1. Full Title: Effects of Hormone Replacement Therapy on Carotid Artery Atherosclerosis

b. Abbreviated Title (Length 26):

HRT and Atherosclerosis

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

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3. Timeline:

Compile and analyze data in the fall of 1999, write manuscript fall 1999

4. Rationale:

The findings regarding the effects of hormone replacement therapies on coronary heart disease and atherosclerosis are mixed. The bulk of the observational studies in humans support a beneficial effect of hormone replacement therapies on CHD, lumen diameter as determined angiographically, and artery wall thickness measured by B-mode ultrasound. However, the recent results from HERS, the first large randomized trial assessing effects of combined HRT on coronary heart disease, showed no overall benefit of HRT. Randomized controlled studies in animal models support a beneficial effect of estrogen therapy, but suggest there may be an antagonism of that benefit by medroxyprogesterone acetate, the progestin used in HERS and the most commonly used progestin in the United States. The first randomized study that will be
able to compare ERT and HRT in humans will be the ERA study, a secondary prevention study with an angiography endpoint that is projected to be complete in 1999. The Women’s Health Initiative (WHI) which is a primary prevention study with CHD events as the outcome measure has both ERT and HRT therapies in the hormone replacement arm, but only hysterectomized women are assigned to ERT and non-hysterectomized women to combined HRT. This study is projected to be complete in 2005.

There are three published cross-sectional studies that have compared estrogen-only therapy (ERT) versus combined hormone replacement therapy (HRT) effects on carotid artery IMT [Jonas et al, 1996; Nabulsi et al, 1996; McGrath et al, 1998]. There were no significant effects of ERT or HRT on carotid artery IMT in the ARIC study at baseline [Nabulsi et al, 1996]. There were significant differences in IMT between hormone users and never users in the CHS cohort study at baseline [Jonas et al, 1996] and in the Australian study [McGrath et al, 1998]. There were no significant differences in carotid artery IMT between ERT and HRT users in any of the studies. The reports by Jonas et al and Nabulsi et al noted many lifestyle differences between ERT and HRT users.

This analysis will differ from the earlier report by Nabulsi et al [1996] since in addition to the baseline data, it will take advantage of the follow-up measurements at Visits 2, 3, and 4. This will allow inclusion of larger numbers of postmenopausal women, particularly in the ERT and HRT treatments. In addition, hormone use will be evaluated across all visits and so duration of use can be included in the analysis.

None of the studies reporting the effects of ERT and HRT on carotid IMT reported lumen diameter. There is evidence that remodeling of arteries to accommodate wall thickening and plaque growth without compromising blood flow is an important compensatory mechanism in atherosclerosis progression [Clarkson et al, 1994; Glagov et al, 1987]. There is also evidence to suggest that hormone replacement therapy might affect the remodeling processes [Baron et al, 1998, Register et al, 1998, Williams et al, 1995] and some suggestion that estrogen-only therapy might have a more beneficial effect on this process than combined HRT [Register et al, 1998]. As part of the proposed analysis we intend to address a hypothesized association between hormone therapies on lumen diameter.

If a progestin, such as MPA, attenuates the benefit of estrogen therapy on atherosclerosis and coronary heart disease, this would have a major public health impact. A woman’s family and personal history, and risk factor status for various diseases should be considered in the decision of whether or not to take postmenopausal hormone replacement, and which type of hormonal therapy to take (e.g. ERT, HRT, or a selective estrogen receptor modulator [SERM] such as Evista). Therefore, it is important to have clear information regarding the risks, benefits, and the magnitude of these effects. While the most unbiased estimates of the effects will come from randomized trials, the only study underway that can provide any information about the relative effectiveness of ERT and HRT for primary prevention of CHD will not be complete until after 2005. Even then, the WHI study will not be able to directly compare the effects of ERT and HRT. Therefore, further information from observational studies will be useful.

5. Main Study Questions:
Our expectation is that medroxyprogesterone acetate, when added to estrogen replacement therapy, will attenuate the beneficial effect of estrogen therapy on atherosclerosis in the carotid arteries (intimal-medial thickness) and on lumen diameter.

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

Inclusion criteria for this analysis will be: female, peri- or postmenopausal status, black or white race. Exclusion criteria will be physician-diagnosed myocardial infarction or stroke reported at any of visits 1, 2, 3, or 4. The rationale for these criteria for exclusion is that physicians may have considered these conditions in prescribing HRT. Another exclusion criterion will be missing outcome data and missing postmenopausal hormone use data.

- Primary outcome variables: carotid artery IMT at visits 1, 2, 3 and/or 4 and carotid artery lumen diameter at these visits.

One or both of the following analyses will be done:

1.) Use carotid artery IMT and lumen diameter at Visit 4 or Visit 3 (the most recent data point or the average if two are available) as the dependent variable, or

2.) Include carotid artery IMT and lumen diameter at Visits 1, 2, 3, and 4 and use repeated measures analysis with HRT exposure as a time-dependent variable, allowing it to vary for an individual across time.

The advantage to option 1 is that it might be more easily interpretable since there will be one measure for each individual. There should be quite a few more individuals using combined HRT at later visits than the 75 available for the report by Nabulsi [1996]. The advantage of option 2 is the larger number of measurements that can be included in a repeated measures design.

- Primary exposure variable: gonadal hormone use at Visits 1, 2, 3, 4.

- Covariates: age, race, center, systolic blood pressure, antihypertensive medication use, lipid lowering medication use, cigarette smoking status, alcohol consumption status, body mass index (BMI), sport index, diabetes status, education level, ultrasound machine