RESEARCH ARTICLES

EFFECTIVENESS OF EZETIMIBE IN ROUTINE CLINICAL PRACTICE

Authors

Enrique Gonzalez Sarmiento, Miguel Martin Asenjo, Javier Miguel Martín Guerra, Cristina Jauset Alcalá

Correspondence:

Miguel Martin Asenjo

Doctor

Email: miguel.martin.asenjo@gmail.com

Abstract

Atherosclerosis is the primary cause of mortality in our field. Secondary prevention trials show that lowering c-LDL is associated with reduced coronary risk. Hence, sometimes, despite the high dosages of statins, the objective which has been recommended by various panels of experts, only achieves results in a modest 10-20% of patients, as is usual in patients with cardiovascular disease (CVD), with elevated risk of sustaining it, or in diabetic patients, for whom most associations suggest an c-LDL <70 mg/dl.

Ezitimibe is the first selective inhibitor of dietary cholesterol and billiary absorption in the intestinal wall, through the absorption of the NPCL1 transporter protein. Monotherapy has achieved an average reduction of 20% in total cholesterol readings (TC), 22% in c-LDL and 10% in TG, with a minimal increase (3%) of c-HDL. Ezetimibe, in monotherapy and in combined therapy, has shown that as well as reducing levels of inflammatory markers, reactive C-protein and ferritin, have improved endothelial functions.

Patients are increasingly in need of lipid-lowering drug treatments, and more intensive ones, in order to achieve their c-LDL objectives. Since the normal statin dosages reduce the concentrations of c-LDL by 30-40%, in some cases monotherapy using statin is insufficient in order to achieve optimum effects, preferably in high-risk patients. Double therapy, statin-ezetimibe, reduces c-LDL levels with greater efficacy than a single statin and is a more effective strategy for achieving objectives.

Introduction

Atherosclerosis is the primary cause of mortality in our field. Its development is closely related, among other risk factors, with the high concentrations of plasmatic lipids and, fundamentally, with those of low-density lipoproteins (LDL). For this reason, nowadays it is well known that hyperlipidaemia is a risk factor for atherosclerosis and cardiovascular risk (CVR)[1,2].

Dyslipidaemia is characterised by an increase in plasmatic concentrations of triglycerides (TG), total cholesterol (TC), and cholesterol of the low-density lipoproteins (c-LDL), alongside a decrease in the cholesterol of the high-density lipoproteins (c-HDL). To prevent CVR, various guides suggest lowering c-LDL levels until they are under 70mg/dl or at least under 50% of the baseline in very high-risk patients, and under 100mg/dl or at least 50% of the baseline in high-risk patients[3,4].

Secondary prevention trials show that lowering c-LDL is associated with reduced coronary risk. Said studies include the Heart Protection Study (HPS)[5], the Cholesterol And Recurrent Events (CARE) trial[6], the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study[7] and the Scandinavian Simvastatin Survival Study[8].

The effectiveness of statins, 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA) enzymes, controlling dyslipidaemia and a reduction of cardiovascular morbimortality, in primary prevention as in secondary prevention, has been clearly shown in multiple studies[9,10], deeming them adequate drugs of choice in the treatment for hypercholesterolemia. This way, the meta-analysis CTT (Cholesterol Treatment Trialists)[11]of 26 clinical trials, including 170,000 patients, showed that the reduction of c-LDL using statins was safe and for every c-LDL reduction of 39 mg/dl the risk of major cardiovascular complications was reduced by 20%, independently from the basal values of c-LDL.

The first dose of statins leads to a 30-50% cholesterol reduction. Its dose-response relationship is curvilineal, showing that the response to an increased dosage is not directly proportional. When the statin dosage is doubled, the reduction of c-LDL is not doubled. Instead, there is usually only an additional 4-6% reduction; this is known as the 6% rule[12].

