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Original Research Article

Dual and triple antithrombotic pharmacotherapy in patients with coronary heart disease complicated with atrial fibrillation after percutaneous coronary intervention

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Abstract

Purpose: *To compare the influence of triple antithrombotic therapy (warfarin + aspirin + clopidogrel) and dual antithrombotic therapy (aspirin + clopidogrel) on the risk of major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with atrial fibrillation (AF) after coronary stent implantation.*
Methods: *A total of 210 patients with coronary heart disease and complicated with AF, who underwent percutaneous coronary intervention (PCI) in The Third Affiliated Hospital of Chongqing Medical University, were enrolled. They were divided into a triple antithrombotic therapy group (TT group) and a dual antithrombotic therapy group (DT group). The risks of hemorrhage and MACCEs were evaluated via follow-up and multivariate regression analysis.*
Results: *Based on the classification criteria for bleeding in Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO), there were 6 and 0 patients with significant hemorrhage in TT and DT groups, respectively, during the one year of follow-up ($p = 0.013$). The total number of MACCEs of 52 and 61 for both groups was not significantly different ($p = 0.213$). Moreover, the results of multivariate Cox regression analysis revealed that the histories of ischemia and stroke ($p = 0.023$), heart failure ($p = 0.007$), and high CHA2DS2-VASc score ($p = 0.004$) were the risk factors for MACCEs.*
Conclusion: *Compared with dual antithrombotic therapy, triple antithrombotic therapy increases the risk of major hemorrhage in AF patients after PCI, but does not noticeably reduce the incidence of MACCEs during one year of follow-up.*

Keywords: *Coronary heart disease, Atrial fibrillation, Percutaneous coronary intervention, Antithrombotic pharmacotherapy*

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INTRODUCTION

Antithrombotic therapy is the basic treatment for coronary heart disease, and it plays an important role in percutaneous coronary intervention (PCI), the effectiveness and safety of which have been confirmed in many studies [1]. Currently, dual antiplatelet therapy with aspirin and clopidogrel is

the gold standard for the prevention of thrombotic events and poor prognosis [2]. About 5 % of patients with coronary heart disease have persistent or permanent atrial fibrillation (AF) which distinctly increases the risk of thrombosis, leading to a variety of serious complications, including stroke [3,4]. For patients with non-valvular AF at moderate or high risk of thrombosis, the more effective triple antithrombotic therapy (vitamin K antagonist + aspirin + clopidogrel) is needed. According to the 2010/2012 European Society of Cardiology (ESC) guidelines for the management of AF, AF patients need to take oral anticoagulants for antithrombotic therapy, in order to reduce the risk of stroke [5,6].

It has been reported that dual antiplatelet therapy combined with anticoagulants may increase the risk of bleeding in AF patients [7]. The most effective way to optimize the antithrombotic therapy for patients with AF after PCI is therefore an important clinical issue. The present study aims to investigate the differences in bleeding and major adverse cardiovascular events (MACEs) and between triple antithrombotic therapy and dual antithrombotic therapy in AF patients after PCI, so as to provide more clinical evidence for the antithrombotic treatment of AF patients.

METHODS

Subjects

The clinical data of 210 patients with coronary heart disease who underwent PCI due to AF in The Third Affiliated Hospital of Chongqing Medical University were collected. According to the $CHADS_2$ score, some of the patients were treated with warfarin anticoagulation before the operation, and the international standardized ratio (INR) was controlled within the standard INR range (2.0 - 3.0).

Inclusion criteria

The electrocardiographic diagnostic criteria for AF were as follows: The absence of P waves which were replaced by irregular AF waves absolute irregular RR intervals in the presence of atrioventricular conduction), including paroxysmal AF (AF that could be terminated by itself within 7 days after the attack or by intervention, with unfixed attack frequency), persistent AF (with duration longer than 7 days) and permanent AF (with duration longer than 12 months); and AF that occurred at least 1 year before coronary stent implantation.

Exclusion criteria

The exclusion criteria were as follows: patients with cardiogenic shock or severe hypovolemia, those with severe respiratory diseases, those with severe liver or renal insufficiency, those with active bleeding or coagulation dysfunction, those with major surgical operation within 30 days, or those with malignant tumor or immunodeficiency.

