Physical Activity and Vascular Events and Mortality in Patients with Vascular Disease

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ABSTRACT

BOSS, H. M., L. J. KAPPELLE, Y. VAN DER GRAAF, M. KOOISTRA, F. L. J. VISSEREN, and M. I. GEERLINGS. Physical Activity and Vascular Events and Mortality in Patients with Vascular Disease. *Med. Sci. Sports Exerc.*, Vol. 47, No. 11, pp. 2359–2365, 2015. **Introduction**: In patients with CAD, moderate levels of leisure time physical activity are associated with lower risk of mortality. However, less is known about the effects in patients with vascular disease other than CAD. In this study, we examined the association between physical activity and risk of future vascular events and all-cause mortality in patients with vascular disease or risk factors and investigated whether these associations were similar across the different manifestations of vascular disease. **Methods**: A total of 9942 consecutive patients with various manifestations of vascular disease or risk factors enroled in the Second Manifestations of ARTerial disease study were included. The amount of physical activity was assessed at baseline in MET-hours per week. **Results**: The study population (mean age, 56.7 yr; male, 67%) had a median level of physical activity of 17.4 MET·h·wk^{-1}. During a median follow-up of 6.7 yr, 1224 vascular events and 1353 cases of all-cause mortality were recorded. Cox regression analyses adjusted for age, sex, smoking, and current alcohol consumption showed that higher levels of physical activity were associated with reduced risk of vascular events (quartile 4 vs quartile 1; hazard ratio, 0.68 (95% confidence interval, 0.58–0.79)) and all-cause mortality (hazard ratio, 0.61 (95% confidence interval, 0.53–0.71)). This reduced risk was observed both in patients with vascular disease and in patients with risk factors. The associations were similar across the different manifestations of vascular disease. **Conclusions**: Higher levels of leisure time physical activity were associated with reduced risk of vascular events and all-cause mortality in patients with CAD and other manifestations of vascular disease, suggesting that physical exercise programs should also be investigated in these other manifestations. **Key Words:** VASCULAR DISEASE, PHYSICAL ACTIVITY, MORTALITY, EPIDEMIOLOGY

It has been well established that moderate and high levels of physical activity are associated with lower risk of CAD, stroke, and mortality in healthy men and women (16,24,33). Therefore, the current guidelines of the American College of Sports Medicine (ACSM) recommend moderate-intensity cardiorespiratory exercise training for at least 30 min on at least 5 d·wk^{-1} or vigorous-intensity cardiorespiratory exercise training for at least 20 min on at least three weekdays or a combination of these activities (5).

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Submitted for publication November 2014.
Accepted for publication March 2015.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.acsm-msse.org).

0195-9131/15/4711-2359/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000000666

In patients with CAD, the beneficial effects of physical activity on mortality have also been well demonstrated. A meta-analysis of randomized controlled trials investigating the effect of the cardiac rehabilitation program found significant reduction in mortality in patients participating in the cardiac rehabilitation program as compared with those in usual care (29). Moreover, in patients with CAD who performed regular physical activity after a myocardial infarction, the risk of subsequent mortality, myocardial infarction, and stroke after 6 months of follow-up was lower than that in patients without regular physical activity (3). Physical activity has also been associated with reduction in mortality in patients with CAD in the long term (8,19,20,28,31).

Evidence for beneficial effects of physical activity in patients with cerebrovascular disease (CBVD) or aneurysm of the abdominal aorta (AAA) is currently lacking. In addition, exercise programs have only been implemented for patients with CAD and peripheral artery disease (PAD) (22,29). In the United States, the estimated prevalence of CBVD was 6.8 million (9). Although this is approximately half of the prevalence of CAD (9), it is still important to investigate the effects of physical activity in this group of patients separately. A number of studies, which also included patients with vascular disease other than CAD, reported an association between physical activity and reduced mortality and nonfatal vascular disease (4,6,7,11,25). However, most studies did not provide information on the different categories of vascular disease present in their population (4,25). Moreover, no studies have described the benefits of physical activity in patients with CBVD, AAA, or multiple manifestations of vascular disease separately.

Furthermore, although benefits of physical activity have been described in patients with diabetes and hypertension (13,14,27), evidence in patients with other risk factors is currently lacking and it is not known whether the association of physical activity with vascular events and mortality is similar in patients with vascular risk factors or vascular disease.

