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Statin Therapy, Fitness, and Mortality Risk in Middle-Aged Hypertensive Male Veterans

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BACKGROUND

Hypertension often coexists with dyslipidemia, accentuating cardiovascular risk. Statins are often prescribed in hypertensive individuals to lower cardiovascular risk. Higher fitness is associated with lower mortality, but exercise capacity may be attenuated in hypertension. The combined effects of fitness and statin therapy in hypertensive individuals have not been assessed. Thus, we assessed the combined health benefits of fitness and statin therapy in hypertensive male subjects.

METHODS

Peak exercise capacity was assessed in 10,202 hypertensive male subjects (mean age = 60.4 ± 10.6 years) in 2 Veterans Affairs Medical Centers. We established 4 fitness categories based on peak metabolic equivalents (METs) achieved and 8 categories based on fitness status and statin therapy.

RESULTS

During the follow-up period (median = 10.2 years), there were 2,991 deaths. Mortality risk was 34% lower (hazard ratio (HR) = 0.66; 95%

confidence interval (CI) = 0.59–0.74; $P < 0.001$) among individuals treated with statins compared with those not on statins. The fitness-related mortality risk association was inverse and graded regardless of statin therapy status. Risk reduction associated with exercise capacity of 5.1–8.4 METs was similar to that observed with statin therapy. However, those achieving ≥8.5 METs had 52% lower risk (HR = 0.48; 95% CI = 0.37–0.63) when compared with the least-fit subjects (≤5 METs) on statin therapy.

CONCLUSIONS

The combination of statin therapy and higher fitness lowered mortality risk in hypertensive individuals more effectively than either alone. The risk reduction associated with moderate increases in fitness was similar to that achieved by statin therapy. Higher fitness was associated with 52% lower mortality risk when compared with the least fit subjects on statin therapy.

Keywords: blood pressure; fitness; hypertension; mortality risk; statins.

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The efficacy of statin therapy in lowering the risk of cardiovascular events and death in secondary prevention of cardiovascular disease (CVD) is well accepted.^{1,2} Several studies also support the use of statins for primary prevention among individuals at high risk for CVD.^{3,4} The health benefits of statin therapy are largely attributed to the lipid-lowering characteristics of statins.⁵ However, pleiotropic properties such as favorable effects on their interaction with the renin-angiotensin system,⁶ endothelial function,⁷

and arterial compliance⁸ have also been suggested. In addition, recent studies,^{9,10} including two meta-analyses of randomized controlled trials,^{5,11} demonstrated a small but clinically relevant reductions in systolic blood pressure (BP) attributable to statin therapy. This evidence, along with the likely coexistence of hypertension and hypercholesterolemia,¹² makes the combination of antihypertensive medication and statins a common course of therapy in such individuals.

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Strong epidemiologic evidence supports an inverse and graded association between increased exercise capacity and mortality in hypertensive individuals regardless of additional comorbidities.^{13–17} Increased physical activity leading to improved fitness status is now recommended for hypertensive individuals as an adjunct to antihypertensive medication to manage BP and lower mortality risk.^{18,19} We have also reported that higher fitness and statin therapy work synergistically to lower mortality risk more than either therapy alone in dyslipidemic individuals.²⁰ However, muscle damage,²¹ mitochondrial dysfunction,²² attenuated cardiorespiratory fitness,²³ and other maladaptive changes that could negatively impact exercise and lifestyle-related health benefits²⁴ have been reported recently with the use of statins. In addition, some studies have shown that exercise capacity is attenuated in hypertensive individuals.^{25,26}

Thus, it is not known whether the health benefits of exercise are attenuated by statin therapy or whether the 2 therapeutic strategies act synergistically to result in better outcomes than either therapy alone for hypertensive individuals. Therefore, the aim of this study was to assess the independent and combined effects of statin therapy and fitness status on mortality risk in individuals with established hypertension.

METHODS

Study design and sample

This prospective cohort study consisted of 10,202 hypertensive male veterans from the Veterans Affairs Medical Centers in Washington, DC, and Palo Alto, California. Of those, 5,947 were black (mean age = 58.9 ± 10.7 years), 3,776 were white (mean age = 62.4 ± 10.3 years), and 479 were other races (i.e., Native Americans and Asians; mean age = 62.3 ± 10.2 years). The cohort reflects individuals from a larger database (>20,000), identified with hypertension defined by International Classification of Diseases coding, who underwent a symptom-limited exercise tolerance test between 1986 and 2011. The exercise tolerance test was administered either as part of a routine evaluation or to assess exercise-induced ischemia. This information, along with the individual's medical history, was electronically stored.

Individuals with any of the following characteristics were excluded: (i) history of an implanted pacemaker; (ii) development of left bundle branch block during the test; (iii) inability to complete the test because of musculoskeletal pain or impairments; (iv) an exercise capacity <2 metabolic equivalents (METs); (v) instability or requirement of emergent intervention; (vi) body mass index (BMI) <15.5 kg/m²; and (vii) an impaired chronotropic response to exercise.

The study was approved by the institutional review board at each institution, and all subjects gave written informed consent before undergoing the exercise tolerance test.

Measurements

Demographic information, clinical characteristics, and medication information (Table 1) were obtained from the subject's electronic medical record just before his exercise tolerance test.

Each individual was asked to verify the computerized information, including history of chronic disease, current medications, and smoking habits. Body weight and height were assessed by a standardized scale and recorded before the test. BMI was calculated as weight (kg) divided by height squared (m²).

The duration of statin therapy was based on the initial and last date statins were prescribed for each patient. Individuals were considered to be on statin therapy if these 2 dates were >3 months apart. Lipid and lipoprotein evaluations reflect the most recent values in the record (Table 1).

