

Clinical outcomes of various continued antiplatelet therapies in patients who were administered DAPT following the implantation of drug-eluting stents and developed gastrointestinal hemorrhage

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Abstract. Although an increasing number of patients accept dual antiplatelet therapy (DAPT) following implantation of drug-eluting stents (DES) for coronary heart disease (CHD), the proportion of patients with DAPT who subsequently develop gastrointestinal hemorrhage continues to increase. To ensure the clinical outcomes from DES, it is important to formulate a novel continued antiplatelet therapy for patients who were administered DAPT and subsequently develop gastrointestinal hemorrhage following DES implantation. The present study aimed to evaluate the effects of continued aspirin, clopidogrel or DAPT use on the incidence of clinical adverse events and gastrointestinal rebleeding in patients who received DAPT and subsequently developed gastrointestinal hemorrhage following implantation of DES for CHD. Between 2004 and 2010, 108 consecutive patients receiving DAPT developed gastrointestinal hemorrhage following DES implantation for CHD at Liuzhou General Hospital (Liuzhou, Guangxi). These patients were divided into three groups according to the novel antiplatelet therapy. The occurrence of major adverse cardiac events (MACE), including cardiac death, non-fatal myocardial infarction, heart failure or target vessel revascularization, net adverse clinical events (NACE), including major bleeding, stroke or MACE, and gastrointestinal rebleeding during clinical follow-up following the initial procedure were compared among these three groups. The results of this analysis demonstrated that the occurrence rate of MACE, NECE and gastrointestinal rebleeding was not significantly different among these groups ($P>0.05$). Furthermore, survival

analysis was performed and although the survival curves of MACE and NECE were not significantly different among these groups, gastrointestinal rebleeding was demonstrated to be significantly different among the three groups ($P<0.05$), and continued aspirin or clopidogrel use was superior to continued DAPT. In conclusion, the results of the present study indicated that there were no significant differences in the clinical effectiveness and safety of continuing antiplatelet monotherapy or DAPT in patients who are administered DAPT and experience gastrointestinal hemorrhage following DES implantation. As for the prevention of recurrent bleeding, antiplatelet monotherapy was demonstrated to be superior to DAPT. Moreover, the treatment of patients who are administered DAPT and experience gastrointestinal hemorrhage following DES implantation must involve an evaluation of the risk of complications, including stent thrombosis, continuous bleeding and recurrent hemorrhage.

Introduction

Coronary artery disease (CAD) is the most prevalent cause of death in patients suffering from cardiovascular diseases (1). It is well-established that the complications of CAD include acute coronary syndrome (ACS), arrhythmias, heart failure and sudden death. ACS, particularly acute myocardial infarction (AMI), is a major public health concern, as it is the cause of ~75% of all CHD deaths and accounts for ~50% of all CHD hospital admissions (2). Percutaneous coronary intervention (PCI) and thrombolytic therapy are currently used in clinics as the predominant methods of treating AMI. Dual antiplatelet therapy (DAPT) is recommended for the treatment of coronary heart disease, which includes aspirin and an ADP receptor blocker (3). Regardless of which therapy is used, patients are recommended to accept anticoagulant or antiplatelet therapies, including aspirin, clopidogrel and warfarin, in order to prevent the onset of recurrent infarction following intervention (4). Bleeding, including intracranial hemorrhage and gastrointestinal hemorrhage, remains the predominant adverse effect of antiplatelet therapy (5). However, physicians cannot terminate antiplatelet therapy due to potential high incidence of recurrent

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Table I. Clinical events observed indicators.

Variable	Group A	Group B	Group C	χ^2 value	P-value
Patients	18	60	25		
MACE, n (%)	1 (5.6%)	3 (5.0%)	1 (4.0%)	0.061	0.972
NACE, n (%)	1 (5.6%)	4 (6.7%)	2 (8.0%)	0.103	0.955
RH, n (%)	2 (11.1%)	5 (10.0%)	4 (16.0%)	1.092	0.582

MACE, major adverse cardiovascular events; NACE, net adverse cardiovascular events; RH, recurrent hemorrhage.

Table II. Survival analysis of clinical events.

