Supplementary material

Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands

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Content list

Supplementary Table 1. Inclusion criteria and exclusion criteria

Inclusion criteria	Definition
One or more of the following cardiovascular diseases or risk factors:	
Cardiovascular disease	
Transient ischemic attack	Sudden onset, ≤24 hours of: *carotid:* temporary motor weakness in one half of the body, language disorder, blindness in one eye *vertebrobasilar*: ≥2 simultaneously: bilateral motor weakness or paraesthesia, dizziness, diplopia, dysphagia, ataxia, dysarthria *unknown vascular region:* hemianopia, dysarthria
Cerebral infarction	Criteria as for TIA, but duration of >24 hours
Subarachnoid haemorrhage	Sudden headache and (temporary) loss of consciousness, often accompanied by neck stiffness, nausea and vomiting, with blood in basal cisterns confirmed by CT or xantochromia in cerebrospinal fluid
Carotid artery stenosis	Duplex ultrasound confirmed stenosis or occlusion of ≥1 carotid artery with diameter reduction ≥50%
Ischemic retinal syndrome	Visual field defect diagnosed as retinal syndrome by ophthalmologist
Angina pectoris	Chest pain with proven stenosis on coronary angiogram
Myocardial infarction	≥2 of following: - Chest pain >20 minutes, not relieved by nitrates; - ST elevation >1 mm in 2 contiguous ECG leads, or left bundle branch block; - Troponin levels >60 ng/L with rise and fall pattern*
Coronary syndrome requiring PCI or CABG	
Abdominal aortic aneurysm	Ultrasound confirmed local dilatation of abdominal aorta with anterior-posterior diameter ≥3 cm and/or distal-proximal ratio of >1,5
Renal artery stenosis	Stenosis of ≥1 renal artery with lumen narrowing ≥50%, caused by atherosclerosis
Peripheral artery disease of the lower limbs	Fontaine classification: - Fontaine II: intermittent claudication: pain (or other symptoms) in one or both legs after certain walking distance, disappearing at rest; - Fontaine III: rest/nocturnal pain; - Fontaine IV: ischemic ulceration, necrosis or gangrene; confirmed by ABI ≤0.90 at rest and/or ≥20% post-exercise decrease
Cardiovascular risk factors	
Hypertension	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hypertension, target organ damage, medical or family history
Hyperlipidaemia	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hyperlipidaemia, suspected lipid metabolism disorder, medical or family history

Diabetes mellitus	Fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L or use of oral antidiabetic agents or insulin
Renal insufficiency	Serum creatinine >120 µmol/L
HIV infection	Chronic infection with human immunodeficiency virus
Family medical history	Positive family history for premature cardiovascular disease in 1st degree relatives
Pre-eclampsia†	Gestational hypertension accompanied by proteinuria, other maternal organ dysfunction or uteroplacental dysfunction
HELLP syndrome†	Haemolysis, elevated liver enzymes, low platelets as a manifestation of pre-eclampsia
Placental abruption†	Gestational hypertension accompanied by placental abruption as an effect of uteroplacental insufficiency
Intrauterine growth restriction†	Gestational hypertension accompanied by fetal growth restriction as an effect of uteroplacental insufficiency
Remaining inclusion criteria	
18 – 90 years of age	
Independent in most daily activities	Rankin scale ≤3[1]
Exclusion criteria	
Pregnancy	
Short life expectancy (per judgement of the treating physician)	
Insufficient understanding and expression of the Dutch language	
No informed consent	
Follow-up impossible	

* In earlier years of the UCC-SMART study, this laboratory item was defined as CK elevation of ≥2x upper limit and MB-fraction >5% of total CK level.
† Hypertensive pregnancy complications are based on the ISSHP criteria[2]

ABI, ankle-brachial index; CABG, coronary artery bypass grafting; CK, creatine kinase; CT, computed tomography; ECG, electrocardiogram; HELLP, haemolysis, elevated liver enzymes and low platelets; HIV, human immunodeficiency virus; ISSHP, International Society for the Study of Hypertension in Pregnancy; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 2. Variables available in UCC-SMART

Health questionnaire	Medication use	Physical examination	Radiology measurements	Laboratory measurements
Medical history	Statins	Weight (kg)	Visceral fat (cm)	Haemoglobin (mmol/L)
Age (years)	Ezetimibe	Height (m)	Subcutaneous fat (cm)	Haematocrit (%)
Sex	Fibrates	Blood pressure (mmHg)	Carotid artery stenosis (%)	Total cholesterol (mmol/L)
Smoking and pack years	Thiazide diuretics	Ankle-brachial index	Carotid intima thickness (mm)	LDL-C (mmol/L)
Alcohol use and number of units	Loop diuretics	Body mass index (kg/m^2)	Aortic artery diameter (cm)	HDL-C (mmol/L)
Level of education	Potassium saving diuretics	Waist circumference (cm)	Kidney size and volume (cm; mL)	Apolipoprotein B (g/L)
Country of birth	ACE-inhibitors	Hip circumference (cm)	Electrocardiography	Triglycerides (mmol/L)
Quality of life*	Angiotensin II-receptor blockers		Echocardiography†	HbA1c (%)
Exercise (MET-hours per week)	Aldosterone antagonists			Fasting glucose (mmol/L)
	Beta-blockers			Fasting insulin (mU/L)
	Calcium antagonists			Creatinine (µmol/L)
	Alpha blockers			eGFR (ml/min/1.73 m^2)
	Central acting antihypertensives			Albuminuria (mg/L)
	Direct vasodilators			Albumin-to-creatinine ratio
	Aspirin			CRP (mg/L)
	Clopidogrel			TSH (mU/L)
	Dipyridamole			Lp(a)
	DOAC			Urine sodium
	Vitamin K antagonists			Urine potassium
	LMWH			
	Oral glucose-lowering therapy			
	Insulin			
	Antidepressants			
	Benzodiazepines			

