



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



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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.

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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-

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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.

3. Results

3.1. Baseline characteristics

Data of 7216 patients with a history of CVD included in the SMART cohort between 1996 and 2014 were used for the present analyses. Mean age was 60 ± 10 years and 74% of patients were male (Table 1). A total of 1190 recurrent MCVE and 1324 deaths occurred during a median follow-up of 6.5 (IQR 3.3–9.9) years.

3.2. Change in prevalence of cardiovascular risk factors between 1996 and 2014

The percentage of current smokers declined from 43% in 1996 to 25% in 2014 (Fig. 1). Systolic blood pressure declined from 147 ± 20 mm Hg in 1996 to 134 ± 18 mm Hg in 2014. The use of blood pressure lowering drugs increased from 59% to 75%. Plasma concentrations of LDL-c declined from 3.7 ± 1.0 mmol/L in 1996 to 2.5 ± 0.9 mmol/L in 2014. The use of lipid-lowering drugs increased from 30% in 1996 to 79% in 2014. Mean BMI of patients increased from 26.3 ± 3.4 kg/m² in 1996 to 27.1 ± 3.6 kg/m² in 2014.

3.3. Change in prevalence of subclinical atherosclerosis between 1996 and 2014

In the period 1996–2014, the prevalence of asymptomatic carotid artery stenosis decreased from 33% to 6%. In the same period, the prevalence of high IMT >0.9 mm remained unchanged: 52% in 1996–1998 and 46% in 2012–2014. The prevalence of CKD decreased from 18% in 1996 to 9% in 2014. The prevalence of ABI <0.9 or >1.3 decreased from 39% in 1996 to 18% in 2014. The prevalence of pulse pressure > 60 mm Hg, an indicator of arterial stiffness, decreased from 61% in 1996 to 30% in 2014 (Fig. 1, Supplemental Table 1).

3.4. Change in incidence rates of recurrent MCVE and all-cause mortality for different time periods between 1996 and 2014

Incidence rates decreased in the period 1996 to 2014 by 53% for recurrent MCVE from 3.68 to 1.73 events per 100 person-years (PY), by 82% for vascular mortality from 2.57 to 0.47 events per 100 PY, and by 82% for all-cause mortality from 4.55 to 0.82 events per 100 PY.

Incidence in recurrent MCVE decreased in patients with coronary artery disease, cerebrovascular disease, peripheral artery disease and polyvascular disease, but remained the same for patients with abdominal aortic aneurysm (Fig. 2; Supplemental Table 2).

3.5. Rate ratios of MCVE and all-cause mortality adjusted for changes in risk factor, medication use and subclinical atherosclerosis in different time periods between 1996 and 2014

The risk for recurrent MCVE adjusted for age and sex changed with –7% per year (rate ratio of 0.93; 95%CI 0.91–0.94). After additional adjustment for risk factors, medication use, and subclinical atherosclerosis, the change in risk for recurrent MCVE was –4% per year (adjusted rate ratio 0.96; 95%CI 0.95–0.98). Thus, for MCVE a risk reduction of 3% per year (36% of total) could be explained by changes in risk factors, medication use, and subclinical atherosclerosis (Fig. 3; Supplemental Table 3).

For vascular mortality, additional adjustment for risk factors, medication use, and subclinical atherosclerosis compared to adjustment for age and sex changed the risk from –13% to –7% per year (adjusted rate ratio 0.93; 95%CI 0.91–0.96). Thus, for vascular mortality a risk reduction of 6% per year (49% of total) could be explained by changes in risk factors, medication use, and subclinical atherosclerosis.

For all-cause mortality, additional adjustment for risk factors, medication use, and subclinical atherosclerosis compared to adjustment for age and sex changed the risk from –11% to –6% per year (rate ratio 0.94; 95% CI 0.93–0.96). Thus, for all-cause mortality a risk reduction of 5% per year (48% of total) could be explained by changes in risk factors, medication use, and subclinical atherosclerosis (Fig. 3; Supplemental Table 3).