Method	MACE		NACE		Recurrent hemorrhage	
	χ^2 value	P-value	χ^2 value	P-value	χ^2 value	P-value
Long-rank	2.929	0.231	3.697	0.157	5.336	0.069
Breslow	1.444	0.486	2.763	0.251	6.909	0.032
Tarone-Ware	1.971	0.373	3.142	0.208	6.419	0.040

Significant differences ($P < 0.05$) are indicated in bold. MACE, major adverse cardiovascular events; NACE, net adverse cardiovascular events.

infarction. Therefore, the present study investigated patients admitted to Liuzhou General Hospital (Liuzhou, Guangxi) between 2004 and 2010, who were suffering from gastrointestinal hemorrhage following DAPT after the implantation of drug eluting stents (DES) in order to compare the efficacy of various types of continued antiplatelet therapy. The results of the present study may help elucidate the most effective method of continued antiplatelet therapy for patients who were treated with DAPT following DES implantation and subsequently developed gastrointestinal hemorrhage.

Materials and methods

Study participants. Patients were eligible for the present study if they had experienced recurrent hemorrhage within one year of DES implantation and DAPT, and had no relevant co-morbidities. A total of 108 patients (aged 38-78 years) were recruited from our hospital between 2004 and 2010. Exclusion criteria included i) The patient died during PCI or within 24 h of the surgery; and ii) the patient exhibited bleeding diathesis or was allergic to antiplatelet drugs. The present study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all study participants.

Grouping. Patients were randomly assigned to three groups: Group A, 100 mg aspirin + proton pump inhibitor (PPI; n=18); group B, 75 mg clopidogrel + PPI (n=60); and group C, DAPT + PPI (n=25). Treatment was administered for 14 (2-25) months. PPI treatment included esomeprazole (20 mg q.d.), rabeprazole (20 mg q.d.), or pantoprazole (40 mg q.d.). Baseline characteristics, including age, ethnicity, basic treatment, condition of PCI surgery, were recorded for all three groups and no significant heterogeneity was detected. Therapies administered post-PCI surgery were identical in each group.

Follow up. All patients were contacted by telephone or attended an out-patient follow up. During follow-up, the patient's state of health and major evaluation criteria were recorded, including: Major adverse cardiovascular events (MACE), which included heart failure, AMI and cardiac death; net adverse clinical events (NACE), which included bleeding stroke and MACE; and recurrent of gastrointestinal hemorrhage. The dates of these incidents were recorded.

Statistical analysis. Student's t-test or analysis of variance was performed to compare continuous variables between populations. Two-tailed Fisher's exact test or χ^2 test was used to compare categorical variables. Survival analysis was used to compare patients' survival data and was performed using the Log-rank, Breslow and Tarone-Ware methods (6-8). Data were presented as the mean \pm standard deviation. $P < 0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA).

Results

DAPT and monotherapy induce similar incidence rates of MACE, NACE and recurrent hemorrhage. The mean follow-up period for the present study was 14 months (range 2-25 months). Five patients were lost to follow-up (changed telephone number or stopped attending out-patient follow-up), resulting in a dropout rate of 4.6%; therefore 103 patients were postoperatively followed-up in the three groups: A (n=18), B (n=60) and C (n=25; Table I). The incidence rates of MACE in groups A (n=1), B (n=3) and C (n=1) were 5.6, 5.0 and 4.0%, respectively ($P=0.97$). Incidence rates of NACE in groups A (n=1), B (n=4) and C (n=2) were 5.6, 6.7 and 8.0%, respectively ($P=0.95$) and the recurrent hemorrhage

Table III. Survival analysis of recurrent hemorrhage.

Variable	Group A		Group B		Group C	
	χ^2 value	P-value	χ^2 value	P-value	χ^2 value	P-value
Long-rank method						
Group A			0.205	0.651	4.054	0.044
Group B	0.205	0.651			2.897	0.089
Group C	4.054	0.044	2.897	0.089		
Breslow method						
Group A			1.215	0.270	3.882	0.049
Group B	1.215	0.270			3.959	0.047
Group C	3.882	0.049	3.959	0.047		
Tarone-Ware method						
Group A			0.796	0.372	3.987	0.046
Group B	0.796	0.372			3.605	0.058
Group C	3.987	0.046	3.605	0.058		

Significant differences ($P < 0.05$) are indicated in bold.

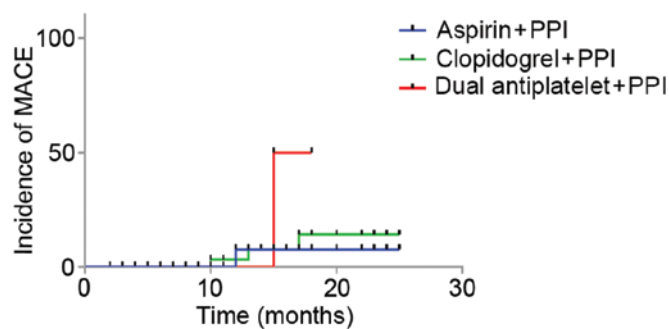


Figure 1. Incidence of major adverse cardiovascular events among the three groups.

