Effect of Converting Enzyme Inhibitor (SQ14,225) on Myocardial Hypertrophy in Spontaneously Hypertensive Rats

SUBHA SEN, PH.D., D.SC., ROBERT C. TARAZI, M.D., AND F. MERLIN BUMPUS, PH.D.

SUMMARY The potent converting enzyme inhibitor (CEI) SQ14,225, which is known to prevent the formation of angiotensin II (AII) has been used to evaluate the role of AII in the development and reversal of cardiac hypertrophy. The present study describes the effect of CEI on blood pressure (BP) and myocardial hypertrophy (prevention and reversal) in the spontaneously hypertensive rat (SHR).

A group of 3-week- and 8-week-old male SHR was treated with CEI (30 mg/kg in drinking water) for 6 weeks. An additional group of SHR was also treated with a combination of CEI and a diuretic (hydrochlorothiazide, 500 mg/liter). Heart weight, BP, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), hydroxyproline, myocardial catecholamines, and plasma renin activity (PRA) were determined.

In the prevention study, we found a significant reduction in the ratio of heart weight to body weight along with the prevention of hypertension (200 vs 145 mm Hg, \( p < 0.001 \)). Similar reductions in BP and heart weights were obtained with the reversal group. A better BP control was noted in the CEI and hydrochlorothiazide group. The reduction of heart weight was associated with a reduction in RNA and hydroxyproline content. In all groups, we found a significant increase in PRA \( (p < 0.001) \) and a slight increase in tissue catecholamine concentration. No change in kidney weight was found in any group. Data clearly showed that oral administration of CEI prevented and reversed cardiac hypertrophy in SHR. Reversal was associated with a decrease in myocardial collagen content. These data indicate that prevention of AII formation in combination with BP control can prevent and reverse cardiac hypertrophy in SHR. Of course, whether or not CEI acts only through the renin angiotension system is still speculative. (Hypertension 2: 169-176, 1980)

KEY WORDS • converting enzyme inhibitor • hypertension • myocardial hypertrophy • angiotensin II

SYSTEMATIC investigation of myocardial hypertrophy in spontaneously hypertensive rats (SHR) led to the suggestion that factors other than blood pressure (BP) may be involved in the development or reversal of myocardial cardiac hypertrophy. \(^1,2\) Recently, we have attempted to dissociate hypertension and myocardial hypertrophy by using antihypertensive drugs, either alone or in combination, to study the possible involvement of humoral factors in either the development or the reversal of hypertrophy. Data suggested the possible involvement of one of three factors: the renin-angiotension (R-A) system, catecholamine and hemodynamic factors, or mechanical actions of the drugs on the heart. \(^1,3\) A good correlation between ventricular hypertrophy and plasma renin activity (PRA) was obtained when SHR were treated with \( \alpha \)-methyldopa or vasodilators. \(^3\) This relationship did not hold, however, when a combination of drugs was administered. \(^3\)

Khairallah et al. \(^4\) suggested involvement of angiotensin II (AII) in stimulation of myocardial protein synthesis. When we attempted to block endogenous AII in SHR by using angiotensin antagonists, the degree of hypertrophy increased with the use of some antagonists. \(^5\) The results of further studies \(^6\) suggested that this increase possibly was due to increase in myocardial catecholamines rather than to direct action of the peptides, since their effect could be prevented by adrenalectomy. No clear-cut data have been obtained to define the possible role of either catecholamines or AII in the development of hypertrophy. The converting enzyme inhibitor (CEI) SQ14,225 is an orally active, potent inhibitor of the R-A system and has lowered BP effectively in both experimental and human hypertension. \(^7,8\)
Materials and Methods

Antihypertensive Therapy

The drugs used in this study were CEI (SQ14,225), hydrochlorothiazide, and a combination of hydrochlorothiazide and CEI. The SHR were divided into 6 groups for drug therapy as follows: 1) prevention of hypertension (3-week-old rats): Group I, control; Group II, CEI, 30 mg/kg; 2) reversal of hypertension (8-week-old rats): Group III, control; Group IV, CEI, 30 mg/kg; Group V, hydrochlorothiazide, 500 mg/liter (drinking water); Group VI, hydrochlorothiazide and CEI, 500 mg/liter (drinking water) and 30 mg/kg respectively.

