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Switching between ticagrelor and clopidogrel in patients who underwent percutaneous coronary intervention: insight into contemporary practice in Chinese patients

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Ticagrelor has been proved to be more effective than clopidogrel; however, little is known about the switching between ticagrelor and clopidogrel in real-world clinical practice. We assessed the prevalence, related factors, dose bridging, compliance, and short-term outcomes of in-hospital switching between ticagrelor and clopidogrel in consecutively recruited patients treated by ticagrelor after percutaneous coronary intervention (PCI). A total of 417 eligible patients administrated with ticagrelor in-hospital after PCI were recruited. Switching between ticagrelor and clopidogrel occurred in 362 (86.8%) patients, with 318 (76.3%) from clopidogrel to ticagrelor occurring mainly after PCI and 44 (10.6%) from ticagrelor to clopidogrel primarily at discharge. History of cerebrovascular disease, final diagnosis of acute coronary syndrome, left main disease, ostial lesion, co-administration with warfarin, CYP2C19 loss-of-function alleles' carriage status, and ticagrelor-related dyspnoea emerged as related factors for the switching between clopidogrel and ticagrelor. Dose bridging between clopidogrel loading dose and ticagrelor maintenance dose (MD) was more frequent in patients switching from clopidogrel to ticagrelor, while the bridging between ticagrelor MD and clopidogrel MD was more likely to occur in patients switched from ticagrelor to clopidogrel. At 6 month follow-up, poor compliance was observed in patients from clopidogrel to ticagrelor (64.8%) or treated only by ticagrelor (50.9%), but perfect compliance in patients from ticagrelor to clopidogrel (100%). After excluding the cases with incompliance, patients switching from ticagrelor to clopidogrel had a relatively lower bleeding risk in comparison with patients with constant ticagrelor treatment and those switching from clopidogrel to ticagrelor (29.5% vs. 50.0% vs. 46.6%, adjusted $P = 0.02$). In-hospital switching between ticagrelor and clopidogrel is frequent in patients undergoing PCI. In comparison with constant ticagrelor treatment, switching from clopidogrel to ticagrelor in ischaemic high-risk patients confers similar antiplatelet efficacy and safety, while switching from ticagrelor to clopidogrel in ischaemic low-risk patients relates to lower hazard for bleeding events.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor is the cornerstone for the prevention of

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thrombo-embolic events in acute coronary syndrome (ACS) patients, and those undergoing percutaneous coronary intervention (PCI).[1–4] In comparison with the traditional P2Y12 receptor inhibitor clopidogrel, the novel antiplatelet agent ticagrelor could achieve a more rapid and consistent antiplatelet effect, with significant reduction in mortality among patients with ACS, without increasing the overall incidence of major bleeding as shown in the results of PLATO (a study of Platelet inhibition and Patient outcomes) study.[5] Accordingly, ticagrelor has now been incorporated into the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for antiplatelet treatment in PCI and ACS patients.[6,7]

Although ticagrelor has been proved to be more effective than clopidogrel in preventing thrombotic cardiovascular events, it has been associated with higher risk of bleeding, more costly, and higher risk of dyspnoea, the off-target side effect.[8–10] Given the existence of different P2Y12 receptor inhibitors, optimizing antiplatelet strategy by switching between the available agents may commonly be a consideration for the patients.[11–14] Even though, the frequency, effectiveness, related factors, and safety of the switching between adenosine diphosphate glucose pyrophospheralase (ADP) receptor inhibitors in routine practice are largely unknown. Ticagrelor was approved for clinical application in China in November 2012, with the contemporarily approved P2Y12 inhibitors including only clopidogrel and ticagrelor. In General Hospital of Chinese People's Liberation Army (GH-PLA), one of the largest comprehensive hospitals in China with patients came from the whole country, we have a unique opportunity to characterize the practice of P2Y12 receptor inhibitors switching between ticagrelor and clopidogrel in China.

Therefore, in the present study, we sought to ascertain the patient features, incidence, timing, dose bridging, compliance, and clinical outcomes associated with the switching between ticagrelor and clopidogrel in Chinese patients undergoing PCI with drug-eluting stent (DES).

