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 of 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-analyzes 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 analyses

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. \(\frac{\text{IMT}_2 - \text{IMT}_1}{\text{time [years]}}\), ‘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 I² 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 (I² = 0%) between the particular cohorts in this analysis, whereas there was moderate, however non-significant, heterogeneity in the general population (I²=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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The first author takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

**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.

Alberico Catapano has received grants from Genzyme, Pfizer, Sanofi Aventis, Mediolanum, Rottapharm, and Sigma Tau; and personal fees from AstraZeneca, Amgen, Aegerion, Eli-Lilly, Genzyme, Pfizer, Sanofi Aventis, Merck MSD, Mediolanum, Rottapharm, Recordati and Sigma Tau.

Oscar H. Franco works in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd.); Metagenics Inc.; and AXA. 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. With regard to potential conflicts of interest, there is nothing to disclose.

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

References


## Tables

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

<table>
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<tr>
<th>Cohort</th>
<th>Country</th>
<th>Total number with two ultrasound scans</th>
<th>Number of subjects with diabetes without previous CVD events</th>
<th>Mean interval between the two ultrasound scans (years)</th>
<th>Mean duration of clinical follow-up (years) after second ultrasound scan</th>
<th>Number of combined endpoint events among subjects with diabetes</th>
<th>Crude event rate of the combined endpoint among subjects with diabetes (per 1000 person years)</th>
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*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

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<th>Average mean CCA-IMT [mm]</th>
<th>Annual mean CCA-IMT progression [mm/year]</th>
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<td>No diabetes (Mean (SD))</td>
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<td>.79 (.12)</td>
</tr>
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<td>.56 (.11)</td>
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<td>.73 (.17)</td>
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<td>Tromsø</td>
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<td>.78 (.14)</td>
</tr>
<tr>
<td>Combined (95% CI)</td>
<td>.041 (.036 to .045)</td>
<td>-.000 (.001 to .001)</td>
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</tbody>
</table>

Note: * adjusted for age and sex

Mean CCA-IMT is not available in BHS, Bruneck and CCC.
Table 3: Average maximal CCA-IMT and annual maximal CCA-IMT progression in persons with and without diabetes

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Average max CCA-IMT [mm]</th>
<th>Annual max CCA-IMT progression [mm/year]</th>
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</thead>
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<td>No diabetes Mean (SD)</td>
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<td>ARIC</td>
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<td>BHS</td>
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<td>BRUNNECK</td>
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<td>CCCC</td>
<td>.79 (.20)</td>
<td>.73 (.18)</td>
</tr>
<tr>
<td>CHS 1</td>
<td>1.09 (.20)</td>
<td>1.03 (.18)</td>
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<tr>
<td>CHS 2</td>
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<td>1.09 (.19)</td>
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<td>CMCS</td>
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<td>.88 (.25)</td>
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<td>KIHD</td>
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<td>1.06 (.22)</td>
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<tr>
<td>NOMAS/INVEST</td>
<td>.93 (.09)</td>
<td>.94 (.09)</td>
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<td>PIVUS</td>
<td>1.12 (.17)</td>
<td>1.06 (.17)</td>
</tr>
<tr>
<td>PLIC</td>
<td>.82 (.13)</td>
<td>.73 (.15)</td>
</tr>
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<td>Rotterdam</td>
<td>1.08 (.17)</td>
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<td>SHIP</td>
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<td>.89 (.19)</td>
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<td>Tromsø</td>
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<td>.97 (.18)</td>
</tr>
<tr>
<td>Combined (CI 95%)</td>
<td>1.04 (.17) to .109 (.20)</td>
<td>.97 (.17) to .95 (.18)</td>
</tr>
</tbody>
</table>

Note: * adjusted for age and sex. * MAX CCA-IMT is not available in CAPS, EAS, EPICARDIAN, EVA, INVADE 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, KIHD, NOMAS/INVEST, PLIC and SAPHIR
## Appendix: Weblables

