Am J Transl Res 2023;15(5):3433-3441
www.ajtr.org /ISSN:1943-8141/AJTR0144985

*Original Article*

# Adjuvant qi-invigorating blood-activating tongmai decoction promotes effect of rosuvastatin on senile diabetes mellitus complicated with atherosclerosis

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Received June 27, 2022; Accepted October 18, 2022; Epub May 15, 2023; Published May 30, 2023

**Abstract:** Objective: This study aimed to explore the efficacy and safety of qi-invigorating blood-activating tongmai decoction combined with rosuvastatin in the treatment of senile type 2 diabetes mellitus (T2DM) complicated with atherosclerosis (AS). Methods: The clinical data of 122 elderly patients with T2DM complicated with AS treated in Hospital of Chengdu University of Traditional Chinese Medicine from February 2020 to November 2021 were retrospectively analyzed. Among them, 57 patients treated with rosuvastatin alone were divided into a Monotherapy group, and 65 patients treated with qi-invigorating blood-activating tongmai decoction adjuvant combined with rosuvastatin were divided into a combined group. The two groups were compared in terms of efficacy after treatment, incidence of adverse reactions after 8 weeks of treatment, and carotid plaque indexes, glucose metabolism indexes and lipid metabolism indexes before and after 8 weeks of treatment. Results: The Combined group showed a notably higher response rate than the Monotherapy group ($P<0.05$), but the two groups showed no significant difference in the incidence of adverse reactions ($P>0.05$). After 8 weeks of treatment, the intima-media thickness (IMT), plaque area, fasting blood glucose, glycosylated hemoglobin (HbA1c), total cholesterol (TC), triacylglycerol (TG) and low-density lipoprotein-cholesterol (LDL-C) in the two groups decreased significantly, and high-density lipoprotein-cholesterol (HDL-C) in them increased significantly. Furthermore, the Combined group showed significantly higher levels of IMT, plaque area, fasting blood glucose, HbA1c, TC, TG and LDL-C, and a significantly lower HDL-C level than the Monotherapy group ($P<0.05$). Conclusion: Qi-invigorating blood-activating tongmai decoction can promote the therapeutic efficacy of rosuvastatin in elderly patients with T2DM complicated with AS.

**Keywords:** Qi-invigorating blood-activating tongmai decoction, type 2 diabetes mellitus, atherosclerosis, rosuvastatin

## Introduction

Cardiovascular and cerebrovascular diseases have always been common and harmful among the elderly, with high morbidity, disability and mortality [1, 2]. Type 2 diabetes mellitus (T2DM), as a crucial chronic non-communicable disease and a risk factor of various cardiovascular and cerebrovascular diseases, also impacts increasing number of elderly patients' health [3]. Diabetes and its related complications have become a major public health problem, causing healthcare and economic burden to the society [4, 5].

Because of the instability of blood glucose and the disorder of lipid metabolism, patients with T2DM face a higher incidence of cardiovascular and cerebrovascular diseases [6]. Among the complications of T2DM, macrovascular disease presents a high incidence, and atherosclerosis (AS) is the most common one. AS is the key cause of coronary heart disease, cerebral infarction and peripheral vascular disease in patients with T2DM, and it can also lead to disability or death in the patients [7, 8]. Although biguanides, sulfonylureas, and statins can benefit patients with both T2DM and AS to some extent, they can't completely and effectively

reduce the vascular lesions and arterial plaques, and further interventions are required for patients [9, 10].

