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
endpoints over time that result from a particular therapy may not predict future clinical events (2,3).

However, we would highlight one potential drawback in the methodology the investigators used—namely that examining the relationship between changes in CIMT and outcomes with death included as a primary endpoint is limiting, given that patients who died during follow-up cannot undergo further serial assessments of CIMT to calculate a “change.”

We recently performed a similar meta-regression analysis, looking at 28 trials of novel cardiovascular therapies to see whether changes in CIMT from these therapies are correlated with nonfatal myocardial infarction (MI) (4). We chose to focus our primary analysis on nonfatal MI, excluding the endpoint of death given the reason described above. Our findings raised similar concerns that changes in CIMT do not consistently predict cardiovascular events. For example, we found that for each 0.01 mm per year smaller rate of change in CIMT, the odds ratio for MI was 0.82 (95% confidence interval: 0.69 to 0.96; p = 0.018), but that no significant relationship between mean change in CIMT and nonfatal MI was noted in randomized controlled trials evaluating statin therapy or those with high CIMTs at baseline (p > 0.20 in both instances).

The results of this meta-analysis as well as others, although provocative, must be interpreted cautiously. Overall, we agree with the authors that larger clinical trials evaluating patient outcomes generally are needed to evaluate new drug therapy.

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Reply

We write this letter to clarify some issues that have arisen regarding our study (1). The purpose of our meta-analysis was mostly driven by the fact that it has been claimed that interventions that reduce intima-media thickness (IMT) progression also reduce cardiovascular events. However, although studies that have shown a relationship between a high IMT and increased risk of cardiovascular events do exist (2–4), there is no study that has ever been powered and published to show such a relationship. IMT prognostic value has always relied on its relationship with other proven surrogate endpoints and never with cardiovascular events. The only study that is often quoted to show a putative relationship between IMT changes and cardiovascular risk is the review of Espeland et al. (2). However, it should be stated that, technically, the Espeland et al. study (2) merely incorporated the addition of change in carotid IMT as a covariate in a regression model of a meta-analysis of some statin trials. In particular, they showed that the change in carotid IMT raised the summary odds ratio of developing a cardiovascular event on statin therapy from 0.48 to 0.64. In addition, they included few studies and only those that directly compared statin therapy with placebo. Therefore, this study cannot be quoted as clear evidence of a significant relationship between change in carotid IMT and cardiovascular risk.

Technical aspects concerning the reproducibility of serial individual changes and lack of standardization of IMT measurements are crucial in understanding the role of this tool in cardiovascular risk assessment. Despite the fact that carotid IMT measurements are prone to generate variability in follow-up studies, in controlled clinical trials, measurement variability has been decreasing due to technical improvements, standardization, and training (5). Nevertheless, we could not find any significant influence of the year of publication. Furthermore, in our meta-analysis, some source of variability could also have come from the inclusion of studies with different imaging protocols. However, we substantially identified 2 major groups: multicenter trials in which images were handled and IMT measurements recorded off-line in a core ultrasound laboratory. However, after performing a sensitivity analysis by excluding studies that did not measure IMT in a central core laboratory, our results again did not significantly change.

The short follow-up of studies included in our meta-analysis may be used to justify the lack of association between IMT changes and cardiovascular risk; however, it becomes troublesome then to explain why short-term changes in low-density lipoprotein do predict cardiovascular risk. Thus, although we recognize that IMT changes perhaps may predict long-term cardiovascular risk, they do not perform as low-density lipoprotein changes in the short term, as we have shown in our paper.

Finally, we would like to point out that, as for all meta-analyses, particularly for those not based on an individual dataset, findings need to be interpreted with caution and are intended to be hypothesis-generating. Nonetheless, we believe that the conclusion from our study can help achieve a better understanding of clinical trials having IMT as endpoint and the planning of future studies.

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