Improvement in Hypertension in Patients With Diabetes Mellitus After Kidney/Pancreas Transplantation

Michael D. Elliott, MD; Ajoy Kapoor, MD; Michele A. Parker, RN, MS; Dixon B. Kaufman, MD, PhD; Robert O. Bonow, MD; Mihai Gheorghiade, MD

Background—Hypertension persists in many patients with diabetes mellitus after kidney transplantation. However, the impact of control of diabetes as well as kidney failure on hypertension by combined kidney and pancreas transplantation has not been studied.

Methods and Results—Between March 1993 and August 1998, 111 patients with type 1 diabetes mellitus underwent successful pancreas transplantation (108 kidney/pancreas transplantation) and another 28 patients with type 1 diabetes mellitus underwent isolated kidney transplantation. Blood pressure measurements and all antihypertensive medications were determined for both groups before transplantation and at 1, 3, 6, and 12 months and at the most recent outpatient evaluation after transplantation. At baseline, the mean blood pressure was 151/88 and 151/83 mm Hg for the kidney/pancreas and isolated kidney transplant patients, respectively. The mean blood pressure decreased to 134/77 mm Hg 1 month after kidney/pancreas transplantation (P<0.001) and decreased further to 126/70 mm Hg (P<0.001) at a mean follow-up of 18 months. This reduction in blood pressure after transplantation occurred despite a decrease in antihypertensive medications and the institution of immunosuppressive agents. At 1 month after kidney/pancreas transplantation, the average number of antihypertensive medications per patient was 0.9±1.0, compared with 2.5±1.1 before surgery (P<0.001). At 18 months after transplantation, 34% of patients were both normotensive (blood pressure ≤130/85 mm Hg) and receiving no antihypertensive medications. In contrast, there was no significant decrease in systolic blood pressure or antihypertensive medication use in the patients receiving an isolated kidney transplant.

Conclusions—Successful kidney/pancreas transplantation results in a marked improvement in hypertension treatment that is not observed in patients undergoing isolated kidney transplantation. These data underscore the importance of diabetes in the pathogenesis of hypertension in patients with diabetes and kidney failure. (Circulation. 2001;104:563-569.)

Key Words: diabetes mellitus ■ hypertension ■ kidney ■ transplantation

Cardiovascular disease is a leading source of morbidity and mortality in patients with diabetes mellitus. 1–5 Hypertension is a major contributor to this excess of cardiovascular disease and is present during the course of nearly all patients with type 1 diabetes mellitus complicated by diabetic nephropathy. Despite the restoration of normal renal function, hypertension remains a significant issue for diabetics who have undergone successful kidney transplantation, with persistent hypertension in up to 60% to 80% of patients. 7,8 Although the high prevalence of hypertension after kidney transplantation may in part be related to the chronic administration of immunosuppressive medications such as cyclosporine, tacrolimus, and prednisone, persistent hypertension may also be the result of diabetes. Successful pancreas transplantation provides normal blood glucose concentrations and normal glycosylated hemoglobin levels for patients with type 1 diabetes mellitus. 9,10 However, the prevalence of hypertension after kidney and pancreas transplantation is not well defined. We hypothesized that treatment of diabetes as well as kidney failure, by combined kidney-pancreas transplantation, would lead to enhanced blood pressure control. Accordingly, we investigated the impact of kidney/pancreas transplantation on blood pressure control in patients with type 1 diabetes mellitus compared with similar patients undergoing isolated kidney transplantation.

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Methods

Patient Population
Between March 1993 and August 1998, 117 consecutive patients with type 1 diabetes mellitus underwent pancreas transplantation at Northwestern Memorial Hospital. Early (<1 month) pancreatic graft loss occurred in 6 patients, who were excluded from analysis. Of the 111 patients who had successful pancreas transplantation, 106
underwent simultaneous kidney and pancreas transplantation, 2 underwent pancreas transplantation after previously successful kidney transplantation, and 3 underwent pancreas transplantation alone. During the same time period, 28 patients with type 1 diabetes mellitus underwent isolated kidney transplantation. All patients had type 1 diabetes, with onset at age 25 years or younger.

