Conservative Drug Treatment in Patients With Moderately Severe Chronic Occlusive Peripheral Arterial Disease

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A double-blind, parallel group, multicenter clinical trial of pentoxifylline compared with placebo enrolled 150 patients with moderately severe chronic occlusive arterial disease (COAD) at three centers in Scandinavia. The study consisted of a 4-6 week single-blind, placebo-controlled run-in phase, during which the stabilization of the initial claudication distance of all patients was assessed before randomization to a 6-month double-blind observation period. The diagnosis of COAD was established by clinical findings, conventional angiography, and noninvasive peripheral Doppler pressure assessment at rest and after exercise. The results of the overall intention-to-treat analysis of the study population show statistically significant superiority of pentoxifylline over placebo for all absolute claudication distance summary and end point measures. By using two clinically relevant parameters, which are a resting ankle/arm pressure ratio 0.8 or less and a duration of COAD for greater than 1 year, a target population could be defined in whom trial results became highly significant. For nontarget patients with mild COAD, we conclude that basic therapeutic measures should include the treatment of risk factors and the initiation of physical training. For target patients, however, a multifactorial therapeutic approach, including the use of pentoxifylline, is justified. (Circulation 1989;80:1549-1556)

Basic measures for the treatment of chronic occlusive arterial disease (COAD) are the avoidance of risk factors and the institution of physical training. However, the decision of whether or not to use vasoactive drugs is controversial, and recommendations differ widely among different schools of medicine mainly because of the difficulty in predicting treatment outcome.

The drug used in this trial, pentoxifylline, is a compound that improves blood fluidity by reducing red cell rigidity and blood viscosity. Furthermore, it inhibits platelet aggregation and, as recently published, diminishes the state of neutrophile granulocyte activation.

The purpose of this Scandinavian study was to compare pentoxifylline and placebo as treatment for COAD. Furthermore, those patients were to be identified in whom treatment with pentoxifylline was especially beneficial. This was to be achieved by identifying relevant patient background variables that are positively associated with a favorable treatment outcome.

Methods

Study Population

A double-blind, placebo controlled, parallel group study was conducted in three centers: Malmö (center 1), Växjö (center 2), and Gentofte (Copenhagen) (center 3). One hundred fifty outpatients of either sex were enrolled. Forty-one of these were recruited by writing to two age cohorts (born in 1922 and 1924), totaling 6,000 subjects living in the Malmö urban area; 44 were known COAD patients from the Malmö hospital outpatient department; and 41 and 24 patients were recruited from the surgical outpatient departments of centers 2 and 3. All patients were at least 40 years of age, suffering from moderately severe COAD with an initial claudication distance (ICD) between 50 and 200 m, as tested on a treadmill, set at a speed of 2 mph (3.2 km/hr) and an inclination of 12.5% (7.1°). All patients had a history of intermittent claudication of at least 6 months in duration. The diagnosis of COAD was established by
clinical examination and by Doppler pressure assessment at rest and after exercise. The diagnosis was confirmed by angiography in all patients.

Design

The study was divided into a 4–6 week single-blind, placebo-controlled, run-in phase and a randomized, double-blind, 6-month observation period. Primary efficacy variables were the ICD and the absolute claudication distance (ACD). The protocol design ensured that patients were randomized to the double-blind phase, only if the ICD was stable at the last two visits of the run-in phase. Stability was defined as a difference of less than 35% in patients with baseline ICD up to 100 m and less than 25% in patients with baseline ICD between 101 and 200 m. This classification into two groups was necessary to homogenize the accepted variation in walking capacity even in rather different baseline ICDS.

Patients were not eligible for the study if any of the following conditions applied: complete occlusion of the aortoiliac segment, the femoral bifurcation, or the popliteal artery without angiographically proven distal refilling of the respective segment; vascular reconstruction or sympathectomy within the last 12 months; peripheral neuropathy, Buerger’s disease; marked postphlebitic syndrome; diabetes; cardiac failure or severe rhythm disorders; major infections; abnormal values for platelets; prothrombin index or partial thromboplastin time; history of xanthine hypersensitivity; addiction to analgesics; malignant disease, or any other condition that limits the patient’s walking ability or the full understanding of the study procedure.

