

# Effect of Mibefradil, a T-Type Calcium Channel Blocker, on Morbidity and Mortality in Moderate to Severe Congestive Heart Failure

## The MACH-1 Study

T. Barry Levine, MD; Peter J.L.M. Bernink, MD; Abraham Caspi, MD; Uri Elkayam, MD; Edward M. Geltman, MD; Barry Greenberg, MD; William J. McKenna, MD; Jalal K. Ghali, MD; Thomas D. Giles, MD; Alon Marmor, MD; Leonardo H. Reisin, MD; Susan Ammon, RN; Elisabet Lindberg, MD

**Background**—Calcium antagonists have proved disappointing in long-term congestive heart failure (CHF) studies. Mibefradil, a new calcium antagonist that selectively blocks T-type calcium channels, has been shown to be an effective antihypertensive, antianginal, and anti-ischemic agent, and because of its different mechanism of action, it may be beneficial as adjunct therapy in CHF patients.

**Methods and Results**—This multicenter, randomized, double-blind study compared mibefradil with placebo as adjunct to usual therapy in 2590 CHF patients (NYHA class II to IV; left ventricular fraction <35%). The initial 50-mg daily dose of mibefradil was uptitrated to 100 mg after 1 month and continued up to 3 years. Patients were monitored at 1 week; 1, 2, and 3 months; and every 3 months thereafter. All-cause mortality, cardiovascular mortality, and cardiovascular morbidity/mortality were analyzed by use of the log-rank test ( $\alpha=0.05$ ). Substudies included exercise tolerance, plasma hormone and cytokines, echocardiography, and quality of life. Total mortality was similar between mibefradil- and placebo-treated patients ( $P=0.151$ ). The 14% increased risk of mortality with mibefradil in the first 3 months was not statistically significant ( $P=0.093$ ). Treatment groups had similar cardiovascular mortality ( $P=0.246$ ), cardiovascular morbidity/mortality ( $P=0.783$ ), and reasons for death or hospitalization. Patients comedicated with mibefradil and antiarrhythmics (class I or III), including amiodarone, had a significantly increased risk of death. Substudies demonstrated no significant differences between treatments.

**Conclusions**—When used as adjunct therapy, mibefradil did not affect the usual outcome of CHF. The potential interaction with antiarrhythmic drugs, especially amiodarone, and drugs associated with torsade de pointes may have contributed to poor outcomes early in the study. (*Circulation*. 2000;101:758-764.)

**Key Words:** mibefradil ■ calcium channels ■ heart failure

Calcium antagonist use in congestive heart failure (CHF) therapy remains controversial. Large clinical trials of calcium antagonists have yielded generally disappointing results<sup>1,2</sup> because their negative inotropy, sympathetic activation, and cytokine mechanisms worsen left ventricular dysfunction.<sup>3,4</sup>

Traditional calcium antagonists act on the L-type calcium channel.<sup>5</sup> However, both L- and T-type channels exist in cardiovascular tissues, albeit with different distributions.<sup>5</sup> L-type channels are found in both adult myocardium and vascular smooth muscle.<sup>6</sup> T-type channels occur in vascular smooth muscle and the sinoatrial node, mediating vascular tone<sup>7</sup> and nodal automaticity.<sup>8</sup> T-type channels occur in the adult myocardium only under pathophysiological conditions<sup>9</sup> and may affect cellular responses to hypertrophic stimuli.<sup>9,10</sup>

Pharmacological manipulation of T-type channels has recently been possible with mibefradil, the prototype of a new class of selective T-type calcium channel blockers. The vasodilatory action of mibefradil<sup>11</sup> without neurohormonal activation<sup>12</sup> or negative inotropy at clinically relevant dosages<sup>13</sup> is of potential clinical benefit. In a variety of experimental and clinical pathophysiological situations, T-channel blockade was demonstrated to be beneficial.<sup>14-16</sup> In clinical trials, mibefradil was found to be an effective antihypertensive, antianginal, and anti-ischemic agent.<sup>17-19</sup> Therefore, the aim of the Mortality Assessment in Congestive Heart Failure Trial (MACH-1) was to assess the impact of the addition of mibefradil to standard therapy on both symptomatic status and mortality in CHF patients with NYHA class II to IV symptomatology.