Materials and methods

Patients' recruitment

The present study was a single-centre, observational, and prospective study focusing on the evaluation of the switching between ticagrelor and clopidogrel in patients who underwent PCI for DES, in the Department of Cardiology, GH-PLA, in Beijing, China, from January 2013 to December 2014. Consented patients more than 18 years were consecutively recruited if they were treated with PCI for DES and administrated with ticagrelor on top of aspirin for DAPT during the hospitalization. To observe the antiplatelet treatment patterns in real-world clinical practice, patients who were enrolled in other research study that guided the selection of an approved or investigated P2Y12 receptor inhibitors were excluded. No treatment intervention was directed by the protocol in the study. Therefore, the physicians made all treatment determinations according to the practice guideline recommendations and local standards of care and practice.

Exclusion criteria were the patients did not receive a PCI for DES placement, those missing angiographic data related to the PCI, in-hospital death, documented contraindications to any of ticagrelor and clopidogrel, those who did not have any record of ticagrelor and clopidogrel, those discharged without the prescription of clopidogrel or ticagrelor, and those without follow-up information after discharge. All patients were informed of the purpose of the study and requested to sign an informed consent form for the anonymous management of their individual data. The study was performed in accordance with the Declaration of Helsinki. Institutional Review Boards in Chinese GH-PLA approved the protocol and participation of the study.

Collection of clinical data

Data on baseline demographics, clinical characteristics, cardiac-related procedures including coronary angiography, type and timing of re-vascularization therapy and use of medications, and major clinical events during the hospitalization were collected from the electronic medical record using a standardized set of data elements and definitions. An emphasis was given to the record about P2Y12 receptor antiplatelet agents, including clopidogrel and ticagrelor, prescribed during hospitalization and at discharge. In particular, the timing of P2Y12 inhibitors administration with respect to PCI, their dose and route of administration, and the switching between different P2Y12 inhibitors were evaluated. Among patients treated initially in-hospital with clopidogrel, switching was defined as discharge from the hospital with ticagrelor. Among patients treated initially in-hospital with ticagrelor, switching was defined as discharge from the hospital with clopidogrel. For patients who were switched between ADP receptor inhibitors more than once during hospitalization, the final P2Y12 receptor inhibitor switch was used in the analysis. All patients were grouped by the P2Y12 receptor inhibitor that was received prior to the final switching.[12] No patients switched more than two times in-hospital. Data were screened upon entry, and only those meeting predetermined criteria for completeness and accuracy were entered into the database for analysis.

Study endpoints and follow-up

All patients were followed up after discharge for 6 months. The primary cardiovascular ischaemic events were defined as major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The secondary cardiovascular ischaemic events included defined or probable stent thrombosis, coronary revascularization, and re-hospitalization for unstable angina. The antiplatelet efficacy analysis focused on the difference of a composite of cardiovascular ischaemic events including MACE and the secondary cardiovascular ischaemic events during follow-up after admission. The safety endpoint of the study was the composite of major and minor bleeding events, defined by the updated Thrombosis in Myocardial Infarction (TIMI) criteria.[15,16] In brief, major bleeding includes any intracranial bleeding, clinically overt signs of haemorrhage associated with a drop in haemoglobin of $\geq$5 g/dL, fatal bleeding that directly results in death within 7 days. Minor bleeding includes clinically overt bleeding (including imaging), resulting in haemoglobin drop of 3 to $<$5 g/dL, requiring medical attention, and any overt bleeding event that does not meet the criteria above. Bleeding events in the settings of coronary artery bypass grafting or other surgery procedures were not included in the endpoints. Major and minor TIMI bleeding events were also included as the additional safety endpoints, respectively. Side effect of ticagrelor-related dyspnoea was defined and justified according to the reported management procedures.[17] A clinical events committee, whose members were unaware of the switching strategies, adjudicated all outcomes. Clinical follow-up was performed through telephone interview at

the outpatient clinics. All collected data and information were input into the database by well-trained staff, with source documentation double-checked to ensure accurate data input.

