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Comparison of therapeutic effects of ticagrelor and clopidogrel on patients with acute myocardial infarction and influence of lncRNA BANCR

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Abstract. – OBJECTIVE: To investigate the therapeutic effects of ticagrelor and clopidogrel on patients with acute myocardial infarction (AMI) and its effect of lncRNA BANCR.

PATIENTS AND METHODS: A total of 169 AMI patients admitted to our hospital from June 2015 to July 2018 were prospectively selected, of which 82 patients treated with clopidogrel were enrolled in the clopidogrel group (CG) and 87 patients treated with ticagrelor were enrolled in the ticagrelor group (TG). The therapeutic effect, serum lncRNA BANCR, platelet count, maximum platelet aggregation rate, serum troponin I (cTnI), serum creatine kinase isoenzyme (CK-MB), and serum high sensitivity C-reactive protein (hs-CRP) levels of the two groups of patients were detected and compared before and after treatment. The incidence of adverse reactions (ADR) and the occurrence of major adverse cardiovascular events (MACE) within 6 months after treatment were recorded and compared, and the predictive value of BANCR on therapeutic effect and MACE occurrence was analyzed.

RESULTS: The therapeutic effect of TG was remarkably better than that of CG ($p<0.05$), and the improvement of serum BANCR, platelet count, maximum platelet aggregation rate, cTnI, CK-MB, hs-CRP levels of the TG were remarkably better than that of CG ($p<0.05$). The incidence of ADR and MACE in the TG were notably lower than the CG ($p<0.05$). The expression of BANCR in the serum of patients with better therapeutic effect was significantly lower than that of patients with invalid treatment ($p<0.05$). The expression of BANCR in the serum of patients without MACE was significantly lower than that of patients with MACE ($p<0.05$). BANCR had high predictive value for both therapeutic effect and occurrence of MACE.

CONCLUSIONS: The effect of ticagrelor on AMI patients is significantly better than clopidogrel, and has higher safety. It can effectively reduce the content of BANCR in the serum of AMI patients, which is worthy of further promotion in clinical practice. Moreover, the predictive value of BANCR for the efficacy of AMI patients and the occurrence of MACE was high.

Key Words:
Ticagrelor, Clopidogrel, Acute myocardial infarction, Therapeutic effect, LncRNA BANCR.

Introduction

Acute myocardial infarction (AMI), as a common cardiovascular disease, is ultimately caused by the failure of the heart to supply oxygen and blood following coronary artery disease[1,2]. Moreover, the occurrence of AMI may further lead to severe complications, such as heart failure or myocardial ischemic shock, which seriously endanger the life safety of patients[3].

Recently, thrombolytic therapy is often used in AMI to treat the ischemic and anoxic state of patients, and vascular stent interventional therapy is used to further alleviate the symptoms of patients[4]. However, many patients still have blood hypercoagulability after thrombolysis and interventional therapy, which will have certain influence on the curative effect of thrombolysis and interventional therapy in the early stage[5].

At present, anti-platelet aggregation therapy is mainly used to treat hemagglutination[6]. Clopidogrel is a clinically common platelet aggregation inhibitor, which has a wide efficacy and can effectively improve the circulatory system[7]. Ticagrelor and clopidogrel have extremely similar mechanisms of action, which can effectively inhibit platelet activation and reduce platelet aggregation in vascular plaques[8,9]. Currently, the clinical comparison of the therapeutic effects of the two drugs on the interventional treatment of AMI has always been controversial. In order to provide more data support for the selection of therapeutic schemes for AMI patients, we have also compared the therapeutic effects of the two drugs. In recent years, there have been increasing researches on LncRNA in cardiovascular diseases. Therefore,

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we wonder whether LncRNA can help us to better evaluate the drug efficacy when it is included in the efficacy evaluation. LncRNA BANCR has been found to have abnormal expression in multiple tumor diseases in the past and Chen et al[10] observed that BANCR regulated the invasion and migration of esophageal squamous cell carcinoma through the Wnt/place-catenin signaling pathway. BANCR also plays an important regulatory role in cardiovascular diseases[11]. Therefore, in order to further evaluate the therapeutic effects of Ticagrelor and clopidogrel and to better predict the therapeutic effects of AMI patients, we also analyzed the changes of BANCR in AMI treatment, thus to provide more data support for the selection of treatment schemes for these patients.

