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ARTICLE

Effects of sartans and low-dose statins on cerebral white matter hyperintensities and cognitive function in older patients with hypertension: a randomized, double-blind and placebo-controlled clinical trial

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Abstract

Cerebral white matter hyperintensities (WMHs) and cognitive impairment are common in elderly hypertensive patients, and more needs to be learned about their prevention and treatment. Our aim was to investigate the effect of low-dose statins on WMH and cognitive function in elderly patients undergoing antihypertensive treatment. A total of 732 elderly hypertensive patients taking hydrochlorothiazide as their baseline medication were randomized using a 2 × 2 factorial design with antihypertensive (telmisartan vs. placebo) and lipid-modulating (low-dose rosuvastatin vs. placebo) arms. Brain magnetic resonance imaging (MRI) and cognitive function data were obtained. After a mean follow-up time of 59.8 (range 12–65) months, there were no differences in WMH progression and cognitive function decline over time between the groups in the antihypertensive arm. The risks of new-incident WMH Fazekas scale scores ≥ 2 and the incidence of cognitive impairment did not differ between the telmisartan and placebo groups. Rosuvastatin use was associated with lower risks of new-incident Fazekas scale scores ≥2 (hazard ratio = 0.500; 95% confidence interval: 0.34–0.74) and cognitive impairment (hazard ratio = 0.54; 95% confidence interval: 0.36–0.80). Telmisartan interacted with rosuvastatin on reducing WMH progression and cognitive function decline. Findings suggest that low-dose rosuvastatin could reduce WMH progression and cognitive function decline in antihypertensive patients, as demonstrated by the interaction between telmisartan and low-dose rosuvastatin to this effect.

Keywords White matter lesions · Cognitive impairment · Neuroprotective effect · Vascular risk factor

Introduction

White matter hyperintensities (WMHs), an important indicator of white matter lesions, are highly prevalent and can be quantified by neuroimaging. WMHs are detected more and more frequently in aging brains owing to the increasing use of magnetic resonance imaging (MRI) [1–6]. WMHs significantly increase the risk of future stroke and dementia [7–9], accounting for 20–30% of all strokes and approximately 45% of dementia cases [8, 9]. With the prolongation of life expectancy, WMH takes an enormous toll on both the individual and the social healthcare system.

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Although the exact etiologies of WMH and dementia are not yet completely understood, evidence has shown that WMH and dementia are most commonly associated with vascular risk factors, especially hypertension [10, 11], hyperlipidemia [10], and aging [12, 13]. Aging is an unavoidable biological process, whereas hypertension and hyperlipidemia can be treated and managed medically. Antihypertensive and anti-lipid therapies are important in this regard and they have been widely accepted as effective management strategies for reducing vascular risk factors [14–18]. However, the current prevention and treatment methods for WMH and dementia are mostly empirical, not evidence based, and are suboptimal or even hazardous in their effect at times [19].

Sartans, as angiotensin II receptor blockers, have been widely used in antihypertensive treatments owing to their longer duration of action, good efficacy, and better tolerability profiles [20]. Numerous studies have demonstrated that sartans are closely associated with reductions in cognitive decline and risk of cerebral small vessel disease [21, 22]. However, comparative trials have reported that sartans do not produce a beneficial effect on the progression of white matter lesions or cognitive decline [3, 23].

Statins are recommended by several major guidelines to modulate the plasma lipid profiles in the primary prevention of cardiovascular disease. In addition, they can also achieve a wider range of non-lipid-lowering pleiotropic effects [17, 18, 24]. Studies have shown beneficial effects of statins on reducing stroke risks, ameliorating dementia, and improving white matter lesions, although disagreements about their benefits on cerebral small vessel disease also exist [17, 18, 25–29].

Recently, sartans and statins have been routinely prescribed together for the comprehensive management of cardiovascular diseases and associated risk factors. However, to our knowledge, the neuroprotective effect of this combination has not been fully evaluated. Our goal was to investigate the effect of telmisartan and low-dose rosuvastatin on the progressions of WMH and cognitive impairment in elderly patients with essential hypertension.

Methods

Study design and participants

A randomized, double-blind, placebo-controlled trial was conducted as previously described [24, 30]. Briefly, between April 2008 and November 2010, 732 hypertensive elderly patients aged 60 years and older were enrolled from community-dwellings in the Shandong area, China. Hypertension was defined as a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mmHg, or self-reported use of blood pressure-lowering medications in the last 2 weeks. Patients with any of the following conditions were excluded: secondary hypertension, definite hypersensitivity or contraindication to the study medications, stroke or transient ischemic attack, Mini-Mental State Examination (MMSE) score ≤23 points, Alzheimer's disease, Parkinson's disease, claustrophobia, bipolar disorder, schizophrenia, seizures, drug or alcohol abuse, malignancy, renal failure and dialysis treatment, liver disease, inability to walk to the clinic, unable to have MRI, or unwillingness to provide informed consent.

The present study was conducted in compliance with the Declaration of Helsinki, adhered to established clinical practice guidelines, and was approved by the Research Ethics Committee of the Institute of Basic Medicine, Shandong Academy of Medical Sciences. Written informed consent was obtained from each patient.

Randomization, masking, and intervention

We used a two-by-two factorial design to randomly assign eligible patients on a 1:1:1:1 ratio into antihypertensive intervention (telmisartan vs. placebo, telmisartan 40 mg increased to 80 mg given once daily if needed) and lipid-modulating intervention (rosuvastatin vs. placebo, rosuvastatin 10 mg given once daily) arms separately, after a 2-week washout period. An open-label medication, hydrochlorothiazide (12.5 mg increased to 25 mg daily if needed), was used as a baseline medication in all treatment arms. We used computer-generated randomization according to the order of recruitment with a block size of eight, without stratification. Members of our institution who were not directly working on the study executed the randomization and supplied study medications. During the double-blind phase, all patients and investigators were masked to treatment assignment. Treatment allocations were not unmasked until the study was completed and after final clinical database lock down, except in cases of emergency.

Procedures

Baseline data were collected at the end of each washout period. Clinical follow-up visits were conducted weekly during the washout period, and then at trial months 1, 3, and 6, and every 6 months thereafter, until the conclusion of the study. The demographic and clinical characteristics of each patient were recorded at clinical follow-up visits. Concomitant use of open-label sartans and/or statins was not allowed. Investigators provided the best medical care to all patients independent of treatment assignment in the washout

and follow-up periods. The targeted blood pressure was defined as <140/90 mm Hg. Medication compliance was assessed by counting the number of tablets taken.

