Relationship Between Left Ventricular Mass and Endothelium-Dependent Vasodilation in Never-Treated Hypertensive Patients

Francesco Perticone, MD; Raffaele Maio, MD; Roberto Ceravolo, MD; Carmela Cosco, MD; Cosima Cloro, MD; Pier Luigi Mattioli, MD

Background—Hypertensive patients are characterized by development of both left ventricular hypertrophy (LVH) and endothelial dysfunction.

Methods and Results—We enrolled 65 never-treated hypertensive patients (36 men and 29 women aged 45.6 ± 6.0 years) to assess the possible relationship between echocardiographic left ventricular mass (LVM) and endothelium-dependent vasodilation. Left ventricular measurements were performed at end diastole and end systole according to the recommendations of the American Society of Echocardiography and the Penn Convention. LVM was calculated with the Devereux formula and indexed by body surface area and height raised to the 2.7th power. The endothelial function was tested as responses of forearm vasculature to acetylcholine (ACh), an endothelium-dependent vasodilator (7.5, 15, and 30 μg · mL⁻¹ · min⁻¹, each for 5 minutes), and sodium nitroprusside (SNP), an endothelium-independent vasodilator (0.8, 1.6, and 3.2 μg · mL⁻¹ · min⁻¹, each for 5 minutes). Drugs were infused into the brachial artery, and forearm blood flow (FBF) was measured by strain-gauge plethysmography. A negative significant relationship between indexed LVM and peak of increase in FBF was found during ACh infusions (r = -0.554; P < 0.0001). In addition, hypertrophic patients had a significantly lower responsive to ACh than patients without LVH (the peak increase in FBF was 9.9 ± 3.7 versus 16.1 ± 8.1 mL per 100 mL of tissue per minute; P < 0.0001). No significant correlation was observed between LVM and FBF during SNP infusion.

Conclusions—Our data provide the first evidence that echocardiographic LVM in hypertensive patients is inversely related to FBF responses to the endothelium-dependent vasodilating agent ACh, but it is likely that both endothelium and LVM are damaged by hypertension. (Circulation. 1999;99:1991-1996.)

Key Words: hypertrophy ■ endothelium ■ hypertension ■ risk factors

Some published studies have reported that electrocardiographic and echocardiographic left ventricular hypertrophy (LVH) is an independent predictor of cardiovascular diseases in the general population and in several clinical conditions, including essential hypertension.1–5 Moreover, recent reports suggest that left ventricular adaptation to human hypertension has been shown to be more complex. In fact, echocardiographic measurements of left ventricular mass (LVM) and relative posterior wall (PW) or interventricular septal (IVS) thickness identify a spectrum of cardiac adaptations to hypertension, including concentric and eccentric hypertrophy, the normal ventricular geometry, and concentric left ventricular remodeling.2,4,6–9

The normal endothelium plays a key role in the local regulation of vascular tone by producing and releasing contracting and relaxing factors.10 One of these is the nitric oxide (NO)11–13 that is released after stimulation of endothelial cells by shear stress14 and some agonists such as acetylcholine (ACh), bradykinin, substance P, and serotonin.15 On the other hand, sodium nitroprusside (SNP) is an endothelium-independent vasodilator compound that produces vasodilation by providing an inorganic source of NO.16

Endothelium-dependent vasodilation has been show to occur in most mammalian species17 and in humans by in vitro studies that used arterial preparations.18,19 Human studies have subsequently confirmed these experimental findings and have demonstrated that this regulatory action of the endothelium is also exerted on resistance vessels.19 Results of recent investigations indicate that endothelial dysfunction exists in some cardiovascular conditions.20–23 Endothelium-dependent vasodilation is impaired in experimental models of hypertension as well as in hypertensive patients. In addition, it was recently reported that hypertensive LVH is associated with endothelial dysfunction in coronary vessels in both white and black patients.24,25

Thus, the purpose of our study was to evaluate the effects of hypertensive LVH on forearm blood flow (FBF) in response to the endothelium-dependent agent ACh and the
endothelium-independent agent SNP in a cohort of a southern Italian never-treated hypertensive patients in comparison with a group of normotensive subjects.