Qi-invigorating blood-activating tongmai decoction is a self-developed prescription formed by syndrome differentiation on the basis of blood-activating tongmai decoction and many years' clinical experience of doctors in our hospital. This traditional Chinese medicine decoction composes of radix astragali, rhizome chuanxiong, safflower and salvia miltiorrhiza, with functions of dredging collaterals, promoting blood circulation, nourishing blood and invigorating qi. The original blood-activating tongmai decoction delivers excellent effect on diabetes mellitus [11]. Besides, statins are frequently adopted clinically to lower the mortality and incidence of coronary heart disease. According to prior research [12, 13], for patients with T2DM with carotid AS, statins could improve the endothelial function of patients, inhibit inflammatory reactions and prevent thrombosis by stabilizing atherosclerotic plaques. This kind of drugs has been extensively applied in the prevention and treatment of cardiovascular and cerebrovascular diseases. With similar mechanisms of action, different statins cause different effects on different types of lipoproteins, and also give rise to the protection effects against inflammatory response and vascular endothelium [14]. Compared with other statins, rosuvastatin can significantly reduce low density lipoprotein-cholesterol (LDL-C) [15, 16]. However, the single application of this western medicine has the limitations of long treatment course, proneness of drug resistance and severe side effects, and the combination of it with traditional Chinese medicine can deliver higher treatment effect and reduce adverse reactions [17].

In this study, we aimed to explore the clinical efficacy and safety of qi-invigorating blood-activating tongmai decoction adjuvant combined with rosuvastatin in the treatment of elderly patients with T2DM complicated with AS.

## Methods and data

### *Patient information*

The clinical data of 122 elderly patients with T2DM complicated with AS treated in Hospital of Chengdu University of Traditional Chinese Medicine from February 2020 to November 2021 were retrospectively analyzed. Among them, 57 patients treated with rosuvastatin alone were divided into a Monotherapy group, including 33 males and 24 females, with a mean age of 70.39±5.91 years, and 65 patients treated with qi-invigorating blood-activating tongmai decoction adjuvant combined with rosuvastatin were divided into a Combined group, including 41 males and 24 females, with a mean age of 71.42±6.33 years. This study was conducted with the permission from the Medical Ethics Committee of Chengdu Qingbajiang District Traditional Chinese Medicine Hospital (ethnical approval number: 20200308).

### *Inclusion and exclusion criteria*

*The inclusion criteria:* Patients who were diagnosed with T2DM according to the diagnostic criteria of T2DM issued by the American Diabetes Association in 2019 [18]; patients with fasting blood glucose ≥7.8 mmol/L or 2 hour postprandial blood glucose ≥11.1 mmol/L; patients who suffered AS symptoms of different degrees according to CT or magnetic resonance imaging and had not received other blood lipid-lowering and antibiotic drugs; patients who were 60 years old or more; patients with detailed case data.

*The exclusion criteria:* Patients with other types of diabetes; patients who were allergic to the treatment drugs; patients with a history of ischemic stroke or cerebrovascular events; patients with severe heart, liver, kidney or other organ functional diseases; patients with unfavorable compliance with treatment or halfway withdrawal of drugs; patients whose aortic dissection was not excluded; patients who were pregnant or in lactating.

### *Treatment methods*

After admission, patients in both groups were given routine treatment, including oral administration or injection of insulin (Novo Nordisk Pharmaceutical Co., Ltd.), and oral administration of hypoglycemic drugs mainly including acarbose tablets (Bayer Pharmaceutical Co., Ltd.) and metformin (Bristol Myers Squibb). The Monotherapy group was orally administrated with rosuvastatin tablets (Lunan BETTER Pharmaceutical Co., Ltd.), 10 mg each time, once a day. Additionally, the Combined group was treated with qi-invigorating blood-activat-

ing tongmai decoction adjuvant (15 g of each astragalus flavone, salvia miltiorrhiza, pseudoginseng, polygonum multiflorum and glossy privet fruit, 12 g of each suberect spatholobus stem and aged Citrus peel, 10 g of each rhizoma chuanxiong and fruit of Chinese wolfberry, 8 g of leech, 6 g of Rhizoma Pinelliae preparatum, and 3 g of liquorice), 1 dose per day. This adjuvant was provided by Chengdu Qingbajiang District Traditional Chinese Medicine Hospital. The medicine was decocted with 800 mL water to get 100 mL of filtered decoction. The operation was repeated once, and the two portions of decoction were mixed and then redivided into two portions. The patient was required to take one portion in the morning and one in the evening. Both groups were treated continuously for 8 weeks.

