Introduction

The role of hypercholesterolemia as a risk factor for cardiovascular (CV) disease has been well-documented. Hypercholesterolemia is the most prevalent modifiable risk factor in Poland. Despite the fact that the benefits of cholesterol lowering have been known for a long time, the therapeutic goals recommended by guidelines are still often not attained in clinical practice. Only 3% of Poles with hypercholesterolemia achieve recommended cholesterol levels, and the rate of reaching recommended goals among patients receiving lipid-lowering drugs is low, approximately 30%. Control of hypercholesterolemia is not satisfactory also in patients with ischemic heart disease. The introduction of new statins, use of higher statin doses, and the evidence pointing to the effectiveness of combination therapy have provided us with effective tools whose broad application in everyday practice may lead to a significant improvement in the control of hypercholesterolemia in Poland.

KEY WORDS
cardiovascular risk, cholesterol, lipid-lowering drugs, statins

ABSTRACT

The role of hypercholesterolemia as a risk factor for cardiovascular disease has been well-documented. Hypercholesterolemia is the most prevalent modifiable risk factor in Poland. Despite the fact that the benefits of cholesterol lowering have been known for a long time, the therapeutic goals recommended by guidelines are still often not attained in clinical practice. Only 3% of Poles with hypercholesterolemia achieve recommended cholesterol levels, and the rate of reaching recommended goals among patients receiving lipid-lowering drugs is low, approximately 30%. Control of hypercholesterolemia is not satisfactory also in patients with ischemic heart disease. The introduction of new statins, use of higher statin doses, and the evidence pointing to the effectiveness of combination therapy have provided us with effective tools whose broad application in everyday practice may lead to a significant improvement in the control of hypercholesterolemia in Poland.

According to the 2007 guidelines of the European Society of Cardiology (ESC) on CV disease prevention, low-risk patients should maintain total cholesterol levels below 5.0 mmol/l (190 mg/dl) and low-density lipoprotein (LDL) cholesterol below 3.0 mmol/l (115 mg/dl). In patients with ischemic heart disease or peripheral artery disease, in those with a history of stroke or transient ischemic attack, as well as in diabetics and other high-risk patients (risk of CV death within 10 years: >5%), the recommended cholesterol levels are lower: total cholesterol <4.5 mmol/l (175 mg/dl) or even <4.0 mmol/l (155 mg/dl), if feasible; LDL cholesterol <2.5 mmol/l (100 mg/dl) or <2.0 mmol/l (80 mg/dl), if feasible. Some experts recommend that the level of high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and triglycerides should be considered as a secondary therapeutic goal. Nevertheless, the ESC experts recommend that HDL cholesterol and triglyceride levels should be regarded only as indices of CV risk: HDL cholesterol <1.0 mmol/l (40 mg/dl) in men and 1.2 mmol/l (45 mg/dl) in women and triglycerides >1.7 mmol/l (150 mg/dl) suggest increased risk of CV events. It should be noted, however, that the relation between blood lipid levels and CV risk is continuous; therefore, any thresholds for increased risk of developing CV disease is always artificial. Although non-HDL
Lipid-lowering drugs and control of hypercholesterolemia...

Of all lipid-lowering drugs, statins have the most compelling evidence for their beneficial effects. They are the most potent lipid-lowering drugs, especially when LDL cholesterol level is considered. The inhibition of cholesterol synthesis in hepatocytes results in greater expression of LDL receptors and, consequently, in the removal of LDL molecules from the blood. Recent studies and analyses have provided additional data regarding the efficacy of these drugs.

The JUPITER study (Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin), completed in 2008, significantly contributed to the scientific evidence on the effectiveness of statins. The study evaluated the effect of rosuvastatin on the incidence of CV events in 17,802 healthy patients (men >50 years and women >60 years of age, without a previous history of CV disease) with normal or only slightly elevated LDL cholesterol (<3.4 mmol/l) but with increased C-reactive protein (CRP) level (≥2 mg/l). When planning the design of the JUPITER trial, it was decided that it would be terminated after the occurrence of 520 CV events (CV death, myocardial infarction, stroke, myocardial revascularization, hospitalization due to unstable angina). The study was stopped prematurely after a total of 393 endpoints occurred (142 in the rosuvastatin group and 251 in the placebo group), i.e., 76% of the number of the initially planned CV events. The study was terminated because otherwise the placebo patients would be exposed to an increased risk of CV events.

