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Application effect of tirofiban on percutaneous coronary intervention in patients with acute coronary syndrome and its postoperative effect on C-X-C motif chemokine ligand 16 level and myocardial perfusion

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Abstract: This study aimed to investigate the application effect of tirofiban on percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS) and its postoperative effect on C-X-C motif chemokine ligand 16 (CXCL16) level and myocardial perfusion. A total of 50 cases of patients diagnosed with acute coronary syndrome and treated in Sunshine Union Hospital (Weifang, China) were included in group A and 30 cases of healthy subjects underwent physical examination in our hospital during the same period were enrolled in group B. Tirofiban was used in group A patients during PCI. Clinical efficacy evaluation criteria were used to evaluate the efficacy after treatment. The level of CXCL16 in serum before and after treatment was detected by qRT-PCR. Receiver operating characteristic (ROC) curve was drawn to analyze the value of C-X-C Motif Chemokine Ligand in diagnosing ACS. Before treatment, CXCL16 level in group A was significantly higher than that in group B (p<0.001). After treatment, patients in TMPG grade 3 in group A were significantly increased (p<0.001). Tirofiban could improve myocardial perfusion in patients with ACS after PCI, reduce adverse events and CXCL16 levels. Serum CXCL16 is expected to be a potential diagnostic and therapeutic predictor of ACS.

Keywords: Tirofiban, acute coronary syndrome, PCI, CXCL16, myocardial perfusion.

INTRODUCTION

Acute coronary syndrome (ACS) is a high-risk disease caused by coronary artery thrombosis due to atherosclerotic plaque rupture, leading to acute myocardial ischemia, and is the main cause of death in developed countries. ACS is a subclass of coronary heart disease (CAD). According to research statistics, 15.5 million people in the United States have CAD (Writing Group Members *et al*., 2016) and the mortality rate in developing countries is also increasing (Sanchis-Gomar *et al*., 2016). Studies have shown that advanced age is an independent predictive factor of poor prognosis of ACS (Dai *et al*., 2016), and prevalence increases with age. Therefore, the society with an increasingly serious aging population urgently needs to strengthen the prevention and treatment measures of ACS.

Due to the rupture of atherosclerotic plaques in patients with ACS, myocardial perfusion is poor, which may lead to myocardial ischemia or even death. Percutaneous coronary intervention (PCI), as the preferred treatment for ACS recommended by foreign guidelines (Yetgin *et al*., 2013), has a considerable curative effect. However, PCI also has limitations, for it may cause damage to blood vessels again during stent implantation, and postoperative no-reflow also has a bad impact on patients' safety (Liang *et al*., 2017). Therefore, antiplatelet therapy is indispensable in operation. Studies have shown that tirofiban can effectively improve myocardial perfusion in patients and reduce the incidence of postoperative complications (Kingma, 2019). Tirofiban is a highly effective and reversible GP αb/βa inhibitor, which can prevent platelet aggregation. It can achieve anti-platelet coagulation effect by preventing the binding of fibrinogen and platelet glycogen receptor and it can also block the shedding of blood clots, reduce the vasoconstrictor factors caused by inflammation, and reduce the thrombosis events of ACS (Yang *et al*., 2019). Therefore, the study of the application of tirofiban in PCI is of great significance for clinical treatment. C-X-C motif chemokine ligand 16 (CXCL16) is a soluble chemokine discovered in recent years, which is involved in the development of inflammation and promotes atherosclerosis (Hu *et al*., 2016). Foreign studies have reported that CXCL16 is expressed in the in time of atherosclerotic plaques obtained from coronary or carotid endarterectomy, but it is not found in normal aortic, endothelial or smooth muscle cells (Nazari *et al*., 2017). Nosseir *et al* (Nosseir, *et al*., 2019) showed that compared with healthy people, the serum CXCL16 level in ACS patients was significantly increased. However, the predictive value of preoperative serum CXCL16 in tirofiban treatment is not clear. It is of great significance to study the effect of tirofiban in PCI and the predictive value of preoperative serum CXCL16 in ACS.

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In a word, this study uses tirofiban to ACS patients undergoing PCI operation, to investigate the therapeutic effect of tirofiban and its effect on myocardial perfusion, and to study the diagnosis, efficacy and predictive value of preoperative serum CXCL16 in ACS.

