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Safety and efficacy of ezetimibe: A meta-analysis

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ABSTRACT

Background: The addition of ezetimibe to statin therapy has been widely demonstrated to significantly reduce low-density lipoprotein cholesterol levels. However, the efficacy of ezetimibe in reducing CV events and its safety has been less investigated. The aim of the current meta-analysis was to report efficacy and safety of ezetimibe from randomized clinical trials.

Methods: Randomized clinical trials with a follow-up of at least 24 weeks, enrolling more than 200 patients, comparing ezetimibe versus placebo or ezetimibe plus another hypolipidemic agent versus the same hypolipidemic drug alone and reporting at least one event among all-cause and CV mortality, myocardial infarction (MI), stroke and new onset of cancer were included in the analysis.

Results: 7 trials enrolling 31,048 patients (median follow-up 34.1 ± 26.3 months; 70% women; mean age 61 ± 8 years) were included in the analysis. Compared to control therapy, ezetimibe significantly reduced the risk of MI by 13.5% (RR: 0.865, 95% CI: 0.801 to 0.934, $p < 0.001$) and the risk of any stroke by 16.0% (RR: 0.840, 95% CI: 0.744 to 0.949, $p = 0.005$), without any effect on all-cause and CV mortality (RR: 1.003, 95% CI: 0.954 to 1.055, $p = 0.908$; RR: 0.958, 95% CI: 0.879 to 1.044, $p = 0.330$; respectively) and risk of new cancer (RR: 1.040, 95% CI: 0.965 to 1.120, $p = 0.303$).

Conclusions: Ezetimibe significantly reduces the risk of MI and stroke without any effect on all-cause and CV mortality and risk of cancer.

1. Introduction

Statins (3 HMG-coA inhibitors) have been proven to reduce cholesterol levels and cardiovascular (CV) events in primary and secondary prevention [1–4]. Subsequent studies have shown that intensive statin therapy, as compared with less intensive statin therapy, reduces low-density lipoprotein cholesterol (LDL-C) further and produces a greater reduction in CV events [5–9]. However, there is a significant risk of recurrent CV events even in patients receiving high dose statins, the use of which has also raised safety concerns, leading to the search of additional lipid-modifying therapies [10–14].

Circulating cholesterol originates from liver synthesis and intestinal absorption, with the latter mechanism increasing its contribution during treatment with statins [15,16]. Ezetimibe markedly reduces the intestinal absorption of cholesterol interacting with the Niemann–Pick C1-Like 1 (NPC1L1) protein [17,18]. This results in a further 20–25% reduction in LDL-C levels among patients treated with statins [19,20]. Should the relationship between LDL-C reduction and cardiovascular events reduction shown by the CTT collaborative study hold true also for ezetimibe [4], this would translate into an additional clinical benefit.

However, a widespread use of ezetimibe has been hindered by the recommendation of the ACC/AHA guidelines to base treatment on statins, in the absence of efficacy data for ezetimibe [21] and by concerns over the safety of this agent, notably over the possibility of an increased incidence of cancer. This originated from the finding of an increased incidence of cancer among patients taking ezetimibe/simvastatin as compared with placebo in the SEAS trial, designed to evaluate the effect of the combination on the progression of aortic stenosis [22]. The publication of a specifically designed safety analysis including data from ongoing trials was not unanimously accepted as appropriate and reassuring [23], leading to a strong controversy [24,25]. This must not have been completely solved, as suggested by the conclusions on the risk/benefit ratio of ezetimibe reached by a recent meta-analysis published [26]. Notably, this analysis did not include data from the IMPROVE-IT trial [27–30]. Since this latter trial followed patients for an average of six years providing more than 100,000 patient-year of safety data, approximately the same amount of the

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combined data included, we thought it would be important to reassess the safety and efficacy of ezetimibe including this essential information.

2. Methods

2.1. Search strategy

This study was designed according to the PRISMA (Preferred Reporting Items for Systematic reviews and meta-analyses) statement [31]. MEDLINE, Cochrane Database, ISI Web of Sciences and SCOPUS were searched for articles published in English and other languages until June 2015. Studies were identified by the following headings: ezetimibe, random, randomized controlled trial, and clinical trial. We used reference lists of the retrieved articles and reviews about the current topic as well information from colleagues to identify additional eligible studies.

2.2. Study selection

According to the aim of the study, i.e., to evaluate the safety and efficacy of ezetimibe *per se*, all trials that reported a comparison between patients receiving the drug vs patients not receiving the drug, independently on background therapy, were eligible for the analysis. Thus, study inclusion criteria were: randomized allocation to ezetimibe versus placebo or ezetimibe plus another hypolipidemic agent versus the same hypolipidemic drug alone; follow-up longer than 24 weeks; enrollment of at least 200 patients; report of at least 1 clinical event among all-cause and CV death, MI, any stroke and new cancer onset.

2.3. Data extraction and quality assessment

Two reviewers (GS and GMDF) independently selected potentially eligible trials, read the full-text of retained studies, which were checked to avoid inclusion of data published in duplicate. Discrepancies were resolved by a third author (GMCR). Corresponding authors were asked to provide full-text papers, if they were not available. From each study, information about the inclusion criteria, year of publication, number of patients in treatment and control arms, duration of follow-up, age, gender, body mass index (BMI), smoking, CV risk factors, coronary artery disease (CAD) and peripheral artery disease (PAD) were abstracted and entered into STATA (version 12.0, StataCorps, College Station, Texas) by one author (GS) and checked by another one (GMDF). Pre-specified outcomes of the analysis included all-cause death, CV death, MI, any stroke and new cancer onset.