The criterion used to establish dosage was effective BP control in SHR. The dosages used were based on pilot experiments in which SHR were given dosages of CEI ranging from 6 mg/kg to 70 mg/kg. Administration of (approximately) 30 mg/kg was found effective for prevention and reversal of hypertension.

All rats were treated for 6 weeks. During this period, whenever BP of the rats tended to rise by approximately 20 mm Hg, the CEI dosage was increased. The 6-week period was chosen for treatment because previous experience showed the need for at least this amount of time for achieving significant reversal of myocardial hypertrophy. Oral administration (in drinking water) was chosen because it had been shown to lower BP effectively and was more convenient than intramuscular injections.

Blood Pressure Measurements

In all rats, arterial pressures were measured using a tail-cuff method similar to that of Friedman and Freed.19 The BP was measured twice a week in each rat by the same person and approximately at the same time of the day.

Results

Effect on Blood Pressure

Prevention Therapy

The effect of oral administration of CEI (30 mg/kg) on the development of hypertension is shown in figure 1. During the 6 weeks of treatment, BP rose from 100 to 148 ± 5 mm Hg, whereas in the untreated controls, BP rose to 198 ± 4 mm Hg (p < 0.001). During the 6 weeks of treatment, BP tended to rise after 3 weeks of therapy. When the CEI dosage was increased to 50 mg/kg, this increase was controlled; however, a further increase to 70 mg/kg did not lower BP below 150 mm Hg. These data showed that development of hypertension could be controlled by oral CEI therapy, but not to the normal level (120 mm Hg).

Reversal of Hypertension

When 8-week-old SHR were treated with CEI (30 and 50 mg/kg), we noted a significant reduction in BP (fig. 1). As in prevention therapy, an increase in dosage was necessary after one week of therapy; and BP fell to 151 ± 3 mm Hg, whereas BP of the untreated, control SHR remained at 193 ± 5 mm Hg. A combination of hydrochlorothiazide (500 mg/liter) and CEI showed better BP control (120 ± 10 mm Hg, p < 0.001) than did CEI (30 mg/kg) alone, and BP remained low during the rest of the experimental period (fig. 1). We noted a slight reduction in BP with diuretic therapy alone (192 ± 8 vs 168 ± 6 mm Hg, p < 0.025) (fig. 1).

Analytical Methods

All rats were killed by decapitation; hearts and kidneys were immediately removed, cleaned, and weighed as described in 1974. The lower part of ventricles was used for biochemical determination and the upper part for determination of tissue catecholamines. Ribonucleic acid (RNA) was determined according to the method of Fleck and Munro,11 an ultraviolet absorption method. Deoxyribonucleic acid (DNA) was determined by the method of Ceriotti.12 Hydroxyproline was determined in the ventricular tissue extract by the colorimetric method with diethylamine benzaldehyde.13

Ventricular catecholamine (norepinephrine) was determined by the fluorometric method of Robinson and Watts.14 A blood sample (0.4 ml) was removed from each rat 1 day before it was killed. The PRA was measured according to the micromethod of Boucher et al.,15 with exogenous substrate prepared from 48-hour bilaterally nephrectomized male rats.

