



# Carotid Intima-Media Thickness Progression and Risk of Vascular Events in People With Diabetes: Results From the PROG-IMT Collaboration

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## OBJECTIVE

Carotid intima-media thickness (CIMT) is a marker of subclinical organ damage and predicts cardiovascular disease (CVD) events in the general population. It has also been associated with vascular risk in people with diabetes. However, the association of CIMT change in repeated examinations with subsequent CVD events is uncertain, and its use as a surrogate end point in clinical trials is controversial. We aimed at determining the relation of CIMT change to CVD events in people with diabetes.

## RESEARCH DESIGN AND METHODS

In a comprehensive meta-analysis of individual participant data, we collated data from 3,902 adults (age 33–92 years) with type 2 diabetes from 21 population-based cohorts. We calculated the hazard ratio (HR) per standard deviation (SD) difference in mean common carotid artery intima-media thickness (CCA-IMT) or in CCA-IMT progression, both calculated from two examinations on average 3.6 years apart, for each cohort, and combined the estimates with random-effects meta-analysis.

## RESULTS

Average mean CCA-IMT ranged from 0.72 to 0.97 mm across cohorts in people with diabetes. The HR of CVD events was 1.22 (95% CI 1.12–1.33) per SD difference in mean CCA-IMT, after adjustment for age, sex, and cardiometabolic risk factors. Average mean CCA-IMT progression in people with diabetes ranged between –0.09 and 0.04 mm/year. The HR per SD difference in mean CCA-IMT progression was 0.99 (0.91–1.08).

## CONCLUSIONS

Despite reproducing the association between CIMT level and vascular risk in subjects with diabetes, we did not find an association between CIMT change and vascular risk. These results do not support the use of CIMT progression as a surrogate end point in clinical trials in people with diabetes.

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Diabetes is an important risk factor for atherosclerosis and its complications, including myocardial infarction (MI), stroke, and vascular death. Compared with subjects without diabetes, diabetes patients have a twofold higher risk of cardiovascular disease (CVD) events (1) and cardiovascular death (1,2); in some cohorts, it is even higher (up to sixfold) and comparable to the event risk in established coronary heart disease (3).

Carotid intima-media thickness (CIMT) is an ultrasound biomarker of atherosclerosis, considered as a marker of subclinical organ damage. People with diabetes exhibit a greater CIMT, as compared with those without diabetes (4–6); on average, common CIMT was found to be 0.13 mm greater in subjects with diabetes (6). People with impaired glucose tolerance but without diabetes also show a higher CIMT, although to a lesser extent (4,6); CIMT seems to increase from people without diabetes to those with impaired glucose tolerance, newly diagnosed diabetes, and established diabetes (4). This increase appears to be steeper for internal than for common carotid artery intima-media thickness (CCA-IMT) (4).

When measured once (at baseline), CIMT is predictive of future CVD events in the general population (7), even when adjusted for a wide range of established CVD risk factors. Recently, a meta-analysis has suggested that a “one-off” measurement of CIMT is also predictive of subsequent

nonfatal vascular events in people with diabetes (8), but the association of CIMT progression with event risk was not evaluated.

In clinical trials (including trials of oral antidiabetic medications [9–13]), CIMT has been frequently used as a secondary outcome. In this context, usually the absolute or annual progression of CIMT, derived from at least two ultrasound scans over 1 or more years, is used (9–13) rather than CIMT measured on a single occasion. However, whether the observed change in CIMT reflects a true change in risk of future CVD events is currently a matter of debate. Two publication-based meta-analyses assessed the surrogacy of CIMT progression for CVD event risk (14,15). Their results showed weak relations and were partially conflicting. In addition, several methodological issues were raised questioning the validity of these findings (16).

A necessary first step is to clarify the association between CIMT progression and CVD event risk. Recently, a large individual participant data–based meta-analysis (as part of the PROG-IMT collaboration) collated 70% of the identified worldwide population data on CIMT progression and CVD event risk. Surprisingly, no association between CIMT progression and CVD events risk was found, although there was a consistent association between “baseline” CIMT and CVD event risk (17). One hypothesis to explain these results is that in the general population, changes in the vessel

wall over time are too small to be captured with ultrasound CIMT scans, even when measurements are performed several years apart. It is therefore plausible to assume that in cohorts of subjects with higher rates of CIMT progression, which also have high CVD event rates (such as those with diabetes), CIMT progression may have a greater impact on risk prediction. The aims of the current study, as part of the PROG-IMT collaboration, were therefore to assess the rate of CIMT progression in people with diabetes compared with the general population, to replicate associations between a single CIMT measure and subsequent CVD events (including fatal end points), and to determine the association between CIMT progression and CVD events in people at high vascular risk due to the presence of diabetes.

