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Comparison of the Efficacy and Safety of Cyp2c19 Gene-guided Oral Administration of Different P2Y12 Inhibitors in Elderly Patients with Acute Coronary Syndrome

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Abstract: Objective To explore the survival prognosis and safety analysis of the cyp2c19 gene-guided ACS elderly patient group using Tegretol and Clopidogrel. Methods Three hundred and eighty-five ACS patients aged ≥65 years were selected, tested for polymorphisms in the cyp2c19 gene, and divided into two groups according to the oral P2Y12 receptor inhibitor: 320 patients in the clopidogrel group and 165 patients in the tegretol group. Patients were followed up for 1 year after discharge from the hospital, with the primary end point being a composite end point of adverse cardiovascular events including cardiac death, nonfatal infarction, or absence of stroke, and the secondary end point including unstable angina, in-stent stenosis, target vessel revascularization, and all-cause mortality, as well as bleeding events. Results The 1-year rate of ischemic events was lower in patients treated with tegretol compared with the clopidogrel group [28.5% (47/165) versus 26.3% (84/320), P = 0.599], and the difference in the 1-year rate of BARC 2, 3, and 5 events between the two groups was not statistically significant [6.0% (10/165) versus 3.4% (11/320), P = 0.179]. P = 0.179]. Conclusion In elderly patients with cyp2c19-directed ACS, there was no significant difference in survival prognosis, ischemic events, or bleeding risk between tegretol and clopidogrel at 1 year.

Keywords: Acute coronary syndrome, Cyp2c19 gene, Clopidogrel, Tegretol, Ischemic events.

1. Introduction

Coronary heart disease (CHD) is a common chronic disease with a high rate of sudden death and serious harm, of which acute coronary syndrome (ACS) is a group of clinical syndromes caused by acute myocardial ischemia. Standardized management of coronary artery disease is the key to improving prognosis and reducing mortality, and antiplatelet therapy is the cornerstone of coronary artery disease management, regardless of whether drug or interventional therapy is adopted. Percutaneous coronary intervention (PCI) is one of the most widely used procedures in the world, and in addition to aspirin, the introduction of thienopyridine-type P2Y12 receptor inhibitors, known as dual antiplatelet therapy (DAPT) [1], has led to a significant reduction in the number of postprocedural thrombotic events [2]. Clopidogrel became the first widely used P2Y12 inhibitor to reduce the risk of thrombotic complications after PCI with an acceptable safety profile. However, the active metabolite production of clopidogrel is unpredictable, leading to significant inter-patient differences in the level of platelet response during treatment [3]. cyp2c19 gene polymorphisms have been identified as contributing, at least in part, to the observed differences in clopidogrel response [4] [5] [6] [7]. However, this difference is ten dangerous for the individual patient, doubling the risk of bleeding despite the fact that tegretol has greater watchfulness and does not require cyp2c19 gene metabolism [8] [9]. Coronary heart disease with the age of morbidity and mortality gradually increased, while the elderly coronary artery lesions are more complex, such studies are less in our country, so it is crucial to explore more personalized and scientific anti-plate program.

2. Data and Methods

2.1. Study population

ACS patients (aged ≥65 years) who were admitted to the Department of Cardiovascular Medicine of Huaqiao Hospital from 2014 to 2020 were divided into the clopidogrel group and the tegretol group according to the type of P2Y12 receptor inhibitor they were taking at discharge, with 165 patients in the tegretol group, aged 73.6±6.4 years, and 59 women (36.2%), and 320 patients in the clopidogrel group, aged 74.9±6.3 years, and 144 women (44.2%). 6.3 years, 144 (44.2%) females.

Patients with the following conditions were also excluded:

1) Combined coagulation dysfunctional diseases (such as nephrotic syndrome, tumor, autoimmune diseases, hematologic diseases, etc.) and those who were bedridden for a long time;

2) Patients with severe renal insufficiency, hepatic insufficiency, abnormal thyroid function;

(3) Patients with newly occurring gastrointestinal bleeding or bleeding from oral antiplate drugs.

4) Patients with incomplete medical record data.

5) Patients with new tumor survival less than 1 year after discharge.

6) Patients who change and stop medication on their own, as well as patients who fail to visit or follow up.

2.2. Research methodology

A retrospective cohort study research method was used, and the admission medical records of patients who met the study criteria were used as the baseline for this study. Information on patients' gender, age, admission time, discharge diagnosis, discharge with medication, and vascular

risk factors (smoking, hypertension, diabetes mellitus, hyperlipidemia) were collected. Patients' concomitant diseases were obtained from past history, medication use and secondary diagnoses. Patients were categorized into clopidogrel and tegretol groups based on their discharge carryover medications. Patients were counted based on outpatient visits, telephone follow-up, or hospitalization. The end point was a composite end point of 1-year post-discharge stroke events in the absence of stenosis, i.e., a composite end point that included cardiac death, cardiac infarction, or stroke in the absence of stenosis. Secondary endpoints were unstable angina, in-stent stenosis, target vessel revascularization, all-cause mortality, and BARC type 2, 3, and 5 events as defined by the BARC Academic Research Consortium (BARC) at 1 year.

2.3. Statistical analysis

SPSS 25.0 software was used to analyze the data, the count data were expressed as the number of cases and percentage, the comparison between groups was performed by chi-square test, the measurement data were expressed as mean±standard deviation, the comparison between groups was performed by ANOVA if it conformed to normal distribution, and the comparison between groups was performed by rank-sum test if it did not conform to normal distribution. $p<0.05$ indicated that the difference was statistically significant.

