Int J Clin Exp Med 2016;9(3):5291-5300
www.ijcem.com /ISSN:1940-5901/IJCEM0019029

Review Article

Comparison of the safety of statin monotherapy and coadministration with fenofibrate in patients with mixed hyperlipidemia: a meta-analysis

Kan Shao[1], Yubin Tang[1], Dong Zhou[2], Shan Huang[1]

[1]Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200336, China; [2]Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Received November 3, 2015; Accepted January 28, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Objective: To compare adverse events of statin monotherapy and combination therapy of statin and fenofibrate. Methods: We searched the online databases of PUBMED and EMBASE for high-quality randomized controlled trials (RCTs). Interested outcomes included discontinuation because of any adverse event, any adverse event, serious adverse events, drug-related adverse events, increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 3 times upper limit of normal (ULN), increase in creatine kinase (CK) ≥ 5 times ULN, increase in creatinine ≥ 50% and above ULN. As the incidence of adverse events was dichotomous, odds ratios (ORs) were calculated for each included trial with a fixed-effects or random-effects model depending on the heterogeneity of the studies. Results: Twelve RCTs covering 5398 participants were included in this meta-analysis. Our results revealed that combination therapy was associated with a significantly higher discontinuation because of any adverse event compared with statin monotherapy (P < 0.00001), but there were no significant difference in any adverse event (P = 0.54), serious adverse events (P = 0.55) and drug related adverse events (P = 0.39). Fenofibrate plus statin did not result in a greater risk of muscle-related adverse events than monotherapy (P = 0.79). However, there were more hepatic enzyme elevation-related adverse events (P = 0.0006) and plasma creatinine elevation-related adverse events (P = 0.0002) in coadministration group than monotherapy group. Conclusions: The pooled evidence showed that combination therapy of statin and fenofibrate is associated with a higher incidence of hepatic and renal abnormality compared with statin monotherapy. Fenofibrate should be used carefully in patients with liver and renal impairment, and function of liver and kidney should be monitored closely within the combination therapy.

Keywords: Combination therapy, drug safety, fenofibrate, statin, meta-analysis

Introduction

Mixed or combined hyperlipidemia is prevalent worldwide because of the advancement of living standards and subsequent abnormality of lifestyle. It is featured by elevated low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and associated with the decrease of high-density lipoprotein cholesterol (HDL-C) [1]. Statins are the most frequently prescribed medications for simple dyslipidemia and have an effective control of LDL-C, but statins alone are insufficient to normalize the remaining lipid parameters in patients with mixed hyperlipidemia. Combination therapy of statins and other lipid-lowering agents serves as an appropriate treatment strategy to standardize all the targeted lipid indexes. Fenofibrate is the most commonly used lipid-lowering drug, a regular dose of which can simultaneously reduce TG and elevate HDL-C. Statin together with fenofibrate can achieve added benefits through alternative pharmacological mechanisms in normalizing the serum lipid [2]. Clinical trials have also proven that patients benefited a lot from the combination therapy of statin and fenofibrate in comparison with monotherapy of either of them [3].

Despite the obvious lipid-lowering effects, safety concerns of combination therapy have made some physicians reluctant to prescribe them [4]. The research by Davidson et al claimed that fenofibrate plus statin was associated with a

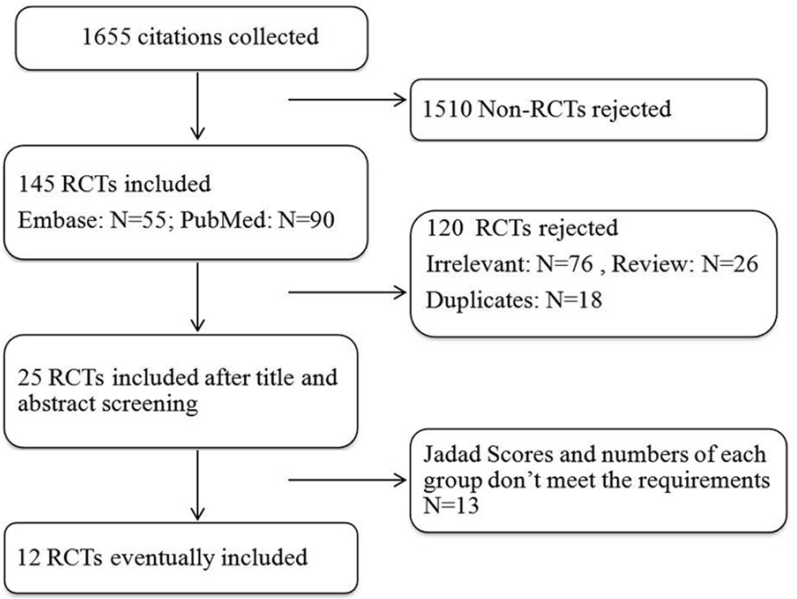

Figure 1. Flowchart of trial selection process.

