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Efficacy of ticagrelor and clopidogrel in treating unstable angina and their effects on serum inflammatory factors

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Abstract: To evaluate the comparative efficacy of Ticagrelor and Clopidogrel in treating patients with coronary heart disease and unstable angina, as well as their effects on serum inflammatory factors, thereby providing a solid foundation for future clinical diagnosis and treatment. The frequency of angina attacks in the Ticagrelor group was lower than in the Clopidogrel group ($P< 0.05$). The duration of angina and shortness of breath were also shorter in the Ticagrelor group ($P<0.05$). The levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-18 (IL-18), matrix metalloproteinase-9 (MMP-9), lipoprotein-associated phospholipase A2 (Lp-PLA2), myeloperoxidase (MPO), type 1 tissue plasminogen activator inhibitor (tPAI-1), homocysteine (Hcy), endothelin-1 (ET-1), tumor necrosis factor-alpha (TNF-α), platelet-derived growth factor (PDGF), brain natriuretic peptide (BNP), soluble CD40 ligand (sCD40L), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule (sLCAM-1), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), as well as the incidence of MACCE events, were all lower in the Ticagrelor group compared to the Clopidogrel group ($P<0.05$), while high-density lipoprotein cholesterol (HDL-C) levels and overall efficacy were higher in the Ticagrelor group ($P<0.05$). Ticagrelor demonstrates superior therapeutic efficacy compared to Clopidogrel in patients with coronary heart disease and unstable angina, effectively reducing serum inflammatory factor levels.

Keywords: Unstable angina, ticagrelor, clopidogrel, angina attacks, serum inflammatory factor levels, blood lipid levels, major adverse cardiovascular and cerebrovascular events (MACCE), bleeding events, adverse reactions.

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INTRODUCTION

Unstable angina is a common acute coronary syndrome in clinical practice. Its pathogenesis involves acute ischemia and necrosis of the myocardium due to the activation and adhesion of platelets in the context of unstable atherosclerotic plaque rupture (Roos *et al*., 2022). Unstable angina is classified into four grades based on the severity of symptoms and their impact on daily activities. Grade I involves angina occurring only with vigorous exertion, while Grade II describes angina that occurs with moderate exertion. Grade III pertains to angina that occurs with mild exertion or during emotional stress and Grade IV indicates angina at rest or with minimal exertion, significantly impacting the patient's quality of life (Byrne *et al*., 2023; Roos *et al*., 2022). Understanding these classifications is vital for tailoring treatment strategies and assessing the prognosis of patients with unstable angina.

Antiplatelet therapy is fundamental in the treatment of unstable angina (Liu *et al*., 2023). Currently, the conventional clinical antiplatelet treatment regimen is Clopidogrel combined with Aspirin, but long-term studies (Kuszynski *et al*., 2022) have found that Clopidogrel has a slow onset, and patients face ischemic risk. Ticagrelor, a new antiplatelet drug, has characteristics such as reversibility and rapid onset, which can improve the prognosis of patients with unstable angina, demonstrating significant clinical efficacy (Kabil *et al*., 2022).

In recent studies, Ticagrelor has shown superior efficacy over Clopidogrel in reducing major adverse cardiovascular events, particularly in high-risk populations. Its unique mechanism of action, which allows for rapid and reversible inhibition of platelet aggregation, provides a more robust therapeutic effect, especially during acute episodes of unstable angina. Furthermore, the ability of Ticagrelor to lower inflammatory markers, such as C-reactive protein and interleukins, suggests that it may address not only the thrombotic but also the inflammatory components of coronary artery disease. This dual action could lead to improved patient outcomes, making it a compelling alternative in the management of unstable angina.

Numerous studies have shown that serum inflammatory factors (C-reactive protein, interleukin IL, lipoprotein-associated phospholipase A2, myeloperoxidase, tumor necrosis factor-α, etc.) play an important role in coronary artery disease, especially in the progression of acute coronary syndromes such as unstable angina (Su *et al*., 2022; Liu *et al*., 2022; Dragan *et al*., 2023).