Statistical analysis

Categorical variables were presented as frequencies (percentages) and compared using χ^2 test and Fisher's exact tests. Continuous variables were summarized as mean $\pm$ standard deviation (SD) and compared using the Student's *t*-test, Mann–Whitney *U* test, or one-way analysis of variance (ANOVA) test, as appropriate. The timing of the switch was defined by whether the second agent was given before the PCI procedure, during the PCI procedure, after the PCI procedure but prior to hospital discharge, or prescribed at the time of hospital discharge. Dose bridging for the switching between clopidogrel and ticagrelor was classified and calculated for the percentage of patients. All the variables, which were statistically significant at univariate analysis, were included in a multivariable logistic regression, to test for an independent association of the P2Y12 receptor inhibitors switching modes between ticagrelor and clopidogrel with the clinical endpoints. All statistical tests were performed with the use of SPSS Statistics 17.0 (SPSS, Inc., Chicago, IL). A two-sided *P*-value was used to test for significance threshold ($P < 0.05$).

Results

Patients' recruitment and clinical characteristics

From 7475 patients under the treatment of DAPT from January 2013 to December 2014 in the Department of Cardiology Chinese GH-PLA, 701 (9.4%) cases were treated by ticagrelor. In the ticagrelor-treated patients, 417 (59.5%) underwent PCI, among whom, 318 (76.3%) experienced the switching from clopidogrel to ticagrelor, 44 (10.6%) from ticagrelor to clopidogrel, and the remaining 55 (13.2%) initiated and continued on ticagrelor treatment without switching (*Figure 1*).

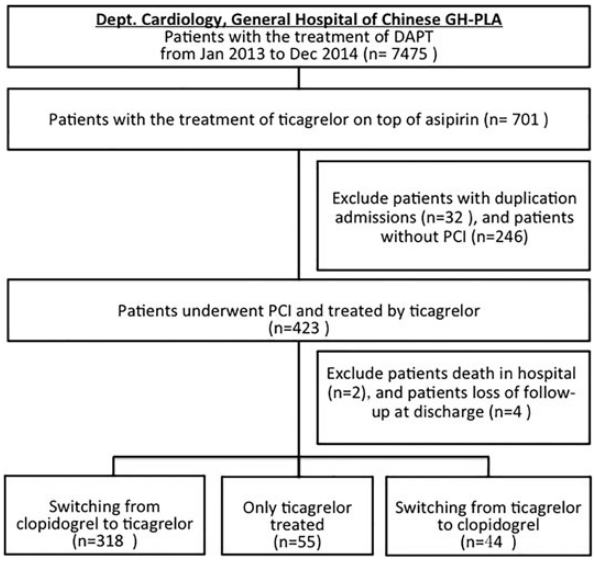

Figure 1 Patients' recruitment. DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; DES, drug- eluting stent.

The demographics and clinical characteristics of the included patients were documented in *Table 1*. Among the patients with the clopidogrel and ticagrelor switching and patients with constant ticagrelor treatment, no difference was found for the demographic factors (age, gender, and body mass index), cardiovascular risk factors (smoking status, hyperlipidaemia, hypertension, diabetes mellitus), and laboratory examinations. Significant difference could be found for the history of cerebrovascular disease ($P = 0.05$), final diagnosis of ACS (for STEMI $P = 0.007$, non-STEMI $P = 0.009$, and unstable angina $P = 0.04$), left main disease ($P = 0.007$), ostial lesion ($P = 0.01$), co-medication with warfarin ($P = 0.03$), carriage status of CYP2C19 loss of function (LOF) alleles ($P = 0.02$), and ticagrelor-related dyspnoea ($P = 0.004$).

Time for the switching between clopidogrel and ticagrelor in hospital

The switching from clopidogrel to ticagrelor occurred before ($n = 103$, 32.4%) or after ($n = 215$, 67.6%) PCI procedures but prior to hospital discharge. Switching from ticagrelor to clopidogrel occurred in 33 patients (75%) at the time of hospital discharge, 2 (4.5%) patients before the PCI procedure, and 9 (20.5%) patients after the PCI procedures but prior to hospital discharge, respectively (*Table 2*).

