Smoking cessation and risk of recurrent cardiovascular events and mortality after a first manifestation of arterial disease

M. Johanneke van den Berg, MD, [a,b] Yolanda van der Graaf, MD, PhD, [c] Jaap W. Deckers, MD, PhD, [d] Wanda de Kanter, MD, [e] Ale Algra, MD, PhD, [f,g] L. Jaap Kappelle, MD, PhD, [g] Gert J. de Borst, MD, PhD, [h] Maarten-Jan M. Cramer, MD, PhD, [i] and Frank L. J. Visseren, MD, PhD [a], on behalf of the SMART study group *Utrecht, Amsterdam, Rotterdam, The Netherlands*

Aims To quantify the relation between smoking cessation after a first cardiovascular (CV) event and risk of recurrent CV events and mortality.

Methods Data were available from 4,673 patients aged 61 ± 8.7 years, with a recent (≤1 year) first manifestation of arterial disease participating in the SMART-cohort. Cox models were used to quantify the relation between smoking status and risk of recurrent major atherosclerotic cardiovascular events (MACE including stroke, MI and vascular mortality) and mortality. In addition, survival according to smoking status was plotted, taking competing risk of non-vascular mortality into account.

Results A third of the smokers stopped after their first CV event. During a median of 7.4 (3.7–10.8) years of follow-up, 794 patients died and 692 MACE occurred. Compared to patients who continued to smoke, patients who quit had a lower risk of recurrent MACE (adjusted HR 0.66, 95% CI 0.49–0.88) and all-cause mortality (adjusted HR 0.63, 95% CI 0.48–0.82). Patients who reported smoking cessation on average lived 5 life years longer and recurrent MACE occurred 10 years later. In patients with a first CV event >70 years, cessation of smoking had improved survival which on average was comparable to former or never smokers.

Conclusions Irrespective of age at first CV event, cessation of smoking after a first CV event is related to a substantial lower risk of recurrent vascular events and all-cause mortality. Since smoking cessation is more effective in reducing CV risk than any pharmaceutical treatment of major risk factors, it should be a key objective for patients with vascular disease. (Am Heart J 2019;213:112-22.)

The percentage of smokers at time of first clinical manifestation of cardiovascular (CV) disease ranges between 30–50%.[1,2] Although the harmful effects of smoking on health are widely known,[3-5] smoking is highly addictive and cessation can be extremely difficult, even after a life-threatening vascular event. A third of the patients with cerebrovascular disease and a quarter of patients with coronary artery disease (CAD) do not (intent to) quit after a CV event.[6,7] In patients with peripheral artery disease, this proportion is most likely even higher.[8] In the last 15 years, the proportion of smokers has only decreased slightly, from 20% to 16% in 2013 in European patients with CAD according to the EUROASPIRE surveys.[9] Due to better treatment options, survival after a first CV event has increased and thus the number of patients with a history of manifest arterial disease.[10,11] Smoking cessation appears to be more effective in reducing CV risk than pharmaceutical treatment of major risk factors such as cholesterol and blood pressure or the use of antiplatelet therapy.[12]

Although presence of CV disease was not taken into account, the British Doctors Study and a more recent study based on the United States Health Interview Survey showed that cessation of smoking, even at the age of 60, was related to improved survival with an average gain of 3 years compared to patients who continued smoking.[13,14] In patients aged ≥65 years, admitted for acute myocardial infarction between 1994 and 1996, cessation of smoking

From the [a]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands, [b]Department of Anesthesiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands, [c]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands, [d]Department of Cardiology, Thoraxcenter Erasmus Medical Centre, Rotterdam, The Netherlands, [e]Department of Thorax oncology, Antoni van Leeuwenhoek, Netherlands Cancer Institute, Amsterdam, The Netherlands, [f]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands, [g]Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands, [h]Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands, and [i]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands.

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Reprint requests: Professor F L J Visseren, MD, PhD, Department of Vascular Medicine, University Medical Center Utrecht, P.O. Box 85500, 3508, GA, Utrecht, The Netherlands.
E-mail: F.L.J.Visseren@umcutrecht.nl
0002-8703

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after the vascular event until the age of 70 years was found to improve survival with 1 year.[15] Though mainly studied in patients with CAD, cessation of smoking is likely to also result in increased life expectancy in patients with other manifestations of arterial disease. Insight and quantification of the potential gain in life years would be helpful in stimulating doctors to better motivate patients to quit smoking, also after onset of CV disease.

The aim of the present study therefore is twofold. First, to describe the prevalence and characteristics of patients after a recent first manifestation of arterial disease according to smoking status. Second, to quantify the relation between smoking status and risk of recurrent CV events and mortality, in a contemporary cohort of patients with a variety of arterial disease manifestations, taking age at onset of a first CV event and type of vascular disease into account.

Methods

Study population

Data were used from the Second Manifestations of ARTerial disease (SMART) study, which is an ongoing prospective cohort study at the University Medical Center Utrecht, the Netherlands. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. A detailed description of the study rationale and design has been published earlier.[16] Patients were enrolled after they had reached a stable situation in the course of their disease. For the present study (Flowchart presented in Figure 1), data were used from 4,673 patients aged ≥45 years, with complete smoking status at baseline who enrolled between September 1996 till March 2015 with a recent (within 1 year prior to baseline) first diagnosis of manifest arterial disease, e.g. cerebrovascular disease, coronary artery disease, peripheral artery disease or aneurysm of the abdominal aorta (definitions can be found in Supplemental Table 1). At inclusion patients completed a health questionnaire, which included questions regarding medical health and lifestyle and underwent a standardized vascular screening.