Patients and Methods

General Data

Totally 169 patients with AMI admitted to our hospital from June 2015 to July 2018 were prospectively selected, including 102 males and 67 females. Patients were aged 56 to 71 years, with a mean age of (63.8±6.4) years. Among them, 82 patients treated with clopidogrel were included in the clopidogrel group (CG), and 87 patients treated with ticagrelor were included in the ticagrelor group (TG). Patients meeting the diagnostic criteria for AMI were enrolled in this research. Patients with serious blood system diseases, other malignant tumor diseases, severe liver and kidney dysfunction, or severe immune system diseases were excluded. This study was conducted with the approval of the hospital Ethics Committee, and all patients and their families had agreed to participate in the study.

Therapies

After interventional therapy, patients in the CG were treated with clopidogrel tablets (Lepu Medical Co., Ltd., Beijing, China; SFDA approval number: H20123115) orally on the basis of basic therapy, with 75 mg each time, once/d. Patients in the TG were treated with ticagrelor (AstraZeneca AB, London, UK; registration number: H20171037) on the basis of basic treatment, strictly following the medication standard of the instructions, with 90 g each time, twice/d. When taking medicine, patients should strictly follow the instructions of medical personnel and take the medicine continuously for 12 weeks without interruption.

QRT-PCR Detection of BANCR Expression

5 ml venous blood of all subjects were taken on an empty stomach, centrifuged at 1500 x g for 10 min at 4°C, and the supernatant was taken for detection after centrifugation. TRIzol was added to the serum to extract total RNA. The purity, concentration, and integrity of total RNA were detected by UV spectrophotometer and agarose gel electrophoresis. cDNA reverse transcription was performed according to the kit instructions (TransGen Biotechnology, Beijing, China), and BANCR detection was performed according to the kit instructions. PCR reaction conditions were as follows: pre-denaturation at 95°C for 30 s, denaturation at 95°C for 5 s, annealing, and extension at 60°C for 15 s, with a total of 40 cycles. GAPDH was used as the internal reference, and the primer sequence are shown in Table I. The experiment was repeated for 3 times.

Detection of Other Relevant Indicators

Before and after interventional therapy, 4 mL of venous blood of patients were extracted on an empty stomach in the morning. Serum was separated by centrifugation. Platelet count was monitored by flow cytometry. The maximum platelet aggregation rate was detected by dynamic translucency turbidimetry. Serum troponin I (cTnI) was detected by immunoturbidimetry. Serum creatine kinase isoenzyme (CK-MB) was detected by DGKC method. High sensitivity C-reactive protein (hs-CRP) was determined by enzyme linked immunosorbent assay (ELISA).

Ticagrelor Indexes

(1) The therapeutic effect of the two groups of patients was compared. Patients were divided into markedly effective [symptoms completely disappeared or basically disappeared, and the electro-

Table I. Primer sequences.

Factor	Upstream primer	Downstream primer
BANCR	5'-ACAGGACTCCATGGCAAACG-3'	5'- ATGAAGAAAGCCTGGTGCAGT-3'
GAPDH	5'-GGGAGCCAAAAGGGTCAT-3'	5'-GAGTCCTTCCACGATACCAA -3'

cardiogram (ECG) showed that the ST segment basically returned to normal, and the frequency and duration of onset decreased by more than 80% compared with before], effective (symptoms were markedly relieved, ECG showed that ST segment was improved but not completely recovered), invalid (symptoms were not improved or even aggravated, ECG showed no evident change compared with before treatment, the incidence frequency of onset was reduced by < 50%). The effective rate of treatment = (number of markedly effective people + number of effective people) / total number x 100%.

(2) The serum BANCR expression before and after treatment was compared between the two groups, and the BANCR levels of patients with different therapeutic effects were compared. ROC was applied to analyze the predictive value of BANCR for therapeutic effects.