Dose bridging for switching between clopidogrel and ticagrelor in hospital

Dose bridging for the switching between clopidogrel and ticagrelor in the patients were classified into four types (*Table 3*). For comparison, patients switching from clopidogrel to ticagrelor were more likely to experience the dose bridging between clopidogrel loading dose (LD) and ticagrelor maintenance dose (MD) (58.2% vs. 4.5%, $P < 0.001$). In contrast, dose bridging between ticagrelor MD and clopidogrel MD was found more likely in patients switching from ticagrelor to clopidogrel (77.3 vs. 9.1%, $P < 0.001$).

Out-hospital compliance to the switching between ticagrelor and clopidogrel

During 6 month follow-ups, patients switched from ticagrelor to clopidogrel had a perfect compliance to the switching strategy (100%). However, for patients switched from clopidogrel to ticagrelor and those treated constantly by ticagrelor, out-hospital no compliance to ticagrelor could be found in 112 (35.2%) and 27 (49.1%) patients, respectively. All patients with no compliance to ticagrelor were administrated with clopidogrel instead for antiplatelet treatment. The reasons for the out-hospital no compliance to ticagrelor include active bleeding (11, 7.9%), ticagrelor-related dyspnoea (4, 2.9%), cost consideration (6, 4.3%), physician's determination (28, 20.1%), and drug unavailability in rural or undeveloped area (90, 64.7%).

Table 1 Demographic and clinical characteristics of the study population ($n = 417$)

Characteristics	From clopidogrel to ticagrelor ($n = 318$)	From ticagrelor to clopidogrel ($n = 44$)	Only ticagrelor treated ($n = 55$)	*P*-value
Median age, years	60.2 ± 10.1	62.1 ± 9.9	59.7 ± 10.0	0.4
Age ≥75 years, no./total no. (%)	31 (9.7)	2 (4.5)	3 (5.5)	0.3
Gender, female, *n* (%)	96 (30.2)	14 (31.8)	14 (25.5)	0.7
Body mass index, kg/m^2	26.0 ± 3.6	26.0 ± 3.2	26.0 ± 2.7	0.9
Cardiovascular risk factor, no. (%)				
Current smoker	102 (32.3)	13 (29.5)	20 (36.4)	0.8
Hyperlipidaemia	98 (30.8)	13 (29.5)	22 (40.0)	0.4
Hypertension	189 (59.4)	30 (68.2)	29 (52.7)	0.3
Diabetes mellitus	92 (28.9)	16 (36.4)	13 (23.6)	0.3
Medical history, no. (%)				
AMI	42 (13.2)	6 (13.6)	5 (13.2)	0.7
PCI	66 (20.8)	14 (31.8)	11 (20.0)	0.2
CABG	7 (2.2)	1 (2.3)	0	0.3
Chronic renal disease	11 (3.5)	1 (2.3)	1 (1.8)	0.7
Cerebrovascular disease	31 (9.7)	6 (13.6)	1 (1.8)	0.05
Peripheral arterial disease	0	1 (2.3)	0	0.1
Chronic lung disease	0	0	0	–
Final diagnosis of ACS, no. (%)				
STEMI	44 (13.8)	4 (9.1)	16 (29.1)	0.007
Non-STEMI	24 (7.5)	1 (2.3)	0	0.009
Unstable angina	215 (67.6)	33 (75.0)	29 (52.7)	0.04
Laboratory examinations				
LV ejection fraction, %	57.4 ± 8.4	58.5 ± 7.2	57.0 ± 6.3	0.7
Platelet count, $\times 10^5/\mu L$	226.6 ± 70.7	218.6 ± 67.7	232.5 ± 62.3	0.7
Serum creatinine, mL/min	77.6 ± 31.6	80.0 ± 20.4	77.0 ± 21.6	0.9
Total cholesterol, mmol/L	4.0 ± 1.1	4.2 ± 1.2	3.9 ± 1.1	0.6
TG ,mmol/L	1.7 ± 1.1	1.9 ± 1.5	1.6 ± 0.8	0.4
HDL, mmol/L	1.0 ± 0.3	1.0 ± 0.2	1.1 ± 0.3	0.7
LDL, mmol/L	2.4 ± 0.8	2.6 ± 1.0	2.4 ± 0.9	0.7
UA, mmol/L	331.8 ± 101.1	362.7 ± 90.8	333.3 ± 94.3	0.2
PCI treatment in hospital, *n* (%)				
Left main disease	65 (20.4)	1 (2.3)	7 (12.7)	0.007
Three-vessel disease	113 (35.5)	11 (25.0)	15 (27.3)	0.2
Stent length >20 mm	198 (62.3)	25 (56.8)	34 (61.8)	0.8
Chronic total occlusions	69 (21.7)	6 (13.6)	16 (29.1)	0.2
Culprit in graft	3 (0.9)	0	0	–
Multi-vessel disease	212 (66.7)	23 (52.3)	34 (61.8)	0.2
Culprit proximal LAD	49 (15.4)	7 (15.9)	9 (16.4)	0.9
Intracoronary thrombus	6 (1.9)	0	3 (5.5)	0.1
Stent thrombosis	3 (0.9)	0	1 (1.8)	0.7
Bifurcation culprit lesion	5 (1.6)	2 (4.5)	2 (3.6)	0.3
Ostial lesion	116 (36.5)	9 (20.5)	11 (20.0)	0.01
Multi-vessel PCI	158 (49.7)	14 (31.8)	23 (41.8)	0.06
No. of PCI procedures at least two during hospitalization	33 (10.4)	2 (4.5)	5 (9.1)	0.5
Antithrombotic treatment in hospital, no. (%)				
Aspirin, *n* (%)	318 (100)	44 (100)	55 (100)	1.0
Glycoprotein IIb/IIIa inhibitor, *n* (%)	153 (48.1)	23 (52.3)	22 (40.0)	0.4
Heparin, *n* (%)	120 (37.7)	10 (22.7)	17 (30.9)	0.1
Warfarin, *n* (%)	2 (0.6)	2 (4.5)	0	0.03
Other medication administered in hospital or at discharge, no. (%)				
β-Blocker	275 (86.5)	35 (79.5)	48 (87.3	0.4
ACE inhibitor	96 (30.2)	11 (25.0)	18 (32.7)	0.7
Angiotensin-II-receptor blocker	35 (11.0)	6 (13.6)	4 (7.3)	0.6
Calcium-channel blocker	126 (39.6)	25 (56.8)	22 (40.0)	0.09
Statins	314 (98.7)	43 (97.7)	55 (100)	0.4
Proton-pump inhibitor	236 (74.2)	30 (68.2)	35 (63.6)	0.2
Morphine use	13 (4.1)	3 (4.8)	1 (1.8)	0.4
Organic nitrate	287 (90.3)	36 (81.8)	45 (12.2)	0.08
CYP2C19 LOF alleles carriers[a]	59 in 86 (68.6)	3 in 9 (33.3)	3 in 9 (33.3)	0.02
Bleeding events	28 (8.8)	7 (15.9)	3 (5.5)	0.2
Ticagrelor-related dyspnoea	6 (1.9)	6 (13.6)	1 (1.8)	0.004