higher morbidity of renal-related adverse events compared with statin monotherapy [5]. The study by Lee et al pointed that combination therapy should be used carefully in individuals with renal dysfunction [6]. Likewise, the systematic review by Geng et al also suggested that the incidence of hepatic and renal related adverse events was significantly higher in the combination group than in the corresponding statin monotherapy group [7]. Warnings of uncertain adverse events about combination therapy of statin plus fenofibrate have limited its broad use in clinical practice. Comprehensive analysis of the safety of combination therapy versus monotherapy could help guide the clinical treatment.

We performed this meta-analysis to critically examine the potential adverse events about statin monotherapy and combination therapy of statin and fenofibrate. We put forward questions that (1) whether combination therapy was associated with more adverse events; (2) Whether patients treated with coadministration were more susceptible to muscle, liver and renal related adverse events than those with monotherapy.

Materials and methods

Search strategies

We searched all RCTs comparing statin monotherapy and coadministration of statin and fenofibrate through the online databases (PUBMED, EMBASE) from January 1990 to December 2014 with language restriction only in English. The key words ("statin" OR "rosuvastatin" OR "simvastatin" OR "pravastatin" OR "cerivastatin" OR "fluvastatin" OR "lovastatin") AND ("fenofibrate" OR "fenofibric acid" OR "FA" OR "ABT-335") AND ("hyperlipidemia") were used in screening the related literatures.

Inclusion criteria/exclusion criteria

All RCTs comparing statin monotherapy and coadministration of statin and finofibrate were included. The experiment group and the control group must adopt the identical statin drug and the dose of statin should be the same. We treated fenofibrate and its active metabolite fenofibrate acid, choline fenofibrae (ABT-335) equally. The inclusion criteria were: (1) the studies were randomized controlled trials, non-randomized controlled trials and quasi-randomized trials were excluded; (2) the number of participants in each group was above 20; (3) the studies presented at least one of the outcomes that we were interested in. The main outcomes were discontinuation because of any adverse event, any adverse event, serious adverse events, drug-related adverse events, increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 3 times upper limit of normal (ULN), increase in creatine kinase (CK) ≥ 5 times ULN, increase in creatinine ≥ 50% and above ULN.

Quality assessment and data extraction

All the studies matching the eligible criteria were evaluated by the Jadad Score System [8]. The highest score is five points. Studies with a score no more than three points were not allowed into the next data extraction stage.

If there were more than one dose of statin used to compare the safety of statin monotherapy and coadministration of statin and fenofibrate,

Table 1. Characteristics of the included studies

Study	NO.		Mean age		Female (%)		Drug and dose (mg)		Follow up (week)	Jadad score
	Statin	Statin + F	Statin	Statin + F	Statin	Statin + F	Statin	Statin + F		
Davidson (2009) [11]	74	73	56.3	54.9	52.70	45.20	Atorva (40)	F (100) + Atorva (40)	12	5
Davidson (2014) [5]	339	337	61	61	32	32	P + Atorva	FA (135) + Atorva	108	4
Derosa (2004) [3]	23	24	59	61	47.80	52	Fluva (80)	F (200) + Fluva (80)	12	4
Farnier (2010) [15]	125	123	58.1	57.8	29.60	30.10	Prava (40)	F (160) + Prava (40)	12	4
Farnier (2007) [10]	179	180	55.2	55	45.99	48.40	Eze/simva (10/20)	F (160) + Eze/Simva (10/20)	12	5
Goldberg (2009) [12]	113	110	53.7	56.2	42.50	50.90	Atorva (20)	ABT-335 (135) + Atorva (20)	16	4
	109	110	56.3	54.9	55	55.50	Atorva (40)	ABT-335 (135) + Atorva (40)		
Grundy (2005) [9]	207	411	53.5	52.3	45.90	50.60	Simva (20)	F (160) + Simva (20)	12	4
Jones (2009) [13]	261	261	53.6	55.6	49.80	56.70	Rosuva (10)	ABT-335 (135) + Rosuva (10)	16	4
	266	261	55.5	54.4	46.60	50.20	Rosuva (20)	ABT-335 (135) + Rosuva (20)		
Jones (2010) [16]	270	272	56.4	54.4	57.40	52.60	P + Atorva (40)/Eze (10)	FA (135) + Atorva (40)/Eze (10)	16	5
Mohiuddin (2009) [14]	119	118	54.3	55.9	56	59	Simva (20)	ABT-335 (135) + Simva (20)	12	4
	116	118	53.7	53.7	61	57	Simva (40)	ABT-335 (135) + Simva (40)		
Roth (2010) [17]	251	253	55.3	56.2	59.80	63.60	Rosuva (5)	FA (135) + Rosuva (5)	12	4
Weinstein (2013) [18]	140	140	67.4	65.1	50.70	55.10	P + Rosuva (5-10)	FA (45) + Rosuva (5-10)	16	5

Atorva: atorvastatin; Fluva: fluvastain; Prava: pravastatin; Simva: simvastatin; Rosuva: rosuvastatin; EZE: Ezetimibe; F: Fenofibrate; FA: fenofibric acid; ABT-335: choline fenofibrate.