Hence, sometimes, despite the high dosages of statins, the objective which has been recommended by various panels of experts, only achieves results in a modest 10-20% of patients, as is usual in patients with cardiovascular disease (CVD), with elevated risk of sustaining it, or in diabetic patients, for whom most associations suggest an c-LDL <70 mg/dl. The EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events)[13] study showed that only 51% of patients receiving lipid-lowering drug treatments achieved the objective, and the REALITY (Return on Expenditure Achieved for Lipid Therapy)[14] study showed that 57% of high-risk patients won't achieve the projected c-LDL goals through statin-based monotherapy. In Spain, the results of the DYSIS-España (Dyslipidemia International Survey-España)[15] study imply that, despite the treatment with statins, only a fifth of patients reach normal lepidic values as recommended by the currently acting clinical practice guidelines. Moreover, the vast majority of high-risk patients, CVD patients, and diabetic patients continue to exhibit one or more parameters of dyslipidemia. DYSIS-España's results show that there are important differences between the recommendations by the clinical practice guidelines and the clinical reality, hence the need for a more intensive and

thorough management of dyslipidemia in patients with high CVR.

The reason for this failure can be attributed to various factors: low therapeutic effect of patients, the biological variability in response to statins, the reluctance of medical professionals when it comes to modifying poorly-controlled patient treatments, the insufficient efficacy of the current statin dosages, its tolerability (rhabdomyolysis, hepatic impairment), and the risks involved for diabetic patients as shown in the JUPITER (The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin[16] and WOSCOPS (The West of Scotland Coronary Prevention Study)[17]studies. This is probably related to the high dosage, showing a 12% risk increase in patients treated with higher dosages compared with patients treated with more moderate dosages of statins[18], alongside the type of statin (primarily atorvastatin and simvastatin[19]) and primarily in patients with pre-diabetes. The independent predictors of newly-appearing diabetes can be identified by basal levels of glucose when fasting; metabolic syndrome; a family history of diabetes; and the duration of observations. The addition of ezetimibe to the statin treatment had a neutral effect on how glucose was metabolized[20]. In these cases, when treatment with statins is insufficient to achieve the desired c-LDL concentrations, new alternatives are being sought. For example, the interaction with fibrates, bile acid resin, or nicotinic acid, with varied results. Some important interaction-related side effects were noted to have limited their efficacy.

Ezetimibe's pharmacokinetics. Ezitimibe is the first selective inhibitor of dietary cholesterol and billiary absorption in the intestinal wall, through the absorption of the NPCL1 transporter protein (protein 1 similar to the Niemann-Pick C-protein)[21]. It influences dietary cholesterol as well as that coming from enterohepatic circulation, which is quantitatively more important, therefore the efficacy of the drug does not depend on the patient's diet. There is a negative correlation between LDL particles and the concentration of plasmatic triglycerides, and a positive correlation with HDL values. This also applies to the cholesteryester transfer enzyme in the transference of the latter from the HDL and the LDL to the triglyceride-rich lipoproteins and transference of triglycerides in the opposite direction. Cholesterol absorption inhibitors reduce the content of the latter in chylomicrons, which can indirectly lead to an LDL reduction and to the inhibition of the cholesteryester transfer enzyme[22].

It does not interfere in the absorption of other substances, such as liposoluble vitamins (A, D, E) or carotenes, fatty acids, bile acids, or triglycerides. Hence, it has a different active mechanism to statins, for which reason its co-administration achieves double inhibition of absorption and synthetisation of cholesterol, leading to greater plasmatic density reductions, which can make up 50% and even 5% in triglycerides[23]. Intestinal cholesterol loss can reach a daily 400mg. Once it has been absorbed, it combines itself with glucuronic acid in the intestine and liver, entering enterohepatic circulation which means that its half-life is quite long, approximately 22 hours. Its elimination is primarily hepatic (78%) and to a lesser extent renal (11%), which means it is not recommended in moderate or grave hepatic deficiencies, with no necessity of modifying the dosage in renal deficiency. The most effective ezetimibe dosage is 10 mg/day, which can be administered once a day with its bio-availability unaffected by food. Its efficacy

stops rising once the dosage is increased above 10 mg/day. It is hepatically metabolised via glucoronidation. It is not metabolised via cytochrome p450, and no important interaction has been described with drugs that are metabolised via CYP 1A2, 2D6, 2C8, 2C9 or 3A4, which suggests low toxicity in its clinical use[24,25]. Lipid-lowering drug action peaks after 2 weeks and is maintained over the course of several months[26].