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Definition of Diabetes Mellitus</th>
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<tbody>
<tr>
<td>AIR</td>
<td>Self reported physician's diagnosis</td>
</tr>
<tr>
<td>ARIC</td>
<td>ADA definition (RPG or FPG or OGTT) or preexisting antidiabetic medication</td>
</tr>
<tr>
<td>BHS</td>
<td>FPG&gt;126mg/dL or preexisting antidiabetic medication</td>
</tr>
<tr>
<td>Bruneck</td>
<td>Record-confirmed physician's diagnosis or HbA1c≥6.5%</td>
</tr>
<tr>
<td>CAPS</td>
<td>Self reported physician's diagnosis</td>
</tr>
<tr>
<td>CCCO</td>
<td>FPG&gt;140mg/dL or preexisting antidiabetic medication</td>
</tr>
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<td>Self reported physician's diagnosis</td>
</tr>
<tr>
<td>CMCS</td>
<td>Self reported physician's diagnosis or preexisting antidiabetic medication</td>
</tr>
<tr>
<td>DIWA</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
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<td>Self reported physician's diagnosis or preexisting antidiabetic medication</td>
</tr>
<tr>
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<td>FPG&gt;126mg/dL or preexisting antidiabetic medication</td>
</tr>
<tr>
<td>EVA</td>
<td>Self reported physician's diagnosis or FPG≥7.8 mmol/L or preexisting antidiabetic medication</td>
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<tr>
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<td>Self reported physician's diagnosis or preexisting antidiabetic medication</td>
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<td>KIHDI</td>
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<td>NOMAS/INVEST</td>
<td>Self reported physician's diagnosis or FPG&gt;126mg/dL or preexisting antidiabetic medication</td>
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<td>PIVUS</td>
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<tr>
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<td>Rotterdam</td>
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</table>

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

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<th>body mass index</th>
<th>total cholesterol</th>
<th>HbA1c</th>
<th>fasting glucose</th>
<th>antihypertensive medication</th>
<th>Lipid lowering medication</th>
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<td>MI or stroke or death</td>
<td>yes</td>
<td>edu</td>
<td>yes</td>
<td>yes</td>
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<td>yes</td>
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<td>MI or stroke or vascular death</td>
<td>missing</td>
<td>ses</td>
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<td>MI or stroke or death</td>
<td>missing</td>
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<td>MI or stroke or vascular death</td>
<td>yes</td>
<td>edu</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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BL = baseline visit  
FU = follow-up visit  
n.a. = not applicable (only total mortality available)  
inc = household income  
edu = education level  
ses = socioeconomic status
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<th>Cohort</th>
<th>CCA landmark</th>
<th>CCA length</th>
<th>Avoid plaques</th>
<th>ECG gated</th>
<th>Angle control</th>
<th>Multiple scans</th>
<th>Central reading</th>
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<td>Beginning of bulbar widening</td>
<td>1cm</td>
<td>No</td>
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<td>Yes</td>
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<td>Beginning of bulbar widening</td>
<td>3cm</td>
<td>Yes</td>
<td>Yes</td>
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<td>up to 4cm</td>
<td>Not specified</td>
<td>No</td>
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<td>1cm</td>
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<td>1cm</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Beginning of bulbar widening</td>
<td>Three single measurements each in 3 segments of 1cm</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<td>Beginning of bulbar widening</td>
<td>1cm</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td>Beginning of bulbar widening</td>
<td>0.5cm</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<td>Beginning of bulbar widening</td>
<td>1cm</td>
<td>Yes</td>
<td>No</td>
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<td>1cm proximal to the tip of the flow divider</td>
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<td>1-5cm</td>
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<td>No</td>
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<td>Yes</td>
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<tr>
<td>Tromso</td>
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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

PubMed research

2,278 publications

Population cohorts

41 cohorts did not reply to screening

163 potentially relevant cohorts

89 cohorts not eligible: Only one ultrasound visit, no clinical follow-up after 2nd ultrasound, or/and no endpoint event among subjects with diabetes

122 cohorts did reply to screening

33 cohorts eligible

20 cohorts included

41 cohorts did not reply to screening

163 potentially relevant cohorts

89 cohorts not eligible: Only one ultrasound visit, no clinical follow-up after 2nd ultrasound, or/and no endpoint event among subjects with diabetes

122 cohorts did reply to screening

33 cohorts eligible

20 cohorts included

459 potentially relevant cohorts

Diabetes cohorts

89 cohorts did not reply to screening

459 potentially relevant cohorts

370 cohorts did reply to screening

370 cohorts did reply to screening

369 cohorts not eligible: No type 2 diabetes cohort, only one ultrasound visit, no clinical follow-up after 2nd ultrasound or/and no endpoint event

