Abstract
The indications for the prescription of statins have broadened over the years. Initial studies supported the use of statins in secondary prevention for cardiovascular disease, or as primary prevention only when the risk of cardiovascular disease was significantly raised. Currently, based on clinical trials, statins also play an important role in myocardial infarction, stroke and peripheral arterial disease. There are still some questions regarding the use of statins in hypertension, heart failure and atrial fibrillation.

Statins improve the postoperative condition and prognosis and decrease the risk of postoperative complications in patients subjected to surgical coronary revascularization. However, there are still a few aspects that need to be explained, especially the role of statins in patients undergoing surgical revascularization and concomitant valve surgery, or valve surgery alone. There is still little knowledge regarding application of statins in patients with heart failure subjected to surgical revascularization.

Key words: complications, prognosis, risk stratification, statins, surgical revascularization.

Introduction
Cardiovascular disease (CVD) is the principal cause of mortality in developed countries; for example in Poland over 50% of all deaths are the result of CVD, outnumbering deaths from neoplasms. The Framingham Heart Study showed that elevated serum cholesterol is an important risk factor for CVD, and low levels of LDL (low-density lipoprotein) cholesterol inhibit the progress of atherosclerosis [1, 2].

Statins are the most effective drugs in the decrease of LDL cholesterol. However, the beneficial effects of statins cannot be solely explained by cholesterol lowering. Many available trials with statins, beginning with 4S (Scandinavian Simvastatin Survival Study) in 1994, suggest that statins exert useful pleiotropic effects [3, 4].

Statins lower cholesterol by inhibiting HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase, the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Inhibition of this enzyme in the liver stimulates LDL receptors, resulting in increased clearance of LDL cholesterol.
Statins in patients subjected to surgical revascularization

ACS, either as a primary or secondary diagnosis, is responsible for more than 1.5 million hospitalizations each year in the United States [12]. Following an ACS, the risk of adverse cardiovascular events is highest in the first 6 months and slowly diminishes over time. There is an almost linear relationship between LDL-cholesterol level and CHD event rate after ACS. Statins, with their pleiotropic effects, including the reduction of systemic inflammation, improvement of endothelial dysfunction and stabilization of atherosclerotic plaque, play a significant role in patients with ACS and should be administered immediately after diagnosis of ACS. ACS is a pan-coronary process with multiple vulnerable or ruptured plaques in addition to the ruptured lesion that caused the ACS. While angioplasty and stenting treatment of a culprit lesion are very effective, potent systemic therapy is also required to passivate other vulnerable sites. Statins, by virtue of their multiple mechanisms of action, especially at very high doses, have become established for management of ACS [13, 14].

As long as the role of statins in ACS is significant and very effective, there are still some questions regarding the application of statins in patients subjected to surgical coronary revascularization (CABG, coronary artery bypass grafting). We should remember that there is a percentage of people with ACS that cannot be treated with PTCA (percutaneous transluminal coronary angioplasty), and they are qualified for urgent or scheduled surgery. However, surgery for patients with cardiogenic shock are associated with very high mortality; thus it is much more favourable (if possible) to perform a planned surgery after intensive pharmacological treatment, when markers of myocardial damage (troponin) are in the range of standard values. According to available knowledge the use of statins in patients subjected to surgical revascularization is useful, because statin application decreases the inflammation associated with advanced coronary disease and the extracorporeal circulation [15, 16].

