ONLINE SUPPLEMENT

## *Common carotid intima-media thickness relates to cardiovascular events in adults under the age of 45 years*

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Supplemental methods

## Statement of Medical Ethical Committee of UMC Utrecht regarding the Non-Medical Research Involving Human Subjects Act complicity of the current study

University Medical Center
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Medical Ethics Review Committee

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Date
May 20th, 2011

Our reference
AvG/rc/11/11083

Subject
METC-protocol number 11-197/C
Advice non-WMO research

Your reference

Dear Ms. Den Ruijter,

The Medical Research Ethics Committee (MREC), recognized on November 11, 1999 ex section 16 of the WMO[1], has considered research proposal number 11-197/C entitled "**The added value of carotid initima media thickness measurements in cardiovascular risk prediction: The USE-IMT Study**", submitted by Ms. H. den Ruijter from Utrecht and commissioned by the University Medical Center Utrecht in Utrecht, in the meeting of May, 10th 2011.

The committee has had the following documents at her disposal:
1. Letter with brief outline of study proposal, dated April 29, 2011
2. Data and materials distribution agreement MESA, dated April 21, 2011
3. MESA Ancillary Study Proposal Form (v6), received on May 3, 2011

The research proposal has been considered with regard to the use of data already assembled in other studies. Since the research proposal does not imply that people will receive particular additional treatment, nor imposes on the behaviour of persons, the MREC concludes that the Medical Research Involving Human Subjects Act (WMO) does not apply.

Therefore, the MREC concludes that for this proposal no WMO-approval by the MREC is needed.

Furthermore the MREC has made sure that the investigators shall take all necessary appropriate measures to safeguard the protection of the participant's privacy, including the adaptation of data in order to ensure sufficient anonymity.

[1] Medical Research Involving Human Subjects Act

1401123

Any change of protocol, however small, must be submitted to the MREC for approval.

On behalf of the METC,

M.A.C. van Groenestijn
Secretary

c.c. Manager Onderwijs en Onderzoek Prof.dr. A.W. Hoes, UMC Utrecht, Divisie Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde, STR6.131

A list of committee members and the committee regulations are available and can be obtained from the METC office.

Supplemental references


1. den Ruijter HM, Peters SA, Groenewegen KA 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.
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8. Ali YS, Rembold KE, Weaver B, Wills MB, Tatar S, Ayers CR, Rembold CM. Prediction of major adverse cardiovascular events by age-normalized carotid intimal medial thickness. *Atherosclerosis*. 2006;187:186-190.
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Supplemental tables

## Table S1. Method section of each cohort[1, 2]

| Study Name | Study design | CV risk factor measurement | Event measurement | CIMT measurement | Reproducibility information |
|---|---|---|---|---|---|
| Carotid Atherosclerosis Progression Study (CAPS)[3]<br><br>2006, Germany | Prospective population based cohort study (n=3889)<br><br>Members of German primary healthcare scheme<br><br>No event (MI or stroke) before baseline visit | CV risk factors obtained using standardized computer-assisted interview technique, examination by a physician trained in vascular medicine and blood sampling | Median follow up: 8.1 years (7.4, 9.1). Follow up time: from date of examination to date of endpoints: first-ever fatal/non-fatal MI, stroke or date of death. Follow up also terminated when patients withdrew from the study or died from other causes. Identification of endpoints using ICD codes for CV events and mortality, questionnaires for participants and information obtained from their physicians. Follow-up time for each patient included in analyses | P700SE, Philips. CCA (20-60mm proximal from flow divider), CB, ICA (0-20mm distally from flow divider), digitally captured during systole. Measured offline, automated (Matlab.) Calibration measurements with phantom in 1 in 100 patients | Gain was adjusted so that least dense arterial wall interface was just visible. Inter-observer reliabilities (15 subjects): ICC 0.97, intra-observer: ICC 0.93 |
| The Firefighters and Their Endothelium Study (FATE)[4]<br><br>2011, Canada | Prospective population based cohort study (n=1441)<br><br>Healthy men at low/intermediate Framingham Risk<br><br>Free from symptomatic CVD at baseline | CV risk factors obtained using a detailed interview and questionnaire and blood sampling. Risk factors defined according to current guidelines | Mean follow up: 7.2 (± 1.7 years). Follow up time: from date of examination to date of first-ever MI, stroke or date of death. Telephone follow up was obtained every 12 months in which next to information on events, also information on withdrawal, loss to follow up and non-end point deaths was documented. Endpoints: composite of CV death; resuscitated cardiac arrest; nonfatal first time MI; revascularization coronary, carotid or peripheral circulation; symptomatic CVD with >50% stenosis documented by angiography and documented stroke or TIA. Identification of endpoints: by documents on events, verified by local site investigator and reviewed by end-point committee. Follow-up time for each patient included in analyses | Acuson/Acoustic Response Technology ART 1 imaging System. Right CCA, proximal to flow divider. Thickest region identified (circumferential scan). Measured manually traced lumen-to-intima and media-to-adventitia interfaces, using locally developed software | Within-observer: ICC 0.89, between-observer: 0.92 |