In this study, we investigated the association of leisure time physical activity with the risk of vascular events (the composite end point of stroke, myocardial infarction, or vascular death), all-cause mortality, stroke, ischemic coronary events, vascular death, and nonfatal vascular events in patients with various manifestations of vascular disease or risk factors. We also investigated whether the associations between physical activity and the outcomes were similar in patients with vascular disease or risk factors and across the different manifestations of vascular disease, with an emphasis on patients with CBVD, PAD, AAA, and multiple manifestations of vascular disease.

METHODS

Participants. Data were used from patients enroled in the Second Manifestations of ARTerial disease (SMART) study, an ongoing single-center prospective cohort study initiated in 1996. Patients newly referred to the University Medical Center Utrecht in the Netherlands for treatment of vascular disease or risk factors were invited to participate (26). During a 1-d visit to our medical center, extensive vascular screening was performed, including a physical examination, ultrasonography of the carotid arteries, overnight fasting venous blood and urine sampling, assessment of risk factors, medical history, and medication use. A written informed consent was obtained from all participants. The study was approved by the medical ethics committee of the University Medical Center Utrecht.

For the present study, the following vascular disease groups were defined: CAD, CBVD, PAD, and AAA. CAD was defined as a history of coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or myocardial infarction either previously or at inclusion. Patients were considered to have CBVD if they experienced a transient ischemic attack or stroke at inclusion or reported history of stroke. PAD was defined as history of surgery or angioplasty of the arteries supplying the lower extremities or intermittent claudication or pain at rest at inclusion. AAA was defined as AAA (distal aortic diameter, ≥3 cm) at inclusion or previous surgery for AAA. Patients with multiple manifestations of vascular disease at baseline were considered as a separate category. Vascular disease was defined as the presence of CAD, CBVD, PAD, and AAA either previously or at inclusion. Vascular risk factors was defined as the presence of risk factors for atherosclerosis, including hypertension, diabetes mellitus, and hyperlipidemia, but no history of vascular disease.

For this current study, 10,128 consecutive patients included between September 1996 and February 2013 were studied. A total of 186 patients had to be excluded because of missing data for physical activity. Therefore, 9942 patients were included in the analysis. In these patients, follow-up was complete in 95.5%.

Physical activity. At baseline, patients completed a questionnaire on their usual pattern of leisure time physical activity during a regular week in the past year. A previously validated questionnaire was used, and one additional question regarding activity in sport was included (23). Patients were asked how many hours per week they spent on leisure time physical activities, which included sport (e.g., swimming, running) or other physical activities (e.g., walking, cycling, gardening, and leisure time physical activity). Housekeeping and work-related physical activity were not included.

To each activity, a specific MET intensity was assigned, derived from the compendium of physical activity (1). The MET intensity is based on the rate of energy expenditure. One MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10 times the resting energy expenditure (brisk walking is estimated to be approximately 3.5–4.0 METs). For each type of leisure time physical activity, the amount per week was calculated by multiplying the time spent on this activity ($h \cdot wk^{-1}$) by the derived MET intensity of the activity ($MET \cdot h \cdot wk^{-1}$). The total amount of physical activity per week was the sum of these values.

Clinical outcomes. Every 6 months, patients were asked to complete a questionnaire on hospitalizations and outpatient clinic visits. If a possible event was reported by the patient or a relative, the hospital discharge letter and the results of relevant laboratory and radiology examinations were obtained and evaluated by three members of the SMART study Outcome Event Committee. Vascular death was defined as death caused by myocardial infarction, stroke, sudden death (unexpected coronary death occurring within 1 h after onset of symptoms or within 24 h (given convincing circumstantial evidence)), congestive heart failure, rupture of abdominal aortic aneurysm, or death from another vascular cause. Stroke was defined as relevant clinical features that caused increase in impairment of at least one grade on the modified Rankin scale (mRS), with or without a new relevant lesion at brain imaging. Ischemic coronary event was defined as myocardial infarction, sudden death, or fatal congestive heart failure.

Outcomes of interest for this study were the composite end point vascular events, which consisted of stroke, myocardial infarction or vascular death, and the end point all-cause mortality (Table 1). The outcomes vascular death, stroke, ischemic coronary events, and nonfatal vascular events were also investigated.

