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Statins and Menopause

Mohammed H. Moghadasian

Division of Clinical Trials, PhenoPharma Research Inc., and Department of Pathology and Laboratory Medicine, The University of British Columbia, Vancouver, British Columbia, Canada

Abstract

During the reproductive period, women generally have lower low-density lipoprotein (LDL) cholesterol and higher high-density lipoprotein cholesterol than age- and diet-matched men. However, these possibly antiatherogenic characteristics of lipoproteins are changed to a potentially atherogenic profile after menopause. Menopause-related changes in lipoprotein profile can be corrected by the administration of hormone replacement therapy (HRT). However, the results of recent studies did not show definite benefits of HRT on coronary heart disease-related mortality rates. On the other hand, several large-scale, long-term clinical trials provide evidence for efficacy and safety of HMG-CoA reductase inhibitors (statins) in both men and women. The results of 19 short-term clinical trials using simvastatin, pravastatin, fluvastatin or lovastatin in postmenopausal women are summarised and discussed. All these investigations reported significant reductions in both total and LDL cholesterol levels. The question of whether statin therapy results in a significant decrease in cardiovascular-related mortality rates along with a better quality of life in postmenopausal women remains to be investigated in large-scale, randomised, double-blind, placebo-controlled clinical trials.

It is believed that production and secretion of estrogen during the reproductive period plays an important role in late onset of coronary heart disease (CHD) in women. Indeed, induction of menopause by surgical means, such as bilateral oophorectomy, significantly increases the risk of CHD in women.[1] Thus, several epidemiological, clinical and experimental studies have suggested hormone replacement therapy (HRT) in both the prevention and treatment of CHD in postmenopausal women.[2-4] However, the potential cardiovascular benefit of HRT should be carefully weighed against their potential serious adverse effects including an increased risk for uterine and breast cancer.[5,6] Alternatively, the lipoprotein profile of postmenopausal women can be beneficially modified by other relatively 'safe' pharmacological means including lipid-lowering agents. This is particularly appropriate in those postmenopausal women at high risk for CHD and with a family history of breast cancer, or in those who are either unable or unwilling to take HRT long-term in the absence of menopausal syndrome.

The aim of this review is to summarise knowledge to date on menopause-associated dyslipidaemia and the potential benefits of HMG-CoA reductase inhibitors (statins). Related articles were selected through a Medline search limited to the period of 1980–2002, and are critically reviewed and discussed in this article.

1. Menopause and Lipoprotein Profile

During the reproductive period, women generally have lower low-density lipoprotein (LDL)

cholesterol and higher high-density lipoprotein (HDL) cholesterol levels than age- and diet-matched men. However, these possibly anti-atherogenic characteristics of lipoproteins are changed to a potentially atherogenic profile after menopause. These changes mainly include decreased HDL and increased LDL cholesterol levels with lower quality, namely an elevated proportion of small and dense LDL particles.[7] Analyses of the data from the Framingham Offspring and Cohort 1971–1974[8] demonstrate an age-dependent variation in plasma lipoprotein cholesterol levels in both men and women (figure 1). As illustrated in figure 1, the total cholesterol levels of postmenopausal women exceed those in men mainly as a result of increases in non-HDL-cholesterol (figure 1). This causes a significant rise in the total/HDL cholesterol ratio in women after the age of 50 years, whereas this ratio is decreased in men after 50 years of age (figure 2). Thus, the net effect of aging is the development of a more atherogenic lipoprotein profile in postmenopausal women. This may be the cause of higher CHD risk in women as observed after 16 years of follow-up of the Framingham Cohort (table I). Similarly, further analysis of the data from the Framingham Cohort indicates that the age-related increment in the risk

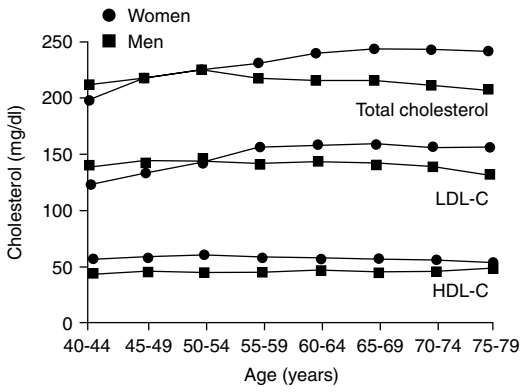

Fig. 1. Age- and sex-dependent variations in plasma lipoprotein cholesterol levels after the age of 40 years. Reproduced with permission from Kannel.[8] **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol.

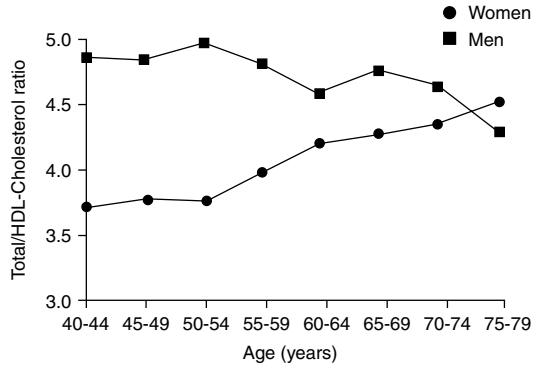

Fig. 2. Estimated total/HDL cholesterol ratio in both men and women more than 40 years of age. Reproduced with permission from Kannel.[8] **HDL-C** = high density lipoprotein cholesterol.

of cardiovascular events is more profound in women than in men (table II).

