Exercise Capacity and Mortality in Hypertensive Men With and Without Additional Risk Factors

Peter Kokkinos, Athanasios Manolis, Andreas Pittaras, Michael Doumas, Angeliki Giannelou, Demosthenes B. Panagiotakos, Charles Faselis, Puneet Narayan, Steven Singh, Jonathan Myers

Abstract—We assessed the association between exercise capacity and mortality in hypertensive men with and without additional cardiovascular risk factors. A cohort of 4631 hypertensive veterans, who successfully completed a graded exercise test at the Veterans Affairs Medical Center in Washington, DC, and Palo Alto, California, was followed for 7.7±5.4 years (35 629 person-years) for all-cause mortality. Fitness categories were established based on peak metabolic equivalent (MET) levels achieved. In each fitness category, we defined individuals with and without additional cardiovascular risk factors. Exercise capacity was the strongest predictor of all-cause mortality. The adjusted mortality risk was 13% lower for every 1-MET increase in exercise capacity. Compared with the very low fit ($\leq 5.0$ MET), the adjusted risk was 34% lower for those achieving 5.1 to 7.0 MET (low fit; hazard ratio: 0.66; CI: 0.58 to 0.76; $P<0.001$), 59% lower for the moderate fit (7.1 to 10.0 MET; hazard ratio: 0.41; CI: 0.35 to 0.50; $P<0.001$), and 71% lower for the high-fit category (>10.0 MET; hazard ratio: 0.29; CI: 0.21 to 0.40; $P<0.001$). Within the very-low-fit category, mortality risk was 47% higher for those with additional risk factors compared with individuals with no risk factors. This risk was eliminated for those in the next fitness category (5.1 to 7.0 MET) and was progressively reduced for the moderate and high-fit categories regardless of the presence or absence of additional risk factors. In conclusion, exercise capacity was the strongest predictor of all-cause mortality in hypertensive men. The increased risk imposed by low fitness and additional cardiovascular risk factors was eliminated by relatively small increases in exercise capacity and declined progressively with higher exercise capacity. (Hypertension. 2009;53:494-499.)

Key Words: hypertension • exercise capacity • mortality • cardiovascular risk factors • cardiovascular disease

Chronic hypertension is considered a risk factor for developing cardiovascular (CV) disease and mortality.1-3 Approximately 7.1 million deaths per year are attributed to hypertension.4 The worldwide prevalence of hypertension is estimated to be as much as 1 billion, with an estimated 60% increase by the year 2025.5

The prevalence of hypertension is perpetuated by lifestyle factors, such as consumption of high-fat and/or high-salt diets, and physical inactivity.4 Conversely, strong evidence supports that lifestyle modifications, including weight loss and increased physical activity, contribute significantly to blood pressure (BP) control.5 An overwhelming number of studies have consistently shown significant reductions in BP achieved by regularly performed aerobic exercise of mild-to-moderate intensity in patients with essential hypertension. The findings of these studies are summarized by a recent review6 and a meta-analysis.7 Consequently, increased physical activity is now strongly recommended as part of the lifestyle modifications alone or as adjunct to pharmacological therapy proposed by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and recent European Society of Hypertension and of the European Society of Cardiology guidelines.3,8

There is also some evidence to support that increased physical activity is associated with lower mortality, even in the presence of hypertension. In relatively small groups of hypertensive individuals, mortality rates were significantly lower in those with higher exercise capacity when compared with those with lower exercise capacity.9-11 However, it is not known whether increased exercise capacity is associated with lower mortality in hypertensive individuals with multiple CV risk factors.

The Veterans Health Administration in the US Department of Veterans Affairs Health Care System is unique in that it ensures equal access to care independent of a patient’s financial status.12 Improved access to care and higher quality health have been demonstrated in the US Department of Veterans Affairs Health Care System.12 In addition, the Veterans Affairs electronic health care database is uniquely suited to determine mortality and other outcomes accurately.
and facilitates risk-adjustment models to study outcomes. The system provides a unique opportunity to assess the association between mortality and exercise capacity while minimizing the influence of disparities in medical care. In this study, we sought to determine the association between exercise capacity and mortality in hypertensive individuals with and without additional risk factors.

