Step-Down of Enalapril Treatment for Arterial Hypertension

José Ramón González-Juanatey, Antonio Pose Reino, José María García-Acuña, Carlos González-Juanatey, Luis Valdes, José Cabezas-Cerrato

Abstract—Enalapril treatment (20 mg every 12 hours) of 24 patients with essential hypertension and left ventricular (LV) hypertrophy established normal blood pressures after 8 weeks, and after 5 years, it had reduced LV mass index by 39% (from 148±34 to 90±16 g/m²) and had normalized LV structure and function and QT dispersion. Stepwise reduction of the enalapril dosage from 40 to 30, 20, 10, and 5 mg/d during the eighth year caused no significant change in blood pressure, LV structure, LV systolic function, or QT dispersion, which all likewise remained unaltered during an additional 2-year period of the 5-mg/d regimen. We conclude that for hypertensive patients in whom prolonged treatment with high doses of enalapril has normalized blood pressure, LV structure, LV function, and QT dispersion, the dose may be reduced as much as 8-fold without detriment to cardiovascular control. The use of smaller doses is evidently advantageous from the point of view of health costs. (Hypertension. 1999;34:1287-1292.)

Key Words: hypertension, essential ■ hypertension, arterial ■ enalapril

The withdrawal of antihypertensive medication from well-controlled hypertensive patients generally leads to the reappearance of hypertension within 6 to 12 weeks.1 Schmieder et al2 found that those patients who do remain normotensive after withdrawal of medication have in common that they are relatively young, nonobese, nondrinkers with low salt intake who were being successfully treated with just a single antihypertensive drug for mild hypertension that had not caused target organ lesions.

Because the reappearance of hypertension is the usual result of withdrawal of medication, the dosage of antihypertensive drug found to be effective for a particular patient is usually maintained indefinitely. Very few studies have examined the effects of dosage reduction.

Arterial hypertension is part of a vicious circle that is completed by structural and functional vascular alterations, such as increased wall thickness and reduced resistance arterial lumen.3,4 The reappearance of hypertension on withdrawal of antihypertensive medication may be interpreted as showing that the antihypertensive drugs used addressed only one aspect of the vicious circle, hypertension. It may be surmised that therapies that simultaneously controlled hypertension and inverted the associated vascular alterations might, once these effects had been achieved, allow permanent withdrawal of medication, or at least the use only of such low levels as might be necessary to offset genetic or environmental factors favoring the reappearance of the disease.

In previous articles,5,6 we reported that prolonged administration of enalapril (with no other drug) to a group of hypertensive patients initially exhibiting left ventricular (LV) hypertrophy not only maintained blood pressure (BP) at the normal values attained within 8 weeks of the start of treatment (normal BP at 8 weeks was a requisite for a patient’s continuing in the study) but also reduced LV mass, improved LV systolic function, and reduced the dispersion of the electrocardiographic QT interval. After the patients were treated for 7 years, the daily dose of enalapril was progressively reduced from 40 to 10 mg without any effect on BP or on indices of LV structure and function. We now report that after 2 years on 5 mg of enalapril daily, the state of these patients remains unchanged.

Methods

We studied 28 previously untreated hypertensive patients (20 men and 8 women aged 50±10 years [range 35 to 64 years]) who gave their informed consent. All were diagnosed as having essential arterial hypertension on the basis of (1) seated diastolic BPs of between 95 and 114 mm Hg in 3 replicate measurements over a period of 3 weeks, (2) absence of symptoms, and (3) absence of signs and history of any other cardiovascular disorder.

All the patients took 20 mg of enalapril every 12 hours for 5 years (59±1 months). At that time, the treatment was interrupted for 8 weeks, after which it was resumed (the dose given every 12 hours was increased progressively from 2.5 to 20 mg). At their 7-year check-ups, all the patients had normal BPs. The enalapril dosage was then reduced to 15 mg twice daily and, at 3-month intervals thereafter, to 10 mg twice daily, 5 mg twice daily, and 5 mg every morning (5 patients were temporarily returned from the 10-mg/d to the 20-mg/d regimen; see Results).

