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Original Article

Effect of three different antithrombotic regimens in patients with coronary heart disease and atrial fibrillation after coronary stent implantation and comparison of long-term follow-up results

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Abstract: Objective: To analyze the effect of applying three different antithrombotic regimens to patients with coronary heart disease and atrial fibrillation after coronary stent implantation. Methods: Based on the order of admission, 155 cases of patients with coronary heart disease combined with atrial fibrillation in our hospital were divided into three groups, including triple antithrombotic group, double antithrombotic groups 1 and 2, and received coronary stent implantation. After the operation, patients in triple antithrombotic group were treated with warfarin, aspirin combined with clopidogrel antithrombotic therapy. Patients in double antithrombotic group 1 were treated with aspirin combined with clopidogrel antithrombotic therapy. Patients in double antithrombotic group 2 were treated with warfarin combined with clopidogrel antithrombotic therapy. All patients in 3 groups were followed up for 12 months and the results were analyzed. Results: There was no significant difference in incidence of cardiac death, recurrent myocardial infarction, stent thrombosis and ischemic stroke among the three groups ($P>0.05$); the incidence of the triple antithrombotic group was significantly lower than the other two groups ($P<0.05$). The incidence of major bleeding, secondary bleeding and minor bleeding in triple antithrombotic group was 1.89%, 3.77% and 3.77%, and in double antithrombotic group 1 was 11.76%, 15.69% and 17.65% and in double antithrombotic group 2 was 13.73%, 19.61% and 19.61%. There was less significant difference in the incidence among the three groups ($P>0.05$), and the incidence of the triple antithrombotic group was significantly lower than the other two groups ($P<0.05$). Conclusion: After patients with coronary heart disease and atrial fibrillation were treated with warfarin, aspirin combined with clopidogrel antithrombotic therapy after coronary stent implantation, the adverse cardiovascular and cerebrovascular events and bleeding events can be significantly reduced, and patient prognosis can also be improved.

Keywords: Antithrombotic regimen, coronary heart disease, atrial fibrillation, coronary stent implantation, follow-up

Introduction

Atrial fibrillation is a kind of tachyarrhythmia characterized by the deterioration of atrial mechanical function caused by the uncoordinated atrial activity. The disease has a relatively high incidence in China and is age-dependent with a significantly higher incidence in the elderly population [1, 2]. According to the statistics, the incidence of atrial fibrillation in people under 60 years of age is less than 2%, while the incidence of atrial fibrillation in people over 80 years of age is more than 30% [3]. With a full name as coronary atherosclerotic heart disease, coronary heart disease is mainly a type of heart disease that coronary atherosclerosis makes the lumen narrow or even occluded, and further causes myocardial hypoxia, ischemia or even necrosis [4, 5].

At present, the number of patients with coronary heart disease and atrial fibrillation is increasing due to multiple risk factors among atrial fibrillation and coronary heart disease [6]. Clinically, patients with confirmed coronary heart disease and atrial fibrillation are more likely to choose surgical treatment or interventional therapy, especially interventional thera-

py. Coronary stent implantation is an important treating method for those patients, and good results have been confirmed in clinical practice [7, 8]. However, it is important to insist on the standard medication, regardless of the method selected. Antithrombotic therapy is an important means to reduce stent thrombosis after coronary stent implantation. There are a variety of clinically available antithrombotic regimens, but there isn't a consolidated conclusion on the best antithrombotic regimen yet to-date [9, 10].

Aspirin and clopidogrel are widely used antithrombotic agents. However, they are extensively applied in antithrombotic therapy of simple coronary heart disease. For patients with coronary heart disease with atrial fibrillation, anticoagulants should be selected to prevent venous thrombosis. Warfarin is a kind of anticoagulant widely used in clinic, but there is no standard conclusion on whether warfarin can combine aspirin and clopidogrel as an antithrombotic regimen for antithrombotic therapy [11, 12]. Based on this, 155 cases of patients with coronary heart disease combined with atrial fibrillation in our hospital were selected in this study to analyze the effect of applying three different antithrombotic regimens.