*Outcome measures*

*Primary outcome measures:* (1) The total response rate was evaluated and compared between the two groups after 8 weeks of treatment. Markedly effective: the clinical symptoms disappeared, and the number and area of plaques decreased by more than 80%; effective: the clinical symptoms were alleviated, and the number and area of plaques decreased by 50%-80%; ineffective: the clinical symptoms were not alleviated, and the number and area of plaques decreased by <50%, or even increased. Total response rate = markedly effective rate + effective rate. (2) The adverse reactions of the two groups during treatment were counted. (3) Carotid artery ultrasound (EPIQ7 color Doppler ultrasonic diagnostic instrument) was adopted to determine the intima-media thickness (IMT) and plaque thickness of carotid artery before therapy and after 8 weeks of treatment.

*Secondary outcome measures:* (1) Fasting venous blood (5 mL) was collected from the two groups of patients, of which 3 mL was subjected to 10-min centrifugation (3000 r/min) and the serum fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) were determined using an automatic biochemistry analyzer. (2) The total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and LDL-C in the two groups before treatment and after 8 weeks of treatment were quantified by a Hitachi 7600 automatic biochemical analyzer.

*Statistical analyses*

This study adopted SPSS20.0 (SPSS Co., Ltd., Chicago, the States) for statistical analyses of all collected data, and GraphPad Prism 7 (GraphPad Software Co., Ltd., San Diego, the States) for visualization of data. Counting data were presented as percentage and analyzed using the Chi-square test. Measurement data were presented by mean ± SD if they were in normal distribution, and the inter-group comparisons were performed by independent sample t-test, and intra-group comparisons by paired t test. $P<0.05$ suggests a significant difference.

## Results

*Baseline data*

According to comparison of baseline data between the two groups, the two groups were not greatly different in sex, age, course of disease, body mass index, hyperlipidemia, smoking history, family history of cardiovascular diseases, systolic blood pressure, diastolic blood pressure and uric acid ($P>0.05$, **Table 1**).

*Comparison of response rate between the two groups*

The total response rate was significantly higher in the Combined group than in the Monotherapy group ($P<0.05$). The Combined group yielded a significantly higher markedly effective rate and a significantly lower ineffective rate than the Monotherapy group ($P<0.05$), but the effective rate was not greatly different between the two groups ($P>0.05$). See **Table 2**.

*Comparison of the incidence of adverse reactions*

During the treatment, headache, diarrhea, muscle pain and pharyngalgia occurred in both groups, and the symptoms were all mild. The total incidence of adverse reactions between the two groups was not greatly different ($P>0.05$, **Table 3**).

*Effects of different treatment schemes on carotid plaque*

In terms of the changes in carotid artery plaque indexes (IMT and plaque area) before and after treatment, the two groups were similar in IMT and plaque area before treatment ($P>0.05$),

**Table 1.** Baseline data

| | Monotherapy group (n=57) | Combined group (n=65) | T/$\chi^2$ value | *P* value |
|---|---|---|---|---|
| Sex | | | 0.342 | 0.559 |
| Male | 33 (57.89) | 41 (63.08) | | |
| Female | 24 (42.11) | 24 (36.92) | | |
| Age (years) | 70.39±5.91 | 71.42±6.33 | 0.925 | 0.357 |
| Course of disease (years) | 6.47±2.05 | 7.05±1.98 | 1.588 | 0.115 |
| BMI (kg/m$^2$) | 24.07±2.01 | 23.97±1.97 | 0.277 | 0.782 |
| Hyperlipemia | | | 0.579 | 0.447 |
| Yes | 33 (57.89) | 42 (64.62) | | |
| No | 24 (42.11) | 23 (35.38) | | |
| Smoking history | | | 0.798 | 0.372 |
| Yes | 21 (36.84) | 19 (29.23) | | |
| No | 36 (63.16) | 46 (70.77) | | |
| Family history of cardiovascular diseases | | | 0.346 | 0.556 |
| Yes | 19 (33.33) | 25 (38.46) | | |
| No | 38 (66.67) | 40 (61.54) | | |
| SBP (mmHg) | 168.08±14.06 | 167.56±14.55 | 0.200 | 0.842 |
| DBP (mmHg) | 110.59±12.36 | 112.61±14.34 | 0.828 | 0.410 |
| Uric acid (μmol/L) | 252.12±51.75 | 250.55±57.66 | 0.157 | 0.875 |

Note: Body Mass Index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP).

