | **0.386** |
| Low | 15/389 | 28/388 | 0.538 (0.286, 1.011) | |
| Medium | 24/400 | 33/409 | 0.789 (0.463, 1.344) | |
| High | 8/129 | 9/121 | 0.681 (0.259, 1.789) | |

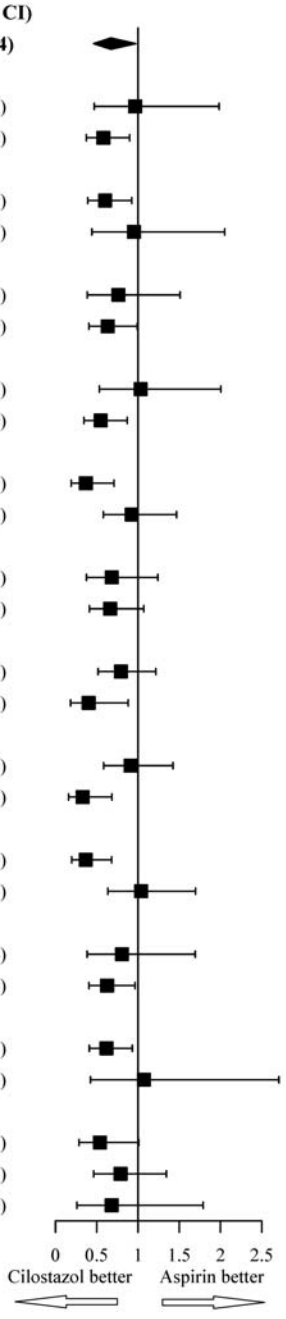


**Fig. 3** Subgroup analysis. MACCE was further analyzed in subgroup analysis. The data in column two or three are shown as No. of events / No. of patients. *Judged by the Gensini score. Specifically, < 40 (the median) was defined as the mild lesions, while ≥ 40 the severe lesions. †Judged by the GRACE discharge score. Specifically, ≤ 88 was defined as the low risk, 89–118 the medium risk, while 119–263 the high risk. ACS, acute coronary syndrome; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; PCI, percutaneous coronary intervention.

## Discussion

In China, cilostazol-based DAPT is widely used among patients with aspirin intolerance after coronary DES implantation. However, few large-scale studies have examined this empirical strategy. To our knowledge, this study is the largest cohort study to explore the efficacy and safety of cilostazol-based DAPT for Chinese patients with aspirin intolerance after coronary DES implantation. We consecutively enrolled 918 patients who received cilostazol-based DAPT, matched with 918 patients who received aspirin-based DAPT. After 15 months of prospective follow-up, the incidence of MACCE in the cilostazol group was lower than that in the aspirin group, without increasing bleeding events.

In fact, there is no uniform definition of "aspirin intolerance" yet. It is often narrowly defined as "aspirin allergy", which is not comprehensive. We believe that aspirin intolerance can be defined as any conditions that prevent patients from long-term use of low-dose aspirin, such as having contraindications or severe adverse drug reactions after taking it. Because of the vague definition, the epidemiology