Exercise assessments

Exercise capacity was assessed by a standard treadmill test using the Bruce protocol at the Veterans Affairs Medical Center in Washington, DC, and an individualized ramp protocol as described elsewhere^{27,28} for subjects assessed at the Veterans Affairs Medical Center in Palo Alto, California. Peak exercise time was recorded in minutes. Peak exercise capacity (METs) was estimated using standardized equations based on peak speed and grade for the ramp protocol²⁸ and on peak exercise time for the Bruce protocol.²⁷ One MET is defined as the energy expended at rest, which is approximately equivalent to an oxygen consumption of 3.5 ml per kg of body weight per minute. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping.²⁹ The use of handrails was allowed only if necessary for balance and safety. Age-predicted peak exercise heart rate was determined using a population-specific equation.²⁸ Medications were not altered before testing.

Four fitness categories were formed (quartiles) based on the peak MET level achieved. Those who achieved a peak level ≤5 METs (lowest 25th percentile of the MET level achieved by the cohort) comprised the lowest fitness category (least fit; n = 2,674); those with a peak MET level of 5.1–6.5 (26th to 50th percentile) comprised the low fit category (low fit; n = 2,489); those with a peak MET level of 6.6–8.4 (51st to 75th percentile) comprised the fit category (moderate fit; n = 3,338), and those with a peak MET level ≥8.5 (>75th percentile), comprised the highest fit category (high fit; n = 1,701). To further explore the combined effects of fitness and statin therapy on mortality, we formed 2 groups (treated with statin and not treated with statin) within each fitness category for a total of 8 fitness/statin categories.

Follow-up and endpoint

The endpoint studied was death from any cause. Dates of death were verified from the Veterans Affairs Beneficiary Identification and the Record Locator System File. This system is used to determine benefits to survivors of veterans and has been shown to be 95% complete and accurate.³⁰ Vital status was determined as of December 2011. No missing cases existed in the sample in terms of vital information.

Statistical analysis

Follow-up time is presented as median, 25th, and 75th percentiles. Mortality rate was calculated as the ratio of events by the person-years of observation. Continuous variables are

Table 1. Demographic and clinical characteristics according to statin therapy

	Entire cohort	Statin therapy		P value
		Yes	No	
No.	10,202	4,529	5,673	
Age, y	60.4 ± 11	59.7 ± 10	60.9 ± 11	<0.01
Weight, kg	91.6 ± 18.2	93.6 ± 17.9	90 ± 18.2	<0.01
BMI, kg/m ²	29.5 ± 5.6	30.1 ± 5.4	29.0 ± 5.7	<0.01
Resting heart rate, beats/min	73 ± 14	72 ± 13	74 ± 14	0.76
Resting systolic BP, mm Hg	135 ± 21	132 ± 18	138 ± 22	<0.01
Resting diastolic BP, mm Hg	81 ± 12	79 ± 12	82 ± 12	<0.01
Peak MET	6.6 ± 2.0	6.9 ± 2.0	6.3 ± 1.9	<0.01
Total cholesterol, mg/dl	189 ± 45	179 ± 44	198 ± 44	<0.01
LDL cholesterol, mg/dl	127 ± 47	114 ± 42	142 ± 47	<0.01
HDL cholesterol, mg/dl	43 ± 12	43 ± 12	44 ± 12	0.05
Triglycerides, mg/dl	144 ± 91	146 ± 95	139 ± 80	0.22
Race				
Black	58.3 n = 5,947	67.1 n = 3,037	51.3 n = 2,910	<0.01
White	37 n = 3,776	30.2 n = 1,363	42.5 n = 1,624	<0.01
Others	4.7 n = 479	26.1 n = 125	6.2 n = 354	<0.01
History of CVD	36.5 n = 3,726	50.6 n = 1,885	35 n = 1,841	<0.01
Dyslipidemia	54.1 n = 5,520	86.7 n = 3,927	28.1 n = 1,593	<0.01
Smoking	31.7 n = 3,237	33.3 n = 1,510	30.4 n = 1,727	<0.01
Type 2 diabetes mellitus	49.2 n = 5,017	57 n = 2,580	43 n = 2,437	<0.01
Insulin	1,237 (12.1)	1,029 (22.7)	208 (3.7)	<0.01
Oral hypoglycemic agents	1,905 (18.5)	1,585 (35)	320 (5.6)	<0.01
Cardiac medication				
Beta-blocker	20.2 n = 2,060	22.5 n = 1,021	18.3 n = 1,039	<0.01
CCB	24.7 n = 2,517	23.6 n = 1,067	25.6 n = 1,450	<0.01
ACE/ARB	27.2 n = 2,770	35.7 n = 1,616	20.3 n = 1,154	<0.01
Diuretics	16.6 n = 943	27.6 n = 1,250	5 n = 246	<0.01
Nitrates/vasodilators	7.1 n = 728	4.1 n = 184	9.6 n = 544	<0.01
Antiarrhythmic agents	2.4 n = 247	4.5 n = 202	0.8 n = 45	<0.01
Drug/alcohol abuse	7.4 n = 750	9.4 n = 424	5.7 n = 5.7	<0.01
MWD	16 n = 1,630	20.8 n = 940	12.2 n = 690	<0.01

Data are mean ± SD or percentage. P values derived using χ^2 test for medication and medical history between statin treatment groups and using *t* test for the rest of variables.

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent; MWD, muscle-wasting disease.

presented as mean values and SD, and categorical variables are presented as relative frequencies (%). Baseline associations between categorical variables were tested using χ^2 tests. One-way analysis of variance and *t* tests were applied to evaluate mean differences of selected variables between individuals on and not on statin therapy. The assumption of equality of variances between groups was tested by Levene's test, and the assumption of normality was evaluated using p-p plots. Hazard ratios (HRs) for all-cause mortality were calculated

for the 4 fitness categories, the 2 statin categories (statin/no statin), and the 8 fitness/statin categories using Cox proportional hazards models. First-order interactions between statin treatment and fitness groups were also evaluated.

