



**Carotid Intima Media Thickness progression and risk of
vascular events in people with diabetes mellitus- results
from the PROG-IMT collaboration**

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Abstract

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 with subsequent CVD events is uncertain, and its use as a surrogate endpoint in clinical trials is controversial. Our aim was to determine the relation of CIMT change with incident CVD events in people with diabetes.

Research Design and Methods: In a comprehensive meta-analysis of individual participant data, we collated data from 3902 adults (age range 33-92) with type 2 diabetes from 21 population-based cohort studies. We calculated the hazard ratio (HR) per standard deviation (SD) difference in mean common carotid artery (CCA) IMT, or in CCA-CIMT progression, for each cohort, and combined the estimates with random effects meta-analysis.

Results: Average annual mean CCA-IMT progression in people with diabetes ranged between -0.09 and 0.04mm/year across cohorts. The HR of CVD events was 1.22 (95% confidence interval 1.12-1.33) per SD difference in mean CCA-IMT, after adjustment for age, sex, and a large set of cardiometabolic risk factors. The corresponding HR per SD difference in annual 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 endpoint in clinical trials in people with diabetes.

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Introduction

Diabetes mellitus is an important risk factor for atherosclerosis and its complications, including myocardial infarction, stroke and vascular death. Compared with subjects without diabetes, diabetes patients have a two-fold higher risk of cardiovascular (CVD) events [1] and cardiovascular death [1,2]; in some cohorts it is even higher (up to 6-fold) 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. Persons with diabetes exhibit a greater CIMT, as compared to those without diabetes [4–6]; on average, common CIMT was found to be 0.13mm 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 persons 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 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 'one-off' measurement of CIMT is also predictive of subsequent non-fatal 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 one 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 (IPD) 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 present study, as part of the PROG-IMT collaboration, were therefore to assess the rate of CIMT progression in people with diabetes compared to the general population, to replicate associations between a single CIMT measure and subsequent CVD events (including fatal endpoints) and to determine the association between CIMT progression and CVD events in people at high vascular risk due to the presence of diabetes.

Methods

Study identification and data management

PubMed was comprehensively searched for publications on observational studies with the following inclusion criteria: (i) prospective longitudinal study design, (ii) investigation of subjects with diabetes, or of the general population, (iii) well-defined and disclosed inclusion criteria and recruitment strategy, (iv) at least two ultrasound visits where carotid IMT was determined, (v) a clinical follow-up after the second ultrasound 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 the 18th 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 analyzes

Only patients with diabetes who were free of myocardial infarction and stroke up to the second CIMT scan were included into the analyzes. The diabetes definitions from the individual studies were adopted; an overview can be found in webtable A1. The Cardiovascular Health Study (CHS) was divided into a Caucasian (CHS1) and an African American (CHS2) cohort, as these had different follow-up times for ultrasound and for clinical endpoints.

Mean IMT in the common carotid artery (CCA-IMT) was calculated as the average of all available values (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 the second ultrasound visit ('average CCA-IMT'), and the annual change between the first and the second ultrasound visit (i.e. $(\text{IMT}_2 - \text{IMT}_1) / \text{time [years]}$, 'annual progression of CCA-IMT'). The principal analysis relied on mean CCA-IMT; for sensitivity analyzes maximal CCA-IMT was also used.

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

For the primary analysis, we used a combined endpoint (myocardial infarction or stroke or vascular death) for clinical events after the second ultrasound scan. In cohorts where the endpoint 'vascular death' was not recorded, 'total mortality' was used instead. For sensitivity analyzes, the endpoint 'total mortality' was analyzed independently. The Cox regression models were adjusted for age and sex (and average CCA-IMT when analysing CCA-IMT progression) (model A), and additionally for ethnicity, socioeconomic status, body mass index, systolic blood pressure, antihypertensive medication, total cholesterol, lipid lowering medication, smoking status, fasting glucose or HbA1c, as available (model B). When these risk factors were available for both visits, both their average and their progression was used for adjustment. The definitions of the combined endpoint and the adjustment variables for each cohort are listed in webtable A2.

The first and the last author had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

During the literature search, 2278 publications were screened (webfigure A1). 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 persons with and without type 2 diabetes; it was also included [18]. One other study dedicated to persons with diabetes was not eligible as no endpoints events were observed in the group of subjects with diabetes and with two ultrasound scans [19]. The mean age at baseline of all included diabetes patients was 60.4 years (range 33-92).

Table 1 gives an overview of the included cohorts, which comprise a total of 3902 persons with diabetes amongst whom 935 CVD events have been recorded during follow-up after the second ultrasound scan. The ultrasound protocols were heterogenous in some respects; details are displayed in webtable A3. The mean interval between the two CIMT measurements on which progression was based was 4 years (ranging from 2 to 7 years).

The CIMT and CIMT progression values are shown in table 2 (mean CCA-IMT) and table 3 (maximal CCA-IMT), which compare progression in persons with and without diabetes. Subjects with diabetes had on average 0.041mm higher (95% CI 0.036-0.045mm, adjusted for age and sex) mean CCA-IMT than subjects without diabetes. For maximal CCA-IMT, the difference was 0.046mm (95% CI 0.041-0.051mm). Average annual mean CCA-IMT progression in people with diabetes ranged from -0.09 mm 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 endpoint per standard deviation (SD) of average mean CCA-IMT, which is the average of the first and the second CIMT measurement. These HRs are clearly and significantly greater than 1: in model A we found a HR of 1.30 (95% CI: 1.22-1.38), 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 confidence intervals of the pooled HRs include 1: in model A the HR is 1.03 (0.96-1.10), in model B 0.99 (0.91-1.08).

In comparison, we assessed the HRs per SD of average mean CCA-IMT for persons without diabetes in the same population cohorts. Here, the HRs were slightly smaller than in persons with diabetes (webfigure A2), but the differences were not statistically significant (tests of interaction $p > 0.2$).

Comprehensive sensitivity analyzes were done, including analysis of maximal CCA-IMT (webfigure A3), and assessment of the clinical endpoint 'total mortality' (webfigure A4). Both of these showed a robust association between average CIMT and risk, but not between CIMT progression and clinical endpoints. We also looked for sex and ethnic differences in the associations (webfigures A5 and A6). 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.

Discussion

Diabetes mellitus is an important risk condition for atherosclerosis and its complications. In July 2014, more than 11000 clinical trials in diabetes mellitus were registered at clinicaltrials.gov. The best standard to evaluate the efficiency of a new antidiabetic drug, of dietary, lifestyle, or other interventions is to observe clinical events, including myocardial infarction, 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 endpoints 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 endpoint events such as myocardial infarction 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 persons with diabetes, as compared with those without, with an average age and sex adjusted difference of 0.04mm. For maximal CCA-IMT, the difference was 0.05mm. In a meta-analysis from Brohall et al. [6], an average difference of 0.13mm (95% CI: 0.12-0.14) was found between persons with diabetes and controls, 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. included both population cohorts and case-control studies, where in the latter long-standing diabetes may predominate, while we used only general population cohorts where diabetes may have been newly diagnosed. In contrast, we found that rates of CCA-IMT progression did not differ substantially between subjects with and without diabetes.

The current analyzes in subjects with diabetes showed a robust and substantial association between average CIMT and the risk of the combined endpoint MI, stroke, or vascular death, which persisted after adjustment for all major cardiovascular risk factors. The HR per SD of mean CCA-IMT we found was identical to the corresponding estimate in the USE-IMT study on diabetes, 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.

