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Original Article

Comparison of hemorrhages of different triple antiplatelet therapies in female patients of acute coronary syndrome associated with diabetes after percutaneous coronary intervention

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Abstract: Antiplatelet therapies using aspirin, P2Y12 receptor blockers, and IIb/IIIa receptor blockers have been termed as triple antiplatelet therapies (TAPTs). Female acute coronary syndrome (ACS) patients with diabetes have higher incidence of hemorrhages after PCI surgery. In the current study, treatment outcomes and side effects associated with different TAPTs on female ACS patients with diabetes were investigated. Clinicopathological information of 119 female ACS patients with diabetes was collected for the current study. Of the 119 patients, 59 cases received treatment of ticagrelor-based TAPT and 60 cases received treatment of clopidogrel-based TAPT. Moreover, 59 male ACS patients with diabetes, treated with ticagrelor-based TAPT, were used as the control group. Treatment outcomes and side effects of different treatments were assessed by GRACE scores, CRUSADE scores, TIMI grades, TMPG grades, and other parameters. Incidence of pre-infarction angina was significantly higher in male patients, compared with female patients, but the hospitalization duration of females was significantly longer. After PCI surgeries, patients with TMPG level 3 were significantly higher in male patients. Incidence of having angina and arrhythmia in female patients treated with clopidogrel-based TAPT was higher than female patients treated with ticagrelor-based TAPT. However, incidence of hemorrhages in female patients treated with ticagrelor-based TAPT was higher than that of female patients treated with clopidogrel-based or male patients. Ticagrelor-based TAPT has stronger improving effects on ACS but a higher risk of hemorrhaging in female patients with diabetes, compared with clopidogrel-based TAPT.

Keywords: Acute coronary syndrome, clopidogrel, diabetes, female, hemorrhage, ticagrelor, triple antiplatelet therapy

Introduction

Impaired glucose metabolism is a major risk factor for the development of arteriosclerosis [1]. Plague fracture, platelet activation, and accumulation in blood vessels form the pathological basis of acute coronary syndrome (ACS) [2]. It has been reported that more than 80% of diabetes related deaths are attributed to the onset of cardiovascular disease (CVD) [1]. Currently, percutaneous coronary interventions (PCIs) are the major handling strategy for symptoms associated with ACS [3, 4]. However, PCI can itself lead to complications, such as slow-flow, non-reflow, or stent thrombosis after PCI surgery, making treatment outcomes of PCI less satisfactory for ACS patients [5, 6]. Moreover, the complications associated with PCI are more severe in ACS patients with diabetes [5, 6]. Additionally, compared with non-diabetes patients, diabetes ACS patients also have a higher chance of developing hemorrhages after PCI treatments. The above obstacles have made the management of ACS patients with diabetes a critical issue.

A well-recognized therapy for treatment of non-flow symptoms associated with PCI is dual antiplatelet therapy (DAPT). It depends on the combined application of aspirin and P2Y12 receptor blockers [7, 8]. The most widely prescribed P2Y12 receptor blocker used to be clopidogrel. Its revascularization effects have been validated by numerous studies [7, 8]. However, due to

patient resistance to long-term use of aspirin and clopidogrel, severe thrombosis has been recorded. Thus, a new generation of P2Y12 receptor blockers has been developed. One of the most promising drugs is ticagrelor [9]. Compared with clopidogrel, the effects of ticagrelor are not influenced by the polymorphism of CYP2C19 genes [10]. It has been proposed as a first-line drug against thrombosis after PCI treatment [7, 8]. However, based on the results of multiple trials, DAPT based on clopidogrel was less effective in treating PCI-associated thrombosis in female ACS patients, especially those with diabetes [5, 6, 11-13]. To increase the treatment efficacy of clopidogrel-based DAPT on female ACS patients with diabetes, the treating strategy was further developed as triple antiplatelet therapy (TAPT).