Statistical Analysis

All data were expressed as mean values ± SEM and multiple comparisons between groups. Comparisons were done by the Kruskal-Wallis rank sum test.
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**Prevention**

The body weight of SHR at the end of preventive therapy was lower than that of untreated controls (208 ± 6 vs 242 ± 6 g, p < 0.001). The mean ventricular weight was significantly lower than that of the untreated controls (0.626 ± 0.05 vs 0.804 ± 0.01 g, p < 0.001). Because the treated SHR weighed less than the controls, however, we also calculated the ratio of heart weight to body weight and found a significant reduction in the ratio (3.3 ± 0.03 vs 3.0 ± 0.03 mg/g, p < 0.001). This showed that the development of hypertrophy was prevented by 6 weeks of CEI therapy. In a separate study, when SHR were treated for 21 weeks (treatment started at 3 weeks and continued till 24 weeks), the ratio of heart weight to body weight in treated SHR was significantly reduced when compared to untreated, 24-week SHR (3.2 ± 0.1 vs 2.5 ± 0.05, p < 0.0001). When compared to age-matched Wistar-Kyoto (WK) rats, the heart weight-to-body weight ratio of treated SHR was not significantly different (2.6 ± 0.06 vs 2.5 ± 0.05, p not significant).

The data on untreated SHR, WKY, and CEI-treated SHR are shown in figure 2. The regression lines of the heart weight-to-body weight ratio of SHR and WKY were drawn from 126 rats during 30 weeks of study and compared to data from CEI-treated (prevention therapy) SHR at 8 weeks and 24 weeks of age. When data were analyzed by Kruskal-Wallis H test, the probability of no significant difference between untreated and treated SHR was 0.013, and the probability of no significant difference between treated SHR and WKY was 0.23. The ratio of kidney weight to body weight was not different (3.4 ± 0.05 vs 3.5 ± 0.03 mg/g, p not significant), which suggests that the reduction in ventricular weight was specific for the heart.

**Reversal**

A slight, but not significant, reduction in body weight (291 ± 6 vs 276 ± 6 g, p < 0.1) was noted after SHR received therapy for 6 weeks (table 1). A significant reduction in absolute ventricular weight and its ratio to body weight was found (0.962 ± 0.02 g vs 0.814 ± 0.02 g; and 3.3 ± 0.06 vs 2.95 ± 0.06 mg/g respectively, p < 0.001). When the heart weight-to-body weight ratio was compared to age-matched WKY, no significant difference was obtained (2.8 ± 0.05 WKY vs 2.95 ± 0.04 in treated SHR, p not significant). The individual data on treated SHR are shown in figure 2. The absolute kidney weight and its ratio to body weight were not different between control and treated SHR (1.0 ± 0.03 vs 0.99 ± 0.03 g; and 3.42 ± 0.07 mg/g vs 3.58 ± 0.07 mg/g respectively, p not significant). This showed that myocardial hypertrophy was reversed by CEI therapy and was specific for the heart.

The water content of both treated and untreated SHR was found to be the same (78% vs 77.5%, p not significant), which suggested that the reduction in heart weight was not due to loss of water. The effect of a combined diuretic and CEI on body weight and organ weight is shown in table 1. When SHR treated with a diuretic alone were used as controls and were compared with SHR treated with a combination of CEI and hydrochlorothiazide, similar changes in body weight and heart weight were found. There was no significant reduction in body weight (282 ± 7 vs 270 ± 6 g, p not significant), and a significant reduction in heart weight and its ratio to body weight was found.
TABLE 1. Effect of the Converting Enzyme Inhibitor (CEI) SQ14,225 on Body and Organ Weight of the Spontaneously Hypertensive Rat (SHR)

