Low-Dose Captopril for the Treatment of Mild to Moderate Hypertension

VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP
ON ANTIHYPERTENSIVE AGENTS

SUMMARY **Short-term results of this double-blind control trial (previously reported) in patients with initial diastolic blood pressures (DBP) in the range of 92–109 mm Hg indicated that doses of 12.5 or 25 mg captopril (C) three times daily (t.i.d.) and 37.5 mg twice daily (b.i.d.) had similar antihypertensive effectiveness as 50 mg t.i.d. After 7 weeks of C, the addition of hydrochlorothiazide (H) to two-thirds of the patients enhanced the antihypertensive response. This report presents the results of unchanged and uninterrupted treatment for 9.5 months in 46 patients taking C alone, and for 7.8 months in 94 patients taking C plus H or H alone. With C alone, reductions in DBP averaged 8.3, 11.0, 15.1, and 17.5 mm Hg with the 12.5, 25, 37.5, and 50 mg doses respectively. The response to the 12.5 mg dose only was significantly less than the 50 mg dose. With H alone, the reduction in DBP averaged 10.6 mm Hg and with C plus H reductions averaged 15.6, 18.1, 16.8, and 18.7 mm Hg with the 12.5, 25, 37.5, and 50 mg doses of C, respectively. Reductions in DBP with C plus H regimens were significantly different from H alone. There was no waning of effectiveness from short to long term except for the 12.5 mg dose of C alone. During the long-term phase, two patients developed rash and one lost the sense of taste. Neutropenia in one patient probably was not drug-related. There were no terminations for elevated DBP > 104 mm Hg on two successive visits. Thus, C was well tolerated and remained effective over the long term. (Hypertension 5 (supp III): III-139–III-144, 1983)**

KEY WORDS • hypertension • captopril • treatment • blood pressure • dosage • toxicity

THE Veterans Administration Cooperative Study Group has presented a preliminary report on the short-term efficacy of captopril (C) with and without a diuretic.[1] A total of 475 patients with entry diastolic blood pressure (DBP) between 92 and 109 mm Hg were randomly assigned, double-blind, to one of five regimens which included placebo or four dose levels of C alone ranging from 12.5 to 50 mg three times daily (t.i.d.). The results of the short-term trial may be summarized as follows: the average reduction of DBP for all patients receiving C alone was 12.2 mm Hg, which was significantly greater than the 2.0 mm Hg reduction obtained in the placebo group. The 12.5, 25, and 37.5 mg doses of C were as effective in reducing DBP over a 7-week period as the 50 mg dose. There was no significant difference between any of the doses of C with respect to reduction of either systolic blood pressure (SBP) or diastolic blood pressure (DBP) in the sitting or standing positions.

After 7 weeks, hydrochlorothiazide (H) 25 mg twice daily (b.i.d.) was added double-blind to all of the placebo group and to two-thirds of the patients receiving C. The remaining third were randomized to C plus H placebo, that is, they continued on C alone. Each patient remained on the originally assigned dose of C. In the patients receiving C alone, the antihypertensive response after 14 weeks was moderately but not significantly less than at 7 weeks for the two lowest doses of C. For the two highest regimens, the effect on DBP was the same or slightly greater. The patients who received C with H exhibited greater reductions of blood pressure than with C alone, and there were no significant differences in the antihypertensive responses between the various doses of C plus H. During this short-term treatment period, only 4% of the patients were terminated from the study because of adverse effects, none of which were life threatening.

Because of a possible waning of the antihypertensive response to the 12.5 and 25 mg doses of C between the 7th and 14th week, an extension of the study for an additional 6 months or more seemed indicated. Also, the extension would permit additional observation for the possible development of toxic reactions.

From the Cooperative Studies Program of the Veterans Administration Medical Research Service, Washington, D.C.

Supported in part by a grant from E. R. Squibb & Sons, Inc.

Address for reprints: Edward D. Freis, M.D., Veterans Administration Medical Center, 50 Irving Street, N.W., Washington, D.C. 20422.

Methods

The present study is essentially a continuation of the short-term trial. The design of the short-term trial will be described in more detail in another communication[2] and will only be briefly summarized here.

