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REVIEW

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safety rev*

DEC 24 1985

DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
MEDICAL OFFICER'S REVIEW

NDA #: 18-998 Safety Up-date

Reviewer: R. E. Keenan, M.D.

M.O. Review #: A

SPONSOR: Merck Sharp & Dohme Research Laboratories

DRUG: enalapril maleate (VASOTEC)

DATE OF CORRESPONDENCE: April 9, 1985; May 2, 1985; August 6, 1985;  
August 23, 1985; November 8, 1985; December 12, 1985

DATE RECEIVED BY REVIEWER: All of Above

DATE REVIEW COMPLETED: December 19, 1985

Resume:

The initial "Safety Update" for enalapril was submitted February 14, 1985 and was reviewed in a letter to the sponsor from Dr. Temple dated November 1, 1985. Dr. Temple's letter also addressed some, but not all, of the issues raised in several of the subsequent "updates" which were submitted on the dates noted above.

This review will deal primarily with the issues of concern contained in the "safety update" information provided by the sponsor since February 12, 1985. For the sake of completeness, however, an overall Table of all serious adverse events submitted to the Agency since the original NDA submission of September 15, 1983 will be included.

All of the "safety updates" received by the Agency contain only those adverse reactions considered "serious" by the sponsor. This includes a complete listing of all deaths but does not (obviously) include adverse reactions judged not to be serious. The absence of "non-serious" adverse reactions is likely of no consequence. However, 2 points should be made prior to departing from this issue:

1. Except for those patients judged to have "serious" adverse reactions, the sponsor has not provided a listing nor reports of all patients discontinued from enalapril for whatever reasons. This omission occurred in spite of a discontinuation rate of at least 6.0% and in spite of a request (albeit informal) for such a listing.

2. Upper respiratory infections and common cold ADR's occurred with sufficient frequency (0.5 to 1.0%) to be included in the proposed labelling. That some of these may or may not have been due to a (relative ?) leukopenia

cannot be determined one-way or the other since reports of these cases were not submitted in any of the "up-dates".

In a great many of the submitted cases of "serious" adverse drug reactions, a relationship between the drug and the reported event appeared tenuous at best and are therefore considered unrelated for the purposes of this review. Of those where a relationship appeared possible or probable (either because of an obvious connection or because of the sheer numbers of times they were reported), the following emerge as being of sufficient importance to require special attention:

1. Hematological disturbances
  - leucopenia
  - agranulocytosis
  - thrombocytopenia
  - aplastic anemia
  - pancytopenia
  - sepsis ? death ?
2. Severe hypotension
  - "first dose"
  - "increased dose"
  - with dehydration
  - with diuretic therapy
  - renal artery stenosis
3. Acute renal failure/oliguria
  - pre-existing renal disease
  - "first dose" phenomenon/death ?
  - associated with hypotension/shock
  - decrease in renal function
4. Angioneurotic edema
  - laryngeal edema/death
  - inconsequential edema of the face and/or mucous membranes of the mouth

The sources from which the serious adverse reactions were derived include:

1. Domestic Controlled Clinical Studies
2. Domestic Compassionate Use Studies
3. International Controlled Clinical Studies
4. International Compassionate Use Studies
5. International Clinical Development Study Program
6. International Local Studies
7. International Marketing
8. International Post-Marketing Surveillance Studies

For the purpose of this review ADR's will be lumped into the four categories noted above rather than by the source (i.e. all angioneurotic edema from all sources will be considered together).

1. Hematological disturbances: In the "Hematologic Update" provided by the sponsor on November 8, 1985, 37 cases were listed and included:

Agranulocytosis	1 case
Anemia	8 cases
Bone marrow depression	6 cases
Leukopenia	12 cases
Neutropenia	2 cases
Pancytopenia	1 case
Thrombocytopenia	7 case
TOTAL	<u>37 cases</u>

All of the cases noted were reviewed in depth with Dr. Bosco (HFN-773) and she has prepared a "worst case" report, now a matter of record. A review of Dr. Bosco's report has been prepared by Dr. Lipicky. Together, the two documents represent an overall view of the data submitted and therefore will not be repeated herein. This reviewer is in agreement with the outcome of the hematologic review as stated in the approved Vasotec package insert.

2. Severe hypotension: The most common form of severe hypotension can be attributed to the pharmacologic effect of the drug. In dehydrated patients (usually due to diuretic therapy) and in renal artery stenosis patients, maintenance of blood pressure is mostly dependent upon the renin-angiotensin system. Inhibition of converting enzyme (obviously) obviates this system and therefore results in severe hypotension, at times leading to shock, renal failure, and death. For example: Dr. Easthope; study 920; patient #52335, a 69 year old male who responded dramatically (CHF) to captopril but was switched to enalapril because of a skin rash. After a single dose of enalapril, hypotension occurred with subsequent anuria and death.

Another example case: Dr. Spencer; study 919; patient #52334, a 53 year old female (CHF) was treated with captopril with good results but developed interstitial nephritis. Captopril was stopped and the patient recovered. After a single dose (2.5mg) of enalapril her BP decreased to 40mmHg systolic (from 70mmHg). In spite of this hypotensive episode, she received a second dose of enalapril (3 days later) and even more severe hypotension occurred this time with anuria and death.

Hypotension (dizziness) associated with enalapril (not the worst case) is exemplified in Dr. Mc Carron; study 38; 39 year old female with mild hypertension assigned to (blinded) enalapril plus hydrochlorothiazide combination (20mg E + 50mg HCTZ/day) suffered severe dizziness and hypotension after the first dose. She recovered uneventfully and was restarted at a lower dose (10mg E + 25mg HCTZ daily) and did well.

A renovascular patient; Dr. Bauer; study # 117; a 61 year old white male with pre-existing angina became (relatively) hypotensive after 8 months on enalapril. Speculation that decrease in BP resulted in decrease coronary perfusion with exacerbation of angina. When enalapril was discontinued, patient recovered.

Another renovascular hypertension patient; Dr. Davidson; study 334; a 30 year old female with diuretic and enalapril; resulted in loss of weight and blood volume (dehydration) and orthostatic hypotension. Serum creatinine rose from 1.9 to 9.0 (BUN to 67). Enalapril and HCTZ were discontinued and she recovered.

3. Acute renal failure (this ADR is frequently preceded by severe hypotension, but by no means always); also includes dose-related cases of decreased renal function. For example: Dr. Vidt; study 48; 72 year old male patient; after 6 months on enalapril 20mg and HCTZ 50mg daily, creatinine rose from 1.6mg/dl to 2.2mg/dl. Dose reduction to E 10mg and HCTZ 25mg daily resulted in creatinine return to 1.6 - 1.9 baseline levels. Another (simple) case: Dr. Schnaper; study 45; a 53 year old male patient with mild hypertension received enalapril 20mg plus HCTZ 50mg daily for approximately 2 months. During therapy the serum creatinine rose from 1.2 to 3.2mg/dl and BUN increased from 1.5 to 55mg/dl. Upon discontinuation of enalapril/HCTZ, both serum creatinine and BUN returned to normal.

An example of the "first-dose" phenomenon occurred in Dr. Sbissa; PMS; a 74 year old male in CHF with many concomitant drugs; after 1 dose of enalapril, he developed oliguria. In spite of oliguria, enalapril was continued for 4 days at which time drug (E) was discontinued. Oliguria disappeared and the patient recovered.

Another patient; Dr. Chapelon; PMS; a 56 year old female diabetic hypertensive received one dose of enalapril and became anuric. Enalapril dose was first doubled but then stopped. Creatinine rose from 0.8 to 4.4 during enalapril Rx. Anuria resolved 12 hours after enalapril discontinuation and creatinine decreased to 1.3mg/dl.

Still another case, Dr. Johnston; study 752; IIN 54219 patient with impaired renal function experienced further elevation of serum creatinine after just 2 doses of enalapril and died.

Dr. Silas; study 538; AO # 19211, a 71 year old female renal hypertensive patient (BP 300/150) is another example of acute renal failure, sepsis and death. Captopril controlled her blood pressure for 3 months but was discontinued because of a skin rash. She was switched to enalapril 5mg/day but after one week her BP was not controlled and creatinine was 1084mol/l. Dose of enalapril was raised to 20mg/day (gradually) and a month later the patient was hospitalized with vomiting, a BP of 150/90, and creatinine elevated to 7304mol/l. All treatment was stopped and IV fluids were given; however, a day later she "collapsed" with a staph septicemia (no hematology available) and, despite heroic measures, she died a few weeks later.

The Doctors Matthys/Dirk patient #52493, a 64 year old female hypertensive is an example of acute renal failure following a single dose of enalapril. Hypotension (BP 65/35) accompanied the anuria which was reversible upon discontinuation of the drug.

4. Angioneurotic edema. Altogether, 31 cases of angioneurotic edema temporally associated with enalapril administration occurred. Of particular concern is the fact that the reaction occurred in 9 cases after the first dose of enalapril, one more case after the second dose, and one more patient after the third dose. Three of the angioneurotic victims died, the one most likely caused by the drug died after receiving a single (first) dose of enalapril.

Among the 31 cases of angioneurotic edema, the ADR was deemed to be severe in 18 cases (60%). Cases considered severe (18) required hospitalization, emergency room treatment or intravenous therapy as required. Edema of the face, lips, tongue, glottis, epiglottis and larynx were most often the affected sites. Edema of the larynx occurred in 7 of the angioneurotic edema patients including the one that died. In 4 of these 7 patients, the laryngeal edema occurred after the first dose of enalapril and all seven patients were in the "severe" category (hospitalization, etc).

Angioneurotic edema in the remaining 13 cases appeared to be of no consequence.

/s/

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Robert E. Keenan, M.D.

cc  
Orig. NDA  
HFN/110  
HFN/110/CSO  
HFN/110/RKeenan/12/20/85;12/24/85

DEC 28 1984

Review and Evaluation of Clinical Data

NDA #: 18-998

Date of Submission: September 15, 1983

Received by the Reviewer: January 23, 1984

Review Completed: March 16, 1984

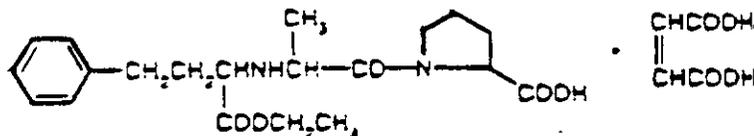
Applicant: Merck Sharp & Dohme Research Laboratories  
West Point, PA 19486  
(215) 661-6352/5000

I. General Information:

Name of Drug: Generic name: Enalapril maleate

Trade name: VASOTEC<sup>TM</sup> Tablets (MSD)

Structural formula:



Chemical name: (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate(1:1) salt.

Empirical formula: C<sub>20</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub> · C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

Molecular weight: 492.53

Enalapril maleate is a white to off-white, non-hygroscopic, slightly photosensitive crystalline powder and melts with decomposition at  $\sim 151^{\circ}\text{C}$  (DTA under nitrogen). It is sparingly soluble in water, soluble in ethanol, and freely soluble in methanol and dimethylformamide. It is slightly soluble in semipolar organic solvents and nearly insoluble in nonpolar organic solvents. The pKa's of enalapril maleate are 3.0 and 5.4.

Two polymorphs of enalapril maleate, designated as Forms I and II, have been detected. The average values for  $T_o$  (uncorr.) obtained from DSC analysis are  $143.4 \pm 3.2^{\circ}\text{C}$  for Form I and  $141.5 \pm 1.5^{\circ}\text{C}$  for Form II.

Pharmacologic Category: Long-acting non-mercapto angiotensin converting enzyme inhibitor.

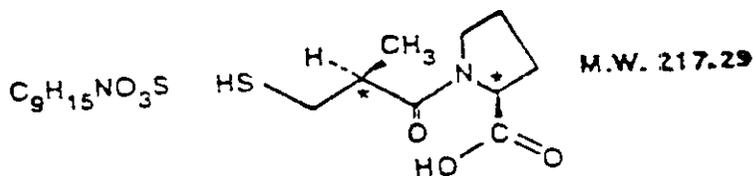
Proposed Indications: "VASOTEC<sup>TM</sup> is indicated for the treatment of essential and renovascular hypertension of all degrees of severity. It may be used alone as initial therapy or concomitantly with other antihypertensive agents, especially diuretics.

VASOTEC<sup>TM</sup> is also indicated in the management of congestive heart failure."

Dosage Forms and Route of Administration: VASOTEC<sup>TM</sup> tablets are barrel shaped, compressed tablets with code numbers on one side and trade name on the other. Products: 5 mg, white, code MSD 712; 10 mg, red, code MSD 713; 20 mg, peach, code MSD 714; 40 mg, yellow, code MSD 715.

The tablets are supplied as follows: bottle of 100 (with desiccant), single unit package of 100, unit of use bottles of 100 (with desiccant), and all intended for oral administration.

Related Drugs: Enalapril maleate is structurally related and has been compared in clinical trials to captopril (NDA 18-343). Captopril, Capoten<sup>TM</sup>, or Lopirin<sup>TM</sup> is 1-(3-mercapto-2-D-methyl-1-oxopropyl)-L-proline (S,S) with Chem. Abstr. Registry Number 62571-86-2.



The asterisks indicate the two S,S optically active centers.

## II. Manufacturing Controls:

Refer to chemistry review.

### III. Pharmacology:

Refer to pharmacology review. For general information the following brief summarization is provided.

Enalapril is the monoethyl ester of the active angiotensin converting enzyme (ACE) inhibitor, MK-0422. Enalapril is an antihypertensive agent that reduces blood pressure in a variety of hypertensive models. Mechanism of action studies have failed to precisely define the principal site where ACE inhibition leads to a reduction in angiotensin II.

The toxicity of enalapril appears to be related principally to the pharmacologic effects of this compound. The exact mechanism of the principal toxic change, renal tubular degeneration, is not known; however, it is believed due to prolonged marked hypotension, an exaggeration of the therapeutic effect. It has been shown that saline supplementation can ameliorate the toxicity of enalapril as well as attenuate its hypotensive effect. This supports the theory that the toxicity may be related to hypotension and argues against a direct toxic effect of enalapril to the renal tubular cells. The possible role of hypotension as a primary cause of toxicity is also supported by the fact that an increased hypotensive effect is seen with combinations of enalapril and hydrochlorothiazide as well as a potentiation of toxicity. The maximum recommended human dose is 40 mg/day (<1 mg/kg/day). Renal lesions were not produced in rats given 90 mg/kg/day for 2 years and in dogs, a more

sensitive species, no drug-induced changes were seen when 15 mg/kg/day was given for 1 year. This demonstrates an adequate margin of safety.

There is no contraindication to the clinical administration of this compound. The results of an extensive series of in vivo and in vitro studies indicate that there is no genotoxic risk associated with enalapril administration. However, because of the adverse effects of enalapril on weight gains and survival of rat F1 pups, and its maternotoxic and fetotoxic potential in rabbits, enalapril should not be used during pregnancy unless the anticipated benefit to the mother outweighs the potential risk to the fetus.

It is noted that no indication of carcinogenic potential was observed in mice or rats treated with high doses of enalapril for 94 or 106 weeks, respectively.

#### IV. Background:

Enalapril was developed following a detailed study of the ACE active site. Because of the toxicity reported with captopril (probably associated with the sulfhydryl radical), it was decided to develop a non-sulfhydryl containing agent with similar therapeutic activity, but, if possible, greater potency and longer duration of action.

Angiotensin converting enzyme (ACE) inhibition leads to a cascade of effects which have clinical usefulness. As ACE is inhibited, angiotensin I (AI) can no longer be converted to angiotensin II (AII), a potent vasoconstrictor. This leads to increases in levels of AI, and decreases of AII.

Decreases in levels of AII cause diminished aldosterone release, and a rise in plasma renin activity. Since ACE, also known as kininase II, is responsible for degradation of bradykinin, levels of bradykinin, a vasodilator, may also rise.

Decreases in AII and, at least theoretically, increases in bradykinin levels, lead to vasodilation, probably largely on the arterial side of the circulation. This leads to reduction in peripheral resistance, blood pressure and an increase in cardiac output. In congestive heart failure, as a result of afterload reduction left ventricular function improves relieving pulmonary congestion and respiratory-related symptoms such as dyspnea.

Unlike most other vasodilators, converting enzyme inhibitors lead to a reduction in aldosterone. This reduces sodium retention and may contribute to control of blood pressure and congestive failure.

V. Clinical Studies:

A. Bioavailability, Metabolism, Disposition.

Twelve biopharmaceutical programs were conducted by MSD to support the projected commercial product. For review and evaluation of these investigations, reference is made to the Division of Biopharmaceutics (HFN-520) assessments.

In the following, a short recapitulation is provided:

Enalapril, (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, is a pro-drug which is converted in vitro to its biologically active diacid: enalaprilat, (N-[(S)-1-carboxy-3-phenylpropyl]-L-alanyl-L-proline). Due to the changes in nomenclature over time, according to MSD, a glossary of names relating to enalapril and enalaprilat is appended here:

Enalapril Maleate

Nonproprietary name adopted by the USAN council; equivalent to the terms L-154,739 and MK-421.

Enalaprilat

Proposed nonproprietary name for the active diacid of enalapril maleate; equivalent to the terms L-154,628, MK-422, and enalaprilic acid.

Enalapril

The monoethyl ester of enalaprilat.

Lisinopril

Proposed nonproprietary name for the lysine analog of enalaprilat (MK-422); equivalent to the terms L-154,826 and MK-521.

Total Drug

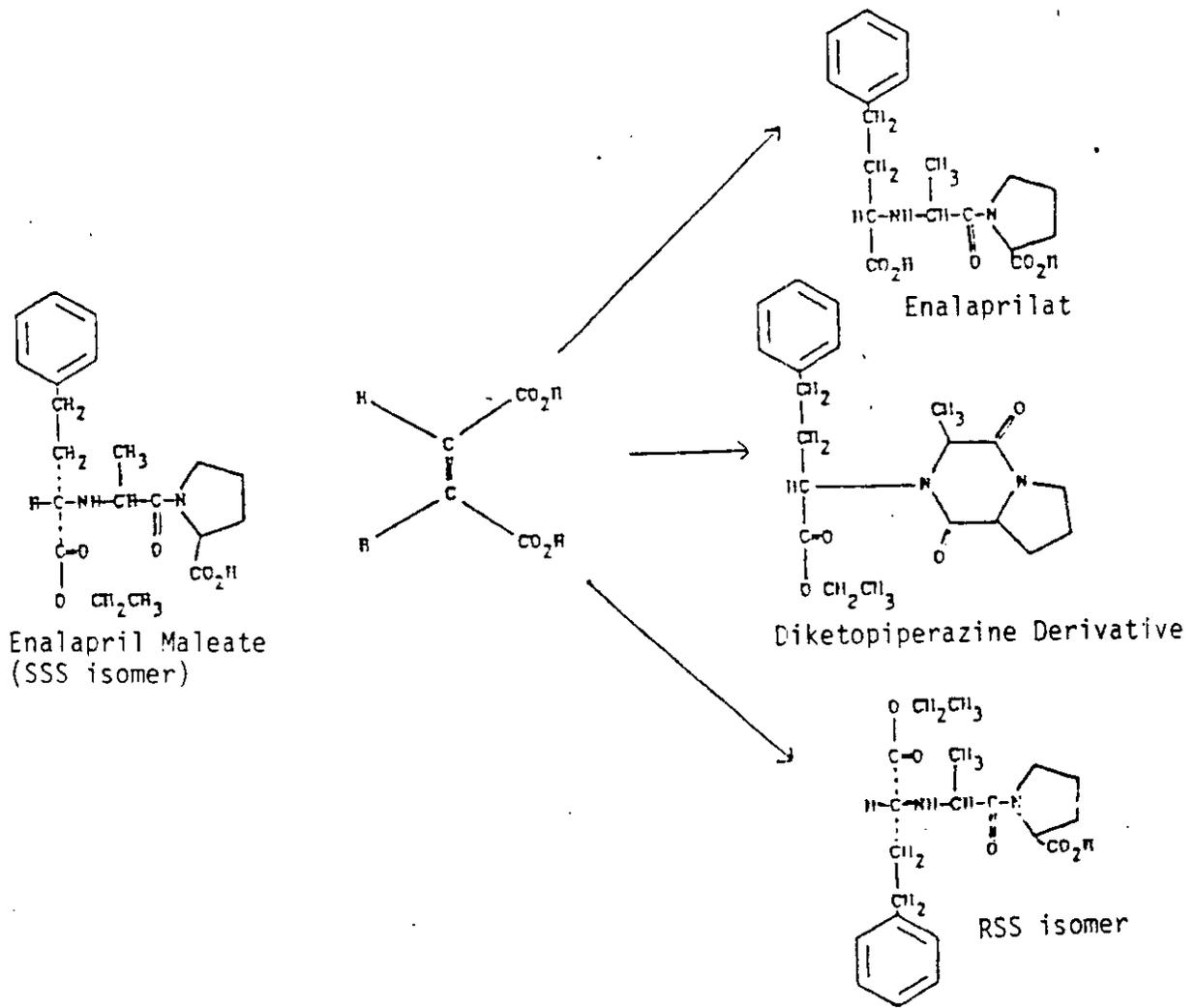
Enalaprilat measured in biological fluids after hydrolysis; represents that which was present in the sample as enalaprilat itself plus that which was present as enalapril maleate.

The principal action of enalapril is the inhibition of angiotensin-converting enzyme (ACE) activity, the biological consequence of which is a reduction in plasma angiotensin II (AII) and aldosterone (ALD) with a simultaneous increase in plasma renin activity (PRA).

There are three potential modes of degradation for enalapril maleate (shown below): hydrolysis of the ethylester to enalaprilat, the active pharmacological species; cyclization to form a diketopiperazine; and inversion at the optically active carbon 1. The stability of enalapril maleate in aqueous solution was studied as a function of pH in the range of 2-7. Maximum solution stability is around pH 3, the native pH of the compound in water. Both the rate of enalapril loss and the mode

of degradation are pH dependent. Optimization of dosage form favors formulation of enalaprilat. The RSS isomer does not form under label storage conditions. Both enalaprilic acid and diketopiperazine derivative remain at less than 5% over the expiration period of the product.

### Mode of Degradation



A summarization (refer to Appendix: Synopsis of Clinical Studies) briefly describes the 12 studies in which a total of 159 healthy volunteers and patients received enalapril/enalaprilat in order to assess the relevant pharmacokinetic and metabolic properties of enalapril maleate in man. The study design, number of subjects receiving enalapril/enalaprilat, dose of enalapril/enalaprilat, and duration of therapy are listed in Table 1.

List of Studies

Table 1

Investigator/ Protocol	No.	Study Purpose	Study Design	No. Subjects In Study	No. Subjects on Enalapril Maleate/ Enalaprilat	Enalapril Maleate (EM)/ Enalaprilat (EA)/ Lisinopril (LI) Doses	Duration
<b>Pharmacokinetics</b>							
Schelling	503	Pilot Bioavailability	Open, 2-period crossover	12	12	EM 10 mg p.o. LI 10 mg p.o.	Single doses
Ferguson	6	Disposition of Enalaprilat	Double-blind, 4-period crossover	12	12	EA 2.5, 5, 10 mg iv.	Single doses
Kukovetz	555	Dose-dependent kinetics	Double-blind, 4-period crossover	13	13	EM 2.5, 10, 40 mg p.o. EA 5 mg i.v.	Single doses
Lant	518	Steady state kinetics	Open, repeated oral dose	12	12	EM 10 mg q.d. p.o.	8 days
Leary	512	<sup>14</sup> C Metabolism	Open, 3-period crossover	6	6	EM 10 mg p.o. EA 10 mg p.o.	Single doses
Lowenthal	118	Disposition-Renal Impairment	Open, parallel, 3 groups	29	29	EM 10 mg p.o.	Single doses
<b>Bioavailability</b>							
Bullery	523	Bioavailability-Capsules	Open, 2-period crossover	12	12	EM 10 mg p.o. EA 5 mg i.v.	Single doses
McMahon	27	Bioavailability-Tablets	Open, 2-period crossover	12	12	EM 10 mg p.o. EA 5 mg i.v.	Single doses
Williams	53	Bioavailability-Caps. vs. Tablets	Open, 3-period crossover	12	12	EM 10 mg capsules EA 5 mg tablet	Single doses
Ferguson	168	Tablet Bioequivalence	Double-blind, 6-period crossover	12	12	EM 5, 10, 20, 40 mg p.o. EM 5 mg i.v.	Single doses
Ferguson	23	Effect of Food on Bioavailability	Open, 2-period crossover	13	13	EM 40 mg p.o.	Single doses
Williams	21	Bioavailability-Enalapril/HClZ	Open, 2-period crossover	14	14	EM 10 mg p.o. EM/HClZ 10 mg/25 mg p.o.	Single doses
TOTAL				159	159		

Table 18 summarized the conclusions for each of the studies noted in the foregoing.

Table 18  
Summary of Results

<u>Investigator/ Protocol</u>	<u>No.</u>	<u>Study Purpose</u>	<u>Conclusions</u>
<u>Pharmacokinetics</u>			
Schelling	503	Pilot Bioavailability	Bioavailability of enalaprilat after enalapril maleate at least 43 pct. absorption of drug at least 61 pct. Total recovery (urine and feces) as enalaprilat and enalapril 894 pct. of dose.
Ferguson	6	Disposition of Enalaprilat	>90 pct. of dose recovered in urine as enalaprilat, serum profiles polyphasic with prolonged terminal phase - same conc. of enalaprilat in terminal phase for all doses; $AUC_{0-\infty}$ linearly related to dose with a positive intercept (subtraction of $AUC^E$ - area related to extrapolated terminal phase - yields an AUC linearly related to dose, with zero intercept); terminal phase likely represents binding of a fixed amount of enalaprillic acid to ACE regardless of dose.
Kukovetz	555	Dose-dependent kinetics	Absorption of enalapril and hydrolysis to enalaprilat are generally independent of dose; disposition of enalaprilat analogous to that seen for i.v. enalaprilat (Study No. 6), i.e., an apparent nonlinear component likely reflecting binding to ACE.
Lant	518	Steady-state kinetics	Little accumulation of enalaprilat following eight daily doses of enalapril maleate; steady state attained by 3rd and 4th dose; effective half-life for accumulation of 11 hours, accumulation ratio of 1.3.
Leary	512	$^{14}C$ Metabolism	No metabolism beyond that to enalaprilat; enalapril maleate better absorbed than enalaprilat; availability of enalaprilat after administration of enalapril maleate 843 pct.
Lowenthal	110	Disposition in renal impairment	Impaired renal function results in elevated serum conc. of enalaprilat and decreased excretion rate of enalaprilat and total drug following enalapril maleate administration; enalaprilat is dialyzable.
<u>Bioavailability</u>			
Dollery	523	Bioavailability - Capsules	Bioavailability of enalaprilat is 54 pct.; absorption of drug is at least 74 pct.
McMahon	27	Bioavailability - Tablets	Bioavailability of enalaprilat is 40 pct.; absorption of drug is at least 59 pct.
Williams	53	Bioavailability - Caps. vs. Tabs.	Capsule and tablet are bioequivalent, bioavailability of enalaprilat is 42 and 40 pct for capsule and tablet, respectively; absorption of drug is at least 61 and 63 pct., respectively.
Ferguson	168	Tablet bioequivalence	Bioavailability and absorption of enalaprilat similar for 5, 10, 20, and 40 mg enalaprilat maleate tablets; bioavailability 38, 44, 38, 36 pct., respectively; absorption 63, 73, 62, 59 pct., respectively.
Ferguson	23	Effect of food on bioavailability	Standardized breakfast does not influence bioavailability of 40 mg tablet.
Williams	21	Bioavailability - Enalapril maleate/HCTZ	The enalapril maleate/HCTZ combination tablet is bioequivalent to the individual components given separately but concurrently.

B. Dose Range Studies.

The effective antihypertensive dose range for enalapril has been determined from dose-ranging and definitive dose-response studies which were conducted here and abroad in 459 patients with essential or renovascular hypertension. Table 1 outlines the study purpose, design, number of subjects participating, dose of enalapril, and duration of treatment for each of these studies. Reference is also made to Appendix: Synopsis of Clinical Studies. Dosing frequencies of once-daily enalapril alone and in combination with hydrochlorothiazide have been compared to twice-daily administration. Data from these studies support a starting dose of enalapril maleate of 10 mg once a day in patients with mild to moderate hypertension. The usual dosage is 10 to 40 mg per day administered in a single or two divided doses.

Dose-ranging studies have also been conducted with enalapril maleate in 38 patients with renovascular hypertension and in 73 patients with congestive heart failure.

Studies Discussed in Dose-Response Section - OES

Study No.	Investigator	Study Design	No. of Subjects Entered*/Completed	MK-421 Dose (mg)	Study Duration
<b>Dose-Range Studies</b>					
1	Ferguson	Single-blind, single dose rising	12/11	2.5, 5, 10, 20	Single doses of MK-421 followed by placebo day
2	Gavras	Open, single-blind, single dose rising	11/11	2.5, 5, 10, 20, 40	Single doses of MK-421 followed by placebo
3	Larochelle	Open, single-blind, single dose rising	13/13	2.5, 5, 10, 20, 10 bid	Single dose of MK-421 followed by placebo
9	Case/Atlas	Open, single-blind, single dose rising	14/14	5, 10, 20, 40, 80	Two to four days per dose
504	Menard	Open label repeated oral doses	52/50	1.25, 2.5, 5, 10, 20 and 40 od	Until satisfactory blood pressure response obtained or up to 40 mg. HCTZ could be added Outpatient six months.
507	Velandia	.	.	.	.
508	Brunner	.	.	.	.
510	Birkenhaefer	.	.	.	.
511	Yetter	.	.	.	.
513	Amery	.	.	.	.
514	Stumpe	.	.	.	.
515	Rosenthal	.	.	.	.
519	Ritz	.	.	.	.
<b>Dose-Response Studies</b>					
61	Gavras	Double-blind, randomized, parallel	139/125	2.5, 10, 20, 40 bid	Eight weeks
62	Guthrie	Placebo controlled	.	.	.
63	Izzo	.	.	.	.
64	Kirkendall	.	.	.	.
65	Weinberger	.	.	.	.
566	Wilhelmsson	Double-blind, incomplete block	91/91	2.5, 5, 10, 20, and 40 bid	DR-I-14 weeks**
579	Berglund	two period crossover	.	.	DR-II-12 weeks
<b>Once vs. Twice Daily</b>					
12	McMahon	Double-blind, two period crossover	32/32	40 qd or 20 bid	12 weeks
13	Lowenthal	.	.	.	.
14	Holland	.	8/7	20 qd or 10 bid	.
522	Velasco	.	56	.	.
524	Wilhelmsson	.	.	.	.
<b>Once vs. Twice Daily With HCTZ</b>					
4	Ferguson	Double-blind, multiple dose, incomplete block study in a crossover design	9/8	Group I: 5 od, HCTZ 50 od, 5 + 50 HCTZ od Group II: 10 od, HCTZ 50 od, 10 + 50 HCTZ od	4 weeks
20	Mitchell/Taylor	Double-blind, multiple dose crossover	22/17	40/50 HCTZ od 20/25 HCTZ bid	14 weeks
22	Ferguson	Double-blind, multiple dose	.	20 bid/HCTZ 25 bid/ 20/25 HCTZ bid (2 wks each)	.

\* = Entered and received enalapril therapy  
 \*\* = Including four-week interim washout  
 ■ = Received enalapril therapy

Table 1

(Continued)

Studies Discussed in Dose Response Section - DES

Study No.	Investigator	Study Design	No. of Subjects Entered*/Completed	PK-421 Dose (mg)	Study Duration				
<b>Dose-Ranging in Renovascular Hypertension.</b>									
534	Fyrhquist	Open-label, single-dose, followed by outpatient period	38/26	1.25 to 40 qd	12 weeks				
533	DeiPortillo								
586	Rosenthal								
526	Karlberg/Robertson								
<b>Dose-Ranging in CHF</b>									
55	Cohn	Open label, single-dose	73/60	1.25, 2.5, 5, 10, 20, 40	16 weeks				
56	Fouad								
57	Williams/Hollenberg								
58	Cody								
59	Franciosa								
72	Chatterjee								
521	Ikram								
533	Turini								
567	Soyland								
568	Dickstein								
591	DeiPortillo								
95	Chrysant					Double-blind, placebo controlled study to evaluate the effects of enalapril in patients with CHF	51 (24)*/ 50	2.5 first dose 5 second dose 10 bid	14 weeks
97	Faxon								
101	Hackshaw								
99	Hassle								
100	McCall								
106	McMahon								
102	Parker								
103	Ribner								
104	Rubin								
105	Sagar								
95	Young								
598	Athanassiadis	Double-blind, placebo controlled study to evaluate the effects of enalapril in patients with CHF	119 (57)* 97	Group I: 5 bid * digitalis and/or diuretic Group II: placebo bid * digitalis and/or diuretics	14 weeks				
621	Bounhour								
674	Denis/Machecourt								
557	Escudero								
574	Espinoza								
578	Faerchtein								
610	Gourgon								
606	Hagmeijer								
616	Harris								
626	Huber								
589	Ikram/Micholls								
632	Jennings								
609	Johnson								
627	Joy								
590	Kleynhans								
620	Mirman								
619	Raynaud								
608	Thomas								
645	Tremblay								
TOTAL			740 (601)*/ 667						

Table 1  
(Cont'd)

\* = Entered and received enalapril therapy  
 † = Received enalapril therapy

1) Hypertension Studies:

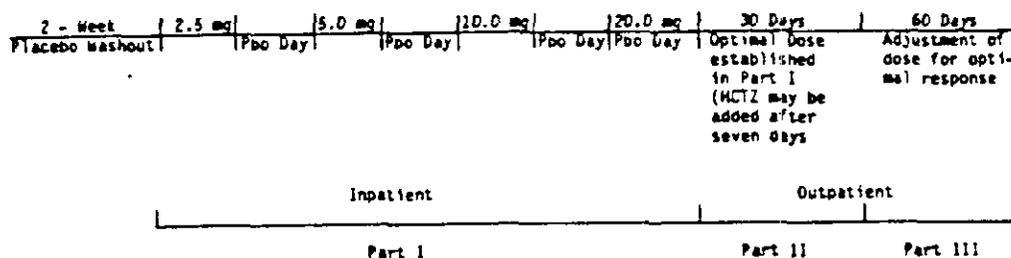
Open Dose-Ranging Studies

a) Single-Dose Studies in Essential Hypertension

Single-dose, open-label, dose-ranging, time course of action studies were carried out in 13 centers (four domestically, nine internationally, Table 1).