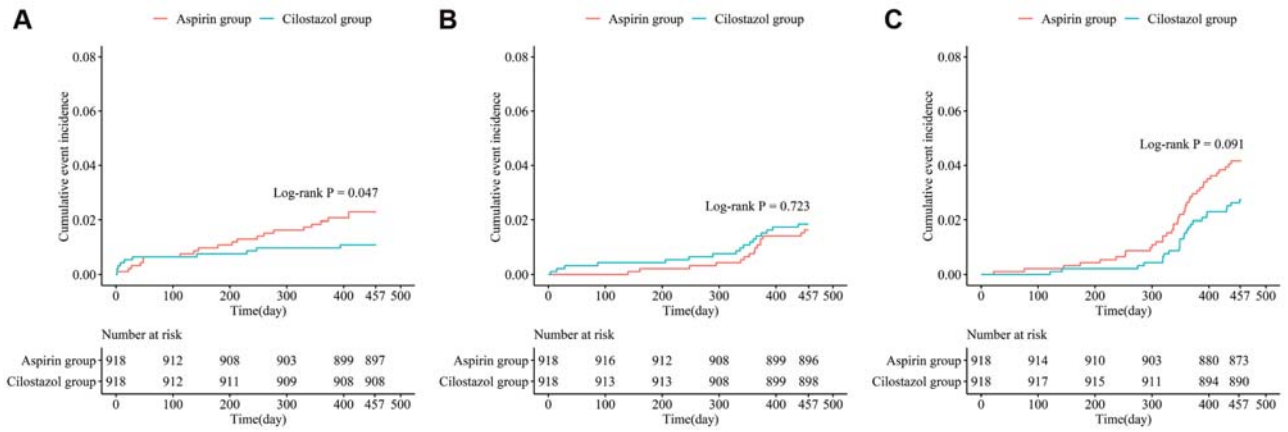


**Fig. 4** Secondary efficacy endpoints in both groups. It shows the cumulative incidence of secondary efficacy endpoints described by the Kaplan–Meier curves. (**A**) A combined endpoint consisting of cardiogenic death, noncardiogenic death, nonfatal myocardial infarction, and nonfatal stroke. Log-rank $p = 0.047$. (**B**) Target lesion revascularization. Log-rank $p = 0.723$. (**C**) Nontarget lesion revascularization. Log-rank $p = 0.091$.

**Table 3** Follow-up angiography in both groups

| | Cilostazol group ($n = 448$) | Aspirin group ($n = 454$) | *p*-Value |
|---|---|---|---|
| Median time for angiographic follow-up (d) | 372 | 379 | 0.206 |
| Clinically driven angiographic follow-up, no. (%) | 102 (22.8) | 139 (30.6) | 0.008 |
| Results of angiography, no. (%) | | | |
| Lesion progression[a] | 78 (17.4) | 107 (23.6) | 0.022 |
| Target lesion | 24 (5.3) | 27 (6.0) | 0.701 |
| Nontarget lesion | 54 (12.1) | 80 (17.6) | 0.019 |

[a]Refers to an increase of more than 30% in lumen stenosis.

**Table 4** Safety endpoints in both groups

| | No. of events (%) | | *p*-Value |
|---|---|---|---|
| | Cilostazol group ($n = 918$) | Aspirin group ($n = 918$) | |
| Bleeding events | | | |
| Minor bleeding events | 20 (2.2) | 56 (6.1) | < 0.001 |
| BARC 1 | 15 (1.7) | 43 (4.7) | |
| BARC 2 | 5 (0.5) | 13 (1.4) | |
| Major bleeding events | 7 (0.8) | 4 (0.4) | 0.364 |
| BARC 3a | 1 (0.1) | 2 (0.2) | |
| BARC 3b | 4 (0.4) | 1 (0.1) | |
| BARC 3c | 0 (0.0) | 0 (0.0) | |
| BARC 4 | 0 (0.0) | 0 (0.0) | |
| BARC 5a | 1 (0.1) | 1 (0.1) | |
| BARC 5b | 1 (0.1) | 0 (0.0) | |
| Other drug-induced symptoms | | | |
| Severe gastric discomfort | 18 (2.0) | 34 (3.7) | 0.024 |
| Dyspnea | 2 (0.2) | 3 (0.3) | 1.000 |
| Palpitation | 6 (0.7) | 0 (0.0) | 0.041 |
| Allergy | 2 (0.2) | 3 (0.3) | 1.000 |
| Gout | 0 (0.0) | 3 (0.3) | 0.083 |

Abbreviation: BARC, Bleeding Academic Research Consortium.

of aspirin intolerance is also unknown. The reported incidence of aspirin allergy was approximately 2.6% in patients with coronary artery disease.[11] However, few studies have focused on the proportion of generalized aspirin intolerance among patient with coronary artery disease in the real world. In Japan, a multicenter observational study involving 947 patients found that up to 30% of patients taking low-dose aspirin clinically showed aspirin intolerance, mainly manifested as severe gastrointestinal reactions or aspirin allergy.[12] In our study, for the first time, we reported the prevalence of aspirin intolerance in Chinese patients with coronary artery disease in a single center. Among the 11,470 patients admitted for coronary angiography, a total of 1,139 (9.9%) patients were treated with cilostazol because of aspirin intolerance. Notably, some patients with aspirin intolerance (especially gastrointestinal intolerance) may adopt other strategies like adding PPIs, rather than replacing aspirin with cilostazol. Thus, the above proportion was actually underestimated. In other words, the incidence of aspirin intolerance might exceed 9.9% in China. As for the causes of aspirin intolerance, up to 76.9% of the patients showed gastrointestinal intolerance, including a history of peptic ulcer, a history of chronic gastritis, and severe gastrointestinal reactions after taking aspirin. The incidence of aspirin allergy was lower than that in Western countries, accounting for only approximately 0.5%.

It should be admitted that some sporadic studies have explored the efficacy and safety of cilostazol-based DAPT in

China, but most of them have been small scale and published domestically. At present, the only one published internationally was conducted by Xue et al.[10] In their study, only 205 patients with aspirin intolerance were enrolled, and it eventually focused on pharmacologic analysis. For the first time, we used a relatively large-sample real-world cohort study to explore the efficacy and safety of cilostazol-based DAPT in patients with aspirin intolerance after DES implantation in China. Ultimately, the efficacy of cilostazol-based DAPT for preventing MACCE was at least similar to the traditional aspirin-based DAPT, and it even reached a "better" level in our study. This conclusion was consistent with the study conducted by Xue et al,[10] although their comparisons did not reach statistical significance.