MATERIALS AND METHODS

Collection of clinical data

Fifty patients with ACS diagnosed and treated in Sunshine Union Hospital (Weifang, China) from January 2017 to March 2018 were selected and included in group A. They were treated with tirofiban during PCI operation. Meanwhile, 30 healthy people underwent physical examination were included in group B. The clinical data of the two groups were completely recorded. This study was approved by the medical ethics committee of Sunshine Union Hospital (Weifang, China).

Inclusion and exclusion criteria of patients

Inclusion criteria: Patients with unstable angina or non-ST elevation myocardial infarction, and the diagnostic criteria were based on the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) (No authors listed, 2016). Patients treated in our hospital with complete clinical data. Patients informed and signed informed consent.

Exclusion criteria: Patients whose systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg. Patients with bleeding within one year. Patients with coagulation disorders. Patients with severe liver and kidney function damage. Patients with blood platelet disorders and platelet count <150000/mm^3. Patients with hemorrhagic retinopathy. Patients in chronic hemodialysis. Patients used other drugs affecting hemostasis. Patients with surgical operation within one month. Patients in lactation.

Treatment plan of patients

All patients were treated with conventional antiplatelet therapy, namely oral clopidogrel bisulfate, taking 300 mg for the first time, once/d, and then taking 75mg, once/d (Lepu Pharmaceutical Co., Ltd., SFDA approval number: H20123116). Along with aspirin enteric-coated tablets 300 mg, once/ d (Shenyang Original Pharmacolabo Co., Ltd., SFDA approval number: H20065051), Hypodermic injection of low molecular weight heparin calcium: 1ml: 5000AXa, once/d (Shenzhen Saibaoer Biological Pharmaceutical co., LTD., SFDA approval number: H20060190).

PCI was performed after continuous antiplatelet therapy for 7 days. Preoperative loading injection of tirofiban (Shandong Xinshidai Pharmaceutical Co., Ltd., SFDA approval number: H20090227) 10g/kg5min was performed, and then maintaining at 0.15g/kg/min24h. Postoperative oral administration of 75mg clopidogrel and 100 mg aspirin continued, once /d.

Detection of CXCL16 level

The enrolled patients were taken 3ml of venous blood on an empty stomach on the second day in the morning. Meanwhile, the same blood samples were taken from subjects of the control group, which were left at room temperature for 30 min and centrifuged at 3000 rpm/min for 10 min. The supernatant was absorbed and stored in the refrigerator at -80℃ for centralized detection.

Total RNA was extracted from the serum using TRIzol (Invitroge, USA, 15596026), and the purity, concentration and integrity of total RNA were detected using a UV spectrophotometer and agarose gel electrophoresis. TaqMan™ MicroRNA Reverse Transcription Kit (Applied Biosystems, USA, 4366596) was used for reverse transcription of total RNA. The procedures of transcription were strictly performed according to the manufacturer's instructions. cDNA was collected, and mirVana™ qRT-PCR miRNA Detection Kit (Invitroge, AM1558, USA) and ABI 7500 (Applied Biosystems, 7500, USA) was used for amplification. The amplification system was as follows: mirVana 5X PCR Buffer 5μL, 50X ROX ™ 0.5μL, cDNA 1μL, upstream primer 0.5μL and downstream primer 0.5μL and finally supplemented with Nuclease-free Water to 20μL. Amplification conditions were as follows: pre-denaturation at 95°C for 3 min, denaturation at 95°C for 15s and annealing extension at 60°C for 30 s, with a total of 40 cycles. Three replicate wells were set for each sample and the experiment was performed 3 times. In this study, GAPDH was used as an internal reference and the data was analyzed using 2-△△ Ct.

Patients follow-up

Patients in group A were followed up for short-term bleeding events and MACE events by telephone and outpatient reexamination, once a week.

Outcome measures

Main outcome measures: the clinical efficacy of patients in group A after treatment was observed, and the evaluation criteria for efficacy were shown in table 1. Total effective rate = n (markedly effective + effective) / n (all patients) × 100%. The changes of CXCL16 level in serum of patients before treatment and 24h after PCI were observed. The changes of TMPG grading before treatment and 7d after PCI (Gibson and Schomig, 2004) were observed and compared. Diagnostic value and predictive value of efficacy of CXCL16 in patients with ACS were observed.