(3) cTnI and CK-MB levels in the two groups were measured after treatment.

(4) The platelet count and maximum platelet aggregation rate before and after treatment were compared between the two groups.

(5) The adverse reactions (ADR) of the two groups during treatment were recorded and compared, including vomiting, bleeding, ecchymoma and ecchymosis.

(6) The patients were followed-up for six months, and the major adverse cardiovascular events (MACE) were recorded and compared between the two groups, including angina pectoris, high risk arrhythmia and acute left ventricular failure.

Statistical Analysis

Statistical analysis of experimental data was performed with SPSS 20.0 (IBM Corp., Armonk, NY, USA). Chi-square test was utilized for counting data, and mean standard deviation was utilized for measurement data. Comparison between the two groups was conducted by *t*-test, and comparison before and after treatment was conducted by paired *t*-test. GraphPad Prism 6 software (La Jolla, CA, USA) was applied for drawing the experimental pictures. When $p < 0.05$, there was a statistical difference.

Results

General Data

There was no remarkable difference in gender, age, BMI, and course of disease between the two groups ($p>0.05$), indicating comparability, as shown in Table II.

Comparison of Therapeutic Effects Between the Two Groups

After the course of treatment, the therapeutic effect in the two groups were compared. In the TG, there were 41 markedly effective patients, 28 effective patients, and 13 invalid patients, with an effective rate of 84.15%. In the CG, there were 53 markedly effective patients, 29 effective patients and 5 invalid patients, with an effective rate of 94.25%. The therapeutic effective rate of the TG

Table II. General data.

Factors	CG n=82	TG n=87	t/χ^2	*p*
Gender			0.026	0.873
Male	50 (60.98)	52 (59.77)		
Female	32 (39.02)	35 (40.23)		
Age (years)	63.34±6.37	63.04±6.41	0.305	0.761
BMI (kg/m²)	23.24±2.11	23.34±2.17	0.304	0.761
Course of disease (year)	3.11±0.32	3.14±0.34	0.591	0.555
Drinking history			0.009	0.926
With	43 (52.44)	45 (51.72)		
Without	39 (47.56)	42 (48.28)		
Smoking history			0.054	0.816
With	40 (48.78)	44 (50.57)		
Without	42 (51.22)	43 (49.43)		
Hypertension			0.006	0.963
With	54 (65.85)	57 (65.52)		
Without	28 (34.15)	30 (34.48)		
Diabetes mellitus			0.001	0.969
With	45 (54.88)	48 (55.17)		
Without	37 (45.12)	39 (44.83)		

Table III. Comparison of therapeutic effect between the two groups.

Therapeutic effective	CG n=82	TG n=87	t/χ^2	*p*
Markedly effective	41 (50.00)	53 (60.92)	2.039	0.153
Effective	28 (34.15)	29 (33.33)	0.012	0.911
Invalid	13 (15.85)	5 (5.75)	4.531	0.033
Total effective rate	69 (84.15)	82 (94.25)	4.531	0.033

was remarkably higher than the CG, and there was a statistically significant difference ($p<0.05$), as shown in Table III.

Comparison of Serum BANCR Expression Before and After Treatment Between the Two Groups of Patients

There was no notable difference in the serum BANCR expression between the two groups of patients before treatment ($p>0.05$). After treatment, the serum BANCR expression of patients in both groups was considerably elevated compared with before treatment ($p<0.05$), and it improved more remarkably in TG than it in CG ($p<0.05$). By analyzing the BANCR level of patients with different therapeutic effects, it was found that the serum BANCR of patients with effective (markedly effective + effective) treatment was remarkably lower than that of patients with invalid treatment ($p<0.05$). ROC analysis found that BANCR had higher value in predicting therapeutic effects, as shown in Figure 1.

