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Decline in risk of recurrent cardiovascular events in the period 1996 to 2014 partly explained by better treatment of risk factors and less subclinical atherosclerosis

Gijs F.N. Berkelmans [a,1], Yolanda van der Graaf [b,1], Jannick A.N. Dorresteijn [a,1], Gert Jan de Borst [c,1], Maarten J. Cramer [d,1], L. Jaap Kappelle [e,1], Jan Westerink [a,1], Frank L.J. Visseren [a,*,1], On behalf of the SMART study group

[a] Department of Vascular Medicine, University Medical Center Utrecht, The Netherlands
[b] Julius Center, University Medical Center Utrecht, The Netherlands
[c] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[d] Department of Cardiology, University Medical Centre Utrecht, The Netherlands
[e] Department of Neurology, University Medical Center Utrecht, Utrecht, The Netherlands

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ABSTRACT

Background: To quantify the decline in recurrent major cardiovascular events (MCVE) risk in patients with clinically manifest vascular disease between 1996 and 2014 and to assess whether the improvements in recurrent MCVE-risk can be explained by reduced prevalence of risk factors, more medication use and less subclinical atherosclerosis.

Methods and results: The study was conducted in the Second Manifestations of ARTerial disease (SMART) cohort in patients entering the cohort in the period 1996–2014. The prevalence of risk factors and subclinical atherosclerosis was measured at baseline. Incidence rates per 100 person-years for recurrent MCVE (including stroke, myocardial infarction, retinal bleeding, retinal infarction, terminal heart failure, sudden death, fatal rupture of abdominal aneurysm) were calculated, stratified by the year of study enrolment. For the attributable risk of changes in risk factors, risk factor treatment, and subclinical atherosclerosis on the incidence rates of recurrent MCVE, adjusted rate ratios were estimated with Poisson regression. 7216 patients had a median follow-up of 6.5 years (IQR 3.4–9.9). The crude incidence of recurrent MCVE declined by 53% between 1996 and 2014 (from 3.68 to 1.73 events per 100 person-years) and by 75% adjusted for age and sex. This improvement in vascular prognosis was 36% explained by changes in risk factors, medication use and subclinical atherosclerosis.

Conclusion: The risk of recurrent MCVE in patients with clinically manifest vascular disease has strongly declined in the period between 1996 and 2014. This is only partly attributable to lower prevalence of risk factors, improved medication use and less subclinical atherosclerosis.

1. Introduction

The incidence of cardiovascular disease (CVD) has decreased in recent decades, and the 2010 Global Burden of Disease study [1] for Western countries has estimated a 20–50% decrease in the years of life lost due to premature mortality as a result of CVD between 1990 and 2010. However, vascular diseases remain the leading cause of premature death [2,3]. The incidence of cardiovascular morbidity and mortality has decreased due to improved primary prevention and by improved vascular revascularisation [4–10]. For example, the 43% decline in coronary heart disease mortality rates between 2000 and 2010 was 49% attributed to improved revascularisation procedures and for 39% attributed to improved risk factor treatment [11].

In addition, secondary prevention measures have improved over the last 10–20 years. Between 2003 and 2008 in patients hospitalized with coronary artery disease, overall adherence to 6 performance measures (start on aspirin within 24 h, discharge on aspirin, discharge on beta-blockers, patients with low ejection fraction discharged on ACE inhibitors, smoking cessation counseling, and use of lipid-lowering medications) increased from 72% to 94% [12]. Mean blood pressure and lipid levels decreased between 1999 and 2013 in patients with coronary artery disease [13]. Also, a steady increase in the use of lipid-

* Corresponding author at: Department of Vascular Medicine, University Medical Centre Utrecht, PO Box 85500, 3508, GA, Utrecht, The Netherlands.
E-mail address: F.L.J.Visseren@umcutrecht.nl (F.L.J. Visseren).
[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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lowering therapy and aspirin has been observed in the periods 1975–1986 and 1997–2007, which likely contributed to an absolute 5% decrease in 2-year all-cause mortality for patients hospitalized after an acute myocardial infarction [14]. However, it is unknown whether the long-term risk decreased for recurrent major cardiovascular events (MCVE) and for all-cause mortality, and to what extent this is caused by improved risk factor management or treatment of less advanced stages of atherosclerosis.

Earlier in life and more widespread use of lipid-lowering and blood pressure-lowering medication for primary and secondary prevention and a decline in smoking may have changed the face of vascular disease to a more benign, stable phenotype. However, as there is a wide variation in the extent of atherosclerotic lesions in the arterial wall between patients with similar risk factors, other factors than the classical risk factors need to be considered [15]. This variation is likely due to a combination of genetic susceptibility, interactions between other risk factors, life-style, and duration of exposure to risk factors [16]. One of the other factors that might give insight into the extent of atherosclerotic lesions might be measures of subclinical atherosclerosis, for example carotid intima-media thickness (cIMT).

The aim of the present study is to quantify the decline in recurrent MCVE-risk in patients with clinically manifest vascular disease between 1996 and 2014 and to assess whether the improvements in recurrent MCVE-risk can be explained by reduced prevalence of risk factors, more medication use and less subclinical atherosclerosis.

