The prospective studies of atherosclerosis (proof-ATHERO) consortium: design and rationale

Tschiderer, L.; Seekircher, L.; Klingenschmid, G.; Izzo, R.; Baldassarre, D.; Iglseder, B.; ... ; Willeit, P.

Gerontology

Clinical Section / Original Paper

Gerontology 2020;66:447–459
DOI: 10.1159/000508498

Received: January 29, 2020
Accepted: May 7, 2020
Published online: July 1, 2020

The Prospective Studies of Atherosclerosis (Proof-ATHERO) Consortium: Design and Rationale

Lena Tschiderer[a] Lisa Seekircher[a] Gerhard Klingenschmid[a] Raffaele Izzo[b] Damiano Baldassarre[c, d] Bernhard Iglseder[e, f] Laura Calabresi[g] Jing Liu[h] Jackie F. Price[i] Jang-Ho Bae[j, k] Frank P. Brouwers[l] Eric de Groot[m] Caroline Schmidt[n] Göran Bergström[o, p] Gülay Aşçi[q] Paolo Gresele[r] Shuhei Okazaki[s] Kostas Kapellas[t] Manuel F. Landecho[u] Naveed Sattar[v] Stefan Agewall[w] Zhi-Yong Zou[x] Christopher D. Byrne[y] Prabath W.B. Nanayakkara[z] Aikaterini Papagianni[A] Miles D. Witham[B] Enrique Bernal[C] Robert Ekart[D] Michiel A. van Agtmael[E] Mario F. Neves[F] Eiichi Sato[G] Marat Ezhov[H] Matthew Walters[I] Michael H. Olsen[J] Radojica Stolić[K] Dorota A. Zozulińska-Ziółkiewicz[L] Markolf Hanefeld[M] Daniel Staub[N] Michiaki Nagai[O] Pythia T. Nieuwkerk[P] Menno V. Huisman[Q] Akihiko Kato[R] Hirokazu Honda[S] Grace Parraga[T] Dianna Magliano[U] Rafael Gabriel[V] Tatjana Rundek[W] Mark A. Espeland[X] Stefan Kiechl[a, Y] Johann Willeit[a] Lars Lind[Z] Jean Philippe Empana[1] Eva Lonn[2, 3] Tomi-Pekka Tuomainen[4] Alberico Catapano[g, 5] Kuo-Liong Chien[6] Dirk Sander[7, 8] Maryam Kavousi[9] Joline W.J. Beulens[β] Michiel L. Bots[γ] Michael J. Sweeting[δ, ε] Matthias W. Lorenz[ζ] Peter Willeit[a, ε] Proof-ATHERO Study Group

[a]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria; [b]Department of Advanced Biochemical Sciences, Federico II University, Naples, Italy; [c]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy; [d]Centro Cardiologico Monzino IRCCS, Milan, Italy; [e]Department of Geriatric Medicine, Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft GmbH Christian-Doppler-Klinik, Salzburg, Austria; [f]Department of Geriatric Medicine, Paracelsus Medical University, Salzburg, Austria; [g]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [h]Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [i]Usher Institute, University of Edinburgh, Edinburgh, UK; [j]Heart Center, Konyang University Hospital, Daejeon, South Korea; [k]Department of Cardiology, Konyang University College of Medicine, Daejeon, South Korea; [l]Department of Cardiology, Haga Teaching Hospital, The Hague, The Netherlands; [m]Imagelabonline and Cardiovascular, Eindhoven/Lunteren, The Netherlands; [n]Wallenberg Laboratory for Cardiovascular Research, University of Gothenburg, Gothenburg, Sweden; [o]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [p]Department of Clinical Physiology, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden; [q]Nephrology Department, Ege University School of Medicine, Bornova-Izmir, Turkey; [r]Division of Internal and Cardiovascular Medicine, Department of Medicine, University of Perugia, Perugia, Italy; [s]Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan; [t]Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, SA, Australia; [u]Department of Internal Medicine, University Clinic of Navarra, Navarra, Spain; [v]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [w]Oslo University Hospital Ullevål and Institute of Clinical Sciences, University of Oslo, Oslo, Norway; [x]Institute of Child and Adolescent Health, School of Public Health, Peking University, Beijing, China; [y]Human Development and Health Academic Unit, Faculty of Medicine, The Institute of Developmental Sciences, University of Southampton – Southampton General Hospital, Southampton, UK; [z]Department of Clinical Neurophysiology, Amsterdam UMC, Amsterdam, The Netherlands; [A]University Department of Nephrology, Hippokration General Hospital, Thessaloniki, Greece; [B]AGE Research Group, NIHR Newcastle Biomedical Research Centre, Newcastle University and Newcastle-upon-Tyne Hospitals Trust, Newcastle, UK; [C]Infectious Diseases

karger@karger.com
www.karger.com/ger

Peter Willeit
Department of Neurology
Medical University of Innsbruck, Anichstrasse 35
AT–6020 Innsbruck (Austria)
peter.willeit@i-med.ac.at

Unit, Reina Sofia Hospital, Murcia, Spain; [D]Department of Dialysis, University Medical Centre Maribor, Maribor, Slovenia; [E]Department of Internal Medicine Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands; [F]Department of Clinical Medicine, State University of Rio de Janeiro, Rio de Janeiro, Brazil; [G]Division of Nephrology, Shinmatsudo Central General Hospital, Chiba, Japan; [H]Laboratory of Lipid Disorders, National Medical Research Center of Cardiology, Moscow, Russia; [I]School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK; [J]Department of Internal Medicine, Holbaek Hospital, University of Southern Denmark, Odense, Denmark; [K]Department of Internal Medicine, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; [L]Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznan, Poland; [M]Center for Clinical Studies, Technical University Dresden, Dresden, Germany; [N]Department of Angiology, University Hospital Basel, Basel, Switzerland; [O]Department of Internal Medicine, General Medicine and Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan; [P]Department of Medical Psychology, Amsterdam UMC – Location AMC, Amsterdam, The Netherlands; [Q]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; [R]Blood Purification Unit, Hamamatsu University Hospital, Hamamatsu, Japan; [S]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [T]Department of Medical Biophysics, Western University, London, ON, Canada; [U]Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, VIC, Australia; [V]National School of Public Health, Instituto de Salud Carlos III, Madrid, Spain; [W]Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA; [X]Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA; [Y]VASCage GmbH, Research Centre on Vascular Ageing and Stroke, Innsbruck, Austria; [Z]Department of Medicine, Uppsala University, Uppsala, Sweden; [1]Paris Cardiovascular Research Centre (PARCC), University Paris Descartes, Paris, France; [2]Department of Medicine and Population Health Research Institute, McMaster University, Hamilton, ON, Canada; [3]Hamilton General Hospital, Hamilton, ON, Canada; [4]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio Campus, Kuopio, Finland; [5]IRCCS Multimedica, Milan, Italy; [6]Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan; [7]Department of Neurology, Benedictus Hospital Tutzing and Feldafing, Feldafing, Germany; [8]Department of Neurology, Technische Universität München, Munich, Germany; [9]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands; [β]Department of Epidemiology and Biostatistics, Amsterdam UMC – Location Vumc, Amsterdam, The Netherlands; [γ]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [δ]Department of Health Sciences, University of Leicester, Leicester, UK; [ε]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; [ζ]Department of Neurology, Goethe University, Frankfurt am Main, Germany

Keywords

Prospective studies · Consortium · Individual-participant data · Atherosclerosis · Repeat measurements · Cardiovascular disease