Methods

Study Population

Hypertensive Group
The study included 65 outpatients referred to Catanzaro University Hospital to evaluate their hypertensive status (36 men and 29 women aged 45.6±6.0 years), each of whom had a well-documented history of primary hypertension (duration of hypertension, 2.7±1.2 years). All patients were white, and causes of secondary hypertension were excluded by the appropriate clinical and biochemical examinations. Each patient underwent standard electrocardiography, routine chemical analyses, and chest radiography. No patient had a history of diabetes, hyperlipidemia, peripheral vascular disease, coagulopathy, or any disease predisposing them to vasculitis or Raynaud’s phenomenon. None of the participants was taking antihypertensive therapy. Fifteen patients (23%) had a history of cigarette smoking (3 to 5 cigarettes daily).

The local ethics committee approved the study, and all participants gave written informed consent for all procedures.

Control Group
The study included 20 normotensive subjects (12 men and 8 women aged 45.7±5.3 years). Normalcy was determined by clinical history, physical examination, routine laboratory analyses, and chest radiography. No patient had a history of diabetes, hyperlipidemia, peripheral vascular disease, coagulopathy, or any disease predisposing them to vasculitis or Raynaud’s phenomenon. None of the participants was taking antihypertensive therapy. Fifteen patients (23%) had a history of cigarette smoking (3 to 5 cigarettes daily).

The local ethics committee approved the study, and all participants gave written informed consent for all procedures.

Echocardiograms
In each patient, measurements of left ventricular dimensions and derived variables were obtained from both M-mode and 2-dimensional echocardiograms. Echocardiographic readings were made in random order by an investigator who had no knowledge of BP or other clinical data for any patient. Only frames with optimal visualization of IVS thickness, PW thickness, and left ventricular internal dimension (LVID) throughout the entire cardiac cycle were considered for reading. The mean values from ≥5 measurements for each parameter per patient were computed.

M-Mode Measurements
Tracings were recorded under 2-dimensional guidance, and measurements were taken at the tip of the mitral valve or just below that point. Left ventricular measurements were performed at end diastole and end systole according to the recommendations of the American Society of Echocardiography and the Penn Convention.26,27 LVM was calculated with the Devereux formula.28 Analyses were performed with the calculated value of LVH indexed by body surface area (meters squared) with the Devereux criteria reported by de Simone et al30 (using height2.7). Partition values for LVH were taken from the Framingham Heart Study (with body surface area used for indexing: normal, <131 g/m2 for men and <100 g/m2 for women,30 with the cutoff value of 125 g/m2 used for both women and men (as suggested by Casale et al31), and with allometric criteria reported by De Simone et al30 (using height2.7 for indexing: normal, <50 g/m2 for men and <47 g/m2 for women).

Patterns of Left Ventricular Geometry
Relative wall thickness (RWT) was measured at end diastole as the ratio of twice the thickness of PW/LVID or, as recently reported by Verdecchia et al,4 as the ratio of twice the thickness of IVS/LVID. The value of 0.45 was considered the cutpoint of RWT.

Four different patterns of left ventricular geometry were identified by categorizing patients according to values of LVM indexed by body surface area (LVMi; 125 g/m2) and end-diastolic RWT. Patients with normal LVMi were considered to have normal left ventricular geometry if their RWT was normal (<0.45) or eccentric remodeling if their RWT was elevated (>0.45). Those with increased LVMi were considered to have concentric LVH if their RWT was elevated (≥0.45) or eccentric hypertrophy if their RWT was normal (<0.45).

