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ARTICLE

Effects of rosuvastatin on serum asymmetric dimethylarginine levels and incidence of long-term cardiovascular events in patients with hyperlipidaemia and H-type hypertension

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Abstract

Aims/Background Rosuvastatin is a common lipid-lowering statin on the market, but its impact on the incidence of long-term cardiovascular events is not well clarified. This study aimed to explore the effects of rosuvastatin on serum asymmetric dimethylarginine (ADMA) levels and the incidence of long-term cardiovascular events in patients with hyperlipidaemia and H-type hypertension.

Methods This retrospective study included 158 patients with hyperlipidaemia and H-type hypertension who were treated in the Hebei Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine from August 2015 to August 2016. The patients were divided into an occurrence group and a non-occurrence group according to the occurrence of long-term cardiovascular events following the resuvostatin treatment. The changes in blood lipids, blood pressure, serum ADMA levels and vascular endothelial function indexes before and after treatment were compared, and the effect of ADMA on the occurrence of long-term cardiovascular events and its predictive efficacy were analysed using the Spearman correlation test and receiver operating characteristics (ROC) curve.

Results After treatment, the levels of serum total cholesterol, low-density lipoprotein cholesterol, triglyceride, serum ADMA and blood pressure became significantly lower ($p < 0.001$), with high-density lipoprotein cholesterol exhibiting no significant difference. Twenty-two cases developed long-term cardiovascular events after the treatment, with an incidence of 13.92%. The occurrence group had significantly higher serum ADMA levels than the non-occurrence group ($p < 0.001$). The rosuvastatin treatment also lowered the levels of endothelin-1 and high-sensitivity C-reactive protein and increased the nitric oxide level ($p < 0.001$). Spearman correlation analysis showed that serum ADMA levels were positively correlated with the occurrence of long-term cardiovascular events (r=0.462, $p < 0.001$). Meanwhile, according to the ROC curve, serum ADMA had a good predictive efficacy for long-term cardiovascular events, with an area under the curve of 0.885 (95% confidence interval 0.808–0.963; $p < 0.001$).

Conclusion Rosuvastatin can reduce ADMA levels and exert vascular protective effects. The increase in serum ADMA levels is closely related to the occurrence of long-term cardiovascular events in patients with hyperlipidaemia and H-type hypertension, serving as a potential clinical predictor to guide disease prevention and treatment.

Key words: Asymmetric dimethylarginine; H-type hypertension; Hyperlipidaemia; Long-term cardiovascular events; Rosuvastatin

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Introduction

Rosuvastatin—a common lipid-lowering statin—can competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase to interfere with endogenous cholesterol synthesis, promote the degradation of low-density lipoprotein cholesterol (LDL-C), and effectively improve the lipid profile (Cortese et al, 2016). A study has reported that rosuvastatin has a remarkable therapeutic effect among East Asian patients with hypercholesterolaemia (Zhang et al, 2020). Additionally, some studies have proved that rosuvastatin has an ideal

curative effect in the treatment of dyslipidemia, hypercholesterolaemia (Boutari et al, 2021), and coronary heart disease (Li et al, 2021). Hyperlipidaemia refers to the increase of blood lipid content caused by abnormal lipid metabolism in the body. H-type hypertension is mainly characterised by homocysteine ≥ 10 μmol/L. High levels of homocysteine can lead to vascular endothelial dysfunction, making patients with H-type hypertension highly susceptible to long-term cardiovascular events (Esse et al, 2019). A large number of data has pointed out that cardiovascular events are often associated with a high risk of disability and mortality, significantly leading to increased burdens on the lives and finances of the affected patients and their families (WHO CVD Risk Chart Working Group, 2019; Son et al, 2020).