Diabetics were excluded from the trial because of the possible influence of a diabetic neuropathy that may mask claudication pain and, thus, hinder an objective evaluation of the patient’s walking ability.

During the run-in phase, all patients received placebo, 1 tablet t.i.d. During the double-blind period and according to a randomization plan, pentoxifylline (400 mg) or matching placebo was administered t.i.d. Randomization was stratified by centers. Patients were reviewed fortnightly during the run-in phase and every 4 weeks during the double-blind period. At each follow-up visit, the following examinations were performed: assessment of ICD and ACD by treadmill testing (2 mph [3.2 km/h], 12.5% [7.1°] inclination), documentation of adverse events and intercurrent illness, assessment of compliance by tablet count, without the patient’s knowledge. In addition, a clinical vascular examination, including the assessment of COAD signs and symptoms, was performed. Ankle/arm pressure ratios and laboratory parameters were checked at 3-month intervals. Laboratory parameters included: red blood cell count, white blood cell count, platelets, mean corpuscular volume, hemoglobin, fibrinogen, prothrombin index, partial thromboplastin time, total bilirubin, SGOT, SGPT, gamma-GT, AP, FBS, creatinine, total cholesterol, and triglycerides.

The trial was performed in accordance with the Declaration of Helsinki, and its protocol was reviewed by the Boards of Health in Denmark and Sweden as well as by the Ethical Committee of each center. The patients gave their informed consent before enrollment in the study.

Statistical Analysis

All baseline variables were analyzed using Wilcoxon’s rank-sum test, two-sample t test, χ² test, or Fisher’s exact test. To analyze drug effects on walking distances, the following variables were used: the last observation carried forward to each visit (LOCF) and, as summary measures, the minimum, mean, and median distances walked at weeks 16–24. The LOCF was used in cases of missing data; the last available test result was carried forward and used as the value for each visit until another result was recorded. In the case of dropouts, data were carried forward to each subsequent visit until the final visit at week 24. The minimum distance for a given time period is identical to the lowest treadmill test result measured within this time period. This measure is independent of spontaneously occurring, nonpersistent improvements and, to a large extent, abolishes the placebo effect.

The trial result analysis was based on the intention-to-treat population, using all data available from the 150 patients randomized to the study.

Efficacy results were reported after adjustment for study site. Comparison of treatment effects was performed with the extended Mantel-Haenszel test with stratification adjustment for site and standardized rank scores. Geometric means of percent change from baseline and 95% confidence intervals were calculated. ANOVA models were used to test interactions of treatment groups and background variables as listed in the Table 1. Laboratory data were classified as normal or abnormal, and changes within each group were analyzed by Wilcoxon’s signed-rank test. Differences in the overall prevalence of side effects were compared between treatment groups with a χ² test. All statistical tests were two sided and were considered significant if p was less than 0.05.

Results

A total of 161 patients entered the single-blind run-in phase, 11 of whom did not qualify for the double-blind phase because of violation of the study’s inclusion and exclusion criteria. The remaining 150 patients were randomized: 76 patients to pentoxifylline and 74 to placebo.

Intention-to-Treat Population

The baseline characteristics for the total study population are shown in Table 1. There were no differences in any of the patients’ characteristics between the two treatment groups. However, ACD was significantly longer in patients receiving placebo. As confirmed by angiography, the distribution of vascular stenoses and occlusions within the
TABLE 1. Patient’s Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pentoxifylline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65±7</td>
<td>64±8</td>
</tr>
<tr>
<td>Male/female</td>
<td>79/21%</td>
<td>80/20%</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.03±0.1</td>
<td>1.05±0.2</td>
</tr>
<tr>
<td>Duration of disease (yr)</td>
<td>4.9±4.9</td>
<td>4.2±4.5</td>
</tr>
<tr>
<td>Ankle/arm pressure ratio</td>
<td>0.58±0.2</td>
<td>0.62±0.2</td>
</tr>
<tr>
<td>Isolated iliac or iliofemoropopliteal lesions</td>
<td>17%</td>
<td>12%</td>
</tr>
<tr>
<td>Isolated femoropopliteal or femoropopliteal/lower leg lesions</td>
<td>72%</td>
<td>68%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37%</td>
<td>35%</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>26%</td>
<td>30%</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>History of angina pectoris</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>Smoking</td>
<td>63%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Values are mean±SD where applicable.