2. Methods

2.1. Study population

Patients originated from the SMART (Secondary Manifest of ARTerial disease) study, an ongoing, single-center, prospective cohort study at the University Medical Centre Utrecht (UMCU). A detailed description of the study rationale and design has previously been published [17]. The study commenced in 1996, after which participating patients, aged 18–80 years, referred to the UMCU with clinically manifest atherosclerotic vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm) or cardiovascular risk factors (hyperlipidemia, diabetes, or hypertension) underwent vascular screening. Screening followed a standardized diagnostic protocol, followed by physical examinations and laboratory testing in the fasting state. For the current study, baseline data of patients included between September 1996 and March 2014, with a history of CVD, were used. Written informed consent was obtained from all participants at baseline. The study was approved by the Medical Ethics Committee of the UMCU.

2.2. Follow-up and endpoints

Patients received bi-annual health questionnaires. When a participant reported a possible event, relevant hospital documents, and laboratory and radiologic findings were collected. Cause of death was verified with general practitioners, medical specialists or relatives. All events were audited by three members of the SMART-study endpoint committee, comprised of physicians from different departments. The outcomes for the present analyses are a composite of MCVE, vascular mortality, and all-cause mortality. A composite of MCVE was established including stroke, myocardial infarction, retinal bleeding, retinal infarction, terminal heart failure, sudden death, and fatal rupture of abdominal aneurysm.

Follow-up duration was defined as the period between enrolment and first MCVE, death from any cause, date of loss to follow-up, or the preselected date of 1 March 2014. Of the 7216 participants in this study, 419 patients (5.8%) were lost to follow-up due to migration or withdrawal from the study; these patients were censored.

2.3. Risk factors and medical treatment of risk factors

Cardiovascular risk factors and the use of medication (antithrombotic, lipid-lowering, or blood pressure-lowering medication) were recorded at baseline, using a standardized diagnostic protocol consisting of a questionnaire, physical examination and laboratory testing in a fasting state. Risk factors measured in this study included age, sex, smoking, pack years, body-mass index (BMI), LDL-c, systolic blood pressure, presence of diabetes mellitus, estimated glomerular filtration rate (eGFR) and duration of CVD. LDL-c in mmol/L was estimated using the Friedewald formula up to triglycerides of 9 mmol/L [18]. Systolic blood pressure was measured every 4 min during a total of 25 min in supine position at the right brachial artery until March 1999 and 2 times in the sitting position at the right and left upper arms from March 1999 onward. In both situations, the highest mean of the blood pressure measurements on one arm was taken. Diabetes mellitus was defined as use of glucose lowering-therapy, self-reported diabetes mellitus, or two times a fasting glucose >7.0 mmol/L. eGFR was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations [19].

2.4. Clinical manifest and subclinical atherosclerosis

Clinical manifest vascular disease was registered at baseline (e.g. coronary, cerebrovascular, peripheral artery disease, and aortic abdominal aneurysm). Screening for subclinical atherosclerosis comprised of multiple clinical and radiological measurements. Direct measurements of subclinical atherosclerosis were defined as a carotid intima-media thickness (cIMT) >0.9 mm [20], an ankle-brachial index (ABI) <0.9 or >1.3, and an asymptomatic carotid artery stenosis of >50%. Subclinical atherosclerosis-associated measurements were chronic kidney disease (CKD), and a pulse pressure > 60 mm Hg (PP). CKD was defined as either 1) an eGFR <45, 2) an eGFR <60 with >30 mg/g albuminuria, or 3) any eGFR with >300 mg/g albuminuria.

2.5. Data analyses

For the descriptive analysis of baseline characteristics in different time periods, year of vascular screening was split into groups of three years, where in further analyses inclusion year as determinant is used as a continuous variable.

Data of cardiovascular risk factors were missing for systolic blood pressure in 17 patients (0.2%), for glucose measurement in 23 patients (0.3%), for diabetes mellitus status in 19 patients (0.3%), for smoking and pack-years in 42 patients (0.6%), for eGFR in 11 patients (0.2%), and for albuminuria in 258 patients (4%). For atherosclerotic burden, IMT was missing in 208 patients (3%), carotid artery stenosis in 136 patients (2%), ABI in 55 patients (0.8%) and pulse pressure in 48 patients (0.7%). Missing data for risk factors and subclinical atherosclerosis were singly imputed by weighted probability matching on the basis of multivariable regression using covariate and outcome data. Trends in cardiovascular risk factor and subclinical atherosclerosis prevalence were plotted. Crude incidence rates for vascular mortality, all-cause mortality, myocardial infarction, stroke, and the composite endpoint of MCVE were calculated stratified for year of vascular screening. To evaluate the effect of cardiovascular risk factors, medication use, subclinical atherosclerosis, and duration of CVD on the incidence rates of MCVE and all-cause mortality, adjustment was performed with Poisson regression in multiple models. In addition, stratified analyses were performed for different groups of CVD-patients separately (i.e. coronary artery disease, cerebrovascular disease, peripheral artery disease, abdominal aneurysm and polyvascular disease). To check whether possible non-proportionality during long-term follow-up did not meaningfully influence the results, a sensitivity analysis was performed in which observations were censored after five year follow-up. All statistical analyses were conducted using R version 3.2.0.

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