## RESEARCH DESIGN AND METHODS

### Study Identification and Data Management

PubMed was comprehensively searched for publications on observational studies with the following inclusion criteria: 1) prospective longitudinal study design; 2) investigation of subjects with diabetes, or of the general population; 3) well-defined and disclosed inclusion criteria and recruitment strategy; 4) at least two ultrasound visits where carotid IMT was determined; and 5) a clinical follow-up after the second ultrasound

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visit, recording MI, stroke, vascular death, or total mortality. Furthermore, we searched the reference lists of all identified papers (including reviews) manually for additional eligible publications. We included publications up to 18 July 2014. When a potentially eligible study was identified, we sent a screening questionnaire to the study team in order to assess the inclusion criteria. If a study fulfilled all inclusion criteria, the study team was invited to join the PROG-IMT collaboration and share a dataset of predefined variables. The datasets underwent central plausibility checks and were harmonized in order to create uniform variable names and coding.

### Statistical Analyses

Only patients with diabetes who were free of MI and stroke up to the second CIMT scan were included into the analyses. The diabetes definitions from the

individual studies were adopted; an overview can be found in Supplementary Table 1. The Cardiovascular Health Study (CHS) was divided into Caucasian (CHS1) and African American (CHS2) cohorts, as these had different follow-up times for ultrasound and for clinical end points.

The analysis of CIMT values was restricted to subjects with at least two CIMT values. Mean CCA-IMT was calculated as the average of all available values of the subject's mean CCA-IMT (left and right, near and far wall, and all insonation angles) for each ultrasound visit. From the resulting CCA-IMT values, we derived the average of the first and second ultrasound visits (average CCA-IMT) and the annual change between the first and second ultrasound visits (i.e.,  $[IMT_2 - IMT_1]/[time, years]$ , "annual progression of CCA-IMT"). The principal analysis relied on mean CCA-IMT; for

sensitivity analyses, maximal CCA-IMT was also used.

For each cohort with at least 20 end point events, separate Cox regression models were fitted. Cohorts with <20 end point events were analyzed together in one Cox regression model, stratified by cohort. The resulting log hazard ratios (HRs) of the end point per SD of average CIMT or annual CIMT progression were combined across all cohorts using random-effects meta-analysis (18). Heterogeneity was assessed using  $I^2$  statistics (19).

For the primary analysis, we used a combined end point (MI or any stroke or vascular death) for clinical events after the second ultrasound scan. In cohorts where the end point "vascular death" was not recorded, "total mortality" was used instead. For sensitivity analyses, the end point "total mortality" was analyzed

**Table 1—Included cohorts with sample size and numbers of end point events**

Cohort	Country	Total number with two ultrasound scans	Number of subjects with diabetes without previous CVD events	Mean interval between the two ultrasound scans (years)	Mean duration of clinical follow-up after the second ultrasound scan (years)	Number of combined end point events among subjects with diabetes	Crude event rate of the combined end point among subjects with diabetes (per 1,000 person-years)
AIR (25)	Sweden	297	12	3.3	5.1	1	16.2
ARIC (26)	U.S.	12,221	1,131	2.9	7.4	281	33.5
BHS (27)	U.S.	554	22	2.4	4.3	2*	21.2*
Bruneck (28)	Italy	633	47	5.0	8.0	11	29.3
CAPS (22)	Germany	3,284	74	3.1	5.2	6	15.7
CCCC (29)	Taiwan	1,285	127	5.1	7.2	8	8.7
CHS1 (30)	U.S.	3,551	896	2.9	8.3	348	46.9
CHS2 (30)	U.S.	297	87	5.9	5.2	25	55.5
CMCS (31)	China	920	57	5.4	4.9	2	7.2
DIWA (20)	Sweden	418	40	5.5	2.1	2	23.4
EAS (32)	U.K.	620	31	6.5	5.2	4	25.0
EPICARDIAN (33)	Spain	161	7	3.0	6.6	1	21.5
EVA (34)	France	922	57	2.0	13.2	19*	25.3*
INVADE (35)	Germany	2,534	488	2.2	3.9	70	36.6
KIHD (36)	Finland	891	29	4.1	11.5	18	54.1
NOMAS/INVEST (37)	U.S.	647	116	3.6	2.9	5	14.8
PIVUS (38)	Sweden	680	53	5.1	1.8	4*	40.8*
PLIC (39)	Italy	1,538	71	2.3	4.0	1	3.5
Rotterdam (40)	The Netherlands	2,610	158	6.4	5.4	51	59.5
SAPHIR (41)	Austria	1,154	35	4.6	9.5	1	3.0
SHIP (42)	Germany	1,751	283	5.2	5.5	50	32.0
Tromsø (43)	Norway	4,003	81	6.3	6.4	25	48.1

