Recent trials of postmenopausal hormone therapy have shown lack of cardiovascular benefit or possible harm among women with and without underlying cardiovascular disease [1-7]. Despite a favorable impact on several cardiovascular risk markers, hormone therapy is thus not recommended for the primary or secondary prevention of cardiovascular disease. [8] Although alternatives are available, hormone therapy remains the most effective treatment for postmenopausal hot flashes and may be indicated for postmenopausal urogenital problems and for prevention and treatment of postmenopausal osteoporosis. [8]

Statins, in contrast, have been shown in randomized, controlled, double-blind trials to reduce coronary heart disease morbidity among women with hyperlipidemia and those at high cardiovascular risk [9]. It has been suggested that statins, when used in conjunction with hormone replacement therapy, may accentuate the apparent beneficial effects of postmenopausal hormone therapy on cardiovascular risk markers and mitigate adverse effects of hormone replacement therapy [10], but data on the interaction between statins and postmenopausal hormone therapy remain limited. This paper will review the available data on combination therapy with statins and hormones.

Statin therapy and sex-hormone levels
Reproductive hormones such as estrogen, progesterone, and testosterone are synthesized from a common cholesterol precursor pathway. It is thus possible that statin therapy could lower reproductive hormone levels. Two recent studies specifically address this issue [11,12]. Ushiroyama et al. treated 121 women (47 premenopausal, 74 postmenopausal) for 5 years with pravastatin and assessed the impact of therapy on the lipid profile and on levels of reproductive hormones [11]. Changes over time in levels of sex gonadotropins and sex steroids (estradiol, estrone, testosterone) were similar to those previously published for women not on statin therapy. Investigators from the Women's Ischemia Syndrome Evaluation (WISE) study analyzed data from 453 women with coronary heart disease risk factors who were referred to participating WISE centers for clinically indicated coronary angiography and who were not on oral contraceptives or postmenopausal hormone therapy [12]. Mean age was 53 years and 27% of the women were on statin therapy. Levels of estradiol, estrone, and progesterone did not correlate with statin therapy among the group overall nor in subgroups of premenopausal, perimenopausal and postmenopausal women. None of the randomized statin trials have measured reproductive hormone levels, but the available data suggests that statins do not adversely impact circulating reproductive hormone levels, at least among middle-aged and older women.

Lipoprotein effects of statin/hormone combination therapy
Orally administered postmenopausal hormone therapy lowers low-density lipoprotein cholesterol (LDL-C) levels, increases high density lipoprotein (HDL-C) levels (estrogen monotherapy to a greater extent than estrogen/progestin therapy), lowers lipoprotein(a) (Lp(a)) levels, but increases triglyceride levels [13,14]. Transdermal hormone replacement regimens have minimal effects on lipid levels. Statins are powerful LDL-C lowering agents, lower triglycerides and modestly increase HDL-C levels, but do not affect Lp(a) levels [15].