Grouping and ethical approval

This study included 137 males and 73 females, aged 40 - 77 years, with an average age of (58.23 ± 9.44) years. According to the types of oral antithrombotic drugs, the patients were divided into a triple antithrombotic therapy group (TT group, n = 105) and a dual antithrombotic therapy group (DT group, n = 105). All patients enrolled were informed and signed the informed consent in accordance with the *Declaration of Helsinki* [8]. This study was reviewed and approved by the Ethics Committee of The Third Affiliated Hospital of Chongqing Medical University, Jeer Hospital (approval no. CN-CQ-19-0016).

Therapies

Patients in both groups received different antithrombotic therapies within 6 - 12 h after coronary stent implantation. The triple antithrombotic therapy included aspirin (100 mg/day), clopidogrel (75 mg/day), and warfarin (starting with 2.5 mg to maintain INR 2.0-3.0). After 6 months of treatment, the therapy was replaced with dual antithrombotic therapy (warfarin + aspirin or clopidogrel) according to the 2010/2012 European Society of Cardiology (ESC) guidelines for the management of AF and then changed to warfarin alone if the disease condition was stable after 12 months of treatment. The dual antithrombotic therapy consisted of aspirin (100 mg/day) and clopidogrel (75 mg/day) for 12 months.

Evaluation of parameters/indices

HAS-BLED and CHA_2DS_2-VASc scores

The HAS-BLED and CHA_2DS_2-VASc scores of all patients were analyzed. The higher the scores, the higher the risks of thrombosis and bleeding in AF patients. The correlations of AF with bleeding and MACEs were also analyzed.

Incidence of bleeding

All patients were followed up for 360 days. The incidence of bleeding in each group was

recorded. Bleeding was evaluated according to the bleeding classification of Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO). The main bleeding sites were the oral cavity, digestive tract, respiratory system, urinary system, skin, vagina, and within the head [9,10]. The TIMI bleeding classification criteria included: *Major hemorrhage:* intracranial hemorrhage or clinically visible hemorrhage (including those observed in imaging) with hemoglobin concentration decline by ≥ 5 g/dL. *Minor hemorrhage:* clinically visible bleeding with hemoglobin concentration decline by 3 - 5 g/dL. *Slight hemorrhage:* clinically visible bleeding with hemoglobin concentration declines by < 3 g/dL. The GUSTO bleeding classification criteria were as follows: *Severe or life-threatening hemorrhage:* intracranial hemorrhage or bleeding that resulted in substantial hemodynamic compromise requiring intervention. *Moderate hemorrhage:* bleeding that required blood transfusion but did not result in hemodynamic compromise. *Slight hemorrhage:* bleeding that did not meet the criteria for severe or moderate bleeding.

Adverse cardiovascular and cerebrovascular events

Adverse cardiovascular and cerebrovascular events were recorded during follow-up, including stent thrombosis, recurrent myocardial infarction, revascularization, ischemic stroke, transient ischemic attack (TIA), and death.

Statistical analysis

The SPSS software (version 26.0) software was utilized for statistical analysis. Measurement data are expressed as mean ± standard deviation (SD), and a *t*-test was performed for intergroup comparison. Enumeration data are expressed in percentage (%) and tested with the χ^2 test or Fisher's exact test. A Multivariate Cox proportional-hazards regression model was used to analyze the factors influencing the MACCEs during one year of follow-up.

RESULTS

There were no statistically significant differences in baseline data between the two groups ($p > 0.05$), as shown in Table 1.

Patients' status during and after PCI

During PCI, the results from coronary angiography revealed that the left anterior descending coronary artery (45.7 %, 48.6 %) and the right coronary artery (32.4 %, 24.8 %) were involved in most of the patients in the TT and DT groups. There were 8 and 10 patients with their left main coronary artery involved, and 15 and 18 patients with their left circumflex branch involved in the TT and DT groups, respectively. There were no significant differences in the distribution of involved vessels between the two groups ($p = 0.648$). During PCI, 14 and 9 patients had femoral artery punctures, and 91 and 96 patients underwent radial artery punctures in the TT group and DT group, respectively, with no statistically significant differences between the two groups ($p = 0.269$), Besides, during PCI, 5 and 7 patients had the intravascular ultrasound, and 2 and 1 patients received intra-aortic balloon pump in the TT and DT groups,

Table 1: Demographics and general clinical data of the studied patients (n = 105)