Furthermore, we found no noteworthy heterogeneity ($I^2 = 0\%$) between the particular cohorts in this analysis, whereas there was moderate, however non-significant, heterogeneity in the general population ($I^2=37\%$) [17]. The association of CIMT and risk was virtually identical for maximal CCA-IMT and the combined endpoint, and a little smaller, but nevertheless robust, for the endpoint '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 endpoint or total mortality were analyzed. Thus, whilst 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 [20], 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 (webtable A3). This hypothesis is supported by the large standard deviation around the mean CIMT progression we observed here and in the general population [17], and would argue for attempting to find an effect in randomised trials, where the specific ultrasound protocols used may measure CIMT progression more precisely.

In our investigation, we assembled almost one thousand CVD event endpoints 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 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.

Conclusion

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 and future event risk. Based on the evidence obtained from populations based cohort studies, none of which specifically designed for assessment of change over time in CIMT, the use of CIMT progression as a surrogate endpoint in clinical trials in people with diabetes is not supported. To further assess whether CIMT could be a valid surrogate endpoint in some circumstances, it will be necessary to determine whether, in randomised trials, an intervention acts on CIMT progression in a similar way as it acts on event risk. Such an analysis is planned in the framework of the PROG-IMT collaboration.

Author contributions

All authors fulfill the ICMJE criteria for authorship. In detail, the study was designed by MWL and SGT, the data were researched by all authors, analyzed by MWL, FS, LG and SGT, interpreted by MWL, JP, CR, MLB, and SGT; the manuscript was drafted by MWL, JP, CR, MLB, and SGT; and double-checked and critically revised by all authors. 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.

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Conflict of interest disclosures

Michiel Bots has received grants from AstraZeneca, Dutch Heart Foundation, Organon, Pfizer, Servier, the Netherlands Organisation for Health Research and Development, and TNO-Zeist, and consultancy fees from AstraZeneca, Boehringer, Organon, Pfizer, Servier, Schering-Plough, and Unilever. He runs the Vascular Imaging Center in Utrecht, a core laboratory for cIMT measurements in national and international observational and intervention studies.

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All other authors declare that they have no conflicts of interest.

References

1. Sarwar N, Gao P, Seshasai SRK, Gobin R, Kaptoge S et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010 ;375: 2215–2222.
2. Woodward M, Zhang X, Barzi F, Pan W, Ueshima H et al. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care* 2003 ;26: 360–366.
3. Haffner SM, Lehto S, Rönkämaa T, Pyörälä K, Laakso M Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N. Engl. J. Med.* 1998 ;339: 229–234.
4. Wagenknecht LE, D'Agostino RB, Haffner SM, Savage PJ, Rewers M Impaired glucose tolerance, type 2 diabetes, and carotid wall thickness: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 1998 ;21: 1812–1818.
5. Temelkova-Kurktschiev TS, Koehler C, Leonhardt W, Schaper F, Henkel E et al. Increased intimal-medial thickness in newly detected type 2 diabetes: risk factors. *Diabetes Care* 1999 ;22: 333–338.
6. Brohall G, Odén A, Fagerberg B Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. *Diabet. Med.* 2006 ;23: 609–616.
7. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007 ;115: 459–467.
8. den Ruijter HM, Peters SAE, Groenewegen KA, Anderson TJ, Britton AR et al. Common carotid intima-media thickness does not add to Framingham risk score in individuals with diabetes mellitus: the USE-IMT initiative. *Diabetologia* 2013 ;56: 1494–1502.
9. Katakami N, Yamasaki Y, Hayaishi-Okano R, Ohtoshi K, Kaneto H et al. Metformin or gliclazide, rather than glibenclamide, attenuate progression of carotid intima-media thickness in subjects with type 2 diabetes. *Diabetologia* 2004 ;47: 1906–1913.
10. Mazzone T, Meyer PM, Feinstein SB, Davidson MH, Kondos GT et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006 ;296: 2572–2581.
11. Hodis HN, Mack WJ, Zheng L, Li Y, Torres M et al. Effect of peroxisome proliferator-activated receptor gamma agonist treatment on subclinical atherosclerosis in patients with insulin-requiring type 2 diabetes. *Diabetes Care* 2006 ;29: 1545–1553.
12. Crouse JR, Raichlen JS, Riley WA, Evans GW, Palmer MK et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA* 2007 ;297: 1344–1353.
13. Lonn EM, Gerstein HC, Sheridan P, Smith S, Diaz R et al. Effect of ramipril and of rosiglitazone on carotid intima-media thickness in people with impaired glucose tolerance or impaired fasting glucose: STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone). *J. Am. Coll. Cardiol.* 2009 ;53: 2028–2035.
14. Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P et al. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *J. Am. Coll. Cardiol.* 2010 ;56: 2006–2020.

15. Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT et al. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. *Am. Heart J.* 2010 ;160: 701–714.
16. Taylor AJ, Bots ML, Kastelein JJ. Vascular disease: meta-regression of CIMT trials - data in, garbage out. *Nat Rev Cardiol.* 2011;8:128-30.
17. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012 ;379: 2053–2062.
18. Behre CJ, Brohall G, Hulthe J, Wikstrand J, Fagerberg B Are serum adiponectin concentrations in a population sample of 64-year-old Caucasian women with varying glucose tolerance associated with ultrasound-assessed atherosclerosis. *J. Intern. Med.* 2006 ;260: 238–244.
19. Becker A, Henry RMA, Kostense PJ, Jakobs C, Teerlink T et al. Plasma homocysteine and S-adenosylmethionine in erythrocytes as determinants of carotid intima-media thickness: different effects in diabetic and non-diabetic individuals. The Hoorn Study. *Atherosclerosis* 2003 ;169: 323–330.
20. Lorenz MW, Kegler S von, Steinmetz H, Markus HS, Sitzer M Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke* 2006 ;37: 87–92.
21. Tivesten A, Hulthe J, Wallenfeldt K, Wikstrand J, Ohlsson C et al. Circulating estradiol is an independent predictor of progression of carotid artery intima-media thickness in middle-aged men. *J. Clin. Endocrinol. Metab.* 2006 ;91: 4433–4437.
22. Chambless LE, Folsom AR, Sharrett AR, Sorlie P, Couper D et al. Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) study. *J Clin Epidemiol* 2003 ;56: 880–890.
23. Li S, Chen W, Srinivasan SR, Bond MG, Tang R et al. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA* 2003 ;290: 2271–2276.
24. Kiechl S, Willeit J The natural course of atherosclerosis. Part I: incidence and progression. *Arterioscler. Thromb. Vasc. Biol.* 1999 ;19: 1484–1490.
25. Lee Y, Lin RS, Sung FC, Yang C, Chien K et al. Chin-Shan Community Cardiovascular Cohort in Taiwan-baseline data and five-year follow-up morbidity and mortality. *J Clin Epidemiol* 2000 ;53: 838–846.
26. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N. Engl. J. Med.* 1999 ;340: 14–22.
27. Liu J, Hong Y, D'Agostino RB, Wu Z, Wang W et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA* 2004 ;291: 2591–2599.
28. Price JF, Tzoulaki I, Lee AJ, Fowkes FGR Ankle brachial index and intima media thickness predict cardiovascular events similarly and increased prediction when combined. *J Clin Epidemiol* 2007 ;60: 1067–1075.
29. Gabriel R, Alonso M, Reviriego B, Muñoz J, Vega S et al. Ten-year fatal and non-fatal myocardial infarction incidence in elderly populations in Spain: the EPICARDIAN cohort study. *BMC Public Health* 2009 ;9: 360.
30. Bonithon-Kopp C, Touboul PJ, Berr C, Magne C, Ducimetière P Factors of carotid arterial enlargement in a population aged 59 to 71 years: the EVA study. *Stroke* 1996 ;27: 654–660.
31. Sander D, Kukla C, Klingelhöfer J, Winbeck K, Conrad B Relationship between circadian blood pressure patterns and progression of early carotid atherosclerosis: A 3-year follow-up study. *Circulation* 2000 ;102: 1536–1541.
32. Salonen JT, Salonen R Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler. Thromb.* 1991 ;11: 1245–1249.
33. Rundek T, Elkind MS, Pittman J, Boden-Albala B, Martin S et al. Carotid intima-media thickness is associated with allelic variants of stromelysin-1, interleukin-6, and hepatic lipase genes: the Northern Manhattan Prospective Cohort Study. *Stroke* 2002 ;33: 1420–1423.

