

The role of statins in patients after heart transplantation

Bożena Szyguła-Jurkiewicz¹, Wioletta Szczurek², Marian Zembala³

¹3rd Chair and Department of Cardiology, Medical University of Silesia in Katowice, School of Medicine with the Division of Dentistry in Zabrze, Silesian Center for Heart Diseases, Poland

²Student Research Club, Poland

³Department of Cardiac Surgery and Transplantation, Medical University of Silesia in Katowice, School of Medicine with the Division of Dentistry in Zabrze, Silesian Center for Heart Diseases, Poland



Kardiologia i Torakochirurgia Polska 2015; 12 (1): 42-47

Abstract

Numerous studies have shown that statin therapy initiated early after heart transplantation improves the short- and long-term prognosis, leading to a reduction in the incidence of cardiac allograft vasculopathy (CAV), acute rejection episodes and significantly lowers the incidence of cancer in this patient population. The molecular mechanisms responsible for the beneficial effects of statins in patients after heart transplantation are complex; the effectiveness of statins is associated not only with their hypolipemic action, but also with their pleiotropic properties. Statins have been shown to exert protective and therapeutic effects against cancer because they act as antiproliferative agents, promoting apoptosis and inhibiting angiogenesis. Moreover, they reduce the number of circulating monocytes, which inhibits the secretion of proinflammatory cytokines, growth factors, adhesion molecules, chemokines, and matrix metalloproteinases, preventing chronic rejection and CAV. For these reasons, statins should be used as part of standard therapy in patients after heart transplantation.

Key words: statins, heart transplantation.

Streszczenie

Liczne badania wykazały, że leczenie statynami rozpoczęte we wczesnym okresie po transplantacji serca poprawia rokowanie wczesne i odległe, prowadzi do zmniejszenia częstości występowania waskulopatii przeszczepionego serca, epizodów odrzucania przeszczepionego narządu oraz znamienne rzadszego rozwoju nowotworów w tej populacji pacjentów. Molekularne mechanizmy odpowiedzialne za korzystne działanie statyn u pacjentów po transplantacji serca są złożone: poza działaniem hipolipemicznym skuteczność statyn związana jest z ich właściwościami pleiotropowymi. Wykazano, że statyny mają działanie protekcyjne i terapeutyczne w odniesieniu do nowotworów, ponieważ działają antyproliferacyjnie, proapoptotycznie i hamują angiogenezę. Ponadto leki te zmniejszają liczbę krążących monocytów, przez co hamują wydzielanie cytokin prozapalnych, czynników wzrostowych, cząstek adhezyjnych, hemokin i metaloprotein macierzy pozakomórkowej i w konsekwencji przyczyniają się do hamowania procesu przewlekłego odrzucania oraz powstawania waskulopatii przeszczepionego serca. Z wymienionych powodów statyny powinny być stosowane jako element standardowej terapii u chorych po transplantacji serca.

Słowa kluczowe: statyny, transplantacja serca.

Introduction

Heart transplantation is a recognized and effective form of treatment for patients with end-stage cardiac insufficiency. Within the last several years, significant improvements have been made in transplantology – anesthesiological and surgical techniques have been perfected, state-of-the-art technology has been employed to store the organs, new immunosuppressive and antiviral agents have been developed, and changes have been introduced to the methodology of monitoring the concentrations of immunosuppressants. All these factors have facilitated the gradual prolongation of post-transplant survival.

Episodes of acute rejection and viral infections are considered to be among the significant causes of heart transplant failures in short-term follow-up. In turn, the long-term complications include chronic transplant rejection, malignant tumors, dyslipidemia, cardiac allograft vasculopathy (CAV), and renal failure [1-3]. The immunosuppressive therapy employed after heart transplantation is indispensable for preventing episodes of acute and chronic rejection; notwithstanding, it is associated with the occurrence of numerous adverse effects [2, 3]. There are many factors which impact the long-term survival of heart transplant patients; among them, the co-occurrence of additional cardiovascu-

Address for correspondence: Assoc. Prof. Bożena Szyguła-Jurkiewicz, 3rd Chair and Department of Cardiology, Medical University of Silesia in Katowice, School of Medicine with the Division of Dentistry in Zabrze, Silesian Center for Heart Diseases, 9 Curie-Skłodowskiej St., 41-800 Zabrze, Poland, phone: +48 60410299, e-mail: centrala4@wp.pl

lar risk factors and the proper selection of pharmacotherapy are considered particularly important [4, 5].

