Changes in IMT and its Association with Cardiovascular Disease

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ABSTRACT

Carotid Intima Media Thickness (IMT) assessed by B-mode ultrasound is an important non-invasive modality for evaluating atherosclerotic disease burden and global cardiovascular (CV) disease risk. A number of studies have examined the relationship between carotid IMT and subsequent cardiovascular disease [O’Leary, 1999; Psaty, 1999; Kuller, 2006 ARIC], and have generally shown a strong relationship. The evidence for a relationship between carotid IMT and future cardiovascular events is strong, especially among younger individuals [Lorenz MW et al. (2006). Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke 37: 87–92]. Carotid (IMT) has been used also as measure of disease progression in clinical trials investigating the efficacy of new pharmacologic products tested for the ability to reduce cardiovascular disease burden [Bots ML et al. (2003)]. Change in IMT has been reported to be associated with several known cardiovascular risk factors [Chambless 2002]. The use of IMT as an image surrogate marker of sub-clinical atherosclerosis and cardiovascular events has several desirable features, as it is easily measurable in all study participants, it is non-invasive, is relatively inexpensive, and, of particular importance in clinical trials, it does not require an extended duration of follow up for cardiovascular events to occur [Demol P and Weihrauch TR (1998)]. Other studies in patients with more severe cardiovascular disease have shown disease regression with the use of statins, indicating a reduction in carotid IMT. Likewise, multiple diabetes [CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone)] and hypertensive medications have been shown to slow the progression of carotid IMT.

However, much more limited evidence is available regarding the association of carotid IMT progression and cardiovascular outcomes in longitudinal studies. A meta-analysis of several longitudinal studies has examined the relationship between IMT and future events, but different studies have used different measurement methods and studied different populations, therefore these data, although important, are difficult to interpret [Lorenz MW Circulation]. A high correlation between the surrogate and the ultimate outcome is desirable for an intermediate outcome measure to be valid. As IMT measurement is associated with a noteworthy amount of measurement error, the effect of measurement error on IMT change can potentially affect the prediction of cardiovascular events and introduce bias.

The Cardiovascular Health Study provides an ideal setting to examine the relationship between cardiovascular events and changes in IMT among a group of relatively healthy participants 65 and older that had carotid IMT measures at baseline, year 5 and year 11 of the study. For this investigation, our primary research hypothesis is to evaluate whether changes in the common carotid IMT and the internal carotid IMT are associated with subsequent clinical coronary heart disease, stroke, and myocardial infarction. We perform our analysis in this observational study by accounting for measurement error bias using risk-set regression calibration (RSRC) methods on both the time independent and time dependent IMT measurements. We also adjust for known baseline confounders in our analyses, such as age, sex, race, smoking status, height, weight, systolic blood pressure, HDL, LDL, LV Mass, Factor VII, fibrinogen, insulin and blood glucose. We also investigate the impact of the measurement error bias by comparing our results to those using standard (naïve) Cox PH.