A recent clinical study has shown that statin can improve blood lipid metabolism, reduce cholesterol synthesis, stabilise atherosclerotic plaques, reduce inflammation, and offer vascular protection (Liberale et al, 2020). As an endogenous inhibitor of nitric oxide synthase (NOS), asymmetric dimethylarginine (ADMA) can competitively inhibit NOS activity and reduce the production of nitric oxide (NO), leading to vascular endothelial dysfunction (Wieczór Anna et al, 2018; Khan et al, 2021). In recent years, a hypothesis that ADMA may be a cardiovascular risk factor has emerged in the picture (Mangoni Arduino et al, 2021). These elements, which currently have inexplicable concerted connections with cardiovascular risk and protection, offer a new research direction, along which we designed a study focusing on 158 patients with hyperlipidaemia and H-type hypertension to explore the efficacy of oral rosuvastatin and the changes of serum ADMA levels, as well as to clarify the correlation between serum ADMA and long-term cardiovascular events.

Methods

Research design and study participants

This study conformed to the principles of the Declaration of Helsinki (2013) (World Medical Association, 2013).

In total of 162 patients with hyperlipidaemia and H-type hypertension who were treated in the Hebei Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine from August 2015 to August 2016 were selected and recruited in this study. After excluding 4 cases that did not meet the inclusion criteria, 158 patients were included. Patients were included only if they fulfilled the following requirements: (1) patients who were diagnosed with hyperlipidaemia and H-type hypertension in adherence with the clinical practice guidelines of the American College of Cardiology/American Heart Association (Grundy et al, 2019); and (2) patients who had never received any lipid-lowering drugs before the rosuvastatin treatment. At the same time, patients who exhibit the following characteristics were excluded from the study: (1) patients with congenital heart disease, cardiomyopathy and other cardiovascular diseases; (2) patients with secondary hypertension; and (3) patients with incomplete medical records. A flow chart depicting patient recruitment, inclusion, exclusion and grouping is presented in **Figure 1**.

The medical staff collected the demographic characteristics and baseline data of the patients. The blood lipid levels, serum ADMA levels, blood pressure, and vascular endothelial function indexes (such as endothelin-1 [ET-1], NO, and high-sensitivity C-reactive protein [hs-CRP]) before and after rosuvastatin treatment were compared. Meanwhile, the clinical efficacy of rosuvastatin was investigated in a comprehensive manner.

These patients were followed up for 6 months after treatment. The occurrence of long-term cardiovascular events, including myocardial infarction (MI), angina pectoris (AP), heart failure (HF), and sudden cardiac death (SCD), was recorded as the endpoint. Due to the possibility of multiple occurrences, long-term cardiovascular events occurring for ≥ 2 times should be recorded as one cardiovascular event for the first time. All patients cooperated with their physicians until the end of the follow-up. These patients were divided into the occurrence group and the non-occurrence group in accordance with the occurrence of long-term cardiovascular events after treatment.

In this study, we compared the changes in serum ADMA levels after treatment, analysed the correlation between serum ADMA and long-term cardiovascular events using the

