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Am J Cardiol. Author manuscript; available in PMC 2010 October 13.

Published in final edited form as:
Am J Cardiol. 2008 June 1; 101(11): 1614–1620. doi:10.1016/j.amjcard.2008.01.046.

Exercise Blood Pressure and the Risk of Incident Cardiovascular Disease (From the Framingham Heart Study)

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Abstract

Exaggerated systolic blood pressure (BP) augmentation with exercise has been associated with impaired endothelial function and cardiovascular risk. However, prior studies have been largely restricted to men, have not evaluated diastolic BP, and have focused on peak exercise measures, which are influenced by effort and fitness level. We sought to determine the association of exercise BP responses with the risk of incident cardiovascular disease (CVD). BP was assessed during Stage 2 of the Bruce protocol and during recovery in 3045 Framingham Study participants (mean age 43, 53% women). The association between exercise BP and CVD events during 20 years of followup was examined using Cox proportional hazards models. In age- and sex-adjusted analyses, exercise systolic and diastolic BP were associated with incident CVD (adjusted-hazards ratios (HR) for top quintile, 1.55 [95% confidence interval, 1.18–2.04] and 1.77 [1.35–2.31], respectively, relative to the lower 4 quintiles; p<0.005). After adjustment for resting BP and conventional risk factors, exercise diastolic BP (HR, 1.41 [1.01–1.95]; p=0.04), but not exercise systolic BP (HR, 0.97 [0.68–1.38]; p=0.86), remained a significant predictor of CVD. Similarly, among post-exercise recovery responses, only diastolic BP (HR, 1.53 [1.08–2.18]; p=0.02) predicted incident CVD in multivariable models. In middle-aged adults, diastolic BP during low-intensity exercise and recovery predicted incident CVD. In conclusion, our findings support the concept that dynamic BP provides incremental information to resting BP, and suggest that exercise diastolic BP may be a better predictor than exercise systolic BP in this age group.

Exercise treadmill testing (ETT) was performed routinely at the second examination of the Framingham Offspring cohort, which provided us the opportunity to investigate the association of exercise BP and incident atherosclerotic cardiovascular disease in apparently healthy,

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middle-aged adults. We examined both systolic and diastolic BP during exercise and recovery, and pre-specified low-level (Stage 2, Standard Bruce Protocol) rather than peak exercise to standardize exercise exposure and reduce confounding by heterogeneity in fitness level and motivation. We hypothesized that exercise systolic and diastolic BP would predict the long-term risk of cardiovascular disease, above and beyond resting BP and other conventional risk factors.

METHODS

In 1971, 5124 offspring and spouses of offspring of Original Cohort Framingham Heart Study participants were enrolled in the Framingham Offspring Study.1 The study design and selection criteria for the original and offspring cohorts have been described in detail elsewhere.1,2 The second examination of the offspring cohort was conducted from 1979 to 1982 and consisted of 3863 participants. Of the attendees, 3447 participants (89%) underwent routine ETT using the standard Bruce protocol. Participants were excluded from the present investigation for the following indications defined at baseline: age <20 or >69 years (n=14); use of antihypertensive medications (n=274);3 prevalent cardiovascular disease, defined by a history of myocardial infarction, coronary insufficiency (angina pectoris lasting ≥20 minutes and accompanied by ischemic ECG changes), heart failure or stroke (n=45); missing data on any of the BP measurements (n=8); inability to attain stage 2 of the Bruce protocol (n=84);4 and systolic BP in stage 1 or stage 2 that was lower than resting systolic BP (n=53). The last two criteria were included because poor exercise tolerance or a hypotensive exercise response may reflect the presence of severe multivessel coronary artery disease or critical valvular disease. The Boston University Medical Center reviewed the Framingham Heart Study protocol and all participants signed informed consent.

At all examinations, participants underwent a physician-obtained medical history and physical examination, anthropometry (including measurement of height and weight and calculation of body mass index [BMI]), and laboratory assessment of cardiovascular risk factors as previously described.1 BPs were measured by physician investigators using a mercury column sphygmomanometer and an appropriate-sized cuff. Resting systolic and diastolic BP were measured in the left arm after participants had been seated for at least five minutes according to a standardized protocol,5 and two readings were averaged. Participants were classified as current cigarette smokers if they smoked cigarettes regularly during the previous year. Criteria for diabetes mellitus were fasting glucose concentration of 126 mg/dL (7.0 mmol/L) or greater, or use of insulin or medications used to treat hyperglycemia. Electrocardiographic left ventricular hypertrophy was defined as increased voltage with accompanying lateral precordial repolarization abnormalities.6 Valvular heart disease was defined by the presence of a systolic murmur of grade 3/6 or greater or any diastolic murmur.