Tirofiban is a type of IIb/IIIa receptor blocker, which has shown potential to strengthen the revascularization effects of DAPT [6, 11, 14, 15]. Thus, it is expected that the combined application of tirofiban and ticagrelor-based DAPT will improve the hemodynamics of female ACS patients with diabetes after PCI surgery. However, based on the trial of Korea acute myocardial infarction Registry-National Institute of Health, treatment of ticagrelor will increase patient risks of hemorrhage, which may restrict application of the drug. According to the above information, the TAPT based combined application of aspirin, ticagrelor, and tirofiban might have better improving effects on hemodynamics of female ACS patients with diabetes. This treatment might also increase patient risk of hemorrhages. To verify the hypothesis, the current study investigated the treatment effects and side effects of different TAPTs on female ACS patients with diabetes after PCI surgeries. Results were further compared with the outcomes of male ACS patients with diabetes treated with ticagrelor-based TAPT. The findings outlined in the current study demonstrate that ticagrelor-based TAPT has better revascularization effects than clopidogrel-based TAPT, but the risk of hemorrhaging in female patients treated with ticagrelor-based TAPT was higher than that of female patients treated with clopidogrel-based or male patients.

Materials and methods

Patients

The current study collected clinicopathological information of 119 female ACS patients with diabetes. Diagnosis of ACS was performed according to ESC guidelines [3] and diabetes was diagnosed according to WHO criteria [16]. All patients received PCI treatment in People's Hospital of Zhengzhou, from January 2015 to November 2017, and were subjected to TAPT treatment. Of the 119 patients, 59 cases received treatment of ticagrelor-based TAPT and 60 cases received treatment of clopidogrel-based TAPT. Moreover, the clinicopathological information of 59 male ACS patients with diabetes that received treatment of ticagrelor-based TAPT was also collected as control information. This study was approved by the Ethics Committee of Southern Medical University for screening, inspection, and data collection of the patients. All works were undertaken following the provisions of the Declaration of Helsinki.

Treatment strategy

For patients receiving ticagrelor-based TAPT, 300 mg aspirin (Bayer, Germany) and 180 mg ticagrelor (Astrazeneca, UK) was orally given daily before PCI surgeries. For patients receiving clopidogrel-based TAPT, 300 mg aspirin and 300 mg clopidogrel (Sanofi, France) was orally given daily PCI surgeries. Tirofiban (10 μg/kg) was injected into coronary arteries during the surgery and the administration was sustained intravenously for 24 hours after PCI surgeries [17]. Upon completion of the surgeries, patients receiving ticagrelor-based TAPT were treated with 100 mg/day aspirin and 180 mg/day ticagrelor for at least 12 months. Patients receiving clopidogrel-based TAPT were treated with 100 mg/day aspirin and 75 mg/day for at least 12 months.

Outcome assessment

To assess the treatment efficacy and side effects associated with patients receiving different therapies, age, gender, heart rate, systolic pressure (SBP), serum creatinine, Killip grading, changes in ST segments, myocardial necrosis marker levels, hematocrit, and history of ACS and diabetes were retrieved from the patient database. Moreover, GRACE scores [18] and CRUSADE scores [19] were calculated for patients. SYNTAX scores were also calculated based on the results of coronary angiograms (CAG). Diameter and length information of stents in different groups was collected for patients. Other information regarding prognosis and side effects during hospitalization was

Table 1. Patient characteristics

	Male patients treated with ticagrelor-based TAPT (59)	Female patients treated with clopidogrel-based TAPT (60)	Female patients treated with ticagrelor-based TAPT (59)	*P*
Age (year)	57.3 ± 6.8	59.2.6 ± 5.8	60.8 ± 4.3	0.789
STEMI [n (%)]	37 (62.71)	38 (63.33)	40 (67.80)	0.819
NSTMI [n (%)]	16 (27.12)	15 (25.00)	15 (25.42)	0.962
UAP [n (%)]	6 (10.17)	7 (11.67)	4 (6.78)	0.650
Hypertension [n (%)]	39 (66.10)	35 (58.33)	33 (55.93)	0.499
Hyperlipidemia [n (%)]	31 (52.54)	40 (66.67)	39 (66.10)	0.201
BMI (kg/m^2)	30.33 ± 3.72	31.27 + 4.12	30.98 + 3.26	0.823
Serum creatinine (mmol/L)	87.6 ± 8.9	90.3 ± 11.2	86.3 ± 13.9	0.763
PCI history [n (%)]	3 (5.36)	2 (3.33)	4 (6.78)	0.086
Preinfarction angina [n (%)]	10 (16.95)	3 (5.00)[a]	2 (3.39)[a]	0.015
CVD history [n (%)]	5 (8.47)	3 (5.00)	8 (11.86)	0.403
GRACE Score				
< 85 [n (%)]	9 (15.25)	7 (11.67)	6 (10.17)	0.689
85~133 [n (%)]	17 (28.81)	19 (31.67)	12 (20.34)	0.352
> 133 [n (%)]	33 (52.52)	34 (56.67)	41 (69.49)	0.147
CRUSADE Score				
1~20 [n (%)]	5 (8.47)	7 (11.67)	7 (11.86)	0.799
21~30 [n (%)]	29 (49.15)	31 (51.67)	27 (45.76)	0.812
31~40 [n (%)]	23 (38.98)	22 (36.67)	23 (38.98)	0.956
41~50 [n (%)]	1 (1.69)	1 (1.67)	1 (1.69)	0.999
> 51 [n (%)]	1 (1.69)	(0)	0 (0)	0.363