For the 4 fitness categories, individuals in the least-fit category (≤ 5 METs) comprised the reference group. For the statin/no statin categories, individuals not on statin therapy comprised the reference group. In the fully adjusted model, we adjusted for age, BMI, ethnicity, CVD, risk factors (type 2

diabetes mellitus, dyslipidemia, and smoking), muscle-wasting diseases (MWD) (cancer, HIV/AIDS, and renal failure), sleep apnea, cardiac medications (beta-blockers, calcium-channel blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antiarrhythmic agents), insulin, oral hypoglycemic agents, and lipid-lowering (nonstatins) agents. All variables included in the models were based on the rationale of their clinical role on the outcome and the main factors of interest. Cox proportional hazards models were also used to assess risk among the 8 fitness/statin categories. The model was adjusted for the aforementioned covariables according to the rationale mentioned. For the latter analysis, the least-fit individuals not on statin therapy (least fit/no statins) comprised the reference group. We also performed a subgroup analysis ($n = 4,848$) to directly assess mortality risk between the least-fit individuals treated with statins (referent) and individuals in the remaining fitness categories (low, moderate, and high fit) not treated with statins. The assumption of proportionality for all Cox proportional hazard analyses was graphically tested by plotting the cumulative hazards of the logarithms of the covariables; the proportionality assumption was fulfilled for each model. All hypotheses were 2-sided, and P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 19.0 (SPSS, Chicago, IL).

RESULTS

The median follow-up period was 10.2 years (25th and 75th percentiles = 5.7 and 14.5, respectively), comprising a total of 107,620 person-years. There were 2,991 deaths (29.3% overall mortality in the cohort), with an average annual mortality of 27.8 events per 1,000 person-years of observation. Significantly higher mortality rates were noted for individuals not treated with statins (35.5% vs. 26.2%; $P < 0.01$) and those with CVD (40.7% vs. 21.9%), MWD (47.5% vs. 25.9%; $P < 0.01$), and smokers (31.4% vs. 28.1%; $P < 0.01$). Those who died were also older (64.8 ± 10 vs. 58.6 ± 10 years; $P < 0.01$) and had higher systolic BP (142 ± 23 vs. 133 ± 20 mm Hg; $P < 0.01$) and lower exercise capacity (5.6 ± 1.7 vs. 7.0 ± 2.0 METs; $P < 0.01$). There was no interaction between site-by-METs ($P = 0.23$) or race-by-METs ($P = 0.06$), and therefore the data were not stratified by site or race. However, there was an interaction between fitness categories and statin use ($P = 0.01$) as well as statin use and peak METs achieved ($P < 0.01$).

Demographic and clinical characteristics for the entire cohort and the 2 statin categories are presented in Table 1. Individuals on statin therapy were slightly younger and had higher BMI and exercise capacity and lower systolic and diastolic BP when compared with those not on statin therapy. The prevalence of CVD, smoking, dyslipidemia, type 2 diabetes mellitus, drug/alcohol abuse, MWD, and the use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antiarrhythmic agents, diuretics, insulin, and oral hypoglycemic agents were also higher in those on statin therapy. The use of nitrates/vasodilators and calcium channel blockers were higher in those not on statin therapy.

The median duration of statin therapy was 77.6 months. Approximately 98% of the individuals in the statin group were treated with statins for at least 12 months, and only 186 individuals (approximately 1.8%) were treated for <12 months.

Significantly more favorable lipid profiles were noted in total cholesterol and low density lipoprotein (LDL) cholesterol among those on statin therapy (Table 1).

Predictors of mortality risk for the entire cohort and according to statin or no statin therapy

In the fully adjusted model, significant predictors for increased all-cause mortality were age (HR = 1.03; 95% confidence interval (CI) = 1.02–1.04; $P < 0.01$), systolic BP (HR = 1.006; 95% CI = 1.004–1.008; $P < 0.01$), smoking (HR = 1.30; 95% CI = 1.20–1.40; $P < 0.01$); type 2 diabetes (HR = 1.43; 95% CI = 1.32–1.56; $P < 0.01$); CVD (HR = 1.28; 95% CI = 1.18–1.38; $P < 0.01$), MWD (HR = 1.82; 95% CI = 1.66–1.98; $P < 0.01$) and drug/alcohol abuse (HR = 1.29; 95% CI = 1.11–1.50; $P < 0.01$). Conversely, lower mortality risk was observed with BMI (HR = 0.98; 95% CI = 0.97–0.99; $P < 0.01$), use of hypoglycemic agents (HR = 0.74; 95% CI = 0.65–0.83; $P < 0.01$), antihypertensive/cardiac medication (HR = 0.74; 95% CI = 0.67–0.81; $P < 0.01$), statin therapy (HR = 0.66; 95% CI: 0.59–0.74; $P < 0.001$), and exercise capacity. For every 1-MET increase in exercise capacity, the adjusted mortality for the entire cohort was 15% lower (HR = 0.85; 95% CI = 0.83–0.87; $P < 0.01$). The influence of exercise capacity was substantially more potent in the statin therapy group. For every 1-MET increase in exercise capacity, the adjusted mortality risk was 19% lower per MET achieved (HR = 0.81; 95% CI = 0.78–0.85; $P < 0.01$) and 14% for those not treated with statins (HR = 0.86; 95% CI = 0.84–0.88; $P < 0.01$). The adjusted mortality risk was significantly lower (34%) for those on statin therapy compared with those not on statin therapy (HR = 0.66; 95% CI = 0.59–0.74; $P < 0.01$).