Methods

Study Design and Population

Between May 1983 and December 30, 2006, a symptom-limited exercise tolerance test was administered to ~15,660 male Veterans at the Veterans Affairs Medical Center in Washington, DC, and the Veterans Affairs Palo Alto Health Care System, either as a routine evaluation or to evaluate for exercise-induced ischemia. The following patients were excluded from the study: (1) those with a history of an implanted pacemaker; (2) those who had or developed left bundle branch block during the test; and (3) those who were unable to complete the test, were unstable, or required emergent intervention. To avoid an overestimation of the impact of exercise capacity on mortality, individuals with impaired chronotropic response, defined as a ratio of <0.8 between the percentage of heart rate (HR) reserve to metabolic reserve achieved at peak exercise, or those who were unable to complete the exercise test. Each individual was also asked to verify the computerized information with regard to history of chronic disease, current medications, and cigarette smoking habits. Body weight and height were recorded before the test. Body mass index (BMI) was calculated as weight (kilograms) divided by height squared (meters squared). Individuals with CV disease (CVD) were defined as those with a history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, and/or peripheral vascular disease. All of the participants gave written consent before the exercise tolerance test. The study was approved by the internal review board at each institution.

We recorded death dates from the Veterans Affairs Beneficiary Identification and Record Locator System File. This system is used to determine benefits to survivors of veterans and is complete and accurate. The Social Security Death Index was used to match all of the subjects with their record according to Social Security number. Vital status was determined as of June 30, 2007.

Exercise Assessments

The exercise capacity for the individuals at the Veterans Affairs Medical Center was assessed by the standard treadmill test using the Bruce protocol. For the individuals assessed at the Veterans Affairs Palo Alto Health Care System, an individualized ramp protocol (treadmill) was used as described elsewhere. Peak exercise time was recorded in minutes. Peak workload was estimated as metabolic equivalents (METs). One MET is defined as the energy expenditure at rest, which is equivalent to an oxygen consumption of 3.5 mL/kg of body weight per minute. Exercise capacity (in METs) was estimated based on exercise time via a commonly used equation for the Bruce protocol and based on American College of Sports Medicine equations for the ramp protocol. Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other indicators of ischemia. The use of handrails during the exercise test was discouraged. Age-predicted peak exercise HR was determined based on standardized methods. Medications were not changed or stopped before testing.

Supine resting HR and BP were assessed once after 5 minutes of rest. Exercise BP was recorded at 2 minutes of each exercise stage, at peak exercise, and within 1, 3, and 5 minutes into recovery (supine position). Diastolic BP was recorded at Phase V. Indirect arm-cuff sphygmomanometry (Model X018, Tyco) was used for all of the BP assessments. ST depression ≥1.0 mm that was horizontal or down sloping was considered to be suggestive of ischemia.

Determination of Fitness Categories

Four fitness categories were established based on the MET level achieved. Those who achieved a peak MET level ≤5 (lowest 25th percentile) of the MET level achieved by the cohort composed the very low fitness category (very low fit; n = 1477); those who achieved between 5.1 and 7.0 MET (25th to 50th percentile) composed the low fitness category (low fit; n = 1335); those who achieved 7.1 to 10.0 MET composed the moderate fitness category (moderate fit; n = 1239), and those who achieved >10.0 MET (75th percentile) composed the highest fit category (high fit; n = 580).

Statistical Analysis

Follow-up time is presented as means ±SDs and medians of years. Mortality rate was calculated as the ratio of events by the number of persons (crude estimate) or by the person-years of observation. Continuous variables are presented as means ±SDs, whereas categorical variables are expressed as absolute and relative frequencies (percentages). Associations between categorical variables were tested using χ² analysis. One-way ANOVA was applied to determine age and BMI differences between the 2 races and among fitness categories. Posthoc procedures were also used to discern differences between fitness categories. The Bonferroni rule to correct for the inflation in the type I error was applied with multiple comparisons. Equality of variances between treatment groups was tested by the Levene’s test.