Cardiac surgery, especially with the application of cardiopulmonary bypass (CPB), significantly intensifies the inflammation process, and in consequence may lead to endothelial dysfunction and destabilization of the atherosclerotic plaque [17]. Many studies have confirmed these observations. Nakamura et al. compared the effects of atorvastatin plus aspirin versus aspirin monotherapy on inflammatory responses, endothelial cell function and the coagulation system in patients undergoing CABG. Reduced total cholesterol in the combined therapy group was seen after short term medication for 14 days. On postoperative day (POD) 14, inhibitory effects of the combined therapy on whole blood aggregation as well as platelet activation assessed by flow cytometry were stronger than those after monotherapy. Furthermore, cytokine, cytokine receptors, C-reactive protein (CRP) and alpha1-acid glycoprotein in the combined therapy group were down-regulated, while E-selectin and transforming growth factor-beta1 were up-regulated. The authors concluded that combined therapy with atorvastatin and aspirin might exert beneficial effects on inflammatory responses, platelet activity, vascular endothelial cell function and the coagulation system in patients subjected to CABG [18].

Surgical revascularizations also increase levels of cardiac troponin, a highly sensitive and specific indicator of myocardial cell death. Available studies suggest that preoperative application of statins may significantly reduce the levels of troponin, and from the bloodstream and a decrease in blood cholesterol levels. The first results can be seen after 1 week of use and the effect is maximal after 4 to 6 weeks. Statins, the most potent cholesterol-lowering agents available, lower LDL cholesterol by as much as 30–50% [5].

The indications for the prescription of statins have broadened over the years. Initial studies, such as the 4S study [6], supported the use of statins in secondary prevention for cardiovascular disease, or as primary prevention only when the risk of cardiovascular disease was significantly raised (as indicated by the Framingham Risk Score) [7]. Indications were broadened by trials such as the Heart Protection Study (HPS) (with simvastatin), which showed preventive effects of statin use in patients with diabetes, and the SPARCL study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) which showed that in patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day significantly reduced the overall incidence of strokes and cardiovascular events [8, 9]. Based on clinical trials, the National Cholesterol Education Program guidelines, and the increasing focus on aggressively lowering LDL cholesterol, the statins continue to play an important role in both the primary and secondary prevention of coronary heart disease (CHD), myocardial infarction (MI), stroke and peripheral arterial disease. There are still some questions regarding the use of statins in hypertension, heart failure and atrial fibrillation, but ongoing trials should answer all doubts. Research continues also into other, non-cardiovascular areas, where statins appear to have a favourable effect: inflammation, dementia, cancer (especially of the colon), nuclear cataracts and pulmonary hypertension [10, 11].
essentially improve the postoperative haemodynamic function of the heart [19].

The first studies regarding the effective role of statins in patients who underwent surgical coronary revascularization were published in the 1990s, and initially concerned the effect of statins in the reduction of graft vessel disease (GVD) in patients after heart transplantation [20, 21].

As early as 1994 Barbir et al. observed that combined hypolipaemic treatment with colestipol and simvastatin or colestipol and bezafibrate were effective and well tolerated in the management of moderate hyperlipidaemia in patients who had undergone CABG [22]. However, the critical study on this subject was the Post Coronary Artery Bypass Graft Trial (Post-CABG), where the authors studied whether aggressive lowering of LDL cholesterol levels or low-dose anticoagulation would delay the progression of atherosclerosis in grafts. They included 1351 patients who had undergone CABG surgery 1 to 11 years before and who had LDL cholesterol levels between 130 and 175 mg/dl and at least 1 patent vein graft as seen on angiography. They used a two-by-two factorial design to assign patients to aggressive or moderate treatment to lower LDL cholesterol levels (with lovastatin and, if needed, cholestyramine) and to treatment with warfarin or placebo. As measured annually during the study period, the mean LDL cholesterol level of patients with aggressive treatment ranged from 93 to 97 mg/dl; with moderate treatment, the range was from 132 to 136 mg/dl (p<0.001). The mean percentage of grafts with progression of atherosclerosis was 27% for patients whose LDL cholesterol level was lowered with aggressive treatment, and 39% for those who received moderate treatment (p<0.001). The rate of revascularization over 4 years was 29% lower in the group whose LDL cholesterol level was decreased aggressively than in the group receiving moderate treatment (6.5% vs. 9.2%, respectively, p=0.03). The authors concluded that the aggressive lowering of LDL cholesterol levels to below 100 mg/dl significantly reduced the progression of atherosclerosis in grafts [23].

