CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020528/S-001

TRADE NAME: Mavik 1 mg, 2 mg and 4 mg Tablets

GENERIC NAME: Trandolapril

SPONSOR: Knoll Pharmaceutical Company

APPROVAL DATE: 07/02/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

D F

NDA 20-528/S-001

JUL 2 1997

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
199 Cherry Hill Road
Parsippany, NJ 07054

Dear Dr. Ashworth:

Please refer to your May 6, 1996 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mavik (trandolapril) 1, 2, and 4 mg Tablets.

We acknowledge receipt of your amendment dated June 6, 1997.

The supplemental application provides for the use of Mavik Tablets in the treatment of patients with post myocardial infarction left ventricular dysfunction or post myocardial infarction heart failure.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included in the June 6, 1997 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HF-2/MedWatch (with labeling)
HFD-2/MLumpkin (efficacy supplements only)
HFD-92 (with labeling)
~~HFD~~-101 (with labeling)
HFD-110
HFD-40 (with labeling)
HFD-613 (with labeling)
HFD-735 (with labeling)
DISTRICT OFFICE
HFD-810/New Drug Chemistry Division Director
HFD-110/Project Manager
HFD-110/GBuehler/6/17/97
sb/6/18/97;7/1/97;7/2/97
R/D: NStockbridge/6/20/97
LCui/6/28/97
KMahjoob/6/30/97
NMorgenstern/6/30/97

Approval Date: 4/26/96

APPROVAL

Labeling: HAT-110

NDA No: 21-135 Rec'd. 2-18-97

Reviewed by: Bouchelle for KS

6/19/97

APPROVED

0983000-3

MAVIK® (Trandolapril Tablets)

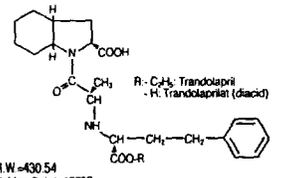
Knoll

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, MAVIK® should be discontinued as soon as possible. See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Trandolapril is the ethyl ester prodrug of a non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor, trandolaprilat. Trandolapril is chemically described as (2S,3aR,7aS)-1-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl] hexahydro-2-indolinecarboxylic acid, 1-ethyl ester. Its empirical formula is $C_{24}H_{34}N_2O_5$ and its structural formula is



R: C_2H_5: Trandolapril
H: Trandolaprilat (diacid)

M.W.=430.54
Melting Point=125°C

Trandolapril is a colorless, crystalline substance that is soluble (>100 mg/mL) in chloroform, dichloromethane, and methanol. MAVIK® tablets contain 1 mg, 2 mg, or 4 mg of trandolapril for oral administration. Each tablet also contains corn starch, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxide, lactose, povidone, sodium stearyl fumarate.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Trandolapril is deesterified to the diacid metabolite, trandolaprilat, which is approximately eight times more active as an inhibitor of ACE activity. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor that also stimulates secretion of aldosterone by the adrenal cortex and provides negative feedback for renin secretion. The effect of trandolapril in hypertension appears to result primarily from the inhibition of circulating and tissue ACE activity thereby reducing angiotensin II formation, decreasing vasoconstriction, decreasing aldosterone secretion, and increasing plasma renin. Decreased aldosterone secretion leads to diuresis, natriuresis, and a small increase of serum potassium. In controlled clinical trials, treatment with MAVIK® alone resulted in mean increases in potassium of 0.1 mEq/L. (See **PRECAUTIONS**.)

ACE is identical to kininase II, an enzyme that degrades bradykinin, a potent peptide vasodilator, whether increased levels of bradykinin play a role in the therapeutic effect of trandolapril remains to be elucidated.

While the principal mechanism of antihypertensive effect is thought to be through the renin-angiotensin-aldosterone system, trandolapril exerts antihypertensive actions even in patients with low-renin hypertension. MAVIK® was an effective antihypertensive in all races studied. Both black patients (usually a predominantly low-renin group) and non-black patients responded to 2 to 4 mg of MAVIK®.

Pharmacokinetics and Metabolism:

Pharmacokinetics Trandolapril's ACE-inhibiting activity is primarily due to its diacid metabolite, trandolaprilat. Cleavage of the ester group of trandolapril, primarily in the liver, is responsible for conversion. Absolute bioavailability after oral administration of trandolapril is about 10% as trandolapril and 70% as trandolaprilat. After oral trandolapril under fasting conditions, peak trandolapril levels occur at about one hour and peak trandolaprilat levels occur between 4 and 10 hours. The elimination half lives of trandolapril and trandolaprilat are about 6 and 10 hours, respectively, but, like all ACE inhibitors, trandolaprilat also has a prolonged terminal elimination phase, involving a small fraction of administered drug, probably representing binding to plasma and tissue ACE. During multiple dosing of trandolapril, there is no significant accumulation of trandolaprilat. Food slows absorption of trandolapril, but does not affect AUC or Cmax of trandolaprilat or Cmax of trandolapril.

Metabolism and Excretion After oral administration of trandolapril, about 33% of parent drug and metabolites are recovered in urine, mostly as trandolaprilat, with about 66% in feces. The extent of the absorbed dose which is biliary excreted has not been determined. Plasma concentrations (Cmax and AUC of trandolapril and Cmax of trandolaprilat) are dose proportional over the 1-4 mg range, but the AUC of trandolaprilat is somewhat less than dose proportional. In addition to trandolaprilat, at least 7 other metabolites have been found, principally glucuronides or deesterification products.

Serum protein binding of trandolapril is about 80%, and is independent of concentration. Binding of trandolaprilat is concentration-dependent, varying from 65% at 1000 ng/mL to 94% at 0.1 ng/mL, indicating saturation of binding with increasing concentration.

The volume of distribution of trandolapril is about 18 liters. Total plasma clearances of trandolapril and trandolaprilat after approximately 2 mg IV doses are about 52 liters/hour and 7 liters/hour respectively. Renal clearance of trandolaprilat varies from 1-4 liters/hour, depending on dose.

Special populations:

Pediatric Trandolapril pharmacokinetics have not been evaluated in patients <18 years of age.

Geriatric and Gender Trandolapril pharmacokinetics have been investigated in the elderly (> 65 years) and in both genders. The plasma concentration of trandolapril is increased in elderly hypertensive patients, but the plasma concentration of trandolaprilat and inhibition of ACE activity are similar in elderly and young hypertensive patients. The pharmacokinetics of trandolapril and trandolaprilat and inhibition of ACE activity are similar in male and female elderly hypertensive patients.

Race Pharmacokinetic differences have not been evaluated in different races.

Renal Insufficiency Compared to normal subjects, the plasma concentrations of trandolapril and trandolaprilat are approximately 2-fold greater and renal clearance is reduced by about 85% in patients with creatinine clearance below 30 ml/min and in patients on hemodialysis. Dosage adjustment is recommended in renally impaired patients. (See **DOSAGE and ADMINISTRATION**.)

Hepatic Insufficiency Following oral administration in patients with mild to moderate alcoholic cirrhosis, plasma concentrations of trandolapril and trandolaprilat were, respectively, 9-fold and 2-fold greater than in normal subjects, but inhibition of ACE activity was not affected. Lower doses should be considered in patients with hepatic insufficiency. (See **DOSAGE and ADMINISTRATION**.)

Drug Interactions Trandolapril did not affect the plasma concentration (pre-dose and 2 hours post-dose) of oral digoxin (0.25 mg). Coadministration of trandolapril and cimetidine led to an increase of about 44% in Cmax for trandolapril, but no difference in the pharmacokinetics of trandolaprilat or in ACE inhibition. Coadministration of trandolapril and furosemide led to an increase of about 25% in the renal clearance of trandolaprilat, but no effect was seen on the pharmacokinetics of furosemide or trandolaprilat or on ACE inhibition.

Pharmacodynamics and Clinical Effects:

A single 2-mg dose of MAVIK® produces 70 to 85% inhibition of plasma ACE activity at 4 hours with about 10% decline at 24 hours and about half the effect manifest at 8 days. Maximum ACE inhibition is achieved with a plasma trandolaprilat concentration of 2 ng/mL. ACE inhibition is a function of trandolaprilat concentration, not trandolapril concentration. The effect of trandolapril on exogenous angiotensin I was not measured.

Hypertension

Four placebo-controlled dose response studies were conducted using once-daily oral dosing of MAVIK® in doses from 0.25 to 16 mg per day in 827 black and non-black patients with mild to moderate hypertension. The minimal effective once-daily dose was 1 mg in non-black patients and 2 mg in black patients. Further decreases in trough supine diastolic blood pressure were obtained in non-black patients with higher doses, and no further response was seen with doses above 4 mg (up to 16 mg). The antihypertensive effect diminished somewhat at the end of the dosing interval, but trough/peak ratios are well above 50% for all effective doses. There was a slightly greater effect on the diastolic pressure, but no difference on systolic pressure with b.i.d. dosing. During chronic therapy, the maximum reduction in blood pressure with any dose is achieved within one week. Following 6 weeks of monotherapy in placebo-controlled trials in patients with mild to moderate hypertension, once-daily doses of 2 to 4 mg lowered supine or standing systolic/diastolic blood pressure 24 hours after dosing by an average 7-10/4-5 mmHg below placebo responses in non-black patients. Once-daily doses of 2 to 4 mg lowered blood pressure 4-6/3-4 mmHg in black patients. Trough to peak ratios for effective doses ranged from 0.5 to 0.9. There were no differences in response between men and women, but responses were somewhat greater in patients under 60 than in patients over 60 years old. Abrupt withdrawal of MAVIK® has not been associated with a rapid increase in blood pressure.

Administration of MAVIK® to patients with mild to moderate hypertension results in a reduction of supine, sitting and standing blood pressure to about the same extent without compensatory tachycardia.

Symptomatic hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted. (See **WARNINGS**.) Use of MAVIK® in combination with thiazide diuretics gives a blood pressure lowering effect greater than that seen with either agent alone, and the additional effect of trandolapril is similar to the effect of monotherapy.

Heart Failure Post Myocardial Infarction or Left Ventricular Dysfunction Post Myocardial Infarction:

The Trandolapril Cardiac Evaluation (TRACE) Trial was a Danish, 27-center, double-blind, placebo controlled, parallel-group study of the effect of trandolapril on all-cause mortality in stable patients with echocardiographic evidence of left ventricular dysfunction 3 to 7 days after a myocardial infarction. Subjects with residual ischemia or overt heart failure were included. Patients tolerant of a test dose of 1 mg trandolapril were randomized to placebo (n=873) or trandolapril (n=876) and followed for 24 months. Among patients randomized to trandolapril, who began treatment on 1 mg, 62% were successfully titrated to a target dose of 4 mg once daily over a period of weeks. The use of trandolapril was associated with a 16% reduction in the risk of all-cause mortality (p=0.042), largely cardiovascular mortality. Trandolapril was also associated with a 20% reduction in the risk of progression of heart failure (p=0.047), defined by a time-to-first-event analysis of death attributed to heart failure, hospitalization for heart failure, or requirement for open-label ACE inhibitor for the treatment of heart failure. There was no significant effect of treatment on other end-points: subsequent hospitalization, incidence of recurrent myocardial infarction, exercise tolerance, ventricular function, ventricular dimensions, or NYHA class.

The population in TRACE was entirely Caucasian and had less usage than would be typical in a U.S. population of other post-infarction interventions: 42% thrombolysis, 16% beta-adrenergic blockade, and 6.7% PTCA or CABG during the entire period of follow-up. Blood pressure control, especially in the placebo group, was poor: 47 to 53% of patients randomized to placebo and 32 to 40% of patients randomized to trandolapril had blood pressures >140/95 at 90-day follow-up visits.

INDICATIONS AND USAGE

Hypertension

MAVIK® is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medication such as hydrochlorothiazide.

In considering the use of MAVIK®, it should be noted that in controlled trials ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients. (See **Warnings: Angioedema**.)

When using MAVIK®, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that MAVIK® does not have a similar risk. (See **WARNINGS**.)

Heart Failure Post Myocardial Infarction or Left-Ventricular Dysfunction Post Myocardial Infarction:

MAVIK® is indicated in stable patients who have evidence of left-ventricular systolic dysfunction (identified by wall motion abnormalities) or who are symptomatic from congestive heart failure within the first few days after sustaining acute myocardial infarction. Administration of trandolapril to Caucasian patients has been shown to decrease the risk of death (principally cardiovascular death) and to decrease the risk of heart failure-related hospitalization (See **CLINICAL PHARMACOLOGY, Heart Failure or Left-Ventricular Dysfunction Post Myocardial Infarction** for details of the survival trial.)

CONTRAINDICATIONS

MAVIK® is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions:

Presumably because angiotensin converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors, including MAVIK®, may be subject to a variety of adverse reactions, some of them serious.

Angioedema:

Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors including MAVIK®. Symptoms suggestive of angioedema or facial edema occurred in 0.13% of MAVIK®-treated patients. Two of the four cases were life-threatening and resolved without treatment or with medication (corticosteroids). Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue or glottis occurs, treatment with MAVIK® should be discontinued immediately, the patient treated in accordance with accepted medical care and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, emergency therapy, including but not limited to subcutaneous epinephrine solution 1:1,000 (0.3 to 0.5 mL) should be promptly administered.** (See **PRECAUTIONS**: Information for Patients and **ADVERSE REACTIONS**.)

Anaphylactoid Reactions During Desensitization Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension:

MAVIK® can cause symptomatic hypotension. Like other ACE inhibitors, MAVIK® has only rarely been associated with symptomatic hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been salt- or volume-depleted as a result of prolonged treatment with diuretics, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating treatment with MAVIK®. (See **PRECAUTIONS**, Drug Interactions, and **ADVERSE REACTIONS**.) In controlled and uncontrolled studies, hypotension was reported as an adverse event in 0.6 percent of patients and led to discontinuations in 0.1% of patients.

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia, and rarely, with acute renal failure and death. In such patients, MAVIK® therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely during the first 2 weeks of treatment and, thereafter, whenever the dosage of MAVIK® or diuretic is increased. (See **DOSAGE and ADMINISTRATION**.) Care in avoiding hypotension should also be taken in patients with ischemic heart disease, aortic stenosis, or cerebrovascular disease.

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of MAVIK® or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis:

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of trandolapril are insufficient to show that trandolapril does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen-vascular disease and/or renal disease should be considered.

Hepatic Failure:

ACE inhibitors rarely have been associated with a syndrome of cholestatic jaundice, fulminant hepatic necrosis, and death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Fetal/Neonatal Morbidity and Mortality:

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of trandolapril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, trandolapril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy.

Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Doses of 0.8 mg/kg/day (9.4 mg/m²/day) in rabbits, 1000 mg/kg/day (7000 mg/m²/day) in rats, and 25 mg/kg/day (295 mg/m²/day) in cynomolgus monkeys did not produce teratogenic effects. These doses represent 10 and 3 times (rabbits), 1250 and 2564 times (rats), and 312 and 108 times (monkeys) the maximum projected human dose of 4 mg based on body-weight and body-surface-area, respectively assuming a 50 kg woman.

PRECAUTIONS

General

Impaired Renal Function:

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be antici-

pated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including MAVIK®, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACE inhibitors have been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or the ACE inhibitor may be required.

Evaluation of hypertensive patients should always include assessment of renal function. (See **DOSAGE** and **ADMINISTRATION**.)

Hyperkalemia and potassium-sparing diuretics:

In clinical trials, hyperkalemia (serum potassium > 6.00 mEq/L) occurred in approximately 0.4 percent of hypertensive patients receiving MAVIK®. In most cases, elevated serum potassium levels were isolated values, which resolved despite continued therapy. None of these patients were discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with MAVIK®. (See **PRECAUTIONS**: Drug Interactions.)

Cough:

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials of trandolapril, cough was present in 2% of trandolapril patients and 0% of patients given placebo. There was no evidence of a relationship to dose.

Surgery/anesthesia:

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, MAVIK® will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema:

Angioedema, including laryngeal edema, may occur at any time during treatment with ACE inhibitors, including MAVIK®. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Symptomatic Hypotension:

Patients should be cautioned that light-headedness can occur, especially during the first days of MAVIK® therapy, and should be reported to a physician. If actual syncope occurs, patients should be told to stop taking the drug until they have consulted with their physician (See **WARNINGS**.)

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting, resulting in reduced fluid volume, may precipitate an excessive fall in blood pressure with the same consequences of light-headedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor that has a long duration of action.

Hyperkalemia:

Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician. (See **PRECAUTIONS**.)

Neutropenia:

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which could be a sign of neutropenia.

Pregnancy:

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

NOTE: As with many other drugs, certain advice to patients being treated with MAVIK® is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy:

As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may experience an excessive reduction of blood pressure after initiation of therapy with MAVIK®. The possibility of exacerbation of hypotensive effects with MAVIK® may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with MAVIK®. If it is not possible to discontinue the diuretic, the starting dose of trandolapril should be reduced. (See **DOSAGE** and **ADMINISTRATION**.)

Agents increasing serum potassium:

Trandolapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes concomitantly with ACE inhibitors can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be used with caution and with appropriate monitoring of serum potassium. (See **PRECAUTIONS**.)

Lithium:

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other:

No clinically significant interaction has been found between trandolapril and food, cimetidine, digoxin, or furosemide. The anticoagulant effect of warfarin was not significantly changed by trandolapril.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted with oral trandolapril administered by gavage to mice (78 weeks) and rats (104 and 106 weeks). No evidence of carcinogenic potential was seen in mice dosed up to 25 mg/kg/day (85 mg/m²/day) or rats dosed up to 8 mg/kg/day (60 mg/m²/day). These doses are 313 and 32 times (mice), and 100 and 23 times (rats) the maximum recommended human daily dose (MRHDD) of 4 mg based on body-weight and body-surface-area, respectively assuming a 50 kg individual. The genotoxic potential of trandolapril was evaluated in the microbial mutagenicity (Ames) test, the point mutation and chromosome aberration assays in Chinese hamster V79 cells, and the micronucleus test in mice. There was no evidence of mutagenic or clastogenic potential in these in vitro and in vivo assays.

Reproduction studies in rats did not show any impairment of fertility at doses up to 100 mg/kg/day (710 mg/m²/day) of trandolapril, or 1250 and 260 times the MRHDD on the basis of body-weight and body-surface-area, respectively.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

Radiolabeled trandolapril or its metabolites are secreted in rat milk. MAVIK® (trandolapril) should not be administered to nursing mothers.

Geriatric Use

In placebo-controlled studies of MAVIK®, 31.1% of patients were 60 years and older, 20.1% were 65 years and older, and 2.3% were 75 years and older. No overall differences in effectiveness or safety were observed between these patients and younger patients. (Greater sensitivity of some older individual patients cannot be ruled out).

Pediatric Use

The safety and effectiveness of MAVIK® in pediatric patients have not been established.

ADVERSE REACTIONS

The safety experience in U.S. placebo-controlled trials included 1067 hypertensive patients, of whom 831 received MAVIK®. Nearly 200 hypertensive patients received MAVIK® for over one year in open-label trials. In controlled trials, withdrawals for adverse events were 2.1% on placebo and 1.4% on MAVIK®. Adverse events considered at least possibly related to treatment occurring in 1% of MAVIK®-treated patients and more common on MAVIK® than placebo, pooled for all doses, are shown below, together with the frequency of discontinuation of treatment because of these events.

ADVERSE EVENTS IN PLACEBO-CONTROLLED HYPERTENSION TRIALS
Occurring at 1% or greater

	MAVIK (N=832) % Incidence (% Discontinuance)	PLACEBO (N=237) % Incidence (% Discontinuance)
Cough	1.9 (0.1)	0.4 (0.4)
Dizziness	1.3 (0.2)	0.4 (0.4)
Diarrhea	1.0 (0.0)	0.4 (0.0)

Headache and fatigue were all seen in more than 1% of MAVIK®-treated patients but were more frequently seen on placebo. Adverse events were not usually persistent or difficult to manage.

Left Ventricular Dysfunction Post Myocardial Infarction:

Adverse reactions related to Mavik®, occurring at a rate greater than that observed in placebo-treated patients with left ventricular dysfunction, are shown below. The incidences represent the experiences from the TRACE study. The follow-up time was between 24 and 50 months for this study.

Percentage of Patients with Adverse Events Greater Than Placebo

Adverse Event	Placebo-Controlled (TRACE) Mortality Study Trandolapril N=876	Placebo N=873
Cough	35	22
Dizziness	23	17
Hypotension	11	6.8
Elevated Serum uric acid	15	13
Elevated BUN	9.0	7.6
PTCA or CABG	7.3	6.1
Dyspepsia	6.4	6.0
Syncope	5.9	3.3
Hyperkalemia	5.3	2.8
Bradycardia	4.7	4.4
Hypocalcemia	4.7	3.9
Myalgia	4.7	3.1
Elevated Creatinine	4.7	2.4
Gastritis	4.2	3.6
Cardiogenic shock	3.8	<2
Intermittent claudication	3.8	<2
Stroke	3.3	3.2
Asthenia	3.3	2.6

Clinical adverse experiences possibly or probably related or of uncertain relationship to therapy occurring in 0.3% to 1.0% (except as noted) of the patients treated with MAVIK® (with or without concomitant calcium ion antagonist or diuretic) in controlled or uncontrolled trials (N=1134) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General Body Function: chest pain.

Cardiovascular: AV first degree block, bradycardia, edema, flushing, hypotension, palpitations.

Central Nervous System: drowsiness, insomnia, paresthesia, vertigo.

Dermatologic: pruritus, rash, pemphigus.

Eye, Ear, Nose, Throat: epistaxis, throat inflammation, upper respiratory tract infection.

Emotional, Mental, Sexual States: anxiety, impotence, decreased libido.

Gastrointestinal: abdominal distention, abdominal pain/cramps, constipation, dyspepsia, diarrhea, vomiting, *pancreatitis*.

Hemopoietic: *decreased leukocytes, decreased neutrophils.*

Metabolism and Endocrine: *increased creatinine, increased potassium,* Increased SGPT (ALT).

Musculoskeletal System: extremity pain, muscle cramps, gout.

Pulmonary: dyspnea.

Angioedema: Angioedema has been reported in 4 (0.13%) patients receiving MAVIK® in U.S. and foreign studies. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with MAVIK® should be discontinued and appropriate therapy instituted immediately. (See **WARNINGS**.)

Hypotension: In hypertensive patients, symptomatic hypotension occurred in 0.6 percent and near syncope occurred in 0.2 percent. Hypotension or syncope was a cause for discontinuation of therapy in 0.1 percent of hypertensive patients.

Fetal/Neonatal Morbidity and Mortality: See **WARNINGS**, Fetal Neonatal Morbidity and Mortality.

Cough: See **PRECAUTIONS**, Cough.

Clinical Laboratory Test Findings

Hematology: (See **WARNINGS**.) Low white blood cells, low neutrophils, low lymphocytes, thrombocytopenia.

Serum Electrolytes: Hyperkalemia (See **PRECAUTIONS**.) hyponatremia.

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.1 percent of patients receiving MAVIK® alone and 7.3 percent of patients treated with MAVIK®, a calcium ion antagonist and a diuretic. Increases in blood urea nitrogen levels occurred in 0.6 percent of patients receiving MAVIK® alone and 1.4 percent of patients receiving MAVIK®, a calcium ion antagonist, and a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See **PRECAUTIONS and WARNINGS**.)

Liver function tests: Occasional elevation of transaminases at the rate of 3X upper normals occurred in 0.8% of patients and persistent increase in bilirubin occurred in 0.2% of patients. Discontinuation for elevated liver enzymes occurred in 0.2 percent of patients.

OVERDOSAGE

No data are available with respect to overdosage in humans. The oral LD_{50} of trandolapril in mice was 4875 mg/Kg in males and 3990 mg/Kg in females. In rats, an oral dose of 5000 mg/Kg caused low mortality (1 male out of 5; 0 females). In dogs, an oral dose of 1000 mg/Kg did not cause mortality and abnormal clinical signs were not observed. In humans the most likely clinical manifestation would be symptoms attributable to severe hypotension.

Laboratory determinations of serum levels of trandolapril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of trandolapril overdose. No data are available to suggest that physiological maneuvers (e.g., maneuvers to change the pH of the urine) might accelerate elimination of trandolapril and its metabolites. Trandolaprilat is removed by hemodialysis. Angiotensin II could presumably serve as a specific antagonist antidote in the setting of trandolaprilt overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of trandolapril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat trandolaprilt overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended initial dosage of MAVIK® for patients not receiving a diuretic is 1 mg once daily in non-black patients and 2 mg in black patients. Dosage should be adjusted according to the blood pressure response. Generally, dosage adjustments should be made at intervals of at least 1 week. Most patients have required dosages of 2 to 4 mg once daily. There is little clinical experience with doses above 8 mg.

Patients inadequately treated with once-daily dosing at 4 mg may be treated with twice-daily dosing. If blood pressure is not adequately controlled with MAVIK® monotherapy, a diuretic may be added.