**Table 2.** Therapeutic efficacy

| | Monotherapy group (n=57) | Combined group (n=65) | $\chi^2$ value | *P* value |
|---|---|---|---|---|
| Markedly effective | 25 (43.86) | 41 (63.08) | 4.516 | 0.034 |
| Effective | 21 (36.84) | 20 (30.77) | 0.502 | 0.479 |
| Ineffective | 11 (19.30) | 4 (6.15) | 4.866 | 0.027 |
| Total response rate | 46 (80.70) | 61 (93.85) | 4.866 | 0.027 |

**Table 3.** Adverse reaction

| | Monotherapy group (n=57) | Combined group (n=65) | $\chi^2$ value | *P* value |
|---|---|---|---|---|
| Headache | 2 (3.51) | 1 (1.54) | | |
| Diarrhea | 3 (5.26) | 1 (1.54) | | |
| Muscle pain | 2 (3.51) | 2 (3.08) | | |
| Pharyngalgia | 2 (3.51) | 3 (4.61) | | |
| Total adverse reactions | 9 (15.79) | 7 (10.77) | 0.672 | 0.413 |

but after 8 weeks of treatment, the IMT and plaque area in both groups decreased significantly (P<0.05). In addition, the Monotherapy group showed significantly larger IMT and plaque area than the Combined group (P<0.05, **Figure 1**).

*Effects of different treatment schemes on glucose metabolism*

According to comparison of the changes in glucose metabolism indexes (FBG and HbA1c) between the two groups before and after treatment, the two groups were similar in FBG and HbA1c before treatment (P>0.05), but after 8 weeks of treatment, the FBG and HbA1c in both groups decreased significantly (P<0.001), and the Monotherapy group showed significantly higher FBG and HbA1c levels than the Combined group (P<0.05, **Figure 2**).

*Effects of different treatment schemes on lipid metabolism*

According to comparison of the changes in lipid metabolism indexes (TC, TG, HDL-C, and LDL-C)