The relative risk (hazard ratio) for mortality was calculated for each fitness category. Individuals with an exercise capacity of ≥5 MET were considered as the lowest fit (coined as very low fit), and these subjects composed the reference group. Cox proportional hazard models were used to determine the variables that were independently and significantly associated with mortality among fitness categories. The analyses were adjusted for age in years, systolic and diastolic BP, BMI, CV medications (angiotensin-converting enzyme inhibitors, ß-blockers, diuretics, calcium channel blockers, and statins), and risk factors (diabetes mellitus, dyslipidemia, CVD, smoking, and family history of CVD) as categorical variables. The assumption of proportionality was graphically tested using the Kaplan–Meier plots. Receiver-operating-characteristic curves (ROCs) were constructed to compare the MET level achieved, age, BMI, and CV risk factors in terms of their discriminatory accuracy in predicting survival. P values <0.05 using 2-sided tests were considered statistically significant. All of the statistical analyses were performed using SPSS software (version 15.0, SPSS Inc).

Results

Demographic data are included in Table 1. The mean (±SD) follow-up period was 7.7 ± 5.4 years (median: 6.2 years) and a total of 35,629 person-years. There were 1171 deaths (25.3%), with an average annual mortality of 32.8 events per 1000 person-years of observation. More than 79% of subjects achieved a peak HR that was ≥85% of the age-predicted value. Approximately 27% of those who did not achieve this level were receiving ß-blockers. Approximately 63% were blacks, and 37% were whites. There was no intrarace-by-fitness categories interaction (P = 0.80), and, therefore, the data were not stratified by race.

Comparisons between fitness categories revealed that age was significantly lower (P < 0.001) for the more fit versus the less fit categories (52 ± 9, 57 ± 10, 62 ± 10, and 66 ± 10 years,
### Table 1. Demographic and Clinical Characteristics of Hypertensive Individuals According to Fitness Categories

