Globally, stroke and myocardial infarction (MI) are two of the most common causes of death and disability among adults [1]. Previous studies have shown a strong correlation between high blood pressure (BP) and an increased risk of stroke and MI [2,3]. The exercise stress test, as an addition to myocardial scintigraphy and coronary angiography, has been used for a long time in clinical practice to evaluate the risk of cardiovascular disease (CVD), especially in terms of coronary events among high-risk patients. During exercise stress tests, symptoms, electrocardiography and a variety of physiological responses to physical activity are assessed, including repeated measurements of BP. BP levels increase physiologically during exercise. For some individuals, SBP may increase beyond 210 mmHg, known as hypertensive responsive to exercise (HRE) [4]. It is well known that resting BP is strongly correlated to the risk of CVD, while knowledge relating to the prognostic value of HRE for CVD, such as stroke and MI, is limited [5–8]. In addition, many but not all patients with hypertension also have an HRE, but there is no common consensus on the predictive value of this response for CVD or other health-related causes in clinical practice, as the results from previous studies diverge [6,9–11]. The aim of the current study was more specifically to identify the role of SBP reactions during maximum workload using an exercise stress test on the long-term risk of stroke and MI.

INTRODUCTION

Long-term risk of stroke and myocardial infarction in middle-aged men with a hypertensive response to exercise: a 44-year follow-up study

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Introduction: Data on the prognostic value of hypertensive response to exercise in cardiovascular disease are limited. The aim was to determine whether SBP reactions during exercise have any prognostic value in relation to the long-term risk of stroke and myocardial infarction (MI).

Patients and methods: A representative cohort of men from Gothenburg, Sweden, born in 1913, who performed a maximum exercise test at age 54 years, \((n = 604)\), was followed-up for a maximum of 44 years with regard to stroke and MI.

Results: Among the 604 men, the mean resting and maximum SBP was 141.5 (SD 18.8) and 212.1 (SD 24.6) mmHg, respectively. For maximum SBP, the risk of stroke increased by 34% (hazard ratio 1.34, 95% confidence interval 1.11–1.61) per 1-SD increase, while no risk increase was observed for MI. The highest risk of stroke among blood pressure groups was observed among men with a resting SBP of at least 140 mmHg and a maximum SBP of at least 210 mmHg with an hazard ratio of 2.09 (95% confidence interval 1.29–3.40), compared with men with a resting SBP of less than 140 mmHg and a maximum SBP of less than 210 mmHg, independent of smoking, blood glucose, cholesterol and BMI.

Conclusion: Among middle-aged men with high resting and maximum blood pressure during maximum exercise workload, an increased risk of stroke was observed but not for MI. Further studies with larger sample sizes are needed to investigate the underlying mechanisms of the increased risk of stroke among individuals with hypertensive response to exercise.

Keywords: blood pressure, cardiovascular disease, epidemiology, exercise test, myocardial infarction

Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HRE, hypertensive reaction to exercise; MI, myocardial infarction

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PATIENTS AND METHODS

Study population
A detailed description of the study population has previously been reported [12,13]. In brief, all men born in 1913 on dates evenly divisible by three and living in Gothenburg, Sweden, in 1962 were invited to participate in a medical examination. Of the 973 invited, 855 men (88%) accepted and were examined in 1963. A re-examination of the men, in which 803 men participated, was performed in 1967. The re-examination included a submaximum exercise test, followed by a maximum exercise test, as described, in which 792 men were eligible [14].

Medical examination and exercise test
Before the exercise test, a medical and physical examination was performed and a medical history was taken. At the time of the study in 1967, a maximum workload test was considered to be a risk for persons with CVD. Therefore, specific conditions were set up to decide whether or not a maximum workload could be applied after a submaximum load. In summary, participants with an established heart disease were subjected only to submaximal testing. Moreover, those with chest pain significant ECG changes, arrhythmias and SBP of more than 300 mmHg or severe airway obstruction during submaximal testing were excluded from performing a maximal exercise test. Participants treated for hypertension were also excluded from maximum exercise testing [14].