Brain MRI was performed on either a 3.0-T GE Signa Horizon scanner (General Electric Medical Systems, Milwaukee, WI, USA), or a 3.0-T Siemens Allegra scanner (Siemens Medical, Erlangen, Germany), using an identical protocol at baseline, the first MRI follow-up (between May 2012 and August 2013), and the second MRI follow-up (between May 2015 and August 2017). All data processing and analyses were conducted separately by experienced neuroradiologists, who were blinded to the clinical and cognitive function data of the patients. Total intracranial volume (ICV) was computed as the sum of white matter, gray matter, and cerebrospinal fluid volumes. Total WMH volume was computed from automated periventricular and subcortical segmentation of fluid-attenuated inversion recovery axial images using Freesurfer [31–33]. The Fazekas scale for total WMH (periventricular and subcortical WMHs) was assessed and dichotomized as <2 vs. ≥2 [34]. WMH fraction (%), correction of total WMH, was calculated as: [total WMH (mL)/total ICV (mL)] × 100%
[16, 35]. The inter-observer agreement was good: the coefficient of variation was 0.86 for WMH volume and the weighted Cohen's κ was 0.87 for the Fazekas scale.

Cognitive function was assessed annually using the Chinese versions of the MMSE and the Mattis Dementia Rating Scale (DRS) by experienced neuropsychology research assistants, who are experts in the measurement of cognitive function. The MMSE is a 30-point test and a reliable and validated tool for diagnosis in the advanced stages of cognitive dysfunction. The DRS is a standardized, valid, and widely used cognitive rating instrument in the elderly [36]. Possible total scores for the DRS range from 0 to 144 points.

Outcomes

The progression of WMH was assessed using the changes in the volume of WMH and WMH fraction as well as new-incident WMH Fazekas scale scores ≥2 across the intervention duration. For the progression of cognitive impairment, the changes in scores of the MMSE and DRS and possible cognitive impairment were used. Possible cognitive impairment was identified using the following: an MMSE score of ≤23 points at any annual follow-up visit or a decline by ≤3 points between any two annual follow-up visits [36, 37], and/or a DRS score ≤123 points at any annual follow-up visit [38].

Statistical analysis

We used the formula: $n = 2\sigma^2 \times f(\alpha, \beta)/(\mu_1 - \mu_2)$ [2] to calculate the sample size [39], where n is the sample size of each intervention arm, σ is the standard deviation (SD) of basic total WMH, μ_1 is the basic value of total WMH, and μ_2 is the desired value of total WMH at the end of the trial. In the present study, α was equal to 0.05, and β was equal to 0.1. Thus, $f(\alpha, \beta)$ was equal to 10.5. Based on a multinational study and our previous study [33, 40, 41], the mean and SD of the basic total WMH in people aged 60 years and older were 6.5 and 3.3 mL, respectively, and the mean progressed by approximately 1.2 mL over 60 months. The missed follow-up rate was demanded by <10%. Thus, a sample size of 175 patients in each intervention arm was required. This study included 183 patients in each group, to achieve 80% power with a level of statistical significance of 0.05 (two-sided P value).

Analyses followed the intention-to-treat principle. All patients with assessment of brain MRI at study entry were included in these analyses. Patient characteristics at baseline are described by antihypertensive groups and lipid-modulating groups separately as means and SD, medians and interquartile ranges (IQRs), or frequencies and percentages, as appropriate. Comparisons of the baseline characteristics and the changes in measured variables between groups in the antihypertensive arm were performed via the Student's t test and Mann–Whitney U test depending on the normality of continuous variables. A χ^2 test was used to compare the differences in categorical variables. These tests were also used for comparing the baseline characteristics and the changes in measured variables between groups in the lipid-modulating arm. A linear mixed model with random intercepts was performed to compare WMH volume and WMH fraction increases and MMSE and DRS score declines over time in the antihypertensive groups and the lipid-modulating groups. We used logistic regression to compare the odds of new-incident Fazekas scale scores ≥2 and possible cognitive impairment for telmisartan vs. matching placebo and rosuvastatin vs. matching placebo. A log-rank test was used to compare time to new-incident Fazekas scale scores ≥2 and possible cognitive impairment by treatment arms. The Cox proportional hazards model was used for assessing whether there was an interaction between telmisartan and low-dose rosuvastatin on new-incident Fazekas scale scores ≥2 and possible cognitive impairment. A two-sided P value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA).

This trial has been retrospectively registered with ChiCTR.org.cn, number ChiCTR-IOR-17013557.

