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# Association of the use of amlodipine with clopidogrel response in Chinese patients undergoing percutaneous coronary intervention

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Until recently, the precise mechanism of clopidogrel resistance remains unclear. Some clinical studies have demonstrated that calcium channel blockers (CCBs) could reduce the antiplatelet effect of clopidogrel in white or black subjects, implicating in clopidogrel resistance. However, that remains to be determined in Chinese patients. In this study, we sought to determine whether there could be a decreased antiplatelet effect of clopidogrel and an increased risk for developing adverse cardiovascular events after concomitant use of different CCBs and clopidogrel in Chinese patients treated with percutaneous coronary intervention (PCI). A subcohort of 249 patients not carrying the *CYP2C19* *2, *3 or *17 variant was identified from a total of 617 consecutive clopidogrel-treated patients undergoing PCI and then categorized into three groups according to various CCB treatments. Baseline data, clinical characteristics and blood samples were collected for all patients. The maximum platelet aggregation (MPA) was measured by light transmittance aggregometry (LTA) to assess the platelet function in blood samples obtained from patients on day 3 after starting daily clopidogrel maintenance doses. The primary clinical end-point was a definite stent thrombosis (ST) episode, whereas secondary end-points were other major adverse cardiovascular events within 12 months after stenting. Of the 249 patients not carrying *CYP2C19* *2, *3 and *17 variants, the ADP-induced MPA differed significantly among the three groups ($P < 0.001$). The MPA values were 1.76 times in the amlodipine group ($41.6 \pm 23.0\%$) than in the No CCB group ($23.7 \pm 14.1\%$) ($P < 0.001$). Moreover, in a linear regression model, the use of amlodipine was independently associated with MPA values ($R = 0.375$, $P < 0.001$), suggesting that the use of amlodipine might link to the increased MPA. However, the incidence of 1-year ST was not significantly higher in the amlodipine group than the No CCB group (OR, 4.80; 95% CI, 0.87 to 26.52; $P = 0.068$), and none of the risks for other adverse cardiovascular events were significantly different across the three groups ($P = 0.11$).

## 1. Introduction

Clopidogrel, an oral antiplatelet agent, has been widely prescribed for the prevention of thrombotic events in patients with acute coronary syndrome or undergoing percutaneous coronary intervention (PCI) (Simon et al. 2009; Zou et al. 2014). However, there are still some substantial adverse cardiovascular events with severe clinical consequences, such as stent thrombosis (ST) and myocardial infarction (MI) after regularly taking clopidogrel as anti-platelet therapy, which is called clopidogrel resistance (Simon et al. 2009; Mega, et al. 2009; Zou et al. 2014). Clopidogrel is a prodrug that needs to be converted *in vivo* into its active metabolite by CYP450 enzymes such as *CYP2C19* and *CYP3A4* (Simon et al. 2009; Mega et al. 2009). Many clinical studies have almost consistently demonstrated that loss-of-function *CYP2C19**2 polymorphisms are associated with a reduced antiplatelet effect of clopidogrel and a higher incidence of major cardiovascular events (Simon et al. 2009; Mega et al. 2009). However, *CYP2C19* polymorphism and clinical factors may explain only a small 12% of clopidogrel resistance (Notarangelo et al. 2013; Geisler et al. 2011; Zou et al. 2013; Yang et al. 2013). Up to now, the precise mechanism of clopidogrel resistance is still unknown.