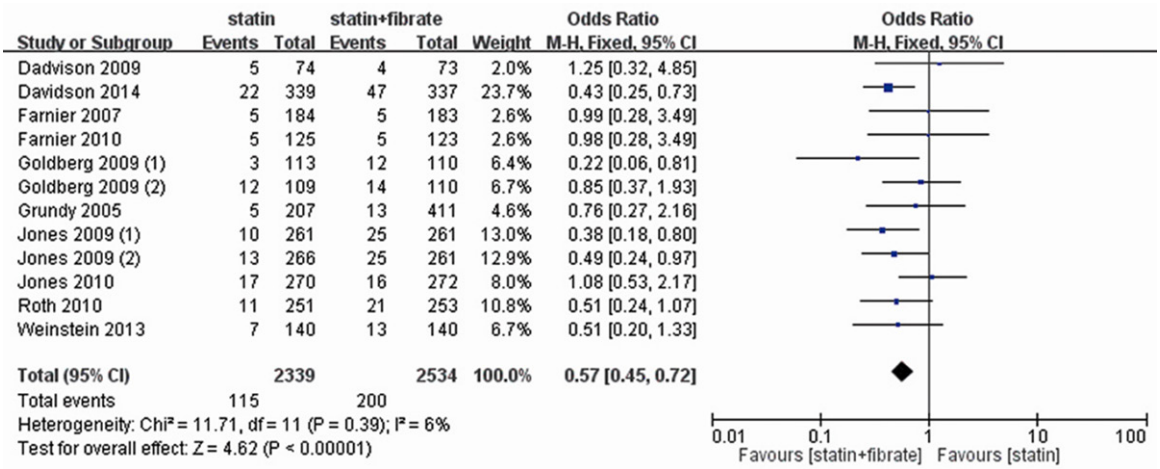

Figure 2. Forest plot of discontinuation because of any adverse event between the monotherapy and coadministration groups.

each dose of pair-wise comparison was used separately in the meta-analysis as if they were from different studies. The following information was extracted from the citations: first author name, year of publication, baseline information of each group (sample size, mean age, ratio of female, type and dose of drug), duration of follow-up, and citation quality (generation of the random sequence, concealment of the allocation, blinding of the outcome assessment, description of the withdrawals and dropouts).

Data analysis

Odds ratio (OR) and 95% confidence interval (CI) were calculated for each article as the data describing adverse events in the compared groups were dichotomous. I^2 value and *P* value were adopted to evaluate the heterogeneity. If there was no notable heterogeneity ($I^2 \leq 50\%$ and $P > 0.1$), a fixed-effects model would be used to test the overall effect size; otherwise a random-effects model would take its place. The sensitivity analysis would be carried out if there was significant heterogeneity among literatures. The data analysis was conducted by Review Manager Software (RevMan 5.3) and the publication bias was tested by Stata 12.0. $P < 0.05$ was considered as significant difference.

Results

Characteristics and selected studies

A total of 1655 articles were firstly collected, within which 145 were RCTs. After scanning the title and abstract, we deleted 26 reviews, 18 duplicates and 76 unrelated ones. The remaining 25 articles were full-text glanced, thus we eventually included 12 RCTs that covered 5398 participants with mixed hyperlipidemia [3, 5, 9-18] (**Figure 1**; **Table 1**). The paper by Goldberg et al [12], Jones et al [13] and Mohiuddin et al [14] reported two doses of statin in the coadministration group and the monotherapy group.

Meta-analysis results

Common adverse events

Ten studies reported the outcomes of discontinuation because of any adverse event, within which two articles involved two different doses of statin [12, 13], so the valid pair-wise comparisons between the monotherapy and coadministration group were twelve. There was significant difference between the compared groups in discontinuation because of any adverse event (OR = 0.57, 95% CI: 0.45-0.72; $P < 0.0001$), patients in coadministration group discontinuing from the therapy due to any adverse event were notably more than those in monotherapygroup. Evidence showed that there was no significant heterogeneity ($I^2 = 6\%$, $P = 0.39$) (**Figure 2**).