Data are presented as percentages or mean ± SD. AMI, acute myocardial infarction; ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; HDL, high density lipoprotein; LDL, low density lipoprotein; LOF, loss of function; LAD, left anterior descending branch; LV, left ventricular; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction; TG, triglycerides; UA, uric acid.

[a]A total of 86 cases in patients switching from clopidogrel to ticagrelor and 9 in patients switching from ticagrelor to clopidogrel were genotyped for CYP2C19 LOF alleles.

Table 2 Time for switching between clopidogrel and ticagrelor

Time for switching between clopidogrel and ticagrelor	Switching from clopidogrel to ticagrelor ($n = 318$)	Switching from ticagrelor to clopidogrel ($n = 44$)	*P*-value
Before the PCI procedure, *n* (%)	103 (32.4)	2 (4.5)	0.002
After the PCI procedure but prior to hospital discharge, *n* (%)	215 (67.6)	9 (20.5)	<0.001
At the time of hospital discharge, *n* (%)	0	33 (75.0)	–

Table 3 Dose bridging for switching between clopidogrel and ticagrelor in PCI patients in hospital

Dose-bridging type[a]	From clopidogrel to ticagrelor ($n = 318$)	From ticagrelor to clopidogrel ($n = 44$)	*P*-value
Clopidogrel LD + ticagrelor LD	17 (5.3%)	0	–
Clopidogrel MD + ticagrelor LD	87 (27.4%)	8 (18.2%)	0.04
Clopidogrel LD + ticagrelor MD	185 (58.2%)	2 (4.5%)	<0.001
Clopidogrel MD + ticagrelor MD	29 (9.1%)	34 (77.3%)	<0.001

LD, loading dose; MD, maintenance dose.
[a]Only the bridging doses of clopidogrel and ticagrelor, not the orders of the drugs for the switching.