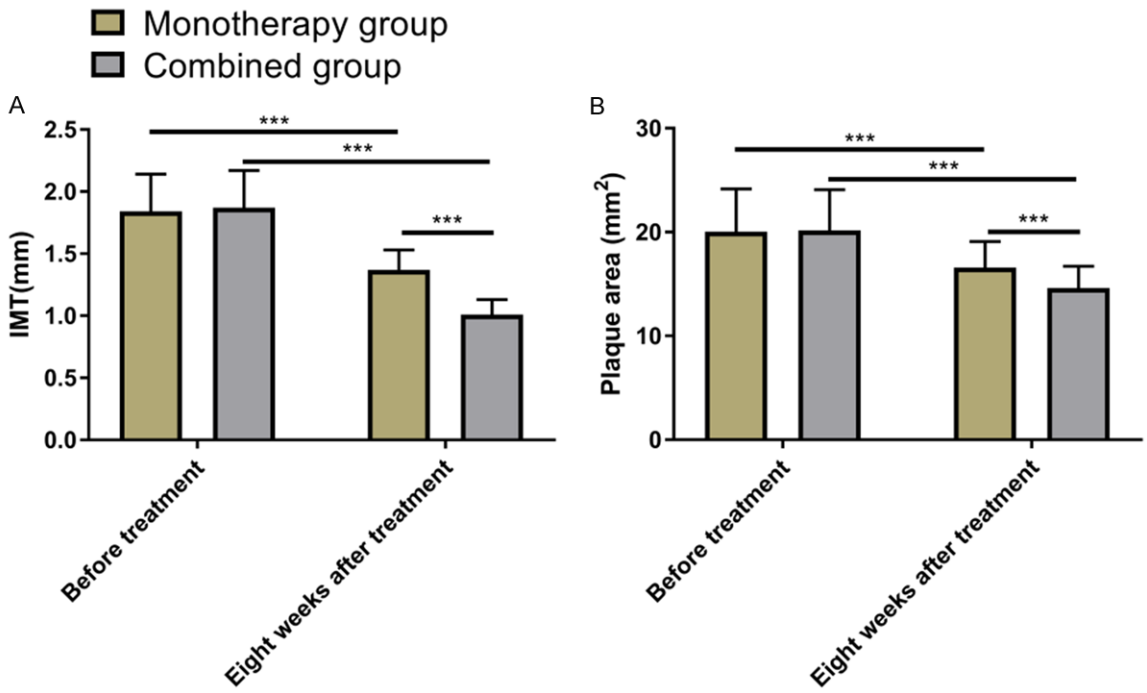


**Figure 1.** Impacts of different treatment schemes on carotid plaque. A. After 8 weeks of treatment, the Monotherapy group showed a significantly larger intima-media thickness (IMT) than the Combined group (P<0.001). B. After 8 weeks of treatment, the Monotherapy group showed a significantly larger plaque area than the Combined group (P<0.001). ***P<0.001.

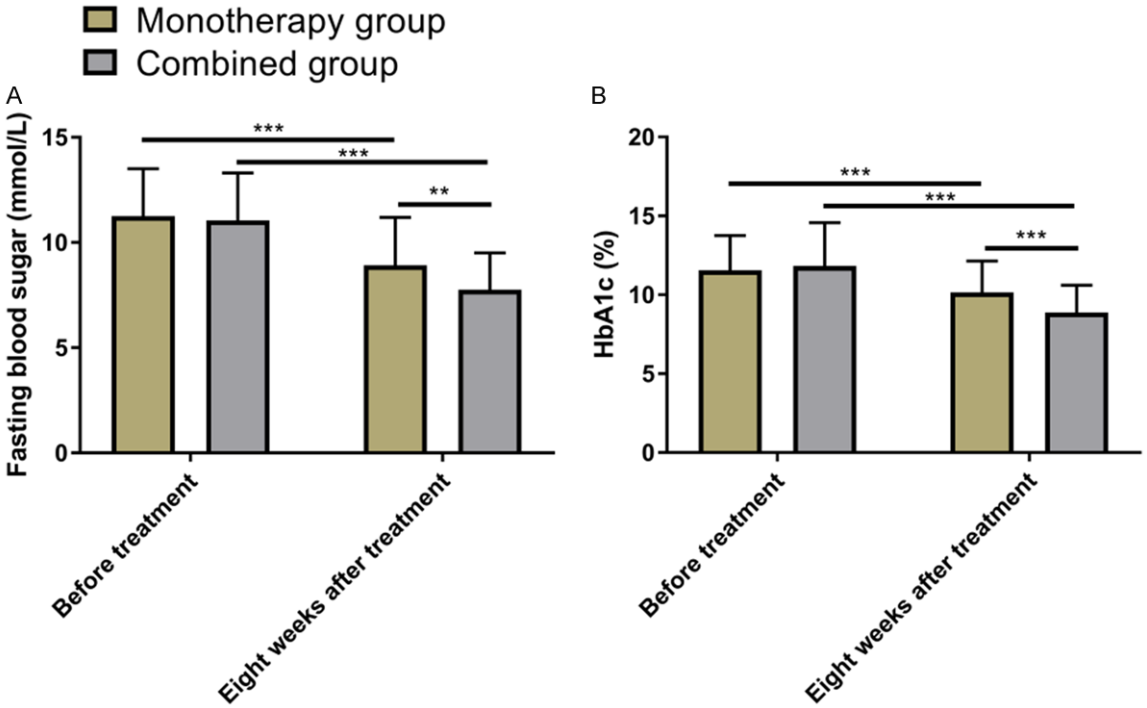


**Figure 2.** Effects of different treatment schemes on glucose metabolism. A. After 8 weeks of treatment, the Monotherapy group showed a significantly higher fasting blood glucose (FBG) level than the Combined group (P<0.01). B. After 8 weeks of treatment, the Monotherapy group showed a significantly higher glycosylated hemoglobin (HbA1c) level than the Combined group (P<0.001). **P<0.01, ***P<0.001.