Table 1 Patient demographic and baseline clinical characteristics

	Total ($n = 732$)	Antihypertensive arm			Lipid-modulating arm		
		Telmisartan group ($n = 366$)	Placebo group ($n = 366$)	*P* value	Rosuvastatin group ($n = 366$)	Placebo group ($n = 366$)	*P* value
Female, *n* (%)	350 (47.8)	182 (49.7)	168 (45.9)	0.301	180 (49.2)	170 (46.4)	0.460
Age, mean (SD) (years)	70.69 ± 6.21	70.62 ± 6.12	70.75 ± 6.31	0.775	70.90 ± 6.28	70.47 ± 6.14	0.354
Smoking, *n* (%)	182 (24.9)	87 (23.8)	95 (26.0)	0.494	97 (26.5)	85 (23.2)	0.305
Alcohol consumption, *n* (%)	238 (32.5)	111 (30.3)	127 (34.7)	0.207	118 (32.2)	120 (32.8)	0.875
Education (years)	7.0 (2.0, 10.0)	7.0 (3.0, 10.0)	7.0 (0.0, 9.0)	0.383	7.0 (1.0, 10.0)	7.0 (3.0, 10.0)	0.708
BMI (kg/m^2)	24.17 ± 3.10	24.07 ± 2.80	24.28 ± 3.38	0.363	24.06 ± 2.81	24.29 ± 3.37	0.330
Blood pressure							
SBP (mmHg)	156.27 ± 9.68	156.09 ± 9.60	156.45 ± 9.77	0.612	156.67 ± 9.75	155.87 ± 9.61	0.264
DBP (mmHg)	71.27 ± 7.76	71.33 ± 7.84	71.22 ± 7.68	0.860	71.11 ± 7.97	71.44 ± 7.54	0.571
Blood laboratory measurements							
Total cholesterol (mmol/L)	5.09 ± 0.65	5.11 ± 0.67	5.10 ± 0.63	0.835	5.13 ± 0.64	5.06 ± 0.66	0.147
Triglycerides (mmol/L)	1.50 ± 0.39	1.49 ± 0.38	1.52 ± 0.41	0.253	1.52 ± 0.41	1.49 ± 0.38	0.331
HDL-c (mmol/L)	1.17 ± 0.21	1.18 ± 0.22	1.17 ± 0.21	0.530	1.16 ± 0.22	1.17 ± 0.21	0.429
LDL-c (mmol/L)	3.24 ± 0.68	3.25 ± 0.68	3.24 ± 0.67	0.751	3.28 ± 0.67	3.21 ± 0.68	0.218
FPG (mmol/L)	5.63 ± 0.74	5.60 ± 0.76	5.66 ± 0.71	0.287	5.66 ± 0.78	5.61 ± 0.70	0.329
Brain magnetic resonance imaging							
Total WMH (mL)	5.28 (3.83, 6.70)	5.15 (3.69, 6.53)	5.54 (1.05, 6.77)	0.075	5.08 (3.82, 6.77)	5.52 (3.84, 6.68)	0.555
WMH fraction (%)	0.43 (0.31, 0.55)	0.43 (0.29, 0.53)	0.44 (0.32, 0.56)	0.114	0.42 (0.31,0.55)	0.44 (0.31, 0.54)	0.600
Fazekas scale ≥2, *n* (%)	76 (10.4)	37 (10.1)	39 (10.7)	0.809	42 (11.5)	34 (9.3)	0.333
Cognitive function							
MMSE score, point	26.0 (25.0, 28.0)	26.0 (25.0, 28.0)	26.0 (25.0, 28.0)	0.477	26.5 (25.0, 28.0)	26.0 (25.0, 28.0)	0.397
DRS score, point	134.0 (129.0, 139.0)	135.0 (129.0, 139.0)	134.0 (129.0, 139.0)	0.387	135.0 (129.0, 139.0)	134.0 (129.0, 139.0)	0.547

Data are *n* (%), mean (SD), or median (IQR)

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *FPG* fasting plasma glucose, *WMH* white matter hyperintensities, *MMSE* Mini-Mental State Examination, *DRS* Dementia Rating Scale

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, preparation, writing and review, or approval of the report. The corresponding author and data analyst had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Demographic and baseline clinical characteristics

Descriptive demographic and baseline clinical characteristics are presented in Table 1. Among the 732 patients, 703 (96.0%) and 676 (92.4%) completed the first and second MRI follow-up assessments, and 725 (99.0%), 714 (97.5%), 703 (96.0%), 686 (93.7%), and 676 (92.4%) completed the first, second, third, fourth, and fifth annual cognitive functional assessments, respectively, over a mean follow-up time of 59.8 (range 12–65) months. The most common reasons for non-complete of the trial were death (31, 55.4%), withdrawal (16, 28.6%), and loss to follow-up (5, 5.4%).

Changes in blood pressure and blood lipids

Compared to baseline, blood pressure levels significantly declined in both treatment arms across the study duration (all $P < 0.001$). There were rapid blood pressure declines during the first 12 months in both arms, followed by steady declining in blood pressure from the 12th month to the end of the study. There were no differences in these declines between the telmisartan and placebo groups or between the rosuvastatin and placebo groups ($P = 0.612$ and 0.264 for systolic blood pressure, $P = 0.860$ and 0.571 for diastolic blood pressure, respectively, Fig. 1). For the changes in blood lipids, there were no differences between telmisartan and placebo groups (all $P > 0.05$, Fig. 2). The declines in total cholesterol, triglycerides, and low-density lipoprotein cholesterol were greater in the rosuvastatin group than in the placebo group ($P < 0.001$, =0.035, and <0.001, respectively, Fig. 2).

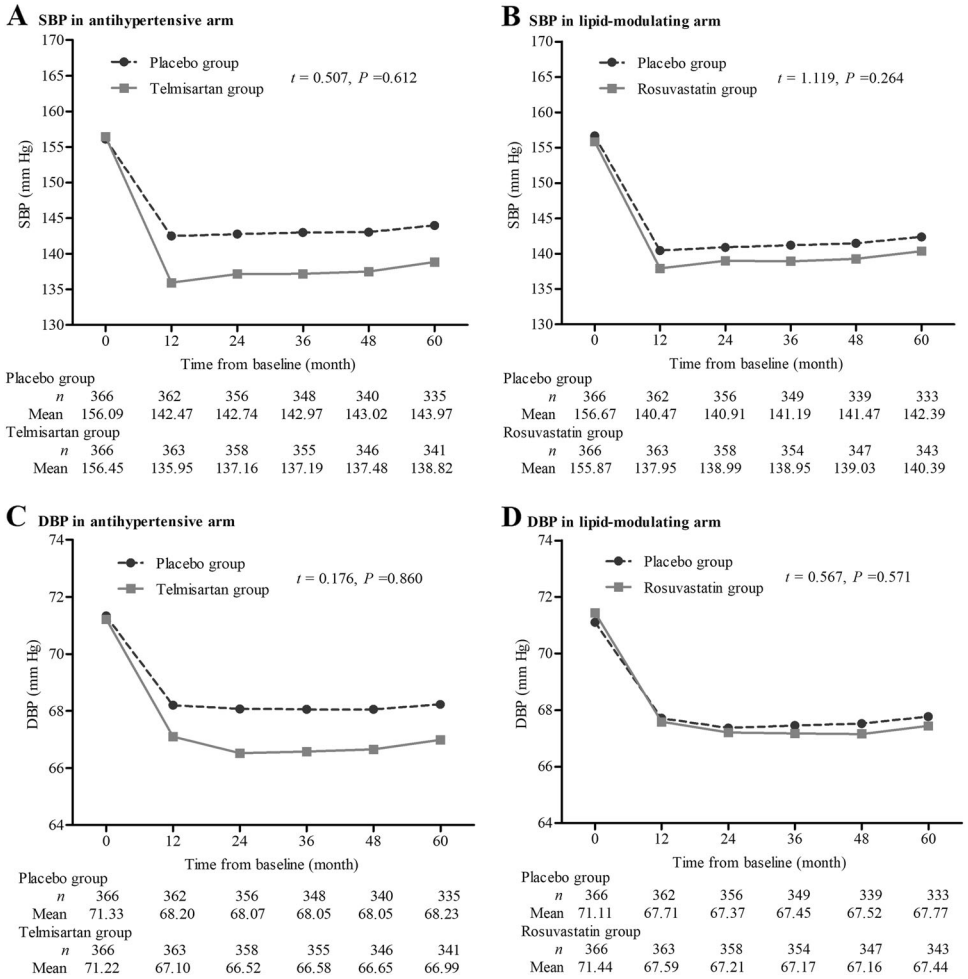
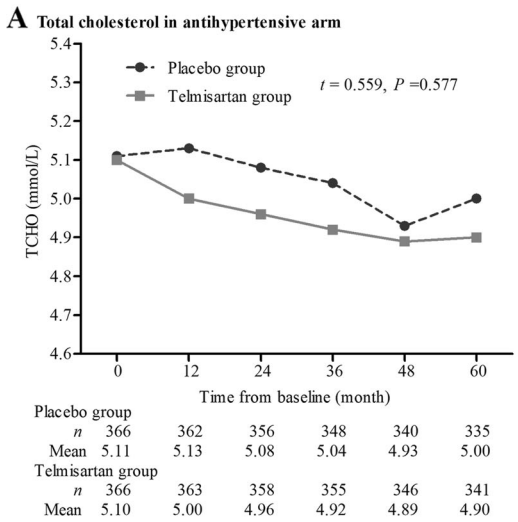