* Based on EQ-5D questionnaire

† Echocardiography will be added to the UCC-SMART program in the near future

ACE, angiotensin converting enzyme; CRP, C-reactive protein; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin type A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMWH, low molecular weight heparin; Lp(a), lipoprotein(a); MET, metabolic equivalent of task; TSH, thyroid stimulating hormone; UCC-SMART, Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Diseas

Supplementary Table 3. Measurements that have been performed in the past

Vascular wall stiffness was determined from 2001 until 2003 using the Wall Track System that captures vascular diameter changes using radio-frequent signals. At the first signal, the position of the anterior and posterior vascular wall of the common carotid artery are marked at 2 cm proximal to the carotid bulb. Then, for five times on both the left and right side, changes in arterial diameter (ΔD) and end-diastolic diameter (D_d) are registered during four seconds, and the mean is calculated. Carotid distension is defined as the change in artery diameter in systole relative to diastolic diameter. Other stiffness indices include β stiffness index ($\ln(SBP/DBP)/(\Delta D/D_d)$), compliance coefficient ($(\pi \times D_d \times \Delta D)/2 \times$pulse pressure), distensibility coefficient ($(2 \times \Delta D/D_d)$/pulse pressure), Peterson's modulus (pressure change required for theoretical 100% increase in diameter) and Young's elastic modulus (pressure per mm^2 required for theoretical 100% extension).
Flow-mediated vasodilatation (FMD) was assessed temporarily starting from March 1999. Here, the Wall Track System described above was used to capture the diameter of the brachial artery in the elbow crease. Following 3 baseline readings, new measurements were taken every 30 seconds for 5 minutes: first after a blood pressure cuff at the forearm was inflated to 100 mmHg above SBP for 4 minutes, and then after sublingual administration of 400 µg of nitroglycerin. Endothelial function was defined as the proportional increase of diameter after nitrate and the baseline-adjusted maximal diameter following ischemia. This examination was stopped in June 2001, since analysis in the first 400 patients showed this measurement was not related to other known measures of atherosclerosis.
Quality of life information was collected through questionnaires based on the 36-Item Short Form Health Survey (SF-36)[3], sent to participants from 2001 until 2019. This quality of life assessment contains scales for 1) limitations in physical activities; 2) limitations in social activities; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality and 8) general health perceptions.
Homocysteine was measured from 1998 until 2011 in fasting blood samples by high performance liquid chromatography with fluorescence detection. Up until 2000, a methionine loading test was performed in patients younger than 50 years. Plasma homocysteine was measured six hours after oral administration of 100mg methionine per kilogram bodyweight.

DBP, diastolic blood pressure; SBP; systolic blood pressure

Supplementary Table 4. Definitions of established cardiovascular disease

Cardiovascular disease	Definition of cardiovascular disease*
Cerebrovascular disease	TIA, cerebral infarction, ischemic retinal syndrome, carotid surgery or angioplasty in medical history
Coronary artery disease	Myocardial infarction, angina pectoris, ≥ 1 vessel disease on coronary angiography, PCI or CABG in medical history
Abdominal aortic aneurysm	Abdominal aortic aneurysm, surgical or endovascular treatment of abdominal aortic aneurysm in medical history
Peripheral artery disease	Fontaine classification ≥ II, amputation, vascular surgery or angioplasty in medical history

* Definitions of these items are listed in Supplementary Table 1.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 5. Definitions of outcome events

Outcome event	Definition of outcome event
	Primary endpoints
Stroke	
Ischemic stroke / haemorrhagic infarction	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale[1], and new (haemorrhagic) infarction on CT or MRI <2 weeks after stroke
Cerebral haemorrhage	Cerebral haemorrhage confirmed with CT, MRI or surgery
Subarachnoid haemorrhage	Subarachnoid haemorrhage confirmed with CT, MRI or surgery
Type not determined	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale, but no brain imaging performed
Retinal syndromes	
Infarction	Associated clinical symptoms, typical fundus changes and/or vision loss, scotoma on perimetry
Haemorrhage	Associated clinical symptoms, typical fundus changes and vision loss
Myocardial infarction	The assessment includes: chest pain >30 minutes, elevated cardiac enzymes, characteristic ECG-changes
STEMI	Acute chest pain with persistent (>20 minutes) ST-elevation
NSTEMI	Acute chest pain without ST-elevation, with elevated troponin
Intervention-related myocardial infarction	New Q wave and elevated troponin <7 days after any intervention (for PCI >3x, for CABG >5x)
Probable myocardial infarction	Typical pain, persistent STT-changes, no documented course of cardiac enzymes
Heart failure	≥2 of the following: dyspnoea, dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, exercise intolerance, pulmonary oedema, increased central venous pressure, third heart tone, hepatojugular reflux, altered hemodynamics, peripheral oedema, cardiomegaly; and (intensified) treatment with loop diuretics or intravenous vasoactive inotropic agents Classified as: systolic heart failure (at least moderate left ventricle dysfunction or LVEF <40%) or heart failure with preserved ejection fraction, due to coronary disease, valve disease or other causes
Rupture of abdominal aortic aneurysm	Rupture abdominal aortic aneurysm, proven by ultrasound, CT or laparotomy
Renal disease	
End-stage renal disease	CKD stage 5 (i.e. persisting eGFR <15ml/min/1.73 m^2 for >3 months and/or need for renal replacement therapy (chronic dialysis or renal transplantation))

