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Research Article
Lipid-altering Efficacy of Ezetimibe/Simvastatin Compared with Rosuvastatin in Hypercholesterolaemic Patients: A Meta-Analysis

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Abstract

Background and Objectives: Ezetimibe/simvastatin and rosuvastatin drugs are two effective lipid-lowering therapies for hypercholesterolemic patients. However, whether the effect of ezetimibe/simvastatin is superior to rosuvastatin is still controversial. Therefore, the purpose of this study was to compare the efficacy between ezetimibe/simvastatin and rosuvastatin for hypercholesterolemia treatment by a meta-analysis. **Materials and Methods:** Based on the predefined searching strategy and selection criteria, the eligible studies were selected. The quality of included study was evaluated using Cochrane Collaboration's tool. The out come assessments indexes including low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterin (HDL-C), total cholesterin (Total C), triglycerides (TG) and apolipoprotein B (Apo B) were analyzed. In addition, the sub-group analysis was performed for comparing the efficacy of two groups with different dosages and sensitivity analysis was performed. **Results:** Totally, six studies were collected in the present study. The quality of the included studies were relatively high. Ezetimibe/simvastatin might result in greater LDL-C, Total C, TG and Apo B reductions than rosuvastatin for hypercholesterolemia. In addition, compared with 10 mg/day rosuvastatin, 10/20 mg/day ezetimibe/simvastatin had a better clinical efficacy in lipid-lowering of LDL-C, Total C, TG and Apo B. Moreover, no obvious changes of lipid-altering were observed between the rosuvastatin 40 mg/day and ezetimibe/simvastatin 10/40 mg/day. **Conclusion:** Ezetimibe/simvastatin was recommended to administrate hypercholesterolemia for providing greater reductions of LDL-C, Total C, TG and Apo B than rosuvastatin. Ezetimibe/simvastatin 10/20 mg/day had a better clinical efficacy than rosuvastatin 10 mg/day, while ezetimibe/simvastatin 10/40 mg/day had the same lipid-lowering than rosuvastatin 40 mg/day.

Key words: Hypercholesterolemia, ezetimibe/simvastatin, rosuvastatin, low-density lipoprotein cholesterol, lipid-lowering, lipid-altering

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Hypercholesterolemia is one kind of hyperlipemia and people who have suffered hypercholesterolemia may have a high-risk for cardiovascular diseases[1]. Cardiovascular disease is one most common cause of death (42.3%) and the cardiovascular disease mortality in familial hypercholesterolaemic patients is significantly higher than non-hypercholesterolemia population[2]. The estimated prevalence of familial hypercholesterolemia in US is 0.40% (1 in 250) and approximately 834,500 US adults have familial hypercholesterolemia in 2012 years[3]. The increased low-density lipoprotein cholesterol (LDL-C) may lead to improve lipid levels in plasma and this is a main cause for hypercholesterolemia and cardiovascular diseases[4,5]. In addition, the reduced high density lipoprotein cholesterin (HDL-C) and increased total cholesterin (Total C),triglycerides (TG), and apolipoprotein B (Apo B) are also important indicators for testing hypercholesterolemia due to lipid altering[6].

Rosuvastatin, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is belonged to statin[7]. Most clinical studies have suggested that rosuvastatin can improve the blood liquid of hypercholesterolaemic patients and it can obviously reduce LDL-C, Total C and TG in patients with hypercholesterolemia than atorvastatin[8-10]. Catapano *et al.*[11] have indicated that ezetimibe/simvastatin can significantly reduce LDL-C, Total C, Apo B and TG levels than rosuvastatin at different dose[11]. However, there are some controversies on the efficacy of ezetimibe/simvastatin in comparison with rosuvastatin in clinical treatment hypercholesterolemia. Moutzouri *et al.*[12] have demonstrated that there is no significant difference between the ezetimibe/simvastatin and rosuvastatin groups[12].