These changes in lipoprotein profile can be corrected by oral administration of estrogen.[9] Transdermal administration of 17β-estradiol lowers plasma cholesterol levels to a lesser extent[10] indicating the importance of the intestine and liver in the regulation of lipoprotein metabolism by estrogen. One possible mechanism is enhanced hepatic cholesterol uptake through LDL receptors, and consequent increases in cholesterol catabolism and bile acid formation.[11] Simultaneous increases in apolipoprotein (apo) AI levels, decreased activity of hepatic lipase and increases in reverse cholesterol transport may further reduce the risk of CHD in postmenopausal women. Estrogen may be beneficial against CHD through other mechanisms as well. These include: (i) positive effects on coronary vasomotor through nitric oxide (NO) generation and endothelium involvement;[12] (ii) antioxidant activities and inhibition of LDL oxidation;[13] (iii) anti-proliferative effects on vascular smooth muscle cells;[14] and (iv) anti-hypertensive properties mediated by reduced angiotensin converting enzyme levels.[15] Despite these potentially beneficial effects of HRT, the Heart Estrogen/Progestin Replacement Study (HERS)[16] showed no significant benefit of HRT on the incidence of CHD-related death compared with placebo over 4.1 years

of follow-up. On the other hand, several small clinical trials have shown benefits from statins alone or in combination with HRT in postmenopausal women. These studies are outlined in section 2.

2. Statin Therapy in Postmenopausal Women

Currently, several classes of lipid-lowering agents are used to reduce plasma lipid levels and potentially decrease the risk for CHD. The choice of drug treatment mainly depends on the nature of dyslipidaemia, the response of the patient, the severity of adverse effects and drug-drug interactions. Statins are widely used and have been shown to be effective with a relatively low incidence of serious adverse effects. These drugs competitively inhibit hepatic cholesterol synthesis and thus upregulate hepatic LDL receptor function resulting in significant reductions in plasma LDL cholesterol levels. Certain statins may cause increases in plasma HDL cholesterol levels and decreases in plasma triglyceride levels by unknown mechanisms. All these lipid modifications as well as nonlipid-related effects, such as antioxidant activity, direct effects on vessel wall function, anti-coagulation effects and other properties, may contribute to the antiatherogenic effects of statins. The effects of various statins on lipoprotein profile have been investigated in postmenopausal women in numerous studies as described in the following subsections and summarised in table III.

Table I. Coronary heart disease risk by total/HDL cholesterol ratio. Sixteen year follow up of the Framingham Study (reproduced with permission from Kannel.[8])

Age (y)	Q5/Q1 Risk ratio	
	Men	Women
49–59	3.4	3.7
60–69	2.9	6.8
70–81	2.3	3.3
All ages	2.4	3.9

Q5/Q1 = ratio of risk for the fifth (highest) quintile compared to the first (lowest) quintile; **HDL** = high-density lipoprotein.

2.1 Simvastatin

A recent study[17] investigated the effects of simvastatin 10 mg/day for 6 months in 50 postmenopausal women (mean age 58 years and mean duration of menopause 67 months) with hypercholesterolaemia (mean plasma total cholesterol 6.45 mmol/L and mean LDL-cholesterol 4.53 mmol/L). Simvastatin therapy for 6 months resulted in 11 and 16% reductions in total and LDL cholesterol levels, respectively, and an 11% increase in HDL cholesterol levels with no change in triglyceride levels. Similar results were obtained when a combination of simvastatin 10 mg/day and HRT (estrogen 0.625mg plus medroxyprogesterone 2.5mg daily) was used in a matched group of 50 postmenopausal women. Similarly, simvastatin 10 mg/day for 8 weeks resulted in 26, 36 and 14% decreases in total and LDL cholesterol and triglyceride levels, respectively, along with a 7% increase in HDL cholesterol levels in 58 postmenopausal women.[18]

Table II. Increment in the risk of cardiovascular events comparing age 35–64 year rates with 65–94 year rates in each sex: 36-year follow up of the Framingham Study (reproduced with permission from Kannel[8])

Age (y)	Average annual rate per 1 000							
	All CV events[a]		CHD		Stroke		CHF	
	Men	Women	Men	Women	Men	Women	Men	Women
35–64	18	9	14	6	3	2	3	2
65–94	43	30	27	17	12	11	11	9
Risk ratio[b]	2.4	3.3	1.9	2.8	4.0	5.5	3.7	4.5

a Also includes peripheral vascular disease.

b (65-94)/(35-64).

CHD = coronary heart disease; **CHF** = congestive heart failure; **CV** = cardiovascular.