a, P < 0.05 vs. Male patients treated with ticagrelor-based TAPT.

analyzed to compare the treatment efficacy and side effects associated with different treatments.

Statistical analysis

Continuous data are represented as mean ± standard deviation (SD) and category data are represented as median with interquartile range or frequency. Differences of parameters between patients receiving different therapies were analyzed with Student's t-test or Chi-squared test. All analyses were performed using SPSS 19.0 with a significance level of 0.05 (two tailed *P* value).

Results

Patient information

The average age was 60.8 ± 4.3 years old (ranging from 53 to 79) for female patients treated with ticagrelor-based TAPT, 59.2.6 ± 5.8 years old (ranging from 51 to 78) for female patients treated with clopidogrel-based TAPT, and 57.3 ± 6.8 years old for male patients treated with ticagrelor-based TAPT (**Table 1**). No significant differences were detected in age among the three groups. The proportion of patients with STEMI, NSTEMI, and UAP in different groups was analyzed, with no significant diferences detected (**Table 1**). However, incidence of pre-infarction angina was significantly higher in male patients treated with ticagrelor-based TAPT, compared with female patients treated the other therapies ($P < 0.05$) (**Table 1**). Regarding GRACE and CRUASDE scores, patients treated with different strategies did not show any differences (**Table 1**). Detailed clinicopathological information is shown in **Table 1**.

Characterization of ACS

No significant differences were detected in ACS characteristics between the three groups before PCI surgeries (**Table 2**). After PCI surgeries, the number of patients with TMPG level 3 was significantly higher in male patients treated ticagrelor-based TAPT, compared with female patients treated with the same therapy ($P < 0.05$) (**Table 2**).

Table 2. Pathological characteristics

	Male patients treated with ticagrelor-based TAPT (59)	Female patients treated with clopidogrel-based TAPT (60)	Female patients treated with ticagrelor-based TAPT (59)	*P*
Single vessel [n (%)]	4 (6.78)	5 (8.33)	7 (11.86)	0.613
Double vessel [n (%)]	6 (10.17)	3 (5.0)	9 (11.25)	0.179
Triple vessel [n (%)]	49 (83.05)	52 (86.67)	43 (72.88)	0.141
Left main [n (%)]	3 (5.08)	2 (3.33)	3 (5.08)	0.868
SYNTAX Score	19.96±7.92	21.83 ± 8.13	20.97 ± 8.87	0.863
PCI target vessel				
Left anterior descending branch [n (%)]	30 (50.85)	26 (43.33)	31 (52.54)	0.564
Left circumflex artery [n (%)]	13 (22.03)	8 (13.33)	12 (12.84)	0.432
Right coronary artery [n (%)]	16 (27.12)	26 (47.33)	16 (27.12)	0.093
Stent diameter (mm, x ± s)	2.71 ± 0.23	2.69 ± 0.27	2.70 ± 0.39	0.873
Stent length (mm, x ± s)	27.37 ± 3.74	28.02 ± 4.01	28.89 ± 4.19	0.823
TIMI grade before PCI				
0 [n (%)]	56 (94.42)	59 (98.33)	57 (96.61)	0.587
1~2 [n (%)]	3 (5.08)	1 (1.67)	2 (3.39)	0.587
3 [n (%)]	0	0	0	
TIMI grade after PCI				
0 [n (%)]	0 (0)[c]	4 (6.67)[a,c]	0 (0.00)[b,c]	0.018
1~2 [n (%)]	2 (3.39)	7 (11.47)[c]	5 (8.67)	0.240
3 [n (%)]	57 (96.61)[c]	49 (81.67)[a,c]	54 (91.53)[c]	0.023
TMPG grade before PCI				
0 [n (%)]	59 (100)	60 (100)	59 (100)	
1~2 [n (%)]	0 (0)	0 (0)	0 (0)	
3 [n (%)]	0	0	0	
TMPG grade after PCI				
0 [n (%)]	1 (1.69)[d]	3 (5.00)[d]	2 (3.39)[d]	0.607
1~2 [n (%)]	2 (3.39)	14 (23.33)[a,d]	8 (13.56)[a,d]	0.006
3 [n (%)]	56 (94.92)[d]	43 (71.67)[a,d]	49 (83.05)[a,d]	0.003