Data and methods

Data

Selected 155 cases of patients with coronary heart disease combined with atrial fibrillation in our hospital from January 2014 to June 2016. The patients received coronary stent implantation and were divided into three groups based on the order of admission: 53 cases in triple antithrombotic group, 51 cases in double antithrombotic group 1 and 51 cases in double antithrombotic group 2. (1) Inclusive criteria: patients with pre-existing definite history of atrial fibrillation or new onset of atrial fibrillation after admission; non valvular atrial fibrillation; successful coronary stent implantation; normal coagulation function; normal cognition; informed consent of patients received; approved by medical ethics committee. (2) Exclusion criteria: cardiogenic shock; used drugs that affect the progress of antithrombotic treatment; active bleeding or bleeding constitution; major surgical procedures within one month; in-hospital death.

Methods

All 3 groups received coronary stent implantation with the same team of doctors. After the operation, triple antithrombotic group selected warfarin, aspirin and clopidogrel for antithrombotic therapy: 100 mg/d aspirin enteric-coated tablets (Specification: 100 mg × 30 tablets, Approval No.: GYZZI: J20130078; Manufacturer: Bayer Healthcare Company Ltd.); 75 mg/d clopidogrel bisulfate tablets (Specification: 25 mg × 7 tablets, Approval No.: GYZZI: H2012-3115; Manufacturer: Lepu Pharmaceuticals Co. Ltd.); Warfarin sodium tablets with an initial dose of 2.5 mg/d (Specification: 2.5 mg × 20 tablets, Approval No.: GYZZI: H37021314; Manufacturer: Qilu Pharmaceutical Co. Ltd.), patients were tested once a week, dosing was adjusted according to the international standardized ratio (INR), and adjusted once a month when INR maintained between 2.0 and 2.5; and patients appropriately adjusted dose when having an adverse reaction.

For double antithrombotic group 1, the antithrombotic therapy of aspirin combined with clopidogrel was selected, and the method of medication was the same as above. In double antithrombotic group 2, warfarin combined with clopidogrel was selected for antithrombotic therapy, and the method of medication was the same as above.

In addition, the patients in all 3 groups used ACEI, ARB, β-adrenergic blocking agent, statin and other drugs as needed. The dosage was administered at the recommended dose of ACC/AHA.

After treatment, all patients in three groups were followed for 12 months. Follow-up included telephone, WeChat and outpatient review.

Observation index

General information: statistics of 3 groups of general data such as patients age, sex, body mass index (BMI), total stent, smoking history, hypertension history, diabetes history, cerebral infarction history, history of heart failure, left ventricular ejection fraction (LVEF), hemoglobin (Hb) level, serum creatinine level (Cr), platelet count, etc.

Adverse cardiovascular and cerebrovascular events: the occurrence of various adverse car-

