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# Ezetimibe: New perspectives in lipid lowering treatment

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## Abstract

*Therapeutic goals for lipid lowering treatment in the prevention of ischemic heart disease are often not reached in clinical practice. Even the highest doses of statins do not guarantee good control of hypercholesterolemia in all patients. Therefore, new lipid lowering drugs are being investigated. One of them is ezetimibe — intestinal cholesterol absorption inhibitor. Treatment with ezetimibe results in significant reduction of total cholesterol and LDL cholesterol levels. It is hoped that concomitant treatment with ezetimibe and other lipid lowering drugs (particularly statins) will be more effective. In large randomized clinical trials, co-administration of ezetimibe with atorvastatin and simvastatin proved to be more effective in lowering cholesterol levels and reaching target therapeutic levels than treatment with statin alone. In addition, combined treatment with ezetimibe and simvastatin was more effective compared to treatment with today's most effectively used statin (rosuvastatin) alone. Reduction of statin dose, due to the combined treatment with ezetimibe, lowers the risk of adverse events. Results of the published studies suggest that ezetimibe is safe and when administered together with statin does not increase the risk of liver or muscle damage. Treatment with ezetimibe may be regarded as a new option in the management of patients who need lipid lowering treatment.* (Cardiol J 2007; 14: 232–237)

**Key words: lipid-lowering drugs, hypercholesterolemia, cardiovascular risk, prevention**

## Introduction

The role of dyslipidemia as a risk factor for cardiovascular disease is well documented. Despite the fact that the benefits of lowering cholesterol levels have been widely known for a long time, therapeutic goals in medical association recommendations concerning the prevention of ischemic heart disease are rarely met in clinical practice [1]. In some reports, it has been shown that only 49% of patients with coronary heart disease meet the criteria of LDL level below 3.5 mmol/L and only in 10% of patients LDL level is decreased below 2.6 mmol/L [1]. It is especially difficult to reach recommended targets in patients with initially very high cholesterol levels. Therefore, alternative modes of treatment are being investigated.

One of the possible options which attracted the attention of investigators is intervention on cholesterol absorption in the small intestine. Dietary cholesterol in the gastrointestinal tract (exogenous) as well as the cholesterol produced by the liver and excreted with bile and cholesterol derived from desquamating epithelial cells (endogenous) is emulsified and accumulated in micelle. It is transported by brush border in this form to enterocytes, where, after esterification, it is packed into chylomicrons [2]. The precise mechanism of cholesterol absorption is not known. Recently the NPC1L1 protein has been identified as a putative cholesterol transporter

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and site of action of the new lipid lowering drug, ezetimibe, in intestinal cells. Ezetimibe is the first drug of the 2-azetidinone group of drugs, which block NPC1L1 protein [3]. The structure of NPC1L1 protein is similar to the structure of NPC1 protein which plays an important role in intracellular cholesterol transport and which gene defect causes lipid storage disease Niemann-Pick type C. The NPC1L1 protein is also expressed in liver cells and probably plays a significant role in the development of diet-induced fatty liver [4].

It is estimated that ezetimibe lowers diet cholesterol absorption in the intestine by over 50% [5]. Ezetimibe-glucuronide is the pharmacologically active form of the drug with bioavailability of 80%, and maximal concentration of the drug is reached in 1–2 hours after administration. The estimated half-time of ezetimibe in the serum is 22 hours [6].

Pharmacological intervention in the process of cholesterol absorption appears to be an important and promising method to improve efficacy of lowering serum cholesterol [7]. Ezetimibe is especially effective when combined with cholesterol synthesis inhibitor-statins. Increased cholesterol synthesis in the liver resulting from cholesterol absorption inhibition in the intestine is prevented by statins. This strategy of simultaneous inhibition of absorption and synthesis of cholesterol seems to be very promising.