Calcium channel blockers (CCBs) are often prescribed for patients under clopidogrel to treat hypertension and angina pectoris (Takenaka, et al. 2014; Wang, et al. 2013). Three recent studies observed that CCBs reduced the antiplatelet effect of clopidogrel and increased the risk of adverse cardiovascular events (Siller et al. 2008; Gremmel, et al. 2010; Harmsze, et al. 2010). However, all these studies were performed in white or black patients. The conclusion may not be fully generalized or extrapolated to the Chinese people due to the marked ethnic variability in the disposition of and response to clopidogrel (Xie et al. 2011). Moreover, the activity of P-glycoprotein (Pgp) is thought to influence the antiplatelet effect of clopidogrel (Taubert et al. 2006). Importantly, some CCBs, such as nifedipine, felodipine and diltiazem, have strong inhibitory effects on Pgp activity (Pgp-inhibiting CCBs), but amlodipine has no inhibitory effect on Pgp activity (Zhou, et al. 2007). Due to these differences within the class of CCBs, different antiplatelet effects and

**Table 1: Baseline and demographic characteristics of the 249 patients with *CYP2C19* wild-type homozygotes for the **2*, **3* and **17* according to the CCB treatments**

| | No CCB (n = 139) | Pgp-CCB (n = 52) | amlodipine (n = 58) | P value |
|---|---|---|---|---|
| MPA, % | 23.7 ± 14.1 | 29.9 ± 20.2 | 41.6 ± 23.0 | 0.001 |
| Age, yr | 63.8 ± 9.0 | 64.5 ± 10.6 | 61.8 ± 6.6 | 0.24 |
| Male, n (%) | 115 (82.7) | 40 (76.9) | 47 (81.0) | 0.66 |
| BMI, kg/m$^2$ | 24.9 ± 2.8 | 24.5 ± 3.6 | 24.4 ± 3.3 | 0.52 |
| Hypertension, n (%) | 99 (71.2) | 40 (76.9) | 49 (84.5) | 0.14 |
| Hyperlipidemia, n (%) | 85 (61.2) | 33 (63.5) | 40 (69.0) | 0.58 |
| Diabetes mellitus, n (%) | 38 (27.3) | 12 (23.1) | 16 (27.6) | 0.82 |
| Current smoking, n (%) | 49 (35.3) | 17 (32.7) | 18 (31.0) | 0.84 |
| Previous MI, n (%) | 19 (13.7) | 9 (17.3) | 14 (24.1) | 0.20 |
| Stable angina, n (%) | 18 (12.9) | 7 (13.5) | 9 (15.5) | 0.89 |
| Unstable angina, n (%) | 107 (77.0) | 38 (73.1) | 36 (62.1) | 0.10 |
| Statins, n (%) | 132 (95.0) | 48 (92.3) | 52 (89.7) | 0.39 |
| ACEI, n (%) | 47 (33.8) | 22 (42.3) | 23 (39.7) | 0.49 |
| Omeprazole, n (%) | 101 (72.7) | 45 (86.5) | 45 (77.6) | 0.13 |
| Platelet count, × 10$^9$/L | 204.0 ± 50.2 | 215.1 ± 46.3 | 209.3 ± 35.8 | 0.33 |
| HDL, mmol/L | 0.98 ± 0.19 | 0.98 ± 0.25 | 1.02 ± 0.22 | 0.44 |
| LDL, mmol/L | 2.51 ± 0.59 | 2.60 ± 0.55 | 2.56 ± 0.61 | 0.63 |
| LVEF (%) | 61.3 ± 5.0 | 63.0 ± 6.1 | 62.2 ± 3.5 | 0.11 |
| Total number of stents | 2.2 ± 1.3 | 2.4 ± 1.1 | 2.0 ± 1.4 | 0.37 |
| Total length of stent, mm | 58.8 ± 32.0 | 58.2 ± 29.0 | 51.6 ± 22.9 | 0.28 |

Data are expressed as mean ± SD, or n (%).
MPA, maximum platelet aggregation; CCBs, calcium channel blockers; BMI, body mass index; MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, Left ventricular ejection fraction.

adverse clinical outcomes relevance of drug interactions with clopidogrel are expected.

Thus, we investigated the impact of co-administration of different CCBs on the antiplatelet effect of clopidogrel and 1-year adverse clinical outcomes in a cohort of patients undergoing PCI after they were treated with clopidogrel.