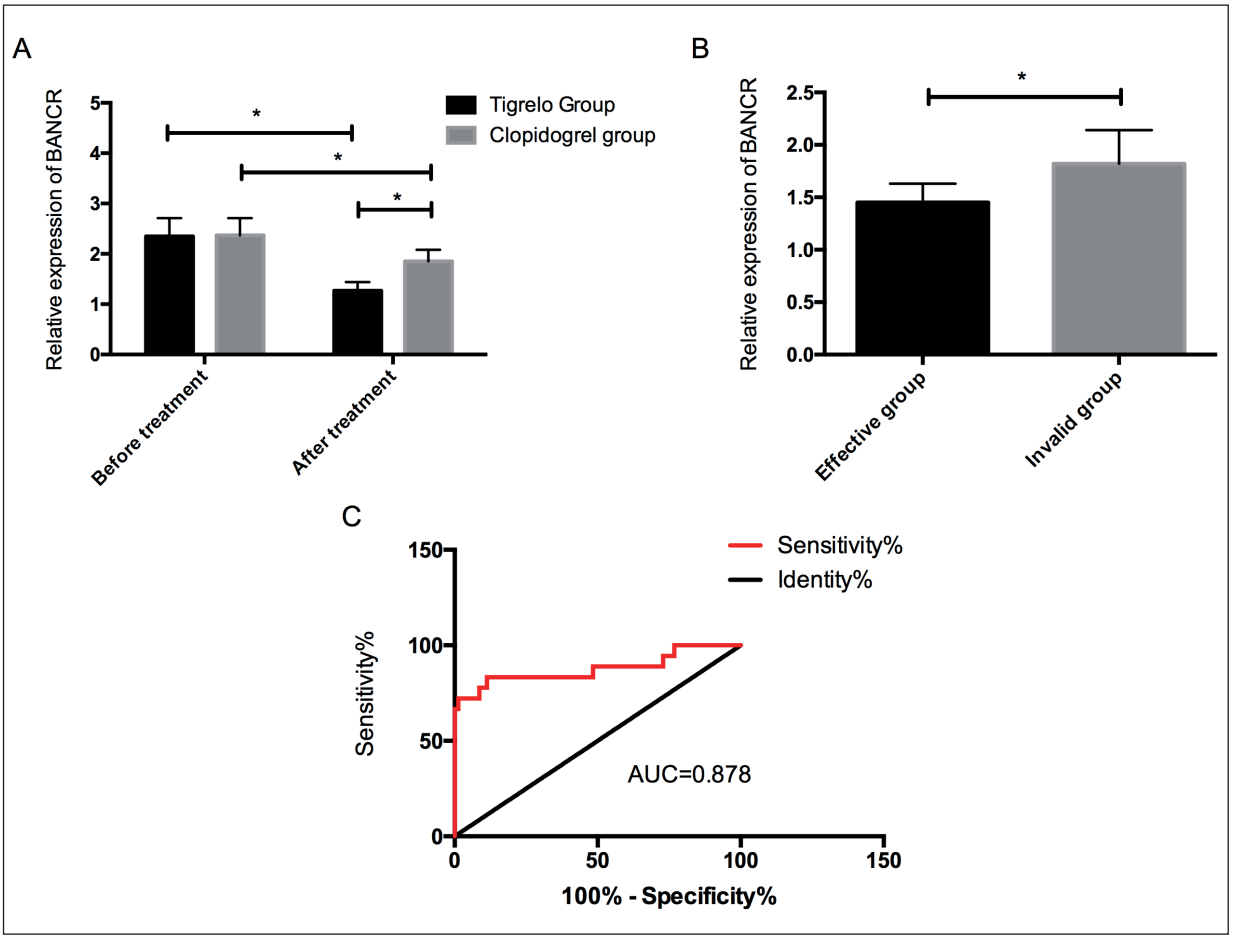

Figure 1. Serum BANCR expression and its predictive value for therapeutic effect. **A**, Serum BANCR expression of two groups of patients before and after treatment. B, BANCR expression in patients with different therapeutic effects. C, ROC of BANCR in predicting therapeutic effect. *denotes $p<0.05$.