Numerous studies have demonstrated that statin treatment introduced early after heart transplantation improves both short- and long-term prognosis, reduces the prevalence of CAV and transplant rejection, and significantly lowers the prevalence of tumors in this patient population (Table I). Molecular mechanisms responsible for the beneficial effect of statins in heart transplant recipients have not yet been fully understood; however, it is known that the effectiveness of statins is associated not only with their hypolipemic action, but also with their pleiotropic properties. In this regard, it is especially noteworthy that their action is antineoplastic and immunomodulatory; it regulates endothelial activity and inhibits the development of CAV [5-8].

Hypolipidemic properties of statins

Dyslipidemia occurs in 60-80% of heart transplant recipients and is associated with the development of CAV. It is believed that its occurrence may be caused by genetic predispositions, infections, concomitant diseases such as diabetes or chronic kidney disease, obesity, heart failure of ischemic etiology, preoperative dyslipidemia, and the use of steroids and immunosuppressants [3, 9, 10].

Statins, whose mechanism of action is based on the competitive inhibition of HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase, play a significant role in the pre-

vention and inhibition of post-transplant dyslipidemia progression [11]. A prospective randomized study conducted by Zakliczyński *et al.* demonstrated that 66% of heart transplant recipients have abnormal lipid profiles; this primarily pertains to elderly patients as well as patients with heart failure of ischemic etiology, obesity, arterial hypertension, and diabetes [4]. Magnani *et al.* analyzed the efficacy and safety of statin use in heart transplant recipients [12]. The patients included in their study were randomized into groups receiving atorvastatin or pravastatin. The study demonstrated a significantly more pronounced reduction of total cholesterol concentration, LDL fraction, and triglycerides in patients treated with atorvastatin as compared with the group receiving pravastatin [12]. In turn, the research conducted by Samman *et al.* indicates the effectiveness of rosuvastatin use in heart transplant recipients in whom previous therapy with other statins did not result in desired effects with regard to regulating their lipid economy [11]. One of the theories explaining the differences in statin action points to their different chemical structure, which determines their hydrophilic or lipophilic nature [13]. Heart transplant recipients often face the development of drug-resistant dyslipidemia; thus, the hypolipemic action of statins may be insufficient. In such cases, therapy employing ezetimibe combined with small doses of HMG-CoA reductase inhibitors may prove effective [14]. An observational study conducted by Quart *et al.* corroborates the efficacy and safety of combined treatment using simvastatin

Tab. I. Major studies assessing the efficacy and safety of statin use in heart transplant recipients