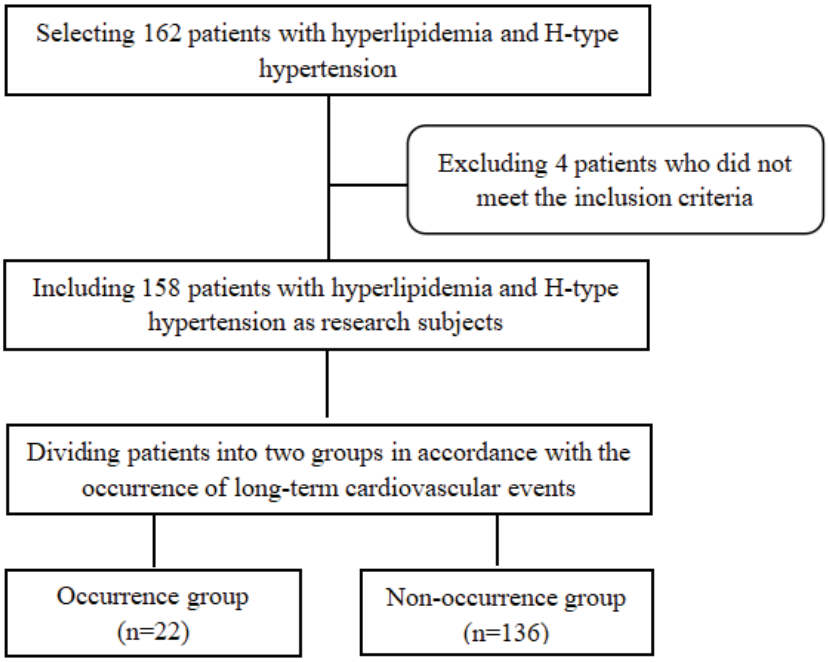

Figure 1. A flow chart depicting patient inclusion and grouping.

Spearman correlation test, and evaluated the predictive efficacy of serum ADMA for long-term cardiovascular events using the receiver operating characteristics (ROC) curve.

Treatment methods

All patients were treated with conventional treatments such as antiplatelet aggregation, thrombolysis and antihypertensive therapy, followed by oral administration of rosuvastatin (specification: 10 mg × 28 tablets; batch no.: 180156; NMPA approval no.: J20160025; AstraZeneca Pharmaceutical [China] Co., Ltd., Taizhou, Jiangsu, China). Each patient was instructed to take oral rosuvastatin once per day (10 mg/day) for a continuous period of 8 weeks.

Detection indicators and methods

The levels of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were measured before and after the rosuvastatin treatment using automatic biochemical analyser (batch no.: 7600-010; Hitachi Limited, Tokyo, Japan).

The diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured before and after the treatment using a sphygmomanometer (batch no.: 20182202; Jiangsu Yuwell Medical Equipment Co., Ltd., Danyang, China).

The serum ADMA levels were detected using enzyme-linked immunosorbent assay (ELISA) reagent kits (batch no.: 8575061; Shanghai Keborui Biotechnology Co., Ltd., Shanghai, China) and a BL-420E ELISA detector (batch no.: JL46600; Chengdu Taimeng Technology Co., Ltd., Chengdu, China) before and after the treatment. The measurement was performed in strict accordance with the manufacturer's instructions.

The levels of ET-1 and NO before and after the treatment were detected by means of radioimmunoassay (Ahmad et al, 2021) and colourimetric detection of nitrate reductase (Bo et al, 2015), respectively, while the hs-CRP levels were detected by ELISA. These biomarkers were measured using a human ET-1 detection kit (batch no.: 7310711; Shanghai Jingkang Biotechnology Co., Ltd., Shanghai, China), NO detection kit (batch no.: 5326783; Shanghai Xuanya Biotechnology Co., Ltd., Shanghai, China), and human hs-CRP ELISA kit (batch no.: 2391563; Shanghai Baililai Biotechnology Co., Ltd., Shanghai, China). The measurements were followed in strict accordance with the manufacturer's instructions.

Statistical analysis

SPSS 22.0 (International Business Machines Corporation, Armonk, New York, USA) was utilised for data analysis and processing. The categorical data are presented as counts and percentages. The Shapiro-Wilk test was used to assess the conformance of data with normal distribution. Non-normal data are expressed as median (25th percentile, 75th percentile) and were analysed using the Mann-Whitney U test. Wilcoxon signed-rank test was performed for comparison within groups. Statistical outputs with $p < 0.05$ were considered statistically significant. In addition, GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) was used to plot the graph used in this paper. The correlation between ADMA and long-term cardiovascular events was analysed using the Spearman correlation test, and the predictive efficacy of ADMA was assessed using the ROC curve.