Monotherapy has achieved an average reduction of 20% in total cholesterol readings (TC), 22% in c-LDL and 10% in TG, with a minimal increase (3%) of c-HDL.

It is a safe drug without significant side-effects. In all controlled studies around ezetimibe its safety has been tested, showing that the secondary effects were much like those caused by the similarly-administered placebo, both in the randomised studies and in the post-launch pharmacovigilance, both in monotherapy and when associated with statins.

Ezetimibe, in monotherapy and in combined therapy, has shown that as well as reducing levels of inflammatory markers, reactive C-protein and ferritin, have improved endothelial functions[27,28,29].

Biochemical efficacy of treatment combining statins and ezetimibe. Ezetimibe has shown its efficacy and adequate clinical tolerability across various studies, where it has been used in combination with diverse statins (lovastatin, simvastatin, atorvastatin, pravastatin, rosuvastatin and pitavastatin). The ezetimibe and statins combination is based on the different, yet complimentary effects of each drug. It is indicated for clinical situations in which statins when performing their function as the drug of choice, cannot attain the necessary therapeutic objectives or the patient presents any form of adverse reaction or side effects (with an EBM level C of evidence)[30]. Co-administration of a daily 10mg of ezetimibe in combination with the 10mg dosage of statin reduced c-LDL levels with the same efficacy as the elevation of statin doses to the maximum recommended dosage. It lowers total cholesterol levels by up to 50% and c-LDL by more than 60%, with the lowest incidence of secondary effects. Hence, co-administering ezetimibe with a statin, in a single step, produces a similar reduction to multiplying the statin dosage 3 or 4 times (6% x 3). It allows a simple, yet efficient control of lipids in comparison with the three-step dosage adjustment in monotherapy with statins[31] without increasing the secondary effects and the hepatic or muscular toxicity, allowing the c-LDL therapeutic objectives to be met in a large percentage of patients.

The VYVA (Vytorin Versus Atorvastatin Study)[32] compares the efficacy of the statin-ezetimibe combination with varying dosages of atorvastin when it comes to achieving therapeutic objectives in 1,902 patients. The combination resulted in a larger reduction of c-LDL than atorvastatin (47-59% compared to 36-53%; $p < 0.001$); a larger number of patients reached c-LDL levels of <100 mg/dl (85% compared to 70%; $p < 0.001$) or <70 mg/dl (45% compared to 21%; $p < 0.001$). Of the patients who received treatment that suffered from coronary disease or had similar risk factors, 64% reached the c-LDL objective of <70mg/dl with the combined treatment, while only 36% with atorvastatin at its maximum dosage did.

Ez PATH by Leiter LA et al[33] found that the percentage of patients who reached the c-LDL therapeutic objective of <70mg/dl after 6 weeks of treatment (70%) is greater than the group who received 10mg of ezetimibe combined with 40mg of atorvastatin, compared to those

who increased their atorvastatin dosage to 80 mg (32%). Specifically, 74% of patients in the combined treatment group achieved the therapeutic objective of c-LDL <70mg/dl compared with 32% of patients in the atorvastatin at maximum dosage monotherapy group, a statistically significant difference of p <1.001.

The ACTE Study[34] evaluated ezetimibe's efficacy in reducing c-LDL when co-administered in patients who had already been treated with 5 or 10mg of rosuvastatin versus the increase on rosuvastatin dosage to 10-20mg in hypocholesterolemic patients with a moderate or high CVR with atherosclerosis. The addition of ezetimibe to the rosuvastatin treatment resulted in major c-LDL reductions compared with the increased dosage of rosuvastatin (-21.5% vs. -7,6% p <0,001) both in the total demographic of the study, as when tested separately on each stratum. Moreover, there were also major reductions noted with the co-administration of ezetimibe as compared to the increase in levels of TC, no-HDL cholesterol, and apoB. Regarding the achievement of the projected goals for the co-administration of ezetimibe and rosuvastatin, a major percentage of patients achieved the desired c-LDL <70mg/dl levels for high CVR with atherosclerosis, following a similar baseline profile for safety and tolerability in all treatment groups.