Author	Statin	Results and observations
Stojanovic <i>et al.</i> , 2005 [1]	Pravastatin	Pravastatin significantly reduces the frequency of graft rejection episodes, inhibits CAV development, and improves 5-year survival.
Fröhlich <i>et al.</i> , 2012 [5]	Simvastatin, fluvastatin, atorvastatin, pravastatin	The observed risk of cancer in the group treated with statins was lower than in the control group (13% vs. 34%). Statins improve overall survival.
Mahle <i>et al.</i> , 2005 [6]	Pravastatin	Pravastatin lowers cholesterol concentration and significantly reduces the risk of CAV development.
Moro <i>et al.</i> , 2007 [9]	Atorvastatin, pravastatin, simvastatin	Adding ezetimibe to statins in the treatment of dyslipidemia significantly reduces the levels of TC and LDL.
Samman <i>et al.</i> , 2005 (11)	Rosuvastatin	Rosuvastatin effectively reduces the levels of LDL, TC, and TG. No significant adverse effects were observed.
Magnani <i>et al.</i> , 2000 [12]	Atorvastatin, pravastatin	Higher efficacy of atorvastatin in reducing TC, LDL, and TG in comparison to pravastatin. Safety and tolerance of both agents were comparable.
Fildes <i>et al.</i> , 2008 [31]	Pravastatin, atorvastatin	Statins reduce the concentration of monocytes in circulation, which are engaged in the mechanism of graft rejection.
Wenke <i>et al.</i> , 2005 [36]	Simvastatin	Chronic simvastatin use after a transplant significantly reduces CAV incidence and improves prognosis.
Kobashigawa <i>et al.</i> , 1995 [37]	Pravastatin	Introducing pravastatin early after a transplant reduces the frequency of acute rejection, inhibits CAV development, and improves survival in 1-year follow-up.
Grigioni <i>et al.</i> , 2006 [39]	Atorvastatin, pravastatin, simvastatin	Statin therapy reduces the risk of CAV development and improves the survival of heart transplant recipients. The observed adverse effects included several cases of rhabdomyolysis, myositis, and increased levels of aminotransferases. Possible interactions of statins with ketoconazole.
Rodríguez <i>et al.</i> , 1999 [42]	Simvastatin, pravastatin	Combining statins with ciclosporin is associated with an increased risk of adverse effects.

TG – triglycerides, TC – total cholesterol, LDL – low density lipoproteins, CAV – cardiac allograft vasculopathy

and ezetimibe, the mechanism of which is based on inhibiting the absorption of cholesterol in the intestines [15]. Due to the different, but complementary mechanisms of these agents' action, combined therapy enables the achievement of better results than monotherapy, especially in patients in whom statin use does not enable the achievement of target lipid values [9]. Considering dose-dependent adverse effects of statins and the prevalence of dyslipidemia refractory to treatment among heart transplant recipients, introducing ezetimibe in monotherapy or in combination with statin should improve prognosis in this group of patients [14-16].

Antineoplastic properties

Neoplasms constitute one of the leading causes of mortality in the long-term follow-up of heart transplant recipients. Their etiology has four potential causes: genetic, environmental, and immunological factors, as well as viral infections. These factors may cause the activation of carcinogenic mechanisms, including damage of strategic DNA fragments, so-called proto-oncogenes, or tumor suppressor genes, changes in the regulation of cell growth, resistance to apoptosis, and sustained angiogenesis. The most important factors influencing the development of tumors in heart transplant recipients are the accumulated effect of immunosuppression (length of use and treatment intensity) and the coexistence of chronic viral infection. Immunosuppressive agents can damage deoxyribonucleic acid, causing neoplastic cell transformation and impairing normal immune mechanisms, which leads to uncontrolled growth and division of tumor cells. In turn, viruses cause neoplastic transformation of cells when they acquire cellular proto-oncogenes into their genome, integrate their genome with that of the host in the vicinity of proto-oncogenes, or encode viral oncogenes [2].

Much evidence has been gathered for the protective and therapeutic action of statins with regard to various neoplasms. This effect is dependent both on their hypolipemic and pleiotropic action. Statins inhibit cholesterol synthesis, primarily in hepatocytes, but also through the mevalonate pathway. By reducing the concentration of cholesterol in circulation, they reduce cholesterol concentration in many types of cells, including neoplastic cells, influencing the microdomains of cellular membranes and steroidogenesis. Furthermore, they inhibit the activity of cholesterol-dependent pathways in neoplastic tumors by influencing their microenvironment. The cholesterol-dependent effects of statin action have been confirmed by epidemiological studies, which demonstrated a positive correlation between hypercholesterolemia and the risk of aggressive prostate tumor development [17, 18]. In turn, *in vitro* studies have demonstrated the antiproliferative, proapoptotic, and antiangiogenic action of statins [19-21]. It has been determined that statins reduce the expression of the antiapoptotic Bcl2 protein and increase the expression of the proapoptotic Bax protein [22], thus intensifying the apoptotic effects of chemotherapeutic agents. Another