## 2. Investigations and results

### *2.1. Baseline characteristics of enrolled patients*

A total of 617 consecutive clopidogrel on-treatment patients were eligible according to the inclusion and the exclusion criteria and enrolled in the study. Many studies reported that carriage of the *CYP2C19* *2, *3, and *17 variants is significantly associated with attenuated platelet response to clopidogrel (Simon et al. 2009; Mega et al. 2009; Yang et al. 2013; Zou et al. 2013). To clarify the effect of amlodipine on the antiplatelet effect of clopidogrel and clinical endpoints, all patients carrying *CYP2C19* loss-of-function genetic variants were excluded from the study population. Of the 617 PCI-treated patients enrolled, 259 were wild-type homozygotes without the *CYP2C19* *2 or *3 loss-of-function variants as described elsewhere (Zou et al. 2013, 2014), of whom 10 patients harboring the *CYP2C19**17 gain-of-function variant was further excluded. Finally, a subcohort of 249 patients not carrying any *CYP2C19* *2, *3, and *17 variants were analyzed.

According to medical records of the CCB prescription claims within 12 months after discharge, 249 clopidogrel-treated patients were categorized into three groups: 139 patients with No CCB treatment, 52 patients used Pgp-inhibiting CCBs (nifedipine, n = 27, mean dose 45.6 ± 16.7 mg; felodipine, n = 6, 6.8 ± 2.2 mg; and diltiazem, n = 19, 147.1 ± 42.3 mg). The remaining 58 patients were treated with amlodipine (mean dose 6.7 ± 1.8 mg), which does not inhibit Pgp. The baseline characteristics of the study population according to CCB treatments are summarized in Table 1. The baseline variables were well balanced among the various CCB treatment groups (P > 0.05).

### *2.2. Amlodipine and maximum platelet aggregation (MPA)*

The median value of ADP-induced MPA was 30.8% (IQR, 15.2 to 50.0%) for the whole cohort of 617 patients. According to the various CCB groups, the median value of MPA was 24.2% (12.1–39.5%) for No CCB, 31.2% (17.9%–43.8%) for Pgp-inhibiting CCBs and 46.5% (22.2%–68.2%) for amlodipine, respectively, which differed significantly among the three groups (P = 0.001). In addition, results derived from a multivariable linear regression model demonstrated that the use of amlodipine

**Table 2: Association of the ADP-induced MPA as the dependent variable with other independent variables as determined by the multivariable linear regression model**

| Independent variable | β Coefficient | | P |
|---|---|---|---|
| | Value | SE | value |
| Use of amlodipine | 6.38* | 2.00 | 0.002 |
| *CYP2C19 *2* or **3* allele carriage | 6.53† | 2.47 | 0.009 |
| Age | 1.33 | 0.51 | 0.90 |
| Sex | 2.45 | 1.76 | 0.32 |
| BMI | 1.49 | 0.91 | 0.26 |
| Hypertension | 1.66 | 0.87 | 0.65 |
| Hyperlipidemia | 1.42 | 0.50 | 0.69 |
| Diabetes mellitus | 1.37 | 0.59 | 0.48 |
| HDL | 2.77 | 1.73 | 0.86 |
| LDL | −5.23 | 4.01 | 0.22 |

MPA, maximum platelet aggregation; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein. * Unadjusted $\beta_{coefficient}$ for the use of amlodipine was 8.21 (SE = 1.93, $P < 0.001$). † Unadjusted $\beta_{coefficient}$ for the *CYP2C19*2* or **3* allele carriage was 9.02 (SE = 2.37, $P < 0.001$).