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|---|---|---|---|---|---|
| Kuopio Ischaemic Heart Disease Risk Factor Study (KHID)[5]<br><br>1991, Finland | Prospective population based cohort study (n=879)<br><br>Eastern Finnish men aged 42,48,54, 60 years<br><br>Free from history of CVD at baseline | CV risk factors obtained using questionnaires and interviews, examination by a study nurse and blood sampling | Median follow up: 14.2 years (13.2, 15.2). Follow up time: from date of examination to date of endpoints: first-ever MI, stroke or date of death. There were no losses to follow up. Identification of endpoints using hospital files, stroke registry and death certificate registry (1984-1992). From 1993, computer linkage to Finnish national hospital discharge registry and death certificate registry using unique Finnish identification number. Endpoints were coded according to the ICD codes for MI and stroke and checked for first time MI/stroke. Follow-up time for each patient included in analyses | ATL UM4 duplex ultrasound system. Right and left CCA and CB, max CIMT located. Measured recorded on videotape. Image Measure morphometry software | Reproducibility: 50 subjects rescanned by same scanner, other reader. Correlation: 0.91. Difference: mean -0.03 mm, SD 0.09, range -0.17=0.16 mm) |
| Osaka Follow-Up Study for Carotid Atherosclerosis 2<br><br>(OSACA 2)[6]<br><br>2007, Japan | Prospective population based cohort study (n=403)<br><br>High risk patients ≥ 40 years of age (>1 CV risk factor)<br><br>Free from history of CVD events, endartectomy or carotid artery stenting | CV risk factors obtained using clinical records and self-reports at time of enrollment, physical examination and blood sampling | Median follow up 4.6 years (3.3, 6.1). Follow up time: from date of examination to date of first-ever MI, stroke or date of death. Follow up also terminated when patients withdrew from the study because of death or for personal reasons. Identification of endpoints: first occurrence of major CV event: nonfatal stroke/TIA, nonfatal MI, hospitalization for AP, arterial revascularization procedure (PCI, bypass graft) or confirmed death from CV causes. Endpoints assessed by investigators blinded to baseline data. Follow-up time for each patient included in analyses | Phillips SONOS 5500 equipped with a 3- to 11-MHz linear-array transducer. CCA, CB, ICA, near and far wall, mean of max-IMT calculated. Measured using electronic caliper on frozen frame of longitudinal B-mode image | In 36 patients: intra-observer correlation 0.98, inter-observer correlation for 47 patients 0.94, differences in both cases not significant |
| Tromsø Study[7]<br><br>2000, Norway | Prospective population based cohort study (n=4240)<br><br>Inhabitants of municipality of Tromsø | Baseline CV risk factors collected using self-administered questionnaires, physical examination and blood sampling | Median follow up 10.7 years (10.4, 11.0). Follow up time: from date of screening to date of endpoints: first-ever fatal/non-fatal MI, stroke or date of death. Follow up also terminated when patients withdrew from study because of migration or death. Identification of endpoints using computer linkage to national and local diagnosis registries (University Hospital of North Norway, outpatient diagnoses included) and National Causes of Death Registry at Statistics Norway using unique Norwegian identification number. Cases were identified according to ICD | Acuson 128 XP/10c ART upgraded. Three images (of CCA and CB) selected for offline reading (with optimal visibility). Measured via offline reading, using automated software (AMS) | No systematic differences between observers or within observers, however precision decreased with increasing CIMT |