Assessment of smoking status

Smoking behavior was classified into four categories: 'never smoked', 'former smoker' (someone who stopped smoking prior to the vascular event), 'quit after vascular event' (someone who stopped smoking in the same year or in year after the vascular event) or 'continued after vascular event'. The number of pack-years was calculated at baseline, with one pack-year defined as smoking 20 cigarettes a day for 1 year. In addition the age at which a person stopped smoking was recorded. In former smokers, the time (in years) between smoking cessation and the vascular event was calculated.

Assessment of covariates

Level of education was assessed at inclusion and based on highest level of completed education and classified into three categories; low (intermediate secondary education or less), moderate (intermediate vocational or high secondary education) and high (higher vocational education or university). The definition of diabetes mellitus is provided in Supplemental Table 1. Body mass index was calculated as weight (kg) divided by height (m) squared (kg/m^2). Office blood pressure was measured with a non-random sphygmomanometer and the average of multiple measurements was taken. Plasma lipids and high-sensitivity C-reactive protein (hs-CRP) were measured. LDL-C was calculated using the Friedewald formula[17] up to a plasma TG level of 9 mmol/l.[18] The estimated glomerular filtration rate (eGFR) was calculated with CKD-EPI formula.[19] Medication use, specifically use of anti-platelets and anticoagulants, blood pressure lowering and cholesterol lowering medication was recorded.