1 cohort eligible

1 cohort included

1 cohort eligible

1 cohort included

41 cohorts did not reply to screening

163 potentially relevant cohorts

89 cohorts not eligible: Only one ultrasound visit, no clinical follow-up after 2nd ultrasound, or/and no endpoint event among subjects with diabetes

122 cohorts did reply to screening

33 cohorts eligible

20 cohorts included
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.
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, KIHD, NOMAS/INVEST and PLIC
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, KIHD, NOMAS/INVEST, PIVUS and SAPHIR
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, KIHD, NOMAS/INVEST, PLIC and SAPHIR.
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
## Appendix: Members of the PROG-IMT Study group

**Status as of 05th November 2014**

<table>
<thead>
<tr>
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<th>Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
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<td>Norwegian School of Sports Sciences, Oslo, Norway</td>
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<td>Tatiana Balakonova, MD, PhD, Prof.</td>
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<td>Ultrasound Vascular Laboratory, Cardiology Research Center, Moscow, Russia</td>
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<td>Damiano Baldassarre, PhD, Prof</td>
<td></td>
<td>Centro Cardiologico Monzino, IRCCS, Milan, Italy and Dipartimento di Scienze Farmacologiche e Biomolecolari, Università di Milano, Milan, Italy</td>
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<tr>
<td>Edith Beishuizen</td>
<td></td>
<td>Department of General Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands</td>
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<td>Oscar Beloqui, MD, PhD</td>
<td></td>
<td>Department of Internal Medicine, University Clinic of Navarra, Navarra, Spain</td>
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<tr>
<td>Gerald Berenson, MD, Prof.</td>
<td></td>
<td>Department of Medicine, Pediatrics, Biochemistry, Epidemiology, Tulane</td>
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<tr>
<td>Göran Bergström, MD, PhD, Prof</td>
<td></td>
<td>Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska Academy, Gothenburg University, Göteborg, Sweden</td>
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<tr>
<td>Sebastijan Bevc, MD, PhD, Assist Prof</td>
<td></td>
<td>Department of Nephropathy, Clinic for Internal Medicine, University Medical Centre Maribor, Maribor, Slovenia</td>
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<tr>
<td>Lokpal Bhala, MB BCh</td>
<td></td>
<td>Faculty of Medicine, Human Development &amp; Health Academic Unit, University of Southampton - Southampton General Hospital, Southampton, UK and Southampton NIHR Biomedical Research Centre, University Hospital Southampton - Southampton General Hospital,</td>
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<td>Horst Bickel, PhD</td>
<td></td>
<td>Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany</td>
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<tr>
<td>Stefan Blankenberg, MD, Prof.</td>
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<td>2nd Department of Medicine, Johannes Gutenberg-Universität, Mainz, Germany and Department of Cardiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany</td>
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<td>Peter J. Blankestijn</td>
<td></td>
<td>Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands</td>
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<td>Lena Bokemark, MD, PhD</td>
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<td>Wallenberg Laboratory for Cardiovascular Research, Institution for Medicin, Department for Molecular and Clinical Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden</td>
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<td>Jackie Bosch, MSc</td>
<td></td>
<td>Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada</td>
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<tr>
<td>Michiel Bots, MD, PhD, Prof</td>
<td></td>
<td>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands</td>
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<tr>
<td>Frank P. Brouwers, MD, PhD</td>
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<tr>
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<td>Faculty of Medicine, Human Development &amp; Health Academic Unit, University of Southampton - Southampton General Hospital, Southampton, UK and Southampton NIHR Biomedical Research Centre, University Hospital Southampton - Southampton General Hospital,</td>
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<tr>
<td>Philip C. Calder, PhD, Prof.</td>
<td></td>
<td>Department of Neurology, Institute of Neuroscience, the Second Affiliated Hospital of Soochow University, Soochow, China</td>
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<tr>
<td>Samuela Castelnuovo, PhD</td>
<td></td>
<td>Centro Dislipidemie E. Grossi Padletti,Ospedale Ca’ Granda di Niguarda, Milan, Italy</td>
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<tr>
<td>Alperico Catapano, PhD, Prof.</td>
<td></td>
<td>IRCSS Multimedica, Milan, Italy and Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy</td>
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<tr>
<td>Ana Rosa Cunha, PhD</td>
<td></td>
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