TABLE 1. Definition of outcomes.

Event	Definition
All-cause mortality	Death from any cause
Vascular death	Death from stroke, congestive heart failure, myocardial infarction, or rupture of abdominal aortic aneurysm
	Sudden death: unexpected cardiac death occurring within 1 h after onset of symptoms or within 24 h given convincing circumstantial evidence
	Vascular death from other causes
Stroke	Relevant clinical features that caused an increase in impairment of at least one grade on the mRS associated with a relevant infarction or bleeding on a repeat brain scan
Ischemic coronary event	Myocardial infarction, sudden death, or fatal congestive heart failure
Vascular event	A composite of stroke, myocardial infarction, and vascular death completed with a probable or definite retinal infarction or bleeding
Nonfatal vascular event	A composite of nonfatal stroke and nonfatal myocardial infarction completed with a probable or definite retinal infarction or bleeding

Covariates and definitions. Covariates included demographic characteristics (age, sex), medical history, and risk factors for vascular disease (current smoking, current alcohol use, hypertension, diabetes, hyperlipidemia, and body mass index (BMI)). Hypertension was defined as the use of blood pressure-lowering drugs or blood pressure >140/90 mm Hg. Diabetes mellitus was defined as a referral diagnosis of diabetes, self-reported diabetes, use of glucose-lowering agents or glucose ≥126 mg·L^{-1}, and glucose-lowering therapy within 1 yr after inclusion. Hyperlipidemia was defined as fasting total cholesterol >193 mg·L^{-1}, fasting LDL cholesterol >124 mg·L^{-1}, or lipid-lowering drug use. Height and weight were measured, and the BMI was calculated (kg·m^{-2}).

Data analysis. We used single imputation methods to reduce missing covariate data for smoking (n = 12 (<1%)), alcohol consumption (n = 21 (<1%)), BMI (n = 15 (<1%)), hyperlipidemia (n = 36 (<1%)), and hypertension (n = 23 (<1%)). Data were analyzed with SPSS version 20.0.

We first calculated baseline characteristics for the total population (n = 9942) and across the quartiles of leisure time physical activity. Second, using Cox regression analysis, we estimated the association of physical activity in quartiles with vascular events and all-cause mortality using the first (lowest) quartile of physical activity as the reference group. Follow-up duration was defined as the period between study inclusion and first occurrence of the defined event, date of loss to follow-up, date of death not due to vascular causes, or end of study (March 1, 2013). Results are expressed as hazard ratios (HR) with 95% confidence intervals (CI). The proportionality assumption was verified with the Schoenfeld test and did not seem to be violated for our main outcomes. In model 1, we estimated this association adjusted for age and sex. In model 2, we additionally adjusted for smoking and current alcohol consumption. In model 3, we additionally adjusted for BMI, presence of diabetes, presence of hypertension, and presence of hyperlipidemia because they could confound the relation but also be intermediates. To investigate whether there were linear trends between the HR values of the quartiles of physical activity, we also considered these categories as ordinal variables in the Cox regression analysis.

Third, to investigate whether the presence of vascular disease, risk factors, or different vascular disease categories influences the association, we stratified for the presence of vascular disease or risk factors and for different categories of vascular disease. For these additional analyses, we combined the second to fourth quartiles of physical activity and used the first quartile as the reference group. We also calculated interaction terms between the level of physical activity and vascular disease or risk factor and vascular disease categories and considered interaction present if $P \leq 0.10$.

Finally, we performed sensitivity analyses to explore the possibility that the associations were due to totally inactive patients by excluding all patients who reported no physical activity at all (n = 1486). The likelihood of reverse causality, referring to the possibility that physical inactivity may be the consequence of the severity of the disease rather than the cause, was also evaluated. Reverse causality will affect short-term rather than long-term results; for that reason, analyses were repeated after exclusion of patients with a follow-up of less than 2 yr. Secondly, we stratified for the severity of the vascular disease at baseline. We defined severe vascular disease (n = 929) as CBVD and an mRS of 2 or more (n = 105), CAD and three-vessel disease or left main CAD (n = 626), AAA with previous surgery (n = 130), and PAD with Fontaine stage 3 or 4 (n = 68).