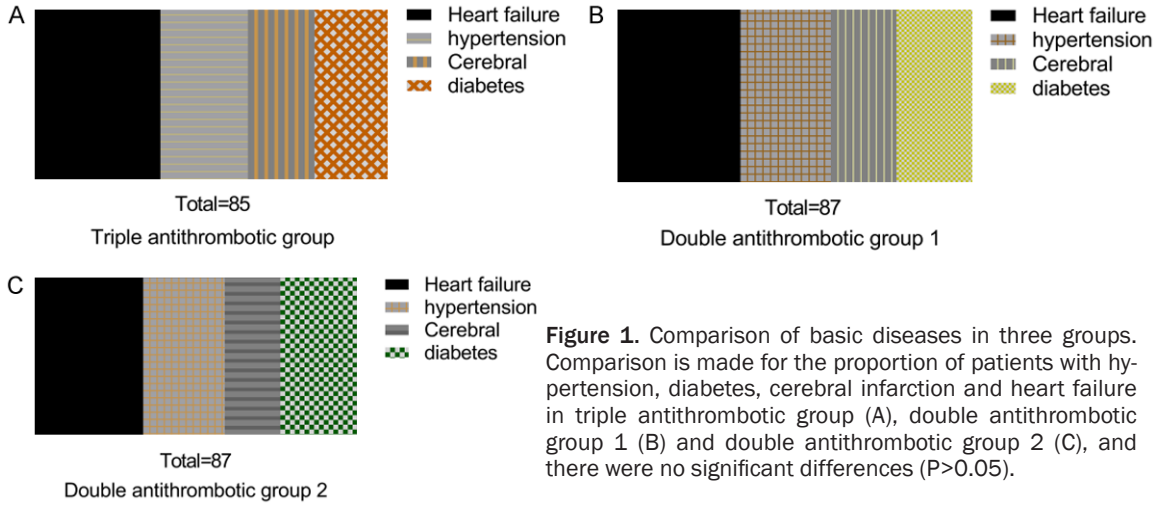

Figure 1. Comparison of basic diseases in three groups. Comparison is made for the proportion of patients with hypertension, diabetes, cerebral infarction and heart failure in triple antithrombotic group (A), double antithrombotic group 1 (B) and double antithrombotic group 2 (C), and there were no significant differences (P>0.05).

diovascular and cerebrovascular events, such as cardiac death, re-emergence of myocardial infarction, stent thrombosis, and ischemic stroke during follow-up period of 12 months after treatment in 3 groups.

Bleeding events: the major bleeding, secondary bleeding and minor bleeding during follow-up period of 12 months after treatment in 3 groups. Judgment criteria [13]: major bleeding: intracranial bleeding or clinically visible bleeding (including imaging) with decreased hemoglobin concentration ≥50 g/L; secondary bleeding: clinically visible bleeding (including imaging) with a 30~50 g/L decrease in hemoglobin concentration; minor bleeding: clinically visible bleeding (including imaging) with decreased hemoglobin concentration <30 g/L.

Statistical method

Carry out data analysis with SPSS23.0, the measurement data is expressed by $\bar{x} \pm sd$, and results are compared by independent sample t test. The count data is represented by [n (%)], and the results are compared by X^2 test, the multipoint comparison is analyzed by ANVOA, and the F test is performed. Graphics is made with Graphpad Prism 8. $P<0.05$ suggests that there is statistically significant difference.

Results

General information

Comparing the proportion of males and females, mean age, BMI, total number of stents and smoking history between the observation group and the control group, there was no statistically significant difference ($P>0.05$); comparing the history of hypertension, diabetes, cerebral infarction and heart failure between the observation group and the control group, there was no statistically significant difference ($P>0.05$) (**Figure 1**); comparing LVEF, Hb, Cr and platelet counts between the observation group and the control group, there was no statistically significant difference ($P>0.05$) (**Table 1**; **Figure 2**).

The adverse cardiovascular and cerebrovascular events of the three groups

After treatment, all patients were followed up for 12 months. During the follow-up period, the incidences of cardiac death, recurrent myocardial infarction, stent thrombosis and ischemic stroke were 0.00% (0/53), 3.77% (2/53), 5.66% (3/53) and 3.77% (2/53) in triple antithrombotic group with 53 cases of patients, 7.84% (4/51), 15.69% (8/51), 19.61% (10/51), and 17.65% (9/51) in double antithrombotic group 1 with 51 cases of patients, and 9.80% (5/51), 17.65% (9/51), 21.57% (11/51), and 21.57% (11/51) in double antithrombotic group 2 with 51 cases of patients. The difference among the three groups was not statistically significant ($P>0.05$), but the incidences of the triple antithrombotic group were significantly lower than those of the other two groups ($P<0.05$) (**Table 2**).