<table>
<thead>
<tr>
<th>Action taken</th>
<th>Body wt. (g)</th>
<th>Ventricular wt. (g)</th>
<th>Water content</th>
<th>Ratio of ventricular wt. to body wt. (g)</th>
<th>Kidney wt. (g)</th>
<th>Ratio of kidney wt. to body wt. (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated SHR (n = 8)</td>
<td>242 ± 4</td>
<td>0.804 ± 0.01</td>
<td>—</td>
<td>3.3 ± 0.03</td>
<td>0.863 ± 0.03</td>
<td>3.4 ± 0.05</td>
</tr>
<tr>
<td>SHR and CEI (n = 8)</td>
<td>208 ± 6</td>
<td>0.626 ± 0.05</td>
<td>—</td>
<td>3.0 ± 0.03</td>
<td>0.750 ± 0.04</td>
<td>3.5 ± 0.03</td>
</tr>
<tr>
<td>Reversal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated SHR (n = 8)</td>
<td>291 ± 4</td>
<td>0.962 ± 0.02</td>
<td>78%</td>
<td>3.3 ± 0.06</td>
<td>1.0 ± 0.03</td>
<td>3.42 ± 0.07</td>
</tr>
<tr>
<td>SHR and CEI (n = 8)</td>
<td>276 ± 6</td>
<td>0.814 ± 0.02</td>
<td>77%</td>
<td>2.95 ± 0.04</td>
<td>0.99 ± 0.03</td>
<td>3.58 ± 0.06</td>
</tr>
<tr>
<td>SHR and Hydrochlorothiazide (n = 8)</td>
<td>282 ± 7</td>
<td>0.876 ± 0.09</td>
<td>78%</td>
<td>3.12 ± 0.09</td>
<td>p = n.s.</td>
<td></td>
</tr>
<tr>
<td>SHR and hydrochlorothiazide + CEI (n = 8)</td>
<td>270 ± 4</td>
<td>0.793 ± 0.02</td>
<td>—</td>
<td>3.91 ± 0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 2. Effect of converting enzyme inhibitor (CEI) on heart weight of the spontaneously hypertensive rat (SHR) on the background of regression lines for the heart weight-to-body weight ratio of SHR and Wistar-Kyoto rats (WKY) (126 rats). Symbols: • = heart weight at the end of 6 weeks and 24 weeks of prevention therapy with CEI; ◆ = ratio of heart weight to body weight at the end of reversal therapy for 6 weeks; † = treatment started; ♦ = treatment started after 6 weeks; □ = treatment stopped after 24 weeks; ⊀ = reversal therapy started; and ⊁ = discontinuation of therapy.
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(0.876 ± 0.09 vs 0.793 ± 0.02 g; and 3.12 ± 0.09 vs 2.91 ± 0.95 mg/g respectively, \( p < 0.005 \)) (table 1).

When untreated SHR were compared with SHR treated with hydrochlorothiazide, the body weight of diuretic-treated rats was slightly lower than that of controls (291 ± 6 vs 282 ± 7 g, \( p \) not significant), and the ventricular weight and its ratio to body weight were not significantly different (0.962 ± 0.02 vs 0.876 ± 0.09 g; and 3.3 ± 0.06 vs 3.1 ± 0.09 mg/g respectively, \( p \) not significant).

**Wistar-Kyoto Control Groups**

We gave CEI to three different groups of normotensive WKY matched with SHR for age and sex. Each of the three groups was followed according to the described protocol for “prevention” or “reversal” treatment. All rats were handled in the same way. No group showed any significant change in BP, and changes in heart weights were inconsistent (table 2). For all three groups (n = 17) considered together, changes in heart weight were not significant; among the three groups considered individually, only one showed a slight reduction in the ratio of heart weight to body weight (5.9% of borderline significance, \( p < 0.04 \)).

**Effect on Biochemical Variables**

The effect of CEI on biochemical variables; namely, myocardial DNA, RNA, and hydroxyproline, is summarized in tables 3 (prevention therapy) and 4 (reversal therapy).

**Prevention Therapy**

The concentrations of DNA and hydroxyproline were increased in the treated group (1.76 ± 0.04 vs 2.05 ± 0.05 mg/g; and 0.58 ± 0.01 vs 0.63 ± 0.01 respectively, \( p < 0.05 \)) whereas the concentration of RNA remained unchanged (3.48 ± 0.08 vs 3.53 ± 0.08, \( p \) not significant. When the total RNA and hydroxyproline content per ventricle were calculated, however, both were significantly reduced (2.8 ± 0.1 vs 2.26 ± 0.08, \( p < 0.005 \); and 0.46 ± 0.01 vs 0.396 ± 0.01, \( p < 0.05 \) respectively), whereas total DNA was not significantly different (1.41 ± 0.05 vs 1.29 ± 0.04, \( p < 0.1 \)).