Several small, short-term studies have investigated the effect of combined statin/hormone therapy among postmenopausal women [16-20]. Davidson and colleagues compared lipoprotein effects of placebo, conjugated estrogen (0.625 mg), pravastatin (20 mg) and the combination of estrogen plus pravastatin in a group of hyperlipidemic postmenopausal women (4 group parallel design, 22 women per group, 16 weeks of treatment) [16]. Pravastatin lowered non-HDL-C (-23.7%) and LDL-C (-25.4%) to a greater extent than estrogen therapy alone (-13% and -13.5%, respectively), while estrogen increased HDL-C to a much greater extent than pravastatin therapy (+22.5% versus +3.7%). Pravastatin lowered triglycerides while estrogen therapy resulted in a small increase. When the two agents were combined, non-HDL-C and LDL-C were lowered to an extent similar to that seen with pravastatin monotherapy and HDL-C increased to a similar extent as that seen with estrogen monotherapy. The combination treatment was "triglyceride-neutral". Similar effects were observed by Sbarouni et al. when combining conjugated estrogen (0.625 mg) plus medoxyprogesterone acetate (2.5 mg).
therapy with simvastatin therapy (20 mg) for 8 weeks [17]. The combination lowered total cholesterol, LDL-C, and apoprotein B to a similar degree as simvastatin monotherapy, increased apolipoprotein A-I by 12% (compared to 11% with hormone therapy alone), and decreased Lp(a) even further than hormone therapy alone (-33% versus -23%). Significantly more women reached their secondary prevention "goal levels" with the combination treatment which was well tolerated in this short-term study. Herrington et al. compared estrogen/progestin therapy, lovastatin therapy and combined therapy in a cross-over design with 6 week treatment periods [18]. Compared to the other treatment regimens, the combination of hormones and statin resulted in the greatest reduction in total cholesterol and LDL-C (-21% and -31%, respectively) and the greatest increase in HDL-C (+17%). The addition of the statin abolished the hormone-mediated increase in triglyceride levels. Ohta and colleagues compared very low doses of pravastatin monotherapy (10 mg daily) versus pravastatin combined with hormone therapy (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) after 4 weeks and 12 weeks of therapy [19]. Women in the combined group had lower LDL-C levels than women in the pravastatin group at 4 weeks, but the difference was no longer significant at 12 weeks. The investigators concluded that the combination regimen lowered LDL-C levels earlier than pravastatin therapy alone, but without net benefit overall. Lemay and colleagues compared 6 months of estrogen/progestin therapy (conjugated estrogens 0.625 mg combined with micronized progesterone 200 mg daily) or statin therapy (pravastatin 40 mg) with 6 months of hormone/statin combination therapy [20]. The investigators showed greater LDL-C reductions and greater HDL-C increases with the combination regimen with proportional changes in apolipoproteins B-100 and A-1. The total/HDL-C ratio decreased from 5.87 to 3.52 with the combination regimen. Triglycerides increased with hormone therapy, decreased with statin therapy, and were similar to baseline on the combined regimen.

These studies suggest that combined hormone/statin therapy accentuates the beneficial changes seen with each regimen alone with a net favorable impact on the lipid profile by decreasing LDL-C, apo B-100, and Lp(a) levels and increasing HDL-C and apolipoprotein A-I levels with minimal changes in serum triglycerides.

### Inflammatory Markers and Endothelial Function

Orally administered hormone therapy has heterogeneous effects on inflammatory markers in postmenopausal women. C-reactive protein tends to increase while levels of soluble adhesion molecules (E-selectin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1)), monocyte chemoattractant protein-1 (MCP-1), and soluble tumor necrosis factor alpha (TNF-alpha) tend to decrease [21]. Matrix metalloproteinase-9, a marker for plaque instability, has been shown to increase with hormone therapy [22]. Whether orally administered hormones are net pro- or anti-inflammatory is unknown and may well vary from individual to individual depending on age, body weight, lifestyle and co-morbidities. In contrast, statins consistently demonstrate anti-inflammatory properties which appear to be at least in part independent of the lipid-lowering effects [15]. Improvements in endothelial function have been documented with hormone therapy and with statin therapy.

Data on combination hormone/statin therapy is limited. Koh et al. compared the effects of conjugated equine estrogen (0.625 mg), simvastatin (10 mg), and the combination of conjugated equine estrogen plus simvastatin on lipoprotein levels, plasminogen activator inhibitor-1 and E-selection levels, and endothelial function in a 6 week study among 28 postmenopausal women [23]. LDL-C levels were reduced to a greater extent by the combination than by estrogens alone. The combination raised HDL-C and lowered Lp(a) levels to a greater extent than statin therapy alone. Only estrogen-containing regimens had a beneficial impact on plasminogen activator inhibitor 1 levels and E-selectin. The improvement in flow-mediated vasodilatation of the brachial artery was similar for estrogen therapy, statin therapy, and the combination; none of the regimens affected endothelial-independent vasodilatation. In a subsequent report from the same dataset, Koh et al. reported that statin therapy attenuated the estrogen-induced rise in C-reactive protein (29% increase on the combination versus 70% increase with estrogen monotherapy) while interleukin-6 levels did not change. Sbarouni et al. analyzed the effect of simvastatin, estrogen/progestin therapy, and the combination of simvastatin with the hormone regimen on inflammatory markers including plasma concentrations of ICAM-1, VCAM-1 and E-selectin [25]. Simvastatin monotherapy had no significant impact on ICAM-1, VCAM-1, or E-selectin levels while hormone therapy lowered ICAM-1, but did not significantly affect VCAM-1 or E-selectin levels. When simvastatin was combined with hormone therapy, ICAM-1 was lowered to a similar degree as with hormone therapy alone. Herrington and colleagues could not demonstrate any added benefit on endothelial function when conjugated equine estrogen and medroxyprogesterone acetate were combined with 20 mg of lovastatin. [18]

