

ARIC Manuscript Proposal #748

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1.a. **Full Title:** Post-menopausal endogenous hormones and atherosclerosis: A case-control study

b. **Abbreviated Title (Length 26 characters):** Hormones and atherosclerosis

2. **Writing Group (list individual with lead responsibility first):**

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3. **Timeline:** Immediate

4. **Rationale:**

The risk of cardiovascular disease increases significantly in post-menopausal women compared to their pre-menopausal counterparts. In observational studies, estrogen users have been found to have a reduced risk of major clinical coronary disease and reduced cardiovascular disease mortality (1). However, a large randomized clinical trial of estrogen replacement therapy (ERT) for secondary prevention of coronary heart disease in postmenopausal women failed to demonstrate a reduced rate of coronary heart disease events (2). Finally, two studies examining the relationship of ERT to subclinical atherosclerosis, assessed by carotid intimal-medial thickness (IMT), have yielded conflicting results (3;4).

Several studies have shown beneficial cardiovascular effects of exogenous estrogen, including lower body weight (4-6), increased HDL-cholesterol and lower LDL-cholesterol (4;7-9), lower fasting insulin and glucose levels (4;7), improvement in brachial artery blood flow (10), and regression of atherosclerotic plaques (11). ERT alters the post-menopausal sex hormone milieu such that sex hormone binding globulin (SHBG) levels increase, indicating less free hormones available to tissues (12). Higher SHBG is associated with less insulin resistance and a more favorable cardiovascular risk factor profile (13-17), which is found in post-menopausal women not on hormone replacement therapy (13;16;17).

Prior to menopause, women have a much lower risk of CVD compared to men of the same age (18). Menopause, however, has been shown to initiate a phase of increased risk (18). At the time of menopause, the endogenous hormonal milieu of the female changes such that there is a relative estrogen deficiency and a relative increase in testosterone levels, compared to the pre-menopausal state. A weaker estrogen, estrone, continues to be synthesized by peripheral conversion from adrenal $\Delta 4$ androstenedione in the fat, liver, and kidney (19). Given what is known about the relationship between estrogens, androgens, and cardiovascular disease in women on ERT, post-menopausal women with significant atherosclerosis and cardiovascular disease would be expected to have lower endogenous estrogen levels and higher endogenous androgen levels than those without significant atherosclerosis.

Studies examining the relationship between the endogenous post-menopausal hormonal milieu and cardiovascular disease have yielded conflicting results. Barrett-Connor found no association between levels of androstenedione, testosterone, estrone, or estradiol, and risk of death from cardiovascular disease (20). Haffner et al., on the other hand, found lower DHEAS levels predictive of ischemic heart disease mortality in postmenopausal women (21). Similarly, two previous studies found no association of SHBG levels (22) and DHEAS levels (23) with cardiovascular mortality. In the Edinburgh Artery Study, the mean levels of total and free testosterone, estradiol, and SHBG were not significantly different in cases of peripheral vascular disease compared to controls (24). Another case-control study found no difference in estrone concentration between women who had angiographically documented atherosclerosis and those who did not (25). One prior study, however, suggests a protective effect of higher free testosterone, DHEAS, and androstenedione on carotid IMT (26).

5. **Main Hypothesis/Study Questions:** Post-menopausal women with significant atherosclerosis will have lower endogenous estrogen levels and higher endogenous androgen levels than post-menopausal women without atherosclerosis.

6. **Data (variables, time window, source, inclusions/exclusions):**

Cases of atherosclerosis and controls were chosen on the basis of carotid artery ultrasound measurements. Post-menopausal women in the ARIC cohort who were not current or ever users of hormone replacement therapy were eligible for this study. Menopause was defined based on Visit 1 interview data conducted in 1987-89.

Endogenous post-menopausal hormone status was assessed by measuring levels of estrone, androstenedione, DHEA-S, total testosterone, and SHBG performed by Yerkes Laboratory on blood collected during visit 2.

Atherosclerosis was assessed using B-mode ultrasound to measure carotid artery IMT. The average IMT for Visits 1 and 2, which were conducted three years apart, was used to determine case-control status. Cases were defined as postmenopausal women with no history of exposure to hormone replacement therapy, who had the highest average of all carotid IMT measurements for Visit 1 and 2. Controls were postmenopausal women with no history of hormone replacement therapy, who had the lowest average IMT values for Visits 1 and 2. One control was chosen per case, and frequency matched on five-year age groups and ARIC center.

Covariates included in the analysis were age, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking history, sports index, fibrinogen, body mass index, and insulin level. Information on historical variables from Visit 1 were used.