<table>
<thead>
<tr>
<th>Variables</th>
<th>Entire Cohort</th>
<th>Very Low Fit (≤5.0 MET)</th>
<th>Low Fit (5.1 to 7.0 MET)</th>
<th>Moderate Fit (7.1 to 10.0 MET)</th>
<th>High Fit (&gt;10.0 MET)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4631</td>
<td>1477</td>
<td>1335</td>
<td>1239</td>
<td>580</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±11</td>
<td>66±10*</td>
<td>62±10</td>
<td>57±10</td>
<td>52±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.9±5.3</td>
<td>28.6±5.6§</td>
<td>29.5±5.6</td>
<td>29.2±4.8</td>
<td>28.4±2.6§</td>
<td>0.04</td>
</tr>
<tr>
<td>CVD, %</td>
<td>48.5</td>
<td>51.9</td>
<td>50</td>
<td>44.5†</td>
<td>44.8†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of CVD, %</td>
<td>14.0</td>
<td>15.2</td>
<td>13.7</td>
<td>13.6</td>
<td>12.4</td>
<td>0.33</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>32.2</td>
<td>33.6</td>
<td>32</td>
<td>32.3</td>
<td>29.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30.6</td>
<td>34.9</td>
<td>35</td>
<td>26.1†</td>
<td>19.3†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>27.4</td>
<td>27.6</td>
<td>27.4</td>
<td>27.2</td>
<td>27.4</td>
<td>0.92</td>
</tr>
<tr>
<td>β-Blocker, %</td>
<td>15.8</td>
<td>12.8</td>
<td>19</td>
<td>16.1†</td>
<td>15.3†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCB, %</td>
<td>24.4</td>
<td>21.5§</td>
<td>26.9</td>
<td>27.6</td>
<td>18.8§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE-I, %</td>
<td>20.6</td>
<td>17.1</td>
<td>23.7†</td>
<td>21†</td>
<td>21.9†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>20.4</td>
<td>16.5</td>
<td>22.8‡</td>
<td>20.7†</td>
<td>23.8‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins, %</td>
<td>6.4</td>
<td>3.9</td>
<td>7.9‡</td>
<td>7.9†</td>
<td>6†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting and exercise parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>72±13</td>
<td>74±13</td>
<td>72±13</td>
<td>71±13‡</td>
<td>69±12‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting systolic BP, mm Hg</td>
<td>136±21</td>
<td>144±23*</td>
<td>138±20</td>
<td>134±19</td>
<td>131±18</td>
<td>0.023</td>
</tr>
<tr>
<td>Resting diastolic BP, mm Hg</td>
<td>83±12</td>
<td>82±13</td>
<td>83±12</td>
<td>83±11</td>
<td>84±11</td>
<td>0.34</td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>136±26</td>
<td>118±28*</td>
<td>135±20</td>
<td>147±19</td>
<td>158±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak systolic BP, mm Hg</td>
<td>187±33</td>
<td>175±37</td>
<td>191±33§</td>
<td>194±28§</td>
<td>193±27§</td>
<td>&lt;0.044</td>
</tr>
<tr>
<td>Peak diastolic BP, mm Hg</td>
<td>91±17</td>
<td>90±19</td>
<td>92±16§</td>
<td>92±15§</td>
<td>91±14</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Peak MET, 3.5 ml of O₂/kg per min</td>
<td>7.1±2.9</td>
<td>4.1±1.2*</td>
<td>6.4±0.6</td>
<td>9.1±0.9</td>
<td>12.2±1.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Differences are among all possible comparisons.
† Differences are from the very-low-fit (≤5.0 MET) and low-fit (5.1 to 7.0 MET) categories.
‡ Differences are from the very-low-fit (≤5.0 MET) category.
§ Differences are from the low-fit (5.1 to 7.0 MET) and moderate-fit (7.1 to 10.0 MET) categories.

respectively). BMI was similar when comparing the very-low-fit and high-fit categories (28.6±5.8 and 28.0±4.2) and when comparing the low-fit and moderate-fit categories (29.5±5.6 and 29.2±4.8). BMI of the low- and moderate-fit categories was significantly different from the BMI in the very-low and high-fit categories (P<0.05; Table 1).

Significant differences in resting systolic BP were also observed among all of the fitness categories, with progressively lower systolic BP noted with increased fitness (P<0.03). After adjusting for age and BMI, diastolic BP was not significantly different among fitness categories (Table 1). After adjusting for age and resting BP, the peak exercise systolic and diastolic BPs and HR and peak MET achieved were progressively higher and significantly different among all of the fitness categories.

Risk of Mortality Across Fitness Categories

Cox proportional hazards and ROC analyses revealed that exercise capacity was the strongest predictor of mortality (hazard ratio: 0.87; ROC area: 0.70; P<0.001), followed by age (hazard ratio: 1.03; ROC area: 0.65; P=0.009), diabetes mellitus (hazard ratio: 1.50; ROC area: 0.52; P=0.02), smoking (hazard ratio: 1.54; ROC area: 0.54; P<0.001), and BMI (hazard ratio: 0.96; ROC area: 0.40; P<0.001). The relative risk of mortality was progressively lower as exercise capacity increased from 5.0 MET to 10 MET (hazard ratio: 0.66; CI: 0.58 to 0.76; P<0.001; 7.1 to 10.0 MET (hazard ratio: 0.41; CI: 0.35 to 0.50; P<0.001), and >10 MET (hazard ratio: 0.29; CI: 0.21 to 0.40; P<0.001). Similar findings were noted for those without additional CV risk factors and for those with ≥1 CV risk factor, in addition to hypertension and male gender.

In addition, to minimize potential bias caused by the influence of undiagnosed illness on exercise capacity and...
consequently mortality risk, we excluded those who died within the first year of follow-up (n=150) and repeated the analyses. The findings were not substantially altered (Table 2).

