Background—Obesity may independently increase the risk of adverse events in hypertension with target-organ damage. We investigated whether body build was independently associated with higher cardiovascular risk and whether treatment with losartan relative to atenolol influenced the impact of body build on the primary composite end point of cardiovascular death, stroke, and myocardial infarction and on cardiovascular death in patients with hypertension and left ventricular hypertrophy in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.

Methods and Results—The population of 9079 patients was divided as follows: thin (body mass index [BMI] <20 kg/m², 2%), normal weight (BMI 20 to 24.9, 24%), overweight (BMI 25 to 29.9, 45%), and obese (class I: BMI 30 to 34.9, 21%; class II: BMI 35 to 39.9, 6%; class III: BMI ≥40, 2%). Incident diabetes increased progressively with BMI and was somewhat higher in the atenolol arm. Differences in gender and race were detected among the body build groups. Rates (Cox proportional hazard analysis) of the primary composite end point did not differ among body build groups after adjustment for age, gender, race, smoking habit, prevalent cardiovascular disease, and left ventricular hypertrophy. Cardiovascular death was more frequent among thin (P<0.05) and pooled class II-III obesity (both P<0.04) than normal-weight groups. Risk was not attenuated significantly by losartan treatment, nor did it interfere with the greater benefit of losartan-based treatment as opposed to atenolol-based treatment.

Conclusions—In the LIFE study, stratification for classes of body build identified increased risk of cardiovascular mortality in both thin and moderately-to-severely obese individuals. This risk was not attenuated significantly by losartan treatment, nor did it interfere with the greater benefit of losartan-based treatment as opposed to atenolol-based treatment. (Circulation. 2005;111:1924-1931.)

Key Words: hypertension ■ obesity ■ drugs ■ risk factors ■ prognosis

There is a general consensus that the prevalence and severity of arterial hypertension increase with increasing body weight and might be particularly severe in advanced (body mass index [BMI] ≥35 kg/m²) obesity.1-4 Obesity predisposes to hypertension because of concomitant metabolic and hemodynamic abnormalities, yielding both increased circulating volume and inadequate lowering of systemic resistance.1,5,6 Hypertension in obesity, therefore, is characterized by combined volume and pressure overload, even more than in normal-weight subjects with hypertension, and the cardiocirculatory burden is thought, generally but not invariably,7 to be more severe. There is extensive evidence that obesity increases cardiovascular risk because cardiovascular risk factors tend to cluster in obese persons,3,8,9 but there is also evidence from epidemiological studies that relatively low body mass predicts higher cardiovascular risk because of associated systemic diseases.10
It is unclear whether obesity also independently increases the risk of cardiovascular events in persons with hypertension-related target-organ damage or other risk factors.\textsuperscript{11,12} This is particularly relevant in the context of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study given the current evidence for local activation of the renin-angiotensin system and its interactions with the endothelin system in obesity.\textsuperscript{13} Accordingly, the present study was designed to assess whether obesity influences the prognosis of hypertensive patients with established target-organ damage independently of prognostically relevant baseline covariates and randomization to losartan- or atenolol-based antihypertensive therapy in the LIFE study.\textsuperscript{14,15}

**Methods**

**Participants**

The present analysis was performed in 9079 participants (of the total population of 9193) in the LIFE study who had available baseline BMI data. Detailed inclusion and exclusion criteria and characteristics of the LIFE study population have been reported previously.\textsuperscript{15} All patients provided written informed consent, and the protocol was approved by relevant ethics committees. Previously treated or untreated outpatients with stage II or III arterial hypertension, between 55 and 80 years of age, were recruited from medical practice settings in Denmark, Finland, Iceland, Norway, Sweden, the United Kingdom, and the United States. Participants were required to have sitting systolic blood pressure 160 to 200 mm Hg or diastolic blood pressure 95 to 115 mm Hg after 1 to 2 weeks of single-blind placebo treatment without other antihypertensive medication. A major inclusion criterion was the presence of ECG-verified left ventricular hypertrophy (by Cornell voltage-duration product or Sokolow-Lyon voltage).\textsuperscript{15} Patients with myocardial infarction or stroke within 6 months, current heart failure or previously known left ventricular ejection fraction was estimated with the Cockcroft-Gault formula,\textsuperscript{17} according to investigator report and plasma glucose level.