Fig. 1 Changes in blood pressure over time. **a** represents the changes in SBP in the placebo and telmisartan groups; **b** the changes in SBP in the placebo and rosuvastatin groups; **c** the changes in DBP in the placebo and telmisartan groups; and **d** the changes in DBP in the placebo and rosuvastatin groups. SBP systolic blood pressure, DBP diastolic blood pressure

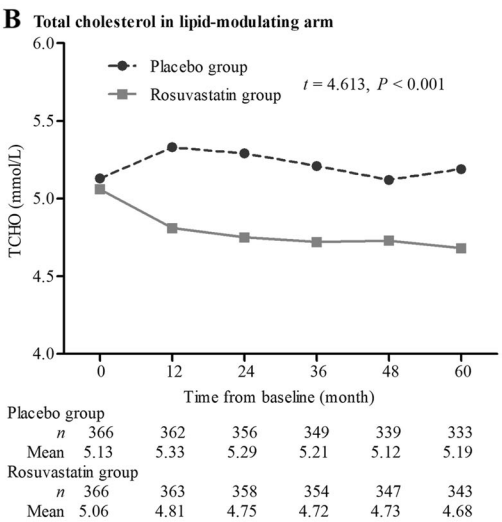
WMH progression over time

WMH volume and WMH fraction were increased in both treatment arms, compared to baseline (all $P < 0.05$). The increases over time in WMH volume and WMH fraction did not differ significantly between the telmisartan and placebo groups ($P = 0.236$ and 0.105, respectively), but did differ significantly between the rosuvastatin and placebo groups ($P = 0.026$ and 0.037, respectively). There were significant interactions between the antihypertensive arm and lipid-modulating arm with respect to increases in WMH volume and WMH fraction over time ($P = 0.020$ and 0.030, respectively, Fig. 3). These results remained after adjustment for age, sex, education, smoking, alcohol consumption, and the differences in time of MRI follow-up visit from baseline (for the increases in WMH volume, $P = 0.239$ for the antihypertensive arm, $P = 0.025$ for the lipid-modulating arm, and $P = 0.022$ for the interaction; for the increases in WMH fraction, $P = 0.107$ for the antihypertensive arm, $P = 0.038$ for the lipid-modulating arm, and $P = 0.031$ for the interaction).

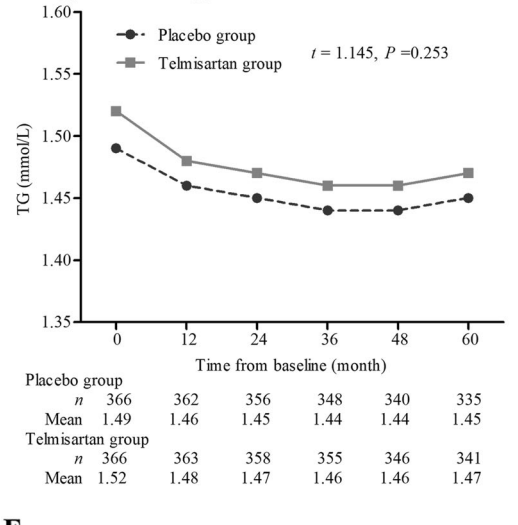
Of the 732 patients, there were 656 (89.6%) patients whose WMH Fazekas scale scores were <2 at baseline, with 634 of these having at least one follow-up MRI assessment. Of these 634, 110 (17.4%) developed a Fazekas scale ≥2 over time. The risk of new-incident WMH Fazekas scale scores ≥2 did not differ between the telmisartan and placebo groups (48 (15.1%) vs. 62 (19.6%), $P = 0.132$), but was significantly lower in the rosuvastatin group than in the placebo group (39 (12.1%) vs. 71 (22.8%), $P < 0.001$). The cumulative hazard ratios (95% confidence interval) were 0.74 (0.50–1.08) for the telmisartan group compared with the placebo group, 0.50 (0.34–0.74) for the rosuvastatin group compared with the placebo group, and there was a significant interaction between the antihypertensive arm and lipid-modulating arm ($P < 0.001$) after adjustment for age, sex, education, smoking, alcohol consumption, and the differences in time of MRI follow-up visit from baseline (Fig. 3 and Table 2).



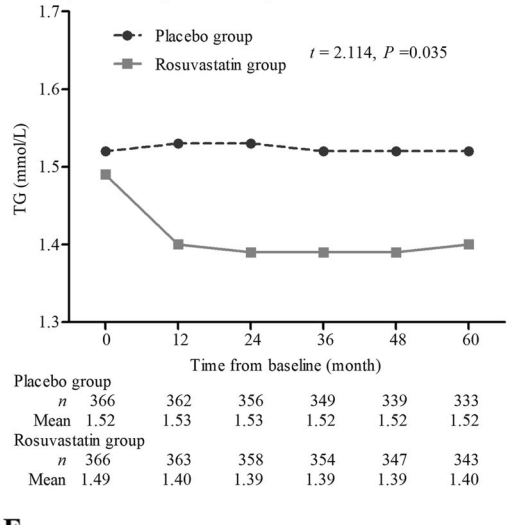
Placebo group						
n	366	362	356	348	340	335
Mean	5.11	5.13	5.08	5.04	4.93	5.00
Telmisartan group						
n	366	363	358	355	346	341
Mean	5.10	5.00	4.96	4.92	4.89	4.90