In the JUPITER study, the use of rosuvastatin reduced the risk of the primary endpoint (CV death, myocardial infarction, stroke, myocardial revascularization, hospitalization due to unstable angina) by 44% with a simultaneous 50% reduction in LDL cholesterol and 37% reduction in CRP levels. Moreover, the use of rosuvastatin was related to a significantly lower incidence of thrombotic/embolic events. Some experts maintain that the results of the JUPITER study provide another evidence for a pleiotropic effect of statins. However, in July 2010, an analysis was published in the American Journal of Cardiology which claimed that the effect of rosuvastatin on CV risk was independent of the initial CRP level. In other words, it could not be proven that the effectiveness of rosuvastatin in reducing CV risk increases with increasing baseline CRP levels. Furthermore, some analyses of the JUPITER study indicated that in the group of patients with only slightly elevated CRP levels (mean: 3.2 mg/l), the efficacy of rosuvastatin was slightly higher than in patients with significantly elevated CRP levels (mean: 5.4 mg/l; P < 0.0001; Figure 3).

It seems that the results of the JUPITER study provide strong argument for those who believe that the primary factor responsible for extending life expectancy in patients treated with statins is the lowering of LDL levels. However, this interpretation contradicts the results of the CORONA study (Controlled Rosuvastatin Multinational Trial in Heart Failure), which showed a beneficial effect of rosuvastatin on the prognosis of patients with ischemic heart failure and CRP greater than 2.0 mg/l, while this beneficial effect was not observed in patients with CRP less than 2.0 mg/l.

Elucidation of this issue would definitively require a study including patients with normal cholesterol and CRP levels. Other pleiotropic effects of statins, such as increased fibrin clot permeability, may contribute to the clinical benefits of statins.

The SEARCH trial (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) included 12,064 post-myocardial infarction subjects with hypercholesterolemia. Treatment with simvastatin (80 mg/day)
did not produce any benefit compared with low dose of simvastatin (20 mg/day). In November 2010, the results of a meta-analysis of 26 trials (170,000 participants), including the SEARCH study, were published. The meta-analysis demonstrated that the reduction of LDL cholesterol level by 1 mmol/l using a statin reduced the risk of death due to coronary heart disease by 20%, due to CV causes by 14%, and due to any causes by 10%. No significant correlation was found between baseline cholesterol levels and the efficacy of statins. A similar relation between cholesterol reduction and decreased risk of CV events was observed in studies comparing statin therapy with placebo and in those comparing varying doses of statins. These results confirm the earlier recommendations regarding the benefits of intensive reduction of cholesterol level and, at the same time, provide another evidence for the benefit of using strong statins in large doses.

It is interesting to compare the registration indications for rosuvastatin in the United States and in Europe. In accordance with the decision of the Food and Drug Administration, indications for rosuvastatin include treatment of hypercholesterolemia and mixed dyslipidemia, slowing the progression of atherosclerosis, prevention of myocardial infarction, stroke, and the need for coronary revascularization in men over 50 and women over 60 years of age who do not suffer from coronary disease, have CRP levels above 2 mg/L, and at least 1 risk factor (hypertension, smoking, low HDL cholesterol, positive family history of premature heart disease). In Europe, indications include primary hypercholesterolemia and prevention of major CV events in patients at a high risk for the primary occurrence of such events. It seems that the European experts, in accordance with the evidence from the JUPITER study, recognized that CRP levels do not affect the efficacy of statins, including rosuvastatin. The European authorities took into consideration both the opinions of experts and the current guidelines of the European medical societies regarding the prevention of CV disease. Following these recommendations, pharmacotherapy with proven preventive efficacy should be used for primary prevention in patients at high CV risk (risk calculated using the SCORE system: risk of CV death ≥5% during 10 years). However, it should be noted that CV risk (calculated using the SCORE or Framingham system) has never been shown to significantly affect relative risk reduction in subjects on rosuvastatin. On the other hand, the absolute risk reduction in patients on statins is proportional to the overall CV risk.