Results

Demographic characteristics and baseline data

Of the patients included in this study (n=158), 85 are males (53.80%) and 73 are females (46.20%). They were aged 41–75 years, with a median and quartile of 60.00 (51.00, 67.00) years. Their body mass index ranged from 22.71 to 28.30 kg/m^2, with a median and quartile of 25.72 (24.24, 26.99) kg/m^2. Fifty-seven patients had a primary school diploma or lower qualifications (36.08%), 82 cases had a secondary school diploma (51.90%), and 19 cases had a college diploma or above (12.03%). A total of 131 cases were married (82.91%), and 27 cases were unmarried/divorced (17.09%). Among them, 47 cases had a history of smoking (29.75%), 24 cases had a history of drinking (15.19%), and 92 cases had diabetes mellitus (58.23%).

Comparison of blood lipid, blood pressure and serum ADMA levels before and after rosuvastatin treatment

The rosuvastatin treatment significantly lowered the levels of TC, LDL-C, TG, serum ADMA and blood pressure ($p < 0.001$), with HDL-C exhibiting no significant difference after the treatment ($p > 0.05$), as shown in Table 1.

Table 1. Comparison of blood lipid, blood pressure and serum asymmetric dimethylarginine levels before and after rosuvastatin treatment

Indicators	Before treatment	After treatment	*Z*	*p*
TC (mmol/L)	5.54 (4.48, 6.67)	4.58 (3.65, 5.61)	–5.487	< 0.001
LDL-C (mmol/L)	3.47 (2.88, 3.90)	2.60 (2.20, 3.05)	–8.729	< 0.001
HDL-C (mmol/L)	1.17 (0.90, 1.45)	1.22 (0.99, 1.47)	–1.390	0.165
TG (mmol/L)	2.13 (1.81, 2.62)	1.80 (1.49, 2.01)	–7.132	< 0.001
SBP (mmHg)	160.00 (152.75, 167.25)	136.00 (129.00, 143.00)	–10.793	< 0.001
DBP (mmHg)	96.00 (90.00, 102.25)	82.00 (76.00, 91.00)	–10.043	< 0.001
ADMA (μmol/L)	3.57 (3.38, 3.69)	2.15 (1.69, 2.61)	–10.482	< 0.001

Note: Data are expressed as median (25th percentile, 75th percentile). Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; DBP, diastolic blood pressure; SBP, systolic blood pressure; ADMA, asymmetric dimethylarginine.

Comparison of vascular endothelial function indexes before and after rosuvastatin treatment

Table 2 shows that after the rosuvastatin treatment, the levels of ET-1 and hs-CRP in patients became lower, while the NO level increased ($p < 0.001$).

Occurrence of long-term cardiovascular events after rosuvastatin treatment

Twenty-two patients developed long-term cardiovascular events after the treatment with rosuvastatin, with an incidence of 13.92%. HF was the most common event in all long-term cardiovascular events, accounting for 45.45% (Figure 2).

Comparison of serum ADMA levels between the occurrence and non-occurrence groups after rosuvastatin treatment

The medians (interquartile ranges) of serum ADMA in the occurrence group and non-occurrence group were 3.42 (3.15, 3.60) μmol/L and 2.06 (1.60, 2.43) μmol/L, respectively. The occurrence group had higher serum ADMA levels than the non-occurrence group ($p < 0.001$) (Figure 3).

Correlation between serum ADMA levels and long-term cardiovascular events

Spearman correlation analysis displayed that serum ADMA levels were positively correlated with the occurrence of long-term cardiovascular events (r=0.462, $p < 0.001$). In other words, a higher ADMA level translates to a higher risk of long-term cardiovascular events.

Table 2. Comparison of vascular endothelial function indexes before and after rosuvastatin treatment

Indexes	Before treatment	After treatment	*Z*	*p*
ET-1 (ng/L)	88.69 (82.41, 96.79)	53.69 (45.84, 60.42)	–10.903	< 0.001
NO (μmol/L)	48.24 (43.80, 53.86)	71.91 (66.80, 78.57)	–10.903	< 0.001
hs-CRP (mg/L)	11.68 (9.65, 14.07)	2.89 (2.19, 3.54)	–10.587	< 0.001

Note: Data are expressed as median (25th percentile, 75th percentile). Abbreviations: ET-1, endothelin-1; NO, nitric oxide; hs-CRP, high-sensitivity C-reactive protein.