Secondary outcome measures: bleeding events and MACE events were observed of patients in group A 30 days after PCI (Zhang *et al*., 2020).

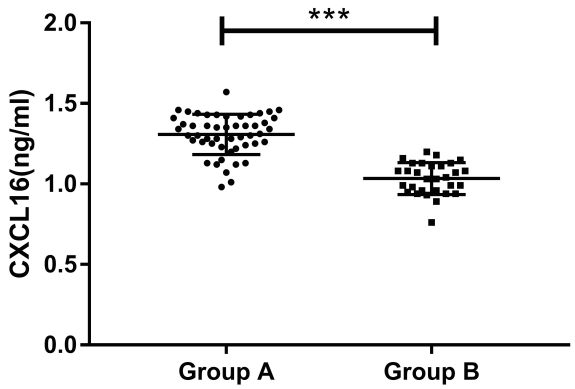
STATISTICAL ANALYSIS

In this study, SPSS20.0 (Cabit information technology Co., Ltd., Shanghai, China) software package was used for statistical analysis of the collected data, and GraphPad Prism 7 (SOFTHEAD. Inc., Shenzhen, China) was used for drawing the data images. N=Z2 × (1-P) / E2 was used to calculate the sample size, where N is the sample size, Z is the statistic size, and E is the error value. Enumeration data utilization (%) was represented by chi-square test, expressed as X2. Normal distribution data were expressed as mean ± standard deviation (Meas±SD). Independent sample t-test was used for comparison between two groups, and paired t-test was used for inter-group comparison. ROC curve was used to analyze the diagnostic value and predictive value of serum CXCL16 in ACS. Significant differences were indicated when $p<0.001$.

RESULTS

Comparison of baseline data between the two groups

The data in table 2 showed that there was no significant difference in age, gender, BMI, smoking history, drinking history and residence between groups A and B ($p>0.05$), suggesting comparability.

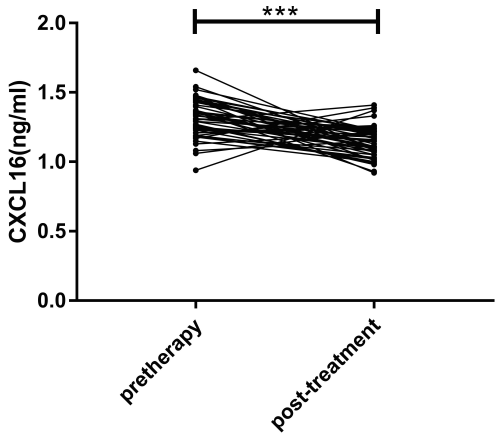


The CXCL16 level in group A (1.302±0.148) was significantly higher than that in group B (1.035±0.118), *** indicated $p<0.001$.

Fig. 1: Comparison of CXCL16 level before treatment in the two groups

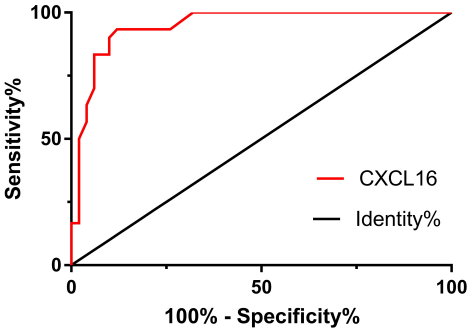
The therapeutic effect of tirofiban and the changes of serum CXCL16 levels in the two groups

The clinical efficacy of patients was evaluated according to the efficacy evaluation criteria. The results showed that 25 patients were markedly effective, 22 were effective, and 3 were ineffective. The total effective rate was 94%. Comparing the CXCL16 level in serum of patients in A, B groups before treatment, it was found that the CXCL16 level in group A (1.302±0.148) was significantly higher than that in group B (1.035±0.118) ($p<0.001$), as shown in fig. 1. The serum CXCL16 level before and after treatment was compared, and it was found that the CXCL16 level of patients after treatment (1.154±0.133) was significantly lower than that before treatment (1.302±0.148) ($p<0.001$), as shown in fig. 2.