34. Lind L, Fors N, Hall J, Marttala K, Stenborg A. A comparison of three different methods to evaluate endothelium-dependent vasodilation in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. *Arterioscler Thromb Vasc Biol* 2005;25:2368-75.
35. Norata GD, Garlaschelli K, Ongari M, Raselli S, Grigore L et al. Effects of fractalkine receptor variants on common carotid artery intima-media thickness. *Stroke* 2006 ;37: 1558–1561.
36. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* 1997 ;96: 1432–1437.
37. Iglseder B, Mackevics V, Stadlmayer A, Tasch G, Ladurner G et al. Plasma adiponectin levels and sonographic phenotypes of subclinical carotid artery atherosclerosis: data from the SAPHIR Study. *Stroke* 2005 ;36: 2577–2582.
38. Sarnowski B von, Lüdemann J, Völzke H, Dörr M, Kessler C et al. Common carotid intima-media thickness and framingham risk score predict incident carotid atherosclerotic plaque formation: longitudinal results from the study of health in Pomerania. *Stroke* 2010 ;41: 2375–2377.
39. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromsø Study. *Stroke* 2007 ;38: 2873–2880.

Tables

Table 1: Included cohorts with sample size and numbers of endpoint events

<i>Cohort</i>	<i>Country</i>	<i>Total number with two ultrasound scans</i>	<i>Number of subjects with diabetes without previous CVD events</i>	<i>Mean interval between the two ultrasound scans (years)</i>	<i>Mean duration of clinical follow-up (years) after second ultrasound scan</i>	<i>Number of combined endpoint events among subjects with diabetes</i>	<i>Crude event rate of the combined endpoint among subjects with diabetes (per 1000 person years)</i>
AIR [21]	Sweden	297	12	3.3	5.1	1	16.2
ARIC [22]	USA	12221	1131	2.9	7.4	281	33.5
BHS [23]	USA	554	22	2.4	4.3	2*	21.2*
Bruneck [24]	Italy	633	47	5.0	8.0	11	29.3
CAPS [20]	Germany	3284	74	3.1	5.2	6	15.7
CCCC [25]	Taiwan	1285	127	5.1	7.2	8	8.7
CHS 1 [26]	USA	3551	896	2.9	8.3	348	46.9
CHS 2 [26]	USA	297	87	5.9	5.2	25	55.5
CMCS [27]	China	920	57	5.4	4.9	2	7.2
DIWA [18]	Sweden	418	40	5.5	2.1	2	23.4
EAS [28]	UK	620	31	6.5	5.2	4	25.0
EPICARDIAN [29]	Spain	161	7	3.0	6.6	1	21.5
EVA [30]	France	922	57	2.0	13.2	19*	25.3*
INVADE [31]	Germany	2534	488	2.2	3.9	70	36.6
KIHD [32]	Finland	891	29	4.1	11.5	18	54.1
NOMAS/INVEST [33]	USA	647	116	3.6	2.9	5	14.8
PIVUS [34]	Sweden	680	53	5.1	1.8	4*	40.8*
PLIC [35]	Italy	1538	71	2.3	4.0	1	3.5
Rotterdam [36]	Netherlands	2610	158	6.4	5.4	51	59.5
SAPHIR [37]	Austria	1154	35	4.6	9.5	1	3.0
SHIP [38]	Germany	1751	283	5.2	5.5	50	32.0
Tromsø [39]	Norway	4003	81	6.3	6.4	25	48.1

*number of deaths among subjects with diabetes

Table 2: Average mean CCA-IMT and annual mean CCA-IMT progression in persons with and without diabetes

Cohort	Average mean CCA-IMT [mm]			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	.86 (.14)	.79 (.12)	.066 (.036)	-.004 (.040)	.001 (.028)	-.005 (.008)
ARIC	.72 (.13)	.56 (.11)	.052 (.003)	.009 (.048)	.011 (.037)	-.001 (.001)
CAPS	.81 (.13)	.73 (.17)	.018 (.018)	-.004 (.035)	.003 (.092)	-.007 (.011)
CHS 1	.90 (.16)	.86 (.14)	.038 (.005)	.006 (.053)	.005 (.045)	.001 (.002)
CHS 2	.94 (.15)	.92 (.16)	.015 (.020)	.005 (.030)	.011 (.028)	-.007 (.004)
CMCS	.85 (.23)	.81 (.19)	.040 (.025)	.037 (.044)	.040 (.041)	-.002 (.006)
DIWA	.94 (.17)	.86 (.15)	.074 (.025)	-.001 (.022)	.004 (.020)	-.005 (.003)
EAS	.87 (.20)	.85 (.19)	.005 (.033)	.030 (.032)	.030 (.045)	.001 (.008)
EPICARDIAN	.78 (.15)	.79 (.21)	-.004 (.079)	-.093 (.101)	-.099 (.133)	.001 (.052)
EVA	.72 (.11)	.66 (.10)	.045 (.014)	.008 (.040)	.006 (.046)	.002 (.006)
INVADE	.86 (.18)	.81 (.17)	.031 (.008)	.012 (.082)	.009 (.075)	.004 (.004)
KIHD	.83 (.12)	.81 (.16)	.010 (.027)	.024 (.022)	.028 (.033)	-.005 (.006)
NOMAS/INVEST	.72 (.09)	.73 (.08)	-.005 (.008)	.007 (.028)	.009 (.030)	-.002 (.003)
PIVUS	.97 (.17)	.92 (.14)	.049 (.021)	.009 (.034)	.009 (.029)	.000 (.004)
PLIC	.74 (.12)	.66 (.13)	.029 (.013)	.009 (.032)	.015 (.036)	-.007 (.004)
Rotterdam	.86 (.15)	.79 (.14)	.046 (.011)	.012 (.024)	.012 (.021)	.000 (.002)
SAPHIR	.91 (.11)	.80 (.12)	.074 (.019)	.024 (.024)	.017 (.019)	.005 (.003)
SHIP	.83 (.16)	.78 (.14)	.031 (.009)	.009 (.037)	.003 (.023)	.001 (.002)
Tromsø	.87 (.16)	.78 (.14)	.053 (.013)	.010 (.034)	.004 (.019)	.006 (.002)
Combined (95% CI)			.041 (.036 to .045)			-.000 (-.001 to .001)