Diabetes was defined by 1985 World Health Organization criteria,\textsuperscript{16} according to investigator report and plasma glucose level. Because 24-hour urinary creatinine excretion was unavailable, creatinine clearance was estimated with the Cockcroft-Gault formula,\textsuperscript{17} which uses estimated ideal body weight.\textsuperscript{18} Prevalent coronary artery disease was identified on the basis of patient and physician report and the presence of ECG Q waves that met Minnesota code criteria.\textsuperscript{14}

**Study Design**

The present analysis was not prespecified as part of the LIFE protocol; therefore, neither selection of patients nor treatment randomization was related to body build. For this analysis, the LIFE population was stratified into 6 categories of body build according to 1998 National Institutes of Health guidelines: \textsuperscript{19} thin (BMI <20 kg/m\textsuperscript{2}, 2\% of patients in this analysis), normal weight (BMI 20 to 24.9, 24\%), overweight (BMI 25 to 29.9, 45\%), and obese (class I: BMI 30 to 34.9, 21\%; class II: BMI 35 to 39.9, 8\%; class III: BMI \geq 40, 2\%). For hazard analyses, classes II and III were pooled.

**End Points and Adjudication**

We analyzed the primary composite end point of cardiovascular mortality, stroke, and myocardial infarction (n=1081), as well as cardiovascular mortality (n=432). End points were adjudicated by an independent committee on the basis of definitions provided in the LIFE study predefined end-point manual.\textsuperscript{20}

**Statistical Analysis**

Data were analyzed with SPSS 12 software. Descriptive statistics were obtained with $\chi^2$ distributions (with Monte Carlo method for computation of exact probability value), 1-factor ANOVA, and the REGW-F post hoc test (Ryan, Einot, Gabriel, & Welsch F test). Log cumulative hazard functions were computed by Cox proportional hazards analysis with enter procedures. Hazard ratios with 95\% CIs and adjusted cumulative incidences of the primary composite end point and cardiovascular mortality were examined. The null hypothesis was rejected at 2-tailed $P\leq0.05$.

**Results**

**Characteristics of Study Population in Relation to Body Build**

A higher level of physical activity, as assessed by questionnaires, was significantly less common in participants with the lowest or highest BMI class. Among overweight individuals, 48\% were women, which increased to 59\% with class I, 69\% with class II, and 79\% with class III obesity. Overweight was present in 45\% of whites, 37\% of blacks, and 47\% of other ethnicities. Class I obesity was present in 21\% of whites, 25\% of blacks, and 17\% of other ethnicities; class II in 5\% of whites, 10\% of blacks, and 8\% of other ethnicities; and class III in 2\% of whites, 6\% of blacks, and 4\% of other ethnicities. Because these differences were statistically significant (all $P<0.001$), gender and ethnicity were considered as covariates in multivariate analyses.

In addition to randomized treatments, other medications were used. In particular, among thin subjects, 36\% were given calcium-channel blockers, 8\% were given diuretics other than hydrochlorothiazide, and 13\% were given other antihypertensive medications. Rates of concomitant treatment were 35\% for calcium-channel blockers, 10\% for diuretics, and 10\% for other antihypertensive medications among normal-weight individuals; 40\%, 12\%, and 12\%, respectively, among overweight subjects; 44\%, 15\%, and 14\% among class I obese subjects; and 46\%, 22\%, and 17\% in pooled class II-III obese subjects.