Acute renal insufficiency – temporary renal replacement therapy	Acute kidney injury requiring temporary renal replacement therapy
Acute renal insufficiency – no renal replacement therapy	Acute kidney injury KDIGO stage 3 (i.e. serum creatinine 3 times baseline creatinine and/or serum creatinine ≥354 µmol/L)
Bleeding	Bleeding requiring outpatient treatment or (prolonged) hospitalization
Major bleeding	*ISTH definition:* fatal bleeding and/or bleeding in critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular causing compartment syndrome), bleeding causing Hb level drop of ≥1.24 mmol/L or leading to transfusion of ≥2 units of blood[4] *BARC type 3:* overt bleeding with Hb level drop of ≥1.86 mmol/L, leading to transfusion, cardiac tamponade, surgical intervention for control or intravenous vasoactive agents, or located intracranial or intraocular compromising vision *BARC type 5:* fatal bleeding[5]
Diabetes	Self-reported diagnosis, confirmed and classified based on a questionnaire. If necessary, additional information is requested from the general practitioner or looked up in the electronic health record.
DM type 1	Insulin needed immediately at onset and absence of oral glucose lowering medication. Supportive but not mandatory: ≤25 years of age, BMI <25 kg/m^2, presence of anti-GAD antibodies
DM type 2	Diagnosed between age 35 and 40 and BMI >33 kg/m^2 or diagnosed after age 40 and BMI >27 kg/m^2
Dementia	Self-reported diagnosis, confirmed and classified based on a questionnaire. Classified as: Alzheimer's disease; vascular dementia; a mix of Alzheimer's disease and vascular dementia; Lewy Body dementia; or frontotemporal dementia.
Vascular mortality	
Fatal cerebral infarction	Cerebral infarction leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal cerebral haemorrhage	Cerebral haemorrhage leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal stroke - type not determined	Stroke without radiological confirmation leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without stroke)
Fatal myocardial infarction	Documented myocardial infarction followed by death (>1 hour after onset of symptoms)

Fatal heart failure	Heart failure leading to death
Fatal rupture abdominal aortic aneurysm	Rupture abdominal aortic aneurysm followed by death
Fatal bleeding	Major bleeding leading to death
Sudden death	Witnessed death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Other	Death without apparent cause in case of cardiovascular history, terminal renal insufficiency, dementia (unless clearly non-vascular), pulmonary haemorrhage*
Non-vascular mortality	Death caused by malignancy, infection, unnatural death or other
All-cause mortality	Death from any cause
	Secondary endpoints
Amputation	Any amputation of a toe or part of the foot or leg due to chronic ischemia. *Excluding:* traumatic amputations, amputation due to sepsis, amputation of fingers.
Vascular intervention†	Percutaneous coronary intervention; coronary artery bypass grafting; carotid endarterectomy, angioplasty or stenting; vertebral artery angioplasty or stenting; vascular surgery or percutaneous transluminal angioplasty of the aorta(bifurcation), iliac arteries, femoral and crural arteries; vascular intervention because of abdominal angina; LVAD. Angioplasty and stenting of other arteries are registered as well.
Vascular intervention of an intracranial aneurysm	Coiling or clipping of an intracranial aneurysm

* In accordance with Antiplatelets Trialists' Collaboration, Lancet 2002
† Excluding interventions already planned before or at inclusion, but including re-interventions and complications of an intervention already planned before or at inclusion.

Anti-GAD, antibodies to glutamic acid decarboxylase; BARC; Bleeding Academic Research Consortium; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; KDIGO, Kidney Disease Improving Global Outcomes; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

Supplementary Table 6. Substudies of UCC-SMART

Substudy	Period in which the patients were included	N	Aim	Key publications	Additional measurements within substudy
ARTEMIS *(ARTErial calcifications of the Media and Intima in SMART)*	2015 - 2017	520	1) To determine whether intima and media calcification differ in their respective associated CVD risks. 2) To elucidate which risk factors and mechanisms lead to the development of these respective types of calcification and in turn to cardiovascular disease	- Zwakenberg, 2020, PloS One[6] - Hoek, 2021, Atherosclerosis[7]	Technique: unenhanced thin-slice CT-scan of the legs (femoral head to feet) Measurement: calcification in the femoral and crural arteries scored as absent, predominant intimal arterial calcification, predominant medial arterial calcification or indistinguishable; calcification volume.
Athero-Express *Added to UCC-SMART study in June 2022*	2002 - present	Patients undergoing a femoral or carotid endarterectomy	To investigate the value of plaque characteristics in relation to cardiovascular outcomes	Verhoeven, 2004, Eur J Epidemiology[8]	During surgery, the atherosclerotic plaque is collected and immunohistochemically stained in order to asses fat, collagen, macrophages and smooth muscle cells
BEST *(BEtter risk factor treatment with STructured agreement)* RCT	2004 - 2006	197 patients with at least 2 modifiable risk factors	To investigate whether a clearly written agreement on risk factor management between general practitioners and hospital improved the vascular risk profile of high-risk patients compared with usual care after 1 year	Brouwer, B.G. 2008. SMART risk factor screening in patients at high vascular risk. Utrecht University, Utrecht[9]	NA
Brown adipose tissue	2014 – 2016	50 patients with clinically manifest CVD	1) To evaluate and optimize a protocol for quantifying brown adipose tissue with MRI and to assess BAT volume per patient. 2) To evaluate the reproducibility of MRI by determining inter-scan, intra-observer and inter-observer variability in BAT volume	- Franssens, 2016, NMR Biomed[10] - Franssens, 2017, J Magn. Reson. Imaging[11]	Technique: 1.5T water-fat MRI of supraclavicular and subcutaneous adipose tissue Measurement: fat signal fraction value, representative of the amount of triglycerides, intracellular water content and capillary