Although these data are promising, it is premature to conclude that statins could counteract potentially adverse effects of hormone therapy on inflammation and plaque stability or that the combination of hormone therapy and statins has net anti-inflammatory effects. It is likely that the net-effect will be variable depending on dose and type of hormone regimen, dose of statin, and patient characteristics including co-morbidities and stage of atherosclerosis.
Subclinical Atherosclerosis
The Asymptomatic Carotid Atherosclerosis Progression Study (ACAPS) randomized patients to lovastatin and warfarin in a factorial design and evaluated progression of carotid intimal medial thickness (IMT) by serial B-mode ultrasounds [26]. Lovastatin significantly decreased progression of carotid IMT over 3 years of follow-up. Estrogen use (non-randomized) among the 186 postmenopausal women enrolled in ACAPS was also associated with decreased progression of carotid IMT, however this effect was only apparent among the women in the placebo group [26]. Estrogen therapy did not enhance the effect of statin on IMT progression. Similar results were reported in 2001 in the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), a prospective study of IMT progression among 222 postmenopausal women randomized to micronized 17 beta estradiol 1mg daily or placebo.[27] Progression rate was lower among patients randomized to estradiol than those randomized to placebo. Placebo patients who were taking lipid-lowering medications had less IMT progression than those not on such therapy. Among estradiol treated patients, statin therapy did not have any additional beneficial impact. Progression rates among estradiol patients not on lipid lowering therapy and placebo patients on lipid-lowering therapy were similar. For prevention of IMT progression, the combination of estrogen plus statin thus does not seem to have any advantages over statin therapy alone.

Clinical Events
In the Heart and Estrogen/progestin Replacement Study (HERS), 1004 women (36.3%) used statins at baseline (evenly distributed between the hormone and placebo groups) and an additional 708 women initiated statin therapy during the trial (385 placebo patients and 323 patients assigned to hormone therapy, p=0.005) [28]. This provided the HERS investigators with an opportunity to explore interactions between estrogen/progestin therapy and statin use. Statin users experienced 22% fewer primary coronary heart disease (CHD) events (myocardial infarction or CHD death) than non-users (p=0.044), had 56% fewer thromboembolic events (p=0.033) and all cause mortality was reduced by 26% (p=0.04). These risk reductions were most pronounced among women who took statins for 3 or more years during the trial.

Statin use did not abolish the increased risk of thromboembolic events attributable to hormone therapy. CHD event rates during year 1 differed significantly by hormone therapy / statin status: women assigned to hormone therapy and not on a statin at baseline had a 75% increase in risk for primary CHD events (RH 1.75, 95% CI 1.02-3.03) while women assigned to hormone therapy who were on a statin at baseline had a lower relative hazard in year 1 which was not statistically significant (RH 1.34, 95% CI 0.63-2.86). This apparent beneficial effect during year 1 did not translate into overall benefit, however: the overall relative hazards for hormone therapy were nearly identical in statin users and non-users (0.99 for non-users, 0.97 for users).

Conclusion
Available data suggest that statin therapy when combined with postmenopausal hormone therapy has added beneficial effects on the lipoprotein profile and may attenuate the adverse impact of hormone therapy on some inflammatory markers. Favorable effects of statin monotherapy and hormone monotherapy on brachial reactivity and carotid IMT progression do not appear to be additive when the two regimens are combined. There is no study specifically designed to assess the impact of combination therapy with hormones and statins on cardiovascular morbidity and mortality. It is unlikely that such a prospective, factorial trial (placebo versus statin versus hormone therapy versus statin/hormone therapy) will ever be done. The post-hoc analyses from HERS suggest that statins may protect against the increased risk of cardiovascular events early after starting hormone therapy, but this early benefit did not translate into a significant impact on the overall outcome of the trial. Similarly, statin use did not abolish the increased risk of thromboembolic events associated with hormone therapy. None of the studies reviewed have shown any adverse impact of adding statins to hormone therapy.

Based on the available data on combination therapy, statin therapy should not be withheld from women who have statin-indications and are already on hormone therapy for non-cardiovascular reasons. Hormone therapy in turn is not a substitute for statins in primary and secondary prevention of cardiovascular disease.

Bibliography

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