ETTs were performed according to the standard Bruce protocol[4] aiming for the attainment of 85% of the target heart rates (age- and sex-predicted maximal response). Systolic and diastolic BPs were recorded by cuff when the subject was standing, immediately before testing and at the midpoint of each 3-minute exercise stage. The recovery phase was for 4 minutes, with BP and heart rate recorded in the upright sitting position at the end of each minute. Twelve-lead ECGs were obtained at rest, at the end of each stage, and each minute for the first 4 minutes of recovery.

We examined exercise BPs as continuous and categorical variables. The categorical variables were defined according to whether exercise systolic and diastolic BPs exceeded the sex-specific 80th percentile (pre-specified cutpoint), obtained at the midpoint of the second stage of exercise. Systolic and diastolic BP change with exercise were defined as (systolic BP at stage 2 – systolic BP at rest) and (diastolic BP at stage 2 – diastolic BP at rest), respectively. Systolic and diastolic

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BPs during recovery were treated similarly; we analyzed BP obtained at the third minute of the recovery to correspond with the timing of previously reported BP and heart rate recovery measurements.[7,8]

A panel of three Framingham investigators adjudicated all suspected cardiovascular events, using information from medical records and Framingham clinic visits. Cardiovascular diagnoses were made on the basis of standardized criteria that have been in use since the inception of the cohort.[9] The composite atherosclerotic cardiovascular disease endpoint included myocardial infarction, coronary insufficiency (unstable angina with documented electrocardiographic changes), stroke, or CVD death. Coronary heart disease events were defined by new onset of angina pectoris, coronary insufficiency, myocardial infarction, or coronary heart disease death.[10]

Pearson correlations between BPs measured at rest, during exercise, and during recovery were estimated. Cox proportional hazards models were used to examine the association between BP variables and the 2 outcomes (total cardiovascular events and coronary heart disease events), after confirming that the assumption of proportionality of hazards was met. Each BP measurement (systolic and diastolic BP during exercise and recovery) was examined separately in multivariable-adjusted models. Exercise and recovery BP's were modeled as continuous variables and as categorical variables (comparing individuals in the top quintile with all others). We used four levels of adjustment: (1) age and sex, (2) age, sex, resting systolic BP, and resting diastolic BP, (3) age, sex, resting systolic BP, resting diastolic BP, BMI, diabetes, current cigarette smoking, total/high density lipoprotein (HDL) cholesterol ratio, valvular heart disease, and electrocardiographic left ventricular hypertrophy, and (4) the third model plus exercise test variables demonstrated to be of prognostic importance: exercise duration,11 ischemic ST-segment response to exercise (>1mm horizontal or downsloping ST-segment depression versus none),12 premature ventricular contractions (present versus absent),13 chronotropic incompetence (present versus absent),14 and abnormal heart rate recovery measured 3-min post-exercise (present versus absent).15

In secondary analyses, we substituted systolic and diastolic BP *change* from rest to the midpoint of stage 2, in place of absolute BP values at stage 2 of treadmill testing. BP changes were then examined in the 4 multivariable-adjusted models described above. Using multiplicative interaction terms, we also tested whether age or sex modified the association between exercise BP and cardiovascular events. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were done using the Statistical Analysis System, version 8.2 (SAS Institute, Cary, N.C.).

RESULTS

The clinical and exercise characteristics of the study cohort are summarized in Table 1 and Table 2. The distributions of BP responses during stage 2 of exercise and at 3 minutes of recovery are shown in Figure 1 and Figure 2, respectively. Resting systolic BP was strongly correlated with systolic BP during stage 2 of exercise ($r=0.60$, $p<0.001$) and at 3 minutes of recovery ($r=0.56$, $p<0.001$). Weaker correlations were observed between diastolic BP at rest and diastolic BP during exercise ($r=0.40$, $p<0.001$) and recovery ($r=0.48$, $p<0.001$). The correlations between systolic and diastolic BP during stage 2 of exercise and at 3 minutes of recovery were 0.58 and 0.38, respectively, ($p<0.001$ for both).