Bleeding events of the three groups

After treatment, all patients were followed up for 12 months. During the follow-up period, the

Table 1. General data comparison of three groups ($\bar{x}$ ± sd)/[n (%)]

Data		Triple antithrombotic group (n=53)	Double antithrombotic group 1 (n=51)	Double antithrombotic group 2 (n=51)	*F*	*P*
Gender	Male	24 (45.28)	27 (52.94)	24 (47.06)	2.163	0.854
	Female	29 (54.72)	24 (47.06)	27 (52.94)		
Age (years)		65.28±10.18	64.19±11.42	65.35±11.47	1.751	0.361
Total number of stents (stents)		1.82±0.63	1.85±0.61	1.83±0.66	0.857	0.527
BMI (kg/m^2)		23.17±2.51	22.76±2.63	22.95±1.98	1.492	0.741
Smoking history	Yes	27 (50.94)	27 (52.94)	25 (49.02)	2.316	0.827
	No	26 (49.06)	24 (47.06)	26 (50.98)		

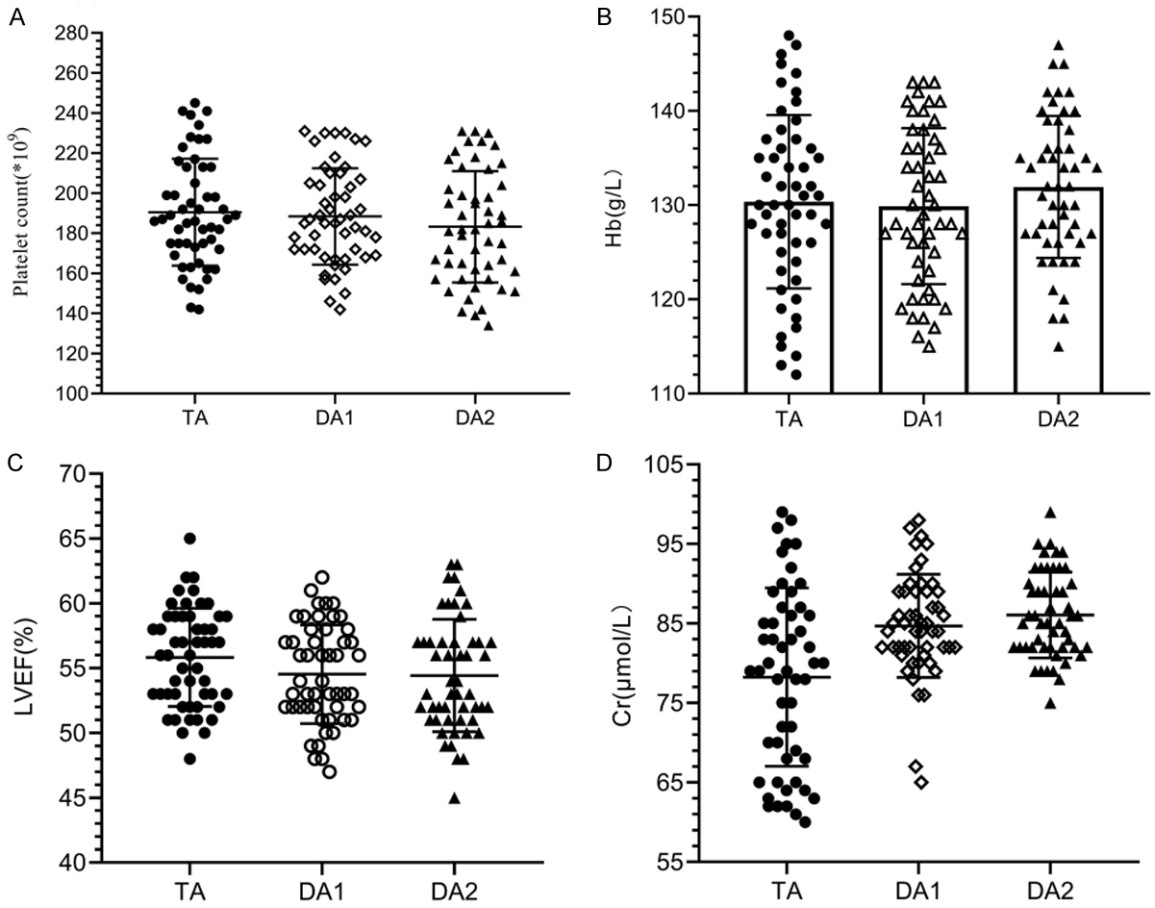

Figure 2. Comparison of indicators in three groups. There were no significant differences in platelet count (*P*>0.05) (A), Hb level (*P*>0.05) (B), LVEF level (*P*>0.05) (C) and Cr level (*P*>0.05) (D) in the three groups.

