FERTILITY AND STERILITY®
VOL. 79, NO. 2, FEBRUARY 2003

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Effect of tibolone treatment on intima-media thickness and the resistive indices of the carotid arteries

Mithat Erenus, M.D., A. Hakan Ilhan, M.D., and Koray Elter, M.D.

Department of Obstetrics and Gynecology, Marmara University School of Medicine, Istanbul, Turkey

Objective: To assess the effect of tibolone treatment on the intima-media thickness (IMT) of the common carotid artery (CCA) and the resistive indices (RIs) of the CCA and internal (ICA) and external (ECA) carotid and the vertebral arteries (VAs) in postmenopausal women as sonographic markers of atherosclerosis.

Design: A prospective study.

Setting: University hospital.

Patient(s): Twenty postmenopausal women who had no cardiovascular disease.

Intervention(s): Noninvasive measurements of the IMT of the CCA and the RI of the CCA, ICA, ECA, and VA were made with ultrasound at baseline and after 12 weeks of tibolone treatment.

Main Outcome Measure(s): IMT of the CCA and RI of the CCA, ICA, ECA, and VA.

Result(s): Three months of tibolone treatment decreased the IMT of the CCA (mean ± SD) from 0.70 ± 0.22 mm (95% confidence interval [CI], 0.60–0.80) to 0.47 ± 0.17 mm (95% CI, 0.39–0.55) by 28%. Resistive indices of the CCA, ICA, and VA also decreased significantly.

Conclusion(s): The present study showed that tibolone treatment decreases both the IMT of the CCA and RI of the CCA, ICA, and VA, which appears to be related to its anti-atherosclerotic effect. Nevertheless, the clinical implications of these findings are yet to be investigated. (Fertil Steril® 2003;79:268–73. ©2003 by American Society for Reproductive Medicine.)

Key Words: Tibolone, intima-media thickness, carotid arteries

Observational studies suggest that hormone replacement therapy (HRT) in healthy postmenopausal women reduces morbidity and mortality from cardiovascular disease (CVD) (1–4). Nevertheless, currently there is some dispute as to the validity of such claims. The presumed protective effect of the estrogens was initially attributed to changes in lipoprotein metabolism (2, 5–7). Subsequently, arterial effects of estrogen have been demonstrated by both endothelium-dependent and -independent mechanisms (8–13). Estrogens also protect the integrity of blood vessels by stimulating endothelial cell proliferation and migration, inhibiting smooth muscle cell growth, and inhibiting intimal thickening (8–10, 14).

Tibolone is a tissue-specific synthetic steroid that relieves menopausal symptoms and osteoporosis but does not stimulate the endometrium (15). Tibolone lowers serum cholesterol and triglyceride levels in healthy postmenopausal women (15). However, concern has arisen about cardiovascular safety because of reductions in high-density lipoprotein cholesterol concentrations. Nonetheless, there are no data on the long-term cardiovascular effects of the drug. Recently, it has been demonstrated in cholesterol-fed ovariectomized rabbits that tibolone exerts a strong dose-dependent anti-atherosclerotic effect compared with estrogens, which is independent of the effect of the drug on circulating cholesterol levels (2). To our knowledge, there has been no human study regarding the long-term vascular effects of tibolone.

The assessment of subclinical atherosclerosis in the carotid arteries can be accomplished noninvasively by means of B-mode ultrasound. The intima-media thickness (IMT) is, at present, the best studied sonographic marker for early atherosclerotic vascular wall lesions (16–21). Previous studies have shown cross-

Received February 14, 2002; revised and accepted June 5, 2002.
Supported by Organon A.S., Istanbul, Turkey.
Reprint requests: Mithat Erenus, M.D., Gulistan sk. 13/6, 81060 Goztepe, Istanbul, Turkey (FAX: 90-216-326-68-09; E-mail: erenus@superonline.com).

0015-0282/03/$30.00
PII S0015-0282(02)04580-6

sectional associations among the common carotid artery (CCA) IMT and cardiovascular risk factors, the prevalence of CVD, and the involvement of other arterial beds with atherosclerosis (16, 17, 22–25). The resistive index (RI) is a hemodynamic parameter that is easily determined by Doppler sonography and basically reflects vascular resistance. Frauchiger et al. (26) demonstrated that the correlation between the RI of the internal carotid artery (ICA) and the risk of atherosclerosis are comparable to those of the well-known IMT.