**Cardiovascular Risk Profile**

Diabetes prevalence increased from 5\% in thin subjects to 7\% in those of normal weight, 12\% in overweight subjects, and 15\%, 24\% and 34\% in those with class I, II, and III obesity, respectively ($P$ for trend $<0.0001$). During follow up, new-onset diabetes was detected in fewer than 1\% of normal-weight subjects, 3\% of thin subjects, 6\% of overweight subjects, and 12\%, 15\%, and 23\% of those with class I, II, and III obesity, respectively ($P<0.0001$ for trend) and was slightly more frequent during treatment with atenolol than with losartan at all body size strata (achieving statistical significance in thin and overweight groups; Table 1). Current smoking was more frequent in thin individuals (43\%) than in normal-weight (24\%), overweight (15\%), or obese (13\%, 11\%, and 12\% in the 3 classes, respectively) subjects ($P<0.0001$). The prevalence of ischemic heart disease at baseline was highest in thin individuals (33\%) and lowest in those with class III obesity (20\%), with intermediate values in the overweight (25\%), class I obesity (22\%), and class II obesity (25\%) groups ($P<0.0001$).

Table 2 shows that participants with class II and III obesity were younger than those in other groups and that thin participants were older than those in all other strata (all $P<0.001$). Mean systolic blood pressure was comparable among strata, but diastolic blood pressure was higher with obesity and lower in thin participants, who also had the
highest pulse pressure (all \(P<0.001\)). Heart rate was higher with class II and III obesity or with thin body build (all \(P<0.001\)). Both total and HDL cholesterol levels were lower in class II or III obesity than in other strata. HDL cholesterol was highest in normal-weight and thin participants. Plasma glucose was lowest in the normal-weight and thin groups and rose progressively with overweight and obesity (all \(P<0.001\)).

### Renal Status

The urinary albumin:creatinine ratio was markedly higher with both class III obesity and thin body build than in all other groups (\(P<0.001\); Table 2). The lowest creatinine clearance was found in thin individuals and in the most obese participants (\(P<0.0001\)). Urine albumin/creatinine ratio and creatinine clearance were not improved significantly by losartan.

### TABLE 1. Risk of New-Onset Diabetes by BMI Categories in 7899 Patients Without Diabetes at Baseline

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline BMI Category, kg/m²</th>
<th>New Diabetes, n, %</th>
<th>New Diabetes, n, %</th>
<th>Hazard Ratio (95% CI)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Losartan</td>
<td>Atenolol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 24.9)†</td>
<td>1121 23 (2.1)</td>
<td>1092 39 (3.6)</td>
<td>0.56 (0.34–0.95)</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>25–29.9</td>
<td>1806 89 (4.9)</td>
<td>1783 131 (7.3)</td>
<td>0.68 (0.52–0.89)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>30–34.9</td>
<td>817 92 (11.3)</td>
<td>801 98 (12.2)</td>
<td>0.92 (0.69–1.22)</td>
<td>0.539</td>
<td></td>
</tr>
<tr>
<td>(\geq 35)</td>
<td>230 34 (14.8)</td>
<td>249 48 (19.3)</td>
<td>0.73 (0.47–1.13)</td>
<td>0.155</td>
<td></td>
</tr>
</tbody>
</table>

Patients with diabetes at baseline were excluded. A hazard ratio \(>1\) favors losartan.

*A global test for treatment effect performed across BMI categories simultaneously indicated that there was a treatment effect in at least 1 subgroup (\(P<0.005\)).

†The “thin” and “normal” body build categories were combined.