Interestingly, we found an obvious intersection when plotting the cumulative incidence curves of MACCE. Landmark analysis was subsequently adopted to split the follow-up time. The results showed that the cumulative incidence of MACCE was lower in the cilostazol group only after 150 days of follow-up. Further analysis revealed more cases of nonfatal stroke and stent thrombosis in the cilostazol group within 48 days of follow-up, which seemed to explain why the advantage of prevention of MACCE in the cilostazol group was not obvious during this period. Since postoperative intensive DAPT is the key to preventing stent thrombosis after coronary DES implantation, we hypothesize that cilostazol (50 mg twice daily)-based DAPT is inferior to the traditional aspirin (100 mg once daily)-based DAPT in terms of preventing early stent thrombosis. More studies are required for validation in the future.

In terms of repeat revascularization, we found that the trend of reduced incidence in the cilostazol group was mainly attributed to non-TLR, rather than TLR. Further, through follow-up angiography, the rate of lesion progression in the cilostazol group was also significantly lower than that in the aspirin group, again mainly driven by the nontarget lesions. This is inconsistent with the conclusions drawn by previous DECLARE studies,[13–15] in which cilostazol could significantly reduce the rate of TLR (mainly in-stent restenosis) after PCI. The different regimen (DAPT vs. triple antiplatelet therapy), dose of cilostazol (50 mg twice daily vs. 100 mg twice daily), and type of coronary stents (second-generation DES vs. bare metal stents and first-generation DES) may account for it. In fact, as a phosphodiesterase inhibitor, cilostazol can reduce the incidence of non-TLR due to its inhibition of primary coronary lesion progression. This ability can be related to its antiplatelet effects, prevention of vascular smooth muscle cell proliferation, regulation of lipids,[16] or even alleviation of clopidogrel resistance.[17]

Compared with other antiplatelet drugs, cilostazol has reversible antiplatelet effects and the ability to protect endothelial cells, which are associated with fewer bleeding events.[18] However, in the current analysis, there was no significant difference in the incidence of major bleeding events between the two groups, although cilostazol-based DAPT was associated with fewer minor bleeding events. In fact, many patients who used cilostazol as an alternative for aspirin had underlying diseases (e.g., severe gastrointestinal ulcers) that were prone to massive hemorrhage, although there was no significant difference in the distributions of CRUSADE scores. Further analysis also showed that the major bleeding events in the cilostazol group were mainly from the digestive tract (data not shown).

### Limitations

First, all the above conclusions should be interpreted with caution because of the retrospective and observational nature of this cohort study. Besides selection bias, we could not adjust for all the potential confounders in this cohort study, although the matching strategy and propensity score analysis were adopted. However, a large-scale randomized controlled trial is planned to be conducted in our hospital. Second, the occurrence of aspirin intolerance was partly self-reported from patients, which made it subjective. Third, the rate of "hard" endpoints like death, myocardial infarction, and stroke was relatively low in the current study. Fourth, although we collected the data on PPIs, they were actually inexact due to the abusive and irregular use in China. Fifth, only approximately 10% of patients were treated with ticagrelor, so the efficacy and safety of cilostazol in these patients still needed to be confirmed, especially in East Asia. Last, our conclusions cannot apply to other races without further research.

## Conclusion

In this retrospective cohort study, compared with the aspirin group, the cilostazol group was associated with lower risks of MACCE, without increasing bleeding events. Cilostazol is a good substitute for aspirin in patients with aspirin intolerance after coronary DES implantation in China. However, large-scale randomized controlled trials are still required for further discovery.

### What is known about this topic?

- Cilostazol-based DAPT is empirically used in Chinese patients with aspirin intolerance after coronary DES implantation without support from strong clinical evidence.
- Several domestic small-scale studies have tried to explore its efficacy and safety.

### What does this paper add?

- In this large-scale retrospective cohort study, compared with aspirin-based DAPT, cilostazol-based DAPT had lower risks of MACCE and same risks of bleeding events.
- The advantage of the cilostazol group in preventing repeat revascularization was mainly attributed to the reduced rate of nontarget lesion progression.
- Cilostazol is a good substitute for aspirin in patients with aspirin intolerance after coronary DES implantation in China. However, large-scale randomized controlled trials are still required to further confirm its efficacy and safety.

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Conflict of Interest
None declared.

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