In the four domestic centers, 50 patients with mild to moderate essential or renovascular hypertension were studied utilizing a common protocol design, as shown below. Following a two-week placebo washout, patients were admitted to the hospital. All 50 patients entered and completed Part I (dose titration period) of these studies; forty patients entered and completed Part II and 26 patients entered Part III. Parts II and III were repeat-dose period. Patients with untreated sitting supine diastolic blood pressure between 95-125 mg were included in the study. Three studies: Ferguson (No.1), Gavras (No. 2), and Larochelle (No.3) administered single rising doses of 2.5, 5, 10, and 20 mg of enalapril with a placebo day between each dose (Part I). In the Case/Atlas study (No. 9), patients were given single rising doses of enalapril from 5 mg to 80 mg for two to four days per dose; there was no placebo washout between doses. Blood pressure was monitored as were safety,

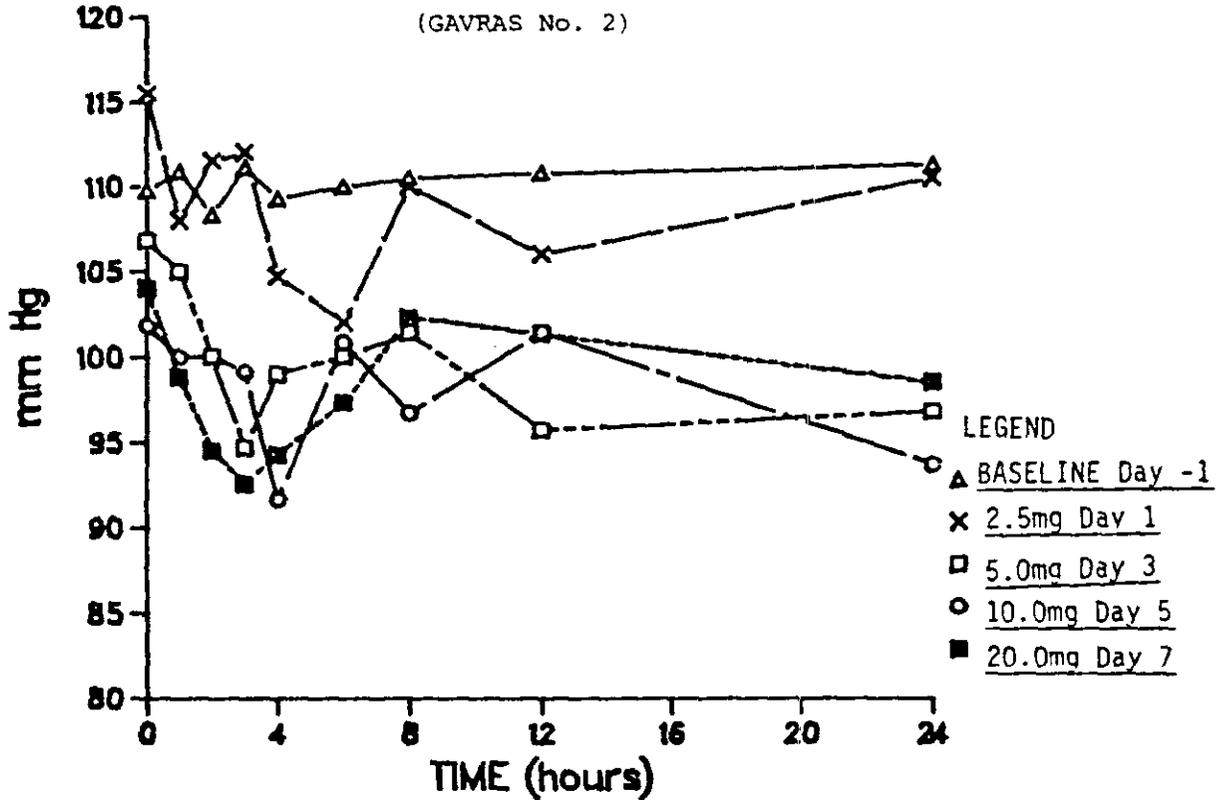
tolerability, and biochemical parameters in all four studies.



In Part II patients received repeat daily doses of enalapril as outpatients to a 30-day total drug exposure at the optimal dose level determined in Part I. If after seven days there was an inadequate effect on blood pressure (defined as a reduction of <10 mmHg from baseline values or a sitting diastolic blood pressure of >90 mmHg for 12 hours), hydrochlorothiazide 50 mg/day was added to the regimen. Part III of the study, an amendment to the original protocol, allowed the extension of Part II to 90 days total enalapril exposure and adjustment of the dose levels to achieve optimum response.

Doses of enalapril (5 to 80 mg) produced significant reductions in mean sitting diastolic pressure with respect to duration of response. Figure 1 shows the effects of single doses of 2.5-20 mg of enalapril and mean sitting diastolic blood pressure (from Study No. 2, Gavras).

**FIGURE 1**  
**MEAN SITTING DIASTOLIC BLOOD PRESSURE (n=8)**  
**PART 1—ACTIVE TREATMENT DAYS**



Supine diastolic blood pressure also continued to decrease with increasing dose ( $p < 0.01$ ). For standing diastolic blood pressure, there was a highly significant dose-related trend from 10 mg per day through 80 mg per day ( $p < 0.01$ ) in the Case/Atlas study (No. 9) where the 80 mg dose was administered.

Many patients maintained control of diastolic blood pressure (sitting diastolic blood pressure  $\leq 90$  mmHg) at the 10 mg to 40 mg per day doses.

Supine systolic blood pressure also decreased with increasing dose. This trend became apparent at 5 mg and statistically significant at 10 mg per day ( $p < 0.01$  at all hours except 0 and 24) and was maintained through 80 mg per day ( $p < 0.01$  all hours). The readings obtained on the last outpatient day were also significantly lower than baseline readings ( $p = 0.001$ ) (Table 2<sup>a</sup>). Decreases in standing systolic blood pressure were very similar to the supine. Standing systolic blood pressure declined with increasing dose [test for linear dose trend through 10, 20, 40, and 80 mg per day ( $p < 0.01$ )].

Table 2

Mean Blood Pressure and Pulse Rates After Continuous Treatment in the Outpatient Setting for Four Weeks (Case/Atlas, No. 9)

Part 2 - Last Outpatient Day

Parameter	Baseline		Last Out-Patient Day		Difference		P-Value
	N	Mean	N	Mean	N	Mean	
Supine Systolic BP	14	170.9	14	136.1	14	-34.8	0.0001**
Supine Diastolic BP	14	106.9	14	86.7	14	-20.2	0.0002**
Standing Systolic BP	14	163.2	14	125.3	14	-37.0	0.0001**
Standing Diastolic BP	14	111.4	14	88.4	14	-23.0	0.0002**
Supine Pulse	14	82.6	14	82.1	14	-0.5	0.9000
Standing Pulse	14	90.4	14	96.4	14	6.0	0.1800

\*\* Difference is statistically significant at  $p < 0.01$ .

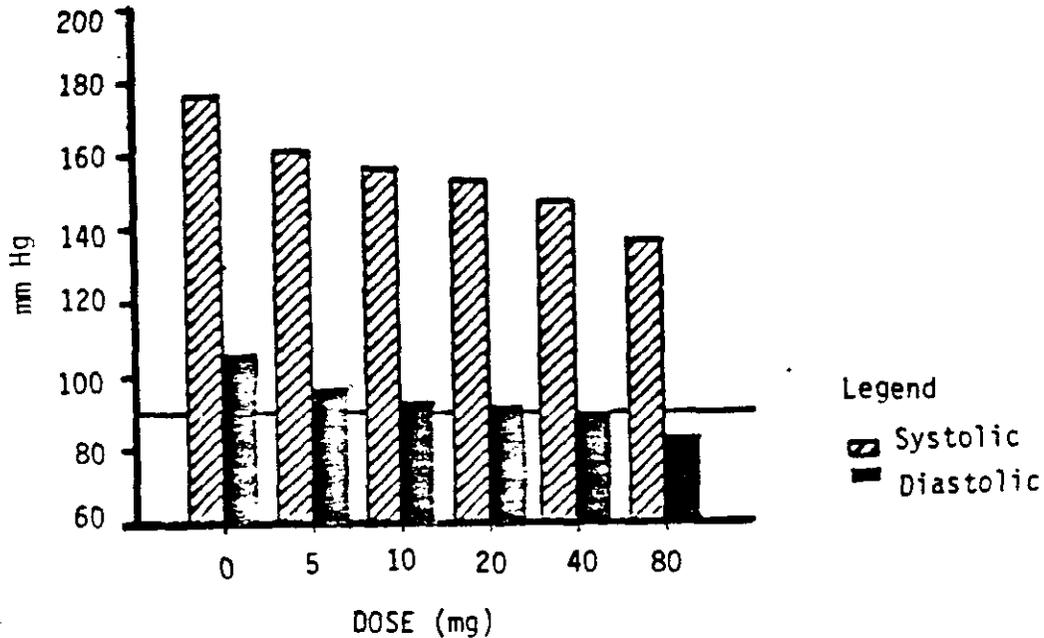
<sup>a</sup>On this last outpatient day, one patient received 10 mg, two received 20 mg, eight received 40 mg, one received 60 mg, and two received 80 mg enalapril. Five patients were receiving concomitant HCTZ.

In the Larochelle (No. 3) study, renovascular hypertensive patients appeared to respond (sitting DBP < 90 mmHg; > 10 mmHg decrease from baseline) to a greater extent than those diagnosed as essential hypertensives. Of the 13 patients who entered Phase I, 5 patients were diagnosed as having renovascular hypertension, 2 (Nos. 1 and 15) entered the outpatient portion of the study. Both of these patients experienced increased responses to treatment with enalapril at doses of 10 and 20 mg. Sitting systolic blood pressure decreased by 30 and 44 mmHg while sitting diastolic pressures decreased by 28 and 20 mmHg for Patients 1 and 15, respectively.

The analysis of standing diastolic blood pressure was also differentiated for renovascular and essential hypertensive patients in Case/Atlas Study No. 9. The results for both groups of patients showed similar mean daily decreases relative to baseline (at even numbered hours 2-12) during Part I. As shown in Figure 2 (n = 9 patients), mean decreases of 11, 12, 15, 19, and 23 mmHg were noted for the 5, 10, 20, 40, and 80 mg doses of enalapril, respectively.

Figure 2

Mean (even hours 2-12) Supine Blood Pressure  
Versus Dose  
(Case/Atlas, No. 9)



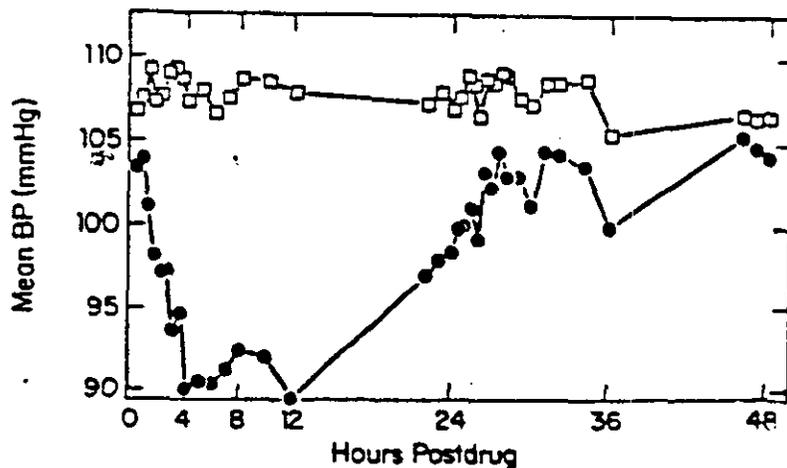
Note: Includes only patients progressing to 80 mg per day dose.

In the international open, pilot, multicenter study of nine investigators (Menard, et al, Nos. 504, 507, 508, 510, 511, 513, 514, 515 and 519) single, oral doses of enalapril maleate (1.25 to 40 mg) were studied in 52 ambulatory patients with essential hypertension. This study design consisted of three successive parts: an (ambulatory) two week, washout period; (in-patient) five-day placebo stabilization period followed by enalapril dose titration; and an (outpatient) six-month follow-up on the effective dose regimen. The mean untreated supine diastolic blood pressure in this group of patients before hospitalization was 118 mmHg (n = 48), and the range was 100-150 mmHg.

Results from this study showed that single, oral doses of enalapril (1.25, 2.5, 10, and 20 mg) reduced supine and erect blood pressures in hospitalized patients. The onset of action--the first statistically significant decrease from placebo baseline--was at one hour postdrug. The peak effects occurred from 3.5 to 8 hours postdosing. At 24 hours postdrug, approximately 50 pct. of the maximal antihypertensive effect was still present (Figure 3).

Figure 3

Mean Supine Diastolic Blood Pressure in Hospitalized Patients After Placebo (□) and Optimal Doses of Enalapril Maleate (●) (2.5 to 20 mg/day) (n=33) (Menard et al)



At six hours after baseline placebo, the mean supine blood pressure was 171/108 mmHg. The optimal dose of enalapril, individualized by titration of each

patient, reduced the supine blood pressure to 140/86 mmHg ( $p < 0.001$ ). No significant changes in heart rate were observed.

Enalapril exhibited a dose dependency on an in-patient blood pressure response in that increasing dosage was required to obtain an optimal response in an increasing proportion of patients. After a placebo check day, dosage was adjusted to obtain an optimal response.

In the outpatient setting, patients were maintained at optimal daily doses of enalapril ranging from 2.5 to 40 mg. The distribution of patients at the various daily doses following 2, 4, and 8 weeks of enalapril therapy are given in Table 3.

Table 3

Outpatient Dose Distribution  
(Menard et al)

Week	Number of Patients on Each Total Daily Dose					Total
	2.5 mg	5 mg	10 mg	20 mg	40 mg	
2	2 (25)	0 (0)	2 (25)	3 (30)	1 (13)	8
4	2 (25)	1 (13)	1 (13)	0 (0)	4 (50)	8
8	0 (0)	1 (17)	1 (17)	1 (17)	3 (50)	6

The numbers in parentheses are the percentages of patients on each dose of MK-421.

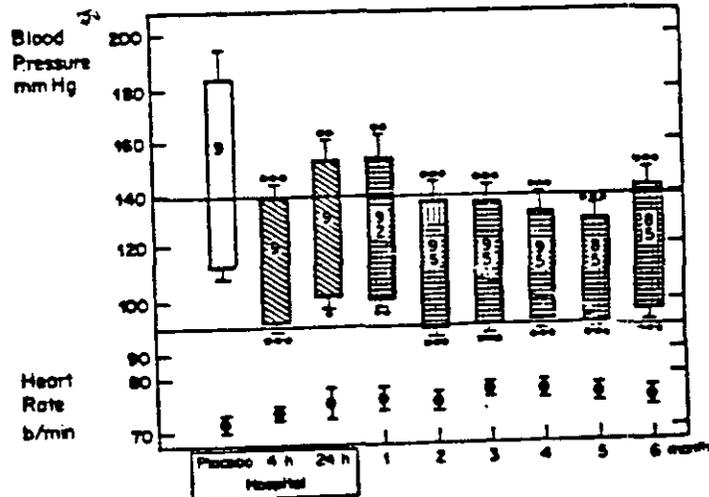
b) Repeat-Dose Studies in Essential Hypertension

In the domestic studies following repeat dosing of enalapril in the outpatient setting (Part III) for periods up to four months, mean supine and standing diastolic blood pressures were lower than baseline by the last outpatient visit (Table 2 from Case/Atlas Study No. 9). There were no changes in pulse with continuous outpatient treatment.

In the international multiclinic study (Menard et al) after the initial titration period in the hospital, patients were treated with enalapril once a day or twice a day for 16 weeks on an outpatient basis. Significant decreases from both outpatient and inpatient baselines in blood pressure were observed during the entire 16-week period. Mean supine blood pressure decreases were greater than erect values. Some of the patients with moderate-severe hypertension, who were not satisfactorily controlled on enalapril alone, required the addition of a diuretic. Some patients (N=9) have been controlled for as long as ten months (Figure 4) on 20 mg enalapril b.i.d. with or without hydrochlorothiazide. One patient has been controlled on a maintenance dose of 2.5 mg once a day.

Figure 4

Long-Term Results in Nine Patients Treated from Four to Six Months with Enalapril 20 mg b.i.d. (Menard et al)



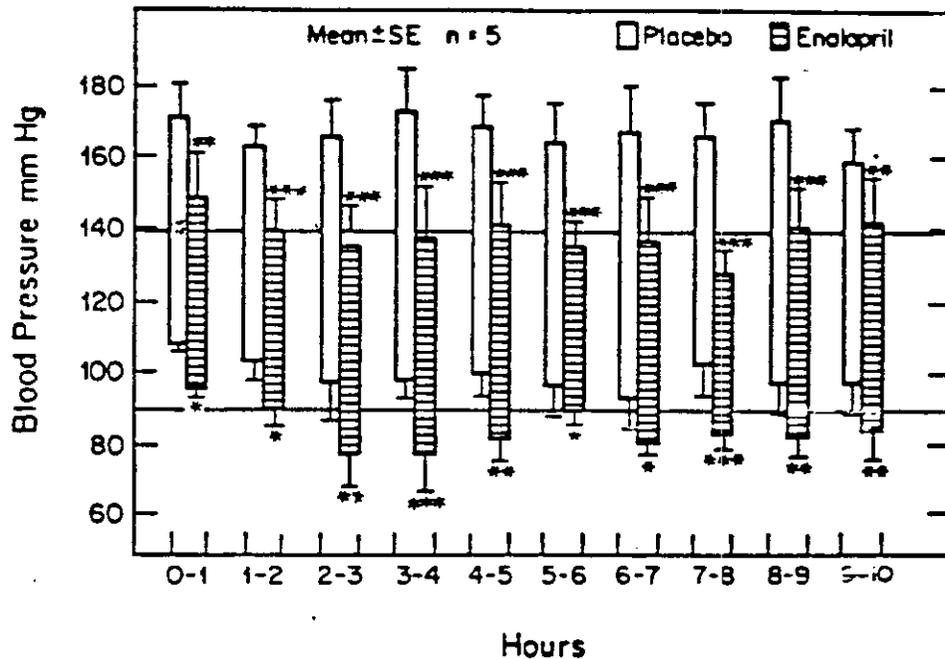
The lower number in the blood pressure columns indicates the number of patients maintained on enalapril and hydrochlorothiazide 50 mg q.d.

Statistical significance versus placebo.  
\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001

In five patients during the outpatient portion of the study, blood pressure profiles were obtained over a 10-hour postdrug period using an ambulatory Remler blood pressure monitoring device while patients were on placebo and after two months of enalapril therapy (Figure 5). At all time intervals, enalapril significantly reduced both supine systolic and diastolic blood pressures compared to placebo (p<0.001 in most cases).

Figure 5

Ambulatory Blood Pressure Reading Before (open columns) and After Two Months Therapy with Enalapril 20 mg b.i.d. (latched columns) (Menard et al)



One patient was maintained on enalapril and hydrochlorothiazide 50 mg q.d.

\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001

Conclusions: These single-and repeat-dose studies in mild to moderate essential hypertension demonstrated that enalapril in single or divided doses of 10 to 40 mg per day is effective in controlling (sitting diastolic blood pressure  $\leq$  90 mmHg) blood pressure. Moderate to severe hypertensives were not controlled and required the addition of a diuretic. Patients

were controlled for as long as ten months at 20 mg enalapril per day with or without hydrochlorothiazide. Data for the few renovascular hypertensives who were studied showed that renovascular hypertensives responded to enalapril to a greater extent than did essential hypertensives. For essential and renovascular hypertensives, blood pressure further declined with increasing dose.

c) Dose Ranging in Patients with Renovascular Hypertension

Additional dose-ranging studies were conducted to specifically describe the enalapril antihypertensive response in patients with renovascular hypertension. A multicenter (Fyhrquist et al, Nos. 534, 553, 586, and 526) study was completed abroad in 38 patients with renovascular hypertension.

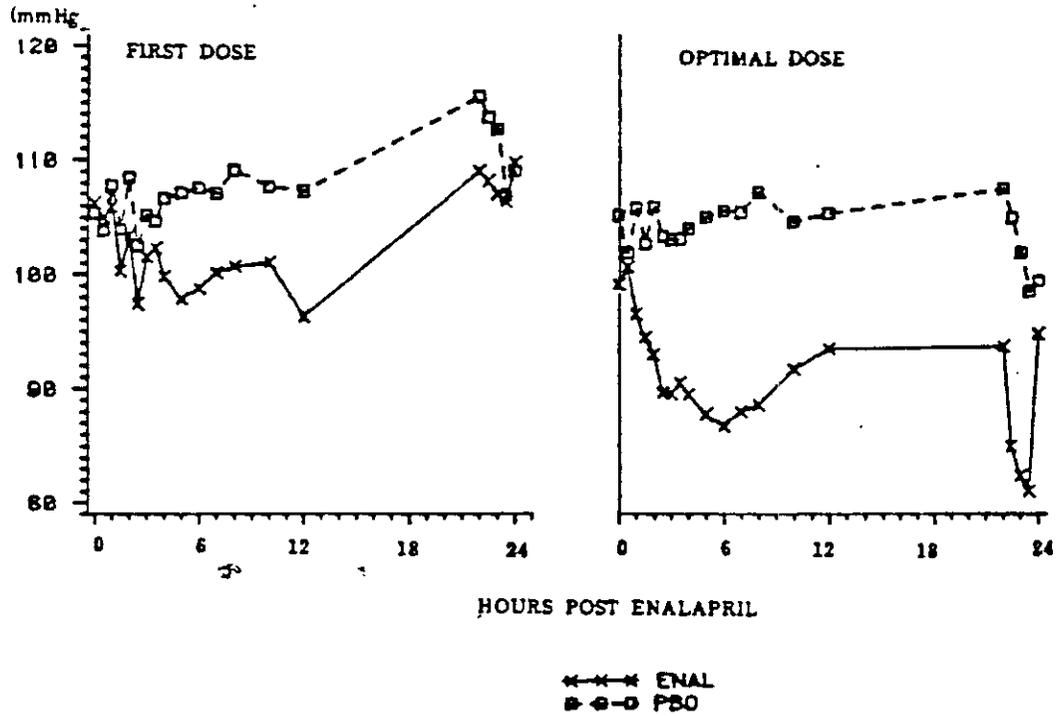
This was an open, pilot study consisting of an inpatient placebo stabilization phase (Period I), an inpatient drug-treatment (single-dose) phase (Period II), and an out-patient drug-treatment (repeat-dose) phase (Period III). Data for 26 of these 38 patients were received by the sponsor at the "study cut-off date" (June 22, 1983) and were included in the submission.

Previous antihypertensive medications were discontinued in these patients and they were hospitalized for a five-day placebo stabilization period. At the end of this time, the mean supine blood pressure was 179/106. The patients then entered an inpatient drug-treatment period and received doses of enalapril ranging from 1.25 mg to 40 mg once a day. The doses most commonly needed to achieve blood pressure control (supine diastolic blood pressure  $\leq 90$  mmHg) in these hospitalized patients were 10 mg per day (35 pct.) and 40 mg per day (42 pct).

There was a significant mean decrease in supine blood pressure as early as 1.5 hours after the first dose. The mean peak decrease in supine blood pressure compared to the last placebo day was 20/11 mmHg occurring at 10 to 12 hours after the first dose of enalapril. After individual titration, the optimal dose produced a mean peak decrease in supine blood pressure of 33/19 mmHg. Decreases were statistically significant as late as 23.5 hours postdose (Figure 6).

Figure 6

Supine Diastolic Blood Pressure in Hospitalized  
Patients with Renovascular Hypertension  
(Fyhrquist et al)

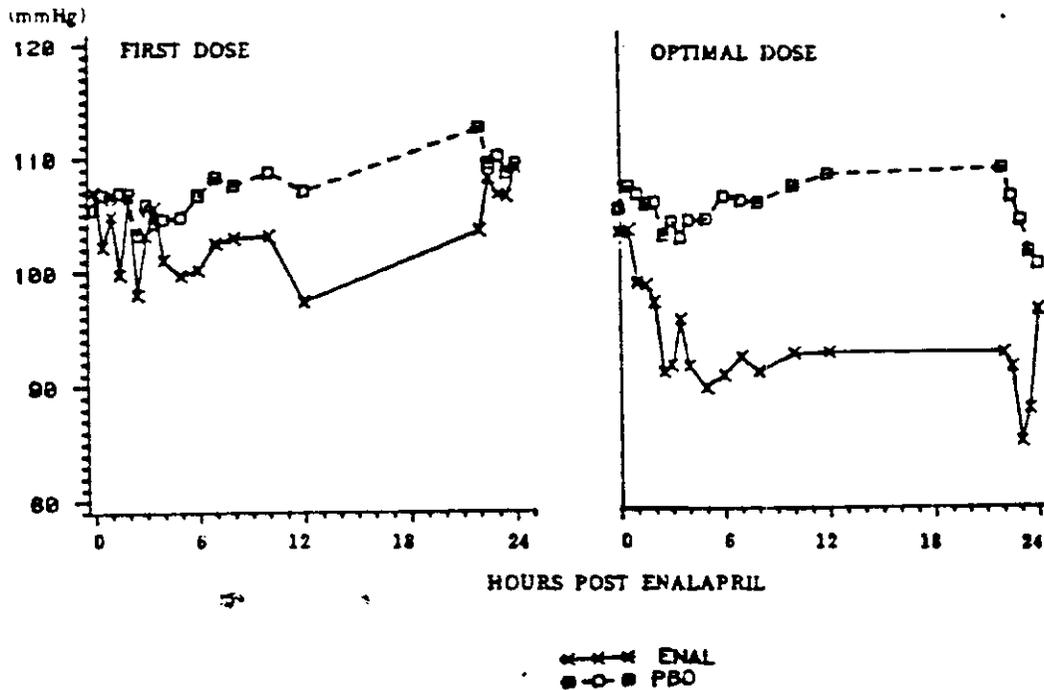


N. B. Patients were asleep during the Hour 22-24 measurement.

Similar results were observed for erect blood pressure, although to a slightly lesser degree (Figure 7).

Figure 7

Erect Diastolic Blood Pressure in Hospitalized Patients with Renovascular Hypertension (Fyhrquist et al)



N.B. Patients were asleep during the hour 22-24 measurement.

After the initial titration period in the hospital, patients were treated with enalapril once a day for three months on an outpatient basis (Table 4). Significant mean decreases compared to the last inpatient placebo day were observed in every blood pressure variable at each monthly observation.

Table 4

Mean Supine and Erect Systolic and Diastolic BP (mmHg) in Outpatients with Renovascular Hypertension (Fyhrquist et al)

n	PRETREATMENT	POSTTREATMENT					
		n	ONE MONTH	n	TWO MONTHS	n	THREE MONTHS
25	Supine 181/107	24	Supine 152/93 ▲-29/-16	24	Supine 142/89 ▲-39/-19	25	Supine 143/89 ▲-38/-18
25	Erect 168/107	24	Erect 146/96 ▲-21/-12	24	Erect 134/91 ▲-32/-17	25	Erect 134/89 ▲-34/-17

By the end of three months of enalapril therapy, 12 of the 25 (one patient, of the 26, underwent surgery) patients (48 pct.) were controlled (supine diastolic blood pressure  $\leq 90$  mmHg), 21 of 25 (84 pct.) responded (decreases compared to placebo of at least 10 mmHg), 11 of 25 (44 pct.) were both controlled and responded, and 22 of 25 (88 pct.) were either controlled or responded. The blood pressure responses were not accompanied by any significant changes in heart rate.

The most-commonly used doses after three months of therapy were 40 mg per day (52 pct.) and 10 mg per day (28 pct.). Most of the patients were controlled with enalapril alone given as a single daily dose. Only two of the 20 patients treated at one center required concomitant diuretic therapy.

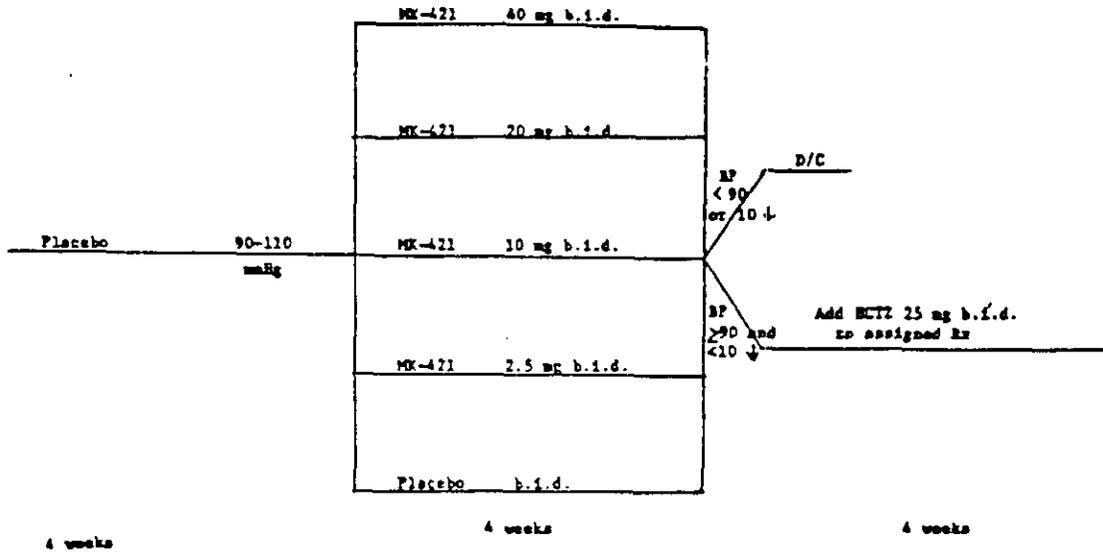
## Controlled Studies

### Dose-Response in Essential Hypertension

To substantiate the antihypertensive efficacy of enalapril as described in the open dose-ranging studies, definitive, randomized controlled dose-response studies were conducted in patients with mild to moderate essential hypertension. Two multicenter studies (Gavras et al, and Wilhelmsson, and Berglund) have been completed describing the dose-response of enalapril maleate in patients with mild to moderate essential hypertension.

1) Gavras et al. Domestic Dose-Response Study.

Five investigators (Gavras et al, Study No. 61-65) participated in the domestic multicenter study and explored the dose range of 2.5 to 40 mg of enalapril. Following a four-week placebo washout period, 139 patients with sitting diastolic blood pressures between 90 and 110 mmHg were randomly assigned to receive enalapril 2.5, 10, 20 or 40 mg b.i.d. or placebo for four weeks. Responders completed the study after four weeks of therapy. Nonresponders had hydrochlorothiazide 25 mg b.i.d. added to their enalapril regimen and continued in the study for an additional four weeks. The following diagram illustrates the study design.



Sitting and standing blood pressure determinations were performed before the morning dose at screening and weekly throughout the placebo baseline and active drug treatment periods. Readings at the end of the fourth week of both the placebo baseline and active drug treatment periods were used to determine antihypertensive efficacy in each treatment group. A patient had an excellent response to the drug if the sitting diastolic blood pressure was  $\leq 90$  mmHg. A patient had a good response if his sitting diastolic blood pressure was lowered at least 10 mmHg from baseline by the end of the period but did not reach 90 mmHg. If a patient met either of these response criteria after four weeks, he was considered to have completed the study. If the patient did not meet these response criteria, hydrochlorothiazide 25 mg

b.i.d. was added to the treatment regimen, and the patient was monitored for an additional four-week period. One hundred and thirty-six patients met blood pressure eligibility criteria and were included in the efficacy analysis. All patients were evaluated for safety.

The five treatment groups were comparable at baseline with respect to age, gender, race, and stratum (i.e., number of patients with mean diastolic blood pressure between 90-99 mmHg and between 100-110 mmHg). Mean sitting and standing, systolic and diastolic blood pressures were evaluated relative to baseline. Significant reductions from baseline were observed at all weeks for all enalapril-treated groups ( $p < 0.01$  in most cases) (Table 5). The placebo group showed a significant reduction from baseline for sitting diastolic pressure only at Week 4 ( $p < 0.01$ ) and Week 1 (0.05). These decreases were of lesser magnitude than the blood pressure reductions in the enalapril groups.

Table 5

Mean Sitting Blood Pressure (Systolic/Diastolic; mmHg)  
at Treatment Weeks 1, 2, 3, and 4  
(Gavras et al)

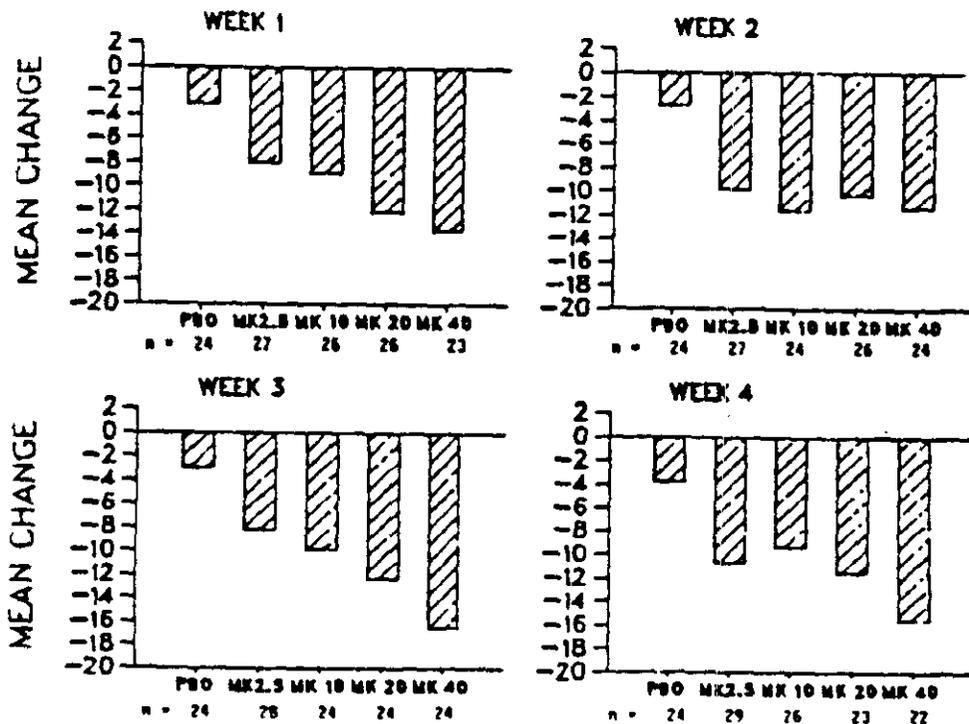
Treatment Weeks	Placebo (n=26)	2.5 mg (n=29)	10 mg (n=28)	20 mg (n=28)	40 mg (n=25)
Baseline	145.2 /97.5 <sup>a</sup>	144.9 /98.1	144.6 /97.7	150.3 /98.9	147.0 /97.5 <sup>b</sup>
1	141.8 /94.4*	135.6**/90.0**	134.0**/88.7**	133.7**/86.7**	132.2**/83.7**
2	142.8 /94.4	132.0**/88.1**	127.6**/85.3**	137.1**/88.4**	136.2**/86.5**
3	140.7**/94.4	135.6**/90.0**	129.9**/86.2**	135.5**/85.8**	129.5**/81.5**
4	141.7**/93.7**	130.7**/87.5**	130.4**/87.3**	133.8**/86.9**	129.5**/82.7**

\*Statistically significant change from baseline within the group, p < 0.05.  
\*\*Statistically significant change from baseline within the group, p < 0.01.  
<sup>a</sup>Baseline n=28.  
<sup>b</sup>Baseline n=26.