Following withdrawal of preexisting antihypertensive drugs for 2 to 4 weeks, men aged 20–69 years were given placebo (t.i.d.) for a maximum of 5 weeks. Placebo counts were carried out and noncompliant patients were excluded. To qualify for randomization, DBP had to be in the range of 92–109 mm Hg and the patients had to be free of any exclusion factors. The acceptable patients were then randomized, double-blinded, to one of five regimens as follows: C 12.5 mg t.i.d., C 25 mg t.i.d., C 37.5 mg b.i.d., C 50 mg t.i.d., and placebo. Seven weeks following randomization, H 25 mg twice daily was added to two-thirds of the C-treated patients while one-third were given H-placebo. Active H was added to all of the placebo-treated patients. These regimens were continued for 7 additional weeks. This completed the short-term phase of the trial.

Because of a protracted recruitment period of 13 months, some patients were completing the short-term trial before others were entering the study. Therefore, although the trial was only of 14 weeks' duration, the clinics were operational for 16.5 months. Approximately midway in the study it was decided to evaluate the patients completing the short-term phase on their present regimens until the termination date of the trial. Late entries, therefore, did not complete long periods of follow-up. Because of limited numbers of patients completing the longest follow-up treatment periods, the 6-month interval was selected for evaluation of the long-term results. Due to the additional 14 weeks for patients on C alone and 7 weeks for patients on C plus H during the short-term phase, the actual periods of continuous treatment were 7.8 months (6 months plus 7 weeks) with combination therapy, and 9.5 months (6 months plus 14 weeks) with C alone. Only patients whose treatment was uninterrupted from the time of randomization were included. Routine laboratory and physical examinations were carried out at 3-month intervals during the long-term period.

Results

A total of 139 patients on C with H regimens entered the long-term treatment phase. Of this number, 94 patients (68%) completed 7.8 months of continuous treatment. In the C alone group, 62 entered, of which 46 (74%) patients completed a total of 9.5 months of continuous treatment.

There were no significant differences between any of the C plus H regimens or the C alone patients with respect to race or mean age (table 1). In the C plus H group, the racial distribution was nearly equal, with 45 whites and 48 blacks; in the captopril alone group, whites moderately outnumbered blacks. The average age of the patients among the various regimens were similar, varying between 54 and 58 years.

TABLE 1. *Race and Age Characteristics Among the Different Long-Term Treatment Groups*

	Captopril (C) regimens with hydrochlorothiazide (H)				
Group	H	C 12.5 + H	C 25 + H	C 37.5 b.i.d. + H	C 50 + H
White	8.0	4.0	9.0	10.0	14.0
Black	13.0	10.0	7.0	9.0	9.0
Other	0.0	1.0	0.0	0.0	0.0
Total	21.0	15.0	16.0	19.0	23.0
Age, mean (yrs)	55.2	55.1	57.8	56.4	53.8
	Captopril (C) regimens without hydrochlorothiazide (H)				
		C 12.5	C 25	C 37.5 b.i.d.	C 50
White		3.0	5.0	10.0	9.0
Black		5.0	1.0	7.0	6.0
Total		8.0	6.0	17.0	15.0
Age, mean (yrs)		55.4	57.0	55.6	56.7

Because the long-term treatment patients represented a relatively small proportion of the total number of patients completing the short-term (7-week) treatment phase, their comparability was investigated with respect to DBP both at baseline and after 7 weeks of treatment. Pretreatment DBP at the time of randomization was closely similar. In each treatment group with or without H, the average DBP did not vary more than 2 mm Hg between the long-term patients and the total short-term group. The average reductions of DBP, however, were somewhat greater at 7 weeks for the long-term subsample than for all patients, the difference averaging 3 mm Hg lower among the long-term patients as compared to the total short-term treatment groups.

Changes in Blood Pressure

Captopril Alone

The changes in blood pressure after 9.5 months of continuous treatment are shown in table 2. The average diastolic reductions were related to dosage and ranged between −8.3 mm Hg for the 12.5 mg dose to −16.5 mm Hg for the 50 mg dose. These changes were essentially the same as the short-term (7-week) reductions except for the 12.5 mg regimen where there was a rise of 4.7 mm Hg in average DBP between the short-term and long-term readings. Systolic reductions also were dose-related. Compared to the 7-week values, the average systolic blood pressure rose by 4.8 and 5.0 mm Hg with the 12.5 and 25 mg regimens, respectively. Such lessening of the antihypertensive effect with time was not seen, however, with the 37.5 b.i.d. and 50 mg t.i.d. doses of C.