A previous meta-analysis have been performed for assessment the lipid efficacy of ezetimibe/simvastatin and rosuvastatin approaches for hypercholesterolemia treatment[13]. Although they have analyzed the lipid efficacy of those two therapies at the different dose comparisons, the several included studies are single sample study or have different control groups. In this meta-analysis, synthetically comparing the efficacy of ezetimibe/simvastatin with rosuvastatin for lipid altering of LDL-C, Total C, Apo B and TG levels were performed and the high quality study with both rosuvastatin and ezetimibe/simvastatin treatment were included. Moreover, a sub-group analysis for comparison different doses of ezetimibe/simvastatin and rosuvastatin groups was performed. The purpose of this study was to select a better therapy method to administrate hypercholesterolemia.

MATERIALS AND METHODS

Data sources and search strategy: Studies were searched from the several English databases such as PubMed, EMBASE, Springer and Cochrane databases. The retrieval time for the present study was up to December, 2016. The searching strategy was "rosuvastatin" and "ezetimibe" and "simvastatin" and "hypercholesterolemia" or "hyperlipidemia" or "HLP" and "random*".

Inclusion and exclusion criteria: The inclusion criteria were strictly established as follows: (1) The experiment object was patient with hypercholesterolemia, (2) The studies were randomized controlled trials (RCTs), (3) During clinical trials, the studies were needed to have two groups including rosuvastatin and ezetimibe/simvastatin groups, (4) The studies could provide or calculate the change percentage of each outcome indicators, (5) At least one of the following outcomes was included: LDL-C, HDL-C, Total C, TG and Apo B.

Exclusion criteria were: (1) The cases were diagnosed with familial hypercholesterolemia, (2) The number of participants was less than 20 in each group, (3) Studies with unavailable data or the reviews, letters and repeat publications were excluded.

Data extraction and quality assessment: Two investigators independently retrieved the databases and selected eligible studies. Then, they independently extracted the information including name of first author, publication time, study region and time, case income criterion, the number of cases in rosuvastatin group and ezetimibe/simvastatin group, dosage, the percentage of average changes and its corresponding standard deviations for each outcome indicators including LDL-C, HDL-C, Total C, TG and Apo B.

After the data extraction, quality assessment for each study was performed by using Cochrane Collaboration's tool to assess risk of bias according to Cochrane Collaboration recommendations[14]. Disagreements were resolved by discussion with a third assessor during the course of data extraction and literature quality assessment.

Statistical analysis: Stata 12.0 (STATA, College Station, TX, USA) and RevMan 5.2 statistical software (Cochrane Collaboration, http://ims.cochrane.org/revman) were utilized

for the statistical analysis of the present meta-analysis. The primary clinical outcome as the percentage of average changes of LCL-C from baseline to endpoint and several secondary outcomes including the percentage of average changes of HDL-C, Total C, TG and Apo B were chosen as the effect indicators. Due to the results of each effect size were continuous data, the pooled effect size was calculated by weighted mean difference (WMD) with 95% confidence intervals. The heterogeneity test was performed using Cochran's Q statistic and I^2 test[15]. If there exist significant heterogeneity among the studies ($p<0.05$ or $I^2>50\%$), the Dersimonian-laird random effects model was applied to combine effect size. Otherwise, the Mantel-haenszel fixed effects model was used with no obvious heterogeneity among the studies ($p\geq0.05$ or $I^2\leq50\%$). In addition, given that the used doses in the two groups were crucial variables for the effect of evaluation, a further sub-group analysis for assessment the efficacy under different dose contrasts between ezetimibe/simvastatin and rosuvastatin groups (10/20 vs.10 mg/day,10/40 vs. 40 mg/day) was conducted. Moreover, a sensitivity analysis via calculating the pooled WMD with its 95%CI for each effect size under both random effects model and fixed effects model was performed to evaluate the reliability of the present meta-analysis.