An antihypertensive dose-response relationship based upon mean decreases in sitting diastolic blood pressure was clearly demonstrated at Weeks 1 and 3 (p<0.01) (Figure 8).

Figure 8

Enalapril (b.i.d.) Dose-Response Study  
Sitting Diastolic Blood Pressure  
(Gavras et al)

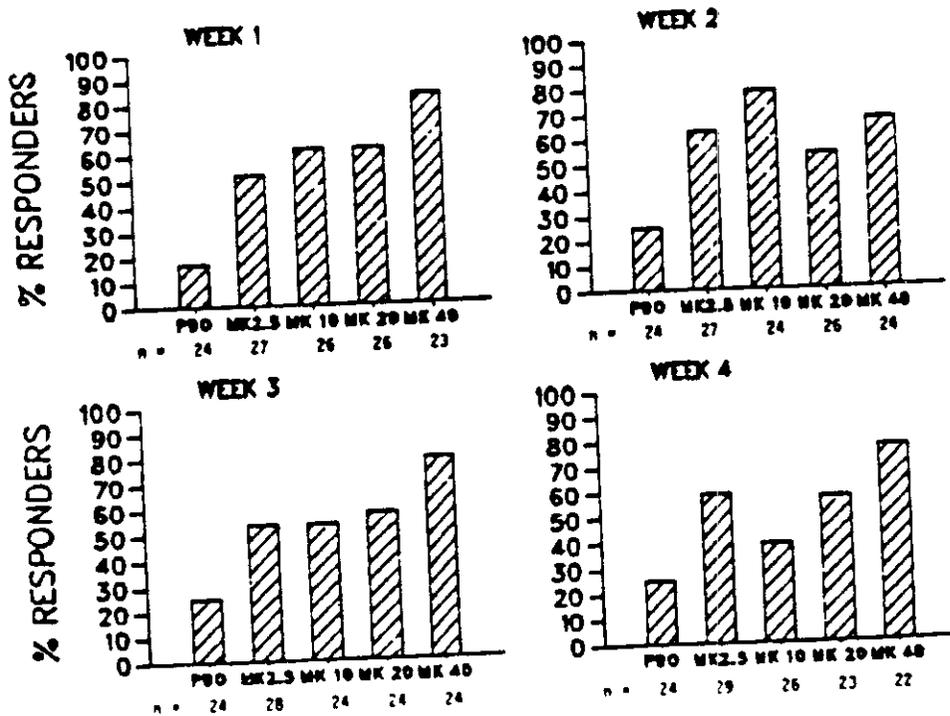


A dose-response relationship was also suggested at Weeks 2 (NS) and 4 ( $p = 0.056$ ), although the 2.5 group had a better response than was expected at these weeks.

Over the dose range tested, more than 50 pct. of patients (with the exception of the 10 mg b.i.d. dose at Week 4) demonstrated an excellent or good response (previously defined) at Week 4 (see Figure 9).

Figure 9

Enalapril Dose-Response Study  
Good or Excellent Response  
(Gavras et al)



The proportion of patients with a good or excellent response was significantly greater in the groups treated with enalapril than in the placebo group for every comparison at every week except enalapril 10 mg (39 pct.) versus placebo (25 pct.) at Week 4. With the exception of the unexplained finding at Week 4, 62, 79 and 54 percent of patients were good or excellent responders to the 10 mg dose at the end of Treatment Weeks 1, 2, and 3, respectively.

The 10 mg dose of enalapril resulted in a 10 mmHg decrease in mean diastolic blood pressure (from 96.2 to 86.2 mmHg) by three weeks of treatment, with approximately 54 percent of the patients achieving an excellent or good response at this dose level.

At completion of the first four treatment weeks, the investigator had the option to prescribe hydrochlorothiazide for patients who were nonresponders (a sitting diastolic blood pressure  $>90$  mmHg, or a decrease of  $<10$  mmHg from baseline). The proportion of enalapril-treated patients requiring the addition of hydrochlorothiazide was significantly less than the proportion of placebo patients requiring hydrochlorothiazide (Table 6) for each dosage.

Table 6

Patients Requiring the Addition of HCTZ  
at the End of Treatment Week 4  
(Gavras et al)

<u>Treatment Group</u>	<u>Requiring HCTZ</u>	
	<u>No.</u>	<u>Percent</u>
Placebo	18/28	64
2.5 mg b.i.d.	9/29*	31
10 mg b.i.d.	8/28**	29
20 mg b.i.d.	8/28**	29
→ 40 mg b.i.d.	4/26**	15

\*Significantly different from  
placebo,  $p < 0.05$ .

\*\*Significantly different from  
placebo  $p < 0.01$ .

- 2) Wilhelmsson and Berglund. International Dose-Response Study.

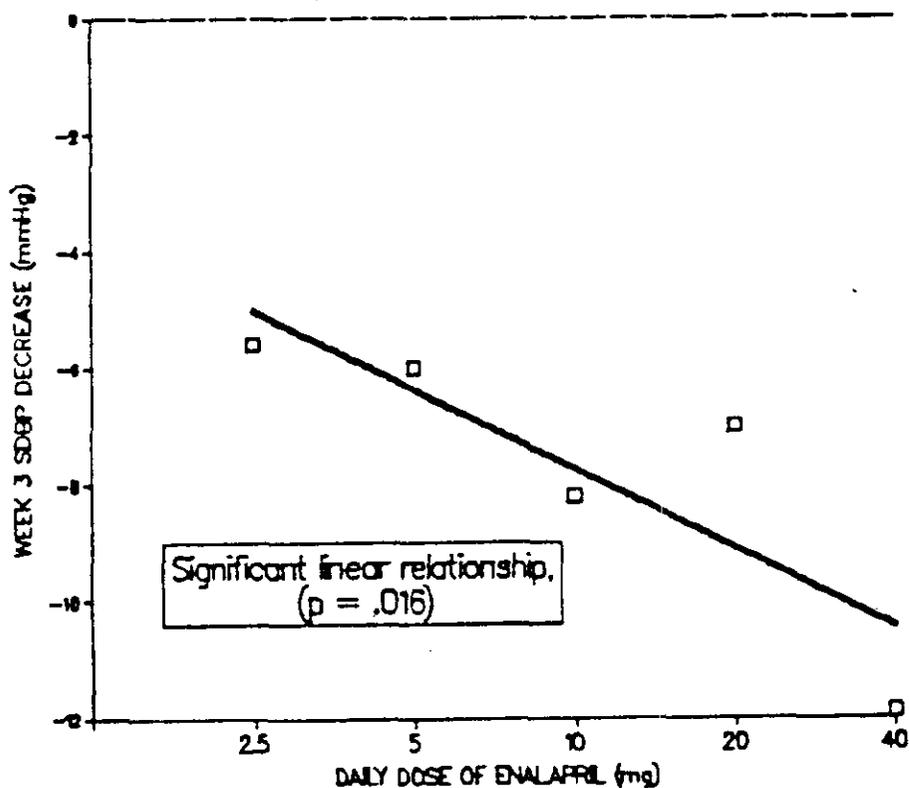
The dose-response relationship of enalapril was studied in a two-part, multicenter international clinical trial in Sweden (Wilhelmsson MA No. 566, Berglund MA No. 579). The first part of the study (DR-I) was a double-blind, balanced, two-period incomplete-block crossover study. Each of 91 patients received two of the following enalapril doses for up to three weeks each preceded by a four-week placebo washout: placebo, 2.5, 5, 10, 20, or 40 mg per day taken b.i.d.

No significant changes from baseline were observed after placebo and significant decreases in every blood

pressure variable [supine systolic (SSBP), diastolic (SDBP) and mean arterial (SMAP), and erect systolic (ESBP), diastolic (EDBP) and mean arterial (EMAP)] were observed after every enalapril dose in an increasing dose-response relationship. The effects of each dose on supine diastolic blood pressure following three weeks of therapy are displayed in Figure 10.

Figure 10

Enalapril Dose-Response Study (Period I) Week 3  
of Parallel Studies Preceded by Four-Week Placebo Washout  
(overall mean SDBP prior to first enalapril dose was 97 mmHg)  
(Wilhelmsson and Berglund, No. 566 and 579)

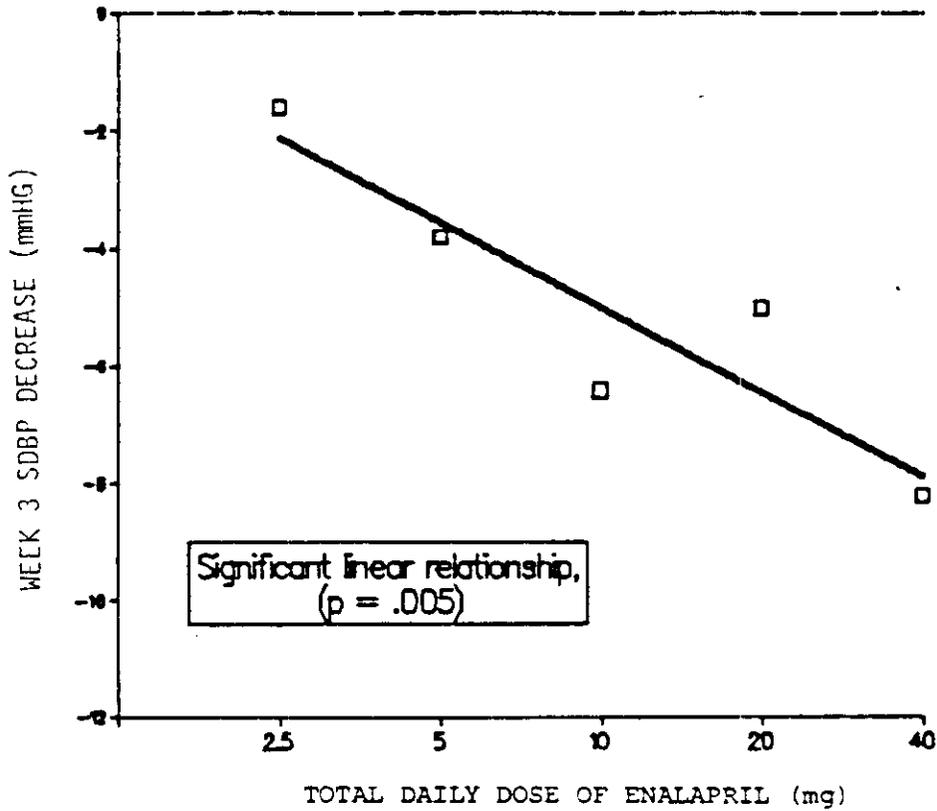


All differences from placebo, except that for ESBP 2.5 mg, were significant; and the linear dose-response relationship was significant ( $p < 0.02$ ) for all but EDBP (for which  $p = 0.12$ ). The slopes of the dose-response relationship were  $-3.3$  and  $-1.4$  mmHg per dose increment for SSBP and SDBP, respectively. Adjusted (for baseline covariance) mean supine blood pressure changes ranged from  $-8/-6$  mmHg for 2.5 mg to  $-21/-12$  mmHg for 40 mg in an increasing dose-response fashion. The results of this study indicate an increasing dose response across the 2.5-40 mg per day range with 2.5 mg per day as the minimum effective dose.

Following the first part of the study (DR-I), a double-blind, parallel (extension) study (DR-II) was set up to further characterize the enalapril dose-response relationship. Specifically, 67 of the 91 patients who participated in DR-I, received, at random, one of the following enalapril doses for up to 12 weeks preceded by a 4-6 week placebo washout: 1.25, 10, 40, or 80 mg per day taken b.i.d. The effects of each dose on mean supine diastolic blood pressure following three weeks of therapy are displayed in Figure 11.

Figure 11

Enalapril Dose-Response at (Period II) Week 3  
(overall mean SDBP prior to first enalapril dose was 95 mmHg)  
(Wilhelmsson and Berglund, No. 566 and 579)



The results of DR-II indicate an increasing dose response from 1.25-10 mg per day but no increase in the dose response above 10 mg per day.

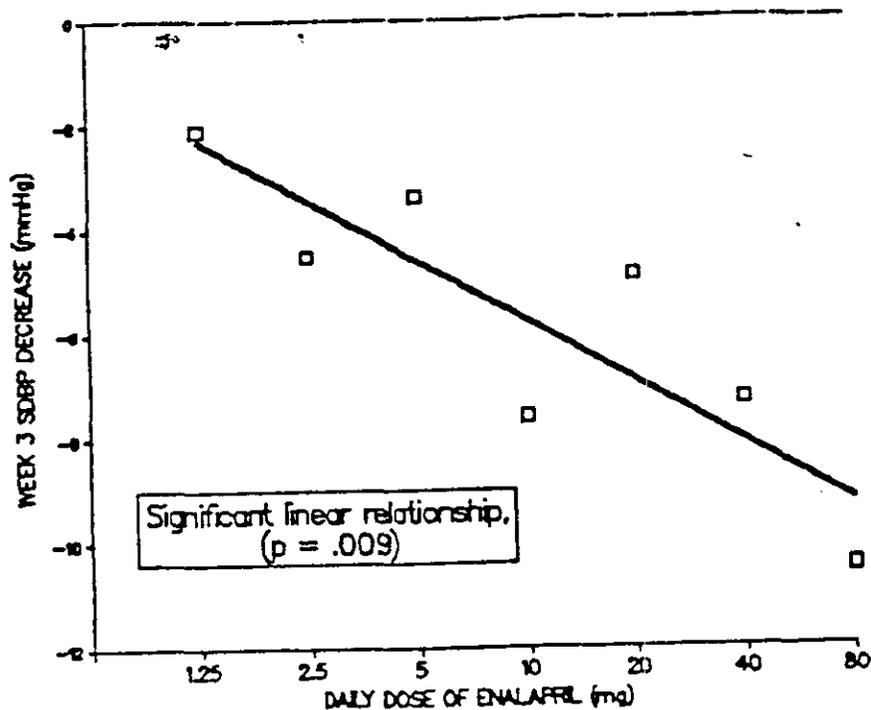
Of the 91 patients who entered DR-I and the 67 who entered DR-II, 57 had complete blood pressure data after three weeks of test therapy in Periods 1 and 2, (DR-I), and 3 (DR-II).

Adjusted mean decreases from baseline were observed in every blood pressure variable after placebo, although

none reached significance (mean supine blood pressure changes were -2/-3 mmHg). SSBP/SDBP mean decreases were significant for 2.5 and 10-80 mg per day and ranged from -4/-2 to -24/-11 mmHg over the 1.25-80 mg per day range. The linear dose-response relationship was significant for every blood pressure variable except EDBP for which  $p = 0.07$  (the slopes for SSBP and SDBP were -3.0 and -1.2 mmHg per dose increment, respectively). The effects of each dose on combined mean sitting diastolic blood pressure after three weeks of therapy in Periods 1 and 2 (DR-I), and 3 (DR-II) are shown in Figure 12.

Figure 12

Enalapril Dose-Response Studies I and II at Week 3  
(overall mean SDBP prior to first enalapril dose was 98 mmHg)  
(Wilhelmsson and Berglund, No. 566 and 579)



When the DR-II results are pooled with DR-I to adjust for possible interpatient differences, after three weeks of b.i.d. therapy, the dose response of enalapril in mild hypertensive patients begins in the 1.25-5 mg per day range and is gradually increasing up through 80 mg per day, the highest dose tested. This data is consistent with results from the domestic parallel design study discussed above and with the analysis of Periods 1 and 2 (DR-I) alone and when combined.

#### Once Vs. Twice Daily Dose Studies

##### a) Once Versus Twice Daily Dosing with Enalapril Alone in Essential Hypertension

Since enalapril is a long-acting compound, studies were conducted domestically and internationally to determine if once-a-day and twice-a-day dosage regimens produced similar results in the control of hypertension.

Dr. Velasco (Study No. 522) and Dr. Wilhelmsson (Study No. 524) conducted a double-blind, two-period crossover study to compare once daily and twice daily regimens of enalapril in outpatients with mild essential hypertension. Fifty-six patients entered

this study after a two-week washout. Patients were then randomly assigned to receive either 20 mg enalapril q.d. in Period 1 and 10 mg enalapril b.i.d. in Period 2 (Group A) or 10 mg enalapril b.i.d. in Period 1 and 20 mg enalapril q.d. in Period 2 (Group B). There was a two-week placebo washout between periods.

There were no significant between-treatment differences in mean supine and erect blood pressure or in change from baseline at Week 4 as can be seen in the following table. Pressure measurements were made within the hour prior to the morning and evening doses.

Table 8

Mean Supine Blood Pressure (Systolic/Diastolic: mmHg)  
(Velasco and Wilhelmsson, No. 522 and 524)

<u>REGIMEN</u>	<u>n*</u>	<u>WEEK 0</u>	<u>WEEK 4</u>	<u>CHANGE**</u>	<u>CHANGE %</u>
q.d.	53	162/104	146/92	-17/-11	-10/-11
b.i.d.	53	161/102	145/92	-16/-11	-10/-11

MEAN ERECT BLOOD PRESSURE (SYSTOLIC/DIASTOLIC; mmHg)

q.d.	53	162/106	142/94	-20/-12	-12/-11
b.i.d.	53	159/105	139/93	-20/-12	-13/-11

\* Three of the 56 patients were excluded from the statistical evaluation, because they were unable to attend their Week 4, Period 2 visits.

\*\* All within-treatment changes were significant ( $p < 0.001$ )

These data suggest that once-a-day and twice-a-day dosage regimens of enalapril (20 mg/day) reduce blood pressure to a similar extent in patients with mild to moderate essential hypertension after 4 weeks of treatment.

Two studies (McMahon No. 12 and Lowenthal No. 13; and Holland No. 14) were conducted domestically. All of the studies were multiple dose, double-blind, crossover design studies, with a baseline washout period followed by two, four-week active treatment periods separated by an interim placebo washout period. The studies differed in the total daily dose of enalapril and length of washout periods. Sitting and supine systolic and diastolic blood pressure, pulse and respirations were monitored at 0 Hour (time of dosing) and then every hour for the next 12 hours on Days -1, 1, and 28; at 14, 16, and 18 hours on Days 1 and 28; and at -1, -1/2, and 0 Hour on Days 2 and 29; and on the day the patients visited clinic at the end of each treatment week.

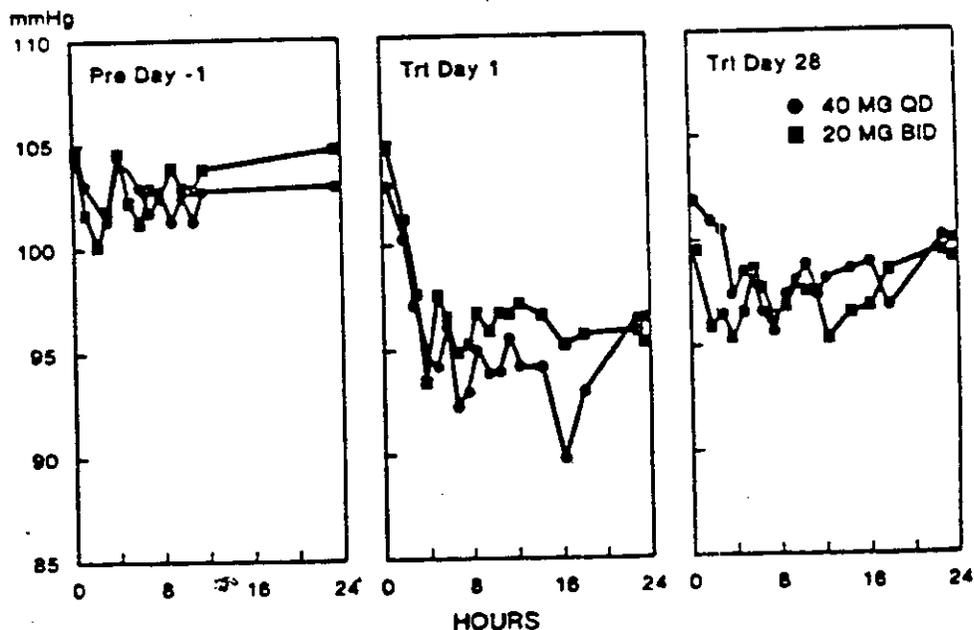
In Study Nos. 12 and 13 conducted by Dr. McMahon and Dr. Lowenthal, respectively, 32 patients with essential hypertension were randomly allocated to receive either 40 mg enalapril q.d. or 20 mg enalapril b.i.d. Each treatment was administered for four weeks with a two-week placebo washout between treatments.

Patients then received the alternate treatment, either 40 mg q.d. or 20 mg b.i.d. for an additional four-week period.

As can be seen in Figure 13, mean standing diastolic blood pressures were similar at almost all hours on Days 1 and 28 of both dosage regimens. Significant decreases from prestudy were observed within both dosage regimens on Day 1 and were still present after four weeks of treatment at most hours.

Figure 13

Mean Standing Diastolic Blood Pressure 40 mg  
Enalapril Once-A-Day vs. 20 mg Enalapril Twice-A-Day  
(n=27)  
(McMahon and Lowenthal, No. 12 and 13)



Note: Not All Patients Present Data at All Times.

Mean standing and supine systolic blood pressure was significantly lower for the q.d. regimen than for the b.i.d. regimen at most hours on Day 1. However, after four weeks of treatment mean systolic blood pressure was similar for both dosage regimens.

No significant differences between or consistent changes within treatment regimens were observed for respirations per minute, pulse, temperature, body weight, or plasma renin activity.

In a similarly designed study (Holland No. 14), mean standing and supine systolic and diastolic blood pressures were comparably reduced by either 10 mg enalapril b.i.d. or 20 mg enalapril q.d. (Table 9). However, because of the small study population (n=7), no statistical analysis of this data was performed.

Table 9

Effects on Once-Daily vs. Twice-Daily Enalapril on Blood (Holland, No. 14<sup>9</sup>)

<u>Parameter</u>	<u>Unit</u>	<u>20 mg Enalapril q.d.</u>				<u>10 mg Enalapril b.i.d.</u>		
		<u>Day</u>	<u>N</u>	<u>Mean</u>	<u>STD</u>	<u>N</u>	<u>Mean</u>	<u>STD</u>
Standing Diastolic Blood Pressure	mmHg	1	7	101	9.04	7	100	7.76
		28	6	89	8.35	7	86	7.95
Standing Systolic Blood Pressure	mmHg	1	7	140	17.94	7	141	19.17
		28	6	130	9.35	7	127	10.95
Supine Diastolic Blood Pressure	mmHg	1	7	99	7.80	5	95	11.86
		28	5	92	9.42	7	87	9.23
Supine Systolic Blood Pressure	mmHg	1	7	141	19.07	5	147	24.11
		28	5	148	18.76	7	138	13.92

A Phase III double-blind, randomized, controlled, dose-finding, multiclinic once-a-day vs. twice-a-day study in a parallel design was conducted by six investigators (Brown et al., DP No. 1). Patients had mild hypertension (supine diastolic blood pressure 90-104 mmHg).

After an initial placebo washout period of four weeks, enalapril once daily (active drug in the morning and placebo in the evening), enalapril twice daily, or placebo twice daily, was administered to 169 patients. Enalapril once daily was titrated from 10 mg q.d. to 20 mg q.d. to 40 mg q.d. at four-week intervals. Enalapril twice daily was titrated from 5 mg b.i.d. to 10 mg b.i.d. to 20 mg b.i.d. at four-week intervals. No upward dose titration occurred if the supine diastolic blood pressure was <80 mmHg. Placebo was titrated at identical intervals.

Compared to placebo, enalapril administered either once daily or twice daily was effective in lowering both systolic and diastolic blood pressure at virtually all time points. Blood pressure reductions tended to be greater in the twice-daily enalapril group than in the once-daily group, but the differences were not statistically significant.

At the end of Week 4 (when both enalapril groups had completed four weeks of 10 mg therapy, i.e., 10 mg q.d. or 5 mg b.i.d.) 46.3 percent of the enalapril 10 mg q.d. group and 44 percent of the enalapril 5 mg b.i.d. group had either an excellent or good response. An excellent response was defined as reduction of supine diastolic blood pressure to 85 mmHg or less. A good response was defined as a reduction of the supine diastolic blood pressure by 10 mmHg from baseline. The proportion of these responses at Week 4 is given in the table below.

Table 10

Proportion of Excellent and Good Responders  
After Four Weeks of Treatment With Total  
Daily Dose of 10 mg Enalapril  
(Domestic Protocol No. 1)

	N	Treatment Week 4			
		Excellent		Good	
		No.	Pct.	No.	Pct.
ENAL 10 mg QD	54	19	35.2	6	11.1
ENAL 5 mg BID	50	20	40.0	2	4.0
PLACEBO	50	9	18.0	1	2.0

In this study, the percent of good or excellent responders was similar, whether enalapril was administered q.d. (10 mg) or b.i.d. (5 mg), and this response rate was comparable to that reported in other studies (deIGreco et al, DP No. 3; Abbott et al, IP No. 1; Brown et al, DP Nos. 4 and 5).

b) Once Daily Versus Twice Daily Dosing With Enalapril and Hydrochlorothiazide in Essential Hypertension

Two enalapril studies were designed to determine the safety, tolerance, and efficacy of enalapril and hydrochlorothiazide, each given alone and concomitantly.

In the first study, Ferguson No. 4, using a once-daily treatment regimen, one group of patients, Group I, received each of the following drugs in random order for two weeks: enalapril 5 mg, hydrochlorothiazide 50 mg, and enalapril 5 mg/hydrochlorothiazide 50 mg. Group II received in random order: enalapril 10 mg, hydrochlorothiazide 50 mg, and enalapril 10 mg/hydrochlorothiazide 50 mg.

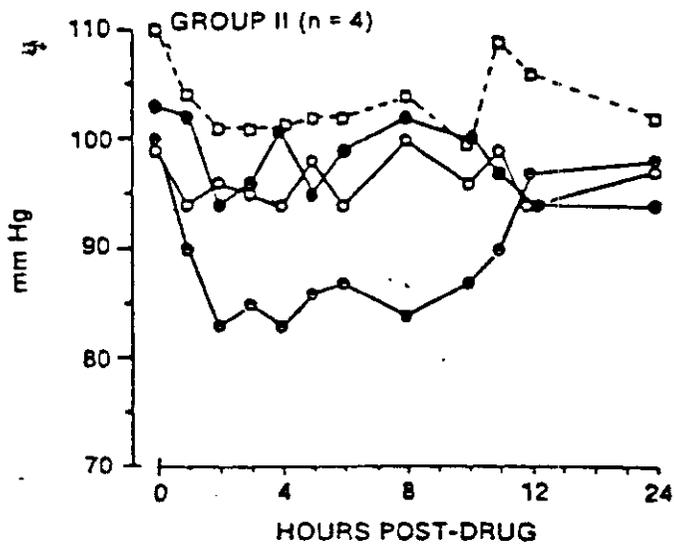
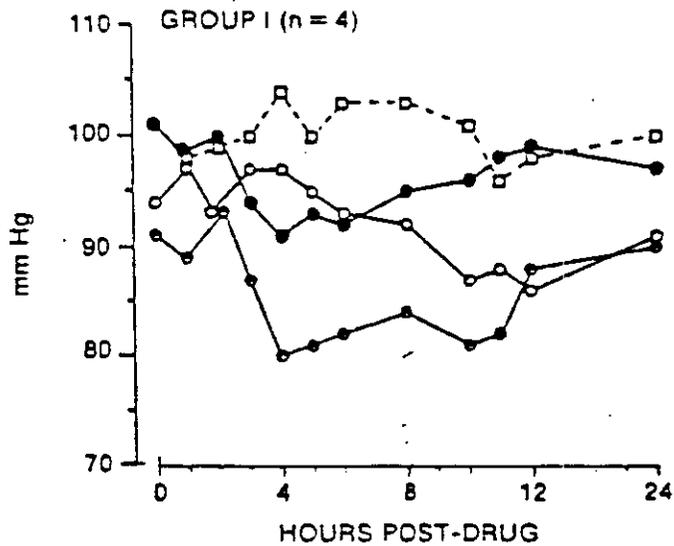
In the second study, Ferguson No. 22, following a two-week no-treatment washout period, each patient received enalapril 20 mg b.i.d., hydrochlorothiazide 25 mg b.i.d., and enalapril 20 mg plus hydrochlorothiazide 25 mg b.i.d. for successive two-week periods.

Results of these studies, one with a q.d. regimen and the other with a b.i.d. regimen, were similar.

In these small studies, mean sitting diastolic blood pressure (SDBP) was significantly decreased from baseline only for the enalapril plus hydrochlorothiazide treatments. For Ferguson No. 4, Figure 14 demonstrates mean SDBP on Day 14 for Group I and Group II, respectively. These treatments were given once a day.

Figure 14

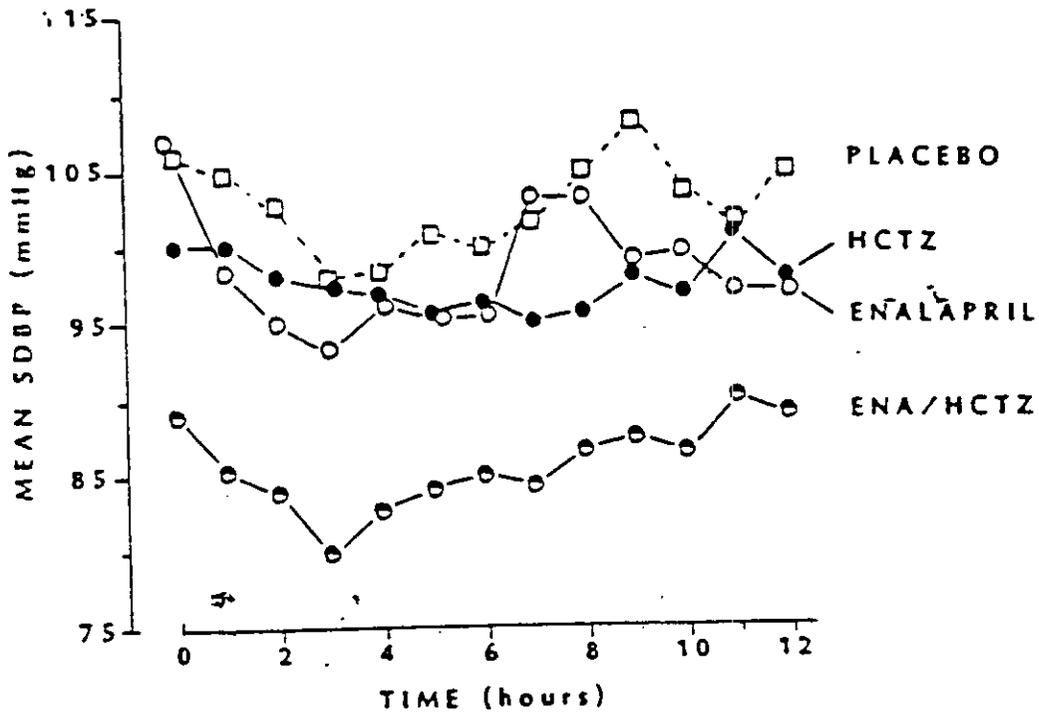
Mean Seated Diastolic Blood Pressure  
Day 14  
(Ferguson No. 4)



Mean seated diastolic blood pressure (SDBP) response at various times after drug on 14th treatment day in the two groups in comparison with baseline (placebo) day. Group I received 5 mg enalapril; Group II, 10 mg Placebo (□); enalapril (●); hydrochlorothiazide (○); the combination (◐).

Figure 15

Antihypertensive Effects of Enalapril, HCTZ, and Their Combination (n=14) (Ferguson No. 22)



Hydrochlorothiazide combined with 5 and 10 mg enalapril controlled blood pressure ( $<90$  mmHg) up to 11 hours; the single entities did not show this control. Figure 15 demonstrates mean SDBP for Ferguson No. 22 study on Day 14 at baseline (placebo)

and following hydrochlorothiazide 25 mg b.i.d., enalapril 20 mg b.i.d., and enalapril 20 mg plus hydrochlorothiazide 25 mg b.i.d. In this study 12-hour blood pressure control (<90 mmHg) was achieved by two patients on the enalapril b.i.d. alone therapy, one patient on the hydrochlorothiazide b.i.d. alone, and 11 patients on the combination.

In light of these findings, a single study, Mitchell No. 20, was conducted to compare a once versus twice-daily regimen of enalapril plus hydrochlorothiazide.

Dr. Mitchell's study was a double-blind, multiple-dose, randomized crossover study to determine the safety, tolerability and efficacy of 40 mg enalapril plus 50 mg hydrochlorothiazide (HCTZ) once daily vs. 20 mg enalapril plus 25 mg HCTZ administered twice daily to 22 patients with essential hypertension. After a three-week placebo washout period, patients meeting entrance criteria were randomly assigned to one of the two dosage regimens for four weeks. Following a three-week interim placebo washout period, patients crossed over to the alternate treatment regimen.