Received April 27, 1999; revision received September 17, 1999; accepted September 23, 1999.

The Appendix provides a complete list of study participants.

Correspondence to T. Barry Levine, MD, Michigan Institute for Heart Failure and Transplant Care, Botsford General Hospital, 28050 Grand River Ave, Farmington Hills, MI 48336.

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## Methods

MACH-1 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, forced-dose titration study conducted in the United States, Canada, Europe, and Israel. Patients gave written informed consent, and the study conformed to the amended Declaration of Helsinki and local regulations and review boards.

Eligible patients randomized between November 1994 and October 1996 had stable CHF, NYHA class II to IV, and left ventricular ejection fraction (LVEF) <35% and were taking clinically optimal doses of loop diuretics and ACE inhibitors with or without vasodilators and/or digitalis. Patients continued their usual medications except calcium antagonists. Exclusion criteria included a scheduled cardiac procedure or transplant; a myocardial infarction, CABG, or coronary angioplasty within 1 month; second- or third-degree AV block without a pacemaker; clinically significant arrhythmias; heart rate <55 bpm; blood pressure (BP) >160/100 mm Hg or systolic <90 mm Hg; a cerebrovascular accident within 3 months; or any clinically significant disease other than CHF. After a 2-week placebo run-in, patients were randomized to placebo or 50 mg/d mibefradil (single tablet). After 1 month, all patients were uptitrated to 2 tablets once daily (placebo or 100 mg mibefradil). Patients with intolerable adverse events were returned to the lower dose.

Follow-up visits were done after 1 week; 1, 2, and 3 months; and every 3 months thereafter or when an event occurred. ECG measurements and vital signs were obtained and adverse events were recorded at each visit. NYHA class assessment, routine laboratory analyses, and physical exams were performed throughout the study. Each critical event (death, hospitalization, or premature withdrawal owing to adverse events) was evaluated and classified by the independent Critical Events Committee.

The primary efficacy parameter was all-cause mortality over a 2- to 3-year period. Mortality was measured by time to death or clinical cutoff. Secondary parameters included cardiovascular mortality (time to death for cardiovascular reasons or clinical cutoff), combined cardiovascular morbidity/mortality, and change in NYHA class (worse than, equal to, or better than baseline). Additionally, signs and symptoms of CHF (orthopnea, paroxysmal nocturnal dyspnea, palpitation during physical activity, edema, fatigue, or dyspnea) were evaluated at baseline and at last available assessment, as were both patient and investigator opinions about CHF status (worse, equal, or better).

### Substudies Performed at Selected Centers

Treadmill<sup>20</sup> (n=406) and bicycle (n=406) exercise tolerance tests (ETTs) were assessed at screening; on day 2; at baseline; and after 1, 3, and 6 months. The main parameter was change in total exercise duration. BP, heart rate, and gas exchange data ( $\dot{V}O_2$ ,  $\dot{V}CO_2$ , and minute ventilation; n=420) were also measured.

Plasma neurohormonal (n=352) and cytokine (n=160) concentrations were measured over the first 6 months of treatment. Norepinephrine was measured by high-performance liquid chromatography,<sup>21</sup> atrial natriuretic peptide by a radioimmunoassay kit (Bühlmann Laboratories AG), and angiotensin II and endothelin-1 by radioimmunoassay with specific antibodies (Hoffmann-La Roche) after C-8 column extraction. ELISA kits were used to measure IL-1 $\beta$ , IL-2R, IL-6, tissue necrosis factor- $\alpha$  (R&D Systems), and big endothelin-1 (Biomedica). LVEF (calculated by use of the modified Simpson rule from 2-dimensional echocardiography) was assessed in 117 patients at baseline and after 1 year. Quality of life was assessed in 327 patients with the Minnesota Living With Heart Failure Questionnaire (total, physical, and emotional scores).

### Statistical Analysis

This event-driven study was stopped when 669 deaths occurred (clinical cutoff). This estimate was based on the expected mortality in placebo-treated patients with NYHA class II to IV, an expected treatment effect of 17% risk reduction, and a desired 80% power by use of a 2-sided log-rank test with  $\alpha=0.05$ . Five interim analyses following a sequential plan according to O'Brien and Fleming<sup>22</sup> were performed by the Independent Safety and Data Monitoring Advisory

Committee biostatistician using the log-rank test to evaluate total mortality. Any significant finding required that the study be terminated and fully evaluated, but the study continued as planned.