RESULTS

At baseline, the mean age of the total population was 56.7 yr (SD, 12.4) and 67% of patients were male (Table 2). The median level of physical activity in the total population was 17.4 MET·h·wk^{-1} (10th to 90th percentile, 0.0–55.5). In the lowest quartile of physical activity, more patients had PAD or diabetes and more patients were current smokers as compared with those in the highest quartile. Patients in the highest quartile of physical activity more often had CAD and were older than patients in the lowest quartile (Table 2).

During a median follow-up of 6.7 yr (10; 90th percentile, 1.4; 13.2), 1224 vascular events (18 per 1000 person-years (p-y)) and 1353 cases of all-cause mortality (19 per 1000 p-y) occurred (Table 3). Cox regression analyses adjusted for age, sex, smoking, and current alcohol consumption showed that a higher level of physical activity was associated with significantly lower risk of recurrent vascular events; the HR (95% CI) of the highest quartile of physical activity versus the lowest quartile was 0.68 (0.58–0.79). For all-cause mortality, HR (95% CI) was 0.61 (0.53–0.71) (Table 3). The relation between physical activity and vascular events and mortality was not different after additional adjustment for BMI, presence of diabetes, presence of hypertension, and presence of hyperlipidemia (Table 3). Physical activity was also significantly associated with reduced risk of vascular death, stroke, and

TABLE 2. Baseline characteristics of the study population.

	Total	Quartiles of Physical Activity (Range, MET·h·wk^{-1}) 1 (<5.9)	2 (5.9–17.4)	3 (17.4–34.2)	4 (>34.2)
n	9942	2482	2487	2488	2485
Age (yr)	56.7 (12.4)	56.8 (12.6)	55.5 (12.3)	55.7 (12.7)	58.9 (11.5)
Sex, male (%)	67	64	65	67	72
Measures of physical activity					
Physical activity (MET·h·wk^{-1})[a]	17.4 (0.0–304.0)	0.0 (0.0–5.9)	11.4 (5.9–17.4)	24.6 (17.4–34.2)	50.8 (34.2–304.0)
Manifestation at baseline (%)					
Vascular risk factors	32	32	36	32	27
CBVD	15	15	15	15	15
CAD	33	25	30	35	41
AAA	3	3	2	2	2
PAD	8	11	8	7	6
Multiple manifestations of vascular disease	11	14	10	9	9
Other variables (%)					
Hypertension[b]	67	69	67	65	68
Diabetes[c]	19	26	19	18	15
Hyperlipidemia[d]	78	81	79	75	75
Current smoking	30	42	30	26	22
Current alcohol consumption	52	37	52	57	63
BMI (kg·m^{-2})	26.8 (4.4)	27.5 (5.0)	26.9 (4.2)	26.6 (4.2)	26.5 (3.9)

Characteristics are presented as mean ± SD unless otherwise specified.
[a]Values are expressed as median (range).
[b]Hypertension is defined as blood pressure-lowering drug use or blood pressure >140/90 mm Hg.
[c]Diabetes mellitus is defined as a referral diagnosis of diabetes, self-reported diabetes, use of glucose-lowering agents, or glucose ≥126 mg·L^{-1} and glucose-lowering therapy within 1 yr after inclusion.
[d]Hyperlipidemia is defined as fasting total cholesterol >193 mg·L^{-1}, fasting LDL cholesterol >124 mg·L^{-1}, or lipid-lowering drug use.

nonfatal vascular events (Table 4). When we used the norm of 500–1000 MET·min·wk^{-1}, as recommended by the ACSM, patients who performed physical activity according to or above the norm had lower risk of vascular events and all-cause mortality than patients performing below the norm (see Figure, Supplemental Digital Content 1, HR for mortality and vascular events according to the ACSM norm, http://links.lww.com/MSS/A535).