Therefore, comparing the efficacy of these two drugs in reducing the frequency of unstable angina attacks and

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improving patient outcomes, particularly in relation to serum inflammatory factors, will provide important insights for clinical practice. This research not only addresses a gap in the existing literature but also offers critical information for optimizing future treatment strategies.

MATERIALS AND METHODS

General data

A total of 122 patients with unstable angina pectoris, treated at the Third Affiliated Hospital of Qiqihar Medical University from June 2022 to June 2024, were randomly assigned to the Ticagrelor or Clopidogrel groups using a computer-generated randomization method to ensure unbiased allocation, with 61 cases in each group.

Inclusion and exclusion criteria

Inclusion Criteria: (1) All patients had normal coagulation function; (2) All met the diagnostic criteria for unstable angina (Byrne *et al*., 2023); (3) All were diagnosed through ultrasound, electrocardiogram, and other examinations.

Exclusion Criteria: (1) Patients with autoimmune diseases; (2) Patients with neurological diseases such as epilepsy; (3) Patients with a history of intracranial hemorrhage.

Procedure

Clopidogrel Group

Patients were administered an oral loading dose of 300mg Clopidogrel once daily, followed by 75mg Clopidogrel orally once daily, in addition to 100mg Aspirin orally once daily, for a duration of three months.

Ticagrelor Group

Patients were administered an oral loading dose of 180 mg Ticagrelor once daily, followed by 90mg Ticagrelor orally twice daily, in addition to 100mg Aspirin orally once daily, for a duration of three months.

Follow-up and evaluation

The follow-up period for all patients was three months from the initiation of treatment. Evaluations of angina status, including the frequency and duration of angina attacks and shortness of breath, were conducted at baseline and then again at the end of the three-month treatment period. Blood tests to measure serum inflammatory factors and lipid levels were performed at the same time points to assess the efficacy of Ticagrelor and Clopidogrel.

Observation indicators

(1) Angina attack status, including frequency of angina attacks, duration of angina, and duration of shortness of breath; (2) Serum inflammatory factor levels, including C-reactive protein (CRP), interleukin-6 (IL-6), IL-18, matrix metalloproteinase-9 (MMP-9), lipoprotein-associated phospholipase A2 (Lp-PLA2), myeloperoxidase (MPO), type 1 tissue plasminogen activator inhibitor (tPAI-1), homocysteine (Hcy), endothelin-1 (ET-1), tumor necrosis factor-α (TNF-α), platelet-derived growth factor (PDGF), brain natriuretic peptide (BNP), soluble CD40 ligand (sCD40L), soluble vascular cell adhesion molecule-1 (sVCAM-1), and soluble intercellular adhesion molecule (sLCAM-1); (3) Blood lipid levels; (4) Incidence of MACCE events and bleeding events; (5) Incidence of adverse reactions. Adverse drug reactions (ADRs) were evaluated using the Naranjo Algorithm. This standardized tool consists of a series of questions aimed at determining the likelihood of an ADR being related to the administered medication. Each question is scored, and the total score categorizes the ADR as "definite," "probable," "possible," or "unlikely." All patients were monitored for ADRs throughout the treatment period, and any identified reactions were assessed using this algorithm to ensure accurate attribution to either Ticagrelor or Clopidogrel.

Efficacy evaluation criteria

Efficacy was evaluated based on the frequency of angina attacks and their impact on daily life. A reduction of 80%-100% without adverse effects on daily life was evaluated as significant efficacy, a reduction of 50%-79% with mild impact on daily life as effective, and a reduction of 0%-49% or an increase in adverse effects on daily life as ineffective (Li *et al*., 2023).

Ethical approval

This study was approved by the Institutional Review Board (IRB) of the Third Affiliated Hospital of Qiqihar Medical University (Approval No.2024LL-16). Informed consent was obtained from all participants prior to the study.