aortoiliac, the femoropopliteal, and the peripheral segment was similar in both groups (Table 1) and was in keeping with the distribution described in the literature for a typical elderly COAD population.19

The mean baseline ICD and ACD values for patients receiving pentoxifylline or placebo were: ICD, 77 and 79 m; ACD, 132 and 155 m, respectively. The results for the overall intention-to-treat analysis of all 150 patients for ICD and ACD are given in Table 2 and Figure 1. Treatment differences for ICD and ACD increased steadily over time in favor of pentoxifylline.

ACD minimum percent improvement for weeks 16–24 favored pentoxifylline significantly (p=0.023). As shown by the 95% confidence intervals in Figure 1, a large interindividual variation in results leads to a p value of 0.06 for ICD. These results are consistent with the ACD data.

TABLE 2. Analysis of Walking Distance for Intention-to-Treat Population

<table>
<thead>
<tr>
<th>weekly measures</th>
<th>Pentoxifylline (n=76)</th>
<th>Placebo (n=74)</th>
<th>p*</th>
<th>Absolute claudication distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial claudication distance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline distance</td>
<td>77±4</td>
<td>79±4</td>
<td>0.613</td>
<td>132±9</td>
</tr>
<tr>
<td>Percent improvement</td>
<td></td>
<td></td>
<td></td>
<td>155±11</td>
</tr>
<tr>
<td>LOCF to wk 20</td>
<td>74±11</td>
<td>56±11</td>
<td>0.233</td>
<td>46±8</td>
</tr>
<tr>
<td>LOCF to wk 24</td>
<td>80±12</td>
<td>60±11</td>
<td>0.268</td>
<td>50±9</td>
</tr>
<tr>
<td>Summary measures</td>
<td></td>
<td></td>
<td></td>
<td>29±8</td>
</tr>
<tr>
<td>Minimum of wk 16–24</td>
<td>54±10</td>
<td>27±8</td>
<td>0.060†</td>
<td>31±8</td>
</tr>
<tr>
<td>Mean of wk 16–24</td>
<td>79±11</td>
<td>57±10</td>
<td>0.101</td>
<td>50±8</td>
</tr>
<tr>
<td>Median of wk 16–24</td>
<td>82±12</td>
<td>60±10</td>
<td>0.134</td>
<td>51±9</td>
</tr>
</tbody>
</table>

Values are geometric mean±SEM.

LOCF, Last observation carried forward.

*p values are based on extended Mantel-Haenszel statistics with stratification for study site and usage of standardized rank scores within site. †0.05<p<0.10, ‡0.01<p<0.05.

FIGURE 1. 95% confidence limits for group differences of percent improvement over baseline; weekly measures and summary measures for weeks 16–24 for all patients (n=150). ICD, initial claudication distance; ACD, absolute claudication distance.

Influence of Background Variables

Twelve patient background variables were tested for interaction with study outcome, of which the most important were investigational site, age, smoking, ankle pressure index, duration of COAD, history of cardiac disease, and baseline ICD.

The interaction of baseline ankle/arm pressure ratio, categorized as 0.8 or less and greater than 0.8 with treatments for ICD outcomes, was the strongest of all interactions tested (p=0.009). Smoking and duration of disease (≤1 year and >1 year) interacted with treatment for ICD outcomes only. Interaction of treatment and baseline ICD (<70 m and ≥70 m) was strongest for ACD outcomes. There was no interaction between treatment out-
come and a history of myocardial infarction or angina pectoris or for the combination of both.