Event-driven parameters were analyzed by the 2-sided log-rank test ( $\alpha=0.0414$  for total mortality and  $\alpha=0.05$  for others) with the intent-to-treat population (all randomized patients) stratified by region. Survival curves and pointwise mortality rates were based on Kaplan-Meier estimates for each treatment group. Risk reductions were estimated by use of a Cox regression model, which included treatment and baseline LVEF, NYHA class, and origin (ischemic versus nonischemic disease) to adjust for baseline differences.

For substudies, the intent-to-treat populations consisted of all randomized patients who received  $\geq 1$  dose of trial medication and who had a valid baseline and  $\geq 1$  postbaseline measurement. Missing values were replaced by carrying the last observation forward, except for quality of life, for which missing values were imputed by use of the mean of available scores. Placebo-corrected treatment effects for ETT duration and gas exchange parameters were estimated with Hodges-Lehmann type estimators (nonparametric). Evaluations of changes in NYHA class and opinions of CHF status used a logistic regression model. Change in quality of life was analyzed by use of ANOVA, with treatment effect, origin, and their interaction included in the linear model; the change in LVEF was analyzed with ANCOVA, with treatment and region effects as factors and baseline LVEF as the covariate. Other parameters were analyzed descriptively and presented as mean  $\pm$  SD.

## Results

### Patients

Baseline patient demographics were similar between mibefradil and placebo groups (Table 1). During the study, the disposition of patients was also similar between groups, as was treatment duration ( $594 \pm 301$  and  $565 \pm 324$  days for placebo and mibefradil, respectively). At 1 month, more placebo (86.4%) than mibefradil (77.8%) patients were successfully uptitrated.

### Morbidity and Mortality

During the study, 350 deaths (27.0%) in the mibefradil and 319 deaths (24.6%) in the placebo groups occurred. All-cause mortality was similar for both groups (Figure 1;  $P=0.151$ , log-rank test). Mibefradil treatment had a 14% increased risk of mortality (95% CI, 2.2% reduction to 33% increase), which was statistically insignificant ( $P=0.093$ , Cox regression). The mortality rate difference between the groups occurred in the first 3 months after randomization and remained constant thereafter (Kaplan-Meier estimates).

Cardiovascular mortality and combined cardiovascular morbidity/mortality were similar in both groups (crude event rates: 22.2% for placebo and 24.0% for mibefradil for cardiovascular mortality,  $P=0.246$ ; 53.4% and 51.6% for cardiovascular morbidity/mortality,  $P=0.783$ ). As with all-cause mortality, the greatest discrepancy between groups occurred within the first 3 months, with an increased risk of 3% to 5% with mibefradil. Reasons for deaths and hospitalizations (Table 2) were similar between groups, except for the slightly higher number of sudden deaths and arrhythmia hospitalizations with mibefradil and CHF hospitalizations with placebo. The number of patients hospitalized for any reason was similar between groups (56.2% for placebo and 53.1% for mibefradil).

Analysis of all-cause mortality risk in subpopulations revealed few differences between mibefradil and placebo