Twelve studies reported the results of any adverse event, within which three articles involved two different doses of statin [12-14], so the valid pair-wise comparisons between the monotherapy and coadministration groups were fifteen. There was no significant differ-

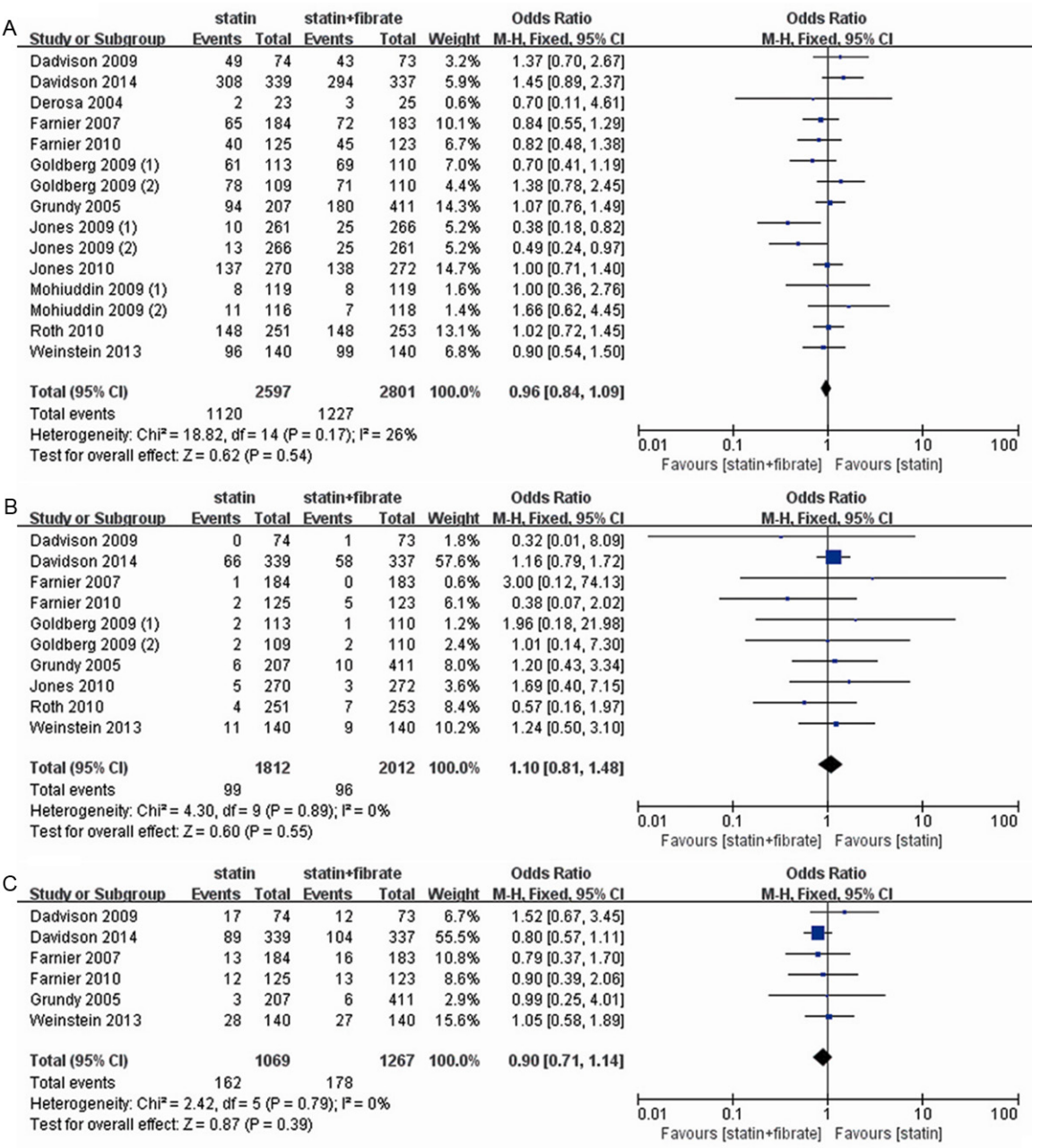

Figure 3. Forest plots of (A) any adverse event, (B) serious adverse event, and (C) drug related adverse event between the monotherapy and coadministration groups.

ence of any adverse event between the two groups (OR = 0.96, 95% CI: 0.84-1.09; P = 0.54). Evidence showed that the heterogeneity was not notable (I^2 = 26%, P = 0.17) (**Figure 3A**).

Nine studies reported the results of serious adverse events, within which one article involved two different doses of statin [12], so the valid pair-wise comparisons between the monotherapy and coadministration groups were ten. There was no significant difference of patients suffering from serious adverse events between the groups (OR = 1.10, 95% CI: 0.81-1.48; P = 0.55). Evidence showed that the heterogeneity was not significant, neither (I^2 = 0%, P = 0.89) (**Figure 3B**).

