European Review for Medical and Pharmacological Sciences 2019; 23: 2302-2310

A comparative meta-analysis of the efficacy of statin-ezetimibe co-therapy *versus* statin monotherapy in reducing cardiovascular and cerebrovascular adverse events in patients with type 2 diabetes mellitus

X.-Y. MIAO, H.-Z. LIU, M.-M. JIN, B.-R. SUN, H. TIAN, J. LI, N. LI, S.-T. YAN

Department of Endocrinology, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing, China

Xinyu Miao and Hongzhou Liu contributed equally to this work

Abstract. – OBJECTIVE: This study evaluates the efficacy of statin-ezetimibe co-therapy compared to statin monotherapy in reducing cardiovascular and/or cerebrovascular disease (CVD) prevalence in diabetes and non-diabetes patients.

PATIENTS AND METHODS: Literature search was conducted in electronic databases and study selection was based on pre-determined eligibility criteria. Random-effects metanalyses were performed to examine the risk of CVD incidence between statin-ezetimibe co-therapy and statin monotherapy and subgroups were performed to examine the significance of differences between diabetic and non-diabetic individuals. A pooled analysis of hazard ratios of statin-ezetimibe combination versus statin monotherapy in the prevalence of CVD reported by the individual studies was also performed.

RESULTS: 8 studies (136893 individuals; 80790 diabetics, 85555 non-diabetics; age 63.5 years [95% confidence interval (CI) 61.2, 65.8]; 61.5% [95% CI 55.2, 67.8] males) were included. Follow-up duration was 45 months [95% CI 27.5, 62.5]. Risk of CVD prevalence was significantly less with ezetimibe-statin than with statin alone in both diabetes (RR 0.69 [95% CI 0.67, 0.73]; *p*<0.00001) and in non-diabetes (RR 0.68 [95% CI 0.52, 0.90]; *p*=0.006) subjects (subgroup difference: chi2=0.00; *p*=0.97). Risk of prevalence of stroke was significantly less with ezetimibe-statin than with statin monotherapy in diabetes (RR 0.74 [95% CI 0.56, 0.98]; *p*=0.03) but non-significantly less in non-diabetes patients (RR 0.74 [95% CI 0.39, 1.41]; *p*=0.39) and this sub-group difference was also not statistically significant (chi2=0.00; *p*=0.99).

CONCLUSIONS: Statin-ezetimibe co-therapy is found more efficacious than statin monotherapy in reducing the incidence of CVD with no significant difference between diabetic and non-diabetic individuals.

Key Words:
Lipid lowering, Statins, Ezetimibe, Cardiovascular, Cerebrovascular.

Introduction

Hyperlipidemia, a state of high levels of lipids in the blood, is a serious health risk to the coronary arteries and related vascular diseases. Individuals with type 2 diabetes mellitus often have elevated levels of low-density lipoprotein cholesterol (LDL-C), small, dense-LDL and triglycerides which increases the risk of cardiovascular and/or cerebrovascular disease (CVD)[1]. In diabetic dyslipidemia, insulin resistance is a major etiological factor, which acts on several lipid metabolism pathways. It induces lipolysis in the adipose tissue with subsequent high free fatty acid levels in the blood[2] and reduces apolipoprotein B100 degradation in the liver[3]. Furthermore, insulin resistance causes the overproduction and secretion of atherogenic very low-density lipoprotein (VLDL) and promotes the production of small dense-LDL while reducing high-density lipoprotein cholesterol (HDL-C) production. Insulin resistance is also associated with enhanced intestinal production of chylomicrons and reduced hepatic clearance of triglyceride-rich lipoproteins[4,5]. For the management of hyperlipidemia, several drugs are used in clinical practice. Among these, statins inhibit

Corresponding Author: Shuangtong Yan, MD; e-mail: ystf@yeah.net

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and thence decrease cholesterol biosynthesis[6,7]; ezetimibe, a Niemann-Pick C1-like1 (NPC1L1) inhibitor, selectively inhibits cholesterol absorption from intestine and reduces its blood levels[8]; fibrates stimulate activation of peroxisome proliferator-activated receptor (PPAR) gamma and consequently decrease fatty acid and triglyceride levels[6]; cholestyramine, colestipol, and colesevelam like bile acids sequestrants inhibit enterohepatic circulation of bile acids by preventing their reabsorption[9]; torcetrapib inhibits cholesterol ester transfer protein to increase the concentration of cholesterol in its protective HDL-C fraction while decreasing the harmful non-HDL fractions[10]; avasimibe, inhibits acyl-CoA which helps cholesterol acyltransferase to form cholesteryl esters and thence decrease concentration of cholesteryl esters within macrophages that constitutes the foam cells for atherogenesis[11]; implitapide, inhibits microsomal triglyceride transfer protein to decrease LDL-C levels[12]; and niacin increases HDL-C levels, lowers triglyceride, LDL-C and lipoprotein levels and reduces atherogenic small, dense LDL particles[13].