During a mean follow up of 19 years, 240 patients experienced a first cardiovascular event. The events included myocardial infarction (n=140), coronary insufficiency (n=18), cerebrovascular accident (n=61), sudden cardiac death (n=12), and other death attributable to CVD (n=9). 181 individuals experienced a first coronary heart disease event. Figure 3 displays

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unadjusted Kaplan-Meier curves for cardiovascular events, according to baseline exercise systolic and diastolic BP.

Results of multivariable models relating exercise BP to the risk of cardiovascular and coronary heart disease events are shown in Table 3. In age- and sex-adjusted models, both systolic and diastolic BP during exercise predicted the risk of cardiovascular events. After adjustment for resting systolic and diastolic BP, exercise diastolic BP remained predictive of cardiovascular events, but exercise systolic BP did not (Table 3). In multivariable-adjusted models incorporating conventional risk factors and other ETT variables, each SD increment in diastolic BP was associated with an adjusted HR of 1.32 (95% CI, 1.11–1.56; p=0.002) for cardiovascular events. An exercise diastolic BP at or above the 80th percentile was associated with an adjusted HR of 1.41 (95% CI, 1.01–1.95; p=0.04) compared to individuals in the lower 4 quintiles. Results for the coronary heart disease endpoint were similar (Table 3).

To assess the prognostic utility of BP *change* with exercise, we substituted systolic and diastolic BP change from rest to the midpoint of stage 2, in place of absolute BP values at stage 2. Continuous diastolic BP change (HR 1.02, 95% CI 1.01–1.04, p<0.001) but not systolic BP change (HR 1.006, 95% CI 0.998–1.01, p=0.12) predicted cardiovascular events in multivariable-adjusted models incorporating conventional risk factors and other ETT variables.

Results of multivariable Cox models relating recovery BP to cardiovascular events are shown in Table 4. Recovery systolic and diastolic BPs were associated with increased risks for cardiovascular events in age- and sex-adjusted models. After adjustment for resting BP alone, or resting BP plus clinical covariates, recovery diastolic BP remained a significant predictor of cardiovascular events in models using the 80th percentile threshold. This association was not significant in models using continuous recovery diastolic BP (Table 4). Recovery systolic BP was not significantly related to risk of cardiovascular disease in any models adjusting for resting BP. Results were similar for coronary heart disease events (Table 4). In secondary analyses, there was a significant, negative interaction between age and exercise diastolic BP (p=0.01) in multivariable models. Interactions of age or sex with other exercise BP variables were not significant.

DISCUSSION

In this prospective, community-based study, elevated diastolic BP during exercise or recovery predicted an increased risk of future cardiovascular disease, above and beyond resting BP and other conventional risk factors. Exercise and recovery systolic BPs were not related to incident cardiovascular events after adjustment for resting BP. The validity of our findings is supported by the use of a large, well-characterized cohort; the availability of 20 years of follow-up; the adjudication of cardiovascular and coronary heart disease events by a blinded panel of investigators; the standardized ETT protocol; and adjustment for other ETT measurements.

Our findings extend the results of prior studies, which have focused on men[16–18] and have examined systolic BP only.16–18 Additionally, studies that have shown an association between exercise-induced hypertension and cardiovascular risk have utilized bicycle ergometry16,17 instead of treadmill ETT, which is the typical exercise testing modality used in the United States. We analyzed BP during an early stage of incremental exercise (stage 2) instead of peak exercise,18 or fixed moderate exercise,16,19 which has been the focus of other studies. Examining the response to low-level exercise standardizes the exercise exposure and reduces confounding by heterogeneity in fitness level and motivation. The prognostic value of low-level treadmill exercise may be of particular value in patients unable to sustain exercise at or beyond stage 2 (6 METs). Moreover, stage 2 exercise correlates with levels of daily physical

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activities, and therefore BP measurements during this stage reflect the BP to which patients are exposed regularly.

Notably, our findings are in contrast to those of reports based on persons with known or suspected coronary artery disease, in whom peak exercise systolic BP is associated with a *lower* incidence of adverse cardiovascular outcomes,[20] lower rates of angiographic coronary artery disease,[20] and lower all-cause mortality.[21] These discrepancies emphasize the differences between unselected, ambulatory cohorts and referral cohorts. Studies that have found a "protective effect" of exercise hypertension were done in older samples with significant burdens of coronary artery disease and lower exercise capacities.[20,22] In these cohorts, inability to augment systolic BP probably reflects inadequate cardiac output in the setting of myocardial ischemia or left ventricular dysfunction.