Six studies reported the results of drug related adverse events. The pooled analysis of the

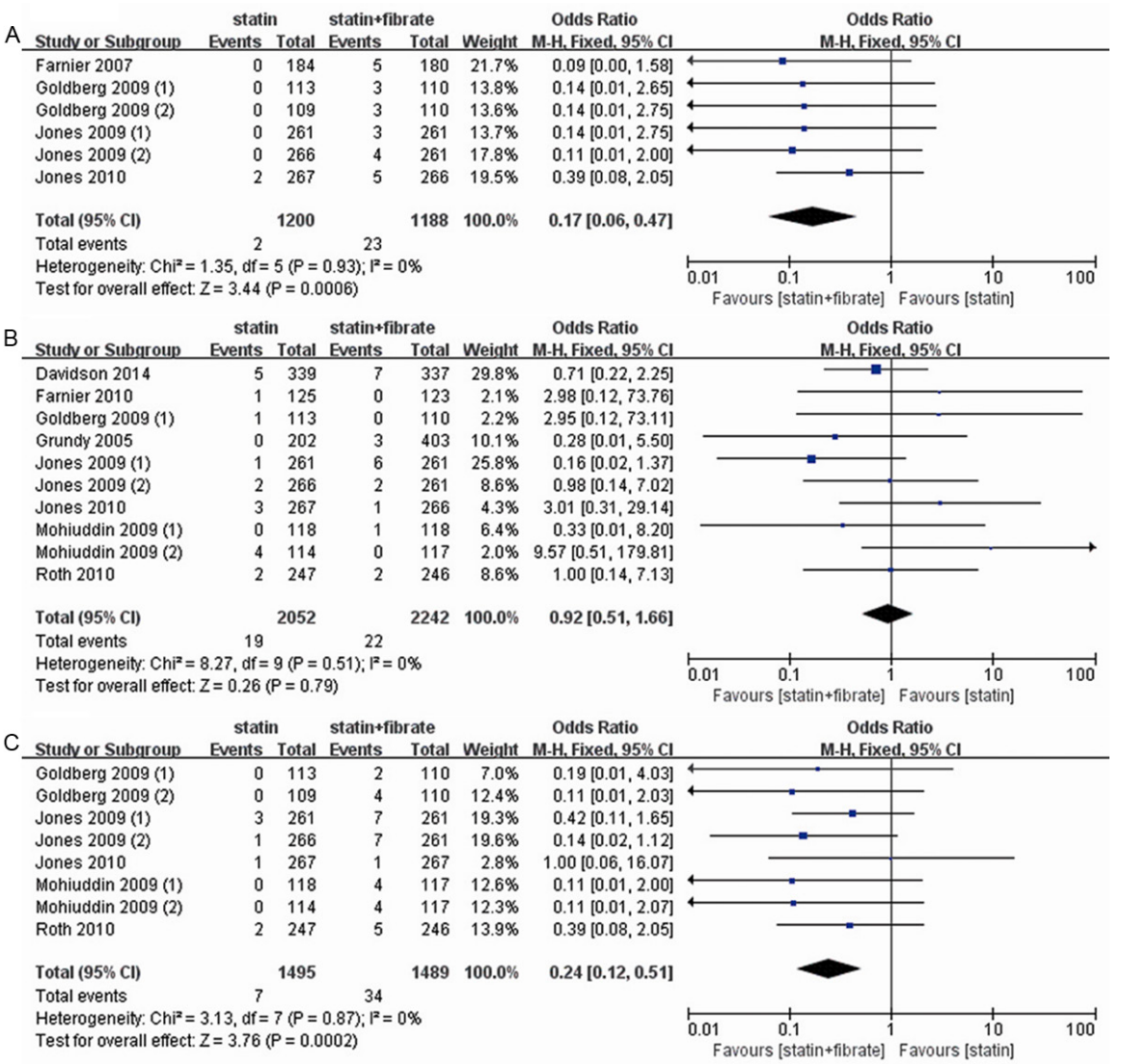

Figure 4. Forest plots of (A) ALT and/or AST > 3ULN, (B) CK ≥ 5ULN, and (C) Creatinine increased ≥ 50% and > ULN between the monotherapy and coadministration groups.

studies showed that there was no significant difference between the groups (OR = 0.90, 95% CI: 0.71-1.14; P = 0.39). Heterogeneity analysis showed that the statistical difference was little (I^2 = 0%, P = 0.79%) (**Figure 3C**).