Statins are efficacious lipid lowering drugs which can reduce primary as well as secondary CVD risk[14]. However, many diabetes patients need combination therapy for lipid lowering for the reduction of CVD risk[15]. One such combination is use of a statin with ezetimibe. A meta-analysis found that, in high-risk patients with an acute coronary syndrome, statin-ezetimibe co-therapy reduced CVD risk in comparison with statin monotherapy[16]. The aim of the present study was to conduct a literature survey for the identification of studies which compared statin-ezetimibe co-therapy with statin monotherapy in diabetes patients and reported the prevalence of CVD with a follow-up of at least 12 months, and to perform a meta-analysis of prevalence rate and risk ratio to examine the significance of difference in CVD prevalence between diabetes and non-diabetes patients.

Patients and Methods

Inclusion and Exclusion Criteria

Inclusion criteria were: a study a) investigated the efficacy and safety of statin-ezetimibe co-therapy by comparing it with statin monotherapy; b) reported the incidence of CVD observed during follow-up period in diabetes patients; c) reported the hazard of the incidence of CVD events between diabetes mellitus and non-diabetes mellitus. A study was excluded if a) reported the incidence of CVD in diabetes patients by evaluating the efficacy of statin-ezetimibe co-therapy by comparing it with placebo; b) reported indicators of cardiovascular risk factors but not CVD events, c) used triple therapy in treated arm or combination therapy in control arm, or c) reported non-numerical information only. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Literature Search

Literature search was conducted in electronic databases (Embase, Google Scholar, Ovid, and PubMed, and Science Direct). Important keywords and MeSH terms used in logical combinations were: Ezetimibe, statin, diabetes, cardiovascular event, cerebrovascular event, major adverse cardiac events (MACE), Vytorin, Zetia, atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, simvastatin, rosuvastatin, coronary syndrome/intervention, myocardial infarction, heart failure, heart disease, atherosclerosis, stroke, and trial. The search encompassed original research articles published before January 2019 in English language. Additionally, the references list of important relevant research and review articles were manually searched.

Data and Analyses

Demographic and anthropometric characteristics of the patients and methodological, analytical, and outcome data of the included studies were obtained from respective research articles of the included studies and were organized in datasheets for qualitative and quantitative information synthesis. Meta-analyses of risk ratio between ezetimibe-statin and statin only treated patients in the incidence of CVD events were performed with RevMan software (version 5.3; Cochrane) under random effects model. Hazard ratios reported by the individual studies were pooled under random-effects using Stata software (Stata Corporation; USA). Overall effect size of each of endpoint was an inverse variance weighted average of the individual studies outcome. I^2 index was used to estimate statistical heterogeneity between the studies.

Results

Eight studies were found to fulfill eligibility criteria (Figure 1). The outcomes of these 8

studies were reported in 11 research articles[17-27]. Three of the included studies were randomized controlled trials (IMPROVE-IT[17,18,21], HIJ-PROPER[22], SANDS[20,23]) and other 5 were retrospective in design. Of the retrospective studies, 2 were database[19,24] and 3 were cohort[25-27] studies. Important characteristics of the included studies are presented in Table I. Overall, these studies reported the outcomes of 136,893 patients of which 80,790 were diabetics and 85,555 were non-diabetics. 30,492 individuals were treated with statin-ezetimibe co-therapy whereas 137,947 were treated with statin monotherapy. Age of these participants was 63.5 years [95% confidence interval (CI) 61.2, 65.8]. Of these patients, 61.5% [95% CI 55.2, 67.8] were males and 39.7% [23.8, 55.6] were smokers. Follow-up duration was 45.0 months [95% CI 27.5, 62.5].

Risk of the incidence of CVD was significantly less with statin-ezetimibe co-therapy in comparison with statin monotherapy in both diabetes (RR 0.69 [95% CI 0.67, 0.73]; $p < 0.00001$) and in non-diabetes (RR 0.68 [95% CI 0.52, 0.90]; $p = 0.006$) individuals. Difference between diabetic and non-diabetic subjects was not significant ($chi^2 = 0.00$; $p = 0.97$; Figure 2). There was no significant difference between diabetes and non-diabetes subjects studied either in RCTs (0.75 [95% CI 0.60, 0.94]; $p = 0.001$ for diabetics *vs* 0.79 [95% CI 0.74, 0.84]; $p = 0.00001$ for non-diabetics; subgroup differences: $Chi^2 = 0.16$; $p = 0.69$) or in retrospective studies (0.58 [0.29, 1.17]; $p = 0.13$ for diabetics *vs* 0.45 [95% CI 0.35, 0.56]; $p = 0.00001$ for non-diabetics; subgroup differences: $Chi^2 = 0.48$; $p = 0.49$). Risk of prevalence of stroke was significantly less with statin-ezetimibe co-therapy in comparison with statin monotherapy in both diabetes (RR 0.74 [95% CI 0.56, 0.98]; $p = 0.03$) and non-significantly less in non-diabetes patients (RR 0.74 [95% CI 0.39, 1.41]; $p = 0.39$). Difference between diabetic and non-diabetic subjects was not statistically significant ($chi^2 = 0.00$; $p = 0.99$; Figure 3). A pooled analysis of hazard ratios between statin-ezetimibe co-therapy and statin monotherapy for the prevalence of cardiovascular events reported by the included studies revealed effect sizes of 0.80 [95% CI 0.73, 0.88] for diabetics studied in RCTs, 0.94 [95% CI 0.88, 0.99] for non-diabetics studied in RCTs, 0.69 [95% CI 0.60, 0.77] for diabetics studied in retrospective studies, and 0.67 [95% CI 0.57, 0.76] for non-diabetics studied in retrospective studies (Figure 4). Risk of the prevalence of CVD was similar between statin-ezetimibe co-therapy and high-intensity

