



WHI Coronary Artery Calcium Study (WHI-CACS): An Introduction for Imaging Centers

(for Imaging Center staff use only; not for participant distribution)

Background: The Women's Health Initiative (WHI) is a multi-component clinical trial (CT) and observational study among 161,808 postmenopausal women at 40 clinical centers across the United States. The CT includes a randomized, placebo-controlled evaluation of the benefits of conjugated equine estrogen (0.625 mg/day) in 10,739 women ages 50 to 79 and with a prior hysterectomy when they joined the study between 1993 and 1998. Primarily because of a persistent increase in stroke, the Estrogen-Alone clinical trial was stopped early (March 1, 2004) after 7.1 years of intervention and follow-up. Secondary analyses revealed that there may be differences in risk for coronary heart disease (CHD) events based on the age at randomization. The WHI-CACS was developed to evaluate a surrogate marker for coronary plaque burden, coronary calcium, in the youngest Estrogen-Alone participants.

Design & Sample: In collaboration with participating WHI clinical centers and their affiliated imaging centers, WHI-CACS will obtain measurements for the presence and extent of coronary calcium in 900 WHI Estrogen-Alone participants who were 50 – 59 years of age at randomization. The clinical centers have developed long-term, close relationships with their participants and, as such, are in an ideal position to recruit these committed women for this WHI sub-study. Once recruited by the clinical center, either the center or the participant will make arrangements with the imaging center for the CT scan to be performed. The resulting images from these scans will be forwarded to a central WHI reading center for analysis of coronary calcium.

Imaging Methods: Electron beam (EBCT) or multi-detector (MDCT) computed tomography will be performed to determine the presence and extent of coronary artery calcification. The imaging will be done at approximately 25-30 experienced imaging centers around the country. The protocol will also utilize phantom scans that will be forwarded to the central reading center. The reading center will conduct brief training sessions by interactive internet and/or teleconferences with CT Technologists from each imaging center prior to the initiation of the study to ensure standardization of methods.

Analytic Plan: The primary hypothesis for this study is that there will be a lower prevalence of any coronary calcium in women in the estrogen-alone arm of the clinical trial compared to those in the placebo arm. An important secondary hypothesis is that women in the estrogen-alone arm will have, on average, a lower amount of coronary calcium than women in the placebo arm. Therefore, this study will use the CT images to compare calcified atherosclerotic burden among these women with primary analyses based on "intention-to-treat" and secondary ("sensitivity") analyses limited to women who had adhered to the study pill regimen.

Implications: The results of this study will advance our understanding of the biological mechanisms underlying the CHD results from the WHI Estrogen-Alone trial. For example, if estrogen-alone treatment is associated with reduced coronary calcium, this finding would support the hypothesis that estrogen, taken in a population of younger women, is associated with reduced atherosclerotic plaque burden in the coronary circulation and thereby a decreased risk for CHD events. If estrogen alone treatment is associated with no differences in the amount of coronary calcium or an increased amount, this finding would provide support for an absence of CHD benefit or a possible increase in coronary risk related to treatment.