The reduced risk of recurrent vascular events and all-cause mortality was similar in men and women; the HR (95% CI) for recurrent vascular events of the second to fourth quartiles of physical activity versus the first quartile was 0.69 (0.60–0.80) in men and 0.70 (0.55–0.89) in women. For all-cause mortality, HR (95% CI) values were 0.64 (0.56–0.73) in men and 0.61 (0.48–0.76) in women. The reduced risk of recurrent vascular events and all-cause mortality was observed both in patients with vascular disease and in patients with risk factors, although the relation between physical activity and risk of vascular events in patients with vascular risk factors was not statistically significant (Fig. 1). There was no evidence for a difference in risk reduction in patients with vascular disease or risk factors; the interaction *P* values were higher than 0.50. In patients with CBVD, AAA, PAD, and multiple manifestations of vascular disease, estimates of the relation between physical activity and vascular events and all-cause mortality were similar in comparison with those in patients with CAD (Fig. 1). Interactions between the level of physical activity and the different categories of vascular disease were not statistically significant. Using CAD as the reference group, *P* values for these interactions were higher than 0.40 for vascular events and for mortality.

When patients with no leisure time physical activity (n = 1486) were excluded from the analysis, physical activity was still associated with reduced risk of vascular events and all-cause mortality (see Table, Supplemental Digital

TABLE 3. HR for vascular events and all-cause mortality according to level of physical activity.

	n	Person-Years	HR (95% CI) Model 1	Model 2	Model 3	*P* Trend
Vascular events						
Quartiles of physical activity (range, MET·h·wk^{-1})						
1 (<5.9)	447	17,349	1.00	1.00	1.00	
2 (5.9–17.4)	269	17,061	0.64 (0.55–0.75)	0.72 (0.62–0.84)	0.74 (0.63–0.86)	
3 (17.4–34.2)	251	16,860	0.58 (0.50–0.68)	0.67 (0.57–0.79)	0.68 (0.59–0.80)	
4 (>34.2)	257	15,149	0.56 (0.48–0.65)	0.68 (0.58–0.79)	0.70 (0.59–0.82)	<0.001
All-cause mortality						
Quartiles of physical activity (range, MET·h·wk^{-1})						
1 (<5.9)	533	18,427	1.00	1.00	1.00	
2 (5.9–17.4)	290	17,768	0.62 (0.53–0.71)	0.69 (0.60–0.80)	0.71 (0.61–0.82)	
3 (17.4–34.2)	256	17,382	0.53 (0.45–0.61)	0.60 (0.52–0.70)	0.61 (0.52–0.71)	
4 (>34.2)	274	15,837	0.51 (0.44–0.59)	0.61 (0.53–0.71)	0.63 (0.54–0.73)	<0.001

Model 1 is adjusted for age and sex.
Model 2 is adjusted for age, sex, smoking status, and current alcohol consumption.
Model 3 is adjusted for age, sex, smoking status, current alcohol consumption, BMI, presence of diabetes, presence of hypertension, and presence of hyperlipidemia.

TABLE 4. HR for specific vascular outcomes according to level of physical activity.

	n	Person-Years	HR (95% CI)	*P* Trend
Stroke				
Quartiles of physical activity (range, MET·h·wk^{-1})				
1 (<5.9)	131	17,874	1.00	
2 (5.9–17.4)	84	17,480	0.78 (0.59–1.03)	
3 (17.4–34.2)	69	17,143	0.65 (0.48–0.87)	
4 (>34.2)	70	15,563	0.65 (0.48–0.87)	0.001
Ischemic coronary events				
Quartiles of physical activity (range, MET·h·wk^{-1})				
1 (<5.9)	217	17,788	1.00	
2 (5.9–17.4)	148	17,280	0.82 (0.66–1.01)	
3 (17.4–34.2)	137	17,072	0.76 (0.61–0.94)	
4 (>34.2)	156	15,329	0.87 (0.70–1.07)	0.10
Vascular death				
Quartiles of physical activity (range, MET·h·wk^{-1})				
1 (<5.9)	282	18,427	1.00	
2 (5.9–17.4)	140	17,768	0.66 (0.53–0.80)	
3 (17.4–34.2)	145	17,382	0.66 (0.54–0.81)	
4 (>34.2)	128	15,837	0.55 (0.44–0.68)	<0.001
Nonfatal vascular events				
Quartiles of physical activity (range, MET·h·wk^{-1})				
1 (<5.9)	244	17,349	1.00	
2 (5.9–17.4)	171	17,061	0.82 (0.67–0.99)	
3 (17.4–34.2)	148	16,860	0.71 (0.58–0.88)	
4 (>34.2)	161	15,149	0.79 (0.64–0.97)	0.007

Cox regression model is adjusted for age, sex, smoking status, and current alcohol consumption (model 2).