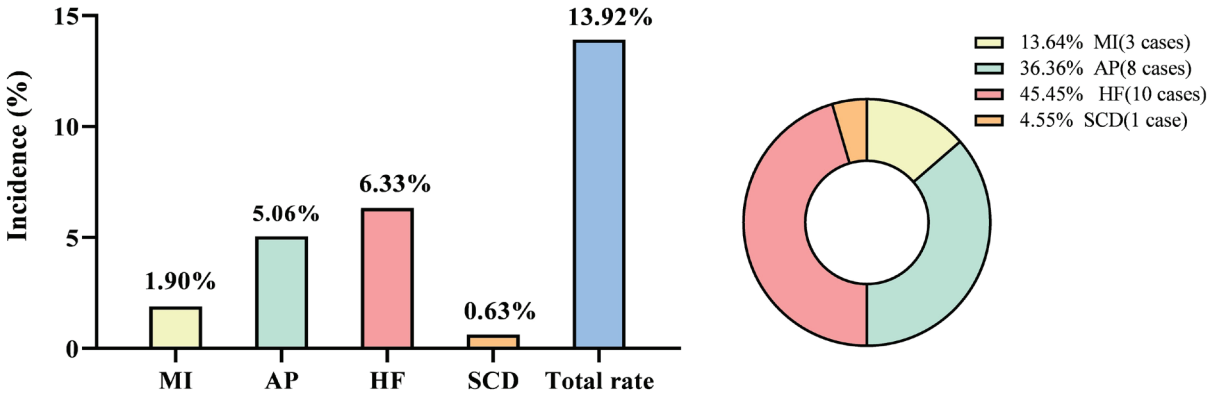

Figure 2. Incidence and distribution of long-term cardiovascular events after rosuvastatin treatment (%). Total rate = (MI + AP + HF + SCD) cases/total cases × 100%. Abbreviations: MI, myocardial infarction; AP, angina pectoris; HF, heart failure; SCD, sudden cardiac death.

Predictive efficacy of serum ADMA for long-term cardiovascular events

The ROC curve showed that serum ADMA had a good predictive efficacy for long-term cardiovascular events, with an area under the curve (AUC) of 0.885 (95% confidence interval 0.808–0.963; $p < 0.001$) (Table 3 and Figure 4).

Discussion

The current study demonstrated that rosuvastatin significantly reduced the levels of TC, LDL-C, TG, SBP, and DBP, suggesting the therapeutic protection confers onto patients with hyperlipidaemia and H-type hypertension. This is because rosuvastatin can reduce plaque lipids, especially endogenous cholesterol and LDL-C (Mehta et al, 2022). For patients with both hyperlipidaemia and hypertension, good blood lipid control can help reduce blood pressure levels through the L-arginine-NO (Chang et al, 2022). Khokhar et al (2022) have found that rosuvastatin can remarkably reduce LDL-C in patients with type 2 diabetes, outperforming atorvastatin in terms of efficacy. Rhee et al (2020) found that rosuvastatin monotherapy is not inferior to nebivolol combined with rosuvastatin in improving SBP,