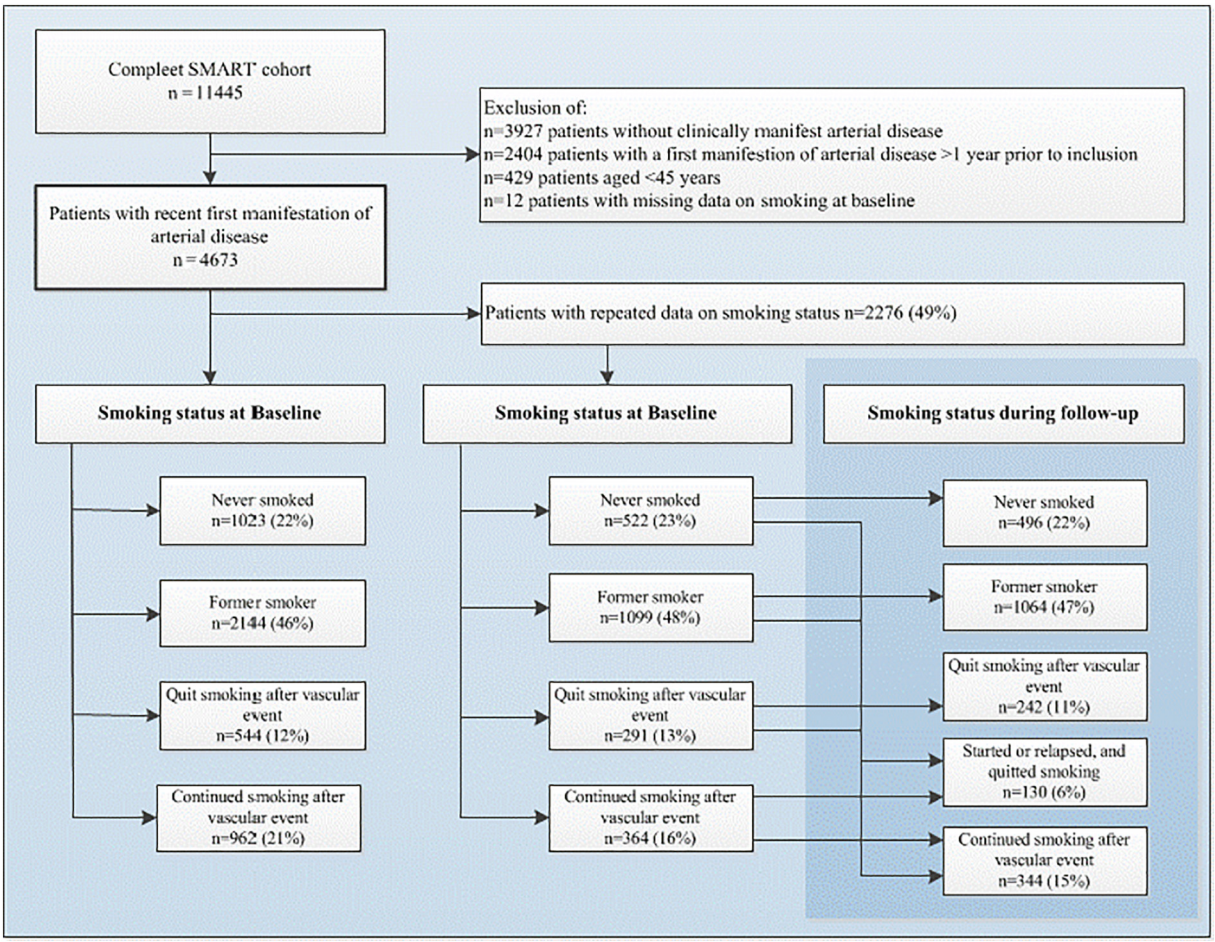
Assessment of outcome during follow-up

From baseline onwards, patients were asked to biannually fill in a short questionnaire regarding hospitalization and outpatient clinic visits. If a patient, family member or general practitioner reported a potential event, relevant data were collected and an outcome committee of three staff members assessed whether the outcome did occur. Outcomes of interest were first, major atherosclerotic cardiovascular events (MACE), a composite of stroke, myocardial infarction and CV mortality. Second, a composite of MACE and vascular interventions, such as open or percutaneous revascularization procedures and amputation of extremities (described in more detail in Supplemental Table 2) and third, all-cause mortality. If a patient had multiple atherosclerotic events, the first recorded event was used in the analyses. Follow-up duration was defined as the period between enrollment and first recurrent CV event, death from any cause, date to loss of follow-up or the preselected date of March 2015.

Reassessment of baseline measures

From January 2006 onwards, participants with a follow-up of at least 4 years were invited for reassessment of all baseline measurements (SMART-2). Approximately 49% of the patients invited for SMART-2 responded and were reassessed. In addition, from October 2015 till March 2016, all participants received an additional questionnaire (SMART-3) with similar questions regarding health and lifestyle. Non-responders received one reminder, which resulted in a total response rate of 79%. Phone calls were made to 284 participants to complete data of returned questionnaires with missing values, which succeeded in 70%. Smoking status during follow-up was reassessed at SMART-2 and SMART-3 and recorded into the following

Figure 1



Flowchart of selection of study population and stratification into smoking status.

categories: 'never smoked', 'former smoker', i.e. quit smoking prior to the vascular event, 'stopped after vascular event', 'started or relapsed, and quit smoking after vascular event' or 'continued after vascular event'.

Data analyses

The proportions of patients who were "never", "former", "quit after vascular event" or "continued after vascular event" smokers were calculated, also according to type of vascular disease and year of inclusion in the SMART-study to detect possible temporal changes. To detect possible misclassification in smoking status, the proportions and change in smoking status during follow-up was also calculated in the subset of patients who participated in SMART-2 or SMART-3. Patient characteristics of the study population are presented according to smoking status at baseline.

Single imputation (performed with the 'AregImpute' function of the 'Hmisc' package in R) was used to reduce missing covariate data. Variables with missing values were: level of education (43%) since it was recorded at baseline from 2004 onwards, BMI (<1%), Systolic blood pressure (<1%).

Three pre-specified sets of models were used, to analyze the effect of smoking status, in particular smoking cessation after a first CV event, on risk of (1) recurrent MACE, (2) recurrent MACE including vascular interventions and (3) all-cause mortality.

First, Cox proportional hazards models with time since event were used to calculate risk of the above mentioned outcomes of interest, according to smoking status at baseline. Hazard ratios with 95% confidence intervals (HR, 95%CI) were adjusted for potential confounders: age, sex, level of education (low, moderate or high), type of vascular disease (cerebrovascular disease, coronary artery disease, aneurysm of abdominal aorta, peripheral artery disease or polyvascular disease), systolic blood pressure, LDL-cholesterol, diabetes, BMI, (log transformed) hs-CRP,

Table I. Patient characteristics according to smoking status at baseline (n = 4,673)

	Continued after vascular event	Quit after vascular event	Former smoker	Never smoked
	962 (21%)	544 (12%)	2144 (46%)	1023 (22%)
Age (years)	57.9 (8.3)	57.2 (7.8)	62.5 (8.4)	62.4 (8.8)
Male sex	676 (70%)	399 (73%)	1664 (78%)	627 (61%)
pack-years*	29.7 (15.7-42.3)	32.4 (10.2-46.2)	15.0 (6.6-29.4)	NA
Age smoking cessation	NA	57 (51-63)	45 (35-55)	NA
Level of education – Low	175 (43%)	88 (28%)	378 (29%)	183 (29%)
Level of education – Moderate	165 (40%)	145 (45%)	520 (40%)	218 (34%)
Level of education – High	71 (17%)	86 (27%)	412 (31%)	239 (37%)
Medical history and medication use				
Diabetes mellitus	132 (14%)	64 (12%)	327 (15%)	164 (16%)
Cerebrovascular disease	259 (27%)	130 (24%)	568 (26%)	280 (27%)
Coronary artery disease	291 (30%)	281 (52%)	1187 (55%)	643 (63%)
Aneurysm of abdominal aorta	53 (6%)	18 (3%)	95 (4%)	14 (1%)
Peripheral artery disease	309 (32%)	85 (16%)	196 (9%)	59 (6%)
Polyvascular disease	50 (5%)	30 (6%)	98 (5%)	27 (3%)
Antiplatelet/anticoagulant therapy	688 (72%)	429 (79%)	1808 (84%)	881 (86%)
Blood pressure-lowering therapy	548 (57%)	384 (71%)	1644 (77%)	819 (80%)
Statin therapy	489 (51%)	359 (66%)	1468 (68%)	704 (69%)
Measurements				
Body mass index (kg/m^2)	26.1 (4.4)	26.8 (4.0)	26.9 (3.6)	26.6 (3.8)
LDL-cholesterol (mmol/l)	3.2 (1.1)	2.9 (1.0)	2.8 (1.0)	2.8 (1.0)
eGFR (CKD-EPI)	83 (70 - 94)	81 (69 - 92)	76 (64 - 87)	74 (63 - 85)
Hs-CRP (mg/l)	3.1 (1.5 – 6.1)	2.0 (1.1 – 4.1)	1.8 (0.9 – 3.9)	1.5 (0.7 – 3.2)