\*Number of deaths among subjects with diabetes. AIR, Atherosclerosis and Insulin Resistance study; ARIC, Atherosclerosis Risk In Communities study; BHS, Bogalusa Heart Study; Bruneck, Bruneck study; CAPS, Carotid Atherosclerosis Progression Study; CCCC, Chin-Shan Community Cardiovascular Cohort; CMCS, Chinese Multi-provincial Cohort Study; DIWA, Diabetes, Impaired glucose tolerance in Women and Atherosclerosis; EAS, Edinburgh Artery Study; EPICARDIAN, Estudio epidemiológico sobre enfermedades y factores de riesgo cardiovasculares en ancianos españoles; KIHD, Kuopio Ischaemic Heart Disease study; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; PLIC, Progression of Lesions in the Intima of the Carotid; Rotterdam, Rotterdam Study; SAPHIR, Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk; Tromsø, Tromsø Study.

independently. The Cox regression models analyzed the time between the second ultrasound scan and the first end point event, or the end of follow-up; they were adjusted for age and sex (and average CCA-IMT when analyzing CCA-IMT progression) (model A), and additionally for ethnicity, socioeconomic status, BMI, systolic blood pressure, antihypertensive medication, total cholesterol, lipid-lowering medication, smoking status, and fasting glucose or HbA<sub>1c</sub>, as available (model B). When these risk factors were available for both visits, both their average and their progression were used for adjustment. The definitions of the combined end point and the adjustment variables for each cohort are listed in Supplementary Table 2.

## RESULTS

During the literature search, 2,278 publications were screened (Supplementary Fig. 1). Of 33 eligible population-based cohorts, 20 were included. The only cohort that appeared as a “diabetes cohort” in the screening process was in fact based on a

population sample as well and represented people with and without type 2 diabetes; it was also included (20). One other study dedicated to people with diabetes was not eligible, as no end point events were observed in the group of subjects with diabetes and with two ultrasound scans (21). The mean age at baseline of all included patients with diabetes was 60.4 years (range 33–92).

Table 1 gives an overview of the included cohorts, which comprise a total of 3,902 people with diabetes, among whom 935 CVD events have been recorded during follow-up after the second ultrasound scan. The ultrasound protocols were heterogeneous in some respects; details are displayed in Supplementary Table 3. The mean interval between the two CIMT measurements on which progression was based was 3.59 years (range 2–7, SD 1.32).

The CIMT and CIMT progression values are shown in Table 2 (mean CCA-IMT) and Table 3 (maximal CCA-IMT), which compare progression in people with and

without diabetes. Subjects with diabetes had on average 0.041 mm higher (95% CI 0.036–0.045, adjusted for age and sex) mean CCA-IMT than subjects without diabetes. For maximal CCA-IMT, the difference was 0.046 mm (95% CI 0.041–0.051). Average annual mean CCA-IMT progression in people with diabetes ranged from –0.09 to 0.04 mm/year across studies and did not differ substantially between subjects with and without diabetes.

Figure 1 shows Forest plots of the HR of the combined end point per SD of average mean CCA-IMT, which is the average of the first and second CIMT measurements. These HRs are clearly and significantly greater than 1: in model A, we found an HR of 1.30 (95% CI 1.22–1.38), and in model B (which adjusts for cardiometabolic risk factors), the HR was 1.22 (1.12–1.33). The  $I^2$  statistics indicate no heterogeneity. Figure 2 displays similar plots for annual mean CCA-IMT progression. Here, the CIs of the pooled HRs include 1: in model A, the HR is 1.03 (0.96–1.10), in model B, it is 0.99 (0.91–1.08). Very similar

