Primary prevention of cardiovascular diseases with statins in women

Kadınlarda statinlerle kardiyovasküler hastalıklardan birincil korunma

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Cardiovascular disease is one of the leading causes of mortality and morbidity in postmenopausal women. Menopausal changes have been shown to be related with an atherogenic lipid profile. The efficiency of statins in reducing the incidence of cardiovascular diseases has been well documented in a variety of randomized, placebo controlled trials. This review outlines the effectiveness of statins both in cardiac events and in some noticeable indications in postmenopausal women.

Key words: Anticholesteremic agents; cardiovascular diseases/prevention & control; hydroxymethylglutaryl-CoA reductase inhibitors/therapeutic use; postmenopause; primary prevention.

Kardiyovasküler hastalıklar menopoz geçirmiş kadınlarda mortalite ve morbiditenin önde gelen nedenlerindendir. Menopozda görülen değişiklikler aterojenik lipit profili ile ilişkilidir. Statinlerin kardivasküler hastalıkları azaltmadaki etkinlikleri birçok randomize, plasebo kontrollü çalışmada gösterilmiştir. Bu derlemede, statinlerin menopoz geçirmiş kadınlarda hem kardiyovasküler hastalıklar, hem de bazı önemli endikasyonlardaki etkinlikleri irdelendi.

Anahtar sözcükler: Antikolesteremik ajan; kardiyovasküler hastalık/önleme ve kontrol; hidroksimetilglutaril-KoA redüktaz inhibitörü/terapötik kullanım; menopoz sonrası; birincil koruma.

Statins, the first line of drugs in the treatment of hypercholesterolemia, are competitive enzyme inhibitors for hydroxymethylglutaryl coenzyme A (HMG-CoA), which acts as the rate-limiting stage in the formation of hepatic cholesterol. These drugs exert their main effect in decreasing total cholesterol (TC) and low density lipoprotein (LDL) cholesterol. However, some of the drugs in this group also play a role in increasing high density lipoprotein (HDL) cholesterol and decreasing triglycerides (TGs). In addition to these basic effects, the drugs also posses pleiotropic (lipid-independent) effects (antioxidant, anti-inflammatory, effect on prevention of endothelial dysfunction, thrombus formation and embolism).

Women, who are protected against cardiovascular (CV) diseases until menopause are exposed to the risk of these disease after menopause. CV diseases are most commonly observed in menopausal women compared to same-age women who have not reach menopause.[1] The current NCEP ATP III guideline recommend statin therapy as a primary preventive measure in women, depending on the CV disease profile and blood LDL-cholesterol level.[1-3] On the other hand, there are data supporting the use of statins in non cardiovascular diseases due to their pleiotropic effects.

In this review, the general use of statins in women as primary protective agents and related studies is being investigated.

Postmenopausal Changes in Lipid Metabolism

The level of TC and LDL-cholesterol is known to increase during menopause, accompanied by a decrease in the level of HDL and an increase in TGs levels.[4] Oxygen deficiency is the main factor associated with these changes. In addition to an increase in cholesterol level, this process also involves the formation of an atherogenic lipid profile.[5]

With the onset of menopause there is also a predisposition to coagulation associated with an increase in procoagulant factor VII, fibrinogen and plasminogen activator inhibitor-1 (PAI-1), in the hemostatic system. This condition explains the sudden increase in ischemic events in postmenopausal women.[6]

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Mechanism of Action of Statins