a, $P < 0.05$ vs. Male patients treated with ticagrelor-based TAPT. b, $P < 0.05$ vs. female patients treated with clopidogrel-based TAPT. c, $P < 0.05$ vs. pre-PCI surgery regarding TIMI. d, $P < 0.05$ vs. pre-PCI surgery regarding TMPG.

Characterization of complications

Compared with male patients, the hospitalization duration of females was significantly longer ($P < 0.05$) (**Table 3**). Moreover, the number of patients diagnosed as Killip III was significantly higher in female patients, compared with male patients ($P < 0.05$) (**Table 3**). Incidence of angina and arrhythmia in female patients treated with clopidogrel-based TAPT was higher than female patients treated with ticagrelor-based TAPT ($P < 0.05$) (**Table 3**). However, incidence of hemorrhages in female patients treated with ticagrelor-based TAPT was higher than that of female patients treated with clopidogrel-based or male patients ($P < 0.05$) (**Table 3**).

Discussion

For female ACS patients, timely PCI treatment can significantly decrease incidence of major adverse cardiovascular events (MACE) [20-22]. However, once impaired by ACS, female patients will always have atypical symptoms, compared with male patients [20]. For example, in the current study, incidence of pre-infarction angina was significantly lower in female patients than in male patients. The typical ACS symptoms normally diagnosed with female patients include discomfort behind the xsternum, nausea, emesis, and debilitation. Moreover, female ACS patients are insensitive to detections of electrocardiogram (ECG) and exercise ECG. The above factors dramatically influence the sensitivity and specificity of diagnosis of ACS in females and delay timely management of symptoms associated with attacks of ACS. This results in higher mortality and morbidity rates in female ACS patients, compared with male patients.

DAPT with aspirin and clopidogrel is a widely prescribed therapy to prevent thrombus [1, 5, 6, 11, 23, 24]. However, this therapy has disadvantages, such as slow and medium effects. Moreover, the treatment efficacy also varies

Table 3. Treatment outcomes and side effects

	Male patients treated with ticagrelor-based TAPT (59)	Female patients treated with clopidogrel-based TAPT (60)	Female patients treated with ticagrelor-based TAPT (59)	*P*
Hospitalization duration (d)	7.9 ± 3.1	10.2 ± 3.3[a]	9.1 ± 2.9[a]	0.036
> 2 stents [n (%)]	12 (20.34)	13 (21.67)	14 (23.73)	0.904
> 2 PCI surgeries [n (%)]	16 (27.12)	10 (16.67)	13 (22.03)	0.387
Post-infarction angina pectoris [n (%)]	5 (8.47)	14 (23.33)[a]	5 (8.47)[b]	0.040
Re-infarction [n (%)]	1 (1.69)	4 (6.67)	3 (5.08)	0.409
Stent thrombosis [n (%)]	2 (3.39)	0 (0)	0 (0)	0.130
Severe arrhythmia [n (%)]	2 (3.39)	9 (15.00)[a]	2 (3.39)[b]	0.019
Killip score > III [n (%)]	2 (3.39)	10 (16.67)[a]	9 (15.25)[a]	0.049
Cardiogenic shock after PCI [n (%)]	0 (0)	4 (6.67)[a]	1 (1.69)	0.073
30-day mortality rate [n (%)]	0 (0)	4 (6.67)[a]	1 (1.69)	0.073
Total hemorrhage num [n (%)]	1 (1.69)	7 (11.67)[a]	16 (27.12)[a,b]	<0.001
Major bleeding [n (%)]	0	0 (0)	2 (3.39)	0.347
Moderate bleeding [n (%)]	0	2 (3.33)	9 (15.25)[a,b]	0.001
Hyporrhea [n (%)]	1 (1.69)	3 (5.00)	5 (8.47)	0.244