Mortality risk according to fitness categories and statin therapy

HRs across fitness categories for the entire cohort and for the statin and no statin therapy groups are presented in Table 2 and illustrated in Figure 1a–c. The partially and fully adjusted mortality risks for the 4 fitness categories are shown, with those in the least-fit category (≤ 5 METs) as the reference group. For the entire cohort in the fully adjusted model (Table 2), the mortality risk was progressively lower as exercise capacity increased, such that individuals with an exercise capacity >5 METs had 27%–69% reductions in risk ($P < 0.01$). Similarly, the fully adjusted risks for individuals treated with statins were progressively lower with increased exercise capacity, ranging 31%–75% for individuals on statin therapy and 24%–64% for those not treated with statins (Table 2).

We also examined the mortality risk according to fitness for individuals with documented CVD and those without CVD (Table 3). In both subgroups, the association between fitness categories and mortality risk was inverse and graded. However, mortality rates for individuals with CVD were substantially higher within each fitness category and the impact of fitness was somewhat attenuated.

Table 2. Hazards ratios for mortality risk of the entire cohort and according to statin therapy

Fitness categories according to peak METs achieved	No. of deaths (%)	Hazard ratio, age-adjusted (95% CI)	Hazard ratio, adjusted for age and resting BP (95% CI)	Hazard ratio, fully adjusted (95% CI)	P value
Entire cohort (n = 10,202)					
≤5 MET (n = 2,674)	531 (51.0)	1.00 (referent)	1.00 (referent)	1.00 (referent)	—
5.1–6.5 MET (n = 2,489)	397 (32.1)	0.68 (0.63–0.75)	0.69 (0.63–0.75)	0.73 (0.67–0.80)	<0.01
6.6–8.4 MET (n = 3,338)	270 (20.5)	0.49 (0.44–0.54)	0.50 (0.45–0.55)	0.56 (0.51–0.62)	<0.01
≥8.5 MET (n = 1,701)	190 (8.5)	0.25 (0.21–0.30)	0.26 (0.22–0.31)	0.31 (0.26–0.38)	<0.01
Individuals on statin therapy (n = 4,529)					
≤5 MET (n = 923)	345 (37.4)	1.00 (referent)	1.00 (referent)	1.00 (referent)	—
5.1–6.5 MET (n = 1,146)	252 (22.0)	0.63 (0.54–0.74)	0.64 (0.55–0.76)	0.68 (0.58–0.80)	<0.01
6.6–8.4 MET (n = 1,510)	180 (11.9)	0.42 (0.34–0.50)	0.43 (0.36–0.52)	0.46 (0.38–0.56)	<0.01
≥8.5 MET (n = 950)	51 (5.4)	0.22 (0.16–0.30)	0.23 (0.17–0.31)	0.25 (0.19–0.34)	<0.01
Individuals not on statin therapy (n = 5,673)					
≤5 MET (n = 1,751)	1,018 (58.1)	1.00 (referent)	1.00 (referent)	1.00 (referent)	—
5.1–6.5 MET (n = 1,343)	548 (40.8)	0.73 (0.66–0.81)	0.73 (0.66–0.82)	0.76 (0.68–0.84)	<0.01
6.6–8.4 MET (n = 1,828)	504 (27.6)	0.53 (0.48–0.60)	0.54 (0.48–0.61)	0.60 (0.54–0.67)	<0.01
≥8.5 MET (n = 751)	93 (12.4)	0.32 (0.25–0.40)	0.32 (0.26–0.40)	0.36 (0.29–0.46)	<0.01

Abbreviations: BP, blood pressure; CI, confidence interval; MET, metabolic equivalent; MWD, muscle-wasting disease.

The model was adjusted for age, resting blood pressure, body mass index, ethnicity, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, antiarrhythmic agents, insulin, oral hypoglycemic agents, history of smoking, cardiovascular disease, dyslipidemia, MWD, sleep apnea, alcohol/drug abuse, diabetes mellitus, and year of entry in the study.

Because there was a significant interaction between fitness categories and statin use, we sought to explore further the combined effect of fitness and statins. For this, we performed additional analyses to assess possible differences in mortality risk between those on statin therapy compared with those not on statin therapy. We used the least-fit individuals not treated with statins (least fit/no statins) as the reference group. The model was adjusted for age, BMI, ethnicity, CVD, risk factors, MWD, sleep apnea, cardiac medications, insulin, oral hypoglycemic agents, and lipid-lowering (non-statin) agents. In the fully adjusted model, the association between fitness and mortality risk was inverse and graded for subjects both treated and not treated with statins. However, the combination of statins and higher fitness was substantially more effective in lowering mortality risk than either treatment alone.

It was also noteworthy that the risk for individuals in the high-fit/no statins category was similar to that in the moderate-fit/statins category (HR = 0.37 vs. 0.35, respectively) and substantially lower than the risk observed for those in the low-fit and least-fit categories on statin therapy (Table 4). To directly compare mortality risks associated with fitness vs. statin therapy, we performed a subgroup analysis (n = 4,848) comparing the least-fit individuals treated with statins (referent) to individuals in the low, moderate, and high fitness categories not treated with statins. The findings revealed similar mortality risks for low-fit subjects (HR = 0.99; 95% CI = 0.83–1.17; P = 0.91). However, the risk was 24% lower for moderate-fit subjects (HR = 0.76; 95% CI = 0.64–0.91; P < 0.01) and 52% lower for individuals in the high-fit category (HR = 0.48; 95% CI = 0.37–0.63; P < 0.01) (Figure 2).