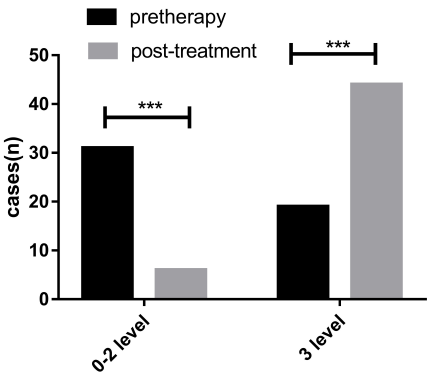
The level of CXCL16 in patients after treatment (1.154±0.133) was significantly lower than before treatment (1.302±0.148), *** indicated $p<0.001$.

Fig. 2: Changes in CXCL16 level before and after treatment



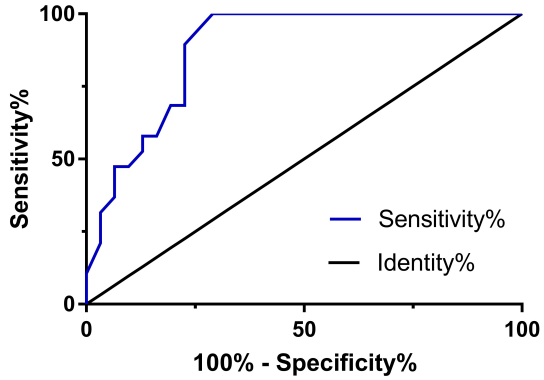
AUC=0.948, 95CI%: 0.901-0.995, sensitivity: 93.33%, specificity: 88.00%, Youden index: 81.33%, cut-off value: ≥1.175.

Fig. 3: ROC curve of CXCL16 in the diagnosis of ACS patients



Treatment was significantly higher than that in TMPG grade 3 patients. *** indicates $p<0.001$

Fig. 4: The expression level of CXCL16 in TMPG grade 0-2 patients before



AUC=0.880, 95CI%: 0.787-0.972, sensitivity: 100%, specificity: 70.97%, Yoden index: 70.97%, cut-off value: <1.16.

Fig. 5: ROC curve for predicting the efficacy of CXCL16 in ACS patients

Diagnostic value of CXCL16 in ACS patients

The expression of CXCL16 in serum before treatment was collected and ROC curve graph was drawn. It was found that the AUC of CXCL16 was 0.948 (95CI%: 0.901-0.995), with sensitivity of 93.33%, specificity of 88.00%, Youden index of 81.33% and cut-off value of ≥1.175, as shown in fig. 3.

Comparison of TMPG grading of patients before and after treatment

Patients were graded according to the TMPG grading system after 7 d of treatment and it was found that there were 31 patients with TMPG grade 0-2, 19 patients with TMPG grade 3 before treatment. After treatment, there were 6 patients with TMPG grade 0-2 and 44 patients with TMPG grade 3. The TMPG grading before and after treatment was statistically different (p<0.001), as shown in table 3.

Efficacy predictive value of CXCL16 in ACS patients

Patients were divided into two groups by TMPG grade 0-2 and TMPG grade 3. The relative expression levels of serum CXCL16 before treatment in two groups of patients were compared, it was found that the expression level of CXCL16 in TMPG grade 0-2 patients before treatment was significantly higher than that in TMPG grade 3 patients (p<0.001), see fig. 4. ROC curve was drawn according to the expression of CXCL16 level in serum of patients in the two groups. The results showed that the AUC was 0.880 (95%CI: 0.787-0.972), the sensitivity was 100%, specificity was 70.97%, Youden index was 70.97% and cut-off value was <1.16. As shown in fig. 5.

Comparison of bleeding events and MACE events in patients 30 days after PCI

According to the statistics results of 30 days follow-up, there were 5 patients with slight bleeding events, 1 patient with moderate bleeding events, and no patient with major bleeding. The total probability of bleeding events was 12.00%. According to the statistical results of MACE events, there were 2 patients with angina pectoris, 1 patient with myocardial infarction, without death events. The total probability of MACE events was 6.00%.

DISCUSSION

The increasing incidence and mortality of ACS is a serious threat to people's life safety, and the incidence is getting younger, which attracts more and more attention from the society. PCI is considered to be the most effective method for the treatment of ACS (Limdi *et al*., 2020). Without proper treatment and management, however, stent thrombosis and serious complications may occur, for which antiplatelet therapy plays an important role.