major bleeding rate, secondary bleeding rate and minor bleeding rate group were 1.89% (1/53), 3.77% (2/53) and 3.77% (2/53) in the triple antithrombotic group with 53 patients, 11.76% (6/51), 15.69% (8/51), and 17.65% (9/51) in double antithrombotic group 1 with 51 patients, and 13.73% (7/51), 19.61% (10/51) and 9.61% (10/51) in double antithrombotic group 2 with 51 patients. The difference among the three groups was not statistically significant (*P*>0.05), but the bleeding event rates of the triple antithrombotic group were significantly lower than those of the other two groups (*P*< 0.05) (**Table 3**).

Discussion

Coronary heart disease is a cardiovascular disease with high incidence, and atrial fibrillation is a common type of arrhythmia. They both be-

Table 2. Comparison of the adverse cardiovascular and cerebrovascular events in three groups [n (%)]

Group	Cardiac death	Recurrent myocardial infarction	Stent thrombosis	Ischemic stroke
Triple antithrombotic group (n=53)	0 (0.00)*	2 (3.77)*	3 (5.66)*	2 (3.77)*
Double antithrombotic group 1 (n=51)	4 (7.84)	8 (15.69)	10 (19.61)	9 (17.65)
Double antithrombotic group 2 (n=51)	5 (9.80)	9 (17.65)	11 (21.57)	11 (21.57)
X^2	2.463	1.967	2.182	1.834
P	1.016	1.038	0.229	0.341

Note: compared with double antithrombotic groups 1 and 2, *P<0.05.

Table 3. Comparison of the incidence of bleeding events in three groups [n (%)]

Group	Major bleeding	Secondary bleeding	Minor bleeding
Triple antithrombotic group (n=53)	1 (1.89)*	2 (3.77)*	2 (3.77)*
Double antithrombotic group 1 (n=51)	6 (11.76)	8 (15.69)	9 (17.65)
Double antithrombotic group 2 (n=51)	7 (13.73)	10 (19.61)	10 (19.6)
X^2	1.285	2.671	2.952
P	1.042	0.139	0.743

Note: compared with double antithrombotic groups 1 and 2, *P<0.05.

long to cardiovascular diseases, so they have multiple similar risk factors such as sleep apnea, smoking, diabetes, obesity, hypertension, etc. [14, 15]. Other works demonstrated that inflammatory response also plays an important role in the pathogenesis of coronary heart disease and atrial fibrillation [16]. Statistics suggest that combined coronary heart disease accounts for about 30% of all patients with atrial fibrillation, and atrial fibrillation accounts for about 5% of all patients with coronary heart disease [17].

Interventional therapy is important for the treatment of coronary heart disease. Double antiplatelet therapy is the standard treatment after interventional operation, in which P2Y12 receptor inhibitor and aspirin are commonly used drugs [18]. However, some studies suggest that, the implementation of antiplatelet therapy is impossible to prevent ischemic stroke in patients with moderate or high risk of atrial fibrillation [19]. Further research found that antiplatelet therapy combined with oral anticoagulant therapy can significantly reduce the risk of ischemic stroke [20]. Patients with coronary heart disease with combined atrial fibrillation should be given anticoagulant, antiplatelet aggregation drugs combined with antiembolism therapy after intervention. With antithrombotic therapy, the prevention of stent thrombosis and the prevention of arteriovenous thrombosis can be realized [6]. Anticoagulants and antiplatelet aggregation drugs are different in pharmacological mechanism and cannot be replaced directly. It will significantly increase the risk of bleeding with combined use. Therefore, the postoperative antithrombotic therapy for patients with coronary heart disease and atrial fibrillation should be focused on minimizing the risk of bleeding on the basis of ensuring the efficacy [21]. However, there are few studies on this aspect, with warfarin as an anticoagulant in previous studies; there is lack of evidence-based medical evidence [22, 23]. Based on the large sample study of patients with atrial fibrillation-combined stent implantation, it is shown that the bleeding event rate of the triple antithrombotic group exceeded 20% within one month, and also showed a continuous increasing trend, and no safe effective treatment window was found. The triple antithrombotic therapy even increased instead of reduced the incidence of ischemic embolism. The study also suggests that, there is no complete explanation for the occurrence of ischemic events due to the fact that the primary endpoint of the study was dominated by bleeding events [8].