protective effect of statins consists in the inhibition of the mevalonate pathway, which, in addition to its participation in cholesterol synthesis, plays a key role in the formation of isoprenoid precursors, necessary for the synthesis of Ras oncogenes. Ras oncogenes encode G proteins, which are responsible for the transmission of cellular information as well as for cellular proliferation, differentiation, and transformation. The inhibitory effect of statins on the mevalonate pathway reduces the concentrations of farnesyl diphosphate, geranylgeranyl diphosphate (GGDP), and dolichol, which are engaged in the post-translational modification of various proteins [23-25]. By inhibiting GGDP production, statins may reduce cell migration and exert an antiproliferative effect. *In vitro* studies on cerivastatin have demonstrated a dose-dependent reduction of the nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) and RhoA, resulting in smaller concentrations of matrix metalloproteinase and urokinase, which play a key role in cell migration [26] and reduce the metastatic potential of neoplastic cells. Fröhlich *et al.* demonstrated that the administration of statins after heart transplantation lowered the risk of tumor development and reduced overall mortality in this group of patients. Significantly, the obtained results were not dependent on the initial level of cholesterol, which indicates statin action that is different from and independent of its hypolipemic effects [5]. What is relevant is statin's influence on the activity of matrix metalloproteinases and the level of cell adhesion molecules such as ICAM-1 and VCAM-1 [27]. The use of HMG-CoA reductase inhibitors results in a lower expression of cell adhesion molecules, which makes it more difficult for neoplastic cells to adhere to blood vessel walls, thus blocking the possibility of metastasis to other organs [8]. It has also been observed that statins inhibit blood vessel proliferation within the tumor, thus reducing the supply of substances required for neoplastic cell growth and, thereby, limiting further tumor growth [28]. Numerous studies demonstrate that the use of statins in heart transplant recipients reduces the risk of large intestine, ovarian, pancreatic, and breast tumors, as well as skin tumors, which are otherwise commonly observed in heart transplant recipients [2, 28]. As a result, the prevalence of all-cause mortality in this patient population is lower [29].

Immunomodulatory properties

Statins influence many components of the immune system. One of the possible immunomodulatory mechanisms of this group of agents is the reduction in the expression of major histocompatibility complex (MHC) class II, which is constitutively present on macrophages, B lymphocytes, and dendritic cells, resulting in a weakened capacity for antigen presentation to T lymphocytes [7]. HMG-CoA reductase inhibitors may also inhibit the expression of MHC II on the surface of endothelial cells stimulated by IFN- γ [30]. The observed reduced activity of this system contributes to the lowering of graft rejection prevalence in patients treated with statins [7, 30]. It has also been demonstrated that

administering statins to heart transplant recipients lowers the circulatory concentration of monocytes, which are engaged in the mechanisms of graft rejection. Lowering the expression of these multi-functional cells of the immune system is associated with inhibiting the secretion of many substances, such as proinflammatory cytokines, growth and adhesion factors, chemokines, and matrix metalloproteinases, contributing to the inhibition of the chronic rejection process [31]. The results of studies conducted to date suggest that statins have a regulatory impact on the mechanisms of humoral and cellular response [1, 7, 32]. It appears that these agents can also be employed as immunomodulators in all those conditions which stem from the abnormal expression of MHC class II molecules [7].