The objective of this study was to assess the effects of tibolone treatment on the IMT and RI of the carotid and vertebral arteries in postmenopausal women as sonographic markers of atherosclerosis.

MATERIALS AND METHODS

Twenty symptomatic postmenopausal women, who presented to the Menopause Outpatient Clinic, Marmara University School of Medicine, Istanbul, Turkey, were included in this prospective study. Written informed consent was obtained from each subject. The study was approved by the Institutional Review Board at Marmara University. Postmenopausal status was defined as the presence of no natural menses for at least 1 year and a serum FSH level of more than 40 IU/L. Exclusion criteria included active cerebrovascular or CVD, hypertension, diabetes, current smoking, thromboembolic disorders, and use of medication containing estrogens, progestins, androgens, lipid-lowering agents, or anticoagulants or products containing aspirin within 6 months of enrollment. Subjects were asked to continue their regular diet, physical activity, and habits.

Medical histories were taken, and all subjects underwent screening mammography and gynecologic examination, including cervical smear. Weight and height were measured, and body mass index (BMI) (weight in kg/height in m^2) was calculated. Fasting blood samples were drawn at baseline for total cholesterol, LDL and HDL cholesterol, and triglyceride determinations.

The IMT of the CCA was performed with a real-time, high-resolution, B-mode ultrasound imager using a 7.5-MHz probe (Toshiba SSA 380 A, Power Vision 7000, Toshiba, Osaka, Japan). Color blood flow imaging of the ICA, external (ECA), and CCA and the vertebral artery (VA) was also carried out using the same Toshiba ultrasound system. The same radiologist performed scanning throughout the study and was blind to the study. As carotid blood flow can be affected by noise, environmental temperature, and diet, all of the Doppler scans were performed at the same time of day in a soundproof room kept at a constant temperature and lighting level 2 hours after the patients had eaten a light meal.

Scanning of the CCA 3 cm proximal to the bifurcation was performed in the anterior-posterior position, with the patient lying on her back with her head on the axis. The ultrasonic image of the vessel was projected in real time on a monitor, and the sound beam was adjusted perpendicularly to the arterial surface of the far wall of the vessel to obtain two parallel echogenic lines corresponding to the lumen-intima and media-adventitia interfaces. The distance between these two interfaces indicates the IMT. Once these interfaces were clearly visible along at least 1 cm of the arterial segment, the IMT was measured. This procedure was repeated twice for both sides, and the average was considered in each subject.

During Doppler scans, five similar and optimal consecutive waveforms were analyzed bilaterally. The resistive indices (1 − [minimum diastolic velocity/maximum systolic velocity]) were calculated electronically. Doppler measurements were also repeated twice for both sides, and the average was considered in each subject. The variability of the ultrasound measurements of IMT and Doppler sonography were studied by performing five measurements over 1 month in 10 volunteers. The coefficients of variation for measurements of IMT and RI were 3% and 3.2%, respectively, which are considered acceptable.

After the above-mentioned baseline evaluations, subjects were administered tibolone, 2.5 mg/day (Livial, Organon, Oss, The Netherlands) for 12 weeks. At the end of the follow-up period, ultrasound measurements were repeated.

Statistical Analysis

A power calculation showed that a sample size of 20 in each group has a power of 95% to detect a 0.23-mm change in IMT between baseline and post-treatment values at the 5% level of significance. Power analysis was made by using StatMate version 1.01 (GraphPad Software, San Diego, CA).

Baseline and after-treatment values were compared by using the paired *t*-test. Pearson's correlation test was performed to analyze any relationship between the percent change in IMT and the baseline clinical characteristics of the subjects, i.e., age, BMI, months since menopause. The Software Package for the Social Sciences (version 10.0; SPSS, Inc., Chicago, IL) was used for these analyses. Values are expressed as means ± SD, and $P<.05$ was considered statistically significant.