**Kidney-Pancreas Transplantation**

The details of organ procurement, preservation, and the surgical technique of kidney/pancreas transplantation with utilization of the whole pancreatocoduodenal allograft have been previously described. Either the left or right kidney was used for transplantation. The kidney was vascularized with the left iliac vessels. The pancreatocoduodenal allograft was vascularized with the right iliac vessels. Pancreas venous drainage was either systemic or intraportal, with the arterial Anastomosis of the Y-graft to the recipient common iliac artery. Pancreatic digestive secretions were drained to the bladder in 97 patients as a 2-layer, hand-sewn duodenocystostomy performed on the dome of the bladder in the intraperitoneal position. In 14 patients, the pancreas secretions were drained enterically.

Immunosuppression was achieved by means of quadruple therapy. All patients received a 7- to 14-day course of induction therapy with antithymocytogenic globulin (ATGAM, Pharmacia and Upjohn Co) or daclizumab (Zeneca, Roche Pharmaceuticals). All patients began on maintenance therapy consisting of azathioprine or mycophenolate mofetil. Dosage adjustments were made on the basis of tolerance to the medication or development of leukopenia. Cyclosporine or tacrolimus was started on postoperative day 1. Corticosteroids were initiated during surgery with methylprednisolone, then prednisone was used and tapered over 1 year to 5 to 7.5 mg/d.

Acute rejection episodes were diagnosed by ultrasound-guided percutaneous renal or pancreas allograft biopsy. Antirejection therapy was relatively consistent independent of the severity of rejection. Acute cellular rejection was treated with a 7- to 14-day course of OKT3 (Orthoclone, Ortho Biotech) or ATG. OKT3 dosing was guided by monitoring circulating OKT3 levels (target level 800 to 1000 ng/mL) and by flow cytometry conducted to determine absolute CD3 circulating levels (target 9%).

Perioperative antimicrobial therapy with vancomycin and piperacillin/tazobactam, (aztreonam and metronidazole for penicillin-allergic patients) was administered for 7 days after surgery. All patients also received daily oral fluconazole (100 mg for 2 weeks) and trimethoprim/sulfamethoxazole. Cytomegalovirus antiviral prophylaxis was administered for 3 months after transplantation and after treatment of a rejection episode. Prophylactic anticoagulation consisted of daily subcutaneous enoxaparin for 3 days with enteric-coated aspirin (325 mg daily). Oral nystatin or mycelox troches, H2 blockers, and bicarbonate supplementation were also prescribed.

**Data Acquisition**

A prospective cardiovascular database was established in 1996 for all type 1 diabetic patients referred for kidney or kidney/pancreas transplantation at Northwestern Memorial Hospital. This database includes baseline demographic information, cardiac risk factors, cardiac history, dialysis status, medication usage, and follow-up clinical data including transplant date, perioperative events, cardiovascular testing, and cardiovascular events. Cardiovascular events included unstable angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, cerebrovascular events, and peripheral vascular surgery, including amputations. Finally, graft function, dialysis status, hospitalizations, medication usage, and deaths were also entered into the database. Patients referred before 1996 were retrospectively entered into the cardiovascular database.

Blood pressure, serum creatinine, weight, antihypertensive medications, and all other medications and their dosages were recorded before transplantation, at 1, 3, 6, and 12-months after transplantation, and at the most recent posttransplantation outpatient visit at the transplant center. The preoperative data were obtained at the time of preoperative cardiology consultation in the majority of patients and at the latest pretransplantation outpatient evaluation in the remaining patients. Blood pressure was measured with a standard sphygmomanometer, with the patient in the seated position.