**Reversal Therapy**

The concentration of all three components in the ventricles remained unchanged after 6 weeks of CEI treatment (DNA, 1.75 vs 1.76; RNA, 3.16 vs 3.23; and hydroxyproline, 0.56 g vs 0.59 g). After reversal of myocardial hypertrophy, however, RNA and hydroxyproline were significantly reduced (3.1 vs 2.58; and 0.53 vs 0.45 respectively, \( p < 0.05 \)). Total DNA was slightly reduced but not statistically significant (1.67 vs 1.46 mg, \( p < 0.2 \)).

In the hydrochlorothiazide- and CEI-treated group, we observed similar changes in RNA and hydroxy-

**Table 2. Converting Enzyme Inhibitor in Normotensive Wistar-Kyoto Rats**

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>BP</th>
<th>Ratio of ht. wt. to body wt. (n = 5)</th>
<th>Treatment schedule</th>
<th>Ratio of ht. wt. to body wt. (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>124 ± 5</td>
<td>2.91 ± 0.01</td>
<td>120 ± 3</td>
<td>2.57 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.5 )</td>
<td>( p &lt; 0.04 )</td>
<td>( p &lt; 0.2 )</td>
<td>( p &lt; 0.47 )</td>
</tr>
<tr>
<td>WKY and CEI</td>
<td>120 ± 7</td>
<td>2.72 ± 0.05</td>
<td>107 ± 4</td>
<td>2.52 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 2 )</td>
<td>( p = n.a. )</td>
<td>( p = n.s. )</td>
<td></td>
</tr>
<tr>
<td>WKY and CEI + hydrochlorothiazide</td>
<td>—</td>
<td>—</td>
<td>108 ± 7</td>
<td>2.52 ± 0.03</td>
</tr>
</tbody>
</table>

**Table 3. Effect of Converting Enzyme Inhibitor (CEI) on Ventricular DNA, RNA, and Hydroxyproline (Prevention Therapy)**

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>RNA</th>
<th>DNA</th>
<th>Hydroxyproline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/g</td>
<td>mg/g</td>
<td>mg/g</td>
</tr>
<tr>
<td>SHR (untreated)</td>
<td>3.48 ± 0.08</td>
<td>1.76 ± 0.05</td>
<td>0.576 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>2.8 ± 0.1</td>
<td>1.29 ± 0.04</td>
<td>0.46 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>( p = n.s. )</td>
<td>( p &lt; 0.005 )</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>SHR and CEI</td>
<td>3.32 ± 0.08</td>
<td>2.05 ± 0.05</td>
<td>0.63 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>2.26 ± 0.88</td>
<td>1.41 ± 0.05</td>
<td>0.396 ± 0.007</td>
</tr>
<tr>
<td>( p &lt; 0.005 )</td>
<td>( p &lt; 0.05 )</td>
<td>( p &lt; 0.001 )</td>
<td></td>
</tr>
</tbody>
</table>
proline (as described above) in the group treated with CEI alone. Data are summarized in table 4. Concentration of DNA was increased (1.65 vs 1.80 mg/g, p < 0.05) and concentrations of RNA and hydroxyproline were not significantly different (3.4 vs 3.23 mg/g; and 0.57 vs 0.60 respectively, p not significant). The total DNA was not significantly different between the treated and control groups (1.45 vs 1.42, p < 0.4); whereas total RNA and OH-proline was decreased (3.04 vs 2.56, p < 0.05; and 0.52 vs 0.48).

Effects on Humoral Factors

The effect of CEI on tissue catecholamines is summarized in table 5.