The exercise test was performed with workloads, using the principles of Astrand and Rodahl, which were the standards at the time of the study [15,16]. One or several maximum workloads above the lowest load were used. Each individual was assumed to perform a total working time of 4–6 min at maximum level. The test was only interrupted due to severe fatigue or dyspnoea or pain in muscles, joints or the chest and electrocardiography changes during exercise. Maximum oxygen uptake (VO2max) was estimated, as previously described, using the determined submaximum and maximum heart rates (HRs) and an internally validated formula based on a subsample of the present material, where maximum oxygen uptake was determined during ergospirometry [12,17].

Definitions of blood pressure groups and other risk factors
Resting BP was recorded in the right arm, with the participant in a sitting position after a 5-min rest, with a mercury sphygmomanometer cuff size of 12 x 23 cm. Normal resting SBP was defined as a BP of less than 140 mmHg. During the exercise test, BP was measured during the fifth minute for each workload at the submaximum workloads and at the maximum load after 2 min of exercise. The HR from electrocardiography was measured initially every minute and then every 30 s to establish the maximum HR. During exercise, the patient reported the rated perceived exertion according to the well established Borg scale [18]. Using the scale steps from 6 (no exertion) to 20 (maximum exertion), it was recorded repeatedly to establish the peak value of maximum exertion. In the current study, an SBP of 210 mmHg or higher during the exercise test was regarded as an HRE, as defined by the American Heart Association [4]. Participants were divided into BP groups depending on SBP at rest and maximum levels during the exercise test.

(1) Group 1: Low rest and low response BP group, defined as less than 140 mmHg SBP at rest and as less than 210 mmHg maximum SBP during the exercise test.
(2) Group 2: Low rest and high response BP group, defined as less than 140 mmHg SBP at rest and as at least 210 mmHg maximum SBP during the exercise test.
(3) Group 3: High rest and low response BP group, defined as at least 140 mmHg SBP at rest and as less than 210 mmHg maximum SBP during the exercise test.
(4) Group 4: High rest and high response BP group, defined as at least 140 mmHg SBP at rest and as at least 210 mmHg maximum SBP during the exercise test.

Body weight was measured with a lever balance to the nearest tenth of a kilogram, while height was measured to the nearest centimetre. BMI was measured as weight (kg)/height (m)². Waist circumference (centimetres) was measured with a soft tape over the umbilicus. After an overnight fast, blood samples for serum cholesterol (measured as mg/100 ml but converted to mmol/l) and blood glucose (measured as mg/100 ml but converted to mmol/l) were drawn from an antecubital vein, with light stasis, and analysed according to standard laboratory procedures. Smoking habits were measured by a questionnaire. Smoking was defined as ongoing smoking or smoking cessation less than 1 month previously.

Follow-up and clinical endpoints
All the participants were followed from baseline after the exercise test in 1967 until the first event of a stroke, MI or until the end of this study, on 31 December 2011 (44-year follow-up). Data on hospital admissions were obtained from follow-up data in the study and from the National Hospital Discharge Register, covering all hospital admissions in the country. Mortality data were obtained from the National Cause of Death Register, covering all deaths domestically or abroad among Swedish residents, whether or not they were citizens. Mortality and hospital discharge diagnoses were classified according to the International Classification of Diseases (ICD) codes ICD 8 until 1986; ICD 9 until 1996 and ICD 10 from 1997 onwards. For stroke, we requested medical records from the hospital where the patient was diagnosed for a stroke according to the National Hospital Discharge Register. These records were then scrutinised and reviewed by specialists in neurology and internal medicine to verify the stroke diagnosis. In 14 strokes, we never received the requested medical records. In these cases, the stroke diagnoses according to the National Hospital Discharge Register were accepted, ICD 8, 9 430–438 and ICD 10 160–164, 169 and G45. For MI, the following discharge diagnosis was used, ICD 8, 9 430 and ICD 10 121. The positive predictive value for discharge diagnosis in the
Swedish National Hospital Discharge registers differs for diagnoses, but it is generally high, 85–95% [19,20].