Abstract

Atherosclerosis – the pathophysiological mechanism shared by most cardiovascular diseases – can be directly or indirectly assessed by a variety of clinical tests including measurement of carotid intima-media thickness, carotid plaque, ankle-brachial index, pulse wave velocity, and coronary artery calcium. The Prospective Studies of Atherosclerosis (Proof-ATHERO) consortium (https://clinicalepi.i-med.ac.at/research/proof-athero/) collates de-identified individual-participant data of studies with information on atherosclerosis measures, risk factors for cardiovascular disease, and incidence of cardiovascular diseases. It currently comprises 74 studies that involve 106,846 participants from 25 countries and over 40 cities. In summary, 21 studies recruited participants from the general population (n = 67,784), 16 from high-risk populations (n = 22,677), and 37 as part of clinical trials (n = 16,385). Baseline years of contributing studies range from April 1980 to July 2014; the latest follow-up was until June 2019. Mean age at baseline was 59 years (standard deviation: 10) and 50% were female. Over a total of 830,619 person-years of follow-up, 17,270 incident cardiovascular events (including coronary heart disease and stroke) and 13,270 deaths were recorded, corresponding to cumulative incidences of 2.1% and 1.6% per annum, respectively. The consortium is coordinated by the Clinical Epidemiology Team at the Medical University of Innsbruck, Austria. Contributing studies undergo a detailed data cleaning and harmonisation procedure before being incorporated in the Proof-ATHERO central database. Statistical analyses are be-

Lena Tschiderer and Lisa Seekircher contributed equally to this work. Members and affiliations of the Collaborators Committee are listed at end of the paper.

ing conducted according to pre-defined analysis plans and use established methods for individual-participant data meta-analysis. Capitalising on its large sample size, the multi-institutional collaborative Proof-ATHERO consortium aims to better characterise, understand, and predict the development of atherosclerosis and its clinical consequences.

Introduction

Cardiovascular diseases (CVD) are the most common cause of death and disability worldwide. According to recent estimates from the Global Burden of Disease Study, about 18 million people die of CVD in a year, which account for over 30% of all global deaths [1]. The pathophysiological mechanism shared by many CVD is atherosclerosis, a gradual and progressive hardening and narrowing of the arteries over the course of life. Initial atherosclerotic alterations can be found as early as in young adulthood [2, 3] and involve endothelial dysfunction, inflammation, and deposition of fat [4]. Advanced atherosclerotic lesions are characterised by the formation of atherosclerotic plaque that can destabilise, rupture, or fissure, and can ultimately lead to acute vessel occlusion or formation of a local thrombus with dislocation into distal arteries and thereby clinical sequelae [4].

Clinical and subclinical atherosclerosis can be directly or indirectly assessed using a range of different clinical tests which are simple, safe, and non-invasive, and therefore amenable for use in large-scale studies (Fig. 1). One of the imaging techniques for atherosclerosis most frequently used is the assessment of carotid intima-media thickness (cIMT). Using B-mode high-resolution ultrasound, the distance between the adventitia-media interface and the intima-lumen interface of the carotid arterial wall is quantified. Spatial resolution of this imaging technique is approximately 50 μm axially and 200 μm laterally. Ultrasound-based cIMT is considered as a marker of the early stage of atherosclerosis. It is related to unfavourable levels of traditional cardiovascular risk factors [5, 6] and has been shown to be in good accordance with "true" cIMT determined in histological studies [7]. Furthermore, increased cIMT has been associated with increased risk of cardiovascular events [8, 9].

Other scalable and commonly available measures to ascertain vessel wall pathology and dysfunction include carotid plaque [10, 11], ankle-brachial index [12], pulse wave velocity [13], and the coronary artery calcium score [14–16] (Fig. 1). As reviewed recently [17], these measures have several strengths and weaknesses. cIMT, carotid plaque, ankle-brachial index, and pulse wave velocity are non-invasive and cost-effective markers, which are therefore relatively easy to implement in large clinical studies. However, disadvantages include measurement error and lack of standardisation in measurement protocols for cIMT, specificity of ankle-brachial index [12], and the error associated with the measurement of travelled distance for pulse wave velocity [18]. The coronary artery calcium score directly quantifies the presence of calcification in coronary arteries [19]. In contrast to the other mentioned markers, coronary artery calcification is assessed with computed tomography, which is more costly and exposes the study participant to radiation, thereby limiting large-scale assessments.

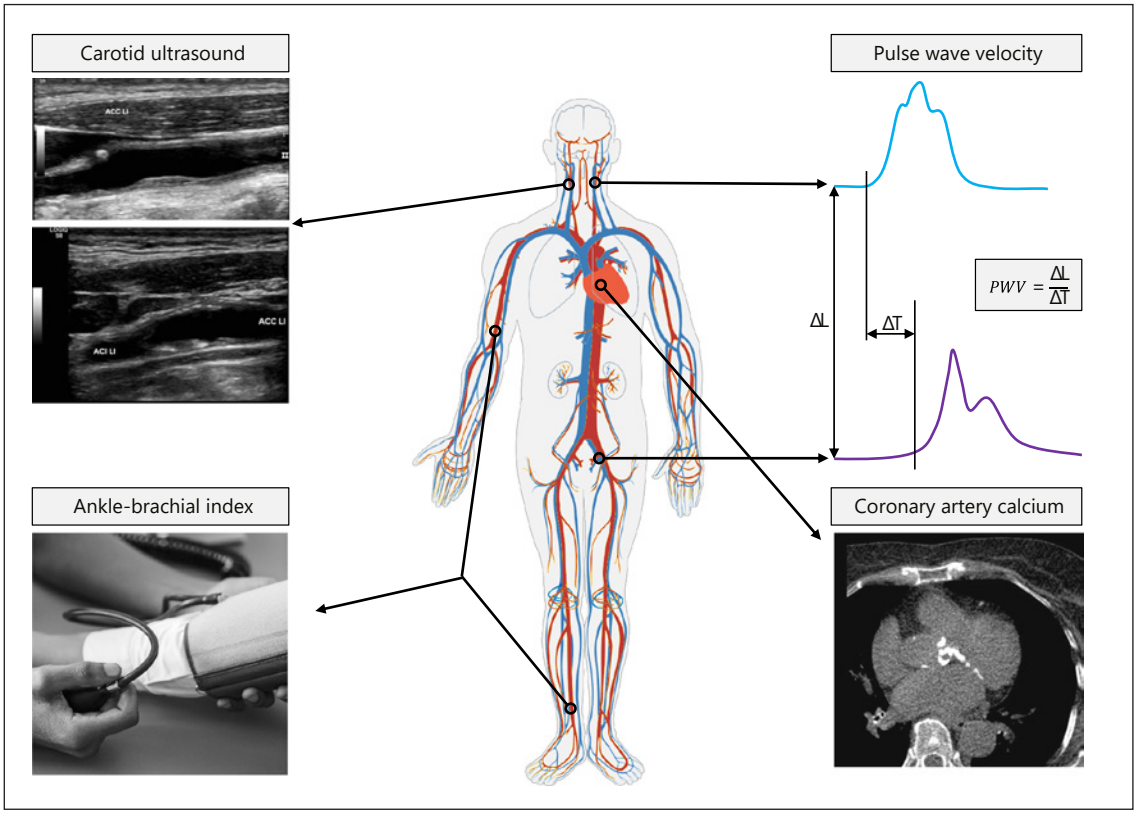
According to the 2019 European Society of Cardiology Guidelines for the diagnosis and management of chronic coronary syndromes, atherosclerotic plaque detection by carotid artery ultrasound, assessment of coronary artery calcium score with computed tomography, and measurement of the ankle-brachial index may be considered as risk modifiers in cardiovascular risk assessment in asymptomatic subjects [19]. Because atherosclerosis typically develops over a long period of time and only causes symptoms at an advanced stage, these measures are important tools in clinical practice to quantify atherosclerosis burden and might help inform treatment decisions.