Data are presented as number (%), mean (standard deviation) or median (interquartile range). * A pack-year is defined as smoking 20 cigarettes a day for one year. Abbreviations LDL-C: low-density lipoprotein-cholesterol, eGFR (CKD-EPI): estimated glomerular filtration rate calculated with the CKD-EPI formula, hs-CRP: high sensitivity C-reactive protein.

and patients who continued smoking after the vascular event were used as reference. In addition, HR were adjusted for health seeking behavior, that is use of preventative medication; anti-thrombotics (anti-platelets and anti-coagulants), cholesterol lowering mediation and blood pressure lowering medication. Since smoking patterns could have changed over time, HR were also adjusted for year of enrollment. Interaction on a multiplicative scale was tested for sex, level of education, type of vascular disease with smoking status for risk of recurrent MACE. Analyses were subsequently stratified when interaction was present.

Second, cumulative incidence curves were created. These were based on Cox proportional hazard models and accounted for non-vascular mortality by applying the Fine-Gray comping risk method.[20] Instead of follow-up time, age at enrolment and age at event were used. This was done in the total study population and in patients aged ≥60 and ≥70 years at time of first CV event. Models were adjusted for previous mentioned confounders. A sensitivity analysis was done in which the effect of smoking status on recurrent MACE free survival was stratified for type of vascular disease at baseline. Due to limited number of patients (n = 266) and events (n = 81), this could not be done in patients with an aneurysm of the abdominal aorta. The assumption of proportionality was visually checked by plotting Schoenfeld residuals. Third, to quantify a possible exposure-response relationship, Cox models were made with restricted cubic splines to enable a non-linear effect of pack-years, age at smoking cessation and time between smoking cessation and first CV event on risk of recurrent MACE and all-cause mortality. Models were first adjusted for age, sex, type of vascular disease, level of education and subsequently also adjusted for the other smoking characteristics; pack-years, age at smoking cessation and time between smoking cessation and first CV event respectively.

Analysis were performed with R statistical software, version 3.3.2 (R Core Team (2016) www.R-project.org/) with the add-on packages 'Hmisc", 'rms', 'cmprsk' and 'survival'.

Results

Smoking status

At the time of the first CV event, 22% of patients had never smoked, 46% was a former smoker and 32% smoked cigarettes. Approximately a third of the smokers (12% of the total population) quit after the vascular event while two-thirds (21% of the total population) persisted to smoke (Figure 1). Importantly, the distribution of smoking status changed considerably during the course of the study, from 1996 through 2015 (Supplemental Figure 1A). The number of never smokers increased (from 15% to 28%), while the proportion of persistent

Table II. Smoking status and risk of recurrent cardiovascular events and mortality

	At risk	Events	Model 1	Model 2	Model 3
Recurrent cardiovascular events					
Continued smoking after vascular event	962	198	1	1	1
Quit smoking after vascular event	544	62	0.59 (0.45-0.79)	0.64 (0.48-0.86)	0.66 (0.49-0.88)
Former smoker	2144	308	0.57 (0.47-0.68)	0.66 (0.54-0.80)	0.68 (0.56-0.83)
Never smoker	1023	124	0.50 (0.39-0.63)	0.59 (0.46-0.75)	0.59 (0.46-0.76)
Recurrent MACE including vascular interventions					
Continued smoking after vascular event	962	448	1	1	1
Quit smoking after vascular event	544	181	0.71 (0.60-0.84)	0.79 (0.66-0.94)	0.81 (0.68-0.96)
Former smoker	2144	734	0.66 (0.58-0.74)	0.80 (0.70-0.91)	0.82 (0.72-0.93)
Never smoker	1023	277	0.51 (0.44-0.60)	0.66 (0.56-0.78)	0.67 (0.57-0.79)
All-cause mortality					
Continued smoking after vascular event	962	260	1	1	1
Quit smoking after vascular event	544	73	0.55 (0.43-0.72)	0.62 (0.48-0.81)	0.63 (0.48-0.82)
Former smoker	2144	331	0.40 (0.34-0.48)	0.52 (0.44-0.63)	0.53 (0.44-0.63)
Never smoker	1023	130	0.34 (0.27-0.42)	0.43 (0.34-0.55)	0.43 (0.34-0.55)

Model 1: adjusted for age, sex, Model 2: model 1 additionally adjusted for level of education, type of vascular disease, diabetes, BMI, systolic blood pressure, LDL-C, and health seeking behavior (use of antiplatelet/anticoagulant, blood pressure lowering medication and statins) and log transformed hs-CRP. Model 3: Model 2 additionally adjusted for year of enrolment in the SMART study.

smokers declined (from 37% to 11%). Patients with peripheral artery disease (61%), with an aneurysm of the abdominal aorta (39%) or with polyvascular disease (39%) were most likely to smoke at the onset of their CV disease manifestation. In addition, these patients were less likely to quit smoking after the vascular event; only 22%, 25% and 38% respectively did so while, among the patients with cerebrovascular disease half of the smokers quitted the habit after the vascular event (Supplemental Figure 1B, Supplemental Table 3).