RESULTS

All 20 subjects were compliant and completed the study. None of them were current smokers. Mean (±SD) age and BMI values were 52.2 ± 5.45 years (range, 44–63 years) and 25.84 ± 3.13 kg/m^2, respectively. The mean (±SD) months since menopause was 63.0 ± 65.81 months. Baseline and after-treatment ultrasound characteristics of the subjects are summarized in Table 1. Three months of tibolone treatment decreased the IMT of the CCA (mean ± SD) by 27.9%, from 0.70 ± 0.22 mm (95% confidence interval [CI], 0.60–0.80; range, 0.40–1.05 mm) to 0.47 ± 0.17 mm (95% CI, 0.39–0.55; range, 0.20–0.80 mm) ($P<.001$, Table 1). Fif-

TABLE 1

Baseline and after-treatment characteristics of the subjects.

	Baseline	After treatment	Mean % change	*P*
IMT of CCA (mm)	0.70 ± 0.22 (0.60–0.80)	0.47 ± 0.17 (0.39–0.55)	27.9	<.001
RI of CCA	0.70 ± 0.06 (0.68–0.73)	0.68 ± 0.06 (0.65–0.70)	3.3	.01
RI of ICA	0.59 ± 0.05 (0.56–0.61)	0.57 ± 0.05 (0.54–0.59)	3.7	.03
RI of ECA	0.79 ± 0.04 (0.77–0.81)	0.78 ± 0.04 (0.76–0.80)	NA	NS
RI of VA	0.65 ± 0.07 (0.62–0.68)	0.62 ± 0.05 (0.60–0.65)	3.7	.03

Note: Values in parentheses are the 95% confidence intervals for the means.
CCA = common carotid artery; ECA = external carotid artery; ICA = internal carotid artery; RI = resistive index; VA = vertebral arteries.

Erenus. Tibolone and atherosclerosis. Fertil Steril 2003.

teen subjects (75%) had a decrease in IMT (Fig. 1A), and five subjects (25%) had either no change (n = 2) or an increase in IMT (n = 3) (Fig. 1A and 1B).

In addition, tibolone administration significantly decreased the RI of the CCA (mean ± SD) from 0.70 ± 0.06 to 0.68 ± 0.06, the RI of the ICA from 0.59 ± 0.05 to 0.57 ± 0.05, and the RI of the VA from 0.65 ± 0.07 to 0.62 ± 0.05 ($P<.05$, Table 1). However, the decrease in the RI of the ECA was not significant ($P>.05$, Table 1). There was no significant relationship between the percent change in IMT and the baseline clinical characteristics of the subjects, i.e., age, BMI, or months since menopause ($P<.05$).