Hypertensive Cardiac Mass and Endothelial Dysfunction

### Table 1. Baseline Demographic, Hemodynamic, and Humoral Characteristics of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives</th>
<th>Casale (LVH (+))</th>
<th>Framingham (LVH (+))</th>
<th>de Simone (LVH (+))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertensives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>33</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.7±5.3</td>
<td>45.6±7.1</td>
<td>45.7±4.9</td>
<td>43.8±6.7</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>8/12</td>
<td>20/13</td>
<td>9/23</td>
<td>9/16</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2±5.2</td>
<td>27.9±7.4</td>
<td>27.9±3.1</td>
<td>27.2±3.7</td>
</tr>
<tr>
<td>VR, U</td>
<td>28.1±5.8</td>
<td>31.9±7.4</td>
<td>36.1±6.8‡</td>
<td>32.4±5.8*</td>
</tr>
<tr>
<td>FBF, mL/100 mL of tissue/min</td>
<td>3.5±0.7</td>
<td>3.7±0.9</td>
<td>3.5±0.7</td>
<td>3.6±0.8</td>
</tr>
<tr>
<td>LVM/LVA, mg/m²</td>
<td>105.5±17.4</td>
<td>102.8±16.7</td>
<td>157.1±21.2</td>
<td>99.6±17.7</td>
</tr>
<tr>
<td>LVM/height², g/m³²</td>
<td>50.8±12.7</td>
<td>49.9±10.1</td>
<td>74.2±12.9</td>
<td>46.8±8.8</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.2±0.4</td>
<td>5.2±0.4</td>
<td>5.3±0.3</td>
<td>5.3±0.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.6±0.6</td>
<td>4.7±0.7</td>
<td>4.7±0.8</td>
<td>4.7±0.6</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.4±0.2</td>
<td>3.5±0.3</td>
<td>3.4±0.2</td>
<td>3.4±0.2</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.0±0.2</td>
<td>1.0±0.2</td>
<td>1.0±0.3</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>Clinical SBP, mm Hg</td>
<td>129.2±5.4</td>
<td>154.0±14.3</td>
<td>160.8±18.8</td>
<td>153.9±13.4</td>
</tr>
<tr>
<td>Clinical DBP, mm Hg</td>
<td>81.0±3.1</td>
<td>94.7±10.7</td>
<td>99.7±10.1</td>
<td>95.8±11.3</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>117.5±4.5</td>
<td>140.4±10.6</td>
<td>150.0±13.3‡</td>
<td>142.5±12.8</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>75.6±3.0</td>
<td>86.0±7.3</td>
<td>90.1±10.2</td>
<td>87.2±8.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±5</td>
<td>70±6</td>
<td>69±4</td>
<td>69±6</td>
</tr>
</tbody>
</table>

BSA indicates body surface area; SBP, systolic BP; and DBP, diastolic BP.

*P<0.05 vs normotensives; †P<0.01 vs normotensives; ‡P<0.05 vs LVH (−).
BP Measurements
Clinical BP measurements were obtained in the morning between 8 AM and noon. BP was measured 3 times with a mercury sphygmomanometer. Hypertension was defined as a systolic BP ≥160 mm Hg, a diastolic BP ≥95 mm Hg, or both. Ambulatory BP monitoring was recorded with an A&K TM 2420 recorder (model 7, Takeda) validated by the British Hypertension Society.31 Recordings were taken every 10 minutes during the day (from 7 AM to 11 PM) and every 20 minutes during the night (from 11 PM to 7 AM).

Vascular Function
All studies were performed at 9 AM after subjects had fasted overnight, with the subjects lying supine in a quiet, air-conditioned room (22° to 24°C); the protocol previously described by Panza et al21 and subsequently used by our group was used for the present study.32

All patients underwent measurement of FBF and BP during intra-arterial infusion of saline, ACh, and SNP at increasing doses. All participants rested ≥30 minutes after artery cannulation to reach a stable baseline before data collection; measurements of FBF and vascular resistance (VR), expressed in units, were repeated every 5 minutes until stable.

Endothelium-dependent vasodilation was assessed by a dose-response curve to intra-arterial ACh infusions (7.5, 15, and 30 µg · mL⁻¹ · min⁻¹, each for 5 minutes). Endothelium-independent vasodilation was assessed by a dose-response curve to intra-arterial SNP infusions (0.8, 1.6, and 3.2 µg · mL⁻¹ · min⁻¹, each for 5 minutes).