### TABLE 2. Baseline Characteristics (n=9079)

<table>
<thead>
<tr>
<th>Category</th>
<th>Thin (BMI&lt;20 kg/m²) (n=200)</th>
<th>Normal Weight (BMI 20–24.9 kg/m²) (n=2190)</th>
<th>Overweight (BMI 25–29.9 kg/m²) (n=4094)</th>
<th>Class I Obesity (BMI 30–34.9 kg/m²) (n=1930)</th>
<th>Class II–II Obesity (BMI (\geq 35) kg/m²) (n=665)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.2 (6.6)</td>
<td>68.2 (7.0)</td>
<td>66.8 (7.0)</td>
<td>66.1 (6.8)</td>
<td>64.8 (7.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>51.1 (6.9)</td>
<td>65.9 (8.3)</td>
<td>77.9 (9.3)</td>
<td>88.9 (10.5)</td>
<td>104.2 (15.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.7 (1.3)</td>
<td>23.3 (1.3)</td>
<td>27.3 (1.4)</td>
<td>32.0 (1.4)</td>
<td>38.9 (4.7)</td>
<td>…</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>153 (76.5)</td>
<td>1169 (53.4)</td>
<td>1951 (47.7)</td>
<td>1144 (59.3)</td>
<td>477 (71.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>177 (88.5)</td>
<td>2057 (93.9)</td>
<td>3824 (93.4)</td>
<td>1773 (91.9)</td>
<td>562 (84.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>177 (88.5)</td>
<td>2057 (93.9)</td>
<td>3824 (93.4)</td>
<td>1773 (91.9)</td>
<td>562 (84.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>18 (9.0)</td>
<td>102 (4.7)</td>
<td>196 (4.8)</td>
<td>130 (6.7)</td>
<td>84 (12.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2.5)</td>
<td>31 (1.4)</td>
<td>74 (1.8)</td>
<td>12 (1.4)</td>
<td>19 (2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>175.6 (12.7)</td>
<td>174.7 (14.2)</td>
<td>173.9 (14.4)</td>
<td>175.0 (14.3)</td>
<td>174.5 (14.4)</td>
<td>0.039</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>95.8 (9.4)</td>
<td>96.8 (9.1)</td>
<td>97.9 (8.8)</td>
<td>98.7 (8.7)</td>
<td>98.6 (9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>79.9 (14.1)</td>
<td>77.9 (15.7)</td>
<td>76.1 (15.6)</td>
<td>76.3 (15.4)</td>
<td>75.9 (14.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76.7 (11.4)</td>
<td>73.6 (11.3)</td>
<td>73.2 (10.9)</td>
<td>74.3 (11.1)</td>
<td>76.1 (11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cornell product, mV · ms · 10⁻²</td>
<td>25.7 (10.7)</td>
<td>27.4 (12.3)</td>
<td>28.1 (9.7)</td>
<td>29.2 (9.3)</td>
<td>29.7 (9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sokolow-Lyon voltage, mV</td>
<td>35.7 (11.6)</td>
<td>33.9 (10.7)</td>
<td>30.1 (9.9)</td>
<td>26.7 (9.2)</td>
<td>24.6 (9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Framingham risk score</td>
<td>17.7 (7.8)</td>
<td>21.5 (9.4)</td>
<td>23.1 (9.5)</td>
<td>22.6 (9.4)</td>
<td>21.8 (8.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>86 (43.0)</td>
<td>463 (21.1)</td>
<td>607 (14.8)</td>
<td>245 (12.7)</td>
<td>75 (11.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum creatinine, (\mu)mol/L</td>
<td>84.1 (21.6)</td>
<td>86.3 (21.1)</td>
<td>87.5 (19.9)</td>
<td>86.9 (19.9)</td>
<td>87.1 (19.2)</td>
<td>0.065</td>
</tr>
<tr>
<td>Creatinine clearance, mg/min</td>
<td>53.2 (15.2)</td>
<td>58.9 (16.6)</td>
<td>60.6 (17.5)</td>
<td>58.0 (17.0)</td>
<td>54.5 (17.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UACR, mg/mmol</td>
<td>18.6 (108.6)</td>
<td>6.6 (29.6)</td>
<td>6.7 (30.7)</td>
<td>8.5 (31.0)</td>
<td>11.2 (31.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.06 (1.19)</td>
<td>6.10 (1.13)</td>
<td>6.05 (1.12)</td>
<td>6.02 (1.14)</td>
<td>5.93 (1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.92 (0.54)</td>
<td>1.64 (0.47)</td>
<td>1.46 (0.42)</td>
<td>1.40 (0.38)</td>
<td>1.37 (0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.4 (1.7)</td>
<td>5.7 (1.9)</td>
<td>5.9 (2.0)</td>
<td>6.3 (2.4)</td>
<td>6.8 (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>13 (6.5)</td>
<td>142 (6.5)</td>
<td>241 (5.9)</td>
<td>96 (5.0)</td>
<td>36 (5.4)</td>
<td>0.321</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>9 (4.5)</td>
<td>168 (7.7)</td>
<td>505 (12.3)</td>
<td>312 (16.2)</td>
<td>186 (28.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; UACR, urinary albumin:creatinine ratio.