Special-interest adverse events

Four studies reported the results of ALT and/or AST > 3ULN, within which two articles involved two different doses of statin [12, 13], so the valid pair-wise comparisons between the monotherapy and coadministration groups were six. The pooled analysis showed that there was significant difference of ALT and/or AST > 3ULN between the groups (OR = 0.17, 95% CI: 0.06-0.47; P = 0.0006), indicating more patients in the monotherapy group suffered an increase in ALT and/or AST above three times ULN. Evidence showed that there was no significant heterogeneity (I^2 = 0%, P = 0.93) (**Figure 4A**).

Eight studies reported the results of CK ≥ 5ULN, within which two articles involved two different doses of statin [13, 14], so the valid pair-wise comparisons between the monotherapy and coadministration groups were ten. The pooled analysis showed that there was no significant difference between the groups in CK ≥ 5ULN (OR = 0.92, 95% CI: 0.51-1.66; P = 0.79). Evidence showed that the heterogeneity was not significant, neither (I^2 = 0%, P = 0.51) (**Figure 4B**).

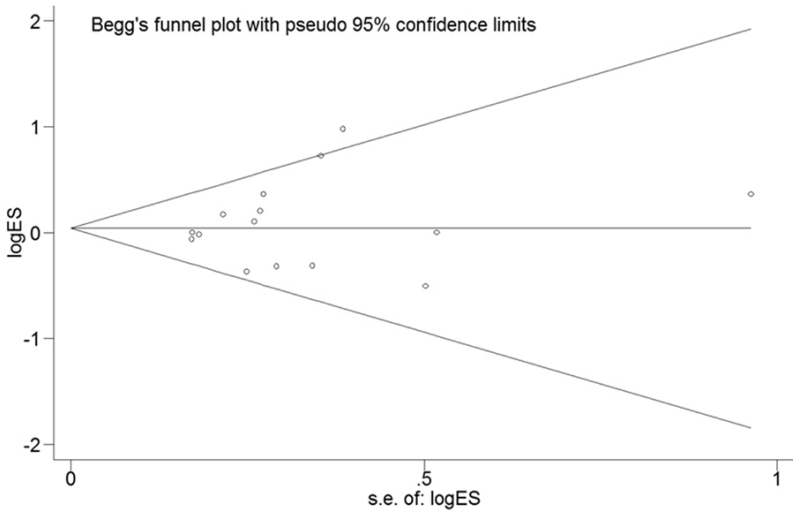

Figure 5. Funnel plot assessing publication bias for any adverse event between monotherapy and coadministration groups.

Five studies reported the incidence of creatinine increased ≥ 50% and > ULN, within which three articles involved two different doses of statin [12-14], so the valid pair-wise comparisons between the monotherapy and coadministration groups were eight. The pooled analysis showed that there was significant difference between the groups in incidence of creatinine increased ≥ 50% and > ULN (OR = 0.24, 95% CI: 0.12-0.51; P = 0.0002). Evidence showed that there was no significant heterogeneity (I^2 = 0%, P = 0.87) (**Figure 4C**).

Publication bias analysis

Publication bias was evaluated by Begg's and Egger's Test with Stata 12.0. Publication bias test was assessed according to the data of any adverse event as this outcome was included in all the studies in our meta-analysis. The results of Begg's and Egger's test showed that there was no clear publication bias of the eligible studies (P = 0.322; P = 0.486). Begg's funnel plot of any adverse event was displayed below (**Figure 5**).

Discussion

Patients with mixed hyperlipidemia are at high risk for cardiovascular diseases [19]. Coadministration of fenofibrate and statin provides an effective control of the multiple lipid parameters compared with either of the monotherapy, thus combination therapy supposed to be an optimal treatment for patients with mixed hyperlipidemia [2]. However, controversies about the safety of coadministration have been arguing without a decision. Physicians feared that the lipid-lowering benefit cannot make up the harm that adverse events might bring, and the concerns have blocked the further clinical practice of combination therapy [4].

Our meta-analysis involving abundant and latest-published RCTs provided concrete adverse events that combination therapy might associate compared with monotherapy. The pooled analysis revealed that combination therapy was associated with a significant higher discontinuation because of any adverse event than statin monotherapy, but there were no notable differences in any adverse event, serious adverse events and drug related adverse events. There were many reasons that might contribute to the discontinuations of participants, such as creatine kinase elevation, aminotransferase elevation, creatinine elevation, and so on.