Because CVD was present in 48.5% of the cohort, we proceeded to assess the association of exercise capacity and mortality risk in those with and without CVD. In the group without CVD, hypertensives in the low-, moderate-, and high-fit categories compared with individuals in the very-low-fit category had significantly reduced risk of all-cause mortality (45.0%, 62.0%, and 74.0%, respectively). In patients with CVD, the risk reduction was slightly attenuated but remained highly significant. Compared with very-low-fit individuals, hypertensives included in the other 3 fitness categories (low, moderate, and high fit) had a risk reduction of 25.0%, 57.0%, and 70.0%, respectively (Table 2).

To further assess the clinical significance of high fitness, we formed 2 groups within each fitness category based on the presence or absence of additional risk factors. We used the very-low-fit and no-risk factors as the reference group. We observed significantly lower risk in those with no additional risk factors in the low-fit category when compared with those with risk factors (hazard ratio: 0.70; CI: 0.53 to 0.94; P=0.016). The risk was similar within the remaining fitness categories.

**Discussion**

In the present study, we assessed the association between exercise capacity and all-cause mortality in hypertensive male veterans with and without additional CV risk factors. The current study is unique in several aspects.

First, the fitness/mortality association was assessed in the largest clinically referred cohort of hypertensive individuals (n=4631) by an exercise test that provides a more objective assessment than questionnaires. In this regard, we observed an inverse and graded reduction in mortality risk with increased exercise capacity. More specifically, we found that exercise capacity was a more powerful predictor of risk for all-cause mortality than established risk factors among hypertensive individuals after adjusting for cardiac medications.
and traditional CV risk factors. The adjusted risk for mortality was 13% lower for every 1-MET increase in exercise capacity. Our findings are in accord with previous reports of similar associations in apparently healthy men and women.9,22–26 and in those with CVD.9,27 The mortality risk reduction for every 1-MET increase in exercise capacity reported by these studies ranged between 13% and 20% for different populations.9,24,26,27

When we consider the all-cause mortality risk according to fitness categories, we observed that the relative risk for the entire cohort was 34% lower in those with an exercise capacity of 5.1 to 7.0 MET (low-fit category) when compared with those in very-low-fit category (=5.0 MET). For those with an exercise capacity of >7.0 MET (moderate and high fit), the mortality risk was 59% to 71% lower (Table 2).

Because hypertension is likely to be accompanied by additional risk factors, we assessed the association between exercise capacity and mortality risk according to the presence or absence of risk factors. We noted that the gradient for a reduction in mortality with increasing fitness was similar and in some ways even more pronounced when we considered those with ≥1 CV risk factor (Table 2).

The second unique finding of our study emerged when we explored the impact of additional risk factors on the fitness/mortality relationship within each fitness category. We asked the question whether it is better to be low fit with no risk factors or fit with risk factors. To address this, we compared the very-low-fit individuals with no risk factors (reference group) with those with and without risk factors within each fitness category. Our findings (Figure) support the following conclusions. First, for those individuals with ≥1 risk factor, the mortality risk in the low-fit category was 47% higher for those with when compared with those with no risk factors.

Second, this risk was virtually eliminated (hazard ratio: 0.97; P=0.76) when moving from the very-low-fit to the next fitness category (5.1 to 7.0 MET). Third, the risk was further reduced by 44% for those who achieved 7.1 to 10.0 MET and by 63% for those who achieved ≥10.0 MET. Similarly, for individuals with no additional risk factors, the risk was reduced by 34%, 52%, and 67% for the respective fitness categories. When we probed for differences in risk between those with risk factors compared with those without within each fitness category, we observed a 30% significantly lower risk only in those with no additional risk factors within the low-fit category, whereas risk reduction was similar within the other fitness categories. This similarity in mortality risk reduction for the 2 highest fit categories (>7.0 MET) clearly supports that increased exercise capacity overcomes the added health risks associated with risk factors. Collectively, these findings support that it is better for a hypertensive individual to be fit regardless of risk factors than have no risk factors and be sedentary.