**Statistical analysis**

For continuous variables, baseline characteristics are shown as the means and SDs, while, for categorical variables, they are shown as numbers (n) and percentages (%). For group comparisons an analysis of variance (continuous variables) and chi-squared (categorical variables) test was used. A P value of less than 0.05 was considered statistically significant. The incidence rate per 1000 person-years was estimated as the total number of events divided by the total follow-up time for stroke and MI separately. A Cox proportional hazard regression model was used to estimate the risk of stroke and MI separately, yielding hazard ratios with 95% confidence intervals (CIs) and a c-index for each model. For continuous variables, resting SBP levels at rest and maximum SBP (standardized), both predictors were simultaneously entered in a forced-entry Cox model adjusted for covariates with interaction effects and a maximum SBP (standardized), both predictors were simultaneously entered in a forced-entry Cox model adjusted for covariates with interaction effects and a P value of less than 0.05 was considered significant. Cubic splines (four knots) were used to estimate resting and maximum SBP for stroke and MI separately per mmHg increase; an SBP of 120 mmHg was used as a reference level for resting and 210 mmHg for maximum SBP. Cumulative risks were estimated after adjusting for competing risk of all-cause mortality using a cumulative incidence function according to the Fine–Gray method and are reported as the cumulative probability. All statistical analyses were implemented with R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) [21].

**Ethics**

Informed consent was given by all participants and followed the Declaration of Helsinki in 1964. Research ethics approval was obtained on several occasions, first from the Research Ethics Committees in Gothenburg and Uppsala, Sweden, and later from the Regional Ethics Review Board, Uppsala, Sweden, No 2011/304.

**RESULTS**

Of the 792 men who were eligible for the exercise test, 136 did not complete the maximum exercise test [12]. Of these, 39 had incomplete data on maximum SBP, nine men were taking prescribed antihypertensive drugs or medications affecting HR and four men had incomplete mortality dates. These men were excluded from the analysis. As a result, the final study population consisted of 604 men.

**Baseline characteristics**

The baseline characteristics of the study population are shown in Table 1. Of the 604 men, the overall mean value for normal resting and maximum SBP was 141.5 (SD 18.8) and 212.1 (SD 24.6) mmHg, respectively. The maximum HR for those performing a maximum exercise test was 172.2 bpm (SD ± 12.1), with an increasing rate for each incremental BP group. Smoking was prevalent in each BP group. A total of 237 men (21.5%) had a resting SBP of at least 140 mmHg and a maximum SBP of at least 210 mmHg. From the first to the last SBP group, DBP,

| TABLE 1. Baseline characteristics of the study population and by blood pressure groups in men aged 54 years |
|-------------------------|
| All, N = 604 | Group 1, N = 144 | Group 2, N = 109 | Group 3, N = 114 | Group 4, N = 237 | P |
| SBP at rest (mmHg) | 141.5 ± 18.8 | 123.0 ± 8.7 | 125.6 ± 7.7 | 148.7 ± 10.0 | 156.6 ± 14.4 | <0.001 |
| Max SBP (mmHg) | 212.1 ± 24.6 | 187.6 ± 13.1 | 223.7 ± 12.2 | 191.0 ± 11.6 | 231.9 ± 16.5 | <0.001 |
| DPP (mmHg) | 89.3 ± 11.1 | 81.9 ± 10.1 | 84.6 ± 8.8 | 92.4 ± 8.9 | 94.4 ± 10.2 | <0.001 |
| Heart rate at rest (bpm) | 66.2 ± 11.4 | 64.7 ± 11.6 | 63.9 ± 10.1 | 67.7 ± 11.2 | 67.5 ± 11.7 | <0.05 |
| Heart rate at max workload (bpm), SD | 172.2 ± 12.1 | 170.1 ± 12.0 | 171.6 ± 12.5 | 172.1 ± 11.9 | 173.9 ± 12.0 | <0.05 |
| VO₂max (l/min) | 2.3 ± 0.3 | 2.2 ± 0.3 | 2.3 ± 0.2 | 2.2 ± 0.2 | 2.3 ± 0.3 | <0.05 |
| S-cholesterol (mmol/L) | 6.3 ± 1.0 | 6.2 ± 1.1 | 6.2 ± 1.0 | 6.4 ± 1.0 | 6.4 ± 1.0 | NS |
| Waist circumference (cm) | 86.8 ± 9.3 | 84.1 ± 8.5 | 87.2 ± 9.4 | 85.8 ± 9.0 | 88.8 ± 9.4 | <0.001 |
| BMI (kg/m²), SD | 25.0 ± 3.1 | 24.0 ± 2.8 | 25.2 ± 3.1 | 24.7 ± 3.1 | 25.7 ± 3.1 | <0.001 |
| Blood glucose (mmol/L) | 3.7 ± 1.1 | 3.7 ± 0.8 | 3.7 ± 1.2 | 3.7 ± 0.7 | 3.8 ± 1.5 | NS |
| Rated perceived exertion | 17.7 ± 1.5 | 17.8 ± 1.5 | 17.8 ± 1.7 | 17.8 ± 1.5 | 17.6 ± 1.5 | NS |
| Smoking, n (%) | 319 (52.8%) | 72 (50.0%) | 61 (56.0%) | 66 (57.9%) | 120 (50.6%) | NS |