- 7.a. Will the data be used for non-CVD analysis in this manuscript? ☐ Yes ☒ No

- b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ☐ Yes ☐ No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

- 8.a. Will the DNA data be used in this manuscript? ☐ Yes ☒ No

- 8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ Yes ☐ No

REFERENCE LIST

- (1) Stampfer MJ, Colditz GA, Willett WC, Manson JE, Rosner B, Speizer FE et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med.* 1991;325:756-62.
- (2) 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.
- (3) 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. Atherosclerosis Risk in Communities (ARIC) Study Investigators [see comments]. *Circulation.* 1996;94:1857-63.
- (4) Manolio TA, Furberg CD, Shemanski L, Psaty BM, O'Leary DH, Tracy RP et al. Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. The CHS Collaborative Research Group. *Circulation.* 1993;88:2163-71.
- (5) Haarbo J, Marslew U, Gotfredsen A, Christiansen C. Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. *Metabolism.* 1991;40:1323-26.
- (6) Kritz-Silverstein D, Barrett-Connor E. Long-term postmenopausal hormone use, obesity, and fat distribution in older women [see comments]. *JAMA.* 1996;275:46-49.
- (7) Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators. *N Engl J Med.* 1993;328:1069-75.
- (8) Vaziri SM, Evans JC, Larson MG, Wilson PW. The impact of female hormone usage on the lipid profile. The Framingham Offspring Study. *Arch Intern Med.* 1993;153:2200-2206.
- (9) Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA.* 1995;273:199-208.
- (10) Koh KK, Blum A, Hathaway L, Mincemoyer R, Csako G, Wacławski MA et al. Vascular effects of estrogen and vitamin E therapies in postmenopausal women. *Circulation.* 1999;100:1851-57.
- (11) Akkad A, Hartshorne T, Bell PR, al Azzawi F. Carotid plaque regression on oestrogen replacement: a pilot study. *Eur J Vasc Endovasc Surg.* 1996;11:347-48.
- (12) Tazuke S, Khaw KT, Barrett-Connor E. Exogenous estrogen and endogenous sex hormones. *Medicine (Baltimore).* 1992;71:44-51.

- (13) Haffner SM, Dunn JF, Katz MS. Relationship of sex hormone-binding globulin to lipid, lipoprotein, glucose, and insulin concentrations in postmenopausal women. *Metabolism*. 1992;41:278-84.
- (14) Soler JT, Folsom AR, Kaye SA, Prineas RJ. Associations of abdominal adiposity, fasting insulin, sex hormone binding globulin, and estrone with lipids and lipoproteins in postmenopausal women. *Atherosclerosis*. 1989;79:21-27.
- (15) Kaye SA, Folsom AR, Soler JT, Prineas RJ, Potter JD. Associations of body mass and fat distribution with sex hormone concentrations in postmenopausal women. *Int J Epidemiol*. 1991;20:151-56.
- (16) Haffner SM, Katz MS, Dunn JF. Increased upper body and overall adiposity is associated with decreased sex hormone binding globulin in postmenopausal women. *Int J Obes*. 1991;15:471-78.
- (17) Goodman-Gruen D, Barrett-Connor E. Sex hormone-binding globulin and glucose tolerance in postmenopausal women. The Rancho Bernardo Study. *Diabetes Care*. 1997;20:645-49.
- (18) Grodstein F, Manson JE, Stampfer MJ. Postmenopausal Hormone Therapy. In: Manson JE, Ridker PM, Gaziano JM, Hennekens CH eds. *Prevention of Myocardial Infarction*. 1st ed. Oxford: Oxford University Press, Inc.; 1996: 413-30.
- (19) Schiff I WB. Menopause. In: Becker K, ed. *Principles and Practice of Endocrinology and Metabolism*. 2nd ed. Philadelphia: J. G. Lippincott Company; 1995: 915-24.
- (20) Barrett-Connor E, Goodman-Gruen D. Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women. *BMJ*. 1995;311:1193-96.
- (21) Haffner SM, Moss SE, Klein BE, Klein R. Sex hormones and DHEA-SO₄ in relation to ischemic heart disease mortality in diabetic subjects. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care*. 1996;19:1045-50.
- (22) Goodman-Gruen D, Barrett-Connor E. A prospective study of sex hormone-binding globulin and fatal cardiovascular disease in Rancho Bernardo men and women. *J Clin Endocrinol Metab*. 1996;81:2999-3003.
- (23) Barrett-Connor E, Goodman-Gruen D. The epidemiology of DHEAS and cardiovascular disease. *Ann N Y Acad Sci*. 1995;774:259-70.
- (24) Price JF, Lee AJ, Fowkes FG. Steroid sex hormones and peripheral arterial disease in the Edinburgh Artery Study. *Steroids*. 1997;62:789-94.
- (25) Cauley JA, Gutai JP, Glynn NW, Paternostro-Bayles M, Cottington E, Kuller LH. Serum estrone concentrations and coronary artery disease in postmenopausal women. *Arterioscler Thromb*. 1994;14:14-18.
- (26) Bernini GP, Sgro' M, Moretti A, Argenio GF, Barlascini CO, Cristofani R et al. Endogenous androgens and carotid intimal-medial thickness in women. *J Clin Endocrinol Metab*. 1999;84:2008-12.