Currently, aspirin and clopidogrel are commonly used antiplatelet drugs in clinical practice. However, studies have found that some patients have resistance to aspirin and continue to develop thromboembolism after treatment (Cai *et al*., 2016). Clopidogrel is widely used in clinical practice due to its advantages of high safety and low risk rate. Whereas its anti-platelet effect is affected in different patients due to genetic defects (Shen *et al*., 2017), and its inhibitory effect is irreversible, which is easy to cause damage to the normal blood function of patients. Therefore, it is particularly important to change drugs or achieve combined treatments. The GPαb / βa receptor antagonists that have appeared in recent years are a kind of drugs with strong antiplatelet effect. Currently, only tirofiban is marketed in China. This study will apply tirofiban to the treatment of ACS patients during PCI, to study the efficacy of tirofiban and its effect on CXCL16 level and myocardial perfusion, so as to provide effective reference for clinical treatment.

All 50 patients enrolled in this study received basic antiplatelet agents and tirofiban during PCI. After treatment, efficacy of patients were divided into marked effect, effective and ineffective in accordance with the evaluation criteria of clinical efficacy. Statistical analysis found that the total effective rate of treatment for patients was 94%, which initially confirmed the effectiveness of tirofiban in the treatment of ACS. We then detected CXCL16 level in serum of patients before and after treatment in both groups. Studies have found that CXCL16 participates in the development of ACS, regulates inflammation, promotes tissue damage and fibrosis, and is highly expressed in cardiovascular diseases (Ma *et al*., 2018), which is positively correlated with the degree of coronary atherosclerotic heart disease (Xing *et al*., 2018). The results of this study showed that the level of CXCL16 in the serum of group A was significantly higher than that of group B before treatment,

but 24 hours after surgery, the level of CXCL16 in patients was significantly lower than that before treatment, which confirmed that the treatment received by the patients could effectively reduce the level of CXCL16 and reduce the pro-inflammatory function. We speculated that the reason might be that the up-regulated expression of CXCL16 in ACS patients promoted the activity of macrophages, enhanced phagocytosis of macrophages (Nemska *et al*., 2016) and intensified inflammatory response. Studies have revealed that CXCL16 is closely related to the vulnerability of atherosclerotic plaques (Jin 2017). Tirofiban can specifically bind to platelet surface receptors, effectively prevent platelet aggregation and adhesion, thus to play a strong role in inhibiting platelet aggregation, reduce thrombus reformation (Li *et al*., 2018), and reduce CXCL16 level. The difference in the expression of CXCL16 in serum between the two groups suggested the diagnostic value of CXCL16 in ACS patients. Hence, we further drew a ROC curve according to the expression level of CXCL16 in ACS patients, and the result showed that the AUC was 0.948, confirming the high diagnostic value of CXCL16. CXCL16 might provide new information in clinical cardiovascular risk assessment (Andersen *et al*., 2019b).

Table 1: Clinical efficacy evaluation criteria

Grade of efficacy	Evaluation criteria
Markedly effect	Clinical symptoms basically disappeared, electrocardiograph examination showed normal
Effective	Clinical symptoms improved to some extent, electrocardiograph improved, but did not return to normal
Ineffective	Clinical symptom and electrocardiograph did not improve or even aggravate

Table 2: Baseline data of patients in the two groups

Factors		Group A (n=50)	Group B (n=30)	t/X^2 value	*p* value
Age (years old)		65.7±8.4	66.2±7.9	0.264	0.793
Gender					
	Male	28(56.00)	17(56.67)	0.003	0.954
	Female	22(44.00)	13(43.33)		
BMI(kg/m^2)		24.67±2.28	25.12±1.98	0.897	0.373
Smoking history					
	Yes	31(62.00)	19(63.33)	0.014	0.905
	No	19(38.00)	11(36.67)		
Drinking history					
	Yes	7(14.00)	3(10.00)	0.274	0.601
	No	43(86.00)	27(90.00)		
Residence					
	Cities	23(46.00)	14(46.67)	0.003	0.954
	Countryside	27(54.00)	16(53.33)		
TC(mmol/L)		4.78±0.88	4.81±0.56	0.167	0.868
Hypertension					
	Yes	37(74.00)			
	No	13(26.00)			
Hyperlipidemia					
	Yes	21(42.00)			
	No	29(58.00)			
Diabetes					
	Yes	19(38.00)			
	No	31(62.00)			
Disease composition					
	Unstable angina	22(44.00)			
	Non-ST elevation myocardial infarction	28(56.00)			
Timi risk score					
	0-2	12(24.00)			
	3-4	31(62.00)			
	5-7	7(14.00)			