Table III. HMG-CoA reductase inhibitor (statin) therapy in postmenopausal women

Study	No. pts	Mean age (y)	Agent (dosage)	Duration	Results (% change from baseline or vs placebo-treated groups when applicable)
Fak et al.[17]	50	58	Simvastatin (10 mg/day)	6m	11% ↓ TC, 16% ↓ LDL, 11% ↑ HDL
Darling et al.[18]	58	61	Simvastatin (10 mg/day)	8 wks	26% ↓ TC, 36% ↓ LDL, 7% ↑ HDL, 14% ↓ TG
Nakajima[19]	122	61	Simvastatin (0.1 mg/kg BW)	1y	20% ↓ TC, 28% ↓ LDL, 25% ↓ TC/HDL ratio
Ohmichi et al.[20]	10	56	Simvastatin (10 mg/day) + HRT	12 wks	21% ↓ TC, 28% ↓ LDL, 24% ↓TG
Sbarouni et al.[21]	16	>1 year after amenorrhea	Simvastatin (20 mg/day)	8 wks	35% ↓ TC, 45% ↓ LDL
Koh et al.[22]	28	57	Simvastatin (10 mg/day)	6 wks	20% ↓ TC, 25% ↓ LDL, 8% ↑ apo AI, 20% ↓TG, 25% ↓ apo B
Wakatsuki et al.[23]	15	55	Simvastatin (5 mg/day)	3m	22% ↓ TC, 33% ↓ LDL
Wakatsuki et al.[24]	18	55	Simvastatin (5 mg/day)	3m	22% ↓ TC, 29% ↓ LDL
Averbuch et al.[25]	16	Not above 60	Simvastatin (10 mg/day) + HRT + Step I diet	6m	24% ↓ TC, 35% ↓ LDL
Gavish et al.[26]	42	54	Simvastatin (20 mg/day)	6m	22% ↓ TC, 31% ↓ LDL, 27% ↓ TC/HDL ratio, 35% ↓ LDL/HDL ratio
Ozsener et al.[27]	12	51	Pravastatin (20 mg/day)	16 wks	19% ↓ TC, 21% ↓ LDL
Lemay et al.[28]	16	57	Pravastatin (40 mg/day)	6m	30% ↓ TC, 30% ↓ LDL, 16% ↓ TG, 25% ↓ apo B
Ushiroyama et al.[29]	74	54	Pravastatin (10 mg/day)	5y	20% ↓ TC, 25% ↓ LDL
Davidson et al.[30]	76		Pravastatin (20 mg/day)	16 wks	25% ↓ non-HDL and calculated LDL
Serruys et al.[31]	70	61	Fluvastatin (80 mg/day)	26 wks	33% ↓ LDL, 28% ↓ apo B, 13% ↓ TG
Marz et al.[32]	35	66	Fluvastatin (40 mg/day)	12 wks	19% ↓ TC, 23% ↓ LDL, 21% ↓ apo B
Clearfield et al.[33]	997	55-73	Lovastatin (20-40 mg/day)	5y	25% ↓ LDL, 9% ↑ HDL, 37% ↓ AMCE rates
Bradford et al.[34]	1930	59	Lovastatin (20-80 mg/day)	48 wks	24–40% ↓ LDL, 9–18% ↓ TG, 7–9% ↑ HDL, 17–28% ↓TC
Herrington et al.[35]	24	>55	Lovastatin (20 mg/day)	6 wks	30% ↓ LDL, 8% ↓ TG, 35% ↓ LDL/HDL ratio, 11% ↑ HDL
Ray et al.[36]	39 842	≥65	Statins	1.1–1.4y	↓ DVT rates

AMCE = acute major coronary events; **apo** = apolipoprotein; **BW** = bodyweight; **DVT** = deep vein thrombosis; **HDL** = high-density lipoprotein; **HRT** = hormone replacement therapy; **LDL** = low-density lipoprotein; **TC** = total cholesterol; **TG** = triglycerides; ↓ indicates decrease; ↑ indicates increase.

One hundred and twenty-two postmenopausal women (mean age 61.4 years) received simvastatin at a median dose of 0.1 mg/kg for 1 year.[19] This resulted in a 20% reduction in total cholesterol, 28% reduction in LDL-cholesterol and an approximately 25% reduction in the total/HDL cholesterol ratio compared with baseline measurements. Seven women experienced drug-related adverse effects. Combination of HRT and simvastatin 10 mg/day in hypercholesterolaemic postmenopausal women (n = 10) who did not respond to HRT alone resulted in a 21% decrease in total cholesterol, a 28% decrease in LDL cholesterol and a 24% decrease in plasma triglycerides with no change in HDL cholesterol.[20] Simvastatin 20mg once daily for 8 weeks resulted in a significant reduction in the levels of plasma total and LDL cholesterol (–35 and –45%, respectively) in 16 postmenopausal women with documented coronary artery disease.[21] However, these changes were not accompanied by significant modifications in the levels of plasma fibrinogen, factor VII or total plasminogen activator inhibitor antigen.[37]

The effects of simvastatin on lipoprotein metabolism were investigated in 28 hypercholesterolaemic postmenopausal women over a 6-week period.[22] Treatment with simvastatin 10mg each night was associated with a 20% reduction in total cholesterol, a 25% reduction in both LDL cholesterol and apo B, a 20% decrease in triglycerides,

and an 8% increase in apo AI.[22] The addition of conjugated equine estrogen 0.625 mg/day to simvastatin did not result in an additional lipid lowering effect. However, estrogen therapy improved markers of fibrinolysis and vascular inflammation.[22] Significant reductions in the LDL/HDL ratio (–30%) and the apo B/apo AI ratio (–30%) along with substantial improvements in endothelial function as measured by flow-mediated dilation were also observed.[22]