Baseline characteristics according to smoking status

The average age of the study population was 61 ± 8.7 years, and three-quarter was male. Patients who quit smoking after the vascular event or persisted smoking were approximately 5 years younger than the never or former smokers (Table I). Patients who continued to smoke after the vascular event were more likely to have a lower level of education, a history of PAD and were less likely to use preventative medication.

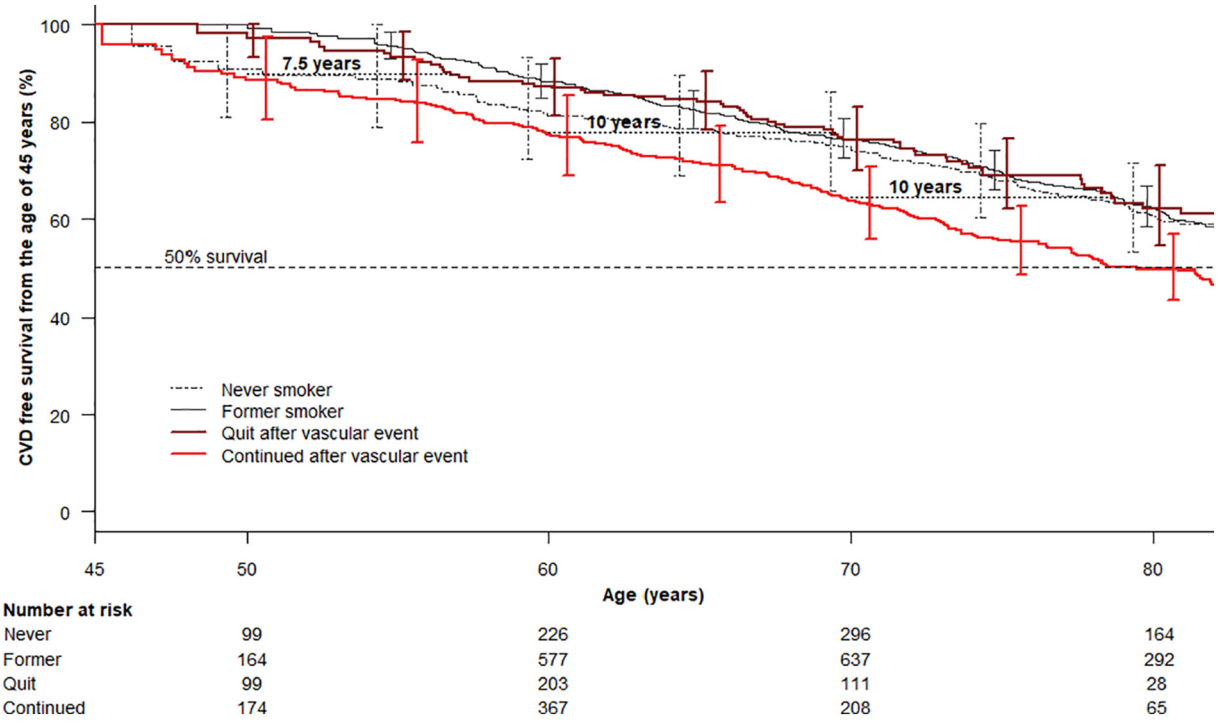
Smoking cessation or continuation and risk of recurrent MACE

During a median follow-up of 7.4 (interquartile range 3.7–10.8) years, 794 (17%) patients died, of which 377 (47%) of a vascular cause, 379 (48%) of a non-vascular and 38 (5%) of an unknown cause. MACE occurred in 692 (15%) patients and MACE including vascular interventions occurred in 1640 (35%) patients. Compared to patients who continued to smoke, patients who quit smoking after the vascular event had a lower risk of recurrent MACE (HR 0.64, 95%CI 0.48–0.86), of recurrent MACE including vascular intervention (HR 0.79, 95%CI 0.67–0.95) and of all-cause mortality (HR 0.62, 95%CI 0.48–0.80) (Table II). Compared to patients who continued to smoke, patients who never smoked had the lowest risk for recurrent MACE (HR 0.56, 95%CI 0.45–0.81), recurrent MACE including vascular interventions (HR 0.65, 95%CI 0.56–0.77) and of all-cause mortality (HR 0.42, 95%CI 0.33–0.53). No interaction was found between smoking status and sex (P-value = 0.61), level of education (P-value = 0.32) or type of vascular disease (*P*-value = 0.17) and risk of recurrent MACE. Supplemental Figure 2 shows a conventional plot of recurrent cardiovascular disease free survival during follow-up, stratified for smoking status.