BP during dynamic exercise is determined by the interaction between increased cardiac output and reduced total peripheral vascular resistance. In healthy individuals, augmentation of cardiac output out of proportion to dilation of resistance vessels in exercising skeletal muscle results in a sharp increase in systolic BP, with a more modest, if any, elevation in diastolic BP.[23] The fact that systolic BP rises markedly during exercise in healthy individuals may explain the weaker association between exercise systolic BP and cardiovascular risk in an ambulatory cohort, as opposed to a referral cohort. In contrast, it may be reasonable to regard large increases in diastolic BP during exercise as "abnormal." Interestingly, secondary analyses indicated a negative interaction between age and exercise diastolic BP, which suggests that a heightened diastolic BP response to exercise may be of particular prognostic significance in younger individuals. This observation is consistent with data from Framingham[24] and other cohorts[25] showing that, at rest, diastolic BP may have greater prognostic value than systolic BP in younger individuals.

The close correlation between resting systolic BP and exercise and recovery systolic BP suggests that systolic BP response to low-level exercise closely mirrors rest systolic BP. In contrast, the weaker correlation between rest diastolic BP and exercise and recovery diastolic BP, coupled with the higher hazard ratios associated with elevated exercise diastolic BP responses, suggests that exercise diastolic BP provides additional information in assessing vascular reactivity in response to low-level exercise.

In addition to reduced arterial compliance, [26] autonomic dysfunction[27] is a putative mediator of exaggerated BP elevation in response to exercise. Exaggerated sympathetic nervous system activation in response to physical activity and attenuated vagal reactivation upon cessation of physical activity[28] may also mediate other findings on ETT that have been related to adverse outcomes, such as ventricular ectopy,[13] and delayed heart rate recovery after exercise.[29] Notably, however, adjustment for these other exercise measurements did not alter the association between exercise and recovery diastolic BP and cardiovascular disease.

Lastly, prior studies suggest that exercise diastolic BP is a stronger predictor of future hypertension than exercise systolic BP.[7] It is possible that the association between exercise diastolic BP and future cardiovascular events was partly mediated by the interim development of hypertension. The development of hypertension might provide another explanation for the apparent superiority of exercise diastolic BP compared with exercise systolic BP as a predictor of cardiovascular disease in this age group.

The reproducibility of exercise BP has not been evaluated in the Framingham Heart Study, but earlier studies have indicated similar BP reproducibility during exercise compared with resting conditions.[30] There are few data on the reproducibility of systolic BP versus diastolic BP during exercise, although the latter is generally regarded as harder to measure given that low frequency Korotkoff sounds may be difficult to hear with the background treadmill noise. Because

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measurement error would tend to create a conservative bias, it cannot explain the stronger association of exercise diastolic BP with cardiovascular risk compared with exercise systolic BP.

Termination of exercise tests when subjects reached 85% of the maximum predicted heart rate may have attenuated inter-individual differences in recovery BPs. This would tend to bias our results against being able to detect an independent association between recovery BPs and cardiovascular events. On the other hand, cessation of exercise at 85% of the maximum heart rate results in a more uniform starting point for the recovery period. In addition, our cohort was young-to-middle aged and of European descent. The generalizability of our data to other ages and ethnicities/races is unknown.

Acknowledgments

From the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195), the Harvard-MIT Clinical Investigator Training Program (Dr. Lewis), a American Heart Association Fellow-to-Faculty Grant (Dr. Lewis), and grants RO1-HC-25195, K23-HL074077 (Dr. Wang), and K24-HL-04334 (Dr. Vasan), from the National Heart, Lung, and Blood Institute of the NIH.