The Prospective Studies of Atherosclerosis (Proof-ATHERO) consortium is an international consortium that brings together individual-participant data from prospective cohorts with detailed information on atherosclerosis, covariates, and incidence of CVD outcomes. The present report provides a description of the broad aims of the Proof-ATHERO consortium and the principal methodology involved in collating, harmonising, and analysing study data.

Design

Objectives

Capitalising on its large sample size and the comprehensive information available, the overarching aims of the Proof-ATHERO consortium are: (i) to better characterise the natural history, communalities, and differences of different atherosclerosis measures; (ii) to provide novel insight into the determinants of atherosclerosis development and progression; and (iii) to investigate clinical consequences of atherosclerosis. In contrast to prior reports in individual studies, the large-scale data of Proof-



Color version available online

Fig. 1. Measures for quantifying atherosclerosis.

ATHERO enables the study team to conduct power-demanding analyses, including (i) characterisation of atherosclerosis trajectories over time; (ii) determination of the shapes of associations (e.g., linear vs. curvilinear vs. threshold effects); (iii) study of potential effect modifiers (e.g., age, sex, medication, or different lifestyle factors such as smoking habit); (iv) direct comparisons of the added predictive value of different atherosclerosis measures over and beyond assessment of conventional risk factors; and (v) reliable evaluation of atherosclerosis measures as surrogate markers for clinically manifest CVD endpoints. Overall, Proof-ATHERO aims to analyse worldwide available data to deliver results based on the highest scientific evidence.

Inclusion Criteria

Prospective cohorts are eligible for inclusion in the Proof-ATHERO consortium if they were observational studies or clinical trials that: (i) have assessed one or more atherosclerosis measures (i.e., cIMT, carotid plaque, ankle-brachial index, pulse wave velocity, and coronary artery calcium) repeatedly (i.e., at two or more time points); (ii) have ascertained comprehensive information on CVD risk factors (e.g., lifestyle, blood-based markers, history of disease, and medication intake); and (iii) have recorded incident CVD outcomes using well-defined criteria.

A crucial foundation for the Proof-ATHERO consortium was provided by the PROG-IMT project [20]. This initiative led by Matthias Lorenz at the Goethe University at Frankfurt am Main had collated and analysed individual-participant data on the progression of cIMT and, for instance, yielded milestone publications on the association of cIMT progression with future CVD risk in the general population [8], in people with type-2 diabetes [21], and in people at high cardiovascular risk [22]. When the PROG-IMT project was completed in 2017, a majority of contributing studies (83%) decided to continue the fruitful collaboration as part of the Proof-ATHERO consortium and to jointly investigate scientific questions which go beyond the initial aims of the PROG-IMT project. The commitment by these studies gave a unique head start to the Proof-ATHERO consortium and enabled efficient data accrual at the beginning of the initiative.

Table 1. Availability of atherosclerosis measures in the Proof-ATHERO consortium as of 24 January 2020

Study acronym or first author	cIMT	Carotid diameter	Carotid plaque	ABI	PWV	CACS	Study acronym or first author	cIMT	Carotid diameter	Carotid plaque	ABI	PWV	CACS
General population							Clinical trials						
AIR	●	●	●	○	○	○	ACAPS	●	○	○	○	○	○
ARIC	●	●	●	●	●	○	ALLO-IMT	●	○	○	○	●	○
BRUN	●	●	●	●	○	○	ASAP-NL	●	●	*	○	○	○
CAPS	●	●	●	○	○	○	ATIC	●	○	○	○	○	○
CCCC	●	○	●	○	○	○	AUDITOR	●	○	○	○	○	○
CHS	●	●	●	●	○	○	BAS	●	○	○	○	●	○
CMCS-BEIJING	●	●	●	○	○	○	BK REGISTRY II	●	○	●	○	○	○
DIWA	●	●	*	○	○	○	CAMERA	●	○	●	○	○	○
EAS	●	○	●	*	○	○	CAPTIVATE	●	●	○	○	○	○
EPICARDIAN	●	●	○	○	○	○	CERDIA	●	○	○	○	○	○
EVA	●	●	●	○	○	○	CONTRAST	●	○	●	○	○	○
HOORN	●	*	○	*	*	○	EGE STUDY	●	○	●	○	*	*
INVADE	●	○	●	●	○	○	ENHANCE	●	○	●	○	○	○
JHS	●	○	●	●	●	●	FACIT	●	●	○	○	○	○
KIHD	●	○	●	○	○	○	GRACE	●	○	*	*	○	○
MESA	●	*	●	●	○	●	Gresele	●	○	○	*	○	○
NOMAS-INVEST	●	●	●	○	○	○	HART	●	○	*	*	○	○
PIVUS	●	●	●	*	○	○	KIMVASC	●	○	○	○	*	○
PLIC	●	○	●	○	○	○	LIFE-ICARUS	●	●	●	○	○	○
ROTTERDAM	●	●	●	*	*	*	Masia	●	○	●	●	○	○
SAPHIR	●	●	●	○	○	○	MAVET	●	○	○	○	○	○
High-risk populations							MEDICLAS	●	●	○	○	*	○
BK REGISTRY	●	○	●	○	○	○	MG600	●	●	●	○	●	○
CREED	●	○	○	○	○	○	Nakamura II	●	●	*	○	*	○
CSN	●	●	●	○	○	○	OPAL	●	*	○	○	○	○
Ekart	●	○	*	○	○	○	PERIOCARDIO	●	●	○	○	*	○
HD-IMT	●	●	○	○	○	○	PREVEND IT	●	○	○	○	○	○
Honda	●	○	○	○	○	○	RADIANCE I	●	●	○	○	○	○
IMPROVE	●	●	●	○	○	○	RADIANCE II	●	●	○	○	○	○
Kato	●	○	●	*	*	○	REGRESS	●	○	○	○	○	○
Landecho	●	○	●	○	○	*	RIS	●	●	*	○	○	○
NIGUARDA-MONZINO	●	●	●	○	○	○	Safarova	●	○	*	*	*	○
OSACA2	●	●	○	○	○	○	SECURE	●	○	*	*	○	○
Papagianni	●	○	●	○	○	○	STARR	●	○	*	*	○	○
POPROSTU	●	●	○	○	○	○	STOP-NIDDM	●	○	○	○	○	○
RIAS	●	○	*	○	○	○	VITAL	●	○	○	○	○	○
SPARC	●	○	●	○	○	○	WELCOME	●	○	●	○	○	○
3SCO	●	●	○	○	○	○							

●, available and provided; *, available but not provided; ○, not available. ABI, ankle-brachial index; CACS, coronary artery calcium score; cIMT, carotid intima-media thickness; PWV, pulse wave velocity. Full study names and references are provided in online supplementary Table S1.

Identification and incorporation of new eligible studies is ongoing, and we invite researchers to contact the coordinating centre if they wish to contribute to the Proof-ATHERO consortium.