Significant reductions in diastolic blood pressure were observed for both treatment regimens on Day 1 (5 to 15 mmHg) with significantly greater reductions seen after four weeks of therapy (12 to 23 mmHg) (Figure 16). Figure 17 demonstrates mean changes in SDBP for the two regimens. Similar results were observed for standing and supine systolic blood pressure.

Figure 16

Mean Standing Diastolic Blood Pressure  
Enalapril Study No. 20 (Mitchell/Taylor) (n=12)  
40 mg Enalapril/50 mg HCTZ q.d. vs.  
20 mg Enalapril/25 mg HCTZ b.i.d.

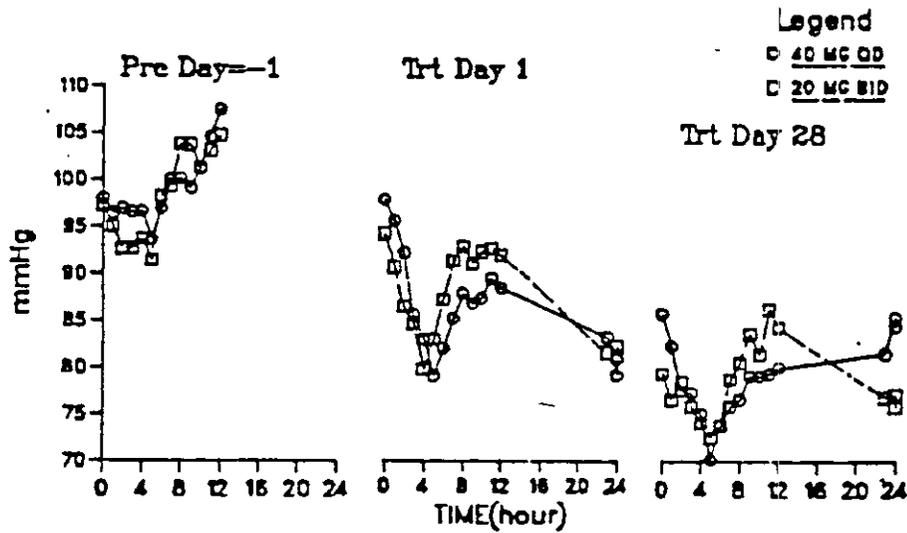
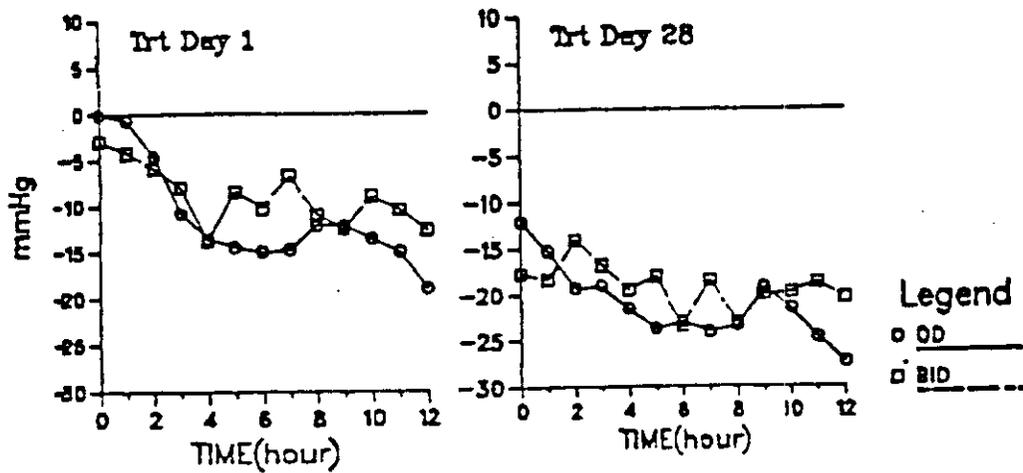


Figure 17

Mean Change in Standing Diastolic Blood Pressure  
Enalapril Study No. 20 (Mitchell/Taylor) (n=12)  
40 mg Enalapril/50 mg HCTZ q.d. vs.  
20 mg Enalapril/25 mg HCTZ b.i.d.



## Tolerability and Safety in Hypertension Studies

### a) Open Dose-Ranging Studies

During the dose ranging portion of the four studies (Ferguson No. 1, Gavras No. 2, Larochelle No. 3, Case/Atlas No. 9), tolerability and safety were assessed by continuous measurements of vital signs and clinical and laboratory adverse experience monitoring.

The most common clinical adverse experiences reported were: tiredness and weakness, dizziness, headache, and nausea. None of these were considered serious or of clinical significance; none of the patients discontinued the study because of the occurrence of an adverse experience. There was no evidence of a dose-related increase in clinical adverse experiences in any of these studies.

There were no dose-related changes in laboratory adverse experiences and none was considered serious or clinically significant.

### b) Controlled Studies

In the controlled, multicenter, dose-range study (Gavras et al), the incidence of adverse clinical

experiences was similar in all treatment groups. Specific reports included: fatigue, diarrhea, leg pain, dizziness, headache and common cold, as can be seen in the following table.

Table 11

Adverse Clinical Experiences in Patients  
on Enalapril or Placebo  
(Gavras et al)

	Enal 2.5 mg		Enal 10 mg		Enal 20 mg		Enal 40 mg		Placebo	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Fatigue	1/29	3.4					2/26	7.7		
Diarrhea							2/26	7.7	1/28	3.6
Leg pain	1/29	3.4	1/28	3.6	1/28	3.6				
Dizziness					2/28	7.1			2/26	7.7
Headache	3/29	10.3	1/28	3.6	4/28	14.3	2/26	7.7	3/28	10.7
Common Cold	1/29	3.4			1/28	3.6			1/28	3.6
Cough	1/29	3.4			1/28	3.6				
Sinusitis	1/29	3.4			1/28	3.6				
Flushing	1/29	3.4					1/26	3.8		
Skin Rash	1/29	3.4	1/28	3.6						

Six patients discontinued therapy due to an adverse experience; one while on placebo, three while receiving 10, 20, and 40 mg of enalapril b.i.d., one while receiving enalapril 2.5 mg plus hydrochlorothiazide, and one while receiving enalapril 20 mg plus hydrochlorothiazide. There was no evidence that higher doses of enalapril were associated with a greater incidence of adverse experiences.

In the multicenter trial in Sweden conducted by Dr. Wilhelmsson (No. 566) and Dr. Berglund (No. 579), 12 of the 91 patients reported 13 adverse clinical experiences. Two patients on placebo had headaches, four had dizziness, one had nausea, and one had

palpitations. One patient on enalapril 5 mg had dizziness. One patient on enalapril 10 mg experienced vertigo. Three patients taking enalapril 20 mg had adverse experiences: one had indigestion, one had dizziness, and one experienced vertigo. None of these clinical adverse experiences was serious and all patients recovered. There was no relationship between dosage and frequency of adverse experiences.

Five patients treated with enalapril had adverse laboratory experiences which consisted in all cases of elevated serum creatinines. None was serious, and there was no relationship to enalapril therapy established.

c) Once Vs. Twice Daily Dose Studies

- 1) In the McMahon (No. 12 ) and Lowenthal (No. 13) study of enalapril 40 mg q.d. versus 20 mg b.i.d., 19 patients reported at least one clinical adverse experience: 16 while or after receiving enalapril 40 mg q.d., and 10 while or after receiving enalapril 20 mg b.i.d. Seven patients reported adverse experiences during both treatment periods. Only one patient reported an adverse experience during the interim placebo period. Patient No. 34 experienced a myocardial infarction which was considered definitely

not drug related.

Thirteen patients had at least one adverse laboratory experience: ten while or after receiving 40 mg q.d. and nine while or after receiving 20 mg b.i.d. Six patients reported adverse laboratory experiences during both treatment periods. This frequency of laboratory adverse experiences was similar for both dosage regimens.

In Dr. Holland's study (No. 14) of enalapril 20 mg q.d. vs. 10 mg b.i.d., three of the eight patients reported clinical adverse reactions, none of which were serious. One of the eight patients had a laboratory value (elevated SGOT) which was considered adverse while receiving enalapril 20 mg q.d. None of the adverse reactions appeared to be dose related.

Of the 56 patients in Dr. Velasco's study (No. 522) and Dr. Wilhelmsson's study (No. 524) enalapril 20 mg q.d. vs. 10 mg b.i.d., two patients who had been taking placebo had adverse experiences, one of which (epigastric pain) was rated as definitely drug related. Six patients taking enalapril had a total of seven clinical adverse experiences. Only one patient had adverse experiences (diarrhea and epigastric pain) which were considered as possibly drug related. One

patient had an adverse experience on both q.d. and b.i.d. regimens, one on q.d. only and four on b.i.d. only. There were no adverse laboratory experiences.

- 2) Eighteen of the 22 patients (82 percent) treated in Dr. Mitchell's study (No. 20), receiving enalapril 40 mg plus hydrochlorothiazide 50 mg q.d. versus enalapril 20 mg plus 25 mg hydrochlorothiazide b.i.d., reported one or more clinical adverse experiences: 10 while or after receiving the once daily regimen and 13 while or after receipt of the twice-daily regimen. Five of these reported clinical adverse experiences during both treatment periods. One patient reported an adverse experience during a placebo washout interval; this was not reflected in these frequencies. The incidence of adverse experiences was similar for the two dosage regimens. The most commonly reported adverse experiences were lethargy, tiredness and fatigue, lightheadedness, dizziness and faintness, muscle cramps and sore muscles and headaches. In most cases, these clinical experiences are characteristic effects of diuretics and may be related to the hydrochlorothiazide component of the treatment.

Twelve patients had at least one laboratory adverse experience that was not noted prestudy: six while on or after receiving 40 mg enalapril with 50 mg hydrochlorothiazide once daily and 12 while or after receipt of 20 mg enalapril with 25 mg hydrochlorothiazide twice daily. Six of these patients had laboratory adverse experiences during both treatment periods. The frequency of laboratory adverse experiences was significantly higher for the twice daily regimen than for the once daily regimen. One hundred fifteen adverse laboratory experiences were noted during drug therapy. Of these, however, 63 had also been noted for the respective patients during prestudy monitoring. Only three of the effects required treatment; these had also been treated prestudy.

Eleven of the effects noted were considered serious. These were all experienced by Patient No. 24.

2) Dose Ranging Studies in Patients with Congestive Heart Failure:

The safety and efficacy of enalapril has also been assessed in 243 patients with congestive heart failure (refer to Table 1).

- a) A pilot study with 11 investigators (Cohn et al) was conducted to determine the effects of repeated single oral doses of enalapril ranging from 1.25 to 40 mg.

This was an open pilot study consisting of three periods: a prestudy screening and stabilization period (Period 1), and inpatient titration period (Period 2) and an outpatient maintenance period of up to four months duration (Period 3).

Seventy-three patients entered and completed Periods 1 and 2; 65 patients entered and 60 completed Period 3. Eight patients did not enter Period 3 due to various reasons which included: death, poor compliance, ineffective therapy, and adverse experiences.

In Period 2, enalapril dosing began at 1.25 mg and was titrated to a maximum of 40 mg per day. The optimum dosage distribution was as follows: 2.5 mg (26 pct.), 5 mg (41 pct.), 10 mg (22 pct.), 20 mg (5 pct.), or 40 mg (3 pct.).

Data from this early dose-ranging study indicate that optimal doses of enalapril ranging from 2.5 to 10 mg produced clinically significant acute hemodynamic changes. Statistically significant improvement from baseline (Day 1, Hour 0) was observed in all

hemodynamic variables (Table 12). Cardiac output and stroke volume were higher and mean arterial blood pressure, heart rate, pulmonary vascular resistance, and pulmonary capillary wedge pressure were lower beginning at one hour post-dose.

MAP reduction was not abrupt. Rather, it was gradual with a nadir of approximately eight hours post-dose. Although CO and SV increased, HR did not increase, and myocardial oxygen demand (as measured by HRPP) was actually reduced.

Table 12

Acute (Optimal Dose) Hemodynamic Efficacy  
(Cohn et al)

<u>Variable</u>	<u>N</u>	<u>Mean Peak<sup>a</sup></u>	<u>95 Pct. Confidence Interval</u>	
HR (bpm)	72	-9.22	11.46	-6.99
SSBP (mmHg)	68	-27.35	-32.12	-22.58
SDBP (mmHg)	68	17.41	-19.74	-15.09
SMAP (mmHg)	72	20.54	-23.26	-17.83
RAP (mmHg)	70	4.91	-5.72	-4.11
SPAP (mmHg)	63	-12.98	-15.23	-10.74
DPAP (mmHg)	63	-8.83	-10.15	-7.50
MPAP (mmHg)	68	-10.18	-11.66	-8.69
PCWP (mmHg)	66	-9.47	-10.87	-8.07
CO (L/min)	71	1.52	1.14	1.91
CI (L/min/M <sup>2</sup> )	71	0.82	0.62	1.02
SVR (dyne sec/cm <sup>5</sup> )	70	-693.54	-796.14	-590.95
SV (ml/beat)	71	26.88	20.82	32.94
SVI (ml/beat/m <sup>2</sup> )	71	14.57	11.43	17.72
SWI (G min/m <sup>2</sup> )	62	36.42	26.94	45.91
PVR (dyne sec/cm <sup>5</sup> )	62	-128.46	-161.15	-95.76
HRPP (mmHg bpm)	68	3111.1	3637.4	2584.8

<sup>a</sup>Maximum change from Day 1, 0 Hour.

The percentage change from baseline at peak effect after the initial dose was -12 percent for PCWP, 14 percent for CI, -20 percent for SVP, -12 percent for MAP, and -3 percent for HR (all  $p < 0.002$ ).

Chronic therapy for periods up to four months resulted in continued significant improvement from baseline (Day 1, 0 Hour) for all hemodynamic variables (Table 13). The optimal daily dose of enalapril was 20 mg (given q.d. or b.i.d.) in 53 percent of the patients, 10 mg in 32 percent.

TABLE 13

CHRONIC HEMODYNAMIC EFFICACY  
(Taken From Tables 8 and 12 of Attachment 2)  
(Cohn, et al)

<u>VARIABLE</u>	<u>n</u>	<u>AT HOUR 0</u>	<u>MEAN PEAK<sup>a,b</sup></u>	<u>95% CONFIDENCE INTERVAL FOR MEAN PEAK</u>	
HR (bpm)	37	-3.54*	-8.68	-11.62,	-5.74
SSBP (mmHg)	37	-11.78***	-20.65	-27.15,	-14.15
SDBP (mmHg)	37	-6.76**	-13.95	-17.83,	-10.07
SMAP (mmHg)	37	-8.43***	-15.92	-19.92,	-11.92
RAP (mmHg)	32	-4.18**	-6.25	-8.79,	-3.71
SPAP (mmHg)	35	-9.97**	-16.83	-23.03,	-10.63
DPAP (mmHg)	35	-6.34**	-10.17	-14.14,	-6.20
MPAP (mmHg)	36	-7.51**	-12.14	-16.58,	-7.70
PCWP (mmHg)	33	-5.21***	-9.42	-11.59,	-7.26
CO (L/min)	34	0.54***	1.07	0.76,	1.38
CI (L/min/m <sup>2</sup> )	34	0.29***	0.58	0.42,	0.74
SVR (dyne·sec/cm <sup>5</sup> )	31	-280.80***	-506.58	-670.09,	-343.07
SV (ml/beat)	34	9.05***	17.48	12.63,	22.33
SVI (ml/beat/m <sup>2</sup> )	34	4.93***	9.57	7.03,	12.11
SWI (G·min/m <sup>2</sup> )	32	11.62+	31.17	18.92,	43.42
PVR (dyne·sec/cm <sup>5</sup> )	32	-44.01**	-112.07	-150.26,	-73.87
HRPP (mmHg·bpm)	37	-1372***	-2439.5	-3096.7,	-1782.2

<sup>a</sup>Maximum change from Day 1, Hour 0

<sup>b</sup>By definition of peak,  $p < 0.001$  for all variables

\*, \*\*, \*\*\* Significant change from Day 1, Hour 0;  $p < 0.05$ ,  $p < 0.01$ ,  $p < 0.001$ , respectively

+ $p = 0.07$

As a further assessment of enalapril efficacy, New York Heart Association functional class was compared prior to and following long term therapy (one to four months) in 32 of the patients (Table 14). The NYHA functional class improved ( $p < 0.01$ ) in 69 percent of the patients, 28 percent showed no improvement and 3 percent (one patient) worsened on class level.

Table 14

Change in NYHA Functional Classification  
After 1-4 Months Therapy (n=32)  
(Cohn et al)

N.Y.H.A. Class (change)	-2	-1	-0.5*	0	1
Number (pct.) patients	5 (16)	14 (44)	3 (9)	9 (28)	1 (3)

\*Result of II-III and III-IV ratings.

Exercise tolerance was also used as a measure of efficacy and improved 32 percent from a mean baseline value of 7.1 minutes to 9.9 minutes after one to four months of enalapril therapy.

- b) In addition to this open label, pilot study, two double-blind, randomized, parallel, placebo-controlled multicenter studies were performed.

A total of 51 patients entered the 14-week domestic study (Chrysant et al), 24 patients were randomly assigned to the enalapril group and 26 to the placebo group. One patient was not randomized to therapy with a study drug.

The baseline period consisted of one or two weeks during which the patient's cardiac status remained stable without changing the dose of digitalis and diuretic (Period 1). The first two to three days of the 12-week double-blind treatment period was an inpatient, open-label titration phase (Period 2). On the first day, patients received 2.5 mg as their first dose and 5 mg as their second dose 12 hours later. Each patient was titrated to a clinically effective dose not to exceed 10 mg b.i.d. enalapril during the next two days. On the third or fourth day of the 12-week treatment period (Period 3), eligible patients were randomized to the double-blind portion of the study to receive either enalapril or placebo according to the allocation schedule. Randomization was further defined by exercise capacity at baseline.

The second double-blind, placebo-controlled study (Athassiades et al) was of similar design with the exception of the 12-week treatment period randomization. In this period, patients were

randomized into two groups: Group 1 received enalapril 5 to 10 mg (in 5 mg tablets) b.i.d. plus the dose of digitalis and/or diuretics; Group 2 received placebo one to two tablets b.i.d. (matching the enalapril tablets) plus the dose of digitalis and/or diuretics as established during baseline.

One hundred nineteen patients entered the treatment period (57 in the enalapril group and 62 in the placebo group). Of this group, 97 patients completed the study (47 in the enalapril group and 50 in the placebo group).

Exercise tolerance as measured by exercise duration (time on treadmill) was the objective endpoint in these two studies. Enalapril was superior to placebo increasing the duration of exercise. Figures 28 and 29 represent the adjusted mean change in duration of exercise in the domestic double-blind study. The changes in exercise duration were similar in the international study.

Figure 28

MK-421 Congestive Heart Failure  
Adjusted Mean Change in Duration of Exercise (Treadmill)  
Baseline NYHA Cardiac Status of 2, 3, or 4  
(Chrysant et al)

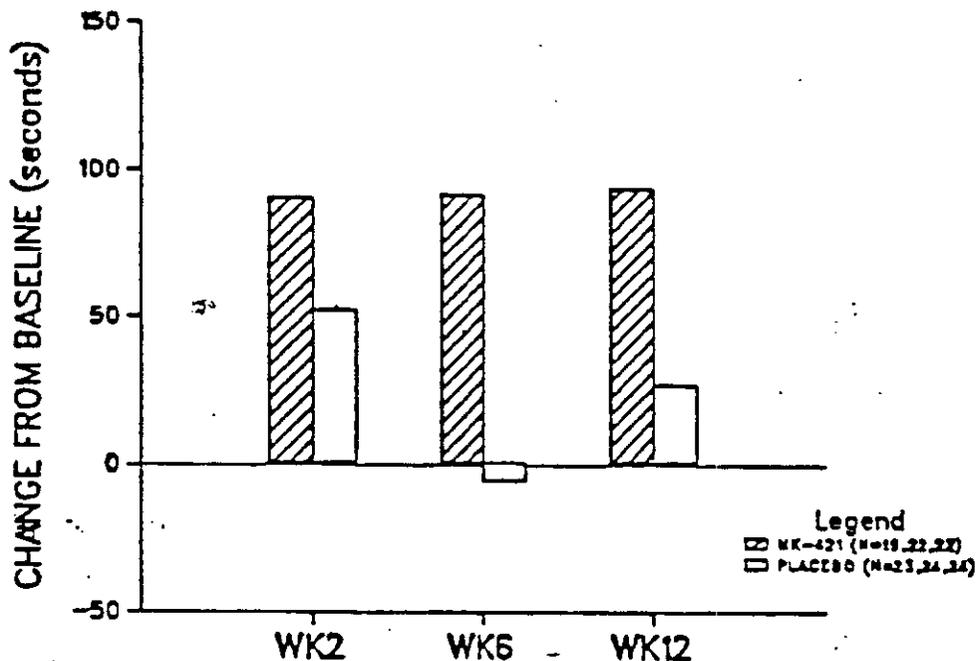
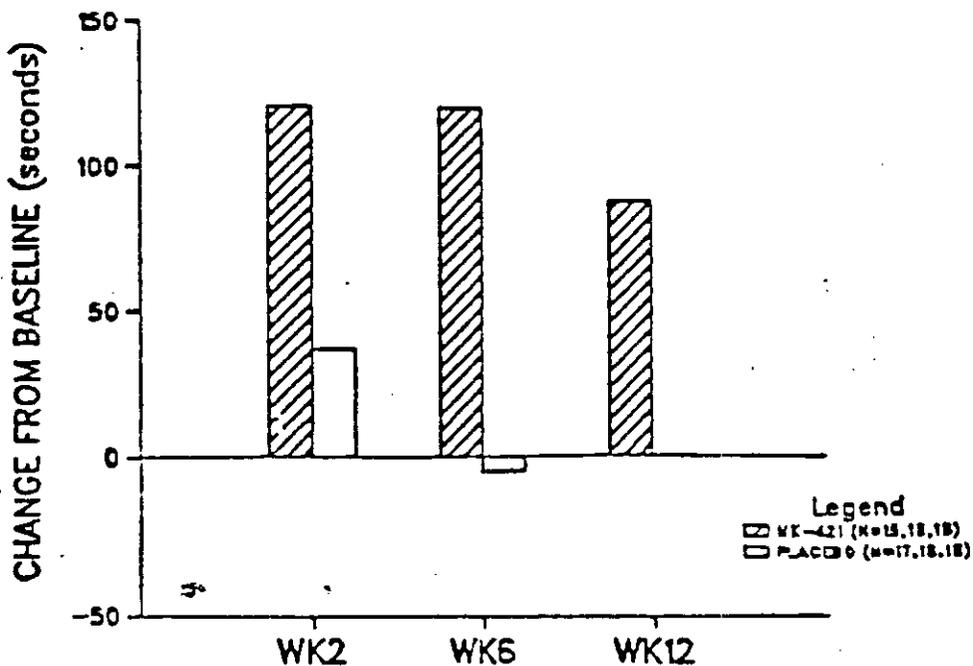


Figure 29

MK-421 Congestive Heart Failure  
Adjusted Mean Change in Duration of Exercise (Treadmill)  
Baseline in NYHA Cardiac Status of 3 or 4  
(Chrysant et al)



It is noted that MSD submitted an NDA Amendment on December 28, 1983. Information on an additional forty patients in the Chrysant et al study became available. Thus with the new cutoff date (12/19/83) the aforementioned data are partly modified as follows:

Twelve investigators participated in the study.

Of 93 patients entered into the titration period, 91 patients to date have entered the double-blind treatment period and 89 patients had completed the study prior to the cutoff date. 43 patients were randomly assigned to the enalapril group, 48 to the placebo group. Treatment related dropouts in the double-blind period included 6 patients on enalapril, 12 patients on placebo.

All 93 patients were evaluated for safety. 89 patients were evaluated for efficacy.

All patients were continued on digitalis and diuretic during a 2-4 day open inpatient titration period. Patients received an initial dose of 2.5 mg enalapril followed by 5 mg enalapril 12 hours later. Each patient was titrated to a maximum dosage of enalapril of 10 mg b.i.d. depending on clinical hemodynamic response and blood pressure reduction. Patients were

then randomized to enalapril or placebo receiving the same number of tablets to which they had been titrated on the last day of the open-label period. Dosage could be increased to a maximum of 20 mg b.i.d. after 2 weeks dependent on clinical response. Dosage could be reduced at anytime if a possible dose related adverse experience occurred. Treatment period was twelve weeks.

Time of exercise duration on powered treadmill was the primary objective measure of cardiac function. Patients receiving enalapril consistently demonstrated greater mean increases from baseline in exercise tolerance at all time periods as compared to placebo.

DURATION OF EXERCISE (In Seconds)  
 (end point analysis - mean values)

<u>Patient Group</u>	<u>Week</u>	<u>N</u>	<u>Enalapril</u>			<u>Adjusted Change</u>	<u>Percent Change</u>
			<u>Pre</u>	<u>Post</u>	<u>Change</u>		
NYHA CLASS 2,3,4 AT BASELINE	2	35	598	672	+ 75**	+ 77	+ 15**
	6	40	589	663	+ 74**	+ 80	+ 18**
	12	42	580	680	+ 99**	+103	+ 21**

<u>Patient Group</u>	<u>Week</u>	<u>N</u>	<u>Placebo</u>			<u>Adjusted Change</u>	<u>Percent Change</u>
			<u>Pre</u>	<u>Post</u>	<u>Change</u>		
NYHA CLASS 2,3,4 AT BASELINE	2	40	560	611	+ 51**	+ 49	+ 12**
	6	43	550	585	+ 35	+ 30	+ 12 $\Delta$
	12	45	547	610	+ 64 $\Delta$	+ 61	+ 17*

<u>Patient Group</u>	<u>Week</u>	<u>N</u>	<u>Enalapril</u>			<u>Adjusted Change</u>	<u>Percent Change</u>
			<u>Pre</u>	<u>Post</u>	<u>Change</u>		
NYHA CLASS 3,4 AT BASELINE	2	22	555	662	+106**	+107	+ 22**
	6	26	554	639	+ 84	+ 86	+ 21
	12	28	545	636	+ 91**	+ 92	+ 22**

<u>Patient Group</u>	<u>Week</u>	<u>N</u>	<u>Placebo</u>			<u>Adjusted Change</u>	<u>Percent Change</u>
			<u>Pre</u>	<u>Post</u>	<u>Change</u>		
NYHA CLASS 3,4 AT BASELINE	2	28	530	580	+ 49*	+ 49	+ 12*
	6	30	530	569	+ 38	+ 37	+ 9
	12	32	527	570	+ 43	+ 42	+ 10

KEY:  $\Delta$  = p<0.10  
 \* = p<0.05  
 \*\* = p<0.01

Improvement in exercise tolerance corresponded with clinical improvement as measured by the composite Yale Scale. There was no clinically significant difference between treatment groups in ejection fraction measurements.

During the randomized, double-blind treatment period 16 of 43 patients on enalapril and 21 of 48 patients on placebo reported at least one clinical adverse experience. One patient in the enalapril group and 8 in the placebo group discontinued the study due to adverse experiences other than death. Two patients in the open titration period were not randomized - one experiencing symptomatic hypotension and the other marked decrease in exercise tolerance. Six deaths occurred - 4 in the placebo group, two in the enalapril group. There were no clinically significant changes in laboratory parameters.

Regarding other measurements of efficacy were changes in NYHA functional classifications and ejection fraction. The proportion of patients with improvement in cardiac status continued to increase throughout the study. In the placebo group the percentage and numbers of patients who improved either their cardiac status or prognosis was insignificant.

Twenty-six of the 73 patients evaluated (36 percent) in the Cohn et al study treated with enalapril improved their NYHA cardiac status by at least one class, whereas 12 out of 76 patients (15 percent) treated with placebo improved their NYHA cardiac status. Improvement in NYHA was more apparent in the international group than the domestic group.

Left ventricular ejection fraction was evaluated by radionuclide gated blood scan or by echocardiogram. Results were variable, and given the small number of patients, were inconclusive.

Of the 57 patients who started their treatment in this study with a daily dose of 10 mg of enalapril (one 5 mg tablet b.i.d.), 39 completed the study on that dose. In nine other patients, the daily dose was increased to 20 mg.

#### Tolerability and Safety in Dose Ranging Studies in Patients with Congestive Heart Failure

Forty-seven patients (30 percent) out of the 154 patients with documented congestive heart failure and treated with enalapril in these three studies had an adverse clinical experience. Twenty-nine patients (32 percent) of the 88 patients treated with placebo had an adverse clinical

experience. Nine of the patients treated with enalapril (5 percent) and 5 (6 percent) of the placebo-treated patients died.

Four patients in the enalapril group in the three studies were withdrawn from the study due to serious adverse experiences as compared to 12 patients in the placebo group. Most patients experienced some decrease in blood pressure. In eight of the patients it was considered clinically significant. One patient had persistent hypotension in the titration period and was not randomized into the treatment period.

In the double-blind studies (Chrysant et al and Athanassiades et al), minor changes in the mean hemoglobin and hematocrit were noted in the treated group at Week 12 as compared with baseline. One patient in the placebo group had an initially low hemoglobin and hematocrit value (7.1 mg pct. and 34 vol pct., respectively). Some clinically relevant increases in serum creatinine and BUN were observed in three patients in the enalapril group. No significant between-group differences were detected. A mean decrease in liver function tests was noted in the enalapril treated group with a mean increase in the placebo. No significant changes in serum potassium have been seen.

In conclusion, enalapril was effective in the treatment of chronic congestive heart failure. In these dose-ranging studies, most patients were monitored at an optimal daily dose of 10 to 20 mg. Improvement in exercise tolerance was sustained during chronic therapy. A decrease was also noted in arterial pressure. Enalapril was well tolerated, and there were no unexpected clinically significant adverse events.

3) Biochemical and Endocrine Parameters of ACE Inhibition in Hypertension Studies:

In support of the dose-ranging and dose-response studies on blood pressure responses described in foregoing, biochemical and endocrine parameters were also evaluated.

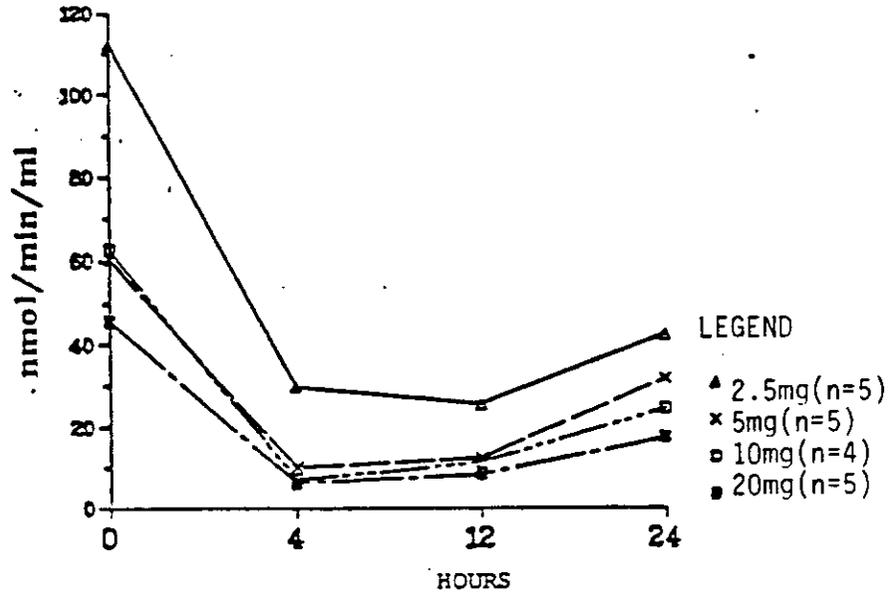
a) Angiotensin Converting Enzyme Activity

Generally, for all the doses discussed above, mean angiotensin converting enzyme (ACE) levels were decreased as a result of enalapril administration.

In the single-dose domestic studies, significant decreases from Hour 0 in ACE levels were seen for the 2.5, 5, 10, and 20 mg doses of enalapril at 4, 12, and 24 hours after drug administration as exemplified in Figure 18 taken from Dr. Gavras' Study No. 2.

Figure 18

Mean Angiotensin Converting Enzyme Activity  
(Gavras No. 2)



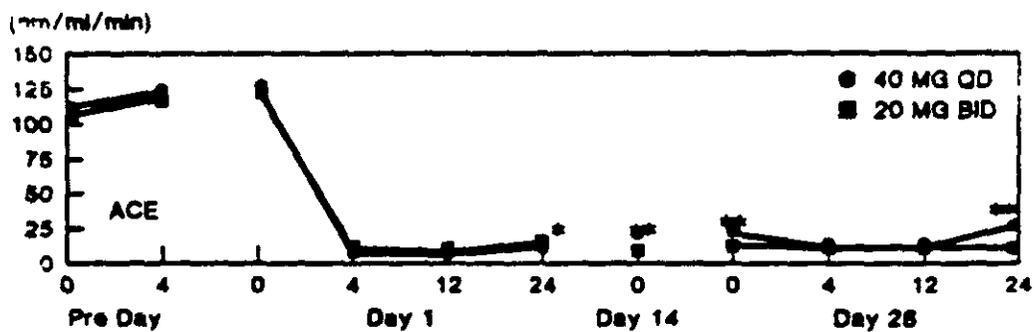
The effects of 10, 20, and 40 mg doses of enalapril were similar by four hours following drug administration (Case/Atlas No. 9). The decrease in ACE activity was noted to last for 24 hours or longer for all dose levels.

Data from the open international studies (Menard et al) showed mean angiotensin converting enzyme activity (CEA) was markedly suppressed following single doses of enalapril and was maintained throughout the repeat-dose, outpatient period.

For the domestic 40 mg enalapril q.d. vs. 20 mg enalapril b.i.d. studies No. 12 and No. 13 (McMahon and Lowenthal), statistically significant differences were found between dosage regimens for mean ACE. Neither dosage regimen was consistently higher or lower than the other. Both dosage regimens produced similar marked and sustained suppression of ACE activity as can be seen in Figure 19.