Clinical outcomes comparison between switching from clopidogrel to ticagrelor and constant ticagrelor treatment after a follow-up of 6 months

After excluding the cases with no compliance, we compared the efficacy and safety outcomes between patients switching from clopidogrel to ticagrelor ($n = 206$), and patients constantly treated by ticagrelor ($n = 28$). The primary ischaemic events were found in no patients. After adjusted for the potential factors related to the switching, in comparison with patients constantly treated by ticagrelor, no significant difference was found for the risk of composited ischaemic outcomes (5.3 vs. 3.6%, adjusted $P = 0.7$). For the safety outcomes, in comparison with patients constantly treated by ticagrelor, no significant difference was found for the risk of any bleeding events (46.6 vs. 50.0% for TIMI-defined composited bleeding events, adjusted $P = 0.6$) (*Table 4*).

Clinical outcomes comparison between switching from ticagrelor to clopidogrel and constant ticagrelor treatment after a follow-up of 6 months

After excluding the cases with no compliance, we compared the efficacy and safety outcomes among patients switching from ticagrelor to clopidogrel ($n = 44$) and patients constantly treated by ticagrelor ($n = 28$). The primary ischaemic events were found in no patients. After adjusted for the potential factors related to the switching, in comparison with patients constantly treated by ticagrelor, no significant difference was found for the risk of composited ischaemic outcomes (6.8 vs. 3.6%, adjusted $P = 0.6$). For the safety outcomes, in comparison with patients constantly treated by ticagrelor, patients with the switching from ticagrelor to clopidogrel associated with a lower risk for TIMI-defined composited bleeding events (29.5 vs. 50.0%, adjusted $P = 0.02$), as well as TIMI minor bleeding events (27.3 vs. 50.0%, adjusted $P = 0.01$) (*Table 4*).

Discussion

The benefits of the novel potent agent ticagrelor over clopidogrel have been confirmed in the PLATO study, particularly for the reduction of all-cause mortalities.[5] Therefore, the practice guidelines in the USA and Europe currently recommend the antiplatelet treatment with ticagrelor in ACS and PCI patients.[6,7] By taking a direct comparison among patients with the switching between ticagrelor and clopidogrel and with only ticagrelor treatment, the present study revealed several novel and important observations regarding the real-world practice of in-hospital application of P2Y12 receptor inhibitors. In ticagrelor-treated patients undergoing PCI, the switching between ticagrelor and clopidogrel was frequent with various dose-bridging types. Preventing thrombosis in high-risk patients and avoiding complications were the common factors for the switching. During 6 month follow-up, poor compliance to ticagrelor could be found in patients switching from clopidogrel to ticagrelor and patients treated only by ticagrelor. Lower bleeding risk seems to relate to the switching from ticagrelor to clopidogrel. Larger number of patients should be included to confirm the potent antiplatelet effects of ticagrelor in comparison with the switching from ticagrelor to clopidogrel.

In the present study, we found that ~76% of ticagrelor-treated patients underwent the switching from clopidogrel to ticagrelor, which was much higher than the rate (46%) reported in PLATO study.[5] As we know, the clinical application of ticagrelor in China was approved in November 2012, which was no more than 1 year before the recruitment of patients in present study. Therefore, due to the relative shorter time for clinical physicians to realize the role of ticagrelor, most of the patients with planned PCI treatment

Table 4 Outcomes for patients switched between ticagrelor and clopidogrel during 6 month follow-up intervals in comparison with patients with continuous ticagrelor treatment