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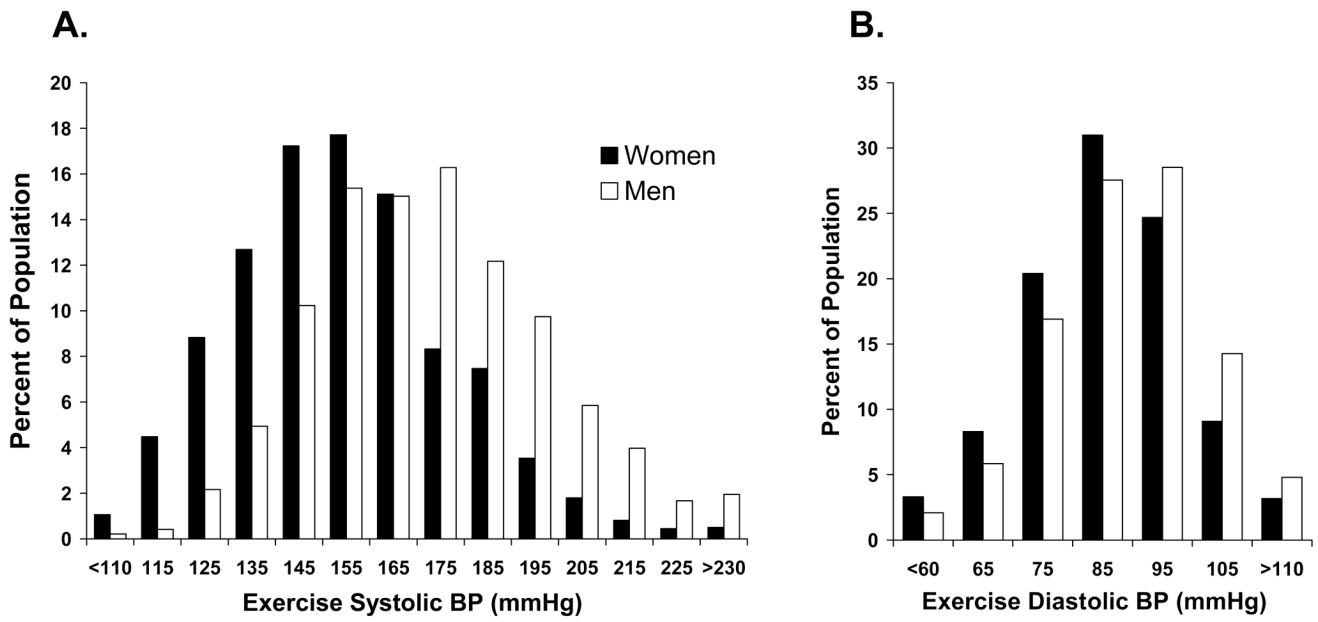

Figure 1. Distribution of Blood Pressures during Exercise

Histograms showing the distribution of systolic and diastolic BP responses (panel A and B, respectively) for men and women at stage 2 of exercise. BP values plotted represent interval midpoints (e.g., 115 mm Hg represents range 110–119 mm Hg).

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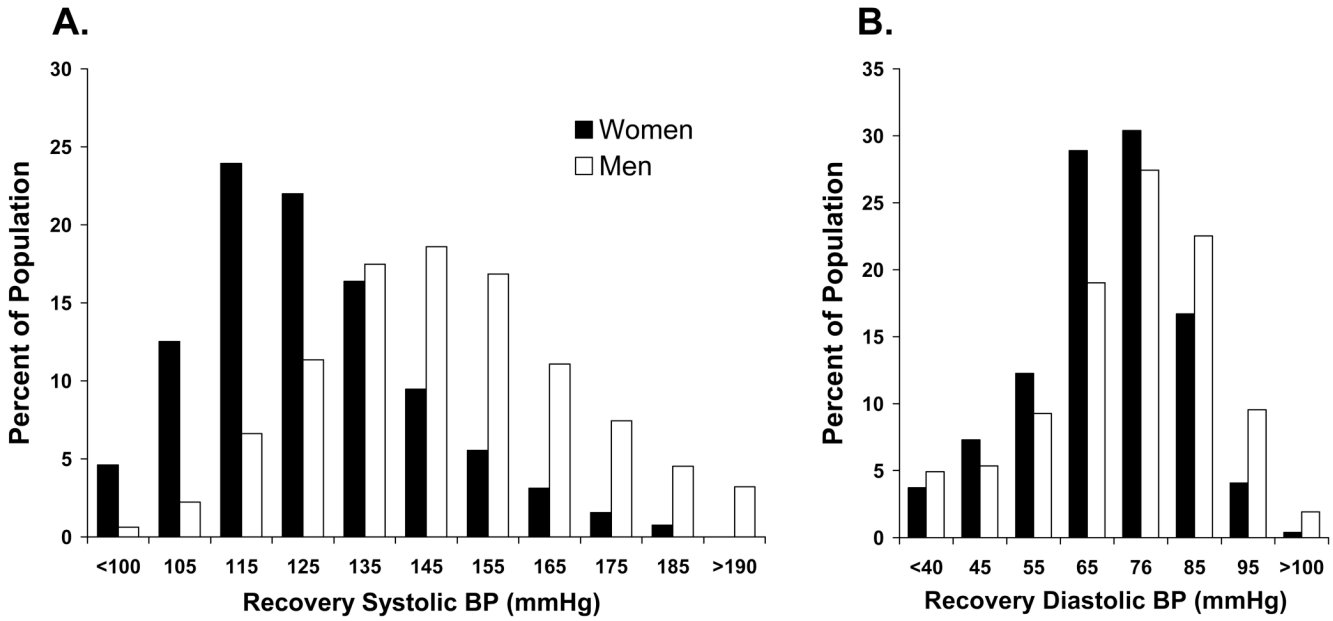