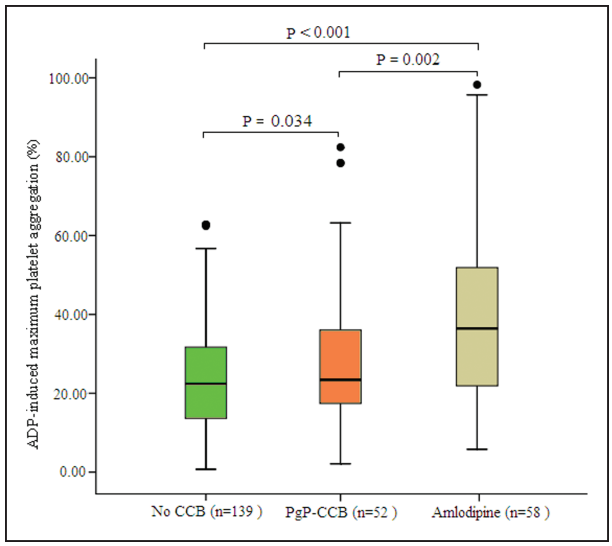


Fig. 1: CCB treatments and maximum platelet aggregation. ADP-induced platelet aggregation (%) in relation to CCB treatments (No CCB; Pgp-inhibiting CCBs; amlodipine). Platelet aggregation values were compared between groups with Mann-Whitney U test.

was independently associated with ADP-induced MPA measurements ($\beta_{coefficient} = 6.38$, SE = 2.00, $P = 0.002$). Moreover, carriage of the *CYP2C19 *2* and **3* was significantly associated with MPA ($\beta_{coefficient} = 6.53$, SE = 2.47, $P = 0.009$) as shown in Table 2.

Of the 249 patients not carrying *CYP2C19 *2*, **3* and **17* variants, the median value of ADP-induced MPA was 25.0% (IQR, 14.9 to 37.0%). The median ADP-induced MPA values among the various CCB groups were as follows: 22.4% (IQR, 13.7 to 31.7%) for the No CCB group, 23.4% (IQR, 17.4 to 33.8%) for the Pgp-CCB group, and 37.0% (IQR, 24.2 to 52.4%) for the amlodipine group. As shown in the Fig. 1, ADP-induced MPA differed significantly among the three groups ($P < 0.001$). The MPA values were 1.76 times in the amlodipine group ($41.6 \pm 23.0\%$) than in the No CCB group ($23.7 \pm 14.1\%$) ($P < 0.001$). Moreover, in a linear regression model, the use of amlodipine was independently associated with MPA values ($R = 0.375$, $P < 0.001$), suggesting that the use of amlodipine might link to the increased MPA**.**

### *2.3. Amlodipine and clinical endpoints*

The primary efficacy endpoint (ie, definite ST within 1 year) occurred in 7 out of 617 PCI patients (1.13%). Of the observed cases, five (71.4%) were diagnosed in hospitalization after the procedure, as described elsewhere (Zou et al. 2014). Moreover, the risk for developing ST events was not significantly different across the three groups ($P = 0.11$; $\chi^2$ test for trend), and the incidence of 1-year ST was not significantly higher in the amlodipine group than the No CCB group (OR, 4.80; 95% CI, 0.87 to 26.52; P = 0.068, $\chi^2$ test for trend).

To further determine the association of the use of amlodipine and ST events, a multiple logistic regression model was used. The results demonstrated that the use of amlodipine was not associated with 1-year ST (OR, 4.37; 95% CI, 0.59 to 18.72; $P = 0.12$). In addition, there were 6 patients with secondary endpoint (2 cases of non-ST-elevation MI and 4 ST-elevation MI) within 1 year post-stenting, as described elsewhere (Zou et al. 2014). Moreover, there was a similar 1-year incidence of MI, mortality rate, TVR, TLR, and composite MACE among the three groups (data not shown).

## 3. Discussion

This study aimed to determine the impact of amlodipine on the antiplatelet effect of clopidogrel and the risk of adverse cardiovascular events in 249 Chinese PCI patients not carrying the *CYP2C19* *2, *3 or *17. We found that amlodipine has a significant impact on the antiplatelet effect (MPA) of clopidogrel in the blood samples, which is in line with previous studies that reported that concomitant use of Pgp-inhibiting CCBs and amlodipine increases on-clopidogrel platelet reactivity (Siller et al. 2008; Gremmel et al. 2010; Harmsze et al. 2010). However, we found that none of the incidences of 1-year adverse cardiovascular events were significantly higher in the amlodipine group than the No CCB group, and there were similar 1-year incidences of ST, MI, mortality rate, TVR, TLR, and composite MACE among the three groups (data not shown), suggesting that the use of amlodipine was not significantly associated with the incidence of 1-year adverse cardiovascular events.