RESULTS

Eligible studies and their characteristics: A total of 283 initially studies were retrieved by database searches in PubMed, Embase and Cochrane library. Then through further screening, 44 repetitive articles, 43 studies irrelevant with the research topic, 36 literature reviews, 11 meeting reports, 8 non-human trails, 28 studies irrelevant with hypercholesterolemia and 94 studies without rosuvastatin vs. ezetimibe/simvastatin were excluded. Subsequently, the remaining 19 articles were reviewed in a full text reading. Among the nineteen studies, the unrelated studies including seven studies using the same data with others, four studies without dividing the rosuvastatin and ezetimibe/simvastatin groups and two without required outcomes were further removed. Finally, total 6 eligible studies conformed to all the inclusion criteria were obtained for the following analysis[11,16-20] (Fig. 1).

A total of 2408 cases including 1197 cases treated with rosuvastatin and 1211 cases treated with ezetimibe/simvastatin were collected in the present meta-analysis. All the included studies were published during the years 2006-2014. In addition, three studies were muti-center and double blinded RCTs[11,16,18] and Farnier *et al.*[16] study involved

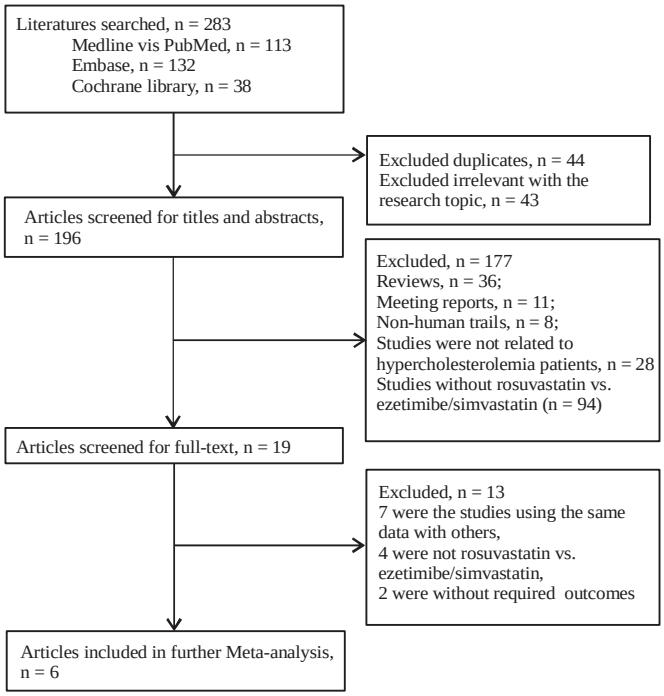

Fig. 1: Flow chart of study selection procedure

Table 1: Characteristics of the selected studies

References	Study type	Study period	Country	Inclusive criteria	No. of cases	Rosuvastatin, (mg/day)	Ezetimibe/ simvastatin, (mg/day)
Catapano *et al.*[13]	Multicenter, double-blind, 6-arm, RCT	10 weeks	214 sites in USA	18-81 years of age, LDL-C ≥145 mg/dL (3.7 mmol/L) and ≤250 mg/dL (6.5 mmol/L)	475/476	10	10//20
Farnier *et al.*[16]	Multicenter, double-blind, RCT	2007.03-2008.03	85 sites in 10 countries	18-80 years of age, patients with documented hypercholesterolaemia and high cardiovascular risk	304/314	10	10//20
Kasmas *et al.*[17]	Open-label, blinded endpoints, RCT	12 weeks	Brazil	30-75 years of age, patients who had an indication for lipid-lowering therapy	58/58	40	10/40
McCormack *et al.*[18]	Double-blind, multicenter, RCT	2007.03-2008.05	34 sites in UK	>18 years of age, with established CVD or diabetes, or were at high risk of CVD	262/261	5 or 10	10/40
Moreira *et al.*[19]	Open-label, blinded endpoints, RCT	12 weeks	Brazil	30-75 years of age, patients who had an indication for lipid-lowering therapy	57/55	40	10/40
Moutzouri *et al.*[20]	Open-label, RCT	2009.07-2010.07	Greece	patients with primary hypercholesterolaemia	45/53	10	10//10