**Statistical Methods**

Continuous data are presented as mean ± SD. Discrete variables were compared between groups by means of $\chi^2$ tests; in cases in which the expected cell count was < 5, Fisher’s exact test was used. Continuous variables were compared between groups by 2-sample t tests. The Bonferroni method was used to allow multiple, between-group comparisons for blood pressure characteristics and antihypertensive medication use as follows: (1) between kidney/pancreas and isolated kidney transplant patients at baseline and 1, 3, 6, and 12 months and the last visit after transplantation; (2) between kidney/pancreas and isolated kidney transplant patients who were taking either cyclosporine or neoral at 1, 3, 6, and 12 months and the last visit after transplantation; (3) between bladder and enteric pancreas drainage for kidney/pancreas transplantation patients at baseline and 1 and 3 months only, because of the recent use of enteric drainage.

Within-group changes in continuous variables were compared with the use of paired t tests and, in discrete variables, with McNemar’s test. The Bonferroni method was used to allow multiple comparisons of baseline values with 1, 3, 6, and 12 months and last follow-up visit values.

All statistical tests were 2-tailed, and a value of $P < 0.05$ was regarded as statistically significant.

**Results**

**Baseline Characteristics**

The preoperative clinical characteristics for the kidney/pancreas and isolated kidney transplantation patients are shown in Table 1. Age was the only significantly different variable between the two groups. The isolated kidney transplant patients were older than the kidney/pancreas transplant patients (45 versus 37 years, $P < 0.001$). Nearly all patients in both groups had a history of hypertension before transplantation. Baseline systolic blood pressures were identical in both groups (mean, 151 mm Hg), and the diastolic blood pressure was slightly higher in the kidney/pancreas transplant patients (88 ± 13 versus 83 ± 10 mm Hg, $P = 0.05$). The percentage of patients who were normotensive while receiving medical therapy, defined as blood pressure < 130/85 mm Hg, did not differ between the two groups (19% versus 14%, $P = 0.05$). The average number of antihypertensive medications per patient (2.5 ± 1.1 versus 2.3 ± 1.1, $P = 0.05$) was not different between the two groups. The percentage of patients with hypertension was 96% in both groups, taking at least one antihypertensive medication before transplantation. Myocardial perfusion imaging was performed in 107 (96%) of the kidney/pancreas transplant patients and in 24 (86%) of the isolated kidney transplant patients. Ischemic perfusion defects were present in 34 (32%) of the kidney/pancreas transplant patients and in 6 (25%) of the kidney transplant patients ($P = 0.05$). Coronary angiography was performed in 41 (37%) of the kidney/pancreas transplant patients, with obstructive (stenosis ≥ 50%) coronary disease identified in 28 (68%) of the patients. Coronary angiography was performed in 12 (43%) of the isolated kidney patients, with obstructive coronary disease present in 9 (75%) of the patients. In addition, 2D echocardiography was performed in 102 (94%) and 19 (68%) of the kidney/pancreas and isolated kidney transplant patients, respectively. Left ventricular systolic dysfunction (ejection fraction < 50%) was identified by
echocardiography in 12 of the kidney/pancreas transplant patients and in 1 of the isolated kidney transplant patients.

**Blood Pressure and Antihypertensive Medication Usage After Transplantation**

Systolic and diastolic blood pressures and the average number of antihypertensive medications per patient before and after kidney/pancreas transplantation are shown in Figure 1.

One month after transplantation, the systolic blood pressure was 134±25 mm Hg and the diastolic blood pressure was 77±16 mm Hg, representing a mean decrease of 17 mm Hg and 11 mm Hg, respectively, compared with pretransplantation values. Both systolic and diastolic blood pressures continued to decline throughout the follow-up period. At the time of the last outpatient evaluation, the mean blood pressure was 126/70 mm Hg. This substantial improvement in blood pressure occurred despite a marked decrease in use of antihypertensive medications. At 1 month after kidney/pancreas transplantation, the average number of antihypertensive medications per patient was 0.9±1.0, compared with 2.5±1.1 before surgery (P<0.001). This decrease in antihypertensive medication usage was maintained throughout the follow-up period, and at 18 months after transplantation, the average number of antihypertensive medications per patient was 0.8±1.0 (P<0.001).