During the 10-year course of the study (123.3±1.9 months), full clinical histories were obtained, arterial BPs were determined (at rest and during exercise), and echocardiography was performed at the following times: after a pretreatment placebo period, at 8 weeks and 1, 3, and 5 years after the initiation of therapy, after the 8-week suspension of therapy, 8 weeks after the resumption of therapy, 6 years (74.2±1.4 months) and 7 years (87.1±1.4 months) after the initiation of treatment, before each successive reduction of the

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dosage, and 3 months, 1 year, and 2 years after initiation of the 5-mg/d regimen.

BP was measured with a mercury sphygmomanometer 12 hours after the latest dose of enalapril. All measurements were made on the same arm. Resting BPs were taken with the patient seated. The values used in subsequent statistical analyses were the means of 3 measurements taken at intervals of at least 5 minutes, starting 10 to 15 minutes after the patient had sat down. Systolic BP and diastolic BP were determined during Korotkoff sounds 1 and 5, respectively. Heart rate (beats per minute) was determined by palpation of the radial artery for 60 seconds. Exercise was performed on a treadmill in accordance with Bruce’s protocol (up to and including stage III). BP was recorded every 3 minutes during exercise and 1, 3, and 6 minutes after exercise had ceased. The values discussed below are those measured during the greatest workload applied. Although the noninvasive technique used is inaccurate for diastolic BP during exercise, we believe that the recorded trends in diastolic BP are probably not incorrect.

Before each reduction of enalapril dosage and at 3 months, 1 year, and 2 years after initiation of the 5-mg/d regimen, ambulatory BPs were recorded every 15 minutes for 24 hours by use of an oscillometric monitor (model 90202, Space-Labs). On each occasion, the daytime, nighttime, and 24-hour mean systolic and diastolic BPs and heart rate were calculated.

M-mode echocardiography with a Siemens Sonoline CD echograph and 2.5-MHz transducer was used to measure (in millimoles) the diastolic thicknesses of the interventricular septum and the posterior wall of the LV and the diastolic and systolic diameters of the cavity; 2-dimensional images taken from longitudinal or transverse parasternal views were used to ensure that all measurements were made at the same level (just above the papillary muscles). The values used in subsequent calculations were the means of 4 to 6 measurements made during successive heartbeats. All echocardiographic recordings were made and interpreted by the same cardiologist (J.R.G.-J.), who was unaware of the patients’ treatments and of their participation in the present study. The intraobserver coefficients of variation of septal thickness (7.2%), LV wall thickness (6.0%), and diastolic LV diameter (3.1%) were calculated as the medians, over all patients, of the coefficients of variation calculated for each patient; these intrapatient coefficients of variation were calculated as 100×(difference between the values measured at the beginning and end of the placebo period/the mean of these 2 values).

LV mass (in grams) was calculated, following the method of Devereux and Reichek, as 1.04×[(diastolic LV diameter + septal thickness + LV wall thickness)³−diastolic LV diameter³]−13.6; LV mass index (in square meters), as LV mass/body surface area; and relative LV wall thickness, as (LV wall thickness + septal thickness)/diastolic LV diameter. LV fractional fiber shortening (percent) was calculated as 100×(diastolic LV diameter − systolic LV diameter)/diastolic LV diameter; circumferential fiber shortening velocity (circumference/second), as LV fractional fiber shortening/(100×ejection time) (LV ejection time in seconds was determined from M-mode measurements of the aortic root); and LV ejection fraction (percent), as 100×(diastolic LV diameter³−systolic LV diameter³)/diastolic LV diameter³.

Standard 12-lead electrocardiograms were recorded at a paper speed of 25 mm/s, and these data were fed into a personal computer in digital form with an optical scanner. For 3 consecutive cycles in the record of each of the 12 electrocardiographic leads, 2 observers blinded to the conditions of the study used calipers to measure QT, which is the interval from the onset of the QRS complex to the end of the T wave (defined as the return to TP baseline; when a U wave was present, the return to baseline was taken as the point of intersection between the baseline and the tangent to the descending limb of the T wave). The QT for each lead was calculated as the mean over the 3 cycles, and the absolute QT dispersion (ΔQT) was calculated by subtracting the shortest of these 12 lead-specific QTs from the longest. This value was converted into a percentage (%ΔQT) by dividing ΔQT by the shortest lead-specific QT interval and multiplying by 100×(%ΔQT=[(QTmax−QTmin)/QTmin]×100).