**TABLE 1. Baseline Demographics**

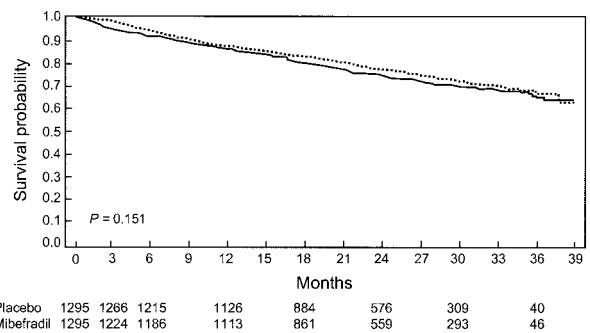
	Placebo (n=1295)	Mibefradil (n=1295)
Age, y	63.0±10.9	62.6±11.0
Sitting systolic BP, mm Hg	120.2±16.9	120.4±17.1
Sitting diastolic BP, mm Hg	74.0±10.3	74.0±10.1
Heart rate, bpm	78.4±12.5	78.3±12.5
6-min walk, m	272.6±91.0	276.8±90.9
LVEF, %	24.6±6.6	24.4±6.6
Sex		
M	79.8	79.0
F	20.2	20.0
Race		
White	83.4	82.6
Black	12.0	12.7
Other	4.6	4.7
NYHA class		
II	25.3	26.0
III	63.7	64.8
IV	11.0	9.2
Medical history		
Previous MI	63.3	62.5
Current stable angina	60.1	61.9
Diabetes mellitus	30.3	31.4
Hypertension	28.3	30.2
Atrial fibrillation	13.7	13.3
Primary cause of CHF		
Ischemic	68.1	67.9
Nonischemic	31.9	32.1
Concomitant medications		
Diuretics	99.7	100
ACE inhibitors	99.5	99.2
Digoxin	67.3	66.9
Aspirin	46.6	47.3
Nitrates	49.8	50.7
β-Blockers	15.3	15.7
Antiarrhythmics (class I, III)	16.2	15.2
Amiodarone	13.4	12.1

MI indicates myocardial infarction. Values are mean±SD or % of patients.

(Figure 2). There was a small but consistently greater risk of death with mibefradil compared with placebo, although only atrial fibrillation at baseline was statistically significant. There was no treatment difference regardless of whether CHF was of ischemic etiology.

### Measures of CHF Status

Approximately 25% of patients had improved NYHA class (Table 2), and about 9% deteriorated during the study, regardless of treatment ( $P=0.756$  for overall treatment effect). Investigator opinions of CHF status changes mirrored NYHA class changes and were similar between groups ( $P=0.924$  for treatment effect). Patient opinion of CHF status changes was also similar between groups, but the percentage



**Figure 1.** Kaplan-Meier survival distribution by time to death (any reason) or clinical cutoff in placebo and mibefradil groups. Number of patients at risk at end of each period is shown.  $P=0.151$  by log-rank test stratified by region.

who felt improved exceeded the investigator assessment (31.8% and 33.9% for placebo and mibefradil, respectively, versus 25.3% and 25.2%). Physician-measured incidences of CHF signs and symptoms were reduced from baseline but were similar between groups for all parameters (data not shown).

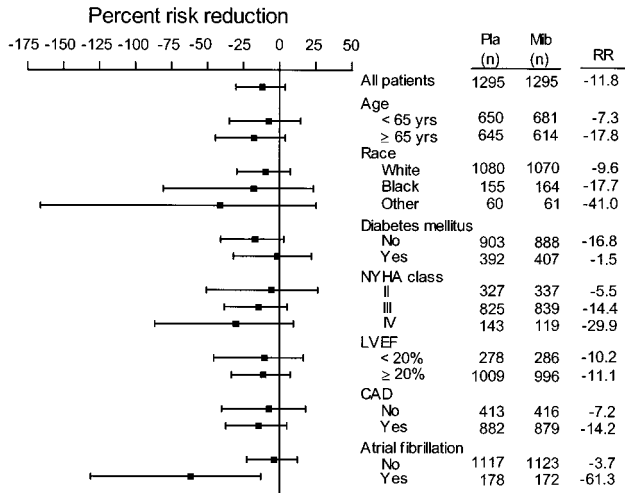
### Substudies

After 6 months of treatment, increases in ETT total exercise duration were similar between groups whether measured via treadmill (treatment effect, 6.80 seconds;  $P=0.600$ ) or bicy-

**TABLE 2. Change in NYHA Class and Reasons for Deaths and Hospitalizations**

	Placebo (n=1289)		Mibefradil (n=1282)	
	n	%	n	%
Change in NYHA class				
Worse	119	9.2	114	8.9
No change	847	65.7	842	65.7
Improved	323	25.1	326	25.4
Deaths (any reason)				
CV deaths	288	90.3	311	88.9
Sudden death	174	54.5	196	56.0
Worsening CHF	88	27.6	88	25.1
Vascular event	7	2.2	14	4.0
Myocardial infarction	10	3.1	9	2.6
Revascularization	2	0.6	...	...
Other CV reasons	7	2.2	4	1.1
Non-CV deaths	31	9.7	39	11.1
Hospitalizations (any reason)				
Hospitalization for CV reasons	815	70.0	813	69.8
Worsening CHF	365	31.3	311	26.7
Angina	107	9.2	108	9.3
Arrhythmia	68	5.8	110	9.5
Syncope	33	2.8	54	4.6
Myocardial infarction	46	3.9	32	2.7
Other CV reasons	196	16.8	198	15.0
Hospitalization for non-CV reasons	350	30.0	351	30.2

CV indicates cardiovascular.