Atherosclerosis Measures

Data have been sought from investigators on carotid ultrasound parameters, ankle-brachial index, pulse wave velocity, and coronary artery calcium at baseline and any subsequent re-examinations during follow-up. Atherosclerosis measures assessed by the individual studies are summarised in Table 1. Parameters based on carotid ultrasound are being collected systematically on up to twelve sites (common carotid artery, carotid bifurcation, and internal carotid artery; left and right side; near and far wall) and include cIMT, vessel diameter, presence of

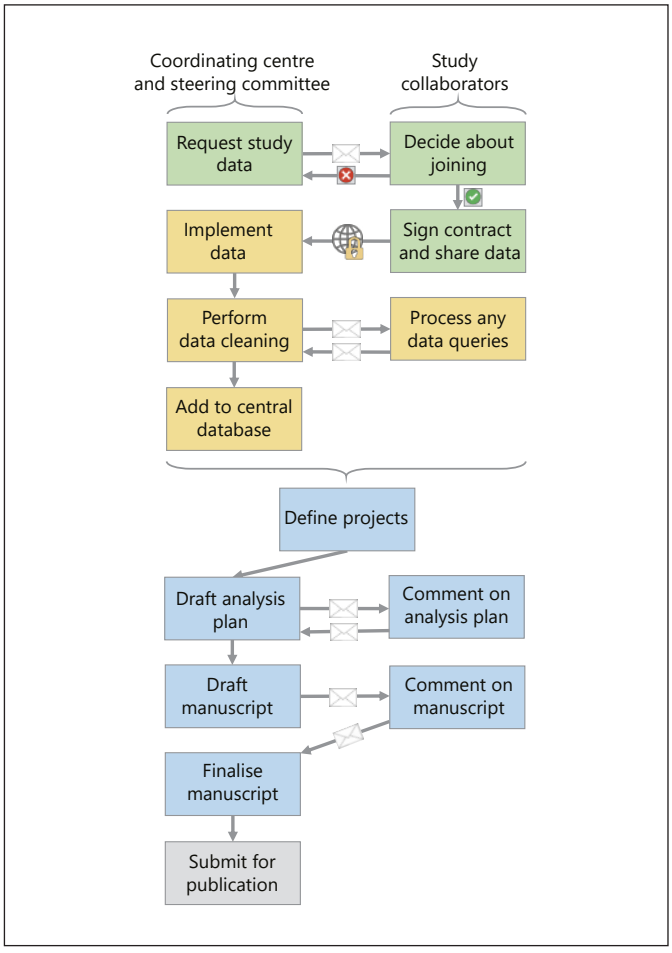


Fig. 2. Data management and analysis workflow in the Proof-ATHERO consortium.

plaques (yes vs. no), number of plaques, plaque thickness (height in mm), plaque area in a longitudinal view (in mm^2), and plaque morphology according to the Gray-Weale classification [23]. The methodologies which studies used to measure cIMT and carotid plaque are summarised in online supplementary Tables S2 and S3 (see www.karger.com/doi/10.1159/000508498 for all online suppl. material), respectively.

Participant Characteristics at the Baseline and Follow-Up Surveys

Data on participant characteristics at baseline and follow-up surveys have been sought from investigators on age, sex, ethnicity, socio-economic status, smoking, systolic and diastolic blood pressure, body mass index, lipid markers (e.g., total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides), markers of inflammation (e.g., C-reactive protein, fibrinogen, leukocyte count), markers of dysglycaemia (e.g., fasting glucose, glycated haemoglobin), use of medication (e.g., antihypertensive, antidiabetic, lipid-lowering medication), and pre-existing diseases (e.g., coronary heart disease, stroke, diabetes, or hypertension). Furthermore, in clinical trials, information on the type of interventions (and dosages, if appropriate) and on adherence to allocated regimens have been collated.

Incident Disease Outcomes

Data on incident disease outcomes have been collated predominantly on fatal and non-fatal CVD events, including myocardial infarction, angina pectoris, and subtypes of stroke. Details on the ascertainment of prevalent and incident CVD are provided in online supplementary Table S4. Studies assessed prevalent CVD at study baseline using self-report only or supplemented by objective criteria. The vast majority of the studies used objective criteria rather than self-report only for assessing incident coronary heart disease (93%) and incident stroke (90%). Outcomes were classified according to International Classification of Diseases-10 coding (e.g., I20–I25 for coronary heart disease and I61–I69 for stroke) or study-specific coding systems. In addition, information on cause-specific death has been sought. In 15 studies, cause of death was ascertained based on the death certificate; 44 studies supplemented the death certificate with information from additional sources (e.g., medical records, autopsy findings).

Coordination of the Consortium

The Proof-ATHERO consortium is coordinated by the Clinical Epidemiology Team at the Medical University of Innsbruck, Austria. An outline of the processes involved in Proof-ATHERO coordination is provided in Figure 2. Standardised data request forms are sent to eligible studies, inviting them to participate in the initiative. Upon receipt of study data, data cleaning and harmonisation are performed by a dedicated data management team using a range of tools for detecting inconsistencies and ambiguities in the data. Any queries arising during this process are clarified through direct correspondence with study investigators. Upon completion of the data management process, study data are stored in a central database at the coordinating centre. The data management system of the coordinating centre has been implemented in SAS 9.4. Proposals for analyses can be submitted by all members of the Proof-ATHERO study group (i.e., all named investigators of studies contributing data to Proof-ATHERO) via

Table 2. Design and descriptive summary of studies in the Proof-ATHERO consortium

Study acronym or first author	Country	Population source	Population type	Years of baseline	n	Female, %	Mean age, years (SD)
General population							
AIR	Sweden	Population register	General population	1995–97	391	0	58 (0.1)
ARIC	USA	Household listings	General population	1986–90	15,121	55	54 (6)
BRUN	Italy	Population register	General population	1990	933	49	59 (11)
CAPS	Germany	Electoral rolls	General population	1995–00	6,970	51	51 (13)
CCCC	Taiwan	Community screening	General population	1990–91	3,602	53	55 (12)
CHS	USA	Medicare lists	General population	1989–93	5,888	57	73 (6)
CMCS-BEIJING	China	Population register	General population	2002	1,324	53	60 (8)
DIWA	Sweden	Population register	General population	2001–04	644	100	64 (0.3)
EAS	Scotland	GP lists	General population	1987–88	1,115	50	64 (6)
EPICARDIAN	Spain	Population register	General population	1993–04	446	59	68 (12)
EVA	France	Electoral rolls	General population	1992–93	1,135	59	65 (3)
HOORN	The Netherlands	Population register	General population	1999–01	780	50	69 (7)
INVADE	Germany	Insurance company	General population	2001–03	3,908	59	68 (8)
JHS	USA	Household listings	General population	2000–04	3,883	63	55 (13)
KIHD	Finland	Population register	General population	1987–89	1,399	0	52 (6)
MESA	USA	Household listings	General population	2000–02	6,814	53	62 (10)
NOMAS-INVEST	USA	Random digit dialling	General population	1993–01	856	62	66 (8)
PIVUS	Sweden	Population register	General population	2001–04	1,016	50	70 (0.0)
PLIC	Italy	Hospital	General population	1998–03	1,782	59	55 (11)
ROTTERDAM	The Netherlands	Population register	General population	1990–93	7,983	61	71 (10)
SAPHIR	Austria	GP lists/advert	General population	1999–02	1,794	37	52 (6)
High-risk populations							
BK REGISTRY	South Korea	Hospital	CHD	2000–07	1,000	44	60 (10)
CREED	Italy	Hospital	On haemodialysis/CAPD	1997–98	138	41	60 (16)
CSN	Italy	GP lists	Hypertension	1980–14	14,158	44	53 (13)
Ekart	Slovenia	Hospital	On haemodialysis	1996–05	54	50	55 (15)
HD-IMT	Serbia	Hospital	On haemodialysis	2004–05	85	39	59 (12)
Honda	Japan	Hospital	On haemodialysis	2005–07	313	39	61 (13)
IMPROVE	Multinational	Hospital/community screening	≥3 CVD RFs	2004–05	3,703	52	64 (5)
Kato	Japan	Hospital	On haemodialysis	2008–09	284	30	64 (12)
Landecho	Spain	Hospital	Early kidney disease	1999–11	250	12	55 (10)
NIGUARDA-MONZINO	Italy	Hospital	Lipid clinic patients/CVD RFs	1984–10	1,564	41	56 (12)
OSACA2	Japan	Hospital	≥1 atherosclerotic RF	2000–03	291	40	65 (9)
Papagianni	Greece	Hospital	On haemodialysis	2001	83	46	58 (15)
POPROSTU	Poland	Hospital	T1DM	1999	96	33	24 (6)
RIAS	Switzerland	Hospital	≥1 CVD RF/CVD	1999–00	145	43	64 (13)
SPARC	Canada	Hospital	Carotid plaque	2006–08	349	43	71 (9)
3SCO	Japan	Hospital	≥1 CVD RF	2007	164	74	80 (6)
Clinical trials							
ACAPS	USA	Mailing lists/ community screening	LDL-C 130–189 mg/dL	1989–90	919	48	62 (8)
ALLO-IMT	Scotland	Hospital	Ischaemic stroke/TIA	2009–10	80	43	68 (10)
ASAP-NL	The Netherlands	Hospital	Heterozygous FH	1997–98	325	61	49 (11)
ATIC	The Netherlands	Hospital	Chronic renal failure	2001–02	93	43	53 (12)
AUDITOR	Multinational	Hospital	Obesity+metabolic syndrome	2005–06	661	49	63 (6)
BAS	China	Community screening	cIMT↑	2010	125	63	57 (5)
BK REGISTRY II	South Korea	Hospital	Coronary stent	2000–03	205	32	60 (10)
CAMERA	Scotland	Hospital/GP lists	CHD	2009–11	173	23	63 (8)
CAPTIVATE	Multinational	Hospital	Heterozygous FH	2004–05	719	NP	NP
CERDIA	The Netherlands	Hospital	T2DM	1999–01	250	53	58 (11)
CONTRAST	Multinational	Hospital	On haemodialysis	2004–09	714	38	64 (14)
EGE STUDY	Turkey	Hospital	On haemodialysis	2005–06	644	46	59 (14)
ENHANCE	Multinational	Hospital	Heterozygous FH	2002–06	720	49	47 (9)
FACIT	The Netherlands	Municipal/blood bank registries	General population	2000–01	819	28	60 (6)
GRACE	Multinational	Hospital	Dysglycaemia+CVD RFs/CVD	2003–05	1,189	36	63 (8)