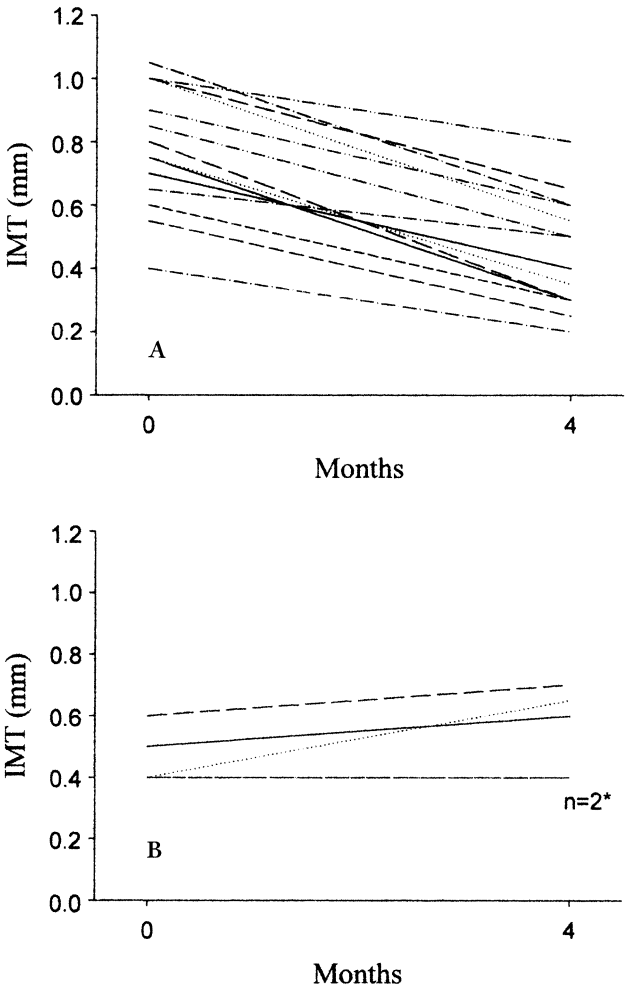
DISCUSSION

CVD is the leading cause of morbidity and mortality for postmenopausal women. Estrogen replacement therapy has been advocated in postmenopausal women with anticipated benefits of alleviating menopausal symptoms, slowing osteoporosis, and preventing heart disease. Nevertheless, estrogen's role in the prevention of heart disease is unclear. Recommendations for postmenopausal women for heart disease prevention are based on observational data, clinical and laboratory studies demonstrating favorable effects of estrogen on cardiovascular risk factors, and experimental arteriosclerosis. Thus, it was a surprise when the Heart and Estrogen/Progestin Replacement Study (HERS) (27) found no overall effect of 4.1 years of treatment with conjugated estrogen plus medroxyprogesterone acetate on the risk of nonfatal myocardial infarction and death from coronary heart disease (CHD) among women with established coronary arteriosclerosis. These results were complicated by an early increase and a late reduction in risk within the overall null effect (27).

Recently, the Estrogen Replacement and Atherosclerosis Trial (28), the first randomized angiographic endpoint trial to test the effect of HRT on the progression of atherosclerosis in postmenopausal women with documented coronary stenosis, showed no benefit of HRT, lending support to the HERS findings. Nevertheless, several studies (10, 29–32)

FIGURE 1

Baseline and after treatment IMT values for each subject. (**A**), Subjects with a decrease in IMT (n = 15). (**B**), Subjects with no change (n = 2) or an increase in IMT (n = 3). An asterisk (*) indicates that two subjects had the same baseline and after-treatment IMT values and therefore were shown as a single line.



Erenus. Tibolone and atherosclerosis. Fertil Steril 2003.

demonstrated that HRT in postmenopausal women decreased carotid artery IMT, which may suggest that HRT is associated with a favorable atherogenic status.

Tibolone (Org ODI4), a synthetic steroid [(7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one] with weak estrogenic, progestogenic, and androgenic properties in laboratory animals, relieves climacteric symptoms, which induces a sense of well-being and prevents osteoporosis in postmenopausal women in the absence of any stimulatory effect on the endometrium (15, 33, 34). The associations between blood lipids and arterial disease are well recognized. Reductions in HDL cholesterol and increases in triglycerides, LDL cholesterol, and Lp(a) are associated with increased CHD rates (15). Tibolone reduces circulating triglycerides and Lp(a) (15). However, it has no effect on LDL cholesterol but does reduce HDL cholesterol (15).

The human data on effects of tibolone on vascular disease in the literature are scarce. Hardiman et al. (35) reported that resting forearm blood flow, the dilator response to anoxic exercise, and heart rate increased significantly after 6 weeks of tibolone treatment. Recently, Lloyd et al. (36) evaluated 10 postmenopausal women with documented coronary artery disease by treadmill exercise electrocardiograms before and 24 hours after the oral administration of tibolone and concluded that tibolone appears to show similar anti-ischemic properties to estrogen. Lehmann et al. (37) stated that oral administration of tibolone had altered the dynamic relationship between structural and functional biophysical properties of the aortic wall in vivo based on the measurement of pulse wave velocity along the thoraco-abdominal aortic pathway by using a noninvasive Doppler ultrasound technique.

Recently, Zandberg et al. (2) evaluated the anti-atherosclerotic effect of tibolone in comparison with oral 17beta-estradiol and ethinyl estradiol (EE) in a rabbit model using a high cholesterol diet. They have observed that both tibolone and EE comparably reduced the accumulation of cholesterol in the aortic arch and the formation of fatty streaks in a dose-dependent manner. E_2 had only a marginal anti-atherosclerotic effect. Analysis indicated that the observed anti-atherosclerotic effects of tibolone and EE were at least partly due to a direct effect on the vessel wall independent of the changes in plasma cholesterol. Recently, Clarkson et al. (38) have compared the effects of two different doses of tibolone with those of conjugated equine estrogens (CEE) with and without medroxyprogesterone (MPA) on coronary atherosclerosis (CAA) of postmenopausal monkeys. CEE and CEE+MPA both significantly reduced CAA by about 62%, whereas tibolone treatment did not cause any difference in CAA, despite the adverse effects on plasma lipoproteins.