Ezetimibe is administered in a single dose of 10 mg *p.o.* in the evening or in the morning without regard to food. Age, sex or race of the patients do not affect ezetimibe efficacy. Ezetimibe does not affect absorption of fatty acids, triglycerides, fat-soluble vitamins or bile acids. Considering the frequent need to use multiple drugs on one patient, it is of note that ezetimibe does not influence the concentration of other drugs such as statins, fibrates, digoxin or warfarin. Gemfibrozil and fenofibrate increase ezetimibe concentration in the serum while resins increase its excretion. Therefore, resins and ezetimibe should be administered a few hours apart [6, 8].

In recent years, the efficacy of ezetimibe has been compared to placebo and other lipid lowering drugs.

## Monotherapy with ezetimibe *vs.* placebo

The results of randomized, multicentre studies comparing the efficacy of ezetimibe with placebo were very promising [9, 10]. Administration of 10 mg of ezetimibe once daily in patients with primary hypercholesterolemia resulted in lowering of LDL cholesterol by 18.2% ($p < 0.01$) and total cholesterol by approximately 12% ($p < 0.01$). Treatment with ezetimibe also resulted in significant reduction of non-HDL cholesterol, triglycerides and apolipoprotein B. The response to ezetimibe administration did not differ significantly between the studied groups. The drug was well tolerated, and its safety profile was similar to the placebo.

## Co-administration of ezetimibe and statin

Studies evaluating the efficacy of concomitant treatment with statin and ezetimibe have been conducted for a few years [11–16]. The recently published meta-analysis of 3 studies [17] which included 3,083 patients with primary hypercholesterolemia, showed that co-administration of ezetimibe and simvastatin compared to treatment with simvastatin alone resulted in greater reduction of LDL cholesterol levels. Twelve weeks of combined treatment with ezetimibe and simvastatin lowered LDL cholesterol by 50%, whereas monotherapy with statin resulted in a reduction of less than 40%. Administration of ezetimibe and simvastatin was associated with a significant increase of percentage of patients who met target LDL cholesterol levels: Nearly 50% more subjects reached treatment goals recommended by ATPIII (Adult Treatment Panel III [18]) — LDL cholesterol concentration < 2.6 mmol/l (79% *vs*. 42%). At the same time, combined treatment resulted in LDL cholesterol level < 1.8 mmol/l 6 times more often compared to treatment with statin alone (37% *vs*. 6%), and such treatment was associated with a significant reduction of non-HDL cholesterol, apolipoprotein B and triglycerides in both young and older patients. The results did not differ significantly between age groups; concomitant treatment with ezetimibe and simvastatin was more effective in both groups: patients > 65 years and < 65 years of age [16].

It has also been demonstrated in the studies that ezetimibe administered with statin significantly lowers LDL cholesterol concentration in patients with chronic renal failure who are also on dialysis. In the UK-HARP-II study (The Second United Kingdom Heart and Renal Protection), the addition of ezetimibe (10 mg) to simvastatin (20 mg) resulted in additional lowering of LDL levels by 21%. Ezetimibe was well tolerated in this group of patients, did not cause an increase in creatinine levels and did not affect absorption of fat-soluble vitamins. Therefore, ezetimibe might also be a valuable treatment in this group of patients [19].

The efficacy of ezetimibe was also evaluated in combination with atorvastatin and, as with simvastatin

combination therapy, was more effective when compared to monotherapy. In one of study which enrolled 450 subjects with LDL cholesterol levels > 2.6 mmol/L, ezetimibe and a placebo were added to the treatment despite administration of atorvastatin (10–20 mg daily). Incidence of reaching target levels of LDL cholesterol (< 2.6 mmol/L) were above 80% of patients in the ezetimibe group and only 20% of patients in the placebo group [20].