Table I. Characteristics of the included studies.

Study	Design	Statin/ dose (mg)	No. of patients					Follow-up (months)	Age	Males %	Smokers %
			Statin alone	Ezetimibe-statin	Total	Diabetic	Non-diabetic				
Bohula et al[17] Cannon et al[18] Giugliano et al[21]	DB-RCT (IMPROVE-IT)	SIMVA 40	9077	9067	18144	13211	4933	72	66±19	75	33
Chang et al[19] Fleg et al[20]	RET Database		16396	4099	20495	0	20495	48	59±9	53	
Howard et al[23]	OL-RCT (SANDS)		204	69	273	0	273	36	57±7	35	21
Hagiwara et al[22]	OL-RCT (HIJ-PROPER)	PITVA 1–4	857	864	1721	1201	520	36	65.6±12	75	63
Ji et al[24]	RET (Database)	ATOR 40–80/ ROSU 20–40	2271	1249	3520	2473	1047	12	61.3±13	78.5	66.1
Lee et al[25]	RET (Cohort)	20	1837	1837	3674	2584	1090	50	70.3±9	54.5	15.6
Liu et al[26]	SIMVA RET (Cohort)	SIMVA 20 /ATOR 40	337	564	901	0	901	34	66.4±11	56	
Wu et al[27]	RET (Cohort)		105914	11703	117617	66086	51531	72	62.5±12	65	

Abbreviations: DB/OL-RCT, double-blind/open-label randomized controlled trial; Improve-it, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; HIJ-PROPER, Heart Institute of Japan PRoper level of lipid lowering with Pitavastatin and Ezetimibe in acute coRonary syndrome; Ret, Retrospective; Sands, Stop Atherosclerosis in Native Diabetics Study; SHARP, Study of Heart and Renal Protection.

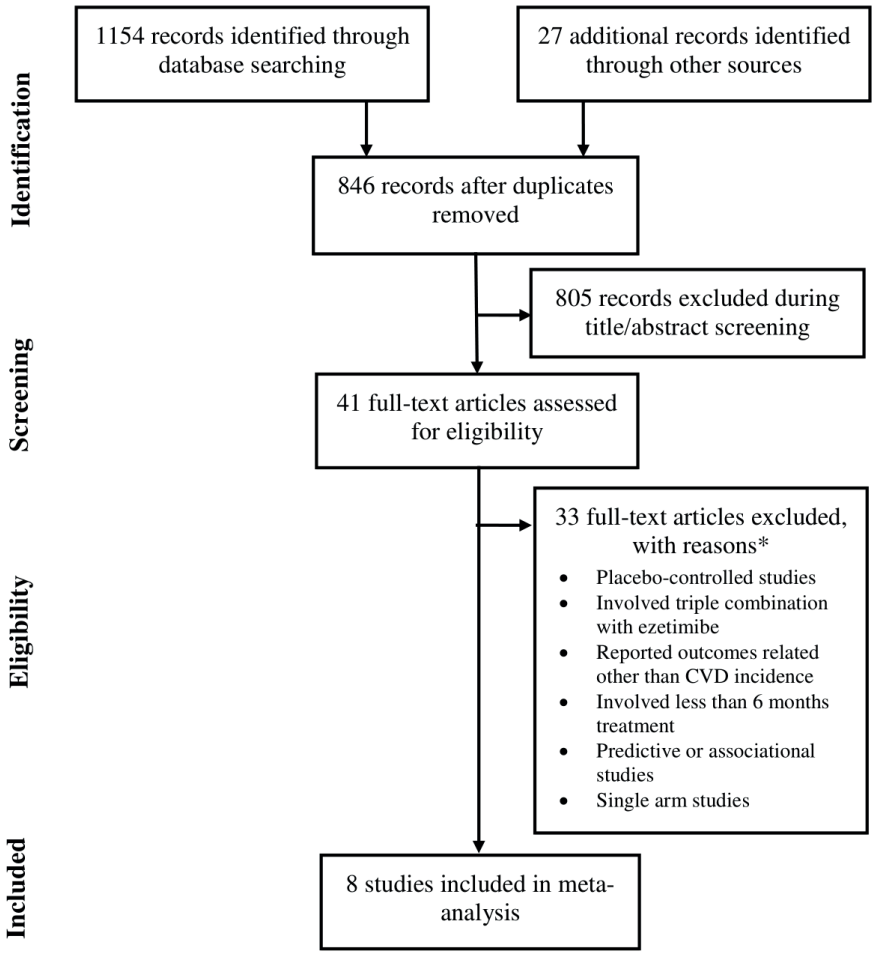

Figure 1. A flowchart of study screening and selection process after literature search.

statin monotherapy (RR 1.12 [0.77, 1.61]; $p = 0.56$) in diabetes patients (2 studies data).