Table 2 (continued)

Study acronym or first author	Country	Population source	Population type	Years of baseline	n	Female, %	Mean age, years (SD)
Gresele	Multinational	Hospital	Peripheral arterial disease	2003–05	442	21	67 (9)
HART	Canada	Hospital/GP lists	CVD/DM+≥1 CVD RF	1999–00	925	24	69 (7)
KIMVASC	Scotland	GP lists	CVD/hypertension/DM	2011–12	80	45	77 (5)
LIFE-ICARUS	Multinational	Hospital	Hypertension+LVH	1996–97	83	27	67 (6)
Masia	Spain	Hospital	HIV+≥2 CVD RFs	2006–07	68	10	52 (11)
MAVET	Australia	Newspaper advert	Smokers	1994–95	408	54	64 (6)
MEDICLAS	Multinational	Hospital	HIV	2003–05	48	0	42 (10)
MG600	Brazil	Hospital	Hypertension	2010–11	35	100	55 (7)
Nakamura II	Japan	Hospital	Chronic renal failure	2001	50	40	53 (7)
OPAL	Multinational	Hospital/GP lists/other[a]	General population	1997–99	866	100	59 (7)
PERIOCARDIO	Australia	Health facilities	Aboriginal Australians	2010–12	273	42	41 (10)
PREVEND IT	The Netherlands	Population register	Microalbuminuria	1998–99	864	35	51 (12)
RADIANCE I	Multinational	Hospital	Heterozygous FH	2003–04	904	51	46 (13)
RADIANCE II	Multinational	Hospital	Mixed dyslipidaemia	2003–06	752	36	57 (8)
REGRESS	The Netherlands	Hospital	CHD+TC 155–310 mg/dL	1989–91	255	0	56 (8)
RIS	Sweden	Hospital	Hypertension+≥1 CVD RF	1987–89	164	0	66 (5)
Safarova	Russia	Hospital	CHD	2007–09	60	0	55 (6)
SECURE	Canada	Hospital	CVD/DM+≥1 CVD RF	1994–95	731	24	66 (7)
STARR	Multinational	Hospital/GP lists/other[b]	Dysglycaemia	2001–03	1,320	55	53 (11)
STOP-NIDDM	Germany	High-risk population screening	Dysglycaemia	1996–98	119	42	54 (7)
VITAL	The Netherlands	Hospital	Indication for statin use	2002–04	199	41	49 (12)
WELCOME	UK	Hospital	NAFLD	2010–11	103	42	51 (11)
Total				**1980–14**	**106,846**	**50**	**59 (10)**

CAPD, continuous ambulatory peritoneal dialysis; CHD, coronary heart disease; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolaemia; GP, general practitioner; HIV, human immunodeficiency virus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NAFLD, non-alcoholic fatty liver disease; NP, not provided; RF, risk factor; SD, standard deviation; TC, total cholesterol; TIA, transient ischaemic attack; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. Full study names and references are provided in online supplementary Table S1. [a]Existing ongoing population-based cohorts and advertisements in local print and broadcast media. [b]Public advertising and news reports in the media, internet items, referral from relatives, poster displays, diabetes screening fairs, and direct mailing campaigns.

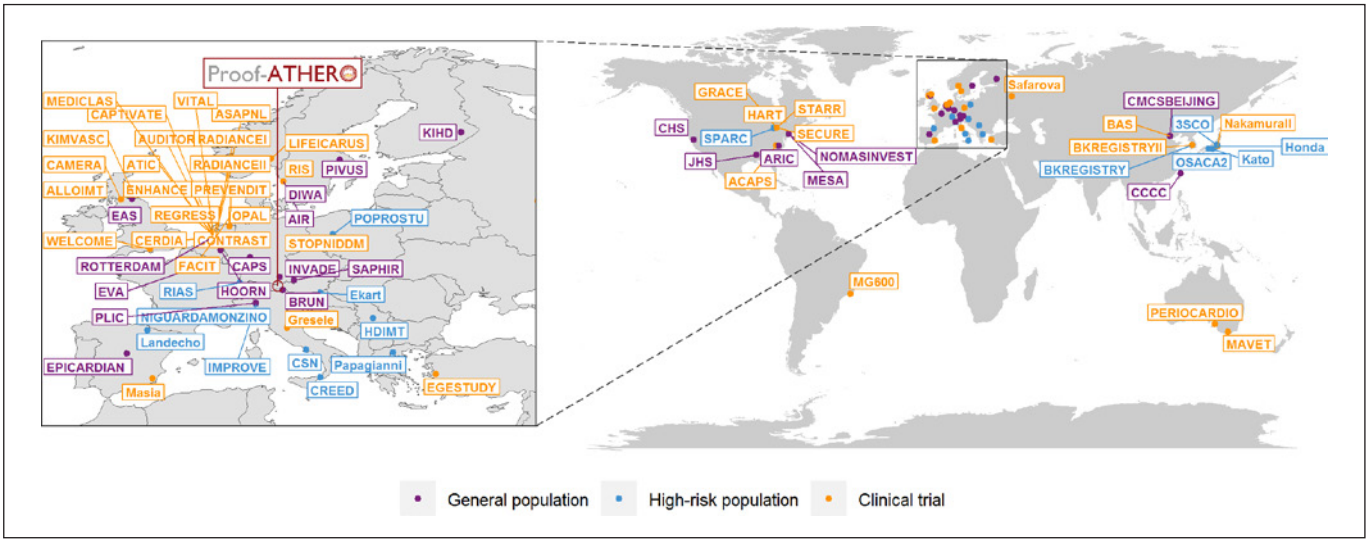
the consortium's webpage. Upon receipt, proposals are reviewed by a dedicated Proof-ATHERO steering committee, which then allocates resources at the coordinating centre according to resource availability and scientific priority of the project. For contractual reasons, data are stored and analysed exclusively at the Proof-ATHERO Coordinating and Statistics Centres (Medical University of Innsbruck and University of Cambridge). At each step, from the development of a statistical analysis plan, to the conduct of statistical analyses, and the creation of a manuscript draft, investigators of contributing studies and expert panels are contacted for feedback and comments, therefore making use of the broad and diverse community of experts in the field involved in the initiative.