					density, of supraclavicular and subcutaneous adipose tissue
DISH *(Diffuse idiopathic skeletal hyperostosis)*	1996 – 2018	4,791 (all patients from SMART with chest X-ray within 3 months of inclusion)	N.A.	- Harlianto, 2021, Rheumatology[12] - Harlianto, 2021, J. Pers. Med.[13]	*Technique:* *Chest X-ray within three months of inclusions (if available in routine clinical care)*
					Measurement: X-rays were scored for DISH using the Resnick criteria.[14] DISH is classified following the presence of ossification of at least four contiguous vertebrae; (relative) preservation of the intervertebral disc height; and the absence of apophyseal joint bony ankylosis or sacroiliac joint erosion. Thoracic aortic calcification subjective score as absent, mild, moderate and severe.
IRIS *(Internet-based vascular Risk factor Intervention and Self-management)* RCT	2008 - 2010	330 patients with a recent clinical manifestation of atherosclerosis of CAD, CeVD or PAD and with ≥ 2 treatable risk factors not at goal (from UMC Utrecht + Rijnstate)	1) To evaluate whether an internet-based vascular risk factor management program promoting self-efficacy on top of usual care is more effective than usual care alone in reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease. 2) To evaluate whether an internet-based vascular risk factor management program for reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease is cost-effective.	- Vernooij, 2012, BMJ[15] - Greving, 2015, BMJ Open[16]	NA

RULE *(Risk management in Utrecht and Leiden Evaluation study)* Two-centre parallel-group comparative investigation	2005 - 2007	604 patients with CAD, CeVD, PAD or T2DM from UMC Utrecht (+ 566 patients from LUMC)	To assess risk factor status after referral in patients with established vascular disease or type 2 diabetes who took part in the multidisciplinary hospital-based vascular screening program SMART, compared with a group who did not participate in such a program	Brouwer, 2010, J of Int Med[17]	NA
Small aneurysms trial (AAA)	1996 - 2005	230 patients with an initial AAA diameter of 30-55mm, who were examined by ≥ 2 AAA diameter measurements and with ≥ 6 months of FU	To estimate overall rupture rates of small AAAs and to investigate a predefined set of demographic characteristics and cardiovascular risk factors for association with AAA growth	Schlosser, 2008, J Vasc Surg[18]	Technique: Ultrasound scanning of the aorta Measurement: AAA diameter and change with initial AAA diameter
SMART-2	2007 - present	1794 patients with a history of CVD or diabetes, a median of 9.9 years after inclusion in UCC-SMART	To study the course of atherosclerosis and vascular risk factors over time, and to evaluate the effects of treatment in the past		NA
SMART HEART	1996 - 2006	536 patients with ≥ 3 years hypertension, but free of known coronary or	To detect patient characteristics related to the development of LVH with special focus on the detection of SNPs that confer an increased susceptibility for the development of LVH, and thus, heart failure	- Meijs, 2007, Neth Heart J[19] - Meijs, 2009, Eur J Prev Cardiol[20] - Vernooij, 2012, Am J Cardiol[21]	Technique: 1.5T cardiac MRI and delayed-enhancement cardiac MRI Measurement: LV mass, LV-end diastolic and end-systolic volumes and left atrial volumes; areas of hyperintense myocardium

		valvular disease		- De Beus, 2015, Eur J Clin Invest[22]	classified as myocardial scar tissue (used to assess the presence of unrecognized myocardial infarction). Infarct size was quantified as scar mass relative to LV mass.
SMART Inform Three-armed hypothesis-blinded RCT	2017 - 2018	303 patients with stable CVD and using a statin	To determine whether communicating personalized statin therapy-effects obtained by prognostic algorithm leads to lower decisional conflict associated with statin use in patients with stable CVD compared with standard (non-personalized) therapy-effects	Jaspers, 2021, BMJ Open[23]	NA
SMART-Junior	Questionnaires sent between 2009-2013 to patients who were included between 2001 and 2012	4,270 (10,564 children)	1) To investigate the presence of cardiovascular risk factors and vascular disease in offspring of patients participating in the SMART cohort. 2) To identify a risk profile of the parent prognostic for the development of traditional cardiovascular risk factors or cardiovascular events in their children.	- Weijmans, 2015, Int J Cardiol[24] - Weijmans, 2015, Am Heart J[25]	- Questions about CV risk factors (incl. dates of risk factor diagnoses): presence of diabetes, hypertension, hypercholesterolemia, smoking behaviour and present weight of the offspring - Questions about CVD (incl. dates of occurrence): whether offspring had experienced MI, PCI, CABG, stroke, PAD, or AAA.
SMART-MR and SMART Medea	2001 - 2005 1st follow-up: 2006-2009 2nd follow-up: 2013-2017	1,309	To investigate brain changes using 1.5T MRI in patients with symptomatic atherosclerotic disease (and 7T MRI in follow-up from 2013-2017)	- Geerlings, 2010, Atherosclerosis[26] - Muller, 2011, Ann Neurol[27] - Conijn, 2011, Stroke[28] - Kloppenborg, 2012, Neurology[29] - Jochemsen 2013, JAMA Neurology[30] - Van der Veen, 2015, Stroke[31]	<u>Technique:</u> - 1.5T brain MRI - 7T brain MRI <u>Measurement:</u> - Total cerebral blood flow (mL/min per 100 mL brain parenchymal volume) - White matter lesions: volume (mL), shape (using the concavity index and fractal dimension[35]) and location were scored