In the secondary analysis of the Post-CABG trial, White et al. tested the hypothesis that a similar decrease in progression of atherosclerosis would also be present in native coronary arteries as measured in the left main coronary artery (LMCA). They included a sample of 402 patients, who had baseline and follow-up views of the LMCA suitable for analysis. Patients treated with the aggressive lipid-lowering strategy (with lovastatin in doses from 40 to 80 mg) had significantly less progression of atherosclerosis in the LMCA as measured by changes in minimum lumen diameter or the maximum percent stenosis, or the presence of substantial progression, or vascular occlusion when compared with the moderate strategy. They showed that a strategy of aggressive lipid lowering results in significantly less atherosclerosis progression than a moderate approach in LMCA, and suggested that such intensive treatment should be prescribed in high-risk patients subjected to CABG [24].

In another study the authors evaluated the effects of pravastatin on the progression of atherosclerosis in the grafts and native coronary arteries in patients after CABG. They included 303 patients who were randomly assigned to either pravastatin or placebo. Paired coronary angiograms were obtained at baseline and after a 5-year follow-up. The LDL cholesterol concentration significantly decreased in the pravastatin group from 141.4 mg/dl to 113.7 mg/dl (−19.6%), compared with 141.1 mg/dl to 133.7 mg/dl (−5.2%) in the control group. On the basis of coronary angiography measurements they also showed that the global change score indicated a significant pravastatin-mediated reduction in plaque progression. The authors concluded that pravastatin could potentially reduce atherosclerotic progression in both the bypass graft and native coronary arteries of patients after CABG [25].

In the post-hoc analysis of the CARE trial (Cholesterol and Recurrent Events), the authors confirmed the role of statins in reducing the risk of postoperative complications. Flaker et al. assessed whether revascularized patients derive significant benefit from hypolipaemic treatment with pravastatin. A total of 2245 patients underwent coronary revascularization before randomization including 1154 patients with PTCA alone, 876 patients with CABG alone, and 215 patients with hybrid procedures. The primary endpoint of CHD death or nonfatal MI was reduced by 4.1% (36% reduction, p=0.001), fatal or nonfatal MI was reduced by 3.3%, post-randomization repeat revascularization by 2.6% and stroke by 1.5% in the pravastatin group. The authors observed that pravastatin was beneficial in both the PTCA and the CABG patients who had undergone revascularization before randomization. They concluded that pravastatin significantly reduced clinical events in revascularized post-MI patients with average cholesterol levels, and such treatment should be indicated in these patients [26].

In a similar study, Pan et al. investigated the influence of preoperative statin therapy on adverse outcomes after primary CABG. Patients were classified into 2 groups: patients receiving preoperative statin therapy and not receiving preoperative anti-hyperlipidaemic treatment. Multivariate logistic regression analysis showed that preoperative statin therapy was independently associated with a significant reduction (approximately 50%) in the risk of 30-day all-cause mortality (3.75 vs. 1.80%; p<0.05); however, it was not independently associated with a reduced risk of postoperative MI, cardiac arrhythmias, stroke or renal dysfunction. In an attempt to further control for selection bias related to the choice of therapy, multivariate analysis of a propensity-matched
A cohort of 1362 patients revealed that preoperative statin therapy was independently associated with a significant reduction in the composite endpoint of 30-day all-cause mortality and stroke (7.1 vs. 4.6%; p<0.05). The authors concluded that preoperative statin therapy may reduce the risk of early mortality after primary CABG surgery with CPB, and confirmed the need for application of statins in patients subjected to cardiac surgery [27].