**Subpopulation With Ankle/Arm Pressure Ratio of 0.8 or Less**

One hundred thirty-one of 150 patients had a baseline resting Doppler ankle/arm pressure ratio of 0.8 or less. In this subset of patients, there was no baseline ACD heterogeneity between the two treatment groups, unlike the overall intention-to-treat population. By the end of the study, summary measures such as minimum improvement during weeks 16–24 were highly significant in favor of pentoxifylline for ICD (p=0.008) and ACD (p=0.006).

The results of ICD and ACD LOCFs to week 20 were significant in favor of pentoxifylline (p<0.05). The same was true for the LOCF to week 24 for both ACD and ICD. The results are summarized in Table 3.

Within the described subpopulation, there was no interaction of the pressure ratio with treatment outcome as described above for the overall intention-to-treat population. Interactions with smoking and baseline ICD were not present. However, the interaction of treatment outcome with the duration of disease still remained significant.

**Subpopulation With a Duration of Disease 1 Year or More**

One hundred twenty-seven of 150 patients had a history of COAD of more than 1 year. In this subset, the differences in ICD and ACD were significant in favor of pentoxifylline for mean and minimum distance walked during weeks 16–24 (p<0.05), whereas weekly results were not significant (Table 3).

**Subpopulation With Ankle/Arm Pressure Ratio of 0.8 or Less and a Duration of Disease for More Than 1 Year**

One hundred nine of 150 patients had a pressure ratio of 0.8 or less and a history of disease of more than 1 year. Baseline ICD and ACD were similar for both treatment groups. All end point measures as well as all summary measures were strongly significant for both ICD and ACD outcomes. The ICD LOCF analysis to week 24 showed improvements of 99% and 47% for pentoxifylline and placebo,
Figure 2. 95% confidence limits for group differences of percent improvement over baseline; weekly measures and summary measures for weeks 16–24 for patients with pressure ratio 0.8 or less and duration of disease 1 year or more (n=109). ICD, initial claudication distance; ACD, absolute claudication distance.

respectively. These results are summarized in Table 4 and Figure 2.

Subpopulation With an Initial Claudication Distance of Less Than 70 Meters

In addition, treatment effects in patients with more severely limited walking distance at baseline (ICD <70 m) were analyzed. Although this subset of patients was only half the size of the intention-to-treat population, which diminished the power to detect treatment effects, the group differences significantly favored pentoxifylline for minimum improvement of weeks 16–24 in ICD (p=0.036) and ACD (p=0.018) (Table 3). These results are in agreement with pentoxifylline data published previously from the United States.20

Angiographic Findings

As seen from Table 1, the distribution of atherosclerotic lesions within the iliacpopliteal and the femoropopliteal segment was comparable in the two treatment groups. When all patients of both groups are considered, the following distribution of lesions emerges. Isolated iliac lesions occurred in 4%; multisegmental disease with main lesion within the iliac segment occurred in 10%; isolated lesions within the femoropopliteal segment occurred in 21%; multisegmental disease with main lesion within the femoropopliteal segment occurred in 48%; isolated lesions of the lower leg trifurcation occurred in 8%; and nonocclusive disease with diffuse multisegmental distribution of plaques only occurred in 9% of patients.

Adverse Events

Twenty-two percent of the patients receiving pentoxifylline and 14% of the patients receiving placebo reported side effects. Adverse events were generally mild and did not lead to exclusion from the trial. The most frequent occurrences were related to the digestive system (13 patients receiving pentoxifylline compared with seven receiving placebo). This difference, however, was not significant. Other side effects were mild in nature, occurred very infrequently, and were seen in similar numbers in the placebo and pentoxifylline groups.

Discussion

Representativeness of Study Results

Pentoxifylline has been used in a large number of clinical trials, most of which are summarized by Rößner and Müller.21 The results of the present study are consistent with the relatively large trial reported by Porter et al22 from the United States as shown in Table 5. There were some differences in the discriminating value of ICD and ACD, which are explained by the high placebo response in this trial.

