Does tibolone exacerbate atherosclerosis?

Thomas B. Clarkson*

Wake Forest University School of Medicine, Comparative Medicine Clinical Research Center, Medical Center Boulevard, Winston-Salem, NC 27157-1040, USA

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This editorial refers to 'The effect of tibolone and continuous combined conjugated equine oestrogens plus medroxyprogesterone acetate on progression of carotid intima–media thickness: the Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) study'† by M.L. Bots et al., on page 746

Tibolone is widely used in many countries (though not in the USA) for the treatment of post-menopausal symptoms and to inhibit post-menopausal bone loss. Tibolone’s popularity likely reflects the observation that it equals traditional hormone therapy in the relief of hot flushes, vaginal dryness, and the prevention of bone loss and, in addition, appears to increase libido. The post-menopausal benefits of tibolone relate to the uniqueness of the metabolism of the parent molecule. In human and non-human primates, tibolone is converted to three metabolites. Two are weak estrogen agonists (the 3-alpha and 3-beta hydroxy metabolites). The third metabolite, the delta-4 isomer, is a molecule that binds both to the progesterone receptor and to the androgen receptor with progestogenic and androgenic effects.

Although tibolone has numerous benefits for post-menopausal women, it markedly lowers plasma concentrations of the HDL with consistent reductions of HDL cholesterol (HDLc) and ApoA1. The magnitude of the reductions is generally 20–30%. Because there is a strong inverse relationship between both HDLc and ApoA1 and the occurrence of coronary heart disease (CHD) among women not taking hormones, there has been concern that tibolone-induced reductions in HDLC and ApoA1 might increase risk for CHD. However, recent studies have shown in women and monkeys that hormone-therapy-induced alterations in HDLC or ApoA1 do not easily translate into changes in CHD risk. For example, in such studies, only ~25–30% of the ability of estrogens to inhibit progression of atherosclerosis relates to changes in plasma lipids/lipoproteins; whereas 70–75% relates to their direct effects on arteries. Those estimates, which are based on estradiol and conjugated equine estrogens (CEE), may not extend to weaker estrogens, such as the 3-alpha and 3-beta hydroxyl metabolites of tibolone. It has thus been uncertain whether tibolone’s adverse HDLc effects should be expected to accelerate atherosclerosis and thereby increase CHD risk.

Bots et al.1 report the effect of tibolone on the progression of carotid artery atherosclerosis, using carotid artery intima–media thickness as the indicator of progression or regression. The comparator group in that trial was CEE plus medroxyprogesterone acetate (MPA), both given continuously. Unfortunately, because of unexplained inconsistencies in the trial outcomes, there remains uncertainty about whether and to what extent tibolone affects atherosclerosis in post-menopausal women. Before commenting on OPAL, it is helpful to consider the comparative and experimental evidence that tibolone is neutral in its effects on atherosclerosis and weigh that evidence in light of the OPAL trial outcomes.

That estrogen administration results in a ‘disconnect’ in the usual relationship between plasma lipid/lipoprotein concentrations and atherosclerosis progression was first shown in pre-menopausal monkeys treated with an oral contraceptive containing ethinyl estradiol and a progestin.2 This hormonal exposure, which markedly reduced HDLC, should have exacerbated atherogenesis but instead reduced lesion extent by 88%. It appeared that the estrogen benefits to arterial metabolism offset the deleterious effects of the reduced HDLC. Additional evidence for a ‘disconnect’ between the plasma lipid concentrations and the progression of coronary artery atherosclerosis came from a study of surgically post-menopausal monkeys that were administered estradiol by way of a silastic implant. Estradiol resulted in a 50% reduction in coronary artery atherosclerosis extent without any significant changes in the plasma lipid/lipoprotein profiles.3 Recently, studies of women have confirmed our findings in the monkey.4 The well-known Estrogen in the Prevention of Atherosclerosis Trial (EPAT) found that only 30% of the beneficial effect of estradiol on carotid artery intima–media thickness progression was due to alterations in HDLC and LDLc.

Studies of surgically post-menopausal cynomolgus monkeys have added to understanding of the effects of tibolone-induced perturbations of plasma lipoproteins on the progression of coronary artery atherosclerosis. Although female monkeys are not women, they closely resemble women in reproductive characteristics and vulnerability to chronic disease. Moreover, using the monkey model, it is possible to obtain direct pathological measurements of extent of coronary artery atherosclerosis. In
contrast, studies of women must rely on a surrogate artery (carotid artery) and on a measurement that includes both the thickness of the media and the thickness of the intimal plaque. Post-menopausal cynomolgus monkeys, which share with post-menopausal women decreases in HDLC following tibolone treatment (40–50% decreases observed with monkeys), were used in a trial to evaluate the effects of two doses of tibolone (LoTib) or 2.5–3.0 mg women’s equivalent dose (HiTib) on coronary and carotid artery atherosclerosis.5 The primary objective was to determine whether tibolone-induced reductions in plasma concentrations of HDLC were associated with exacerbation of coronary and carotid artery atherosclerosis. There were two comparator groups: CEE given at a women’s equivalent of 0.625 mg/day and CEE + MPA with the same CEE dose and women’s equivalent of 2.5 mg MPA/day. Both CEE and CEE + MPA resulted in reduced atherosclerosis extents. Despite the tibolone-treated monkeys having reduced plasma concentrations of HDLC, atherosclerosis was neither exacerbated in the coronary nor common and internal carotid arteries compared to the control group. A metabolic explanation for this observation was sought by measuring the cholesterol efflux potential of each monkey’s serum using 3H-labelled cholesterol and Fu5AH cells.6 With a 30% reduction in HDLC, there was no reduction in the efflux potential. Even with a 50% reduction in HDLC, there was only a 14% reduction in efflux. It was concluded that even though HDLC was reduced by tibolone, reverse cholesterol transport was not compromised and thus atherosclerosis was not exacerbated, consistent with reports of von Eckardstein et al.7 who found no detriment in cholesterol efflux capacity of post-menopausal women despite reductions of ~30% in HDLC following tibolone treatment.

