Is Measuring Risk Marker Progression Useful for Cardiovascular Disease Prediction?

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Dear Editor,

There has been much debate on whether measuring the progression of carotid intima-media thickness (cIMT) adds further predictive information for future CVD events than simply utilizing single baseline measures. Pertinent studies have been conducted in various settings, including pooled projects of observational studies (general populations [1], diabetics [2], and high-risk individuals [3], see Table 1). Many, but not all, of these observational studies have reported null associations between progression, defined as the difference in cIMT measured at 2 separate time points, and risk of CVD events. In contrast, a recently published meta-analysis of clinical trial data [4] showed a significant association of cIMT progression with risk of CVD events with smaller cIMT progression per year associated with lower risk [4]. In the face of this apparent inconsistency, the authors of the meta-analysis stated that the null associations previously reported “could be explained by the challenges of precisely estimating cIMT progression in individuals over time,” and that focusing “on groups of patients in RCTs is better suited” for assessing the value of cIMT progression [4].

Certainly, a study with low reproducibility of cIMT measurements is likely to result in a null association. However, there is no clear reason why RCTs are superior to observational studies with respect to precision of cIMT measurement. In a meta-analysis or pooled analysis of individual participant data, heterogeneity among assessed studies may result in failure to capture the true association [5], although we have no reason to believe that heterogeneity is always less in RCTs than in observational studies. As for other possibilities, a small true change in cIMT over time, due to either a short duration between the first and second measurement or to the use of low-risk versus high-risk populations, will likely result in a low signal-to-noise ratio [6]. This possibility, however, seems unlikely to explain the inconsistent results on the association between cIMT progression and CVD risk at least among recent studies because the average duration between cIMT measurement and the annualized change in cIMT were similar across those studies (Table 1).

We would like to raise another possibility that differences in statistical models used among the studies may, at least in part, explain the inconsistency. In particular, most [1–3], but not all [7], studies reporting null associations adopted a model that simultaneously included “progres-

Table 1. Studies that examined the relationship between change in cIMT over time and cardiovascular disease risk

First author or research group	Study design	Time between first and second cIMT measurement, years	Annualized change in cIMT	Outcome	Statistical model	Was “progression” associated with outcome?
PROG-IMT and Proof-ATHERO [4]	Meta-analysis of clinical trials	Average of 3.7	9.1 $\mu\text{m}/\text{yr}$ in control arms, 1.0 $\mu\text{m}/\text{yr}$ in intervention arms (mean common cIMT, mostly)	Combined CVD endpoint (myocardial infarction, stroke, revascularization procedures, or fatal CVD)	Difference in annualized progression between intervention versus control group (meta-regression)	Yes
Suita Study [15]	A community-based cohort study	5	<24 $\mu\text{m}/\text{yr}$ in lowest quartile, >44 $\mu\text{m}/\text{yr}$ in highest quartile (max cIMT)	CVD	Progression (per 1 mm over 5 years) alone	Yes
PROG-IMT [3]	Meta-analysis of individual participant data (from observational studies of high-risk individuals)	3.6	10 $\mu\text{m}/\text{yr}$ (mean common cIMT)	Combined CVD endpoint (myocardial infarction, stroke, or vascular death)	Annualized progression + average	No
PROG-IMT [2]	Meta-analysis of individual participant data (from observational studies of patients with type 2 diabetes)	2–7 (mean 3.6)	9 $\mu\text{m}/\text{yr}$ in diabetics, 10 $\mu\text{m}/\text{yr}$ in no diabetics (mean common cIMT) 13 $\mu\text{m}/\text{yr}$ in diabetics, 15 $\mu\text{m}/\text{yr}$ in no diabetics (maximal common cIMT)	Combined CVD endpoint (myocardial infarction or any stroke or vascular death)	Annualized progression + average	No
Okayama et al. [11]	Cohort study of type 2 diabetic patients free of CVD	2.9/3.0 (for those with/without CV events)	30 $\mu\text{m}/\text{yr}$ (mean common cIMT)	CVD events (cardiovascular death, nonfatal myocardial infarction, unstable angina, and new-onset stable angina)	Progression (dichotomized by median) with or without baseline cIMT (dichotomized by 1.10 mm)	Yes (with or without adjustment for baseline cIMT)
PROG-IMT [1]	Meta-analysis of individual participant data (from observational studies of a general population)	2–7 (median 4)	1–30 $\mu\text{m}/\text{yr}$ for common cIMT, 1–65 $\mu\text{m}/\text{yr}$ for maximal common cIMT, 0–23 $\mu\text{m}/\text{yr}$ for maximal cIMT	Combined CVD endpoint (myocardial infarction, stroke, or vascular death)	Annualized progression + average	No
Goldberger et al. [16]	Meta-analysis of randomized control trials	Not described	14.2 $\mu\text{m}/\text{yr}$ in control arms, 5.5 $\mu\text{m}/\text{yr}$ in intervention arms*	Nonfatal myocardial infarction	Difference in annualized progression between intervention versus control group	Yes (except for subgroups evaluating statin therapy and those with high baseline cIMT)
Costanzo et al. [7]	Meta-analysis of randomized controlled trials	Not described	8.0 $\mu\text{m}/\text{yr}$ in control arms, 3.7 $\mu\text{m}/\text{yr}$ in intervention arms** (mean common cIMT, mostly)	Coronary heart disease events (acute coronary syndrome, coronary heart death, revascularization, and angina pectoris)	Difference in annualized progression between intervention versus control group with or without adjustment for baseline cIMT	No