Age at first cardiovascular event, smoking status and survival

In Figure 2, CV disease free survival according to smoking status is presented for patients aged ≥45 years at onset of CV disease. At the age of 60 years, patients who quit smoking after a first vascular event, on average had a recurrent CV event 10 years later. Irrespective of age, patients who quit smoking after a first CV event had a longer life expectancy, while patients who continued to smoke on average lived 5 years longer compared to patients who quit smoking after the event (Figure 3). Although the difference in CV disease free survival between patients who quit versus those who persisted to smoke after a first CV event at the age of ≥60 or ≥70 years was less pronounced, patients who persisted to smoke after a first CV event at the age of ≥60 or ≥70 years, had significantly worse overall survival compared to patients who quit (Figure 4). Sensitivity analyses in which recurrent MACE free survival was plotted according to type of vascular disease at baseline showed comparable

Figure 2



Risk of recurrent MACE in patients with a recent first cardiovascular event aged ≥45 years (n = 4,673) according to smoking status. Survival curve with 95% confidence intervals, adjusted for sex, level of education, type of vascular disease, systolic blood pressure, BMI, LDL-C, diabetes, log transformed (hs-CRP), use of antiplatelet/anticoagulant, blood pressure-lowering medication and statins. Dotted black lines indicate an average of 7.5 to 10 years less recurrent MACE free survival for patients who continue to smoke compared to patients who quit smoking after a first cardiovascular event.

benefit of smoking cessation on survival (Supplemental Figures 2, 3 and 4).

Pack-years of smoking, years since smoking cessation, and age at smoking cessation and risk of recurrent MACE and all-cause mortality

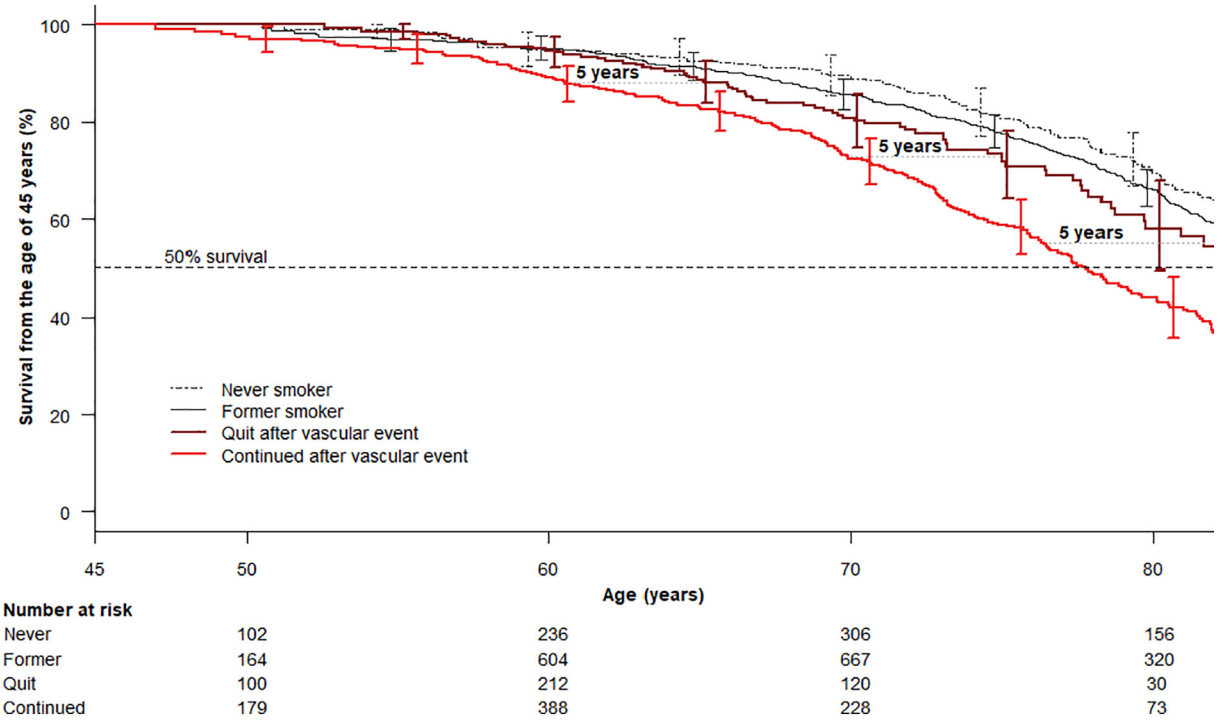
Pack-years of smoking, years since smoking cessation and age at smoking cessation all had a linear relation with risk of recurrent MACE (Supplemental Figure 5). The risk of recurrent MACE decreased when the number of years since smoking cessation was higher or when patients were younger when they quit smoking. Compared to patients who smoked >5 pack-years, smoking ≤5 pack-years was associated with a lower risk of recurrent MACE (HR 0.73, 95%CI 0.61–0.88). Additional adjusting for pack-years only slightly attenuated the risk of recurrent MACE for years since smoking cessation and age at smoking cessation. pack-years of smoking, years since smoking cessation and age at smoking cessation also had a linear relationship with risk of all-cause mortality (Supplemental Figure 6). Additional adjustment for pack-years only slightly attenuated risk of all-cause mortality for years since smoking cessation and age at smoking cessation respectively.

Discussion

Smoking is a major health issue in the current era.[21] The present study shows that, irrespective of age, cessation of smoking after a first CV event is related to a much lower risk of recurrent vascular events and all-cause mortality, compared to patients who continued smoking. Patients who quit smoking after their first CV event were found to live on average 5 years longer than patients who continued to smoke and lived on average 10 more years without recurrent CV events.