The data from the US trial22 and this Scandinavian trial are comparable in respect to patient demographic variables such as age, sex ratio, the prevalence of risk factors (except for diabetes, which was an exclusion criterion in this trial), and the severity of COAD as measured by the pressure ratio. The results of all subgroup analyses disclose

<p>| Table 5. Results of the Study by Porter et al22 Compared With the Present Trial |
|-------------------------------------------------|-------------------------------------------------|-----------------|-----------------|-----------------|
| Study by Porter et al22 | Present study |</p>
<table>
<thead>
<tr>
<th>Tretal</th>
<th>Placebo</th>
<th>p</th>
<th>Tretal</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial claudication distance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF wk 20</td>
<td>47</td>
<td>19</td>
<td>0.038</td>
<td>74</td>
<td>56</td>
</tr>
<tr>
<td>LOCF wk 24</td>
<td>47</td>
<td>26</td>
<td>0.042</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>Minimum wk 16–24</td>
<td>36</td>
<td>9</td>
<td>0.030</td>
<td>54</td>
<td>27</td>
</tr>
<tr>
<td>Absolute claudication distance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF wk 20</td>
<td>35</td>
<td>21</td>
<td>0.214</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>LOCF wk 24</td>
<td>33</td>
<td>20</td>
<td>0.316</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>Minimum wk 16–24</td>
<td>23</td>
<td>9</td>
<td>0.079</td>
<td>31</td>
<td>9</td>
</tr>
</tbody>
</table>

Percent improvement over baseline is given as the geometric mean.
satisfactory agreement of both trials' results, confirming the validity of both studies. Furthermore, there is good comparability of these data with the prevalence of background variables in COAD patients as published in the international literature, suggesting that the results from the study by Porter et al and from ours can be generalized to patients at large.

Gallus et al and Reilly et al report negative results from double-blind trials of pentoxifylline. However, when analyzing these reports, possible explanations for their results can be found. A general criticism of both trials is the small number of patients included. With approximately 15 patients per group, the power to detect a significant difference between treatments is unacceptably low. Furthermore, Gallus et al used a cross-over design without including a washout period. Positive effects seen in the first trial phase were leveling out later probably due to a carry-over effect.

**Trial Design**

This trial has been designed in accordance with the European Community guidelines, which take into account the major problems of clinical trials in intermittent claudication, which are the wide variation in treatment response, and the magnitude of the placebo response to be expected. The guidelines require protocols to ensure that the sample population is representative, the clinical symptomatology is homogeneous, the initial claudication distance is stable, and a minimum study period of 6 months is observed.

In this trial, additional methodology to reduce the variation of claudication distance results and the magnitude of the placebo response was used. As described by Gillings et al, summary measures such as the minimum distance walked during weeks 16–24 abolishes spontaneously occurring nonpersistent improvement and also, to a large extent, the placebo effect. Furthermore, this measure tends to underestimate the true effect of the treatment scheme under evaluation.

**Clinical Relevance of Treadmill Test Results**

Treadmill tests are to be performed under standardized conditions which are widely accepted, such as a walking speed of 2 mph (3.2 km/hr) and an inclination of 12.5% (7.1°). These conditions are feasible for the testing procedure but do not resemble the every day life of an elderly COAD patient, who walks at a much lower speed. Consequently, a multiplication factor should be used for the conversion of treadmill test results to daily walking activity. In the guidelines for exercise testing and prescription of the American College of Sports Medicine, the energy requirements of test subjects are compared under different test conditions. From the comparison of horizontal treadmill walking at 2 mph (3.2 km/hr) and walking at 2 mph (3.2 km/hr) plus 12.5% (7.1°) inclination, respectively, energy requirements on the inclined treadmill were shown to increase by a factor of 2.4.

One known effect of enforced exercise on the muscle metabolism in patients with COAD is, that energy stores such as creatinine phosphate and ATP are depleted much earlier than would occur in healthy subjects. It follows that these assumptions, although derived from stress testing in healthy volunteers, should be valid for patients with COAD, too. However, the appropriate correction factor may well be higher in COAD patients than in normal subjects. A clinical trial to determine the validity of this hypothesis is in progress, and its results will be reported elsewhere in due course. Independent of the interpretation of treadmill results, a validated quality of life assessment scheme is not available for COAD patients and is required urgently.