Figure 19

Mean Angiotensin Converting Enzyme Activity  
40 mg Enalapril Once vs. 20 mg Enalapril Twice-A-Day  
(n=27)  
(McMahon and Lowenthal, No. 12 and 13)



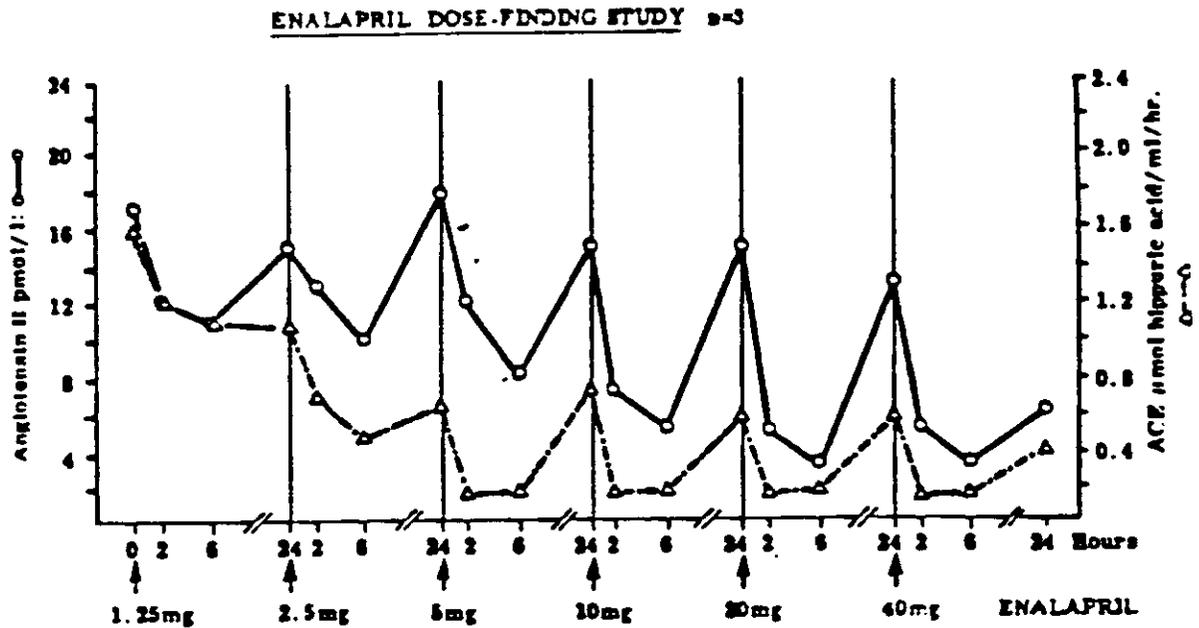
In the q.d. vs. b.i.d. with hydrochlorothiazide study (Mitchell No. 20), mean ACE was significantly reduced within both dosage regimens and no consistent differences between regimens were observed.

Data from the renovascular hypertension study (Fyhrquist et al) showed that suppression of ACE was progressively more marked and more sustained as the dose of enalapril increased from 1.25 to 40 mg per day

as seen in Figure 20 which also demonstrates Angiotensin II (AII) response.

Figure 20

Effects of Single Daily Doses of Enalapril in Hospitalized Patients with Renovascular Hypertension on Angiotensin II and Angiotensin Converting Enzyme Activity (Fyhrquist et al)

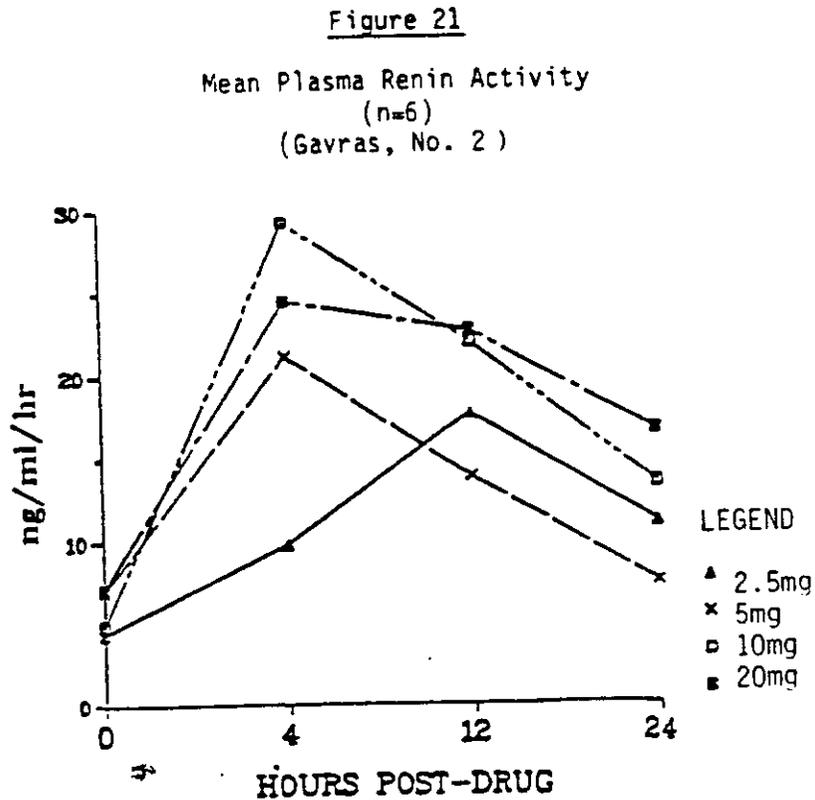


b) Plasma Renin Activity (PRA)

As expected, mean PRA values increased following enalapril administration in the dose-ranging and dose-response studies in hypertension.

In the single-dose Gavras study, No. 2, mean PRA values in response to enalapril administration were significantly higher than mean baseline values at all time points measured, up to Hour 14. These appeared

to be a dose-related effect of enalapril on PRA (Figure 21, from Gavras No. 2).



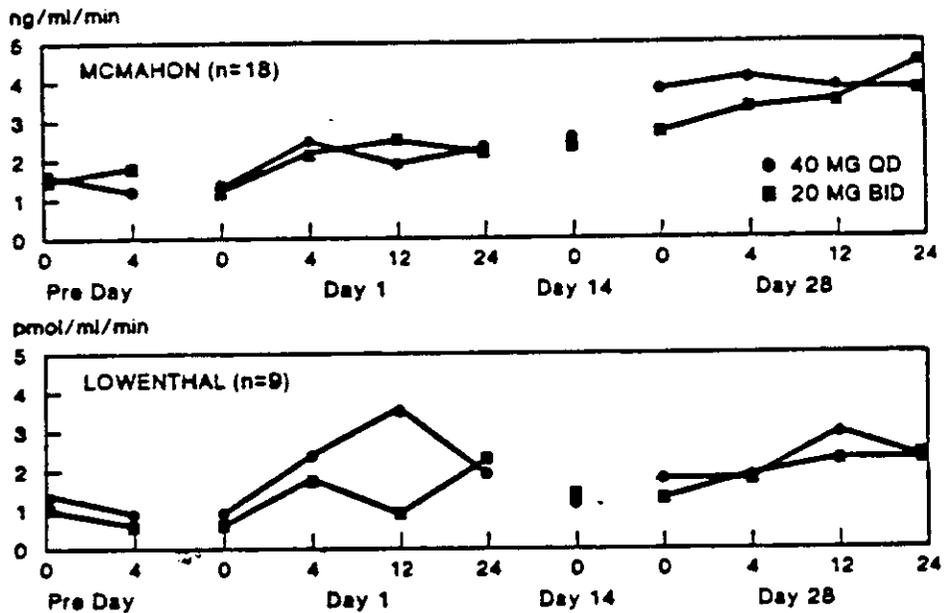
Following repeat doses of enalapril in the open international studies by Drs. Brunner (No. 508) and Birkenhaefer (No. 510), (Menard et al) mean PRA increased significantly and remained elevated with continuous treatment.

No significant difference in mean PRA between dosage regimens was observed in either Dr. McMahon's (No. 12) or Dr. Lowenthal's (No. 13) study of 40 mg enalapril

q.d. vs. 20 mg enalapril b.i.d. (Figure 22). Similar results were noted in the Mitchell study (No. 20), q.d. vs. b.i.d. with hydrochlorothiazide.

Figure 22

Mean Plasma Renin Activity  
40 mg Enalapril Once vs. 20 mg Enalapril Twice A Day  
(n=27)  
(McMahon, No. 12 and Lowenthal, No. 13)



Note: Not All Patients Present Data at All Times.  
No Significant Differences Between Treatment Means.

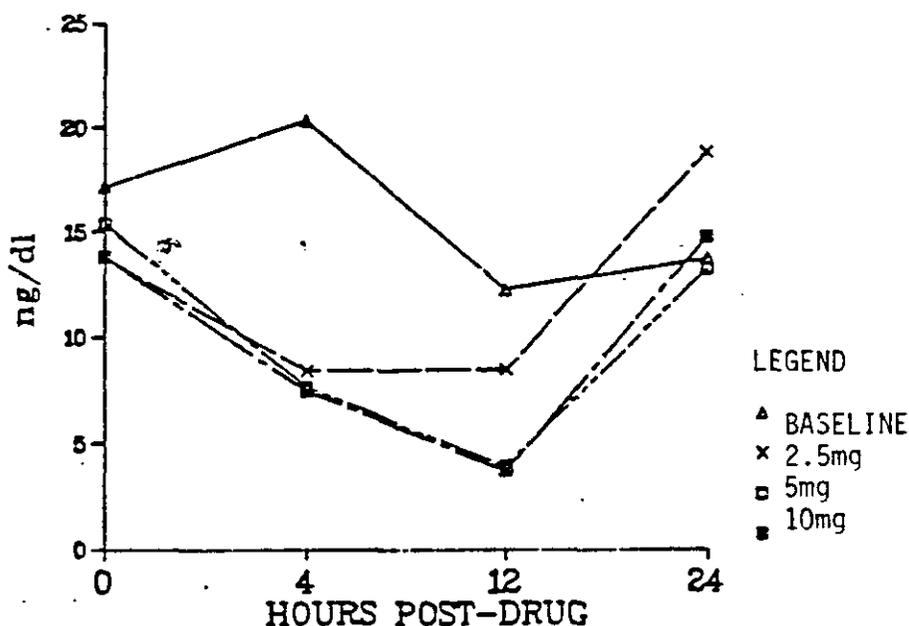
In the renovascular study, mean PRA rose progressively with increasing doses of enalapril (from 1.25 mg to 40 mg).

c) Plasma Aldosterone (PA)

Plasma aldosterone decreased for most patients following the administration of single doses of enalapril 2.5, 5, 10, and 20 mg (see Figure 23 from Ferguson Study No. 1).

Figure 23

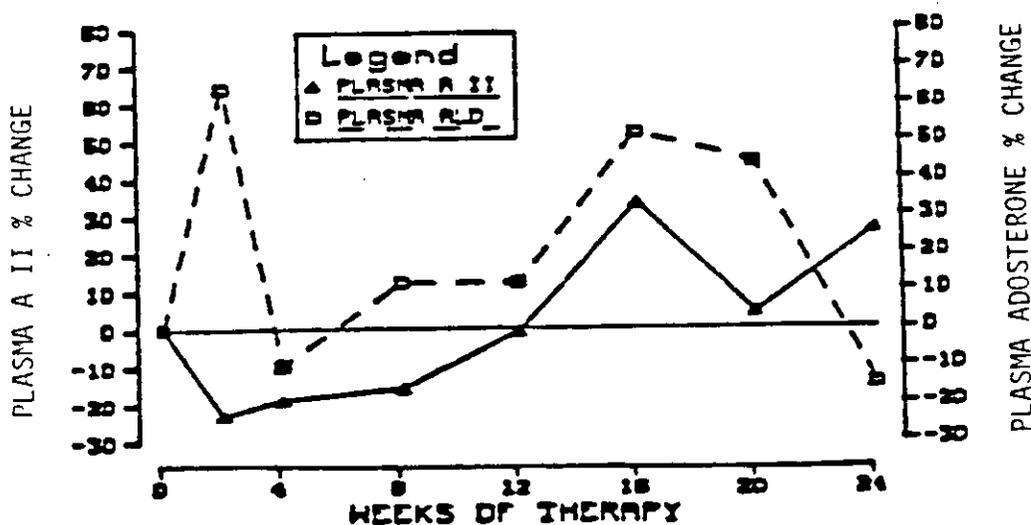
Mean Aldosterone (ng/dl) at 0, 4, 12, and 24 Hours After Dosing During the Inpatient Dose Titration Period (Ferguson, No. 1)



With repeat doses of enalapril (open, international, multicenter study), (Menard et al), PA levels demonstrated a bimodal elevation at the end of Treatment Weeks 2 and 16 (Figure 24) which also demonstrates plasma AII response.

Figure 24

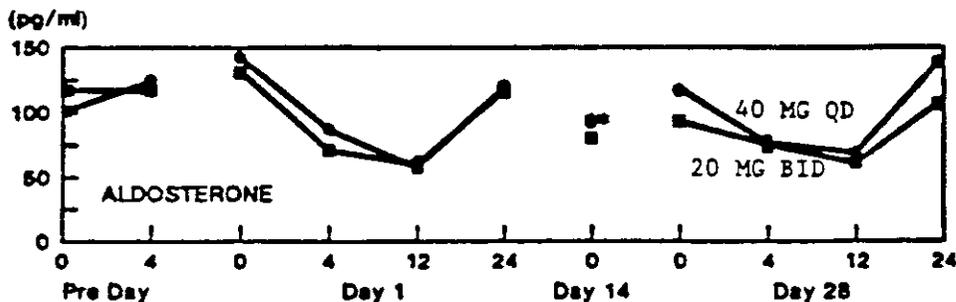
Changes in Plasma Aldosterone and Plasma Angiotension II After Long-Term Therapy with Enalapril (Menard et al)



With 40 mg enalapril q.d. vs. 20 mg enalapril b.i.d. dosing (McMahon No. 12, Lowenthal No. 13), no significant differences between dosage regimens were observed for mean PA except at Hour 0 on Day 28 (q.d. significantly higher). Figure 25 demonstrates mean PA for the two dosage regimens.

Figure 25

Mean Plasma Aldosterone  
 40 mg Enalapril q.d. vs. 20 mg Enalapril b.i.d.  
 (McMahon No. 12/Lowenthal No. 13)



Note: Not All Patients Present Data at All Times.  
 --- Significant Difference Between Treatment Means  $p < 0.05$ ,  $p < 0.01$

In the q.d. vs. b.i.d. study with hydrochlorothiazide (Mitchell No. 20), mean PA did not change in any consistent manner throughout the study and no significant differences were observed between the q.d. and b.i.d. regimens.

Mean PA was also reduced by acute and long-term therapy in renovascular hypertension study.

d) Angiotensin II (AII)

As expected with converting enzyme inhibitor therapy, plasma AII was suppressed in the dose-ranging studies where it was measured.

In the open, repeat-dose, international dose-range studies conducted by Dr. Brunner (No. 508) and Dr. Birkenhaeger (No. 510) (Menard et al), AII was suppressed for the first 12 weeks of therapy with increases in levels with continuing therapy. In the renovascular hypertension study, decreases in AII appear progressively more marked and more sustained as the dose of enalapril increased from 1.25 to 40 mg per day (see Figure 20).

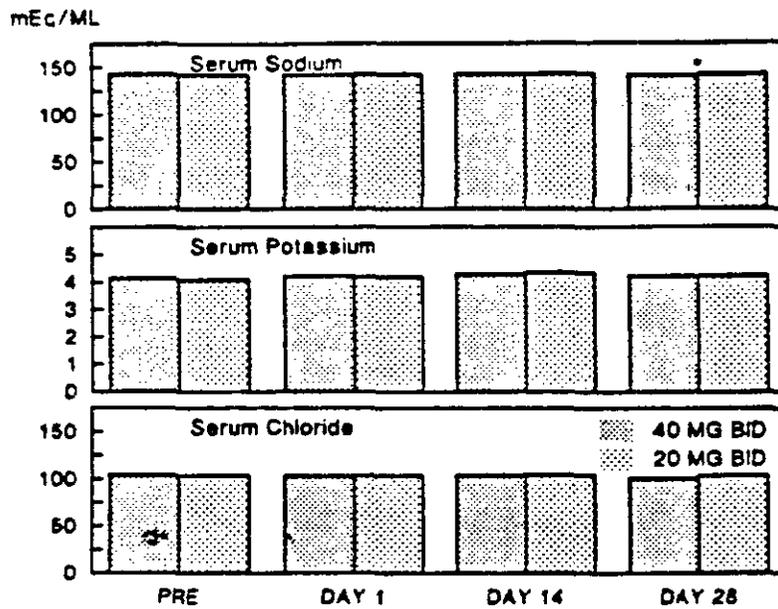
e) Other Biochemical Parameters

In the single-dose, open studies (Nos. 1, 2, 3, and 9), few significant differences were seen from baseline in urine, sodium, potassium or chloride excretion rates following administration of enalapril over the dose range tested in these studies. Cumulative (0-24 hour) urine, sodium, potassium and chloride excretion was also not significantly greater than baseline. Neither a dose-related response nor a difference between renovascular and essential hypertensive patients was evident.

In the once vs. twice daily studies of McMahon (No. 12) and Lowenthal (No. 13), mean serum electrolytes (Na, K, and Cl) and creatinine were similar for the two dosage regimens with one exception: mean Na (mEq) was slightly but yet significantly higher for the 20 mg b.i.d. regimen than for the 40 mg q.d. regimen on Day 28 (Figure 26).

Figure 26

Mean Serum Electrolyte Parameters  
40 mg Enalapril Once vs. 20 mg Enalapril Twice-A-Day  
(n=25)  
(McMahon No. 12 and Lowenthal No. 13)

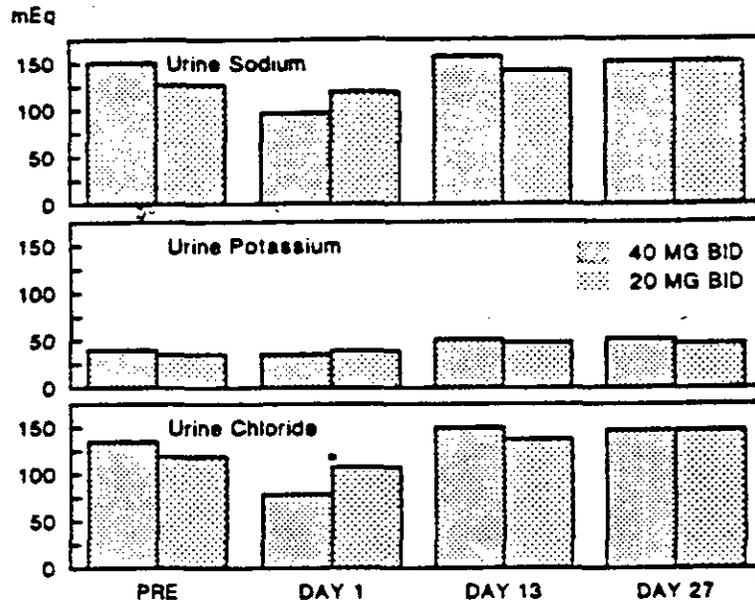


Note: Not All Patients Present Data at All Times.  
\* Significant Difference Between Treatment Means. (P < 0.05)

Significant mean increases in 24-hour urine K were observed on Days 13 and 27 within both dosage regimens. Mean urine Na and Cl were significantly decreased on Day 1 within the 40 mg q.d. dosage regimen but were similar to prestudy after 2 and 4 weeks of treatment. Mean urine creatinine increased over time. Mean urinary electrolyte excretion was similar for both dosage regimens except for chloride on Day 1 which was significantly higher after enalapril 20 mg b.i.d. than after enalapril 40 mg q.d. (Figure 27).

Figure 27

Mean Urinalysis Daily Excretion Parameters  
40 mg Enalapril Once vs. 20 mg Enalapril Twice-A-Day  
(n=25)  
(McMahon No. 12 and Lowenthal No. 13)



Note: Not All Patients Present Data at All Times.  
\* Significant Difference Between Treatment Means. (P < 0.05)

In the once vs. twice-a-day study with hydrochlorothiazide (Mitchell No. 20), significant increases from pre-Day 1 were seen the first day of therapy for urine volume and urine sodium, potassium and chloride excretion. No significant differences between regimens were observed for urine volume or electrolyte excretion with the crossover analyses. In the Period 1 analyses of all patients, urine volume and potassium excretion were significantly higher for the once daily than the twice daily regimen on the first day of treatment.

C. Controlled Studies in Hypertension

These were designed to document the efficacy and safety of enalapril as an antihypertensive agent. Seven multiclinic studies (5 conducted in USA, 2 abroad) were submitted. The following tabulation outlines the program:

Study	No. of Sites	Location	No. of Patients	
			Total	On Enalapril
A. Hypertension				
1. Enal. q.d. vs b.i.d. vs Placebo	6	USA	169	113
2. Enal. vs HCTZ vs Enal/HCTZ	24	USA	546	324
3. Enal. + HCTZ vs Propranolol + HCTZ	29	International	485	242
4. Enal. + HCTZ vs. Metoprolol + HCTZ	6	USA	150	75
5. Enal/HCTZ + Aldomet vs propranolol/HCTZ/Hydralazine	22	International	269	136
6. HCTZ + Enal + Timolol or Aldomet vs HCTZ + Captopril + Timolol or Aldomet	18	USA	175	85
7. Renovascular. Enalapril vs Triple Therapy	10	USA	29	14

Reference is also made to Appendix: Synopsis of Clinical Studies.

1. Enalapril Once Daily vs Twice Daily vs Placebo (Mild Hypertension). Chrysant et al.

Study Design:

This double-blind placebo controlled study was conducted in 169 patients with a diagnosis of mild essential hypertension. Patients entered had supine diastolic blood pressures between 90 and 104 mmHg at the end of a four-week

baseline placebo period. Fifty-seven patients were allocated to begin treatment with enalapril 10 mg in the morning, placebo in the evening, 56 to begin treatment with enalapril 5 mg b.i.d., and 56 to receive placebo b.i.d. At intervals of four weeks dosage was doubled to 20 and then 40 mg daily, (with corresponding increase in number of placebo capsules), if the patient had not achieved a supine diastolic blood pressure of  $<80$  mmHg.

Efficacy:

Table 1 documents the mean blood pressures in all three groups at Weeks 4, 8, and 12 of study. The treatment groups were similar at baseline except that the enalapril q.d. group had a lower baseline systolic pressure than the other two groups.

Both enalapril treatment groups showed significant reductions in systolic and diastolic blood pressures (Figure 1). The proportions of patients with a good or excellent response (i.e., supine diastolic blood pressure  $<85$  mmHg or 10 mmHg decrease from baseline) were also similar for both active treatment groups (Figure 2).

TABLE 1  
 MEAN BLOOD PRESSURE (mmHg)  
 (SYSTOLIC/DIASTOLIC)  
 AT TREATMENT WEEKS 4, 8 AND 12

		ENAL QD			
		SUPINE		STANDING	
TREATMENT WEEK	N	BASELINE	TREATMENT	BASELINE	TREATMENT
4	54	142.4/95.2	136.6**/89.0**	140.4/97.8	134.6**/92.3**
8	54	142.4/95.2	134.9**/88.1**	140.4/97.8	134.3*/92.4**
12	52	142.4/95.2	135.4**/86.5**	140.0/97.7	134.3**/91.6**

		ENAL BID			
		SUPINE		STANDING	
TREATMENT WEEK	N	BASELINE	TREATMENT	BASELINE	TREATMENT
4	50	148.0/95.4	139.4**/88.1**	147.8/98.7	137.7**/91.9**
8	50	148.1/95.3	138.9**/86.6**	148.1/98.9	138.9**/91.2**
12	46	147.0/94.9	137.0**/86.6**	147.2/98.5	135.6**/89.9**

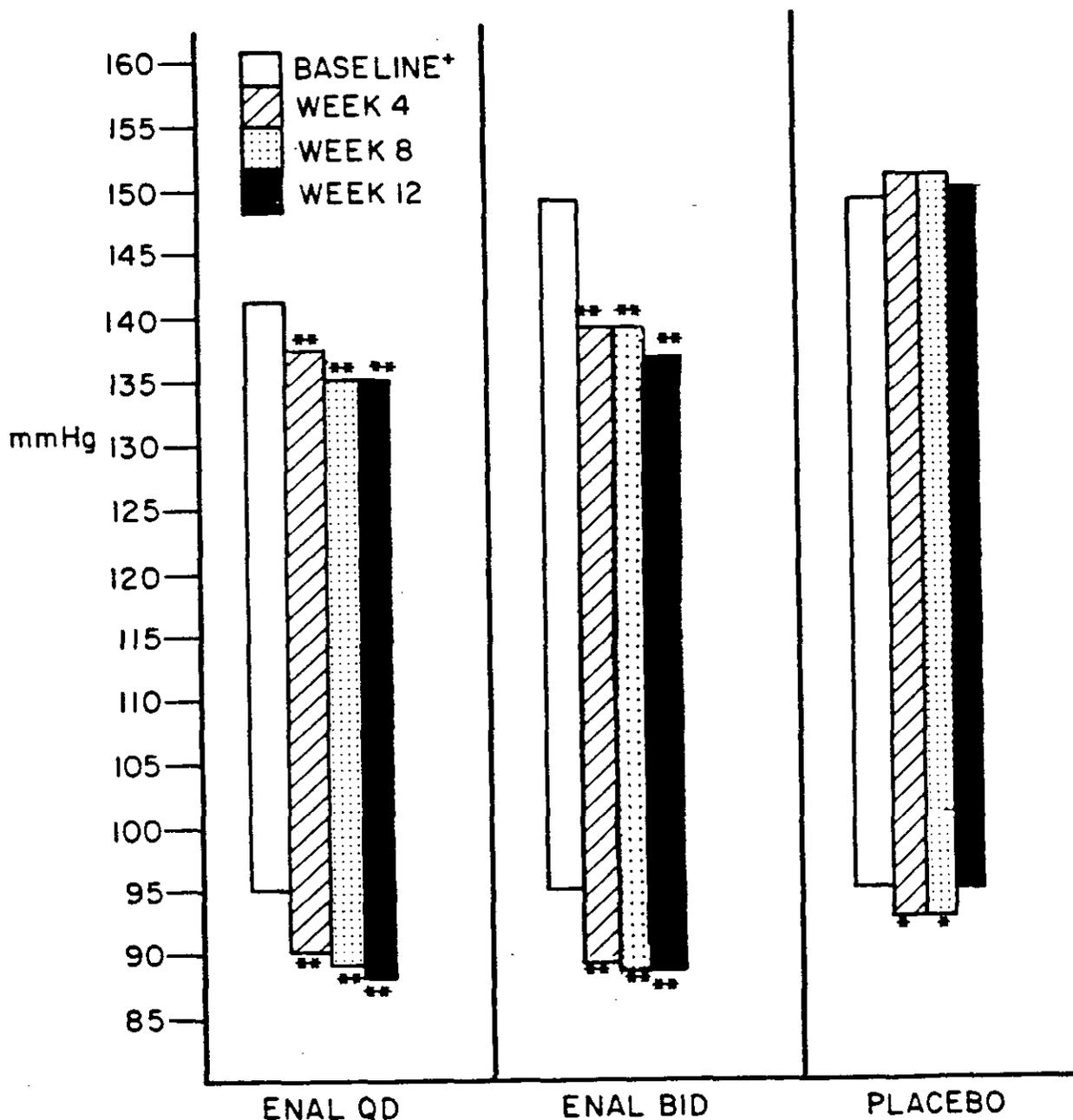
  

		PLACEBO			
		SUPINE		STANDING	
TREATMENT WEEK	N	BASELINE	TREATMENT	BASELINE	TREATMENT
4	50	147.8/95.4	149.8/93.6*	148.3/98.4	149.8/99.0
8	44	148.1/95.1	150.0/93.4*	148.2/98.3	148.5/98.1
12	40	146.0/95.3	149.6/94.5	146.6/98.3	150.0/98.4

\*STATISTICALLY SIGNIFICANT FOR CHANGE FROM BASELINE WITHIN THE GROUP,  
 p < 0.05.  
 \*\*STATISTICALLY SIGNIFICANT FOR CHANGE FROM BASELINE WITHIN THE GROUP,  
 p < 0.01.

THE DIFFERENCES BETWEEN ENALAPRIL (QD AND BID) AND PLACEBO WERE SIGNIFICANT AT TREATMENT WEEKS 4, 8 AND 12 (p < 0.05) FOR EACH PARAMETER, WITH REGARD TO CHANGE FROM BASELINE.

FIGURE 1  
MEAN SYSTOLIC AND DIASTOLIC  
SUPINE BLOOD PRESSURE



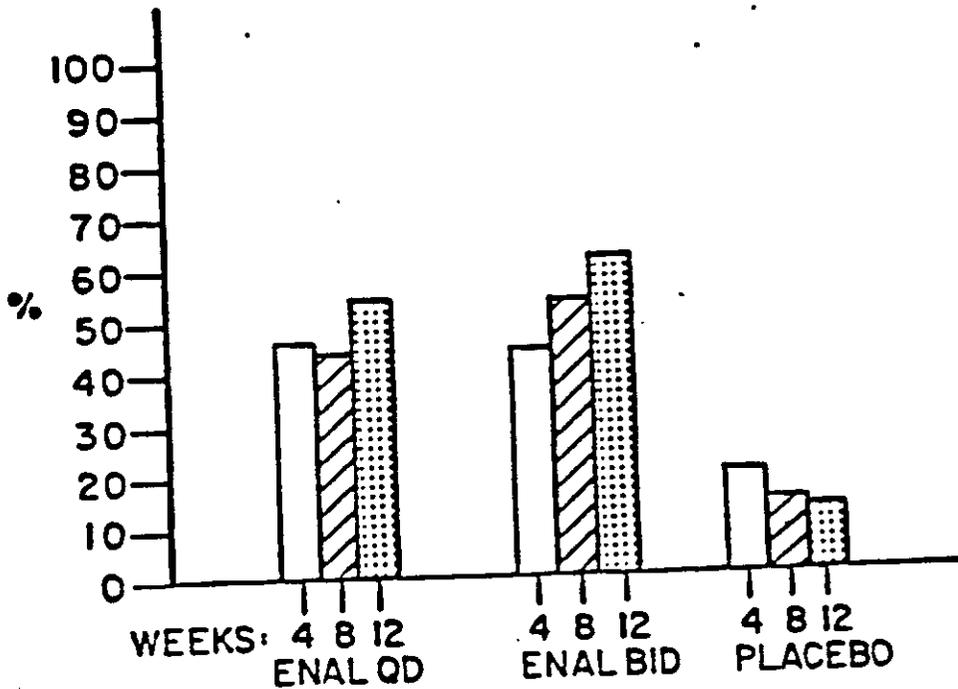
\*STATISTICALLY SIGNIFICANT CHANGE FROM BASELINE WITHIN THE GROUP,  $p < 0.05$ .

\*\*STATISTICALLY SIGNIFICANT CHANGE FROM BASELINE WITHIN THE GROUP,  $p < 0.01$ .

†MEAN VALUES FOR ALL PATIENTS WITH DATA AT ANY SUBSEQUENT TIME POINT.

FIGURE 2

GOOD AND EXCELLENT RESPONDERS\*



\* SDBP  $\leq$  85 mmHg or  
 $\downarrow$  10 mmHg from baseline

Safety:

Clinical Adverse Experiences.

The overall incidence of clinical adverse experiences was similar in all three groups. Two patients in the placebo group were discontinued from therapy, one because of angina, the other because of nervousness. Two patients, one in each of the enalapril groups,

were discontinued, one because of angina (present in baseline), the other because of abdominal cramps. None of these were considered serious by the investigator.

#### Laboratory Evaluation.

One patient on enalapril and concomitant lithium therapy developed acute renal insufficiency with signs of lithium toxicity. These reversed rapidly on discontinuation of test drug. No other serious laboratory abnormalities were noted. Significant small mean increases in serum potassium were seen in both enalapril groups, as were occasional small mean decreases in hemoglobin and hematocrit. No significant mean changes were seen in white cell count or liver function tests.

#### Conclusion:

Enalapril was a safe and effective antihypertensive agent when used alone in the treatment of mild essential hypertension. It was effective as a once or twice daily treatment regimen.

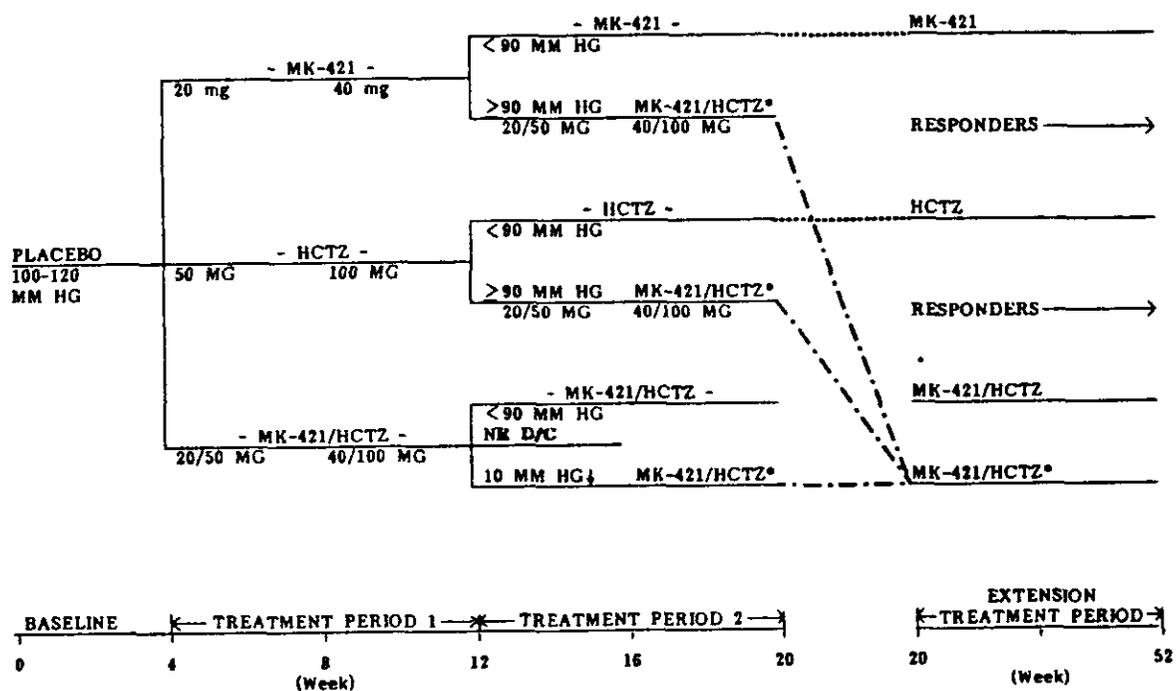
2. Enalapril vs Hydrochlorothiazide vs Enal/HCTZ  
(Mild/Moderate Hypertension). Bauer et al.