To the best of our knowledge, this is the first study to report the impact of amlodipine on the occurrence of clinical adverse outcomes in Chinese clopidogrel-treated patients undergoing PCI. The association between the use of amlodipine and adverse cardiovascular events was not explored in these studies (Siller et al. 2008; Gremmel et al. 2010; Harmsze et al. 2010).

In addition, some limitations of our study need to be discussed. First, we cannot completely exclude the possible bias by patients' characteristics and various risk factors, the presence of other coexisting diseases, comedication and drug transporters as confounding factors might contribute to the changes examined in this study. Nonetheless, the multivariate adjustment models confirmed the primary analyses. Second, in terms of the small number of patients undergoing PCI in the present study and relatively uncommon ST episodes, further studies would be needed to corroborate the present results in a large number of patients, or in patients of other ethnic backgrounds.

## 4. Experimental

### *4.1. Baseline characteristics of enrolled patients*

The present study was performed in Han Chinese patients treated with drug-eluting stent (DES) placement in a single-center, prospective observational cohort in the Department of Cardiology, Nanjing First Hospital, Nanjing Medical University, China. The inclusion period lasted from January 2008 until December 2010. For this study, continuous administration of clopidogrel was confirmed at the assigned different time points of the follow-up period. Patients who discontinued the use of clopidogrel for any reasons other than the occurrence of major adverse cardiovascular events (MACE) or death were in advance excluded from this study. the exclusion criteria were as follows: previous ST, active bleeding and bleeding diathesis, platelet count $< 100 \times 10^9$/L, severe renal or hepatic disorders, hematological disorders, inflammatory diseases, and prior coronary artery bypass grafting (CABG), active malignancy, body mass index (BMI) < 18.5 or > 40 kg/m$^2$, use of hormone replacement therapy or contraceptives, contraindications to aspirin or clopidogrel treatment, remature clopidogrel or aspirin cessation and prior treatment with glycoprotein IIb/IIIa inhibitors during the 10 days before the PCI. The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of Nanjing Hospital, Nanjing Medical University, China. All patients signed their written informed consent for the intervention, platelet function testing prior to participation, as was performed as described previously (Zou et al. 2013; Yang et al. 2013).

### *4.2. Study protocol*

All of the patients (aged 18–75 years) included were pretreated with a loading dose of 300 mg clopidogrel (Plavix®, Hangzhou Sanofi-aventis Minsheng Pharmaceuticals Co. Ltd., Hangzhou, China) before PCI with DES, followed by aspirin (100 mg daily, for long-life) and clopidogrel (75 mg daily, for 12 months). And other medication such as angiotensin-converting enzyme inhibitor (ACEI), statin or calcium-channel blocker (CCB) were also administered. The blood samples were drawn in the morning on day 3 but before intake of clopidogrel using tubes containing 3.8 % sodium-citrate (NanGeer Biomedical Co., Ltd, Sichuan, China). Blood samples for aggregation testing were processed within 2 h after blood collecting. Information on age, gender, BMI, systolic and diastolic pressure, diabetes,

dyslipidemia, smoking status, family history of disease and medications in use were recorded or derived from hospital admission records.