The formation of cholesterol involves a series of complex processes including various biochemical pathways and *feedback* mechanisms in the liver. Statins competitively inhibit the HMG-CoA reductase enzyme, which acts as the rate-limiting stage in the formation of hepatic cholesterol. This enzyme catabolizes the conversion of HMG-CoA to mevalonic acid (MVA), and through this inhibition statins prevent the formation of cholesterol from MVA.[7] The number of LDL-cholesterol receptors in hepatocytes increase in response to a decrease in the formation of cholesterol and also due to the resulting fall in the level of plasma cholesterol. Consequently, there is an increase in the purgation of plasma LDL-cholesterol leading to a fall in plasma cholesterol.[8] On the other hand, statins increase the formation of apolipoprotein A-1 (Apo A-1), leading to a decrease in the level of plasma TGs and an increase in the level of plasma HDL-cholesterol.[9] In addition to these antilipidemic effects, they also have pleiotropic effects such as the preservation and regulation of endothelial function, stabilization of atheromatous plagues, and decrease in inflammation and oxidative stress.[10] The prevention of MVA destruction by statins prevents the formation of isoprenoids such as farnesylpyrophosphate (FPP) and geranylgeranyl-pyrophosphate (GGPP). These isoprenoids play a role in the post-transformational changes of proteins which take part in cell growth such as Ras, Rho Rac and Rap and also in signal transfer.[11] This association with isoprenylation explains the effect of statins on cell growth, cellular multiplication and apoptosis.

Safety of Statins

Long term treatment with statins is generally well tolerated and the incidence of side effects is low. The most commonly encountered side effects are increases in hepatic and skeletal muscle enzymes. The three-fold asymptomatic increase in hepatic enzymes above normal values is generally temporary, dose-related and typically reverts to normal. Skeletal muscle disorders such as benign muscle pain, muscle disease (a 10-fold increase in muscle enzymes together with muscle pain and muscle weakness) and atrophy (the incidence of muscle disease is 0.1-0.5%, whereas incidence of muscle atrophy is 0.02-0.04%) are dose-dependent and the risk increases with the used of medications which slow statin metabolism.[12,13] On the other hand, these side effects are usually mild and may regress with discontinuation of treatment or sometime even without discontinuation of treatment. The benefits from long-term statin therapy overweigh the risks of side effects.

Cardiovascular Diseases

The relationship between CV diseases and statin use in patients with various levels of serum cholesterol and with various risks of coronary artery disease has been investigated in studies conducted on various patient groups. Outstanding controversial reports are known to exist concerning the primary preventive use of statins. A total of 42848 patients were investigated in a collective analysis involving basic studies on this topic, and in which the primary and secondary prevention arms were also included in the study criteria (Table 1). A 29.2% reduction in the rate was reported in important coronary events, 14.4% reduction in important cerebrovascular events and a 33.8% reduction in revascularization procedures following the administration of statin therapy.[14] There was a 22.6% reduction in the rate of cardiovascular deaths which did not attain statistical significance, whereas no significant reduction was observed in the rate of death due to all causes. On the other hand, no increase was reported in the incidence of cancer cases, or in the level of hepatic and muscle enzymes.

The effect of daily lovastatin 20-40 mg administration in the prevention of the first important acute coronary event (fatal or non-fatal myocardial infarction (MI), unstable angina pectoris, or sudden cardiac death) was investigated in a total of 6605 asymptomatic patients (997 menopausal women, age range of 45-73 in men and 55-73 in women) with mean TC and LDL-cholesterol, only in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) which included the primary prevention arm of patients. A significant decrease in the level of TC, LDL-cholesterol and TG was obtained, compared to the control group. On the other hand, a 37% decrease was observed in the prevention of the first important acute coronary event with lovastatin. Although the decreased rate was similar in women and men, this result was not found to be statistically significant as a result of a low incidence of events. However, evaluation of decreased death rate in this study was scheduled separately in the men and the women groups.[15,16]

In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study with the only second study on primary prevention, where 10297 hypertensive patients (1942 females) with moderate or low cholesterol levels and at least three cardiovascular risk factors were randomized to either the atorvastatin or placebo arm, the risk of fatal or non-fatal MI was reduced by 36%. Evaluation of female patients alone revealed 19 events in the atorvastatin arm and 17 events

Table 1. Randomized, controlled trails (adapted from reference number 14) evaluating the use of statins in primary prevention