RCT: Randomized controlled trial, LDL-C: Low density lipoprotein cholesterin, CVD: Cardio vascular disorder

85 centers of 10 countries. All the patients in the included studies were diagnosed as hypercholesterolemia with high risk of cardiovascular disease. The doses of rosuvastatin were differently administrated[11,16,18,20] with 5[19], 10 and 40 mg/day[17,19] and in the comparison, the doses of ezetimibe/simvastatin were administrated[20] with 10/10, 10/20[11,16] and 10/40 mg/day[17-19] (Table 1).

Quality assessment of the included studies: The result of Cochrane quality assessment showed that the studies had a relatively high quality except for the high risk of the blinding of participants and personnel in Kasma *et al.*[17], Moreira *et al.*[19] and Moutzouri *et al.*[20] study and the high risk of selective reporting in Mccormack *et al.*[18] study. Since three studies by Kasma *et al.*[17], Moreira *et al.*[19] and Moutzouri *et al.*[20] were open-label trials and only blind method was carried out for statistical data, which lead to the high risk of bias with lacking of blinding of participants and studying personne (Fig. 2).

Comparison of the treatment outcomes between rosuvastatin and ezetimibe/simvastatin: In the present meta-analysis, all the included studies contained the primary outcome as LDL-C and the secondary outcomes such as HDL-C, Total C, TG and Apo B were used to compare the efficacy of rosuvastatin and ezetimibe/simvastatinon treating hypercholesterolaemic patients. A significant heterogeneity was detected in LDL-C ($p<0.01$, $I^2 = 93\%$), Total C ($p<0.01$, $I^2 = 89\%$) and Apo B ($p<0.01$, $I^2 = 89\%$) respectively, thus a random effects model was utilized and a fixed effects model was chosen to merge HDL-C ($p = 0.74$, $I^2 = 0\%$) and TG ($p = 0.40$, $I^2 = 2\%$) due to no remarkable heterogeneity found.

Compared with the rosuvastatin group, ezetimibe/simvastatin group had a greater reduced LDL-C (WMD = 7.13, 95% CI: 0.44, 13.82, $p = 0.04$, Fig. 3a), a greater reduced Total C (WMD = 6.05, 95% CI:1.30, 10.79, $p = 0.01$, Fig. 3c), a greater reduced TG (WMD = 3.21, 95% CI: 0.91, 5.50, $p<0.001$, Fig. 3d) and a greater reduced Apo B (WMD = 5.01, 95% CI: 0.33, 9.69, $p = 0.04$, Fig. 3e), indicating that the ezetimibe/simvastatin treatment could achieve better efficacy on decreasing LDL-C, total C, TG and Apo B levels than rosuvastatin treatment. In addition, there was no significant difference in HDL-C between ezetimibe/simvastatin and rosuvastatin groups, showing that ezetimibe/simvastatin and rosuvastatin had the same efficacy to control the HDL-C level (Fig. 3b).

Subgroup analysis: In order to analysis the efficacy of two groups under the different doses contrast, two sub-groups