The sequence of administration of ACh and SNP was randomized to avoid any bias related to the order of drug infusion. The drug infusion rate, adjusted for forearm volume of each subject, was 1 mL/min.

Drugs
ACh (Sigma Chemical Co) was diluted in saline immediately before infusion. SNP (Malesci) was diluted in 5% glucose solution and protected from light with aluminum foil.

Statistical Analysis
ANOVARs for clinical and biological data were performed, and differences between means were compared by unpaired Student’s t test as appropriate. The responses to ACh and SNP were compared by ANOVA for repeated measurements, and when analysis was significant, the Tukey test was applied. The percentage of increase of FBF was analyzed as a categorical variable by a stepwise multiple regression analysis.

The responses to ACh and SNP were compared by ANOVA for repeated measurements, and when analysis was significant, the Tukey test was applied. The percentage of increase of FBF was analyzed as a categorical variable by a stepwise multiple regression analysis.

Results
Demographic, clinical, and hemodynamic characteristics of the study population stratified by hypertensive status and LVH (using all 3 partitioning systems) are reported in Table 1. These demonstrated comparability between groups for age, sex, BMI, heart rate, and lipid profile. Both clinical and monitored BP values were significantly (P<0.0001) lower in normotensive subjects than in hypertensives. Hypertensive patients with LVH had higher clinical and monitored BP values than patients without LVH, but differences between groups were statistically significant only for 24-hour systolic BP when the cutpoint of 125 g/m² reported by Casale et al1 was used.

Normotensive Versus Hypertensive Group
In hypertensive patients, FBF responses to ACh were markedly impaired compared with those in the normotensive control group (Figure 1). In hypertensives, FBF increased 1.9±1.0, 3.7±2.5, and 9.4±6.7 mL · 100 mL⁻¹ · min⁻¹ of tissue · min⁻¹ in response to ACh 7.5, 15, and 30 µg · mL⁻¹ · min⁻¹. In normotensive subjects, FBF increased 2.2±1.3, 7.9±2.4, and 21.5±4.5 mL · 100 mL⁻¹ · tissue · min⁻¹ in response to ACh 7.5, 15, and 30 µg · mL⁻¹ · min⁻¹, respectively. Similarly, VR was significantly decreased in hypertensive compared with normotensive subjects, but this decrease was significantly less in hypertensive patients than in the control group (Figure 1).

In contrast, FBF responses to SNP were similar in hypertensive patients and normotensive subjects. In the hypertensive group, FBF increased 2.0±1.3, 4.1±1.5, and 6.8±2.1 mL · 100 mL⁻¹ · tissue · min⁻¹ in response to SNP 0.8, 1.6, and 3.2 µg · mL⁻¹ · min⁻¹, respectively; in normotensive subjects, FBF increased 2.1±1.2, 4.5±1.2, and 7.4±1.1 mL · 100 mL⁻¹ · tissue · min⁻¹ in response to SNP 0.8, 1.6, and 3.2 µg · mL⁻¹ · min⁻¹, respectively. Similarly, no significant differences in VR decrease between groups were observed (Figure 1).

Hypertensive Group
Endothelium-Dependent Vasodilation
Incremental doses of ACh infusions induced a significant increase in FBF in hypertensive patients with and without
LVH. However, patients with LVH had a significantly lower responsiveness to ACh than patients without LVH, independent of the partitioning system used, as shown in Figure 2. No significant differences were observed during SNP infusions. The relationship between peak increase in FBF after ACh infusion and LVMI is shown in Figure 3. Hypertensive patients demonstrated a negative significant linear relationship between the independent variables, such that $y = 658.218 - 3.014x$, where $y$ is the percent increase in FBF after ACh infusion and $x$ is the LVMI ($r = -0.554$; $P < 0.0001$). A similar relationship was obtained when LVM was indexed by height$^{2.7}$ ($r = -0.552$; $P < 0.0001$).