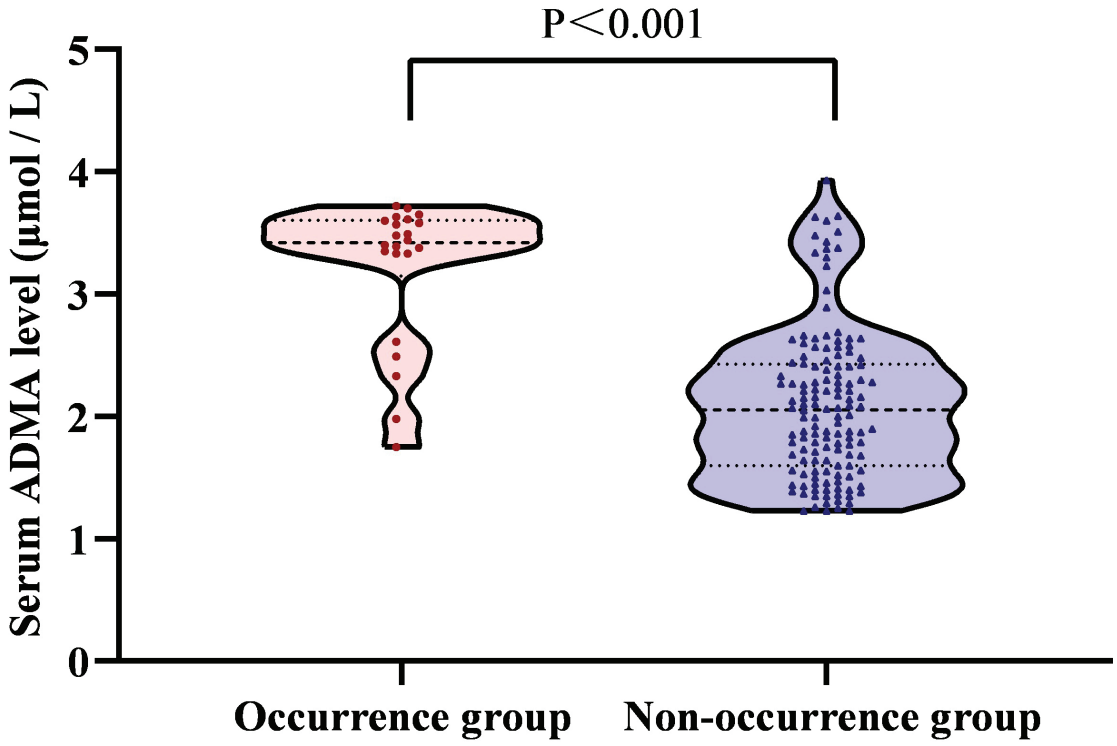

Figure 3. Comparison of serum asymmetric dimethylarginine levels after rosuvastatin treatment. Note: Data are expressed as median (25th percentile, 75th percentile). Abbreviation: ADMA, asymmetric dimethylarginine.

Table 3. Predictive efficacy of serum asymmetric dimethylarginine for long-term cardiovascular events

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	95% CI		p
					Lower limit	Upper limit	
Serum ADMA	0.885	3.315	77.30	92.60	0.808	0.963	< 0.001

Abbreviations: ADMA, asymmetric dimethylarginine; AUC, area under the curve; CI, confidence interval.