Note: [&] adjusted for age and sex

Mean CCA-IMT is not available in BHS, Bruneck and CCCC

Table 3: Average maximal CCA-IMT and annual maximal CCA-IMT progression in persons with and without diabetes

Cohort	Average max CCA-IMT [mm]			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 (.17)	.98 (.16)	.062 (.046)	.006 (.062)	.014 (.042)	-.008 (.013)
ARIC	.83 (.16)	.76 (.13)	.054 (.004)	.015 (.055)	.015 (.044)	.000 (.002)
BHS	.91 (.22)	.75 (.12)	.092 (.019)	-.006 (.102)	.001 (.048)	-.009 (.008)
BRUNECK	1.02 (.15)	.95 (.18)	.004 (.022)	.022 (.032)	.028 (.027)	-.004 (.004)
CCCC	.79 (.20)	.73 (.18)	.032 (.015)	.023 (.048)	.019 (.049)	.004 (.004)
CHS 1	1.09 (.20)	1.03 (.18)	.050 (.007)	.013 (.070)	.009 (.060)	.004 (.002)
CHS 2	1.11 (.18)	1.09 (.19)	.020 (.024)	-.006 (.035)	.004 (.035)	-.010 (.005)
CMCS	.92 (.29)	.88 (.25)	.043 (.034)	.051 (.053)	.053 (.057)	-.002 (.008)
DIWA	1.07 (.23)	.98 (.18)	.088 (.030)	.001 (.026)	.008 (.026)	-.007 (.004)
KIHD	1.08 (.17)	1.06 (.22)	.004 (.038)	.063 (.041)	.066 (.049)	-.002 (.009)
NOMAS/INVEST	.93 (.09)	.94 (.09)	-.002 (.001)	.008 (.029)	.009 (.032)	-.002 (.003)
PIVUS	1.12 (.17)	1.06 (.17)	.056 (.025)	.020 (.043)	.015 (.036)	.005 (.005)
PLIC	.82 (.13)	.73 (.15)	.032 (.015)	.003 (.038)	.009 (.043)	-.006 (.005)
Rotterdam	1.08 (.17)	1.01 (.16)	.047 (.013)	.012 (.020)	.016 (.023)	-.004 (.002)
SHIP	.98 (.20)	.89 (.19)	.036 (.011)	.002 (.032)	.000 (.031)	.001 (.002)
Tromsø	1.09 (.21)	.97 (.18)	.082 (.017)	.014 (.043)	.005 (.025)	.009 (.003)
Combined (CI 95%)			.046 (.041 to .051)			-.000 (-.002 to .001)

Note: [&] adjusted for age and sex. * MAX CCA-IMT is not available in CAPS, EAS, EPICARDIAN, EVA, INVAD and SAPHIR

Figures

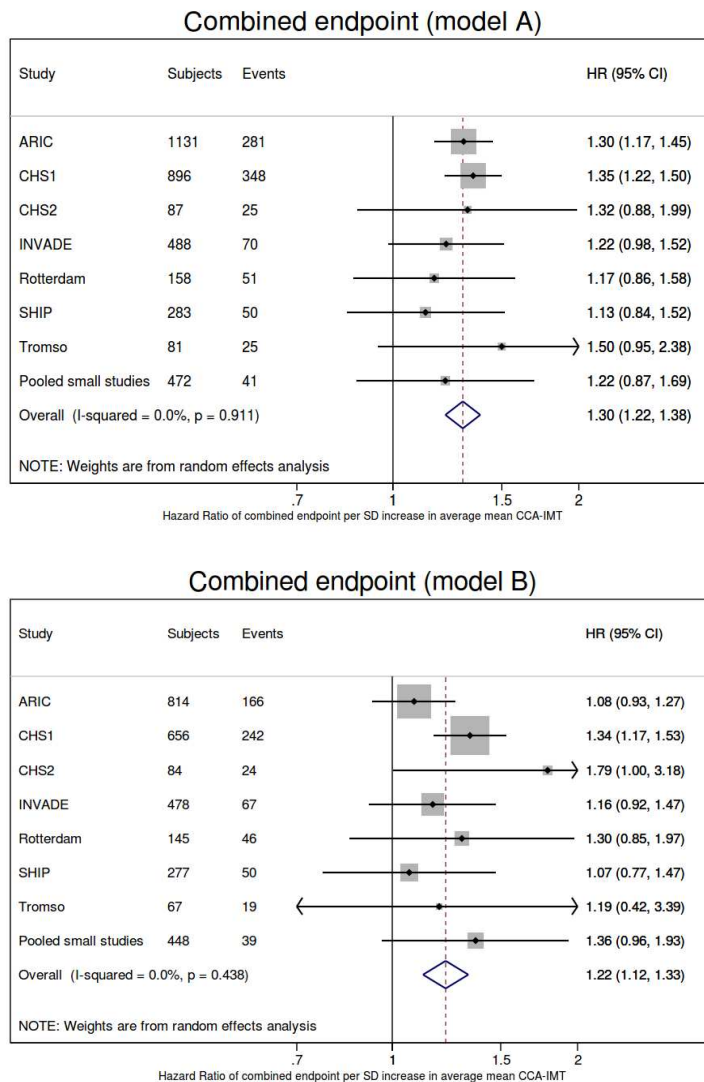


Figure 1: Forest plot of HR of the combined endpoint (MI or stroke or vascular death) per SD of average mean CCA-IMT, in subjects with diabetes

Note: pooled small studies included: AIR, CAPS, CMCS, DIWA, EAS, EPICARIDIAN, KIHD, NOMAS/INVEST, PLIC and SAPHIR

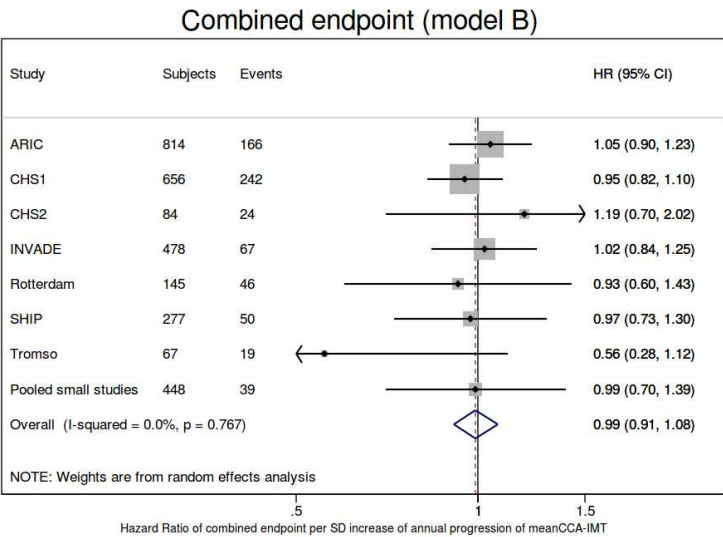
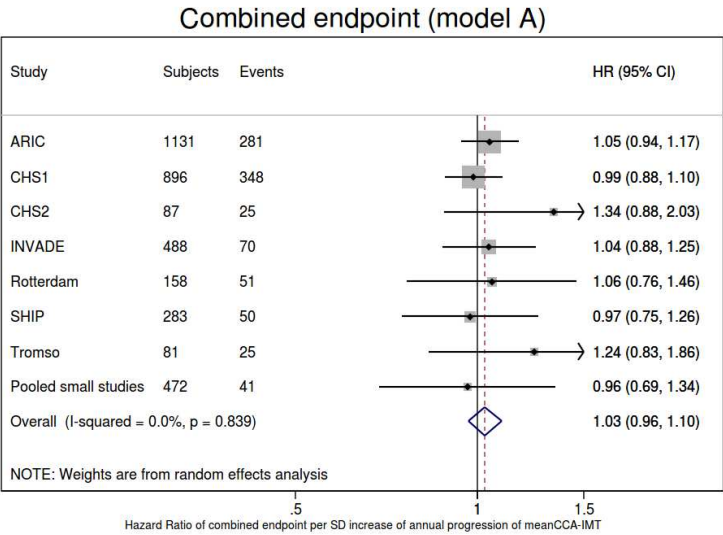