Discussion

This meta-analysis of 82884 diabetic and 92731 non-diabetic patients found that a) statin-ezetimibe co-therapy is more efficacious than standard statin monotherapy, and b) there is no statistically significant difference between diabetes and non-diabetes patients in the statin-ezetimibe co-therapy *vs* statin monotherapy in the prevalence of cardiovascular or cerebrovascular adverse events. A pooled analysis of the hazard ratios of the incidence of cardiovascular or cerebrovascular adverse events between statin-ezetimibe co-therapy *vs.* statin monotherapy reported by the individual studies also revealed the similar outcomes. These outcomes are similar to the findings of some other studies as well. In an RCT, Baigent et al[28] found no significant difference between diabetic and non-diabetic individuals in the prevalence of CVD in a follow-up period of 4 years of ezetimibe-simvastatin co-therapy *vs.* placebo (Hazard ratio: diabetes 0.78 [0.64, 0.94] *vs.* non-diabetes 0.86 [0.74, 1.13]; $\chi^2 = 0{\cdot}58$; $p = 0{\cdot}45$). In a secondary cross-sectional analysis of a subset of over 1000 outpatients with diabetes (The Dyslipidemia International Study; DYSIS), Leiter et al[29] found that diabetic patients taking ezetimibe with statin had no difference of CVD incidence in comparison with non-diabetic patients (12% *vs.* 11.7%). In their study, diabetic patients taking formulation of ezetimibe-statin also had no difference of CVD prevalence in comparison with non-diabetic patients (5.2% *vs.* 5.0%). In a prospective study of 95 patients with acute coro-

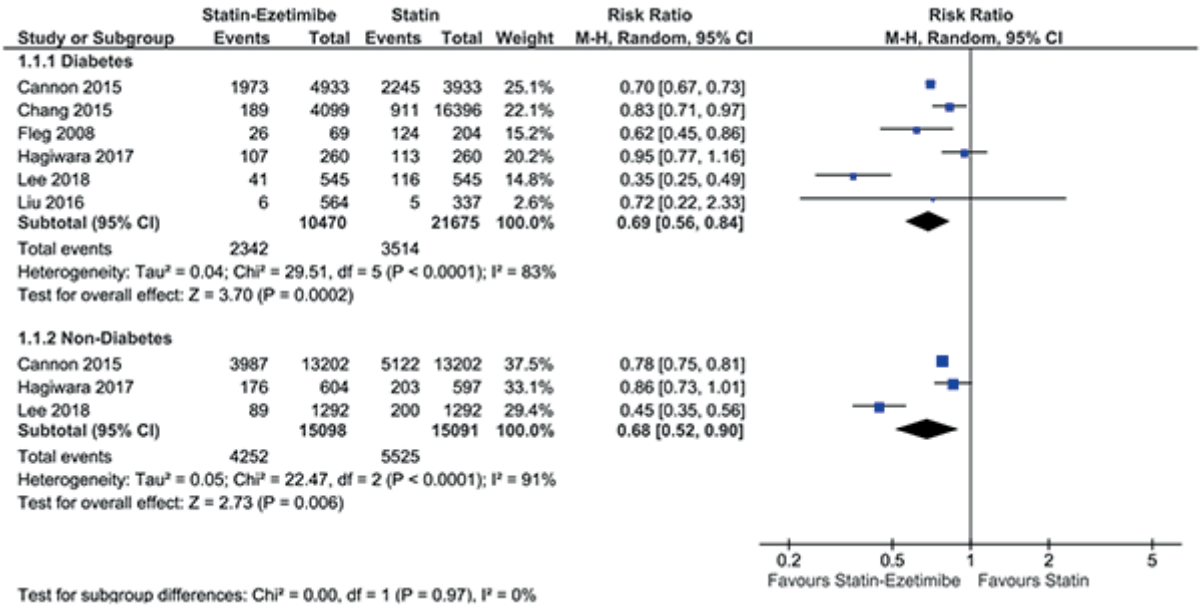

Figure 2. A forest graph showing the outcomes of a meta-analysis of risk ratios between ezetimibe-statin co-therapy and statin monotherapy in the prevalence of CVD events and subgroup differences for diabetes and non-diabetes individuals.