Inhibiting the development of cardiac allograft vasculopathy

Despite advances in immunosuppressive treatment, CAV is one of the leading causes of death in heart transplant recipients who have survived the first year after the transplant, along with graft insufficiency and cancer [33]. CAV pathogenesis has not yet been fully elucidated; nonetheless, CAV is considered to be a multifactorial condition, in which the key role is played by the mechanisms of congenital and acquired immune response as well as by non-immune mechanisms, which may modify the response of the immune system to the transplanted organ. Endothelial dysfunction, hyperlipidemia, as well as the increased expression of adhesion molecules, proinflammatory cytokines, and the recently discovered toll-like receptors contribute to the development of diffuse vasculopathic changes in the transplanted organ, which may lead to graft dysfunction [32, 34]. A high concentration of total cholesterol concomitant with a low HDL concentration or the isolated occurrence of one of the listed factors increase the risk of CAV development in the population of heart transplant recipients [4]. An important role in the described process is also played by other factors, including HLA mismatch between the donor and the recipient, immunosuppressive agents, and cytomegalovirus infection [1]. It is also important to note the significant difference between atherosclerosis developing for years in native coronary vessels, which pertains to all layers of proximal epicardial artery segments, and changes within the coronary vessels of a transplanted heart, which develop very rapidly, in a diffuse and concentric manner, and without calcifications, involving the internal layer of both arteries and veins in their medial and distal segments [35]. Thus, the options of interventional treatment are limited in the case of cardiac allograft vasculopathy. The management strategy for heart transplant recipients should, therefore, aim to prevent and treat the factors which favor CAV occurrence.

Prophylaxis based on inhibiting the excessive activity of endothelial vessels is of particular importance. It has been established that simvastatin and pravastatin inhibit CAV development by reducing cholesterol concentrations, exerting a favorable influence on the endothelium (in-

dependent of their hypolipidemic action) and exhibiting direct anti-inflammatory activity [1, 36-38]. The results of an analysis performed by Mahle *et al.* confirm the favorable role of statins in children after heart transplantation. The authors of the mentioned study demonstrated that the use of pravastatin was associated with a significant reduction in cholesterol concentration and CAV prevalence [6]. A study conducted by Grigioni *et al.* also confirmed the efficacy of statins in preventing the development of cardiac allograft vasculopathy in transplanted hearts [39]. It should be underscored that the impairments in myocardial perfusion caused by CAV contribute significantly to graft failure [25]. Based on retrospective observations, Stojanovic *et al.* reached the conclusion that the use of pravastatin in heart transplant recipients improves survival, lowers the risk of CAV, and reduces the prevalence of hemodynamically significant episodes of graft rejection in 5-year follow-up [1]. Wenke *et al.* demonstrated significantly better prognosis in heart transplant recipients treated with statins over the period of 11 years of follow-up [36]. For the enumerated reasons, statins should be employed as an element of standard therapy in heart transplant recipients [32, 39].

Adverse effects of statins

The most frequent adverse effects of statins consist in their influence on skeletal muscles and liver function. Statins may cause myopathy, myositis, or rhabdomyolysis, which may, in turn, result in acute kidney injury [11, 39, 40].

Toxic liver disease may also develop, expressed by increased transaminase activity in serum [41]. Other potential adverse effects include autoimmune conditions, dysrhythmias, conduction disorders, as well as gastrointestinal and urinary tract dysfunctions of various intensity [42]. Susceptibility to the occurrence of adverse effects is the highest among patients treated with large doses of statins, elderly patients, as well as individuals receiving medication metabolized by cytochrome P450 3A4 (CYP3A4), which is also responsible for the metabolism of some statins [11, 13].

Interactions with other agents

Using statins concurrently with enzymatic CYP3A4 inhibitors (cyclosporin, macrolide antibiotics, azole antifungal agents, calcium channel blockers, fibrates, niacin, acetaminophen) leads to an increased risk of toxic liver disease and myopathy. Also noteworthy are the interactions between statins and agents acting as CYP3A4 inducers (rifampicin, phenytoin, phenobarbital, dexamethasone); they accelerate the metabolism of statins and reduce their effectiveness [43]. Adverse effects resulting from drug interactions are more often encountered in the case of lipophilic statins (simvastatin, lovastatin, atorvastatin) metabolized primarily by CYP3A4 than in the case of hydrophilic statins (fluvastatin, pravastatin, rosuvastatin) using other metabolic pathways [39]. The most frequent adverse effects resulting from interactions between immunosuppressants and statins pertained to cyclosporin. Studies indicate that concurrent statin and cyclosporin treatment is associated with