STATISTICAL ANALYSIS

The sample size was determined based on a power analysis using previously published studies that reported the efficacy of Ticagrelor and Clopidogrel in treating unstable angina (Dragan *et al*., 2023). To achieve a statistical power of 80% and an alpha level of 0.05, we estimated that a total of 122 patients would be required. This calculation accounted for a 10% dropout rate, resulting in 61 patients per group. SPSS 28.0 was used for statistical analysis, with count data expressed as rate/percentage and analyzed using the chi-square test or rank-sum test, and measurement data expressed as mean ± standard deviation ($x \pm s$) and analyzed using the t-test. The test level was set at $\alpha=0.05$.

RESULTS

Baseline characteristics of included paptients

The comparison of general data between the two groups showed no significant differences ($P>0.05$) (table 1).

Table 1: Comparison of general data between the two groups

Item	Category	Ticagrelor Group (n=61)	Clopidogrel Group (n=61)	$t/\chi^2/Z$	*P* 值
Age (years)		56.23±9.56	55.75±9.02	0.285	0.776
Gender	Female	28 (45.90%)	29 (47.54%)	0.033	0.856
	Male	33 (54.10%)	32 (52.46%)		
Body Mass Index (kg/m²)		23.17±1.01	23.25±0.96	0.448	0.655
Course of Disease (years)		4.66±1.15	4.74±1.42	0.342	0.733
Disease Grading	I	22 (36.07%)	21 (34.43%)	0.163	0.871
	II	17 (27.87%)	18 (29.51%)		
	III	12 (19.67%)	11 (18.03%)		
	IV	10 (16.39%)	11 (18.03%)		
Underlying Diseases	Hypertension	30 (49.18%)	31 (50.82%)	0.074	0.964
	Hyperlipidemia	29 (47.54%)	28 (45.90%)		
	Diabetes	11 (18.03%)	10 (16.39%)		

Table 2.1: Comparison of angina incidence between the two groups

Group	Time	Ticagrelor Group (n=61)	Clopidogrel Group (n=61)	t	P
Number of Angina Attacks (times/day)	Before Medication	5.64±1.83	5.36±1.55	0.912	0.364
	After Medication	3.01±1.00	4.65±1.20	8.2	<0.001
Duration of Angina (min/attack)	Before Medication	7.31±1.62	7.17±1.52	0.492	0.624
	After Medication	5.20±1.35	5.71±1.27	2.149	0.034
Duration of Shortness of Breath (days)	Before Medication	5.63±1.38	5.58±1.44	0.196	0.845
	After Medication	3.64±0.51	3.91±0.46	3.07	0.003

Table 2.2: Comparison of inflammatory markers between the two groups

Group	Time	Ticagrelor Group (n=61)	Clopidogrel Group (n=61)	t	P
IL-6 (pg/ml)	Before Medication	30.11±5.42	30.14±5.58	0.03	0.976
	After Medication	13.03±2.24	22.12±3.32	17.727	<0.001
IL-18 (ng/L)	Before Medication	95.61±12.30	96.10±11.90	0.224	0.823
	After Medication	68.60±10.78	92.50±13.48	10.815	<0.001
MMP-9	Before Medication	145.95±16.87	144.53±16.83	0.465	0.643
	After Medication	85.56±9.02	101.66±11.35	8.674	<0.001
Lp-PLA2	Before Medication	512.23±85.20	510.25±85.46	0.128	0.898
	After Medication	253.23±41.25	336.23±50.23	9.974	<0.001
MPO (μg/L)	Before Medication	589.53±64.70	590.66±65.21	0.096	0.924
	After Medication	211.73±25.17	305.37±32.83	17.679	<0.001
tPAI-1 (ng/ml)	Before Medication	69.04±7.13	68.81±7.07	0.179	0.858
	After Medication	55.82±5.61	61.12±6.20	4.951	<0.001
Hcy	Before Medication	25.51±2.40	25.94±2.64	0.941	0.348
	After Medication	7.83±0.94	11.67±1.23	19.374	<0.001
ET-1	Before Medication	115.06±25.17	114.14±24.25	0.206	0.838
	After Medication	71.34±10.92	84.22±12.03	6.192	<0.001
TNF-α (ng/mL)	Before Medication	6.00±0.36	5.96±0.28	0.685	0.495
	After Medication	3.14±0.77	4.61±0.90	9.693	<0.001
PDGF (ng/L)	Before Medication	40.01±7.27	41.30±7.10	0.992	0.323
	After Medication	30.51±5.48	44.40±7.07	12.128	<0.001
BNP (μg/L)	Before Medication	952.23±99.23	949.45±96.23	0.157	0.875
	After Medication	172.23±20.31	291.52±49.36	17.455	<0.001
sCD40L (pg/ml)	Before Medication	558.56±18.85	560.35±17.02	0.551	0.583
	After Medication	240.02±19.75	321.45±21.05	22.034	<0.001
sVCAM-1	Before Medication	421.23±24.26	420.12±21.52	0.267	0.79
	After Medication	232.25±10.02	314.56±16.35	33.524	<0.001
sLCAM-1	Before Medication	425.23±75.23	424.25±76.25	0.072	0.943
	After Medication	30.23±5.26	32.56±5.14	2.474	0.015