Because of the relatively small sample sizes, particularly in the two lowest dose groups, it was possible that the variations noted among doses with respect to blood pressure reduction may not have been representative of the true long-term differences. Therefore, additional comparisons were made utilizing the readings taken at three long-term clinic visits at 6.5, 9.5, and

TABLE 2. *Blood Pressure Changes During Long-Term Treatment in Patients taking Captopril Alone*

	Dose of captopril (mg)			
	12.5	25	37.5 b.i.d.	50
No. of patients	8	6	17	15
Mean DBP (mm Hg)				
Randomization	96.3	98.7	96.1	96.0
After 9.5 mos treatment	88.0	87.7	81.1	79.5
Change	−8.3	−11.0	−15.1	−17.5
After 7 wks treatment	83.3	88.0	80.3	80.7
Change, 7 wks to 9.5 mos	+4.7	−0.3	+0.8	−1.2
Percent < 90 mm Hg	50	50	100	93
Mean SBP (mm Hg)				
Randomization	136.5	149.3	145.6	146.8
After 9.5 mos treatment	135.8	137.7	124.7	125.3
Change	−0.8	−11.7	−20.9	−21.5
After 7 wks treatment	131.0	132.7	123.4	128.9
Change 7 wks to 9.5 mos	+4.8	+5.0	+1.3	−3.6

12.5 months following randomization. There were no significant differences at the 0.05 level between any of the regimens at any of the three visits. There was a questionably significant difference between the C 12.5 and C 50 mg regimens at the 0.10 level at all three visits. However, there were no significant differences between the C 25 mg and the C 50 mg doses at any of these visits. Furthermore, the DBP with the C 25 mg dose averaged lower at the 6.5- and 12.5-month visits than at the 9.5-month visit. Thus, the only consistent change from short-term to long-term follow-up was a moderate waning of the antihypertensive effect of the 12.5 mg dose, which was not present with the other doses.

The percentage of patients achieving a reduction of DBP to below 90 mm Hg with the 12.5 mg dose was 60% at 6.5 months, 50% at 9.5 months, and 67% at 12.5 months. With the 25 mg regimen, it was 75%, 50%, and 100% at each of these time intervals. With the two highest doses, the response rate varied between 76% and 100% at each of the three visits.

Captopril plus Hydrochlorothiazide

The reductions in DBP recorded after 7.8 months of continuous treatment with C plus H regimens were greater than with H alone (table 3) or with comparable doses of C alone (table 2). The reductions in DBP were significantly greater with the C 25 + H ($p = .03$) and the C 50 + H ($p = 0.01$) regimens than with H alone. The SBP was also lower with the combined drugs than with the single entities, the differences from the comparable dose of C alone being significant with C 12.5 mg ($p = 0.05$) and C 50 mg ($p = 0.04$) doses. The above changes in DBP and SBP at 7.8 months appeared to be representative as they were essentially the same as those recorded at 4.8 and 10.8 months.

The changes in blood pressure from short-term (7 weeks) treatment to long-term (7.8 months) treatment are also shown in table 3. The average DBP reductions at each of these two points in time are nearly identical except for the C 12.5 + H regimen, which exhibited an insignificant increase of 2.9 mm Hg. SBP reductions also showed no essential change from short-term to long-term readings, including the C 12.5 mg dose.

The percentage of patients attaining the goal DBP of < 90 mm Hg varied between 79% and 94% with the various C plus H regimens and was not dose-related.[1] There also were no significant differences in response between blacks and whites.

Terminations

Terminations during the first 6 months of the long-term treatment phase were classified as medical and administrative (table 4). There was no correlation between either medical or administrative terminations

TABLE 3. *Blood Pressure Changes During Long-Term Treatment in Patients taking Captopril (C) with Hydrochlorothiazide (H)*

	H	C 12.5 + H	C 25 + H	C 37.5 b.i.d. + H	C 50 + H
No. of Patients	21	15	16	19	23
Mean DBP (mm Hg)					
Randomization	96.6	97.2	99.8	98.8	99.5
After 7.8 mos treatment	86.0	81.6	81.6	82.0	80.8
Change	−10.6	−15.6	−18.1	−16.8	−18.7
After 7 wks treatment	81.9	78.7	82.4	82.4	80.3
Change 7 wks to 7.8 mos	+4.1	+2.9	−0.8	−0.4	+0.5
Percent < 90 mm Hg	76	93	94	79	91
Mean SBP (mm Hg)					
Randomization	143.6	150.3	150.0	149.8	150.1
After 7.8 mos treatment	128.6	120.5	121.4	124.7	121.7
Change	−15.0	−29.7	−28.6	−25.1	−28.3
After 7 wks treatment	124.9	122.4	120.1	117.7	124.5
Change 7 wks to 7.8 mos	+3.7	−1.9	+1.3	+7.0	−2.8