**Table 2—Average mean CCA-IMT and average annual mean CCA-IMT progression in people with and without diabetes**

Cohort	Average mean CCA-IMT (mm)			Average annual mean CCA-IMT progression (mm/year)		
	Diabetes, mean (SD)	No diabetes, mean (SD)	Difference, mean (SE)&	Diabetes, mean (SD)	No diabetes, mean (SD)	Difference, mean (SE)&
AIR	0.86 (0.14)	0.79 (0.12)	0.066 (0.036)	–0.004 (0.040)	0.001 (0.028)	–0.005 (0.008)
ARIC	0.72 (0.13)	0.56 (0.11)	0.052 (0.003)	0.009 (0.048)	0.011 (0.037)	–0.001 (0.001)
CAPS	0.81 (0.13)	0.73 (0.17)	0.018 (0.018)	–0.004 (0.035)	0.003 (0.092)	–0.007 (0.011)
CHS1	0.90 (0.16)	0.86 (0.14)	0.038 (0.005)	0.006 (0.053)	0.005 (0.045)	0.001 (0.002)
CHS2	0.94 (0.15)	0.92 (0.16)	0.015 (0.020)	0.005 (0.030)	0.011 (0.028)	–0.007 (0.004)
CMCS	0.85 (0.23)	0.81 (0.19)	0.040 (0.025)	0.037 (0.044)	0.040 (0.041)	–0.002 (0.006)
DIWA	0.94 (0.17)	0.86 (0.15)	0.074 (0.025)	–0.001 (0.022)	0.004 (0.020)	–0.005 (0.003)
EAS	0.87 (0.20)	0.85 (0.19)	0.005 (0.033)	0.030 (0.032)	0.030 (0.045)	0.001 (0.008)
EPICARDIAN	0.78 (0.15)	0.79 (0.21)	–0.004 (0.079)	–0.093 (0.101)	–0.099 (0.133)	0.001 (0.052)
EVA	0.72 (0.11)	0.66 (0.10)	0.045 (0.014)	0.008 (0.040)	0.006 (0.046)	0.002 (0.006)
INVADE	0.86 (0.18)	0.81 (0.17)	0.031 (0.008)	0.012 (0.082)	0.009 (0.075)	0.004 (0.004)
KIHD	0.83 (0.12)	0.81 (0.16)	0.010 (0.027)	0.024 (0.022)	0.028 (0.033)	–0.005 (0.006)
NOMAS/INVEST	0.72 (0.09)	0.73 (0.08)	–0.005 (0.008)	0.007 (0.028)	0.009 (0.030)	–0.002 (0.003)
PIVUS	0.97 (0.17)	0.92 (0.14)	0.049 (0.021)	0.009 (0.034)	0.009 (0.029)	0.000 (0.004)
PLIC	0.74 (0.12)	0.66 (0.13)	0.029 (0.013)	0.009 (0.032)	0.015 (0.036)	–0.007 (0.004)
Rotterdam	0.86 (0.15)	0.79 (0.14)	0.046 (0.011)	0.012 (0.024)	0.012 (0.021)	0.000 (0.002)
SAPHIR	0.91 (0.11)	0.80 (0.12)	0.074 (0.019)	0.024 (0.024)	0.017 (0.019)	0.005 (0.003)
SHIP	0.83 (0.16)	0.78 (0.14)	0.031 (0.009)	0.009 (0.037)	0.003 (0.023)	0.001 (0.002)
Tromsø	0.87 (0.16)	0.78 (0.14)	0.053 (0.013)	0.010 (0.034)	0.004 (0.019)	0.006 (0.002)
Combined (95% CI)*	0.82 (0.17)	0.71 (0.18)	0.041 (0.036–0.045)	0.009 (0.052)	0.010 (0.047)	–0.000 (–0.001 to 0.001)

Mean CCA-IMT is not available in Bogalusa Heart Study (BHS), Bruneck study (Bruneck), or the Chin-Shan Community Cardiovascular Cohort (CCCC). AIR, Atherosclerosis and Insulin Resistance study; CMCS, Chinese Multi-provincial Cohort Study; DIWA, Diabetes, Impaired glucose tolerance in Women and Atherosclerosis; EAS, Edinburgh Artery Study; EPICARDIAN, Estudio epidemiológico sobre enfermedades y factores de riesgo cardiovasculares en ancianos españoles; KIHD, Kuopio Ischaemic Heart Disease study; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; PLIC, Progression of Lesions in the Intima of the Carotid; Rotterdam, Rotterdam Study; SAPHIR, Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk; Tromsø, Tromsø Study. &Adjusted for age and sex by multiple regression. \*Combined means and SDs weighted by sample size; differences between people with and without diabetes combined by random-effects meta-analysis.