Table 2.3: Comparison of lipid levels between the two groups

Group	Time	Ticagrelor Group (n=61)	Clopidogrel Group (n=61)	t	P
LDL-C (mmol/L)	Before Medication	5.16±0.23	5.18±0.34	0.381	0.704
	After Medication	1.63±0.36	3.14±0.40	21.915	<0.001
HDL-C (mmol/L)	Before Medication	1.33±0.28	1.25±0.27	1.606	0.111
	After Medication	3.20±0.40	2.01±0.32	18.144	<0.001
TC (mmol/L)	Before Medication	6.32±0.81	6.28±0.74	0.285	0.776
	After Medication	2.63±0.48	4.22±0.62	15.838	<0.001
TG (mmol/L)	Before Medication	2.97±0.30	3.02±0.25	1	0.319
	After Medication	1.07±0.24	1.98±0.31	18.129	<0.001

Note: LDL-C—Low-Density Lipoprotein Cholesterol; HDL-C—High-Density Lipoprotein Cholesterol; TC—Total Cholesterol; TG—Triglycerides.

Table 3: Comparison of clinical efficacy between the two groups [n (%)]

Group	n	Markedly Effective	Effective	Ineffective	Total Effective Rate
Ticagrelor Group	61	31 (50.82)	28 (45.90)	2 (3.28)	59 (96.72)
Clopidogrel Group	61	20 (32.79)	25 (40.98)	16 (26.23)	45 (73.77)
χ^2					12.774
P					<0.001

Table 4: Comparison of the incidence of MACCE and bleeding events between the two groups [n (%)]

Group	n	MACCE Events					Bleeding Events
		Arrhythmia	Stroke	Acute Coronary Syndrome	Recurrent Hospitalization	Total Incidence	
Ticagrelor Group	61	1 (1.64)	0 (0.00)	1 (1.64)	1 (1.64)	3 (4.92)	20 (32.79)
Clopidogrel Group	61	6 (9.84)	1 (1.64)	4 (6.56)	4 (6.56)	15 (24.59)	14 (22.95)
χ^2						9.385	1.468
P						0.002	0.226

Table 5: Comparison of adverse reaction rates between the two groups [n (%)]

Group	n	Nausea and Vomiting	Headache	Dyspnea	Total Incidence
Ticagrelor Group	61	3 (4.92)	0 (0.00)	3 (4.92)	6 (9.84)
Clopidogrel Group	61	3 (4.92)	3 (4.92)	4 (6.56)	10 (16.39)
χ^2					1.151
P					0.283

Comparison of angina pectoris incidence, serum inflammatory factors and lipid levels between the two groups