\(P\) values are from a \(\chi^2\) test for categorical variables or ANOVA for continuous variables.
treatment compared with atenolol-based therapy (both \( P>0.3 \)).

**Left Ventricular Hypertrophy**

The Sokolow-Lyon voltage decreased with increasing BMI, from thin to class II and III obesity (\( P<0.0001 \)). In contrast, the Cornell voltage-duration product was progressively higher from thin to obese participants (\( P<0.0001 \)). In an ANOVA post hoc evaluation, Cornell voltage-duration product was statistically indistinguishable in thin and normal-weight groups, and it was lower than in overweight or obese groups (all \( P<0.01 \)) in both. Cornell voltage-duration product was similar in the 3 classes of obesity but higher than in the overweight group (all \( P<0.01 \)).

**Cardiovascular Events in Relation to Body Build**

The crude incidences of the primary composite end point did not differ among the 6 body build strata (17% in thin, 12% in normal weight, 12% in overweight, and 10%, 12%, and 11% in class I, class II, and class III obesity, respectively), whereas cardiovascular mortality was highest in thin individuals (10%), and lower in the other groups (5% in normal weight, thin, or overweight; 4%, 5%, and 2% in class I, class II, and class III obesity, respectively; \( P=0.09 \) for overall \( \chi^2 \) distribution).

**Proportional Hazard Analysis**

Hazard ratios for the primary composite end point in relation to the strata of body build were examined in Cox proportional hazard analysis with adjustment for age, Sokolow-Lyon voltage, Cornell voltage-duration product, gender (1 = women, 2 = men), ethnicity (black and other races relative to whites), smoking habit (1 = nonsmokers, 2 = former smokers, 3 = current smokers), diabetes, and prevalent cardiovascular disease. After controlling for covariates, the large group of overweight individuals had a 17% higher risk of the primary composite end point than normal-weight patients (Table 3). The composite event rate was 35% higher in pooled class II and III obesity. Risk of the primary composite end point was also related to older age, diabetes, current smoking, male gender, prevalent cardiovascular disease, and both ECG indices of left ventricular hypertrophy.

Risk of cardiovascular mortality was higher among thin individuals (\( P<0.05 \)) and those with classes II and III obesity (\( P<0.004; \) Table 3) than among those with normal body build. Other predictors of cardiovascular death were older age, diabetes, current smoking, black race, male gender, prevalent cardiovascular disease, and both ECG indices of left ventricular hypertrophy. The Figure displays adjusted cumulative incidence of the primary composite end point and of cardiovascular mortality for categories of body build, showing the higher cardiovascular mortality rate in thin participants and those with class II or III obesity.

**Therapy and Body Build**

Although randomization was not stratified by body weight, treatment allocation to losartan or atenolol was similar in all body build groups: losartan was given to 54% of thin, 50% of normal-weight, 50% of overweight, 50% of class I obese, and 46% of class II obese, and 52% of class III obese patients (\( P=0.525 \)). The effect of randomized treatment was tested by the introduction of treatment into the Cox proportional hazard model. Table 4 shows that the increased risks of either the primary composite end point or cardiovascular mortality associated with body build were not modified substantially by treatment and that losartan maintained a protective effect compared with atenolol in reducing the risk of the primary composite end point by 15%, independent of body build and the considered covariates.