Each lead-specific QT was “corrected” for the patient’s heart rate using Bazett’s formula [%ΔQTc=QT (ms)/1000 ms⁻¹ × RR (ms)]¹², with an absolute QTc dispersion (ΔQTc) was calculated by subtracting the shortest lead-specific QTc from the longest and was then expressed as a percentage: [%ΔQTc=[(QTcmax−QTcmin)/QTc-min]×100]. The QT dispersion ratio (ΔQT/r) was calculated as QT dispersion (ΔQT) divided by the cycle length in milliseconds and multiplied by 100. The reliability of QT measurements was checked by numbering and duplicating 20 electrocardiograms in which QT intervals were then measured independently by the 2 observers. The average percentage differences in QT measurements for the same ECG were 4% to 5% for within-observer variability and 5% to 7% for between-observer variability.

Results

Two of the 28 patients abandoned the study in its early stages: one after 2 months because of irritant cough and the other after 4 months because of gastrointestinal problems. Two more were excluded during the sixth year when they were taken off enalapril and put on a calcium antagonist because their persistently hypertensive BPs (diastolic BPs >100 mm Hg) had failed to respond to the combination of enalapril and a low dose of a thiazide. A fifth patient underwent surgery for breast cancer after 4 years of enalapril treatment but is still in the study group.

One of the criteria for inclusion in the study had been that a normal BP should be achieved within 8 weeks of the start of enalapril treatment. Only 2 patients required <40 mg/d to achieve normal BP; these 2 exceptions achieved normal BP with 20 mg/d within 6 weeks of treatment but, like the others, took 40 mg/d thereafter. After 5 years, all the patients remained normotensive, but suspension of treatment for 8 weeks sufficed to return resting BP to values that, for the group as a whole, did not differ significantly from pretreatment values (150±16/101±10 mm Hg after 5 years, 156±14/105±6 mm Hg before treatment; see Table 1). Only 6 patients remained normotensive, with diastolic BPs <95 mm Hg. Eight weeks after the resumption of enalapril therapy, all the patients were normotensive again, with resting BPs of 128±12/82±5 mm Hg.

At the end of 3 months on 15 mg enalapril twice daily and at the end of 3 months on 10 mg enalapril BID, all the patients were still normotensive, and there were no significant differences in BP with respect to the last evaluation under the 20 mg BID regime. At the end of 3 months on 5 mg twice daily, BPs had increased with respect to their values at the previous evaluation; although the increase was not significant in the group as a whole, 3 patients had diastolic BPs >90 mm Hg, and 2 patients had systolic BPs >140 mm Hg. These patients were returned to the 20-mg/d regime pending analysis of their ambulatory hemodynamics, but when these were found to be normal (see below), the observed elevation of in-clinic BPs was deemed to be a “white-coat” effect, and the patients in question were put on 5 mg/d in accordance with the preestablished schedule. After 3 months on 5 mg/d enalapril, the group as a whole exhibited no significant changes in BP; 2 patients had diastolic BPs >90 mm Hg, but their ambulatory BPs were normal. After 1 year and 2 years on 5 mg/d enalapril, there was no significant BP change in the group as estimated by the Friedman test. Proportions were compared using the Fisher test.

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0.01 and $P < 0.05$, respectively). At no subsequent examination was there any significant difference from the values recorded at 5-year follow-up; in particular, the 8-week suspension of treatment following the 5-year follow-up had no significant effect (Table 2).

There were no significant differences among the 7 ambulatory records regarding daytime, nighttime, or 24-hour mean BPs or heart rate, and in all cases, daytime, nighttime, and 24-hour mean BPs were within the normal ranges (daytime mean $< 135/85$ mm Hg, night-time mean $< 120/80$ mm Hg).