**Definition of a Target Population**

We hypothesized that it should be possible to select a target population in whom the probability for a successful treatment outcome would be higher than in a general COAD population. Parameters used for this definition must be of obvious clinical relevance. Furthermore, they should be supported by the results of the treatment outcome and patient background variable interaction analysis.

As shown in detail in the “Results” section, the strongest interaction found was between treatment outcome and the pressure ratio (cutoff point 0.8). Furthermore, treatment outcome interacted with the duration of disease (cutoff point, 1 year), even if a multivariate analysis approach was used. In patients with a pressure ratio less than 0.8, the treatment outcome by duration of disease interaction remained unchanged, in contrast to the treatment and smoking and the treatment and investigator interaction, which was no longer observed. Consequently, these two background variables (pressure ratio cutoff point, 0.8; duration of disease cutoff point, 1 year) should be given preference over others for the required definition of a target population.

A duration of disease of 1 year corresponds in clinical terms, to the time by which major spontaneous collateralization has taken place. It is common clinical experience that within this time period there is a high probability of improvement of walking ability, either spontaneously or induced by physical training. Consequently, additional drug treatment may not be necessary during the first year of symptoms. The duration of disease is subjective information from the patient, and its objective value may be doubted. However, the interaction of this background variable with treatment outcome emphasizes its clinical importance.

If the pressure ratio is used to define a target population, a value should be chosen that is clearly in the pathologic range and that may distinguish patient groups who need special attention from those hemodynamically mild cases in whom the
treatment of risk factors and the initiation of physical training may be sufficient. Resting pressure ratios above 0.95 are considered to be normal, although they will not exclude vascular disease that is hemodynamically insignificant at rest. Pressure ratio values below 0.5 clearly describe severe ischemia, whereas the pressure ratio range between 0.5 or 0.6 and 0.9 is characteristic of moderate disease.58

This medical and statistical information suggests that a target population should include COAD patients with a duration of symptomatic disease of more than 1 year and an ankle/arm pressure ratio of 0.8 or less. This group includes 73% of the overall intention-to-treat population for this study. Comparing results in Tables 2 and 4, the validity of the hypothesis that these patients have better treatment outcomes was confirmed. Because of a minimization of ICD and ACD test variations over time, all weekly and summary measures become highly significant in favor of pentoxifylline.

In absolute terms, an improvement in the range of 80–100 m (equivalent to 1.1–1.3 New York city blocks) above placebo results can be expected if a factor of approximately two is used to convert treadmill results into everyday walking activity of a COAD patient as clearly shown above.

Conclusions

For patients with a history of COAD disease of more than 1 year, with an ankle/arm pressure ratio of 0.8 or less the use of pentoxifylline will lead to a high probability of a successful and clinically relevant treatment outcome. However, for patients suffering from COAD with a short history of less than 1 year or mild hemodynamic impairment (pressure ratio >0.8), the treatment of choice should be the avoidance of risk factors and the initiation of physical training.

Acknowledgments

The statistical analysis has been performed in close cooperation with Prof. Dennis Gillings, University of North Carolina, Chapel Hill, North Carolina. We are grateful to Yvonne Fröberg, Grete Ljunglov, and Monika Sjöö-Boquist for their technical assistance. The pentoxifylline preparation used in this trial was Trental 400, which was supplied by Hoechst AG Werk Albert, Wiesbaden, Federal Republic of Germany.

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**KEY WORDS** • claudication distance • pentoxifylline • Doppler pressure ratio • target population • arterial occlusive diseases • clinical trials
Conservative drug treatment in patients with moderately severe chronic occlusive peripheral arterial disease. Scandinavian Study Group.
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Circulation. 1989;80:1549-1556
doi: 10.1161/01.CIR.80.6.1549

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/80/6/1549