**Table 3—Average maximal CCA-IMT and average annual maximal CCA-IMT progression in people with and without diabetes**

Cohort	Average max CCA-IMT (mm)			Average annual max CCA-IMT progression (mm/year)		
	Diabetes, mean (SD)	No diabetes, mean (SD)	Difference, mean (SE)&	Diabetes, mean (SD)	No diabetes, mean (SD)	Difference, mean (SE)&
AIR	1.04 (0.17)	0.98 (0.16)	0.062 (0.046)	0.006 (0.062)	0.014 (0.042)	−0.008 (0.013)
ARIC	0.83 (0.16)	0.76 (0.13)	0.054 (0.004)	0.015 (0.055)	0.015 (0.044)	0.000 (0.002)
BHS	0.91 (0.22)	0.75 (0.12)	0.092 (0.019)	−0.006 (0.102)	0.001 (0.048)	−0.009 (0.008)
Bruneck	1.02 (0.15)	0.95 (0.18)	0.004 (0.022)	0.022 (0.032)	0.028 (0.027)	−0.004 (0.004)
CCCC	0.79 (0.20)	0.73 (0.18)	0.032 (0.015)	0.023 (0.048)	0.019 (0.049)	0.004 (0.004)
CHS1	1.09 (0.20)	1.03 (0.18)	0.050 (0.007)	0.013 (0.070)	0.009 (0.060)	0.004 (0.002)
CHS2	1.11 (0.18)	1.09 (0.19)	0.020 (0.024)	−0.006 (0.035)	0.004 (0.035)	−0.010 (0.005)
CMCS	0.92 (0.29)	0.88 (0.25)	0.043 (0.034)	0.051 (0.053)	0.053 (0.057)	−0.002 (0.008)
DIWA	1.07 (0.23)	0.98 (0.18)	0.088 (0.030)	0.001 (0.026)	0.008 (0.026)	−0.007 (0.004)
KIHD	1.08 (0.17)	1.06 (0.22)	0.004 (0.038)	0.063 (0.041)	0.066 (0.049)	−0.002 (0.009)
NOMAS/INVEST	0.93 (0.09)	0.94 (0.09)	−0.002 (0.001)	0.008 (0.029)	0.009 (0.032)	−0.002 (0.003)
PIVUS	1.12 (0.17)	1.06 (0.17)	0.056 (0.025)	0.020 (0.043)	0.015 (0.036)	0.005 (0.005)
PLIC	0.82 (0.13)	0.73 (0.15)	0.032 (0.015)	0.003 (0.038)	0.009 (0.043)	−0.006 (0.005)
Rotterdam	1.08 (0.17)	1.01 (0.16)	0.047 (0.013)	0.012 (0.020)	0.016 (0.023)	−0.004 (0.002)
SHIP	0.98 (0.20)	0.89 (0.19)	0.036 (0.011)	0.002 (0.032)	0.000 (0.031)	0.001 (0.002)
Tromsø	1.09 (0.21)	0.97 (0.18)	0.082 (0.017)	0.014 (0.043)	0.005 (0.025)	0.009 (0.003)
Combined (CI 95%)*	0.96 (0.22)	0.87 (0.20)	0.046 (0.041–0.051)	0.013 (0.055)	0.015 (0.043)	−0.000 (−0.002 to 0.001)

Max CCA-IMT is not available in CAPS, Edinburgh Artery Study (EAS), Estudio epidemiológico sobre enfermedades y factores de riesgo cardiovasculares en ancianos españoles (EPICARDIAN), INVADE, and Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk (SAPHIR). AIR, Atherosclerosis and Insulin Resistance study; CCCC, Chin-Shan Community Cardiovascular Cohort; CMCS, Chinese Multi-provincial Cohort Study; DIWA, Diabetes, Impaired glucose tolerance in Women and Atherosclerosis; KIHD, Kuopio Ischaemic Heart Disease study; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; PLIC, Progression of Lesions in the Intima of the Carotid; Rotterdam, Rotterdam Study; Tromsø, Tromsø Study. &Adjusted for age and sex by multiple regression. \*Combined means and SDs weighted by sample size; differences between people with and without diabetes combined by random-effects meta-analysis.

results were obtained for CCA-IMT progression when no adjustment was made for the average of the two CCA-IMT measurements.

In comparison, we assessed the HRs per SD of average mean CCA-IMT for people without diabetes in the same population cohorts. Here, the HRs were slightly smaller than in people with diabetes (Supplementary Fig. 2), but the differences were not statistically significant (tests of interaction  $P > 0.2$ ).

Comprehensive sensitivity analyses were performed, including analysis of maximal CCA-IMT (Supplementary Fig. 3) and assessment of the clinical end point “total mortality” (Supplementary Fig. 4). Both of these showed a robust association between average CIMT and risk, but not between CIMT progression and clinical end points. We also looked for sex and ethnic differences in the associations (Supplementary Figs. 5 and 6). The HR for average CIMT for women was greater than that for men, adjusting only for age, but this difference was no longer convincing after adjusting for cardiometabolic risk factors. There were no other clear differences according to sex or ethnic group.