LV mass index fell by 39% during the first 5 years of treatment, from 148±34 to 90±16 g/m$^2$ ($P < 0.001$), and septal thickness and LV wall thickness also fell significantly during this time, whereas LV fractional fiber shortening and LV ejection fraction were both significantly greater after 5 years of treatment than during the pretreatment placebo phase ($P < 0.01$ and $P < 0.05$, respectively). At no subsequent examination did either LV mass index or any index of LV structure or function exhibit any significant difference from the values recorded at the 5-year follow-up; in particular, the 8-week suspension of treatment following the 5-year follow-up had no significant effect (Table 2).

Serum glucose, cholesterol, creatinine, and Na$^+$ concentrations remained unaltered over the 10 years of the study (during which no patient received antihyperlipemiant treatment). K$^+$ concentration underwent a marginally significant increase from 4.1 to 4.9 mEq/L during the first year ($P = 0.048$) but thereafter returned to lower levels. There were no statistically significant changes in blood cell count and related parameters (hemoglobin, hematocrit, platelet count, and total and specific leukocyte counts).

During the placebo phase, LV mass was significantly correlated with both ΔQT ($r = 0.65$, $P < 0.0001$) and ΔQTc ($r = 0.62$, $P < 0.0001$). Tables 3 and 4 show the evolution of QT and related parameters over the following 9 years. The 5-year enalapril treatment was accompanied by a progressive fall in QT, QTc, and the dispersion measures to significantly lower values ($P < 0.01$), which were maintained during the following 2 years. Like the measures of LV structure and function, QT, QTc, and their dispersions were not significantly affected by the 8-week suspension of treatment that was tried after 5 years and was found to cause a return of BP to pretreatment values, and at no subsequent examination was any significant difference from the values recorded at 5-year follow-up detected.

None of the patients suffered any clinically detectable cardiovascular accident at any time during the 10-year duration of the study.

**Discussion**

In the present study, hypertensive patients who initially exhibited LV hypertrophy and whose BPs were normal within 8 weeks of starting enalapril therapy (20 mg twice daily) were treated for a further 10 years with the same drug. Apparently, normal LV structure and systolic function and improved myocardial electrophysiological homogeneity (as reflected by QT dispersion) were achieved by 5 years of treatment at the initial dosage (40 mg/d). Progressive reduc-

**TABLE 1. Body Weight, BP, and Heart Rate During 10 Years of Enalapril Treatment**

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Systolic BP, mm Hg</th>
<th>Diastolic BP, mm Hg</th>
<th>Heart Rate, bpm</th>
<th>Body Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>156±14</td>
<td>105±6</td>
<td>72±5</td>
<td>78±10</td>
</tr>
<tr>
<td>8 wk (57±5 d)</td>
<td>134±12*</td>
<td>84±5*</td>
<td>70±5</td>
<td>77±10</td>
</tr>
<tr>
<td>1 y (11±1 mo)</td>
<td>129±14*</td>
<td>82±6*</td>
<td>73±5</td>
<td>79±9</td>
</tr>
<tr>
<td>3 y (37±1 mo)</td>
<td>127±13*</td>
<td>84±5*</td>
<td>74±5</td>
<td>81±8</td>
</tr>
<tr>
<td>5 y (59±1 mo)</td>
<td>128±11*</td>
<td>84±5*</td>
<td>72±6</td>
<td>83±8</td>
</tr>
<tr>
<td>8 wk without treatment (56±3 d)</td>
<td>150±16</td>
<td>101±10</td>
<td>74±4</td>
<td>84±8</td>
</tr>
<tr>
<td>8 wk with treatment (96±4 d)</td>
<td>133±13*</td>
<td>86±6*</td>
<td>72±6</td>
<td>84±8</td>
</tr>
<tr>
<td>6 y (74±1 mo)</td>
<td>130±11*</td>
<td>83±5*</td>
<td>71±6</td>
<td>82±9</td>
</tr>
<tr>
<td>7 y (87±1 mo)</td>
<td>130±11*</td>
<td>84±5*</td>
<td>74±5</td>
<td>83±9</td>
</tr>
<tr>
<td>7 y+3 mo (15 mg/12 h)</td>
<td>132±12*</td>
<td>85±6*</td>
<td>72±6</td>
<td>84±8</td>
</tr>
<tr>
<td>7 y+6 mo (10 mg/12 h)</td>
<td>133±12*</td>
<td>85±5*</td>
<td>73±6</td>
<td>83±9</td>
</tr>
<tr>
<td>7 y+9 mo (5 mg/12 h)</td>
<td>136±14*</td>
<td>87±7*</td>
<td>73±6</td>
<td>83±9</td>
</tr>
<tr>
<td>9 y (112±2 mo) (5 mg/24 h)</td>
<td>134±13*</td>
<td>86±5*</td>
<td>74±5</td>
<td>84±9</td>
</tr>
<tr>
<td>10 y (123±2 mo) (5 mg/24 h)</td>
<td>133±12*</td>
<td>85±6*</td>
<td>71±6</td>
<td>83±8</td>
</tr>
</tbody>
</table>