In the VYVA study (Vytorin vs Atorvastatin) [21], it was demonstrated that co-administration of ezetimibe with atorvastatin (atorvastatin doses of 10, 20, 40 and 80 mg) resulted in greater reduction of LDL cholesterol levels (47–59% depending on the dose of atorvastatin) compared to monotherapy with atorvastatin (36–53%). Similarly, triglyceride levels were significantly further reduced in the group treated with both ezetimibe and atorvastatin. The target level of LDL cholesterol (according to ATP III recommendations) was reached in more patients in the group treated with two drugs. In addition, co-administration of ezetimibe and simvastatin (20 mg), as compared to the treatment with atorvastatin (20 mg) in 435 patients with LDL cholesterol > 2.6 mmol/L (despite previous treatment with atorvastatin 10 mg), more often resulted in a reduction of LDL cholesterol levels. Moreover, LDL cholesterol concentrations < 2.6 mmol/l were more often observed in the group of patients treated with two drugs [22].

In a recent American study EASE (Ezetimibe Add-on Statin for Effectiveness) [23] which included 3,030 patients with hypercholesterolemia, it was found that adding ezetimibe (10 mg) to statin therapy resulted in additional reduction of LDL cholesterol levels by 25.8%. Statins used in this study were: atorvastatin (in 37.6% of studied subjects), simvastatin (29.4%), pravastatin (20.4%), lovastatin (6.9%) and fluvastatin (5.3%). Co-administration of ezetimibe and statin resulted in significantly more patients (71% in the group treated with two drugs *vs*. 20.6% in statin monotherapy group) reaching target LDL cholesterol levels after 6 weeks of treatment.

The results of meta-analysis of 14 studies comparing monotherapy with rosuvastatin (5, 10, 20 and 40 mg) with combination therapy — ezetimibe and simvastatin (10 mg/10 mg, 10 mg/40 mg, 10 mg/80 mg; ezetimibe and simvastatin doses, respectively) in patients with primary hypercholesterolemia [23] are also very interesting. Meta-analysis results suggest that therapy with ezetimibe added to simvastatin is more effective than monotherapy with rosuvastatin alone. Percentage reductions from baseline in LDL-cholesterol were 50.6% and 47.4% for ezetimibe/simvastatin 10 mg/10 mg and rosuvastatin 5 mg, respectively. Similar results were observed in patients treated with higher doses. In view of the above mentioned results, head-to-head studies comparing the efficacy of rosuvastatin (the most effective statin currently used) and combination therapy with ezetimibe and simvastatin are needed [24].

Currently, further studies are being performed to evaluate the efficacy of combination therapy — SHARP (Study of Heart and Renal Protection), SEAS (Simvastatin and Ezetimibe in Aortic Stenosis), ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) and IMPROVE IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) [25].

## Combination therapy with ezetimibe and fibrate

High incidence of mixed hyperlipidemia forced the investigators to evaluate the efficacy of combination therapy with ezetimibe and fibrate. Data on co-administration of ezetimibe and fibrate are scarce but promising. In one study, which included 626 patients with mixed hyperlipidemia [26], the efficacy of 10 mg ezetimibe, 160 mg fenofibrate and 10 mg ezetimibe co-administered with 160 mg of fibrate and placebo were evaluated. After 12 weeks of therapy, in the combination therapy group a significant reduction of triglyceride levels (44%) and an increase in HDL levels (by 19%) were observed. Co-administration of ezetimibe and fenofibrate resulted in greater reduction of LDL-cholesterol (by 20.4%), non-HDL cholesterol (by 30.4%) and apolipoprotein B levels compared to monotherapy with fenofibrate or ezetimibe.

## Effects of ezetimibe on endothelium

Lipid lowering therapy constitutes the basis of cardiovascular disease prevention, particularly in high-risk patients. The beneficial effects of treatment with statins on cardiovascular morbidity and mortality are well known. However, this is due not only to the lipid lowering effects of statins but also to their pleiotropic activity [27] — beneficial effect on endothelium, inflammation, oxidative stress and smooth muscle cells proliferation [28]. There is a need to evaluate whether or not ezetimibe has similar properties.