and the dosage of captopril. There were seven medical terminations, two in patients taking C alone and five in the patients receiving H regimens. There were two instances of pruritic maculopapular rash. One occurred 9 months after C 50 + H was begun. The rash cleared after the drug was stopped and recurred promptly when reinstituted. The second patient had received C alone 37.5 mg b.i.d. for 9 months prior to the appearance of the rash. Another patient receiving captopril 25 + H developed loss of taste. A black patient receiving 37.5 mg C alone was terminated because of neutropenia. The white blood count was 2.6 × 1000/mm^3 with 38 segmented leucocytes. However, since this patient was an alcoholic and exhibited a low white blood count of 3.6 × 1000/mm^3 prior to randomizations, the relationship to captopril is problematical. The remaining medical terminations were due to unrelated causes such as impotence, weakness, headache, and atrial fibrillation. There were no terminations resulting from elevation of blood pressure, the criterion for which was an elevation of DBP to 105 mm Hg or higher on two successive clinic visits.

There were 16 terminations for administrative reasons, eight among the C alone patients, and eight in the C plus H group. The most frequent causes were failure to return to clinic, tardiness in returning to the clinic so that treatment was interrupted, or the patient's request to terminate.

Laboratory Examinations

The major laboratory change observed during the short-term trial was a statistically significant but clinically unimportant rise in serum potassium with C alone and a slightly lessened reduction with C plus H as compared to H alone. The changes in serum potassium were similar during the long-term treatment period (table 5). C alone resulted in a slight rise in serum potassium levels averaging 0.11 mEq/liter. H alone was associated with a significant reduction averaging 0.54 mEq/liter, which was significantly greater ($p < 0.001$) than the average fall of 0.39 mEq/liter with C plus H.

Serum uric acid concentration rose significantly by an average of 1.40 mg/dl with H alone, which was

TABLE 4. *Terminations During Long-Term Treatment*

	Regimens with hydrochlorothiazide (H)					
Termination	H	C 12.5 + H	C 25 + H	C 37.5 b.i.d. + H	C 50 + H	Total
Medical	1	0	3	0	1	5
Administrative	0	2	3	2	1	8
Total	1	2	6	2	2	13
	Regimens with captopril (C) alone					
		C 12.5	C 25	C 37.5 b.i.d.	C 50	Total
Medical		0	0	2	0	2
Administrative		2	3	2	1	8
Total		2	3	4	1	10

TABLE 5. *Changes in Laboratory Tests During Long-Term Treatment with Captopril (C) and Hydrochlorothiazide (H)*

Laboratory test	C alone	C + H	H alone
Serum potassium (mEq/liter)			
Baseline	4.18 ± 0.06	4.21 ± 0.05	4.23 ± 0.09
Change	0.11 ± 0.06†	−0.39 ± 0.06*‡	−0.54 ± 0.09†
Serum creatinine (mg/dl)			
Baseline	1.14 ± 0.03	1.18 ± 0.03	1.17 ± 0.03
Change	−0.06 ± 0.03	−0.02 ± 0.03	0.09 ± 0.11
Uric acid (mg/dl)			
Baseline	6.27 ± 0.18	6.69 ± 0.13	6.53 ± 0.25
Change	0.38 ± 0.18*‡	1.17 ± 0.14*‡	1.40 ± 0.32†
Cholesterol (mg/dl)			
Baseline	228.9 ± 6.6	223.0 ± 4.6	210.7 ± 8.5
Change	2.2 ± 4.4	−3.8 ± 3.5	−0.7 ± 8.6
Urine protein (mg/24 hrs)			
Baseline	134.9 ± 14.4	127.5 ± 12.3	123.5 ± 24.0
Change	−2.2 ± 20.0	−15.5 ± 13.1	25.0 ± 38.8

*Significant change from baseline, $p < 0.05$.
†Significant change from baseline, $p < 0.001$.
‡Significant difference in the extent of change between groups, $p < 0.001$.

significantly greater than the average increase of 1.17 mg/dl observed with C plus H. Unlike the short-term findings, serum cholesterol did not rise with H alone or with the combination of C plus H. There were no significant changes in serum creatinine or 24-hour urine protein excretion. Other routine biochemical and hematological tests revealed no significant changes.

