Comparison of triple antithrombotic therapy and dual antiplatelet therapy for patients with atrial fibrillation after percutaneous coronary stenting

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Abstract: The aim of this study was to evaluate the safety and efficacy of triple antithrombotic therapy with warfarin, aspirin and clopidogrel in patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI). We retrospectively reviewed clinical and follow-up data of 156 consecutive patients with atrial fibrillation after percutaneous coronary stenting. Patients were followed up at 2 and 12 months. A total of 156 consecutive patients were identified. There were 70 patients (dual antiplatelet therapy group, DAPT), warfarin was not used and 86 patients (triple antithrombotic therapy group, TT), both dual antiplatelet therapy and warfarin therapy were prescribed. The baseline data and PCI data were similar in the two groups. The outcome events were similar in the two groups except for bleeding events. There was a significant difference in bleeding risk in the two groups. In summary, triple antithrombotic therapy increases the bleeding risk. Dual antiplatelet therapy decreased this bleeding risk but tended to increase the risk of stroke.

Keywords: Warfarin, anticoagulation, bleeding, percutaneous coronary intervention.

INTRODUCTION

Dual antiplatelet therapy, aspirin and clopidogrel should be used for 1 months to patients after percutaneous coronary intervention (PCI) to prevent acute in-stent thrombosis and should be used for 2 to 6 months after drug-eluting stenting (Barry and Ackman 2012; Rubboli 2012;Andrade *et al*. 2013; Cahill *et al*. 2015; Lee *et al*. 2015; Yung *et al*. 2015; Zheng*et al*. 2015). Triple antithrombotic therapy, warfarin, aspirin and clopidogrel, is used in patients in whom both are indicated on the assumption that the net benefit of the triple antithrombotic therapy outweighs the increased risk of bleeding (Andrade *et al*. 2013). However, there are no recommendations from the guidelines, proposed by European Society of Cardiology, the American Heart Association and the American College of Cardiology, on management of antithrombotic treatment of patients with atrial fibrillation after percutaneous coronary stenting (Bertrand *et al*. 1998; Gilard *et al*. 2009; Srour and Smetana 2011; Cahill *et al*. 2015; Dobson *et al*. 2015; Ghoneum *et al*. 2015; Mellotte *et al*. 2015; Sandri *et al*. 2015; Sterling *et al*. 2015;). Triple antithrombotic therapy for patients with atrial fibrillation after percutaneous coronary stenting is controversial in clinical practice (Rossini *et al*. 2008; Bruera *et al*. 2015; Kowgier *et al*. 2015; Othman *et al*. 2015; Smithers *et al*. 2015). Some author reported that triple antithrombotic therapy is better than dual antiplatelet therapy, however, some author founded that triple antithrombotic therapy is not better than dual antiplatelet therapy but coupled with severe bleeding events. The present study analyzed the safety and the efficacy of triple antithrombotic therapy in patients with atrial fibrillation after coronary stenting.

METHODS

This retrospective research was approved by the Ethics Committee of our institution. The need for informed consent from all patients was waived because of its retrospective nature.

From January 2010 to September 2012, 156 consecutive patients with atrial fibrillation undergoing PCI in our institution were included in the study. Patients were retrospectively assessed for the main risk factors, such as dyslipidemia, hypertension, and type 2 diabetes mellitus, a family history of coronary artery disease, previous acute coronary syndrome and revascularization by PCI. The indication for PCI were acute coronary syndrome, using the CHADS2 score (Congestive heart failure, Hypertension, Age >75 years, Diabetes mellitus, and previous Stroke or transient ischemic attack) (Bruera *et al*. 2015; Kowgier *et al*. 2015; Othman *et al*. 2015; Rossini *et al*. 2008; Smithers *et al*. 2015).

Clinical data were collected during hospitalization. Follow-up data were collected by outpatient at 2 and 12 months after PCI. Acute coronary syndrome was defined as any troponin elevation or suggestive symptoms detected. Ischemic stroke was confirmed by clinical assessment and imaging-confirmed infarct. Bleeding complications were classified using the criteria proposed by the Global Use of Strategies to Open Coronary Arteries (GUSTO) study group. Mild was defined as not requiring transfusion. Moderate was defined as requiring

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Table 1: Baseline data

	DAPT (*n*=70)	TT (*n*=86)	*P* value
Age (y)	62.30±8.42	64.01±10.30	0.357
Gender (Male: Female)	46:24	51:35	0.632
History			
Hypertension	36	49	0.716
Diabetes mellitus	14	17	0.971
Hyperlipidemia	40	52	0.675
Previous cardiac insufficiency	7	9	0.924
Previous acute coronary syndrome	4	7	0.556
Previous stroke	1	1	0.883
Indication of PCI			
Acute coronary syndrome ST-	31	40	0.781
Acute coronary syndrome ST+	39	46	0.354

Table 2: PCI data

	DAPT (*n*=70)	TT (*n*=86)	*P* value
Lesions treated per patient	1.36±0.25	1.56±0.16	0.236
Stents per patient	1.65±0.36	1.48±0.45	0.360
Patients who underwent drug-eluting stents	61	78	0.479
Coronary artery narrowing			
Left anterior descending	36	42	0.747
Right descending	25	30	0.914
Circumflex	16	20	0.953
Marginal artery	16	19	0.909
Left ventricular function <40%	21	19	0.261
Mean INR on PCI	-	2.01±0.78	-

INR = international normalized ratio.

transfusion. Severe was defined as fatal or intracerebral bleeding or with substantial hemodynamic compromise requiring treatment.