The results of the COSMOS study (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) are quite interesting. The study compared the effect of rosuvastatin treatment on the progression of coronary atherosclerosis in Asian patients with stable coronary disease. After 76 weeks of treatment, intracoronary ultrasound revealed a reduction in the volume of atherosclerotic plaque. The ASTEROID study (Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden), conducted in North America, Europe and Australia, provided similar results. Because it is believed that one of the principle mechanisms that accounts for the beneficial effects of statins is the inhibition of the development and progression of arteriosclerotic plaques, the results of the ASTEROID and COSMOS studies suggest that rosuvastatin can also be an effective drug for patients with symptomatic atherosclerosis.

The results of the PLANET I and PLANET II studies were published in 2010. These studies compared the effects of rosuvastatin (10 mg/day and 40 mg/day) and atorvastatin (80 mg/day) on albuminuria in patients with LDL cholesterol levels above 2.3 mmol/l, high albuminuria, and diabetes (PLANET I), and with albuminuria but without diabetes (PLANET II). In both studies, atorvastatin was associated with the reduction in albuminuria, while this effect was not demonstrated in the groups treated with rosuvastatin. Rosuvastatin, especially at a dose of 40 mg/day, was associated with a slightly faster decrease of the glomerular filtration rate compared with atorvastatin. On the other hand, one of the analyses of the JUPITER study database showed that rosuvastatin decreased CV risk in subjects with moderate chronic renal disease to a similar extent as in patients with the glomerular filtration rate equal to or exceeding 60 ml/min/1.73 m² (45% vs. 43%, P = nonsignificant). It should be noted that the prognostic value of changes in albuminuria in response to statins is unclear. It has also been shown that not achieving the recommended cholesterol levels is associated with a significantly worse prognosis. Thus, when initiating lipid-lowering therapy in patients with albuminuria, the choice of a specific statin should be based on a careful analysis of the potential risks and benefits. Based on the results of the PLANET studies, it can be concluded that rosuvastatin should not be the statin of choice for people with significant albuminuria. It seems that the statin of choice for this group may be atorvastatin. As reviewed recently by Piecha et al., statins should be prescribed to patients with chronic kidney disease.

Statins were shown to significantly improve prognosis in elderly subjects with coronary artery disease. The JUPITER study showed that rosuvastatin (20 mg/day) decreased CV risk in patients aged 70 years or older without overt CV disease but with elevated CRP levels. The absolute risk reduction was greater in this group than in younger patients (<70 years). Although statins reduce CV risk in subjects after ischemic stroke (including reduction in recurrent strokes and coronary events), they were not shown to affect overall mortality. It was also shown that lipid-lowering therapy did not improve prognosis in patients with heart failure.
A comparison of various statin doses in relation to the expected reduction of LDL cholesterol levels is shown in the Table.22 Only a dose of 80 mg/day atorvastatin and a dose of 20 mg/day rosuvastatin reduce LDL cholesterol levels by more than 50%, and only with a dose of 40 mg/day rosuvastatin a 55% reduction can be expected.