Similarly, outcomes were obtained in the Multicenter Study of Perioperative Ischemia (MCSP) Epidemiology II Study, where the authors tried to determine whether preoperative statin therapy is associated with a reduced risk of early cardiac death or nonfatal, in-hospital postoperative MI after primary, elective CABG surgery requiring CPB. The study consisted of a pre-specified subset of all subjects divided into patients receiving (n=1352) and not receiving (n=1314) preoperative statin therapy. To control for potential bias related to use of statin therapy, the study estimated propensity scores by logistic regression to determine the predicted probability of inclusion in the “statin” group. Multivariate, stepwise logistic regression was performed, controlling for patient demographics, medical history, operative characteristics and propensity score to determine whether preoperative statin therapy was independently associated with a reduction in the risk of early cardiac death and/or nonfatal, in-hospital postoperative MI. They showed that preoperative statin therapy was independently associated with a significant reduction in the risk of early cardiac death after primary, elective CABG surgery, but not associated with a reduced risk of postoperative nonfatal, in-hospital MI. Discontinuation of statin therapy after surgery was independently associated with a significant increase in late all-cause mortality compared with continuation of statin therapy (2.64 vs. 0.60%; p<0.01) and associated with a significant increase in late cardiac mortality (1.91 vs. 0.45%; p<0.01) [16]. Similar results were also obtained in another study [28] where in a subsample of patients undergoing valve-only surgery, preoperative treatment with statins did not result in a significant reduction in 30-day morbidity and mortality.

**Statins and reduction in postoperative complications**

**Thrombocytosis**

Besides the influence on postoperative mortality, statins may be highly effective in the reduction of risk of major postoperative complications in patients subjected to surgical revascularization. One study [31] evaluated whether preoperative therapy with simvastatin reduced the risk of postoperative thrombocytosis, a potential marker of worse prognosis [32]. They included 77 patients with symptomatic CHD and hypercholesterolaemia, planned for CABG, who where randomly assigned to undergo CABG without preoperative hypolipaemic treatment or with simvastatin therapy (20 mg daily). They showed that postoperative thrombocytosis (platelet count ≥400 000/microl) occurred significantly more frequently in the group without active treatment (81%) compared with 3% in the group receiving simvastatin. MI after the 7th postoperative day and transient renal failure were more often diagnosed in the control group (respectively 14 vs. 0% and 24 vs. 8%; p<0.05) compared with the simvastatin group. For the first time the authors showed that lipid control with simvastatin prior to CABG reduced the risk of postoperative thrombocytosis, thus lowering the risk of thrombotic complications [31].

**Stroke**

Aboyans et al. aimed to determine factors predicting the occurrence of stroke during CABG with...
a special interest focused on preoperative therapies. They prospectively enrolled 810 consecutive patients subjected to CABG. During the first postoperative month, stroke occurred in 11 cases and transient ischaemic attack (TIA) in 4 additional cases (cumulative rate: 1.85%). After multivariate analysis, the following factors remained significant in the predictive model: redo cardiac surgery (7.45), unstable cardiac status (4.74), past history of cerebrovascular disease (4.14), and past history of peripheral arterial disease (3.55), whereas the presence of preoperative statins was protective. The authors confirmed that preoperative treatment with statins might significantly decrease the risk of stroke in patients subjected to cardiac surgery [33].

Atrial fibrillation

Atrial fibrillation (AF) is one of the most common complications following cardiac surgery [34]. According to various authors, it occurs with a frequency of 20 to 60%, depending on the definition and diagnostic method [35]. AF usually appears between 2 and 4 days after surgery, and often returns during the first 30 days of the postoperative period. According to the current ACC/AHA/ESC guidelines (2006) we usually diagnose first detected or paroxysmal AF. Recently AF has been noted more often, which is probably connected with the fact that more patients are subjected to surgery in advanced age and worse cardiac condition. More postoperative arrhythmias are also connected with the broadening of the group of patients undergoing open-heart operations, as a result of reduction in contraindications. Suitable treatment and prevention of postoperative AF is important for improved health, faster rehabilitation and the reduction of hospitalization costs [36, 37].