Outcomes	Switching from clopidogrel to ticagrelor ($n = 206$)	Switching from ticagrelor to clopidogrel ($n = 44$)	Only ticagrelor treated ($n = 28$)	Adjusted *P*-value	
				P_1	P_2
Efficacy outcomes					
Primary ischaemic events	0	0	0	–	–
Secondary ischaemic events	11 (5.3%)	3 (6.8%)	1 (3.6%)	0.7	0.6
Composited ischaemic events	11 (5.3%)	3 (6.8%)	1 (3.6%)	0.7	0.6
Safety outcomes					
TIMI major bleeding events	0	1 (2.2%)	0	–	–
TIMI minor bleeding events	96 (46.6%)	12 (27.3%)	14 (50.0%)	0.6	0.01
Composited TIMI-defined bleeding events	96 (46.6%)	13 (29.5%)	14 (50.0%)	0.6	0.02

The primary cardiovascular ischaemic events defined as MACE including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The secondary cardiovascular ischaemic events included defined or probable stent thrombosis, coronary revascularization, and re-hospitalization for unstable angina. The antiplatelet efficacy analysis focused on the difference of a composite of cardiovascular ischaemic events including MACE and cardiovascular ischaemic events during follow-up after admission. A composite of bleeding events are defined by the updated TIMI criteria.[15,16] Adjusted *P*-values are from multivariable logistic regression analysis with the adjustment of the potential factors related to the switching between clopidogrel and ticagrelor, including age, gender, diagnosis of ACS, left main disease, ostial lesion, multi-vessel PCI, number of PCI procedures, co-administration of heparin, warfarin, calcium-channel blocker, CYP2C19 LOF carrier status, and ticagrelor-related dyspnoea. P_1 indicates the comparison between the patients switching from clopidogrel to ticagrelor vs. the patients under only ticagrelor treatment. P_2 indicates the comparison between the patients switching from ticagrelor to clopidogrel vs. the patients under only ticagrelor treatment.

tended to be administrated initially with clopidogrel. The rate of patients with the in-hospital switching from the novel P2Y12 inhibitor to clopidogrel (10.6%) in present study is similar to the previous studies in PCI-treated AMI patients (11.5 and 13.6%, respectively).[12,13]

The potential reasons for the switching from clopidogrel to ticagrelor have been summarized as clopidogrel allergy/hypersensitivity, clinical failure/stent thrombosis, and high recurrent thrombotic risk (STEMI, diabetes) in previous studies.[14] As for the real-world clinical practice in the present study, we found the main reasons for the switching from clopidogrel to ticagrelor attributed to the complex coronary lesions and the existence of coronary or stent thrombosis. These factors related to the switching could reasonably explain why the time for the switching from clopidogrel to the more potential agent ticagrelor was near the time for the PCI procedure. The potential clinical reasons for the switching from ticagrelor to clopidogrel have been summarized as unrecognized prior intracranial haemorrhage, off-target adverse effects (dyspnoea, bradycardia), active bleeding or increased bleeding risk (concomitant anticoagulant use), and cost considerations.[14] For the present study, patients treated by oral anticoagulant or presented with ticagrelor-related dyspnoea were more prone to experience the switching from ticagrelor to clopidogrel in hospital at discharge.

Given the relatively lower rate of in-hospital ischaemic and bleeding events in present cohort of patients, the switching from ticagrelor to clopidogrel at discharge might largely based on physicians prediction of the possible risk of events and side effects, as well as the cost consideration of the novel agent for the patients. During 6 month follow-up intervals, we found poor compliance to ticagrelor in at least one-third of the patients with the switching from clopidogrel to ticagrelor and nearly half of the patients with constant ticagrelor treatment. Cost considerations, bleeding, and side effects as well as the physician's determination were the well-known related factors for the out-hospital switching from ticagrelor to clopidogrel. However, one of the special main reasons for the out-hospital poor compliance to ticagrelor in the present study was drug unavailable for the patients from the rural countryside or lower economic areas in China.

