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CORRESPONDENCE

Letters to the Editor

Carotid Intima-Media Thickness Progression and Cardiovascular Disease Risk

Costanzo et al. (1) concluded that slowed progression of carotid intima-media thickness (CIMT) with drug therapies does not predict reduced cardiovascular disease (CVD) risk. Unfortunately, their analytical technique, meta-regression, is not suitable for evaluating this relationship. The limitations of meta-regression are well-known (2). Major pitfalls of their study include the following:

1. CIMT is not a standardized technology. Their meta-regression included studies with different imaging and measurement techniques. By grouping them, the authors created a null bias. Furthermore, some laboratories have highly reproducible techniques and excellent quality assurance procedures. Those laboratories have reliably reported strong relationships between changes in CVD risk factors, changes in CIMT, and CVD risk. But, some laboratories have poor measurement accuracy and reproducibility. Because the meta-regression lumped widely differing methodologies together, it is no surprise that they did not find a relationship among all the noise from the individual trials. Adjusting for the year of the study, the authors' proposed solution, does not address this problem.
2. Short follow-up duration. CIMT progression studies are experiments that evaluate one biological effect of an intervention—change in carotid atherosclerosis burden (or more precisely, change in wall thickness, a measure of arterial injury). CIMT progression studies are performed to obtain information about the effect of an intervention on the arterial wall in a shorter time period than usually is needed to observe differences in CVD event rates. The short-term events analyzed by the authors may not reflect the anatomic substrate measured by CIMT testing, because short-term events are more related to inflammation and thrombosis than atherosclerosis burden. Proponents of CIMT imaging as a research tool do not claim that CIMT changes perfectly reflect CVD risk, especially in the short term. Their analysis attacks a red herring and faults a technique for not predicting events that are not mediated by what it measures. Indeed, the Cholesterol Lowering Atherosclerosis Study showed a significant relationship between CIMT changes and lipid treatment after 2 years, but the relationships between changes in lipids, CIMT, and CVD events took many more years to be identified (3,4). The studies analyzed by Costanzo et al. (1) were, for the most part, only 1 to 2 years in duration.
3. The meta-regression was performed on summary data, not data from individual study participants, and there were a lot of missing data—especially important considerations given the small number of CVD events they analyzed relative to the large number of covariates and studies in their models.

No surrogate is perfect, but the vast majority of interventions that reduce CIMT progression also reduce CVD events. Exceptions include small, poorly conducted studies or interventions where the beneficial effect on CIMT was observed in different individuals than those with increased CVD risk (i.e., hormone replacement therapy). The limitations of meta-regression, short follow-up duration, and data limitations explain why the authors did not observe a relationship between CIMT changes and CVD events. It is noteworthy that another analysis that focused on high-quality CIMT studies of statins came to a different conclusion (5).

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Carotid Intima-Media Thickness as a Surrogate Endpoint

We read with great interest the recently published meta-analysis by Costanzo et al. (1) investigating whether changes in carotid intima-media thickness (CIMT) affect major cardiovascular endpoints, including cardiovascular-related and all-cause mortality. The study was carefully executed and reported that changes in CIMT in response to drug therapy do not translate into changes in major cardiovascular events. The analysis adds to the growing understanding that although surrogate endpoints such as CIMT at baseline may be correlated with clinical outcomes, changes in these