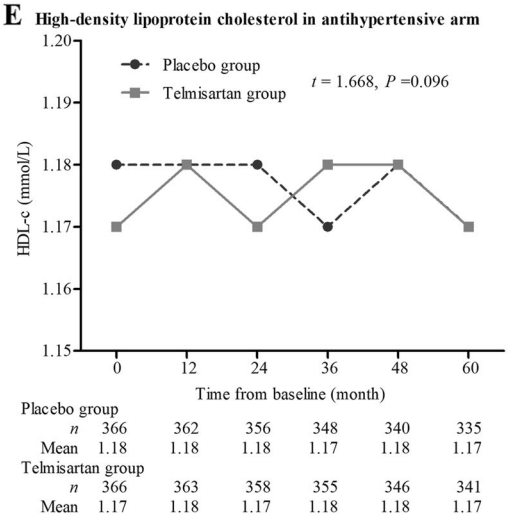
Placebo group						
n	366	362	356	349	339	333
Mean	5.13	5.33	5.29	5.21	5.12	5.19
Rosuvastatin group						
n	366	363	358	354	347	343
Mean	5.06	4.81	4.75	4.72	4.73	4.68



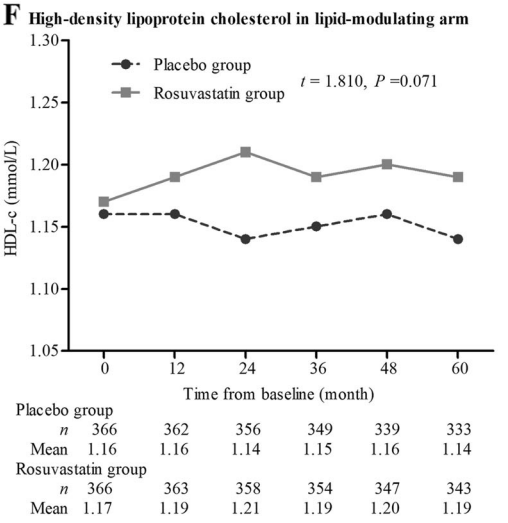
Placebo group						
n	366	362	356	348	340	335
Mean	1.49	1.46	1.45	1.44	1.44	1.45
Telmisartan group						
n	366	363	358	355	346	341
Mean	1.52	1.48	1.47	1.46	1.46	1.47



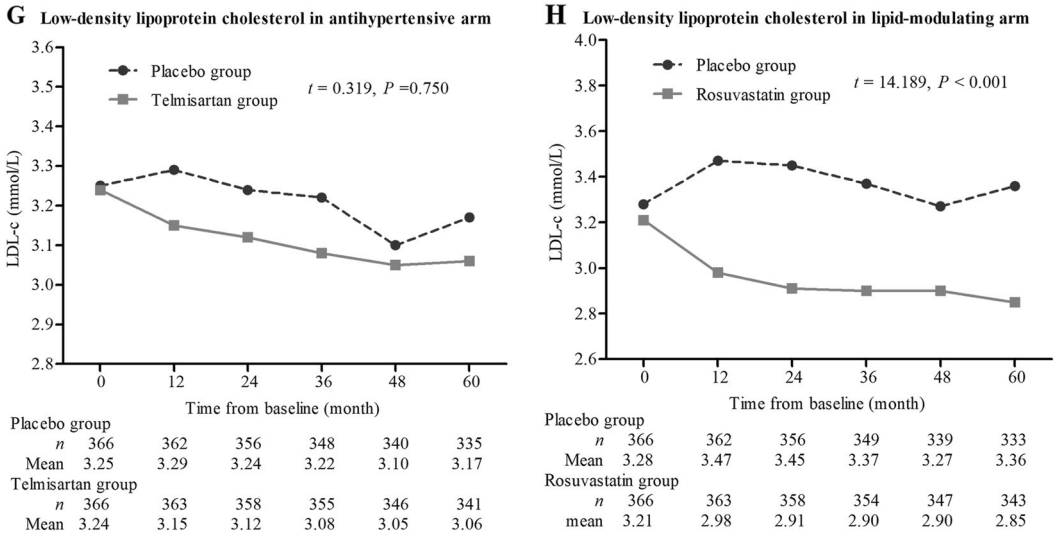
Placebo group						
n	366	362	356	349	339	333
Mean	1.52	1.53	1.53	1.52	1.52	1.52
Rosuvastatin group						
n	366	363	358	354	347	343
Mean	1.49	1.40	1.39	1.39	1.39	1.40



Placebo group						
n	366	362	356	348	340	335
Mean	1.18	1.18	1.18	1.17	1.18	1.17
Telmisartan group						
n	366	363	358	355	346	341
Mean	1.17	1.18	1.17	1.18	1.18	1.17



Placebo group						
n	366	362	356	349	339	333
Mean	1.16	1.16	1.14	1.15	1.16	1.14
Rosuvastatin group						
n	366	363	358	354	347	343
Mean	1.17	1.19	1.21	1.19	1.20	1.19



Placebo group						
n	366	362	356	348	340	335
Mean	3.25	3.29	3.24	3.22	3.10	3.17
Telmisartan group						
n	366	363	358	355	346	341
Mean	3.24	3.15	3.12	3.08	3.05	3.06

Placebo group						
n	366	362	356	349	339	333
Mean	3.28	3.47	3.45	3.37	3.27	3.36
Rosuvastatin group						
n	366	363	358	354	347	343
mean	3.21	2.98	2.91	2.90	2.90	2.85

Fig. 2 Changes in blood lipids over time. **a** presents the changes in total cholesterol in the placebo and telmisartan groups; **b** the changes in total cholesterol in the placebo and rosuvastatin groups; **c** presents the changes in triglycerides in the placebo and telmisartan groups; **d** the changes in triglycerides in the placebo and rosuvastatin groups; **e** presents the changes in high-density lipoprotein cholesterol in the placebo and telmisartan groups; **f** the changes in high-density lipoprotein cholesterol in the placebo and rosuvastatin groups; **g** presents the changes in low-density lipoprotein cholesterol in the placebo and telmisartan groups; and **h** the changes in low-density lipoprotein cholesterol in the placebo and rosuvastatin groups

Cognitive function decline over the time

The MMSE and DRS scores declined in both treatment arms compared to baseline (all $P < 0.05$). The declines over time in MMSE and DRS scores did not differ significantly between the telmisartan and placebo groups ($P = 0.081$ and 0.718, respectively). However, the declines in the MMSE and DRS scores were significantly lower in the rosuvastatin group than in the placebo group ($P < 0.001$ and 0.029, respectively). There was a significant interaction between telmisartan and rosuvastatin in preventing declines in MMSE and DRS scores ($P = 0.031$ and 0.037, respectively). These results remained after adjustment for age, sex, education, smoking, and alcohol consumption (for the declines in MMSE score, $P = 0.239$ for the antihypertensive arm, $P = 0.025$ for the lipid-modulating arm, and $P = 0.033$ for the interaction; for the declines in DRS scores, $P = 0.107$ for the antihypertensive arm, $P = 0.038$ for the lipid-modulating arm, and $P = 0.039$ for the interaction, Fig. 2).