Another issue is the safety of statins. There are no large studies comparing, for example, the risk of developing myopathy after using comparable doses of various statins. Nevertheless, one might expect that hydrophilic statins (such as rosuvastatin or fluvastatin) are less likely to cause myopathy. This is one of the reasons why the use of fluvastatin or rosuvastatin is recommended in patients at a high risk for developing myopathy.23 In 2010, a meta-analysis was published which assessed the risk of cancer in patients treated with statins.11 The results demonstrated unequivocally that the use of statins is not associated with an increased risk of developing cancer.11 Recently published studies have indicated that the use of statins may be related to a higher frequency of diabetes (by about 9%).24 Some experts believe that “postdrug” diabetes may affect the patient’s prognosis to a lower extent than “classic” diabetes. It should be stressed that the benefits of statins are much greater than the potential risk related to higher incidence of diabetes; therefore, the fear that statins may have detrimental effect on glucose metabolism should not be the reason for not prescribing statin therapy. It should also be remembered that such side effects of statins as myopathy symptoms may decrease the quality of life. Although the clinical consequences of the inhibitory effect of statins on coenzyme Q₁₀ synthesis is not clear, it should be underlined that rosuvastatin preserves its level, unlike atorvastatin.25

Ezetimibe Instead of administering large doses of potent statins to obtain target LDL cholesterol levels, a selective inhibitor, ezetimibe, can be added to statin treatment. It has been demonstrated that the transport protein, NPC1L1, is the critical factor in intestinal cholesterol absorption and the target of ezetimibe’s action.24 It is estimated that ezetimibe reduces the intestinal absorption of cholesterol by almost 50%27 and serum cholesterol levels by about 18%.26 Moreover, ezetimibe significantly reduces the levels of triglycerides and apolipoprotein B. A recently published study has indicated that the use of ezetimibe may cause detrimental changes in the size of LDL molecules, which might counteract the benefits from cholesterol reduction.28

Ezetimibe is particularly effective in combination with statins because the inhibition of cholesterol synthesis in the liver by statins causes an increase in cholesterol absorption in the intestines. An analysis of 3 studies including a total of 3083 patients with primary hypercholesterolemia showed that combination of ezetimibe and simvastatin significantly reduced LDL cholesterol levels compared with the use of simvastatin alone.29 Combination therapy reduced LDL cholesterol levels by more than 50%, while monotherapy by less than 40%. It was shown that the lipid-lowering effect of ezetimibe (10 mg/day) combined with simvastatin (40 mg/day) did not differ from that of atorvastatin (40 mg/day).30 Ezetimibe may be combined with any statin, and its strong, synergistic, hypolipidemic effect in combination with statins makes it possible to successfully reduce LDL cholesterol levels using lower doses of statins. This is especially beneficial in patients who do not tolerate higher doses, who have suffered adverse effects of statins, and in whom the use of the maximum tolerable statin dose still does not help to achieve the recommended LDL cholesterol level. The INFORCE study showed that target cholesterol levels were achieved more frequently when ezetimibe was added to simvastatin than when the dose of statin was doubled.31 The use of a combined preparation (simvastatin and ezetimibe in 1 tablet) is especially practical. Ezetimibe is well tolerated and its safety profile is similar to placebo.

Recently, the results of the SHARP study (Study of Heart and Renal Protection) were reported.32 The study included 9438 patients with chronic renal insufficiency (patients on dialysis or patients with creatinine level above 1.7 mg/dl for men and 1.5 mg/dl for women).32 In this study group, simvastatin therapy (20 mg/day) combined with ezetimibe (10 mg/day) was associated with a reduction in LDL levels by approximately 30%. It also reduced the risk of a primary endpoint by about 17%. In the previously published SEAS study (Simvastatin and Ezetimibe in Aortic Stenosis), a 22% decrease in the occurrence of ischemic CV events was achieved using combination therapy consisting of simvastatin (40 mg/day) and ezetimibe (10 mg/day).33 However, because the control groups were not treated with statins, it is not known to what degree

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the effect observed in both studies resulted from statin or ezetimibe use. The safety of the combination therapy should be underlined: the risk of myopathy, hepatocytotoxic damage, cholecystitis, pancreatitis, and neoplasms was similar to placebo.32