A lower dose of simvastatin (5 mg/day for 3 months) also significantly reduced plasma levels of total and LDL cholesterol along with significant reductions in the levels of apo B, apo C-II and apo E in 15 postmenopausal women.[23] Similarly, this dose of simvastatin (5 mg/day) for 3 months produced 22 and 29% reductions in plasma total and LDL cholesterol levels, respectively, in 18 postmenopausal hypercholesterolaemic patients.[24]

Sixteen postmenopausal women who did not respond to combination of American Heart Association Step I diet and HRT were additionally treated with simvastatin 10 mg/day for 6 months. The addition of simvastatin to the Step I diet and HRT regimens resulted in a rapid reduction in both total (–24%) and LDL (–35%) cholesterol levels.[25]

In another study, the efficacy and safety of simvastatin 20 mg/day were investigated in 42 postmenopausal women (mean age 54 years) as well as 58 men (mean age 60 years) with hypercholesterolaemia and type II diabetes mellitus but not receiving any HRT.[26] Simvastatin therapy for 6 months resulted in a significant reduction in plasma total cholesterol, LDL-cholesterol, the LDL/HDL ratio and the total cholesterol/HDL ratio compared with baseline measurements.[26] However, the treatment did not cause any significant changes in the levels of plasma triglycerides, fibrinogen or lipoprotein(a). The adverse effects of simvastatin therapy as determined by mild creatine phosphokinase (CPK) elevation, two times the upper limit of normal CPK elevation, liver function abnormalities and clinical myopathy in all 100 treated participants was 3, 1, 1 and 1%, respectively. Over an 18-month follow-up, the incidence of all cardiovascular events was 6% with one death and no acute myocardial infarction. Of non-cardiovascular events, one case of pneumonia was reported. It is of interested that this study reported a 50% greater reduction in incidence of overall events in women participants than men.[26]

2.2 Pravastatin

Pravastatin 20 mg/day for 16 weeks significantly decreased total and LDL cholesterol levels by 19 and 21%, respectively, in 12 postmenopausal patients with hypercholesterolaemia.[27] The addition of HRT did not enhance the cholesterol-lowering effects of pravastatin.[27] After 4 months of dietary management, pravastatin 40 mg/day was given to 16 postmenopausal women for 6 months.[28] The statin produced significant reductions in total and LDL cholesterol levels (–30% each), a 25% reduction in apo B and a 16% reduction in triglyceride levels.[28]

Seventy-four postmenopausal women with mean plasma total cholesterol levels of 255 mg/dl (6.59 mmol/L) and no CHD symptoms were treated with pravastatin 10 mg/day for 5 years.[29] This treatment resulted in a sustained reduction in total and LDL cholesterol levels by 20 and 25%, respectively.[29] It is of interest that, compared with baseline values, pravastatin therapy was associated with a 39% reduction and an 8% increase in triglyceride levels in hypertriglyceridaemic and normotriglyceridaemic women, respectively. No serious adverse effects were reported over the 5 year study period.

The effects of pravastatin 20 mg/day alone or in combination with HRT were investigated in 76 postmenopausal women with hypercholesterolaemia in a double-blind, randomised, placebo-controlled trial.[30] An approximately 25% reduction in both non-HDL and calculated LDL cholesterol levels was observed in pravastatin-treated group. The addition of HRT did not significantly decrease these parameters; however, it significantly increased HDL cholesterol levels by 21%.

2.3 Fluvastatin

One hundred and forty-six women were included in a cohort of 834 participants with a mean age of 61 years and moderate hypercholesterolaemia (mean total cholesterol levels 5.8 mmol/L). The women were divided into two groups receiving either fluvastatin (70 women) or placebo (76 women) matched for several demographic characteristics including lipid profile, anginal status, relevant medical history, body mass index and extent of coronary artery disease.[31] Fluvastatin 80 mg/day resulted in a sustained 33% reduction in LDL cholesterol levels over 26 weeks. This was accompanied by a 28% reduction in apo B and a 13% decrease in triglyceride levels as compared with baseline values, but no changes in apo AI, HDL cholesterol or LP(a) levels. Although fluvastatin treatment was associated with a decrease in overall mortality and myocardial infarction at 40 weeks after percutaneous transluminal coronary angioplasty, the results of this investigation showed no benefits of fluvastatin in the prevention of restenosis.[31]

Thirty-five postmenopausal women with combined hyperlipidaemia and elevated dense LDL particles were treated with fluvastatin 40 mg/day for 12 weeks.[32] Fluvastatin therapy resulted in significant decreases in total cholesterol (–19%), intermediate-density lipoprotein cholesterol (–35%), LDL cholesterol (–23%), apo B (–21%) and apo B in dense LDL (–42%) compared with those in placebo-treated group (n = 17).

2.4 Lovastatin

A recent analysis of AFCAPS/TexCAPS (Air-Force/Texas Coronary Arthrosclerosis Prevention Study) data demonstrated that lovastatin 20–40 mg/day was associated with a 37% reduction in first acute major coronary events in a total of 997 postmenopausal women and 5 608 men. These participants had average LDL cholesterol but below average HDL cholesterol levels with no clinical evidence of cardiovascular disease.[33] The reductions in clinical events were accompanied by a 25% reduction in LDL cholesterol and a 9% increase in HDL cholesterol levels in postmenopausal participants. Furthermore, it was concluded that both men and postmenopausal women similarly benefited from lovastatin treatment.