	WOSCOPS	AFCAPS/ TexCAPS	PROSPER	ALLHAT-LLT	ASCOT-LLA	HPS	CARDS
Number of patients (Statin/control)	3302 / 3293	3304 / 3301	1585 / 1654	5170 / 5185	5168 / 5137	1455 / 1456	1428 / 1410
Mean follow-up period (yrs)	4.9	5.2	3.2	4.8	3.3	4.8	3.9
Number of patients in the primary prevention group (%)	83.8	100	100	85.8	81.5	100	100
Drug and dosage (mg/dl)	Pravastatin 40	Lovastatin 20-40	Pravastatin 40	Pravastatin 20-40	Atorvastatin 10	Simvastatin 40	Atorvastatin 10
Age (years)	55.3	58.0	75	66.4	63.1	No data	61.5
Male (%)	100	85	42	51	81.1	No data	68
Diabetes mellitus (%)	1.0	3.8	12.2	34.4	24.3	100	100
Cigarette smoking (%)	44	13	33.4	23.3	33.2	No data	22

WOSCOPS: West of Scotland Coronary Prevention Study – Male patients with hyperlipidemia;
AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study – Patients with moderate or less than moderate cholesterol levels;
PROSPER: Prospective Study of Pravastatin in the Elderly at Risk – Elderly patients with at least one cardiovascular risk factor;
ALLHAT-LLT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – Patients with hypertension, moderate hyperlipidemia and at least one cardiovascular risk factor;
ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm – Patients with hypertension, moderate or low cholesterol levels and at least three cardiovascular risk factors;
HPS: Heart Protection Study - diabetic subgroup publication – Subgroup study with high risk diabetic patients;
CARDS: Collaborative Atorvastatin Diabetes Study – Patients with non-high risk LDL-cholesterol level.

in the placebo arm; however, this did not reach statistical significance.[17]

In the recent Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, a total of 17802 individuals (6801 females) with <130 mg/dl of LDL-cholesterol levels and ≥2 mg/dl of highly sensitive C-reactive protein (hsCRP) levels were randomized into rosuvastatin and placebo groups and were hospitalized due to MI, stroke, arterial revascularization, unstable angina pectoris, or followed up for composite primary end points of death. At the end of the 1.9-year follow-up period, a 44% reduction was observed in the primary end points of all study groups following administration of 20 mg/dl of rosuvastatin; the rate was fond to be 46% in the female subgroup.[18]

In conclusion, there is no evidence in the AFCAPS/TexCAPS and ASCOT-LLA studies showing that statins reduce the risk of coronary death in women through primary prevention. However, the risk reduction obtained is similar to that in men. In addition, in the recently published JUPITER study it was also demonstrated that statin therapy as primary prevention reduced the risk of death in the female arm. On the other hand, updated NCEP ATP III guidelines recommend the use of statins in women with LDL-cholesterol levels above certain risk values, even in the absence of confirmed coronary artery disease. The updated guidelines did not include the JUPITER study; however, considering that fact that these results would be included in the subsequent guidelines, new recommendations concerning primary prevention may be added to the already exiting guidelines.

Atrial fibrillation: Atrial fibrillation is the most commonly encountered cardiac arrhythmia. Despite recent advancements in diagnosis and treatment, it remains a life threatening condition. The association of factors such as age, obesity and hypertension which are considered as risk factors for atherosclerosis, with AF suggests that there might be an associated between AF and atherosclerotic vascular diseases.[19] In addition, increased activity of the renin-angiotensin system is thought to have a relationship with the development of AF. Angiotensin II contributes to the development of AF through its growth-stimulating effect on cardiac myocytes, vascular smooth muscles cells and fibroblast, associated with atrial remodeling and increased fibrosis.[20] The possible decrease in the incidence of AF following suppression of the renin-angiotensin system

supports this finding.[21] Evidence of the relationship between dyslipidemia and the renin-angiotensin system, coupled with reduction of cholesterol level and oxidative stress by statins accounts, for the antiarrhythmic effects of statins in the prevention of AF.[22,23] On the other hand, presence of a regulatory effect of statins on the autonomic nervous system especially supports the antiarrhythmic effect of statins in the prevention of AF associated with postoperative increase in sympathetic activity.[24]