Values are mean±SD.

a whole, and no patient had an in-clinic systolic BP $> 140$ mm Hg or an in-clinic diastolic BP $> 90$ mm Hg.
medication from well-controlled hypertensive patients has been
of life, the total or partial withdrawal of antihypertensive
dosage to be effected without detriment to BP control and
5-mg/d level. After 7 years of treatment, these patients were
Follow-Up LV Mass, g LV Mass Index, g/m² Septal Thickness, mm LV Wall Thickness, mm Diastolic LV Diameter, mm LV Fractional Fiber Shortening, % LV Ejection Fraction, %
Placebo 271±40 148±34 12.8±1.3 11.5±1.0 48.7±5.1 41.1±4.1 74.6±5.1
8 wk (57±5 d) 259±38 142±29 12.4±1.1 11.2±0.9 48.5±5.2 41.2±4.3 74.8±5.4
1 y (11±1 mo) 230±33* 127±26† 11.7±1.2* 10.6±0.8 48.1±5.3 42.0±5.1 75.1±6.2
3 y (37±1 mo) 193±25‡ 106±18‡ 10.5±1.1‡ 9.3±0.7‡ 48.2±5.1 43.6±5.8* 76.4±5.2
5 y (59±1 mo) 166±23‡ 90±16‡ 9.3±0.8‡ 8.1±0.5‡ 48.0±4.9 45.9±6.3‡ 77.6±5.0*
8 wk without treatment (56±3 d) 174±28‡ 95±20‡ 9.5±0.9‡ 8.2±0.6‡ 49.6±5.2 45.7±6.9‡ 77.5±5.9*
8 wk with treatment (96±4 d) 167±29‡ 92±19‡ 9.3±0.9‡ 8.2±0.6‡ 48.5±5.0 43.8±6.8* 76.9±5.5*
6 y (74±1 mo) 160±30‡ 90±18‡ 9.2±0.9‡ 8.1±0.5‡ 48.2±5.6 44.2±7.0* 77.2±5.1*
7 y (87±1 mo) 164±28‡ 91±18‡ 9.3±0.9‡ 8.2±0.7‡ 48.3±5.5 44.6±6.8* 77.6±5.2*
7 y+3 mo (15 mg/12 h) 165±30‡ 92±19‡ 9.3±1.1‡ 8.1±0.7‡ 48.2±5.3 45.1±7.1* 76.8±5.5*
7 y+6 mo (10 mg/12 h) 161±25‡ 91±19‡ 9.2±1.2‡ 8.1±0.7‡ 48.1±5.7 45.8±7.1* 77.4±5.6*
7 y+9 mo (5 mg/12 h) 168±27‡ 93±20‡ 9.3±1.2‡ 8.2±0.8‡ 48.7±6.0 45.6±7.4* 76.4±5.9*
9 y (112±2 mo) (5 mg/24 h) 165±26‡ 92±19† 9.3±1.2‡ 8.2±0.7‡ 48.4±5.5 45.7±7.3* 77.0±5.6*
10 y (123±2 mo) (5 mg/24 h) 166±27‡ 91±19† 9.2±1.2‡ 8.1±0.7‡ 48.3±5.8 45.6±7.2* 77.2±5.7*

Values are mean±SD.
*P<0.05, †P<0.01, and ‡P<0.001 vs the pretreatment placebo period.

of the dosage from 40 to 5 mg daily during the eighth year had no significant effect on BP, QT dispersion, or the indices of LV structure and function, which all likewise remained constant during a further 2-year period at the 5-mg/d level. After 7 years of treatment, these patients were thus in a condition allowing a gradual 8-fold reduction in dosage to be effected without detriment to BP control and without inversion of the improvements in cardiac structure and function that had been achieved. Although the group of patients is small, it is worth noting that none of them has exhibited any signs of cardiovascular accident at any time during the 10 years since the start of the study.