For myocardial infarction and stroke separately, similar results were seen as for MCVE after additional adjustment for risk factors, medication use, and subclinical atherosclerosis compared to adjustment for age and sex (Supplemental Table 4).

Sensitivity analyses limiting the follow-up to 5 years for each patient after inclusion showed similar results for recurrent MCVE (adjusted rate ratio 0.96; 95% CI 0.93–0.98), for vascular mortality (adjusted rate ratio 0.95; 95% CI 0.92–0.98), and for all-cause mortality (adjusted rate ratio 0.97; 95% CI 0.95–1.00) adjusted for age, sex, cardiovascular risk factors, medication use, and subclinical atherosclerosis (Supplemental Table 5).

Table 1
Patient characteristics of the study population at baseline according to inclusion periods.

	1996–1998 (n = 748)	1999–2001 (n = 1178)	2002–2004 (n = 1333)	2005–2007 (n = 1529)	2008–2010 (n = 1369)	2011–March 2014 (n = 1059)
Number of fatal and non-fatal vascular events/person years	284/7724	347/12,086	255/11,591	175/10,603	100/5969	29/1677
Age (y)	61.3 (10.7)	59.9 (10.3)	58.7 (10.5)	59.8 (10.4)	60.8 (10.0)	60.4 (9.9)
Sex (male)	553 (74%)	915 (78%)	976 (73%)	1103 (72%)	1005 (73%)	767 (72%)
Never smoked	120 (16%)	205 (17%)	264 (20%)	334 (22%)	310 (23%)	266 (25%)
History of smoking	309 (41%)	524 (44%)	605 (45%)	775 (51%)	669 (49%)	531 (50%)
Current smoking	319 (43%)	449 (38%)	464 (35%)	420 (27%)	390 (28%)	262 (25%)
Smoking (pack-years)	25 (20)	24 (20.4)	21 (20)	19 (20)	19 (20)	18 (18)
Body mass index (kg/m ²)	26 (3.7)	26 (4)	27 (4)	27 (4)	27 (4)	27 (4)
Diabetes mellitus	175 (23%)	247 (21%)	300 (23%)	349 (23%)	297 (22%)	216 (20%)
Systolic blood pressure (mm Hg)	147 (20)	139 (22)	143 (22)	141 (21)	137 (20)	134 (18)
Diastolic blood pressure (mm Hg)	79 (11)	80 (11)	83 (12)	83 (11)	81 (11)	79 (11)
Hypertension	611 (82%)	998 (85%)	1167 (88%)	1357 (89%)	1200 (88%)	887 (84%)
Blood pressure-lowering agents	439 (59%)	821 (70%)	973 (73%)	1200 (78%)	1092 (80%)	790 (75%)
Anti-platelet/anti-coagulant agents	544 (73%)	866 (74%)	1040 (78%)	1322 (86%)	1260 (92%)	932 (88%)
Statin use	225 (30%)	531 (45%)	896 (67%)	1178 (77%)	1138 (83%)	834 (79%)
Total cholesterol (mmol/L)	5.8 (1.1)	5.5 (1.2)	5.0 (1.1)	4.4 (1)	4.5 (1.1)	4.5 (1.1)
HDL-C (mmol/L)	1.1 (0.3)	1.1 (0.3)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)
LDL-C (mmol/L)	3.7 (1.0)	3.4 (1.0)	2.9 (1.0)	2.5 (1.0)	2.6 (0.9)	2.5 (0.9)
Triglycerides (mmol/L)	2.0 (1.2)	2.1 (2.1)	1.8 (1.1)	1.5 (1.3)	1.4 (0.9)	1.6 (1.1)
eGFR (CKDepi)	73 (19)	76 (18)	77 (18)	76 (18)	75 (17)	79 (17)

All data are displayed as mean \pm SD, median (interquartile range) or number (%). HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol.