Figure 2: Forest plot of HR of the combined endpoint (MI or stroke or vascular death) per SD of annual mean CCA-IMT progression, in subjects with diabetes
Note: pooled small studies included: AIR, CAPS, CMCS, DIWA, EAS, EPICARIDIAN, KIH, NOMAS/INVEST, PLIC and SAPHIR

Appendix: Webtables

Cohort	Definition of Diabetes Mellitus
AIR	Self reported physician's diagnosis
ARIC	ADA definition (RPG or FPG or OGTT) or preexisting antidiabetic medication
BHS	FPG>126mg/dL or preexisting antidiabetic medication
Bruneck	Record-confirmed physician's diagnosis or HbA1c≥6.5%
CAPS	Self reported physician's diagnosis
CCCC	FPG>140mg/dL or preexisting antidiabetic medication
CHS	Self reported physician's diagnosis
CMCS	Self reported physician's diagnosis or preexisting antidiabetic medication
DIWA	Oral glucose tolerance test
EAS	Self reported physician's diagnosis or preexisting antidiabetic medication
EPICARDIAN	FPG≥126mg/dL or preexisting antidiabetic medication
EVA	Self reported physician's diagnosis or FPG≥7.8 mmol/L or preexisting antidiabetic medication
INVADE	Self reported physician's diagnosis or preexisting antidiabetic medication
KIHD	Self reported physician's diagnosis or preexisting antidiabetic medication
NOMAS/INVEST	Self reported physician's diagnosis or FPG>126mg/dl or preexisting antidiabetic medication
PIVUS	Self reported physician's diagnosis or FPG≥7.0 mmol/L
PLIC	Self reported physician's diagnosis or preexisting antidiabetic medication
Rotterdam	Self reported physician's diagnosis or preexisting antidiabetic medication
SAPHIR	Self reported physician's diagnosis or preexisting antidiabetic medication
SHIP	Self reported physician's diagnosis or HbA1c>6.5% or preexisting antidiabetic medication
Tromsø	Self reported physician's diagnosis or preexisting antidiabetic medication

Webtable A1: Definition of diabetes mellitus by cohort

ADA = American Diabetes Association

RPG = random plasma glucose

FPG = fasting plasma glucose

OGTT = oral glucose tolerance test

Study	definition of the combined endpoint	ethnicity	Socio-economic status	systolic blood pressure		body mass index		total cholesterol		HbA1c		fasting glucose		antihypertensive medication		Lipid lowering medication		smoking	
		BL	BL	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
AIR	MI or stroke or vascular death	yes	missing	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
ARIC	MI or stroke or death	yes	inc	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
BHS	n.a.	yes	edu	yes	yes	yes	yes	yes	yes	yes	missing	yes	yes	yes	yes	yes	yes	yes	yes
Bruneck	MI or stroke or vascular death	yes	ses	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	missing	missing	yes	yes
CAPS	MI or stroke or death	missing	edu	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
CCCC	MI or stroke or death	yes	ses	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	missing	missing	missing	yes	missing
CHS_1	MI or stroke or vascular death	yes	edu	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
CHS_2	MI or stroke or vascular death	yes	inc	yes	yes	yes	missing	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
CMCS	MI or stroke or vascular death	yes	edu	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
DIWA	MI or stroke or vascular death	yes	edu	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	missing	yes	missing	yes	missing
EAS	MI or stroke or vascular death	missing	ses	yes	yes	yes	yes	yes	missing	missing	missing	yes	yes	yes	missing	missing	missing	yes	yes
EPICARDIAN	MI or stroke or vascular death	missing	missing	yes	missing	yes	missing	yes	missing	missing	missing	yes	missing	missing	missing	yes	missing	yes	missing
EVA	n.a.	missing	missing	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
INVADE	MI or stroke or death	missing	edu	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
KIHD	MI or stroke or vascular death	yes	edu	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
NOMAS/INVEST	MI or stroke or vascular death	yes	edu	yes	missing	yes	missing	yes	yes	missing	missing	yes	yes	yes	missing	yes	missing	yes	missing
PIVUS	n.a.	missing	ses	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
PLIC	MI or stroke or vascular death	missing	missing	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	missing	missing	yes	yes
Rotterdam	MI or stroke or death	yes	edu	yes	yes	yes	yes	yes	yes	missing	missing	missing	yes	yes	yes	yes	yes	yes	yes
SAPHIR	MI or stroke or vascular death	missing	ses	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes	yes	yes	yes	yes	yes	yes
SHIP	MI or stroke or death	missing	edu	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	missing	missing	yes	yes
Tromso	MI or stroke or vascular death	yes	edu	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

Webtable A2: Definition of the combined endpoint, and available adjustment variables by cohort

BL = baseline visit
FU = follow-up visit
n.a. = not applicable (only total mortality available)
inc = household income
edu = education level
ses = socioeconomic status