Dose bridging is inevitable for the switching between ticagrelor and clopidogrel. Despite the compelling evidence that ticagrelor provide faster and higher antiplatelet effect compared with clopidogrel,[5,18] clopidogrel 600 mg remains the most common drug administered before hospital admission or in emergency cases in China. Switching from clopidogrel to either a ticagrelor MD or LD was associated with a further reduction in platelet reactivity.[19] However, little evidence is available regarding the optimal method for switching and reloading with these drugs at the early phase of PCI. In the present study, more than half of the cases switching from clopidogrel to ticagrelor underwent the dose bridging from clopidogrel LD to ticagrelor MD. It indicated that most of the switching from clopidogrel to ticagrelor might occur immediately after the PCI procedure, for the complex coronary lesions or the detection of thrombosis. Previous study also found that no difference for platelet aggregation between ACS patients switching from clopidogrel MD to ticagrelor MD or LD.[20] Even though, for the sake of bleeding risk, relatively less patients switched to ticagrelor with the bridging dose of ticagrelor LD, especially when clopidogrel LD was administrated in advance. Dose bridging for patients switching from ticagrelor to clopidogrel is mostly concerning with the bridging between the MD of both ticagrelor and clopidogrel, occurring frequently at discharge. It remains uncertain about the influence of diverse dose bridging between clopidogrel and ticagrelor

at different time points on the clinical outcomes in PCI-treated patients.

After a follow-up of 6 months, we evaluated the clinical outcomes related to the switching between clopidogrel and ticagrelor and only ticagrelor treatment. The results for the outcomes analysis were partly in co-ordinated with one previous study, in which ADP receptor inhibitors switching between clopidogrel and prasugrel does not appear to be significantly associated with increased hazard of major adverse cardiovascular events (MACE) or bleeding.[13] As a matter of fact, compared with the patients under constant ticagrelor treatment, the switching between clopidogrel and ticagrelor had no different effect on ischaemic events, but patients switching from ticagrelor to clopidogrel had a significant lower risk of bleeding events. Due to the shorter follow-up intervals and relatively lower prevalence of the composite ischaemic events, it is not power enough for the present study to reveal the different antiplatelet effect exerted by the switching between P2Y12 receptor inhibitors.

It has been reported in a case study that dyspnoea contributed to the ticagrelor discontinuation and sub-acute stent thrombosis occurred during the early phase of switching therapy.[21] In our present study, six cases presented with the symptom of ticagrelor-related dyspnoea in hospital, and all of them experienced the switching from ticagrelor to clopidogrel. During the follow-up of 6 months, we did not find any ischaemic adverse events for these patients. The consequence of the switching with longer follow-ups is still waiting to be elucidated.

Several limitations should be mentioned for the present study. Firstly, the comparisons of the observational baseline characteristics might be biased due to unmeasured covariates; therefore, the factors related to the P2Y12 receptor inhibitors switching in the present study should be considered investigative and hypothetical. Secondly, the immediate effect of the related dose bridging at the time of the switching between clopidogrel and ticagrelor, as well as longer-term outcomes, could not be ascertained in the study. Thirdly, the small sample size potentially limits the power to detect differences in clinical outcomes. Fourthly, as mentioned above, the patients in our hospital came from vary sites across China. Due to the various government drug coverage plans, patients from underdeveloped province/area might have to discontinue ticagrelor treatment after discharge for the unavailability of the novel agent. Finally, since the period of study is from July 2013 to December 2014, the current rates for switching between ticagrelor and clopidogrel in 2015 may be different with more availability of ticagrelor.

Conclusions

In ticagrelor-treated patients undergoing PCI, in-hospital switching between clopidogrel and ticagrelor was frequent with various dose-bridging types. Preventing thrombosis after PCI in complex coronary lesions and avoiding bleeding as well as side effects are the most apparent factors related to the switching of P2Y12 receptor inhibitors. In comparison with constant ticagrelor treatment, switching from clopidogrel to ticagrelor in ischaemic high-risk patients confers similar antiplatelet efficacy and safety, while switching from ticagrelor to clopidogrel in ischaemic low-risk patients relates to similar antiplatelet efficacy but lower hazard for bleeding events. The consequence of poor compliance to ticagrelor out-hospital warrants further investigation.

Authors' contributions

X.W. contributed to the clinical data collection, data processing, and follow-up visiting. S.X. participated in the patients' recruitment and follow-up visiting. J.L. and J.J. contributed to the statistical analysis and data analysis. T.Y. and Y.C. contributed to the whole study design and manuscript drafting and editing. All authors have approved the final article.

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