Other studies also have quantified the life expectancy of smokers and quitters. According to these reports, non-smokers on average lived 10 years longer than smokers and cessation of smoking between the age of 45 and 55 improved survival by approximately 5 years.[13,14] A smaller benefit of 1–3 life-years gained by smoking cessation has been reported in patients with coronary artery disease.[22-24] These studies however, were based on patients with an average age of 72 years,[15] and in which

Figure 3



Number at risk				
Never	102	236	306	156
Former	164	604	667	320
Quit	100	212	120	30
Continued	179	388	228	73

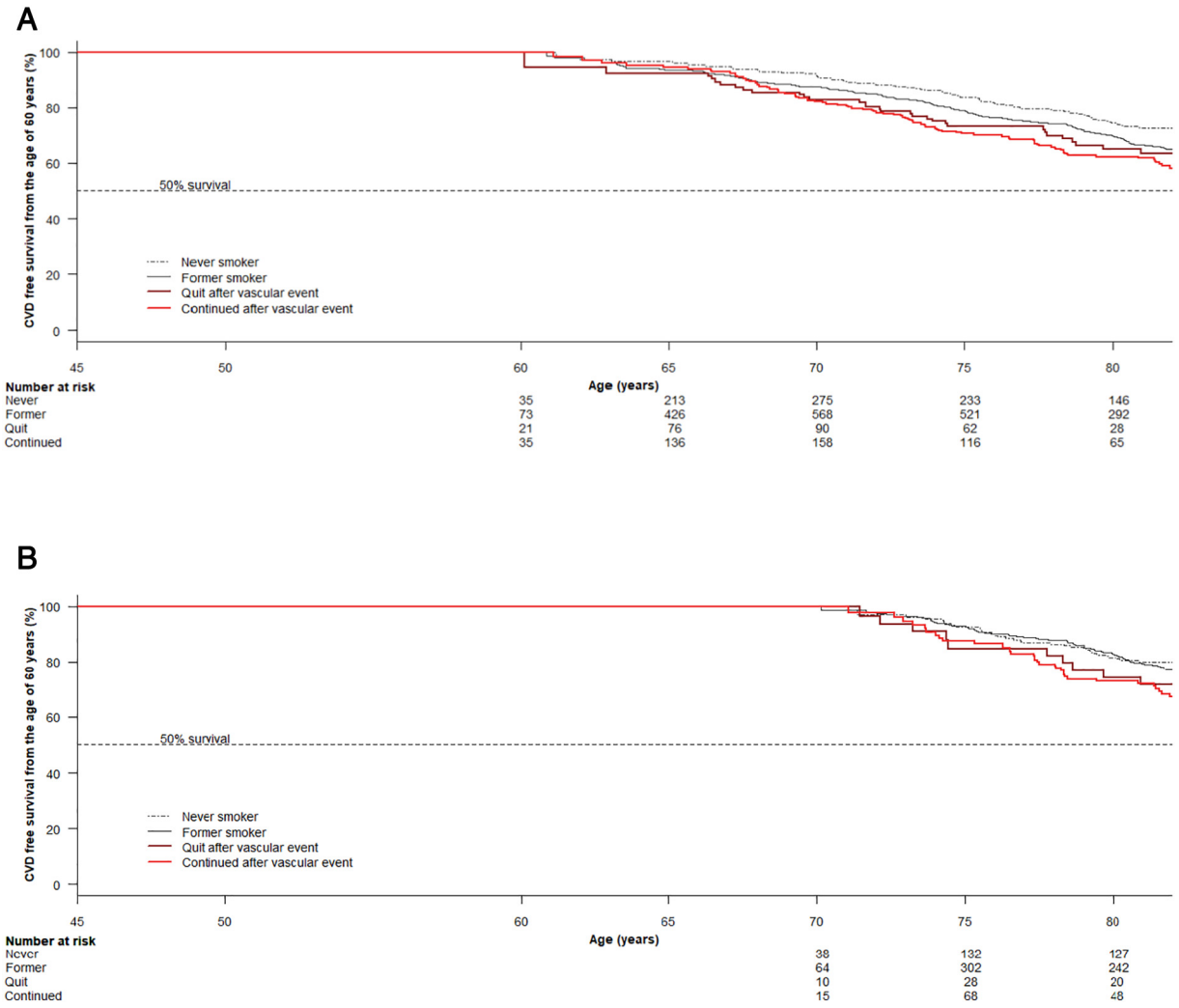
Risk of all-cause mortality in patients with a recent first cardiovascular event aged ≥45 years (n = 4,673) according to smoking status. Survival curve with 95% confidence intervals, adjusted for sex, level of education, type of vascular disease, systolic blood pressure, BMI, LDL-C, diabetes, log transformed (hs-CRP), use of antiplatelet/anticoagulant, blood pressure-lowering medication and statins. Dashed line indicates 50% survival and dotted grey lines indicate an average of 5 years lost for patients who continue to smoke compared to patients who quit smoking after the first cardiovascular event.

data collection took place between 1971 and 1980[24] and 1980 and 1985.[23] Since then, both treatment and secondary prevention measures have improved considerably and consequently, survival of patients with manifest arterial disease has improved. Contrary to these findings, a more recent study from the Spanish FRENA registry reported that cessation of smoking did not improve survival in patients with peripheral artery disease.[8] Although these analyses took place in a large group of patients, results were not adjusted for confounders. In the present study, no interaction was found between type of vascular disease, smoking status and the risk of recurrent MACE nor mortality. In addition, we found that also in a subset of patients with peripheral artery disease, patients who persisted to smoke had the poorest survival (Supplemental Figure 4), which is line with other studies.[25,26]