This was also shown in the EASEGO (The Ezetimibe And Simvastatin versus doublE statin reach new lipid treatment GOals study)[35] study, involving patients with hypercholesterolemia and coronary and/or type 2 diabetics who did not meet the c-LDL objectives set by the monotherapy with statins. These individuals switched over to ezetimibe/simvastatin, which significantly reduced c-LDL and TC levels compared to the increased statin dosage. The patients who switched over to ezetimibe/simvastatin from their base-dosage of statin, simvastatin of 20mg or atorvastatin of 10mg experienced an additional average c-LDL reduction of 29.1% after 12 weeks. On the other hand, patients who increased their simvastatin or atorvastatin dosages only experienced an average c-LDL reduction of 11.5% after 12 weeks. The difference in c-LDL reduction was statistically significant (p <0.001) in favour of the change to ezetimibe/simvastatin.

In Dai Yun-Yan's study[36], 202 patients suffered from acute coronary syndrome (ACS) and percutaneous coronary intervention was required. Between May and July of 2016 they were assigned to 3 groups, according to the lipid reduction strategy: a group receiving moderate intensity statins, a group receiving a combination of ezetimibe and moderate-dosage statins, and the intensive statin group. They were tracked over 6 months. The percentages of CT and c-LDL reduction were significantly higher in the group receiving a combination of ezetimibe and moderate-dosage statins compared to the moderate-intensity statin group (p <0.001). The proportion of patients that reached the projected drop in c-LDL was greater in group receiving the combination of ezetimibe and moderate-dosage statins (69.1%, p =0.007) in comparison with the group receiving moderate-intensity statins (67.9%, p =0.047) and the group receiving intensive statins (46.9%). There were no significant differences among the three groups in terms of the level of hepatic enzymes, the kinease creatine levels, and the frequency of muscular symptoms.

This demonstrates the efficacy of an ezetimibe-simvastatin combination treatment in cholesterol reduction, despite the morbimortality studies that have been carried

out to this date having frequently produced discording results, which has triggered certain controversy in terms of their true usefulness.

Effects on cardiovascular morbimortality of the combined treatment of statins and ezetimibe. The benefit of these results on vascular damage was called into question due to the results obtained in the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia enhances Atherosclerosis Regression) study[37]. This study proved that the addition of ezetimibe to simvastatin did not reduce the intima-media thickness in 720 patients who suffered from familial hypercholesterolemia**,** who were observed over two years. Despite significant c-LDL and C-reactive protein reductions, and due to the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis)[38] study in which said interaction did not reduce the combination of events associated with aortic valvuloplasty and ischemic events in patients with aortic stenosis, it did reduce the incidence of ischemic cardiovascular events.

In this same line of research was the ARBITER-6 HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) study[39]. 315 coronary disease patients, or patients with similar c-LDL<100mg/dl conditions who were receiving statins treatments, were observed for 14 months and were randomly assigned ezetimibe (10 mg/day) or slow release niacin (2,000 mg/day). There was a significant difference between the groups receiving the treatment with ezetimibe and niacin over average CIMT changes, which favoured niacin, both for the CIMT average (p =0.016) as for the maximum CIMT values (p =0.01), proving that niacin reduces regression in a superior manner to ezetimibe. Kiyoshi et al.[40] carried out a randomised, prospective, open-label study in 10 medical centres. 128 patients without statins with ACS who underwent an intravascular echography (IVUS). The patients were randomized to receive 2mg/day of pitavastatin plus 10mg/day of ezetimibe or 2mg/day of pitavastatin. The primary end-point was the percentage change in the volume of plaque that could be seen in the Doppler echocardiography. The combined treatment of ezetimibe and statins produced no significant change in coronary plaque regression or tissue components compared to statin alone.