General Approach to Statistical Analyses

For each scientific project, statistical analyses will be performed according to a pre-specified analysis plan. Statistical analyses will follow established methods in the analysis of individual-participant data [24–29]. Generally, the multi-level structure of data (e.g., multiple cohorts) will be taken into account by combining study-specific estimates using meta-analytical methods or by using mixed regression models with appropriate specification of random effects. Analyses will also involve assessments of between-study heterogeneity. More details on specific analytical methods will be provided in publications resulting from each scientific project.

Characteristics of Contributing Studies

As of 24 January 2020, a total of 74 studies involving 106,846 participants are part of the Proof-ATHERO consortium. The designs of contributing studies and key study-level characteristics are shown in Table 2. In summary, 21 studies recruited participants from the general population, 16 studies were conducted in patient popula-



Color version available online

Fig. 3. Location of studies contributing data to the Proof-ATHERO consortium as of 24 January 2020. Full study names and references are provided in online supplementary Table S1.

tions with specific pre-existing diseases (e.g., with diabetes), and 37 studies were randomised controlled trials covering a range of different patient populations. The numbers of people enrolled in these three types of studies were 67,784, 22,677, and 16,385, respectively. Baseline years ranged from April 1980 to July 2014; the last follow-up was in June 2019. Mean age at baseline was 59 years (standard deviation: 10); 50% of participants were female. Figure 3 demonstrates the geographical location of contributing studies (full study names and references are provided in online supplementary Table S1). Study locations were spread across four continents and are based in 25 countries and over 40 cities. The median duration of follow-up (i.e., the time from baseline to first event or end of follow-up) was 6.1 years (interquartile range: 2.7–10.4). Over a total of 830,619 person-years of follow-up, 17,270 incident CVD events and 13,270 deaths were recorded, corresponding to cumulative incidences of 2.1% and 1.6% per annum, respectively. As Proof-ATHERO evolves further, up-to-date information on contributing studies are being made available on the consortium's webpage at https://clinicalepi.i-med.ac.at/research/proof-athero/.

Initial Set of Hypotheses to Be Tested

The large sample size and variety of data in Proof-ATHERO will enable us to test several hypotheses that are particularly power-hungry and could therefore not be addressed by previous studies. For instance, it is unclear whether cIMT progression could serve as a surrogate marker for hard cardiovascular outcomes in clinical trials [30–32]. Second, given conflicting results of prior individual studies [33–39], the comparative predictive value of cIMT measurements at different locations of the carotid artery remains to be determined in detail. Third, building on the initial insights of our recent literature-based meta-analysis [40], Proof-ATHERO will characterise in detail the association of cIMT with long-term risk of developing carotid plaque. In general, as a large-scale consortium of patient-level data, the high statistical power and consistent approach to statistical analysis and outcome definitions of Proof-ATHERO will help to address the aforementioned and other questions more reliably than previously possible.

Strengths and Limitations

Proof-ATHERO is a large consortium with a huge amount of data on atherosclerosis, applying consistent approaches to data harmonisation and analysis. By inclusion of data from 25 countries and different clinical settings, the generalisability of findings will be of particular value. Our study also has several limitations. First, there were some differences between studies in how they assessed atherosclerosis measures and clinical outcomes. To address this issue, we collect meticulously a variety of study-specific characteristics, enabling us to quantify and better understand the impact of these differences in future analyses. Second, comprehensive data cleaning and harmonisation is a serious, often underestimated challenge. However, we managed to

develop a sophisticated data management system that enables us to transparently and effectively handle various datasets with different structures provided by the individual studies. Third, the current focus of available data lies on cIMT due to participation of multiple studies previously involved in the PROG-IMT project [20]. Fourth, there exist several other markers for atherosclerosis, such as the assessment of endothelial function [41] with flow-mediated dilation or peripheral arterial tone, which have not been collected within Proof-ATHERO yet. Since the consortium is designed to continuously collect new data as they become available, coverage of other atherosclerosis markers will be expanded over time.

Conclusion

The Proof-ATHERO consortium is a multi-institutional collaborative project that is coordinated at the Medical University of Innsbruck, Austria. The consortium brings together large-scale data from prospective studies in the field of atherosclerosis. Proof-ATHERO combines data on CVD risk factors, repeat assessments of atherosclerosis, and clinical outcomes with cutting-edge data management and analytical tools. Building on these strengths, Proof-ATHERO will help to better characterise, understand, and predict the development of atherosclerosis and its clinical consequences.

Acknowledgements

This paper was prepared using data of the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Jackson Heart Study (JHS), and the Multi-Ethnic Study of Atherosclerosis (MESA) obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) and does not necessarily reflect the opinions or views of the ARIC, CHS, JHS, MESA, or NHLBI. An anonymised individual-participant data dataset from CREED was kindly provided by Prof. Zoccali, Prof. Tripepi, and Prof. Mallamaci from the Institute of Biomedicine (CNR), Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, Reggio Calabria, Italy, on the basis on their "public use" policy. We thank the CREED group for sharing their valuable data. We are grateful to the team members of the VASCage project (FFG COMET K-Project 843536) for their support.

Statement of Ethics

All studies contributing data to Proof-ATHERO have previously reported results and have obtained relevant local ethics approval and participants' consent. The data provided by each study remain entirely the property of the principal investigators of that study and are held in confidence by the Proof-ATHERO coordinating centre. To safeguard the identity of individuals at all stages of the analysis and to ensure compliance with data protection legislation and confidentiality guidelines, study data are transferred to the coordinating centre using encrypted connections. De-identified data are being stored securely in a central database at the coordinating centre, protected by firewalls and accessible only to authorised staff. Participants and collaborating studies have the right to withdraw from the Proof-ATHERO consortium at any time and without giving reasons.

Disclosure Statement

L. Tschiderer reports grants from the Dr.-Johannes-and-Hertha-Tuba Foundation during the conduct of the study and non-financial support from Sanofi outside the submitted work. L. Seekircher reports non-financial support from Sanofi outside the submitted work. G. Klingenschmid reports non-financial support from Sanofi and Pfizer outside the submitted work. N. Sattar reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Sanofi, and Pfizer and grants from Boehringer Ingelheim outside the submitted work. S.E. Kjeldsen reports personal fees from Merck Darmstadt, MSD Whitehouse Station, Sanofi Paris, and Takeda Chicago outside the submitted work. S. Kiechl reports grants from Austrian Promotion Agency FFG outside the submitted work. G.D. Norata reports grants from Pfizer and Amgen and personal fees from Sanofi, Amgen, Alnylam, and Novartis outside the submitted work. P. Willeit reports grants from the Dr.-Johannes-and-Hertha-Tuba Foundation and the Austrian Science Fund FWF during the conduct of the study. Other authors have no conflicts of interest.