The IMT measurement by carotid ultrasound is a safe, standardized, and validated method that is useful in screening for atherosclerosis and in providing a surrogate measure for response to disease interventions (16–25). A thickening of the intima-media complex not only reflects local alterations, mostly of the CCA, but also corresponds to generalized atherosclerosis. O'Leary et al. (39) showed a direct correlation between IMT and the risk of myocardial infarction and stroke in patients without a history of vascular disease.

Previously, conflicting results have been reported about the relationship between HRT and carotid artery IMT. Most of the studies (10, 40, 41) have reported a protective effect of HRT on thickening of the IMT of the carotid artery. Nevertheless, Nabulsi et al. (42) have reported no association with HRT (42). Recently, Hashimoto et al. (43) investigated the endothelial function of the brachial artery with ultrasound measurement and carotid IMT in a controlled study. Improvement of the flow-mediated dilation was observed at 3 months and preserved up to 36 months in the HRT group. IMT has not changed significantly in either the HRT group or the control group at the end of 12 months.

The RI according to Pourcelot is a hemodynamic parameter that is easily determined by Doppler sonography and basically reflects vascular resistance (26). In the renal arteries, the RI has been studied thoroughly as a surrogate marker of atherosclerotic alterations. Age, vascular risk factors, and clinically demonstrated vascular diseases are associated with an increase in RI (26, 44–46). Recently, Frauchiger et al. (26) have studied the correlation between carotid RI and the degree of atherosclerosis and concluded that the RI of the ICA can be assessed as a surrogate marker of generalized atherosclerosis, complementary to IMT.

In this study, we have demonstrated that 3 months of tibolone treatment in postmenopausal women decreased the IMT of the CCA by 28% in comparison with baseline values. Similarly, RIs of CCA, ICA, and VA decreased significantly, but by smaller increments. To our knowledge, this is the first study on the effects of tibolone on the IMT of the CCA as a sonographic marker of atherosclerosis.

We do not yet have data on the long-term vascular effects of tibolone in postmenopausal women. The decrease in cholesterol, LDL, Lp(a), and triglycerides after tibolone administration can be considered in light of decreasing atherosclerosis, but the fact that HDL concentrations may also decrease has been considered as an adverse effect. However, the significance of this HDL decrease on the risk of CHD has been disputed (47). Currently, the effect of tibolone treatment in postmenopausal women on the risk of CHD is best evaluated with an assessment of atherosclerotic lesions by sonographic markers. The present study has shown the potential beneficial effects of tibolone on arteriosclerosis. However, the limited number of subjects is the weakness of this study.

In conclusion, the present study showed that tibolone treatment causes thinning of the IMT of the CCA and improves CCA and ICA blood flows and thus appears to be useful in preventing atherosclerosis. Nevertheless, the clin-

ical implications of these findings are yet to be investigated. Future studies with larger groups are needed to assess the potential beneficial effects of tibolone on arteriosclerosis in postmenopausal women.