The efficacy and tolerability of lovastatin 20–80 mg/day were investigated in 1 930 postmenopausal women with moderate hypercholesterolaemia.[34] Lovastatin treatment induced significant reductions in total (17–28%), LDL (24–40%) and triglyceride (9–18%) levels along with an average 8% increase in HDL cholesterol levels compared with baseline measurements. The lipid-lowering effects of lovastatin were dose-dependent. The addition of HRT to lovastatin did not significantly change the lipid values. Up to 0.4% of lovastatin recipients experienced serious drug-related adverse effects. Lovastatin 20 mg/day for 6 weeks also significantly reduced both total and LDL cholesterol levels in 24 postmenopausal women.[35] These changes were accompanied by moderate improvements in brachial artery flow-mediated vasodilator capacity.

2.5 Atorvastatin

Aggressive lipid-lowering therapy with atorvastatin 80 mg/day and its effects on atherosclerotic plaque burden is being evaluated in 600 postmenopausal women.[38] This multicentre, randomised, double-blind, parallel-group study is designed to address the actual incidence of CHD in postmenopausal women and to evaluate the extent of lipid-lowering strategies (aggressive vs moderate) on progression of atherosclerosis.

2.6 Other Trials

In a retrospective study of 125 862 elderly individuals, including 72 398 women (aged 65 years or older),[36] the women were divided into three groups and treated with thyroid replacement hormones (n = 29 286), statins (n = 39 842) or non-statin lipid-lowering agents (n = 6 270). These postmenopausal individuals who were free of a history of angina, myocardial infarction, peripheral vascular disease, cancer diagnosis or a diagnosis of

deep vein thrombosis (DVT) within 36 months of enrolment were followed up for development of DVT over 8 years.[36] During a period of observation (1.1–1.4 years), statin therapy was associated with the lowest rate of DVT in postmenopausal women with 8.1 cases of DVT per 1 000 person-years. This rate was higher in the two other groups of women, namely non-statin lipid-lowering group and thyroid replacement therapy, with 10.1 and 12 cases of DVT per 1 000 person-year, respectively. The study reported that women receiving statin therapy benefited more from the treatment than participant men. Parallel to this study, a cohort of women only (mean age 73.5 years) were divided into four groups and treated with the three above-mentioned treatments or estrogen therapy. Whereas the incidence rate for DVT was again the lowest in the statin-treated group, the estrogen-treated group had the highest rate. Both arms of the study indicated a lower adjusted hazard ratio for statin therapy than for the other treatments in postmenopausal women.[36]

3. Potential Benefits from Statin Therapy Beyond Cholesterol-Lowering Effects

3.1 Effects on Endothelial Cells

Endothelial dysfunction is one of the earliest manifestations of atherosclerotic vascular disease. Abnormalities in synthesis, release and activity of endothelium-derived NO are the main feature of endothelial dysfunction resulting in impaired vessel wall function. Hypercholesterolaemia induces endothelial dysfunction and acute reductions in LDL cholesterol levels by LDL apheresis improves endothelium-dependent vasodilatation.[39] This indicates that statin therapy may enhance endothelial function by reducing plasma LDL cholesterol. However, other studies suggest that beneficial effects of statins on endothelial function may be independent of their LDL-cholesterol lowering effects. For example, restoration of endothelial function was noticed before significant reductions in plasma cholesterol levels.[40] Statin therapy was also associated with up-regulation of endothelial NO synthase leading to increased bioavailability of NO.[41] As superoxide anion can inactivate NO and cause vasoconstriction, antioxidant properties of the statins may also increase NO bioavailability by inhibiting the production of reactive oxygen substances resulting in enhanced endothelium-dependent vasodilation.[42] Moreover, Kureishi et al.[43] have shown that simvastatin promotes angiogenesis in ischaemic limbs of normocholesterolaemic rabbits, an effect similar to that of vascular endothelial growth factor (VEGF).

3.2 Effects on Vascular Smooth Muscle Cells

Migration and proliferation of vascular smooth muscle cells are among major events in the pathogenesis of atherosclerotic vascular disease. Statins may inhibit vascular smooth muscle cell proliferation by arresting the cell cycle.[44] This is most likely mediated through Ras and Rho (two small guanine triphosphate [GTP]-binding proteins implicated in cell cycle regulation) mechanisms. Evidence suggests that this effect of stains on vascular wall cells is due to inhibition of synthesis of isoprenoid intermediates but not cholesterol synthesis.

This mechanism may also contribute to the potential anti-osteoporosis effects of statins.[45] It should be noted that anti-osteoporosis effects of statins are still controversial as several studies failed to observe a close association between statin therapy (at cholesterol-lowering dosages) and a significant reduction in risk of bone fracture.[45,46] Nevertheless, osteoporosis is another most common chronic disorder in postmenopausal women.

3.3 Potential Anti-Inflammatory Effects

Numerous inflammatory elements are implicated in the pathogenesis of atherosclerosis. It is believed that migration of monocytes into the subendothelial space and foam cell formation is an early stage in the development of atherosclerotic lesions. Cytokines produced by these inflammatory cells (macrophages and T cells) may influence endothelial function, smooth muscle cell proliferation, collagen degradation and the thrombotic

process.[47] Statin therapy may be associated with reductions in the number of inflammatory cells within the atherosclerotic lesions.[48] This may be mediated through the inhibition of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), which is totally independent of the inhibition of HMG-CoA reductase.[49] Moreover, further analysis of CARE (Cholesterol and Recurrent Events) and AFCAPS/TexCAPS trials showed that statin therapy was associated with a significant reduction in plasma hs-CRP (C reactive protein measured by high sensitivity assay) levels,[50,51] and elevated levels of hs-CRP are a predictive of increased risk for CHD in women.[52] A recent study by Koh et al.[53] has reported that the addition of simvastatin to estrogen may attenuate estrogen-induced increases in the level of CRP in postmenopausal women.