Results on continuous variables are expressed as mean ± SD. Group 1: Low rest response blood pressure group, defined by less than 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 2: Low rest/high response blood pressure group, defined by less than 140 mmHg resting SBP and at least 210 mmHg maximum SBP. Group 3: High rest/high response blood pressure group, defined by at least 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 4: High rest response blood pressure group, defined by at least 140 mmHg resting SBP and at least 210 mmHg maximum SBP.
Risk of stroke, myocardial infarction and death according to blood pressure groups

The correlation between resting and maximum SBP was modest ($r = 0.4, P < 0.01$). By combining resting and maximum SBP cut-offs, four categorical BP groups were created. Table 3 shows the incidence rates of stroke, MI and all-cause mortality by BP groups, while Fig. 2 shows the probability of an event adjusted for competing risk of death. The incidence rate of stroke increased for each level of BP groups, from 6.20 (95% CI 3.98–9.23) in the first group to 11.60 (8.95–14.78) per 1000 person-years in the last group. The incidence of MI between BP groups was less pronounced, 3.64 (95% CI 2.10–5.37) in the first group to 5.90 (4.22–7.96) per 1000 person-years. Similar trend for BP groups was observed for all-cause mortality but with an overall higher incidence rate (27.29 per 1000 person-years, 95% CI 34.34–40.43) than both stroke and MI.

The risk of stroke was similar among the different BP groups during the first years, but it started to differ after 10 years (Fig. 2). At the end of the study (44 years of follow-up), the risk of stroke was 16% in the first group, 22% in the second group, 21% in the third group and 27% in the last group. For MI, the risk between BP groups started to differ after 10 years of follow-up. The corresponding risk of MI before the end of the study was 27, 34, 26 and 32%, respectively.

Table 4 shows the risk of stroke, MI and all-cause mortality by BP groups. In overall terms, the highest risk of stroke was observed among men with a resting SBP of at least 140 mmHg and a maximum SBP of at least 210 mmHg, with an hazard ratio of 2.08 (95% CI 1.30–3.32). The risk remained after adjusting for smoking, blood glucose, cholesterol and BMI (hazard ratio 2.09, 95% CI 1.29–3.32). The analysis did not suggest any risk for BP levels on MI or all-cause mortality. A sensitivity analysis with adjustment for $\text{VO}_2\text{max}$ in addition to other comorbidities was performed with similar results; HRE remained predictive for stroke during a maximum exercise load, but not for MI or all-cause mortality (data not shown).