Although the main safety concern of fenofibrate is the potential increased muscle-related AE [20], our research showed that there was no significant difference in incidence of elevation of creatine kinase over five times ULN. Fenofibrate plus statin did not result in a greater risk of muscle-related adverse events. However, there were more hepatic enzyme elevation-related adverse events and plasma creatinine elevation-related adverse events in coadministration group than monotherapy group. Similar to previous studies of renal function with fenofibrate, there were indeed more adverse effects related to plasma creatinine elevation. Evidence showed that fenofibrate could increase plasma creatinine concentration [21] and clinical trials also proved that creatinine would fall to baseline level when the combination treatment was stopped [22]. Previous observations pointed that patients in the fenofibrate plus statin treatment group were more vulnerable to renal related adverse

events than those in the monotherapy group [23]. Besides, our study revealed that combination therapy of statin and fenofibrate was detected with hepatic abnormality, and there were significantly more patients suffering from elevation of ALT and/or AST above three times ULN in coadministration group than in monotherapy group. It is noteworthy that fenofibrate should undergo first-pass hepatic metabolism and then turn into the active metabolite of fenofibric acid. Fenofibrate and its active metabolite are primarily excreted via urine, when the intake dosage is out of limit or the filtration rate of glomerular is too slow, extra metabolite will exert toxicity on liver and muscles. Therefore, fenofibrate should be used carefully in patients with renal impairment, and function of liver and kidney should be monitored closely within the combination therapy. Dose adjustment of fenofibrate should be made once the renal function is inefficient [24].

There are some limitations in our meta-analysis. Firstly, we readjusted the criteria of interventions between the compared groups, RCT will be included only if the experiment group involved the combination of statin with fenofibrate and the controlled group involved statin, regardless of the other commonly added drugs, such as Ezetimibe. Secondly, there are three studies containing multiple pair-wise doses of statin in monotherapy and coadministration groups, we divided them into equal independent studies which might narrow the heterogeneity of the included articles. Thirdly, because of the non-identical experimental schemes and research purposes, there may be some disagreements on evaluation systems of the various adverse events between different RCTs, which probably exerted an unknown and unpredictable impact on our research results. Regardless of these, we believe that we made some progresses over the previous studies. Our meta-analysis was the latest one systematically comparing adverse events of statin monotherapy and combination therapy of statin and fenofibrate. We treated fenofibrate, its new formulation and active metabolite equally, interventions about either of them plus statin versus statin monotherapy were totally included. We integrated abundant RCTs than either of the previously published meta-analyses [7, 25], thus our results provided more powerful and accurate conclusions. Besides, every included citation was no less than 4 points according to the Jadad Score, data from two newly published RCTs were also extracted to enrich the existing information [5, 18]. We have reasons to believe that our study is well worth convincing. We think our research could provide useful information for physicians to bravely prescribe the combination therapy of statin and fenofibrate.

Conclusion

In conclusion, combination therapy of statin and fenofibrate is associated with a higher incidence of hepatic and renal abnormality compared with statin monotherapy. Fenofibrate should be used carefully in patients with liver and renal impairment, and function of liver and kidney should be monitored closely within the combination therapy.

Acknowledgements

This work was supported by Science Foundation of Shanghai Municipal Commission of Health and Family Planning (No. 20124248).

Disclosure of conflict of interest

None.

Address correspondence to: Shan Huang, Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200336, China. Tel: +86-21-52039999*72233; Fax: +86-21-62906478; E-mail: shanhuangsh@126.com

References

[1] Fazio S. Management of mixed dyslipidemia in patients with or at risk for cardiovascular disease: a role for combination fibrate therapy. Clin Ther 2008; 30: 294-306.

[2] Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ; Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. J Am Coll Cardiol 2004; 44: 720-732.

[3] Derosa G, Cicero AE, Bertone G, Piccinni MN, Ciccarelli L and Roggeri DE. Comparison of fluvastatin+ fenofibrate combination therapyand fluvastatin monotherapy in the treatment of combined hyperlipidemia, type 2 diabetes mellitus, and coronary heart disease: a 12-month, randomized, double-blind, controlled trial. Clin Ther 2004; 26: 1599-1607.

[4] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-3421.

[5] Davidson MH, Rosenson RS, Maki KC, Nicholls SJ, Ballantyne CM, Mazzone T, Carlson DM, Williams LA, Kelly MT, Camp HS, Lele A and Stolzenbach JC. Effects of Fenofibric Acid on Carotid Intima-Media Thickness in Patients With Mixed Dyslipidemia on Atorvastatin Therapy Randomized, Placebo-Controlled Study (FIRST). Arterioscler Thromb Vasc Biol 2014; 34: 1298-1306.

[6] Lee SH, Cho KI, Kim JY, Ahn YK, Rha SW, Kim YJ, Choi YS, Choi SW, Jeon DW, Min PK, Choi DJ, Baek SH, Kim KS, Byun YS and Jang Y. Non-lipid effects of rosuvastatin-fenofibrate combination therapy in high-risk Asian patients with mixed hyperlipidemia. Atherosclerosis 2012; 221: 169-75.