3. Results

3.1 Comparison of baseline data between the two groups, out of 385 patients, 320 were treated with clopidogrel and 165 patients were treated with tegretol. There was a difference in the age of the patients in the two groups, and the average age of patients using Tegretol was lower than that of clopidogrel, and the differences between the two groups in terms of gender, smoking history, history of hypertension, history of diabetes mellitus, and hyperlipidemia were not statistically significant ($P>0.05$) and comparable, as can be seen in Table 1.

Table 1. Clinical baseline information for older adults

Characteristic	Clopidogrel （n=320）	Ticagrelor （n=165）	t/X²	P-value
Age	74.9±6.3	73.6±6.4	2.13	0.033
Male	144（44.2%）	59（36.2%）	2.85	0.092
Hypertension	252（77.3%）	121（74.2%）	0.57	0.452
DM	110（34.6%）	57（35.4%）	0.06	0.805
Peptic ulcer	10 （3.1%）	3 （1.8%）	0.25	0.619
Strokehistory	46（14.1%）	19（11.7%）	0.57	0.451
Previous PCI	72（22.1%）	29（17.8%）	1.22	0.269
Smoking history			5.24	0.073
Non-smoker	247（75.8%）	108（66.3%）		
Quit	41（12.6%）	26（16%）		
Did not quit	38（11.7%）	67（13.7%）		
Platelets	213.4±59.3	217.0±62.3	0.63	0.527
TC	4.8±1.5	3.0±1.0	0.96	0.336
LDL-C	2.7±1.0	2.8±0.8	1.79	0.075
TG	1.57±1.04	1.74±1.88	1.27	0.205
LVEF	57.1±11.6	56.3±12.9	0.61	0.543
Medication				
Statin	316（96.9%）	157（96.3%）	0.13	0.719
Betablocker	254（79.5%）	134（82.2%）	1.04	0.208
ACEI/ARB	233（71.5%）	119（73%）	0.13	0.722
CCB	119（36.5%）	51 （31.3%）	1.30	0.254

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ALT, alanine transaminase;AST, aspartate transaminase;DM, diabetes mellitus ;eGFR, estimate glomerular filtration rate;CTNI, cardiac troponin I;CCB, Calcium channel blocker;PCI, percutaneous coronary intervention; HDL-C,High-density cholesterol; LDL-C,low density cholesterol; TC, total cholesterol ;TG, triglycerides; LVEF, left ventricular ejection fraction.

3.2 After 1 year of follow-up observation, the incidence rates of bleeding events in patients treated with Tegretol and Clopidogrel in the two groups were 6.0% and 3.4%, respectively, with Tegretol slightly higher than Clopidogrel, and the difference was not statistically significant (P=0.179). The incidence rates of ischemic events were 28.5% and 26.3% respectively, including 12 cases of cardiac death, 10 cases of cerebral infarction, and 4 cases of myocardial infarction, but there was no statistically significant difference in the rates of ischemic events between the two groups (P=0.599), see Table 2.

Table 2. Primary endpoints, secondary endpoints, and safety endpoint events in older adults

Events	Clopidogrel(n=320)	Ticagrelor(n=165)	X^2	P-value
Ischemic events	84(26.3%)	47(28.5%)	0.28	0.599
Primary Endpoint				
Cardiac death	7(2.2%)	5(3.0%)	0.07	0.797
Nonfatal infarction	1(0.3%)	3(1.8%)	1.46	0.227
Ischemic stroke	8(2.5%)	2(1.2%)	0.37	0.543
Secondary endpoint				
Unstable chest pain	52(16.3%)	24(14.5%)	0.24	0.625
TVR	12(3.8%)	11(6.7%)	2.05	0.152
In-stent restenosis	4(1.3%)	2(1.2%)	0.00	1.000
All-cause mortality	5(1.6%)	3(1.8%)	0.00	1.000
Bleeding events				
Bleeding	11(3.4%)	10(6%)	1.81	0.179

TVR, Target vessel revascularization

4. Discussion

Dual antiplatelet therapy for ACS has been the current classic treatment strategy, at present clopidogrel is still the most widely used P2Y12 (purinergic receptor) P2Y12 inhibitor in China, China's cardiovascular disease prevention guidelines and so on are still prioritized clopidogrel. Based on the results of the TRITON-TIMI 38 trial and the PLATO trial two studies have shown that Tegretol is superior to clopidogrel in reducing cardiovascular deaths, myocardial infarction, etc. [10] [11], but with advancing age, patients are at a higher risk of hemorrhagic and thrombotic events, which makes the optimal choice of antithrombotic therapy challenging [12] [13]. Although current guidelines recommend tegretol as the first choice of antithrombotic in patients with ACS [14]. However, large-scale, multicenter evidence-based studies have been conducted mainly in developed countries in Europe and the United States, and East Asian populations may have a higher risk of stroke than Western populations [15]. Moreover, some studies have shown that the problem of insufficiency is more prominent in elderly patients [16]. Therefore, when choosing an antiplatelet regimen for elderly ACS patients, it is important to reduce both thrombotic risk and bleeding risk. In conclusion, the results of this study did not show a significant survival benefit of tegretol over clopidogrel, but it also did not show a significant increase in the risk of hemorrhage. Limitations of this study: the trial population was small, and it was a single-center, only regional study, and there are still fewer large-scale clinical trials of tegretol and clopidogrel in China for patients with ACS in their own country, so more large-scale, multicenter clinical studies are needed to confirm this.

5. Conclusion

In elderly patients with cyp2c19-directed ACS, there was no significant difference in survival prognosis, ischemic events, or bleeding risk between tegretol and clopidogrel at 1 year.

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