Funding Sources

This work was funded by the Austrian Science Fund (FWF) (P 32488) and the Dr.-Johannes-and-Hertha-Tuba Foundation. Funders of individual studies contributing to the present analysis are listed on the Proof-ATHERO webpage (https://clinicalepi.i-med.ac.at/research/proof-athero/studies/).

Author Contributions

L. Tschiderer, L. Seekircher, G. Klingenschmid, and P. Willeit are part of the coordinating centre and are responsible for data management and data analysis of the Proof-ATHERO consortium. L. Tschiderer and L. Seekircher drafted the manuscript, conducted the analyses, and interpreted the data. G. Klingenschmid interpreted the data. M.J. Sweeting provided supervision for statistical analyses. P. Willeit is responsible for the conception and design of the work, drafted the manuscript, conducted the analyses, and interpreted the data. All other authors were responsible for data acquisition. All authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Collaborators Committee

Maria V. Manzi[1], Costantino Mancusi[1], Helmuth Steinmetz[2], Matthias Sitzer[2,3], Mauro Amato[4], Fabrizio Veglia[4], Elena Tremoli[4], Samuela Castelnuovo[5], Dong Zhao[6], Miao Wang[6], Stela McLachlan[7], Moo-Sik Lee[8,9], Hyun-Woong Park[9], Salim Yusuf[10,11], Diederick E. Grobbee[12], Frank L. J. Visseren[13], John J. P. Kastelein[14], Wiek van Gilst[15], Folkert W. Asselbergs[16], Muriel P. C. Grooteman[17], Peter J. Blankestijn[18], Ercan Ok[19], Giuseppe Guglielmini[20], Rino Migliacci[21], Lena Bokemark[22], Kazuo Kitagawa[23], Michael Skilton[24], Lisa M. Jamieson[25], Oscar Beloqui[26], David Preiss[27], Philip C. Calder[28,29], Lokpal Bhatia[28,29], Pieter M. ter Wee[17], Chrysostomos Dimitriadis[30], Radovan Hojs[31,32], Sebastjan Bevc[31,32], Peter Reiss[33,34], Marit G. A. van Vonderen[35], Ana R. Cunha[36], Mayuko Amaha[37], Tsukasa Nakamura[37], Tatyana Balakhonova[38], Maya Safarova[39], Jesse Dawson[40], Peter Higgins[40], Kristian Wachtell[41], Sverre E. Kjeldsen[41], Aleksandar Jovanovic[42], Tatjana Lazarevic[43], Aleksandra Araszkiewicz[44], Aleksandra Uruska[44], Dariusz Naskręt[44], Beat Frauchiger[45], Heiko Uthoff[46], Kazuomi Kario[47], Satoshi Hoshide[47], Erik Stroes[14], Edith Beishuizen[48], Tadao Akizawa[49], Thapat Wannarong[50,51], Sophia Zoungas[52], John McNeil[52], Alfonsa Friera[53], Carmen Suarez[54], Femke Rutters[55], Petra Elders[56], Coen D. A. Stehouwer[57], Moise Desvarieux[58,59], Pierre Ducimetiere[60], Matthieu Plichart[61,62], Hertzel C. Gerstein[10,11], Ari Voutilainen[63], Jussi Kauhanen[63], Liliana Grigore[64], Giuseppe D. Norata[64,65], Ta-Chen Su[66], Pei-Chun Chen[67], Hung-Ju Lin[66], Holger Poppert[68], Horst Bickel[69], and M. Arfan Ikram[70].

Affiliations of Members of the Collaborators Committee

[1]Department of Advanced Biochemical Sciences, Federico II University, Naples, Italy; [2]Department of Neurology, Goethe University, Frankfurt am Main, Germany; [3]Department of Neurology, Klinikum Herford, Herford, Germany; [4]Centro Cardiologico Monzino IRCCS, Milan, Italy; [5]Centro Dislipidemie, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [6]Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [7]Usher Institute, University of Edinburgh, Edinburgh, UK; [8]Department of Preventive Medicine, Konyang University, Daejeon, South Korea; [9]Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, South Korea; [10]Department of Medicine and Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [11]Hamilton General Hospital, Hamilton, Ontario, Canada; [12]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; [13]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands; [14]Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; [15]Department of Experimental Cardiology, University Medical Center Groningen, Groningen, the Netherlands; [16]Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands; [17]Department of Nephrology, Amsterdam UMC, Amsterdam, the Netherlands; [18]Department of Nephrology, University Medical Center Utrecht, Utrecht, the Netherlands; [19]Nephrology Department, Ege University School of Medicine, Bornova-Izmir, Turkey; [20]Division of Internal and Cardiovascular Medicine, Department of Medicine, University of Perugia, Perugia, Italy; [21]Division of Internal Medicine, Cortona Hospital, Cortona, Italy; [22]Wallenberg Laboratory for Cardiovascular Research, University of Gothenburg, Gothenburg, Sweden; [23]Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan; [24]Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Sydney, NSW, Australia; [25]Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, SA, Australia; [26]Department of Internal Medicine, University Clinic of Navarra, Navarra, Spain; [27]MRC Population Health Research Unit, Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK; [28]Faculty of Medicine, University of Southampton – Southampton General Hospital, Southampton, UK; [29]Southampton NIHR Biomedical Research Centre, University Hospital Southampton – Southampton General Hospital, Southampton, UK; [30]University Department of Nephrology, Hippokration General Hospital, Thessaloniki, Greece; [31]Department of Nephrology, University Medical Centre Maribor, Maribor, Slovenia; [32]Faculty of Medicine, University of Maribor, Maribor, Slovenia; [33]Department of Global Health, Amsterdam UMC- Location AMC, Amsterdam, the Netherlands; [34]Amsterdam Institute for Global Health and Development, University of Amsterdam, Amsterdam, the Netherlands; [35]Department of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, the Netherlands; [36]Department of Clinical Medicine, State University of Rio de Janeiro, Rio de Janeiro, Brazil; [37]Division of Nephrology, Shinmatsudo Central General Hospital, Chiba, Japan; [38]Ultrasound Vascular Laboratory, National Medical Research Center of Cardiology, Moscow, Russia; [39]Atherosclerosis Department, National Medical Research Center of Cardiology, Moscow, Russia; [40]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [41]Department of Cardiology, Oslo University Hospital, Oslo, Norway; [42]Faculty of Medicine, University of Prishtina, Prishtina\ Kosovska Mitrovica, Serbia; [43]Faculty of Medicine, University of Kragujevac, Kragujevac, Serbia; [44]Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznan, Poland; [45]Department of Internal Medicine, Kantonsspital Frauenfeld, Frauenfeld, Switzerland; [46]Department of Angiology, University Hospital Basel, Basel, Switzerland; [47]Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; [48]Department of Internal Medicine, HMC+ (Bronovo), the Hague, the Netherlands; [49]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [50]Stroke Prevention & Atherosclerosis Research Centre, Western University, London, Canada; [51]Department of Internal Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [52]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; [53]Radiology Department, Universidad Autónoma de Madrid, Madrid, Spain; [54]Internal Medicine Department, Universidad Autónoma de Madrid, Madrid, Spain; [55]Department of Epidemiology & Biostatistics, Amsterdam UMC- Location Vumc, Amsterdam, the Netherlands; [56]Department of General Practice, Amsterdam UMC- Location Vumc, Amsterdam, the Netherlands; [57]Department of Internal Medicine and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, the Netherlands; [58]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA; [59]METHODS Core, Centre de Recherche Epidémiologie et Statistique Par-

is Sorbonne Cité (CRESS), Institut National de la Santé et de la Recherche Médicale (INSERM) UMR 1153, Paris, France; [60]Faculty of Medicine, University Paris Descartes, Paris, France; [61]Paris Cardiovascular Research Centre (PARCC), University Paris Descartes, Paris, France; [62]Assistance Publique, Hôpitaux de Paris, Hôpital Broca, Paris, France; [63]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio Campus, Kuopio, Finland; [64]SISA Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo, Italy; [65]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [66]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [67]Clinical Informatics & Medical Statistics Research Center, Chang Gung University, Taoyuan, Taiwan; [68]Department of Neurology, Technische Universität München, Munich, Germany; [69]Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany; [70]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands.