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|---|---|---|---|---|---|
| | Exclusion of persons with previous history of MI or stroke | | codes for MI and stroke. Adjudication of endpoints by endpoint committee consisting of experienced physicians. Follow-up time for each patient included in analyses | | |
| Charlottesville Study[8]<br><br>2006, USA | Prospective population based cohort study (n=610)<br><br>Exclusion of persons with prior history of MI or stroke | Assessment of baseline CV risk factors using questionnaires and a physical examination. Blood samples were obtained retrospectively | Mean follow up 4.1 years (2.7, 5.0). Follow up time: from date of examination to date of first-ever fatal/non-fatal MI, stroke or date of death. Telephone follow up was obtained in which adjacent to information on events, also information on withdrawal and loss to follow up was documented . Endpoint: MACE: new MI, arterial revascularization, (PCI, bypass graft), or stroke/TIA. Identification of endpoints by telephone interviews with participants and subsequent confirmation via medical records and consistent with AHA/ACC diagnostic criteria | Toshiba PLM-703AT, Toshiba Powervision 6000SSA370A. Near and far wall CCA (5mm distal to bulb), near far wall bulb, far wall internal (5mm distal to bulb) end diastole, bilateral | - |

Abbreviations: CV: cardiovascular; CVD: cardiovascular disease CCA: common carotid artery; ICA: internal carotid artery; CB: carotid bifurcation; CIMT: carotid intima-media thickness; ICD: International Statistical Classification of Diseases and Related Health Problems; MI: myocardial infarction; TIA: transient ischemic attack; AP: Angina Pectoris; PCI: percutaneous intervention; ICC: intraclass correlation; SD: standard deviation; AHA/ACC American Heart Association/American College of Cardiology

**Table S2. Definition of MI and stroke for each cohort**

| Study Name | Definition of MI | Definition of stroke |
|---|---|---|
| Carotid Atherosclerosis Progression Study (CAPS)[3]<br><br>2006, Germany | MI was defined according to the ICD-9 classification:<br><br>- cardiac infarction<br>- coronary artery embolism, occlusion, rupture or thrombosis<br>- infarction of heart, myocardium or ventricle<br>- rupture of myocardium or ventricle<br>- ST elevation (STEMI) and non-ST elevation (NSTEMI) MI | Stroke was defined according to the ICD-9 classification:<br><br>- (non-traumatic) subarachnoid hemorrhage<br>- (non-traumatic) intracerebral hemorrhage<br>- other and unspecified non-traumatic intracranial hemorrhage<br>- occlusion and stenosis of pre-cerebral arteries<br>- occlusion of cerebral arteries<br>- acute, but ill-defined cerebrovascular disease<br>- other and ill-defined cerebrovascular disease<br>- late effects of cerebrovascular disease |
| The Firefighters and Their Endothelium Study (FATE)[4]<br><br>2011, Canada | MI was defined according to the AHA classification[9]:<br><br>- detection of typical rise and gradual fall of cardiac troponin or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:<br>  o symptoms of ischemia<br>  o development of pathological Q waves on the ECG<br>  o ECG changes indicative of ischemia (e.g. ST segment elevation or depression)<br>  o Identification of an intracoronary thrombus by angiography or autopsy<br><br>All nonfatal cases were confirmed using coronary angiography | Stroke was defined as the presence of typical neurological symptoms supported by abnormalities on neurovascular imaging. All cases were confirmed by a stroke neurologist |
| Kuopio Ischaemic Heart Disease Risk Factor Study | MI was defined according to the ICD-9 and ICD-10 classification:<br><br>- cardiac infarction<br>- coronary artery embolism, occlusion, rupture or thrombosis | Stroke was defined as a sudden onset of focal/global neurological deficit that leads to death or lasts for at |