**Figure 2.** Effect of mibefradil compared with placebo on all-cause mortality in various baseline subpopulations. Reduction in risk is plotted; horizontal lines represent 95% CIs. CIs that do not cross zero risk indicate significant treatment effect, and negative risk reduction indicates worse outcome. Pla indicates placebo; Mib, mibefradil; RR, risk reduction; and CAD, coronary artery disease.

cle (treatment effect,  $-9.99$  seconds;  $P=0.267$ ). Mibefradil slightly decreased diastolic BP, heart rate, and double product (systolic BP times heart rate) compared with placebo in both ETTs at rest and exercise termination (data not shown). Mibefradil caused statistically insignificant greater increases from baseline in  $\dot{V}O_2$ ,  $\dot{V}CO_2$ , and minute ventilation than placebo (Table 3).

After 6 months of treatment, no increase in neurohormones occurred in either group. For 4 hormones, plasma concentrations changed  $\leq 10\%$  from baseline in both groups. Angiotensin II concentration increased similarly in both groups. Plasma concentrations of IL-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  were slightly decreased and IL-2R was slightly increased after 6 months of treatment in both groups with no significant differences.

Echo LVEF decreased slightly and equivalently in both groups after 12 months of treatment. Quality-of-life measures were virtually unchanged during the course of the study in both groups ( $P=0.447$  for treatment difference in total score).

**Safety and Tolerability**

The number of patients with  $\geq 1$  treatment-related adverse event or serious adverse event and the number of patients

**TABLE 3. Data From Substudies on Exercise, Hormones, Cytokines, Echocardiography, and Quality of Life**

	Baseline		Change From Baseline to 6 Months	
	Placebo	Mibefradil	Placebo	Mibefradil
Exercise parameters	208	198	208	198
Treadmill exercise duration, s	454.2 $\pm$ 186.4 (n=200)	459.1 $\pm$ 192.2 (n=206)	41.0 $\pm$ 154.4 (n=200)	48.5 $\pm$ 142.8 (n=206)
Bicycle exercise duration, s	360.3 $\pm$ 161.6 (n=215)	372.4 $\pm$ 158.3 (n=205)	32.0 $\pm$ 114.6 (n=215)	27.8 $\pm$ 111.0 (n=205)
$\dot{V}O_2$ , mL $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$	12.48 $\pm$ 3.66	12.83 $\pm$ 3.74	0.65 $\pm$ 3.52	0.83 $\pm$ 3.18
$\dot{V}CO_2$ , mL $\cdot$ min $^{-1}$ $\cdot$ kg $^{-1}$	12.85 $\pm$ 4.20	13.12 $\pm$ 4.00	0.64 $\pm$ 3.93	0.87 $\pm$ 3.56
Minute ventilation, L/min	41.27 $\pm$ 14.79	41.91 $\pm$ 13.93	1.07 $\pm$ 11.09	2.21 $\pm$ 10.66
Respiratory quotient ( $\dot{V}CO_2/\dot{V}O_2$ )	1.026 $\pm$ 0.138	1.024 $\pm$ 0.141	-0.003 $\pm$ 0.131	0.001 $\pm$ 0.155
Plasma hormones	181	171	181	171
Angiotensin II, pg/mL	13.438 $\pm$ 20.001	14.708 $\pm$ 22.948	3.463 $\pm$ 26.460	6.016 $\pm$ 45.755
Endothelin-1, pg/mL	16.163 $\pm$ 7.246	15.612 $\pm$ 6.821	1.304 $\pm$ 9.043	0.677 $\pm$ 7.923
Big endothelin-1, pg/mL	5.034 $\pm$ 4.487	5.364 $\pm$ 5.575	0.538 $\pm$ 6.998	0.275 $\pm$ 7.317
Atrial natriuretic peptide, pg/mL	160.69 $\pm$ 115.13	161.09 $\pm$ 122.80	-11.09 $\pm$ 107.95	-13.86 $\pm$ 112.46
Norepinephrine, pg/mL	468.27 $\pm$ 363.98	481.87 $\pm$ 354.47	6.78 $\pm$ 301.09	22.26 $\pm$ 383.04
Plasma cytokines, pg/mL	95	65	95	65
IL-1 $\beta$	0.407 $\pm$ 0.696	0.366 $\pm$ 0.517	-0.051 $\pm$ 0.226	-0.047 $\pm$ 0.275
IL-2R	1055.37 $\pm$ 588.84	1143.08 $\pm$ 721.70	58.77 $\pm$ 384.17	39.94 $\pm$ 470.89
IL-6	4.606 $\pm$ 2.668	4.534 $\pm$ 2.581	-0.042 $\pm$ 2.339	-0.156 $\pm$ 2.145
TNF- $\alpha$	4.886 $\pm$ 2.349	4.884 $\pm$ 2.006	-0.134 $\pm$ 1.972	-0.155 $\pm$ 2.146
Echocardiography variable	56	61	56	61
LVEF, %	28.8 $\pm$ 7.9	29.7 $\pm$ 6.7	-0.6 $\pm$ 10.0*	-0.1 $\pm$ 7.7*
Quality-of-life measures	167	160	167	160
Total score	37.9 $\pm$ 23.7	37.7 $\pm$ 22.4	-0.4 $\pm$ 22.8†	1.5 $\pm$ 19.5†
Physical score	17.9 $\pm$ 11.2	17.6 $\pm$ 9.9	-0.5 $\pm$ 10.5†	0.2 $\pm$ 8.6†
Emotional score	8.1 $\pm$ 6.9	7.7 $\pm$ 6.8	0.0 $\pm$ 6.3†	0.4 $\pm$ 6.3†