Study Design:

This double-blind comparative study was conducted in 546 outpatients with supine diastolic blood pressures from 100-120 mmHg at the end of a 4-week placebo baseline. Patients were randomly allocated in a ratio of 2:2:1 to receive enalapril 10 mg b.i.d. (221 patients), hydrochlorothiazide (HCTZ) 25 mg b.i.d. (222 patients), or enal/HCTZ 10/25 mg b.i.d. (103 patients). After 4 weeks, dosage could be doubled, if the supine diastolic blood pressure was 90 mmHg or more. At the end of 8 weeks, non-responders to enalapril or HCTZ were treated single-blind with enal/HCTZ. A flow chart of the study is given in Figure 3.

FIGURE 3

MK-421 VS. HCTZ VS. MK-421/HCTZ  
MILD TO MODERATE HYPERTENSION



(\*) SINGLE BLIND

Efficacy:

Blood pressure was significantly reduced by each of the three treatments with the greatest mean reductions being seen in the enal/HCTZ group. Race was found to be a significant factor in determining response to enalapril; therefore, all analyses were performed for blacks and non-blacks separately, as well as for all races combined. Increasing age in non-blacks was also a negative factor in determining response to enalapril. Table 2 shows the mean reductions in supine diastolic blood pressure after 4 and 8 weeks of treatment, for all races, blacks, and non-blacks. All reductions from baseline were statistically significant ( $p < 0.01$ ).

Table 2

SUPINE DIASTOLIC BLOOD PRESSURE						
MEAN CHANGES FROM BASELINE (mmHg)						
	Week	Group	No. Pts.	Baseline	Treatment	CHANGE
<u>All Races</u>	4	Enal.	197	105.1	93.7	-11.4
		HCTZ	197	105.1	93.8	-11.4
		Enal/HCTZ	94	104.4	84.4	-19.9***
	8	Enal.	176	105.1	93.6	-11.5
		HCTZ	189	105.1	91.8	-13.2
		Enal/HCTZ	90	104.4	83.0	-21.4***
<u>Blacks</u>	4	Enal.	76	105.3	96.5	- 8.8
		HCTZ	100	105.6	92.9	-12.6
		Enal/HCTZ	44	105.6	86.2	-19.5***
	8	Enal.	66	105.8	99.0	- 6.8
		HCTZ	97	105.5	90.9	-14.6**
		Enal/HCTZ	41	105.8	84.8	-21.0**
<u>Non-Blacks</u>	4	Enal.	121	105.0	91.9	-13.0*
		HCTZ	97	104.6	94.6	-10.0
		Enal/HCTZ	50	103.2	82.9	-20.3***
	8	Enal	110	104.7	90.4	-14.3
		HCTZ	92	104.6	92.8	-11.8
		Enal/HCTZ	49	103.3	81.6	-21.7***

\*, \*\* Significantly greater than HCTZ,  $p < 0.05$ ,  $< 0.01$ , respectively.  
 \*, \*\* Significantly greater than Enal.,  $p < 0.05$ ,  $< 0.01$ , respectively.

Figure 4 shows the mean decreases in supine diastolic blood pressure at Week 8 and the effect of race. The influence of age in non-blacks at the same time point is shown in Figure 5.

FIGURE 4

MEAN DECREASE IN SUPINE DIASTOLIC  
BLOOD PRESSURE (mmHg)  
BY TREATMENT GROUP AND RACE

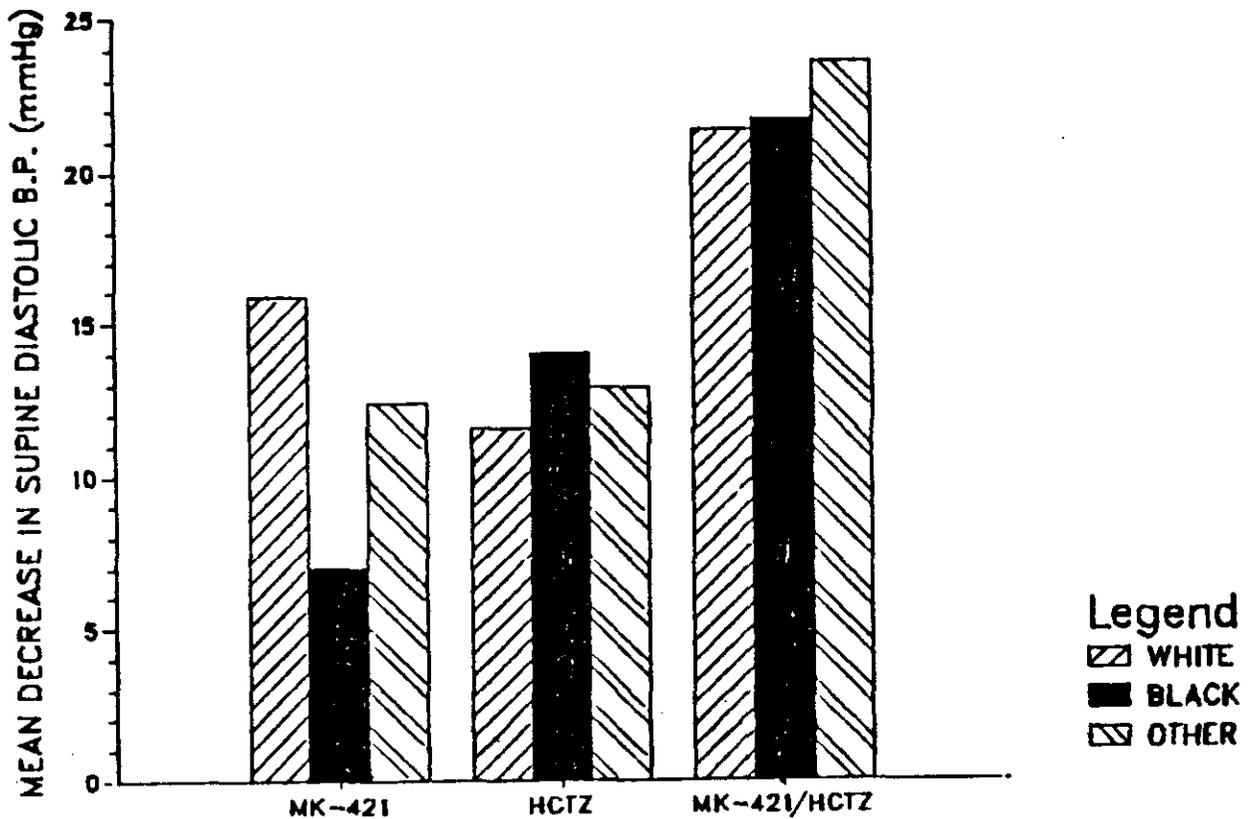


FIGURE 5

MEAN DECREASE IN SUPINE DIASTOLIC  
BLOOD PRESSURE (mmHg)  
BY TREATMENT GROUP AND AGE  
NONBLACKS ONLY

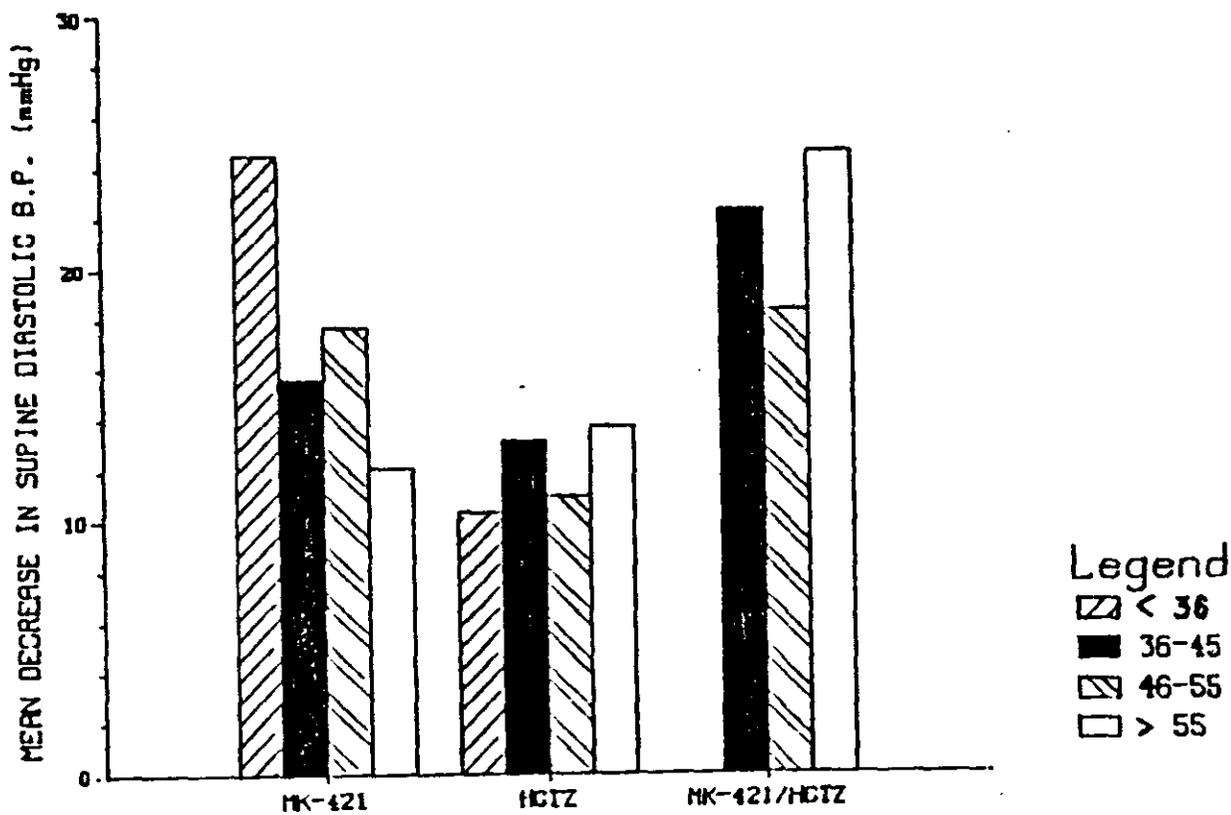
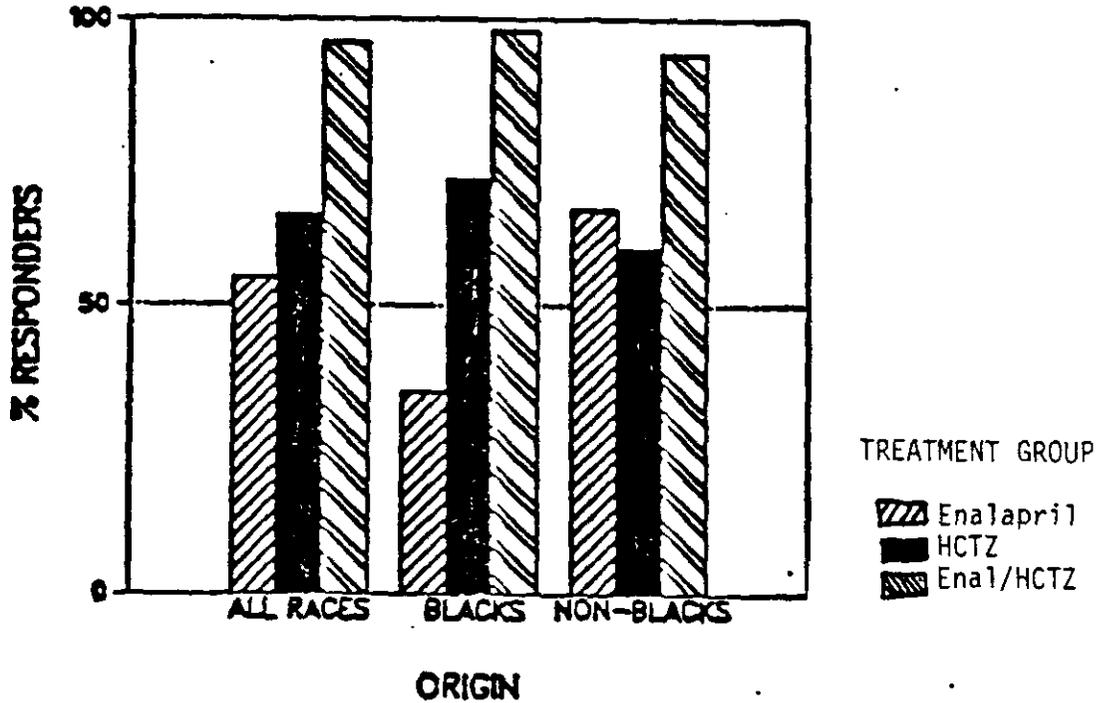


Figure 6 shows the percentage of patients at Week 8 who achieved a good or excellent response (supine diastolic blood pressure  $\leq 90$  mmHg or 10 mmHg decrease from baseline) for all races, blacks and non-blacks.

Figure 6

PERCENT OF PATIENTS WITH A GOOD-EXCELLENT RESPONSE AFTER 8 WEEKS, BY ORIGIN



Safety:

Clinical Adverse Experiences.

The overall frequency of adverse experiences was similar in all three groups, and the frequencies did not show any consistent variation with increasing age. Adverse experiences rated as serious were seen

in 6 patients on enalapril, 5 on HCTZ, and 17 on enal/HCTZ. Drug was discontinued: in 6 patients on enalapril, 9 patients on HCTZ and 30 patients on enal/HCTZ. One patient on enalapril died of a myocardial infarction. Two patients, one on HCTZ and one on enal/HCTZ, suffered myocardial infarctions during study. Two patients experienced episodes of angioneurotic edema on enal/HCTZ. Orthostatic hypotension, palpitations, arrhythmia, diarrhea, dyspepsia, nausea, muscle weakness, insomnia, dyspnea, rash and taste perversion were each seen in from 0.5 - 1.8 percent of patients on enalapril. Those seen more frequently were muscle cramps (2.3 percent), dizziness (5.4 percent), headache (7.7 percent), and cough (2.3 percent).

#### Laboratory Evaluation.

One patient on enal/HCTZ was discontinued because of a low hematocrit. Two patients on enal/HCTZ experienced drops in white blood cell count below  $2.5 \text{ ths/mm}^3$ ; both returned to normal despite continued treatment. Mean white blood cell counts remained stable or increased in all treatment groups. No changes of clinical importance were seen in up to 48 weeks of therapy.

In indices of renal function, some small but statistically significant mean changes were seen. Urinary protein levels fell in all treatment groups. Mean serum creatinine and BUN rose slightly in all three treatment groups, enal/HCTZ>HCTZ>enalapril. Two patients were discontinued from treatment with enal/HCTZ because of increased creatinine levels. One of these had a serum creatinine of 3.7 mg percent with associated renal glycosuria, which resolved on treatment with HCTZ alone; the second patient had a maximum serum creatinine of 3.2 mg percent without associated symptoms or findings. Mean changes in serum uric acid, fasting blood glucose, and serum cholesterol were seen only in those patients on HCTZ or enal/HCTZ, and the changes were reflective of the diuretic therapy. Mean serum potassium decreased on HCTZ significantly more than on enal/HCTZ suggesting that enalapril may attenuate the potassium wasting associated with thiazide treatment. Hyperkalemia (5.7 mEq/L) caused discontinuance in one patient who was using high-potassium salt substitute while on therapy with enal/HCTZ.

Conclusion:

Looking at all races combined, enalapril at doses 10 or 20 mg b.i.d. was as effective as HCTZ in a dose of 25 or

50 mg b.i.d. in the treatment of mild/moderate hypertension. Combined treatment at these doses was significantly more effective than with either single entity, and may attenuate some of the biochemical changes seen with HCTZ treatment alone.

3. Enalapril vs Propranolol  $\pm$  HCTZ

(Mild/Moderate Hypertension). Abbott et al.

Study Design:

Twenty-nine investigators participated in this double-blind, randomized, active drug-controlled parallel study in 485 patients with mild to moderate (supine diastolic blood pressure of 95-114 mmHg) hypertension. A four-week baseline-placebo period was followed by a 12-week titration period. The initial dose of enalapril was 5 mg b.i.d. and the maximum dose was 20 mg b.i.d. The initial dose of propranolol was 40 mg b.i.d. and the maximum dose was 120 mg b.i.d. The extension period which covered study weeks 17 to 30 was a 14-week active treatment period during which hydrochlorothiazide could be added in dosages of 25 to 50 mg once a day concomitantly with either enalapril or propranolol.

**Efficacy:**

Table 3 summarizes the results after 12 and 26 weeks of study in terms of mean supine and standing blood pressure changes. The groups at Week 26 include both patients on single therapy, and patients receiving concomitant hydrochlorothiazide. Figure 7 depicts the mean decreases from baseline in supine diastolic blood pressure at monthly intervals from Week 2 through Week 26 of therapy. At weeks beyond Week 12, a proportion of both groups were receiving additional HCTZ, 25 or 50 mg daily. The group receiving enalapril + HCTZ showed significantly greater reductions from baseline at Weeks 22 and 26 than the group on propranolol + HCTZ. Figure 8 represents the percentages of patients on single therapy and with 25 or 50 mg of additional HCTZ at Weeks 18 and 26.

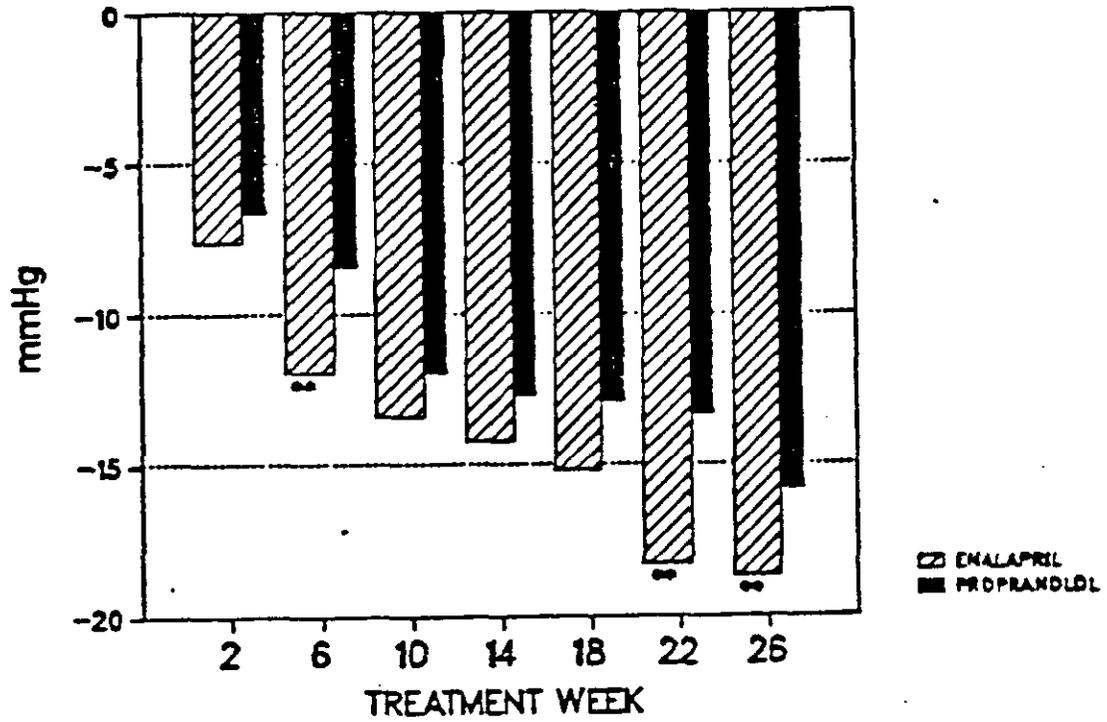
TABLE 3  
 Mean Blood Pressure (mmHg)  
 At Treatment Weeks 12 and 26

	WEEK 12 EVALUATION				WEEK 26 EVALUATION			
	NUMBER OF PATIENTS	BASELINE mmHg	WEEK 12	DIFFERENCE	NUMBER OF PATIENTS	BASELINE mmHg	WEEK 26	DIFFERENCE
<u>Enalapril</u>								
<u>Supine</u>								
Systolic	183	164.4	143.0	-21.4**	97	163.4	132.9	-30.5**
Diastolic	183	103.8	91.0	-12.8**	97	104.1	85.4	-18.7**
<u>Standing</u>								
Systolic	184	162.0	140.2	-21.8**	98	162.0	130.9	-31.2**
Diastolic	183	106.8	94.4	-12.4**	97	108.4	91.0	-17.5**
<u>Propranolol</u>								
<u>Supine</u>								
Systolic	184	162.7	145.5	-17.2**	99	161.4	139.2	-22.2**
Diastolic	184	103.6	92.3	-11.3**	99	103.6	87.8	-15.8**
<u>Standing</u>								
Systolic	185	159.0	143.3	-15.7**	99	157.4	135.9	-21.5**
Diastolic	184	105.9	95.1	-10.8**	99	105.8	91.8	-14.1**

\*\*p < 0.01 Significant change from pretreatment within the indicated treatment group

Figure 7

MEAN REDUCTIONS IN SUPINE DIASTOLIC BLOOD PRESSURE  
INTERNATIONAL PROTOCOL 1



\*\*Significant difference between treatment groups in change from pre-treatment,  $p < .01$ .

Figure 8

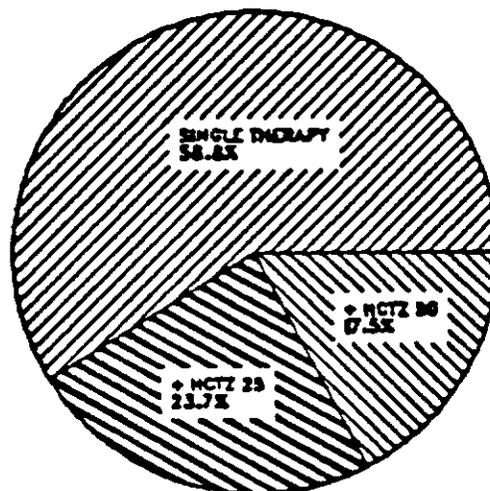
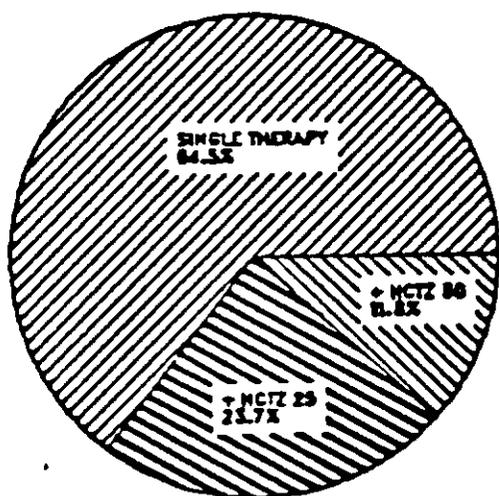
PERCENT OF PATIENTS ON SINGLE THERAPY  
AND WITH HCTZ ADDED

WEEK 18

WEEK 26

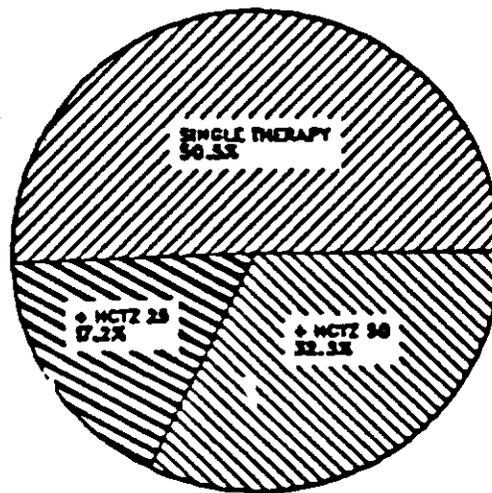
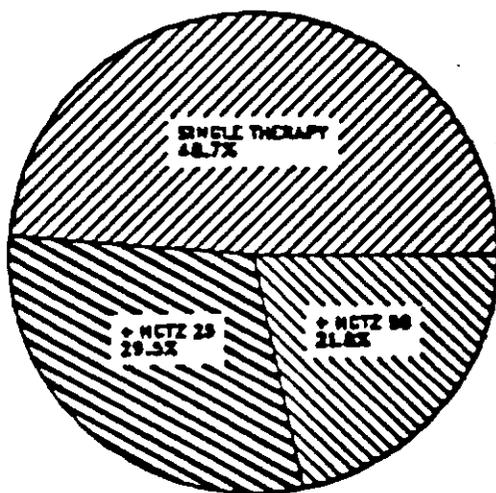
ENALAPRIL

ENALAPRIL



PROPRANOLOL

PROPRANOLOL



**Safety:**

**Clinical Adverse Experiences.**

The overall incidence of adverse experiences was similar in the two treatment groups. Nine patients on enalapril and 12 on propranolol were discontinued because of clinical adverse experiences; two on enalapril and 3 on propranolol were rated as serious. One patient on enalapril suffered a myocardial infarction, one developed atrial fibrillation. On propranolol, one patient had a myocardial infarction, one experienced pulmonary edema, and one patient was discovered to have a malignant brain tumor early in the course of the study.

**Laboratory Evaluation.**

Few clinically significant laboratory adverse experiences were seen in the study. One patient on enal/HCTZ was discontinued because of hypokalemia (serum  $K^+$  = 3.4 mEq/L); one patient on enalapril was discontinued because of serum creatinine values of 1.6 and 1.8 mg percent, and proteinuria of 1-3 gm/24 hrs.

Slight, clinically insignificant changes in serum potassium, uric acid and total WBC were seen in a few other patients on enalapril with or without HCTZ.

**Conclusion:**

Enalapril at doses from 5 mg to 20 mg b.i.d. was as effective as propranolol at doses from 40 mg b.i.d. to 160 mg b.i.d. in the treatment of mild/moderate hypertension. Fewer patients on enalapril than on propranolol required the addition of HCTZ to achieve blood pressure control.

4. Enalapril vs Metoprolol

(Mild/Moderate Hypertension). Del Greco et al.

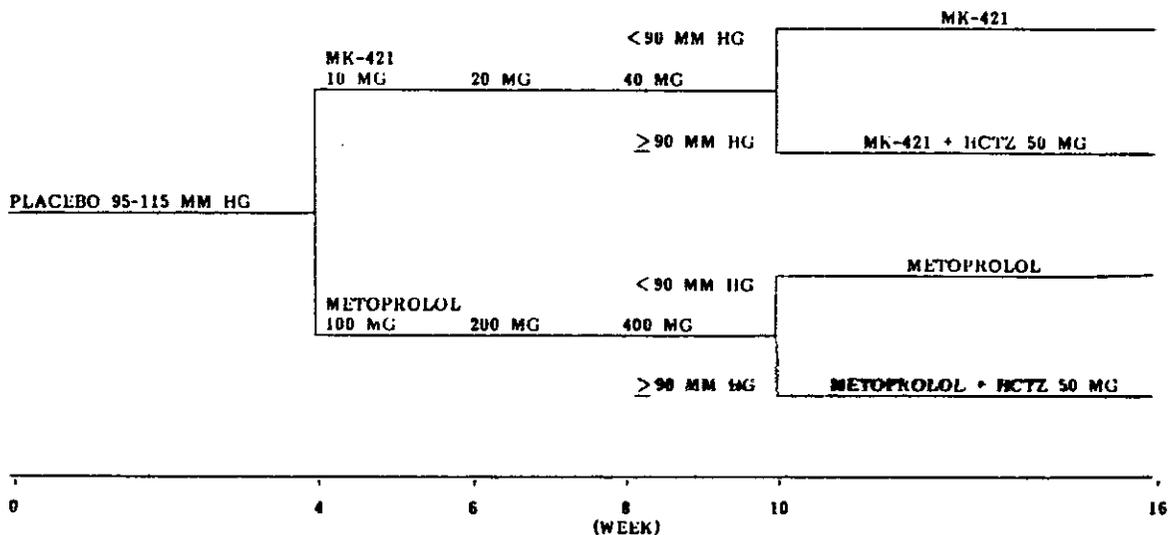
**Study Design:**

Six investigators participated in this double-blind, randomized, parallel controlled study in 150 patients with mild to moderate (95-115 mmHg) hypertension.

After a four-week placebo washout period, patients were randomly assigned to receive enalapril or metoprolol twice a day. Enalapril was titrated from 5 mg b.i.d. to 10 mg b.i.d. to 20 mg b.i.d. at two-week intervals. Metoprolol was titrated from 50 mg b.i.d. to 100 mg b.i.d. to 200 mg b.i.d. at two-week intervals. There was no upward dose titration if supine diastolic blood pressure was <90 mmHg. After six weeks, responders (SDBP <90 mmHg) continued on

their optimum dose for an additional six weeks; non-responders (SDBP  $\geq 90$  mmHg) had hydrochlorothiazide 50 mg once daily added to their regimen, and continued for an additional six weeks. A flow chart of the study is shown in Figure 9.

Figure 9  
MK-421 VS. METOPROLOL  
MILD TO MODERATE HYPERTENSION



Efficacy:

Significant reductions in supine diastolic blood pressure were seen in both single entity groups in the first 6 weeks of treatment. These reductions continued in both groups from Weeks 7 to 12 in those patients continuing single therapy. See Tables 4 and 5 and Figures 10 and 11.

TABLE 4

Mean Supine Blood Pressures (Systolic/Diastolic mmHg)  
First Treatment Period - All Patients

Treatment Week	Treatment Group					
	Enalapril			Metoprolol		
	Baseline	Treatment	No. of Patients	Baseline	Treatment	No. of Patients
2	159.6/101.5	147.1**/94.2**	(62)	158.3/101.2	148.2**/91.5**	(67)
4	158.1/101.6	142.6**/91.3**	(59)	158.6/101.2	148.0**/90.9**	(61)
6	158.6/101.4	140.8**/89.6**	(62)	158.0/101.0	146.4**/89.6**	(59)

\*\* - Significant change from baseline,  $p < 0.01$ .

FIGURE 10

Mean Reductions from Baseline in Supine Blood Pressure  
First Treatment Period

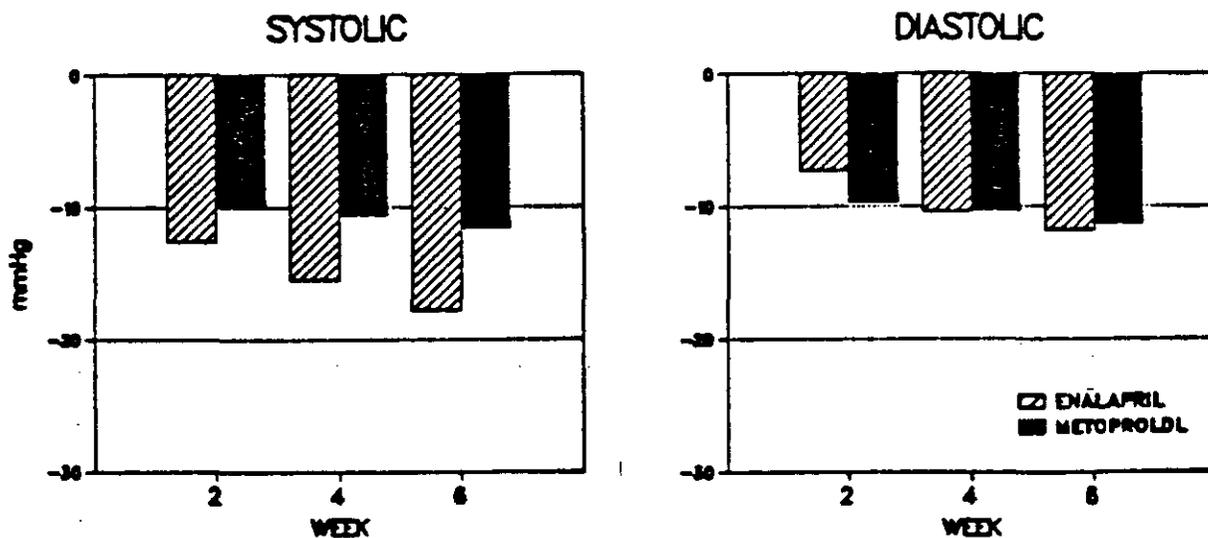


TABLE 5

Mean Supine Blood Pressures for Patients Who Continued on the Single Entities During the Second Treatment Period

Treatment Week	Treatment Group					
	Enalapril		No. of Patients	Metoprolol		No. of Patients
	Baseline	Treatment		Baseline	Treatment	
8	153.7/99.5	135.6**/85.6**	(39)	154.0/99.7	142.6**/87.9**	(34)
10	153.6/99.4	134.6**/85.3**	(37)	151.4/99.0	136.1**/84.0**	(34)
12	154.1/99.4	131.7**/83.4**	(39)	150.3/98.8	135.5**/84.0**	(31)

\*\* - Significant change from baseline, p < 0.01.