Comparison of Serum cTnI, CK-MB and hs-CRP Levels Between the Two Groups Before and After Treatment

Before the treatment, there was no notable difference in serum cTnI, CK-MB, and hs-CRP levels between the two groups ($p>0.05$). After treatment, all of the three reduced remarkably in both groups ($p<0.05$), and the expression of the three in TG improved more notably than that of patients in CG ($p<0.05$), as shown in Figure 2.

Platelet Count and Maximum Platelet Aggregation Rate of the Two Groups Before and After Treatment

Before treatment, there was no remarkable difference in platelet count and maximum platelet aggregation rate between the two groups ($p>0.05$). While the platelet count and the maximum platelet aggregation rate of patients in both groups decreased remarkably after treatment ($p<0.05$), and the two of the TG improved more significantly than those of the CG ($p<0.05$), as shown in Figure 3.

Comparison of ADR Between the Two Groups

We recorded and compared the ADR of patients in both groups during treatment. The results revealed that the number of patients in CG suffering from vomiting, bleeding, ecchymoma, and ecchymosis was 2, 3, 3 and 3, respectively, and the occurrence of ADR was 13.41%. The number of patients in the TG suffering from vomiting, bleeding, ecchymoma, and ecchymosis was 0, 0, 1 and 1, respectively, and the occurrence of ADR was 2.30%. The occurrence of ADR was remarkably higher in the CG than in the TG ($p>0.05$), as shown in Table IV.