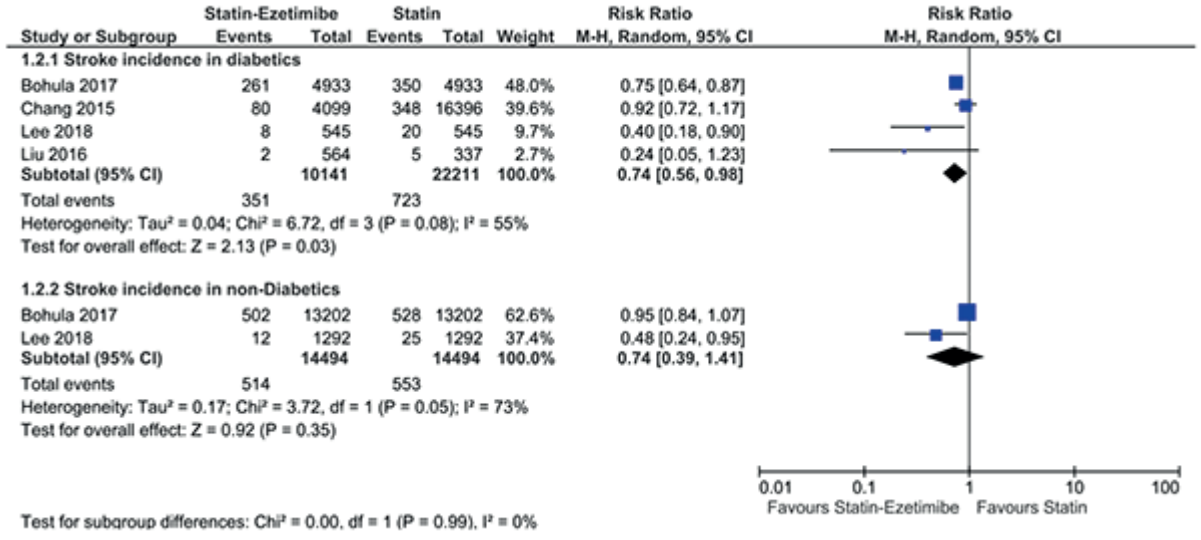

Figure 3. A forest graph showing the outcomes of a meta-analysis of risk ratios between ezetimibe-statin co-therapy and statin monotherapy in the prevalence of stroke and subgroup differences for diabetes and non-diabetes individuals.

nary syndrome, Nakajima et al[30] found that ezetimibe-statin combination decreased serial intravascular ultrasound measured plaque volume in right coronary artery, left circumflex artery, and anterior interventricular artery significantly more than statin alone after 24 weeks of treatment, but difference was not significant between diabetic and non-diabetic patients. On the other hand, a pooled analysis of 27 previously published, randomized, double-blind, active- or placebo-controlled clinical trials comprising 6541 diabetic and 15253 non-diabetic subjects receiving statin-ezetimibe co-therapy or statin monotherapy for 4–24 weeks reported that statin-ezetimibe co-therapy was more effective than statin monotherapy in improving LDL-C, total cholesterol, HDL-C, triglycerides, non-HDL-C, apolipoprotein B and high-sensitivity C-reactive protein and diabetic individuals achieved more reductions in LDL-C, TC and non-HDL-C compared with non-diabe-