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of MAVIK®. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with MAVIK®. (See **WARNINGS**.) Then, if blood pressure is not controlled with MAVIK® alone, diuretic therapy should be resumed. If the diuretic cannot be discontinued, an initial dose of 0.5 mg MAVIK® should be used with careful medical supervision for several hours until blood pressure has stabilized. The dosage should subsequently be titrated (as described above) to the optimal response. (See **WARNINGS**, **PRECAUTIONS**, and **Drug Interactions**.)

Concomitant administration of MAVIK® with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. (See **PRECAUTIONS**.)

Heart Failure Post Myocardial Infarction or Left-Ventricular Dysfunction Post Myocardial Infarction:

The recommended starting dose is 1 mg, once daily. Following the initial dose, all patients should be titrated (as tolerated) toward a target dose of 4 mg, once daily. If a 4 mg dose is not tolerated, patients can continue therapy with the greatest tolerated dose.

Dosage Adjustment in Renal Impairment or Hepatic Cirrhosis:

For patients with a creatinine clearance <30 mL/min. or with hepatic cirrhosis, the recommended starting dose, based on clinical and pharmacokinetic data, is 0.5 mg daily. Patients should subsequently have their dosage titrated (as described above) to the optimal response.

HOW SUPPLIED

MAVIK® tablets are supplied as follows:

1 mg tablet – salmon colored, round shaped, scored, compressed tablets, with code KNOLL 1 on one side.
NDC (0048-5805-01 - bottles of 100)
NDC (0048-5805-41 - unit dose packs of 100)

2 mg tablet – yellow colored, round shaped, compressed tablets with code KNOLL 2 on one side.
NDC (0048-5806-01 - bottles of 100)
NDC (0048-5806-41 - unit dose packs of 100)

4 mg tablet – rose colored, round shaped, compressed tablets, with code KNOLL 4 on one side.
NDC (0048-5807-01 - bottles of 100)
NDC (0048-5807-41 - unit dose packs of 100)

Dispense in well-closed container with safety closure.

Storage: Store at controlled room temperature: 20-25°C (68-77°F) see USP.

Caution: Federal law prohibits dispensing without prescription.

Revised: June 1997

Knoll Pharmaceutical Company
3000 Continental Drive - North
Mount Olive, New Jersey 07828-1234

BASF Pharma

knoll®

0983000-3

DF

JUN 19 1997

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-528
3. Name and Address of Applicant (City & State) Knoll Pharmaceutical Company Parsippany, NJ 07054		4. Supplement(s) Number(s) Date(s) S-001LR 6 May 96
5. Drug Name Mavik Tablets	6. Nonproprietary Name Trandolapril	7. Amendments & Other (reports, etc) - Dates Amendment 20 Dec 96 Amendment 25 Mar 97 Amendment 23 Apr 97 Amendment 6 Jun 97
8. Supplement Provides For: The amendment of 6 Jun 97 provides Final Printed Labeling (FPL) for a revised Package Insert (PI).		
9. Pharmacological Category Antihypertensive	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) TCM	13. Potency(ies) 1, 2, 4 mg	
14. Chemical Name and Structure		15. Records/Reports Current [X] Yes [ ] No Reviewed [X] Yes [ ] No

16. Comments

S-001 provides for a new indication, tratment of post-infarction left ventricular dysfunction, for Mavik. The revised PI is dated June, 1997 (0983000-3). The DESCRIPTION and HOW SUPPLIED sections are unchanged, and remain satisfactory.

17. Conclusions and Recommendations

APPROVAL is recommended as far as the technical aspects of the labeling are concerned.

18. REVIEWER

Name James H. Short Signature James H. Short Date Completed 13 Jun 97

Distribution: [ ] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

jhs/6/13/97/N20-528.S01

R/D init: RWolters/

RWolters 6/19/97

DF

JUL 2 1997

LABELING REVIEW

NDA 20-528/S-001 Mavik (trandolapril) 1,2, and 4 mg Tablets

Sponsor: Knoll Pharmaceutical Company
199 Cherry Hill Road
Parsippany, NJ 07054

Date of Original Submission: May 6, 1996

Date of FPL Submission: June 6, 1997

BACKGROUND

This supplemental application provides for the use of Mavik Tablets in the treatment of patients with post myocardial infarction left ventricular dysfunction or post myocardial infarction heart failure. On May 15, 1997 an approvable issued to Knoll requesting FPL to be submitted that was identical to the enclosed marked-up draft. On June 6, 1997 Knoll submitted FPL.

REVIEW

The FPL was reviewed and found to be in accordance with the marked-up draft included with the May 15, 1997 approvable letter. An approval letter will be drafted for Dr. Temple's signature.

Gary Buehler
Project Manager

Orig NDA
HFD-110
HFD-110 KBongiovanni
HFD-110 SBenton

DF

MAY 13 1997

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : APR 21 1997

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval of NDA 20-528/S-001, trandolapril for left ventricular dysfunction post-myocardial infarction, Knoll Pharmaceutical Company

TO : Director, Office of Drug Evaluation I, HFD-101

As you remember, in September, 1996 we issued an approvable letter for this supplement, stating the indication was approvable provided that Knoll submit follow-up information for patients not accounted for in the Trandolapril Cardiac Evaluation (TRACE) trial, and as much as they could regarding 18 controlled clinical trials related to the use of trandolapril in congestive heart failure that were not part of the original submission.

In March, 1997, Knoll completed submission of all items requested, along with a draft package insert that includes (except as noted on the draft label in the transmittal package) all suggestions that were included in the September, 1996 approvable letter.

Your memorandum of September 9, 1996 (included in this transmittal package) summarizes your thoughts at the time.

In the transmittal package, there is a medical review of the items submitted. Nothing unusual was seen and these studies do not alter any aspect of the previous assessment related to the efficacy or safety of trandolapril when used for ventricular dysfunction post myocardial infarction.

Knoll has responded to our inquiry about follow-up status of patients lost to follow-up in the TRACE trial. The data came from Knoll's inquiry to the Danish registry. There were, indeed, 5 new deaths, all in the placebo group. So, it was worth finding out what happened to patients lost to follow-up. The original finding is strengthened.

Dr. Stockbridge, having read your memorandum of September 9, 1996, sticks with his original recommendations. I also stick with mine and am in agreement with your memorandum of September 9, 1996. I see no reason to amplify reasons for agreement or disagreement.

All concerned parties conclude that TRACE demonstrated a treatment effect and trandolapril, therefore, should be approved.

Another approvable letter is attached for your signature. We could approve, on marked-up draft. Considering that Knoll is currently still in administrative turn-over and that they took 18 months to respond to what appeared to be not very complicated requests, I suggest we go the approvable route.

cc:
NDA 20-528/S-001
HFD-110
HFD-110/KBongiovanni

MAY 15 1997

Lu Cui, Ph.D. & Norman Stockbridge, M.D., Ph.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
Rockville, MD 20857

5600 Fishers Lane
Tel (301) 594-5329 FAX: (301) 594-5494

Memorandum

N Stockbridge 5/12/97
Lu Cui 5/12/97

DATE: 12 May 1997

TO: Dr. Robert Temple, Director, Office of Drug Evaluation I

CC: Dr. Ray Lipicky, Director, Division of Cardio-Renal Drug Products
NDA 20-528/S001

SUBJECT: Office Director's TRACE study memo, dated 5 May 1997.

With regard to the confusion over percentages of use of β-blockers, the clinical reviewers note the following: the trial description that is in the label was derived from the clinical review dated 26 July 1996, but apparently the sponsor transcribed 6% instead of 16%. The clinical reviewers' assessment of 16% came from the baseline usage of β-blockers (op cit, Table 5). The sponsor's originally proposed label said 26%, likely derived from on-treatment usage of concomitant β-blockers during the index hospitalization. This latter rate compares well with the usage rate you estimated for the active treatment group from Table 28 in the clinical review (33% or, estimated the same way, 30% on placebo). There was no longer-term collection of data on concomitant medications.

With regard to the revised estimate of mortality reduction and statistical significance, the clinical reviewers present results in Table 1 below.

Table 1. Original and revised all-cause 2-year mortality analyses.

Stratification	Original analyses			Revised analyses		
	P	RR	95% CI	P	RR	95% CI
None	0.038	0.840	0.712 to 0.990	0.042	0.843	0.715 to 0.994
WMI	0.049	0.847	0.719 to 0.999	0.053	0.850	0.721 to 1.002
WMI, center	0.042	0.840	0.710 to 0.994	0.045	0.842	0.712 to 0.997

In interpreting this table, note the following points: (A) The original protocol called for analysis stratifying by baseline WMI only. (B) Because of interim analyses, the results must be judged against α=0.045, not α=0.05. (C) One-sided p-values appeared in the original review.

As can be seen, 5 additional deaths in the placebo group had the effect of increasing the p-value, rather than lowering it as might intuitively have been expected. The reason for this is that these deaths increased the time period over which these subjects were known to be alive. Previously, these subjects were censored at the time of their last visit (50 to 645 days after randomization); now they are included up to the later time of their deaths (797 to 1312 days after randomization).

Your memo misrepresents the Medical Officer's assessment of secondary support for the major finding in the TRACE study, based, one assumes, on his comments on page 7 of the medical review of 7 April 1997. The following comments are intended to put the record straight. All parties appear to agree that studies other than TRACE were not helpful. The original clinical review of 26 July 1996 presented a wordier assessment of the TRACE results (pages 30 and 33). That assessment acknowledged treatment effects on the pre-specified end point of progression of heart failure, but it ignored, with some reason, support from cause-specific mortality or hospitalizations (whether pre-specified or not), and it denied treatment effects on other pre-specified end points—re-infarction, exercise tolerance, NYHA class, and three others without reported data or analyses. The clinical reviewers do not believe the TRACE mortality finding was wholly without secondary support; the finding was weak, it was further weakened by the 5 newly reported deaths in the placebo group, and, even if real, its applicability to the North American population is questionable.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DF

Food and Drug Administration
Rockville MD 20857

NDA 20-528/S-001

MAY 15 1997

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
199 Cherry Hill Road
Parsippany, NJ 07054

Dear Dr. Ashworth:

Please refer to your May 6, 1996 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mavik (trandolapril) 1, 2, and 4 mg Tablets.

We acknowledge receipt of your amendments dated December 20, 1996, March 25 and April 23, 1997.

The supplemental application provides for the use of Mavik Tablets in the treatment of patients with post myocardial infarction left ventricular dysfunction or post myocardial infarction heart failure.

We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit sixteen copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this supplemental application.

These changes may not be implemented until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5334

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA
HFD-2/MLumpkin (efficacy supplements only)
HFD-101 (efficacy supplements only)
~~HFD-92~~
HFD-110
DISTRICT OFFICE
HFD-40/DDMAC (with labeling)
HFD-110/KBongiovanni
sb/4/22/97;4/28/97
R/D: NStockbridge/4/22/97
JShort/4/22/97
RWolters/4/22/97
EBelair
ADeFelice/4/25/97
FZielinski/4/2/97
LCui/4/25/97
KMahjoob/4/25/97
AParekh/4/28/97
NMorgenstern/4/28/97

Approval Date: 4/26/96

APPROVABLE

APR 28 1997

RHPM Review of Labeling

NDA: 20-528/S-001 Mavik (trandolapril) Tablets

Date of submission: March 25, 1997

Date of receipt: March 31, 1997

Applicant: Knoll Pharmaceuticals

Background: We issued an approvable letter on September 18, 1996, for this supplement, that asked for additional information on the 18% of subjects without mortality status for the full prospectively-defined period of follow-up, and for information on all studies on the use of trandolapril in the treatment of patients with congestive heart failure and/or post-myocardial infarction. The letter included language for the labeling that would be likely, following our review of the additional data, and provided that the new information does not alter our current thinking.

Knoll responded with a submission dated December 20, 1996, that included information on additional studies and a partial response to the request for additional mortality data. We issued a letter dated January 14, 1997, asking for the remainder of this information. Knoll responded with a submission dated March 25, 1997, including additional follow-up data, debarment certification, a request for exemption from the requirement for an Environmental Assessment, and revised draft labeling.

Review:
The submitted draft labeling differs from the draft labeling included in the approvable letter as follows:
INDICATIONS AND USAGE, Heart Failure or Left-Ventricular Dysfunction Post Myocardial Infarction: The reference at the end of this subsection has been corrected to "(See CLINICAL PHARMACOLOGY, Heart Failure or Left-Ventricular Dysfunction Post Myocardial Infarction for details of the survival trial.)"

The rest of the revised labeling is identical to that included in the approvable letter.

Recommendation: The subheadings for the revisions under CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION are "Heart Failure or Left-Ventricular Dysfunction Post Myocardial Infarction." I recommend that this be changed to "Heart Failure Post Myocardial Infarction or Left-Ventricular Dysfunction Post Myocardial Infarction" for clarity. In addition, I recommend the inclusion of an additional subheading, Hypertension, under CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.

I will prepare an approvable letter for this supplement for Dr. Temple's signature.

Kathleen F. Bongiovanni 4-28-97

cc: 20-528/S-001
HFD-110
HFD-110/KBongiovanni
HFD-110/SBenton
HF-2/MedWatch
kb/4/28/97.

DF

APR 7 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Medical Officer's Review

NDA: 20-528 (Mavik®, Trandolapril for post-MI CHF)

Sponsor: Knoll Pharmaceutical Co.

Submission:

Submission	Volumes	Submitted	Received
Amendment to supplement	20.1 to 20.28	20 Dec 1996	23 Dec 1996
Amendment to supplement	21.1	25 Mar 1997	31 Mar 1997

Review date: 7 April 1997.

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution:
NDA 20-528
HFD-110/CSO
HFD-110
HFD-110/Stockbridge

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

1. Introduction

1.1. Background

Trandolapril is the pro-drug for a long-acting ACE inhibitor approved for the treatment of hypertension. The results of the TRACE study were submitted by Knoll in May 1996 in support of a new indication in the treatment of heart failure post-myocardial infarction. An 'approvable' letter was issued pending the submission of two types of data.

The clinical review noted that there were a number of studies in addition to TRACE that had been conducted with trandolapril in the same or a related population. The Agency requested a report of those studies.

The clinical review noted that a number of subjects had a last study visit significantly earlier than the date of last follow-up for mortality, the TRACE study's primary end point. The sponsor indicated that all subjects had follow-up for the full prospective period provided through the Danish central registry of vital statistics. The Agency requested evidence that such an inquiry was made and asked for performance data or other data indicative that the Danish registry would likely have had timely information for this inquiry.

In response, Knoll submitted in December 1996, 28 volumes intended to address these issues. This response included full study reports for 8 studies not previously submitted to FDA. Reviews of these studies are contained in appendices to this document and are summarized more concisely in section 2 on page 3.

The December 1996 submission also addressed the mortality follow-up in TRACE, but the information was substantially less than originally requested, necessitating a second request of the sponsor. The sponsor's second response was received in March 1997. The available follow-up information is summarized in section 3 on page 5.

2. Additional studies

The sponsor has identified 21 study protocols (3 more than previously known to the reviewer) with trandolapril in a population with myocardial infarction or heart failure, as of a cut-off date of 15 September 1996. A summary of these studies, sorted by the number of enrolled subjects, is given in Table 1 below.

Table 1. Reported MI/CHF studies with trandolapril.

Study	Review	N	Days	Design*	Comment[a]
UK/91/570/119	—	292	112	R, DB, PC, ‖	...[P]atients with congestive heart failure (NYHA class II and III). Study ongoing.
FF/90/570/99	page 14	280	385	R, OL, AC, ‖	This was a positive-controlled, open-label study of approximately one year duration. No statistical analyses were performed, but the differences between treatment groups were fairly small. The one-year mortality rate in this study was approximately one-third of that observed in the TRACE study.
S/93/570/186	—	119	21	R, DB, PC, ‖	...[P]atients with a recent myocardial infarction and ventricular systolic dysfunction. Preparation of study report in progress. There were 5 deaths on trandolapril and 2 deaths on placebo.
ZA/90/570/96	—	97	90	R, DB, PC, ‖	...[S]tudy to evaluate exercise capacity and invasive cardiac hemodynamic profile and tolerance in patients with NYHA class III congestive heart failure. Preparation of final study report in progress.
ZA/90/570/96B	—	88	180	OL	Extension to protocol ZA/90/570/96.... Preparation of final report in progress.
UK/89/570/70	page 21	50	112	R, DB, PC, ‖	This was a pilot double-blind, placebo-controlled study evaluating multiple dose levels of trandolapril in an appropriate target population. The study was marred by a high incidence of inappropriately randomized subjects, but in no way suggestive of bias. The results provide scant evidence of a beneficial effect of trandolapril on subjects with heart failure.
UK/91/570/160	—	46	168	R, DB, PC	...[S]tudy stratified with respect to LVEDP, type of surgery and beta-blocker medication. Treatment administered prior to cardiac surgery. Study terminated due to low recruitment and increasing delays in cardiac surgery. Preparation of study report in progress. Information is being awaited from Roussel UCLAF.
UK/91/570/130	—	30	175	R, DB, AC, ‖	...[S]tudy to compare the effects of trandolapril, captopril, and isosorbide dinitrate on exercise, tolerance, cardiac output, hemodynamics and skeletal muscle metabolism in patients with congestive heart failure. Preparation of study report in progress. Information is being awaited from Roussel UCLAF.
J/92/570/180	—	27	70	OL	...[P]atients with congestive heart failure. Preparation of study report in progress.
FF/91/570/154[b] F/91/570/154 ZA/91/570/154	page 17	19	10	OL	The pharmacokinetic parameters for trandolapril and its active metabolite trandolaprilat in a group of subjects with heart failure was similar to those in a population of normal volunteers.
NL/89/570/84	—	19	1	DB, PC, ‖	...[S]tudy to assess acute anti-ischemic effects in patients with coronary artery disease. Study terminated after interim analysis showed no difference between treatments. Preparation of final study report in progress.
NL/89/570/81	—	18	1	OL	...[A]cute coronary, hemodynamic, and vasodynamic changes following i.v. dose in patients with coronary artery disease. Preparation of final study report in progress.
NL/89/570/81B	—	15	180	OL	...[O]pen extension to study NL/89/570/81. Preparation of final study report in progress.
I/91/570/139	page 19	14	90	R, DB, PC, ‖	Only limited safety data were reported. Holter data were not reported. The only serious adverse event was development of complete A-V block by one subject on trandolapril after 90 days of treatment.
F/88/570/34	page 10	12	84	OL	This was a small, open-label study of renal and cardiac hemodynamics. The results should have given the sponsor little encouragement.
NL/89/570/84B	—	12	180	OL	Open extension to study NL/89/570/84 evaluating safety in patients with coronary artery disease. Preparation of final study report in progress.
UK/91/570/171	—	10	21	R, OL, ‖	...[P]harmacokinetics after repeated doses in patients with congestive heart failure. Preparation of study report in progress.
B/91/570/141	page 8	7	182	R, DB, AC, ‖	Only 7 of the planned 30 subjects were enrolled. One subject was withdrawn at 8 weeks. The other 6 subjects completed 6 months, as specified in the amended protocol. Four of the enrolled subjects did not meet enrollment criteria. The sponsor performed no efficacy analyses. There were no serious adverse events.
F/91/570/155	page 13	4	1	R, DB, PC, ‖	Four subjects (one in each treatment group) were enrolled and completed study. Two subjects did not meet protocol-specified criteria for heart rate in the presence of atrial fibrillation. Another subject did not meet protocol-specified criteria for stability and did not have assessments made at planned times. There were no serious adverse events.
CDN/89/570/75	page 9	2	1	OL	This was a pilot open dose-escalation study of hemodynamics. Only 2 subjects were recruited. There were no safety concerns.
UK/91/570/120	—	—	—	—	Study not conducted.

AC=active control; DB=double blind; OL=open label; PC=placebo controlled; R=randomized; ‖=parallel group

a. For reviewed studies, the comments are those of the reviewer; for the rest, they are the sponsor's study description.

b. This study was known by several study numbers.

Discounting one 16-week study (UK/91/570/119, with n=292) said to be ongoing (since 1991?), there are 19 studies completed with trandolapril in a population similar to that in the TRACE study. Eight studies have now been reported by the sponsor, with a total enrollment of 388 subjects. The 11 studies for which the study report is 'in progress' have a total enrollment of 482 subjects. The unreported studies include 3 of the 5 largest studies (after TRACE) in the target population. The expected exposure in the one ongoing study is 32,704 subject-days, for the reported studies, it is 117,138 subject-days, and for the report-pending studies, it is 47,044 subject-days. By comparison, the expected follow-up in TRACE would be 1,276,770 subject-days. Thus, the unreported experience of 79,748 subject-days represents <6% of the potentially available exposure in the heart failure population.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

3. Long-term follow-up in TRACE

3.1. Background

The reviewers analyzed mortality in the TRACE study by censoring a subject's data at the time of the last observation. The sponsor maintained that mortality status was known for all randomized subjects for the full period of follow-up, through inquiries made to the Danish Civil Registration Service, which maintains vital data for all Danish citizens. The difference in treatment affects 309 of 1749 subjects (18%) randomized.

The 'approvable' letter to Knoll asked the firm to provide evidence of the query and evidence that the Danish authorities would likely have provided accurate data on mortality.

3.2. Danish Civil Registration Service

The sponsor's submission of 20 December 1996 describes some aspects of the Civil Registration Service (CRS). Some of the descriptive information was provided by the CRS. All Danish citizens are issued a unique Personal Identification Number (PIN), which is used in tracking changes in status. Information maintained by CRS includes name, address, marital status, kinship, disability, profession, membership in the Lutheran Church of Denmark, voting rights, and vital status. The CRS data are not publicly available, but there is a mechanism in place to allow researchers to determine vital status through structured inquiries made using PINs.

From the information provided, it is not clear how all information is collected by CRS. At least some vital status data are obtained from parish records. The document does not mention whether hospitals directly report vital data.

The sponsor's submission of March 1997 contains a statement by CRS that it takes an average of 6 days for that agency to be notified of a death. There is no indication of the lag between death and registration of the event in the database.

3.3. Inquiries made to CRS

The sponsor provided to CRS a fixed format, line-per-subject, ASCII record containing, among other things, a field containing the PIN and a field containing the subject identification number used in the TRACE study. CRS returned to the sponsor another fixed format, line-per-subject, ASCII dataset containing the PIN, the subject identification number, a coded field indicating vital status, and (where applicable) the date and time of death.

The sponsor has provided some of the cover letters pertaining to exchanges between the CRS and the sponsor. The timing of 3 inquiries (June 1991, February 1992, and July 1993) corresponded to planned interim analyses.

The final inquiry was apparently made in July 1994. A letter from the sponsor to CRS indicates a target date of 15 July 1994 for the last follow-up, but there are no documents from which one can determine exactly when the inquiry was actually made or when was the effective date of the reply. The last subject was screened for TRACE on 7 July 1992.

The actual datasets returned by CRS cannot legally be provided to FDA, because they contain the subjects' PINs. The Agency requested that the PIN be purged from the dataset returned with the final inquiry made to the CRS and that dataset be submitted. Such a dataset was sent in the submission of March 1997.

3.4. Observed lags in mortality reporting

In the datasets returned by the Danish registry, there is apparently no field indicating the date on which a death was registered, so there is no direct way to assess the lags in reporting and registration.

The sponsor's statistical consultant, compared dates of death in the third interim analysis (June 1993) and the final analysis (July 1994) and found two subjects whose deaths occurred prior to the cut-off for the interim analysis but who were not registered until sometime later. These two events occurred 2 and 3 days before the interim cut-off date.

The final CRS listing of vital status as of 15 July 1994 includes 5 deaths not previously included in the sponsor's analyses of mortality. This new listing appears to have been generated sometime after the one used in the original mortality analyses, but there is no record of when this second 'final' inquiry was made. The 5 new events (all in the placebo group) occurred 4, 8, 8, 51, and 85 days prior to the final cut-off date. The older 'final' analysis showed 12 deaths (6 on placebo and 6 on trandolapril) in the last 85 days of the study, ranging from 31 to 85 days from the cut-off date.

The last 7 known deaths in the TRACE study were all in the placebo group, 4 to 51 days prior to the end of the study.

The final CRS listing of vital status as of 15 July 1994 includes 2 subjects whose vital status code is neither 0 (alive) nor dead (9). These subjects (one in each treatment group) were assumed to be alive.

4. Summary and recommendation

The original clinical review (dated 26 July 1996) recommended that the TRACE study be described in the clinical pharmacology section only, because of concerns about the applicability of the findings to the US population, the lack of support from other studies or secondary end points in TRACE, and missing information about the status of some subjects in TRACE and about other studies in a similar population.

The sponsor has now accounted for most of the clinical experience with trandolapril in a similar population.

The newly-discovered mortal events in TRACE were all in the placebo group, so no re-analysis was performed to confirm the statistical significance of the treatment effect. There are some remaining ambiguities about TRACE follow-up, but it seems unlikely than any further information will substantially change the results.