Of the 732 patients, 725 had at least one annual cognitive function assessment. Of these 725, 107 (14.8%) developed cognitive impairment, as defined by changes in the MMSE score and/or DRS score. The incidence of cognitive impairment did not differ between the telmisartan and placebo groups (59 (16.3%) vs. 48 (13.2%), $P = 0.243$), and was significantly lower in the rosuvastatin group than in the placebo group (68 (18.8%) vs. 39 (10.7%), $P = 0.002$). The cumulative hazard ratios (95% confidence interval) were 0.76 (0.52–1.11) for the telmisartan group compared with the placebo group, 0.54 (0.36–0.80) for the rosuvastatin group compared with the placebo group, and there was a significant interaction between the antihypertensive arm and lipid-modulating arm ($P = 0.002$) after adjustment for age, sex, education, smoking, and alcohol consumption (Fig. 4 and Table 2).

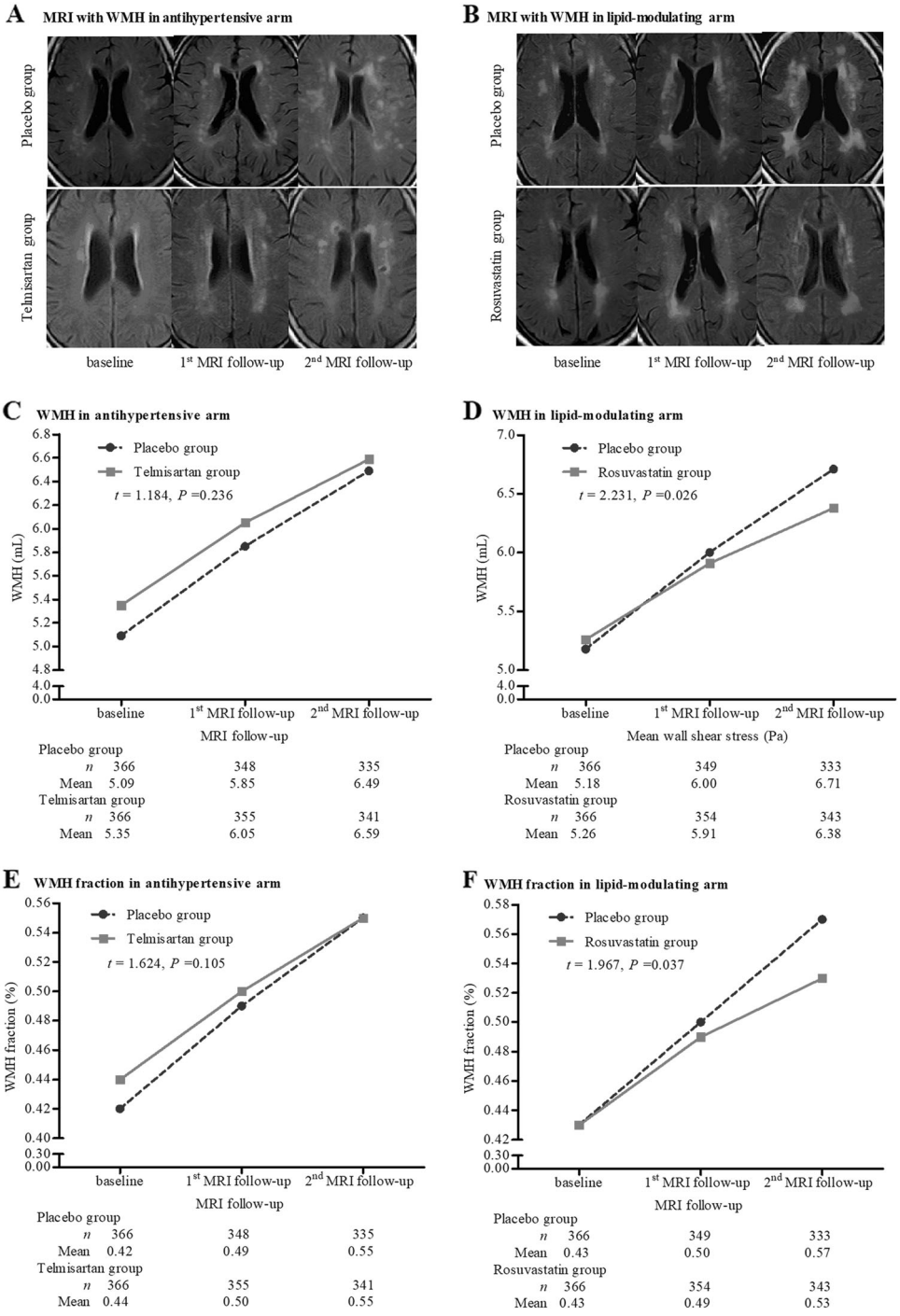
Discussion

In this randomized study, the major findings can be summarized as follows: WMH volume and WMH fraction increased, and MMSE and DRS scores declined in both treatment arms during the follow-up period. However, there were no significant differences in WMH progression and cognitive decline over time between the telmisartan and matching placebo group; the rosuvastatin group was associated with lower risks of WMH progression and cognitive decline when compared with the matching placebo group; and there was a synergistic interaction between low-dose rosuvastatin and telmisartan on ameliorating WMH progression and cognitive decline in elderly (≥60 years of age) hypertensive patients.