For statistical analysis, SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used. For variables following normal distribution, data were presented as mean and standard deviations and were analyzed by student *t* test. For variables following non-normal distribution, data were expressed as median and range and were compared by Mann–Whitney *U*-test. Differences of semiquantitative results were analyzed by Mann-Whitney *U*-test. Differences of qualitative results were analyzed by chi-square test or Fisher exact test where appropriate. $P<0.05$ was considered statistically significant.

RESULTS

Two groups were individualized according to whether warfarin was used. In 70 patients (dual antiplatelet therapy group, DAPT), warfarin was not used and dual antiplatelet therapy, aspirin and clopidogrel, was mandatory. In 86 patients (triple antithrombotic therapy group, TT), both dual antiplatelet therapy and warfarin therapy were continued. There were no significant differences in the baseline characteristics ($P>0.05$) (table 1). There were no significant differences in terms of procedure ($P>0.05$) characteristics (table 2).

In the 156 patients, 150 were followed up at 2 months and 147 were followed up at 12 months. There were no significant differences when comparing the outcome events ($P>0.05$), except for bleeding events (table 3). The incidence of stent thrombosis and stroke were similar in the 2 groups ($P>0.05$).

Moderate bleeding occurred in 6 patients. Severe bleeding occurred in 8 patients, with a significant difference between the two groups: 7 patients in TT and 1 in DAPT ($P=0.013$) (table 4). Table 5 lists the severe bleeding accidents. The risk of bleeding persisted and continued to increase during follow-up in the TT (tables 3 and 4).

DISCUSSION

Our study has confirmed that triple antithrombotic therapy increases the peri- and post-PCI bleeding risk. Previous studies have analyzed the effect of triple therapy (Helft *et al*. 2006; Apostolakis and Dougenis 2015; Breitenbuecher *et al*. 2015; Dagher *et al*. 2016; Freeman and Terracina 2016; Horgan *et al*. 2016; Morise *et al*. 2016). Some author reported that triple antithrombotic

Table 3: discharge and follow-up data

	DAPT (*n*=70)	TT (*n*=86)	*P* value
At discharge			
Acute coronary syndromes	1	1	0.883
Bleeding	3	3	0.808
Mild	1	1	0.883
Moderate	0	1	0.365
Severe	0	0	-
Stroke	1	0	0.918
Stent thrombosis	1	1	0.883
At 2 months			
Acute coronary syndromes	1	1	0.883
Bleeding	4	5	1.000
Mild	2	3	1.000
Moderate	0	1	0.365
Severe	1	1	0.883
Stroke	1	0	0.918
Stent thrombosis	1	0	0.918
At 12 months			
Acute coronary syndromes	2	1	0.865
Bleeding	1	12	0.005
Mild	1	2	1.000
Moderate	0	4	0.187
Severe	0	6	0.066
Stroke	3	0	0.176
Stent thrombosis	1	1	1.000

Table 4: Severe bleeding complications at follow-up

	DAPT (*n*=70)	TT (*n*=86)	*P* value
At 2 months			
Intracranial bleeding	0	1	1.000
Gastrointestinal bleeding	1	0	1.000
Urinary bleeding	0	0	1.000
At 12 months			
Intracranial bleeding	0	2	0.570
Gastrointestinal bleeding	0	3	0.321
Urinary bleeding	0	1	0.321

therapy is better than dual antiplatelet therapy, however, some author founded that triple antithrombotic therapy is not better than dual antiplatelet therapy but coupled with severe bleeding events. When PCI and stenting are required in a patient with atrial fibrillation, the clinical situation is difficult. Whether triple antithrombotic therapy should be prescribed is controversial (Tapp *et al*., 2011). Previous study compared dual antiplatelet therapy versus triple antithrombotic therapy in elective cohorts. They demonstrated that a significant net benefit in terms of safety and efficacy for dual antiplatelet therapy (Singh *et al*., 2011). There was no randomized clinical study supporting the triple antithrombotic therapy. Thus, it was preferable to continue dual antiplatelet treatment, aspirin and clopidogrel, after coronary stenting.

In previous published studies, the incidence of 30-day minor bleeding and major bleeding with triple antithrombotic therapy were in the range of 5% to 11% and 1% to 15% respectively (Manzano-Fernández *et al*. 2008; Singh *et al*. 2011; Saheb *et al*. 2013). With regard to efficacy, no patients treated with triple therapy had experienced stent thrombosis or major cardiovascular events at 30 days. The safety and efficacy of longer term triple antithrombotic therapy is uncertain. In published studies, all major bleeding occurred at 2 to 10 months (Naruse *et al*., 2013). Neither stent valve thrombosis nor thromboembolic events were observed in the long term follow up with triple antithrombotic therapies.

CONCLUSION

In our study, the severity of bleeding was our attention. The incidence of moderate and severe bleeding was similar to other reports (Guo *et al*., 2013). It was notable that the bleeding rate increased during the follow-up

period in patients receiving triple antithrombotic therapy. The stroke incidence was similar in the two groups. The stroke incidence in patients who underwent PCI varied from 0.11% to 0.38%, according to the sample size. Our research showed a tendency for the stroke rate to increase in the triple antithrombotic therapy group. However, our study lacked power to demonstrate a possible significant increase.

Our study has several limitations. The main limitation of our study is that the relatively small sample and the findings were retrospective, making determination of the results more difficult than perspective study. So we cannot exclude bias from patients and therapies selection. This limitation should be taken into account when interpreting the results. In conclusion, triple antithrombotic therapy increases the bleeding risk. Dual antiplatelet therapy decreased this bleeding risk but tended to increase the risk of stroke.

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