DISCUSSION

The findings of this study support the concept that both statin therapy and higher fitness lower mortality risk in hypertensive individuals, independently and synergistically. More specifically, the overall risk reduction related to statin therapy was 34%. The fitness-related reduction in mortality risk was inverse and graded. Relative to individuals with an exercise capacity ≤5 METs, mortality risk was 27%, 43%, and 69% lower for the moderate-fit, fit and high-fit individuals, respectively (Table 2). The trend was similar for those treated and not treated with statins (Table 2). As illustrated in Figure 1b, approximately 90% of the individuals in the high-fit category on statin therapy were still alive at 15 years of follow-up compared with approximately 80% of those within the same fitness category not treated with statins (Figure 1c). Similarly, for individuals in the least-fit category treated with statins, approximately 65% were still alive at 15 years compared with approximately 55% for those in the same fitness category not treated with statins. These findings are in accord with previous reports regarding statin therapy in primary or secondary prevention of mortality in individuals at high CVD risk.^{1–4} The inverse and graded association between fitness and mortality risk in hypertensive individuals has also been described previously.^{13–15,17} We have also reported on the combined effects of statin therapy and fitness in dyslipidemic individuals.²⁰ Because approximately 54% of our cohort in this study was dyslipidemic, some overlapping exists between the cohort of this study and our previous work.²⁰ However, given the likely coexistence of hypertension and dyslipidemia¹² and the use of statins in combination with

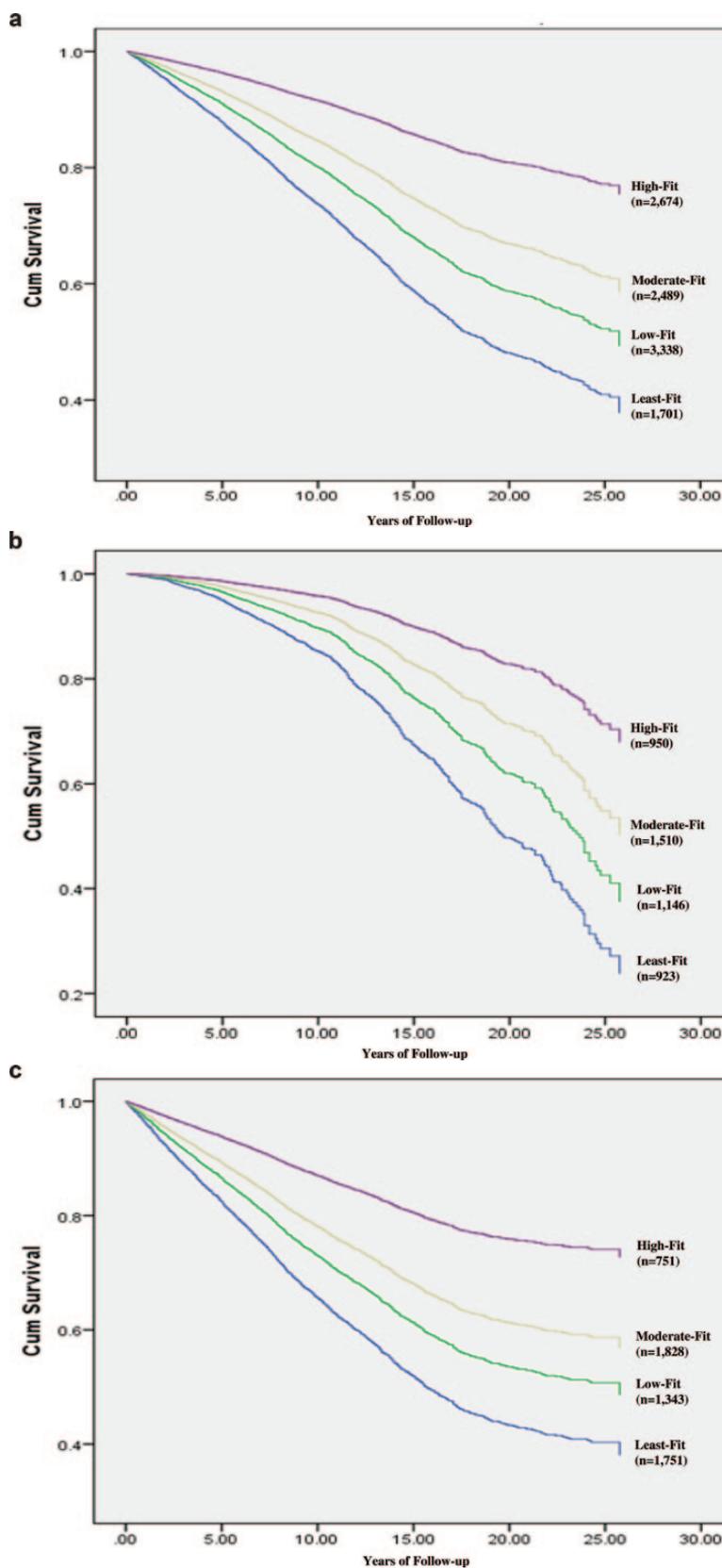


Figure 1. Mortality risk in hypertensive individuals. (a) Mortality risk in hypertensive individuals according to fitness categories. (b) Mortality risk in hypertensive individuals on statin therapy according to fitness categories on statin therapy. (c) Mortality risk in hypertensive individuals on statin therapy according to fitness categories on statin therapy.

Table 3. Hazards ratios for mortality risk according to cardiovascular disease status

Fitness categories according to peak METs achieved	No CVD (n = 6,167)			CVD (n = 4,035)		
	No. of deaths (%)	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	No. of deaths (%)	P value
≤5 MET	564 (42.8)	1.00 (referent)	—	1.00 (referent)	799 (58.9)	—
5.1–6.5 MET	351 (23.9)	0.67 (0.59–0.77)	<0.001	0.77 (0.69–0.87)	449 (43.9)	<0.01
6.6–8.4 MET	362 (16.4.0)	0.54 (0.47–0.62)	<0.001	0.57 (0.49–0.65)	322 (28.5)	<0.01
≥8.5 MET	72 (6.1)	0.26 (0.20–0.34)	<0.001	0.36 (0.28–0.46)	72 (13.7)	<0.01

Abbreviations: CI, confidence interval; MET, metabolic equivalent; MWD, muscle-wasting disease.