The OPAL trial was similar to the monkey study in overall design except for the measured endpoint. The dose of tibolone used in the OPAL trial was comparable to the ‘HiTib’ dose in the monkey study and the doses of CEE + MPA were comparable in the two studies. In the monkey study, atherosclerosis extent was quantified using standard morphometric techniques. In the OPAL trial, carotid artery intima–media thickness was determined by B-mode ultrasound and two measures were derived. One was the mean carotid artery intima–media thickness (mean CIMT) and the other was the mean of maximal carotid artery thicknesses (meanMax CIMT). The authors state that they were uncertain whether mean CIMT or meanMax CIMT was the better of the predictors of risk. Nonetheless, the primary emphasis in the report is on mean CIMT.

What was learnt from the OPAL trial? When all women were considered together, both tibolone and CEE + MPA were found to increase CIMT. Separating them into US and European women reveals a problem. Neither tibolone nor CEE + MPA treatment adversely affected carotid artery atherosclerosis of US women if mean CIMT or meanMax CIMT was used as the outcome measurement. Both tibolone and CEE + MPA increased mean CIMT, but not meanMax CIMT, of European women. The differences in outcomes between US and European women remain unexplained. Figure 1 depicts the major differences in outcomes between the US and the European women and compared those outcomes with two similar trials, EPAT and ACAPS.6,9 The differences in outcomes between the US and the European women are striking. Although it might seem reasonable to statisticians to combine those two groups for an outcome for ‘all subjects’, as was done in Figure 2 of the report by Bots et al.,1 it does not seem biologically appropriate to a cardiovascular pathobiologist.

Several issues are unexplained: there appears to be no explanation for the placebo group of European women having experienced reduced mean CIMT progression; it is unknown whether the women having been ~10 years post-menopausal affected outcome or whether it mattered that nearly half of them were prior hormone users.

There are no other data suggesting that CEE + MPA increases mean CIMT more than placebo in older post-menopausal women. Byington et al.10 found no difference in change from baseline in mean CIMT among women receiving placebo or CEE + MPA in HERS.

In summary, the authors1 correctly conclude that neither tibolone nor CEE + MPA has favourable effects on atherosclerosis as measured by change from baseline in carotid artery intima–media thickness. That either of the two treatments exacerbates atherosclerosis progression is not supported convincingly by the OPAL data.

Conflict of interest: none declared.

References


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**Clinical vignette**

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**Combined cardiac congenital anomalies assessed by multi-slice spiral computed tomography**

Teresa Rius1,2*, Martin Goyenechea1, and Michael Poon1

1Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York, New York; 2Instituto de Medicina y Cardiologia, Centro Medico Teknon, Barcelona 08022, Spain

*Corresponding author. E-mail address: teresarius@hotmail.com

Case presentation: A 27-year-old male was admitted for work-up of severe hypertension unresponsive to medical therapy. Chest X-ray was normal except for slight enlargement of the vessels in the superior mediastinum. A thoracic aortogram demonstrated a focal aortic coarctation in the descending thoracic aorta with large intercostal and internal mammary artery collaterals (Panels A and B). Patient was referred for pre-operative coronary evaluation with multi-slice computed tomography (MSCT). Non-invasive coronary angiography was performed on 16-MSCT using a standard retrospective ECG-gated protocol. The study confirmed the presence of an aortic coarctation distal to the left subclavian artery with severe luminal narrowing (80% lumen reduction) combined with extensive collaterals distal to the aortic coarctation (Panels C and D), anomalous origin of the right coronary artery from the left coronary sinus coursing between the right ventricular outflow tract and the ascending aorta and no evidence of obstructive coronary artery disease (Panel E). MSCT represents a useful non-invasive diagnostic tool for the assessment of possible concomitant cardiac anomalies that may warrant additional surgical intervention at the time of the repair of the coarctation.

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Thoracic X-ray aortogram.

Panel A. A-P projection shows focal descending aortic coarctation.

Panel B. A-P projection demonstrates withdrawal of a catheter to the proximal descending aortic arch.

Panel C. MSCT images with three-dimensional volume rendering (3D-VR) reconstruction. A sagittal view shows coarctation of the aorta (blue arrow) distal to the left subclavian artery.

Panel D. Coronal view of the chest highlights extensive bilateral collaterals to the intercostal and vertebral arteries from the descending aorta.

Panel E. A 3D-VR reconstruction image of the heart. A cranial view of the aorta (Ao) shows anomalous origin of the right coronary artery (RCA) arising from the left coronary sinus (LCS).