TRACE was a single study conducted in a homogeneously Caucasian population against a background of clinical practice distinctly different from that recommended in the US. While there was a statistically significant treatment benefit in mortality in TRACE, there was little interpretive support obtained from secondary findings. Based upon the data submitted by the sponsor in December 1996 and March 1997, there is no reason to alter the above recommendation.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

A. Individual study reports

A1. Study B/91/570/141

A1.1. Title

Double-blind study comparing the efficacy of trandolapril (2 mg) and atenolol (50 mg) in the reversal of left ventricular hypertrophy associated with hypertension, following a single-blind placebo run-in.

A1.2. Source documents

Study report: vol 20.22, CRFs: none.

A1.3. Investigators

This study was conducted at a single center in Belgium. The principal investigator was Prof. Clement, Gent.

A1.4. Study dates

September 1993 to October 1994.

A1.5. Study design

This study description is based upon the 'final' protocol dated 18 May 1993. Amendment 1 (25 June 1993) made numerous minor changes to study procedures and inclusion and exclusion criteria. Amendment 2 (4 October 1994) called for termination of the study (because of poor recruitment) after 6 months of follow-up, rather than the originally specified 1 year.

Subjects underwent an 8-week single-blind placebo withdrawal period and qualified on the basis of stable blood pressure. Subjects were randomized to atenolol 50 mg or trandolapril 2 mg and were to be followed for 52 weeks. If blood pressure was not adequately controlled, the dose could be doubled at 4 weeks and HCTZ could be added at 12 or 26 weeks. Follow-up was at 4, 8, 12, 18, 26, 34, 42, and 52 weeks. The primary end point was LV mass index, assessed using echocardiography. The goal was to enroll 30 subjects.

Subjects were to be males or females at low risk of pregnancy, with off-treatment diastolic blood pressure 95 to 120 mmHg, and echocardiographic evidence of left ventricular hypertrophy indicated by LV mass index >134 g/m^2 (men) or >110 g/m^2 (women). Exclusion criteria were (1) creatinine >1.5 mg/dL, (2) impaired liver function, (3) any history of myocardial infarction, unstable angina, or heart failure, (4) secondary causes of hypertension, (5) malignant hypertension, (6) stroke within 6 months, (7) clinically relevant valvular disease or cardiomyopathy, (8) valvular surgery, (9) Potassium outside 3.2 to 5.2 mM or sodium outside 132 to 148 mM, (10) WBC <4000/nL, (11) proteinuria > 1.2g/d, (12) atrial fibrillation within 3 months, (13) contraindications to study drugs, (14) weight >130% ideal, (15) pacemaker, (16) known non-response to either study drug, (17) blacks, (18) enzyme inducers, and (19) metabolic disease requiring treatment.

A1.6. Results

Only 7 of the planned 30 subjects were enrolled. One subject was withdrawn at 8 weeks. The other 6 subjects completed 6 months, as specified in the amended protocol. Four of the enrolled subjects did not meet enrollment criteria. The sponsor performed no efficacy analyses. There were no serious adverse events.

APPEARS THIS WAY
ON ORIGINAL

A2. Study CDN/89/570/75

A2.1. Title

An open study to measure the haemodynamic effects after oral administration of single doses (0.25, 0.5, 1, 2, and 4 mg) of trandolapril in patients with congestive heart failure.

A2.2. Source documents

Study report: vol 20.6, CRFs: none.

A2.3. Investigators

This study was conducted at two centers in Canada. The investigators were WJ Kostuk (London, Ontario) and JW Warnica (Calgary, Alberta).

A2.4. Study dates

May 1991 to January 1992.

A2.5. Study design

This study description was based upon the final study report dated November 1995.

This was a single-dose escalation study. Five treatment groups of 6 subjects were to undergo 24 hours of baseline hemodynamic studies following single-blind placebo administration, followed by successively higher doses of trandolapril and a second day of hemodynamic study.

Subjects were to have heart failure NHYA class III or early class IV, with LVEF <0.35 and PAWP >18 mmHg.

A2.6. Efficacy results

Only 2 subjects enrolled. Both were males, NYHA class III, recruited at the Ontario site. Both received trandolapril 0.25 mg.

A2.7. Safety

No adverse events were reported.

A2.8. Summary

This was a pilot open dose-escalation study of hemodynamics. Only 2 subjects were recruited. There were no safety concerns.

A3. Study F/88/570/34

A3.1. Title

Acute and long-term systemic and renal haemodynamic effects of trandolapril in patients with congestive heart failure.

A3.2. Source documents

Study report: vol 20.2 to 20.5, CRFs: none.

A3.3. Investigators

This study was conducted at a single center in the Netherlands. The investigator was WJ Remme, Rotterdam.

A3.4. Study dates

May 1989 to May 1992.

A3.5. Study design

This study description was based upon the protocol dated September 1988. There was an amendment in 1990 which led to doubling the doses indicated below. Several other amendments had less impact on the study.

This was an open-label study targeted for 15 subjects with NYHA class III or IV heart failure. During the first 4 days, subjects were stabilized on a fixed dose of diuretics and digoxin as necessary. This was followed by placebo-controlled studies of systemic and renal hemodynamics and neurohormones over a 4 day period in a coronary care unit. Subjects were then discharged on trandolapril and followed up at 8 to 10 weeks. This was followed by another 4-day period of assessment of hemodynamics and neurohormones.

Subjects were to be males and post-menopausal or surgically sterilized females with idiopathic, ischemic, or hypertensive cardiomyopathy, NYHA class III or IV, with cardiothoracic ratio > 0.5, LVEF ≤0.35, PAWP >15 mmHg, and <130% of ideal body weight. Exclusions were made for (1) rapid progression toward end-stage class IV, (2) BP >170/100 or <90/— mmHg, (3) clinically significant stenotic valvular disease, (4) absolute need for long-acting nitrates, (5) severe hepatic disease, (6) severe metabolic disorders, (7) inability to withdraw other cardiovascular medication or K-sparing diuretics, (8) severe ventricular dysrhythmias, (9) Na^+ ≤125 mEq/L, K^+ ≥5,5 mM, creatinine ≥250 μM, and (10) leukopenia <2500/mm^3.

During the hemodynamic studies, subjects received single-blind placebo on day 1, trandolapril 0.5 mg on day 2, and, depending on the hemodynamic response observed, trandolapril 0.25 to 1 mg on day 3. Subjects received trandolapril 0.25 to 1 mg (determined from hemodynamic response) during the outpatient phase, and then the same dose during the final in-hospital hemodynamic study.

Conventional cardiac catheterization data were obtained on heart rate, pulmonary artery pressures, right atrial pressure, systemic pressures, cardiac output, and derived measures. "Success" (during either the first or second assessments) was considered to be a 20% decrease in PAWP, 20% increase in CI, or 5% increase in EF (by MUGA scan).

Safety assessments included 12-lead ECG, CBC with differential and platelet count, and routine chemistry.

A3.6. Efficacy results

Five subjects received a maximum dose of 1 mg (prior to the dose-doubling amendment) and 7 subjects received a maximum dose of 2 mg. The study was terminated because of poor enrollment.

Four subjects discontinued. Reasons for discontinuation were (1) protocol violation, (2) lack of efficacy and subsequent death, (3) lack of efficacy and exacerbation of CHF, and (4) intercurrent illness.

Data from one subject (protocol violation) were excluded from analyses.

Demographics of the two treatment groups are shown in Table 2. below.

Table 2. Demographics and baseline characteristics (Study F/88/570/34).

	Low dose n=5	High dose n=7		Low dose n=5	High dose n=7
Gender			NYHA class		
Male	3	7	III	5	6
Female	2	0	IV	0	1
Age-mean±se	68±3.8	67±2.0	Race		
			Caucasian	5	6
			Other	0	1
Prior medication			Etiology		
ACE inhibitor	2	5	Ischemic	4	5
Vasodilator	5	6	Idiopathic	1	2

Some of the primary end-point data are shown in Table 3. below. These data give little reason to believe there are dose-related effects or that effects are sustained during long-term treatment. Most of the remaining analyses performed by the sponsor involved only the high-dose subjects "with complete data". These subgroup analyses (not reproduced here) appear to show sustained improvements in PAWP but not cardiac index, and reductions in pulmonary artery pressure, but not most other hemodynamic indices.

Table 3. Primary hemodynamic data (Study F/88/570/34).

	Low-dose				High-dose			
	Plcbo	0.5	1	LT[a]	Plcbo	1	2	LT
PAWP (Δ%)	-41	-35	-55	-24	-22	-22	-31	-31
CI (Δ%)	19	25	27	9	33	48	27	24

a. Long-term

Of the neurohormonal data, again analyzed only for 5 "completing" subjects in the high-dose group, there were nominally statistically significant reductions in angiotensin II and epinephrine, but no significant effect on renin, aldosterone, norepinephrine, and dopamine.

Of the renal hemodynamic data, again analyzed only for 5 "completing" subjects in the high-dose group, there were no statistically significant effects on renal blood flow, renal vascular resistance, or GFR. Filtration fraction was marginally significantly decreased long-term.

Systolic and diastolic pressures generally fell during study, but the sponsor performed no statistical analysis for all subjects.

A3.7. Safety

There was one death during study: a 75-year old female subject died on day 14 of probable respiratory infection and worsening heart failure. Relationship to treatment was considered remote.

A second subject discontinued at one month with a skin rash, diagnosed as leucocytoclastic vasculitis. He died one month later from worsening heart failure.

Other adverse events included dizziness which led to a dose reduction, worsening heart failure which led to discontinuation and ventricular tachycardia.

A3.8. Summary

This was a small, open-label study of renal and cardiac hemodynamics. The results should have given the sponsor little encouragement.

A4. Study F/91/570/155

A4.1. Title

Double-blind placebo-controlled study of the dose-haemodynamic effect relationship of trandolapril administered in a single oral dose to patients with congestive heart failure.

A4.2. Source documents

Study report: vol 20.23, CRFs: none.

A4.3. Investigators

This study was conducted at 1 center in France. The investigator was E Aliot, Nance[1].

A4.4. Study dates

October 1993 to May 1994.

A4.5. Study design

This study description was based upon the protocol dated 10 February 1993. There appear to have been no amendments.

This was a double-blind study of acute hemodynamics and pharmacokinetics among subjects with stable heart failure (PAWP >18 mmHg and cardiac index <2.2 L/min/m^2). Measurements were to be made at baseline and over 24 hours following a single dose of placebo or trandolapril 0.25, 1, and 4 mg. Planned enrollment for 40 subjects (10 per treatment group).

A4.6. Results

Four subjects (one in each treatment group) were enrolled and completed study. Two subjects did not meet protocol-specified criteria for heart rate in the presence of atrial fibrillation. Another subject did not meet protocol-specified criteria for stability and did not have assessments made at planned times. There were no serious adverse events.

[1] Three other French centers enrolled no subjects.

A5. Study FF/90/570/99

A5.1. Title

Open, one-year multicenter study to evaluate the safety and efficacy of trandolapril in patients with congestive heart failure (NYHA class II, III, and IV): a randomized study with an enalapril control group.

A5.2. Source documents

Study report: vol 20.9 to 20.21, CRFs: none.

A5.3. Investigators

This study was conducted at 38 centers in Europe and South Africa.

A5.4. Study dates

1992 to 1994.

A5.5. Study design

This study description was based upon the amended protocol dated 29 April 1992. Amendment 1 (3 February 1993) replaced the quality of life questionnaire with the Minnesota Living with Heart Failure questionnaire. Amendment 2 (7 July 1993) allowed a sub-study of renal hemodynamics at one center. Amendment 3 (10 January 1993) extended the period of enrollment of NYHA class IV subjects (who then had less total follow-up) at 18 centers. Amendment 4 extended the period of enrollment of subjects in the single-center sub-study of renal hemodynamics. Amendment 5 shortened the study by 2 months, to allow safety data to be evaluated at the same time as the data from TRACE.

There was a pre-selection phase, lasting at least 2 weeks, during which subjects were to be on stable doses of ACE inhibitor, diuretics, digoxin, and nitrates. Subjects were then randomized to either trandolapril or enalapril and followed for 55 weeks. Subjects not already on ACE inhibitor were up-titrated to the targeted dose of trandolapril 4 mg over 5 weeks or enalapril 20 mg over 2 weeks. Post-titration follow-up was to occur at weeks 7, 11, 15, 23, 31, 39, 47, and 55. The goal was to recruit 300 subjects (200 on trandolapril).

Subjects were to be males or post-menopausal or surgically sterilized females, with NYHA class II to IV heart failure from left ventricular dysfunction (EF <0.40), with seated systolic pressure ≥100 mmHg, and weight between 50% and 150% of ideal. Exclusion criteria were (1) non-cardiac causes of heart failure, (2) right heart failure from pulmonary disease, (3) uncorrected valvular disease or outflow obstruction, (4) myocardial infarction with 2 months, (5) unstable angina, (6) CVA within 6 months, (7) uncontrolled life-threatening dysrhythmia, (8) renal impairment (creatinine >200 µM), (9) liver function abnormalities, (10) digitalis toxicity, (11) potassium outside 3.0 to 5.5 mM, (12) neutropenia (<2500/nl), (13) other severe chronic disease, (14) known hypersensitivity or lack of response to ACE inhibitors, (15) history of angioneurotic edema, (16) solitary kidney, or (17) unilateral or bilateral renal artery stenosis. Use of the following was discouraged: NSAIDs, antiarrhythmics, enzyme inducers, potassium-sparing diuretics. Use of other ACE inhibitors was prohibited.

Efficacy criteria were NYHA class, and clinical signs and symptoms of heart failure. There were also plans to evaluate ejection fraction (2D echo or MUGA), cardio-thoracic ratio, and, at some centers, exercise tolerance, neurohormonal levels, and Holter monitoring. Also planned, but not listed as efficacy criteria were QOL questionnaires, subject and investigator global assessments, mortality, and hospitalization. No end point is identified as primary.

Safety assessments included 12-lead ECG, CBC with differential and platelet count, and routine chemistry.

A5.6. Efficacy results

Two hundred ninety-two subjects were recruited and randomized. Twelve subjects from one German center were excluded from analysis because of irregularities in recording. Centers enrolled from 1 to 20 subjects.

Demographics of the two treatment groups are shown in Table 4 below.

Table 4. Demographics and baseline characteristics (Study FF/90/570/99).

	Enal n=93	Tran n=187		Enal n=93	Tran n=187
Gender			Race		
Male	77	158	Caucasian	84	178
Female	23	29	Other	9	9
Age-mean±sd	63±1.1	62±0.7	Etiology		
Prior medication			MI	48	95
Diuretics	73	156	Ischemic	7	16
Digoxin	42	99	Hypertension	13	23
Antiarrhythmics	19	39	Cardiomyopathy	20	36
Vasodilator	43	93	Valvular	1	6
NYHA class			Other	2	0
II	44	89	Unknown	2	11
III	37	76			
IV	12	22			

At least 75% of subjects achieved titration to the 4 mg dose of trandolapril. The proportion of enalapril subjects at the highest dose (20 mg) was somewhat higher. There were few protocol violations of inclusion criteria. On-treatment compliance was estimated to be >80% for 98% of subjects in each treatment group.

Reasons for withdrawal were similarly distributed for the two treatment groups. Early study termination affected 27% of enrollment.

End point data are summarized in Table 5 below. The sponsor performed no statistical analyses comparing treatment groups.

Table 5. End points (Study FF/90/570/99).

	Enal n=93	Tran n=187		Enal n=93	Tran n=187
CHF symptoms (Δ%)			CHF signs (Δ%)		
Dyspnea at rest	-9	-12	Cyanosis	-1.1	-2.2
Dyspnea on daily activity	-14	-11	Edema	-9.2	-8.7
Orthopnea	-15	-10	Neck vein distension	-7.6	-9.3
Nocturnal dyspnea	-8	-9	Third heart sound	-5.4	-8.2
Fatigue	-19	-11	Mitral regurg murmur	-3.2	0.0
Angina	-3	+2	Other cardiac sound	-5.5	0.5
			Hepatic vasc congestion	-3.3	-6.0
Killip class (Δ%)			Ejection fraction (Δ)	0.06	0.06
1	+20	+16	Cardio-thoracic ratio (Δ)	-0.01	-0.01
2	-20	-16	Subjects hospitalized (%)	22	35
3	0	-0.5	Death (%)	6.5	8.6
4	0	0	Cardiovascular	5.4	7.5
			QOL score (Δ%)	-7.5	-8.9

A5.7. Safety

There were a total of 22 deaths during the study (6.5% on enalapril and 8.6% on trandolapril). Nineteen of these deaths were cardiovascular (7 progression of heart failure, 6 myocardial infarctions, 4 arrhythmias, 1 stroke, and 1 'other').

Forty-three subjects withdrew from treatment because of treatment-emergent adverse events, with a similar rate in the two treatment groups. About half of these events were cardiovascular in nature.

Treatment-emergent serious adverse events were reported by 37% of trandolapril subjects vs. 26% of enalapril subjects. The events were generally of a type common in the population at risk. The only event with at least a 5% incidence was heart failure, reported for 10% of subjects in each group.

Adverse events with at least a 5% incidence in a treatment group are listed in Table 6 below. There was little difference between treatment groups.

Table 6. Adverse events (%) reported for >5% in a treatment group (Study FF/90/570/99).

	Enal n=93	Tran n=187		Enal n=93	Tran n=187		Enal n=93	Tran n=187		Enal n=93	Tran n=187
Any	72	73									
Hypotension	12	13	Cough	7	7	Asthenia	5	5	Infection	5	4
Heart failure	12	11	Bronchitis	7	6	Chest pain	1	5	Angina	8	4
Dyspnea	2	8	Upper resp inf	9	5	Dizziness	9	4	Dyspepsia	5	1

A5.8. Summary

This was a positive-controlled, open-label study of approximately one year duration. No statistical analyses were performed, but the differences between treatment groups were fairly small. The one-year mortality rate in this study was approximately one-third of that observed in the TRACE study.

A6. Study FF/91/570/154

A6.1. Title

Tolerance and pharmacokinetics of trandolapril after oral administration of a repeated dose of 1 mg/day for 10 days in patients with congestive heart failure.

A6.2. Source documents

Study report: vol 20.25 to 20.27, CRFs: none.

A6.3. Investigators

This study was conducted at 2 centers in Sweden and South Africa. The investigators were D Marx, Bloemfontein and G Ulvenstam, Goteborg.

A6.4. Study dates

June 1992 to April 1993.

A6.5. Study design

This study description was based upon the protocol dated April 1992. There was one amendment (undated) which made minor changes in implementation at the Swedish center.

This was an open-label, uncontrolled study. Subjects underwent a washout period of 7 to 14 days, which was optionally placebo-controlled. All study subjects were to take trandolapril 1 mg q.d. for 10 days. Trandolapril and trandolaprilat levels were assayed several times on days 1 and 10, daily at trough on days 2 to 9, and then at intervals up to 17 days after the last dose. Timed urine collections were to be made at baseline, on day 1, and for several days after the last dose. Blood pressure and plasma ACE activity were to be measured at times of pharmacokinetic sampling. The goal was to recruit 15 subjects.

Subjects were to males or females, Caucasian, within 25% of ideal weight, with a 3-month history of heart failure, NYHA class III, on stable treatment for at least 8 weeks, with LVEF <0.35, and systolic pressure >100 mmHg. Exclusion criteria were (1) myocardial infarction or unstable angina within 3 months, (2) symptomatic ventricular arrhythmia, (3) aortic stenosis or other symptomatic valvular disease, (4) potassium outside 3.0 to 5.5 mM or sodium outside 127 to 150 mM, (5) creatinine >200 μM, (6) chronic obstructive pulmonary disease leading to right ventricular failure, (7) CVA within 3 months, and (8) abnormal liver function.

Safety assessments included 12-lead ECG, CBC with differential and platelet count, and routine chemistry.

A6.6. Efficacy results

Nineteen subjects were enrolled (11 in South Africa and 8 in Sweden). All were Caucasian. There were few significant deviations from enrollment criteria. One subject was administratively terminated on day 2 because of failure to meet baseline requirements for heart failure.

Pharmacokinetic data are summarized in Table 7 below.

Table 7. Pharmacokinetic data (Study FF/91/570/154).

	Trandolapril		Trandolaprilat			ACE inhibition	
	Day 1	Day 10	Day 1	Day 10		Day 1	Day 10
C_{max} (mg/mL)	1.7±0.2	1.6±0.2	1.8±0.1	3.9±0.3*	I_{max} (%)	66±4.5	86±2.5*
T_{max} (h)—median min, max	0.5 0.5, 1	0.75 0.4, 2	5 1, 12	3* 1.5, 12	TI_{max} (h)—median min, max	7 1, 24	5 2, 24
AUC (ng/mL h)	2.6±0.6	1.8±0.2*	33.4±1.9	63±3.2*	I_{24h} (%)	54±2.6	63±4.1*

*p<0.05 for comparison between days

Table 7. Pharmacokinetic data (Study FF/91/570/154).*(Continued)*

	Trandolapril		Trandolaprilat			ACE inhibition	
	Day 1	Day 10	Day 1	Day 10		Day 1	Day 10
$t_{1/2}$ (h)	0.76±0.06	0.59±0.06*	—	—			
$Ae_{0\text{-}24h}$ (mg)	—	—	60±13	151±9*			
$Clr_{0\text{-}24h}$ (L/h)	—	—	1.8±0.4	2.5±0.2			
$\frac{AUC_{Day10}}{AUC_{Day1}}$	0.8*		1.9*				

*p<0.05 for comparison between days

A6.7. Safety

There were no deaths. Two subjects developed atrial fibrillation which was treated by cardioversion. There were no other serious adverse events.

A6.8. Summary

The pharmacokinetic parameters for trandolapril and its active metabolite trandolaprilat in a group of subjects with heart failure was similar to those in a population of normal volunteers.

A7. Study I/91/570/139[1]

A7.1. Title

Efficacy and safety of trandolapril in heart failure: study of the antiarrhythmic effect in patients with complex ventricular arrhythmias.

A7.2. Source documents

Study report: vol 20.24, CRFs: none.

A7.3. Investigators

This study was conducted at 1 center in Italy. The principal investigator was P. Rizzon.

A7.4. Study dates

Not stated.

A7.5. Study design

This study description was based upon the final protocol dated 3 November 1992. There was one amendment (13 December 1993) to allow inclusion of subjects with atrial fibrillation.

This was a double-blind, placebo-controlled, parallel-design study. Subjects underwent a 15-day in-hospital stabilization period with single-blind administration of placebo. Subjects were then randomized equally to placebo or trandolapril, the dose of which was force-titrated from 0.5 to 2 mg over 5 days, and followed for 90 days, the first 6 days being in-hospital. Subjects were followed for an additional 30 days on single-blind placebo. Planned enrollment was for 40 subjects.

Subjects were to men and women with adequate contraception with a 3-month history of heart failure, NYHA class III, from idiopathic dilated cardiomyopathy, ischemic heart disease, or hypertension, LVEF <0.40, VPBs >30/h but no runs >3 on 24-hour Holter, normal sinus rhythm, and weight <130% of ideal. Exclusion criteria included (1) nonsustained or sustained ventricular tachycardia, (2) atrial fibrillation, (3) unrepaired valvular disease, (4) hypertrophic or restrictive heart disease, (5) right ventricular dysfunction from restrictive bronchopneumonia, (6) supine systolic pressure outside 100 to 160 mmHg, (7) myocardial infarction or stroke within 4 months, (8) awaiting cardiac transplantation, (9) grade II or III A-V block or sick sinus syndrome, (10) pacemaker, (11) chronic obstructive pulmonary disease, (12) neutropenia, (13) potassium outside 3.6 to 5.5 mM, (14) dermatosis, (15) connective tissue disease, (16) allergy or hypersensitivity to ACE inhibitors, and (17) other severe chronic disease.

The primary end point was a >70% decrease in VPB rate on a 24-hour Holter monitor or an improvement in Lown class if there are couples or runs at baseline. Monitoring was to start 2 h after dosing. Secondary efficacy criteria included NYHA class, exercise tolerance, cardio-thoracic ratio, plasma renin activity, and ACE inhibition.

Efficacy criteria were NYHA class, and clinical signs and symptoms of heart failure. There were also plans to evaluate ejection fraction (2D echo or MUGA), cardio-thoracic ratio, and, at some centers, exercise tolerance, neurohormonal levels, and Holter monitoring. Also planned, but not listed as efficacy criteria were QOL questionnaires, subject and investigator global assessments, mortality, and hospitalization. No end point is identified as primary.

Safety assessments included 12-lead ECG, CBC with differential and platelet count, and routine chemistry.

A7.6. Results

Fourteen subjects were screened and randomized (7 to placebo and 7 to trandolapril). One subject on placebo withdrew during the double-blind treatment period. All subjects were Caucasian and all but one was male.

---

[1] Also identified as study I/91/570/10.

Only limited safety data were reported. Holter data were not reported. The only serious adverse event was development of complete A-V block by one subject on trandolapril after 90 days of treatment.

A8. Study UK89/570/70

A8.1. Title

A placebo-controlled dose ranging study of the efficacy and safety of trandolapril in the treatment of patients with congestive heart failure (NYHA class II & III).

A8.2. Source documents

Study report: vol 20.7 to 20.8, CRFs: none.