**DISCUSSION**

The main finding in the current study showed that HRE increased the risk of stroke but not of MI or all-cause mortality.
Hypertensive response and long-term cardiovascular disease risk

FIGURE 1 Cubic spline models for continuous variables of resting and maximum SBP and the risk of stroke. Panel (a) shows the risk of stroke and myocardial infarction per unit increase in SBP at rest, while panel (b) shows SBP at max (mmHg).

mortality. This was independent of BP at rest or other CVD risk factors among men and was consistent in both the linear and the category model during a 44-year follow-up.

In the current study, we observed that the risk of stroke was two times higher among men with an HRE and a high resting SBP (resting SBP of ≥140 mmHg and maximum SBP of ≥210 mmHg) when compared with a normotensive group and a normal response to exercise (SBP of <140 mmHg and maximum SBP of <210 mmHg). This categorical analysis is further supported by cubic spline analysis, which showed that, for resting SBP, the excess risk of stroke was observed after 135 mmHg, close to the well established cut-off of

| Events, person-years at risk and incidence rates with 95% confidence intervals of stroke, myocardial infarction and all-cause mortality by SBP groups |
|-----------------------------------------------|
| **Stroke** |   |   |   |   |
| Events, n (%) | Person-years | Incidence rate per 1000 person-years | Lower 95% CI | Upper 95% CI |
|----------------|--------------|--------------------------------------|--------------|--------------|
| Group 1  | 24 (17.5%) | 3868 | 6.20 | 3.98 | 9.23 |
| Group 2  | 24 (17.5%) | 2856 | 8.40 | 5.38 | 12.50 |
| Group 3  | 24 (17.5%) | 2779 | 8.64 | 5.53 | 12.85 |
| Group 4  | 65 (47.4%) | 5605 | 11.60 | 8.95 | 14.78 |
| All       | 137         | 15 108 | 9.07 | 7.61 | 10.72 |
| **Myocardial infarction** |   |   |   |   |
| Events, n (%) | Person-years | Incidence rate per 1000 person-years | Lower 95% CI | Upper 95% CI |
|----------------|--------------|--------------------------------------|--------------|--------------|
| Group 1   | 39 (21.3%) | 3963 | 9.84 | 7.00 | 13.45 |
| Group 2   | 37 (20.2%) | 3031 | 12.21 | 8.60 | 16.83 |
| Group 3   | 30 (16.4%) | 2878 | 10.42 | 7.03 | 14.88 |
| Group 4   | 77 (42.1%) | 5923 | 13.00 | 10.26 | 16.25 |
| All       | 183         | 15 795 | 11.59 | 9.97 | 13.39 |
| **All cause-mortality** |   |   |   |   |
| Events, n (%) | Person-years | Incidence rate per 1000 person-years | Lower 95% CI | Upper 95% CI |
|----------------|--------------|--------------------------------------|--------------|--------------|
| Group 1   | 140 (23.8%) | 3970 | 35.27 | 29.67 | 41.62 |
| Group 2   | 107 (18.2%) | 2973 | 35.99 | 29.50 | 43.50 |
| Group 3   | 110 (18.7%) | 2870 | 38.32 | 31.50 | 46.19 |
| Group 4   | 231 (39.3%) | 5956 | 38.78 | 33.94 | 44.12 |
| All       | 588         | 15 769 | 37.29 | 34.34 | 40.43 |

Group 1: Low rest/low response blood pressure group, defined by less than 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 2: Low rest/high response blood pressure group, defined by less than 140 mmHg resting SBP and at least 210 mmHg maximum SBP. Group 3: High rest/low response blood pressure group, defined by at least 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 4: High rest/high response blood pressure group, defined by at least 140 mmHg resting SBP and at least 210 mmHg maximum SBP. CI, confidence interval.
140 mmHg, and, for maximum SBP, an excess risk of stroke was found after 230 mmHg (Fig. 1). Exercise SBP or HRE has been shown to increase mortality, but with conflicting results regarding the correlation to CVD risk [6,22–24]. Our findings suggest that the elevation of SBP during exercise is associated with an increased risk of stroke, independent of CVD risk factors, but not of MI. Our results are in line with those of a previous study from eastern Finland that showed an increased stroke risk for those with HRE during (and post) exercise [25].