| | | |
|---|---|---|
| (KHID)[5]<br><br>1991, Finland | - infarction of heart, myocardium or ventricle<br>- rupture of myocardium or ventricle<br>- ST elevation (STEMI) and non-ST elevation (NSTEMI) MI<br>- myocardial infarction specified as acute or with a stated duration of 4 weeks (28 days) or less from onset | least more than 24 hours and of apparent vascular cause |
| Osaka Follow-Up Study for Carotid Atherosclerosis 2<br><br>(OSACA 2)[6]<br><br>2007, Japan | MI was defined as a nonfatal MI or confirmed death from MI.<br><br>2 of the following 3 criteria had to be met:<br><br>- a significant rise in serum CK level (more than two times the upper limit of the normal level)<br>- symptoms of chest pain or compression lasting for at least 30 minutes<br>- ECG changes indicative of ischemia (ST segment elevation more than 0.1 mV in ≥1 limb leads or in ≥2 precordial leads) | Stroke was defined as a sudden onset of clinical symptoms suggestive for neurological impairment and of apparent vascular cause. All cases were confirmed using neurovascular imaging. |
| Tromsø Study[7]<br><br>2000, Norway | MI was defined according to an algorithm comprising the following:<br>- clinical signs (typical, atypical or ill-described) and changes on the ECG suggestive for MI<br>- clinical signs (typical) and a significant rise in the levels of myocardial enzymes/troponin<br>- clinical signs (atypical or ill-described) and a significant rise in the levels of myocardial enzymes/troponin and changes on the ECG suggestive for MI<br>- Identification of a recent MI by autopsy | Stroke was defined as a sudden onset of focal/global neurological deficit that leads to death or lasts for at least more than 24 hours and of apparent vascular cause |
| Charlottesville Study[8]<br><br>2006, USA | MI was defined according to the AHA classification[9]:<br><br>- detection of typical rise and gradual fall of cardiac troponin or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:<br>  o symptoms of ischemia<br>  o development of pathological Q waves on the ECG<br>  o ECG changes indicative of ischemia (e.g. ST segment elevation or depression) | Stroke was defined as a sudden onset of focal/global neurological deficit that leads to death or lasts for at least more than 24 hours and of apparent vascular cause |

- identification of an intracoronary thrombus by angiography or autopsy

| Characteristic | 'Adjusted' mean common CIMT< 50th percentile‡ *(n = 1465)* | 'Adjusted' mean common CIMT ≥ 50th percentile‡ *(n = 1602)* | P value‖ |
|---|---|---|---|
| Age (years), median (IQR)* | 37 (32, 42) | 37 (32, 42) | |
| Sex, male (%) | 870 (59.4) | 958 (59.8) | |
| BMI (kg/m2), median (IQR)* | 24.7 (22.5, 27.1) | 25.3 (23.2, 28.1) | <0.001§ |
| Systolic blood pressure (mmHg), median (IQR)* | 120.0 (112.0, 129.0) | 124.0 (115.0, 132.0) | <0.001§ |
| Diastolic blood pressure (mmHg), median (IQR)* | 74.0 (65.0, 80.0) | 75.0 (70.0, 85.0) | <0.001§ |
| Cigarette smoking status, yes (%) | 403 (27.5) | 448 (28.0) | 0.80 |
| Total cholesterol level (mmol/L), median (IQR)* | 5.2 (4.6, 5.9) | 5.4 (4.7, 6.1) | <0.001§ |
| HDL cholesterol level (mmol/L), median (IQR)* | 1.4 (1.2, 1.7) | 1.4 (1.1, 1.7) | <0.001§ |
| Hypertension, yes (%)† | 108 (7.4) | 194 (12.1) | <0.001§ |
| Diabetes, yes (%) | 5 (0.3) | 15 (0.9) | 0.06§ |
| Use of antihypertensive medication, yes (%) | 47 (3.2) | 93 (5.8) | <0.001§ |
| Use of lipid lowering medication, yes (%) | 20 (1.4) | 33 (2.1) | 0.61 |

Abbreviations: ICD: International Statistical Classification of Diseases and Related Health Problems; MI: myocardial infarction; CK-MB: Creatine Kinase MB ECG: Electrocardiogram; ACC/AHA: American College of Cardiology / American Heart Association

**Table S3. Study population characteristics using 'adjusted common CIMT' <50th and ≥50th percentile**

* IQR: interquartile range, BMI: body mass index, HDL: high-density lipoprotein, CIMT: carotid intima-media thickness, MI: myocardial infarction

† Defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or use of antihypertensive medication

‡ CIMT value adjusted for age categories, sex and study. Median <50th percentile 'adjusted' CIMT = 0.6 mm, median ≥ 50th percentile 'adjusted' CIMT = 0.7 mm