A8.3. Investigators

This study was conducted at a single center in the UK. The investigator was WJ McKenna, London.

A8.4. Study dates

February 1990 to December 1993.

A8.5. Study design

This study description was based upon the amended protocol dated 11 June 1990. There were no substantial changes effected in amendments.

This was a double-blind, placebo-controlled, parallel-group design. There was a 1-to-6-week pre-selection phase during which subjects underwent repeated exercise tolerance testing until there was <10% variation in peak oxygen consumption. This was followed by a 1-week run-in phase during which baseline exercise and safety data were obtained. Subjects were randomized to once-daily placebo or trandolapril 0.25, 1, or 4 mg, and followed for 16 weeks. Subjects randomized to 1 mg received 0.5 mg for the first 2 weeks. Subjects randomized to 4 mg received 0.5 mg for 2 weeks and 1 mg for 2 weeks. Forty-eight subjects were to complete study, with replacement of withdrawals.

Subjects were to be males and post-menopausal or surgically sterilized females with at least a 3-month history of stable CHF, NYHA class II or III. Exclusions were made for (1) blood pressure < 90/50 mmHg, (2) >140% ideal body weight, (3) peak VO_2 >80% predicted or >15% variation between last 2 measurements, (4) ejection fraction outside 20 to 40%, (5) clinically significant renal dysfunction, (6) neutropenia <2500/mm^3, (7) clinically significant stenotic valvular disease, (8) pacemaker-limited exercise tolerance, (9) myocardial infarction within 4 months, (10) sustained or symptomatic arrhythmias on 24-hour Holter monitoring, (11) significant chronic obstructive pulmonary disease, (12) other significant systemic disease, (13) modified-Bruce exercise tolerance outside stage 0.5 to 4[1], (14) angina-limited exercise, (14) significant hepatic dysfunction unrelated to CHF, (15) Na^+ ≤130 mEq/L, K^+ ≥5,5 mM or <3.0 mM, (16) evidence of digoxin toxicity, (17) hypersensitivity to ACE inhibitors or history of angioneurotic edema, (18) need for concomitant vasodilators, enzyme inhibitors or inducers, NSAIDs, glucocorticosteroids, estrogen or progesterone, β-blockers, or K-sparing diuretics.

The primary end point was exercise duration. Peak oxygen consumption was a secondary end point.

Safety assessments included 12-lead ECG, CBC with differential and platelet count, and routine chemistry.

A8.6. Efficacy results

Because of recruitment problems, the study was terminated with 50 subjects enrolled, 8 withdrawn, and 42 completed. Subjects were not assigned treatments in the originally allocated order; this was, in part, a deliberate attempt to redress an imbalance in the number of subjects per group. Two subjects were not included in the ITT analysis; one withdrew at the randomization visit and the other at 14 days.

Sixty to 92% of subjects in each treatment group had at least one major deviation in adherence to protocol specified inclusion or exclusion criteria. These deviations included ejection fraction >40% or missing (n=18), cardio-thoracic ratio <0.5 or missing (n=20), exercise duration <3 or >12 minutes or peak VO_2 >80% predicted

[1] 3 to 12 minutes

(n=4), no diuretic (n=13), and no exercise test post-baseline (n=2). "Minor" violations in enrollment are described for another 8 subjects.

Demographics of the two treatment groups are shown in Table 8 below.

Table 8. Demographics and baseline characteristics (Study UK89/570/70).

	Plcbo n=10	0.25 mg n=14	1 mg n=13	4 mg n=13		Plcbo n=10	0.25 mg n=14	1 mg n=13	4 mg n=13
Gender					NYHA class				
Male	10	12	10	12	II	8	12	10	10
Female	0	2	3	1	III	2	2	3	3
Age-mean±sd	54±11	60±8.3	61±7.3	60±7.9	Race				
					Caucasian	9	11	12	11
					Other	1	3	1	2
Prior medication					Etiology				
ACE inhibitor	1	3	3	1	Ischemic	8	12	10	9
Vasodilator	3	0	1	2	Idiopathic	2	2	3	4

Changes from baseline in exercise time are shown in Table 9 below. These data give little reason to believe there are dose-related effects.

Table 9. Changes in exercise tolerance (Study UK89/570/70).

	Plcbo	Trandolapril		
		0.25	1	4
Exercise (Δsec)	70±72	54±77	24±191	52±132
VO_2max (Δml/kg/min)	0.9±2.4	1.2±4.6	2.0±4.6	-1.0±3.5

A variety of signs and symptoms were analyzed for dose-dependent effects from baseline to the end of study (orthopnea, dyspnea, NYHA class, JVP, gallop, rales, liver size, edema). Treatment effects were generally not observed.

A8.7. Safety

There was one death during study: a subject in the placebo group had a sudden death on study day 55.

Two subjects were withdrawn because of dizziness (on 0.25 and 1 mg). One subject withdrew with angina, considered possibly related to treatment (1 mg) and one subject withdrew with a TIA, considered unlikely to be related to treatment (0.25 mg). The only other serious adverse event was one case of hemoptysis, considered unlikely to be related to treatment.

Forty-three treatment-emergent adverse events were reported by 25 subjects, with little to suggest dose-relatedness. No specific event was reported by more than 2 subjects in a treatment group. In general the observed events were common to the at-risk population.

A8.8. Summary

This was a pilot double-blind, placebo-controlled study evaluating multiple dose levels of trandolapril in an appropriate target population. The study was marred by a high incidence of inappropriately randomized subjects, but in no way suggestive of bias. The results provide scant evidence of a beneficial effect of trandolapril on subjects with heart failure.

D-F

JUL 26 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Joint Clinical Review

/S-001

NDA: 20-528 (Mavik®, Trandolapril post-myocardial infarction).

Sponsor: Knoll Pharmaceutical Company

Submission:

Submission	Volumes	Submitted	Received
S-001; new indication based on TRACE study	17.1	6 May 1996	10 May 1996
Response to reviewer questions 24 June 1996	17.1	16 July 1996	18 July 1996

Review date: 26 July 1996.

Reviewers: L. Cui, Ph.D., HFD-710 — L. Cui 7/26/96

N. Stockbridge, M.D., Ph.D., HFD-110 — [signature] 26JUL96

Concurrences: G. Chi, Ph.D., HFD-710 — [signature] 7/26/96

Distribution:

NDA 20-528
HFD-110
HFD-710/Cui
HFD-110/Stockbridge
HFD-110/CSO
HFD-710/Chi
HFD-710/Mahjoob
HFD-701/Anello

Table of contents

1. Submission

The original submission consists of a single volume containing the study protocol and amendments, blank case report forms, the publication which describes the study results, and a SAS data tape.

1.1. Study protocol

The description of the study is based upon the 'final' study protocol, dated 17 April 1990 and 4 amendments[1]. The formal name of the study was "Study of trandolapril in patients with reduced left ventricular function after acute myocardial infarction", DK/89/570/57.

This was a multi-center, double-blind, parallel-group, placebo-controlled study of mortality at 1 year (amended to 2 years) in 1500 subjects (planned) with left ventricular systolic dysfunction 1 to 5 days after myocardial infarction.

1.1.1. Enrollment

Subjects were to be men and women >18 years old with a myocardial infarction and left ventricular systolic dysfunction.

The definition of myocardial infarction included elevated enzymes plus typical symptoms, ECG changes, or both. Symptoms included severe discomfort in the anterior chest, back, jaw, neck, or shoulder, lasting more than 30 minutes, unless relieved by morphine or meperidine. Any of the following were considered electrocardiographic evidence of myocardial infarction: (1) new abnormal Q-waves, without bundle branch block, lasting 30 ms in 2 contiguous leads not including V1 and aVR or R/S ratio≥1 in V1 or V2, (2) >50% reduction in R-waves, without bundle branch block, in 2 contiguous leads, (3) ST elevation, without bundle branch block, ≥0.1 mV 80 ms after the J-point (≥0.2 mV in V1 or V2) or upright T-wave ≥0.5 mV (≥1 mV in V1 or V2) where R-wave <1 mV, (4) ST depression, without bundle branch block, ≥0.1 mV 80 ms after the J-point, (5) with right bundle branch block, Q-wave ≥30 ms in 2 contiguous leads, ST elevation or upright T-wave ≥0.2 mV, or (6) with left bundle branch block, Q-wave ≥40 ms in leads other than V1, V2, and aVR, or ST elevation ≥0.2 mV in leads with a predominant R-wave.

Enzymatic evidence of myocardial infarction was to exclude subjects with other causes for enzyme elevation (such as rhabdomyelitis, muscular dystrophy, trauma, seizures, hypothyroidism, or multiple defibrillations). Elevation in CKMB was preferred, unfractionated CK next, then SGOT or LDH if neither of the first two were available. The threshold was, in all cases, twice upper limit of normal for the local laboratory, within 48 hours of symptom onset.

Left ventricular systolic dysfunction was indicated by wall motion index (WMI) ≤1.2 1 to 5 days after infarction. Wall motion index is calculated from the average qualitative echocardiographic assessment of wall motion in 9 areas of the left ventricle, where each area is scored as -1=pronounced paradoxical motion, -0.5=slight paradoxical motion, 0=akinesia, 0.5=pronounced hypokinesia, 1=moderate

[1] Amendment 1 (10 September 1990) made minor changes to the ETT sub-study protocol and named the Events Committee.
Amendment 2 (undated) made minor changes in the follow-up during up-titration.
Amendment 3 (23 September 1992) called for minimum follow-up of 24 months, rather than 12 months, and shifted the time of the third interim analysis to the time when all subjects had completed 12 months (about 9 months from the date of the amendment).
Amendment 4 (5 April 1994) established a Reinfarction Committee, provided details concerning the Holter monitoring sub-study, and altered the secondary end-points so there would be separate analyses of cardiovascular mortality, sudden death, recurrent infarction, and severe or resistant heart failure. Non-cardiovascular mortality was dropped as a secondary end-point.

hypokinesia, 1.5=slight hypokinesia, 2=normokinesia, 2.5=slight hyperkinesia, and 3=pronounced hyperkinesia. This method is said to show very little inter-observer variability and to have a high inverse correlation with survival after myocardial infarction.

Exclusion criteria were (1) intolerance of a test dose of trandolapril 0.5 mg, (2) need for an ACE inhibitor, (3) clinical shock—systolic pressure <80 mmHg for 30 minutes, peripheral vascular contraction, and low urinary output within 24 hours of randomization, (4) ketoacidosis from uncontrolled diabetes mellitus at time of randomization, (5) sodium <125 mM, (6) serum creatinine >0.2 mM, (7) pregnancy, lactation, or lack of approved method of contraception, (8) acute pulmonary embolism, (9) intolerance of ACE inhibitors or history of angioneurotic edema, (10) collagen vascular disease, (11) significant non-ischemic obstructive heart disease, (12) solitary kidney, (13) unstable angina leading to acute procedure or transfer, (14) uncontrolled hypertension—>220/130 mmHg, (15) severe liver disease, (16) neutropenia, (17) need for immunosuppressive or antineoplastic therapy or expectation of death from other causes during study, (18) alcohol or drug abuse or other conditions apt to interfere with study participation, and (19) chronic treatment with an investigational drug, including unapproved uses.

1.1.2. Procedures

1.1.2.1. Concomitant medication

Prior to randomization, "unnecessary" treatment with an ACE inhibitor or other cardiovascular and non-cardiovascular medications was to be discontinued. Heart failure was to be treated with digoxin and diuretics. Shock was to be treated with vasodilators, vasoconstrictors, inotropic drugs, or fluid as deemed indicated. Pain was to be treated with opiates, anginal pain with nitrates or diltiazem. Hypertension was to be treated with diuretics, vasodilators, and β-blockers.

After randomization, heart failure was to be treated with study drug or vasodilators. Absolute need for an ACE inhibitor required withdrawal from the study. Shock, angina, and hypertension were to be treated without the use of other ACE inhibitors.

1.1.2.2. Screening

Data to be collected were medical history, physical exam, ECG, echocardiography, and cardiac enzymes. Subject eligibility was to be ascertained no later than 5 days after myocardial infarction.

All subjects were to receive a single dose of open-label trandolapril 0.5 mg prior to randomization. This dose was considered tolerated if it did not lead to "annoying" symptoms or to inability to stand or walk.

1.1.2.3. Randomization

Subjects were stratified according to WMI (<0.8 and 0.8 to 1.2) and then randomized 1:1 (fixed blocks of 4) to active drug or matching placebo.

1.1.2.4. Dosing

Active treatment group subjects received trandolapril 1 mg on study days 1 and 2, to be administered with breakfast. Subjects not tolerating this dose were withdrawn from the study. Subjects not withdrawn received 2 mg on days 3 to 28. If tolerated, subjects were subsequently to receive 4 mg q.d. The first 100 subjects titrated to 4 mg were to have blood pressure monitored in the clinic for 4 hours after the first dose and to have serum creatinine checked at 2 days.

Study drug could be reduced (but not below 1 mg) in the presence of elevated serum creatinine. Study drug could be interrupted for up to 2 weeks if deemed clinically indicated.

1.1.2.5. Follow-up

After hospital discharge, subjects were to seen in the clinic at 1, 3, 6, 9, and 12 months, and then at intervals of 3 months thereafter[2].

1.1.3. Organization

Up to 24 centers were to participate. The recruitment period was 15 months. With a minimum follow-up period of 12 months, the total study time was expected to be 27 months.

---

[2] Amendment 3 increased the minimum (end-point) follow-up to 24 months.

There was an 8-member Steering Committee responsible for ongoing study management.

There was a 3-member Safety Committee, whose members were not otherwise associated with the conduct of the study. Prior to the start of the study, they were to establish stopping rules. They were to meet regularly and review unblinded results.

There was a 3-member Events Committee charged with setting cause for deaths.

1.1.4. End-points

The primary study end-point was all-cause mortality at 24 months. Cardiovascular and non-cardiovascular deaths were to be separately analyzed.

Morbidity (any hospitalization or contact with physician) was to be monitored. Causes were to be categorized as cardiovascular or non-cardiovascular.

Specific secondary end-points pre-specified were (1) cardiovascular mortality and sudden death, (2) reinfarction, (3) morbidity attributed to heart failure, (4) exercise tolerance, and (5) arrhythmias.

The analysis plan named other secondary end-points: (6) WMI and left ventricular diameter, (7) NYHA class, and (8) Killip class.

In some centers, there were sub-studies conducted—exercise tolerance[3], Holter monitoring[4], and radionuclide cardiography[5].

Study amendment 4 added an end-point of severe or resistant heart failure, described as (a) death attributed by the Mortality Committee to heart failure and in the absence of a recurrent myocardial infarction in the preceding 7 days, (b) hospitalization for heart failure, according to the investigator, or (c) withdrawal to permit open-label ACE inhibitor for treatment of heart failure. The analysis plan called for a log-rank test of time to first qualified event with stratification by center and baseline WMI. Deaths or withdrawals for other reasons were to be considered censoring events.

1.1.5. Statistical analysis plan

1.1.5.1. Sample size

Sample size was based upon a one-year placebo mortality rate of 30% and a reduction of 25% in the trandolapril group. The planned 1500 subjects gave the study 90% power.

1.1.5.2. Interim analyses

The expectation was that enrollment would proceed at about 100 subjects per month. Three interim analyses were planned, at 9, 15, and 21 months. The plan was to perform a stratified log-rank analysis of all-cause mortality at these times. The proposal was to calculate two one-sided *p*-values and compare them against the Bonferroni-type boundaries shown in Table 1 below.

1.1.5.3. Final analysis

The protocol called for overall, cardiovascular, and non-cardiovascular mortality each to be compared. A significant treatment effect in favor of trandolapril required an overall one-sided *p*-value <0.025. A significant treatment effect in favor of placebo required an overall *p*-value <0.25. Both comparisons were made after adjustment for interim analyses.

---

[3] The protocol called for monitoring maximal exercise tolerance at months 1, 3, 6, 9, and 12. Sample size was not indicated.

[4] The protocol called for monitoring ventricular arrhythmias (PVCs, pairs or runs of PVCs, ventricular tachycardia, or ventricular fibrillation), supraventricular arrhythmias (premature depolarizations, atrial fibrillation, and atrial flutter), conduction defects (atrio-ventricular or sino-atrial block), silent ischemia, or ST segment elevation or depression during 24-hour recordings at baseline, and after 1, 3, 6, and 12 months. The planned sample size was 400 subjects.

[5] The protocol called for one center to compare left ventricular ejection fraction as estimated by radionuclide cardiography with WMI in 100 subjects.

Table 1. Interim and final statistical analysis boundaries for all-cause mortality.

Month	*P*-value in favor of	
	Tran	Plcbo
9	0.0000	0.025
15	0.0001	0.050
21	0.0024	0.075
27	0.0225	0.100
Sum	0.0250	0.250

The primary basis of assessing efficacy was to be an intent-to-treat log-rank analysis of overall mortality, stratified by center and WMI.

1.1.5.4. Supportive analyses

Supportive analyses of Kaplan-Meier survival rates at 1, 3, 6, and 12 months were planned. Exploratory analyses were planned to investigate effects of previous infarctions, sex, age, smoking history and dose of trandolapril.

1.2. Publication

The only narrative description of the study results is the publication "A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction", Køber L. et al., *New Eng J Med* (1995) **333**:1670-1676.

The publication indicates that the decision to increase the duration of the study from 12 months to 24 months was made by the Steering Committee on the basis of the published results in the SAVE study and without knowledge of interim results in this study.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

2. Results

Except where noted, all results are from the reviewers' analyses, based upon the electronic datasets submitted.

2.1. Trial management

The TRACE study was conducted at 27 centers in Denmark. Screening took place between 1 May 1990 and 7 July 1992. Seven thousand and one consecutive myocardial infarctions were screened (involving 6676 patients), from which 2606 subjects were deemed eligible for trial participation and 1749 subjects were enrolled, as shown in Table 2 below. Individual centers randomized from 21 to 140 subjects.

Table 2. Enrollment.

Screening	N=7001	Eligibility	N=2606	Enrollment	N=1749
Disqualification		Exclusions		Randomized to placebo	873
WMI[a]>1.2	3920	Mandatory ACE inhibitor	150	Randomized to trandolapril	876
WMI not done	475	Cardiogenic shock	101		
Remaining	2606	Death prior to randomization	70		
		Renal failure or solitary kidney	65		
		Intolerance to trandolapril	39		
		Not consenting	218		
		Other	216		
		Remaining	1749		

a. Wall motion index; see definition on page 1.

Three interim analyses of mortality were performed with enrollment at 673, 1209, and 1745. There was no submitted documentation for the Safety Committee, but analyses are said to have not met stopping criteria.

2.2. Baseline comparability

As expected for a trial of this size, the two treatment groups were generally well matched for demographic and baseline disease factors, as shown in Table 3 to Table 6 below, and for maximum screening laboratory values, as shown in Table 7 below.

Table 3. Comparability of demographics.

	Placebo N=873	Trandol N=876		Placebo N=873	Trandol N=876
Age—% subjects			Race—% subjects		
<40	1.1	0.8	Caucasian	99.7	99.9
40 to 50	4.7	3.5	Black	0.1	0
50 to 60	17	16	Oriental	0.1	0.1
60 to 70	32	33	Eskimo	0	0
70 to 80	36	36	Other	0.1	0
≥80	9.9	11			
Gender—% subjects			Weight—% subjects		
Male	71	72	<60 kg	12	9.7
Female	29	28	60 to 70	22	21
BMI[a]—mean±SD	25.6±3.9	25.8±3.7	70 to 80	31	31
			≥80	35	39

a. Body mass (kg) divided by square of height (m).

Data concerning revascularization procedures do not appear to have been collected.

Table 4. Comparability of clinical history (% subjects).

	Placebo N=873	Trandol N=876		Placebo N=873	Trandol N=876
Hypertension	23	23	Intermittent claudication	9.9	8.2
Diabetes	14	13	CVA or transient ischemia	7.8	9.7
Angina pectoris	44	47	Renal disease	1.3	0.8
Previous MI	34	37	Conduction or rhythm disorder	1.7	1.9
Heart failure	23	21	Pacemaker	0.5	0.7
Current/previous smoker	75	73	Ventricular arrhythmia	1.9	1.7
COPD or asthma	14	12	Supraventricular arrhythmia	8.8	7.6
Hyperlipidemia	4.6	5.3			

Table 5. Comparability of history and treatment of index infarction.

	Placebo N=873	Trandol N=876		Placebo N=873	Trandol N=876
Infarct location—% subjects			Thrombolysis—% subjects		
Anterior Q-wave	47	47	None	55	55
Inferior Q-wave	18	19	Streptokinase	41	43
Non-Q-wave	15	14	tPA	2.7	1.8
Other or mixed	11	13	APSAC	0.3	0.3
ECG abnormalities—% subjects			Baseline medications—% subjects		
Intraventricular block	17	14	Aspirin	90	92
>1st degree A-V block	0.2	1.5	β-blocker	15	17
Signs of ischemia	62	64	Calcium antagonist	28	28
ST elevation	59	60	Diuretic	68	64
ST depression	34	38	Nitrates	50	56
Pathological Q-wave	78	79	Digoxin	29	26
Pathological R-wave	55	57			
Pathological T-wave	70	72			

2.3. Compliance and protocol violations

Most subjects were titrated to and maintained on the protocol-specified 4-mg dose of study drug or placebo, as shown in Figure 1 below[6], although a lower percentage of subjects were maintained on the target dose of the active drug. For this figure, subjects who died or withdrew from treatment were placed in the censored category.

Two subjects were enrolled with WMI>1.2[7].

2.4. Subject disposition

The disposition of subjects through the course of the first 12 months of follow-up is shown in Figure 2 below.

---

6. This graph can be described as a continuous stacked bar chart. All subjects are, at each point in time, characterized by a unique category in a finite set. The number of subjects in a category at any moment in time is given by the height of a region between two boundary lines. In the first 30 to 45 days, most subjects were on 2 mg. After that time, most subjects are either on 4 mg or they are censored. After the first few days, a higher proportion of subjects were in 0, 1, or 2 mg categories in the trandolapril treatment groups than were in those categories in the placebo group, but these categories remained small for both treatment groups throughout the first year.

7. Subject 07-159 with WMI=1.6, assigned to trandolapril, and subject 19-164 with WMI=1.5, assigned to placebo.

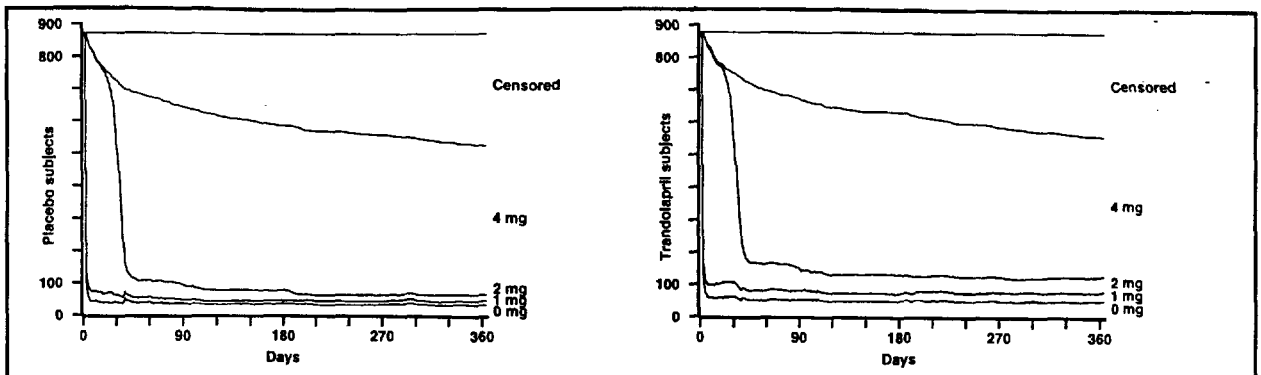


Figure 1. Dosing of subjects.

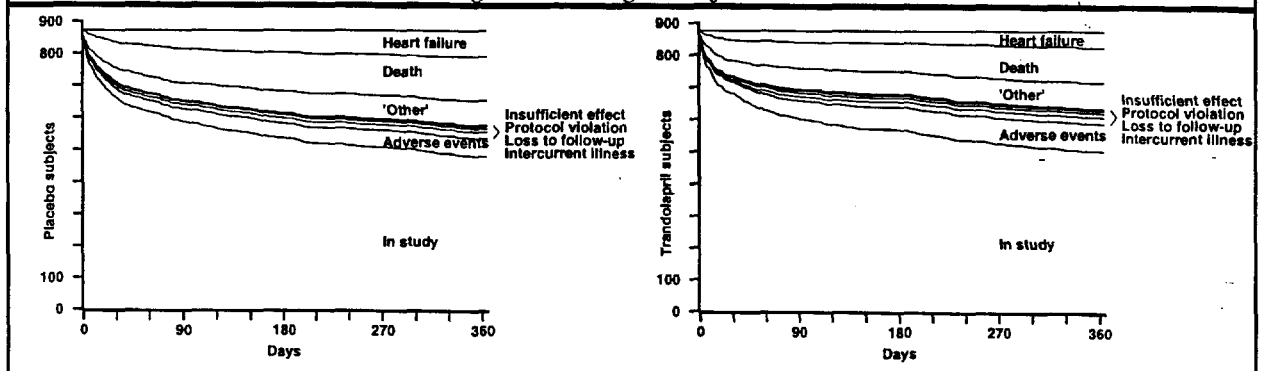


Figure 2. Disposition of subjects.