				- Zwartbol, 2019, Stroke[32] - Ghaznawi 2021, Neurology[33] - Rissanen, 2021, Neurology[34]	- Brain parenchymal fraction (% of intracranial volume (ICV) that is occupied by brain tissue), an indicator for global brain atrophy - Ventricular enlargement (% of ventricular volume of the total ICV), an indicator for subcortical brain atrophy - Cortical gray matter fraction (% cortical gray matter volume of the total ICV), an indicator of cortical brain atrophy - Infarcts: location, affected flow territory and type were scored
					<u>Neuropsychological assessment (from 2003):</u> - 15-learning word test[36] - Rey-Osterrieth Complex Figure test[37] - Visual Elevator test[38] - Brixton Spatial Anticipation test[39] - Verbal Fluency test (letter)[40] - Dutch version of the National Adult Reading test[41] <u>From 2006:</u> - MMSE[42] - Verbal Fluency test (animals)[40] - Digit Symbol Substitution Test[43] - Forward Digit Span and Backward Digit Span[44]
SMART-ORACLE *(Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk*	2012 - present	1.182 (until Dec 2021; ongoing) patients with a history of symptomatic vascular	1) To determine whether there is additional value of performing CAC score, CTCA, total aorta calcification, burden as compared to traditional risk factors in the risk stratification in predicting any cardiovascular event. 2) To	- Franssens, 2017, Eur J of Prev Cardiol[45] - Van 't Klooster, 2020, IJC Heart & Vasculature[46]	<u>Technique:</u> Cardiac non-contrast enhanced CT and CTA of the heart and the carotids to the circle of Willis

for a cardiovascular event)		disease, T2DM or hypertension	estimate the additional value of CTCA and CAC score on top of traditional risk factors in predicting cardiac events. 3) To determine the value of soft plaque burden in the carotid and coronary arteries in predicting acute vascular events		Measurement: - Radiodensity and volume of epicardial adipose tissue - Coronary artery calcium (scored using the Agatston method[47]) - Calcifications on heart valves and in the thoracic aorta (quantified using a pseudo-mass score: mean calcium houndsfield units × region of interest volume) - CAD-RADS[48] - Carotid stenosis
SPAIN *(Selfmanagement of vascular Patients Activated by Internet and Nurses)*	2005	50 patients with computer facilities	1) To evaluate the feasibility of an Internet-based vascular risk reduction program in terms of accessibility, frequency and pattern of use of an individualized website for patients with a recent clinical manifestation of arterial disease. 2) To evaluate whether the use was related to a change in vascular risk factors after 6 months	Goessens, 2008, Patient education and counseling[49]	NA
TEMPUS *(The Evening versus Morning Polypill Utilization Study)* Randomized open blinded endpoint crossover trial	1996 - 2009. Patients were screened between 2012 - 2013	78 patients with established CVD or those at intermediate to high risk of CVD with indication for the use of cardiovascular medication, according to the current	1) To assess whether there is a difference in the morning or evening administration of a cardiovascular polypill, an FDC formulation containing aspirin, simvastatin, lisinopril and hydrochlorothiazide, on LDL-C and mean 24-hour systolic BP levels in individuals at high risk of cardiovascular disease. 2) To assess the effect of the polypill on LDL-C, ambulatory BP, anti-platelet function, adherence and patients'	- Lafeber, 2014, Eur J Prev Cardiol[50] - Lafeber, 2014, Int J Cardiol[51]	At baseline and at the end of each treatment period: medical history, anthropometric parameters, laboratory blood tests, office BP, 24-hour ambulatory BP monitoring, platelet function, pulse wave analysis, adherence to therapy, and questionnaires

		Dutch guidelines	preference as compared to the administration of the individual, identically dosed components of the polypill administered at different times of the day, as is currently recommended in clinical care.		
VENUS *(Vascular prEvention by NUrses Study)* RCT	Patients included between May 2002 and October 2003	236 patients with ≥ 2 modifiable risk factors	To investigate whether risk factor management in the hospital improved with nurse practitioner care plus usual care compared with usual care	- Goessens, 2006, Eur J Cardiovasc Prev Rehabil[52] - Sol, 2009, Eur J C Nurse[53]	Questionnaire about social support using a social support questionnaire for Dutch CHD patients: - Structural support: whether they have a spouse and whether they have someone they could turn to about their health problems - Functional support: statements about active involvement, protective buffering and overprotection.