FIGURE 11

Mean Reductions from Baseline in Supine Blood Pressures Second Treatment Period - Patients on Single Entities

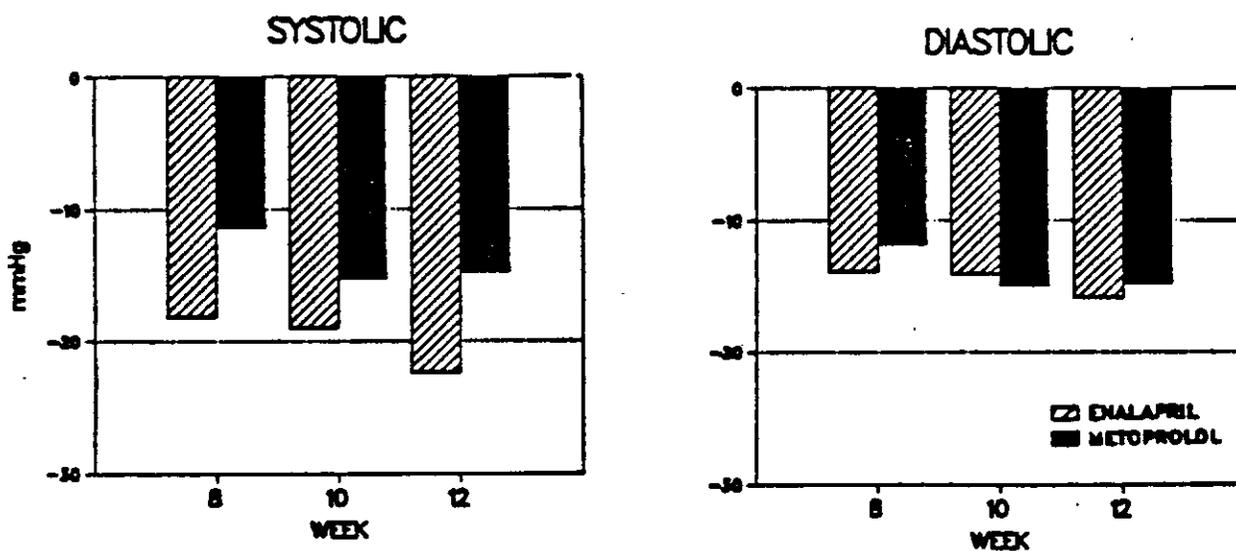


TABLE 6

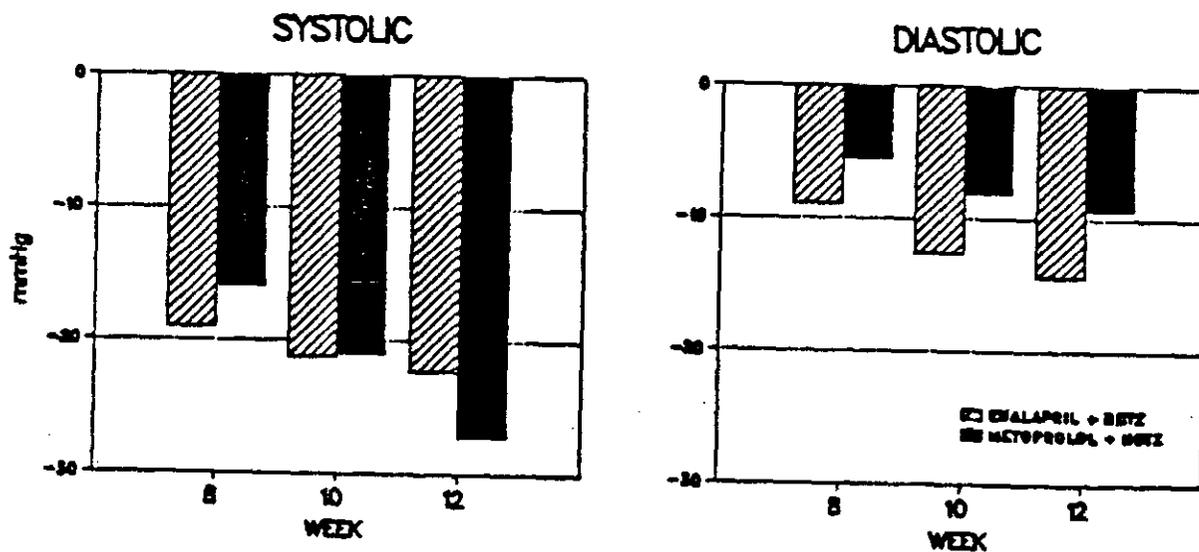
Mean Supine Blood Pressures for Patients Who Had Hydrochlorothiazide Added During the Second Treatment Period

Treatment Week	Treatment Group					
	Enalapril			Metoprolol		
	Week 6	Treatment	No. of Patients	Week 6	Treatment	No. of Patients
8	159.7/103.2	140.7* /94.3*	(15)	162.7/97.2	146.8**/91.7*	(22)
10	155.7/102.3	134.5* /89.6*	(17)	166.3/98.6	145.4**/90.4*	(23)
12	157.6/102.4	135.4**/88.0**	(16)	167.3/98.8	140.1**/89.5*	(16)

\*, \*\* - Significant change from Week 6, p < 0.05, 0.01, respectively.

FIGURE 12

Additional Mean Reductions from Week 6 in Supine Blood Pressures  
Second Treatment Period - Patients Who Had HCTZ Added



In both groups of patients, the addition of HCTZ to non-responders led to substantial additional mean decreases in blood pressure. Table 6 and Figure 12 (above) show the responses at Week 12 for those patients in whom HCTZ was added, compared to Week 6 baseline.

**Safety:**

**Clinical Adverse Experiences.**

Drug was discontinued in two enalapril patients because of serious clinical adverse experiences; one myocardial infarction, one transient cerebral ischemia; both patients recovered. One metoprolol patient suffered agitation and confusion, rated as probably drug-related; drug was discontinued. Seven patients, four on enalapril, 3 on metoprolol had significant clinical adverse experiences but completed study.

The expected reduction in mean pulse rate was seen in the metoprolol group.

Laboratory Evaluation.

Slight mean increases were seen in BUN. No clinically significant hypo- or hyperkalemia occurred. Changes seen in mean and individual hematologic parameters were of no clinical significance.

Conclusion:

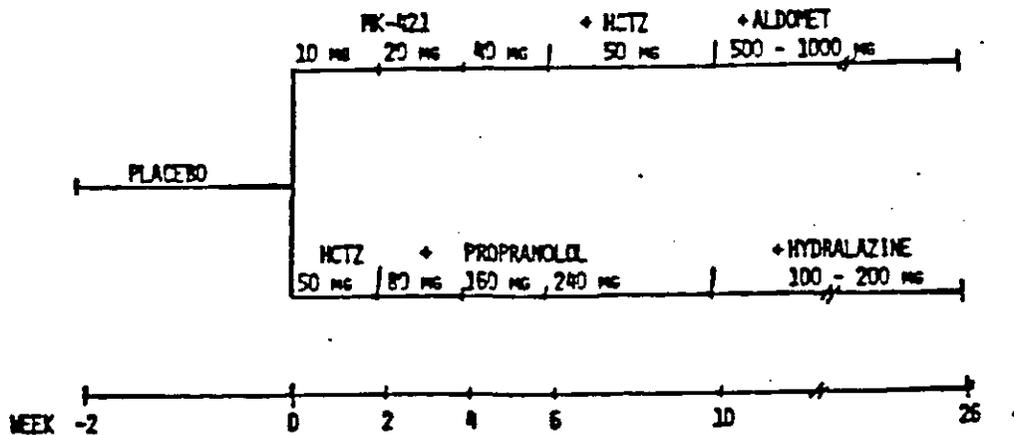
Compared to metoprolol, at doses of from 50 mg b.i.d. to 200 b.i.d., enalapril at doses of from 5 mg b.i.d. to 20 mg b.i.d. was as effective an antihypertensive agent. The addition of HCTZ increased that effectiveness.

5. Enalapril + HCTZ + Aldomet vs HCTZ + Propranolol + Hydralazine (Moderate/Severe Hypertension). De Plaen et al.

Study Design:

This double-blind controlled study was conducted in 269 patients with a supine diastolic blood pressure  $\geq 100$  mmHg after at least 3 days on placebo. One hundred thirty-six patients were assigned to the enalapril group, beginning treatment with enalapril 5 mg b.i.d. (ETT). One hundred thirty-three patients were assigned to the control group, beginning treatment with HCTZ 50 mg once daily (CTT). The sequence of subsequent treatment is illustrated in the schematic study design in Figure 13.

Figure 13



Efficacy:

Because of the study design, it is not possible to make single entity comparisons. Table 7 displays the changes from baseline in mean supine diastolic blood pressure at Weeks 2 through 26 of treatment, without regard for whether the patient was then on one, two, or three medications. Figure 14 shows the percentage of patients who became normotensive (supine diastolic blood pressure  $\leq 90$  mmHg) on each of the two regimens at Weeks 12 and 26 of treatment; more patients in the enalapril than in the control group were considered responders. Figure 15 gives a breakdown by treatment regimen at those same time points; fewer patients on enalapril than on propranolol required triple therapy.

Table 7

SUMMARY OF SUPINE DIASTOLIC BLOOD PRESSURE (mmHg)

WEEK	ENALAPRIL GROUP				CONTROL GROUP			
	N	PRE	POST	CHANGE	N	PRE	POST	CHANGE
2@@	127	115.3	104.6	-10.7###	126	116.1	105.9	-10.1###
4**	128	115.1	101.9	-13.2###	122	115.9	98.4	-17.4###
6	117	114.7	96.3	-18.5###	116	115.9	95.5	-20.3###
8	120	114.9	91.8	-23.1###	119	115.8	92.4	-23.4###
10	114	115.4	88.9	-26.5###	107	115.5	90.4	-25.1###
12	117	114.8	88.2	-26.6###	109	115.9	89.0	-27.0###
14	109	115.4	88.8	-26.6###	107	115.9	88.7	-27.3###
16	116	115.3	86.8	-28.4###	103	116.4	87.6	-28.8###
18	106	115.0	87.3	-27.7###	99	116.1	87.1	-29.0###
20	104	115.2	86.7	-28.5###	104	115.8	86.9	-28.9###
22*	104	115.1	84.1	-31.0###	91	115.8	88.0	-27.8###
24*	101	115.1	84.3	-30.8###	92	115.8	86.8	-29.0###
26	98	115.4	85.7	-29.8###	83	115.4	88.0	-27.4###

@@Significant interaction between treatment and investigator in change from pretreatment,  $p < 0.01$

\*,\*\*Significant difference between treatment groups in change from pretreatment,  $p < 0.05$ ,  $p < 0.01$ , respectively

###Significant change from pretreatment within the indicated treatment group,  $p < 0.001$

Figure 14

### Percent of Patients who Became Normotensive

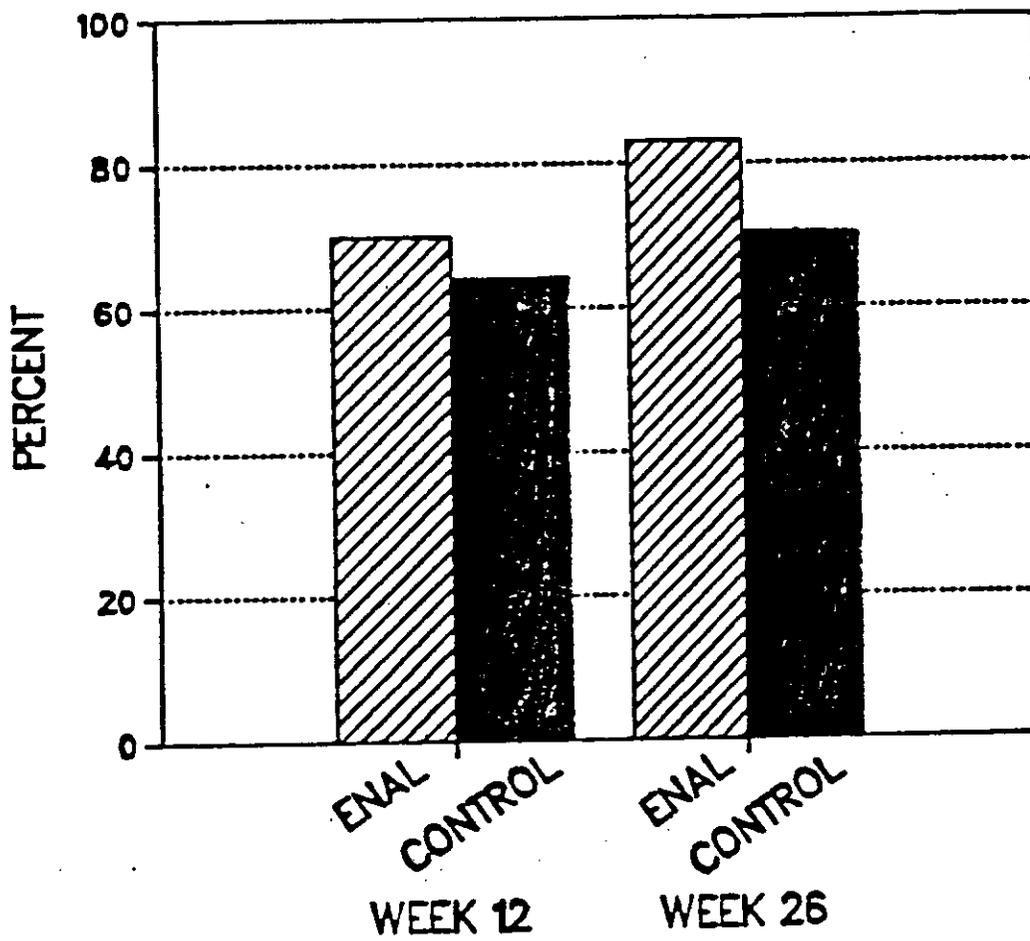
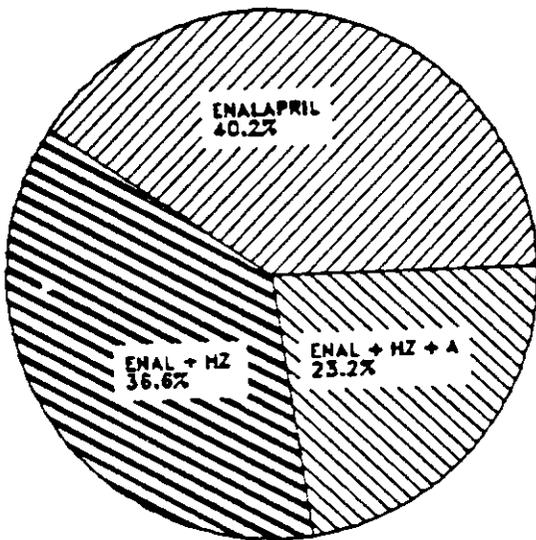


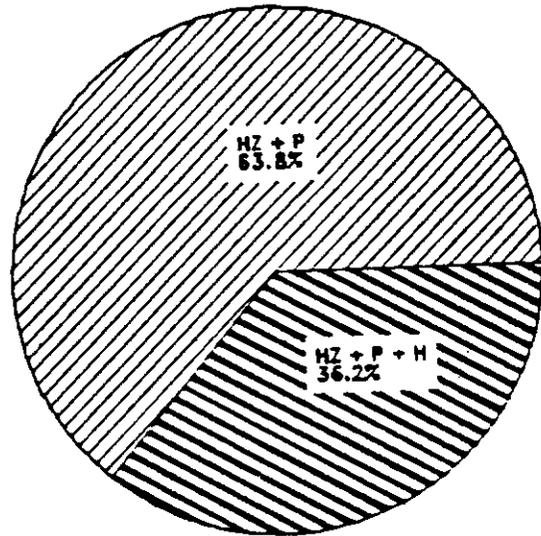
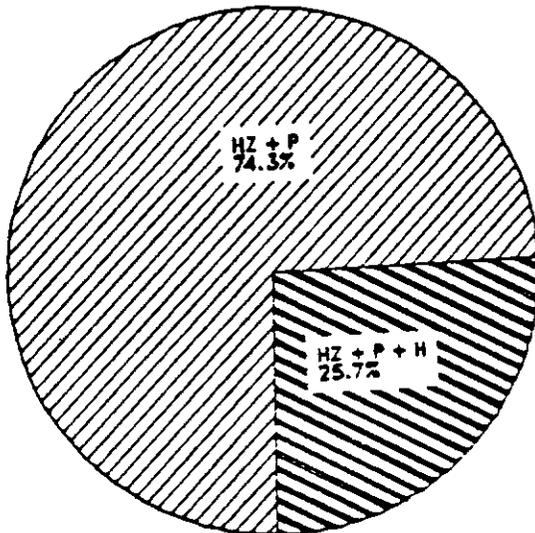
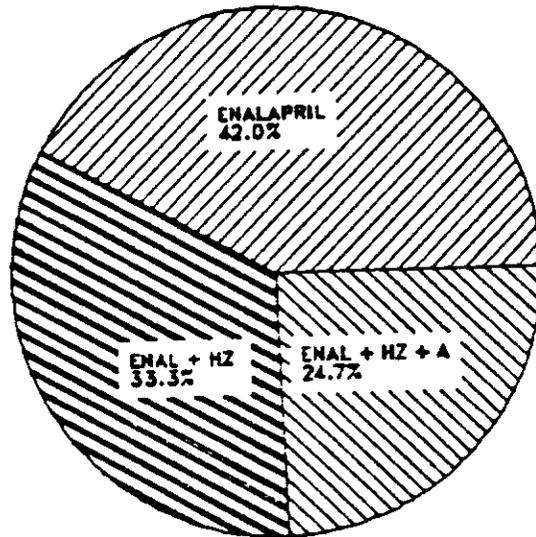
FIGURE 15

INTERNATIONAL PROTOCOL 2  
PERCENT OF PATIENTS WHO BECAME NORMOTENSIVE  
By Treatment Regimen

WEEK 12



WEEK 26



Enal = enalapril  
HZ = hydrochlorothiazide  
A = methyldopa  
P = propranolol  
H = hydralazine

**Safety:**

**Clinical Adverse Experiences.**

The incidence of adverse experiences was similar in the two groups. Five patients in the ETT group and 8 patients in the CTT group were discontinued because of clinical adverse effects. Orthostatic hypotension was more frequent in the ETT group, dizziness and headache more frequent in the CTT group, although the differences were not statistically significant.

**Laboratory Evaluation.**

One patient in the ETT group developed an elevated ANA titer during therapy; one patient in the CTT group had an elevation of urinary protein values to 2240 mg/12 hours after 14 weeks of treatment. The mean changes in other laboratory variables, although sometimes statistically significant, are not of clinical relevance. Serum potassium  $\leq 3.5$  mEq/L developed in 39 of 115 patients in the ETT group and in 60 of 108 patients in the CTT group.

**Conclusion:**

Both the ETT regimen and the CTT regimen were effective in lowering blood pressure. A higher percentage of the ETT group were controlled at Week 26, and fewer of them required triple therapy.

6. HCTZ + Enalapril ± Timolol or Aldomet vs HCTZ + Captopril ± Timolol or Aldomet (Moderate/Severe Hypertension).

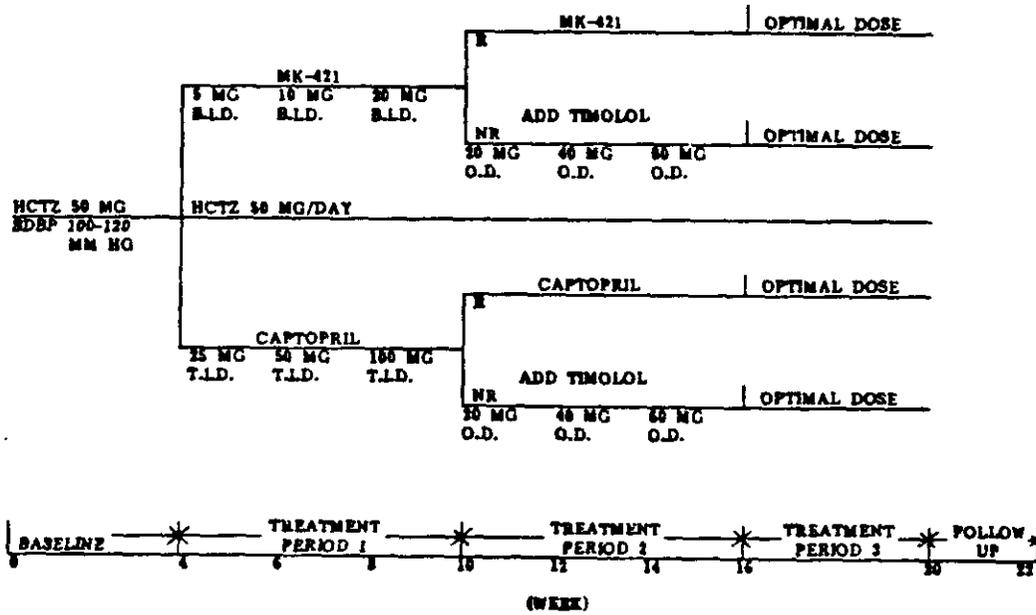
Brown et al.

Study Design:

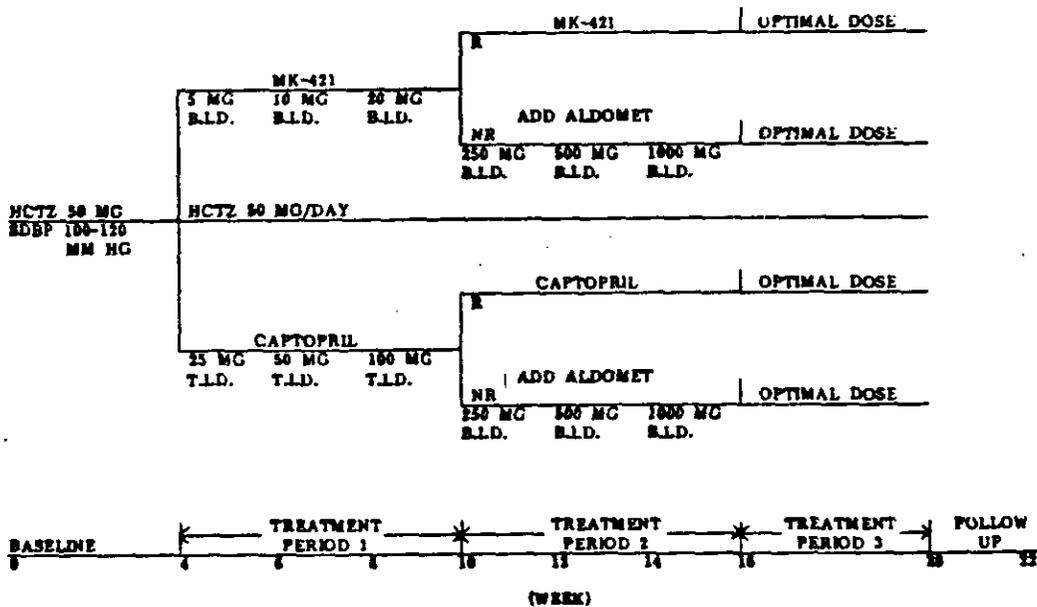
This double-blind, captopril controlled clinical study was conducted by seventeen investigators in 175 outpatients with diastolic blood pressures of 100 mmHg or more after at least 2 weeks of HCTZ 50 mg/day. Ninety patients were randomized to receive additional captopril beginning at 25 mg t.i.d., while 85 patients received enalapril 5 mg b.i.d. Dose could be doubled at 2 and again at 4 weeks to a maximum of 20 mg b.i.d. of enalapril or 75 mg t.i.d. of captopril depending on clinical response; the target supine diastolic blood pressure was <90mmHg. After six weeks of therapy with HCTZ + enalapril or captopril, timolol or Aldomet could be added; nine investigators adding each. Schematic study designs are shown in Figure 16.

FIGURE 16

HCTZ + MK-421 + TIMOLOL VS. HCTZ + CAPTOPRIL + TIMOLOL  
MODERATE TO SEVERE HYPERTENSION



HCTZ + MK-421 + ALDOMET VS. HCTZ + CAPTOPRIL + ALDOMET  
MODERATE TO SEVERE HYPERTENSION



**Efficacy:**

The mean reductions in blood pressure seen with HCTZ plus enalapril were very similar to those seen with HCTZ plus captopril, as were the proportions of patients demonstrating excellent or good response on double therapy at Weeks 6 and 16 of treatment. The addition of timolol or Aldomet led to further small mean reductions in blood pressure. These results are summarized in Table 8.

TABLE 8

Group	Weeks	No. of Patients	Response and Number (Percentage) of Patients				Mean Supine Blood Pressure (mmHg)	
			1	2	3	4	Baseline	Period
H + ENAL	6	79	52 (66)	20 (23)	12 (15)	5 (6)	159/105	137/89
H + CAPL	6	82	49 (60)	20 (24)	7 (9)	6 (7)	156/106	135/89
H + ENAL	16	30	27 (90)	0	3 (10)	0	152/104	129/85
H + CAPL	16	19	18 (95)	1 (5)	0	0	155/104	133/84
H + ENAL + TM	16	5	2 (40)	2 (40)	0	1 (20)	152/97 (1)	144/94
H + CAPL + TM	16	10	6 (60)	2 (20)	1 (10)	1 (10)	143/95 (1)	139/91
H + ENAL + MD	16	13	7 (54)	3 (23)	2 (15)	1 (8)	154/97 (2)	146/93
H + CAPL + MD	16	14	7 (50)	3 (21)	3 (21)	1 (8)	143/95 (1)	141/92

- 1 = Excellent - a supine diastolic blood pressure (SDBP) of 90 mmHg or less
- 2 = Good - a reduction in SDBP of 10 mmHg or more, but not to 90 mmHg
- 3 = Fair - a reduction in SDBP of 5 to 9 mmHg, but not to 90 mmHg
- 4 = Inadequate - a reduction in SDBP of 4 mmHg or less, or an increase

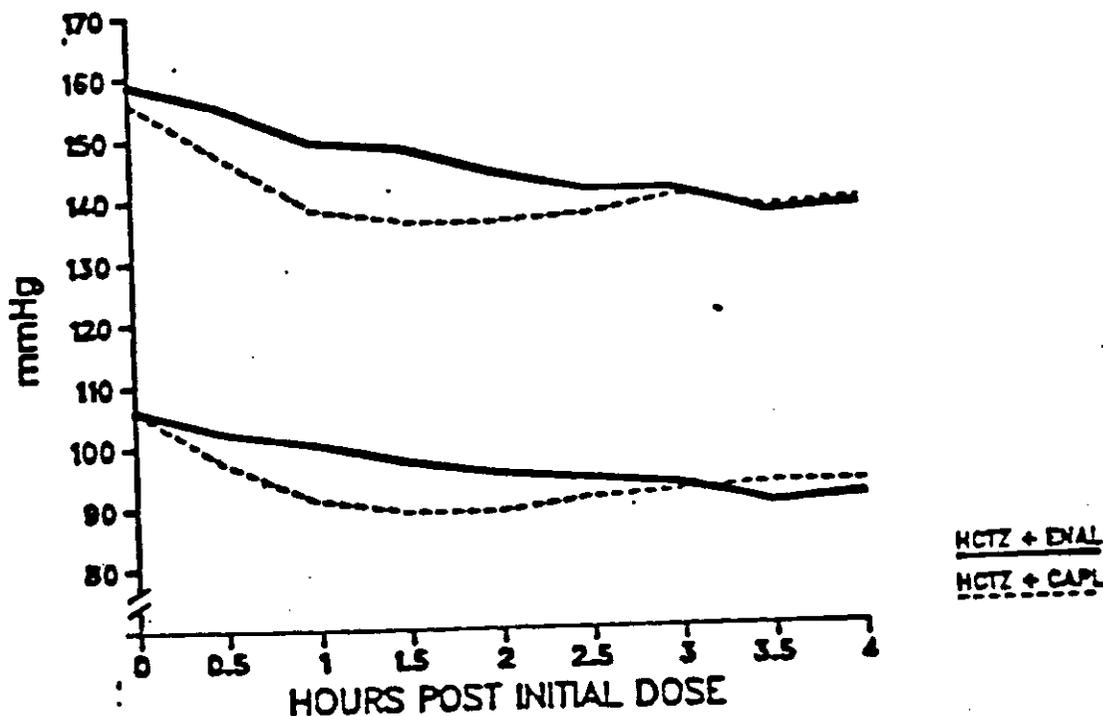
The reductions from the H baseline in supine and standing systolic and diastolic blood pressures were statistically significant ( $p < 0.01$ ) after 2, 4, 6, 8, 10, 12, 14 and 16 weeks of treatment for the groups receiving double therapy. The reductions from the double therapy baseline (1) for the triple therapy groups were statistically significant ( $p < 0.05$  or  $p < 0.01$ ) for a majority (60 pct.) of the measured points and a majority of these patients had an excellent or good response.

(1) = Week 6 when the patients were receiving H + ENAL or H + CAPL.

The major difference observed in blood pressure response was the time to development of maximal effect following the first dose, which was, as expected, more gradual for enalapril than for captopril-treated patients. Figure 17 displays this response over the first 4 hours of treatment.

Figure 17

Mean Supine Blood Pressure  
30-Minute Monitoring After Initial Dose



**Safety:**

**Clinical Adverse Experiences.**

The overall incidence of adverse experiences was similar in two treatment groups. One patient on enalapril was discontinued because of an adverse experience (anxiety disorder-not considered serious), while 8 were discontinued in the captopril group; two of these were considered serious (one was hypotension following the first dose, the other abdominal pain and vomiting after 4 weeks of treatment). Taste loss was reported by 5 patients in the captopril group, and by one patient transiently in the enalapril group. Rash occurred with equal frequency in both groups (2 patients in each).

**Laboratory Evaluation.**

Small mean changes were seen in both groups in laboratory parameters; none of these was considered of clinical significance. One patient in the enalapril group was found to have variable serum creatinine levels during study (<2.3 mg percent). She was subsequently found to have bilateral renal artery disease, and had surgery, following which she continued on enalapril plus HCTZ for persistent

hypertension. One patient on captopril developed iron-deficiency anemia during treatment, probably as a result of excessive menstrual loss. No clinically significant changes were otherwise seen in hematologic indices; and no proteinuria was observed.

Conclusion:

Enalapril at doses of from 5 mg b.i.d. to 20 mg b.i.d. plus HCTZ 50 mg daily was as effective as captopril at doses of from 25 to 100 mg t.i.d. plus HCTZ in the treatment of moderate/severe hypertension.

- 7) Enalapril + HCTZ vs Triple Therapy (Renovascular Hypertension). Anderson et al.

Study Design:

This double-blind controlled study was conducted in twenty-nine patients with documented renovascular hypertension who had supine diastolic blood pressures  $\geq 95$  mmHg at the end of a one week HCTZ baseline period. Fourteen patients randomly assigned to enalapril began with 5 mg b.i.d., which could be titrated to 20 mg b.i.d. Fifteen patients randomly allocated to triple therapy began

with timolol 10 mg b.i.d. which could be increased to 30 mg b.i.d. and to which hydralazine could be added. HCTZ was continued in both groups. A schematic design of the study is shown in Figure 18.

Figure 18

BASELINE	TITRATION			MAINTENANCE	FOLLOW-UP
HCTZ 100 MG EDBP > 95 MM HG	ME-421 8 MG B.I.D. HCTZ 50 MG Q.D. PLACEBO/TIMOLOL B.I.D.	30 MG B.I.D. 50 MG Q.D. B.I.D.	30 MG B.I.D. 50 MG Q.D. B.I.D.	OPTIMAL THERAPY	OFF DRUG
	HCTZ 50 MG Q.D. TIMOLOL 10 MG B.I.D. HYDRALAZINE 50 MG B.I.D.	50 MG Q.D. 30 MG B.I.D. 100 MG B.I.D.	50 MG Q.D. 30 MG B.I.D. 150 MG B.I.D.	OPTIMAL THERAPY	OFF DRUG
1 WEEK	8 DAYS	8 DAYS	8 DAYS	6 WEEKS	3 WEEKS

Efficacy:

The mean reductions from baseline in supine systolic and diastolic blood pressure at the end of the six week maintenance period are shown in Table 9. There were no significant differences between treatment groups.

TABLE 9

SUPINE SYSTOLIC BLOOD PRESSURE (mmHg)

<u>Treatment</u>	<u>Baseline</u>	<u>Maintenance</u>	<u>Change</u>		<u>P-Value</u>		
			<u>N</u>	<u>Mean</u>	<u>Mean</u>	<u>Mean</u>	
HCTZ + MK-421			12	165.7	143.8	-21.9	<.01
HCTZ + Timolol + Hydralazine			12	<u>173.3</u>	<u>155.8</u>	<u>-17.5</u>	<.05
Difference Between Groups				- 7.6	-12.0	-4.4	NS

SUPINE DIASTOLIC BLOOD PRESSURE (mmHg)

<u>Treatment</u>	<u>Baseline</u>	<u>Maintenance</u>	<u>Change</u>	<u>P-Value</u>
	<u>N</u>	<u>Mean</u>	<u>Mean</u>	
HCTZ + MK-421	12	94.9	84.1	NS
HCTZ + Timolol + Hydralazine	12	<u>99.0</u>	<u>83.8</u>	<u>-15.2</u>
Difference Between Groups		- 4.1	-1.3	- 4.4

Safety:

Clinical Adverse Experiences.

One enalapril patient suffered muscle cramps during study. Three patients on triple therapy had adverse experiences; one suffered fatigue and skin flushing, one nausea and headache, and one angina, dyspnea and headache. None was considered serious by the investigator.

Laboratory Evaluation.

No unexpected mean changes were seen in the laboratory measurements made.

Mean serum potassium, BUN and serum creatinine rose in both groups. One patient on enalapril had a single serum potassium level of 5.7 mEq/L recorded, for which no action was taken. One patient on triple therapy had a serum potassium of 2.6 mEq/L; once again, no action was taken.

Conclusion:

Enalapril plus HCTZ was an effective therapy in the treatment of renovascular hypertension.

VI. Safety:

The definition of safety in the studies was based on evaluation of adverse experiences observed by the physicians or reported by the patients, and by analysis of laboratory tests designed to demonstrate adverse hematologic and biochemical changes. These tests generally included full blood count and white cell differential, serum creatinine, blood urea nitrogen, aspartate

transferase, alkaline phosphatase, serum glucose, serum uric acid, serum sodium and potassium, and urinalysis. Other tests were done less frequently and included alanine transferase, antinuclear antibody titer and creatine phosphokinase levels.

#### Clinical Adverse Experiences.

Clinical adverse experiences in general occurred with no greater frequency in the enalapril than in the control groups, and usually those that occurred were transient and not serious. In the combined domestic/international experience of 1878 patients treated with enalapril alone, headache, dizziness and fatigue were seen in from 3-6 percent of patients, diarrhea, nausea, rash, cough, and hypotension in from 1-3 percent, and muscle cramps, muscle weakness, orthostatic hypotension and angioedema in less than 1 percent. The overall incidence of adverse experiences (i.e., the proportions of patients having one or more adverse experiences) was no greater with enalapril than with placebo.

#### Laboratory Evaluation.

In hematologic indices no consistent mean decreases were seen in total white cell counts or neutrophil counts, and review of individual abnormalities did not support a negative effect of enalapril on granulopoiesis. Slight, but clinically insignificant, mean decreases were seen in several studies in hemoglobin and hematocrit. Liver function tests showed no

tendency to hepatotoxicity, and serum creatinine and blood urea nitrogen were not elevated as a result of enalapril treatment, although concomitant administration with thiazide occasionally was associated with mild reversible increases in these variables. In other variables normally influenced by thiazide therapy, such as serum glucose, serum uric acid, serum potassium and serum cholesterol, there was consistent evidence that concomitant administration of enalapril with thiazide, attenuated the deleterious effects of the thiazide alone. On urinalysis, including quantitative protein measurement, no mean increases were seen, and the few isolated instances where elevated protein levels were seen did not suggest a drug effect.