### 4.3. Determination of MPA

We obtained the predischarge samples after PCI, which were drawn in the morning on day 3, but before intake of the maintenance dose of clopidogrel using tubes containing 3.8% sodium citrate. All blood samples used for platelet aggregation testing were processed within 2 h of collection. The antiplatelet response to clopidogrel was evaluated by detection of MPA, which was measured by light transmittance aggregometry (LTA) in platelet-rich plasma (PRP) after stimulation with 20 μmol/L ADP (Sigma-Aldrich, Munich, Germany) using a four-channel LBY-NJ aggregometer (PuLiSheng, Beijing, China) (Bouman et al. 2010). Briefly, the PRP was prepared by centrifugation of citrated venous blood at 150 g for 15 min, and platelet-poor plasma (PPP) by centrifugation at 1,500 g for 20 min. PRP was adjusted to $200 \sim 250 \times 10^9$ platelets/L by dilution with autologous PPP. Aggregation results were expressed as percentage of maximal light transmission using PPP from the same patient as reference (100% transmission). *Ex vivo* platelet function testing was performed as described previously (Zou et al. 2013; Yang et al. 2013).

### 4.4. Study endpoints and definitions

We measured the occurrence of clinical end points over up to 12 months of follow-up. The primary clinical endpoint of the study was the 1-year incidence of definite ST, which was defined as the presence of an acute coronary syndrome with angiographic confirmation of thrombosis according to the Academic Research Consortium (ARC) criteria (Cutlip et al. 2007). The secondary end point was the occurrence of MI, 1-year cardiac death, target vessel revascularization (TVR), target lesion revascularization (TLR), or major adverse cardiovascular events (MACE) 12 months after dose. Of them, MI was diagnosed if increased plasma levels of creatine kinase-MB (CK-MB) doubled its baseline value immediately before stenting in acute MI patients or new abnormal Q-wave appeared in the electrocardiogram (ECG) tracing. All death cases were considered cardiac unless otherwise documented. TVR, TLR and MACE were defined according to the ARC definitions (Mauri et al. 2007). The clinical endpoints were analyzed and adjudicated by the members of an independent committee blinded to the study protocol.

### 4.5. Data collection and follow-Up

This cohort study was conducted using data from hospital discharge and follow-up records provided by the Department of Cardiology, Nanjing First Hospital, Nanjing Medical University. Patients stayed in the hospital for at least three days after study inclusion and also after PCI, and their demographic characteristics and baseline data were evaluated, including gender, age, BMI, lifestyle habits, biochemical testing, potential risk factors (e.g., hypertension, diabetes mellitus, dyslipidemia, and cigarette smoking) and concurrent medications (e.g.,CCB, proton-pump inhibitors, and statins) over 12-month follow-up period. The medication before and after discharge, in particular the CCB, was reviewed for all patients for this analysis. Patient data were collected and input into the electronic database by the well-trained staff blinded to the study protocol, and all information from the attending physicians, relatives, and hospital managers was retrieved. Original records were double checked to ensure high-quality data. Data quality was randomly monitored to determine whether there were any inconsistencies and errors between electronic database and actual clinical datasets. Data collection for this study was approved by the hospital institutional review board, and subsequently data audits were performed at a regular interval. In the hospital, the follow-up angiography was routinely scheduled at 6 and 12 months after PCI, but if necessary, it was performed earlier than scheduled. Clinical follow-up data was obtained through prescription records, reviewing of hospital medical records, outpatient clinical visits, written questionnaires, and telephone interview at the outpatient clinic during 12 months after stent placement, respectively, as was performed as described previously (Zou et al. 2013, 2014).

### 4.6. Statistical analysis

Frequencies of categorical variables were given as counts (percentages) and continuous variables either as mean ± SD or as median with interquartile range (IQR). Categorical variables were analyzed with Chi-square test. Continuous variables with a Gaussian distribution were compared by means of the unpaired 2-tailed *t* test or ANOVA for > 2 groups, whereas continuous variables with a non-Gaussian distribution were compared by Kruskal-Wallis test or Mann-Whitney U test. Correlations between various CCB groups and MPA were performed using multivariate linear regression analysis; the independent associations between various CCB groups and clinical adverse cardiovascular events during the follow-up period were assessed after adjusting for other potential confounding factors using multivariate logistic regression analysis. All statistical analyses were performed with SPSS 16.0 (SPSS Inc, Chicago, III, USA). A value of $P < 0.05$ was considered to indicate statistical significance.

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