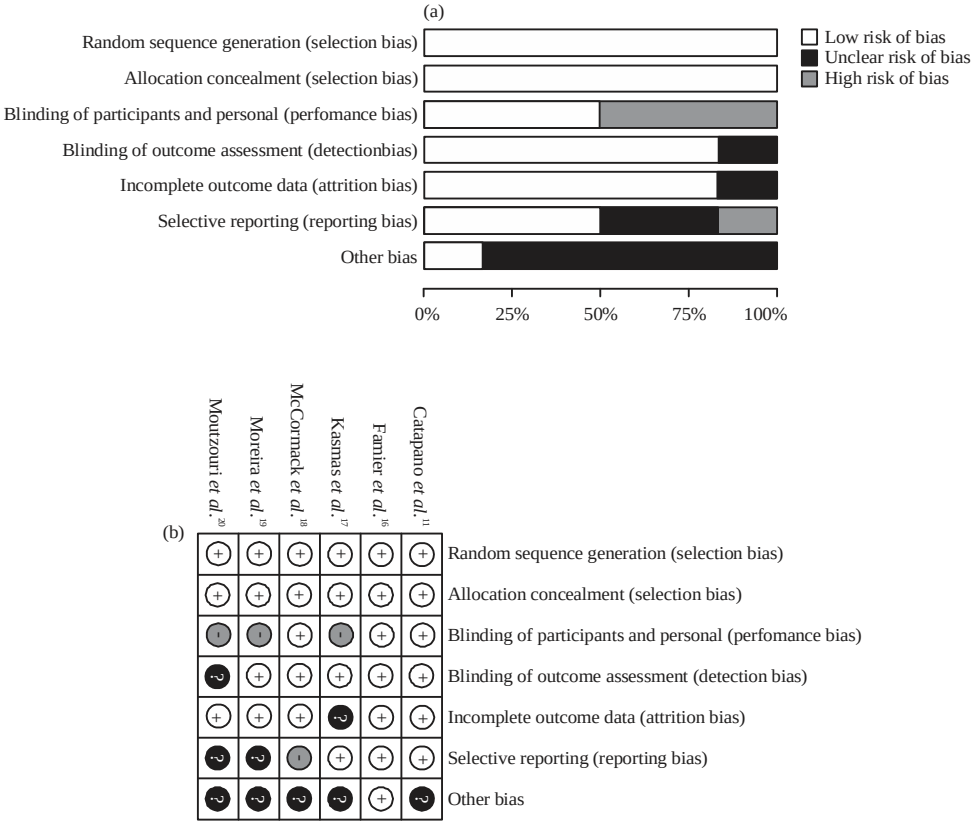

Fig. 2(a-b): Quality assessments of the included studies, (a) Bias risk of the all identified studies for each bias item presented as percentages and (b) Each risk of bias item of the 6 included studies.
"+" indicates Low risk of bias, "?" indicates unclear risk of bias, "–" indicates high risk of bias

Table 2: Sub-group analyses stratified by dosage

	Heterogeneity		Effect size	
Outcomes	P_H	I^2 (%)	WMD (95% CI)	p-value
10 vs. 10/20 mg/day				
LDL-C	0.01	84	7.94 (2.98, 12.90)	<0.01
HDL-C	0.42	0	-0.03 (-1.25, 1.19)	0.96
Total C	0.05	75	5.50 (2.70, 8.30)	<0.01
TG	0.46	0	3.71 (0.77, 6.64)	0.01
Apo B	0.03	79	5.93 (2.25, 9.62)	<0.01
40 vs. 10/40 mg/day				
LDL-C	0.73	0	-4.41 (-13.47, 4.65)	0.34
HDL-C	0.63	0	-0.95 (-4.86, 2.96)	0.63
Total C	0.90	0	-3.35 (-14.07, 7.36)	0.54
TG	0.98	0	-5.05 (-22.25, 12.15)	0.56
Apo B	0.82	0	-1.51 (-8.51, 5.48)	0.67

LDL-C: Low density lipoprotein cholesterin, HDL-C: High density lipoprotein cholesterin, Total C: Total cholesterin, TG: Triglycerides, Apo B: Apolipoprotein B, WMD: Weighted mean difference, CI: Confidence interval

were divided. In compared with rosuvastatin (10 mg/day), the level of LDL-C (WMD = 7.94, 95%CI: 2.98, 12.90, p<0.01), total C (WMD =5.50, 95%CI: 2.70, 8.30, P<0.01), TG (WMD = 3.71, 95% CI: 0.77, 6.64, p = 0.01) and Apo B (WMD = 5.93, 95% CI: 2.25, 9.62, p<0.01) were significantly lower under ezetimibe/simvastatin treatment with10/20 mg/day (Table 2) and no significant difference in HDL-C was observed (WMD = -0.03, 95% CI: -1.25, 1.19, p = 0.96). However, no obviously difference on LDL-C (WMD = -4.41, 95% CI: -13.47, 4.65, p = 0.34), total C (WMD = -3.35, 95% CI: -14.07, 7.36,