Table 6. Comparability of clinical status at randomization.

	Placebo N=873	Trandol N=876		Placebo N=873	Trandol N=876
Time from MI—% subjects			Wall motion index—% subjects		
<2 days	20	20	<0.8	18	17
2 to 3	35	33	0.8 to 0.9	12	11
3 to 4	20	21	0.9 to 1.0	17	17
4 to 5	10	10	1.0 to 1.1	27	31
5 to 6	8	7	1.1 to 1.2	26	24
≥6	7	8	>1.2	0.1	0.1
Symptoms—% subjects			Symptoms—% subjects.		
Dyspnea	36	35	Pulmonary congestion or edema	20	19
Orthopnea	5.1	4.5	Peripheral edema	3.4	2.8
Paroxysmal nocturnal dyspnea	4.0	2.3	Neck vein distension	1.8	1.6
Cough	11	11	Ventricular gallop	1.9	1.9
Angina	19	20	Cyanosis	0.3	0.7
Dizziness	6.6	7.9	Hepatomegaly	1.2	0.7
Fatigue	65	61			
Killip class—% subjects			NYHA class—% subjects		
1	79	80	I	39	42
2	20	19	II	42	42
3	1.2	1.1	III	13	12
4	0	0	IV	4.8	4.1
Vital signs (mean±SD)					
Systolic pressure	121±18	122±18			
Diastolic pressure	75±11	76±11			
Heart rate	81±14	81±13			

Table 7. Maximum screening laboratory values.

	Placebo N=873		Trandolapril N=876			Placebo N=873		Trandolapril N=876	
	n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$		n	$\bar{x} \pm SD$	n	$\bar{x} \pm SD$
SGOT	77	247±238	78	242±168	CK	304	1811±1755	297	1813±1567
LDH	76	1456±803	84	1602±940	CKMB	43	69±59	44	67±67
LD1	177	959±753	181	846±610	CKB	699	97±122	697	98±94
CRE	873	106±28	876	105±26					

2.5. Blood pressure control

Interpretation of a treatment-related difference in mortality would be affected as well by differences in blood pressure control post-randomization. Data from periodic measurements of blood pressure and heart rate are shown in Figure 3 below[8]. The fraction of subjects whose blood pressure as a function of time was ≥140 mmHg systolic or ≥95 mmHg diastolic is shown in Figure 4 below. These data suggest that blood pressure control was substantially better in the trandolapril treatment group.

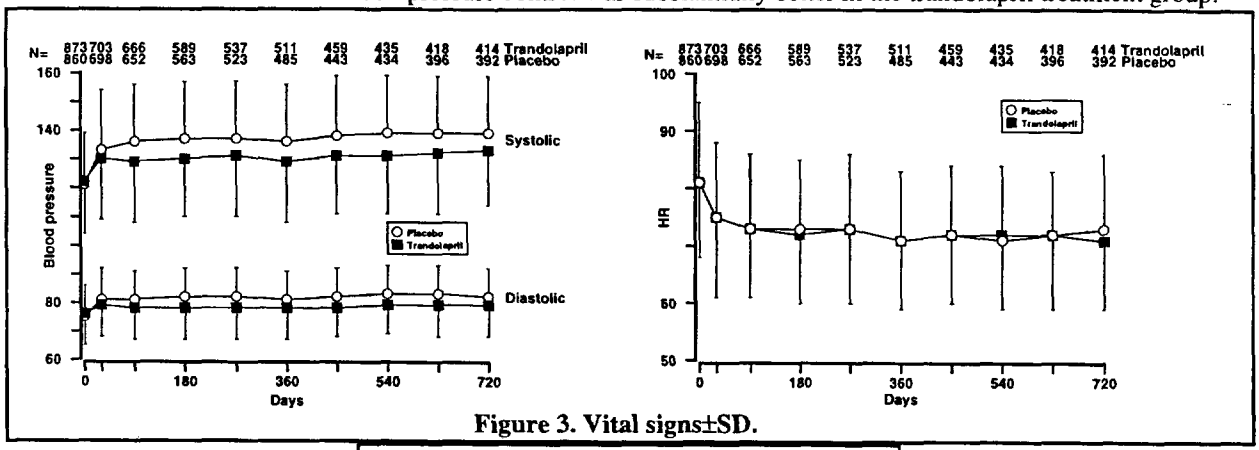


Figure 3. Vital signs±SD.

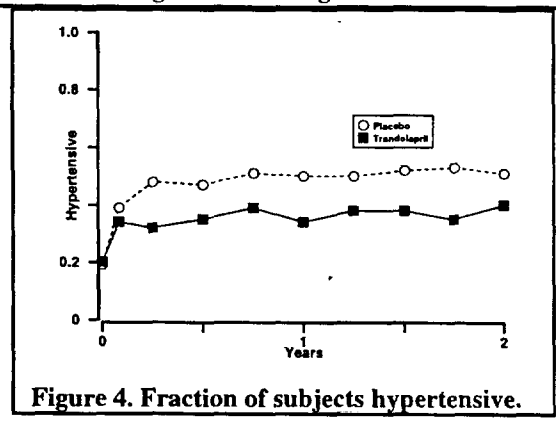


Figure 4. Fraction of subjects hypertensive.

2.6. Efficacy assessments

2.6.1. Mortality

2.6.1.1. Primary efficacy analyses

Survival status for TRACE was determined through the Danish Home Office which maintains vital data on all Danish citizens. The TRACE study final report (dated July

[8]. It is not clear where on the case report forms there was an opportunity to collect these data, but they were in the SAS datasets.

1995), only a portion of which was submitted to the agency in the submission of 16 July 1996, indicates that all subjects had mortal status ascertained as of the closing date of the study (30 June 1994), but what was entered into the database and available, in some sense, for verification by the reviewer were dates of death and not a separate indicator of survival as of the study closing date. Therefore, the reviewers' analyses described below were based upon censoring observations at the time of the last ascertainable follow-up.

The Kaplan-Meier survival curve for mortality is shown in Figure 5 below. A subject's data were censored at the time of the last known dose of study drug, the last follow-up visit, or at the closing date of the study. Differences between treatment groups were assessed with a log-rank test. Statistical analyses were performed for the full period of available follow-up and for the protocol-specified (24 month) period of follow-up. Differences in event rates at 24 months were also assessed using a χ^2 test. Results of statistical analyses are shown in Table 8 below.

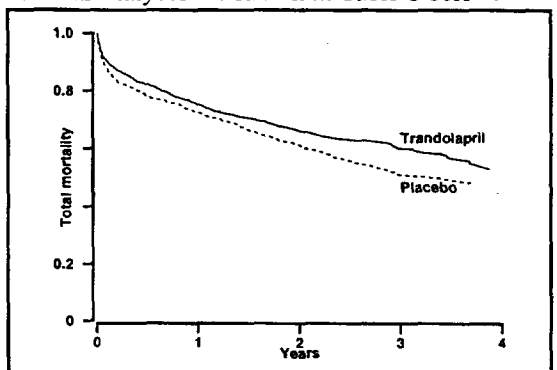


Figure 5. Total mortality.

Table 8. Statistical analyses of mortality.

	Log-rank p[a]		Relative risk (95% CI)		Events over 24 months		
	2 year	All	2 year	All	Placebo (%) N=873	Trandol (%) N=876	Two-sided χ^2 p
All-cause mortality	0.0188*	0.0028*	0.840 (0.712 to 0.990)	0.807 (0.693 to 0.939)	308 (35)	261 (30)	0.014
Stratified by WMI	0.0245	0.0034	0.847 (0.719 to 0.999)	0.811 (0.697 to 0.944)			
Stratified by WMI, center	0.0211*	0.0029*	0.840 (0.710 to 0.994)	0.803 (0.688 to 0.939)			
Cardiovascular mortality	0.0165*	0.0058*	0.811 (0.669 to 0.984)	0.793 (0.661 to 0.950)	230 (26)	188 (22)	0.017
Stratified by WMI	0.0218*	0.0076*	0.820 (0.676 to 0.994)	0.799 (0.667 to 0.958)			
Sudden death	0.0746	0.0254	0.817 (0.621 to 1.075)	0.775 (0.600 to 1.002)	113 (13)	93 (11)	0.131
Stratified by WMI	0.0901	0.0304	0.829 (0.630 to 1.091)	0.783 (0.606 to 1.011)			

a. One-sided p-value for active treatment better than placebo. *Statistically significant at α=0.0225 for all-cause mortality or α=0.025 for other comparisons.

The result for all-cause mortality was statistically significant compared with the threshold for significance given in Table 1 on page 4.

Because of the lack of the usual supporting documentation for subjects believed to have survived to the end of the study, the reviewers also analyzed time to death or 'loss to follow-up', based upon dates in the dataset. When mortality plus loss to follow-up[9] was analyzed, there was no statistical significance to the difference between treatment groups.

2.6.1.2. Cardiovascular mortality

The Kaplan-Meier survival curve for cardiovascular deaths (causality classified by the investigator) is shown in Figure 6 below. A subject's data were censored at the time of the last known dose, the last follow-up visit, the date of death from non-cardiovascular causes, or the closing date of the study.

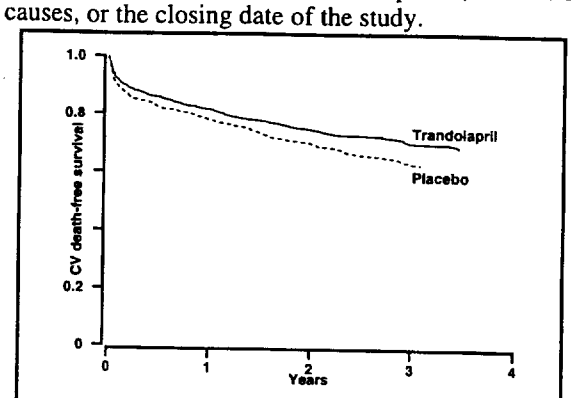


Figure 6. Cardiovascular death-free survival.

2.6.1.3. Sudden death

The Kaplan-Meier survival curve for sudden deaths (protocol-specified as death within 1 hour of onset of symptoms) is shown in Figure 7 below. A subject's data were censored at the time of the last known dose, the last follow-up visit, the date of death >1 hour after symptoms, or the closing date of the study.

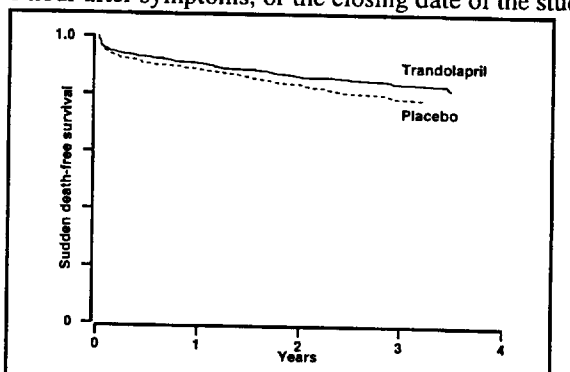


Figure 7. Sudden death-free survival.

2.6.1.4. Risk factors

Subjects who died were compared with the randomized population with respect to some potential risk factors, as shown in Table 9 below. The two treatment groups did not differ significantly with respect to these factors. Compared with the randomized population, the subjects who died were, on average, a few years older, a little more likely to have had a previous myocardial infarction, a little less likely to have had an anterior myocardial infarction, and they were substantially less likely to have received thrombolytic therapy.

The estimated death rate and relative risk (based on the proportional hazards model) were calculated separately for males and females, as shown in Table 10 below. The data show a numerically higher mortality rate in women; the power is perhaps inadequate to determine if a clinically significant difference exists in the benefit of treatment.

---

[9] This is less conservative than the usual test which is applied to mortality analysis—i.e., assume lost control group subjects lived to the closing date and lost active group subjects died at the time of loss to follow-up.

Table 9. Potential risk factors for mortality.

	All rand N=1749	Deaths		
		Plcbo N=369	Trand N=304	All N=673
Age (±SD)	68±11	70±12	72±10	71±11
Weight (±SD)	75±13	74±14	74±13	74±14
Male (%)	71	69	67	68
Previous MI (%)	36	40	43	41
Q-wave MI (%)	65	60	57	58
Anterior MI (%)	46	41	36	39
Thrombolysis (%)	44	33	34	33
WMI (±SD)	1.02±0.22	0.95±0.19	0.97±0.36	0.96±0.28

Table 10. Estimated death rate and relative risk by sex.

	Placebo			Trandolapril			Proportional Hazards Relative Risk (95% Confidence)
	N	Deaths		N	Deaths		
		n	%		n	%	
Males	621	256	41	627	203	32	0.776 (0.645 to 0.933)
Females	252	113	45	249	101	41	0.890 (0.680 to 1.164)

The estimated death rate and relative risk (based on the proportional hazards model) were calculated separately for different age groups, as shown in Table 11 below. The data show a numerical increase in mortality in older subjects, and suggest that the benefit of treatment may be less in older subjects.

Table 11. Estimated death rate and relative risk by age.

	Placebo			Trandolapril			Proportional Hazards Relative Risk (95% Confidence)
	N	Deaths		N	Deaths		
		n	%		n	%	
Age<65	321	90	28	305	57	19	0.645 (0.463 to 0.899)
65≤Age<75	299	134	45	335	115	34	0.725 (0.565 to 0.930)
Age≥75	250	142	57	235	131	56	1.042 (0.822 to 1.322)

Females had a higher death rate and less of a treatment effect than did males. Older subjects also had a higher death rate and less of a treatment effect. To see if the effect of sex could be explained by differences in age, the age distribution by gender and treatment was calculated, as shown in Figure 8 below. It seems likely that much of the apparent effect of sex is actually a result of females being somewhat older at the time of their index myocardial infarction.

Randomization was stratified on the basis of baseline WMI. The estimated death rate and relative risk (based on the proportional hazards model) were calculated separately for the two WMI strata, as shown in Table 12 below. The data show a numerical increase in mortality in subjects with lower WMI, but the estimated magnitude of treatment effect is similar in the two strata.

The estimated death rate and relative risk (based on the proportional hazards model) were calculated separately for sub-groups based upon the use of thrombolytics, as

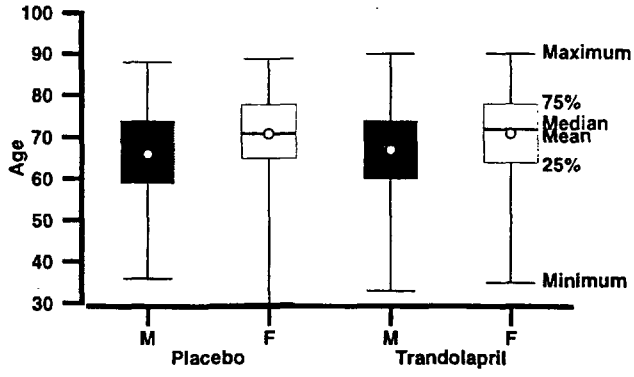


Figure 8. Age distribution by sex and treatment group.

Table 12. Estimated death rate and relative risk by baseline WMI.

	Placebo			Trandolapril			Proportional Hazards Relative Risk (95% Confidence)
	N	Deaths		N	Deaths		
		n	%		n	%	
WMI<0.8	159	104	65	146	82	56	0.803 (0.601 to 1.073)
WMI≥0.8	711	262	37	729	221	30	0.819 (0.684 to 0.979)

shown in Table 13 below. The data show an increase in mortality in subjects whose index infarction was not treated with thrombolysis, but the estimated magnitude of treatment effect is similar in the two sub-groups.

Table 13. Estimated death rate and relative risk by use of streptokinase.

	Placebo			Trandolapril			Proportional Hazards Relative Risk (95% Confidence)
	N	Deaths		N	Deaths		
		n	%		n	%	
No thrombolysis	477	245	51	472	200	42	0.794 (0.658 to 0.957)
Streptokinase	359	110	31	376	96	26	0.847 (0.644 to 1.113)

The estimated death rate and relative risk (based on the proportional hazards model) were calculated separately for sub-groups based upon whether the index infarction was Q-wave or non-Q-wave, as shown in Table 14 below. The data show an increase in mortality in subjects whose index infarction was non-Q-wave, and the estimated magnitude of treatment effect is numerically smaller for non-Q-wave infarctions.

Table 14. Estimated death rate and relative risk by Q-wave.

	Placebo			Trandolapril			Proportional Hazards Relative Risk (95% Confidence)
	N	Deaths		N	Deaths		
		n	%		n	%	
Non-Q-wave	302	145	48	298	128	43	0.886 (0.699 to 1.112)
Q-wave	564	220	39	571	172	30	0.758 (0.621 to 0.926)

The estimated death rate and relative risk (based on the proportional hazards model) were calculated separately for sub-groups based upon baseline NYHA class, as shown in Table 15 below. The data show an increase in mortality in subjects whose NYHA class was high, but the estimated magnitudes of the treatment effects cannot be reliably distinguished.

Table 15. Estimated death rate and relative risk by NYHA class.

	Placebo			Trandolapril			Proportional Hazards Relative Risk (95% Confidence)
	N	Deaths		N	Deaths		
		n	%		n	%	
NYHA I	345	100	29	366	92	25	0.863 (0.650 to 1.146)
NYHA II	367	167	46	361	141	39	0.826 (0.660 to 1.033)
NYHA III	108	63	58	107	52	49	0.870 (0.602 to 1.257)
NYHA IV	41	32	78	36	16	44	0.561 (0.308 to 1.023)

Because a substantial blood pressure difference develops between treatment groups during the course of treatment, the reviewers analyzed crude mortality by the blood pressure at the 90-day visit. The results are shown in Table 16 below. In each stratum of diastolic or systolic pressure, there was a numerically lower death rate on active treatment than on placebo, suggesting that the effects of trandolapril may not be entirely attributable to effects on blood pressure. There is a numerical trend towards a reduction in mortality with increases diastolic pressure at 90 days; the basis for this finding is unknown.

Table 16. Deaths ≥90 days by blood pressure at 90 days.

Diastolic pressure	Placebo			Trandolapril			Systolic pressure	Placebo			Trandolapril		
	N	n	%	N	n	%		N	n	%	N	n	%
≤70	146	48	33	241	51	21	≤115	112	36	32	215	43	20
71 to 80	239	63	26	220	50	23	116 to 130	207	51	25	204	47	23
81 to 89	77	20	26	53	11	21	131 to 145	112	29	26	118	21	18
≥90	184	40	22	142	24	17	≥146	215	58	27	123	27	22

2.6.2. Hospitalization

2.6.2.1. Index event

The distribution of times from onset of symptoms to hospital admission is shown in Figure 10 below (not separated by treatment group). As shown in Table 6 on page 7, subjects in the two treatment groups had a similar distribution of time from index myocardial infarction to randomization. The times from randomization to hospital discharge were compared in Figure 10 below, for subjects who survived until discharge. The dashed curves are for the placebo group.

There appears to have been no effect of treatment on the duration of the original hospitalization.

2.6.2.2. Subsequent hospitalizations

Although any hospitalization or contact with a physician was a pre-defined secondary end-point, the case report forms solicited information with regard to hospitalization only for the index myocardial infarction. The only information collected with regard to subsequent hospitalization was whether adverse events were treated by hospitalization. A total of 1722 adverse events in the placebo group and 1691 events in the trandolapril group were associated with hospitalization[10]. The number of

[10] This is a mean of 1.97 events per subject associated with hospitalization in the placebo group and 1.93 events per subject in the trandolapril group.

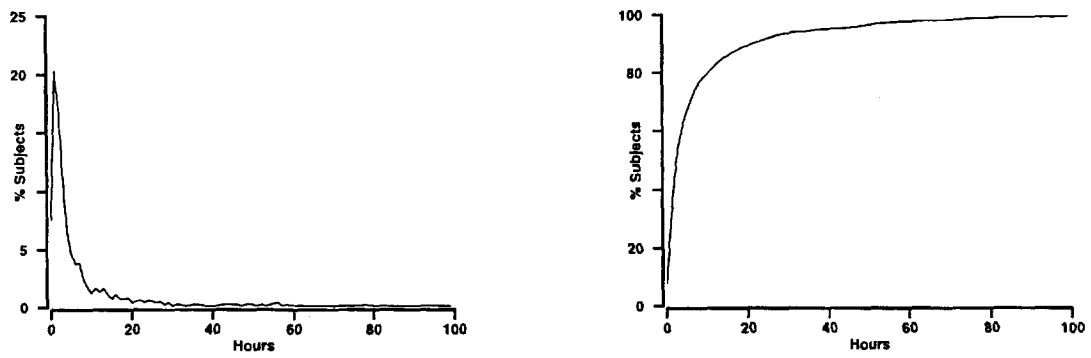


Figure 9. Distribution of delays from onset of symptoms to the original hospitalizations.
LEFT: Histogram of times from onset of symptoms to hospitalization.
RIGHT: Cumulative distribution of times from onset of symptoms to hospitalization.

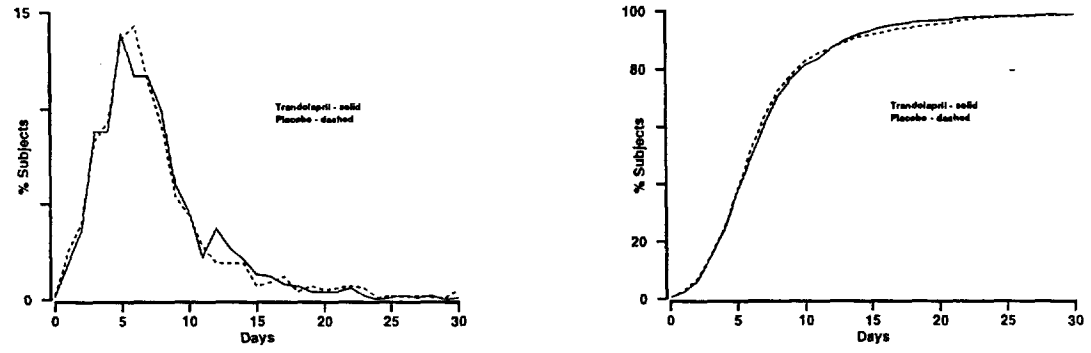


Figure 10. Distribution of durations of original hospitalizations.
LEFT: Histogram of times from randomization to hospital discharge by treatment group.
RIGHT: Cumulative distribution of time from randomization to hospital discharge.

subjects hospitalized at least once was 538 for the placebo group (62%) and 528 for trandolapril (60%). Neither the number of unique hospitalizations nor the duration of hospitalizations could be determined; the dates of the onset and resolution of the adverse events were collected, but the dates of hospitalization were not. What data there are do not suggest a significant benefit of trandolapril on hospitalization.

2.6.3. Recurrent myocardial infarction

Recurrent myocardial infarctions are described in Table 17 and Figure 11 below. Most of the myocardial infarctions reported by investigators were validated by the Reinfarction Committee. More than 50% of recurrent infarctions were not typed as Q-wave or non-Q-wave infarctions, and only about 25% were characterized as to location. Somewhat fewer recurrent infarctions were reported in the trandolapril treatment group, but the risk of reinfarction showed no consistent treatment effect (one-sided log-rank p=0.18; relative risk = 0.874 with 95% confidence limits 0.655 to 1.166[11]). The figure shows the re-infarction-free survival time (censored at time of death, last dose, or last known visit) for the placebo group (dashed line) and the trandolapril group (solid line).

2.6.4. Progression of heart failure

The reviewers' analysis began with selection of qualified events for each component of the combined end-point. Hospitalizations for heart failure were determined from the adverse events dataset (ADVERSE), with selection of subjects with adverse events labelled 'heart failure', 'left ventricular dysfunction', 'congestive heart failure', or 'cardiogenic shock', together with a treatment code indicative of hospitalization. Mortality from progression of heart failure was determined from the mortality dataset

[11] After stratification for WMI: log-rank p=0.172; relative risk=0.870 with confidence limits 0.652 to 1.161. Both analyses are based upon the available period of follow-up.

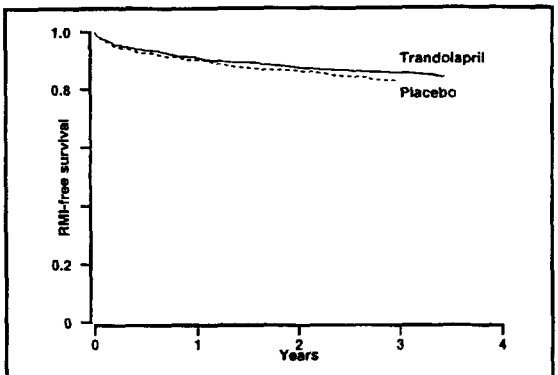


Figure 11. Recurrent myocardial infarctions.