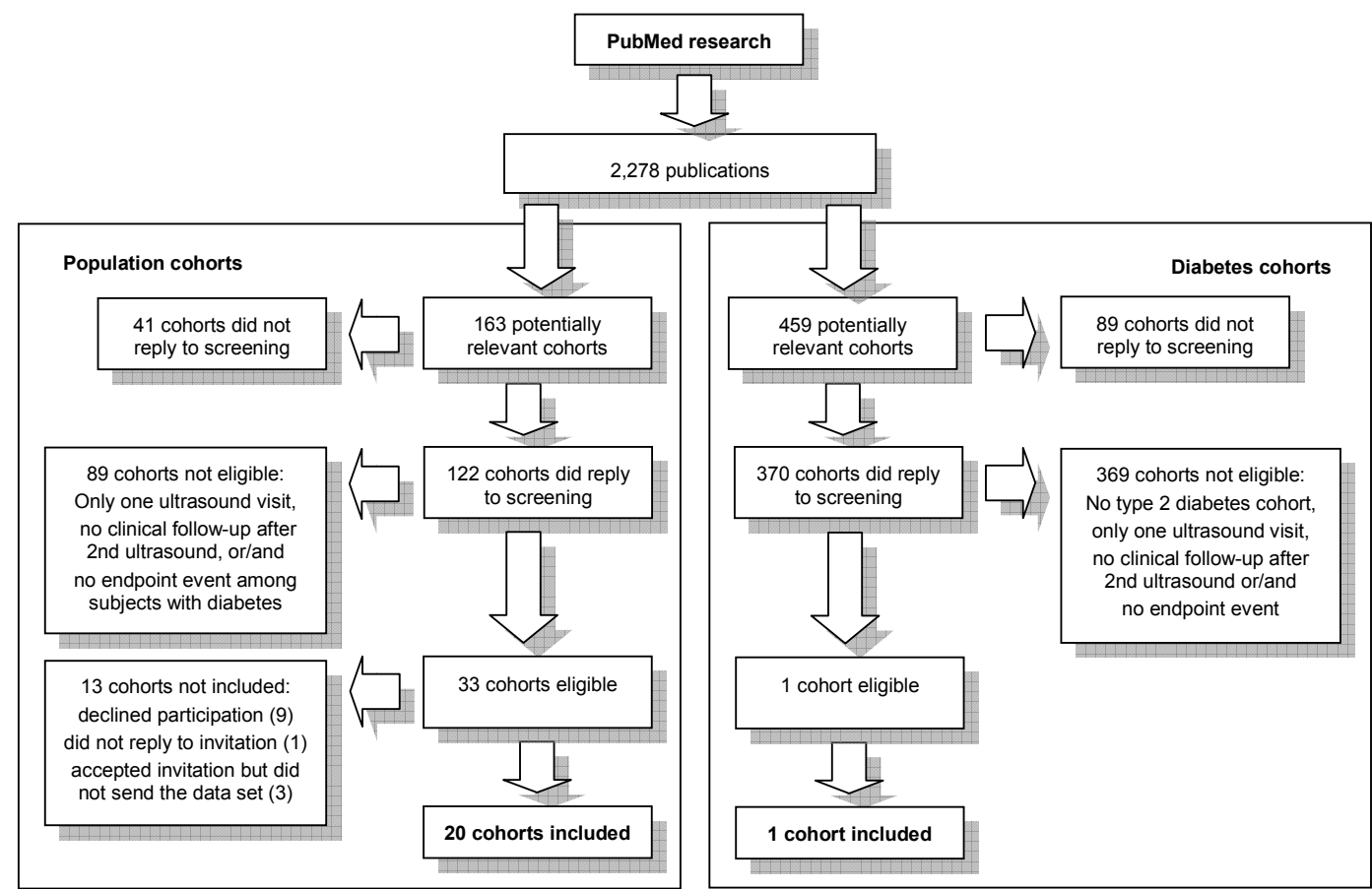
Cohort	CCA landmark	CCA length	Avoid plaques	ECG gated	Angle control	Multiple scans	Central reading	Edge detection algorithm
AIR	Beginning of bulbar widening	1cm	No	Yes	No	No	Yes	Yes
ARIC	Beginning of bulbar widening	1cm	No	Yes	Yes	Yes	Yes	No
BHS	Beginning of bulbar widening	1cm	No	Yes	Yes	Yes	Yes	No
Bruneck	Beginning of bulbar widening	3cm	Yes	Yes	Yes	No	No	No
CAPS	2cm proximal to the tip of the flow divider	up to 4cm	Not specified	No	No	No	Yes	Yes
CCCC	1cm proximal to the tip of the flow divider	1cm	Yes	Yes	Yes	Yes	No	No
CHS	Beginning of bulbar widening or (if not determinable) 1cm proximal to the tip of the flow divider	1cm	No	No	No	No	Yes	No
CMCS	Beginning of bulbar widening	Three single measurements each in 3 segments of 1cm	Yes	No	No	No	Yes	No
DIWA	Beginning of bulbar widening	1cm	No ⁺	Yes	No	No	Yes	Yes
EAS	Beginning of bulbar widening	0,5cm	Yes	No	No	No	Yes	No
EPICARDIAN	Beginning of bulbar widening	1cm	Yes	No	Yes	Yes	No	No
EVA	2cm proximal to the tip of the flow divider	2cm	Yes	No	Yes	No	Yes	Yes
INVADE	1cm proximal to the tip of the flow divider	1cm	Yes	No	Yes	Yes	Yes	Yes
KIHD	Beginning of bulbar widening	1-5cm	No	No	No	No	Yes	Yes
NOMAS/INVEST	1cm proximal to the tip of the flow divider	1cm	Yes	No	Yes [#]	No	Yes	Yes
PIVUS	Beginning of bulbar widening	1cm	Not specified	Yes	No	No	Yes	Yes
PLIC	2cm proximal to the tip of the flow divider	2cm	Yes	Yes	No	No	Yes	Yes
Rotterdam	Beginning of bulbar widening	1cm	No	Yes	No	Yes	Yes	Yes
SAPHIR	8 mm proximal to the tip of the flow divider	8mm	Yes	No	Yes	Yes	No	No
SHIP	Beginning of bulbar widening	1cm	No	No	No	No	Yes	Yes
Tromsø	Beginning of bulbar widening	1cm	No ⁺	Yes	No	Yes	Yes	Yes

Webtable A3: Ultrasound protocols

*vessel wall parallel to transducer interface

[#]internal landmarks in computer aided navigation⁺plaques purposely included

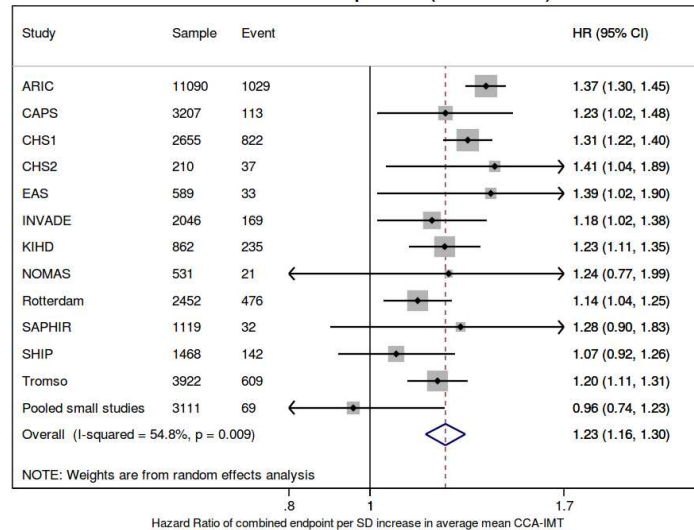
Appendix: Webfigures



Webfigure A1: Flowchart showing numbers of screened and included publication and cohorts

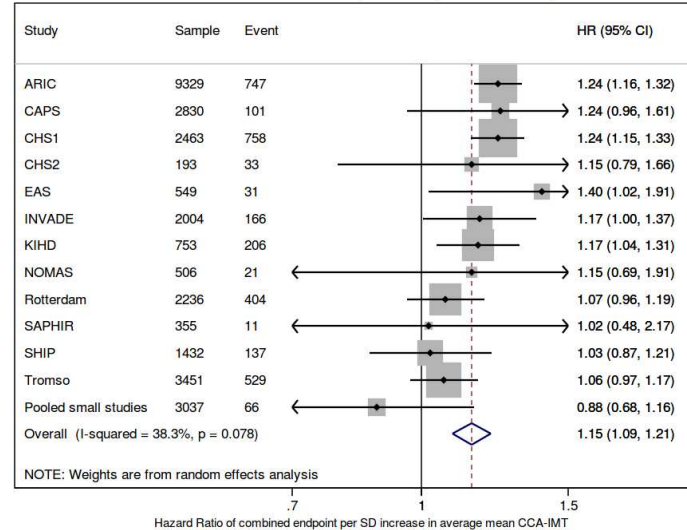
Panel 1

Combined endpoint (model A)