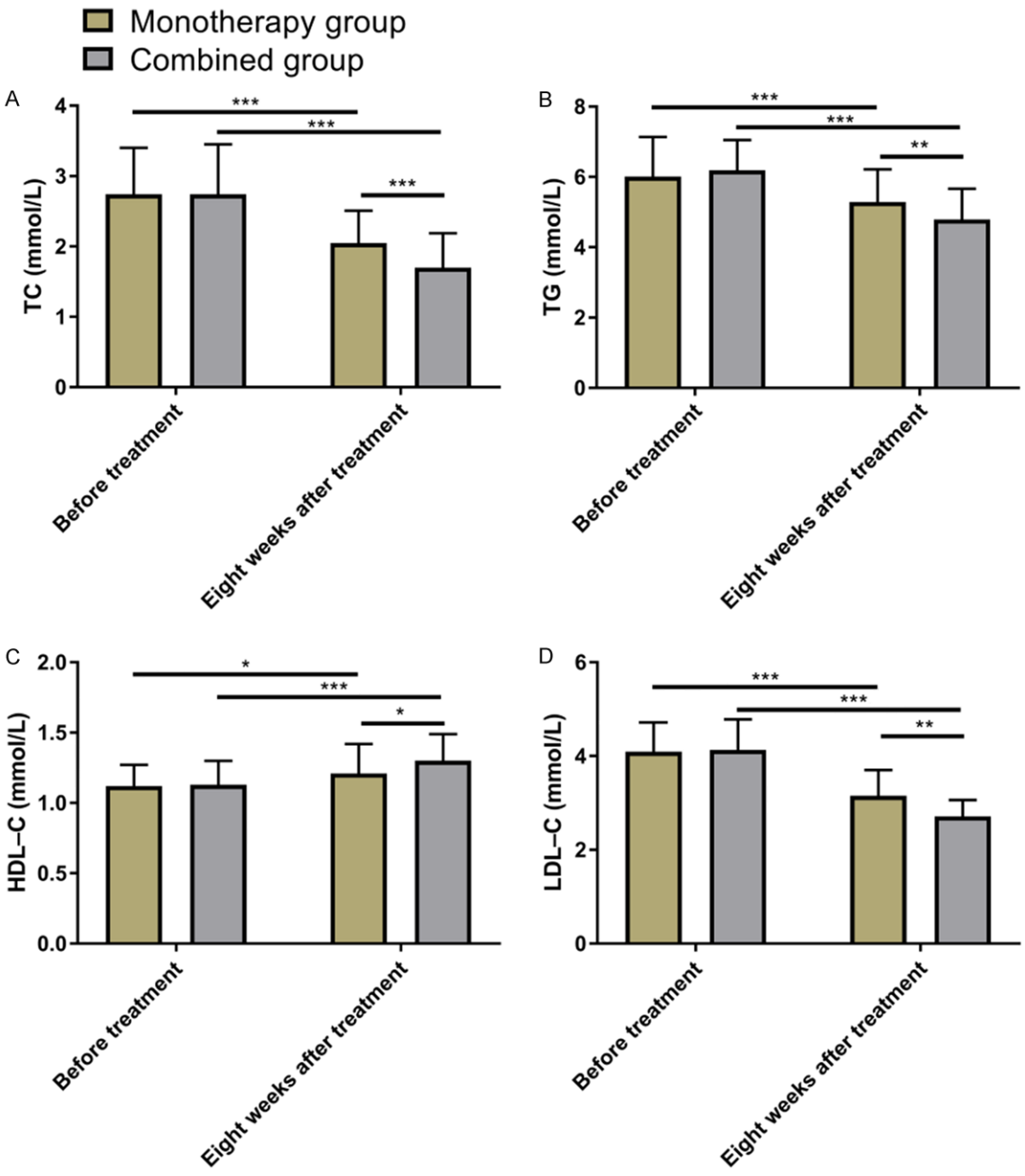


**Figure 3.** Effects of different treatment schemes on lipid metabolism. A. After 8 weeks of treatment, the Monotherapy group showed a significantly higher total cholesterol (TC) level than the Combined group (P<0.001). B. After 8 weeks of treatment, the Monotherapy group showed a significantly higher triacylglycerol (TG) level than the Combined group (P<0.01). C. After 8 weeks of treatment, the Monotherapy group showed a significantly lower high-density lipoprotein-cholesterol (HDL-C) level than the Combined group (P<0.05). D. After 8 weeks of treatment, the Monotherapy group showed a significantly higher low-density lipoprotein-cholesterol (LDL-C) level than the Combined group (P<0.01). *P<0.05, **P<0.01, ***P<0.001.

between the two groups before and after treatment, the two groups were similar in TC, TG, HDL-C and LDL-C before treatment (P>0.05), but after 8 weeks of treatment, TC, TG, and LDL-C in both groups decreased significantly (P<0.001), while HDL-C in both groups increased significantly. In addition, the Monotherapy group showed lower TC, TG and LDL-C levels but a higher HDL-C level than the Combined group (P<0.01, **Figure 3**).

## Discussion

Previous studies have found that qi-invigorating blood-activating tongmai decoction has an effect on preventing AS, because the astragalus polysaccharide and other components can reduce blood lipid levels and inhibit oxidative stress damage, thereby significantly protecting vascular endothelial cells [19, 20]. In this study, it was found that the combined group showed significantly higher total response rate and significantly smaller IMT and plaque area after 8 weeks of treatment than those in the Monotherapy group, but there was no statistical difference in the total adverse reaction rate between the two groups. This suggests that adjusant qi-invigorating blood-activating tongmai decoction can improve the efficacy and plaque elimination effect of rosuvastatin without increasing the incidence of adverse reactions.