In contrast, there was no significant decrease in systolic blood pressure at long-term follow-up for patients undergoing isolated kidney transplantation (Figure 1). At the last outpatient visit, the systolic blood pressure was 148±26 mm Hg, compared with 151±23 mm Hg before transplantation. The diastolic blood pressure decreased after transplantation to a similar degree as that observed in the kidney/pancreas transplant patients. However, in contrast to the kidney/pancreas transplant patients, there was no significant change in the need for antihypertensive medications after isolated kidney transplantation. At 1 month after kidney transplantation, the average number of antihypertensive medications per patient was 2.2±1.2, not significantly different from the pretransplantation value of 2.3±1.1, and at the last outpatient visit, the average number of antihypertensive medications per patient was 2.0±1.3 (P=NS).

Figure 2 indicates the percentage of normotensive patients, defined as those having blood pressure ≤130/85 mm Hg.
were taking antihypertensive medications, compared with transplantation, only 51% of the kidney/pancreas transplant patients were taking at least one antihypertensive medication. One month after transplantation, 96% of both the kidney/pancreas and the isolated kidney transplant patients receiving any antihypertensive medication. Before transplantation, 28% of the patients were both normotensive and not using antihypertensive medications, which increased to 34% at 18 months.

Table 2 displays the use of antihypertensive medications by class before transplantation, at 3 months after transplantation, and at the last outpatient visit for the isolated kidney transplant patients. There was no significant change in use of calcium channel blockers, the most commonly used antihypertensive medications, or diuretics. The usage of β-blockers increased from 25% before transplantation to 54% at last visit after transplantation. In contrast, there was a marked decrease in use of all classes of antihypertensive medications after kidney/pancreas transplantation, with the exception of a slight increase in the usage of β-blockers (Table 2).

**Immunosuppressive Medications**

Mean daily dosages of all immunosuppressive medications including prednisone, azathiaprine, cyclosporine, neoral, mycophenolate mofetil, and tacrolimus were similar or greater in the kidney/pancreas transplant patients at all times in comparison to the isolated kidney transplant patients. The mean prednisone doses (mg) for the kidney/pancreas and isolated kidney transplant patients were: 27.1 ± 10.5 versus 18.7 ± 4.4 at 1 month, (P = 0.0001), 19.6 ± 7.2 versus 14.9 ± 3.8 at 3 months, (P = 0.0001), 15.4 ± 4.8 versus 11.9 ± 2.2 at 6 months, (P = 0.0001), 10.5 ± 3.0 versus 9.2 ± 2.1 at 12 months, (P = 0.09), and 10.5 ± 7.5 versus 8.2 ± 3.1 at last evaluation, (P = 0.02).

Owing to the more frequent use of a cyclosporine-based immunosuppression regimen in the isolated kidney transplant patients, a comparison of blood pressure values and antihypertensive medication use was performed for those kidney and kidney/pancreas transplant recipients receiving cyclosporine or neoral. This comparison is shown in Table 3 at 3 months and last outpatient visit after transplantation. The kidney/pancreas transplant patients tended to have lower systolic blood pressures, a higher percentage of normotensive patients, and less require-

**TABLE 2. Antihypertensive Medication Use According to Type of Transplant**

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Kidney-Pancreas</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Baseline (n=111)</td>
<td>3 mo After Tx (n=109)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>62%</td>
<td>27%</td>
</tr>
<tr>
<td>Diuretic</td>
<td>57%</td>
<td>14%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>47%</td>
<td>0%</td>
</tr>
<tr>
<td>Angiotensin II antagonist</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Other antihypertensive*</td>
<td>38%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Includes patients taking aldomet, clonidine, doxazosin, hydralazine, minoxidil, prazosin, nitrates, or terazosin.
†P < 0.05 between kidney/pancreas and isolated kidney transplant patients after adjusting for comparisons at multiple times by Bonferroni method (see Methods).
Weight loss occurred early (1 month) after kidney/pancreas transplantation, with mean weight decreasing from 67.5 ± 12.2 kg before transplantation to 65.7 ± 12.5 kg (P < 0.05). However, an increase in average weight was observed at subsequent follow-up evaluations. The mean weight at 6 months after kidney/pancreas transplantation increased to 69.0 ± 11.7 kg (P = 0.06). At baseline, the mean weight for the isolated kidney transplant patients was 73.3 ± 19.7 kg. A similar magnitude of weight gain occurred by 6 months after transplantation, with an increase to 76.1 ± 21.0 kg (P = 0.2). No significant difference in mean serum creatinine between the kidney/pancreas and isolated kidney transplant patients was observed after transplantation. At the last outpatient evaluation, the mean serum creatinine was 2.1 ± 1.4 in the kidney/pancreas patients and 1.8 ± 0.9 in the isolated kidney transplant patients.