Panel 2

Combined endpoint (model B)

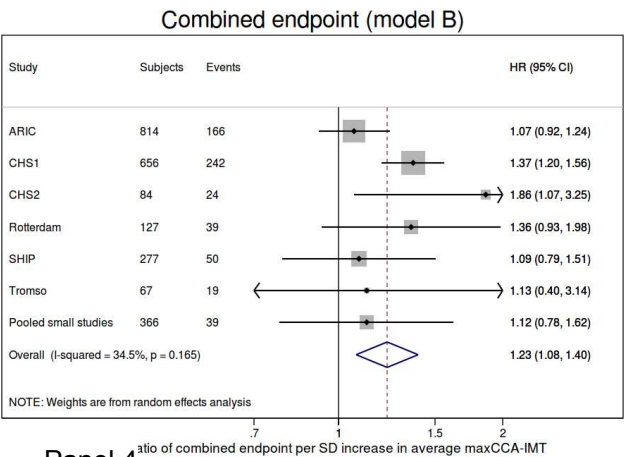
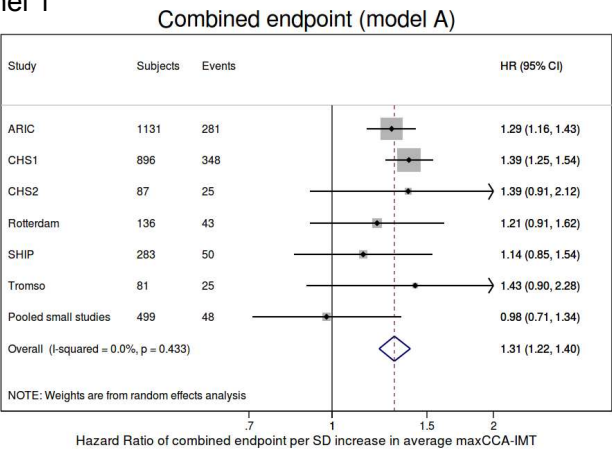


Webfigure A2: Forest plot of HR of the combined endpoint (MI or stroke or vascular death) per SD of average mean CCA-IMT (panels 1 and 2) in subjects without diabetes

Note: pooled small studies included: AIR, CMCS, DIWA, EPICARDIAN and PLIC

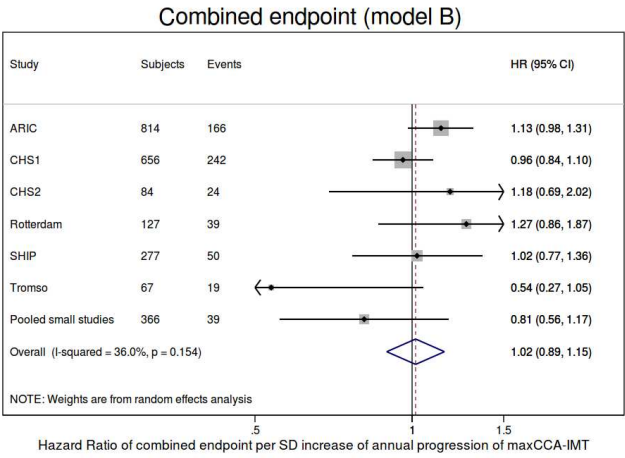
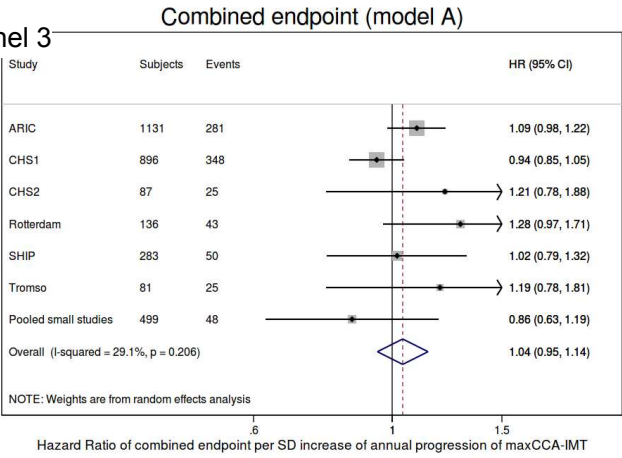
Panel 2

Panel 1



Panel 4

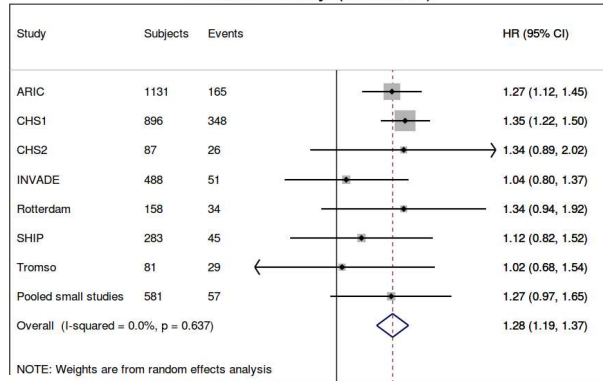
Panel 3



Webfigure A3: Forest plot of HR of the combined endpoint (MI or stroke or vascular death) per SD of average maximal CCA-IMT (panels 1 and 2) and annual maximal CCA-IMT progression (panels 3 and 4)
Note: pooled small studies included: AIR, BRUNECK, CCCC, CMCS, DIWA, KIH, NOMAS/INVEST and PLIC

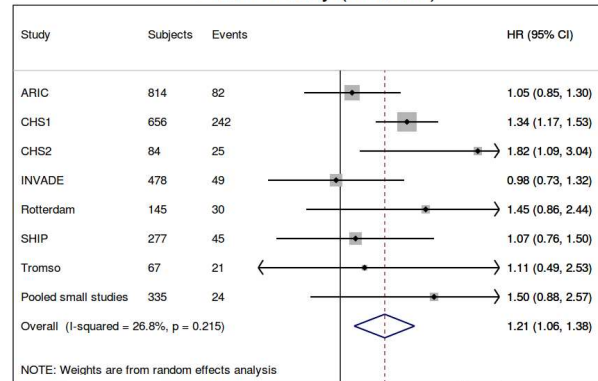
Panel 1

Total mortality (model A)



Panel 2

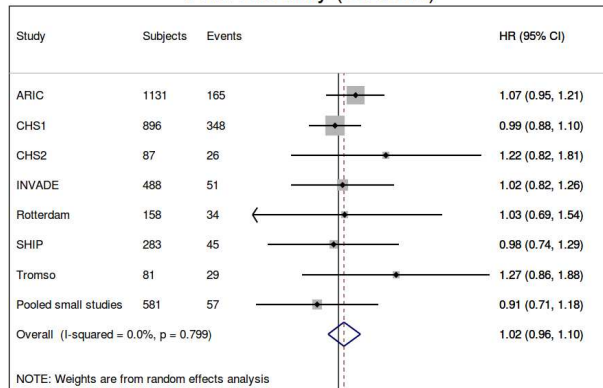
Total mortality (model B)