TNF indicates tumor necrosis factor. Values are mean $\pm$ SD.

\*Change from baseline to 12 mo; †change from baseline to clinical cutoff.

**TABLE 4. Incidence of Adverse Events, Serious Adverse Events, and Premature Withdrawals Because of Adverse Events**

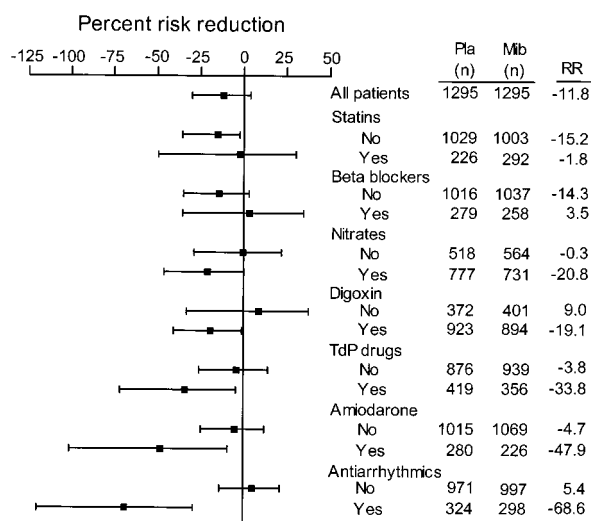
	Placebo (n=1295)		Mibefradil (n=1295)	
	n	%	n	%
<b>Adverse events (&gt;3%)</b>				
Worsening CHF	243	18.8	232	17.9
Hypotension	81	6.3	116	9.0
Dizziness	75	5.8	118	9.1
Angina pectoris	90	6.9	63	4.9
Dyspnea	60	4.6	63	4.9
Bradycardia	14	1.1	97	7.5
Fatigue	43	3.3	61	4.7
Bradycardia on ECG	9	0.7	57	4.4
Total patients with $\geq 1$ adverse event	685	52.9	799	61.7
<b>Serious adverse events (&gt;2%)</b>				
Worsening CHF	161	12.4	150	11.6
Sudden death	63	4.9	65	5.0
Angina pectoris	57	4.4	43	3.3
Total patients with $\geq 1$ serious adverse event	339	26.2	382	29.5
<b>Premature withdrawals because of adverse events (&gt;1%)</b>				
Worsening CHF	36	2.8	31	2.4
Total patients withdrawn because of adverse events	98	7.6	133	10.3

Only events with an incidence greater than the given percentage are listed.

withdrawn because of adverse events were slightly greater for mibefradil than placebo (Table 4). Worsening of CHF was the most prevalent event in all 3 categories and occurred more often with placebo. There was little difference between groups, except for a higher incidence of bradycardia, hypotension, and dizziness with mibefradil. Heart rate decreased from baseline by  $6.8 \pm 13.0$  bpm with mibefradil compared with  $0.8 \pm 13.1$  bpm with placebo.