Later, there is more related study on the application of triple antithrombotic therapy in patients with coronary heart disease and atrial fibrillation. Some studies suggested the adding

warfarin could increase the risk of bleeding. Some studies also found that the occurrence of bleeding was not directly related to warfarin [24, 25]. In this study, with the comparative study of the tree groups, in the triple antithrombotic therapy group treated with warfarin, aspirin and clopidogrel, there were no cases of internal death, and it had a significantly lower incidence of recurrent myocardial infarction, stent thrombosis and ischemic stroke than that of double antithrombotic group 1 and double antithrombotic group 2, and lower rate of major bleeding, secondary bleeding and minor bleeding than those of the two groups ($P<0.05$). Compared with the double antithrombotic therapy of warfarin combined with clopidogrel and double antithrombotic therapy of aspirin combined with clopidogrel, the triple antithrombotic therapy of warfarin, aspirin and clopidogrel can obtain better results. It can reduce the risk of bleeding while reducing the occurrence of cardiovascular adverse events. From a similar randomized controlled study, it is found that by comparing the main end point time between the triple antithrombotic treatment that lasted for half a year and the same triple antithrombotic treatment that lasted for six weeks, there were no significant differences. It confirmed the value of triple antithrombotic treatment [26]. Research showed that, the triple antithrombotic group has a significantly lower incidence of ischemic stroke than those of the double antithrombotic group with clopidogrel and aspirin [27]. Compared with the above studies, it is possible that patients had better basic conditions, higher effectiveness of interventional therapy, and better dose control during antithrombotic treatment, so this study had a more explicit value embodiment for the triple antithrombotic therapy. Triple antithrombotic regimens showed better results than double antithrombotic regimens, which was analyzed to be attributed to the fact that the triple antithrombotic regimens could further reduce the peak and average speed of thrombin production, prolong the peak time of thrombin production, and synergistically enhance the inhibition of platelet aggregation induced by tissue factors. Thereinto, aspirin can inhibit thrombin-induced platelet activation *in vitro*, and this effect is even more significant when combined with the other two drugs. In addition, triple antithrombotic regimens can reduce thrombotic formation and thrombin-dependent thrombin production, thus reducing the expression of platelet-related proteins. Some studies showed that the double antithrombotic regimens with aspirin and with clopidogrel may significantly increase the incidence of ischemic stroke compared with the triple antithrombotic regimens. In some studies, it is found that after the application of double antithrombotic regimens including clopidogrel and aspirin and triple antithrombotic regimens, there were no significant differences in the incidence of adverse cardiovascular and cerebrovascular events [28].

In conclusion, compared with double antithrombotic regimen, applying triple antithrombotic therapy of warfarin, aspirin and clopidogrel to patients with coronary heart disease and atrial fibrillation after coronary stent implantation can effectively reduce cardiovascular adverse events and bleeding events, and the application value of triple antithrombotic regimen was confirmed. This study has the following shortcomings: fewer subjects were included, the risk rating of subjects before treatment was not conducted, and this study is a retrospective study. All of the above points may have affected the representativeness and referentiality of the results. In the future, a larger sample size, deeper and more comprehensive study should be carried out. In addition, interventional treatment before antithrombotic therapy, technical level, etc. may also affect the effect of postoperative antithrombotic treatment, which should also be paid with more attention in the future research.

Disclosure of conflict of interest

None.

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