Discussion

The major objective of the present study was to determine whether C either alone or combined with H would maintain its antihypertensive effectiveness unabated or whether there would be some waning of its activity with the passage of time. The results indicated that the antihypertensive effect is maintained over the long-term with the exception of the smallest (12.5 mg t.i.d.) dose of C alone. This was not the case, however, with C plus H where all doses including the 12.5 mg maintained unabated antihypertensive activity as compared to short-term results. That this was not due to the action of H alone is indicated by the fact that all of the combined regimens lowered DBP to a significantly greater degree than did H alone. Despite the moderate rise of blood pressure from short-term to long-term with the 12.5 mg dose of C alone, it should be noted that 50% of the patients maintained control of DBP after 9.5 months of continuous treatment.

The long-term results are more subject to bias than was the case in the short-term study where the great majority of the randomized patients were followed to completion of the short-term trial. The patients in the long-term study, on the other hand, represent a residual of short-term patients who chose to enter the long-term trial. Therefore, they may represent the patients who responded the best in terms of DBP reduction. In this regard, during the short-term treatment period, there was a 3 mm Hg greater reduction in DBP among the long-term patients than in the short-term treatment group as a whole. Therefore, they may represent to some extent at least a selected group of responders. Within these limitations, however, it is apparent that drug resistance did not develop over the long-term.

A further limitation of the long-term trial was that when subdivision was made into nine different regimens, four with C alone and five with H-containing regimens, some of the sample sizes became quite small, particularly with the smallest doses of C alone. This deficiency was partly compensated for by evaluating the results not only 6 months into the long-term phase but also at 3 and 9 months of long-term follow-up. Since the blood pressure changes at these two other time periods confirmed the results observed at the 6-month interval, it seems likely that the results probably are valid in spite of the small size of some of the samples.

It has been suggested that the antihypertensive effect of a combination of C with a diuretic should have a synergistic effect.[2] Loss of sodium and water with diuretics stimulates the production of angiotensin and aldosterone, which in turn should limit the sodium loss. When this defense reaction is inhibited by C, the diuretic-induced loss of sodium and water might be greater than normal, leading to a considerable fall in blood pressure. In the present trial, however, as well as in other smaller studies,[3,4] the reduction in blood pressure did not exceed the sum of the antihypertensive effects of C and H given separately.

There were relatively few terminations due to adverse reactions. They occurred in only 3.5% of the patients during the 6-month period of long-term follow-up. Furthermore, only three reactions, none of which was severe, appeared to be drug-related. It is doubtful that the single case of neutropenia was related to C. The patient was a heavy consumer of alcohol, which could in itself produce neutropenia, and had already exhibited a reduced white blood count at the time of randomization. The absence of the more serious reactions associated with C such as pancytopenia[5] and glomerulopathy[6] may be due to the exclusion of patients with severe hypertension, renal disease, or immune system disorders, and also to the fact that the doses of C were relatively low.[6]

Captopril given alone has been associated with significant elevations in serum potassium concentrations.[7] These elevations occurred, however, mostly in patients with renal impairment or with high doses of C. In the present trial, there was only a small rise from baseline in serum potassium with C alone. There was, however, a significantly smaller reduction in serum potassium levels with the combination of C with H than with H alone. The combination did not block the reduction completely, but rather reduced its extent. A similar blunting of the H-induced hypokalemia response has been reported by Weinberger,[8] who also noted a diminution in the degree of elevation in serum uric acid and cholesterol associated with administration of thiazides. A similar slight but significant effect on serum uric acid was noted in the present long-term trial which was not found in the short-term phase. In the short-term phase of the present study, a moderating effect of C on the H-induced increase in serum cholesterol was confirmed. However, in the long-term phase, the H group did not exhibit a rise in serum cholesterol, which may account for the failure to observe a significant difference between the diuretic alone and the combination. An increase in serum cholesterol with administration of thiazides is not a constant finding[9,10] and, if present, may disappear with long-term treatment.[11]

Captopril represents a new approach to the treatment of hypertension in that its principal action is to inhibit the renin-angiotensin system. This novel drug has now been added to the three existing categories of antihypertensive agents, namely, diuretics, sympatholytics, and vasodilators. While C resembles the vasodilators in its effects on the cardiovascular system, there are some important differences. There is no significant reflex tachycardia with C and no tendency toward retention of salt and water.