an increase in the risk of myositis and rhabdomyolysis due to the inhibitory effect of ciclosporin on the system of the P450 cytochrome [44]. There are also cases of statin-treated patients in whom the introduction of antifungal ketoconazole therapy was associated with the occurrence of rhabdomyolysis [41]. It has been suggested that ciclosporin and gemfibrozil may increase the concentration of all statins through mechanisms independent of the P450 cytochrome. For this reason, statin interactions with these agents should warrant special attention. In order to minimize the risk of serious side effects, monitoring the levels of aminotransferases and creatine kinase is recommended [39].

Conclusions

In view of the presented studies, it appears that statins should be an integral part of standard therapy after heart transplantation (Table I). The clinical benefits of statin use after heart transplantation significantly exceed the risk of potential adverse effects, as demonstrated by numerous studies. Notwithstanding, when introducing statins into the treatment regimen, one should consider the possible drug interactions, especially in patients undergoing long-term therapy with many agents. It is also of fundamental importance to properly select the type and dose of statins in order to reduce the risk of adverse effects and increase the effectiveness and safety of the conducted treatment.

Disclosure

Authors report no conflict of interest.

References

- Stojanovic I, Vrtovec B, Radovancevic B, Radovancevic R, Yazdanbakhsh AP, Thomas CD, Frazier OH. Survival, graft atherosclerosis, and rejection incidence in heart transplant recipients treated with statins: 5-year follow-up. *J Heart Lung Transplant* 2005; 24: 1235-1238.
- Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. *Transplantation* 2005; 80: S254-264.
- Marzoa-Rivas R, Crespo-Leiro MG, Paniagua-Marin MJ, Llinares-García D, Muñiz-García J, Aldama-López G, Piñón-Esteban P, Campo-Pérez R, Castro-Beiras A. Safety of statins when response is carefully monitored: a study of 336 heart recipients. *Transplant Proc* 2005; 37: 4071-4073.
- Zakliczynski M, Boguslawska J, Wojniak E, Zakliczynska H, Ciesla D, Nozynski J, Szygula-Jurkiewicz B, Zeglen S, Zembala M. In the era of the universal use of statins dyslipidemia's are still common in heart transplant recipients: a cross-sectional study. *Transplant Proc* 2011; 43: 3071-3073.
- Fröhlich GM, Rufibach K, Enseleit F, Wolfrum M, von Babo M, Frank M, Berli R, Hermann M, Holzmeister J, Wilhelm M, Falk V, Noll G, Lüscher TF, Ruschitzka F. Statins and the risk of cancer after heart transplantation. *Circulation* 2012; 126: 440-447.
- Mahle WT, Vincent RN, Berg AM, Kanter KR. Pravastatin therapy is associated with reduction in coronary allograft vasculopathy in pediatric heart transplantation. *J Heart Lung Transplant* 2005; 24: 63-66.
- Mach F. Statins as immunomodulatory agents. *Circulation* 2004; 109: III5-17.
- Kobashigawa JA. Statins in solid organ transplantation: Is there an immunosuppressive effect? *Am J Transplant* 2004; 4: 1013-1018.
- Moro J, Almenar L, Martínez-Dolz L, Izquierdo M, Agüero J, Sánchez-Lazaro I, Ortiz V, Salvador A. Ezetimibe in heart transplantation: initial experience. *Transplant Proc* 2007; 39: 2389-2392.
- Bozbas H, Altin C, Yildirim A, Sade E, Gulmez O, Gultekin B, Sezgin A, Muderisoglu H. Lipid profiles of patients with a transplanted heart before and after the operations. *Transplant Proc* 2008; 40: 263-266.
- Samman A, Imai C, Straatman L, Frolich J, Humphries K, Ignaszewski A. Safety and efficacy of rosuvastatin therapy for the prevention of hyperlipidemia in adult cardiac transplant recipients. *J Heart Lung Transplant* 2005; 24: 1008-1013.
- Magnani G, Carinci V, Magelli C, Potena L, Reggiani LB, Branzi A. Role of statins in the management of dyslipidemia after cardiac transplant: randomized controlled trial comparing the efficacy and the safety of atorvastatin with pravastatin. *J Heart Lung Transplant* 2000; 19: 710-715.