Table 17. Recurrent myocardial infarctions.

	Events		Subjects			Confirmed events	
	Placebo N=873	Trandol N=876	Placebo N=873	Trandol N=876		Placebo N=873	Trandol N=876
Confirmation					Type		
Suspected	204	173	143	133	Q-wave	19	18
No confirmation	96	74	—	—	Non-Q-wave	58	54
Symptoms + enzymes only	62	53	—	—	Not determined	31	27
ECG changes + enzymes only	1	2	—	—	Locations[a]		
New Q-wave + symptoms only	3	0	—	—	Anterior	14	19
Any confirmation	108	99	96	89	Lateral	28	27
					Postero-inferior	11	12
					Not determined	60	46

a. Events could be associated with more than one location.

(DEATH), with selection of subjects with either an immediate cause of death or a precipitating cause of death coded as heart failure, where a re-infarction within 7 days was not indicated. Need for ACE inhibitor was determined from two sources: the concomitant medications dataset (CONMED) was searched for subjects taking an ACE inhibitor[12] for the specific indication of heart failure, and the adverse events dataset (ADVERSE) was searched for subjects with event code 0922, generally labelled as 'need for ACE inhibitor'. The breakdown of subjects located by these criteria is shown in Table 18 below.

Table 18. Progression of heart failure by component end-point.

	Events		Subjects	
	Plcbo N=873	Trand N=876	Plcbo N=873	Trand N=876
Hospitalizations for heart failure	199	176	199	168
Death from heart failure	116	94	116	94
ACE inhibitor for heart failure (CONMED)	108	67	108	66
ACE inhibitor for heart failure (ADVERSE)	50	38	50	38
Any event	—		211	175[a]

a. Two-sided χ^2 p=0.035.

12. From the list of medications, the following drugs were used by at least one subject: captopril or capoten, enalapril or renitec, ramipril or ramace, and lisinopril or zestril.

The time to first event analysis is shown in Figure 12 and Table 19 below. When analyzed with stratification by WMI, the treatment benefit was significant at 2 years and quite significant at the study end[13].

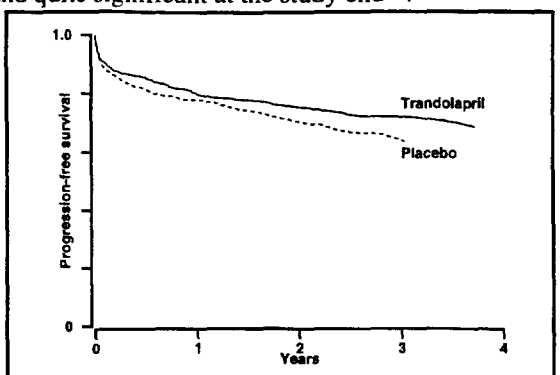


Figure 12. Time to first progression event.

Table 19. Progression of heart failure statistical analysis.

	Log-rank p[a]		Relative risk (95% CI)	
	2 year	All	2 year	All
Without stratification	0.0253	0.0104	0.819 (0.670 to 1.001)	0.800 (0.662 to 0.967)
Stratification by WMI	0.0238	0.0093	0.817 (0.668 to 0.998)	0.796 (0.659 to 0.963)

a. One-sided *p*-value for active treatment better than placebo.

2.6.5. Exercise tolerance

Exercise tolerance data were reported for 675 sessions involving 267 subjects at 9 centers. Total exercise tolerance times are shown in Table 20 below, by treatment group and time after randomization. There was, of course, no baseline assessment. Around 75% of subjects in this sub-study had measurements at around 30 days and then again at around 1 year. The last measurements of subjects were compared between treatment groups, and the result was not statistically significantly different.

Table 20. Exercise tolerance times.

	Placebo		Trandolapril	
	n	Seconds ±SD	n	Seconds ±SD
At 14 to 52 days	126	500±220	128	526±212
At 72 to 147 days	109	540±224	107	554±221
At 169 to 198 days	4	592±273	3	475±220
At 338 to 466 days	104	581±229	92	592±217

2.6.6. Arrhythmia

Holter monitoring was performed on subjects enrolled at some centers. These data do not appear in the submitted SAS datasets.

2.6.7. Wall motion index

Data from serial echocardiographic assessments of wall motion index are shown in Table 20 below. The last measurements of subjects were compared between treatment groups, and the result was not statistically significantly different.

2.6.8. Ventricular diameter

Data from serial echocardiographic assessments of ventricular dimensions—end systolic volume (ESD) and end diastolic volume (EDD)—are shown in Table 22

[13] Similar results were obtained when subjects with a 'progression' event at randomization were treated as having the event on day 1 or when these subjects were excluded from analyses.

Table 21. Wall motion index.

	Placebo		Trandolapril	
	n	WMI±SD	n	WMI±SD
At baseline	873	1.0±0.2	876	1.0±0.2
At < 110 days	550	1.1±0.2	573	1.1±0.2
At 110 to 139 days	33	1.0±0.3	28	1.2±0.3
At 140 to 243 days	517	1.1±0.3	540	1.2±0.2
At >243 days	474	1.2±0.3	474	1.2±0.2

below. The amount of follow-up was inadequate to assess the effect of treatment on ventricular dimensions.

Table 22. Ventricular dimensions.

	End systolic diameter (mm±SD)				End diastolic diameter (mm±SD)			
	Placebo		Trandolapril		Placebo		Trandolapril	
	n	ESD	n	ESD	n	EDD	n	EDD
At baseline	141	30.1±22.9	125	30.1±23.6	141	36.1±27.0	126	36.6±27.8
At < 110 days	78	42.5±8.9	60	41.5±8.2	78	53.2±7.2	60	52.0±7.8
At 110 to 243 days	34	42.3±7.7	39	42.1±8.7	34	52.9±6.7	39	52.5±8.7
At >243 days	29	40.7±15.6	20	43.7±9.2	29	50.4±16.6	20	53.5±7.7

2.6.9. NYHA class

NYHA class was apparently collected at scheduled followed-up visits, and the data appear in the VITALS dataset, although there was no interim visit case report form submitted. Table 23 below shows percentages of subjects in each class at quarterly visits over the first 2 years. When the improvement rates were compared between treatment groups using the Cochran-Mantel-Haenszel method controlling by WMI, the result was not statistically significant at α=0.05.

Table 23. NYHA class (% of subjects) by 90-day period.

NYHA class	0-89		90-179		180-269		270-359		360-449		450-539		540-629		730-719	
	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran
1	40	42	42	42	42	44	48	48	47	47	49	53	51	50	51	53
2	45	45	49	49	48	48	44	46	46	45	44	41	45	45	43	40
3	11	10	8.4	7.8	8.5	6.6	7.1	6.1	6.0	6.9	6.5	6.1	4.1	5.3	5.1	6.0
4	3.2	2.7	1.2	0.6	0.7	0.7	0.4	0.4	0.2	0.6	0.5	0.4	0.2	0.7	0.5	0.2

2.6.10. Killip class

Killip class was apparently collected at scheduled followed-up visits, and the data appear in the VITALS dataset, although there was no interim visit case report form submitted. Table 23 below shows percentages of subjects in each class at quarterly visits over the first 2 years. Although no formal analysis was performed by the reviewers, there does not appear to have been any effect of treatment on Killip class.

2.7. Safety

2.7.1. Non-cardiac deaths

Few details were recorded for subjects said to have died from non-cardiovascular causes, as shown in Table 25 below.

2.7.2. Adverse events

Characteristics of the adverse events are shown in Table 26 below. Events were not rated by seriousness.

Table 24. Killip class (% of subjects) by 90-day period.

Killip class	0-89		90-179		180-269		270-359		360-449		450-539		540-629		730-719	
	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran	Plcb	Tran
1	84	86	93	94	96	97	96	97	96	97	96	98	97	98	97	98
2	15	13	6.6	5.4	4.1	3.2	4.2	3.0	3.7	2.7	3.4	1.5	2.3	1.8	2.5	1.7
3	0.8	0.7	0.3	0.2	0.2	0.2	0	0	0	0	0	0	0	0	0	0.2
4	0	0	0.2	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 25. 'Non-cardiovascular' deaths.

Placebo				Trandolapril			
Subject	Age	Precip cause	Immed cause	Subject	Age	Precip cause	Immed cause
02-143	81	—	—	01-189	72	—	—
02-198	74	—	—	04-012	70	—	Pulmonary embolus
04-181	73	—	Cerebral damage	04-160	81	Heart failure	Pulmonary embolus
05-190	—	—	—	06-192	62	—	—
06-172	67	Heart failure	—	07-168	57	—	Cerebral anoxia sequelae
07-189	72	—	—	07-190	84	Heart failure	Pneumonia
07-194	69	—	Pneumonia	07-195	77	—	—
10-158	78	—	Pneumonia	09-122	77	—	—
11-001	82	—	—	09-130	83	—	—
11-167	73	Heart failure	Pneumonia	13-155	68	—	—
12-184	74	—	—	13-176	76	—	—
13-159	60	—	—	13-185	78	—	—
13-170	81	Heart failure	Sepsis	15-193	61	—	Aortic aneurysm rupture
15-010	64	—	GI hemorrhage	16-172	70	—	Mesenteric artery thrombus
16-166	74	—	—	20-138	69	—	—
21-182	70	Heart failure	Sepsis	21-170	76	—	—
21-193	79	Heart failure	Pulmonary embolus	22-148	70	—	—
22-140	79	—	—	23-008	75	Heart failure	Uremia
22-156	73	—	—				
22-511	64	—	—				
27-187	69	—	—				

Adverse events reported by at least 2% of subjects in the trandolapril treatment group are listed in Table 27 below. Differences between groups in the incidence of cough, dizziness, hypotension, syncope, hyperkalemia, hypertension, and reduced renal function (elevation in BUN and creatinine) are plausibly attributable to known properties of trandolapril or other ACE inhibitors.

2.7.3. Concomitant medications

Concomitant medications were captured on a case report form, apparently only through the period of the initial hospitalization. These were evaluated by treatment group and 12-digit drug code, and sorted by frequency. Table 28 below shows counts of subjects receiving specific drugs, where the drug was used by >5% of subjects in a treatment group.

The only diuretic in common use was furosemide. Its rate of usage was about 8% higher in the placebo group. The number of subjects on at least one drug for a given indication is shown in Table 29 below.

Table 26. Characteristics of adverse events.

	Plcbo N=873	Trand N=876		Plcbo N=873	Trand N=876
Severity			Drug relatedness		
Mild	5277	5820	Related	80	222
Moderate	6781	7346	Not related	10386	10270
Severe	1514	1430	Uncharacterized	6129	7095
Uncharacterized	3023	2991	Total events	16595	17585
Total events	16595	17585			
Action taken			Outcome		
None	12362	13253	Recovery	3303	3438
Decreased dose	150	314	Sequelae	3747	3850
Dose interruption	243	316	Continuing	6052	6928
Discontinuation	688	579	Disabling	34	22
Uncharacterized	3152	3125	Death[a]	451	362
Total events	16595	17585	Uncharacterized	3008	2987
			Total events	16595	17585

a. Subjects could have more than one adverse event ongoing at the time of death.

Table 27. Adverse events (>2% in the active treatment group).

	Plcbo N=873	Trand N=876		Plcbo N=873	Trand N=876		Plcbo N=873	Trand N=876
Heart failure	536	511	↓Calcium	34	41	Gout	34	28
Angina	389	389	Myalgia	27	41	Nausea	25	27
Cough	196	305	↑Creatinine	21	41	Fever	24	26
Dizziness	151	204	Bronchitis	61	40	COPD	38	25
Myocardial infarction	192	180	Diabetes	42	40	Pain	23	25
Pneumonia	210	162	↓Albumin	40	40	TIA	<2%	25
↑Uric acid	116	127	Pulmonary edema	44	38	Rash	22	24
Atrial fibrillation	132	116	Anemia	37	37	Gastric ulcer	23	24
Hypotension	59	99	Gastritis	31	37	Prostate disease	<2%	23
↑BUN	66	79	Need for ACEI	48	36	Uremia	<2%	23
Cystitis	77	71	Dyspnea	47	36	↓Platelets	<2%	22
V tachycardia	69	69	Chest pain	42	36	Flu symptoms	<2%	21
Sudden death	80	65	Hypertension	68	35	Constipation	25	20
PTCA/CABG	53	64	Death	47	35	Diarrhea	<2%	20
Dyspepsia	52	56	↑PVCs	40	35	Hematemesis	<2%	20
Syncope	29	52	SVT	38	34	Cardiac arrest	30	19
V fibrillation	69	49	Cardiogenic shock	<2%	33	Atrial flutter	<2%	19
↑Cholesterol	47	46	Intermit claudication	<2%	33	Back pain	<2%	19
↑Potassium	24	46	Stroke	28	29	Hernia	<2%	18
Bradycardia	38	41	Asthenia	23	29			

2.7.4. Laboratory data

Treatment group differences in laboratory data were examined in plots of changes from baseline, as shown in Figure 13 to Figure 19 below. The analysis is most sensitive to systematic changes in a parameter over time, but has the shortcoming of all but hiding significant outliers. Placebo group plots are in the left column and active treatment group plots are in the right column. Both plots are scaled to the same limits and encompass, in all but one case, the full range of laboratory results for all subjects.

Table 28. Concomitant drugs during hospitalization.

	Placebo N=873	Trandol N=876		Placebo N=873	Trandol N=876
Nitroglycerin	821	859	Penicillin	119	99
Aspirin (SR)	822	844	Terbutylene	130	90
Furosemide	794	729	Halcion	82	78
Isosorbide dinitrate	702	723	Heparin	90	77
Potassium chloride	681	613	Pondocillin	62	70
Bendrofluazide (antihypertensive)	385	418	Vepicombin (?)	67	61
Cimetidine	343	343	Magnesia	48	57
Digoxin	374	329	Sotalol	45	57
Morphine	229	257	Atropine	55	54
Paracetamol	183	198	Apozepam	55	53
Nicomorphine	199	194	Levomepromazine	51	52
Metoprolol	170	180	Atenolol	43	51
Ketobemidone (pain)	147	176	Benzodiazepin	58	51
Metoclopramide (gastrointestinal)	150	171	Captopril	56	47
Lidocaine	166	147	Nitrazepam	43	47
Diltiazem	145	134	Dobutamine	44	45
Verapamil	157	127	Ibuprophen	38	44
Erythrityl tetranitrate (angina)	106	127	Spironolactone	43	23

Table 29. Subjects on drugs by indication.

	Placebo N=873	Trandol N=876		Placebo N=873	Trandol N=876
Myocardial infarction	821	838	Arrhythmia	370	336
Heart failure	709	693	Adverse event	73	57
Angina	668	690	Other	785	773
Concomitant disease	667	651			

There were, in both treatment groups, decreases in ALAT, ASAT, bilirubin, glucose, urea, and leukocytes, and increases in albumin, calcium, cholesterol, HDL cholesterol, LDL cholesterol, potassium, protein, sodium, triglycerides, and uric acid, but no treatment related differences were observed.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

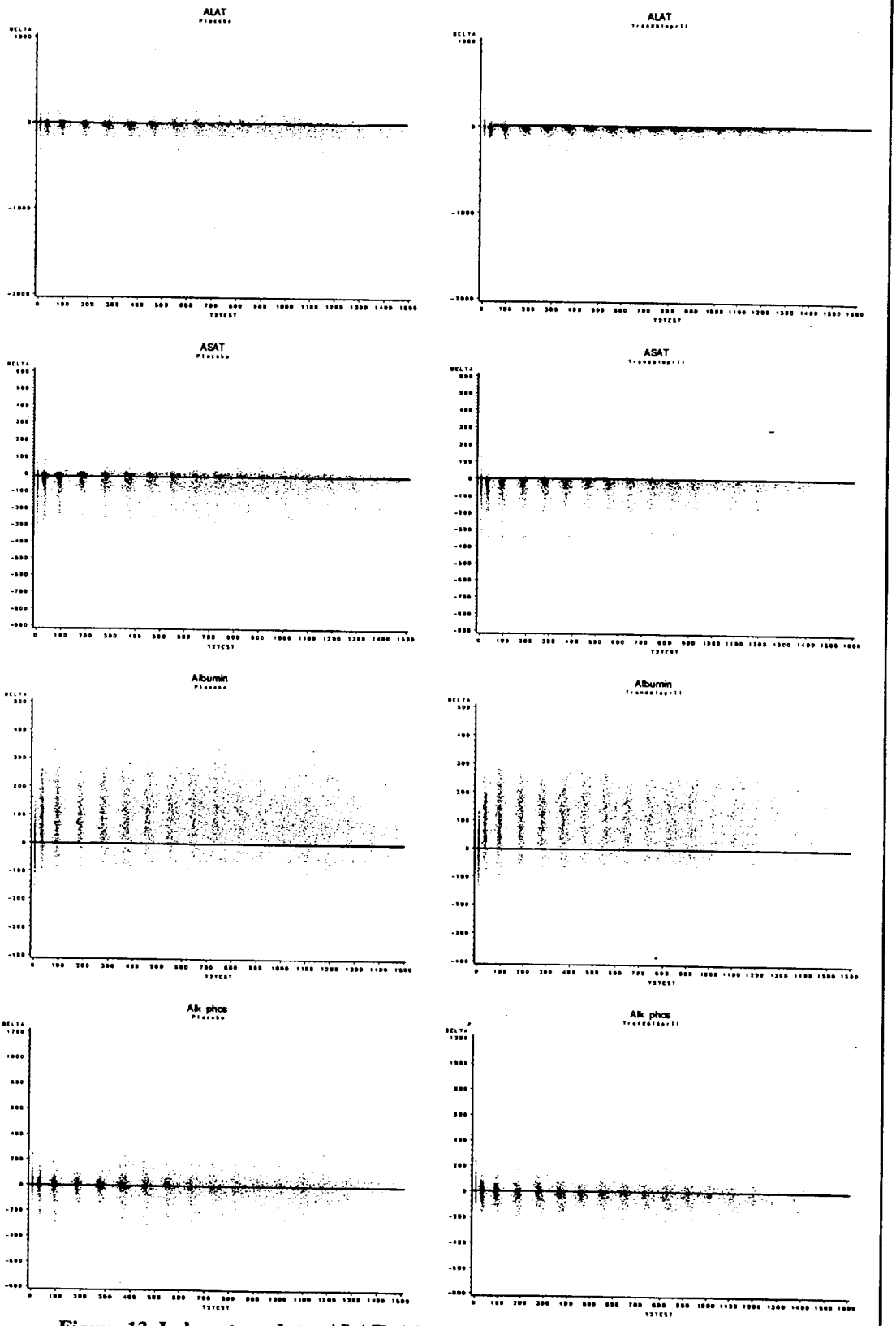


Figure 13. Laboratory data: ALAT, ASAT, albumin, and alkaline phosphatase.

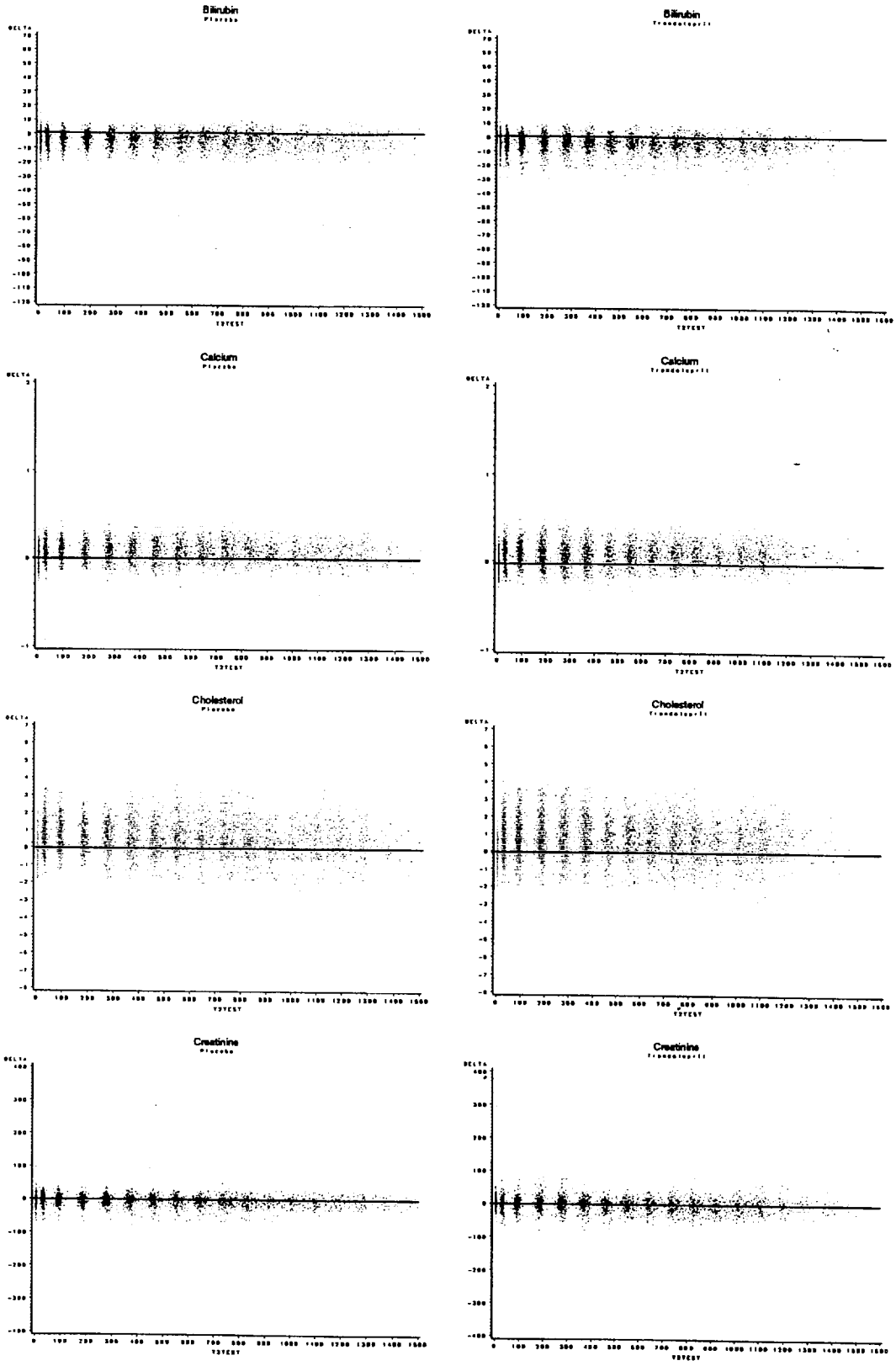


Figure 14. Laboratory data: bilirubin, calcium, cholesterol, and creatinine.

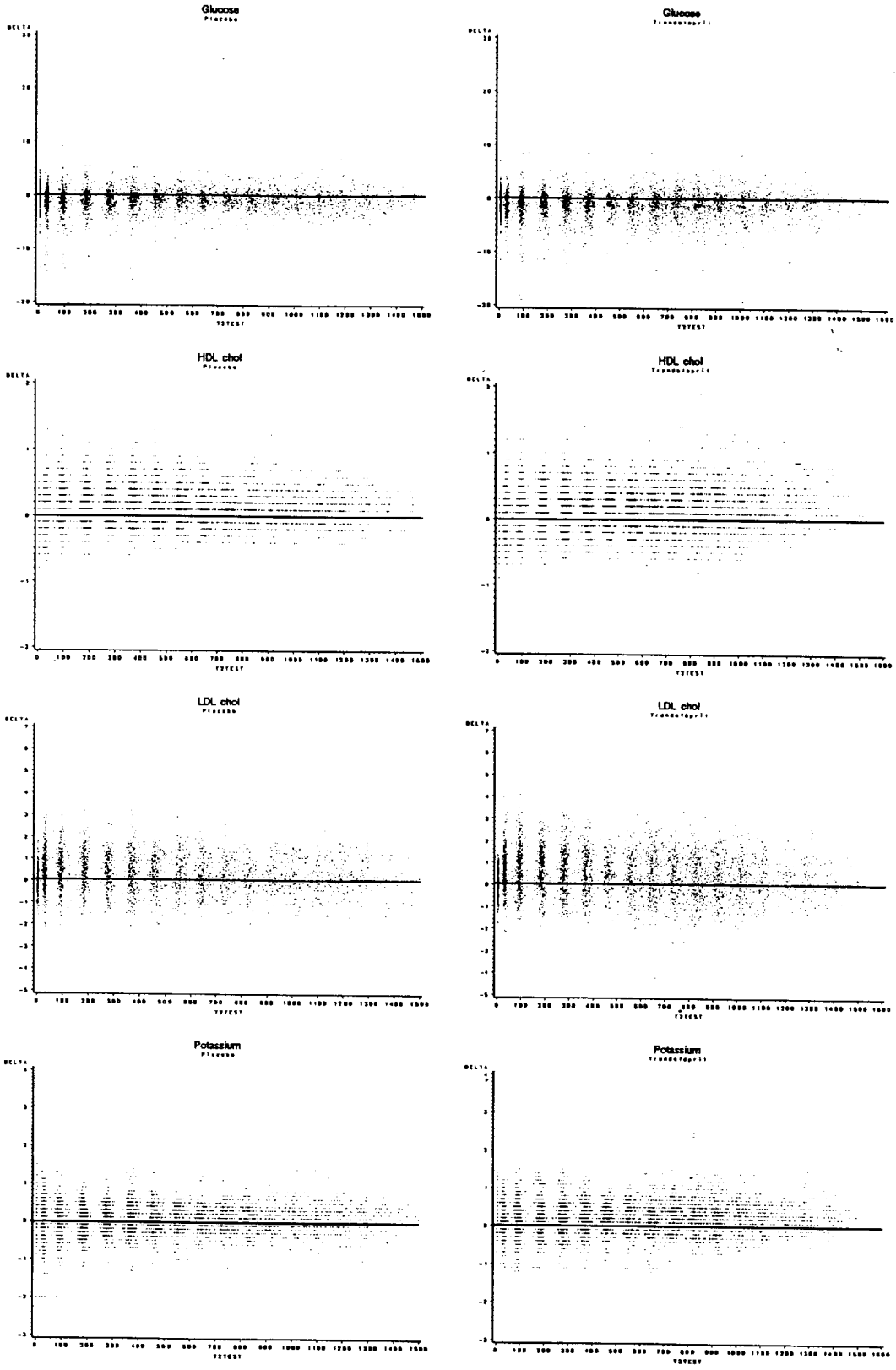


Figure 15. Laboratory data: glucose, HDL cholesterol, LDL cholesterol, and potassium.