3.4 Effects on Thrombus Formation and Embolism

Plaque rupture and thrombus formation account for most of acute coronary events. Platelet activity and the nature of plaque fibrous cap play an important role in the incidence of acute coronary events. Statins can contribute to plaque stability by several mechanisms including reducing plaque size, decreasing the number of inflammatory cells in the plaque and reducing the production of collagen-degrading enzymes, such as matrix metalloproteinases (MMPs), and inhibition of tissue factor production. Statins can reduce expression of MMPs and tissue factor by both cholesterol-dependent and -independent mechanisms.[54] Statins can also reduce the production of thromboxane A2 resulting in decreased platelet function.[55] Several animal studies have suggested inhibition of platelet deposition and platelet thrombus formation by statins.[56] Altogether, beneficial effects of statins on hemostasis may play a significant role in the overall reduction of cardiovascular risk.[57]

4. Discussion

The effects of aging on cardiovascular disease development vary between men and women. While cardiovascular disease is the leading cause of death in men by age 40 years, it is not so in women until age 70 years. This may be explained, at least in part, by dramatic changes in the quality of lipoproteins associated with the menopause. Postmenopausal women develop an atherogenic lipoprotein profile which can be beneficially modified by HRT. However, data from HERS showed unfavourable effects of HRT in secondary prevention of CHD in postmenopausal women. In addition, HRT may also be associated with severe adverse effects. Thus, there is a need for a better tolerated and more effective therapy to correct dyslipidaemia in postmenopausal women. In this regard, in addition to the total/HDL cholesterol ratio (as a dyslipidaemic risk), presence of additional risk factors, including a history of myocardial events, obesity and type II diabetes, should be considered in the pharmacological management of CHD in postmenopausal women.

Although recent large clinical trials with statins[58-61] have shown safety and efficacy in both primary and secondary prevention in middle-age adults, the long-term effects of these agents in elderly populations await further documentation. Approximately half of the participants of the 4S study (Scandinavian Simvastatin Survival Study)[58] were over 60 years of age and treatment with simvastatin in this age group resulted in a significant 27% reduction in mortality rate along with a 29% reduction in coronary events. In particular, the coronary event rate in simvastatin-treated women (n = 407) was 30% lower than that in placebo-treated women (n = 420) [14.5 vs 21.6%]. CARE[59] was another secondary prevention trial which recruited patients with a history of myocardial infarction with a mean age of 59 years. Subgroup analysis of this trial revealed similar benefits from pravastatin therapy in patients below and above 60 years of age. However, coronary events were more common in treated women (39 of 290) than in the placebo group (23 of 286). Of 1 516 women who participated in LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) study,[60] 756 women were treated with pravastatin

and the rest (n = 760) received placebo. Ninety coronary events were reported in the pravastatin-treated group and 104 coronary events in the placebo-control group. The AFCAPS/TexCAPS[61] reported 1.4 and 2.6% coronary event rates in the lovastatin-treated and placebo-control women, respectively, in a primary prevention setting.

These primary and secondary prevention studies along with the clinical pharmacology of the statins have been summarised elsewhere.[62,63] Furthermore, several small-scale clinical trials (as discussed in section 2) have shown substantial LDL cholesterol lowering effects of statins in postmenopausal women. All these data suggest a place for statins in management of dyslipidaemia associated with menopause. It should be noted that unlike HRT,[64] statins do not reduce lipoprotein(a) levels.[26,31] Plasma levels of this potentially atherogenic lipoprotein are increased after menopause.[65] Thus, several lines of evidence suggest cardiovascular benefits from the combination of statins with HRT in postmenopausal women.[22,35,53,57,64]

5. Conclusion

Postmenopausal-associated dyslipidaemia and its potential cardiovascular implications can be corrected pharmacologically. In this regard, evidence for the safety and efficacy of statins is strong. However, whether statin therapy results in a lower rates for cardiovascular events and a better quality of life in postmenopausal women must be answered by randomised, placebo-controlled, large-scale, double-blind clinical trials. Similarly, several remaining questions regarding safety and efficacy of HRT are being addressed by large ongoing clinical trials.[66,67]