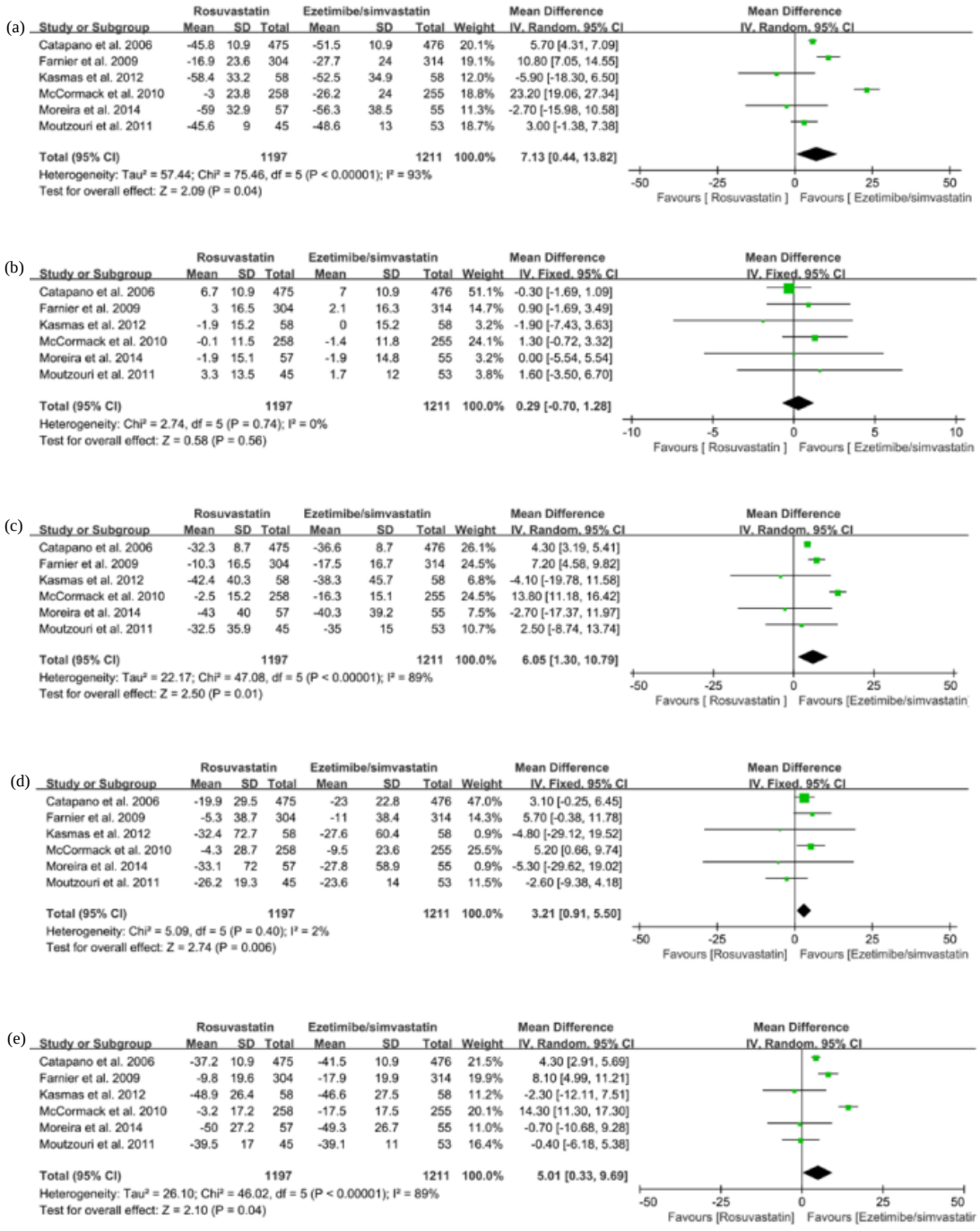

Fig. 3(a-e): Results of the comparison of outcome assessments indexes between ezetimibe/simvastatin and rosuvastatin groups, (a) Forest plot of the comparison of LDL-C between ezetimibe/simvastatin and rosuvastatin groups, (b) Forest plot of the comparison of HDL-C between ezetimibe/simvastatin and rosuvastatin groups, (c) Forest plot of the comparison of total C between ezetimibe/simvastatin and rosuvastatin groups, (d) Forest plot of the comparison of TG between ezetimibe/simvastatin and rosuvastatin groups and (e) Forest plot of the comparison of Apo B between ezetimibe/simvastatin and rosuvastatin groups. Squares denote the study-specific outcome estimates and the size of the square represents the study-specific weight. Horizontal lines and figures in parentheses represent the 95% CI. Diamonds indicate the pooled effect size with the corresponding 95% CI

LDL-C: Low-density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterin, Total C: Total cholesterin, TG: Triglycerides, Apo B: Apolipoprotein B

Table 3: Sensitivity analysis (random effect model vs. fixed effect model)

	Random effect model		Fixed effect model	
Outcomes	WMD (95% CI)	p-value	WMD (95% CI)	p-value
LDL-C	7.13 (0.44,13.82)	0.04	7.27 (6.09, 8.45)	<0.01
HDL-C	0.29 (-0.70, 1.28)	0.56	0.29 (-0.70, 1.28)	0.56
Total C	6.05 (1.30, 10.79)	0.01	5.83 (4.89, 6.77)	<0.01
TG	3.20 (0.85, 5.54)	<0.01	3.21 (0.91, 5.50)	<0.01
Apo B	5.01 (0.33, 9.69)	0.04	5.88 (4.75, 7.01)	<0.01