There is no consensus on the definition of HRE. Some authors suggest cut-offs to define HRE, while others are more descriptive [24,25]. Some studies suggest an SBP of at least 210 mmHg in men and more than 190 mmHg in women, while others define HRE at least 215 or at least 230 mmHg [23,26,27]. High BP or hypertension is the main risk factor for stroke (population attributable risk of 49%) and less pronounced for MI (population attributable risk 18%) [2,3]. The BP reaction during maximum working capacity in the current study further emphasises the risk of stroke in contrast to the risk of MI. These differences in the risk of MI and stroke separately by HRE could be related to the fact that stroke and MI share similar risk factors, but the impact of CVD risk factors differs [2,3,28]. The underlying mechanism is unknown. One possible explanation for the HRE could be a combination of an increased risk of endothelial dysfunction, left ventricular hypertrophy and arterial stiffness in the blood vessels [29–31]. Another factor might be that HRE might cause, or be a result of, a lower aerobic physical working capacity (i.e. VO\textsubscript{2max}).

### TABLE 4. Proportional hazards regression of risk of stroke, myocardial infarction and all-cause mortality by four different blood pressure groups

|                  | Model 1 |                  | Model 2 |                  |
|------------------|---------|------------------|---------|------------------|
|                  | HR      | Lower 95% CI     | Upper 95% CI | HR      | Lower 95% CI     | Upper 95% CI |
| Stroke           |         |                  |          |                  |
| Group 1          | Ref.    |                  |          | Ref.              |                  |
| Group 2          | 1.38    | 0.78             | 2.43     | 1.45              | 0.81             | 2.57        |
| Group 3          | 1.54    | 0.87             | 2.71     | 1.56              | 0.88             | 2.76        |
| Group 4          | 2.08    | 1.30             | 3.32     | 2.09              | 1.29             | 3.40        |
| Myocardial infarction | Ref.      |                  |          | Ref.              |                  |
| Group 2          | 1.23    | 0.78             | 1.93     | 1.17              | 0.74             | 1.85        |
| Group 3          | 1.19    | 0.74             | 1.91     | 1.13              | 0.70             | 1.82        |
| Group 4          | 1.44    | 0.98             | 2.12     | 1.29              | 0.87             | 1.92        |
| All cause mortality | Ref. |                  |          | Ref.              |                  |
| Group 2          | 1.04    | 0.81             | 1.33     | 1.04              | 0.80             | 1.34        |
| Group 3          | 1.23    | 0.96             | 1.58     | 1.19              | 0.93             | 1.53        |
| Group 4          | 1.21    | 0.98             | 1.49     | 1.11              | 0.90             | 1.38        |

Model 1 = unadjusted, Model 2 = adjusted for smoking, BMI, cholesterol and blood glucose. Group 1: Low rest/low response blood pressure group, defined by less than 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 2: Low rest/high response blood pressure group, defined by less than 140 mmHg resting SBP and at least 210 mmHg maximum SBP. Group 3: High rest/low response blood pressure group, defined by at least 140 mmHg resting SBP and less than 210 mmHg maximum SBP. Group 4: High rest/high response blood pressure group, defined by at least 140 mmHg resting SBP and at least 210 mmHg maximum SBP. CI, confidence interval, HR, hazard ratio, Ref., reference group.
which was a strong negative and independent predictor of total mortality in these men [12,32]. Consequently, physical maximum working capacity was a strong, independent, positive factor associated with reaching both 90 and 100 years in the study of men born in 1913, in Gothenburg, Sweden [33,34].

The use of an exercise test for coronary risk prediction is decreasing in favour of other methods, such as coronary angiography, scintigraphy and coronary computed tomography [35]. The results of the current study suggest that an exercise test may contain important information beyond the maximum aerobic capacity. The data suggest that the high BP response to exercise provides additional prognostic information beyond the well established relationship between SBP at rest and the risk of stroke.