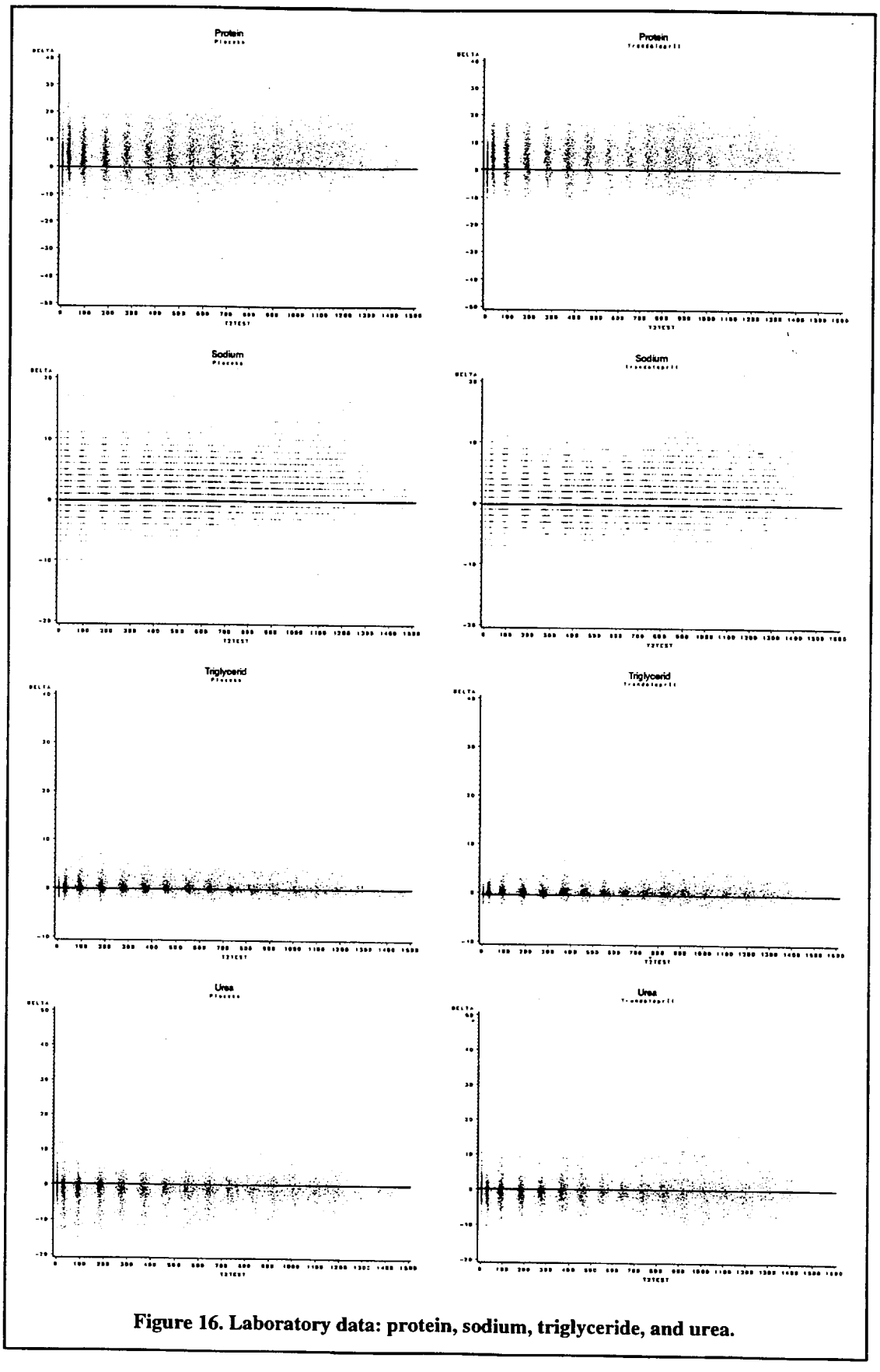


Figure 16. Laboratory data: protein, sodium, triglyceride, and urea.

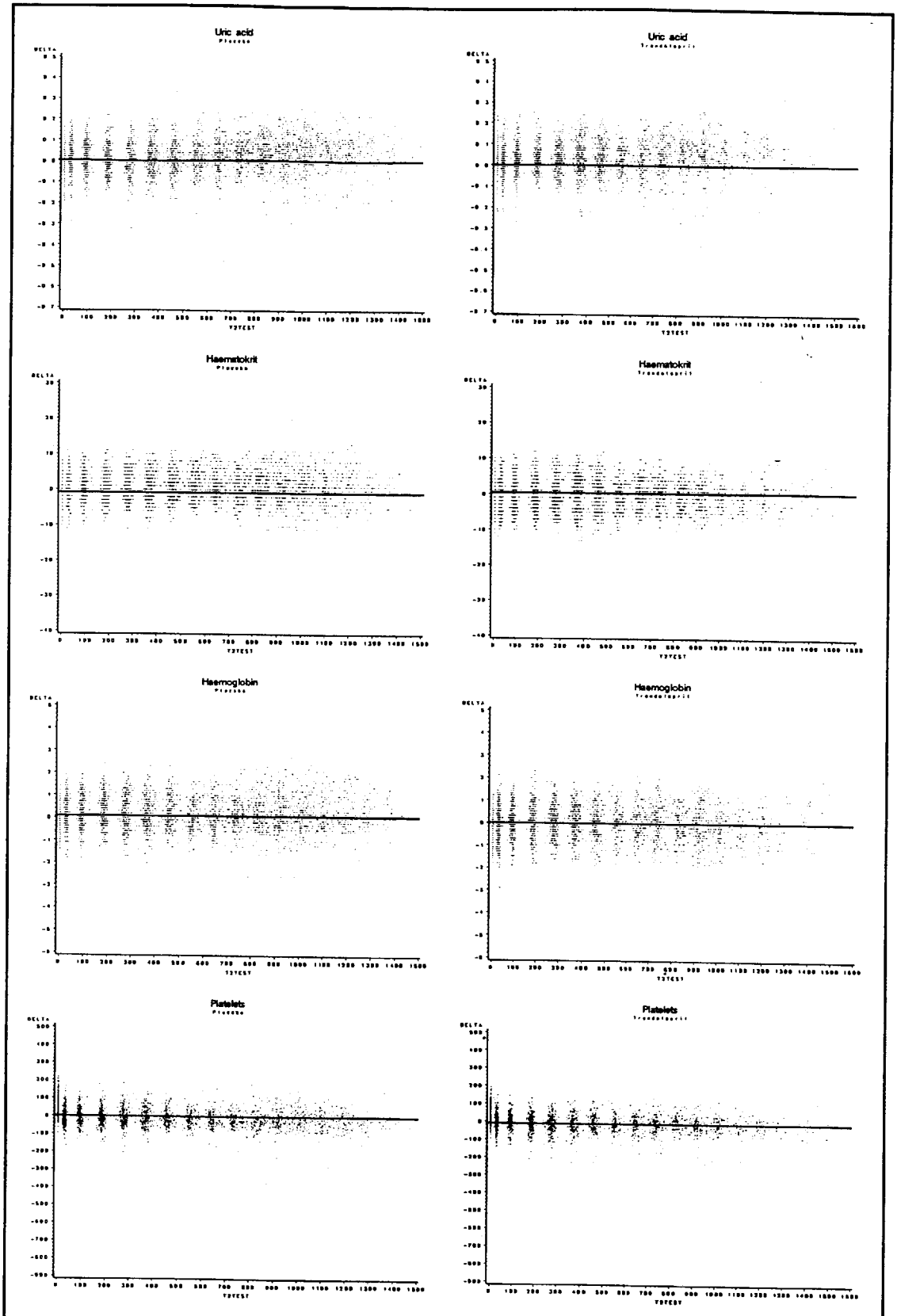


Figure 17. Laboratory data: uric acid, hematocrit, hemoglobin, and platelets.

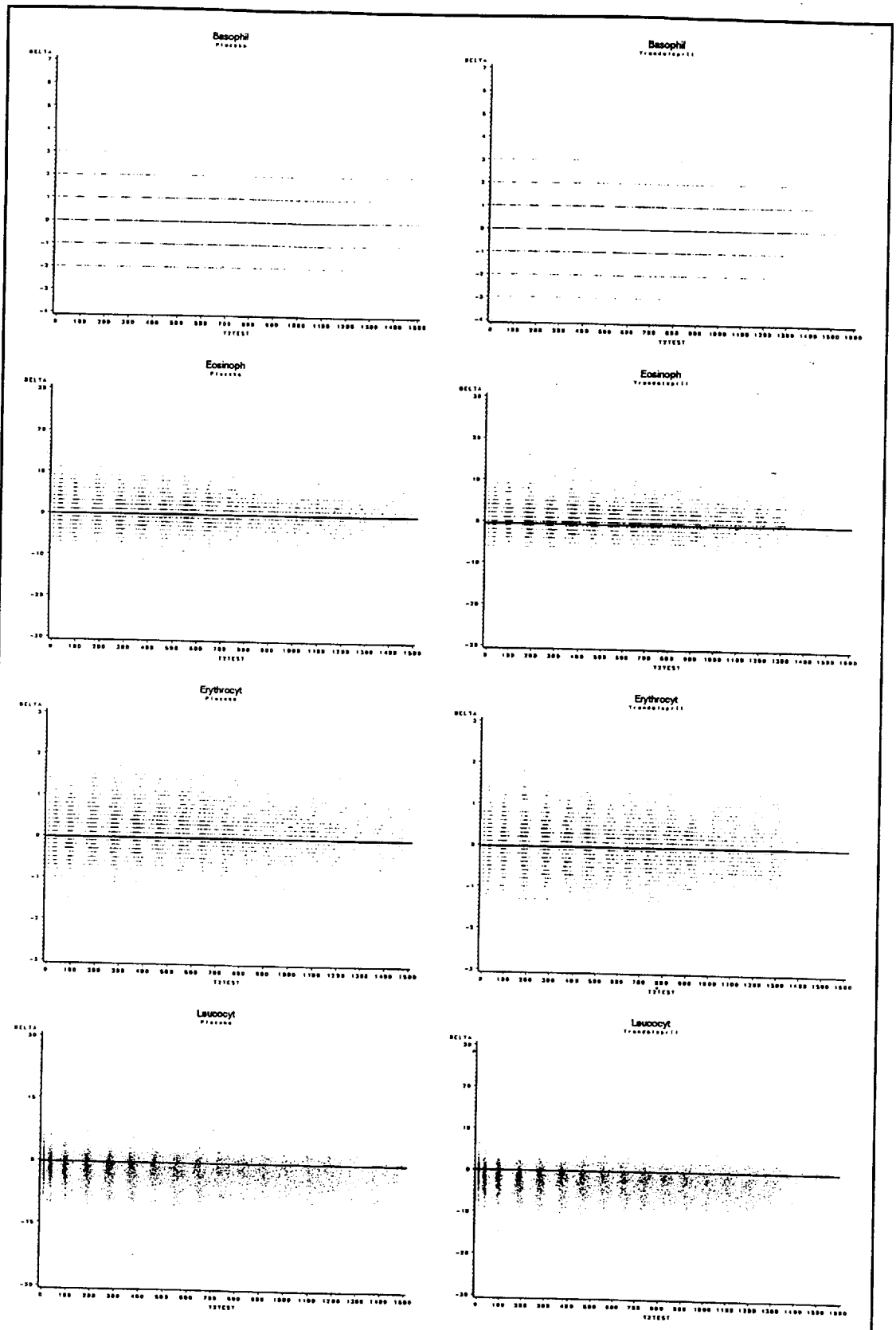


Figure 18. Laboratory data: basophils, eosinophils, erythrocytes, and leukocytes.

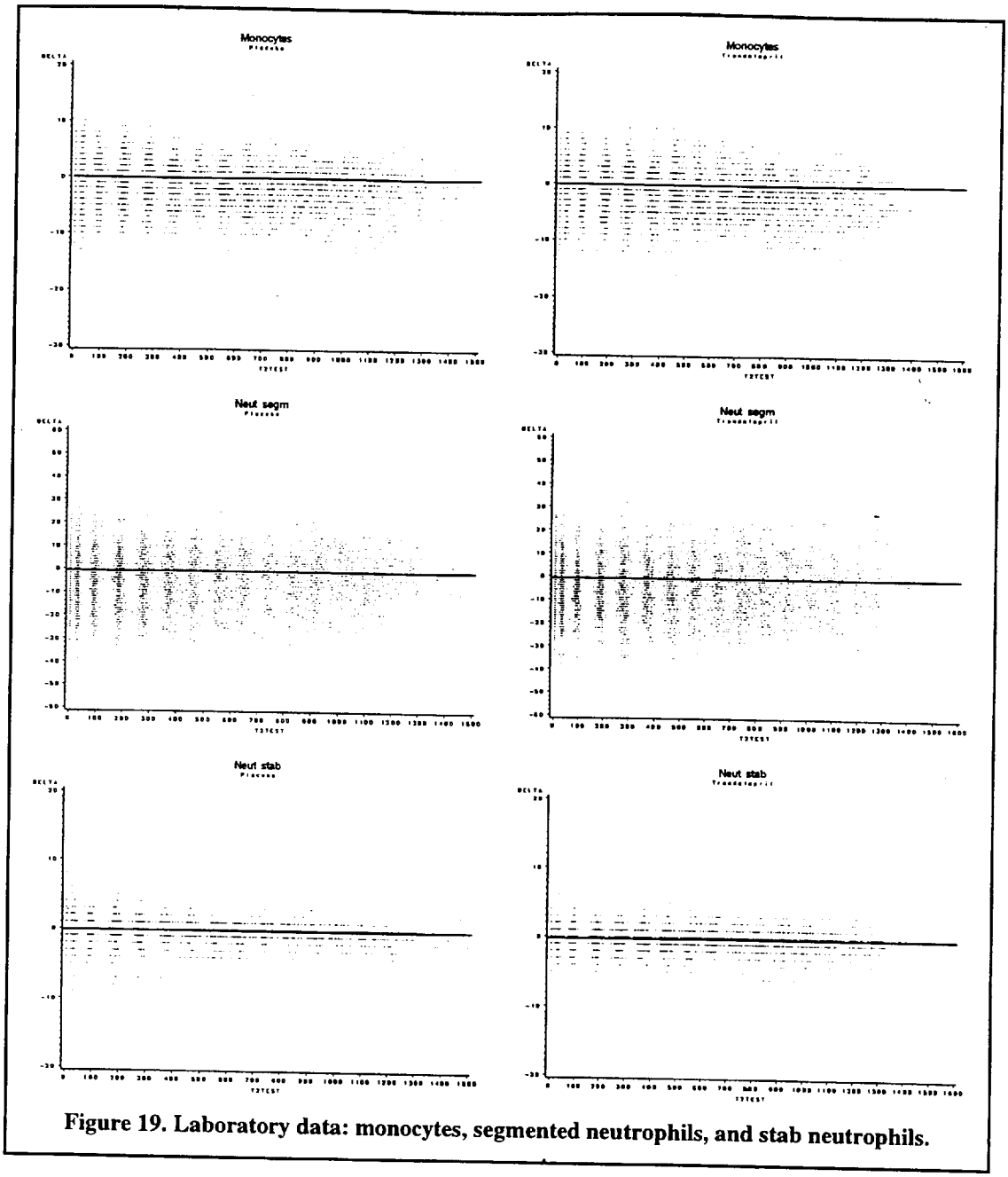


Figure 19. Laboratory data: monocytes, segmented neutrophils, and stab neutrophils.

Subjects with at least one laboratory measurement outside an extended normal range, but within normal range at baseline, were counted, as shown in Table 30 below. Compared with the placebo group, the active treatment group had a higher incidence of abnormally low values for hematocrit, hemoglobin, and RBC, and a higher incidence of abnormally elevated creatinine, potassium, BUN and uric acid. Abnormalities in potassium, creatinine, and BUN are probably a reflection of known renal effects of this class of drugs. Abnormalities in hematocrit and hemoglobin have been reported with enalapril, where they are of unknown significance; there was no excess in hemorrhagic events or strokes in the trandolapril treatment group.

Table 30. Counts of subjects with deviations from the normal range in laboratory data.

	Lower limit			Upper limit				Lower limit			Upper limit		
	Thresh	Plcbo	Trand	Thresh	Plcbo	Trand		Thresh	Plcbo	Trand	Thresh	Plcbo	Trand
ALAT	—	—	—	150 U/L	14	10	Triglyceride	—	—	—	5 mM	63	56
ASAT	—	—	—	165 U/L	3	7	Urea	—	—	—	8 mM	112	161
Albumin	400 µM	14	16	—	—	—	Uric acid	150 µM	12	9	450 µM	181	225
Alk phos	—	—	—	420 U/L	30	19	Hematocrit	35%	80	100	52%	27	13
Bilirubin	5 µM	154	147	35 µM	6	8	Hemoglobin	7.0 mM	67	78	10.5 mM	25	24
Calcium	1.8 mM	1	0	3.0 mM	0	0	RBC	3.7/pL	67	100	5.9/pL	19	5
Cholesterol	3.1 mM	0	0	6.2 mM	246	289	Platelets	100/nL	11	16	450/nL	47	31
Creatinine	—	—	—	180 µM	20	51	WBC	3/nL	5	3	12/nL	57	50
Glucose	2.5 mM	10	12	14 mM	30	25	Basophil	—	—	—	2%	54	67
HDL-chol	—	—	—	2 mM	34	28	Eosinophil	—	—	—	5%	205	220
LDL-chol	—	—	—	4.2 mM	231	255	Lymphocyte	15%	39	55	50%	144	160
Potassium	3.5 mM	46	23	5.0 mM	68	104	Monocyte	—	—	—	11%	41	51
Protein	50 g/L	1	1	—	—	—	Neutr segm	45%	173	175	75%	110	106
Sodium	129 mM	12	10	146 mM	10	9	Neutr stab	—	—	—	5%	11	22

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

3. Summary

3.1. Trial design

This was a well-designed and well-controlled mortality study conducted at multiple centers in Denmark. The most serious flaw, and one it shares with most similar studies, is that it provides no information concerning the appropriateness of the dose selected. The case report forms did not capture data adequate to properly evaluate heart failure hospitalizations, and data from the arrhythmia sub-study were not submitted. A substantial amount of information was to be obtained during the initial hospitalization for the index myocardial infarction, but much less data were collected at subsequent follow-up visits, a problem which further complicates interpretation.

3.2. Trial conduct

Very few subjects were apparently enrolled in contravention of pre-specified criteria; these are not likely to have affected the study outcome. As expected for a trial of this size, the baseline differences between the two treatment groups were small. The great majority of subjects were able to be titrated to the target dose for the active drug.

In contrast to other major mortality trials, 18% of subjects (309 of 1749) did not have mortality status for the full prospectively defined period of follow-up, as far as can be determined from the submitted data. Were this to be considered a significant failing, one might consider (1) asking for better documentation of the request made to the Danish Home Office for mortality status, (2) making some independent assessment of the quality of the data collected by the Danish Home Office, or (3) auditing investigative sites for medical records of subjects believed to have survived to the closing date.

The most striking difference between the study population and US target population is that the study group was essentially all Caucasian. There were several differences in the treatment of subjects in this study compared with usual US practice: (1) Fewer than 50% of subjects received thrombolytic treatment, and of those who did, more than 90% received streptokinase. (2) Only about one-sixth of subjects received a β-blocker. (3) Hypertension was not very aggressively treated.

3.3. Efficacy results

The primary end-point was all-cause mortality at 24 months. The reviewers' analyses are consistent with a statistically and clinically significant benefit of treatment on mortality at 24 months or the full period of actual follow-up. This result was, however, critically dependent upon how subjects with less than the protocol-specified period of follow-up were handled. An analysis of time to death or loss to follow-up showed no statistically significant benefit for trandolapril. In comparison, other major mortality trials have had so much better follow-up for mortality that their results were completely insensitive to handling of losses to follow-up.

The treatment effect was substantially a reduction in cardiovascular death. There was a non-statistically significant treatment-related reduction in the risk of sudden death.

Older subjects and those with a low baseline WMI had a high mortality and less of an apparent benefit of treatment.

Within the first 90 days, a mean blood pressure difference of approximately 7/4 mmHg developed between the treatment groups, and this difference was maintained throughout the remainder of the study. This time course roughly corresponds to that for the development of differences in all-cause mortality. Half of the placebo subjects

and one-third of trandolapril subjects were hypertensive at follow-up visits from 90 days after randomization to the end of the study.

The distribution of times in hospital for the index myocardial infarction were very similar in the two treatment groups. The two groups also had similar proportions of subjects subsequently hospitalized at least once, but the numbers of hospitalizations could not be compared.

The risk of reinfarction was similar in the two treatment groups.

Progression of heart failure was based upon death attributed to heart failure (more than 7 days from a recurrent myocardial infarction), hospitalization for heart failure, and the use of an ACE inhibitor for heart failure. For each component, there was a numerical benefit associated with treatment with trandolapril. The overall time to first event analysis demonstrated a significant benefit of active treatment.

Around 20% of subjects participated in periodic assessment of exercise tolerance. Exercise times were similar in the two treatment groups.

Another sub-study involved periodic Holter monitoring on subjects enrolled at certain centers. These data were not submitted.

Echocardiographic assessment of the wall motion index was performed serially. At no time was there a significant difference between treatment groups.

End systolic and end diastolic ventricular diameters were measured serially. At no time were there significant differences between treatment groups.

An analysis of NYHA class and Killip class demonstrated no effect of treatment.

3.4. Safety results

Causes of death were similar in the two treatment groups, and were those expected in the population studied.

Adverse events which were more common in the active treatment group—cough, dizziness, hypotension, elevated potassium, and elevated creatinine or BUN—were predictable for an ACE inhibitor.

3.5. Context

3.5.1. ACE inhibitors for heart failure

Other ACE inhibitors have been studied in the disease spectrum which runs from asymptomatic left ventricular dysfunction to NYHA class IV heart failure, in populations substantially or completely post-myocardial infarction. Some of the principal results of these studies are described in Table 31 below. The nominal study results are given; not all of these 'findings' resulted in labelling changes.

The recent approval for ramipril is, arguably, the weakest, with only the mortality effect being mentioned in the product label. Other findings judged too weak to include in label were improvements in exercise tolerance and hemodynamics.

The TRACE study differs somewhat in design from other post-myocardial infarction studies. SAVE included subjects with left ventricular dysfunction, measured with a different technique, but excluded subjects with overt heart failure. AIRE recruited subjects who were all symptomatic. The TRACE study subjects all had left ventricular dysfunction and ranged from asymptomatic to NYHA class IV.

There are some other reasons to be cautious about extrapolation of these results to the population at large. (1) The subject population was entirely Caucasian. (2) The

Table 31. Studies of other ACE inhibitors.