**Discussion**

The present analysis addresses the effect of body build strata on prognosis in a large population of hypertensive patients at high risk because of the presence of ECG left ventricular hypertrophy. This study also examines the potential interaction between body build and benefit of losartan-based antihypertensive treatment. Major new findings are that in the

![Table 3. Cox Proportional Hazard Analysis](https://example.com/table3.png)

HR indicates hazard ratio.

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Table 3 shows the Cox Proportional Hazard Analysis for the primary composite end point. Variables such as age, body weight, and obesity class significantly affect the risk of the primary composite end point, with higher risks observed in younger age groups and increased BMI levels. The table also highlights the protective effect of losartan treatment compared to atenolol in reducing cardiovascular mortality risk, especially in thin individuals.
Severe Obesity as an Independent Prognostic Predictor
The evidence that obesity is related to high cardiovascular risk is strong, in large part because most obese persons have several major risk factors, often satisfying criteria for the metabolic syndrome. In unselected populations, obesity contributes to increased cardiac workload and thereby to development of left ventricular hypertrophy, which in turn is associated with adverse prognosis. In the LIFE study population, the association of obesity with increased cardiovascular mortality remained significant even after adjustment for ECG indices of left ventricular hypertrophy. Thus, after accounting for major confounders even in a context (by design) of high cardiovascular risk, obesity plays an independent role in the evolution of cardiovascular disease. Although the ECG is not optimally sensitive for detecting left ventricular hypertrophy in obese subjects, sensitivity was improved by combination of Cornell product and Sokolow-Lyon voltage criteria. As a result, the proportion of LIFE participants with left ventricular hypertrophy by one or both criteria was similar in all groups defined by body mass index (74% to 78%, \( P=0.70 \)).

Kaplan-Meier curves according to class of body build after adjustment for age, gender, race, diabetes, smoking habit, prevalent cardiovascular disease, and ECG indices of left ventricular hypertrophy (Sokolow-Lyon voltage and Cornell voltage-duration product). A, Primary composite end point; B, Cardiovascular mortality.
The design of the LIFE study does not provide information about mechanisms of obesity-related risk. There is, however, growing evidence that severe obesity is associated with activation of inflammatory mechanisms, increase in vascular thromboxane receptor gene expression, and increased fibrinogen levels that might be involved in precipitating arterial thromboxane receptor gene expression, and increased fibrinogen levels might be involved in precipitating cardiovascular disease events, especially when cardiovascular risk is high or very high. Activation of circulating markers of inflammation is most evident with central body fat distribution, whereas in more severe obesity, additional biological mechanisms make increased adiposity harmful beyond established cardiovascular risk factors or preclinical cardiovascular disease.

### Thin Individuals and Hypertension

Another interesting aspect of the present findings is that thin hypertensive individuals (BMI < 20 kg/m²) with ECG left ventricular hypertrophy have a high risk of cardiovascular death as those with severe obesity. This is not surprising, because thin participants in the LIFE study had more prevalent cardiovascular disease and risk factors, including a higher prevalence of smokers, higher pulse pressure, hypercholesterolemia, albuminuria, and lower creatinine clearance. The low BMI in these subjects may be, at least in part, a consequence of more severe cardiovascular impairment. Previous epidemiological studies have documented an association of low body weight with cardiovascular events, and in these studies, as well as in the LIFE study, thin body build remained an independent predictor, even when risk profile was taken into account. Thus, the risk associated with low body weight in the LIFE study may be related, at least in part, to the presence of underlying disease.

An aspect that linked the 2 extreme BMI classes is the association with renal dysfunction. Levels of circulating creatinine were not substantially different among the different body size groups, despite the widely different body weight, which suggests a more severe renal impairment in the older, thin individuals. In fact, in this population sample of hypertensive patients with ECG signs of left ventricular hypertrophy, estimated creatinine clearance was significantly reduced in thin individuals to a level comparable to the reduction detected in class II-III obesity.