Parameter	TT group	DT group	*P*-value
Gender (male/female)	71/34	66/39	0.562
Age (years)	57.67±9.39	59.35±9.62	0.202
LVEF (%)	57.12±11.53	55.85±12.41	0.443
Triglycerides (mmol/L)	1.68±0.47	1.62±0.40	0.320
Low-Density Lipoprotein (mmol/L)	2.74±0.76	2.59±0.58	0.109
Smoking history	25 (23.8%)	21 (20.0%)	0.617
Previous history and risk factors			
Hemorrhage history	8 (7.6%)	6 (5.7%)	0.783
Ischemic /Stroke history	12 (11.4%)	9 (8.6%)	0.646
Hypertension	63 (60.0%)	58 (55.2%)	0.577
Diabetes Mellitus	19 (18.1%)	24 (22.9%)	0.494
Hyperlipemia	37 (35.1%)	33 (31.4%)	0.661
Heart failure	16 (15.2%)	13 (12.4%)	0.690
Coronary heart disease family history	18 (17.1%)	22 (21.0%)	0.598
CHA_2DS_2-VASc score (points)	3.8±2.4	3.4±2.5	0.141
HAS-BLED score (points)	3.5±1.8	3.2±2.2	0.281

Notes: TT: Aspirin + Clopidogrel + Warfarin; DT: Aspirin + Clopidogrel; LVEF: Body Mass Index; LVEF: Left ventricular ejection fraction

respectively, with no statistically significant differences between the two groups (p = 0.552, p = 0.561). The peak value of CK-MB in the TT and DT groups at 24 h after operation were 138.75 ± 20.79 and 143.69 ± 24.64 mmol/L, respectively, with no statistically significant difference between the two groups (p = 0.118) (Table 2).

Bleeding risk during the follow-up period

Based on the TIMI classification criteria for bleeding, major bleeding occurred in 6 and 0 patients in TT and DT groups, respectively during the 1 year of follow-up (p = 0.013). In addition, there were 31 and 24 cases of minor bleeding, and 51 and 40 cases of slight bleeding in the TT and DT groups, respectively, (p = 0.272, p = 0.126).

Based on the GUSTO classification criteria for bleeding, major bleeding occurred in 6 and 0 patients in TT and DT groups, respectively, during the 1 year of follow-up. There was a statistically significant difference in the incidence of severe bleeding between the two groups (p = 0.013). Moderate bleeding occurred in 34 and 25 patients, while mild bleeding occurred in 47 and 37 patients in TT and DT groups (p = 0.167, p = 0.159) (Table 3).

Effectiveness in both groups during the follow-up period

One year after follow-up, it was found that one patient developed stent thrombosis in the DT group, and the difference in the incidence of stent thrombosis was not statistically significant between the two groups (p = 0.316). Besides, 18 and 22 patients had a recurrent myocardial infarction in TT and DT groups, respectively, with no statistically significant difference in the incidence of recurrent myocardial infarction between the two groups (p = 0.482). Repeat revascularization was performed in 19 and 16 patients in the TT and DT groups, respectively, and there was no statistically significant difference in the repeat coronary revascularization rate between the two groups (p = 0.579). In addition, ischemic stroke occurred in 10 and 13 patients, and TIA occurred in 4 and 6 patients in the TT and DT groups, respectively. There were no statistically significant differences in the incidence of ischemic stroke and TIA between the two groups (p = 0.507, p = 0.517). Moreover, 1 and 3 patients died in the TT and DT groups, respectively, and there was no statistically significant difference in the mortality rate between the two groups (p = 0.313). A total of 113 patients had cardiovascular and cerebrovascular events, with 61 in the DT group and 52 in the TT group.

Table 2: Comparison of levels of operative indices of patients (n = 105, %)

Parameter	TT group	DT group	*P*-value
Coronary artery lesion			0.648
Left main coronary artery	8 (7.6)	10 (9.5)	
Left anterior descending coronary artery	48 (45.7)	51 (48.6)	
Left circumflex artery	15 (14.3)	18 (17.1)	
Right coronary artery	34 (32.4)	26 (24.8)	
Site of puncture			0.269
Femoral artery	14 (13.3)	9 (8.6)	
Radial artery	91 (86.7)	96 (91.4)	
Use of intravascular ultrasound	5 (4.8)	7 (6.7)	0.552
Use of intra-aortic balloon pump	2 (1.9)	1 (1.0)	0.561
24 h postoperative CK-MB peak value (mmol/L)	138.75±20.79	143.69±24.64	0.118