In contrast, the controlled, prospective, randomised, multicentral PRECISE-IVUS (The Plaque REgression with Cholesterol absorption Inhibitor or Synthesis inhibitor Evaluated by IntraVascular UltraSound) trial[41] was the first to prove a reduction in coronary atherosclerosis, in patients who underwent a percutaneous coronary intervention, with the dual lipid reduction therapy of ezetimibe and statins when compared to statins by themselves. Patients were randomly assigned to only-atorvastatin, or atorvastatin plus ezetimibe (10 mg/day). Both strategies had acceptable secondary effect profiles, with a low incidence of anomalies and cardiovascular events.

More recently, the SHARP (Study of Heart and Renal Protection) study[42] proved that the reduction of c-LDL achieved via the combination of 20mg of simvastatin and 10mg of ezetimibe safely reduced the incidence of major atherosclerotic events in patients with advanced chronic renal disease and without previous signs of vascular disease.

The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study[43] is a randomised, double-blind, placebo-controlled trial. 18,144 patients of both sexes, above 50 years of age, who had been

hospitalised in the 10 previous days due to acute coronary syndrome (including myocardial infarcts with or without TS segment elevations or a high risk of unstable angina) with c-LDL levels between 50 and 125 mg/dl, participated. They were randomised to placebo/simvastatin 40mg or ezetimibe/simvastatin 10/40mg. They were followed for an average of 6 years for the primary component of cardiovascular death, myocardial infarct, hospitalisation due to unstable angina, coronary revascularisation ≥30 days and cerebrovascular accidents. It was shown that the addition of ezetimibe to the simvastatin treatment produced additional benefits both in men and women, with a good safety profile, no different to the placebo group. This backed the use of intensive, combined, and lipid reduction therapy to optimise cardiovascular results.

A sub-analysis of this study[44] proved that the ezetimibe/simvastatin combination was associated with an absolute reduction of 5.5% (HR 0.86, IC 95% 0.78-0.94) at the final primary endpoint compared to simvastatin monotherapy in diabetic patients, without modifying the metabolical parameters, hence it can be considered a positive interaction in the treatment for said patients.

However, the anti-atherosclerotic effect of ezetimibe continues to be controverted as can be seen in other studies. Kiyoshi et al.[45] showed in patients without previous statins treatments for ACS, that the combined treatment of ezetimibe and statins (2mg/day of pitavastatin plus 10mg/day ezetimibe, or 2mg/day of pitavastatin) there was no significant change in coronary heart regression, or tissue makeup, in comparison with statins alone. Other research such as the SANDS (Stop Atherosclerosis in Native Diabetics Study) clinical trial[46] yielded similar results. This trial was carried out on adults with type 2 diabetes and without previous signs of cardiovascular disease, and concluded that the beneficial effects of the ezetimibe/statin treatment on carotid atherosclerosis were similar to those of the statin monotherapy in patients with a similar c-LDL reduction rate.

In a recent meta-analysis[47] of 8 clinical trials, with a special focus on IMPROVE-IT showed that in patients with a high risk of cardiovascular events, ezetimibe combined with statins was associated with a likely nonlethal myocardial infarct risk reduction, a possible reduction in nonlethal cerebrovascular accidents, and no impact on myopathy, or on mortality for all the aforementioned causes and cardiovascular death, and possibly no impact on cancer. The authors' conclusion was that the addition of ezetimibe to moderate dosages of statins probably prevented 18 infarcts and possibly 6 cerebrovascular accidents in the 1,000 patients treated over 6 years, but it is unlikely to have reduced mortality rates for all the reasons or cardiovascular death. No reference was made to specific major damage associated with the addition of ezetimibe to statins.

In recent years, various studies in everyday medical practice have shown cardiovascular benefits in various clinical situations, confirming the results of the aforementioned clinical trials. In France, Ferrieres et al.[48] evaluated the impact of ezetimibe in real life over morbidity and cardiovascular mortality in a total of 3215 patients, followed over an average of 2.9 years. They estimate the number of nonfatal and fatal cardiovascular events that could be prevented and the number of the patients who need ezetimibe treatment to prevent such an event in 5 years. The predicted frequency reductions related to CV events (fatal and nonfatal) compared to no treatment, or to statin (combined therapy) were, respectively, 8,

2, and 12 in every 1,000 patients treated over 5 years, with a global NNT of 143 patients.