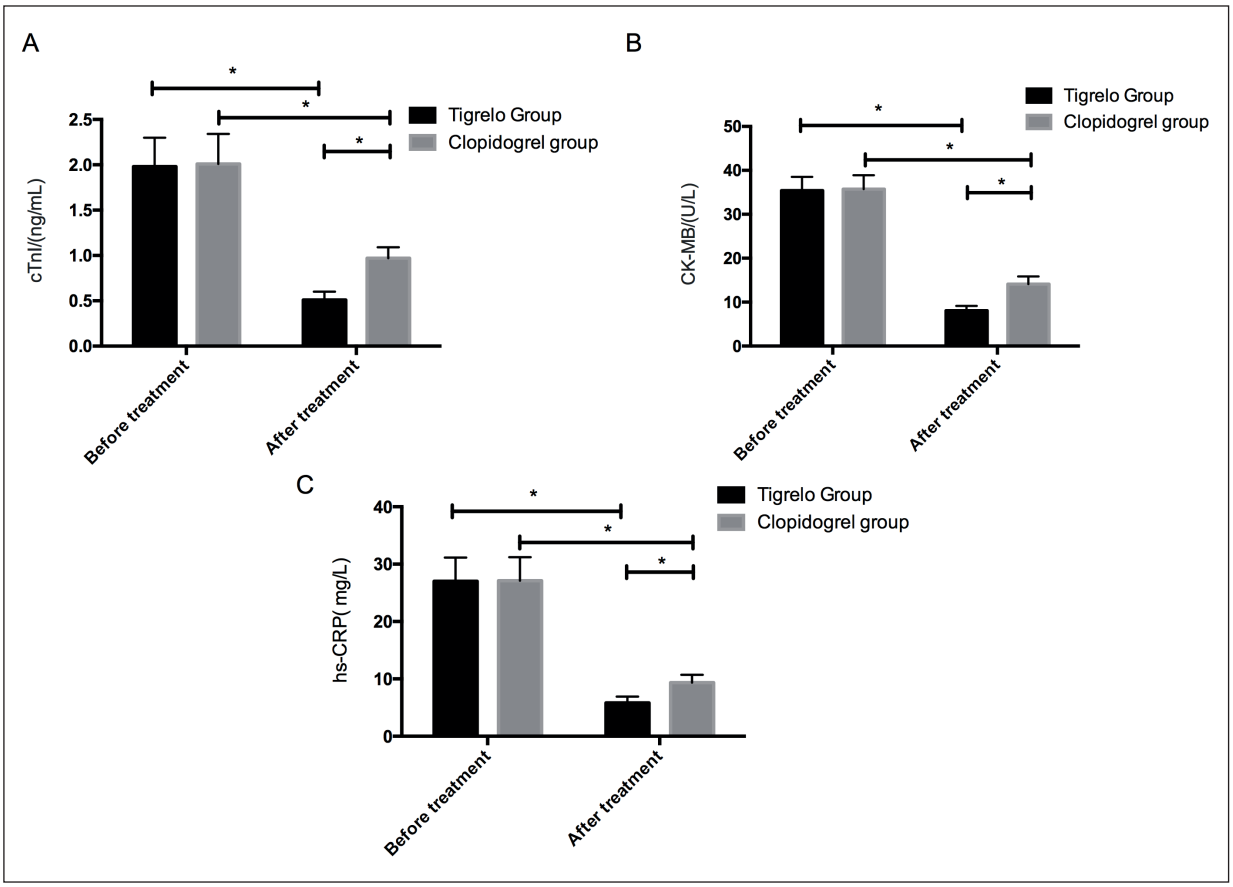

Figure 2. Comparison of serum cTnI, CK-MB and hs-CRP levels between the two groups before and after treatment. **A**, Comparison of serum cTnI levels between the two groups before and after treatment. **B**, Comparison of serum CK-MB levels between the two groups before and after treatment. **C**, Comparison of serum hs-CRP levels between the two groups before and after treatment. *denotes $p<0.05$.

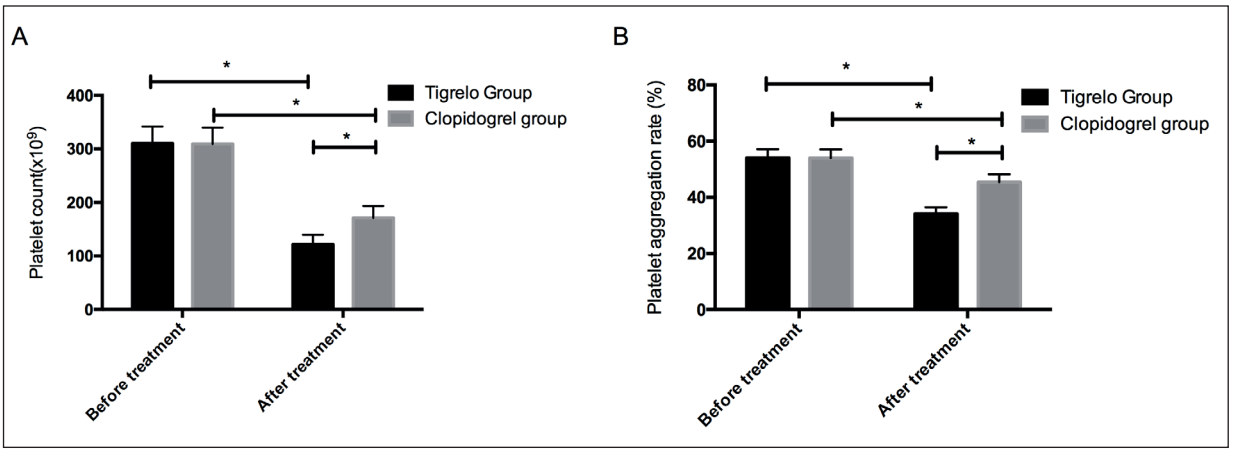

Figure 3. Platelet count and maximum platelet aggregation rate of two groups of patients before and after treatment. **A**, Platelet counts of two groups of patients before and after treatment. **B**, Maximum platelet aggregation rate of the two groups of patients before and after treatment. * denotes $p<0.05$.

Comparison of Prevalence of MACE Between Two Groups of Patients

We recorded and compared the MACE events of patients in both groups during treatment. The results revealed that the number of patients with angina pectoris, high-risk arrhythmia and acute left ventricular failure in the CG was 6, 7 and 7, respectively, and the prevalence of MACE events was 24.39%. The number of patients with angina pectoris, high-risk arrhythmia and acute left ventricular failure in the TG was 2, 2 and 2, respectively, and the prevalence of ADR was 6.90%. The prevalence of MACE events was notably lower in the TG than in the CG ($p>0.05$), as shown in Table V.