TT: Aspirin + Clopidogrel + Warfarin; DT: Aspirin + Clopidogrel; CK-MB: Creatine kinase-MB

Table 3: Comparison of 1-year hemorrhage events on patients between the two studied groups (n = 105, %)

Parameter	TT group	DT group	*P*-value
TIMI hemorrhage assessment			
Major hemorrhage	6 (5.7)	0 (0)	0.013
Minor hemorrhage	31 (29.5)	24 (22.9)	0.272
Slight hemorrhage	51 (48.6)	40 (38.1)	0.126
GUSTO hemorrhage assessment			
Severe hemorrhage	6 (5.7)	0 (0)	0.013
Moderate hemorrhage	34 (32.4)	25 (23.8)	0.167
Slight hemorrhage	47 (44.8)	37 (35.2)	0.159

TT: Aspirin + Clopidogrel + Warfarin; DT: Aspirin + Clopidogrel; CK-MB: Creatine kinase-MB; TIMI: Thrombolysis in myocardial infarction; GUSTO: Global Use of Strategies to Open Occluded Coronary Arteries

Table 4: Comparison of 1-year levels of therapeutic effect indices of patients between the two studied groups (n = 105, %)

Parameter	TT group	DT group	*P*-value
Stent thrombosis	0 (0)	1 (1.0)	0.316
Recurrence of myocardial infarction	18 (17.1)	22 (21.0)	0.482
Target lesion revascularization	19 (18.1)	16 (15.2)	0.579
Ischemic stroke	10 (9.5)	13 (12.4)	0.507
Transient Ischemic Attack	4 (3.8)	6 (5.7)	0.517
Death	1 (1.0)	3 (2.9)	0.313
Total MACCEs	52 (49.5)	61 (58.1)	0.213

TT: Aspirin+ Clopidogrel+ Warfarin; DT: Aspirin + Clopidogrel; CK-MB: Creatine kinase-MB; MACCEs: Major adverse cardiovascular and cerebrovascular events

Table 5: Multivariable Cox Regression analysis of MACCE for atrial fibrillation patients who received the percutaneous coronary intervention

Parameter	HR	95%CI	*P*-value
LVEF<40%	1.534	0.748-2.474	0.431
Smoking history	1.997	0.852-2.960	0.320
Hemorrhage history	2.021	0.968-2.893	0.535
History of ischemic and Stroke	3.173	1.215-7.384	0.023
Hypertension	2.105	0.812-2.792	0.204
Diabetes mellitus	1.804	0.709-2.107	0.259
Hyperlipemia	2.274	0.838-2.941	0.306
Heart failure	3.781	1.189-9.143	0.007
family history of coronary heart disease	1.674	0.759-2.548	0.488
High CHA_2DS_2-VASc score	4.662	1.339-11.905	0.004
High HAS-BLED score	2.117	0.985-2.514	0.365

MACCE: Major adverse cardiovascular and cerebrovascular events; LVEF: Left ventricular ejection fraction; HR: Hazard ratio; CI: Confidence interval

There was no statistically significant difference in the incidence of cardiovascular and cerebrovascular events between the two groups (p = 0.213, Table 4).

Results of multivariate analysis of MACCEs during the follow-up period

Factors such as LVEF < 40 %, histories of smoking, bleeding, ischemic stroke, hypertension, diabetes and hyperlipidemia, heart failure, family history of coronary heart disease, and high CHA_2DS_2-VASc and HAS-BLED scores were included in the multivariate Cox regression analysis. The results revealed that histories of ischemia and stroke {hazard ratio (HR): 3.173, 95 % confidence interval (CI): 1.215-7.384, p = 0.023}; heart failure (HR: 3.781, 95 % CI: 1.189-9.143, p = 0.007), and high CHA_2DS_2-VASc score (HR: 2.117, 95 % CI: 0.985-2.514, p = 0.004) were the risk factors for MACEs (Table 5).

DISCUSSION

Patients with AF are often complicated by coronary heart disease. In clinical practice, about one-third of AF patients are complicated with coronary heart disease, and some of them usually need PCI [11]. The AF significantly increases the incidence of stroke and thrombotic events. Moreover, non-standard oral antithrombotic therapy increases the annual incidence of stroke or death in patients with non-valvular AF by at least 5 - 10 times [12]. When AF patients with coronary heart disease need PCI or stent implantation, it could easily lead to a high risk of thrombus burdens such as foreign body inflammatory response, local coagulation and platelet activation, and chronic inflammatory response stimulation. According to the 2010/2012 ESC guidelines for AF management, AF patients should receive short-term triple antithrombotic therapy, so as to reduce the incidence of thrombosis and stroke [5,6].