## CONCLUSIONS

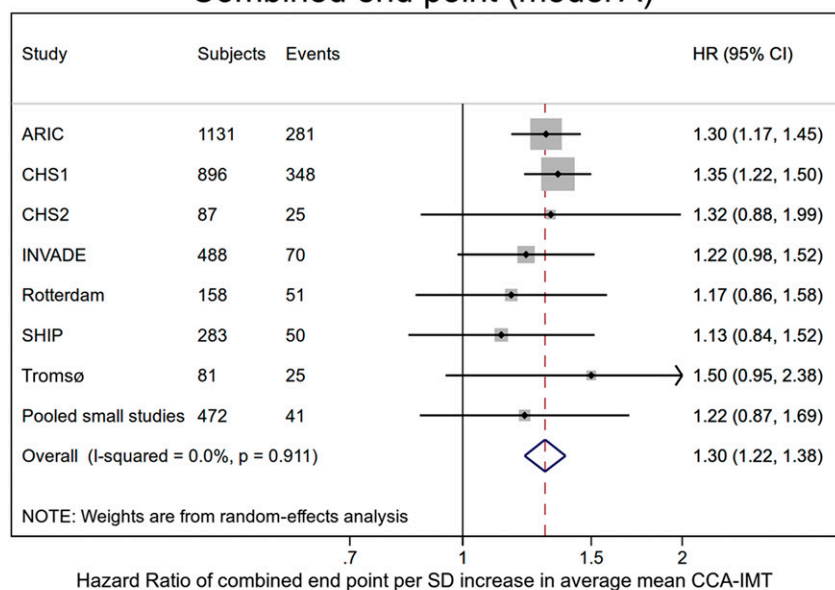
Diabetes is an important risk condition for atherosclerosis and its complications. In July 2014, more than 11,000 clinical trials in diabetes were registered at [clinicaltrials.gov](http://clinicaltrials.gov). The best standard to evaluate the efficacy of a new antidiabetic drug or of dietary, lifestyle, or other interventions is to observe clinical events, including MI, stroke, and death. The existence of a subclinical marker to evaluate change in risk is highly desirable in the development of new therapies, as such surrogate end points in trials often yield results years before sufficient numbers of true clinical events occur. This may save both costs and lives, speeding up the progress of drug development.

CIMT is a measurement of subclinical organ damage, a marker located halfway between risk factors and “hard” clinical end point events such as MI and stroke. Given its good predictive value, CIMT is an excellent candidate for such a surrogate marker. If CIMT were a valid surrogate of vascular events, one would expect both single-time CIMT and CIMT change to be independent predictors of future clinical

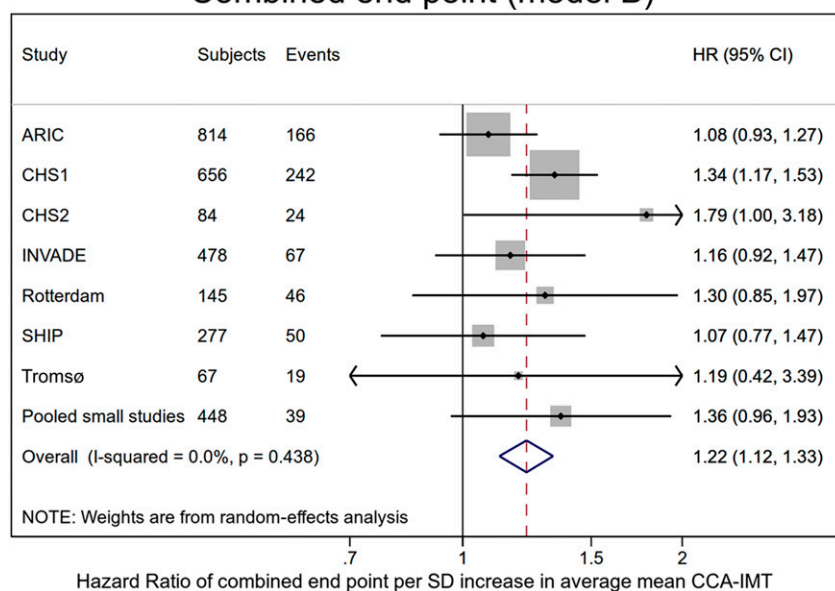
events. However, recent findings suggest no association between CIMT progression and CVD event risk in the general population, despite a consistent association between “baseline” CIMT and CVD event risk (17). Given our hypothesis that such an association may be more evident in “high-risk” populations, i.e., people with diabetes, we first set out to assess differences in CCA-IMT and CCA-IMT progression in subpopulations with and without diabetes before investigating the association of these measures with incident vascular events. We found a systematically higher mean CCA-IMT in people with diabetes, as compared with those without, with an average age- and sex-adjusted difference of 0.04 mm. For maximal CCA-IMT, the difference was 0.05 mm. In a meta-analysis from Brohall et al. (6), an average difference of 0.13 mm (95% CI 0.12–0.14) was found between people with diabetes and control subjects, although this meta-analysis relied on published estimates, and therefore intermingled mean and maximal CCA-IMT. The difference may also be explained by the fact that Brohall et al. (6) included both population cohorts and