- Schindler C, Thorns M, Matschke K, Tugtekin SM, Kirch W. Asymptomatic statin-induced rhabdomyolysis after long-term therapy with the hydrophilic drug pravastatin. *Clin Ther* 2007; 29: 172-176.
- Le VV, Racine N, Pelletier GB, Carrier M, Cossette M, White M. Impact of ezetimibe on cholesterol subfractions in dyslipidemic cardiac transplant recipients receiving statin therapy. *Clin Transplant* 2009; 23: 249-255.
- Quarta CC, Potena L, Grigioni F, Scalone A, Magnani G, Coccolo F, Fallani F, Russo A, Branzi A. Safety and efficacy of ezetimibe with low doses of simvastatin in heart transplant recipients. *J Heart Lung Transplant* 2008; 27: 685-688.
- Crespo-Leiro MG, Paniagua MJ, Marzoa R, Grille Z, Naya C, Flores X, Rodriguez JA, Mosquera V, Franco R, Castro-Beiras A. The efficacy and safety of ezetimibe for treatment of dyslipidemia after heart transplantation. *Transplant Proc* 2008; 40: 3060-3062.
- Murtola TJ, Tammela TL, Määttänen L, Huhtala H, Platz EA, Ala-Opas M, Stenman UH, Auvinen A. Prostate cancer and PSA among statin users in the Finnish prostate cancer screening trial. *Int J Cancer* 2010; 127: 1650-1659.
- Mondul AM, Weinstein SJ, Virtamo J, Albanes D. Serum total and HDL cholesterol and risk of prostate cancer. *Cancer Causes Control* 2011; 22: 1545-1552.
- Lee KW, Bode AM, Dong Z. Molecular targets of phytochemicals for cancer prevention. *Nat Rev Cancer* 2011; 11: 211-218.
- Duncan RE, El-Sohemy A, Archer MC. Statins and cancer development. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1897-1898.
- Cho SJ, Kim JS, Kim JM, Lee JY, Jung HC, Song IS. Simvastatin induces apoptosis in human colon cancer cells and in tumor xenografts, and attenuates colitis-associated colon cancer in mice. *Int J Cancer* 2008; 123: 951-957.
- Spampanato C, De Maria S, Sarnataro M, Giordano E, Zanfardino M, Baiano S, Carteni M, Morelli F. Simvastatin inhibits cancer cell growth by inducing apoptosis correlated to activation of Bax and down-regulation of BCL-2 gene expression. *Int J Oncol* 2012; 40: 935-941.
- Liao JK. Isoprenoids as mediators of the biological effects of statins. *J Clin Invest* 2002; 3: 285-288.
- Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature* 1990; 343: 425-430.
- Holstein SA, Wohlford-Lenane CL, Hohl RJ. Isoprenoids influence expression of Ras and Ras-related proteins. *Biochemistry* 2002; 41: 13698-13704.
- Denoyelle C, Vasse M, Körner M, Mishal Z, Ganné F, Vannier JP, Soria J, Soria C. Cerivastatin, an inhibitor of HMG-CoA reductase, inhibits the signaling pathways involved in the invasiveness and metastatic properties of highly invasive breast cancer cell lines: an in vitro study. *Carcinogenesis* 2001; 22: 1139-1148.
- Zembala M, Wojnicz R, Zakliczynski M, Wojarski J, Nozynski J, Knapik P, Biatkowski J, Foremny J, Rozek M. Cellular adhesion molecules changes in myocardium during first year post heart transplant. *Ann Transplant* 1997; 2: 16-19.
- Vallianou NG, Kostantinou A, Kougiaris M, Kazazis C. Statins and Cancer. *Anticancer Agents Med Chem* 2014; 14: 706-712.
- Clarke NW, Brown MD. Should all patients receive statins to reduce cancer risk after heart transplantation? *Circulation* 2012; 126: 391.
- Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med* 2000; 6: 1399-1402.
- Fildes JE, Shaw SM, Mitsidou A, Rogacev K, Leonard CT, Williams SG, Yonan N. HMG-CoA reductase inhibitors deplete circulating classical and non-classical monocytes following human heart transplantation. *Transpl Immunol* 2008; 19: 152-157.
- Schmauss D, Weis M. Cardiac allograft vasculopathy: recent developments. *Circulation* 2008; 117: 2131-2141.
- Taylor DO, Edwards LB, Boucek MM, Trulock EP, Waltz DA, Keck BM, Hertz MI. Registry of the international Society for Heart and Lung Transplantation: twenty-third official adult heart transplantation report: 2006. *J Heart Lung Transplant* 2006; 25: 869-879.
- Tona F, Marra MP, Fedrigo M, Famoso G, Bellu R, Thiene G, Gerosa G, Angelini A, Iliceto S. Recent developments on coronary microvasculopathy after heart transplantation: a new target in the therapy of cardiac allograft vasculopathy. *Curr Vasc Pharmacol* 2012; 10: 206-215.