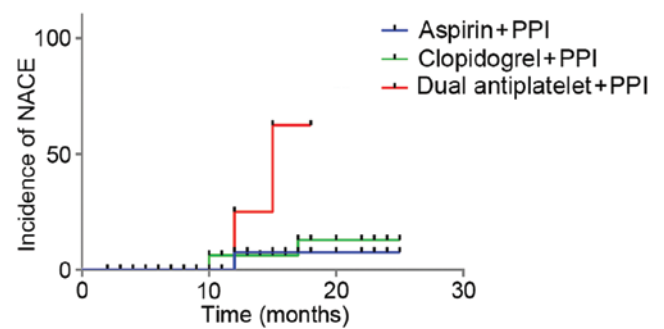


Figure 2. Incidence of net adverse cardiovascular events among the three groups.

rates in groups A ($n=2$), B ($n=5$) and C ($n=4$) were 11.0, 10.0 and 16.0%, respectively ($P=0.58$). No significant differences in the incidence rates of MACE, NACE and recurrent hemorrhage were detected among the three groups ($P > 0.05$).

DAPT increases gastrointestinal rebleeding rates. Survival analysis was performed using the Log-rank, Breslow and Tarone-Ware methods. As demonstrated in Table II, survival analysis of MACE and NACE outcomes demonstrated that there were no significant differences between groups A, B and C. The P-values of MACE in groups A, B and C were 0.231, 2.763 and 3.142, respectively; whereas the P-values of NACE were 0.157, 0.251 and 0.208, respectively. Significant differences in the frequencies of recurrent hemorrhage were detected among the A, B and C groups ($P=0.069$, 0.032 and 0.040, respectively). Furthermore, comparing the survival times of patients among the three groups demonstrated that there were significant differences (Table III). The Long-rank and Tarone-Ware methods demonstrated a significant difference between groups A and C, whereas the Breslow method presented a statistical difference between groups A and C,

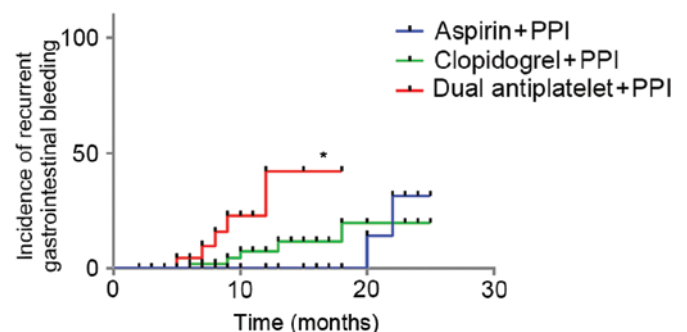


Figure 3. Incidence of recurrent hemorrhage among the three groups. * $P < 0.05$ vs. the aspirin + PPI and clopidogrel + PPI groups.

and groups B and C. Taken together, these findings indicated that the patients in group A had significantly shorter survival times, as compared with groups B and C. Survival curves are presented in Figs. 1-3. No statistical differences in survival duration after MACE and NACE were detected among three groups, whereas the DAPT group exhibited a significantly reduced survival rate after recurrent hemorrhage.