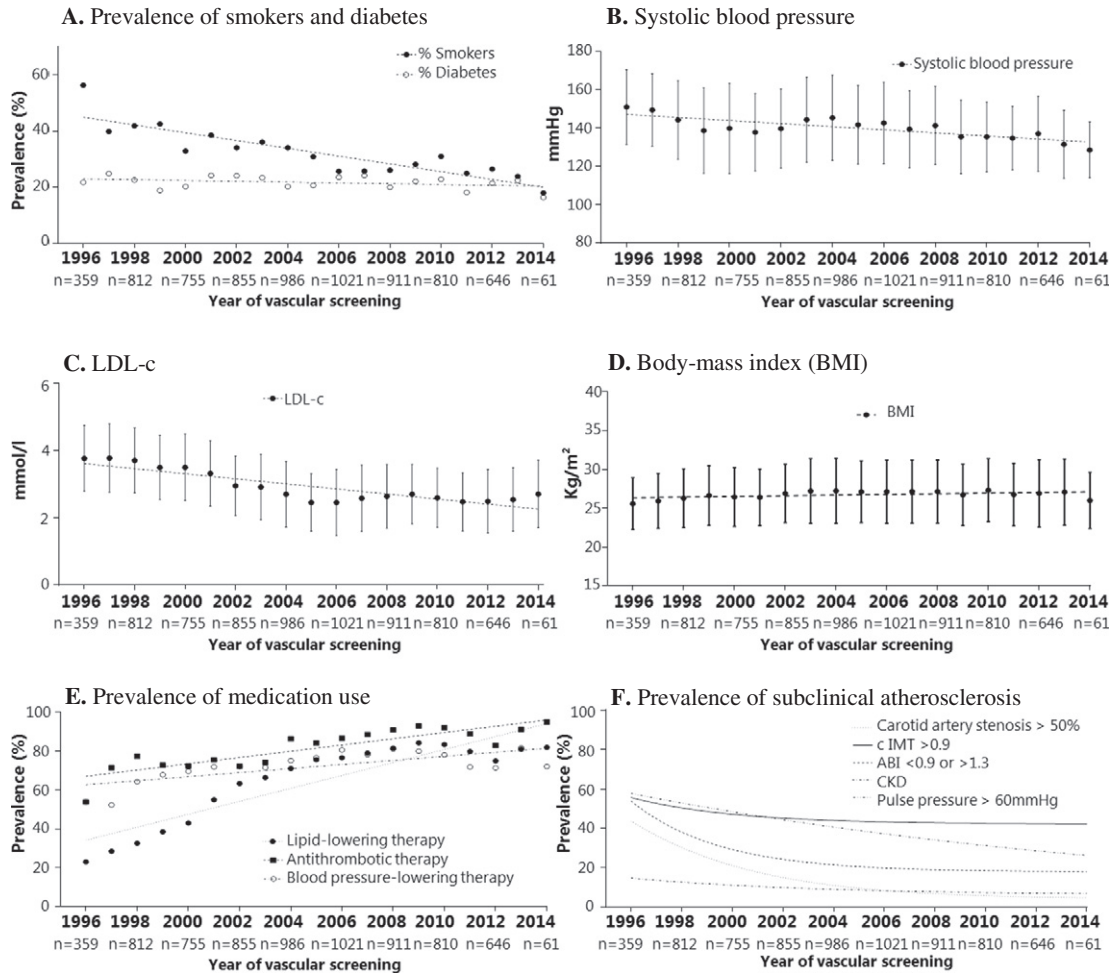


Fig. 1. Trends in risk factors (A, B, C and D), risk factor management (E) and subclinical atherosclerotic burden (F) at baseline.