a, $P < 0.05$ vs. Male patients treated with ticagrelor-based TAPT. b, $P < 0.05$ vs. female patients treated with clopidogrel-based TAPT.

with individuals due to gene polymorphisms [10, 12, 17]. Thus, novel treatment agents are necessary. Compared with clopidogrel, ticagrelor is a recently developed P2Y12 receptor blocker characterized by fast and strong effects. The agent can also benefit ACS patients by increasing blood flow in coronary arteries. Moreover, ticagrelor can be an alternative treatment strategy for patients having no response to clopidogrel [10]. It has been proposed as a first-line therapy for handling ACS [3, 4, 25].

Although DAPTs using aspirin and P2Y12 receptor blockers have shown their effects on ACS, severe side effects have also been detected with the application of the therapies, especially for female ACS patients with diabetes [20, 21]. ACS patients with diabetes have a significantly higher chance of impairment by slow-flow, non-reflow, or other MACEs than diabetes-free patients [1, 5, 6, 11, 23]. To prevent non-flow and slow-flow symptoms after PCI treatment, TAPTs based on combined application of IIb/IIIa receptor blockers and DAPTs have been introduced in clinic. IIb/IIIa receptor blockers, such as tirofiban, can effectively decrease patient incidence of impairment by MACEs [15]. The current study used GRACE scores, CRUSADE scores, TIMI grades, and TMPG to assess ischemia events associated with different treatment strategies [18]. No significant differences in GRACE and CRUSADE scores were detected. For TIMI grades, no significant differences were detected between female patients treated with different strategies or male and female patients treated ticagrelor-based TAPT. However, after PCI surgeries, the number with TMPG level 3 was significantly higher in male patients treated ticagrelor-based TAPT, compared with female patients treated with the same therapy. TMPG grades are used to assess the reperfusion levels of myocardial function [1, 6, 11, 23, 24]. Moreover, compared with males, female patients had an average longer hospitalization duration and higher incidence of heart failure, indicating that females were less sensitive to TAPT treatment than males. For female patients treated with clopidogrel-based TAPT, incidence of post-infarction angina pectoris and arrhythmia was significantly higher than female patients treated with ticagrelor-based TAPT. This indicates that ticagrelor-based TAPT was more effective in attenuating ACS symptoms than clopidogrel-based TAPT in female ACS patients with diabetes.

Although no significant differences were detected among the three groups in CRUSADE scores, incidence of hemorrhages after PCI surgery was significantly higher in female patients treated with ticagrelor-based TAPT than patients in the other two groups. Results indicated that treatment with ticagrelor-based TAPT might increase risk of hemorrhaging in female ACS patient with diabetes. In studies based on European populations, it was inferred that application of ticagrelor-based therapy would increase hemorrhage risks in some popula-

tions while having no influence on hemorrhage risks in other populations. Present results were partially consistent with these studies but were performed with Chinese populations. Compared with European populations, it has been reported that Chinese populations have a higher chance of hemorrhages and a lower chance of ischemia [12, 26, 27]. This was supported in the current study.

In conclusion, findings outlined in the current study demonstrated that female ACS patients with diabetes had more complications than male patients. Additionally, ticagrelor-based TAPT had stronger improving effects on ACS but a higher risk of hemorrhage in female patients with diabetes, compared with clopidogrel-based TAPT. However, the sample size of the current study was relatively small and male patients treated with clopidogrel-based TAPT were not investigated. To promote the understanding of the application of TAPTs in treatment of ACS, more comprehensive work is necessary in the future.

Disclosure of conflict of interest

None.

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