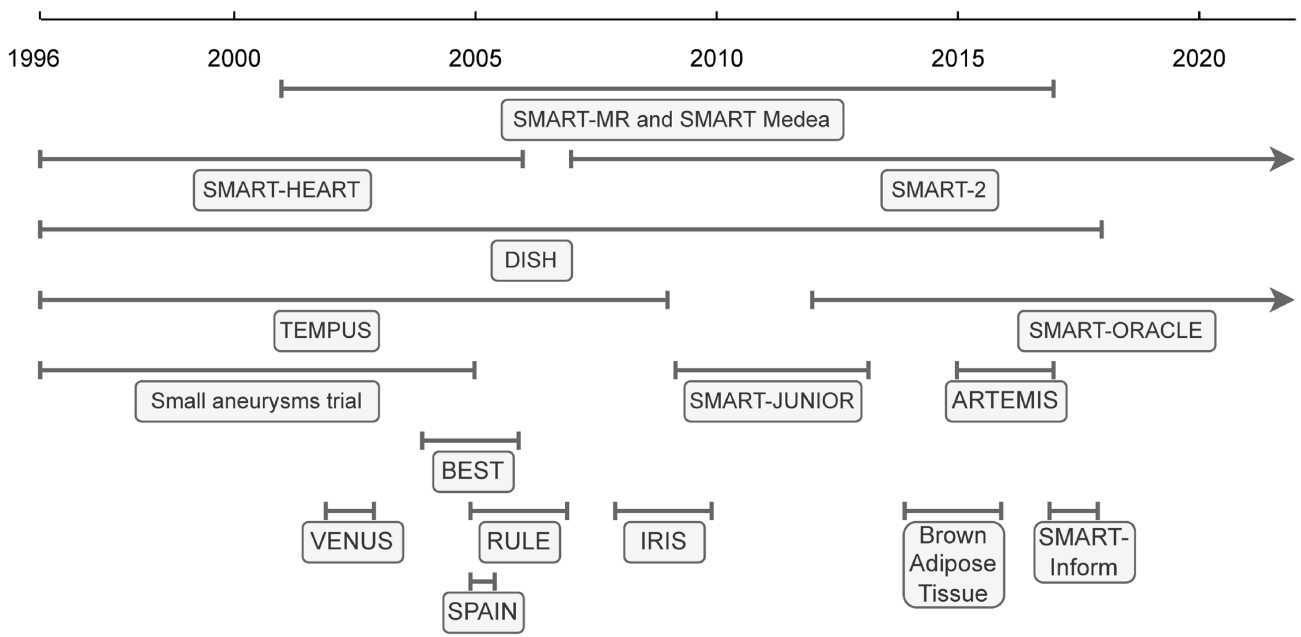
AAA, aortic abdominal aneurysm; BAT, brown adipose tissue; BP, blood pressure; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease, CAD-RADS, CAD-reporting and data system, CeVD, cerebrovascular disease; CHD, coronary heart disease; CT, computed tomography; CTA, CT angiography; CTCA, CT coronary angiography; CV, cardiovascular; CVD, cardiovascular disease; DISH, diffuse idiopathic skeletal hyperostosis; FDC, fixed dose combination; FU, follow-up; LDL-c, low-density lipoprotein cholesterol; LUMC, Leiden University Medical Center; LV, left ventricle; LVH, left ventricle hypertrophy; MI, myocardial infarction; MRI, magnetic resonance imaging; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SMART, Second Manifestations of Arterial Disease; SNP; single nucleotide polymorphism; T2DM, type 2 diabetes mellitus; UCC-SMART, Utrecht Cardiovascular Cohort–SMART; UMC, University Medical Center

Supplementary Table 7. Baseline characteristics of participants with complete follow-up and participants without complete follow-up

	Participants with complete follow-up (n = 13,284)	**Participants without complete follow-up (n = 1,546)**
Age (years)	57 ± 12	55 ± 14
Male sex	8,736 (66)	894 (57)
Previous or current smoking	9,285 (70)	1,065 (69)
Established cardiovascular disease	8,270 (65)	913 (59)
Diabetes mellitus	2,272 (17)	336 (22)
Lipid-lowering therapy	7,529 (57)	724 (47)
Antihypertensive therapy	9,053 (68)	977 (63)
Oral anticoagulant therapy	1,145 (9)	121 (8)
Systolic blood pressure (mmHg)	140 ± 22	144 ± 23
Diastolic blood pressure (mmHg)	83 ± 13	84 ± 13
Body mass index (kg/m^2)	26.9 ± 4.4	27.1 ± 4.8
Non-HDL-cholesterol (mmol/L)	3.8 ± 1.3	4.0 ± 1.5
eGFR (ml/min/1.73 m^2)	53 ± 41	48 ± 43
HbA1c (mmol/mol)	38 (36 - 42)	40 (36 - 48)
CRP (mg/L)	2.0 (1.0 - 4.3)	2.2 (1.0 - 4.4)

Data are presented as number (percentage), mean ± standard difference or median (interquartile range).

Supplemental Figure 1. Timeline of substudies of UCC-SMART



1.5T brain MRIs have been performed between 2001 and 2005. Follow-up of 1.5T MRI was performed between 2006 and 2009 and from 2013 to 2017. During the second follow-up, a 7T brain MRI was added in a subsample. A detailed overview of the substudies is provided in Supplementary Table 5.

ARTEMIS, ARTErial calcifications of the Media and Intima in SMART (Second Manifestations of Arterial Disease)[6]; BEST, BEtter risk factor treatment with STructured agreement[9]; Brown Adipose Tissue[10]; DISH, Diffuse idiopathic skeletal hyperostosis[12]; IRIS, Internet-based vascular Risk factor Intervention and Self-management[15]; RULE, Risk management in Utrecht and Leiden Evaluation study[17]; SMART HEART[19]; SMART Inform[23]; SMART-JUNIOR[24]; SMART-MR[26]; ORACLE; Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk for a cardiovascular event[45]; SPAIN,

Self-management of vascular Patients Activated by Internet and Nurses[49]; TEMPUS, The Evening versus Morning Polypill Utilization Study[50]; VENUS, Vascular prEvention by NUrses Study[52].