### Combined end point (model A)



### Combined end point (model B)



**Figure 1**—Forest plot of HR of the combined end point (MI, stroke, or vascular death) per SD of average mean CCA-IMT in subjects with diabetes. Note that pooled small studies included Atherosclerosis and Insulin Resistance study (AIR); CAPS; Chinese Multi-provincial Cohort Study (CMCS); Diabetes, Impaired glucose tolerance in Women and Atherosclerosis (DIWA); Edinburgh Artery Study (EAS); Estudio epidemiológico sobre enfermedades y factores de riesgo cardiovasculares en ancianos españoles (EPICARDIAN); Kuopio Ischaemic Heart Disease study (KIHD); NOMAS/INVEST; Progression of Lesions in the Intima of the Carotid (PLIC); and Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk (SAPHIR).

case-control studies, where in the latter long-standing diabetes may predominate, whereas we used only general population cohorts where diabetes may have been newly diagnosed. The average annual progression of mean and maximal CCA-IMT in subjects with and without diabetes was very low. In contrast with CCA-IMT, we found that rates of CCA-IMT

progression did not differ substantially between subjects with and without diabetes.

The current analyses in subjects with diabetes showed a robust and substantial association between average CIMT and the risk of the combined end point MI, stroke, or vascular death, which persisted after adjustment for all major

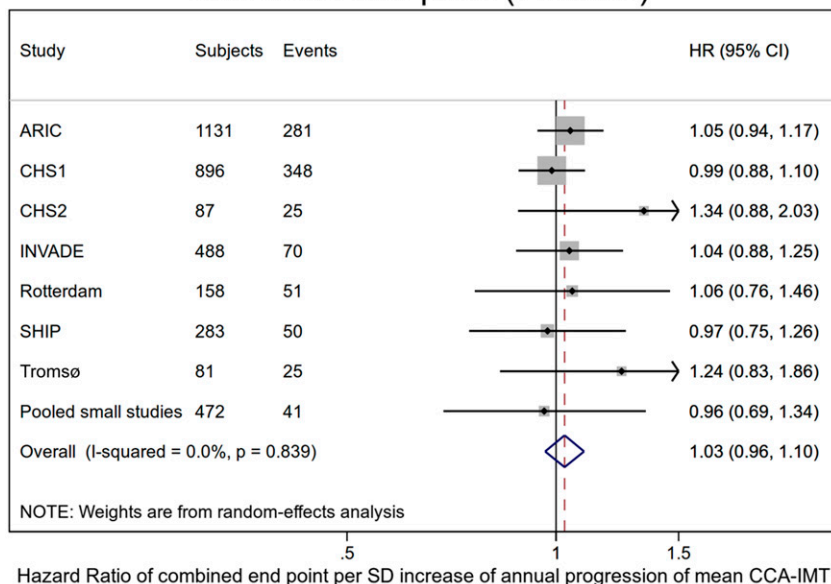
cardiovascular risk factors. The HR per SD of mean CCA-IMT that we found was identical to the corresponding estimate in the USE-IMT study on diabetes (8), which is not surprising, as the cohorts included have considerable overlap. In our data, the HR in people with diabetes was a little higher than in people without diabetes (1.22 vs. 1.15), although this difference was not statistically significant.

There were some differences in the methods between the cohorts, including the ultrasound protocols and the diabetes and end point definitions (see Supplementary Tables 1–3). As we found no noteworthy heterogeneity ( $I^2 = 0\%$ ) between the particular cohorts in this analysis, we do not rate these minor differences influential on the main effects. The association of CIMT and risk was virtually identical for maximal CCA-IMT and the combined end point, and a little smaller, but nevertheless robust, for the end point “total mortality.”

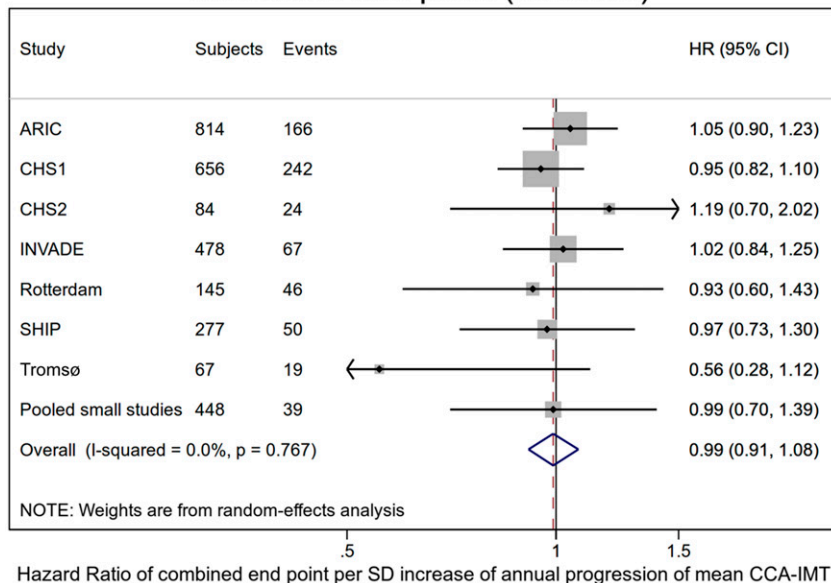
A statistically significant association between CIMT progression and event risk was found neither for mean nor for maximal CCA-IMT, nor when either the combined end point or total mortality was analyzed. Thus, although the association between (single-time) carotid IMT and the risk of vascular events has been shown many times, in subjects with diabetes (8) as well as in general population samples (7) and in all age-groups (22), in both the present analysis of people with diabetes and the recent analysis of the general population (17), an association between CIMT progression and CVD risk remained unproven. One possible explanation for this apparent discrepancy may be that single-time CIMT reflects a history of decades of exposure to risk factors, whereas CIMT progression relates to a time frame of only a few years. Another hypothesis is that a true association between CIMT change and risk is diluted by measurement error, despite the fact that all included studies made efforts to increase reproducibility using different techniques (Supplementary Table 3). This hypothesis is supported by the large SD around the mean CIMT progression that we observed here and in the general population (17), and would argue for attempting to find an effect in randomized trials, where the specific ultrasound protocols used may measure CIMT progression more precisely.