§ p<0.2

|| p value of model

**Table S4. Relation between quartiles of mean common CIMT and first-time MI/stroke**

| Per quartile of CIMT | mean common CIMT (mm)* Q1 | mean common CIMT (mm)* Q2 | mean common CIMT (mm)* Q3 | mean common CIMT (mm)* Q4 |
|---|---|---|---|---|
| Range of CIMT (mm) | 0.285 - 0.560 | 0.563 - 0.624 | 0.625 - 0.680 | 0.682 - 1.175 |
| Person years | 7330 | 6738 | 6767 | 6744 |
| Number of events (MI/stroke) | 5 | 9 | 15 | 26 |
| Age and sex adjusted hazard ratio (reference: Q1)† | - | 1.49 (0.49, 4.50) | 2.36 (0.84, 6.64) | 3.29 (1.21, 8.94) |
| Multivariable hazard ratio (reference: Q1)†‡ | - | 1.49 (0.49, 4.53) | 2.22 (0.78, 6.29) | 3.04 (1.11, 8.32) |

* Q: quartile, SD: standard deviation, CIMT: carotid intima-media thickness, MI: myocardial infarction
† Values are standardized hazard ratios (HR) with 95% confidence intervals
‡ Multivariable model is adjusted for age, sex, body mass index, smoking, diastolic blood pressure, total cholesterol level, HDL cholesterol level, presence of diabetes, use of antihypertensive medication, use of lipid lowering medication and for study

**Table S5. Relation between cardiovascular risk factors and mean common CIMT adjusted for SBP instead of DBP**

| Cardiovascular risk factors | Mean common CIMT (ln(mm))*†‡** | P value\|\| |
|---|---|---|
| Age, per 1 SD increase* | 0.042 (0.037, 0.048) | <0.001§ |
| Sex (reference: female) | 0.005 (0.001, 0.017) | 0.04§ |
| Smoking (reference: nonsmoker) | 0.005 (-0.005, 0.016) | 0.33 |
| SBP, per 1 SD increase* | 0.015 (0.009, 0.021) | <0.001§ |
| BMI, per 1 SD increase* | 0.012 (0.007, 0.018) | <0.001§ |
| Total Cholesterol, per 1 SD increase* | 0.009 (0.004, 0.014) | <0.001§ |
| HDL-Cholesterol, per 1 SD increase* | -0.069 (-0.013, -0.001) | 0.02§ |
| Diabetes mellitus (reference: no diabetes) | 0.048 (-0.011, 0.106) | 0.11 |
| Antihypertensive medication use (reference: no use) | 0.008 (-0.016, 0.032) | 0.52 |
| Lipid lowering medication use (reference: no use) | -0.006 (-0.048, 0.036) | 0.77 |

* SD: standard deviation, CIMT: carotid intima-media thickness, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, HDL: high density lipoprotein
† Values are standardized beta's with 95% confidence intervals
‡ Adjusted for all risk factors included in the model and for study
§ p<0.05
|| p value of fully adjusted model
** In this variable natural logarithmic transformation was performed

**Table S6. Relation between mean common CIMT and first-time myocardial infarction/stroke adjusted for SBP instead of DBP**

| Cardiovascular risk factors | Multivariable hazard ratio (HR)†‡ | P value\|\| |
|---|---|---|
| Mean common CIMT, per 1 SD increase* | 1.38 (1.09, 1.73) | 0.006§ |
| Age, per 1 SD increase* | 1.35 (0.90, 2.03) | 0.15 |
| Sex (reference: female) | 1.34 (0.59, 3.02) | 0.48 |
| Smoking (reference: nonsmoker) | 0.91 (0.50, 1.67) | 0.77 |
| SBP, per 1 SD increase* | 1.27 (0.97, 1.67) | 0.09 |
| BMI, per 1 SD increase* | 0.84 (0.61, 1.15) | 0.28 |
| Total Cholesterol, per 1 SD increase* | 0.96 (0.73, 1.26) | 0.80 |
| HDL-Cholesterol, per 1 SD increase* | 0.91 (0.64, 1.30) | 0.60 |
| Diabetes mellitus (reference: no diabetes) | 2.25 (0.50, 10.11) | 0.29 |
| Antihypertensive medication use (reference: no use) | 2.98 (1.34, 6.63) | 0.008§ |
| Lipid lowering medication use (reference: no use) | 5.01 (1.38, 18.22) | 0.01§ |

* SD: standard deviation, CIMT: carotid intima-media thickness, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, HDL: high density lipoprotein
† Values are standardized hazard ratios (HR) with 95% confidence intervals
‡ Adjusted for all risk factors included in the model and for study
§ $p<0.05$
|| p value of fully adjusted model

Supplemental acknowledgements

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