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References

1. Colditz GA, Willett WC, Stampfer MJ, et al. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987; 316: 1105-10
2. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses's Health Study. N Engl J Med 1991; 325: 756-62
3. Stampfer MJ, Colditz GA. Estrogen replacement and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991; 20: 47-63
4. American College of Physicians. Guidelines for counseling postmenopausal women about preventive hormone therapy. Ann Intern Med 1992; 117: 1038-41
5. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995; 332: 1589-93
6. Belchetz PE. Hormonal treatment of postmenopausal women. N Engl J Med 1994; 330: 1062-71
7. Brown SA, Hutchinson R, Morrisett JD, et al. Plasma lipid, lipoprotein cholesterol, and apoprotein distributions in selected US communities: the Atherosclerosis Risk in Communities (ARIC) study. Arterioscler Thromb 1993; 13: 1139-58
8. Kannel WB. Prospects for prevention of cardiovascular disease in the elderly. Prev Cardiol 1998; 1: 32-9
9. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. JAMA 1995; 273: 199-208
10. Walsh BW, Schiff I, Rosner B, et al. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med 1991; 325: 1196-204
11. Sacks FM, Walsh BW. Sex hormones and lipoprotein metabolism. Curr Opin Lipidol 1994; 5: 236-40
12. Collins P, Rosano GMC, Sarrel PM, et al. 17β-estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. Circulation 1995; 92: 24-30
13. Sack MN, Rader DJ, Cannon RO. Oestrogen and inhibition of oxidation of low-density lipoproteins in postmenopausal women. Lancet 1994; 343: 269-70
14. Vargas R, Wroblewska B, Rego A, et al. Oestradiol inhibits smooth muscle proliferation of pig coronary artery. Br J Pharmacol 1993; 109: 612-7
15. Proudler AJ, Ahmed AIH, Crook D, et al. Hormone replacement therapy and serum angiotensin-converting-enzyme activity in postmenopausal women. Lancet 1995; 346: 89-90
16. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998; 280: 605-13
17. Fak AS, Erenus M, Tezcan H, et al. Effects of simvastatin only or in combination with continuous combined hormone replacement therapy on serum lipid levels in hypercholesterolemic postmenopausal women. Eur Heart J 2000; 21: 190-7
18. Darling GM, Johns JA, McCloud PI, et al. Estrogen and progestin compared with simvastatin for hypercholesterolemia in postmenopausal women. N Engl J Med 1997; 337: 595-601
19. Nakajima K. Sex-related differences in response of plasma lipids to simvastatin: the Saitama Postmenopausal Lipid Intervention Study. S-POLIS Group. Clin Ther 1999; 21: 2047-57
20. Ohmichi M, Ikegami H, Kurachi H, et al. Effects of bezafibrate and simvastatin on plasma lipoproteins in hypercholesterole-

mia resistant to hormone replacement therapy. Maturitas 2001; 38: 279-86
21. Sbarouni E, Kyriakides ZS, Kremastinos DTH. The effect of hormone replacement therapy alone and in combination with simvastatin on plasma lipids of hypercholesterolemic postmenopausal women with coronary artery disease. J Am Coll Cardiol 1998; 32: 1244-50
22. Koh KK, Cardillo C, Bui MN, et al. Vascular effects of estrogen and cholesterol-lowering therapies in hypercholesterolemic postmenopausal women. Circulation 1999; 99: 354-60
23. Wakatsuki A, Okatani Y, Ikenoue N. Effects of combination therapy with estrogen plus simvastatin on lipoprotein metabolism in postmenopausal women with type IIa hypercholesterolemia. Atherosclerosis 2000; 150: 103-11
24. Wakatsuki A, Ikenoue N, Izumiya C, et al. Effect of estrogen and simvastatin on low-density lipoprotein subclasses in hypercholesterolemic postmenopausal women. Obstet Gynecol 1998; 92: 367-72
25. Averbuch M, Ayalon D, Eckstein N, et al. Hormone replacement and simvastatin in the therapy of hypercholesterolemic postmenopausal women. J Med 1998; 29: 343-50
26. Gavish D, Leibovitz E, Shapira I, et al. Bezafibrate and simvastatin combination therapy for diabetic dyslipidaemia: Efficacy and safety. J Intern Med 2000; 247: 563-9
27. Ozsener S, Sendag F, Koc T, et al. A comparison of continuous combined hormone replacement therapy, HMG-CoA reductase inhibitor and combined treatment for the management of hypercholesterolemia in postmenopausal women. J Obstet Gynecol Res 2001; 27: 353-8
28. Lemay A, Dodin S, Turcot L, et al. Estrogen/progesterone replacement versus pravastatin and their sequential association in hypercholesterolemic postmenopausal women. Maturitas 2001; 40: 247-57
29. Ushiroyama T, Ikeda A, Ueki M. Beneficial effects of pravastatin in pre- and post-menopausal hyperlipidemic women: a 5 year study on serum lipid and sex hormone levels. Maturitas 2001; 37: 201-8
30. Davidson MH, Testolin LM, Maki KC, et al. A comparison of estrogen replacement, pravastatin, and combined treatment for the management of hypercholesterolemia in postmenopausal women. Arch Intern Med 1997; 157: 1186-92
31. Serruys PW, Foley DP, Jackson G, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restonosis after successful coronary ballon angioplasty. Eur Heart J 1999; 20: 58-69
32. Marz W, Scharnagl H, Abletshauser C, et al. Fluvastatin lowers atherogenic dense low-density lipoproteins in postmenopausal women with the atherogenic lipoprotein phenotype. Circulation 2001; 103: 1942-8
33. Clearfield M, Downs JR, Weis S, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAP/TexCAPS): efficacy and tolerability of long-term treatment with lovastatin in women. J Womens Health Gend Based Med 2001; 10: 971-81
34. Bradford HB, Downton M, Chremos AN, et al. Efficacy and tolerability of lovastatin in 3390 women with moderate hypercholesterolemia. Ann Intern Med 1993; 118: 850-5
35. Herrington DM, Werbel BL, Riley WA, et al. Individual and combined effects of estrogen/progestin therapy and lovastatin on lipids and flow-mediated vasodilation in postmenopausal women with coronary artery disease. J Am Coll Cardiol 1999; 33: 2030-7
36. Ray JG, Mamdani M, Tsuyuki RT, et al. Use of stains and the subsequent development of deep vein thrombosis. Arch Intern Med 2001; 161: 1405-10
37. Sbarouni E, Melissari E, Kyriakides ZS, et al. Effects of simvastatin or hormone replacement therapy, or both, on fibrinogen, factor VII, and plasminogen activator inhibitor levels in postmenopausal women with proven coronary artery disease. Am J Cardiol 2000; 86: 80-3
38. Raggi P, Callister TQ, Davidson M, et al. Aggressive versus moderate lipid-lowering therapy in postmenopausal women with hypercholesterolemia: rationale and design of the Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES) trial. Am Heart J 2001; 141: 722-6
39. Tamai O, Matsuoka H, Itabe H, et al. Single LDL apheresis improves endothelium-dependent vasodilatation in hypercholesterolemic humans. Circulation 1997; 95: 76-82
40. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme a: reductase inhibitor, improves endothelial function within 1 month. Circulation 1997; 95: 1126-31
41. Laufs U, La Fata V, Plutzky J, et al. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998; 97 (12): 1129-35
42. Rikitake Y, Kawashima S, Takeshita S, et al. Antioxidant properties of fluvastatin, an HMG-CoA reductase inhibitor, contribute to prevention of atherosclerosis in cholesterol-fed rabbits. Atherosclerosis 2001; 154: 87-96
43. Kureishi Y, Luo Z, Shiojima I, et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. Nat Med 2000; 6: 1004-110
44. Yang Z, Kozai T, van der Loo B, et al. HMG-CoA reductase inhibition improves endothelial cell function and inhibits smooth muscle cell proliferation in human saphenous veins. J Am Coll Cardiol 2000; 36: 1691-7
45. Moghadasian MH, Frohlich JJ. Statins and bones. Can Med Assoc J 2001; 164: 803-5
46. Van Staa TP, Wegman S, de Vries F, et al. Use of statins and risk of fractures. JAMA 2001; 285: 1850-5
47. Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995; 91: 2844-50
48. Vaughn CJ, Gotto AM, Basson CT. The evolving role of statins in the management of atherosclerosis. J Am Coll Cardiol 2000; 35: 1-10
49. Niwa S, Totsuka T, Hayashi S. Inhibitor effect of fluvastatin, an HMG-CoA reductase inhibitor, on expression of adhesion molecules on human monocyte cell line. Int J Immunopharmacol 1996; 18: 669-75
50. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of statin therapy in primary prevention of acute coronary events. N Engl J Med 2001; 344: 1959-65
51. Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein: the Cholesterol and Recurrent Events (CARE) Investigators. Circulation 1999; 100: 230-5
52. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836-43
53. Koh KK, Schenke WH, Waclawiw MA, et al. Statin attenuates increases in C-reactive protein during estrogen replacement therapy in postmenopausal women. Circulation 2002; 105: 1531-3
54. Aikawa M, Rabkin E, Sugiyama S, et al. An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macro-