35. Knollmann FD, Stühmer F, Lehmkuhl H, Felix R, Hetzer R. Progression of coronary atherosclerosis after heart transplantation on electron-beam computed tomography. *Acad Radiol* 2009; 16: 194-199.
36. Wenke K, Meiser B, Thiery J, Reichart B. Impact of simvastatin therapy after heart transplantation an 11-year prospective evaluation. *Herz* 2005; 30: 431-432.
37. Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, Chia D, Terasaki PI, Sabad A, Cogert GA, Trosian K, Hamilton MA, Moriguchi JD, Kawata N, Hage A, Drinkwater DC, Stevenson LW. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1995; 333: 621-627.
38. Shimizu K, Aikawa M, Takayama K, Libby P, Mitchell RN. Direct antiinflammatory mechanisms contribute to attenuation of experimental arteriosclerosis by statins. *Circulation* 2003; 108: 2113-2120.
39. Vasudevan AR, Hamirani YS, Jones PH. Safety of statins: effects on muscle and the liver. *Cleve Clin J Med* 2005; 72: 990-993, 996-1001.
40. Patel DN, Pagani FD, Koelling TM, Dyke DB, Baliga RR, Cody RJ, Lake KD, Aaronson KD. Safety and efficacy of atorvastatin in heart transplant recipients. *J Heart Lung Transplant* 2002; 21: 204-210.
41. Grigioni F, Carigi S, Potena L, Fabbri F, Russo A, Musuraca AC, Coccolo F, Magnani G, Ortolani P, Leone O, Arpesella G, Magelli C, Branzi A. Long-term safety and effectiveness of statins for heart transplant recipients in routine clinical practice. *Transplant Proc* 2006; 38: 1507-1510.
42. Sadowitz B, Seymour K, Costanza MJ, Gahtan V. Statin therapy Part II: Clinical considerations for cardiovascular disease. *Vasc Endovascular Surg* 2010; 44: 421-433.
43. Barylski M. Atorvastatin and rosuvastatin in cardiovascular system diseases – why, when and whom they should be given? *Geriatrics* 2012; 6: 166-182.
44. Rodríguez JA, Crespo-Leiro MG, Paniagua MJ, Cuenca JJ, Hermida LF, Juffé A, Castro-Beiras A. Rhabdomyolysis in heart transplant patients on HMG-CoA reductase inhibitors and cyclosporine. *Transplant Proc* 1999; 31: 2522-2523.