4. Discussion

In this cohort study, the risk of recurrent vascular events in patients with clinical manifest vascular disease declined with 53% in the period between 1996 and 2014. The risk of vascular and all-cause mortality both decreased with 82%. These reductions are similar in patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease and polyvascular disease. In patients with abdominal aortic aneurysm a decrease in risk of recurrent events was not observed, but numbers were small. During this period, the prevalence of risk factors

and prevalence of subclinical atherosclerosis (carotid artery stenosis, cIMT, CKD, ABI, and pulse pressure) declined as well. The observed reductions in recurrent vascular events and all-cause mortality could only partially be explained by improved risk factor management and changes in the prevalence of subclinical atherosclerosis.

In the present study, the reduced risk of recurrent CVD is partially explained by improved risk factor management including a decline in the prevalence of smoking as well as a reduction of concomitant subclinical atherosclerosis indicating less advanced stages of atherosclerosis at the time of a clinical vascular event. As expected, over the years, evidence based improvements in risk factor management have resulted in improved outcome after a first cardiovascular event [3,14,21]. The improvement of risk factor management is further supported by the unchanged risk of recurrent events in patients with abdominal aortic aneurysms. In these patients, stratified analyses of risk factor levels and prevalence by year of vascular screening showed less improvement in risk factor management (data not shown).

The EUROASPIRE studies reported similar improved risk factor management and reduced prevalence of risk factors in different time periods (1994–1995, 1999–2000, 2006–2007, and 2012–2013) [13, 22]. For example, from 1999 and 2000, the prevalence of hypertension (systolic blood pressure > 140 and/or diastolic blood pressure > 90 mm Hg) decreased from 54% to 45% when compared to 2012–2013. The prevalence of LDL-c > 2.5 mmol/L decreased by 62% (from 96% to 34%) over the period 1994–2013, as a result of increased use of lipid-lowering therapy in general (18% to 90%) and in the use of high intensity statin regimens (23% to 45%) [13,22]. This is in line with the findings in the present study regarding risk factor prevalence and risk

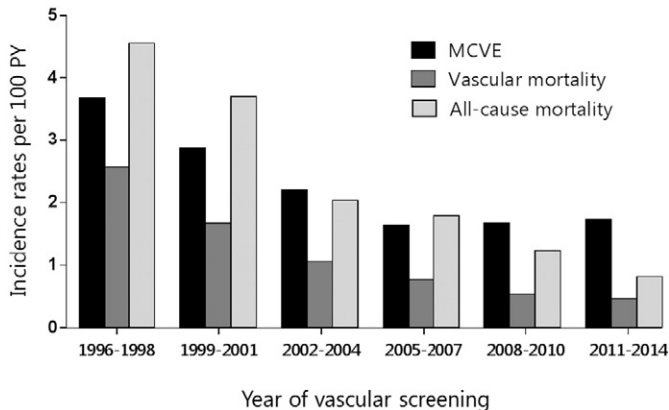


Fig. 2. Crude incidence rates of recurrent major cardiovascular events.