Analysis of BANCR's Predictive Value for MACE

Patients were divided into a MACE group and a non-MACE group in line with the occurrence of MACE. After detecting the serum BANCR of patients in the two groups, it was found that the serum BANCR expression of patients in MACE group was remarkably higher than that in non-MACE group ($p<0.05$). Then, ROC showed that BANCR had high predictive value for the occurrence of MACE, as shown in Figure 4.

Discussion

AMI is a common cardiovascular disease. For the past few years, with the arrival of an aging society, the incidence of AMI is getting higher and higher, posing a serious threat to health and life of the majority of the elderly population[12]. For AMI patients, thrombolytic therapy is an extremely important method to change the hypoxic-ischemic state of them. Interventional therapy can be used to further alleviate the symptoms when patients' condition is stable[13,14]. However, some patients still have blood coagulation after interventional therapy[15,16], which has a great influence on the curative effect of interventional therapy. In view of this situation, antiplatelet aggregation drugs are commonly used in clinic at present, and ticagrelor and clopidogrel are common drugs[17].

Table IV. Comparison of ADR between the two groups.

Factors	CG n=82	TG n=87	t/χ^2	*p*
Vomiting	2 (2.44)	0	2.147	0.143
Bleeding	3 (3.66)	0	3.240	0.072
Ecchymoma	3 (3.66)	1 (1.15)	1.150	0.284
Ecchymosis	3 (3.66)	1 (1.15)	1.150	0.284
Total occurrence rate (%)	11 (13.41)	2 (2.30)	7.346	0.007

Table V. Comparison of ADR between the two groups.

Factors	CG n=82	TG n=87	t/χ^2	*p*
Angina pectoris	6 (7.32)	2 (2.30)	2.357	0.125
High risk arrhythmia	7 (8.54)	2 (2.30)	3.258	0.071
Acute left ventricular failure	7 (8.54)	2 (2.30)	3.258	0.071
Total incidence rate	20 (24.39)	6 (6.90)	9.924	0.001

In our study, the therapeutic effects of ticagrelor and clopidogrel in AMI patients were compared. The therapeutic effect of ticagrelor on AMI patients was significantly better than clopidogrel, suggesting that the effect of ticagrelor was better only in terms of curative effect alone. Clopidogrel is a commonly used P2Y12 inhibitor drug, which can play an anti-platelet aggregation role, but it needs to be metabolized by the liver. However, due to different metabolic levels of clopidogrel, individual drug tolerance varies greatly, and drug resistance may occur in some patients, leading to poor efficacy[18]. Ticagrelor is a P2Y12 receptor antagonist with high drug availability, which can directly act on ADP receptor P2Y12 of patients and can rapidly inhibit platelet aggregation[19]. The above also explains the reason why the curative effect of ticagrelor is better than clopidogrel. In order to adjust the treatment plan according to the patient's situation, it is also important to predict the therapeutic effect. In recent years, there are increasing related researches on LncRNA in cardiovascular diseases, so it is also an important direction to select LncRNA to predict and evaluate the therapeutic effect of drugs[20]. We tested the LncRNA BANCR in the serum patients in both groups. The results revealed that after treatment, the expression of BANCR in the serum of patients in both groups decreased significantly, but the decrease degree of serum BANCR in the TG was greater than that in the CG. Subsequently, we also detected the expression of BANCR in the serum of patients with different therapeutic effects. The results showed that the expression of BANCR in the serum of patients with better therapeutic effects was notably lower than that of patients with invalid treatment. Therefore, we further conducted ROC analysis and found that BANCR had higher value for the therapeutic effects of drugs on AMI patients.

Then, in order to further analyze the effect of ticagrelor and clopidogrel on AMI patients, we also compared the serum cTnI, CK-MB, hs-CRP, platelet count and platelet aggregation rate of patients in both groups before and after treatment. The results revealed that the serum cTnI, CK-MB, hs-CRP, platelet count, and platelet aggregation rate of patients in both groups improved significantly after treatment, and the improvement effect of ticagrelor was significantly better than clopidogrel.