Recently many authors have focused on the selection of predictors of postoperative AF and have tried to explain the pathogenesis of postoperative arrhythmias. Inflammation, as a response to hypoxia during surgery, ischaemia-reperfusion injury after cardiac surgery, or as a result of use of extracorporeal circulation, is the most popular hypothesis of postoperative AF [38]. For that reason many authors suggested that preoperative use of statins, due to their anti-inflammatory characteristics, might decrease the risk of postoperative AF [39].

An important study on this subject was the ARMYDA-3 study (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery). The authors included 200 patients undergoing elective cardiac surgery with CPB, without previous statin treatment or history of AF. Patients were randomized to atorvastatin (40 mg daily) or placebo starting 7 days before operation. The primary end point was incidence of postoperative AF; secondary end points were length of stay, 30-day major adverse cardiac and cerebrovascular events, and postoperative CRP variations. They showed that atorvastatin significantly reduced the incidence of AF versus placebo (35 vs. 57%, p=0.003). Accordingly, length of stay was longer in the placebo versus atorvastatin arm (6.9±1.4 vs. 6.3±1.2 days, p=0.001). Peak CRP levels were significantly lower in patients without AF, irrespective of randomization assignment. Multivariable analysis showed that atorvastatin treatment conferred a 61% reduction in risk of AF, whereas high postoperative CRP levels were associated with increased risk. The authors concluded that preoperative treatment with atorvastatin at a dose of 40 mg daily significantly reduced the incidence of postoperative AF after elective cardiac surgery with CPB and shortened the hospital stay. What is more, these results might influence practice patterns with regard to adjuvant pharmacological therapy before cardiac surgery [40].

These results were also confirmed, among others, in the study by Mariscalco et al., where the authors assessed the efficacy of preoperative statins in prevention of AF in patients after CABG. 405 consecutive patients who underwent isolated CABG procedures were included in the study. Postoperative AF occurred in 29.5% of the patients with preoperative statin therapy compared with 40.9% patients without such treatment (p=0.021). They observed that preoperative statins were associated with a 42% reduction in risk of AF development after CABG surgery. This study confirmed the result of the ARMYDA-3 study, and showed that preoperative statins could significantly reduce postoperative AF after CABG [41].

Renal failure

Postoperative renal failure is still a very important problem in patients undergoing cardiac surgery. It is especially important when the kidney disease co-exists in patients who qualify for open-heart surgical treatment, because an operation with extracorporeal circulation is a burden for the kidneys and there is a huge risk of intensifying existing failure [42]. Therefore, many authors tried to decrease the risk of postoperative renal failure. Statins seem to be a method of treatment which might really improve the postoperative kidney condition [43].

In the study by Tabata et al., the authors evaluated the renoprotective effect of statins in patients subjected to CABG. Two propensity score-matched cohorts each of 641 patients (statin and non-statin groups) were constructed. In a matched analysis, the statin group had a significantly (p=0.01) lower incidence of new renal insufficiency than the non-statin group. Multivariate logistic regression analysis including all patients showed that preoperative statin use was significantly associated with a low incidence of new postoperative renal insufficiency. The authors concluded that preoperative statin use might be renoprotective after CABG. However, further studies
should be performed in order to confirm these results [44].

Conclusions

Statins seem to improve postoperative outcome and decrease the risk of postoperative complications, such as MI, stroke, renal failure and AF in patients subjected to isolated coronary surgical revascularization. However, some aspects still need to be explained, especially the role of statins in patients undergoing CABG and concomitant valve surgery, or valve surgery alone. In our opinion, and based on the recently published CORONA trial (COnrolled ROSuvastatin multiNAtional trial in heart failure) we still do not know what is the role of statins in patients with heart failure, and there is still a lack of statin studies on patients with heart failure subjected to surgical coronary revascularization [45-47].

References