Because in the LIFE study, thin body build was as predictive of cardiovascular death as morbid obesity, renal dysfunction might play a role as an accelerator of impairment of arterial system. Although the 2 extremes of the body build distribution appear to be prognostically similar, participants with normal weight, overweight, and even class I obesity (ie, BMI 20 to 35 kg/m²) did not differ substantially in cardiovascular event rate. This risk pattern confirms the findings of large epidemiological studies of association of mortality with body size.

### Treatment Effect

The increased cardiovascular risk associated with the extremes of body build distribution was not influenced substantially by treatment, although the hazard ratios associated with thin or severely obese body build lost significance when the effect of losartan was considered in the predictive model. The receiver operating characteristic curves, confirmed that specificity of BMI ≥ 35 kg/m² for central fat distribution was 99.8% and 98% in men and women, respectively.
small fluctuations of hazard ratios did not reveal any interaction between body build and the effect of losartan treatment. This observation cannot be extrapolated automatically to other angiotensin II type 1 receptor inhibitors. Losartan presents some functional differences from other angiotensin receptor blockers, because its activity is not specific for angiotensin II type 1 receptor inhibition. The losartan metabolite EXP3179 is detectable in patients in concentrations that exhibit antiinflammatory and antiaggregatory properties in vitro, through block of thromboxane receptors, a characteristic that might be very useful in obesity.

Conclusions

In the LIFE study, stratification for classes of body build identified increased risk of cardiovascular mortality in both thin and moderately-to-severely obese individuals. This risk was not attenuated significantly by losartan treatment, nor did it interfere with the greater benefit of losartan-based treatment as opposed to atenolol-based treatment. Aggressive treatment of patients at extremes of body build distribution to lower targets for blood pressure or other risk factors may be needed to reduce cardiovascular mortality.

Acknowledgments

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Disclosure

Drs Beevers, Dahlöf, de Faire, Devereux, Fyhrquist, Ibsen, Kjeldsen, Julius, Lederballe-Pedersen, Lindholm, Nieminen, Omvik, Oparil, and Wachtell have received grants from Merck & Co, Inc, etc. Darcy Hille is an employee of Merck & Co, Inc.

Drs Beevers has served on the Advisory Boards of Merck & Co, Inc, and AstraZeneca. Dr Dahlöf has served as a consultant to Pfizer, Novartis, Boehringer, and Merck, and has had speaking engagements with Pfizer, Novartis, Boehringer, Merck, AstraZeneca, Bayer, Bristol-Myers Squibb, and Servier. Dr Fyhrquist has received honoraria for lecturing at symposia arranged by Merck Sharp & Dohme. Dr Kjeldsen has received honoraria from AstraZeneca, Bayer, Merck, Novartis, Pharmacia, and Pfizer. Dr Omvik has received honoraria from Merck & Co, Inc, Pfizer, Novartis, Pharmacia, and AstraZeneca. Dr Oparil is the recipient of grants-in-aid from Abbott Laboratories, AstraZeneca, Aventis, Bioway, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Encysive (previously Texas Biotechnology Corporation), Forest Laboratories, GlaxoSmithKline, Monarch, Novartis, Merck & Co, Inc, Pfizer, Sanofi Pharma, Sanofi-Synthelabo, Schering Plough, Scios, and Wyeth. Dr Oparil is a consultant for Bristol-Myers Squibb, Bioway, Merck & Co, Inc, Pfizer, Reliant, Sanofi, Novartis, The Salt Institute, and Wyeth, and she is a member of the Board of Directors for Encysive Pharmaceuticals. Dr Devereux has received honoraria for speaking engagements from and is a paid consultant for Merck & Co, Inc.

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Body Build and Risk of Cardiovascular Events in Hypertension and Left Ventricular Hypertrophy: The LIFE (Losartan Intervention For Endpoint reduction in hypertension) Study

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