Prevention

After 6 weeks of CEI therapy, the ventricular catecholamine norepinephrine (NE) was significantly elevated (573 ± 39 vs 814 ± 54 mg/g, p < 0.01). The total NE content was not significantly different, however, between the treated and control groups (456 ± 31 vs 509 ± 37 ng, p < 0.4).

Reversal

The ventricular NE concentration varied in all groups and no significant change was noted. In the CEI-treated group, the concentration of ventricular NE was 829 ± 69 ng/g compared to 727 ± 65 ng/g in the control group. The total NE content was also found to be similar (692 ± 56 vs 676 ± 53 ng/g, p not significant).

Similarly, in the hydrochlorothiazide-and-CEI- and CEI-treated groups, both NE concentration and contents were the same (715 ± 96 ng/g vs 978 ± 121 ng/g, and 625 ± 45 vs 774 ± 96 ng/g respectively).

Effect on Plasma Renin Activity (PRA)

The effect of CEI on PRA is shown in table 5. In both CEI-treated groups, i.e., CEI alone and in combination with diuretic, we found a five- to tenfold increase in PRA.

In the prevention group, PRA rose from 49.5 ± 6 to 254 ± 54 ng/ml/hr (p < 0.001) during 6 weeks of treatment. Similarly, in the reversal group a significant increase in PRA was found (38.4 ± 7 vs 182 ± 24, p < 0.001).

Discussion

The results from this study clearly showed that orally-administered CEI (SQ14,225) prevented the development of hypertension when given early, controlled BP when given late, and lowered ventricular weight in both cases.

When CEI was administered in combination with a diuretic, a similar degree of reversal of hypertrophy and hypertension was achieved, and a better BP control was maintained; in fact, a BP was normalized

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### Table 4. Effect of Converting Enzyme Inhibitor (CEI) on Ventricular Biochemical Composition (Reversal Therapy)

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>RNA (mg/g)</th>
<th>DNA (mg/g)</th>
<th>Hydroxyproline (mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHR (untreated)</td>
<td>3.2</td>
<td>1.76 ± 0.06</td>
<td>0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.1</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>p = n.s.</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.1</td>
</tr>
<tr>
<td>SHR and CEI</td>
<td>3.1</td>
<td>1.75</td>
<td>0.59</td>
</tr>
<tr>
<td>SHR and hydrochlorothiazide</td>
<td>3.4</td>
<td>1.65</td>
<td>0.566</td>
</tr>
<tr>
<td>SHR and hydrochlorothiazide + CEI</td>
<td>3.23</td>
<td>1.80</td>
<td>0.60</td>
</tr>
</tbody>
</table>

### Table 5. Effect of Converting Enzyme Inhibitor (CEI) on Humoral Factors

<table>
<thead>
<tr>
<th>Factors</th>
<th>Control</th>
<th>Prevention</th>
<th>SHR and CEI</th>
<th>Control</th>
<th>Reversal</th>
<th>SHR and CEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamine (ng/g)</td>
<td>573 ± 39</td>
<td>p &lt; 0.01</td>
<td>814 ± 54</td>
<td>727 ± 65</td>
<td>p = n.s.</td>
<td>829 ± 69</td>
</tr>
<tr>
<td>Total content</td>
<td>456 ± 31</td>
<td>p &lt; 0.4</td>
<td>509 ± 37</td>
<td>692 ± 54</td>
<td>p = n.s.</td>
<td>676 ± 53</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>49.5 ± 6.09</td>
<td>p &lt; 0.001</td>
<td>254.5 ± 54</td>
<td>38.4 ± 7</td>
<td>p &lt; 0.001</td>
<td>182 ± 24</td>
</tr>
</tbody>
</table>
The underlying mechanism for reversal of hypertrophy by CEI is not clear. Whether CEI acts exclusively through the R-A system or otherwise is speculative; whatever the case, the CEI SQ14,225 appears to be a potent antihypertensive drug in spontaneous hypertension, with the added advantage that it can reverse myocardial hypertrophy.

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