The model was adjusted for age, resting blood pressure, body mass index, ethnicity, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, antiarrhythmic agents, insulin, oral hypoglycemic agents, history of smoking, dyslipidemia, MWD, sleep apnea, alcohol/drug abuse, diabetes mellitus, and year of entry in the study.

Table 4. Hazards ratios for mortality risk for the combined fitness and statin categories

Groups	No. of Deaths (%)	Hazard ratio, age-adjusted (95% CI)	Hazard ratio, adjusted for age and resting BP (95% CI)	Hazard ratio, fully adjusted (95% CI)	P value
Least fit/no statins (n = 1,748)	1,017 (58.2)	1.00 (referent)	1.00 (referent)	1.00 (referent)	—
Least fit/statins (n = 923)	345 (37.4)	0.70 (0.62–0.79)	0.70 (0.66–0.82)	0.75 (0.65–0.87)	<0.01
Low fit/no statins (n = 1,346)	549 (40.8)	0.73 (0.66–0.82)	0.74 (0.66–0.82)	0.76 (0.68–0.84)	<0.01
Low fit/statins (n = 1,146)	252 (22)	0.45 (0.39–0.52)	0.46 (0.40–0.53)	0.51 (0.44–0.60)	<0.01
Moderate fit/no statins (n = 1,830)	504 (27.2)	0.54 (0.48–0.60)	0.54 (0.49–0.61)	0.60 (0.53–0.67)	<0.01
Moderate fit/statins (n = 1,511)	180 (11.7)	0.29 (0.24–0.34)	0.29 (0.25–0.35)	0.35 (0.29–0.42)	<0.01
High fit/no statins (n = 749)	93 (12.4)	0.33 (0.26–0.40)	0.33 (0.27–0.41)	0.37 (0.30–0.46)	<0.01
High fit/statins (n = 949)	51 (5.4)	0.15 (0.11–0.19)	0.15 (0.11–0.20)	0.18 (0.13–0.25)	<0.01

Abbreviations: BP, blood pressure; CI, confidence interval; MET, metabolic equivalent; MWD, muscle-wasting disease.

The model was adjusted for age, resting blood pressure, body mass index, ethnicity, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, antiarrhythmic agents, insulin, oral hypoglycemic agents, history of smoking, cardiovascular disease, dyslipidemia, MWD, sleep apnea, alcohol/drug abuse, diabetes mellitus, and year of entry in the study.

antihypertensive medication in such individuals, the combined effects of fitness and statins in hypertensive individuals merits special consideration. Therefore, these findings add to the expanding body of information on this issue.

Our findings suggest that higher fitness combined with statin therapy was the most effective approach in lowering mortality risk in hypertensive individuals. More specifically, the mortality risks for least-fit (≤5 METs), low-fit (5.1–6.5 METs), moderate-fit (6.6–8.4 METs), and high-fit individuals (≥8.5 METs) on statin therapy were 25%, 49%, 65%, and 82% lower, respectively, when compared with the least-fit individuals not treated with statins (Table 4). It is also noteworthy that low-, moderate-, and high-fit individuals not treated with statins exhibited 24%, 40%, and 63% lower mortality risk, respectively (Table 4). This suggests that higher fitness may be at least as effective as statin therapy in lowering mortality risk in hypertensive individuals. To further assess this, we performed a subgroup analysis (n = 4,848) comparing the least-fit individuals on statin therapy (reference group) to the individuals in the remaining fitness categories not treated with statins. This analysis revealed similar risk for the low-fit individuals. However, mortality risk for moderate-fit and high-fit individuals was 24% and

52% lower compared with the least-fit individuals on statin therapy (P < 0.01) (Figure 2).

These findings are clinically relevant because a substantial number of individuals may not tolerate statins. For individuals who cannot tolerate statin therapy for various reasons, a relatively moderate increase in fitness may provide an alternative and effective way to lower mortality risk. The exercise capacity >5 METs that was associated with similar risk reduction to that provided by statin therapy is easily achievable by most middle-aged or older individuals. Thus, these findings lead to the salient concept that physical activity is an efficacious and cost-effective way to prevent premature mortality in hypertensive individuals and therefore should be promoted by health-care providers.

Several other aspects of this study are noteworthy. This is the only evaluation to our knowledge to assess the association between the combination of statin therapy and fitness for the treatment of hypertensive individuals. The statin–fitness–mortality association was assessed in the largest clinically referred cohort of hypertensive individuals (n = 10,202), >58% of whom were black, with a follow-up time of 107,620 person-years. Despite recent reports of unfavorable effects of statin therapy on cardiorespiratory fitness,²³ exercise