Figure 4 demonstrates the responses of FBF to ACh in hypertensive patients with and without LVH using LVMI according to both Casale et al and the Framingham criteria as well as by allometric criteria and LVM indexed by height$^{2.7}$. Responses to ACh were significantly lower in patients with LVH than in those without LVH.

Multivariate linear regression was performed to relate the dependent variable, peak response to ACh, to age, sex, BMI, systolic and diastolic BP, duration of hypertension, and LVMI. Only LVMI was significantly associated with the peak response to ACh (Table 2). Finally, we tested the possible influence of both hypertension status and LVH alone, as well as the consequence of their interaction on FBF, by multivariate ANOVA (Table 3). These data indicate an independent effect of both hypertension and LVH on FBF, but no significant interaction was detected in our population.

Endothelium-Independent Vasodilation

During increasing infusions of SNP, the FBF and VR values were similar in hypertensive patients with and without LVH. Baseline and peak FBF values in hypertrophic patients were $3.5 \pm 0.8$ and $9.8 \pm 2.3$ mL $\cdot$ min$^{-1} \cdot$ tissue $\cdot$ min$^{-1}$, respectively; in hypertensive patients without LVH, the values were $3.7 \pm 0.8$ and $10.9 \pm 2.3$ mL $\cdot$ 100
Impaired endothelium-dependent vasodilation in response to ACh is well reported in essential hypertension and in several other pathological states. In addition, the predictive value of LVH for subsequent cardiovascular morbidity and mortality is well established. Finally, recent published data provided evidence that hypertensive LVH is associated with depression in coronary vascular relaxation during the peak effect of the endothelium-dependent and endothelium-independent agonists ACh and adenosine.

The present study confirms that hypertensive patients have blunted endothelium-dependent vasodilation compared with a normotensive control group; moreover, it provides the first evidence that echocardiographic LVM in hypertensive patients is inversely related to FBF responses to the endothelium-dependent vasodilating agent ACh. In our hypertensive patients, endothelial dysfunction reflects the effects of chronic hypertension on the forearm vessels. However, when we tested the effect of other well-established risk factors for impairment of endothelium-dependent vasodilation, only LVMI was an independent predictor of endothelial dysfunction. The present data also demonstrate that this endothelial dysfunction is more marked in hypertensive patients with LVH than in patients without LVH, and when we classify patients on the basis of their pattern of left ventricular geometry, a higher decrease in peak response to ACh is evident in patients with concentric LVH. Our clinical study does not enable us to clearly state whether LVH affects endothelial dysfunction or rather the impaired endothelium-dependent vasodilation affects cardiac LVH; however, it is more likely that both the endothelium and the left ventricle are damaged by hypertension.

### TABLE 2. Effects of Variables Associated with Endothelial Dysfunction Tested by Multiple Linear Regression

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-5.471</td>
<td>3.294</td>
<td>-12.058, 1.115</td>
</tr>
<tr>
<td>Duration of hypertension</td>
<td>-5.798</td>
<td>3.516</td>
<td>-12.828, 1.231</td>
</tr>
<tr>
<td>BMI</td>
<td>-11.019</td>
<td>6.165</td>
<td>-23.346, 1.308</td>
</tr>
<tr>
<td>LVMI</td>
<td>-3.028</td>
<td>0.600</td>
<td>-4.227, -1.830</td>
</tr>
<tr>
<td>Intercept</td>
<td>1246.521</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mL⁻¹ of tissue · min⁻¹, respectively. Baseline and peak VR values, respectively, were 35.7±8.6 and 13.4±3.9 U in hypertrophic patients and 32.0±6.8 and 11.6±3.8 U in hypertensive patients without LVH. No significant differences were observed regardless of the hypertrophy partitioning system used.

### Discussion

Impaired endothelium-dependent vasodilation in response to ACh is well reported in essential hypertension and in several other pathological states. In addition, the predictive value of LVH for subsequent cardiovascular morbidity and mortality is well established. Finally, recent published data provided evidence that hypertensive LVH is associated with depression in coronary vascular relaxation during the peak effect of the endothelium-dependent and endothelium-independent agonists ACh and adenosine.