The glucose metabolism of the two groups was also compared in this study. After 8 weeks of treatment, the FBG and HbA1c in both groups decreased significantly, with significantly higher FBG and HbA1c levels in the Monotherapy group than those in combined group. Chen et al. [21] mentioned that qi-invigorating blood-activating tongmai decoction could effectively lower the blood glucose and glycosylated hemoglobin of diabetic rats, which may be achieved by regulating podocyte autophagy and promoting the degradation of advanced glycation end products through mTOR/S6K1/LC3 pathway. According to comparison of lipid metabolism of patients, the Monotherapy group showed significantly higher levels of TC, TG and LDL-C, and a significantly lower HDL-C level than the combined group after 8 weeks of treatment. This suggests that qi-invigorating blood-activating tongmai decoction adjuvant combined with rosuvastatin has a better lipid-lowering effect. In addition, codonopsis pilosula, salvia miltiorrhiza and pseudo-ginseng have the effects of enriching blood, promoting blood circulation and invigorating qi, and various chemical components of codonopsis pilosula and safflower can reduce lipid oxidation, improve the blood lipid level and inhibit inflammatory reaction [22, 23]. Moreover, rhizoma chuanxiong and safflower can alleviate oxidative stress, improve endothelial function, reduce platelet aggregation and lower the degree of AS [24].

However, this study has the following limitations. Firstly, HbA1c can only reveal the blood glucose control of patients for 2-3 months. However, the data of patients in this study were only data acquired at admission and from treatment testing, so it was difficult to have a comprehensive understanding of the long-term blood glucose control of patients. Secondly, if the patient's blood glucose was at a high level for a long time before treatment, the long-term abnormal glucose metabolism may cause many aspects of cardiovascular damage, so we hope that the cardiovascular benefits of long-term blood glucose control can be discussed in later studies. Finally, corresponding basic research is needed in the future for exploring the specific mechanism of qi-invigorating blood-activating tongmai decoction, so as to provide a basis for clinical practice.

To sum up, for senile patients with T2DM complicated with AS, qi-invigorating blood-activating tongmai decoction adjuvant combined with rosuvastatin can improve the curative effect and has good safety.

## Disclosure of conflict of interest

None.

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