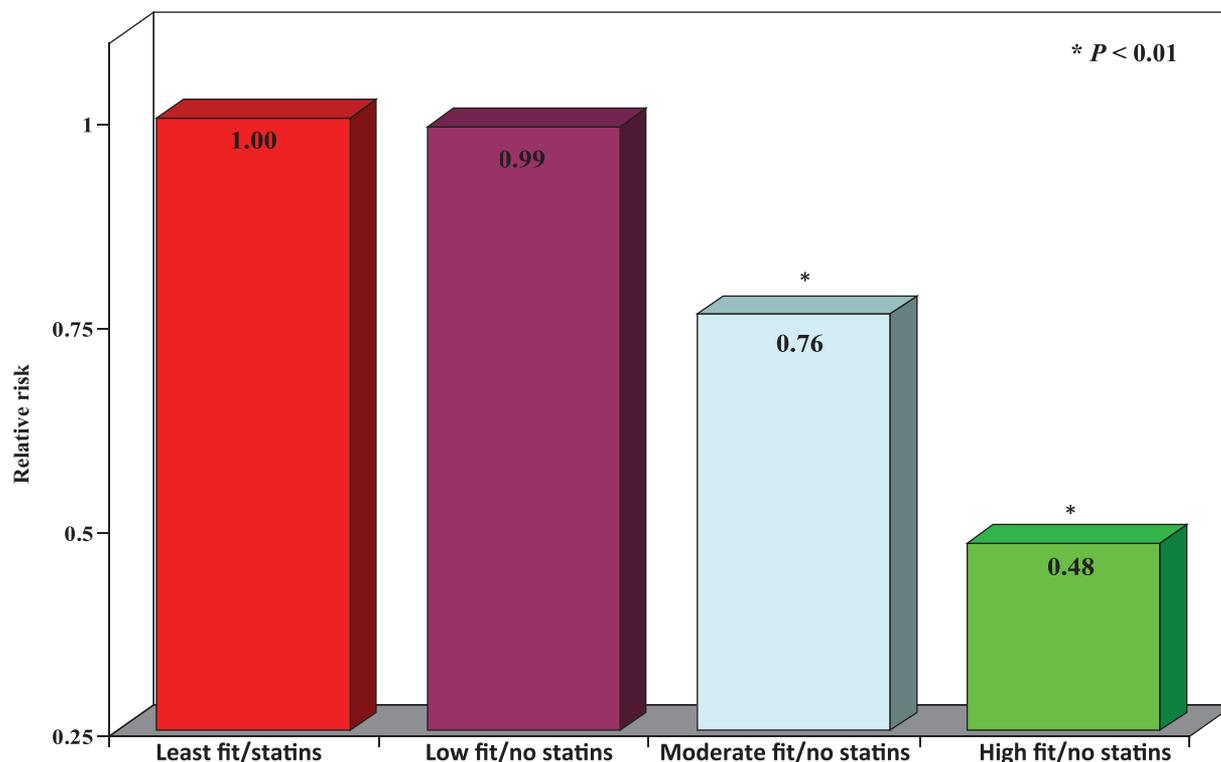


Figure 2. Mortality risk according to fitness for those not treated with statins compared with the least-fit group treated with statins.

capacity among individuals on statin therapy was significantly higher than that among those not treated with statins in this study (Table 1). Significantly lower systolic BP and diastolic BP were also observed in those treated with statins. This is in accord with previous findings suggesting a modest BP-lowering effect of statins.^{5,9–11}

Our cohort is unique. Veterans have equal access to care independent of a patient's financial status provided by the Veterans Health Administration. This permits epidemiologic evaluations while minimizing the influence of disparities in medical care.^{31,32} This, along with the existence of electronic health records within the Veterans Affairs Healthcare System, enables detailed observation of prior history and alterations in health status. Because mortality rates in individuals with MWD were significantly higher vs. the rest of the cohort (47.5% vs. 25.9%) and exercise capacity was lower (6.7 ± 2.0 vs. 6.2 ± 1.8 METs; $P < 0.001$), Cox proportional hazard models were constructed with these individuals included and excluded from the analyses. The models did not change substantially. This, along with the exclusion of those with an exercise capacity < 2 METs, lowers the likelihood of reverse causality and supports the validity of the fitness–statin therapy and mortality risk association in hypertensive individuals.

This study has several limitations because of its design. We only had information on all-cause mortality and did not have data on cardiovascular interventions or cardiovascular mortality. Our cohort was comprised of male veterans only, which limits the ability to generalize the findings to women. Fitness levels were based on 1 assessment, and follow-up data on the fitness status of the participants were not available.

The 2 different exercise protocols used to assess fitness is also a potential limitation. Our previous work suggests that the ramp protocol is somewhat more accurate in predicting measured METs.^{15,33} However, separate analyses from the 2 locations yielded similar results, suggesting that the differences in protocols had minimal impact.

We have no data regarding adverse effects of statins to discern whether statin therapy may have influenced exercise capacity. In this regard, the use of statins was progressively higher with higher fitness (least-fit group = 34.5%; fit group = 46%; moderate-fit group = 45.2%; and high-fit group = 55.8%). Finally, the onset of chronic diseases, their severity, and duration of therapy were not evaluated, and dietary information was not available in our records.

Our findings support the concept that both statin therapy and higher fitness are effective in lowering premature all-cause mortality in hypertensive individuals. The combination of the 2 was more efficacious in lowering mortality in hypertensive individuals than either alone. Thus, despite reports of muscle damage and impaired cardiorespiratory fitness as a result of statin therapy, our findings suggest that the 2 therapeutic strategies can be used effectively in lowering mortality risk for hypertensive individuals.

Interestingly, a modest increase in fitness status alone (5.1–8.4 METs) was associated with a 24%–40% lower mortality risk, similar to the 25% lower risk observed with statin therapy alone (least fit/statins; Table 4; Figure 2). Furthermore, mortality risk was significantly lower among individuals in the highest fitness categories (exercise capacity ≥ 8.5 METs) not treated with statins compared with the least-fit group on statin therapy (Figure 2). This suggests that if statin therapy

is not an option, higher fitness provides protection that is similar or even greater than that achieved by statin therapy in unfit individuals. The exercise capacity necessary to realize these health benefits (>5 METs) is achievable by many middle-aged and older adults by daily exercise such as brisk walking.¹⁶ Thus, improved fitness may provide an attractive adjunct therapy to statins and even an alternative when statin therapy cannot be prescribed.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