Balut et al. [29] performed an interesting study concerning the influence of treatment with various

lipid lowering drugs on endothelium function evaluated by measuring forearm blood flow in 14 male patients with metabolic syndrome. Endothelium-dependent vasodilatation and an increase in blood flow were better with combination therapy (ezetimibe 10 mg and atorvastatin 10 mg) *vs*. treatment with atorvastatin alone even at higher doses (40 mg).

On the other hand, Landmesser et al. [30] did not observe any significant pleiotropic effect of ezetimibe. In this study, 20 patients with chronic heart failure were treated with ezetimibe or simvastatin for four weeks. Endothelial function improved significantly only in the group treated with simvastatin. The authors observed that treatment with simvastatin increased the number of progenitor cells whereas ezetimibe had no such effect [29]. Similar results were observed in another study by Fichtlscherer et al. [31]. In four groups of patients with ischemic heart disease, four different methods of lipid lowering therapy were used: ezetimibe 10 mg, ezetimibe 10 mg and simvastatin 20 mg, and atorvastatin in increasing doses 10–40 mg and atorvastatin 40 mg. After four weeks, endothelial function was evaluated. Neither ezetimibe in monotherapy nor ezetimibe combined with 20 mg simvastatin were associated with an increase in forearm blood flow. This effect was only observed in two groups treated with statins. Therefore, it was suggested that adding ezetimibe to statin might abolish its pleiotropic activity [32]. Further studies to elucidate the possible influence of ezetimibe on endothelial function are needed.

## Effects of ezetimibe on C-reactive protein level

Significant association between C-reactive protein level (CRP) — inflammation marker and cardiovascular risk has been found in many studies [33]. CRP level can be reduced by statins, which is thought to be the mechanism of their pleiotropic activity. Ezetimibe, however, can have a similar effect. Sager et al. [34] investigated the effect of simvastatin and combination therapy with statin and ezetimibe on CRP concentration in over 1,000 patients. Adding ezetimibe to simvastatin resulted in a two-fold greater reduction in CRP concentration compared to treatment with simvastatin alone. Treatment with 10 mg ezetimibe and 80 mg simvastatin resulted in a 40% reduction in CRP level compared to a 20% reduction with 80 mg simvastatin alone. Similar observations were made by Feldman et al. [17] in the meta-analysis in which the efficacy of co-administration of ezetimibe and simvastatin with respect to CRP levels in different age groups was examined. As it has been found that monotherapy with ezetimibe does not lower CRP levels [35]; the mechanism of the synergistic effect of ezetimibe and simvastatin is not clear. Possibly ezetimibe increases its beneficial effect on CRP levels by increasing the lipid-lowering activity of statin. This issue will be the subject of future studies and publications.

## Side effects of ezetimibe

The high lipid lowering efficacy of ezetimibe in combination with statin raises question of its safety. In large studies, the safety profile of ezetimibe was good. It seems that ezetimibe in combination with statin does not increase the risk of muscle or liver damage. In some studies a slight increase in liver enzymes or creatine kinase was observed in 1–2% of studied subjects, and they returned to normal after drug was stopped [17, 36]. Side effects with statin (administered alone) occurred in 3–4% of patients [37]. Moreover, in the VYVA study, a long lasting increase in liver enzymes was observed significantly more often in the group treated with atorvastatin alone (doses 10, 20, 40, 80 mg) *vs*. group of patients treated with ezetimibe and simvastatin (10, 20, 40, 80 mg, respectively) [25]. Nevertheless, rare cases of serious liver damage during treatment with ezetimibe have been reported. Two types of side effects were observed: serious cholestatic hepatitis and acute immune hepatitis [36]. Three cases of myopathy were reported during treatment with ezetimibe (one of them in a patient treated with ezetimibe and atorvastatin) [38] and two during monotherapy with ezetimibe [39]. The underlying mechanism remains unknown.