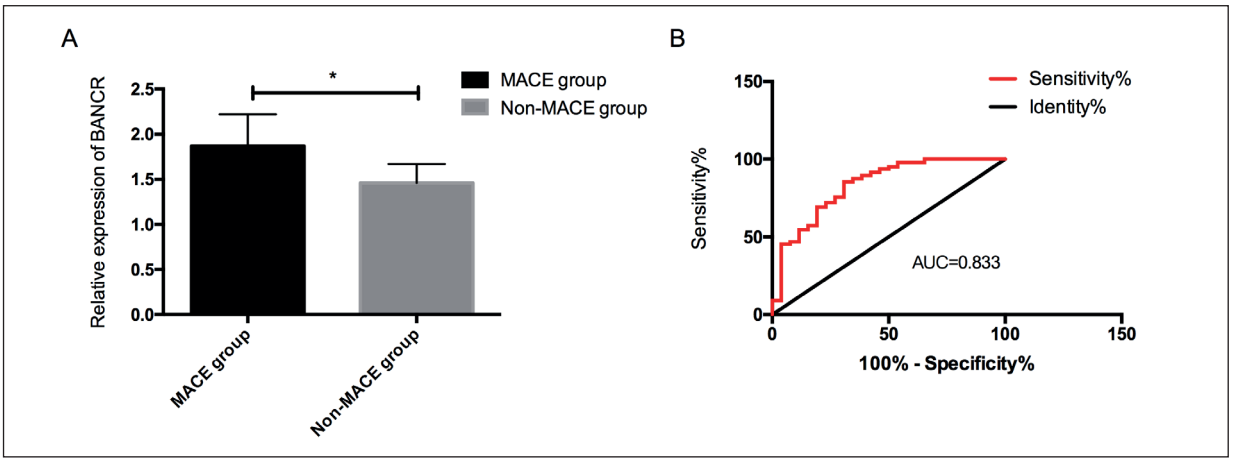

Figure 4. Analysis of BANCR's predictive. **A**, BANCR expression of patients with different MACE occurrence. **B**, ROC analysis of BANCR's prediction of MACE. * denotes $p<0.05$.

The changes of serum cTnI, CK-MB, and hs-CRP showed that the effect of ticagrelor on myocardial improvement in AMI patients was stronger than that of clopidogrel, possibly because ticagrelor has a stronger anti-platelet effect and thus a stronger protective effect on the myocardium and blood vessels[21]. The change of platelet quantity and platelet aggregation rate also proves this point. Ticagrelor has good stability[22,23], which can better restore the blood supply of coronary artery-related myocardium to reduce the area of myocardial infarction, and it can also exert anticoagulant effect to further improve the blood supply and oxygen supply of myocardium to reduce the myocardial damage for the excessive oxidative stress.

For drug therapy, safety should be considered in addition to curative effect, so we also compared the ADR of the two drugs. The results exhibited that the ADR of patients treated with ticagrelor were significantly lower than that of clopidogrel, which suggested that ticagrelor have good curative effect and good safety at the same time.

Finally, we also compared the MACE occurrence rate of patients in both groups within 6 months after treatment. The results expressed that the MACE prevalence rate of patients treated with ticagrelor was notably lower than that of clopidogrel. In order to provide better reference for the later treatment of AMI patients, we analyzed the predictive value of BANCR for MACE. It turns out that the serum BANCR expression of patients with MACE was considerably higher than that of patients without MACE, and ROC analysis results showed that BANCR also had higher predictive value for the occurrence of MACE.

Conclusions

To sum up, ticagrelor is significantly better than clopidogrel in therapeutic effect for AMI patients, and has higher safety. We found for the first time that ticagrelor can effectively reduce the content of BANCR in serum of AMI patients, and the predictive value of BANCR for the efficacy of AMI patients and the occurrence of MACE is relatively high, which may be one of the potential clinical indicators for AMI patients. This provides a certain direction for the subsequent research on the molecular mechanism of AMI development. However, there are still some limitations in this study. We have not conducted an *in vitro* research on the effect of BANCR on myocardial cells, so the effect of BANCR on AMI still needs to be further explored.

Conflict of Interests

The authors declare that they have no conflict of interest.

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