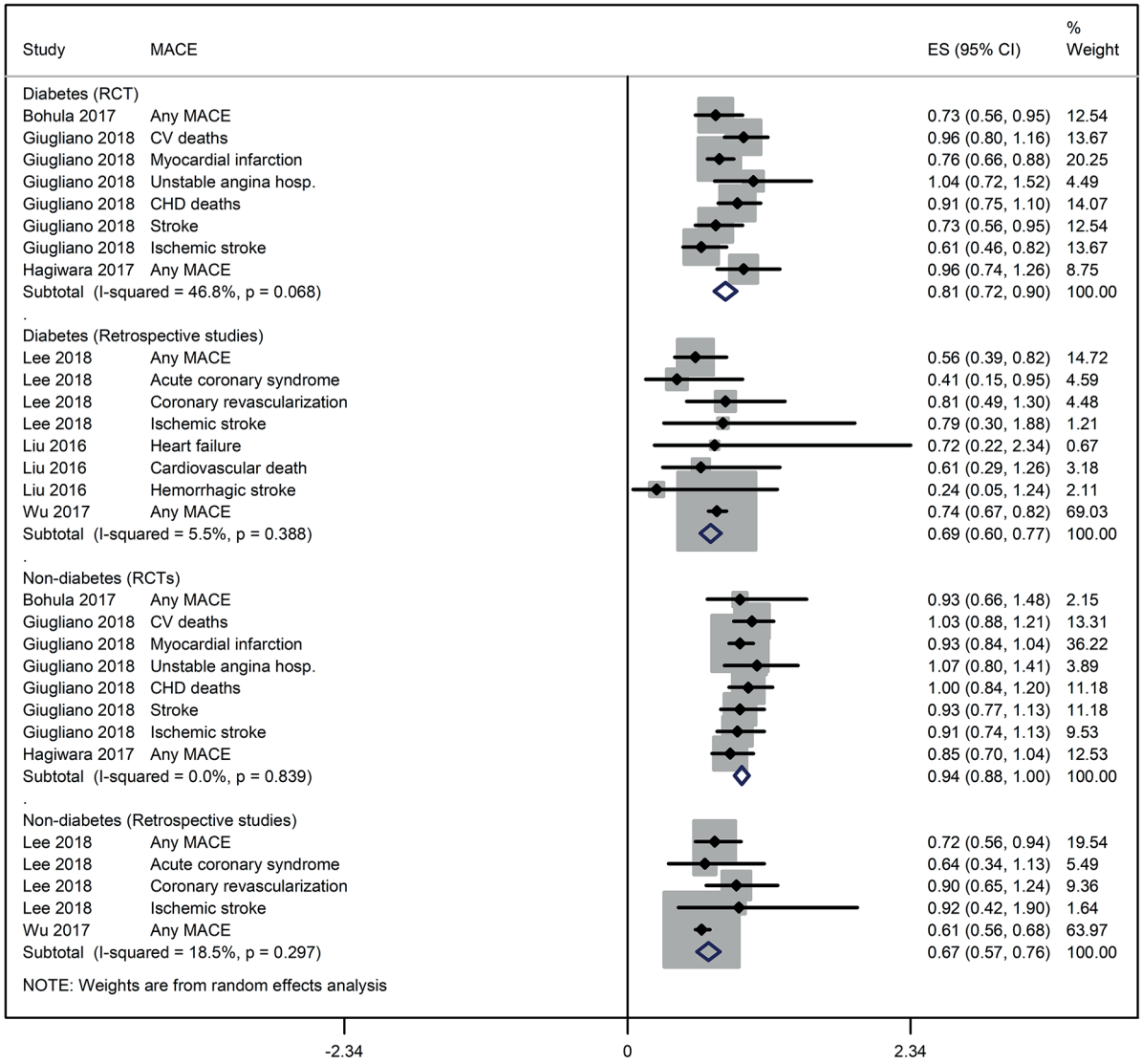

Figure 4. A forest graph showing the outcomes of a pooled meta-analysis of hazard ratios between ezetimibe-statin co-therapy and statin monotherapy reported by the individual studies and subgroup differences for diabetes status and study design.

tic patients[31]. A recently published meta-analysis which also compared statin-ezetimibe co-therapy efficacy in diabetic *vs* non-diabetic individuals in the prevalence of major adverse cardiovascular events based mainly on un-published data concluded that statin-ezetimibe co-therapy works better in diabetes individuals[32]. However, in both these studies statistical analyses to assess the significance of difference between diabetic and non-diabetic individuals was not involved. Although, a similar trend of the efficacy of statin-ezetimibe co-therapy has also been observed in the present study, but the outcomes were found statistically non-significant between diabetic and non-diabetic individuals in subgroup analyses. Less data were available for the risk assessment of the prevalence of cardiovascular adverse event between statin-ezetimibe co-therapy with high-intensity statin monotherapy according to which both regimens were similar in efficacy in diabetes patients. A single study data suggested that intense statin monotherapy was superior than statin-ezetimibe co-therapy in non-diabetes patients but not in diabetes patients[24]. Several studies have reported that high-intensity statin therapy (in comparison with moderate intensity) is associated with significantly higher risk of incident diabetes in prediabetic individuals[33-35]. Whereas this risk is not found to

be associated with statin-ezetimibe co-therapy[35]. Many studies suggest that ezetimibe, either added to statin or as monotherapy, does not adversely affect glucose metabolism[36,37] rather may improve metabolic markers such as hepatic steatosis and insulin resistance[38]. Secretory phospholipase A2 (sPLA2) is an enzyme that plays an important role in the pathogenesis of atherosclerosis and adverse cardiovascular events. Higher serum levels of secretory phospholipase A2 (sPLA2) are associated with recurrent CVD events in patients with acute coronary syndromes[39,40]. Ezetimibe-atorvastatin co-therapy for 8 weeks has been reported to decrease sPLA2 activity[41].

Conclusions

This meta-analysis of 82884 diabetics and 92731 non-diabetics individuals who were followed for approximately 45 months after statin-ezetimibe co-therapy compared to statin monotherapy, has found statin-ezetimibe co-therapy more efficacious than standard statin monotherapy, and there is no statistically significant difference between diabetes and non-diabetes patients in the efficacy outcomes with regards to the prevalence of cardiovascular or cerebrovascular adverse events. Because, statistically non-significant differences between diabetes and non-diabetes individuals exist, therefore, more data from future studies should refine these outcomes.

Conflict of interest

The authors declare no conflicts of interest.