[7] Geng Q, Ren J, Chen H, Lee C and Liang W. Adverse events of statin-fenofibric acid versus statin monotherapy: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2013; 29: 181-8.

[8] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ and McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.

[9] Grundy SM, Vega GL, Yuan Z, Battisti WP, Brady WE and Palmisano J. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). Am J Cardiol 2005; 95: 462-468.

[10] Farnier M, Roth E, Gil-Extremera B, Mendez GF, Macdonell G, Hamlin C, Perevozskaya I, Davies MJ, Kush D, Mitchel YB; Ezetimibe/Simvastatin + Fenofibrate Study Group. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J 2007; 153: 335. e18.

[11] Davidson MH, Rooney MW, Drucker J, Eugene Griffin H, Oosman S, Beckert M; LCP-AtorFen Investigators. Efficacy and tolerability of atorvastatin/fenofibrate fixed-dose combination tablet compared with atorvastatin and fenofibrate monotherapies in patients with dyslipidemia: a 12-week, multicenter, double-blind, randomized, parallel-group study. Clin Ther 2009; 31: 2824-2838.

[12] Goldberg AC, Bays HE, Ballantyne CM, Kelly MT, Buttler SM, Setze CM, Sleep DJ and Stolzenbach JC. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. Am J Cardiol 2009; 103: 515-522.

[13] Jones PH, Davidson MH, Kashyap ML, Kelly MT, Buttler SM, Setze CM, Sleep DJ and Stolzenbach JC. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: a phase 3 study. Atherosclerosis 2009; 204: 208-215.

[14] Mohiuddin SM, Pepine CJ, Kelly MT, Buttler SM, Setze CM, Sleep DJ and Stolzenbach JC. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3, randomized, controlled study. Am Heart J 2009; 157: 195-203.

[15] Farnier M, Ducobu J and Bryniarski L. Efficacy and Safety of Adding Fenofibrate 160 mg in High-Risk Patients With Mixed Hyperlipidemia Not Controlled by Pravastatin 40 mg monotherapy. Am J Cardiol 2010; 106: 787-792.

[16] Jones PH, Goldberg AC, Knapp HR, Kelly MT, Setze CM, Stolzenbach JC and Sleep DJ. Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia. Am Heart J 2010; 160: 759-66.

[17] Roth EM, Rosenson RS, Carlson DM, Fukumoto SM, Setze CM, Blasetto JW, Khurmi NS, Stolzenbach JC and Williams LA. Efficacy and safety of rosuvastatin 5 mg in combination with fenofibric acid 135 mg in patients with mixed dyslipidemia-a phase 3 study. Cardiovasc Drugs Ther 2010; 24: 421-8.

[18] Weinstein DL, Williams LA, Carlson DM, Kelly MT, Burns KM, Setze CM, Lele A and Stolzenbach JC. A Randomized, Double-Blind Study of Fenofibric Acid Plus Rosuvastatin Compared With Rosuvastatin Alone in Stage 3 Chronic Kidney Disease. Clin Ther 2013; 35: 1186-1198.

[19] Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, Ceska R, Chapman MJ, Dodson PM, Fioretto P, Ginsberg HN, Kadowaki T, Lablanche JM, Marx N, Plutzky J, Reiner Z, Rosenson RS, Staels B, Stock JK, Sy R, Wanner C, Zambon A and Zimmet P. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. Am J Cardiol 2008; 102: 1K-34K.

[20] Davidson MH. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic drug interactions. Expert Opin Drug Saf 2006; 5: 145-56.

[21] Dierkes J and Westphal S. Effect of drugs on homocysteine concentrations. Semin Vasc Med 2005; 5: 124-139.

[22] Mychaleckyi JC, Craven T, Nayak U, Buse J, Crouse JR, Elam M, Kirchner K, Lorber D, Marcovina S, Sivitz W, Sperl-Hillen J, Bonds DE and Ginsberg HN. Reversibility of fenofibrate therapy-induced renal function impairement in ACCORD type 2 diabetic participants. Diabetes Care 2012; 35: 1008-1014.

[23] Keech A, Simes R, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; FIELD study investigators. FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trials. Lancet 2005; 366: 1849-1861.

[24] Moutzouri E, Kei A, Elisaf MS and Milionis HJ. Management of dyslipidemias with fibrates, alone and in combiantion with statins: role of delayed-release fenofibric acid. Vasc Health Risk Manag 2010; 6: 525-539.

[25] Guo J, Meng F, Ma N, Li C, Ding Z, Wang H, Hou R and Qin Y. Meta-analysis of safety of the coadministration of statin with fenofibrate in patients with combined hyperlipidemia. Am J Cardiol 2012; 110: 1296-301.