In the Heart and Estrogen-Progestin Replacement Study (HERS), involving 2673 menopausal women with known coronary artery disease the rate of baseline AF and the number of patients who developed AF during the study were both found to be low in patients undergoing statin therapy.[25] However, the fact that AF follow-up in this study was performed only by yearly electrocardiography, and the subsequent inability to adequately identify attacks of AF was a limitation of this study.

Osteoporosis

The effects of statins on bone metabolism are similar to the cytotoxic effects of biophosphonates on osteoclasts.[26] Statins reduce FPP and GGPP by preventing the formation of mevalonate, whereas biophosphonates inhibit FPP and GGPP which promote osteoclastic activation by inhibiting FPP synthase.[27] In addition, statins activate bone morphology protein-2, which provide osteoclastic differentiation and as a result bone formation.[28]

No randomized, placebo controlled study has been conducted to investigate the effects of statins on bone mineral density. On the other hand, observational studies which have been conducted are controversial. In a retrospective study conducted by Chung et al,[29] where 69 diabetic patients (36 using statins) were evaluated during a 15-months follow-up period, a significant 0.88% increase in bone density of the femur neck was observed in patients treated with statins, whereas a 1.03% reduction was observed in the control group. In the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) Study conducted in Finland, 620 women (age range, 53-64) were followed up for a period of 2.8-5.4 years.[30] Patients were divided into four groups according to women with regular statin use (n=55), women with intermittent statin use (n=63), hypercholesterolemic women who did not use statins (n=142), and non-hypercholesterolemic women who did not use statins (n=360). No difference was observed between the groups at the end of the follow-up period in respect of changes in both spinal and femoral yearly bone density. In another study in which the effects of fluvastatin and pravastatin were investigated, no increase was observed with any of the two drugs in respect of whole body bone density at the end of the one-year follow-up period; however, there was a 1% increase in vertebral bone density was observed with fluvastatin use, whereas there was a 2% decrease in the group with pravastatin use.[31]

In the Geelong Osteoporosis study, the fracture risk of statins use was investigated in a total of 1375 women.[32] 16 of the 573 patients in the fracture group used statins, whereas 53 of the 802 patients in the non-fracture group did not use statin. Results obtained demonstrated that there was a 60% reduction in the risk of fractures associated with statin use; however, there were limitations to these findings due to the small patient-population.

In another study (The Women's Health Initiative Observational Study) conducted at 40 clinical centers, data concerning hip, wrist and other fractures were investigated in 93716 menopausal women. However, no association was found between statin use and reduction in the risk of fracture at the end of the 3.9-year follow-up period.[33]

In the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study the effect of pravastatin on fracture was investigated; no difference was found between pravastatin and placebo in all study groups as well as in the women subgroup. These results were similar to those observed with ≥65 years-old patients.[34]

In the MRC/BHF Heart Protection Study-HPS study, the effects of simvastatin and placebo were compared and no difference was obtained between the groups in respect of any fracture and of hip, wrist, or shoulder fractures associated with osteoporosis.[35]

A collective analysis investigating the effect of statin on the risk of fractures demonstrated that there was a positive effect in the case and cohort studies (23% reduction in fracture risk). However, in the *post-hoc* analyses of randomized studies (LIPID, 4S, AFCAPS/TexCAPS, HPS) no similar findings were obtained.[36]

Statins may have a positive effect on metabolism; however, no definite result concerning their effect on reducing the risk of fractures has yet been reported. Randomized, prospective studies are required to investigate the effect of statins in the prevention of fractures or in the treatment of osteoporosis.