The high frequency of mixed hyperlipidemia led researchers to study the effectiveness of ezetimibe combined with a fibrate. A study conducted by Farnier et al.34 compared the efficacy of a 10 mg dose of ezetimibe, a 160 mg dose of fenofibrate, a 10 mg dose of ezetimibe combined with 160 mg of fenofibrate, and placebo. After 12 weeks of therapy, a significant reduction (44%) of triglyceride levels and elevation (19%) in HDL cholesterol levels were observed in the combination therapy group. The important finding was that the combination of ezetimibe and fenofibrate resulted in a greater reduction of LDL cholesterol (20.4%), non-HDL cholesterol (30.4%), and apolipoprotein B level than the treatment with fenofibrate or ezetimibe alone.34

Fibrates Fibrates are a group of lipid-lowering drugs used both for primary and secondary prevention of CV disease. These drugs are known to effectively reduce triglyceride levels and increase HDL cholesterol levels. Therefore, fibrates are used to treat patients with hypertriglyceridemia and mixed hyperlipidemia as well as patients with low HDL cholesterol levels. However, fibrates are not the drugs of choice in the treatment of hyperlipidemia, especially in patients with ischemic heart disease, after stroke, or those with diabetes. This approach was confirmed by the results of meta-analysis of 18 studies, which was published in 2010 and included a total of 45,058 patients.35 The results suggest that although fibrates moderately reduce the risk of serious CV events (by 10%) and coronary events (13%), they do not affect the risk of stroke, CV death, or all-cause death. The observed increase in the risk of death from non-CV causes (by 10%, P = 0.06) is somewhat worrisome.35

One of the goals of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial was to test the effectiveness of combining fenofibrate with statin in patients with type 2 diabetes.36 The study group (5518 subjects) was followed up for almost 5 years. Addition of fibrate to statin therapy did not produce any significant effect on the risk of serious CV events (the analysis of the subgroups revealed a beneficial effect of fenofibrate in subjects with low HDL cholesterol levels and increased triglyceride levels, but also a trend to a detrimental effect on the progression in women – the interaction with sex was significant).36 It should be noted that even high dose of a statin does not reduce CV risk completely (the CV risk in patients prescribed a statin is called residual risk). It was suggested that residual risk could be reduced using a fibrate if HDL levels were low and/or triglyceride levels were high despite statin treatment. It should be remembered, however, that residual risk is also the effect of coexistence of other risk factors such as smoking, hypertension, diabetes, and others. Although fibrates reduce fasting as well as postprandial triglyceride levels more effectively than statins,37 experts from the European medical societies recommend that triglyceride levels should not be regarded as a target of lipid-lowering therapy and should only be used in a thorough assessment of CV risk. Very recently, the European Medicines Agency’s Committee for Medicinal Products for Human Use has advised to avoid fibrates as first-line drugs. It was shown that HDL cholesterol levels may have no prognostic value in patients treated with potent statins.38

Nicotinic acid Nicotinic acid (niacin) and its analogues inhibit adipose tissue lipolysis, reduce LDL cholesterol and triglyceride levels, and increase HDL cholesterol levels. This drug is usually used in combination with a statin if the cholesterol level achieved when treated with statin alone is unsatisfactory. Despite its efficacy, a major drawback of nicotinic acid is the fact that it often causes adverse effects such as face and neck flushes, heat waves, hypotonia and palpitations, although a pharmaceutical preparation consisting of nicotinic acid and laropiprant (a selective prostaglandin D2 receptor antagonist) is available in some countries.39 In a study published in 2009, patients with HDL cholesterol levels below 40 mg/dl, diabetes, and ischemic heart disease or atherosclerosis of the carotid and/or peripheral arteries were treated with a statin combined with a 2 g modified-release nicotinic acid. After 12 months of treatment, the group receiving nicotinic acid had HDL cholesterol levels elevated by 23% and LDL cholesterol levels decreased by 19%. Moreover, the study results suggested inhibition of atherosclerotic progression.40 Another study, also published in 2009, compared the effects of niacin and ezetimibe on the carotid intima–media thickness (IMT) in patients treated with a statin.41 Niacin, but not ezetimibe, had a beneficial effect on IMT. Very similar results were observed in the prematurely interrupted ARBITER 6-HALTS study (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis).42