References

1) Chehade JM, Gladysz M, Mooradian AD. Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management. Drugs 2013; 73: 327-339.
2) Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. Am J Physiol Endocrinol Metab 2003; 285: 906-916.
3) Taghibiglou C, Rashid-Kolvear F, Van Iderstine SC, Le-Tien H, Fantus IG, Lewis GF, Adeli K. Hepatic very low-density lipoprotein-ApoB overproduction is associated with attenuated hepatic insulin signaling and overexpression of protein-tyrosine phosphatase 1B in a fructose-fed hamster model of insulin resistance. J Biol Chem 2002; 277: 793-803.
4) Vergès B. Pathophysiology of diabetic dyslipidaemia: where are we? Diabetologia 2015; 58: 886-899.
5) Scicali R, Di Pino A, Ferrara V, Urbano F, Piro S, Rabuazzo AM, Purrello F. New treatment options for lipid-lowering therapy in subjects with type 2 diabetes. Acta Diabetol 2018; 55: 209-218.
6) Pahan K. Lipid-lowering drugs. Cell Mol Life Sci 2006; 63: 1165-1178.
7) Feng Y. Efficacy of statin therapy in patients with acute respiratory distress syndrome/acute lung injury: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2018; 22: 3190-3198.
8) van Heek M, Farley C, Compton DS, Hoos L, Davis HR. Ezetimibe selectively inhibits intestinal cholesterol absorption in rodents in the presence and absence of exocrine pancreatic function. Br J Pharmacol 2001; 134: 409-417.
9) Takebayashi K, Aso Y, Inukai T. Role of bile acid sequestrants in the treatment of type 2 diabetes. World J Diabetes 2010; 1: 146-152.
10) Barter PJ, Nicholls SJ, Kastelein JJ, Rye KA. Is cholesteryl ester transfer protein inhibition an effective strategy to reduce cardiovascular risk? CETP Inhibition as a strategy to reduce cardiovascular risk: the pro case. Circulation 2015; 132: 423-432.
11) López-Farré AJ, Sacristán D, Zamorano-León JJ, San-Martín N, Macaya C. Inhibition of acyl-CoA cholesterol acyltransferase by F12511 (Eflucimibe): could it be a new antiatherosclerotic therapeutic? Cardiovasc Ther 2008; 26: 65-74.
12) Rizzo M. Lomitapide, a microsomal triglyceride transfer protein inhibitor for the treatment of hypercholesterolemia. Drugs 2010; 13: 103-111.
13) Guyton JR. Extended-release niacin for modifying the lipoprotein profile. Expert Opin Pharmacother 2004; 5: 1385-1398.
14) Ruscica M, Macchi C, Morlotti B, Sirtori CR, Magni P. Statin therapy and related risk of new-onset type 2 diabetes mellitus. Eur J Intern Med 2014; 25: 401-406.
15) Tonkin AM, Chen L. Effects of combination lipid therapy in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Circulation 2010; 122: 850-852.
16) Nubaumer B, Glechner A, Kaminski-Hartenthaler A, Mahlknecht P, Gartlehner G. Ezetimibe-statin combination therapy. Dtsch Arztebl Int 2016; 113: 445-453.
17) Bohula EA, Wiviott SD, Giugliano RP, Blazing MA, Park JG, Murphy SA, White JA, Mach F, Van de Werf F, Dalby AJ, White HD, Tershakovec AM, Cannon CP, Braunwald E. Prevention of stroke with the addition of ezetimibe to statin therapy in patients with acute coronary syndrome in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation 2017; 136: 2440-2450.
18) Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im

K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372: 2387-2397.

19) Chang SH, Wu LS, Lee CH, Kuo CT, Liu JR, Wen MS, Chen WJ, See LC, Yeh YH. Simvastatin-ezetimibe combination therapy is associated with a lower rate of major adverse cardiac events in type 2 diabetics than high potency statins alone: a population-based dynamic cohort study. Int J Cardiol 2015; 190: 20-25.

20) Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, Silverman A, Galloway JM, Henderson JA, Weir MR, Wilson C, Stylianou M, Howard WJ. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol 2008; 52: 2198-2205.

21) Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, Park JG, White JA, Bohula EA, Braunwald E; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from improve-it (improved reduction of outcomes: Vytorin Efficacy International Trial). Circulation 2018; 137: 1571-1582.

22) Hagiwara N, Kawada-Watanabe E, Koyanagi R, Arashi H, Yamaguchi J, Nakao K, Tobaru T, Tanaka H4, Oka T, Endoh Y, Saito K, Uchida T, Matsui K, Ogawa H. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. Eur Heart J 2017; 38: 2264-2276.

23) Howard BV, Roman MJ, Devereux RB, Fleg JL, Galloway JM, Henderson JA, Howard WJ, Lee ET, Mete M, Poolaw B, Ratner RE, Russell M, Silverman A, Stylianou M, Umans JG, Wang W, Weir MR, Weissman NJ, Wilson C, Yeh F, Zhu J. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA 2008; 299: 1678-1689.

24) Ji MS, Jeong MH, Ahn YK, Kim SH, Kim YJ, Chae SC, Hong TJ, Seong IW, Chae JK, Kim CJ, Cho MC, Rha SW, Bae JH, Seung KB, Park SJ; other Korea Acute Myocardial Infarction Registry Investigators. Clinical outcome of statin plus ezetimibe versus high-intensity statin therapy in patients with acute myocardial infarction propensity-score matching analysis. Int J Cardiol 2016; 225: 50-59.