Although the proportion of patients who smoked at onset of CV disease has decreased in the past 20 years, a substantial proportion of patients with vascular disease continues to smoke. In our study population of patients with a variety of CV disease, the percentage of smokers was approximately 20%, and decreased to approximately 10% in 2013–2014. Comparative studies are scarce, however, tobacco use is more prevalent in patients with peripheral artery disease or aneurysm of abdominal aorta than in patients with coronary artery disease or cerebrovascular disease.[26-29] Although the average age did not differ, the number of pack-years was considerably higher in patients with peripheral artery disease than in patients with cerebrovascular of coronary artery disease. Moreover, patients with a first acute myocardial infarction appear to be more successful in smoking cessation than patients with peripheral artery disease.[8,25,29] Perhaps because a myocardial infarction is considered to be more life threatening than lower limb ischemia. Another explanation could be that peripheral artery disease is associated with lower social economic status,[30] which subsequently is related to a higher prevalence of smoking and lower rate of successful smoking cessation.[31,32]

Apart from social disparity, genome wide association studies have identified genes associated with heavy smoking and likelihood of smoking cessation failure, also in patients with coronary artery disease.[33,34] In future clinical practice, these genetic markers could perhaps assist to optimize allocation of intensive smoking cessation interventions.

Figure 4



Risk of all-cause mortality in patients with a recent first cardiovascular event in A) patients aged ≥60 years (n = 2,536) and B) patients aged ≥70 years (n = 894) according to smoking status. Survival curves with 95% confidence intervals, are adjusted for sex, level of education, type of vascular disease, systolic blood pressure, LDL-C, BMI, diabetes, log transformed (hs-CRP), use of antiplatelet/anticoagulant, blood pressure-lowering medication and statins.

The present study adds to the body of evidence that cessation of smoking should be top priority in every CV prevention setting. The effect of smoking cessation on CV risk reduction is substantially larger in magnitude than the medical treatment effect of a single major risk factor.[35-40] Communication of the health benefits of smoking cessation by health care providers must be emphasized, regardless of the patient' age or the age at first manifestation of CV disease, in order to encourage patients to quit. In addition to psychosocial counseling, which enhances motivation to quit smoking and builds coping skills to avoid relapse, pharmacotherapy can be given to relieve nicotine withdrawal symptoms.[41,42] Secondhand (smoke from burning tobacco products) and possibly also third hand smoking; i.e. residual nicotine and other chemicals left on indoor surfaces by tobacco smoking, are related to an increased risk of (lung) cancer and cardiovascular disease.[5,43] Cessation of smoking thus will also benefit the next of kin, colleagues and others in close proximity of the patient. Patient advocacy organizations, health insurance companies and policy makers should also have increased awareness of the gain in life years by smoking cessation, because of their role in effectuating a society free from tobacco-related disease. For instance by increasing funding for in- and out hospital smoking cessation units, prevention programs, restriction of tobacco marketing and retail and expansion of clean (indoor) air laws and regulations.[44]

Interestingly, patients with a CV event at a relative young age (<60 years) who had never smoked, appeared to have a worse survival compared to patients who quit smoking, even after adjusting for traditional CV risk factors. This could be the result of or unmeasured confounders, such as an unfavorable genetic predisposition or residual confounding such as more advanced atherosclerosis in the non-smokers at the time of clinical disease manifestation. In smokers, however, smoking can be the driver of a CV event even in the absence of generalized atherosclerosis.[45,46]

Strength of our study are the prospective design and relative long duration of follow-up, up to 20 years with limited loss to follow-up (5%). Moreover, the SMART-study is a contemporary cohort reflecting clinical practice that includes patients with a variety of manifestations of arterial disease. Limitations also need to be addressed. Smoking status at baseline was used in the analysis and patients who persisted to smoke could have stopped, while patients who stopped after the vascular event could have started again. Both scenarios however would have resulted in an underestimation of the effect of smoking cessation on mortality and recurrent CV events. To estimate the extent of misclassification, smoking status during follow-up (SMART-2 and/or SMART-3) was assessed and although approximately 6% of the patients started or relapsed and quitted again, the majority of patients reported that they did not change their smoking behavior. Another potential cause for misclassification could be that smoking status was based on self-reported data and not objectified by measuring urine cotinine[47,48] or carbon monoxide concentrations in breath as done in the EUROASPIRE surveys.[9] In the analyses, we have only adjusted for baseline and not follow-up variables, which could resulted in potential residual confounding. Although CV disease is a male dominated disease, other limitations include the limited number of female patients, which may limit the generalizability of our findings. Lastly, although only patients with a recent CV event who reached a stable course in their disease were included, the risk of death might be biased in the first year. However, we found the yearly incidence of mortality in the first four years to be 1%.

In conclusion, patients who quitted smoking after a first CV event on average gained 5 life years and delayed the occurrence of new CV events with 10 years, compared to patients who continued smoking. Irrespective of age, cessation of smoking after a first CV event should be a key objective for both patients and physicians to lower the risk for recurrent vascular events.

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Contributors

MJB, FLJV and YG designed the study. MJB performed the statistical data analysis and drafted the paper. All authors discussed and contributed to the theoretical framework, interpretation of the results, and revised and gave final approval of this manuscript.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.03.019.

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