Previous studies have demonstrated that hypertension is associated with an increased risk of cerebral small vessel disease and dementia, and adequate antihypertensive treatment can ameliorate the progression of white matter lesions and cognitive impairment [2, 3, 14, 16]. However, it remains unclear whether similar effects are true among different hypertensive medications. In this study,

telmisartan performed slightly better than the matching placebo on alleviating the progression of WMH and cognitive impairment, although we did not find a significant difference between the two groups. One explanation for this could be the dampening effect of hydrochlorothiazide, which was used as a background antihypertensive medication in all the participants, leading to significantly reduced baseline blood pressure levels in both groups. Therefore, further blood pressure reductions by telmisartan did not reach statistical significance between the two groups. Our findings, however, further substantiate the important role that blood pressure levels play in the development of white matter lesions and cognitive impairment.

In a randomized clinical trial, known as the Regression of Cerebral Artery Stenosis study, simvastatin was implicated in having ameliorating effects on cerebral WMH progression in patients with a severe initial WMH burden [27]. Similarly, in our lipid-modulating trial arm, we found



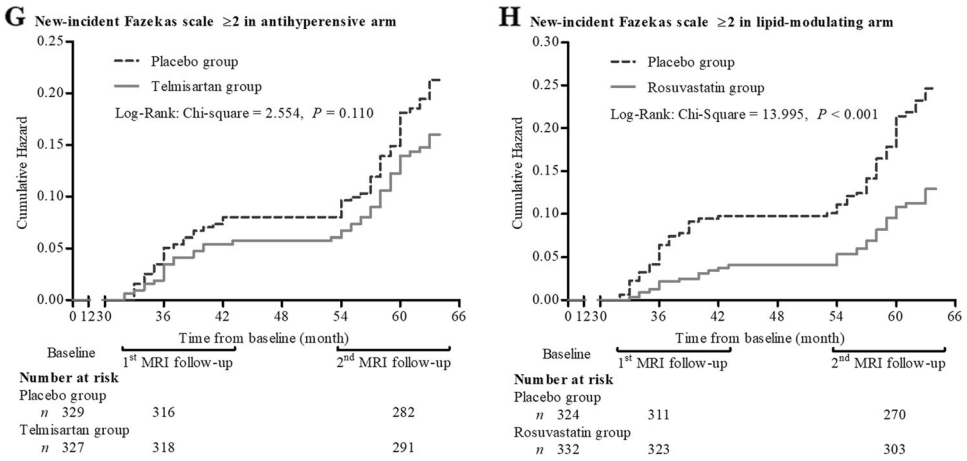


Fig. 3 Effects of telmisartan and low-dose rosuvastatin on WMH progression over time. **a** presents the MRI with WMH in placebo and telmisartan groups; **b** the MRI with WMH in placebo and rosuvastatin groups; **c** presents the changes in WMH volume in placebo and telmisartan groups; **d** the changes in WMH volume in placebo and rosuvastatin groups; **e** the changes in WMH fraction in placebo and telmisartan groups; **f** the changes in WMH fraction in placebo and rosuvastatin groups; **g** cumulative hazard of new-incident Fazekas scale ≥2 in placebo and telmisartan groups; and **h** cumulative hazard of new-incident Fazekas scale ≥2 in placebo and rosuvastatin groups. WMH white matter hyperintensities, MRI magnetic resonance imaging

Table 2 Possible risk of new-incident Fazekas scale ≥2 and incidence of cognitive impairment over the time

	New-incident Fazekas scale ≥2				Incidence of cognitive impairment			
	OR (95% CI)	*P* value	HR (95% CI)	*P* value	OR (95% CI)	*P* value	HR (95% CI)	*P* value
Antihypertensive arm								
Placebo group	Ref.		Ref.		Ref.		Ref.	
Telmisartan group	0.721 (0.472–1.102)	0.131	0.737 (0.503–1.082)	0.119	0.758 (0.499–1.152)	0.194	0.758 (0.518–1.114)	0.156
Lipid-modulating arm								
Placebo group	Ref.		Ref.		Ref.		Ref.	
Rosuvastatin group	0.466 (0.302–0.720)	0.001	0.496 (0.335–0.735)	<0.001	0.513 (0.334–0.790)	0.002	0.538 (0.362–0.800)	0.002
Antihypertensive arm ×lipid-modulating arm	0.592 (0.445–0.786)	<0.001	0.614 (0.473–0.796)	<0.001	0.649 (0.492–0.855)	0.002	0.666 (0.515–0.860)	0.002

All models were adjusted for age, sex, education, smoking and alcohol consumption

OR odd ratio, *CI* confidence interval, *HR* hazard ratio

that the rosuvastatin group was associated with a lower risk of WMH progression over the follow-up period when compared to the placebo group. Furthermore, the incidence of cognitive impairment was significantly lower in the rosuvastatin group than in the placebo group. These findings could mainly be the result of the lipid-modulating effect of rosuvastatin. However, some studies have demonstrated that blood lipid levels are inversely associated with WMH burden [42, 43]. This inconsistency in findings may be due to the fact that the patients in our study differed from those in the previous studies [27, 42–44]. For example, the patients our study were hypertensive Han Chinese patients without a history of ischemic stroke. In addition, low-dose rosuvastatin was used in this study. Low-dose statins do not lower blood lipids drastically, but significantly reduce the side effects [45–47].

Our results show that telmisartan significantly interacted with low-dose rosuvastatin on WMH progression and cognitive decline. Studies have shown that sartans, as well as statins, exhibit pleiotropic and protective effects on the cardiovascular system [24, 45]. Although these effects have been shown to act through different mechanisms, some fundamental processes are similar to both drug types, that is, anti-inflammatory, antioxidative, and anti-thrombotic effects, in addition to their unique intrinsic actions [45]. WMHs are considered to be a subtype of small vessel ischemic disease and are closely associated with vessel wall inflammation, degeneration, and oxidative stress [48]. In a previous study [24], we showed that combining telmisartan and rosuvastatin induced an additive and synergistic effect on attenuating inflammatory processes independent of their intrinsic actions. Rizos et al. [49] reported that the