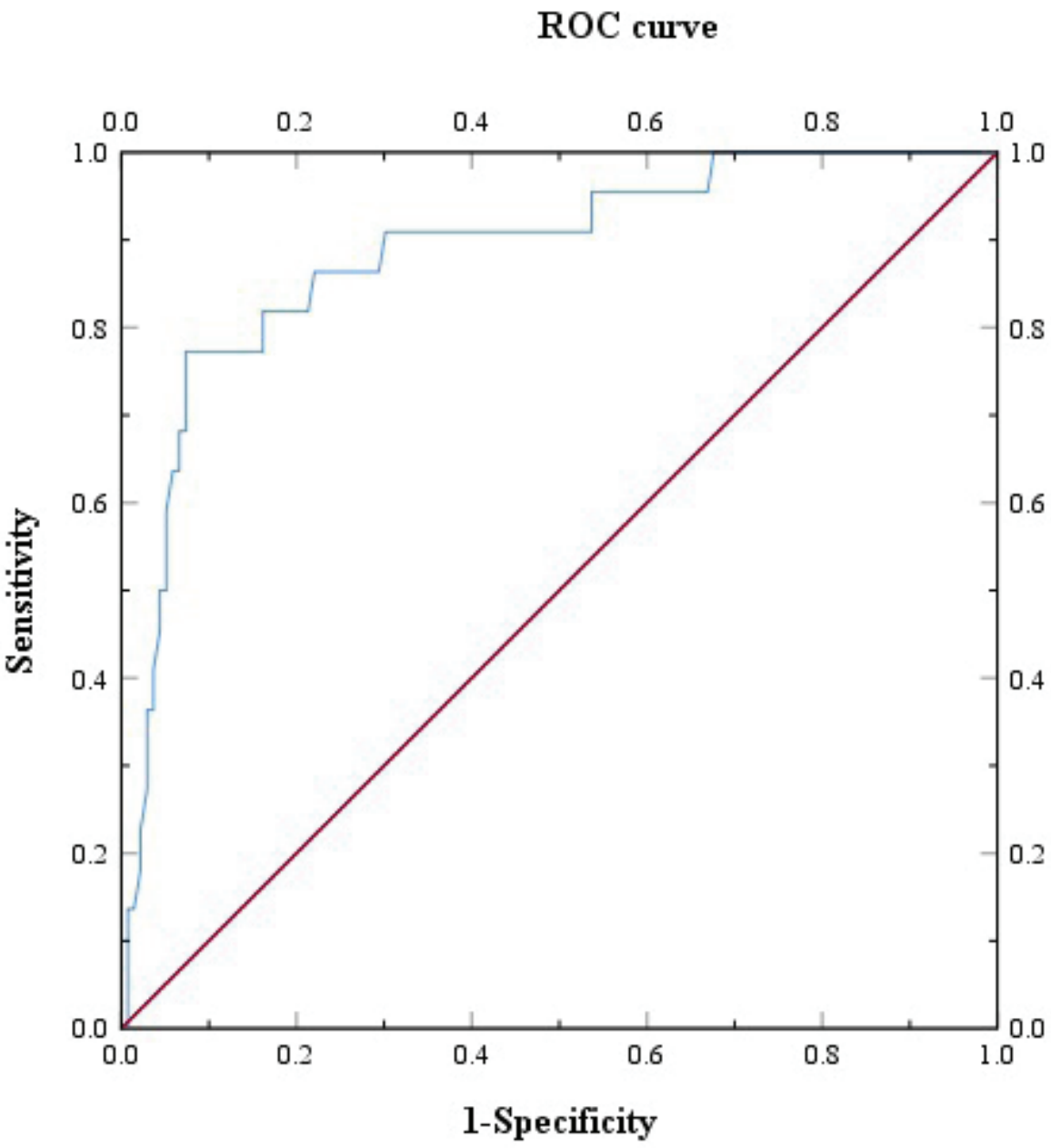

Figure 4. Receiver operating characteristics curve depicting the efficacy of serum asymmetric dimethylarginine in predicting long-term cardiovascular events. Abbreviation: ROC, receiver operating characteristics.

DBP and LDL-C in patients with hypertension and hyperlipidaemia. This study not only observed the changes of BP and LDL-C, but also analysed the anti-inflammatory effect of rosuvastatin.

Vascular endothelial dysfunction is closely related to the occurrence and development of cardiovascular disease. ET-1 is a sensitive indicator reflecting the function of vascular endothelial cells, which play a role in blood vessel contraction, smooth muscle proliferation and leukocyte adhesion (Cai et al, 2021). Clinically, NO is regarded as the primary molecule involved in the maintenance of vascular structure and function; therefore, it is used as an indicator for evaluating vascular endothelial function in this study, along with ET-1. Generally, patients with hyperlipidaemia and hypertension are subject to vascular endothelial injury, which results in an inflammatory response (Lai et al, 2022). To explore the biological pleiotropic effects of rosuvastatin, we employed hsCRP, a cardiovascular

inflammatory lesion marker, in this study to aid in the observation of the reversal and protective effects of rosuvastatin on blood vessels. The results displayed that after 8 weeks of oral rosuvastatin treatment, the levels of ET-1 and hs-CRP in patients were significantly decreased, and the NO level was significantly increased, indicating that rosuvastatin can alleviate the inflammatory response and protect the vascular endothelial function.