Glycemic Control
There were 37 (33%) kidney/pancreas patients who had HbA1C measurements before (≥ 24 hours before transplantation) and after transplantation. The mean baseline HbA1C was 10.0 ± 2.2% (range, 6.1% to 13.9%). At 17.3 ± 13.0 months after transplantation, the mean HbA1C had decreased to 5.9 ± 1.1% (range, 3.9% to 8.8%, P < 0.0001). For the 64 (58%) kidney/pancreas transplant patients who had HbA1C values measured on admission for transplantation, the mean

### TABLE 3. Blood Pressure Characteristics Among Patients Taking Cyclosporine or Neoral According to Type of Transplant

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type of Transplant</th>
<th>Kidney-Pancreas</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mo After Tx</td>
<td>Last Visit After Tx</td>
<td>3 mo After Tx</td>
</tr>
<tr>
<td></td>
<td>(n=37)</td>
<td>(n=23)</td>
<td>(n=24)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133±17</td>
<td>130±19</td>
<td>142±25</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83±10</td>
<td>72±13</td>
<td>76±11</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mm Hg, %</td>
<td>32</td>
<td>49</td>
<td>26</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>1.4±1.3</td>
<td>1.1±1.3</td>
<td>2.3±1.2</td>
</tr>
<tr>
<td>Cyclosporine dose</td>
<td>556±183</td>
<td>581±270</td>
<td>410±171</td>
</tr>
<tr>
<td>Neoral dose</td>
<td>507±143</td>
<td>366±134</td>
<td>373±115</td>
</tr>
</tbody>
</table>

*P < 0.05 between kidney/pancreas and isolated kidney transplant patients after adjusting for comparisons at multiple times by Bonferroni method (see Methods).

### TABLE 4. Blood Pressure Characteristics Among Kidney/Pancreas Transplant Patients According to Type of Pancreas Drainage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type of Pancreas Drainage</th>
<th>Bladder</th>
<th>Enteric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 mo After Tx</td>
<td>3 mo After Tx</td>
</tr>
<tr>
<td></td>
<td>(n=97)</td>
<td>(n=95)</td>
<td>(n=90)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>150±25</td>
<td>135±26</td>
<td>127±20</td>
</tr>
<tr>
<td>Diastolic</td>
<td>88±12</td>
<td>77±16</td>
<td>76±13</td>
</tr>
<tr>
<td>Blood pressure ≥130/85 mm Hg, %</td>
<td>21</td>
<td>45</td>
<td>57</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>2.5±1.1</td>
<td>0.9±1.1</td>
<td>0.8±1.0</td>
</tr>
<tr>
<td>Any antihypertensive drug</td>
<td>95%</td>
<td>52%</td>
<td>50%</td>
</tr>
</tbody>
</table>