Triple-drug therapy In some cases, it is not possible to obtain target lipid levels even despite prescribing the maximum dose of a strong statin or combined therapy consisting of 2 lipid-lowering drugs. In such cases, a good solution may be to apply a triple-drug therapy consisting of a statin, ezetimibe, and a fibrate or a statin, ezetimibe, and niacin. The effectiveness and safety of triple-drug hypolipidemic therapy was evaluated in a double-blind study which included 611 patients with mixed hyperlipidemia.33 A reduction of LDL cholesterol levels by 46%, non-HDL cholesterol by 51%, triglycerides by 50% and an increase of apolipoprotein A, by 11% were achieved.
The experiment showed that the addition of fenofibrate to the combination of ezetimibe and simvastatin therapy did not produce any further reduction in LDL cholesterol but caused an elevation of HDL cholesterol and a reduction of triglycerides. Fenofibrate (both when used alone and in combination with a statin and ezetimibe) reduced the fraction of atherogenic “small dense” LDL particles. Similarly, the addition of niacin to simvastatin and ezetimibe had a relatively minor effect on LDL cholesterol but significantly increased HDL cholesterol levels and reduced triglyceride levels. However, it should be underlined that polytherapy may have negative aspects including increased risk of drug interactions and reduced patients’ compliance.

Summary
Currently, treatment of dyslipidemia is one of the main methods of CV prevention. There is a substantial body of evidence pointing to the benefit of cholesterol reduction (especially with statins). Many studies have shown that achieving recommended blood lipid values reduces the risk of CV events. Despite a significant improvement in the control of hypercholesterolemia compared with the late 20th century, there are still too many people with high cholesterol levels in Poland. The introduction of the most potent statin (rosuvastatin) and the evidence pointing to the effectiveness of combination therapy of dyslipidemia has provided us with effective tools, whose wide application in everyday practice may lead to a significant improvement in the control of hypercholesterolemia in Poland. Presently, we do not have any evidence to support a thesis that clinical efficacy (measured by reduced risk of CV events) of combined therapy is better than that of a high statin dose. It should also be underlined that lifestyle modification is always fundamental to treating dyslipidemia. It often allows to avoid pharmacotherapy altogether or at least to avoid higher doses of a lipid-lowering drug.

REFERENCES


ARTYKUŁ POGŁĄDOWY

Leki hipolipemizujące i kontrola hipercholesterolemii w Polsce – wyniki najnowszych badań

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STRESZCZENIE

Rola hipercholesterolemii jako czynnika ryzyka sercowo-naczyniowego jest dobrze udokumentowana. Hipercholesterolemia jest najbardziej rozpowszechnionym modyfikowalnym czynnikiem ryzyka w Polsce. Mimo że korzyści wynikające z obniżania stężenia cholesterolu są znane od dawna, cele terapeutyczne zalecane przez towarzystwa naukowe nadal często nie są osiągane w praktyce klinicznej. Jedynie 3% Polaków z hipercholesterolemią osiąga zalecane stężenie cholesterolu, a częstość osiągania zalecanych celów wśród osób leczonych lekami hipolipemizującymi mała – wynosi około 30%. Również wśród osób z chorobą niedokrwieniową serca kontrola hipercholesterolemii nie jest zadowalająca. Obecnie, dzięki wprowadzaniu na polski rynek coraz silniejszych statyn i stosowaniu coraz większych dawek oraz dzięki dowodom na skuteczność leczenia skojarzonego, dysponujemy efektywnymi narzędziami, których szerokie zastosowanie w codziennej praktyce prawdopodobnie pozwoli na istotną poprawę sytuacji epidemiologicznej w zakresie kontroli hipercholesterolemii w Polsce.

SŁOWA KLUCZOWE

cholesterol, leki hipolipemizujące, ryzyko sercowo-naczyniowe, statyny
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Zamówienia: tel. 0800 888 000, http://ksiegarnia.mp.pl