- Pedersen TR, Olsson AG, Faergeman O, Kjekshus J, Wedel H, Berg K, Wilhelmsen L, Haghfelt T, Thorgeirsson G, Pyorala K, Miettinen T, Christophersen B, Tobert JA, Musliner TA, Cook TJ. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998; 97:1453–1460.
- Sacks FM, Moye LA, Davis BR, Cole TG, Rouleau JL, Nash DT, Pfeffer MA, Braunwald E. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial. *Circulation* 1998; 97:1446–1452.
- Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, Sattar N. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med* 2010; 170:1024–1031.
- Taylor F, Ward K, Moore TH, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2011; 2011:CD004816.
- Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure?: a meta-analysis of randomized, controlled trials. *Hypertension* 2007; 49:792–798.
- Nickenig G, Baumer AT, Temur Y, Kebben D, Jockenhovel F, Bohm M. Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. *Circulation* 1999; 100:2131–2134.
- Wolfgram S, Jensen KS, Liao JK. Endothelium-dependent effects of statins. *Arterioscler Thromb Vasc Biol* 2003; 23:729–736.
- Ferrier KE, Muhlmann MH, Baguet JP, et al. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol* 2002; 39:1020–1025.
- King DE, Mainous AG 3rd, Egan BM, Player M, Geesey ME. Use of statins and blood pressure. *Am J Hypertens* 2007; 20:937–941.
- Morgado M, Rolo S, Macedo AF, Castelo-Branco M. Association of statin therapy with blood pressure control in hypertensive hypercholesterolemic outpatients in clinical practice. *J Cardiovasc Dis Res* 2011; 2:44–49.
- Briasoulis A, Agarwal V, Valachis A, Messerli FH. Antihypertensive effects of statins: a meta-analysis of prospective controlled studies. *J Clin Hypertens (Greenwich)* 2013; 15:310–320.
- Smith SC Jr, Blair SN, Bonow RO, Brass LM, Cerqueira MD, Dracup K, Fuster V, Gotto A, Grundy SM, Miller NH, Jacobs A, Jones D, Krauss RM, Mosca L, Ockene I, Pasternak RC, Pearson T, Pfeffer MA, Starke RD, Taubert KA. AHA/ACC Guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol* 2001; 38:1581–1583.
- Faselis C, Doumas, Panagiotakos D, Kheirbek R, Korshak L, Manolis A, Pittaras A, Tsioufis C, Papademetriou V, Fletcher R, Kokkinos P. Body mass index, exercise capacity, and mortality risk in male veterans with hypertension. *Am J Hypertens* 2012; 25:445–450.
- Kokkinos P, Doumas M, Myers J, Faselis C, Manolis A, Pittaras A, Kokkinos JP, Papademetriou V, Singh S, Fletcher R. A graded association of exercise capacity and all-cause mortality in males with high-normal blood pressure. *Blood Press* 2009; 18:261–267.
- Kokkinos P, Manolis A, Pittaras A, Doumas M, Giannelou A, Panagiotakos D, Faselis C, Narayan P, Singh S, Myers J. Exercise capacity and mortality in hypertensive men with and without additional risk factors. *Hypertension* 2009; 53:494–499.
- Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. *Circulation* 2010; 122:1637–1648.
- Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346:793–801.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Matterson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206–1252.
- Mancia G, De Backer G, Dominiczak A, Task Force for the Management of Arterial Hypertension of the European Society of Hypertension. 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; 28:1462–1536.
- Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. *Lancet* 2013; 381:394–399.
- Bouitbir J, Charles AL, Rasseneur L, Dufour S, Piquard F, Geny B, Zoll J. Atorvastatin treatment reduces exercise capacities in rats: involvement of mitochondrial impairments and oxidative stress. *J Appl Physiol* 2011; 111:1477–1483.
- Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial. *Arch Intern Med* 2012; 172:1180–1182.
- Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, Fletcher J, Meers GM, Ruebel M, Laughlin MH, Dellsperger KC, Fadel PJ, Thyfault JP. Simvastatin impairs exercise training adaptations. *J Am Coll Cardiol* 2013; 62:709–714.
- Rautio N, Jokelainen J, Oksa H, Saaristo T, Peltonen M, Vanhala M, Puolijoki H, Moilanen L, Tuomilehto J, Keinänen-Kiukaanniemi S, Uusitupa M. Do statins interfere with lifestyle intervention in the prevention of diabetes in primary healthcare? One-year follow-up of the FIN-D2D project. *BMJ Open* 2012; 2:e001472.
- Missault L, Duprez D, de Buyzere M, de Backer G, Clement D. Decreased exercise capacity in mild essential hypertension: non-invasive indicators of limiting factors. *J Hum Hypertens* 1992; 6:151–155.
- Modesti PA, Olivo G, Carrabba N, Guarnaccia V, Pestelli F, Malfanti PL, Gensini GF. Early impairment of the cardiopulmonary exercise capacity of hypertensive patients. *Int J Cardiol* 1994; 44:163–169.
- Foster C, Jackson AS, Pollock ML, Taylor MM, Hare J, Sennett SM, Rod JL, Sarwar M, Schmidt DH. Generalized equations for predicting functional capacity from treadmill performance. *Am Heart J* 1984; 107:1229–1234.
- Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, Froelicher VF. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol* 1991; 17:1334–1342.
- Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. *J Am Coll Cardiol* 1993; 22:175–182.
- Boyle CA, Decoufle P. National sources of vital status information: extent of coverage and possible selectivity in reporting. *Am J Epidemiol* 1990; 131:160–168.
- Kizer KW, Demakis JG, Feussner JR. Reinventing VA health care: systematizing quality improvement and quality innovation. *Med Care* 2000; 38:17–16.
- Selim AJ, Berlowitz DR, Fincke G, Rosen AK, Ren XS, Christiansen CL, Cong Z, Lee A, Kazis L. Risk-adjusted mortality rates as a potential outcome indicator for outpatient quality assessments. *Med Care* 2002; 40:237–245.
- Kokkinos P, Myers J, Faselis C, Panagiotakos D, Doumas M, Pittaras A, Manolis A, Kokkinos JP, Karasik P, Greenberg M, Papademetriou V, Singh S, Fletcher R. Exercise capacity and mortality in older men: a 20-year follow-up study. *Circulation* 2010; 122:790–797.