LDL-C: Low density lipoprotein cholesterin, HDL-C: High density lipoprotein cholesterin, Total C: Total cholesterin, TG: Triglycerides, Apo B: Apolipoprotein B, WMD: Weighted mean difference, CI: Confidence interval

p = 0.54), TG (WMD = -5.05, 95% CI: -22.25, 12.15, p = 0.56), HDL-C (WMD = -0.95, 95% CI: -4.86, 2.96, p = 0.63)and Apo B(WMD = -1.51, 95% CI: -8.51, 5.48, p = 0.67) were found between rosuvastatin 40 mg/day and ezetimibe/simvastatin 10/40 mg/day (Table 2).

Sensitive analysis: The results of LDL-C, HDL-C, Total C, TG and Apo B random effects model and fixed effects model were consistent, which indicated that the outcomes of this meta-analysis were stable (Table 3).

DISCUSSION

In the present study, the efficacy of ezetimibe/simvastatin with rosuvastatin on lipid altering for the hypercholesterolemia treatment was compared. The data of LDL-C, HDL-C, Total C, TG and Apo B levels acted as indicators for assessment lipid altering. As a result, ezetimibe/simvastatin significantly resulted in greater LDL-C, Total C, TG and Apo B reductions than rosuvastatin. No significant change in HDL-C was achieved between the two groups. In addition, compared with rosuvastatin (10 mg/day), the 10/20 mg/day ezetimibe/simvastatin had a better clinical efficacy in lipid-lowering of LDL-C, Total C, TG and Apo B. However, no obvious changes of LDL-C, HDL-C, Total C, TG and Apo B were found between the rosuvastatin 40 mg/day and ezetimibe/simvastatin 10/40 mg/day.