Before medication, there were no significant differences between the two groups in terms of angina pectoris incidence, CRP, IL-6, IL-18, MMP-9, Lp-PLA2, MPO, tPAI-1, Hcy, ET-1, TNF-α, PDGF, BNP, sCD40L, sVCAM-1, sLCAM-1 levels and lipid levels (P>0.05). After medication, the number of angina pectoris attacks in the ticagrelor group was lower than that in the clopidogrel group (P<0.05). The duration of angina pectoris and shortness of breath were shorter in the ticagrelor group than in the clopidogrel group (P<0.05). Levels of CRP, IL-6, IL-18, MMP-9, Lp-PLA2, MPO, tPAI-1, Hcy, ET-1, TNF-α, PDGF, BNP, sCD40L, sVCAM-1, sLCAM-1, LDL-C, TC and TG were lower in the ticagrelor group than in the clopidogrel group (P<0.05), while HDL-C levels were higher in the ticagrelor group (P<0.05) (table 2).

Comparison of clinical efficacy between the two groups

The overall effective rate in the Ticagrelor group was higher than that in the Clopidogrel group (P<0.05) (table 3).

Comparison of the incidence of MACCE and bleeding events between the two groups

The incidence of MACCE in the Ticagrelor group was lower than that in the Clopidogrel group (P<0.05), but there was no significant difference in the incidence of bleeding events between the two groups (P>0.05) (table 4).

Comparison of adverse reaction rates between the two groups

There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05) (table 5).

DISCUSSION

In this study, we compared the efficacy of Ticagrelor and Clopidogrel in treating patients with unstable angina. Our results indicate that Ticagrelor significantly reduces the frequency of angina attacks and serum inflammatory markers compared to Clopidogrel. The lower incidence of MACCE in the Ticagrelor group further supports its superior therapeutic profile. Clopidogrel is a commonly used antiplatelet drug in clinical practice, but it has a relatively slow onset of action, which may increase the risk of ischemia (Watanabe *et al*., 2024). Ticagrelor can inhibit thrombosis by selectively inhibiting the P2Y12 receptor (Wang *et al*., 2018). Additionally, it can reversibly bind to the P2Y12 receptor, with effects dissipating quickly after discontinuation, allowing for rapid recovery of platelet function, thus offering higher safety (Laurent *et al*., 2022). For patients with myocardial infarction or acute coronary syndrome, ticagrelor can effectively prevent atherosclerotic thrombosis events. Studies have shown that ticagrelor therapy results in lower mortality in acute coronary syndrome patients compared to clopidogrel (van Nunen *et al*., 2023), though the reasons remain unclear. Research has indicated that ticagrelor has a stronger antiplatelet effect than clopidogrel, due to its faster onset of action and the fact that it does not require hepatic biotransformation. However, major adverse cardiovascular events may increase when platelet function is excessively suppressed (Sanderson *et al*., 2021). Another study demonstrated that in elderly patients with unstable angina, ticagrelor does not increase the risk of bleeding and has higher tolerability and safety (Gimbel *et al*., 2020).

The results of this study indicate that the number of angina attacks in the Ticagrelor group was lower than that in the Clopidogrel group, the duration of angina and shortness of breath were shorter, and the levels of CRP, IL-6, IL-18, MMP-9, Lp-PLA2, MPO, tPAI-1, Hcy, ET-1, TNF-α, PDGF, BNP, sCD40L, sVCAM-1, sLCAM-1, LDL-C, TC, TG, and the incidence of MACCE were lower, while HDL-C levels and overall effectiveness were higher, indicating that ticagrelor can reduce serum inflammatory factor levels without increasing the incidence of major adverse cardiovascular events. A study demonstrated that Ticagrelor significantly reduced the risk of MACCE compared to Clopidogrel in patients with acute coronary syndrome, reinforcing the notion of its superior efficacy in high-risk populations (Wang *et al*., 2018). Moreover, a meta-analysis found that Ticagrelor not only reduces the incidence of ischemic events but also has a favorable effect on lipid profiles, which can further mitigate cardiovascular risks. This is consistent with our results showing lower levels of LDL-C and TC in the Ticagrelor group (Lee *et al*., 2021). This may be because ticagrelor increases extra cellular adenosine levels, thereby reducing the release of pro-inflammatory factors such as IL-6; it also inhibits the release of inflammatory mediators from platelets, such as thromboxane A2, thereby reducing the degree of damage to the vascular endothelium; additionally, it inhibits CD40L expression, thereby suppressing plaque rupture and further development of atherosclerosis.