In our analyses, only the common carotid CIMT was reported, and differences

### Combined end point (model A)



### Combined end point (model B)



**Figure 2**—Forest plot of HR of the combined end point (MI, stroke, or vascular death) per SD of annual mean CCA-IMT progression in subjects with diabetes. Note that pooled small studies included Atherosclerosis and Insulin Resistance study (AIR); CAPS; Chinese Multi-provincial Cohort Study (CMCS); Diabetes, Impaired glucose tolerance in Women and Atherosclerosis (DIWA); Edinburgh Artery Study (EAS); Estudio epidemiológico sobre enfermedades y factores de riesgo cardiovasculares en ancianos españoles (EPICARDIAN); NOMAS/INVEST; Progression of Lesions in the Intima of the Carotid (PLIC); and Salzburg Atherosclerosis Prevention program in subjects at High Individual Risk (SAPHIR).

may have been seen with more extensive evaluation, i.e., of the IMT in the internal carotid artery or the carotid bifurcation. We refrained from these additional analyses a priori to avoid multiple testing issues. In our statistical analyses, we appropriately adjusted CIMT progression for the average of the first and second CIMT

values, rather than the first CIMT alone, to avoid biases due to regression to the mean (23,24).

In our investigation, we assembled almost 1,000 CVD event end points by collating individual data from 21 cohort studies, being a large proportion of the globally available data on CIMT progression

and CVD events in diabetes. Although this is a large number of CVD events, it is possible that an even larger dataset is required to demonstrate a relationship of CIMT progression with CVD events.

#### Summary

In a large individual participant data meta-analysis, we pooled a large proportion of the global data to determine the association between CIMT progression and vascular risk in people with diabetes. We reproduced and substantiated the association between single-time CIMT level and event risk in people with diabetes. Despite this, we did not find an association between CIMT progression over a mean time of 3.6 years and future event risk. As such, our results do not support the use of CIMT as a surrogate end point in clinical trials in people with diabetes. However, the lack of association between CIMT progression and clinical events may at least partially be explained by considerations of statistical power and measurement error, and further definitive analysis may require even larger studies. To more fully answer the question of whether CIMT is a valid surrogate end point, it will also be informative to determine whether, in randomized trials, an intervention acts on CIMT progression in the same way as it acts on vascular risk. Such an analysis is planned in the framework of the PROG-IMT collaboration (a full list of members can be found in the Supplementary Data online).

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Nestlé Nutrition (Nestec Ltd.), Metagenics Inc., and AXA had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

**Author Contributions.** M.W.L. and S.G.T. designed the study; researched, analyzed, and interpreted data; and drafted, double checked, and critically revised the manuscript. J.F.Pr., C.R., and M.L.B. researched and interpreted data and drafted, double checked, and critically revised the manuscript. J.F.Po., H.P., M.K., M.Dö., E.S., P.D., K.R., S.K., M.S., T.R., L.L., J.L., G.B., L.Gr., L.B., A.F., D.Y., H.B., M.A.I., H.V., S.H.J., J.P.E., T.-P.T., P.W., H.S., M.De., W.X., C.Sc., G.D.N., C.Su., D.S., A.H., U.S., E.M., M.P., J.K., J.W., R.L.S., S.M., D.Z., B.F., A.L.C., R.G., O.H.F., A.B., and A.P. researched data and double checked and critically revised the manuscript. F.S. and L.Ga. researched and analyzed data and double checked and critically revised the manuscript. All authors fulfill the International Committee of Medical Journal Editors criteria for authorship. All authors gave final approval of the manuscript as submitted. All authors agreed to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. M.W.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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