## Summary

Ezetimibe appears to be a promising new lipid lowering drug. It has been found that lowering total cholesterol by 1% decreases all-cause mortality by 1.1% and coronary heart disease mortality by 1.5% [40]. Assuming that ezetimibe reduces total cholesterol concentration by around 12%, treatment with this drug could result in a 13% reduction in total mortality and 18% in coronary heart mortality. However, there is continuing debate about the overall clinical benefit of ezetimibe. In order to elucidate the role of ezetimibe in atherosclerosis prevention, further large studies evaluating its effect on cardiovascular risk are needed. In some countries, ezetimibe (10 mg) is already on the market.

In the US and a few European countries, a combination of ezetimibe (10 mg) and simvastatin (in 10, 20, 40 and 80 mg doses) is already registered. Last year ezetimibe was also registered in Poland.

It appears that combination therapy may be the treatment of choice in hyperlipidemia in patients not tolerating statins in high doses. The other group of patients who may benefit from ezetimibe treatment are those who do not respond to statins probably due to increased absorption of dietary cholesterol. In this group of patients, endogenous cholesterol synthesis (with HMG-CoA reductase) has less influence on its serum level [41]. It should be noted, however, that margarines which have been available in Poland for some years contain stanols — semi-synthetic phytosterols (steroids contained in plant products) derivatives [42]. Stanols also suppress cholesterol absorption in the intestine and reduce serum cholesterol levels by several percent. In contrast to ezetimibe, stanols make "dietary pharmacotherapy" possible as they can be added to food products. Nevertheless, treatment with ezetimibe opens new therapeutic options for patients who need lipid lowering therapy.

## References


1. Kawecka-Jaszcz K, Jankowski P, Pajak A. Determinants of appropriate lipid management in patients with ischaemic heart disease. Cracovian Program for Secondary Prevention of Ischaemic Heart Disease. Int J Cardiol, 2003; 91: 15–23.
2. Bays H. Ezetimibe. Expert Opin Investig Drugs, 2002; 11: 1587–604.
3. Altmann SW, Davis HR Jr., Zhu LJ et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science, 2004; 303: 1201–1204.
4. Yamagishi S, Nakamura K, Matsui T, Sato T, Takeuchi M. Inhibition of intestinal cholesterol absorption by ezetimibe is a novel therapeutic target for fatty liver. Med Hypotheses, 2006; 66: 844–846.
5. Sudhop T, Lutjohann D, Kodal A et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation, 2002; 106, 1943–1948.
6. Kosoglou T, Statkevich P, Johnson-Levonas AO, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet, 2005; 44: 467–494.
7. Pikto-Pietkiewicz W, Pasierski T. Ezetimibe — intestinal cholesterol absorption inhibitor. Kardiol Pol, 2006; 64: 1434–1441.
8. Lammert F, Wang DQ. New insights into the genetic regulation of intestinal cholesterol absorption. Gastroenterology, 2005; 129: 718–734.
9. Knopp RH, Dujovne CA, Le Beaut A, Lipka LJ, Suresh R, Veltri EP. Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia: a pooled analysis from two controlled phase III clinical studies. Int J Clin Pract, 2003; 57: 363–368.
10. Knopp RH, Gitter H, Truitt T et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J, 2003; 24: 729–741.
11. Gagne C, Bays HE, Weiss SR et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol, 2002; 90: 1084–1091.
12. Bays HE, Ose L, Fraser N et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther, 2004; 26: 1758–1773.
13. Davidson MH, McGarry T, Bettis R et al. Ezetimibe co-administered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol, 2002; 40: 2125–2134.
14. Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and safety of ezetimibe co-administered with simvastatin in patients with primary hypercholesterolemia: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc, 2004; 79: 620–629.
15. Farnier M, Volpe M, Massaad R, Davies MJ, Allen C. Effect of co-administering ezetimibe with on-going simvastatin treatment on LDL-C goal attainment in hypercholesterolemic patients with coronary heart disease. Int J Cardiol, 2005; 102: 327–332.
16. Dujovne CA, Ettinger MP, McNeer JF et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol, 2002; 90: 1092–1097.
17. Feldman T, Davidson M, Shah A et al. Comparison of the lipid-modifying efficacy and safety profiles of ezetimibe co-administered with simvastatin in older versus younger patients with primary hypercholesterolemia: a post hoc analysis of subpopulations from three pooled clinical trials. Clin Ther, 2006; 28: 849–859.
18. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA, 2001; 285: 2486–2497.
19. Landray M, Baigent C, Leaper C et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: a randomized controlled study of the biochemical safety and efficacy of adding

ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis, 2006; 47: 385–395.
20. Cruz-Fernandez JM, Bedarida GV, Adgey J, Allen C, Johnson-Levonas AO, Massaad R. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. Int J Clin Pract, 2005; 59: 619–627.
21. 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: 464–473.
22. Barrios V, Amabile N, Paganelli F et al. Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20 mg/day compared to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease. Int J Clin Pract, 2005; 59: 1377–1386.
23. Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc, 2005; 80: 587–595.
24. Catapano A, Brady WE, King TR, Palmisano J. Lipid altering-efficacy of ezetimibe co-administered with simvastatin compared with rosuvastatin: a meta-analysis of pooled data from 14 clinical trials. Curr Med Res Opin, 2005; 21: 1123–1130.
25. Vasudevan AR, Jones PH. Effective use of combination lipid therapy. Curr Atheroscler Rep, 2006; 8: 76–84.
26. Farnier M, Freeman MW, Macdonell G et al. Efficacy and safety of the co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. Eur Heart J, 2005; 26: 897–905.
27. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors. Arterioscler Thromb Vasc Biol, 2001; 21: 1712–1719.
28. Tsiara S, Elisaf M, Mikhailidis DP. Early vascular benefits of statin therapy. Curr Med Res Opin, 2003; 19: 540–556.
29. Bulut D, Hanefeld C, Bulut-Streich N, Graf C, Mugge A, Spiecker M. Endothelial function in the forearm circulation of patients with the metabolic syndrome — effect of different lipid-lowering regimens. Cardiology, 2005; 104: 176–180.
30. Landmesser U, Bahlmann F, Mueller M et al. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. Circulation, 2005; 111: 2356–2363.
31. Fichtlscherer S, Schmidt-Lucke C, Bojunga S et al. Differential effects of short-term lipid lowering with ezetimibe and statins on endothelial function in patients with CAD: clinical evidence for «pleiotropic» functions of statin therapy. Eur Heart J, 2006; 27: 1182–1190.
32. Kłosiewicz-Latoszek L. Skuteczne skojarzone leczenie hipolipemizujące — komentarz do artykułu. Kardiologia po Dyplomie, 2006; 5: 35–36.
33. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med, 2000; 342: 836–843.
34. Sager PT, Capece R, Lipka L et al. Effects of ezetimibe co-administered with simvastatin on C-reactive protein in a large cohort of hypercholesterolemic patients. Atherosclerosis, 2005; 179: 361–367.
35. Ridker PM, Rifai N, Clearfield M et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. N Engl J Med, 2001; 344: 1959–1965.
36. Stolk MF, Becx MC, Kuypers KC, Seldenrijk CA. Severe hepatic side effects of ezetimibe. Clin Gastroenterol Hepatol, 2006; 4: 908–911.
37. Newman CB, Palmer G, Silbershatz H, Szarek M. Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients. Am J Cardiol, 2003; 92: 670–6.
38. Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Can J Cardiol, 2006; 22: 141–144.
39. Havranek JM, Wolfsen AR, Warnke GA, Phillips PS. Monotherapy with ezetimibe causing myopathy. Am J Med, 2006; 119: 285–6.
40. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation, 1998; 97: 946–952.
41. Thompson GR. Poor responders to statins: A potential target for stanol esters. Eur Heart J, 1999; 1 (suppl. S): S114–S117.
42. Jankowski P, Bilo G, Kawecka-Jaszcz K, Bryniarski L, Bryniarska-Mirek E, Pająk A. Stanole — nowa perspektywa w leczeniu hipercholesterolemii? Przegl Lek, 2000; 57: 655–658.