There were no significant differences in blood pressure characteristics or antihypertensive medication use according to type of pancreas drainage.
HbA1C was 10.2±2.2% (range, 6.1% to 14.4%). Posttransplantation HbA1C values were available for 66 (60%) of the kidney/pancreas transplant patients. The mean HbA1C was 5.9±0.9% (range, 3.9% to 8.8%) for all measurements obtained after transplantation (mean, 22±17 months). The average for the last HbA1C level obtained after transplantation (mean, 25±17 months) for these patients was 5.8±0.9%. In comparison, the mean HbA1C level for the isolated kidney transplant patients (n=17, 61%) at a mean follow-up of 31±21 months was 10.2±2.7% (range, 7.4% to 17.2%). Fasting serum glucose levels were available for all kidney and kidney/pancreas transplant patients at transplantation at the follow-up intervals of 1, 3, 6, 12 months and last outpatient evaluation. The mean glucose levels for the kidney/pancreas transplant patients were 116, 114, 110, 99, and 103 mg/dL, respectively. The mean glucose levels for the isolated kidney transplant patients were 205, 190, 168, 200, and 182 mg/dL, respectively (P<0.05). Most (90% to 95%) kidney/pancreas transplant recipients remained insulin-independent at all follow-up intervals, including 91% of the patients at the time of the last outpatient visit.

Discussion

This study demonstrates a substantial decrease in blood pressure after successful kidney/pancreas transplantation despite a marked reduction in the use of antihypertensive therapy. The number of antihypertensive medications per patient decreased to one third of the number before transplantation despite a 3-fold increase in the percentage of patients who were normotensive. Only half of the patients were taking any antihypertensive medications, and ~33% were normotensive without antihypertensive medications. This remarkable improvement in hypertension treatment was observed early (1 month) after transplantation and was maintained at long-term follow-up (mean, 18.2 months). It is noteworthy that this improvement in hypertension treatment occurred despite the addition of immunosuppressive agents known to aggravate hypertension.

In contrast, persistent hypertension was prevalent for the type 1 diabetics after successful isolated kidney transplantation despite reversal of chronic kidney failure, with no significant change in mean systolic blood pressure, the percentage of patients requiring antihypertensive medications, the average number of antihypertensive medications per patient, or the percentage of normotensive patients compared with pretransplantation values.

An excess of cardiovascular disease and cardiac mortality is well established in patients with type 1 diabetes mellitus. Hypertension is causally related to this excessive cardiovascular risk and is a nearly ubiquitous finding in type 1 diabetics with diabetic nephropathy. Recent studies have emphasized the importance of intensive treatment of hypertension to reduce cardiovascular events in this vulnerable population. The Hypertension Optimal Treatment (HOT) study demonstrated an impressive 51% reduction in major cardiovascular events (myocardial infarction, stroke, and cardiovascular death) in hypertensive diabetic patients randomly assigned to achieve a target diastolic blood pressure of ≤80 mm Hg compared with the group with a target of ≤90 mm Hg. A modest 4 mm Hg separated the mean diastolic blood pressures between these two groups (85.2 versus 81.1 mm Hg).

The increase in usage of β-blockers after transplantation for both groups may in part be related to the treatment of coronary artery disease that was first addressed during their preoperative evaluation for transplantation. Additionally, at last outpatient visit, 8 kidney/pancreas transplant patients were receiving angiotensin II receptor antagonists for the purpose of treating posttransplantation inappropriate erythro-
poiesis. For 5 of these patients, the angiotensin II receptor antagonist was the only antihypertensive medication they were taking. No patients in the kidney transplant group were receiving an angiotensin II receptor antagonist for inappropriate erythropoesis after transplantation.

Conclusions
Successful kidney/pancreas transplantation results in a marked improvement in hypertension treatment manifested by a reduction in blood pressure and decreased need for antihypertensive medications. This improvement in hypertension treatment is observed as early as 1 month after transplantation and is maintained at long-term follow-up. The short-term improvement in hypertension treatment is similar for both surgical methods of excocrine pancreatic drainage (bladder and enteric). These data suggest that the markedly elevated risk of cardiovascular events in type 1 diabetics with nephropathy may be reduced by the improved blood pressure control that occurs after kidney/pancreas transplantation. Our data also underscore the importance of diabetes in the pathogenesis of hypertension in patients with type 1 diabetes mellitus and diabetic nephropathy.

References
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Circulation. 2001;104:563-569
doi: 10.1161/hc3001.093434

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

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