Figure 2. Distribution of Blood Pressures during Recovery from Exercise

Histograms showing the distribution of systolic and diastolic BP responses (panel A and B, respectively) for men and women at the third minute of recovery following exercise. BP values plotted represent interval midpoints (e.g., 115 mm Hg represents range 110–119 mm Hg).

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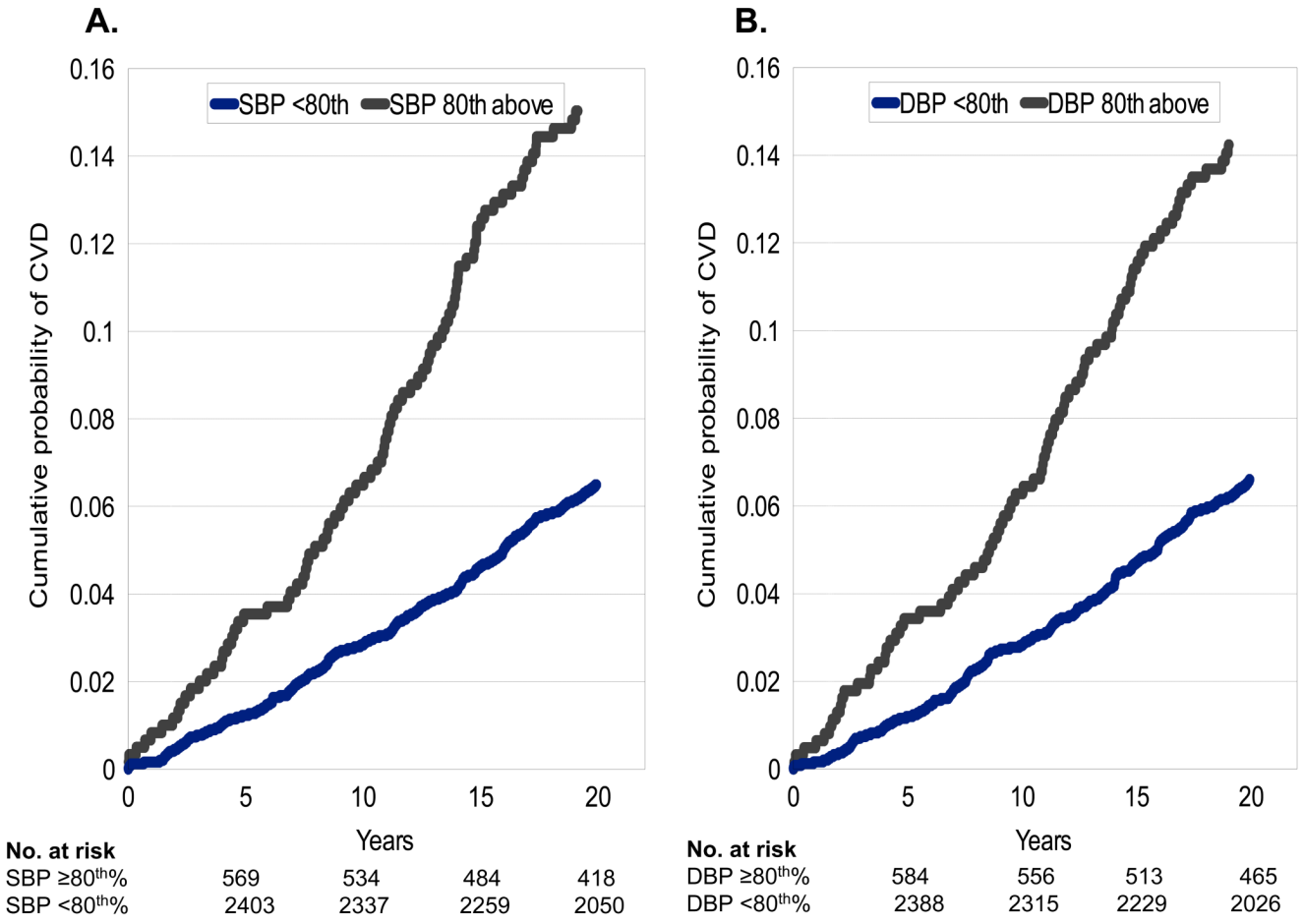