Table 1 (continued)

First author or research group	Study design	Time between first and second cIMT measurement, years	Annualized change in cIMT	Outcome	Statistical model	Was “progression” associated with outcome?
Hodis et al. [17]	Long-term follow-up of the Cholesterol-Lowering Atherosclerosis Study (2-year cholesterol-lowering intervention for patients with coronary bypass graft surgery)	2 (during the trial)	21 $\mu\text{m}/\text{yr}$ in control arms, –24 $\mu\text{m}/\text{yr}$ in intervention arms (mean common cIMT)	Incident coronary event (nonfatal acute myocardial infarction, coronary death, and coronary artery revascularization)	Annualized progression + absolute cIMT at the end of trial	Yes

Presented were studies that examined cIMT progression in relation to cardiovascular risk, with statistical methods being verifiable. cIMT, carotid intima-media thickness; CVD, cardiovascular disease. * Since summary value was not reported, we computed median values based on 18 studies with annualized change presented among 32 studies assessed in the study. cIMT segments across the 32 studies varied. ** Since summary value was not reported, we computed median values based on 39 studies with annualized change in mean IMT presented among 44 studies assessed in the study.

sion” and “average” of the 2 cIMT values assessed at 2 separate time points (“progression-average model”), whereas many studies reporting a significant positive association did not adopt such a model, including the aforementioned meta-analysis (Table 1).

To illustrate why the “progression-average model” matters, suppose a simple regression model: CVD risk = $\text{beta1} \times \text{RF1} + \text{beta2} \times \text{RF2}$, where RF denotes a risk factor or marker. If a risk factor assessed at time points 1 and 2 (RF1 and RF2, respectively) has a similar strength of association with CVD risk in the model, then the regression coefficient of progression (RF2 – RF1) in the “progression-average model” is determined to be small, close to zero, because the coefficient is mathematically equivalent to $(\text{beta2} - \text{beta1})/2$ [8]. A near-zero regression coefficient for progression obtained from the “progression-average model” is likely to be statistically nonsignificant. In fact, even for a conventional risk factor such as systolic blood pressure, the association between progression and CVD risk can be either null or positive depending on the model used: a null (i.e., nonsignificant) association observed in the “progression-average model” flipped to be significantly positive when based on models without the average term [9, 10]. As such, previously reported “null associations” may be just artifacts derived from the “progression-average model.” Thus, we are concerned that the null findings, based on the “progression-average model,” may provide a biased impression that the second time measurement of the risk marker has no value, which indeed means, when based on the simple model, that the second time measurement predicts CVD events to a similar degree to the first measurement.

What would be the “correct model” then? In our opinion, there is no single “correct model” that is suitable for every case. The answer also depends on the aim of a study. If the aim is to examine the predictive property of RF2 for CVD risk, then stratification according to cIMT levels at baseline (RF1) and at second measure (RF2) to assess how CVD risk differs across the strata would be a simple and easy-to-understand model [11, 12]. Alternatively, the “simple regression model” described above may be acceptable if correlation between RF1 and RF2 is not a concern. When the aim is to examine the additive value of the repeated measurement(s) for CVD prediction, multiple options without using the “progression” variable have been proposed such as use of the average [13], cumulative value or trajectory patterns of risk factor/marker over time [14].

To conclude, in order to assess the usefulness of risk factors/markers assessed at different time points in pre-

dicting CVD events, one needs to carefully choose an appropriate statistical model. Otherwise, this debate will not be settled, and we will continue without substantial progress in this dispute.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.F. conceived and drafted the first version of the manuscript and revised. M.Z. and E.B.-M. assisted collecting published articles, critically reviewed earlier versions of the draft, and contributed to revision. All the authors approved the final version.

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