This way, other authors[49] have shown the clinical benefits of a combination of statins and ezetimibe on a total of 212,110 patients with ACS and multiple comorbidities. The patients of the statin group, more so than the ezetimibe group had a significantly lesser risk of being admitted to hospital with ACS (risk ratio adjusted [RR] =0.64, confidence interval [CI] =95%: 0.60-0.69) and revascularization (CRR =0.69, CI 95%: 0.63-0.76) than those who were in the statin-only group. There were also significant interactions between the combination with ezetimibe, sex, and mellitus diabetes.

The MOBS (The Model-Observational-Bridging Study)[48] study was launched to study ezetimibe's impact on health, after it was approved for sale to the public in France. Its primary objective was to estimate the number of fatal and nonfatal cardiovascular events which could be prevented by ezetimibe. 3,395 patients were recruited due to hypercholesterolemia who had been taking ezetimibe over a minimum of 3 months before being included in the study. They concluded that ezetimibe combined with statin could prevent 12 CVEs for every 1,000 patients over 5 years compared to statins alone.

Conclusion. Epidemiological studies have revealed that the increase in serine cholesterol can be associated with a greater risk of cardiovascular morbidity and mortality. Patients are increasingly in need of lipid-lowering drug treatments, and more intensive ones, in order to achieve their c-LDL objectives. Since the normal statin dosages reduce the concentrations of c-LDL by 30-40%, in some cases monotherapy using statin is insufficient in order to achieve optimum effects, preferably in high-risk patients. Double therapy, statin-ezetimibe, reduces c-LDL levels with greater efficacy than a single statin and is a more effective strategy for achieving objectives. Its side effects are similar to those of a placebo. In conclusion: although statins continue being the treatment of choice in dyslipidemic patients, the interaction between statins and ezetimibe are suggested as a more effective treatment for those patients who do not achieve their c-LDL objectives via monotherapy or cannot tolerate higher dosages of statins.

Bibliography.

1. Kannel WB. Range of serum cholesterol values in the population developing coronary artery disease.Am J Cardiol. 1995; 76:69-77
2. Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, Shih J, Stamler J, Wentworth D. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Tria Research Group. Arch Intern Med. 1992; 152:1490-500
3. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I1, Verschuren WMM, Binno S; ESC Scientific Document Group.The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal, 2016;37:2315–2381
4. Lobos Bejarano JM, Galve E, Royo-Bordonada MÁ, Alegría Ezquerra E, Armario P, Brotons Cuixart C, Camafort Babkowski M, Cordero Fort A, Maiques Galán A, Mantilla Morató T, Pérez Pérez A, Pedro-Botet J, Villar Álvarez F, González-Juanatey JR; Spanish Interdisciplinary Committee for Cardiovascular Disease Prevention; Spanish Society of Cardiology. Spanish Interdisciplinary Committee for Cardiovascular Disease Prevention and the Spanish Society of Cardiology Position Statement on Dyslipidemia Management. Differences Between the European and American Guidelines. Rev Esp Cardiol. 2014; 67:913–919
5. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002; 360:7-22
6. Pfeffer MA, Sacks FM, Moyé LA, Brown L, Rouleau JL, Hartley LH, Rouleau J, Grimm R, Sestier F, Wickemeyer W, et al.Cholesterol and Recurrent Events: a secondary prevention trial for normolipidemic patients. CARE Investigators. Am J Cardiol. 1995; 76:98-106
7. LIPID Study Group (Long-term Intervention with Pravastatin in Ischaemic Disease). Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet. 2002; 359:1379-87
8. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344:1383-9

9. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. JAMA. 1997; 278:313-21
10. La Rosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a metaanalysis of randomized controlled trials. JAMA. 1999; 282:2340-6
11. Cholesterol Treatment Trialists' (CTT) Collaboration1, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376:1670-81
12. Knopp RH. Drug treatment of lipid disorders. N Engl J Med. 1999; 341:498-511
13. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. Eur Heart J. 2001; 22:554-72
14. Van Ganse E1, Laforest L, Alemao E, Davies G, Gutkin S, Yin D. Lipid-modifying therapy and attainment of cholesterol goals in Europe: The Return on Expenditure Achieved for Lipid Therapy (REALITY) study. Curr Med Res Opin. 2005;21:1389-99
15. González-Juanatey JR, Millán J, Alegría E, Guijarro C, Lozano JV, Vitale GC. Vitale Prevalence and characteristics of lipid abnormalities in patients treated with statins in primary and secondary prevention in Spain. DYSIS-Spain Study. Rev Esp Cardiol. 2011; 64:286-94
16. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; 103:357-62
17. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al.Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359:2195-207
18. Sattar N. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials Lancet. 2010; 375:735–42.
19. Aleesa A Carter, Tara Gomes, Ximena Camacho, David N Juurlink, Baiju R Shah, Muhammad M Mamdani. Risk of incident diabetes among patients treated withstatins: population-based study. BMJ. 2013; 346:1-11
20. Barkas Fotios, Elisaf Moses, Liberopoulos Evangelos, Klouras Eleftherios, Liamis George, Rizos Evangelos C. Statin therapy with or without ezetimibe and the progression to diabetes. J Clin Lipidol. 2016; 10:306-13
21. Filippatos TD, Mikhailidis DP. Lipid-lowering drugs acting at the level of the gastrointestinal tract. Curr Pharm Des. 2009; 15:490-516
22. Scheffer PG, Bakker SJ, Heine RJ, Teerlink T. Measurement of LDL particle size in whole plasma and serum by high performance gel-filtration chromatography using a fluorescent

lipid probe. Clin Chem. 1998; 44:2148-51

23. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, LeBeaut AP, Suresh R, Yang B, Veltri EP; Ezetimibe Study Group. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J. 2003; 24:729-41.
24. Jurado J. Effectiveness of ezetimibe in clinical practice. Am J Cardiol.2004;93:641
25. Pascual Izuel JM, Rodilla Sala E, Sánchez Juan C. Clinical efficacy of ezetimibe and combined use with statins. Rev Clin Esp. 2005; 205:496-8
26. Knopp RH, Gitter H, Truitt T, Bays H, Manion CV, Lipka LJ, LeBeaut AP, Suresh R, Yang B, Veltri EP; Ezetimibe Study Group. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J. 2003; 24:729-41.
27. Pesaro AE, Serrano CV Jr, Fernandes JL, Cavalcanti AB, Campos AH, Martins HS, Maranhão RC, de Lemos JA, Souza HP, Nicolau JC.Pleiotropic effects of ezetimibe/ simvastatin vs. high dose simvastatin. Int J Cardiol 2012; 158:400-4
28. González Sarmiento E, Zurro Hernández J, Fernández Galante I. Effectiveness of ezetimibe in routine clinical practice. Effect on lipid profile and other laboratory parameters. Endocrinol Nutr. 2008; 55:165-9
29. Sager PT, Melani L, Lipka L, Strony J, Yang B, Suresh R, et al. Ezetimibe Study Group. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. Am J Cardiol. 2003; 92:1414-8
30. European Association for Cardiovascular Prevention & Rehabilitation1, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011; 32:1769-818
31. Stein E. Results of phase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. Eur Heart J Suppl 2001;3:E11-E16
32. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. Am Heart J. 2005; 149:464-73.
33. Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME, Tomassini JE, Tershakovec AM. Efficacy and Safety of Ezetimibe Added on to Atorvastatin (40 mg) Compared with Uptitration of Atorvastatin (to 80 mg) in Hypercholesterolemic Patients at High Risk of Coronary Heart Disease. Ez PATH Trial. Am J Cardiol 2008; 102:1495-501