Figure 3. Kaplan-Meier Plot: Blood Pressure

Kaplan-Meier plot of survival free of cardiovascular events according to the presence of systolic and diastolic BP in excess of the sex-specific 80th percentile (Panel A and B, respectively), obtained at the midpoint of the second stage of exercise.

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Table 1

Baseline clinical characteristics of study subjects

Characteristics	Men (n=1437)	Women (n= 1608)
Age (years)	43±10	43±10
Systolic blood pressure (mmHg)	122±18	116±18
Diastolic blood pressure (mmHg)	79±12	74±11
Body mass index (kg/m^2)	26.5±3.5	24.2±4.4
Diabetes mellitus	2.5%	1.0%
Current tobacco use	43.5%	35.5%
Total/HDL cholesterol ratio	5.0±1.6	3.9±1.3
Valvular heart disease	0.3%	0.6%
Electrocardiographic left ventricular hypertrophy	1.7%	0.6%

Results are expressed as mean ± SD or percentage

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Table 2

Exercise characteristics of study participants

Characteristics	Men n = 1437	Women n = 1608
Exercise duration (minutes)	10.4±2.7	8.3±2.3
Resting heart rate (bpm)	71±11	77±11
Peak heart rate (bpm)	166±12	165±12
Attained target heart rate*	80%	76%
Systolic blood pressure, mmHg		
Mean, stage 2 exercise	171±25	153±23
80th percentile stage 2 exercise	190	170
Mean recovery (3 minutes)	146±21	125±18
80th percentile recovery (3 minutes)	162	138
Diastolic blood pressure (mmHg)		
Mean stage 2 exercise	87±13	84±13
80th percentile stage 2 exercise	98	92
Mean recovery (3 minutes)	70±17	67±21
80th percentile recovery (3 minutes)	82	78
Ischemic ST-segment response to exercise	10%	10%
Exercise premature ventricular complexes (per minute)	2.2±9.5	2.0±8.3
Chronotropic incompetence	1%	1%
Abnormal heart rate recovery (3 minutes)	20%	20%

Results are expressed as mean ± SD or percentage.

*Target heart rates were 85% of the age- and sex-predicted maximal heart rate.

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Table 3

Exercise blood pressure and cardiovascular outcomes, multivariable models

Blood Pressure Parameter	Cardiovascular disease events		Coronary heart disease events	
Models using continuous blood pressure variables (per SD increment in BP)				
Exercise Systolic BP	**Adjusted HR (95% CI)**	**P-value**	**Adjusted HR (95% CI)**	**P-value**
Age and sex-adjusted	1.39 (1.22–1.58)	<0.0001	1.40 (1.21–1.63)	<0.0001
+ Rest Systolic BP and Diastolic BP	1.20 (1.02–1.42)	0.03	1.26 (1.04–1.52)	0.02
+ Multivariable	1.13 (0.95–1.33)	0.17	1.15 (0.95–1.40)	0.15
+ Exercise Tolerance Test Variables	1.15 (0.95–1.38)	0.15	1.18 (0.95–1.46)	0.13
Exercise Diastolic BP				
Age and sex-adjusted	1.47 (1.28–1.68)	<0.0001	1.47 (1.26–1.73)	<0.0001
+ Rest Systolic BP and Diastolic BP	1.35 (1.15–1.58)	0.0002	1.39 (1.16–1.67)	0.0005
+ Multivariable	1.31 (1.12–1.54)	0.0009	1.34 (1.11–1.61)	0.0002
+ Exercise Tolerance Test Variables	1.32 (1.11–1.56)	0.002	1.34 (1.10–1.63)	0.003
Models using categorical blood pressure variables (>80th percentile)				
Exercise Systolic BP	**Adjusted HR (95% CI)**	**P-value**	**Adjusted HR (95% CI)**	**P-value**
Age and sex-adjusted	1.55 (1.18–2.04)	0.002	1.65 (1.21–2.26)	0.0017
+ Rest Systolic BP and Diastolic BP	1.11 (0.80–1.53)	0.54	1.24 (0.86–1.79)	0.25
+ Multivariable	1.03 (0.75–1.43)	0.84	1.12 (0.78–1.62)	0.55
+ Exercise Tolerance Test Variables	0.97 (0.68–1.38)	0.86	1.08 (0.72–1.61)	0.71
Exercise Diastolic BP				
Age and sex-adjusted	1.77 (1.35–2.31)	<0.0001	1.70 (1.25–2.32)	0.0008
+ Rest Systolic BP and Diastolic BP	1.42 (1.05–1.92)	0.02	1.39 (0.98–1.97)	0.07
+ Multivariable	1.40 (1.04–1.90)	0.03	1.36 (0.96–1.92)	0.09
+ Exercise Tolerance Test Variables	1.41 (1.01–1.95)	0.04	1.39 (0.96–2.02)	0.08