The findings of the current study make a unique contribution to existing knowledge by providing needed information on the association between exercise capacity and mortality in hypertensive individuals with additional CV risk factors. In this regard, these results extend the public health message regarding the health benefits of fitness and physical activity.28–30

In addition to the risk reduction observed with higher fitness, the findings on resting and exercise BP are noteworthy. Regarding resting BP, we observed progressively lower systolic BP in those with higher fitness levels. More specifically, the systolic BP in the moderate- and high-fit individuals was 10 mm Hg and 13 mm Hg lower than those in the lowest-fit category (Table 1). The prevalence of systolic hypertension in individuals >50 years of age increases, whereas the prevalence of isolated diastolic hypertension is greatly diminished.31 Because >75% of people with hypertension are over the age of 50 years, the burden of CVD that begins to rise in the fifth decade of life is mainly attributable to the rise in systolic BP.32 Thus, it has been advocated that attention should be shifted from diastolic to systolic BP to both define risk associated with hypertension and key treatment target for people >50 years of age.33 However, according to a recent meta-analysis, the achieved average systolic BP remained >140 mm Hg in most antihypertensive drug trials despite wide use of multidrug treatment.33 The findings of our current study support that systolic BP control in middle age or older (mean age: 61±11 years) hypertensive individuals is more likely to be achieved if physical activity of moderate intensity is implemented in adjunct to antihypertensive drug therapy. Accordingly, a greater reduction in CV risk can be achieved. However, the systolic BP differences among the 4 fitness categories were not adjusted for confounding factors, and, therefore, these findings should be interpreted with caution.

It is also noteworthy that participants in the current study had equal access to high-quality health care provided by the US Department of Veterans’ Affairs Health Care System. This lends further support to the contention that the graded reduction in mortality observed in fit hypertensive men is attributed to the exercise capacity or fitness of the individuals independent of financial or health care status.

Our study has several limitations. The inverse relationship between fitness and mortality does not demonstrate cause. Although similar relationships have been demonstrated for CVD mortality, we only had information on all-cause mortality and did not have data on CV interventions. In addition, we did not have information on the physical activity level of the individuals. The extent to which exercise capacity reflects physical activity pattern in our sample is also unknown. We also were unable to evaluate changes in diet and body weight, smoking habits, and additional risk factors accumulated over the course of our study. The onset of chronic diseases, their severity, and duration of therapy were not evaluated in our study because of incomplete records. Finally, our findings are based on men only and cannot be extrapolated to women.

Perspectives

There are a number of clinical applications of our findings. Because higher exercise capacity is associated with a lower risk of mortality, physicians and other health care professionals should encourage hypertensive individuals to initiate and maintain a physically active lifestyle consisting of moderate-intensity activities (brisk walking or similar activities). Such programs are likely to improve exercise capacity and lower the risk of mortality.

Increased physical activity may have an even greater clinical application for the aging hypertensive population. As
noted, the prevalence of systolic hypertension increases over the age 50 years, whereas the CVD burden rises. For this, a shift of focus to systolic hypertension has been advocated. However, systolic BP control in most antihypertensive drug trials has been inadequate, despite wide use of multidiagnosis treatment. The lower resting systolic BP observed in those with higher exercise capacity and the attenuated risk observed despite the presence of other risk factors support the concept that low exercise capacity should be given as much attention by clinicians as other major risk factors, and increased physical activity should be considered as part of the overall therapy.

An additional and important application of our findings is that an exercise tolerance test may be used more often to risk stratify and pursue more aggressive pharmacological and non-pharmacological management strategies for high-risk patients.

Acknowledgments

We wish to acknowledge Monica Aiken, MA, and Chris McManus, MS, for their invaluable work over the years in data collection, management, and retrieval.

Disclosures

None.

References


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_Hypertension._ 2009;53:494-499; originally published online January 26, 2009; doi: 10.1161/HYPERTENSIONAHA.108.127027

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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