34. Harold E. Bays Safety and Efficacy of Ezetimibe Added on to Rosuvastatin 5 or 10 mg Versus Up-Titration of Rosuvastatin in Patients with Hypercholesterolemia (the ACTE Study), Am J Cardiol 2011;108:523-30
35. Roeters van Lennep HW, Liem AH, Dunselman PH, Dallinga-Thie GM, Zwinderman AH, Jukema JW. The efficacy of statin monotherapy uptitration versus switching to ezetimibe/simvastatin: results of the EASEGO study. Curr Med Res Opin. 2008; 24:685-94
36. Dai YY, Zhang HS, Zhang XG, Guan QG, Gao Y, Li YZ, Zhang YL, Jia DL, Sun YX, Qi GX, Tian W. Statin-ezetimibe versus statin lipid-lowering therapy in patients with acute coronary syndromes undergoing percutaneous coronary intervention. J Thorac Dis. 2017; 9:1345-1352
37. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de Groot E; ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008; 358:1431-43.
38. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008; 359:1343-56.
39. Villines TC, Stanek EJ, Devine PJ, Turco M, Miller M, Weissman NJ, Griffen L, Taylor AJ. The ARBITER 6-HALTS Trial (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis): final results and the impact of medication adherence, dose, and treatment duration J Am Coll Cardiol. 2010; 55:2721-6.
40. Hibi K, Sonoda S, Kawasaki M, Otsuji Y, Murohara T, Ishii H, Sato K, Koshida R, Ozaki Y, Sata M, Morino Y, Miyamoto T, Amano T, Morita S, Kozuma K, Kimura K, Fujiwara H. Effects of Ezetimibe-Statin Combination Therapy on Coronary Atherosclerosis in Acute Coronary Syndrome. Circ J 2018; 82:757-766
41. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, et al. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: The multicenter randomized controlled PRECISE-IVUS Trial. J Am Coll Cardiol 2015;66: 495-507
42. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al., 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 randomized placebo-controlled trial. Lancet. 2011; 377:2181-92
43. Kato ET, Cannon CP, Blazing MA, Bohula E, Guneri S, White JA, Murphy SA, Park JG, Braunwald E, Giugliano RP. Efficacy and Safety of Adding Ezetimibe to Statin Therapy Among Women and Men: Insight From IMPROVE-IT (Improved Reduction of

Outcomes: Vytorin Efficacy International Trial). J Am Heart Assoc. 2017:18;6.

44. Filippatos TD, Florentin M, Georgoula M, Elisaf MS. Pharmacological management of diabetic dyslipidemia. Expert Rev Clin Pharmacol. 2017; 10:187-200.
45. Hibi K, Sonoda S, Kawasaki M, Otsuji Y, Murohara T, Ishii H, Sato K, Koshida R, Ozaki Y, Sata M, Morino Y, Miyamoto T, Amano T, Morita S, Kozuma K, Kimura K, Fujiwara H; Effects of Ezetimibe-Statin Combination Therapy on Coronary Atherosclerosis in Acute Coronary Syndrome. Circ J. 2018:82:757-766
46. Russell M, Silverman A, Fleg JL, Lee ET, Mete M, Weir M, Wilson C, Yeh F, Howard BV, Howard WM. Achieving lipid targets in adults with type 2 diabetes: the Stop Atherosclerosis in Native Diabetics Study. J Clin Lipidol.2010 ;4:435-43
47. Fei Y, Guyatt GH, Alexander PE, El Dib R, Siemieniuk RAC, Vandvik PO, Nunnally ME, Gomaa H, Morgan RL, Agarwal A, Zhang Y, Bhatnagar N, Spencer FA. Addition of Ezetimibe to statins for patients at high cardiovascular risk: Systematic review of patient-important outcomes. J Eval Clin Pract. 2018; 24:222-231
48. Ferrières J, Dallongeville J, Rossignol M, Bénichou J, Caro JJ, Getsios D, Hernandez L, Abenhaim L, Grimaldi-Bensouda L. Model-observational bridging study on the effectiveness of ezetimibe on cardiovascular morbidity and mortality in France: A population-based study. J Clin Lipidol. 2016; 10:1379-1388
49. Lin Wu FL, Wang J, Ho W, Chou CH, Wu YJ, Choo DW, Wang YW, Chen PY, Chien KL, Lin ZF. 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