References

1. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May;19(5):604–7.
2. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive Disorders of Pregnancy. Hypertension. 2018 Jul;72(1):24–43.
3. Ware JEJ, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473–83.
4. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005 Apr 4;3(4):692–4.
5. Mehran R, Rao S V, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011 Jun;123(23):2736–47.
6. Zwakenberg SR, De Jong PA, Hendriks EJ, Westerink J, Spiering W, De Borst GJ, et al. Intimal and medial calcification in relation to cardiovascular risk factors. PLoS One. 2020;15(7 July):1–14.
7. Hoek AG, Zwakenberg SR, Elders PJM, de Jong PA, Spiering W, Bartstra JW, et al. An elevated ankle-brachial index is not a valid proxy for peripheral medial arterial calcification. Atherosclerosis. 2021;323(March):13–9.
8. Verhoeven BAN, Velema E, Schoneveld AH, de Vries JPPM, de Bruin P, Seldenrijk CA, et al. Athero-express: differential atherosclerotic plaque expression of mRNA and protein in relation to cardiovascular events and patient characteristics. Rationale and design. Eur J Epidemiol. 2004;19(12):1127–33.
9. Brouwer BG. SMART risk factor screening in patients at high vascular risk [dissertation]. Utrecht University; 2008.
10. Franssens BT, Eikendal AL, Leiner T, van der Graaf Y, Visseren FLJ, Hoogduin JM. Reliability and agreement of adipose tissue fat fraction measurements with water-fat MRI in patients with manifest cardiovascular disease. NMR Biomed. 2016;29(1):48–56.
11. Franssens BT, Hoogduin H, Leiner T, van der Graaf Y, Visseren FLJ. Relation between brown adipose tissue and measures of obesity and metabolic dysfunction in patients with cardiovascular disease. J Magn Reson Imaging. 2017;46(2):497–504.
12. Harlianto NI, Oosterhof N, Foppen W, Hol ME, Wittenberg R, van der Veen PH, et al. Diffuse idiopathic skeletal hyperostosis is associated with incident stroke in patients with increased cardiovascular risk. Rheumatology. 2021;1–8.
13. Harlianto NI, Westerink J, Foppen W, Hol ME, Wittenberg R, Van Der Veen PH, et al. Visceral adipose tissue and different measures of adiposity in different severities of diffuse idiopathic skeletal hyperostosis. J Pers Med. 2021;11(7):1–11.
14. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). Radiology. 1976 Jun;119(3):559–68.
15. Vernooij WP, Kaasjager HAH, Van Der Graaf Y, Wierdsma J, Grandjean HMH, Hovens MMC, et al. Internet based vascular risk factor management for patients with clinically manifest vascular disease: Randomised controlled trial. BMJ. 2012;344(7863):1–13.
16. Greving JP, Kaasjager HAH, Vernooij JWP, Hovens MMC, Wierdsma J, Grandjean HMH, et al. Cost-effectiveness of a nurse-led internet-based vascular risk factor management programme: Economic evaluation alongside a randomised controlled clinical trial. BMJ Open. 2015;5(5):1–8.
17. Brouwer BG, Visseren FLJ, Algra A, Van Bockel JH, Bollen ELEM, Doevendans PA, et al. Effectiveness of a hospital-based vascular screening programme (SMART) for risk factor management in patients with established vascular disease or type 2 diabetes: A parallel-group comparative study. J Intern Med. 2010;268(1):83–93.
18. Schlösser FJV, Tangelder MJD, Verhagen HJM, van der Heijden GJMG, Muhs BE, van der Graaf Y, et al. Growth predictors and prognosis of small abdominal aortic aneurysms. J Vasc Surg. 2008;47(6):1127–33.
19. Meijs MFL, Bots ML, Vonken EJA, Cramer MJM, Melman PG, Velthuis BK, et al. Rationale and design of the SMART Heart study. Netherlands Hear J. 2007;15(9):295–8.

20. Meijs MF l., Vergouwe Y, Cramer MJ m., Vonken EJA, Velthuis BK, Verton DJ, et al. A prediction model for left ventricular mass in patients at high cardiovascular risk. Eur J Prev Cardiol. 2010;17(6):621–7.
21. Vernooij JWP, Cramer MJM, Visseren FLJ, Korndewal MJ, Bots ML, Meijs MFL, et al. Relation between abdominal obesity, insulin resistance and left ventricular hypertrophy diagnosed by electrocardiogram and magnetic resonance imaging in hypertensive patients. Am J Cardiol. 2012;110(2):227–33.
22. de Beus E, Meijs MFL, Bots ML, Visseren FLJ, Blankestijn PJ, Algra A, et al. Presence of albuminuria predicts left ventricular mass in patients with chronic systemic arterial hypertension. Eur J Clin Invest. 2015;45(6):550–6.
23. Jaspers NEM, Visseren FLJ, Van Der Graaf Y, Smulders YM, Damman OC, Brouwers C, et al. Communicating personalised statin therapy-effects as 10-year CVD-risk or CVD-free life-expectancy: Does it improve decisional conflict? Three-armed, blinded, randomised controlled trial. BMJ Open. 2021;11(7):1–8.
24. Weijmans M, Van Der Graaf Y, De Borst GJ, Asselbergs FW, Cramer MJ, Algra A, et al. Prevalence and risk of cardiovascular risk factors and events in offspring of patients at high vascular risk and effect of location of parental vascular disease. Int J Cardiol. 2015;195:195–202.
25. Weijmans M, Van Der Graaf Y, De Borst GJ, Asselbergs FW, Cramer MJ, Algra A, et al. The relation between the presence of cardiovascular disease and vascular risk factors in offspring and the occurrence of new vascular events in their parents already at high vascular risk. Am Heart J. 2015;170(4):744-752.e2.
26. Geerlings MI, Appelman APA, Vincken KL, Algra A, Witkamp TD, Mali WPTM, et al. Brain volumes and cerebrovascular lesions on MRI in patients with atherosclerotic disease. The SMART-MR study. Atherosclerosis. 2010;210(1):130–6.
27. Muller M, Van Der Graaf Y, Algra A, Hendrikse J, Mali WP, Geerlings MI. Carotid atherosclerosis and progression of brain atrophy: The SMART-MR Study. Ann Neurol. 2011;70(2):237–44.
28. Conijn MMA, Kloppenborg RP, Algra A, Mali WPTM, Kappelle LJ, Vincken KL, et al. Cerebral small vessel disease and risk of death, ischemic stroke, and cardiac complications in patients with atherosclerotic disease: The second manifestations of arterial disease-magnetic resonance (SMART-MR) study. Stroke. 2011;42(11):3105–9.
29. Kloppenborg RP, Geerlings MI, Visseren FL, Mali WPTM, Vermeulen M, Van Der Graaf Y, et al. Homocysteine and progression of generalized small-vessel disease :The SMART-MR study. Neurology. 2014;82(9):777–83.
30. Jochemsen HM, Muller M, Visseren FL, Scheltens P, Vincken KL, Mali WP, et al. Blood pressure and progression of brain atrophy the SMART-MR study. JAMA Neurol. 2013;70(8):1046–53.
31. Van Der Veen PH, Muller M, Vincken KL, Hendrikse J, Mali WPTM, Van Der Graaf Y, et al. Longitudinal Relationship between Cerebral Small-Vessel Disease and Cerebral Blood Flow. Stroke. 2015;46(5):1233–8.
32. Zwartbol MHT, Van Der Kolk AG, Ghaznawi R, Van Der Graaf Y, Hendrikse J, Geerlings MI, et al. Intracranial Vessel Wall Lesions on 7T MRI (Magnetic Resonance Imaging): Occurrence and Vascular Risk Factors: The SMART-MR Study. Stroke. 2019;50(1):88–94.
33. Ghaznawi R, Geerlings MI, Jaarsma-Coes M, Hendrikse J, de Bresser J. Association of White Matter Hyperintensity Markers on MRI and Long-term Risk of Mortality and Ischemic Stroke: The SMART-MR Study. Neurology. 2021;96(17):e2172–83.
34. Rissanen I, Lucci C, Ghaznawi R, Hendrikse J, Kappelle LJ, Geerlings MI. Association of Ischemic Imaging Phenotype With Progression of Brain Atrophy and Cerebrovascular Lesions on MRI: The SMART-MR Study. Neurology. 2021;97(11):e1063–74.
35. Ghaznawi R, Geerlings MI, Jaarsma-Coes MG, Zwartbol MHT, Kuijf HJ, van der Graaf Y, et al. The association between lacunes and white matter hyperintensity features on MRI: The SMART-MR study. J Cereb Blood Flow Metab. 2019;39(12):2486–96.
36. Brand N, Jolles J. Learning and Retrieval Rate of Words Presented Auditorily and Visually. J Gen Psychol. 1985 Apr 1;112(2):201–10.