Similarly, a study highlighted that Ticagrelor's rapid onset and broader anti-inflammatory effects contribute to better clinical outcomes in unstable angina and myocardial infarction patients (Kuszynski *et al*., 2022). Conversely, a randomized trial on older patients indicated that although Ticagrelor showed improved efficacy, it also presented a higher risk of adverse reactions, particularly dyspnea and bleeding (Gimbel *et al*., 2020). This underscores the importance of patient selection and individualized treatment strategies when considering antiplatelet therapies. Additionally, on study emphasized the role of serum inflammatory markers in predicting outcomes in acute coronary syndromes. Their findings suggest that elevated levels of inflammatory factors correlate with poorer prognoses, thus supporting our results that demonstrate Ticagrelor’s ability to lower these markers effectively (Byrne *et al*., 2023).

Antiplatelet drugs are commonly used in the treatment of unstable angina. Clopidogrel is a frequently used antiplatelet drug, but its use in treating unstable angina has drawbacks such as slow onset and an increased risk of myocardial ischemia events. Ticagrelor, with its stronger antiplatelet effect, can protect patients' heart function and reduce the risk of cardiovascular events, though it also has adverse reactions such as bleeding, dyspnea, hyperuricemia and elevated creatinine. It is important to note that the study did not account for the potential effects of concurrent medications on angina status and blood test results. For instance, the observed reductions in LDL levels in the Ticagrelor group, which reached one-third of baseline values, may not solely be attributed to Ticagrelor itself. Other medications, such as statins, were also prescribed to patients and could significantly influence lipid profiles and overall cardiovascular outcomes. Future studies should consider a comprehensive assessment of all medications taken by participants to better isolate the effects of Ticagrelor and provide a clearer understanding of its impact on serum lipid levels and angina management. Research into the differences in efficacy between ticagrelor and clopidogrel, as well as monitoring serum inflammatory factors, can better guide drug use in clinical practice, provide personalized treatment for patients, and improve patient health and well-being, yielding significant social benefits. Understanding the efficacy differences between ticagrelor and clopidogrel in treating unstable angina and monitoring serum inflammatory factors can facilitate personalized treatment and avoid blind medication use, reducing the occurrence of MACCE and bleeding events. Overall treatment costs

and insurance fund expenditure can be effectively controlled, further reducing the consumption of medical resources. This therapy is worthy of clinical promotion, with significant economic benefits.

Given the superior efficacy of Ticagrelor over Clopidogrel in treating unstable angina and its impact on reducing serum inflammatory factors, future clinical practice should prioritize the use of Ticagrelor in high-risk patients with coronary heart disease. Additionally, further studies are needed to explore long-term outcomes and potential side effects associated with prolonged Ticagrelor therapy, particularly in diverse populations. It is also essential to assess the influence of concurrent medications on the efficacy of antiplatelet treatments to ensure comprehensive patient management. Implementing personalized treatment strategies that consider individual patient profiles may enhance therapeutic outcomes and reduce the incidence of major adverse cardiovascular events (MACCE). Lastly, ongoing education for healthcare providers regarding the latest guidelines and evidence-based practices related to antiplatelet therapy can further optimize patient care in unstable angina management.

CONCLUSION

In conclusion, the treatment effect of ticagrelor in patients with coronary heart disease and unstable angina is better than that of clopidogrel, as it more effectively reduces serum inflammatory factor levels and is worthy of promotion.

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