Breast cancer

Statins are known to stop the development of cancer cells at the G1-S phase of the cell cycle under *in vitro* environments.[37,38] The apoptotic effects of statins are due to inhibition of isoprenylation.[39] In *in vivo* studies lovastatin and simvastatin were reported to reduce tumor formation and prevent metastasis in mouse breast tumor models.[40,41]

In the Cholesterol and Recurrent Events (CARE) study where the secondary preventive effect of pravastatin on coronary artery disease was evaluated over a 4 to 6.2 follow-up period, 12-fold increased risk of breast cancer was observed with statin treatment.[42] However, this result was associated with the less than anticipated number of cancer cases in the placebo arm of the study.[43] In another study with pravastatin, no increase was observed in the risk of breast cancer, and no similar findings were reported from the other important randomized studies involving statins.[44-46]

In the retrospective analysis of the health reports from the Saskatchewan region of Canada, the relationship between statin therapy and breast cancer was investigated. In the study conducted between 1989 and 1997 involving women of the same age group, comparison was made between 13592 women who used statins at least once and 53880 women who did not use statins. A total of 879 breast cancer cases were observed among all women. No relationship was demonstrated between statin use and breast cancer in women <55 years of age. However, a statistically non-significant increase was observed in women >55 years old who used statins.[47]

In another study (The Nurses' Health Study), where 75828 women were evaluated over a follow-up period of 12 years, no relationship was demonstrated between statin use and the risk of breast cancer.[48]

In the Women's Health Initiative study on 156351 menopausal women, development of breast cancer was reported in 4383 women over a 6.7-year follow-up period. Breast cancer was 4.09 in 1000 women years, in women treated with statins, and was 4.28 in women who were not treated with statins. However, women who were treated with hydrophobic statins were reported to have an 18% reduced risk of breast cancer.[49]

In conclusion, the relationship between statin use and breast cancer is so far limited to observational studies and retrospective analyses. Beneficial results obtained from observational studies have not so far been clearly revealed in retrospective analyses. There is a need for prospective, randomized, placebo controlled studies investigating the relationship between statins (especially hydrophobic statins) and breast cancer.

Alzheimer's disease

Alzheimer's disease (AD) is characterized by the presence of a pool of neutrophils and by the intra- and extravascular accumulation of beta-amyloid proteins.[50] The degree of cortical atrophy is associated with the degree of dementia in AD. In Alzheimer's disease beta-amyloid proteins which take part in the formation of amyloid plague in the brain, cholesterol plays a role in the formation of amyloid precursor proteins. The cholesterol transport protein, apolipoprotein E type 4 (APOE4) polymerase, is known to be related with increased risk in the formation of atherosclerosis and amyloid plague.[51,52] On the other hand, epidemiologic studies have demonstrated a relationship between high cholesterol levels and AD.[53,54] In an experimental study, lovastatin and simvastatin were shown to decrease the level of beta-amyloid protein in cortical neuronal and hippocampal cell cultures.[55] In patients with hypercholesterolemia, treatment with lovastatin doses of 20, 30, 40, or 60 mg demonstrated a relationship between decreased beta-amyloid protein levels and increased dosage of lovastatin.[56] In mild to moderate AD patients, positive results were obtained from the use of atorvastatin in clinical scales (such as geriatric depression scale, AD evaluation scale), compared to placebo.[57] However, the positive findings obtained in patients treated with atorvastatin was found in patients with high cholesterol levels, patients who demonstrated apolipoprotein E genotype, and during the early stages of AD.[58]

Conclusion

The current NCEP ATP III guidelines recommend statin therapy as a primary preventive measure in women. The administration of statin therapy as primary prevention under optimal conditions is gaining importance, taking into consideration the increased incidence of CV diseases during the postmenopausal period. The JUPITER study has demonstrated that statin therapy should also be considered in respect of LDL-cholesterol targets and highly sensitive C-reactive protein (hsCRP) levels. On the other hand, apart from cardiovascular diseases, randomized, prospective controlled studies are required to investigate the use of statins.

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