A recent study has shown that statins not only have lipid-lowering effects, but also have inhibitory and/or stimulatory effects on the NOD-like receptor pyrin domain containing 3 inflammasome and Toll-like receptor (Koushki et al, 2021). It can be seen that rosuvastatin can reduce the activity of inflammatory cells, decrease the release of platelet-derived inflammatory factors, and then avoid thrombosis. At the same time, it can also reduce the serum ADMA levels, accelerate the release of NO from endothelial cells, and promote the vasodilation.

Cholesterol control, as one study pointed out, is one of the predominant methods of cardiovascular disease prevention—a strategy that can ease the burden of atherosclerotic plaques and mitigate the risk of cardiovascular disease (Quispe et al, 2021). Serum ADMA is an L-arginine analogue, mainly synthesised and released by vascular endothelial cells, which can be hydrolysed into monomethylamine, dimethylamine and citrulline by dimethylarginine dimethylaminohydrolase. The pathophysiological mechanism underlying the development of hyperlipidaemia and H-type hypertension is implicated in the inactivation of dimethylarginine dimethylaminohydrolase and the increased plasma levels of ADMA, which can reduce the synthesis of NO and causing vascular endothelial dysfunction, promoting the development of long-term cardiovascular events (Singh et al, 2022). Therefore, patients with high serum ADMA levels are more susceptible to long-term cardiovascular events.

Several limitations of this study should be acknowledged. Firstly, the findings from this retrospective study, involving a small sample size, have low representativeness and cannot be generalised to other populations. Secondly, the present set of findings did not offer any fundamental data concerning the dosage of rosuvastatin that can deliver the best possible therapeutic effect. Thirdly, the current study is unable to clarify the effect of drugs on the incidence of cardiovascular events. Therefore, to address the gaps mentioned above, it is necessary to carry out prospective studies using a larger sample.

Conclusion

In addition to its capability to lower blood lipid and blood pressure, rosuvastatin has a protective effect on vascular endothelial function, making it an ideal drug for the treatment of hyperlipidaemia coupled with H-type hypertension. Serum ADMA has an excellent predictive efficacy for the occurrence of long-term cardiovascular events. The increase in ADMA levels predicts endothelial dysfunction and a higher risk of long-term cardiovascular events in patients with hyperlipemia and H-type hypertension. These findings underscore the need for clinical application of rosuvastatin and monitoring of serum ADMA level changes to accomplish early prevention and treatment of long-term cardiovascular events in patients with hyperlipidaemia and H-type hypertension.

Key points

- Rosuvastatin has a significant beneficial effect in reducing blood lipids and blood pressure.
- Rosuvastatin has a protective effect on vascular endothelial function in patients with hyperlipidaemia and H-type hypertension.
- Rosuvastatin can reduce serum ADMA levels in patients with hyperlipidaemia and H-type hypertension.
- Serum ADMA can predict the occurrence of long-term cardiovascular events in patients with hyperlipidaemia and H-type hypertension, essentially guiding the early prevention and treatment of long-term cardiovascular events.

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Availability of data and materials

The corresponding author will provide the data that underpin the study's conclusions with a reasonable application.

Author contributions

JZJ and WYT designed the study. All authors conducted the study. WM and HG collected and analysed the data. HG participated in drafting the manuscript, and all authors contributed to the critical revision of the manuscript for important intellectual content. All authors gave final approval of the version to be published. All authors participated fully in the work, take public responsibility for appropriate portions of the content, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

This study has been approved by the ethics committee of Hebei Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine (Approval No. 2021014). Patients were aware of the purpose and significance and signed an informed consent.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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