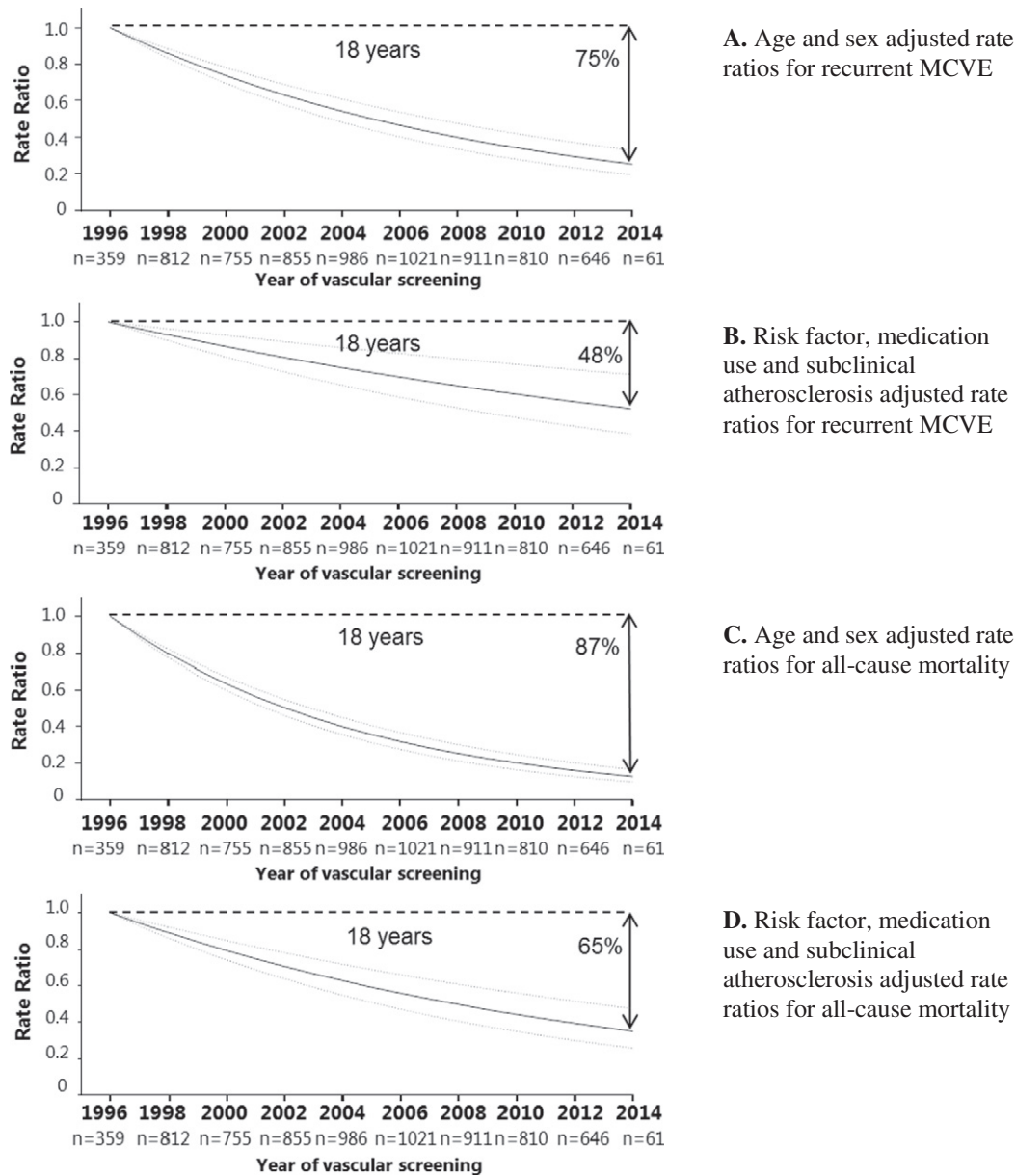


Fig. 3. Rate ratios of recurrent major cardiovascular events and all-cause mortality in the period 1996–2014.

factor management, illustrating the potential gain from adherence to lipid guidelines. It is important to note that in primary prevention this potential gain from better adherence to guidelines is even larger [23]. The change in prevalence of risk factors and improved risk factor management could be a reflection of improved adherence to guidelines such as the Recommendations of the Task Force of European and other Societies on Coronary Prevention [24,25], lower blood pressure targets, availability of statins, more attention to a healthy life-style, and public health campaigns encouraging to stop smoking.