It is well-known that statins such as rosuvastatin, pravastatin and simvastatin are the rate-limiting enzyme for cholesterol synthesis, thus they play a crucial role on lipid lowering. Recently, the usage of statins is firstly recommended to reduce LDL-C level for treating hypercholesterolemia and cardiovascular diseases[21]. Brown *et al.*[22] have demonstrated that 10 mg of rosuvastatin can lead to greater LDL-C reduction than 20 mg of simvastatin or 20 mg of pravastatin in hypercholesterolaemic patients. Viigimaa *et al.*[23] have indicated that the combined therapy of ezetimibe/simvastatin (10/20 mg/day) provides superior LDL-C, Total C and Apo B reductions in patients with hypercholesterolemia. Similarly, Averna *et al.*[24] have obtained the same results that for hypercholesterolaemic patients treated with ezetimibe/simvastatin, is obviously more effective than rosuvastatin at lowering LDL-C, Total C and Apo B. It was consisted with the findings of this study, which showed ezetimibe/simvastatin (10/20 mg/day) offered a better clinical efficacy in lowering LDL-C, Total C, TG and Apo B rosuvastatin (10 mg/day) in hypercholesterolaemic patients.

In addition, the result of this study showed that the lipid-lowering induced by ezetimibe/simvastatin was greater than rosuvastatin via integrating the results of different doses (ezetimibe/simvastatin 10/10, 10/20 mg, 10/40 mg vs rosuvastatin 10, 10, 5 or 10 and 40 mg). Notably, Catapano *et al.*[13] have suggested that greater LDL-C, Total C, TG and Apo B reductions in ezetimibe/simvastatin group were found compared with rosuvastatin group at the different dose-response (ezetimibe/simvastatin 10/10, 10/20, 10/40 and 10/80 mg vs rosuvastatin 5, 10, 20 and 40 mg). One reasonable explanation is that ezetimibe/simvastatin combines two lipid-lowering medicines and block the two sources of plasma cholesterol and it is more effective than monotherapy with the double statin dose[25]. Nevertheless, in this study, no significant difference of LDL-C, HDL-C, Total C, TG and Apo B were observed between the rosuvastatin 40 mg/day and ezetimibe/simvastatin 10/40 mg/day. Therefore, the usage of dose in the two groups was a main influence factor for evaluation the efficacy for hypercholesterolemia treatment.

In the present study, significant heterogeneity among the included studies for Total C, LDL-C and Apo B were detected. Although a sub-group analysis was conducted, there still existed significant heterogeneity in the subgroup (ezetimibe/simvastatin 10/40 mg/day vs rosuvastatin 10 mg/day). The reasons for the high heterogeneity might be: (1) Before random grouping with double-blind, the included cases with hypercholesterolemia were administrated with different statins, (2) The included cases were come from different countries such as Greece, Brazil, UK and USA and their different health and living conditions might lead to strikingly heterogeneity.

Although the sensitive analysis indicated that the results were stable and all the treatments were well tolerated, the present study was limited by several factors. Only six studies were eligible and the comparison of the efficacy of the two therapies with more different dose were failed to conduct. In addition, the adverse reactions and safety of the two treatment groups were not considered. Thus, further studies with larger sample sizes and adverse reactions and safety assessment are needed which might provide a more accurately outcomes.

CONCLUSION

In summary, ezetimibe/simvastatin was superior to LDL-C, Total C, TG and Apo B reductions compared with rosuvastatin. The sub-group analysis indicated that the 10/20 mg/day ezetimibe/simvastatin had a relativegreater LDL-C, Total C, TG and Apo Breductions than 10 mg/day rosuvastatin and the changes of LDL-C, HDL-C, Total C, TG and Apo B were not significant between the rosuvastatin 40 mg/day and ezetimibe/simvastatin 10/40 mg/day treatment for hypercholesterolaemic patients.

SIGNIFICANCE STATEMENT

This study discovers the 10/20 mg/day ezetimibe/ simvastatin produces better outcomes than 10 mg/day rosuvastatin in patients with hypercholesterolemia and the effect of 40 mg/day ezetimibe/simvastatin and 40 mg/day rosuvastatin is comparable. The present evidence will inform further investigations and clinical selections of drugs and their dose usage for hypercholesterolemic patients treatment.

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