37. Osterrieth PA. Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire. [Test of copying a complex figure; contribution to the study of perception and memory.]. Arch Psychol (Geneve). 1944;30:206–356.
38. Robertson IH, Ward T, Ridgeway V, Nimmo-Smith I. The structure of normal human attention: The Test of Everyday Attention. J Int Neuropsychol Soc. 1996 Nov;2(6):525–34.
39. Burgess PW, Shallice T. Bizarre responses, rule detection and frontal lobe lesions. Cortex. 1996 Jun;32(2):241–59.
40. Wilkins AJ, Shallice T, McCarthy R. Frontal lesions and sustained attention. Neuropsychologia. 1987;25(2):359–65.
41. Schmand B, Geerlings MI, Jonker C, Lindeboom J. Reading ability as an estimator of premorbid intelligence: does it remain stable in emergent dementia? J Clin Exp Neuropsychol. 1998 Feb;20(1):42–51.
42. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.
43. Lezak MD, Howieson DB, Loring DW, Fischer JS. Neuropsychological assessment. Oxford University Press, USA; 2004.
44. Wechsler D. Wechsler adult intelligence scale. Arch Clin Neuropsychol. 1955;
45. Franssens BT, Nathoe HM, Leiner T, Van Der Graaf Y, Visseren FLJ. Relation between cardiovascular disease risk factors and epicardial adipose tissue density on cardiac computed tomography in patients at high risk of cardiovascular events. Eur J Prev Cardiol. 2017;24(6):660–70.
46. van 't Klooster CC, Nathoe HM, Hjortnaes J, Bots ML, Isgum I, Lessmann N, et al. Multifocal cardiovascular calcification in patients with established cardiovascular disease; prevalence, risk factors, and relation with recurrent cardiovascular disease. IJC Hear Vasc. 2020;27:100499.
47. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte MJ, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990 Mar;15(4):827–32.
48. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, et al. Coronary Artery Disease - Reporting and Data System (CAD-RADS): An Expert Consensus Document of SCCT, ACR and NASCI: Endorsed by the ACC. JACC Cardiovasc Imaging. 2016 Sep;9(9):1099–113.
49. Goessens BMB, Visseren FLJ, de Nooijer J, van den Borne HW, Algra A, Wierdsma J, et al. A pilot-study to identify the feasibility of an Internet-based coaching programme for changing the vascular risk profile of high-risk patients. Patient Educ Couns. 2008;73(1):67–72.
50. Lafeber M, Grobbee DE, Bots ML, Thom S, Webster R, Rodgers A, et al. The Evening versus Morning Polypill Utilization Study: The TEMPUS rationale and design. Eur J Prev Cardiol. 2014;21(4):425–33.
51. Lafeber M, Grobbee DE, Schrover IM, Thom S, Webster R, Rodgers A, et al. Comparison of a morning polypill, evening polypill and individual pills on LDL-cholesterol, ambulatory blood pressure and adherence in high-risk patients; A randomized crossover trial. Int J Cardiol. 2015;181:193–9.
52. Goessens BMB, Visseren FLJ, Sol BGM, de Man-Van Ginkel JM, Van Der Graaf Y. A randomized, controlled trial for risk factor reduction in patients with symptomatic vascular disease: The multidisciplinary Vascular Prevention by Nurses Study (VENUS). Eur J Prev Cardiol. 2006;13(6):996–1003.
53. Sol BGM, van der Graaf Y, Goessens BMB, Visseren FLJ. Social support and change in vascular risk factors in patients with clinical manifestations of vascular diseases. Eur J Cardiovasc Nurs [Internet]. 2009;8(2):137–43. Available from: http://dx.doi.org/10.1016/j.ejcnurse.2008.10.005