phages expressing matrix metalloproteinases, and tissue factor in vivo and in vitro. Circulation 2001; 103: 276-383
55. Schror K. Platelet reactivity and arachidonic acid metabolism in type II hypercholesterolemia and its modification by cholesterol-lowering agents. Eicosanoids 1990; 3: 67-73
56. Alfon J, Royo T, Garcia-Moll X, et al. Platelet deposition on eroded vessel walls at a stenotic shear rate is inhibited by lipid-lowering treatment with atorvastatin. Arterioscler Thromb Vasc Biol 1999; 19: 1812-7
57. Koh KK. Effects of HMG-CoA reductase inhibitor on hemostasis. Int J Cardiol 2000; 76: 23-32
58. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9
59. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. N Engl J Med 1996; 335: 1001-9
60. LIPID Study Group: Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study group. N Engl J Med 1998; 339: 1349-57
61. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. Air force/Texas coronary atherosclerosis prevention study. JAMA 1998; 279: 1615-22
62. Moghadasian MH, Mancini GBJ, Frohlich JJ. Pharmacotherapy of hypercholesterolemia: statins in clinical practice. Exp Opin Pharmacother 2000; 1: 683-95
63. Moghadasian MH. Clinical pharmacology of 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors. Life Sci 1999; 65: 1329-37
64. Soma MR, Osnago-Gadda I, Paoletti R, et al. The lowering of lipoprotein(a) induced by estrogen plus progesterone replacement therapy in postmenopausal women. Arch Intern Med 1993; 153: 1462-8
65. Jenner JL, Ordovas JM, Lamon-Fava S, et al. Effects of age, sex, and menopausal status on plasma lipoprotein(a) levels: the Framingham Offspring Study. Circulation 1993; 87: 1135-41
66. The Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. Controlled Clin Trials 1998; 19: 61-109
67. Kmietowicz Z. Women's health study signs up million women. BMJ 2000; 321: 981

Correspondence and offprints: Dr *Mohammed H. Moghadasian*, 180 Healthy Heart Program, St. Paul's Hospital, 1081 Burrard Street, Vancouver, BC, V6Z 1Y6, Canada.
E-mail: mhmoghad@interchange.ubc.ca