Content 2, HR after excluding patient with no leisure time physical activity, http://links.lww.com/MSS/A536). In addition, the reduced risks were still observed when patients with less than 2 yr of follow-up were excluded (see Table, Supplemental Digital Content 3, HR after excluding patients with less than 2-yr follow-up, http://links.lww.com/MSS/A537). Risk reduction was also observed in patients with severe vascular disease (n = 929) and in patients without severe vascular disease (see Table, Supplemental Digital Content 4, HR in patients with severe or without severe vascular disease, http://links.lww.com/MSS/A538).

DISCUSSION

In this large prospective cohort study of almost 10,000 patients with vascular disease or vascular risk factors, we observed that a higher level of leisure time physical activity at baseline was associated with strongly reduced risk of new vascular events and all-cause mortality during a median of 6.7 yr follow-up. Patients who performed a light-to-moderate level of physical activity, such as walking 2–3 h·wk^{-1} (second quartile of physical activity), already had 28% lower risk of vascular events and 31% lower all-cause mortality in comparison with patients with less than 2 h·wk^{-1} (first quartile).

To our knowledge, this is the first prospective cohort study that examined the influence of leisure time physical activity on recurrent vascular events and mortality in patients with CBVD, AAA, and multiple manifestations of vascular disease within one cohort and also examined these associations across various manifestations of vascular disease and vascular risk factors. Our results show that a higher level of physical activity similarly reduces the risk of vascular events and all-cause mortality across all disease groups and indicate that the relation of physical activity with reduction in poor outcome is not restricted to patients with CAD. In patients with CBVD and even in patients with multiple manifestation of vascular disease, a patient population at a particularly high risk of recurrent vascular events and mortality, these associations were significant. The reduced mortality that we found in patients with PAD is in line with earlier studies (6,7). In our study, the estimates for new vascular events in patients with PAD and the estimates in patients with AAA were similar to those in patients with CAD but the CI were broader and not significant probably because of the smaller number of patients in these groups. No studies have previously investigated the effect of physical activity in patients with AAA. However, before an elective operation for AAA, a lower exercise capacity, which is presumably associated with less physical activity, was associated with higher mortality (12). These same associations have been observed in patients with CAD and PAD (18,21).

The risk reductions of 20%–30% that we found for light or moderate levels of physical activity are in line with earlier studies in patients with CAD (8,19,20). In addition, we observed that increasing levels of physical activity (third and fourth quartiles) were associated with further risk reduction of less than 10%. This additional risk reduction was relatively small compared with the difference between the first and second quartile and did not change after the third quartile.

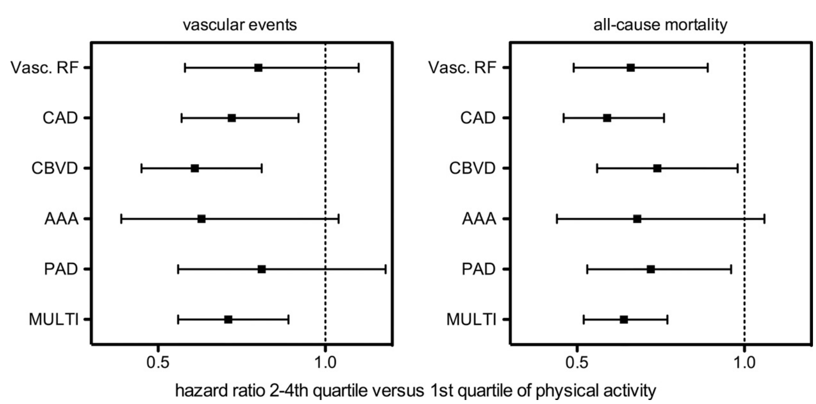

FIGURE 1—HR for vascular events and all-cause mortality according to level of physical activity in different categories of vascular disease or risk factors. The Cox regression model is adjusted for age, sex, smoking status, and current alcohol consumption (see Table, Supplemental Digital Content 5, HR displayed in Figure 1, http://links.lww.com/MSS/A539). MULTI, multiple manifestations of vascular disease; vasc. RF, vascular risk factors.