Drug	Study	Population	Findings[a]
Enalapril	SOLVD-T	65% previous MI symptomatic CHF	↓mortality ↓CHF mortality ↓MI ↓CHF hospitalizations
	SOLVD-P	80% previous MI LVEF ≤35% Asymptomatic	Ømortality ↓CHF hospitalization ↓progression to CHF
	VHeFT-II (+control)	50% previous MI LVEF<45% Symptomatic	↓mortality ↓sudden death
	Consensus-I	50% previous MI NYHA class IV	↓mortality
	Consensus-II	Acute MI	Ømortality ØCHF hospitalization ØMI
	Other	'Heart failure'	↓SVR, ↓PAWP, ↓heart size, ↑CO, ↑ETT, ↓NYHA class, ↓symptoms
Captopril	BHJ '93	Acute MI	↓LVEDV ↓LVESV ØETT
	SAVE	Acute MI LVEF≤40%	↓mortality ↓CHF hospitalization ↓symptoms ↓MI
	Other	'Heart failure'	↓SVR, ↓PAWP, ↓PVR, ↑CO, ↑ETT
Lisinopril		Acute MI	↓mortality
	Various	'Heart failure'	↓SVR, ↓PAWP, ↑CO, ↓symptoms, ↓NYHA class
Quinapril	Various	'Heart failure'	↓SVR, ↓PAWP, ↑CO, ↑ETT, ↓symptoms, ↑QOL, ↓NYHA class
Fosinopril	Various	'Heart failure'	↓SVR, ↓PAWP, ↑CO, ↑SV, ↑ETT, ↓symptoms, ↓NYHA class, ↓CHF hospitalizations
Ramipril	AIRE	Heart failure post-MI	↓mortality ↓CHF hospitalization ↓symptoms

a. Ø=no effect; ↓=decrease in the active treatment group relative to control; ↑=increased in the active treatment group.

majority of subjects received no thrombolysis (42% in TRACE vs. 59% in AIRE); of those who did receive a thrombolytic, the vast majority received streptokinase. (3) Only 16% of TRACE subjects were on β-blockers, compared with 22% in AIRE and 36% in SAVE. (4) It is not clear whether revascularization procedures were available in the period between the presenting myocardial infarction and randomization. In TRACE, only 6.7% of subjects underwent PTCA or CABG during the entire period of follow-up[14]. (5) Survivors' blood pressures rose significantly in the weeks following the index myocardial infarction, with a substantial number of subjects having a blood pressure most US physicians would consider worthy of treatment. (6) Follow-up out to the protocol-specified 24-month end-point was missing from the dataset for hundreds of subjects[15].

[14] While data on the rates of usage of PTCA and CABG post-myocardial infarction are not known to the reviewers, numerous articles attest to its large and growing popularity. As a primary treatment, several studies place its one-year survival value in a range comparable to thrombolytic therapy. In GUSTO (only 56% US), the revascularization rate was >22% at 30 days (8 to 9% CABG, 22% PTCA on first cardiac catheterization, 8% on second cardiac catheterization).

The low rate of usage of thrombolytics can be placed in some perspective. Streptokinase is labelled for use up to 24 hours after infarction; 91% of TRACE subjects were admitted to a coronary care unit within 24 hours of the onset of symptoms, and 82% were admitted in the first 12 hours[16]. French et al.[17] have reported a 53% rate of eligibility for thrombolysis in a prospective series of about 1000 definite or probable myocardial infarctions at 4 centers in New Zealand. These subjects had an incidence of admission within 12 hours of 85% and an incidence of ST elevation of about 62%; corresponding rates for TRACE were 82% and 60%, respectively. In the New Zealand study, 82% of subjects considered eligible, i.e. admission within 12 hours and ST elevation, or 45% overall, received thrombolysis, which compares with 42% in TRACE.

3.5.2. Other studies with trandolapril

During the course of evaluation of the NDA submission for trandolapril for hypertension, it became apparent that some studies were not adequately reported by the sponsor. The sponsor provided some description of known studies in submissions to the NDA dated 30 June 1995 and 7 February 1996. From these lists, the studies listed in Table 32 below appear to have been pertinent to the evaluation of trandolapril for a post-myocardial infarction or heart failure indication[18].

Table 32. Other potentially pertinent studies of trandolapril.

Study	Description
F/88/570/34	CHF, renal hemodynamics
NL/89/570/84	CAD, hemodynamics
GB/89/570/70	CHF
FF/90/570/99	Chronic CHF, comparison with enalapril
UK/91/570/119	CHF
J/92/570/180	CHF
S/93/570/186	Recent MI and reduced LVF, neurohormones
ZA/91/570/154	CHF, pharmacokinetics
UK/91/570/171	CHF, pharmacokinetics
CDN/89/570/75	CHF, hemodynamics
NL/89/570/81	CAD, coronary hemodynamics
NL/89/570/81B	CAD, open safety evaluation
NL/89/570/84B	CAD, open safety evaluation
UK/91/570/120	Acute MI, LV function
I/91/570/139	CHF, antiarrhythmic effects
UK/91/570/130	Chronic CHF, comparison with captopril and nitrates
F/91/570/155	Acute CHF, dose-ranging
UK/91/570/160	LVD after cardiac surgery

Perhaps in addition to these, but perhaps one of the UK or GB studies listed above, is an unreported but published study: Walsh JT, et al., 1995. Failure of effective treatment for heart failure to improve customary activity. *Br. Med. J.* **74**(4): 373-376[19].

---

15. There are, as noted in this review, metadata indicative of complete ascertainment of mortality. If one does not have confidence in the metadata, then it is appropriate to compare the hundreds of subjects 'lost to follow-up' with missing follow-up in 2 out of 2569 subjects in SOLVD-T, 7 out of 4228 subjects in SOLVD-P, or 1 out 1986 subjects in AIRE.
16. See Figure 10 on page 14.
17. French JK, et al. 1996. Prospective evaluation of eligibility for thrombolytic therapy in acute myocardial infarction. *Br. Med. J.* **312**:1637-1641.
18. Not included in this list are studies, some of which were described by the sponsor as being for indications other than hypertension, about which so little is known that their pertinence to this indication cannot be guessed.

The sponsor did not submit reports for any of the above named studies with this efficacy supplement. The Division provided some guidance concerning the form of submission of the TRACE study results, but there was no discussion pertaining to other studies.

3.6. Recommendation

The TRACE study demonstrated a benefit of treatment upon its primary end-point, all-cause mortality, when observations were censored at the time of apparent loss to follow-up. Among potentially corroborative secondary end-points, only time to a combined end-point of progression of heart failure was somewhat supportive; NYHA and Killip classes, the incidence of hospitalizations, the incidence of recurrent myocardial infarctions, exercise tolerance, wall motion index, and ventricular dimensions provided no additional support. This situation is most similar to the support for ramipril for heart failure post-myocardial infarction. Most deaths were considered cardiovascular in nature; the benefit of treatment was comparably evident for all-cause and cardiovascular mortality. Second, there are problems extrapolating the results of the TRACE study to the US; the conditions of the TRACE study do not match well with practices here, with respect to the ethnic mix, the use of β-blockers, the use of thrombolytic agents, the use of revascularization procedures, and the aggressiveness of control of blood pressure. Finally, there is the problem of interpreting the results of TRACE when there appear to be at least 18 studies—all non-IND—conducted in a comparable heart failure or myocardial infarction population, but never submitted for review. The reviewers propose that this application is 'approvable', pending satisfactory follow-up for mortality and submission and review of missing studies, but only for inclusion in the label of a description of the trial. Differences in practices with regard to the treatment of myocardial infarction render it impossible to conclude that the results of the Danish TRACE study would be manifest in US clinical practice. Therefore no new indication for trandolapril should be granted.

APPEARS THIS WAY
ON ORIGINAL

[19] This brief publication refers to 18 subjects, some of whom were in a study comparing captopril with ibopamine, and some were in a study comparing trandolapril with isosorbide mononitrate. Its only utility is as an indicator for an unreported study of trandolapril.

APR 25 1997

CONFIDENTIAL REVIEW

ENVIRONMENTAL ASSESSMENT -- NDA 20-528 S-001

1, 2 and 4 mg Mavik (trandolapril) Tablets
Knoll Pharmaceutical Company
Efficacy Supplement
(Treatment of Post Myocardial Infarction Left Ventricular Dysfunction
or Post Myocardial Infarction Heart Failure)

Submission Type	Doc Date	CDER Date	Assigned Date	Completed
Suppl Amend	Mar 25, 97	Mar 31, 97	April 7, 97	April 25, 97
Suppl Amend (fax)	Apr 23, 97		Apr. 25, 97	April 25, 97

Brief History:
The preparation of an Environmental Assessment (EA) is required for an efficacy supplement to an existing NDA. Knoll Pharmaceutical Company states that the only changes described in the supplement are the new indications namely, (1) treatment of post myocardial infarction left ventricular dysfunction and (2) treatment of post myocardial infarction heart failure. The indication approved in the original NDA was hypertension.

The applicant refers to the FONSI for the same active moiety, trandolapril, prepared by Florian Zielinski and approved by Nancy Sager on April 17, 1996. The first three (3) pages of the FONSI are attached.

The only change in the original EA is due to an increase in the production and use of the drug substance for the additional indications. The original estimate (April 4, 1996) of the total annual market volume in the fifth year after NDA approval (MV_t) was stated to be The revised MV_t estimate provided by FAX on April 23, 1997 is for all indications.

Evaluation:
It is well known that trandolapril, a pro-drug, is extensively and rapidly metabolized in the liver to the diacid, trandolaprilat. The Maximum Expected Environmental Concentration (MEEC) is well below 1 part per billion.

Summary: No significant impact expected due to approval of the supplement.

Florian Zielinski 4/25/97
Florian Zielinski
Review Chemist
April 25, 1997

Distribution:
Original NDA file 20-528 S-001
HFD 110 Division File
HFD 110 Florian Zielinski
HFD 110 CSO, Kathleen Bongiovanni
Initialed by RJ Wolters

4/25/97

CONF.

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

MAVIK TABLETS

(trandolapril)

NDA 20-528

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF
CARDIO-RENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-528

MAVIK TABLETS

[Trandolapril]

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Mavik Tablets, Knoll Pharmaceutical Company conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a (a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Trandolapril is a chemically synthesized angiotensin converting enzyme (ACE) inhibitor which is administered as an oral tablet for the treatment of hypertension. The drug substance is manufactured by The drug product is manufactured and packaged by Knoll Pharmaceutical Company, Whippany, New Jersey. Tablets are packaged into blister packs by The finished drug product will be used in hospitals, clinics and by patients in their homes.

The drug substance, trandolapril, is a pro-drug that is rapidly and extensively hydrolyzed in the liver to the diacid, trandolaprilat. The drug substance and its metabolites are excreted into the sewer system. Chemical and physical test results indicate that they will be restricted to the aquatic environment. The maximum expected environmental concentration (MEEC), based on production estimates for the 5th year after approval of the NDA, is well below 1 part per billion.

The Minimum Inhibitory Concentration (MIC) of trandolaprilat is 400 mg/L for Nostoc Sp. in the Microbial Growth Inhibition Test (TAD 4.02). The MIC is more than 1000 mg/L for molds, ascomycetes and bacteria. Based on structure activity relationships, both trandolapril and its diacid metabolite, trandolaprilat, are highly susceptible to biodegradation by hydrolytic enzymes and peptidases in domestic sewage and in the waste water treatment works.

Disposal includes out of specification lots, returned, unused or expired product, empty or partly used product and packaging. These will be disposed at licensed incineration facilities and landfills. Empty or partially empty packages generated in American hospitals and clinics will be disposed according to their regulations. Empty or partially empty containers from home use will be disposed in the community solid waste management system which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product may be manufactured, used and disposed without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

April 17, 1996 Florian Zielinski

DATE PREPARED BY: Florian Zielinski,
Review Chemist, New Drug Chemistry I

4/17/96 Robert Wolters

DATE CONCURRENCE: Robert J Wolters,
Office of Drug Evaluation I, Center for Drug Evaluation and Research

4/17/96 Nancy B. Sager

DATE APPROVED: Nancy B. Sager, Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheets (trandolapril and trandolaprilat)

Original: NDA 20-528
HFD-357 FONSI File [NDA # 20-528]
HFD-004 Docket File
HFD-205 FOI COPY
HFD-110 Division File
HFD-110 CSO, Kathleen Bongiovanni
HFD-110 Review Chemist, Florian Zielinski

Knoll Pharmaceutical Compa.,

ORIGINAL

knoll®

March 25, 1997

BASF Pharma

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, 5th Floor
Rockville, MD 20852

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 3 1 1997
HFD-110

Subj: **MAVIK (trandolapril)**
NDA 20-528/S-001

NDA SUPPL AMEND
SE1-001
AM

Dear Dr. Lipicky:

Reference is made to your letter of January 20, 1997 regarding our pending supplement to the subject NDA. In order to complete our December 20, 1996 amendment, we are attaching:

1. A diskette forwarded by which contains the data received from the Danish Register in response to the request for the final analysis. The diskette includes the mortality status for all 1749 patients and specifies randomization number (the study number (001), center #, patient #) mortality status (9 represents death) and date of death. File BDY23.P14 is in an ASCII file and can be read through Winword. A printout of the information contained on the diskette is provided for your convenience.

   When this data was compared with data base analyzed by PRA at the end of the study, five discrepancies were identified. The five patients not included in the PRA analysis all received placebo and are identified as follows:

Patient ID	Date of Death
00101133	07/07/94
00115134	07/11/94
00123192	07/07/94
00101176	05/25/94
00106171	06/21/94

   Patients 00104185 and 00122176, given a status of "7" and "8" respectively, were alive at the final study censoring date -- July 15, 1994.

2. An excerpt of a document from the Danish Ministry of the Interior which addresses the timely maintenance of data by the Central Persons Register. According to a 1996 survey it required an average of 6 days for the CPR to be notified about deaths.

ORIGINAL

99 Cherry Hill Road, Parsippany, New Jersey 07054 (201) 426-2600

3. A comparison of the mortality status of patients in the third interim CPR data base (1993) with that of the final CPR data base (1994) revealed that two patients (158 and 152) who had died before the censoring date (July 15, 1993) had no CPR death dates. In the final data base, the CPR death dates were listed as July 12, and July 13, 1993.

4. Debarment Certification.

5. Three copies of revised draft labeling in accordance with the wording (highlighted) of the September 18, 1996 approvable letter.

Knoll hereby requests an exemption from the Environmental Assessment requirement on the basis that the incremental use of the product in the intended population will not materially affect the exposure levels (Tier 0) provided in the assessment included in the original application.

Sincerely,

Robert W. Ashworth

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA:dsb

cc: Kathleen Bongiovanni

mavik.doc

Knoll Must provide estimate of production 5 years after approval of supplement. Knoll notified of this requirement by phone on 11/21/97.

Knoll Pharmaceutical Company

BASF Pharma

April 23, 1997

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products (HFD-110)
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, 5th Floor
Rockville, MD 20852

SUBJECT: **MAVIK (trandolapril)**
NDA 20-528/S-001

Dear Dr. Lipicky:

Reference is made to the pending supplement to the subject NDA and to our correspondence of March 25, 1997.

Pursuant to Florian Zielinski's request, our estimate of the fifth year production quantity for trandolapril has been revised from (see Environmental Assessment Report - 04/16/96) to to reflect the usage of trandolapril for all of the indications covered by the subject NDA.

Sincerely,

Robert W. Ashworth

Robert W. Ashworth, Ph.D.
Director, Regulatory Affairs

RWA:dsb
mavik10.7

199 Cherry Hill Road, Parsippany, New Jersey 07054 (201) 426-2600

DF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-528/S-001

JUL 3 1996

Knoll Pharmaceutical Company
Attention: Robert W. Ashworth, Ph.D.
199 Cherry Hill Road
Parsippany, NJ 07054

Dear Dr. Ashworth:

Please refer to your May 6, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mavik (trandolapril) 1, 2, and 4 mg Tablets.

We note that the cover letter for the supplemental new drug application contains a request for a waiver of the requirements for the submission of paper case report forms and case report tabulations.

We have completed our review of this request and have concluded that under 21 CFR 314.90(b)(2), you alternative electronic submission justifies a waiver of the "hard copy" requirements of 21 CFR 314.50(f). Consequently, your waiver requests are granted.

Should future retrieval be deemed necessary, and as a condition of granting these waivers, you are required to maintain the paper copies of the case report forms as required under 21 CFR 312.57(b). In addition, you must be able to generate case report tabulations for the same timeframe.

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc
Orig. NDA
HFD-070/DMoss
HFD-110
HFD-110/KBongiovanni
sb/2/22/96;7/3/96

NO REPLY NECESSARY (NR)

N 21-528

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: SEP - 9 1996

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Trandolapril for post-infarction LV dysfunction

TO: Dr. Raymond Lipicky, Division of Cardio-Renal Drug Products, HFD-110

I agree with your conclusion that the results of TRACE belong in labeling as an indication, not merely added to the Clin Pharm section without an indication. This study is (or is likely to be, once the mortality data are complete) about as persuasive as data supporting other outcome claims now in other ACEI labeling. I've therefore worked on the "Lipicky" version of the letter. But let's be very clear on the matter of sticking a study of a new use in Clin Pharm: It doesn't change anything; there is no distinction between the support needed for a claim in Indications and a claim placed into Clin Pharm, the legal standard is the same. The Law refers only to the effect it purports or is represented to have under the conditions of use prescribed, recommended, as suggested in the proposed labeling. It says nothing about where the claim is put. If we (other FDA units) have tried to hide new uses not up to speed in Clin Pharm, we shouldn't have.

I am somewhat surprised by the high level of concern about applicability of the results to a U.S. population. This is hardly the first Scandinavian study we've seen.

The level of other intervention in TRACE can be compared with interventions in SAVE, a pretty similar U.S. study. The following table is not complete but is informative already:

Intervention	TRACE	SAVE(meds within 24 hour before randomization)
Thrombolysis	42%	33%
Beta-blockers	16%	35%
Aspirin at infarct	91%	?
Aspirin later	?	59%
PTCA or CABG		26% prior
BP control >140/95	32-40% T, 47-53%Pl	?
Mortality, 1 year	26%	18%

On the whole, I do not believe these differences in practice undermine TRACE at all. Thrombolysis, a procedure with a major influence on survival and possibly cardiac function, was similar to the SAVE rate. The greater use of beta-blockers in the U.S. presumably would lower the untreated mortality rate, possibly decreasing absolute, but probably not relative benefit. A concern more difficult to resolve fully is whether the effect of the ACEI could be substantially related to better BP control. Patients cannot be randomized to level of BP control, of course (it's not a baseline characteristic) but the analysis on page 13 (Table 16) is reassuring. Mortality was reduced by trandolapril for all BP groups. All in all, the study seems as applicable to a U.S. population as GISSI, the ISIS studies, CONSENSUS, the Scandinavian timolol study, the 4S study, WOSCOPS, etc. I see no clear explanation for the idea that the study is unusually questionable in that respect.

The question of generalizability is always interesting and usually is hard to address. In fact, the real issue isn't, I think, generalizability, but rather individualization. We would like to know how (if) the intervention works in demographic subsets (age, sex, race), in the presence of other drugs or interventions, in the presence of various risk factors and characteristics of the AMI (BP, cholesterol, prior infarction, location of infarction, extent of vessel disease, smoking history, EF, heart rate, diabetes). Unfortunately, we have little power to answer any of those questions and they stress even the largest meta-analysis. What to do? We should keep looking, of course, but, as Yusuf has said, the best estimate of the effect in a subgroup is the overall effect in the study, not the observed effect in the subgroup. Put another way,

documented directional changes in subgroup effects are very unusual. The main concern is that if a drug had a lethal risk, it could be more important as the magnitude of actual benefit (as opposed to risk reduction) fell; aspirin, e.g., probably has a net adverse effect (intracranial bleeds) in a group at low risk for a thrombolytic event.

The above is a long introduction to what I think TRACE shows: trandolapril has joined the group of ACEI's for which a well-designed outcome study has shown benefit in patients with poor ventricular function. Although we continue to label the drugs only for what has actually been shown (still a reasonable course, I believe) it seems likely that ACEI benefits have similar pathophysiological origins, whether we observe them in various grades of CHF or in post-infarction ventricular dysfunction.

Within TRACE there is actually considerable evidence of the expected consistency in various subgroups, in addition to the effects in BP subgroups noted above. Table 2 of the paper, as well as Tables in Dr. Stockbridges' review, show reasonably similar benefits over and under age 65, for anterior and other infarcts, for previous/no previous infarct, for use or non-use of aspirin, beta-blockers, and nitrates, for use or non-use of thrombolysis. In many cases both of the pairs of subgroup are significant (CI upper bound $\leq$ 1.0). This should add to our confidence that the results are applicable to our population.

The ADR assessment may represent an important new information source for uncommon events in the CHF population and there are some surprises (at least I'm surprised). What about adding a table like this:

In the TRACE, the following adverse events were relatively frequent (at least 2%) and substantially more common in the trandolapril group:

Event	Trandolapril	Placebo
Dizziness	23.3	17.3
Hypotension	11.3	6.8
Syncope	5.9	3.3
Increased potassium	5.3	2.7

Myalgia	4.7	3.1
Cardiogenic shock	3.8	?
Intermittent claudication	3.8	?
TIA	2.9	?

What do you think?

When we were missing safety and other study data for the initial evaluation of trandolapril, we nonetheless sent an approvable letter because the discovery of data leading to non-approvability would have been a significant surprise. The CHF studies we are asking for, as we should, now include many, probably most, that could not alter our conclusion. Shouldn't this be an approvable letter?

Assuming that the patients with missing vital status can be found, this study seems to provide as much support as any single study can, with two largely independent endpoints (total mortality, CHF combined endpoint) and a high degree of consistency across subsets.

Robert Temple

Robert Temple, M.D.

cc: NDA 20-528/S-001
HFD-110
HFD-110/NStockbridge
HFD-111/KBergjovanni

N 20-528

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : AUG 21 1996

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approvability of NDA 20-528/S-001, Trandolapril for left ventricular systolic dysfunction, post-myocardial infarction. Knoll Pharmaceuticals

TO : Director, Office of Drug Evaluation I, HFD-101

Well this is another one, from three points of view.

1. Trandolapril is an ACE inhibitor that has statistically favorable effects on mortality (compared to placebo) when administered to patients who have survived a myocardial infarction, when started 1 to 5 days post-myocardial infarction.

2. Trandolapril for the treatment of hypertension was not approved as quickly as it might have been because Knoll did not submit all of the data they had for the hypertension claim until we asked for it. True for the left ventricular dysfunction claim also. There are at least 18 other trials (none of the details are known) dealing with the effects of trandolapril in patients with congestive heart failure that were non-IND studies (done in Europe) that have not been submitted.

3. The study in post-infarction patients (TRACE) was conducted entirely in Denmark. There is reason to question its applicability for predicting what will happen in a U.S. population.

TRACE is an acronym for the "TRAndolapril Cardiac Evaluation - Study of trandolapril in patients with reduced left ventricular function after acute myocardial infarction." Out of 7,000 screened patients 2,606 were eligible and 1,749 were randomized (873 to placebo and 876 to trandolapril). Of the patients randomized 99.8 % were caucasian, 22% had a history of heart failure, 55% had no thrombolysis in the treatment of their infarction, 91% were receiving aspirin, 16% beta-blockers and 66% were receiving diuretics. Most patients were NYHA class II or less, but greater than 36% were symptomatic, in one way or anther. Ejection fraction was not measured, rather left ventricular systolic dysfunction was documented using wall motion index (an echocardiographic criterion that I am not very familiar with).

All analyses that are contained in the attached combined medical/statistical review were performed using the sponsor supplied raw data (SAS data tape); being guided by the study protocol and amendments as well as by a publication (NEJM 333: 1670-1676, 1995). The protocol's prespecified primary endpoint was all-cause mortality at 24 months after randomization. The data tapes contained mortality data for longer than the 24 months (so, the review contains analyses that include a duration longer than 24 months).

All-cause mortality was reduced in the trandolapril-treated group (relative risk 0.84) with a p of 0.0188 (which when one considers the interim looks and requires 2-tailed testing, should be compared to a p of 0.0225). There is absolutely no question about the primary result, regardless of how one divides up the deaths, how one stratifies, etc.

There are a large number of other analyses that are elucidated in the attached review. Of most interest, to me, was the lack of effect on exercise tolerance, the increased heart size in the trandolapril-treated group and the lack of effect on recurrent myocardial infarction. None-the-less, these are not dispositive in any sense of the word.

There is little question in my mind that the results of TRACE should not get incorporated into labelling until the other 18 trials in patients with congestive heart failure have been submitted and reviewed. Although there is some mystique about mortality and myocardial infarctions, since the requirement for randomization was to have evidence of left ventricular dysfunction and 36 % were actually symptomatic, the therapy must in some way be related to the treatment of congestive heart failure. Moreover, since there was no effect on reinfarction, it seems unlikely that the treatment is oriented toward the treatment of coronary artery disease. So, the other 18 trials need to be reviewed (they were for ramipril, in addition to the AIRE trial, for the same reasons).

The results of TRACE certainly deserve something (other than publication in the New England Journal). The generalizability of clinical trial results is always a question mark. In this case, the combined medical/statistical review makes the question mark somewhat bigger. However, I do not feel compelled by the arguments presented. I would think an Indication was appropriate.

There are two different not-approvable letters attached. Take your pick.

cc:
NDA 20-528/S-001
HFD-110
HFD-110/NStockbridge
HFD-710/KMahjoob/LCui
HFD-111/KBongiovanni
HFD-110/RLipicky
sb/8/19/96
R/D: LCui/8/15/96
KMahjoob/8/15/96
NMorgenstern