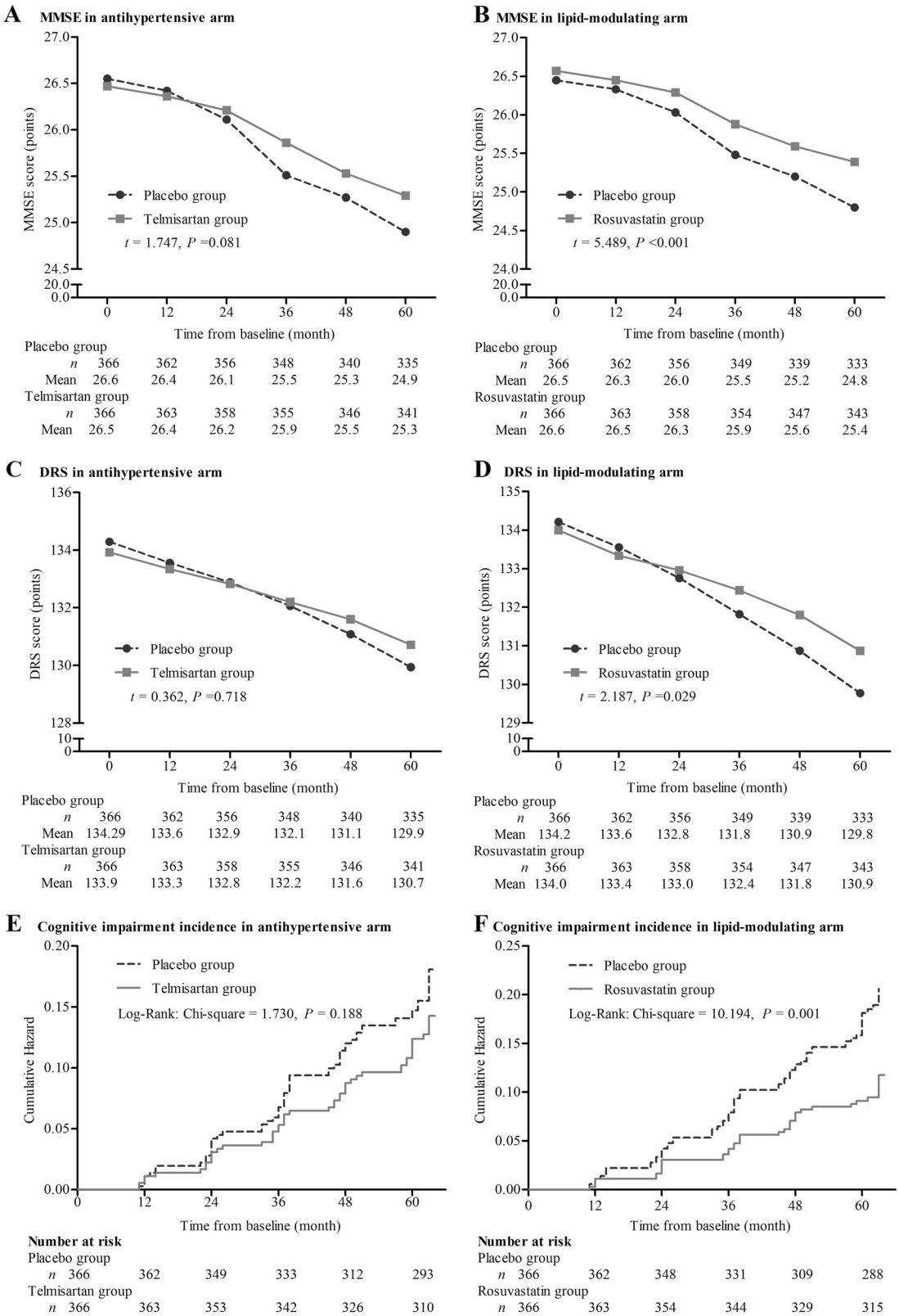


Fig. 4 Effects of telmisartan and low-dose rosuvastatin on cognitive impairment over time. **a** presents the changes in MMSE scores in the placebo and telmisartan groups; **b** the changes in MMSE scores in the placebo and rosuvastatin groups; **c** the changes in DRS scores in the placebo and telmisartan groups; **d** the changes in DRS scores in the placebo and rosuvastatin groups; **e** cumulative hazard of the incidence of cognitive impairment in the placebo and telmisartan groups; and **f** cumulative hazard of the incidence of cognitive impairment in the placebo and rosuvastatin groups. MMSE Mini-Mental State Examination, DRS Dementia Rating Scale

combination of telmisartan and rosuvastatin is significantly associated with a decrease in the levels of oxidative stress. Based on this, we hypothesize that one possible explanation of these synergistic neuroprotective effects could be a reduction of chronic inflammation and oxidative stress on the small vessel wall.

A major strength of this study is that our study was a randomized, double-blind, and placebo-controlled prospective trial with an adequate sample size and suitable longitudinal follow-ups. Another is that low-dose rosuvastatin was administered. As described above, low-dose rosuvastatin causes fewer potential side effects but has more beneficial pleiotropic effects than at higher doses [30, 45, 46, 50]. Long-term low-dose rosuvastatin use may reduce WMH progression and cognitive impairment through its pleiotropic mechanisms.

The genetic factors of patients were not assessed in this study, which could pose a major limitation. All our participants were of Han Chinese ethnicity. WMH burden and the effect of statins on dementia are both subjected to strong genetic influences [25, 51]. Multinational and multiracial clinical trials are needed to further understand such effects. Another potential limitation is that hydrochlorothiazides were used as a background baseline medication in this study. Hydrochlorothiazide is an effective antihypertensive medication and can significantly lower the blood pressure levels of hypertensive patients. When it was used as a baseline medication in this study, it may have had a blunting effect on the subsequent administration. It is therefore difficult to distinguish differences in the progressions in WMH and cognitive impairment between the telmisartan and placebo groups in this study. Third, defining cognitive impairment in terms of the MMSE and/or the DRS scores opens the possibility of conflicting results between the scales, likely resulting in over-definition of cognitive impairment. Finally, we did not assess any possible anti-inflammation and antioxidative stress effects or anti-thrombogenesis effects in our patients, although those mechanisms could have played an important role in the interactions among telmisartan, rosuvastatin, and the progression of WMH and cognitive decline.

Conclusions

In conclusion, our findings indicated that low-dose rosuvastatin could significantly ameliorate brain WMH progression and cognitive decline in elderly hypertensive patients undergoing antihypertensive treatment. Furthermore, there was a synergistic interaction between telmisartan and low-dose rosuvastatin. The combination of telmisartan and low-dose rosuvastatin may be an effective management strategy for the development and progression of white matter lesions and cognitive impairment.

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Author contributions ZL, HZ, YC, and YZ planned and initiated the trial and had full access to all the data in the study and had final responsibility for the decision to submit for publication. HZ and YZ contributed to the management of the data. ZL and HZ contributed to the analysis and interpretation of the data. HZ, YC, and ZL contributed to drafting the manuscript. ZL, GG, and QC contributed to critical revision of the manuscript for important intellectual content. All authors contributed to data collection. All authors interpreted the data, critically reviewed the manuscript, and approved the final version of the manuscript submitted for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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