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### TABLE 3. Effects of Hypertensive Status and LVMI on Endothelium-Dependent Vasodilation by Multivariate ANOVA

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension effect</td>
<td>101.405</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVMI</td>
<td>4.636</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Interaction effects</td>
<td>1.855</td>
<td>NS</td>
</tr>
</tbody>
</table>

The 3 partitioning criteria used for the definition of LVH resulted in no significant differences in the major findings. Both the Casale and Framingham criteria, however, resulted in a lower identification rate than the de Simone criteria. These findings are expected because indexing by body surface area can result in underestimation of LVH in obese subjects, whereas indexing by height provides a better allometric normalization of LVM.

### Cardiac and Vascular Adaptation in Hypertension

Pressure overload induces parallel cardiac and vascular adaptive modifications in hypertensive patients, such as hypertrophy of large capacitance arteries and left ventricle. In particular, previous data demonstrated that vascular hypertrophy may occur earlier and/or be more prevalent than LVM increase in human hypertension. In hypertensives, LVH develops because of increased cardiac afterload, and as a result, LVH systolic function is preserved. However, clinical studies do not show a close relation between BP values and the degree of LVH. In addition, left ventricular adaptation to high BP has been shown to be more complex in humans, because hypertensives with mild to moderate hypertension exhibit normal LVM and wall thickness, whereas other patients have eccentric LVH that is not related to systolic dysfunction but rather to increased preload and cardiac output. Finally, recent data indicate a strong association between LVH and increased arterial stiffness and/or carotid atherosclerosis, even if the mechanism underlying this association remains unclear.

### Hypertension and Vascular Function

Arterial endothelium plays a very important role in the regulation of vascular tone through the release of different vasoactive substances. It is well established that endothelium-dependent vasodilation is impaired in an experimental model of hypertension as well as in hypertensive patients. This endothelial dysfunction can be attributed variably to abnormalities in the NO pathway, decreased endothelium-derived hyperpolarizing factor, or increased release of vasoconstrictor products of cyclooxygenase. A dysfunctional endothelium reduces its protective effect on the vascular system by keeping vessels in a dilatory state and preventing platelet aggregation and smooth muscle cell migration and proliferation, thus playing a key pathophysiological role in the development of atherosclerosis.

### Clinical Implications

Depressed endothelium-dependent vasodilation is considered an earlier modification, present in some cardiovascular risk factors, that may promote the atherosclerotic process by stimulating the proliferation of smooth muscle cells and fibroblasts. The association between LV and vascular dysfunction, as reported in the present study, provides a potential and earlier pathophysiological link to explain the increased risk of vascular events in hypertensive patients with LVH. In addition, our evidence that LVH is an independent predictor of depressed ACh-mediated vasodilation may reflect the known positive relation between BP and LVM and the possibility that LVM may be a better measure of long-term hypertension, as reported by previous studies. At pres-
ent, however, both LVH and endothelial dysfunction in hypertensive patients may be considered indicative of pre-clinical cardiovascular disease that may be reversed by some effective therapeutic interventions.34,39 Although the impact of LVH regression on clinical outcomes has not been conclusively established, recent data indicate that the decrease in LVM brought about by antihypertensive therapy is associated with a reduced risk for subsequent events.40 Thus, the demonstration that hypertension-associated endothelial dysfunc-
tion and LVH may be reversed by a pharmacological treatment may represent a new target for therapeutic inter-
vention in essential hypertension.

Finally, previous prospective studies demonstrated that pa-
ents with concentric LVH as opposed to eccentric LVH develop a higher incidence of cardiovascular events. The lowest endothelium-dependent vasodilation observed in our patients with concentric LVH confirms the highest risk for cardiovascular morbidity and mortality reported in these patients.

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doi: 10.1161/01.CIR.99.15.1991

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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