Besides improved risk factor management and lower risk of recurrent events, it has been shown that the amount of atherosclerotic burden predicts MCVE [26]. In the present study we observed a decreasing atherosclerotic burden at the time of a clinical manifestation of vascular disease in the period 1996 to 2014. Lower atherosclerotic burden at the time of diagnosis could be a reflection of the absolute reduction in risk factors, lower exposure time to risk factors, or a reflection of enhanced detection of cardiovascular disease in an earlier stage of disease. For example, in patients suspected of coronary artery disease troponin has been implemented as a sensitive diagnostic biomarker for

the diagnosis of myocardial infarction [27]. Therefore, smaller myocardial infarctions may be detected, which were previously undetected, in patients with less atherosclerotic burden.

An important finding in our study is the still largely unexplained reduction in recurrent MCVE after adjustment for cardiovascular risk factors and subclinical vascular disease. A clearer understanding of this unexplained risk reduction could provide new opportunities for a further decrease in MCVE risk in patients with clinical manifest vascular disease. It could be speculated that part of the unexplained risk reduction could be related to unmeasured improved lifestyle changes such as lower salt intake, less saturated fatty acids, or increased physical activity [28,29]. Also, technical improvements in cardiovascular interventions (such as drug-eluting stents), and more frequent performance of revascularization may have contributed to lower risk. Early detection and improved techniques may contribute to a lower need for re-interventions and/or a lower risk for cardiovascular events after an intervention [30]. Despite the large relative reduction in the risk of recurrent MCVE, the incidence in patients with clinical manifest vascular disease remains high. In the present study the recurrent MCVE risk

was 1.7 per 100 PY, which translates to a 17% 10-year risk. Therefore, it remains of major importance to identify those patients at the highest risk for recurrent MCVE [31], and find (new) targets for risk reduction. The latest ESC/EAS guidelines of the management of dyslipidaemias suggest even lower LDL-c targets (<1.8 mmol/L for patients with CVD), stricter life-style recommendations, and intensive advice to patients with regard to all risk factors compared to previous guidelines. Also, drug adherence is even more emphasized in these guidelines, with important suggestions to improve the adherence to (multiple) drug therapies. These recommendations should further decrease future MCVE-risk [32].

Incidence of cardiovascular events in patients with and without CVD in the Netherlands decreased by 51% for men and 46% for women between 1997 and 2007. This decrease in CVD is explained for 32% by improved secondary prevention and for 44% by improvement in emergency medicine and is in line with our findings in our cohort [33]. The similarity of findings in our SMART cohort and the Dutch population, show that the SMART cohort is a good representation of patients with manifest vascular disease. Therefore, the findings of our study are generalizable to a population with clinical manifest vascular disease.

The strengths of this study include the prospective nature of the cohort, yearly inclusion of patients over a substantial time period, long follow-up, and the use of a standardized diagnostic protocol, which enabled the direct comparison of risk factors and prevalence of subclinical atherosclerosis in patients included in different time periods without bias due to changed measurement techniques. Some limitations of the study should be considered. Risk factors and subclinical atherosclerosis were only measured at baseline and may have changed during follow-up. However, patients included at the start of the cohort would have had more or improved risk factor therapy during follow-up, which would have led to fewer events during follow-up. Therefore, the event rates of these patients might be underestimated. The actual decrease in risk between patients included at the start of the cohort and patients included later might therefore have been even larger than observed in our study.

Secondly, the measurements used to estimate subclinical atherosclerosis in patients are surrogate, dichotomized measures. This does not completely reflect the biological process and progress of atherosclerosis in patients.

Lastly, the number of patients and number of events in the stratified analyses for different vascular locations are small, especially in the group of patients with an AAA. This makes it more difficult to draw conclusions based on these subgroups and should be taken with caution.

In conclusion, in patients with clinically manifest arterial disease, the risk of recurrent MCVE between 1996 and 2014 strongly decreased. This was partially due to lower risk factors and lower prevalence of subclinical atherosclerosis. However, 10-year risk for recurrent events in patients with clinically manifest vascular disease remains high (average 17%) and a better understanding of the in part unexplained reduction in recurrent MCVE may provide new treatment targets.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2017.07.026>.

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