The limitations of this study are the sample size and the fact that only men from one single city were studied. However, they were all of the same age, 54 years at start, and, consequently, no age adjustment was needed. The study was design in 1962. At that time the knowledge on the impact of cardiovascular risk factors was scares, and no power calculation was performed. The lack of association found between hypertensive response to exercise and MI might simply be due to a type-2 error. Furthermore, changes in risk factors and the standard of care in the treatment of them over time were inevitable. The strengths are the prospective design, including a random sample from the general population, and the unique follow-up time of 44 years. On the contrary, only a single resting BP was available. The homogenous cohort from the same geographical area might further limit the generalization of the results. The aim was, however, to investigate whether a BP measurement during an exercise test in midlife was able to predict the risk of stroke and MI over time (P for interaction NS).

In conclusion, a hypertensive response to a maximum exercise test in men at age 54 predicted stroke, but not MI, during a 44-year follow-up. The results provide additional prognostic information beyond the well established relationship between SBP at rest and the risk of stroke. The clinical implications are twofold; first, a maximum exercise test is of importance in cardiovascular risk prediction. Second, for better risk intervention not only resting but also BP after exercise should be managed, for example by individual advice linked to the degree of physical exercise.

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**Conflicts of interest**

P.L. is an employee of AstraZeneca R&D.

**REFERENCES**

1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392:1736–1788.

2. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet 2004; 364:937–952.

3. O’Donnell MJ, Chin SL, Ranganaraj S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 52 countries (INTERSTROKE): a case–control study. Lancet 2016; 388:761–775.

4. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013; 128:875–934.

5. Fagard R, Staessen J, Thijss J, Amery A. Prognostic significance of exercise versus resting blood pressure in hypertensive men. Hypertension 1991; 17:574–578.

6. Filipovsky J, Ducimetiere P, Safar ME. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. Hypertension 1992; 20:535–539.

7. Lewis GD, Gona P, Larson MG, Plehn JF, Benjamin EJ, O’Donnell CJ, et al. Exercise blood pressure and the risk of incident cardiovascular disease (from the Framingham Heart Study). Am J Cardiol 2008; 101:1614–1620.

8. Skeetelberg PT, Grundvold I, Kjeldsen SE, Engeseth K, Liestol K, Eriksen G, et al. Seven-year increase in exercise systolic blood pressure at moderate workload predicts long-term risk of coronary heart disease and mortality in healthy middle-aged men. Hypertension 2013; 61:1134–1140.

9. Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass? The Framingham Heart Study. Ann Intern Med 1992; 116:203–210.

10. Tsumura K, Hayashi T, Hamada C, Endo G, Fujii S, Okada K. Blood pressure response after two-step exercise as a powerful predictor of hypertension: the Osaka Health Survey. J Hypertens 2002; 20:1507–1512.

11. Goldtiener JS, Brown J, Zohlich J, Fletcher RD. Left ventricular hypertrophy in men with normal blood pressure: relation to exaggerated blood pressure response to exercise. Ann Intern Med 1990; 112:161–166.

12. Ladenfell P, Persson CJ, Mandalamikis Z, Wilhelmsen L, Grimby G, Svardsudd K, et al. Low aerobic capacity in middle-aged men associated with increased mortality rates during 45 years of follow-up. Eur J Prev Cardiol 2016; 23:1557–1564.

13. Hansson PO, Welin L, Tibblin G, Eriksson H. Deep vein thrombosis and pulmonary embolism in the general population. ‘The Study of Men Born in 1913. Arch Intern Med 1997; 157:1665–1670.

14. Grimby G, Bjure J, Aurell M, Ekstrom-Jodal B, Tibblin G, Wilhelmsen L. Work capacity and physiologic responses to exercise. Men born in 1931. Am J Cardiol 1972; 30:57–62.

15. Astrand PO. Human physical fitness with special reference to sex and age. Physiol Rev 1950; 36:907–935.

16. Astrand P, Rodahl K. Textbook of work physiology. New York: McGraw-Hill; 1970; 660.

17. Grimby G, Wilhelmsen L, Ekstrom-Jodal B, Aurell M, Bjure J, Tibblin G. Aerobic power and related factors in a population study of men aged 54. Scand J Clin Lab Invest 1970; 26:287–294.

18. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970; 2:92–98.

19. Koster M, Asplund K, Johannson A, Stegmayr B. Refinement of Swedish administrative registers to monitor stroke events on the national level. Neuroepidemiology 2013; 40:240–246.

20. Ludvigsson JF, Andersson E, Ekdorn A, Feychtling M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish National Inpatient Register. BMC Public Health 2011; 11:450.

21. R Core Team (2019). R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019. https://www.R-project.org/.
22. Weiss SA, Blumenthal RS, Sharrett AR, Redberg RF, Mora S. Exercise blood pressure and future cardiovascular death in asymptomatic individuals. *Circulation* 2010; 121:2109–2116.

23. Laukkanen JA, Kurl S, Salonen R, Lakka TA, Rauramaa R, Salonen JT. Systolic blood pressure during recovery from exercise and the risk of acute myocardial infarction in middle-aged men. *Hypertension* 2004; 44:820–825.

24. Schultz MG, Otahal P, Cleland VJ, Blizzard L, Marwick TH, Sharman JE. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. *Am J Hypertens* 2015; 28:557–566.

25. Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Systolic blood pressure response to exercise stress test and risk of stroke. *Stroke* 2001; 32:2036–2041.

26. Allison TG, Cordeiro MA, Miller TD, Daida H, Squires RW, Gau GT. Prognostic significance of exercise-induced systemic hypertension in healthy subjects. *Am J Cardiol* 1999; 83:371–375.

27. Hietanen HJ, Paakkön R, Salomaa V. Ankle blood pressure and pulse pressure as predictors of cerebrovascular morbidity and mortality in a prospective follow-up study. *Stroke Res Treat* 2011; 2011:729391–729391.

28. Giang KW, Bjorck L, Novak M, Lappas G, Wilhelmsen L, Toren K, et al. Stroke and coronary heart disease: predictive power of standard risk factors into old age – long-term cumulative risk study among men in Gothenburg, Sweden. *Eur Heart J* 2013; 34:1068–1074.

29. Stewart KJ, Sung J, Silber HA, Fleg JL, Kelemen MD, Turner KL, et al. Exaggerated exercise blood pressure is related to impaired endothelial vasodilator function. *Am J Hypertens* 2004; 17:314–320.

30. Tzemos N, Lim PO, MacDonald TM. Exercise blood pressure and endothelial dysfunction in hypertension. *Int J Clin Pract* 2009; 63:202–206.

31. Sharman JE, Hare JL, Thomas S, Davies JE, Leano R, Jenkins C, et al. Association of masked hypertension and left ventricular remodeling with the hypertensive response to exercise. *Am J Hypertens* 2011; 24:898–905.

32. Prasad VK, Drenowatz C, Hand GA, Lavie CJ, Sui X, Demello M, et al. Association between cardiorespiratory fitness and submaximal systolic blood pressure among young adult men: a reversed J-curve pattern relationship. *J Hypertens* 2015; 33:2239–2244.

33. Wilhelmsen L, Svardsudd K, Eriksson H, Rosengren A, Hansson PO, Welin C, et al. Factors associated with reaching 90 years of age: a study of men born in 1913 in Gothenburg, Sweden. *Int J Epidemiol* 2011; 40:441–451.

34. Wilhelmsen L, Dillborg M, Welin L, Svardsudd K. Men born in 1913 followed to age 100 years. *Scand Cardiovasc J* 2015; 49:45–48.

35. Wolk MJBS, Doherty JU, Douglas PS, Hendel RC, Kramer CM, Min JK, et al., American College of Cardiology Foundation Appropriately Use Criteria Task Force. ACCF/AHA/ASE/ASNC/HRS/HFSA/SCAI/SCCT/SCMR/STS2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease. *J Am Coll Cardiol* 2014; 63:380–406.