However, in recent years, it has been suggested in many clinical antithrombotic studies that triple antithrombotic therapy may increase the incidence of bleeding and hemorrhagic stroke in AF patients [13-16]. The results of the ACTION registration study [17] revealed that the triple antithrombotic therapy involving warfarin, aspirin, and clopidogrel will significantly increase the risk of massive hemorrhage during the 2 years of follow-up. According to the clinical registration study of ICAS, in contrast with triple antithrombotic therapy, dual antithrombotic with aspirin and clopidogrel significantly reduces the risk of massive hemorrhage [18]. However, some other studies did not find a remarkable difference in the risk of massive hemorrhage between triple antithrombotic therapy and dual antithrombotic

therapy. The results of the CREDO-Kyoto revealed that there were no significant differences in the risk of massive hemorrhage between DT and TT groups [19]. The study of Ho *et al*. [20] also demonstrated that there was no significant difference in the risk of massive hemorrhage between triple antithrombotic therapy and dual antithrombotic therapy. The results of this study showed that the triple antithrombotic therapy consisting of warfarin, aspirin, and clopidogrel significantly increased the risk of massive hemorrhage, while there were no significant differences in the risks of minor bleeding and slight bleeding between the two therapies.

Some studies have found that there is no distinct difference in the incidence of ischemic events between dual antithrombotic therapy and triple antithrombotic therapy. In the WOEST clinical study, it was found that after 1 year of follow-up, there was no significant difference in the incidence of ischemic events, including stent thrombosis, cerebral ischemic stroke and myocardial infarction between the DT and TT groups [21], in line with the results of this study. Although previous studies have revealed that there is no statistically significant difference in the effect of dual antithrombotic therapy and triple antithrombotic therapy on the incidence of adverse cardiovascular and cerebrovascular events, the dual antithrombotic therapy of clopidogrel combined with aspirin increases the risk of ischemic stroke caused by AF. According to the REAL clinical registration study, the dual antithrombotic therapy of clopidogrel combined with aspirin can significantly increase the incidence of ischemic stroke [22]. Meanwhile, a meta-analysis of the results of previous studies demonstrated that the incidence of ischemic stroke in the TT group is significantly lower than that in the DT group [23,24]. The results of this study also showed that the risk of ischemic stroke caused by AF was higher in the treatment with dual antithrombotic therapy, but the difference was not statistically significant. Therefore, although the dual antithrombotic therapy of clopidogrel and aspirin can reduce the risk of massive hemorrhage, it can also lead to an increase in the risk of cerebral ischemic stroke caused by AF. So, it is necessary to select the optimal antithrombotic therapy according to the individual condition of the patient. The results of the multivariate analysis revealed that the histories of ischemia and stroke, heart failure, and high CHA_2DS_2-VASc score (≥ 2) were significantly correlated with MACEs, which was consistent with the results of Dewilde *et al* [21] and Seivani *et al* [25]. It was suggested that when paying attention to the stratification of risk factors and the risk score of bleeding and thrombus, selecting dual antithrombotic therapy effectively reduces the risk of bleeding in AF patients without increasing the incidence of MACEs.

Limitations of this study

There are some shortcomings in this study. The number of subjects was limited, the follow-up period was not long enough, and the self-reported bleeding and thrombus events might be subjective. In addition, the blood coagulation INR in patients was not monitored accurately and timely, so possible bleeding or thrombus events were not prevented or controlled in time. In the future, more rigorous prospective multi-center randomized studies with large samples are needed to confirm the conclusions of this study.

CONCLUSION

Dual antithrombotic therapy and triple antithrombotic therapy significantly increase the risk of massive hemorrhage in AF patients after PCI and does not significantly reduce the incidence of MACCEs after 1 year of follow-up. Histories of ischemia and stroke, heart failure, and high CHA_2DS_2-VASc score are the risk factors for MACCEs.

DECLARATIONS

Acknowledgements

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Ethical approval

This study was reviewed and approved by the Ethics Committee of The Third Affiliated Hospital of Chongqing Medical University, Jeer Hospital (approval no. CN-CQ-19-0016).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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