Given its implications for the health budget and patient quality of life, the total or partial withdrawal of antihypertensive medication from well-controlled hypertensive patients has been the subject of surprisingly little research, especially in recent years. In 1981, Finnerty9 reported that reduction of the number of drugs prescribed to a group of 51 hypertensive patients in whom normal BPs had been achieved and maintained with various combinations of antihypertensive drugs was followed by improved observance of the therapeutic regimen and a decrease in adverse side effects without detriment to BP control during at least the following 2.5 years, with the consequent improvement of the cost/benefit ratio. In 1984, the US Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure merely noted that gradual reduction of drug dosages might be attempted, under close surveillance, for patients whose BPs had been controlled for 6 to 12 months.10 In the 1985 Dietary Intervention Study in Hypertension,11 remission of hypertension varied between 35% and 60% among 496 hyper-

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>RR, ms</th>
<th>QTRmax, ms</th>
<th>QTRmin, ms</th>
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<td>423±38</td>
<td>362±37</td>
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<tr>
<td>8 wk (57±5 d)</td>
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<td>360±35</td>
<td>447±36</td>
<td>389±25</td>
</tr>
<tr>
<td>1 y (11±1 mo)</td>
<td>822±63</td>
<td>395±30</td>
<td>350±31</td>
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<tr>
<td>3 y (37±1 mo)</td>
<td>811±60</td>
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<td>338±29</td>
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</table>

Values are mean±SD.
*P<0.05 and †P<0.01 vs the pretreatment placebo period.
tensive patients followed up for 13 months after being put on weight-reducing low-sodium diets accompanied by progressive reduction of antihypertensive medication. In 1987, the Framingham study reported that although a small percentage of well-controlled hypertensive patients remained normotensive for at least 4 years after withdrawal of antihypertensive medication, almost all suffered a return to hypertensive BPs. More recently, a short study in which patients were treated for 4 weeks with either trandolapril (2 mg/d) or perindopril (4 mg/d) found that when treatment was interrupted, reversion to pretreatment BPs was least among those who had achieved best BP control during treatment and that BP during treatment was a predictor of posttreatment BP control. In none of these studies was any criterion other than the degree and/or duration of BP control used to determine the time at which medication was withdrawn.

In this, the longest published study of patients treated with angiotensin-converting enzyme (ACE) inhibitors, we withdrew medication twice from patients in whom several years of treatment had achieved not only control of BP but also the regression of structural and functional cardiac anomalies. The results of the first 5 years of the study show the time course of the regression of hypertensive LV hypertrophy in enalapril-treated patients. Withdrawal of medication was first attempted when this process appeared to have terminated, ie, when both parts of the vicious circle constituted by hypertensive disease appeared to be under control (high BP on the one hand and cardiovascular alterations on the other). However, this first attempt was unsuccessful: sudden total withdrawal caused BP to rise to pretreatment levels within 8 weeks in all but 6 patients, and enalapril treatment was accordingly reintroduced. In keeping with the characterization by Schmieder et al of patients likely to remain normotensive after withdrawal of medication, the 6 patients who remained normotensive during the 8-week trial suspension weighed 2.0 to 8.5 kg less than at the start of the study, whereas most of the other patients had gained weight, but these 2 groups did not differ significantly regarding percentage fall in LV mass index during treatment.

When withdrawal was attempted for a second time, after a further 2-year consolidation of the improvement in cardiac structure and function, it was affected by reducing the dosage by 10 mg/d every 3 months. Furthermore, withdrawal was incomplete, with a dosage of 5 mg/d being maintained. This residual dosage (just one eighth of the dosage required by all but 2 of the patients at the start of the study) has sufficed to maintain normal BP and cardiac parameters for the last 2 years; as far as we know, this is the first study in which such a marked reduction in dosage has been effected with such success, at least regarding patients being treated with ACE inhibitors.