Table 3: Comparison of TMPG grading of patients before and after treatment

Groups	TMPG grade 0-2	TMPG grade 3
PCI before operation	31 (62.00)	19 (38.00)
PCI after operation	6 (12.00)	44 (88.00)
X^2	26.81	
p	<0.001	

The level of myocardial perfusion in ACS patients was poor, so we evaluated the level of myocardial perfusion by studying the TMPG grading of patients before and after treatment, so as to understand the influence of tirofiban on the level of myocardial perfusion during PCI. The results of this study showed that the number of patients with TMPG grade 3 was small before treatment, and the number of patients with TMPG grade 3 was significantly increased after treatment, suggesting that tirofiban intervention therapy could significantly improve the myocardial perfusion level of patients and accelerate the improvement of their condition. We analyzed the reason is that tirofiban can improve the microcirculation perfusion in the coronary arteriosclerosis area by inhibiting platelet aggregation, thereby improving myocardial perfusion. Then we studied the predictive value of CXCL16. The patients were divided into two groups in accordance with TMPG grade 0-2 and TMPG grade 3. ROC curve was drawn according to the expression of CXCL16 level in serum of the patients in the two groups, and the results showed that the AUC was 0.880. This indicated that we could we can distinguish the TMPG grade of patients after treatment according to the difference in the expression level of CXCL16 in patients to predict the efficacy. Andersen *et al* (Andersen *et al*., 2019a) also reported CXCL16 as an independent predictor of ACS mortality and fatality rate.

Thrombocytopenia is a complication of tirofiban, and its process may cause alveolar or gastrointestinal bleeding, which may endanger the safety of patients (Vayne *et al*., 2020). Therefore, we conducted statistical analysis on the bleeding events and MACE events of patients 30 days after PCI through follow-up. The results showed that the incidence of bleeding events and MACE events was 12.00% and 6.00% respectively, which was basically consistent with the results of Han *et al* (Han *et al*, 2015), indicating that tirofiban did not increase the risk of bleeding and MACE events in patients. The reason why the risk of bleeding was not increased may be that the dose of tirofiban during PCI was too small to induce severe thrombocytopenia and routine anticoagulant therapy was adopted for subsequent postoperative treatment, with reasonable treatment plan, reducing the risk of bleeding. Qin *et al* (Jia *et al*., 2017) found that tirofiban increased the risk of bleeding in patients, but its effect was better than conventional drugs. This study used standard-dose tirofiban for treatment, without doing half-dose studies, but there was no increased risk of bleeding compared to conventional anticoagulant therapy. Moreover, clopidogrel pretreatment before PCI (He *et al*., 2020) can improve the efficacy without increasing the risk of bleeding, which also indicates that tirofiban with standard dose is more effective in the treatment of ACS. The results of MACE events are basically consistent with those of Wei *et al* (Wei *et al*., 2016). Tirofiban did not increase the incidence of MACE events in patients with better therapeutic outcomes. Therefore, tirofiban is safer and more effective in PCI than conventional anticoagulants.

The efficacy of tirofiban has been widely recognized clinically, but there are still some limitations in this study. Due to time limitation, the sample size of this study was small and the follow-up time was short. The accuracy of the results was still lacking. Therefore, we hope to conduct more in-depth and perfect research in the future, by observing the efficacy of tirofiban and other antiplatelet therapy drugs, and extending the follow-up time to observe the longer-term prognosis of patients.

CONCLUSION

In summary, tirofiban treatment can improve myocardial perfusion in patients with ACS after PCI, reduce the probability of bleeding events and MACE events and the level of CXCL16 after treatment is significantly reduced. The detection of serum CXCL16 may be used to diagnose ACS and the level of serum CXCL16 before treatment may be used as a predictor of efficacy.

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