Methodological quality of trials was assessed by Detsky method, scoring the following items: method of randomization (1 point), adequate description of method of randomization (2 points), blindness (2 points), adequate description of outcome (1 point) and of outcome assessment (2 points), as well as inclusion/exclusion criteria (2 points), number of patients excluded and reasons (2 points), description of therapy in treatment and control groups (4 points) and appropriateness of statistical analysis (up to 5 points) [32].

2.4. Data synthesis and analysis

Relative risks (RRs) of the effect of randomized treatments were calculated using the metan routine (STATA Statacorp, version 14.0) to account for the probability of events occurring in the treatment group versus the control group. The RR and 95% Confidence Interval (CI) for each outcome were separately calculated for each trial, with grouped data, using the intention-to-treat principle [33]. Overall estimates of effect were calculated with a fixed-effects model or with a random-effects model when heterogeneity could not be explained [34]. The assumption of homogeneity between the treatment effects in different trials was tested with the Q and I^2 statistics. A significant heterogeneity was defined by a $p \le 0.05$ at Q statistic; i2 ranging from 0% to 40% might indicate not important heterogeneity, from 30% to 60% might represent moderate heterogeneity, from 50% to 90% might indicate substantial heterogeneity and from 75% to 100% might represent considerable heterogeneity [35]. The significance level for all outcome and heterogeneity analyses was set at $p \le 0.05$.

2.4.1. Sensitivity analysis

To verify the consistency of outcome meta-analysis results, the influence of each individual study on the summary effect estimate was assessed by the 1-study removed sensitivity analysis using the "metaninf" command (STATA) [36].

2.4.2. Publication bias

Publication bias was assessed with the command "metafunnel" using plots of study results against precision of the study (funnel plots) for each outcome. Symmetry of the funnel plots was tested using the Egger linear regression method [37].

3. Results

3.1. Characteristics of included trials

Of 3037 papers identified in the initial search, 167 were retrieved for more detailed evaluation. 160 studies were subsequently excluded. Therefore, 7 trials [22,30,38–42] were finally included in the analysis, which enrolled 31,048 patients (70% males; mean age 61 ± 8 years; mean follow-up 34.1 ± 26.3 months), 15,586 of which were assigned to ezetimibe and 15,462 patients to control therapy (Fig. 1). Baseline characteristics of 7 trials included in the meta-analysis are shown in table 1.

3.2. Methodological quality

Methodological aspects varied across trials, with some quality items of Detsky score not fulfilled in some studies. The median Detsky score was 95% (interquartile range: 90–95%). No trial satisfied all Detsky score items. No trial was triple-blinded, whereas 4 (57%) were double-blinded [22,30,38,41], 2 (29%) were open-label [39,40] and in 1 (14%) blindness was not properly described [42]. In only 1 trial of 7 (14%) included in our study, the sample size was not calculated [39].

3.3. Outcomes analysis

Table 2 summarizes the event rates for each outcome for each trial.

MI occurred in 7.3% of patients allocated to ezetimibe compared to 8.4% of those randomized to control therapy. Thus, ezetimibe significantly reduced the risk of MI by 13.5% compared to control (RR: 0.865, 95% CI: 0.801 to 0.934, comparison $p < 0.001$, heterogeneity $p = 0.785$, Fig. 2), resulting in 1.1% absolute risk reduction (AAR).

Any stroke was reported in 3.0% of patients randomized to ezetimibe compared to 3.6% of those enrolled in control group. Thus, the risk of stroke was significantly reduced by 16.0% in patients receiving ezetimibe as compared to the ones randomized to control therapy (RR: 0.840, 95% CI: 0.744 to 0.949, comparison $p = 0.005$, heterogeneity $p = 0.686$, Fig. 2), resulting in 0.6% ARR.

All-cause death occurred in 15.8% of patients allocated to ezetimibe compared to 15.9% of the ones randomized to control therapy. Thus, no difference in risk of all-cause death was reported between ezetimibe and control therapy (RR: 1.003, 95% CI: 0.954 to 1.055, comparison $p = 0.908$, heterogeneity $p = 0.487$, Fig. 3).

CV death was reported in 6.2% of patients enrolled to receive ezetimibe compared to 6.5% of those randomized to control therapy. Thus, no difference in risk of CV death was reported between ezetimibe and control therapy (RR: 0.958, 95% CI: 0.879 to 1.044, comparison $p = 0.330$, heterogeneity $p = 0.384$, Fig. 3).

New cancer onset occurred in 8.7% of patients allocated to ezetimibe compared to 8.4% of the ones randomized to control therapy. Thus, no difference in risk of new cancer was reported between ezetimibe and control groups (RR: 1.040, 95% CI: 0.965 to 1.120, comparison $p = 0.303$, heterogeneity $p = 0.065$, Fig. 4).

3.4. Sensitivity analysis

When meta-analyses were repeated removing 1 study at the time, the removal of IMPROVE-IT [30] trial only approximated the statistical significance for the reduction of the risk of MI induced by ezetimibe (RR: 0.814, 95% CI: 0.660 to 1.004, comparison $p = 0.054$). After the removal of SHARP trial [41] the reduction of risk of stroke induced by ezetimibe was no longer significant (RR: 0.883, 95% CI: 0.764 to 1.021, $p = 0.092$).

3.5. Publication bias

No publication bias was reported for each outcome.

4. Discussion

The findings of the current meta-analysis indicate that ezetimibe significantly reduces the risk of MI and stroke without any significant effect on overall and CV mortality and risk of cancer.

A recent meta-analysis including 7 randomized clinical trials showed a non-significant effect of ezetimibe added to statin on all-