References

1 Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al.; GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018 Nov;392(10159):1736–88.

2 Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea; preliminary report. J Am Med Assoc. 1953 Jul;152(12):1090–3.

3 McNamara JJ, Molot MA, Stremple JF, Cutting RT. Coronary artery disease in combat casualties in Vietnam. JAMA. 1971 May; 216(7):1185–7.

4 Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011 May;473(7347): 317–25.

5 Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. Stroke. 1999 Apr; 30(4):841–50.

6 Müller-Scholden L, Kirchhof J, Morbach C, Breunig M, Meijer R, Rücker V, et al. Segment-specific association of carotid-intima-media thickness with cardiovascular risk factors - findings from the STAAB cohort study. BMC Cardiovasc Disord. 2019 Apr;19(1):84.

7 Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation. 1986 Dec;74(6): 1399–406.

8 Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, et al.; PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet. 2012 Jun;379(9831):2053–62.

9 Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012 Aug; 308(8):796–803.

10 Kiechl S, Willeit J. The natural course of atherosclerosis. Part I: incidence and progression. Arterioscler Thromb Vasc Biol. 1999 Jun;19(6):1484–90.

11 Kiechl S, Willeit J; Bruneck Study Group. The natural course of atherosclerosis. Part II: vascular remodeling. Arterioscler Thromb Vasc Biol. 1999 Jun;19(6):1491–8.

12 Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al.; Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008 Jul;300(2):197–208.

13 Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014 Feb;63(7):636–46.

14 Kramer CK, Zinman B, Gross JL, Canani LH, Rodrigues TC, Azevedo MJ, et al. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. BMJ. 2013 Mar;346:f1654.

15 Kavousi M, Desai CS, Ayers C, Blumenthal RS, Budoff MJ, Mahabadi AA, et al. Prevalence and Prognostic Implications of Coronary Artery Calcification in Low-Risk Women: A Meta-analysis. JAMA. 2016 Nov; 316(20):2126–34.

16 Chaikriangkrai K, Jhun HY, Palamaner Subash Shantha G, Bin Abdulhak A, Sigurdsson G, Nabi F, et al. Coronary artery calcium score as a predictor for incident stroke: systematic review and meta-analysis. Int J Cardiol. 2017 Jun;236:473–7.

17 Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, et al. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: Endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. Atherosclerosis. 2015 Aug;241(2):507–32.

18 Rajzer MW, Wojciechowska W, Klocek M, Palka I, Brzozowska-Kiszka M, Kawecka-Jaszcz K. Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph. J Hypertens. 2008 Oct;26(10):2001–7.

19 Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2019;100:106.

20 Lorenz MW, Bickel H, Bots ML, Breteler MM, Catapano AL, Desvarieux M, et al.; PROG-IMT Study Group. Individual progression of carotid intima media thickness as a surrogate for vascular risk (PROG-IMT): rationale and design of a meta-analysis project. Am Heart J. 2010 May;159(5):730–736.e2.

21 Lorenz MW, Price JF, Robertson C, Bots ML, Polak JF, Poppert H, et al. Carotid intima-media thickness progression and risk of vascular events in people with diabetes: results from the PROG-IMT collaboration. Diabetes Care. 2015 Oct;38(10):1921–9.

22 Lorenz MW, Gao L, Ziegelbauer K, Norata GD, Empana JP, Schmidtmann I, et al.; PROG-IMT study group. Predictive value for cardiovascular events of common carotid intima media thickness and its rate of change in individuals at high cardiovascular risk - Results from the PROG-IMT collaboration. PLoS One. 2018 Apr;13(4):e0191172.

23 Gray-Weale AC, Graham JC, Burnett JR, Byrne K, Lusby RJ. Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. J Cardiovasc Surg (Torino). 1988 Nov-Dec;29(6):676–81.

24 Thompson S, Kaptoge S, White I, Wood A, Perry P, Danesh J; Emerging Risk Factors Collaboration. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. Int J Epidemiol. 2010 Oct;39(5):1345–59.

25 Jackson D, White I, Kostis JB, Wilson AC, Folsom AR, Wu K, et al.; Fibrinogen Studies Collaboration. Systematically missing confounders in individual participant data meta-analysis of observational cohort studies. Stat Med. 2009 Apr;28(8):1218–37.

26 Pennells L, Kaptoge S, White IR, Thompson SG, Wood AM, Tipping RW, et al.; Emerging Risk Factors Collaboration. Assessing risk prediction models using individual participant data from multiple studies. Am J Epidemiol. 2014 Mar;179(5):621–32.

27 Sanderson J, Thompson SG, White IR, Aspelund T, Pennells L. Derivation and assessment of risk prediction models using case-cohort data. BMC Med Res Methodol. 2013 Sep; 13(1):113.
28 White IR. Multivariate random-effects meta-analysis. Stata J. 2009;9(1):40–56. Available from: http://www.stata-journal.com/article.html?article=st0156
29 Riley RD, Price MJ, Jackson D, Wardle M, Gueyffier F, Wang J, et al. Multivariate meta-analysis using individual participant data. Res Synth Methods. 2015 Jun;6(2):157–74.
30 Espeland MA, O'leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. Curr Control Trials Cardiovasc Med. 2005 Mar;6(1):3.
31 Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT, Nallamothu BK. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. Am Heart J. 2010 Oct;160(4):701–14.
32 Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, et al. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. J Am Coll Cardiol. 2010 Dec;56(24):2006–20.
33 O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med. 1999 Jan; 340(1):14–22.
34 Chambless LE, Folsom AR, Clegg LX, Sharrett AR, Shahar E, Nieto FJ, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol. 2000 Mar; 151(5):478–87.
35 Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke. 2006 Jan;37(1):87–92.
36 Polak JF, Szklo M, O'Leary DH. Associations of Coronary Heart Disease with Common Carotid Artery Near and Far Wall Intima-Media Thickness: The Multi-Ethnic Study of Atherosclerosis. J Am Soc Echocardiogr. 2015 Sep;28(9):1114–21.
37 Lind L, Gigante B, Borne Y, Mälarstig A, Sundström J, Ärnlöv J, et al. The plasma protein profile and cardiovascular risk differ between intima-media thickness of the common carotid artery and the bulb: A meta-analysis and a longitudinal evaluation. Atherosclerosis. 2020 Feb;295:25–30.
38 Bots ML, de Jong PT, Hofman A, Grobbee DE. Left, right, near or far wall common carotid intima-media thickness measurements: associations with cardiovascular disease and lower extremity arterial atherosclerosis. J Clin Epidemiol. 1997 Jul;50(7):801–7.
39 Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC. Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J. 2002 Jun;23(12):934–40.
40 Tschiderer L, Klingenschmid G, Seekircher L, Willeit P. Carotid intima-media thickness predicts carotid plaque development: meta-analysis of seven studies involving 9341 participants. Eur J Clin Invest. 2020 Apr; 50(4):e13217.
41 Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation. 2007 Mar; 115(10):1285–95.