VII. Summary and Conclusions:

Enalapril is an angiotensin converting enzyme inhibitor with a gradual onset and long duration of action.

Bioavailability, Metabolism, Disposition.

Twelve studies were conducted in 159 patients to determine the pharmacokinetics and bioavailability of enalapril in humans.

The active diacid, enalaprilat, is poorly absorbed orally. The maleate salt of its ethyl ester, enalapril maleate (subsequently

referred to as enalapril), is the prodrug used in the clinical studies reported. Schelling studied the pharmacokinetics of both enalapril and enalaprilat at 10 mg single doses in human volunteers. Based upon urinary recovery of total drug, at least 61 percent of the dose of enalapril was absorbed, and 43 percent of the dose was excreted in the urine as enalaprilat. After six hours, only enalaprilat was present in the urine. Ninety-four percent of the administered dose was recovered in the urine or feces.

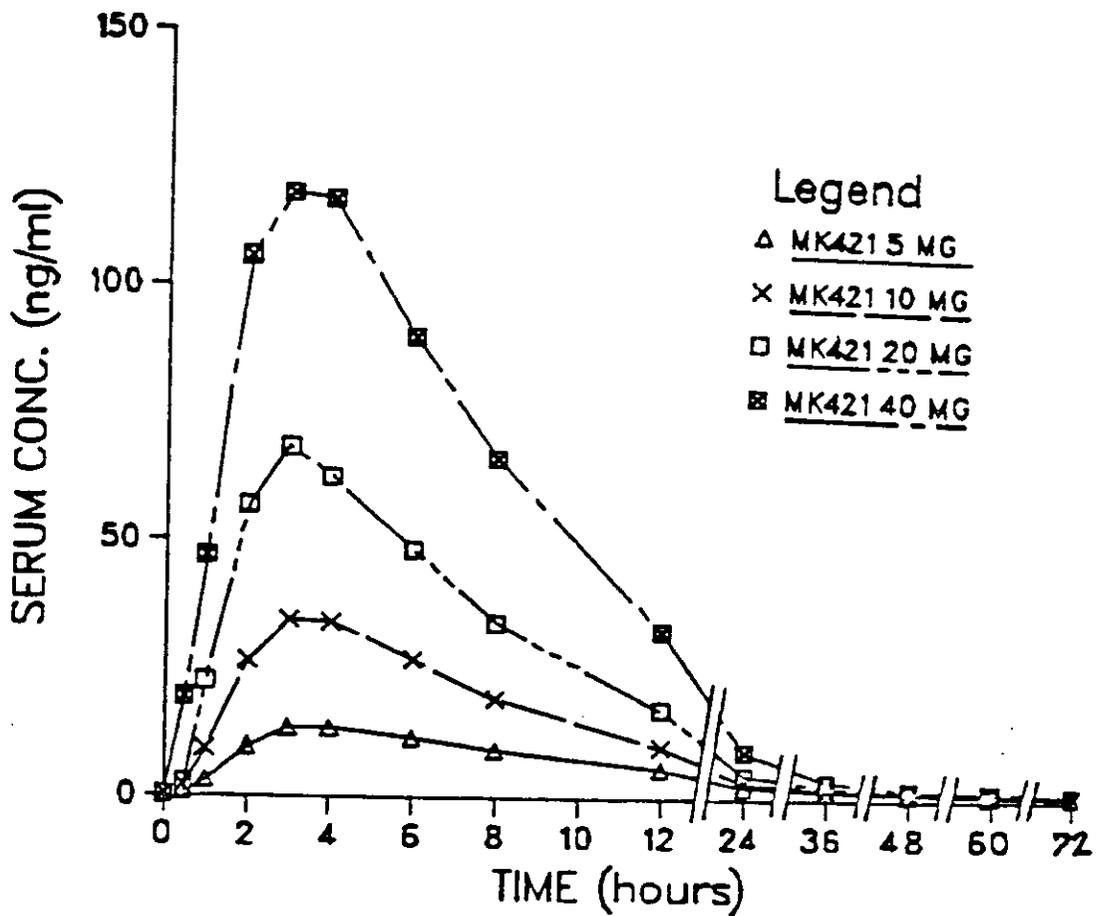
Serum profiles of enalaprilat from oral dosing of enalapril or intravenous enalaprilat have consistently shown a poly-exponential pattern with a prolonged terminal phase, thought to be due to binding to circulating angiotensin converting enzyme. This appears to have little biological significance (Kukovetz, Ferguson). A standard breakfast has no effect on the bioavailability of enalapril (Ferguson).

Lowenthal gave 10 mg single doses of enalapril to normal subjects, and to two groups of patients, one with creatinine clearances <3 ml/min (dialysis patients), the other with creatinine clearances from 10-79 mg/min. As expected, plasma levels were greater in the renally impaired patients, and significantly greater in those severely impaired as compared to those moderately impaired. Enalaprilat was found to be dialyzable, as evidenced by arterial-venous enalaprilat concentration differences during hemodialysis.

Figure 2 demonstrates the mean serum concentrations of enalaprilat at each of 4 doses of enalapril in market image, in 9 healthy volunteers (Ferguson). Results of this study indicate 59-73 percent absorption and 36-44 percent bioavailability of enalaprilat from these 4 dosage strengths.

Figure 2

Mean Serum Concentration Profile of Enalapril  
for Each Dose of Enalapril Maleate  
(Ferguson - Study No. 168)



**Dose Ranging Studies.**

The doses of enalapril studied have ranged in general from 2.5 mg to 40 mg per day with a few patients receiving lower doses and some up to 80 mg daily in single or divided doses.

In early single dose ranging studies, for example, Gavras and Case demonstrated a slight antihypertensive dose response from 2.5 mg to 20 mg, and from 5 mg to 80 mg respectively. All doses of enalapril substantially inhibited angiotensin converting enzyme activity. This appeared to be the primary mechanism involved, leading to reduced angiotensin II levels and consequently decreased peripheral resistance, reduced aldosterone levels, and increases in plasma renin activity.

In an open study (Menard), nine investigators conducted single dose evaluations of enalapril, followed by chronic outpatient maintenance, with clinically appropriate dose titration. The most common maintenance dose was 20 mg b.i.d., in some cases with diuretic, but a few patients responded to lower doses.

In congestive heart failure, invasive hemodynamic monitoring revealed that, in 73 patients inadequately controlled by digitalis and diuretics, substantial improvements occurred in pulmonary capillary wedge pressure (reductions) and cardiac index (increased) acutely and after up to 3 months of enalapril treatment with all doses. This was an open pilot study conducted worldwide (Chatterjee). Patients were treated

initially as inpatients. Enalapril was given in single doses from 2.5 mg to 40 mg and chronic daily doses in the same range given as a single or two divided doses. The most common daily maintenance dose was 20 mg. In the same study, exercise capacity increased by a mean of over 32 percent, and NYHA classification improved in 69 percent of patients.

In two double-blind placebo controlled multiclinic studies in congestive heart failure, mean exercise time increased by 94 to 109 seconds on enalapril, while significantly smaller changes occurred on placebo. NYHA classification improved in one but not the other placebo-controlled study.

#### Controlled Clinical Studies.

Double-blind controlled antihypertensive studies have been conducted under seven protocols in 115 sites worldwide comparing enalapril to placebo, hydrochlorothiazide, propranolol, metoprolol, captopril, and standard triple therapy.

The antihypertensive efficacy of enalapril, in these studies, has compared favorably to the standard antihypertensive agents used as controls. In all cases, enalapril was at least as effective as the active control drugs. Mean reductions in both diastolic and systolic blood pressure have been consistently seen, those in supine diastolic blood pressure varying from about 6 mmHg to 16 mmHg depending to some extent on initial severity of hypertension.

The addition of HCTZ led to substantial further falls to as much as 30 mmHg mean reduction from baseline. In terms of the percentage of patients showing a reduction in supine diastolic blood pressure to 90 mmHg or less or a fall of at least 10 mmHg from baseline: this varied from 54 percent with enalapril alone at optimal dosage, to as high as 96 percent with concomitant HCTZ.

Clinical adverse experiences occurred infrequently, were seldom serious, and/or required discontinuation of therapy.

Laboratory changes associated with therapy did not indicate toxicity of enalapril with relation to hematologic, renal or hepatic function. Concomitant therapy with enalapril may attenuate the undesirable laboratory changes associated with hydrochlorothiazide treatment; i.e., changes in serum potassium, glucose, uric acid and cholesterol.

#### Regulatory Conclusions.

The proposed labeling for the new drug complies with 21 CFR Parts 201 and 202.

VIII. Recommendation:

NDA 18-998 is approvable because the applicant has found substantial evidence of safety and effectiveness in the aforementioned clinical trials.

*A. A. Solymosy, M.D.*  
A. A. Solymosy, M.D.

Enclosure: Synopsis of Clinical Studies

*N.C.C. 18, 998*

APPENDIX

Synopsis of Clinical Studies

A). BIOAVAILABILITY, METABOLISM, DISPOSITION

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>																														
R. Williams, #53	Single	Randomized, single-dose 3-way crossover in which the bio-availability of single, oral doses of MK-421 tablets (10 mg) and MK-421 capsules (10 mg) were determined using a single i.v. dose of MK-422 (5 mg) as a standard.	12	0	-	Based on urinary recovery of MK-422 and total drug. The bioavailability of MK-422 following MK-421 tablets and capsules is the same in healthy, male volunteers. All treatments were well-tolerated.																														
Lowenthal, #110	Single	Open-label, single dose (10 mg enalapril) parallel study comparing bioavailability in healthy volunteers and patients with mild to moderate and severe renal insufficiency.	29	0	-	A single 10 mg enalapril dose caused a greater decrease in blood pressure in patients with renal insufficiency than in healthy patients. Treatment was well tolerated.																														
Ferguson, #168	Single	Crossover study with six single dose drug treatment periods consisting of the following treatments: 5, 10, 20 and 40 mg enalapril maleate tablets, 5 mg. i.v. enalapril maleate and 5 mg. i.v. enalaprilic acid. Each treatment was separated by a six-day washout.	10	0	-	Bioavailability of enalaprilic acid was similar for all enalapril maleate p.o. doses. The extent of hydrolysis of enalapril to enalaprilic acid was approximately 30% less than that for the tablets. All treatments were well tolerated.																														
R. Williams, #21	Single	Open label, single-dose, 2-period crossover to assess bioavailability of MK-421 and HCTZ from a tablet containing 10 and 25 mg of these compounds vs. the separate entities. Both the comb. & sep. entities were well tolerated.	14	0	-	<table border="0"> <tr> <td></td> <td><u>COMB.</u></td> <td><u>SEP. ENT.</u></td> </tr> <tr> <td><u>AUCO-72</u></td> <td>492±78</td> <td>477±110</td> </tr> <tr> <td><u>Urin. Rec.</u></td> <td></td> <td></td> </tr> <tr> <td>L-154,628</td> <td>47±6</td> <td>48±12</td> </tr> <tr> <td>Total L-154,628</td> <td>68±7</td> <td>69±13</td> </tr> <tr> <td>HCTZ</td> <td>61±12</td> <td>60±10</td> </tr> <tr> <td><u>Renal Clear.</u></td> <td></td> <td></td> </tr> <tr> <td>L-154,628</td> <td>153±27</td> <td>155±29</td> </tr> <tr> <td>HCTZ</td> <td>322±89</td> <td>378±91*</td> </tr> <tr> <td></td> <td colspan="2">*(p&lt;0.05)</td> </tr> </table>		<u>COMB.</u>	<u>SEP. ENT.</u>	<u>AUCO-72</u>	492±78	477±110	<u>Urin. Rec.</u>			L-154,628	47±6	48±12	Total L-154,628	68±7	69±13	HCTZ	61±12	60±10	<u>Renal Clear.</u>			L-154,628	153±27	155±29	HCTZ	322±89	378±91*		*(p<0.05)	
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	*(p<0.05)																																			
Ferguson, #23	Single	Open label, 2-way crossover study. Each volunteer received one 40 mg MK-421 tablet while in the fasting state and another tablet one min. following a standardized breakfast.	12	0	-	A 40 mg MK-421 tablet was well tolerated and the standardized breakfast did not influence the rate or extent of absorption of the single 40 mg. dose.																														

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience

BIOAVAILABILITY, METABOLISM, DISPOSITION

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Leary, #512	Single	Open label, randomized, single-dose 3-period crossover study where treatments with MK-421 (9.51 mg), MK-422 (8.62 mg) and MK-521 (9.32 mg) were separated by 1 week intervals.	6	0	-	MK-421 was the most rapidly absorbed. MK-422 was poorly absorbed. MK-421 was extensively metabolized to its active diacid, MK-422. All treatments were well tolerated.
Schelling, #503	Single	Open-label, single dose 2-period crossover study where treatments with MK-421 (10 mg) and L-154,628 (10 mg) were separated by a 1-week washout interval.	12	0	-	MK-421 was rapidly absorbed and metabolized to its diacid L-154,628. MK-421 was more rapidly absorbed than L-154,628. Both significantly lowered blood pressure while being well tolerated.
Lant, #518	Single	Open label study in which each subject received 8 single daily doses of 10 mg MK-421 p.o.	12	0	-	MK-421 increased urinary sodium, potassium and chloride excretion and was well tolerated.
Ferguson, #6	Single	Double-blind, single-dose randomized crossover design. Each volunteer received either < .5, 5, 10 mg of i.v. MK-422 or placebo on each of 4 study days.	12	0	-	MK-422 was safe and effective at all tested dosages.
Dollery, #523	Single	Open label, single-dose, 2-period crossover study where patients received the following treatments separated by a 2-week interval: L-154,628 5 mg i.v. and MK-421 10 mg p.o.	12	0	-	Bioavailability of L-154,628 from MK-421 is 54% and the absorption is 74%. Both MK-421 and L-154,628 were well tolerated.
McMahon, #27	Single	Open label, single-dose, two-period randomized, crossover to determine bioavailability.	12	0	-	The bioavailability of L-154,628 (MK-422) from the 10 mg MK-421 tablet is 40%. The absorption of total drug from the tablet formulation is 59%.

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

BIOAVAILABILITY, METABOLISM, DISPOSITION

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Kukovetz, #555	Single	Double-blind, single-dose, 4-period crossover study where patients received the following treatments between 10 day washout periods: MK-421 (2.5 mg p.o.), MK-421 (10 mg p.o.), MK-421 (40 mg p.o.), and MK-422 (5 mg i.v.)	12	0	-	Bioavailability for 10 and 40 mg MK-421 doses was greater than that for the 2.5 mg dose. All treatments were well tolerated.
Kukovetz, #539	Single	Open label, randomized, single-dose, 2-period crossover study where patients received Inderal (40 mg tablets) and propranolol MSD (40 mg tablets) between a 1-week washout interval.	12	0	-	Propranolol MSD 40 mg tablets are bioequivalent to Inderal, 40 mg tablets to within 20%.

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

B). MECHANISM OF ACTION

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Melby, #10	Single	An open-label, randomized, 3 way, repeat-dose study in parallel groups of healthy patients comparing 10 mg q.d. enalapril, 10 mg q.d. enalapril plus 50 mg q.d. HCTZ and 50 mg q.d. HCTZ alone treatment.	18	1	-	Enalapril was well tolerated and there were no consistent differences in the antihypertensive effects of the three therapies.
Melby, #11	Single	Open-label, randomized, repeat-dose study of 2 groups comparing 10 mg doses of enalapril with 10 mg enalapril plus 50 mg HCTZ daily.	20	1	-	Both treatments resulted in decreases in blood pressures and both were well tolerated.
Oates, #73	Single	Single-blind, multiple dose (20 mg q.d. or b.i.d. of enalapril) mechanism of action study.	8	0	-	Enalapril 20 mg q.d. had an initial onset of activity at 4 to 6 hours with an increasing antihypertensive response during the first 6 days.
Reid, #530	Single	Double-blind, crossover study involving single doses of 10 mg MK-421 p.o., 10 mg MK-521 p.o. and placebo.	9	0	-	10 mg of MK-421 decreased blood pressure from 2 to 12 hours while 10 mg of MK-521 reduced blood pressure from 4 to 24 hours.
Williams/ Hollenberg, #25 A1/A2	Single	Open-label, mechanism of action study in which patients received single and increasing doses of 2.5, 5, 10 and 20 mg enalapril over 4 days while on high or low sodium diets.	22	1	-	Enalapril lowered blood pressure in patients on both low and high sodium diets. Enalapril is well tolerated.
	A3 Single	Open-label, mechanism of action study in which patients received a single 5 mg dose of enalapril followed by 2, once daily, doses of 10 mg enalapril.	8	0	-	Enalapril 10 mg was effective for at least 22 hours. Single doses of 5 and 10 mg enalapril were well tolerated.

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

MECHANISM OF ACTION

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Frohlich, #24	Single	Open label dose ranging study. Patients had dose of enalapril increased weekly to achieve an optimum antihypertensive response. Possible doses: 5 mg q.d. (initial) 10 mg q.d., 20 mg q.d., 40 mg q.d., 20 mg b.i.d. and 20 mg b.i.d. plus 50 mg HCTZ q.d.	8	0	-	Enalapril is well tolerated in 5 mg to 40 mg daily doses. Enalapril therapy decreases blood pressure, peripheral resistance and converting enzyme activity while maintaining cardiac output. The addition of HCTZ further decreased blood pressure.
Isben, #74	Single	Double-blind, randomized, two-way, single-dose, crossover study to evaluate hemodynamic effects and baroflex sensitivity of single dose 20 mg MK-421 therapy.	12	0	-	A 20 mg enalapril dose decreased blood pressure and peripheral resistance and increased stroke volume and cardiac index. Baroflex sensitivity to blood pressure change was enhanced and treatment was well tolerated.
Lant, #525	Single	Double-blind, 4-period crossover study where subjects received single oral doses of either 20 mg MK-421 or placebo under either low or high sodium diets. There was a 2-month interval between diet changes and a 2-week interval between treatment changes.	8	0	-	MK-421 increased sodium excretion regardless of diet and reduced blood pressure up to 24 hours (more so on the low salt diet). MK-421 was well tolerated.
Robertson, #563	Single	Double-blind, randomized, 3-period crossover study involving the following 8-day treatments: 10 mg q.d. enalapril p.o., 10 mg q.d. MK-521 p.o., and placebo.	12	1	-	Both active treatments lowered blood pressure for 24 hours.

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

MECHANISM OF ACTION

<u>Study Name//</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Johnston, #509	Single	Double-blind, single dose cross-over study involving normal and low sodium diets and the following treatments: 10 mg MK-421 and placebo.	13	0	-	A single dose of 10 mg MK-421 reduced blood pressure from 2 to 24 hours regardless of diet; however, reductions were greater on the low sodium diet.
Ferguson, #111	Single	Single-blind study to evaluate single dose and repeated dose effects of 20 mg q.d. of enalapril.	8	1	-	Enalapril 20 mg significantly reduced blood pressures in hypertensive patients after 2 weeks of treatment. Blood pressure reductions were associated with reductions in systemic vascular resistance and forearm vascular resistance. Converting enzyme activity was suppressed and mean plasma epinephrine levels were reduced. Enalapril 20 mg q.d. was well tolerated.
Fouad, #52	Single	Long-range study to determine effects of 20 mg b.i.d. of enalapril. Part I: single-blind study in hospital patients, Part II: open label 12 week study, Part III: 24 month extension, patients maintained on enalapril 10 mg q.d. to 20 mg b.i.d. with or without HCTZ.	10	4	-	Enalapril 20 mg b.i.d. effectively lowers mean arterial pressure and total peripheral resistance while increasing cardiac index (after 1 month) without increasing heart rate or expanding total blood volume.

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

C). DOSE RANGE STUDIES

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Open Pilot Study Menard, et al.	Multiclinic	Open Label 1.25 mg-40 mg	52	2	-	1 MI(#12, 1 CVA(#4) Leukopenia in 1 case (#53) 2.5 mg minimal effective dose
Once Daily vs Twice Daily Velasco/Wilhelmsson	Multiclinic	2 Period Crossover 20 mg o.d. vs 10 mg b.i.d.	56	-	-	Both regimens well-tolerated Once and twice daily equally effective.
Once Daily vs Twice Daily McMahon/Lowenthal	Multiclinic	2 Period Crossover 40 mg o.d. vs 20 mg b.i.d.	32	2	-	Both well tolerated Once and twice daily equally effective.
Once Daily vs Twice Daily Holland	Multiclinic	2 Period Crossover 20 mg o.d. vs 10 mg b.i.d.	8	-	-	Well-tolerated No stat. evaluation
Once Daily vs Twice Daily with HCTZ Mitchell #20	Single	2 Period Crossover MK-421/HCTZ 40/50 mg o.d. vs 20/25 mg b.i.d.	22	7	-	Clinical AE's similar both regimens. Lab. AE's higher in b.i.d. group. Both groups- similar efficacy.

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

DOSE RANGE STUDIES

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Brunner, #501	Single	Open labeled, single dose, dose-ranging parallel study with MK-421 and L-154,826 and L-154,628.	21	0	-	MK-421 and L-154,826 were more effective than L-154,628. All three were well tolerated.
Ferguson, #4	Single	Double-blind, multiple-dose study in which patients received either 1) 5 mg MK-421, 50 mg HCTZ, and 5 mg MK-421 plus 50 mg HCTZ daily with treatment regimen in random order or 2) 10 mg MK-421, 50 mg HCTZ and 10 mg MK-421 plus 50 mg HCTZ daily in random order.	9	1	-	All treatments, 5 and 10 mg MK-421, 50 mg HCTZ and both combined MK-421 and HCTZ treatments, decreased blood pressure. The combined treatments produced the largest decreases and the longest duration of action. All treatments were well tolerated.
Ferguson, #22	Single	Single-blind, multiple dose crossover study consisting of the following treatment regimens: MK-421 20 mg b.i.d. HCTZ 25 mg b.i.d., and MK-421 20 mg b.i.d. plus HCTZ 25 mg b.i.d.; with a 2 week no treatment washout period.	14	0	-	The combination MK-421 and HCTZ regimen was more effective than either entity alone when given after the separate entities. All treatments were well tolerated.
MacGregor, #506	Single	Double-blind, randomized 3-period crossover study involving single doses of placebo, 5 mg MK-421, and 20 mg MK-421.	9	0	-	Both active treatments significantly lowered blood pressure. There was no evidence of a dose response. Both were well tolerated.

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

DOSE RANGE STUDIES

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Multiclinic Dose Response Gavras, et al	Multiclinic	Parallel/Double-blind				Lab and Clinical Safety Comparable SDBP + 10.7 mmHg + 7.0 mmHg + 11.5 mmHg + 15.5 mmHg + 3.8 mmHg
		Enalapril 2.5 mg b.i.d.	29	1	-	
		10 mg b.i.d.	28	1	-	
		20 mg b.i.d.	28	2	-	
		40 mg b.i.d.	26	1	-	
		Placebo	28	1	-	
Multiclinic Dose Response Wilhelmsson/Berglund	Multiclinic	Parallel/Double-blind				No serious AE's. SDBP + 1 mmHg + 11 mmHg + 10 mmHg + 10 mmHg
		Enalapril 0.625 mg b.i.d.	11	-	-	
		5 mg b.i.d.	14	-	-	
		20 mg b.i.d.	15	-	-	
		40 mg b.i.d.	21	-	-	
Study continued for 6 week extension.						
Single/Rising Dose Case/Atlas, #9	Single	Single/Rising dose 5-80 mg/day	14	-	-	No significant AE's 5-80 mg/day is effective dose range.
Single/Rising Dose Then Multiple Doses Ferguson, #1	Single	Single doses 7.5-20 mg/day Effective dose for 1 week	12	-	-	No significant AE's Higher doses increase duration.
Single/Rising Dose Then Multiple Doses Gavras, #2	Single	Single doses 2.5-20 mg/day Effective dose given chronically.	11	-	-	No significant AE's Significant reduction in BP all doses. Duration dose dependent.
Single/Rising Dose Then Multiple Doses Laroche, #3	Single	Single doses 2.5-20 mg/day Then chronic dose	13	-	-	No significant AE's Dose related decrease in BP.
Multiclinic Dose Response-Renovascular Hypertension Robertson, et al.	Multiclinic	Open. Repeated single doses.	25	-	-	No significant AE's 10-40 mg/day is effective in reducing blood pressure in renovascular hypertension patients.

\* Maximum number of patients evaluated for efficacy.  
 \*\* Drop-outs as result of adverse experience.

D). CONGESTIVE HEART FAILURE STUDIES

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
<u>Phase IIB &amp; III</u>						
Enalapril Open Label CHF Hemodynamic Evaluation Chatterjee, et al.	Multiclinic	Open-Label Acute and Chronic hemodynamics Dose 2.5 mg-40 mg daily	73	5	6	AE's expected in severe CHF PCWP +9.5 mmHg acute 9.4 mmHg chronic SVR +694 dynes/sec/cm <sup>5</sup> acute 507 dynes/sec/cm <sup>5</sup> chronic
Enalapril vs Placebo (CHF) Chrysant, et al.	Multiclinic	Double-blind Digoxin/Diuretics + Enalapril 7.5-20 mg/day or Placebo	19 23	0 7	1 3	Overall AE - 54% placebo 33% enalapril Exercise Duration +93.8 secs. Exercise Duration +27.3 secs. NYHA: No significant difference.
Enalapril vs Placebo (CHF) Athanassiades, et al.	Multiclinic	Double-blind Digoxin/Diuretics + Enalapril 5-10 mg b.i.d. or Placebo	46 47	5 2	2 2	AE. Incidence similar both groups. Exercise duration +111.2 secs. Exercise duration + 29.8 secs. Significant improvement NYHA status

\* Maximum number of patients evaluated for efficacy.

\*\* Drop-outs as result of adverse experience.

E). HYPERTENSION STUDIES

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
<u>Phase IIB &amp; III</u>						
Enalapril o.d. vs b.i.d. vs Placebo SDBP 90-104 mmHg Chrysant, et al.	Multiclinic	Parallel/Double-blind				Clinical AE's similar Acute renal insufficiency (#78) SDBP +8.3 mmHg SDBP +8.7 mmHg SDBP +< 1 mmHg
		Enalapril 5-20 mg b.i.d.	50	1	-	
		Enalapril 10-40 mg o.d. Placebo	54 50	1 2	- -	
Enalapril vs HCTZ vs Enalapril/HCTZ SDBP 100-120 mmHg Bauer, et al.	Multiclinic	Parallel, Double-blind				Overall AE's similar Dizziness 10% on Enal/HCTZ SDBP Enal - +11.5 mmHg HCTZ - +13.2 mmHg E/H - +21.4 mmHg
		Enalapril - 10-20 mg b.i.d.	197	8	1(#201)	
		HCTZ - 25-50 mg b.i.d. E/H 10/25-20/50 b.i.d.	197 94	7 24(a)	- -	
Enalapril vs Propranolol + HCTZ SDBP 95-114 mmHg Abbott, et al.	Multiclinic	Parallel/Double-blind				Clinical AE's similar SDBP +12.8 - 18.7 <sup>b</sup> mmHg +11.3 - 15.8 <sup>b</sup> mmHg
		Enal. 5-20 mg b.i.d.	183	10	-	
		Prop. 40-120 mg b.i.d. + HCTZ 25-50 mg if nec.	184	14	-	
Enalapril vs Metoprolol + HCTZ SDBP 95-115 mmHg del Greco, et al.	Multiclinic	Parallel/Double-blind				Clinical AE's similar 1 MI each group SDBP +11.8 mmHg SDBP +11.4 mmHg
		Enalapril 5-20 mg b.i.d.	62	4	-	
		Metop. 50-200 mg b.i.d.	67	6	-	
Enalapril ± HCTZ ± ALDOMET vs HCTZ + Propranolol + HYDRALAZINE SDBP 110-130 mmHg De Plaen, et al.	Multiclinic	Parallel/Double-blind				Overall AE's similar SDBP +26.5 mmHg SDBP +25.1 mmHg (at Wk. 26 on optimal treatment)
		Enalapril 5-20 mg b.i.d.	127	8	-	
		Prop. 40-120 mg b.i.d. (as part of triple therapy as required)	126	12	-	
HCTZ + Enalapril ± ALDOMET or BLOCADREN vs HCTZ + Captopril ± ALDOMET or BLOCADREN SDBP 100-120 on HCTZ Brown, et al.	Multiclinic	Parallel/Double-blind				Overall AE's similar Taste loss 5-Capt., 1 Enal. SDBP +16 mmHg SDBP +17 mmHg
		HCTZ + Enalapril 5-20 mg b.i.d.	79	2	-	
		HCTZ + Capt. 25-100 mg t.i.d. + ALDOMET or BLOCADREN if nec.	82	9	-	

a) Includes patients initially randomized to E or H, but switched to E/H as a result of non-response

b) With HCTZ if needed

\* Maximum number of patients evaluated for efficacy

\*\* Drop-outs as result of adverse experience

RENOVASCULAR HYPERTENSION

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
<u>Phase III</u>						
HCTZ + Enalapril vs Standard Triple Therapy Renovascular H/T Anderson, et al.	Multiclinic	Parallel/Double-blind HCTZ + Enal. 5-20 mg b.i.d. Timolol 10-30 mg b.i.d. + Hydralazine 50-150 mg b.i.d.	14 15	0 1	- -	Overall AE's similar SDBP+ -10.8 mmHg SDBP+ -15.2 mmHg

\* Maximum number of patients evaluated for efficacy

\*\* Drop-outs as result of adverse experience.

F). DRUG INTERACTION

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
DeSchepper, #618	Single	Open label, randomized, single crossover study in which the following treatments were administered to healthy subjects: 10 mg of enalapril maleate, 80 mg furosemide, and 10 mg of enalapril plus 80 mg of furosemide.	12	0	-	The pharmacokinetics of enalapril maleate were not effected by the concomitant use of furosemide. This combination, however, was associated with more adverse experiences than either agent alone.
Dresse, #570	Single	Open label, randomized, single-dose, 3-period crossover study involving the following treatments: 10 mg MK-421, 80 mg Inderal, and 10 mg enalapril plus 80 mg Inderal.	12	0	-	The bioavailability of Inderal seemed enhanced by coadministering MK-421.
Oparil, #109	Single	Single-blind, multiple dose, randomized study with 3 parallel treatment groups receiving 20 mg MK-421 b.i.d., MK-421 plus 200 mg of Clinoril, and the MK-421 and Clinoril regimen plus Indocin 50 mg b.i.d.	29	2	-	The addition of Indocin and/or Clinoril did not effect the anti-hypertensive response to MK-421 therapy. All treatments were well tolerated.
Ryan, #151	Single	Open label, non-randomized study comparing 3 treatments: Coumadin (sodium warfarin) 2.0-7.5 mg dose, Coumadin plus enalapril 10 mg b.i.d., and Coumadin plus 5 mg Vitamin K.	10	0	-	Enalapril does not appear to affect the anticoagulative action of sodium warfarin (in subtherapeutic doses) as measured by prothrombin in healthy volunteers. This combination was also safe and well tolerated.
Ryan, #152	Single	Single-blind, randomized, single dose, 3-way crossover study with the following active treatment regimens: 500 mg Aldomet q.d., 20 mg enalapril q.d., and 500 mg Aldomet q.d. plus 20 mg enalapril q.d.	16	4	-	The combination of enalapril and Aldomet lowers systolic blood pressure more than either enalapril or Aldomet alone. All treatments lowered blood pressure and were well tolerated.

\* Maximum number of patients evaluated for efficacy

\*\* Drop-outs as result of adverse experience

DRUG INTERACTION

<u>Study Name/#</u>	<u>Multicentric/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Combined Summary Timolol Interaction Huikko, #595 Jaatiela, #588 Seppala, #587	Multiple	A parallel, double-blind study in which all patients received either 10 mg b.i.d. of Timolol or 10 mg of Timolol b.i.d. and then 10 mg b.i.d. of Timolol plus 10 mg b.i.d. of enalapril.	22	0	-	In patients uncontrolled by Timolol alone, the addition of enalapril further reduced blood pressure. The combination Timolol + enalapril is well tolerated.
Combined Summary Timolol Interaction Kaarsalo, #577 Wilhelmsson, #676	Multiple	A parallel, double-blind study in which all patients received either 1) 10 mg b.i.d. of enalapril or 2) 10 mg b.i.d. of enalapril and then 10 mg b.i.d. of enalapril plus 10 mg b.i.d. of Timolol.	27	1	-	Enalapril alone was effective in reducing blood pressure, however, the combination (enalapril and Timolol) seems more effective in reducing diastolic blood pressure than enalapril alone. The combination is well tolerated.
Williams, #17	Single	Double-blind, randomized 3-way crossover study consisting of the following treatments: 10 mg MK-421 b.i.d., 25 mg HCTZ b.i.d., and 10 mg MK-421 b.i.d. plus 25 mg HCTZ b.i.d.; with each treatment separated by a 10-day washout period and 3-day placebo period.	12	1	-	In healthy normal volunteers the MK-421 & the combination treatment lowered blood pressure similarly. Multiple doses of MK-421 and HCTZ have little or no effect on bio-availability of either compound.
Darragh, #634	Single	Open label, randomized, single-dose, crossover study in which the following treatments were administered between 2-week washout periods: 10 mg enalapril maleate p.o., 0.25 mg digoxin p.o., and 10 mg enalapril maleate p.o. plus 0.25 mg digoxin p.o.	12	0	-	Digoxin (0.25 mg) did not alter the effects of enalapril maleate. All treatments were well tolerated.

\* Maximum number of patients evaluated for efficacy

\*\* Drop-outs as result of adverse experience

G). COMPASSIONATE

<u>Study Name/#</u>	<u>Multiclinic/Single</u>	<u>Design Dose/Frequency</u>	<u># Pts.* Evaluated</u>	<u>Drop** Outs</u>	<u>Deaths</u>	<u>Results Safety/Efficacy</u>
Compassionate Use Study	Multiclinic	Open-Label Patients with previous captopril adverse experience (mostly rash)	52	7	2 (both off treatment)	Rash recurred in only a very few patients on enalapril.

\* Maximum number of patients evaluated for efficacy  
 \*\* Drop-outs as result of adverse experience.