Discussion

It has previously been demonstrated that the administration of any of the commonly recommended basic antiplatelet strategies (5), including aspirin + PPI, clopidogrel + PPI; DAPT + PPI, is associated with a significant reduction of recurrent infarction (9). However, postoperative antiplatelet therapies are associated with digestive tract diseases, resulting in hemorrhage and peptic ulcers, and cardiovascular disease, which may result in MACE (10). As demonstrated in previous large clinical trials (11-16), as compared with aspirin monotherapy, clopidogrel (300 mg followed by 75 mg daily in all except for one of the trials) plus aspirin reduces the risk of composite vascular events [absolute risk reduction, 0.9-6.7%; relative risk reduction, 8.9-41.9%]. However, this improvement was associated with an increase in major bleeding events [absolute risk increase, 0.6-2.1%; relative risk increase, -54.5-37.0%] over variable periods from 8 days to 12 months. The mechanism of how aspirin may result in digestive diseases, particularly peptic ulcers, can be summarized by the following two points: i) Aspirin directly stimulates the phospholipid layer of gastric mucosa, which damages the hydrophobic protection barrier of the stomach (17), in addition to the increased release of cytotoxic substances (such as leukotrienes), which may also damage the gastric mucosa; ii) aspirin inhibits cyclooxygenase (COX)-1 and COX-2 in gastric mucosa (18). It is well-known that prostaglandin (PG) synthesis requires COX in gastric mucosa, and PGs can increase the blood flow of gastric mucosa and promote the synthesis of the mucus-HCO₃ barrier (19). Therefore, when patients are administered aspirin as antiplatelet therapy, COX is inhibited by aspirin and the gastric mucosa loses the protection of the mucus-HCO₃ barrier and peptic ulcers may subsequently develop. Aspirin inhibits platelet aggregation in a dose-dependent manner, and Patrono *et al* (20) have previously demonstrated that the risk of bleeding increases by 4-6- times when patients are treated with higher doses of aspirin. Conversely, the antiplatelet function of clopidogrel predominantly relies on the irreversible inhibition of the P2Y₁₂ subtype of adenosine (5). Although clopidogrel does not damage the gastric mucosa directly, it may inhibit the release of platelet derived growth factor and vascular endothelial growth factor, resulting in the inhibition of angiogenesis and the healing of peptic ulcers.

Following PCI treatment, various complications may affect the patients' prognosis, particularly bleeding, which may reduce the patients' heart function and lead to MACE. The reason for this can be summarized by the following four points: i) Massive hemorrhage reduces the intravascular volume and increases the heart rate, resulting in an increase of myocardial oxygen consumption and a decrease in myocardial perfusion; ii) in order to treat a massive hemorrhage anticoagulation, antiplatelet and antithrombotic therapy is terminated, which increases the risk of myocardial ischemia and stent thrombosis; and iii) blood transfusion therapy may trigger the release of inflammatory mediators which, in turn, may increase the onset of stent thrombosis (21).

The most salient finding of the present study is that neither monotherapy nor combination therapy was able to induce statistically significant differences in MACE, NACE and recurrent hemorrhage in patients who suffered from gastrointestinal

bleeding after PCI surgery and DAPT. These findings may deviate from the results of previous studies; however, the present results can be explained by the combination therapy of PPI. Yasuda *et al* (22) have previously demonstrated that combination therapy with DAPT and PPI decreases the effect of DAPT; however, the combination therapy was shown to decrease the risk of recurrent hemorrhage. Moreover, previous studies (23-26) have also demonstrated that combination therapy with PPI and clopidogrel reduced the antiplatelet effect of clopidogrel. Therefore, whether combination therapy with clopidogrel and PPI is reasonable remains controversial, and further clinical trials are required.

The present survival analysis results demonstrated that there were significant differences between the aspirin + PPI, clopidogrel + PPI and DAPT + PPI groups. The effect of aspirin + PPI and clopidogrel + PPI combination therapy were demonstrated to be superior to DAPT + PPI combination therapy. No significant differences were detected between the aspirin + PPI and clopidogrel + PPI combination therapy groups. Therefore, we hypothesise that antiplatelet monotherapy is suitable for patients who demonstrate a high risk of gastrointestinal hemorrhage, as compared with DAPT. Furthermore, aspirin is more cost-effective than clopidogrel and patients may prefer it. A 1996 CAPRIE trial (27) demonstrated that upper digestive tract hemorrhage was significantly reduced in patients treated with clopidogrel, as compared with aspirin. These findings are inconsistent with the results of the present study; this may be due to the small number of patients in the aspirin and clopidogrel groups. Cheung *et al* (28) demonstrated that patients with AMI who are complicated by peptic ulcer hemorrhage should not continue aspirin where viable; whereas patients who are at low risk of peptic ulcers following PCI treatment should regard aspirin as the preferable choice.

The results of the present study indicated that patients who developed gastrointestinal hemorrhage following treatment with DAPT after DES implantation should continue to use antiplatelet monotherapy or DAPT, as no significant differences in the rates of clinical incidents, as determined by MACE, NACE and recurrent hemorrhage, or the results of survival analysis, were detected between the treatment groups. As for the prevention of recurrent bleeding, antiplatelet monotherapy was demonstrated to be superior to DAPT. The treatment of patients who are administered DAPT and experience gastrointestinal hemorrhage following DES implantation must involve an evaluation of the risk of complications, including stent thrombosis, continuous bleeding and recurrent hemorrhage.

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