The multivariable model adjusts for age, sex, resting systolic BP, resting diastolic BP, BMI, diabetes, current cigarette smoking, total/HDL cholesterol ratio, valvular heart disease, and electrocardiographic left ventricular hypertrophy. The ETT model adjusted for all of the covariates in the multivariable model and exercise duration, ischemic ST-segment response to exercise (>1mm horizontal or downsloping ST-segment depression versus none), premature ventricular contractions (present versus absent), chronotropic incompetence (present versus absent), and abnormal heart rate recovery measured 3-min post-exercise (present versus absent).

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Table 4

Recovery blood pressure and cardiovascular outcomes, multivariable models

Blood Pressure Parameter	Cardiovascular disease events		Coronary heart disease events	
Models using continuous blood pressure variables (per SD increment in BP)				
Post-Exercise recovery Systolic BP	**Adjusted HR (95% CI)**	**P-value**	**Adjusted HR (95% CI)**	**P-value**
Age and sex-adjusted	1.33 (1.18–1.51)	<0.0001	1.30 (1.13–1.51)	0.0003
+ Rest Systolic BP and Diastolic BP	1.16 (0.99–1.35)	0.07	1.14 (0.95–1.36)	0.15
+ Multivariable	1.11 (0.95–1.31)	0.19	1.08 (0.90–1.29)	0.42
+ Exercise Tolerance Test Variables	1.16 (0.98–1.38)	0.09	1.12 (0.92–1.36)	0.26
Post-Exercise recovery Diastolic BP				
Age and sex-adjusted	1.22 (1.06–1.40)	0.006	1.20 (1.02–1.41)	0.030
+ Rest Systolic BP and Diastolic BP	1.08 (0.92–1.27)	0.34	1.07 (0.89–1.28)	0.48
+ Multivariable	1.10 (0.94–1.29)	0.24	1.09 (0.91–1.30)	0.37
+ Exercise Tolerance Test Variables	1.08 (0.92–1.28)	0.35	1.03 (0.85–1.24)	0.80
Models using categorical blood pressure variables (>80th percentile)				
Post-Exercise recovery Systolic BP	**Adjusted HR (95% CI)**	**P-value**	**Adjusted HR (95% CI)**	**P-value**
Age and sex-adjusted	1.56 (1.18–2.05)	0.002	1.58 (1.15–2.17)	0.004
+ Rest Systolic BP and Diastolic BP	1.11 (0.80–1.53)	0.53	1.17 (0.80–1.69)	0.42
+ Multivariable	1.03 (0.74–1.43)	0.88	1.03 (0.70–1.51)	0.89
+ Exercise Tolerance Test Variables	1.16 (0.81–1.66)	0.39	1.17 (0.78–1.76)	0.46
Post-Exercise recovery Diastolic BP				
Age and sex-adjusted	1.75 (1.33–2.30)	<0.0001	1.79 (1.31–2.45)	0.0003
+ Rest Systolic BP and Diastolic BP	1.43 (1.04–1.97)	0.03	1.50 (1.04–2.17)	0.03
+ Multivariable	1.44 (1.04–2.00)	0.03	1.52 (1.04–2.21)	0.03
+ Exercise Tolerance Test Variables	1.53 (1.08–2.18)	0.02	1.58 (1.05–2.36)	0.03

ETT indicates Exercise Tolerance Test. Covariates included in the multivariable and ETT models are detailed in Table 3.