Panel 3

Hazard Ratio of total mortality per SD increase in average mean CCA-IMT

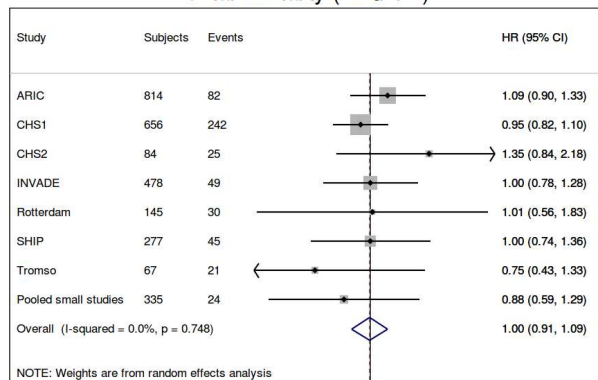
Total mortality (model A)



Panel 4

Hazard Ratio of total mortality per SD increase in average mean CCA-IMT

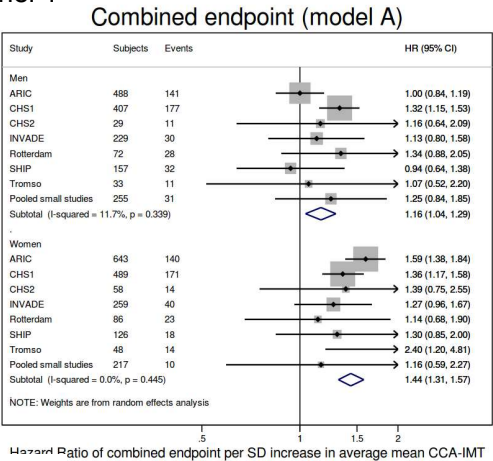
Total mortality (model B)



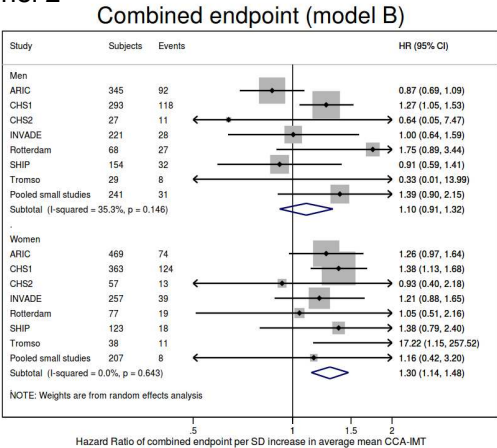
Webfigure A4: Forest plot of HR of total mortality per SD of average mean CCA-IMT (panels 1 and 2) and annual mean CCA-IMT progression (panels 3 and 4)

Note: pooled small studies included: AIR, CAPS, CMCS, DIWA, EAS, EPICARDIAN, EVA, KIH, NOMAS/INVEST, PIVUS and SAPHIR

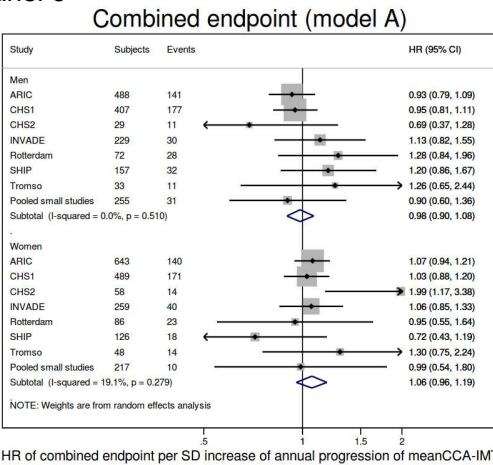
Panel 1



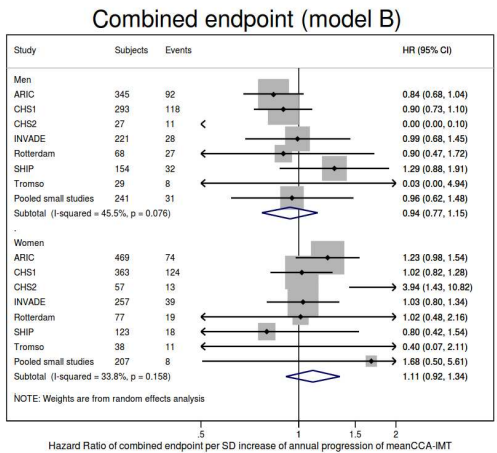
Panel 2



Panel 3



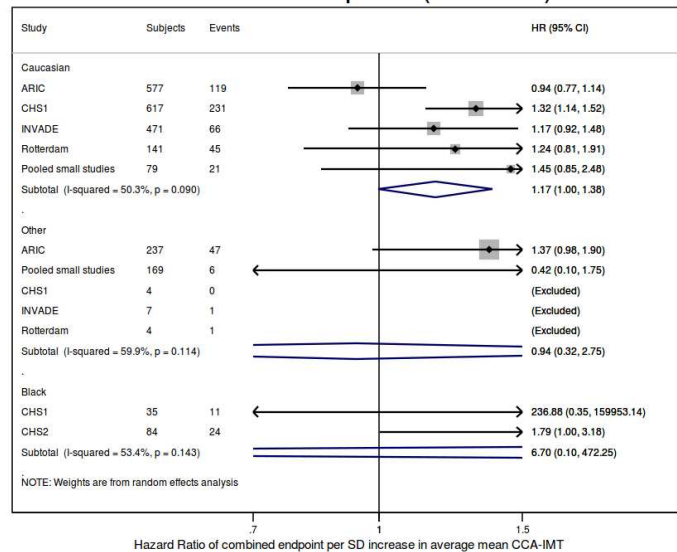
Panel 4



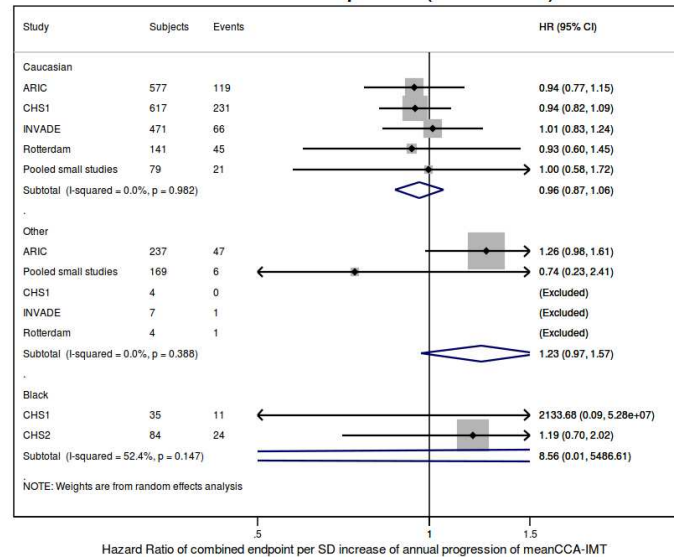
Webfigure A5: Forest plot of HR of the combined endpoint per SD of average mean CCA-IMT (panels 1 and 2) and annual mean CCA-IMT progression (panels 3 and 4), stratified by sex

Note: pooled small studies included: AIR, CAPS, CMCS, DIWA, EAS, EPICARDIAN, KIH, NOMAS/INVEST, PLIC and SAPHIR

Panel 1 Combined endpoint (model B)



Panel 2 Combined endpoint (model B)



Webfigure A6: Forest plot of HR of the combined endpoint (model B) per SD of average mean CCA-IMT (panel 1) and annual mean CCA-IMT progression (panel 2), stratified by ethnicity

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