References

1. Seed M. Postmenopausal hormone replacement therapy, coronary heart disease and plasma lipoproteins. Drugs 1994;47(Suppl 2):25–34.
2. Zandberg P, Peters JLM, Demacker PN, de Reeder EG, Smit MJ, Meuleman DG. Comparison of the antiatherosclerotic effect of tibolone with that of estradiol and ethinyl estradiol in cholesterol-fed, ovariectomized rabbits. Menopause 2001;8:96–105.
3. Barrett-Connor E. The menopause, hormone replacement, and cardiovascular disease: the epidemiologic evidence. Maturitas 1996;23:227–34.
4. Kafonek SD. Postmenopausal hormone replacement therapy and cardiovascular risk reduction. Drugs 1994;47(Suppl 2):16–24.
5. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. JAMA 1991;265:1861–7.
6. Bush TL, Barrett-Connor E, Cowan LD, Criqui MH, Wallace RB, Suchindran CM, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. Circulation 1987;75:1102–9.
7. Mendelsohn ME, Karas RH. Estrogen and the blood vessel wall. Curr Opin Cardiol 1994;9:619–26.
8. Vidovic IP, Demarin V, Grubisic G, Kuna K, Huzjan AL. Carotid artery intima thickness and flow velocity after discontinuation of hormone replacement therapy in postmenopausal women: follow-up study. Croat Med J 2001;42:54–7.
9. Tremollieres FA, Cigagna F, Alquier C, Cauneille C, Pouilles J, Ribot C. Effects of hormone replacement therapy on age-related increase in carotid artery intima-media thickness in postmenopausal women. Atherosclerosis 2000;153:81–8.
10. Westendorp IC, in 't Veld BA, Bots ML, Akkerhuis JM, Hofman A, Grobbee DE, et al. Hormone replacement therapy and intima-media thickness of the common carotid artery: the Rotterdam study. Stroke 1999;30:2562–7.
11. Signorelli SS, Salvatore S, Luigi D, Pia CM, Giuseppe P, Sarina C. Serum lipids and lipoproteins and carotid artery wall intima-media thickness in a population of menopausal women. Menopause 1999;6:230–2.
12. Griewing B, Romer T, Spitzer C, Ludemann J, Gunther A, Kessler C. Hormone replacement therapy in postmenopausal women: carotid intima-media thickness and 3-D volumetric plaque quantification. Maturitas 1999;32:33–40.
13. Anderson HV. Estrogen therapy, atherosclerosis, and clinical cardiovascular events. Circulation 1996;94:1809–11.
14. Muscat Baron Y, Brincat M, Galea R. Carotid artery wall thickness in women treated with hormone replacement therapy. Maturitas 1997;27:47–53.
15. Moore RA. Livial: a review of clinical studies. Br J Obstet Gynaecol 1999;106(Suppl 19):1–21.
16. O'Leary DH, Polak JF, Kronmal RA, Kittner SJ, Bond MG, Wolfson SK Jr., et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. The CHS Collaborative Research Group. Stroke 1992;23:1752–60.
17. Allan PL, Mowbray PI, Lee AJ, Fowkes FG. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease. The Edinburgh Artery Study. Stroke 1997;28:348–53.
18. Blankenhorn DH, Rooney JA, Curry PJ. Noninvasive assessment of atherosclerosis. Prog Cardiovasc Dis 1984;26:295–307.
19. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399–406.
20. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke 1993;24:1297–304.
21. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: a population-based ultrasonography study in Eastern Finnish men. J Intern Med 1991;229:225–31.
22. Poli A, Tremoli E, Colombo A, Sirtori M, Pignoli P, Paoletti R. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients: a new model for the quantitation and follow-up of preclinical atherosclerosis in living human subjects. Atherosclerosis 1988;70:253–61.
23. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. Stroke 1997;28:518–25.
24. Bots ML, Breslau PJ, Briet E, de Bruyn AM, van Vliet HH, van den Ouweland FA, et al. Cardiovascular determinants of carotid artery disease: the Rotterdam Elderly Study. Hypertension 1992;19:717–20.
25. Burke GL, Evans GW, Riley WA, Sharrett AR, Howard G, Barnes RW, et al. Arterial wall thickness is associated with prevalent cardiovascular disease in middle-aged adults. The Atherosclerosis Risk in Communities (ARIC) Study. Stroke 1995;26:386–91.