With respect to the association between increasing levels of physical activity and mortality, conflicting results in patients with CAD have been found. One study found higher risk of cardiovascular mortality in daily active patients in comparison with that in patients who were active 2–4 times a week (20). However, our results agree with other studies that also found further risk reduction of approximately 10%–20% with increasing levels of physical activity (4,8,19).

The reduced risk of vascular events and mortality associated with physical activity may partially be attributed to its effects on the traditional risk factors for vascular disease, as it improves the lipid profile (10), lowers blood pressure (32), and improves glycemic control and insulin resistance (2). It has also been postulated that the positive effects of physical activity are mainly caused by its direct effects on the vasculature function and structure (30). In the present study, we found no evidence for an intermediate effect of the traditional risk factors on the relation between physical activity and vascular events and mortality, suggesting that the indirect effect through traditional risk factors may not be the main mechanism and other mechanisms such as direct effects on the vasculature may be more important.

The found associations may have been caused by the severity of disease in those who are physically inactive and not by physical activity itself. After excluding patients without any leisure time physical activity, the associations remained significant. In addition, exclusion of patients with less than 2 yr of follow-up and stratified analyses for the severity of the vascular disease resulted in only minor differences in the association with physical activity.

The major strengths of our study are the large study population, prospective design, nearly complete follow-up, and intense monitoring of outcomes, which allowed us to precisely investigate the association of physical activity with the study outcomes. Second, the information on manifestations of vascular disease at baseline allowed us to investigate this association in these different disease categories. Third, extensive information on risk factors allowed us to investigate whether this association was independent of these possible confounders.

Our study also has several limitations. First, physical activity was measured by a self-report questionnaire, which can be biased by the recall of patients and social desirability (15). This could have led to misclassification, especially in the most physically active group, and this could have led to underestimation of the benefits of physical activity. However, we tried to minimize this by using a validated questionnaire (23). Second, the MET value used in the calculation was established using primarily middle-age persons, and reflect an absolute intensity level, without taking relative intensity into account. Relative intensity may be a better predictor, as low levels of absolute intensity may be a high relative intensity in persons with poor cardiorespiratory fitness. Indeed, in older men, the relative intensity of physical activity was a stronger predictor of lower CHD rates than absolute intensity (METs) (17). Third, physical activity was only assessed at baseline and some of the participants may have changed their level of physical activity, which leads to a higher probability of misclassification. In approximately 20% of patients with CAD, changes have been reported (8,20,28,31).

In summary, in this large cohort of patients with various manifestations of vascular disease or vascular risk factors, light-to-moderate levels of leisure time physical activity were already associated with significantly reduced risk of recurrent vascular events and mortality. This association was not restricted to patients with CAD but was also observed in patients with CBVD, AAA, and PAD as well as in patients with multiple manifestations of vascular disease. These results support the recommendations on physical activity in patients with vascular disease. These recommendations apply similarly to patients with CAD, CBVD, PAD, and AAA. These results also indicate that the cardiac rehabilitation program, which is offered to patients with CAD, should also be investigated in patients with other manifestations of vascular disease.

Funding for this article was received as part of a grant from the Netherlands Organization for Scientific Research—Medical Sciences (NWO-MW, project number 904-65-095). The Netherlands Organization for Scientific Research—Medical Sciences had no role in the design, data collection, data analyses, and data interpretation of the study or writing of the article.

The authors conducted this study on behalf of the SMART Study Group. The members of the SMART Study Group are as follows: A. Algra, M.D., Ph.D., Y. van der Graaf, M.D., Ph.D., D. E. Grobbee, M.D., Ph.D., and G. E. H. M. Rutten, M.D., Ph.D., Julius Center for Health Sciences and Primary Care; F. L. J. Visseren, M.D., Ph.D., Department of Vascular Medicine; F. L. Moll, M.D., Ph.D., Department of Vascular Surgery; L. J. Kappelle, M.D., Ph.D., Department of Neurology; W. P. T. M. Mali, M.D., Ph.D., Department of Radiology; and P. A. Doevendans, M.D., Ph.D., Department of Cardiology.

The authors declare that they have no conflicts of interest to disclose.

The results of the present study do not constitute endorsement by American College of Sports Medicine.

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