25) Lee YH, Hong N, Lee CJ, Park SH, Lee BW, Cha BS, Kang ES. Differential association of ezetimibe-simvastatin combination with major adverse cardiovascular events in patients with or without diabetes: a retrospective propensity score-matched cohort study. Sci Rep 2018; 8: 11925.

26) Liu CH, Chen TH, Lin MS, Hung MJ, Chung CM, Cherng WJ, Lee TH, Lin YS. Ezetimibe-simvastatin therapy reduce recurrent ischemic stroke risks in type 2 diabetic patients. J Clin Endocrinol Metab 2016; 101: 2994-3001.

27) Wu FL, Wang J, Ho W, Chou C, Wu Y, Choo D, Wang Y, Chena P, Chien K, Lin Z. Effectiveness of a combination of ezetimibe and statins in patients with acute coronary syndrome and multiple comorbidities: a 6-year population-based cohort study. Int J Cardiol 2017; 233: 43-51.

28) Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181-2192.

29) Leiter LA, Lundman P, da Silva PM, Drexel H, Junger C, Gitt AK; DYSIS investigators. Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. Diabet Med 2011; 28: 1343-1351.

30) Nakajima N, Miyauchi K, Yokoyama T, Ogita M, Miyazaki T, Tamura H, Nishino A, Yokoyama K, Okazaki S, Kurata T, Suwa S, Daida H. Effect of combination of ezetimibe and a statin on coronary plaque regression in patients with acute coronary syndrome: ZEUS trial (eZEtimibe Ultrasound Study). IJC Metabol Endocrine 2014; 3: 8-13.

31) Leiter LA, Betteridge DJ, Farnier M, Guyton JR, Lin J, Shah A, Johnson-Levonas AO, Brudi P. Lipid-altering efficacy and safety profile of combination therapy with ezetimibe/statin vs. statin monotherapy in patients with and without diabetes: an analysis of pooled data from 27 clinical trials. Diabetes Obes Metab 2011; 13: 615-628.

32) Hong N, Lee YH, Tsujita K, Gonzalez JA, Kramer CM, Kovarnik T, Kouvelos GN, Suzuki H, Han K, Lee CJ, Park SH, Lee BW, Cha BS, Kang ES. Comparison of the effects of ezetimibe-statin combination therapy on major adverse cardiovascular events in patients with and without diabetes: a meta-analysis. Endocrinol Metab (Seoul) 2018; 33: 219-227.

33) Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011; 305: 2556-2564.

34) Dormuth CR, Filion KB, Paterson JM, James MT, Teare GF, Raymond CB, Rahme E, Tamim H, Lipscombe

L; Canadian Network for Observational Drug Effect Studies Investigators. Higher potency statins and the risk of new diabetes: multicentre, observational study of administrative databases. BMJ 201429; 348: g3244.

35) Barkas F, Elisaf M, Liberopoulos E, Klouras E, Liamis G, Rizos EC. Statin therapy with or without ezetimibe and the progression to diabetes. J Clin Lipidol 2016; 10: 306-313.

36) Toth PP, Catapano AL, Farnier M, Foody J, Tomassini JE, Jensen E, Polis AB, Hanson ME, Musliner TA, Tershakovec AM. Effect on fasting serum glucose levels of adding ezetimibe to statins in patients with nondiabetic hypercholesterolemia. Am J Cardiol 2016; 118: 1812-1820.

37) Saito I, Azuma K, Kakikawa T, Oshima N, Hanson ME, Tershakovec AM. A randomized, double-blind, placebo-controlled study of the effect of ezetimibe on glucose metabolism in subjects with type 2 diabetes mellitus and hypercholesterolemia. Lipids Health Dis 2015; 14: 40.

38) Zafrir B, Jain M. Lipid-lowering therapies, glucose control and incident diabetes: evidence, mechanisms and clinical implications. Cardiovasc Drugs Ther 2014; 28: 361-377.

39) Mallat Z, Steg G, Benessiano J, Tanguy ML, Fox KA, Collet JP, Dabbous OH, Henry P, Carruthers KF, Dauphin A, Arguelles CS, Masliah J, Hugel B, Montalescot G, Freyssinet JM, Asselain B, Tedgui A. Circulating secretory phospholipase A2 activity predicts recurrent events in patients with severe acute coronary syndromes. J Am Coll Cardiol 2005; 46: 1249-1257.

40) Mallat Z, Benessiano J, Simon T, Ederhy S, Sebella-Arguelles C, Cohen A, Huart V, Wareham NJ, Luben R, Khaw KT, Tedgui A, Boekholdt SM. Circulating secretory phospholipase A2 activity and risk of incident coronary events in healthy men and women: the EPIC-Norfolk study. Arterioscler Thromb Vasc Biol 2007; 27: 1177-1183.

41) Azar M, Valentin E, Badaoui G, Kassab R, Sarkis A, Azar RR. Comparison of the effects of combination atorvastatin (40 mg) + ezetimibe (10 mg) versus atorvastatin (40 mg) alone on secretory phospholipase A2 activity in patients with stable coronary artery disease or coronary artery disease equivalent. Am J Cardiol 2011; 107: 1571-1574.