Even though the withdrawal of antihypertensive medication has generally met with failure, mechanisms have been proposed to explain the persistence of subhypertensive BPs in those cases in which it has been successful. One possibility mooted many years ago is that the drug-induced maintenance of normal BP for any considerable period of time may cause the carotid barostat mechanism to be reset to lower levels than those permitted during hypertension. Although this may well be so, it seems unlikely that lasting remission of hypertension can occur without prior remission of the structural and functional vascular alterations with which hypertension is associated, especially those affecting resistance arteries. The regression of these alterations after treatment with ACE inhibitors and some other antihypertensive drugs has been observed in several studies. For example, it has recently been shown that in hypertensive patients enalapril improves coronary flow reserve (whereas calcium channel blockers may not). Similarly, Schiffrin et al observed an improvement in the media/lumen ratio of resistance arteries in patients who took the ACE inhibitor cilazapril for 1 year but not in those who took the β-blocker atenolol (although no such improvement was observed by Thurmann et al among patients taking either the ACE inhibitor spirapril or the calcium channel blocker isradipine, both of which reduced LV mass but not the media/lumen ratio of resistance arteries). We did not monitor vascular alterations in the present study.

### Table 4. QT and QTc Dispersion During 10 Years of Enalapril Treatment

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>ΔQT, ms</th>
<th>%ΔQT</th>
<th>ΔQTc</th>
<th>%ΔQTc</th>
<th>ΔQTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>61±21</td>
<td>17±6</td>
<td>67±27</td>
<td>17±7</td>
<td>7.3±2.2</td>
</tr>
<tr>
<td>8 wk (57±5 d)</td>
<td>52±18</td>
<td>14±5</td>
<td>59±24</td>
<td>15±6</td>
<td>6.1±2.0</td>
</tr>
<tr>
<td>1 y (11±1 mo)</td>
<td>46±15*</td>
<td>13±5*</td>
<td>48±20</td>
<td>14±6</td>
<td>5.6±1.8</td>
</tr>
<tr>
<td>3 y (37±3 mo)</td>
<td>41±15*</td>
<td>13±4*</td>
<td>46±18*</td>
<td>13±5*</td>
<td>5.1±1.7*</td>
</tr>
<tr>
<td>5 y (59±1 mo)</td>
<td>40±14†</td>
<td>12±4†</td>
<td>43±17†</td>
<td>12±4†</td>
<td>4.8±1.7†</td>
</tr>
<tr>
<td>8 wk without treatment (56±3 d)</td>
<td>40±14†</td>
<td>12±4†</td>
<td>44±17†</td>
<td>12±4†</td>
<td>4.7±1.6†</td>
</tr>
<tr>
<td>8 wk with treatment (96±4 d)</td>
<td>39±14†</td>
<td>12±4†</td>
<td>44±17†</td>
<td>12±4†</td>
<td>4.8±1.7†</td>
</tr>
<tr>
<td>6 y (74±1 mo)</td>
<td>38±14†</td>
<td>11±4†</td>
<td>42±16†</td>
<td>11±4†</td>
<td>4.7±1.6†</td>
</tr>
<tr>
<td>7 y (87±1 mo)</td>
<td>37±13†</td>
<td>11±4†</td>
<td>41±16†</td>
<td>11±4†</td>
<td>4.6±1.7†</td>
</tr>
<tr>
<td>7 y+3 mo (15 mg/12 h)</td>
<td>37±13†</td>
<td>11±4†</td>
<td>41±16†</td>
<td>11±4†</td>
<td>4.7±1.6†</td>
</tr>
<tr>
<td>7 y+6 mo (10 mg/12 h)</td>
<td>36±13†</td>
<td>11±4†</td>
<td>42±16†</td>
<td>11±4†</td>
<td>4.7±1.6†</td>
</tr>
<tr>
<td>7 y+9 mo (5 mg/12 h)</td>
<td>36±13†</td>
<td>11±4†</td>
<td>42±16†</td>
<td>11±4†</td>
<td>4.7±1.6†</td>
</tr>
<tr>
<td>9 y (112±2 mo) (5 mg/24 h)</td>
<td>36±13†</td>
<td>11±4†</td>
<td>42±16†</td>
<td>11±4†</td>
<td>4.6±1.6†</td>
</tr>
<tr>
<td>10 y (123±2 mo) (5 mg/24 h)</td>
<td>37±14†</td>
<td>11±4†</td>
<td>42±16†</td>
<td>11±4†</td>
<td>4.7±1.7†</td>
</tr>
</tbody>
</table>