Captopril may be used as a Step 1, Step 2, or Step 3 drug. Because of the great effectiveness of a diuretic plus C in doses as low as 12.5 mg, it would appear to

be most useful as a Step 2 agent. The effectiveness of small doses of C with H would seem to be a most important consideration in view of the observation that toxicity is associated more with high doses of the drug.[6, 12] Possibly other converting-enzyme blockers currently under study will provide additional therapeutic benefits. However, with accumulating experience as to dosage and selection of patients, it is apparent that C itself represents a major therapeutic advance.

Acknowledgments

Participants

Co-Chairmen: Edward D. Freis, M.D. (Washington, D.C.); Barry J. Materson, M.D. (Miami, Florida).

Participating Investigators: William W. Neal, M.D. (Dallas, Texas); Richard E. Borreson, M.D. (Houston, Texas); James T. Taguchi, M.D. (Dayton, Ohio); Bangshi Mukherji, M.D. (Topeka, Kansas); H. Mitchell Perry, M.D. (St. Louis, Missouri); K. C. Mezey, M.D. (East Orange, New Jersey); Walter Flamenbaum, M.D. and Robert Hamburger, M.D. (Boston, Massachusetts).

Nurses or Physician Assistants: Betsy Munze, P.A. and Pat Melly, P.A. (Dallas, Texas); Ruth Collins, R.N. (Houston, Texas); Margaret Curry, R.N. (Dayton, Ohio); Pat Ulrich, P.A. (Topeka, Kansas); Robert Berry, R.N. and Margery Schiffman, R.N. (St. Louis, Missouri); Mary Fitzgerald, R.N. (East Orange, New Jersey); Anne Faiella, R.N. (Boston, Massachusetts); Barbara Gregory, R.N. (Washington, D.C.).

Biostatistical Center: Sharon Anderson, Ph.D.; Thomas Tosch, Ph.D.; Jane Foregger (Hines, Illinois).

Central Laboratory: Walter Flamenbaum, M.D. and Robert Hamburger, M.D. (Boston, Massachusetts).

Central Research Pharmacist: Larry Young, R.Ph. (Albuquerque, New Mexico).

Executive Committee: Barry J. Materson, M.D.; Edward D. Freis, M.D.; Sharon Anderson, Ph.D.; Thomas Tosch, Ph.D.; H. Mitchell Perry, M.D.; Richard E. Borreson, M.D.; Walter Flamenbaum, M.D.; Robert Hamburger, M.D.; Larry Young, R.Ph. (Ad Hoc).

Operations Committee: Walter M. Kirkendall, M.D., Chairman (Houston, Texas); W. McFate Smith, M.D. (San Francisco, California); C. Mort Hawkins, Sc.D. (Houston, Texas).

Consultants: John Alexander, M.D.; Jeffrey Stritar, M.D.; Joseph Meyer, Ph.D. (Squibb Institute for Medical Research).

Hines Cooperative Studies Program Coordinating Center Human Rights Committee: Jennie McKoy, B.S.N., M.S.; Patrick J. Moran; Mary Davidson, Ph.D.; Kenneth C. Elmer; Rev. Douglas D. Hall.

Cooperative Studies Program Central Administration: James A. Hagans, M.D., Ph.D. (Miami, Florida); Ping Huang, Ph.D. (Washington, D.C.); William G. Henderson, Ph.D. (Hines, Illinois); Mike Sather, R.Ph., M.S. (Albuquerque, New Mexico).

This paper was written by Dr. Freis and prepared by Linda Archie.

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Discussion

DISCUSSANTS: G. MACGREGOR
E. FREIS
J. LEDINGHAM

MACGREGOR: We have been presented three very large-scale American studies on captopril, which are obviously important in determining long-term treatment safety. I don't want to be aggressive, but do we need this size of study in order to show the correct dose of the drug and the correct amount of diuretic? This goes back to what Dr. Brunner was showing earlier in a few normotensives. Surely the pharmacology of the drug can be shown in many fewer subjects using careful, randomized crossover studies.

FREIS: I don't agree. It depends on the degree of precision — if this is to be high, you need a more representative sample than merely 20 or 30, or even 50, especially if you're subdividing them into smaller groups.

LEDINGHAM: You also need a sizable placebo group to demonstrate the placebo effects.

FREIS: I agree.