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


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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\(^2,3\) 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 cholestrol (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
Ezetimibe-statin in diabetes vs. non-diabetes patients

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3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and thence decrease cholesterol biosynthesis; ezetimibe, a Niemann-Pick C1-like 1 (NPC1L1) inhibitor, selectively inhibits cholesterol absorption from intestine and reduces its blood levels; fibrates stimulate activation of peroxisome proliferator-activated receptor (PPAR) gamma and consequently decrease fatty acid and triglyceride levels; cholestyramine, colestipol, and colesvelam like bile acids sequestrants inhibit enterohepatic circulation of bile acids by preventing their reabsorption; 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; 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; implitapide, inhibits microsomal triglyceride transfer protein to decrease LDL-C levels; and niacin increases HDL-C levels, lowers triglyceride, LDL-C and lipoprotein levels and reduces atherogenic small, dense LDL particles.

Statins are efficacious lipid lowering drugs which can reduce primary as well as secondary CVD risk. However, many diabetes patients need combination therapy for lipid lowering for the reduction of CVD risk. 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. 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) 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. I² 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\textsuperscript{17-27}. Three of the included studies were randomized controlled trials (IMPROVE-IT\textsuperscript{17,18,21}, HIJ-PROPER\textsuperscript{22}, SANDS\textsuperscript{20,23}) and other 5 were retrospective in design. Of the retrospective studies, 2 were database\textsuperscript{19,24} and 3 were cohort\textsuperscript{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]; \textit{p} < 0.00001) and in non-diabetes (RR 0.68 [95% CI 0.52, 0.90]; \textit{p} = 0.006) individuals. Difference between diabetic and non-diabetic subjects was not significant (\textit{p} = 0.00; \textit{p} = 0.97; Figure 2). There was no significant difference between diabetes and non-diabetic subjects studied either in RCTs (0.75 [95% CI 0.60, 0.94]; \textit{p} = 0.001 for diabetics vs 0.79 [95% CI 0.74, 0.84]; \textit{p} = 0.00001 for non-diabetics; subgroup differences: \textit{Chi}^2 = 0.16; \textit{p} = 0.69) or in retrospective studies (0.58 [0.29, 1.17]; \textit{p} = 0.13 for diabetics vs 0.45 [95% CI 0.35, 0.56]; \textit{p} = 0.00001 for non-diabetics; subgroup differences: \textit{Chi}^2 = 0.48; \textit{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]; \textit{p} = 0.03) and non-significantly less in non-diabetes patients (RR 0.74 [95% CI 0.39, 1.41]; \textit{p} = 0.39). Difference between diabetic and non-diabetic subjects was not statistically significant (\textit{Chi}^2 = 0.00; \textit{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 diabetes studied in RCTs, 0.94 [95% CI 0.88, 0.99] for non-diabetes studied in RCTs, 0.69 [95% CI 0.60, 0.77] for diabetes studied in retrospective studies, and 0.67 [95% CI 0.57, 0.76] for non-diabetes studied in retrospective studies (Figure 4). Risk of the prevalence of CVD was similar between statin-ezetimibe co-therapy and high-intensity

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Statin dose (mg)</th>
<th>Statin alone</th>
<th>Ezetimibe statin</th>
<th>Total</th>
<th>Diabetic</th>
<th>Non-diabetic</th>
<th>Follow-up (months)</th>
<th>Age</th>
<th>Males %</th>
<th>Smokers %</th>
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<td>Bohula et al\textsuperscript{17}</td>
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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.
Ezetimibe-statin in diabetes vs. non-diabetes patients

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 al28 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]; χ² = 0.58; p = 0.45). In a secondary cross-sectional analysis of a subset of over 1000 outpatients with diabetes (The Dyslipidemia International Study; DYSIS), Leiter et al29 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-
nary syndrome, Nakajima et al\textsuperscript{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 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.
Ezetimibe-statin in diabetes vs. non-diabetes patients

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. 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. 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. Whereas this risk is not found to...
be associated with statin-ezetimibe co-therapy. Many studies suggest that ezetimibe, either added to statin or as monotherapy, does not adversely affect glucose metabolism rather may improve metabolic markers such as hepatic steatosis and insulin resistance. 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. Ezetimibe-atorvastatin co-therapy for 8 weeks has been reported to decrease sPLA2 activity.

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

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.
Ezetimibe-statin in diabetes vs. non-diabetes patients


34) Dorrnsfurh CR, Filion KB, Paterson JM, James MT, Terear GF, Raymon CB, Rahme E, Tamam H, Lipscombe