Values are mean±SD. *P<0.05 and †P<0.01 vs the pretreatment placebo period.
but in view of the above findings by others, it seems likely that the improvement in cardiac mass, mechanical efficiency, and electrophysiological homogeneity that occurred in our patients (and that is in keeping with, for example, with the finding that ACE inhibitors reverse myocardial fibrosis in rats\(^2\)\(^2\)) will have been accompanied by parallel improvements in vascular structure and performance.

Although ACE inhibitors take their name from the inhibition of the enzyme converting angiotensin I to angiotensin II, they also inhibit the degradation of kinins, which have vasodilatory and antiproliferative activities.\(^21\),\(^22\) Because continuous inhibition of ACE eventually induces the activation of alternative metabolic pathways for synthesis of angiotensin II, there must come a time, during prolonged ACE inhibitor treatment, at which only the kinin-protecting activity of the ACE inhibitor is effective. The ability of a daily dose of just 5 mg of enalapril to maintain the improved BP and cardiac status of the patients in the present study may therefore have been due to its having been sufficient to afford kinin protection, which requires much smaller doses of ACE inhibitors than does their ACE-inhibiting activity.\(^23\),\(^24\)

The above findings and considerations raise a number of questions: Is even the low dosage that these patients are now receiving necessary? If not, was the failure of the attempted total withdrawal of medication after 5 years due to withdrawal having been abrupt rather than gradual (in which case, gradual total withdrawal would have been successful at that time), or was it due to vascular structure and/or function being defective in spite of the regression of cardiac abnormalities having been completed (in which case total withdrawal would probably not have been successful even if gradual)? If the current maintenance dosage of 5 mg/d is necessary, would a reduction of the dosage to this level have been successful after 5 years of treatment, ie, as soon as cardiac abnormalities had disappeared? Indeed, if the current 5 mg/d is necessary and corresponds to the maintenance of kinin protection, would it have been possible to maintain the patients on 5 mg/d as soon as a rise in angiotensin II level showed that the ACE-inhibiting activity of the drug was being bypassed? More fundamentally, if the current 5 mg/d or some similarly low dosage is necessary, does this mean that it is a genetically or environmentally determined deficiency in kinin protection (or a similarly determined excess of kinin destruction) that predisposes this kind of patient to hypertensive disease? It remains for future research to answer these questions.

In conclusion, 3 years after 5 years of treatment with 20 mg enalapril twice daily had achieved regression of the initial LV hypertrophy of a group of 24 patients with essential hypertension; gradual reduction of the dosage to 5 mg daily (just one eighth of the original dosage) caused no worsening of BP, LV structure, LV systolic function, or the electrophysiological homogeneity of the myocardium, nor did maintenance of this low dosage for a further 2 years. These results, and certain others published in the literature, suggest that in the case of hypertensive patients whose BPs are well controlled by high ACE inhibitor dosages and who exhibit no signs of target organ damage, dosage should be adjusted periodically under appropriate surveillance, with the dosage required for long-term control probably being significantly lower than the dosage required initially. This practice would considerably reduce the economic costs associated with one of the most common of diseases. Evaluation of the possibility of lowering dosages, which in recent years has been the subject of surprisingly little research, should be investigated in depth.

References

Step-Down of Enalapril Treatment for Arterial Hypertension
José Ramón González-Juanatey, Antonio Pose Reino, José María García-Acuña, Carlos González-Juanatey, Luis Valdes and José Cabezas-Cerrato

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