26. Frauchiger B, Schmid HP, Roedel C, Moosmann P, Staub D. Comparison of carotid arterial resistive indices with intima-media thickness as sonographic markers of atherosclerosis. Stroke 2001;32:836–41.
27. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, 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.
28. Herrington DM, Reboussin DM, Brosnihan KB, Sharp PC, Shumaker SA, Snyder TE, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med 2000;343:522–9.
29. Jonas HA, Kronmal RA, Psaty BM, Manolio TA, Meilahn EN, Tell GS, et al. Current estrogen-progestin and estrogen replacement therapy in elderly women: association with carotid atherosclerosis. CHS Collaborative Research Group. Cardiovascular Health Study. Ann Epidemiol 1996;6:314–23.
30. McGrath BP, Liang YL, Teede H, Shiel LM, Cameron JD, Dart A. Age-related deterioration in arterial structure and function in postmenopausal women: impact of hormone replacement therapy. Arterioscler Thromb Vasc Biol 1998;18:1149–56.
31. Punnonen R, Jokela H, Heinonen PK, Aine R, Dastidar P. Hormone replacement therapy and atherosclerosis. J Reprod Med 1995;40:267–72.
32. Espeland MA, Applegate W, Furberg CD, Lefkowitz D, Rice L, Hunninghake D. Estrogen replacement therapy and progression of intimal-medial thickness in the carotid arteries of postmenopausal women. ACAPS Investigators. Asymptomatic Carotid Atherosclerosis Progression Study. Am J Epidemiol 1995;142:1011–9.
33. Albertazzi P, Di Micco R, Zanardi E. Tibolone: a review. Maturitas 1998;30:295–305.
34. Rymer JM. The effects of tibolone. Gynecol Endocrinol 1998;12:213–20.
35. Hardiman P, Nihoyannopoulos P, Kicovic P, Ginsburg J. Cardiovascular effects of Org OD 14—a new steroidal therapy for climacteric symptoms. Maturitas 1991;13:235–42.
36. Lloyd GW, Patel NR, McGing EA, Cooper AF, Kamalvand K, Jackson G. Acute effects of hormone replacement with tibolone on myocardial ischaemia in women with angina. Int J Clin Pract 1998;52:155–7.
37. Lehmann ED, Hopkins KD, Parker JR, Turay RC, Rymer J, Fogelman I, et al. Aortic distensibility in post-menopausal women receiving Tibolone. Br J Radiol 1994;67:701–5.
38. Clarkson TB, Anthony MS, Wagner JD. A comparison of tibolone and conjugated equine estrogens effects on coronary artery atherosclerosis and bone density of postmenopausal monkeys. J Clin Endocrinol Metab 2001;86:5396–404.
39. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14–22.
40. Espeland MA, Applegate W, Furberg CD, Lefkowitz D, Rice L, Hunninghake D. Estrogen replacement therapy and progression of intimal-medial thickness in the carotid arteries of postmenopausal women. ACAPS Investigators. Asymptomatic Carotid Atherosclerosis Progression Study. Am J Epidemiol 1995;142:1011–9.
41. Muscat Baron Y, Galea R, Brincat M. Carotid artery wall changes in estrogen-treated and -untreated postmenopausal women. Obstet Gynecol 1998;91:982–6.
42. Nabulsi AA, Folsom AR, Szklo M, White A, Higgins M, Heiss G. No association of menopause and hormone replacement therapy with carotid artery intima-media thickness. Circulation 1996;94:1857–63.
43. Hashimoto M, Miyao M, Akishita M, Hosoi T, Toba K, Kozaki K, et al. Effects of long-term and reduced-dose hormone replacement therapy on endothelial function and intima-media thickness in postmenopausal women. Menopause 2002;9:58–64.
44. Pontremoli R, Viazzi F, Martinoli C, Ravera M, Nicolella C, Berruti V, et al. Increased renal resistive index in patients with essential hypertension: a marker of target organ damage. Nephrol Dial Transp 1999;14:360–5.
45. Ishimura E, Nishizawa Y, Kawagishi T, Okuno Y, Kogawa K, Fukumoto S, et al. Intrarenal hemodynamic abnormalities in diabetic ne-

phropathy measured by duplex Doppler sonography. Kidney Int 1997; 51:1920–7.
46. Frauchiger B, Nussbaumer P, Hugentobler M, Staub D. Duplex sonographic registration of age and diabetes-related loss of renal vasodilatory response to nitroglycerine. Nephrol Dial Transplant 2000;15:827–32.
47. Ginsburg J, Prelevic GM. Tibolone and the serum lipid/lipoprotein profile: does this have a role in cardiovascular protection in postmenopausal women? Menopause 1999;6:87–9.