Virtually all patients exhibited  $\geq 1$  ECG abnormality at baseline. Both treatment groups were comparable, with  $\approx 60\%$  exhibiting ST-T changes, 50% showing evidence of myocardial infarction, and 25% to 28% exhibiting left axis deviation and left bundle-branch block, respectively, among others. During the study, ECG changes occurred in 66.2% and 69.9% of patients treated with placebo and mibefradil, respectively. Incidences of most abnormalities were similar between groups with the notable exceptions of higher incidences of first-degree AV block (25.9% versus 14.2%) and sinus bradycardia (24.4% versus 5.3%) with mibefradil.

Subpopulation analyses of patients on comedications showed that use of digoxin, class I or III antiarrhythmics, amiodarone, or drugs associated with torsade de pointes significantly increased risk of death with mibefradil compared with placebo (Figure 3). Conversely, mibefradil without these comedications did not increase risk. Because amiodarone was the most frequently taken drug in these categories (Table 5), a post hoc analysis of total mortality stratified by amiodarone comedication showed mibefradil plus amiodarone to significantly increase mortality (crude rate, 38.5%;  $P < 0.05$ ) compared with mibefradil without amiodarone (24.6%) or placebo (23.6% without, 28.2% with amiodarone) (Figure 4).



**Figure 3.** Effect of mibefradil compared with placebo on all-cause mortality in subgroups of patients concomitantly taking selected drugs during study. Reduction in risk is plotted; horizontal lines represent 95% CIs. CIs that do not cross zero risk indicate significant treatment effect, and negative risk reduction indicates worse outcome. Pla indicates placebo; Mib, mibefradil; RR, risk reduction; and TdP, torsade de pointes.

## Discussion

As adjunct therapy in patients with CHF, mibefradil did not alter disease outcome. Treatment with mibefradil did not significantly increase mortality, myocardial infarctions, heart failure-related hospitalizations, or CHF symptoms. However, the study did show a negative trend, with slightly higher

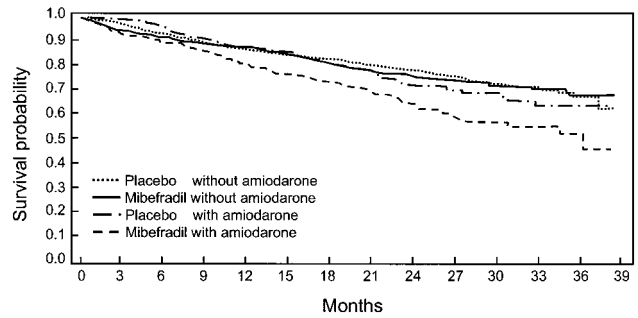
**TABLE 5. Patients Taking Class I and III Antiarrhythmics and Drugs Associated With Torsade de Pointes**

	Placebo (n=1295)	Mibefradil (n=1295)
Antiarrhythmics, n	324	298
Amiodarone	280	226
Lidocaine	41	69
Procainamide	17	17
Mexiletine	16	14
Quinidine	11	10
Propafenone	10	6
Bretylium	3	4
Flecainide	3	2
Disopyramide	2	2
Encainide	1	2
Ibutilide	2	...
Moracizine	1	1
Ajmaline	...	1
TdP drugs, n	419	356
Amiodarone	280	226
Erythromycin	62	54
Amitriptyline	33	42
Cisapride	29	20
Sotalol	21	14
Procainamide	17	17
Quinidine	11	10
Terfenadine	9	9
Doxepin	4	5
Fluvoxamine	5	4
Imipramine	5	2
Astemizole	4	2
Clomipramine	4	1
Disopyramide	2	2
Dosulepin	...	3
Lofepramine	2	1
Desipramine	1	...
Maprotiline	...	1

TdP indicates torsade de pointes.

mortality in patients on mibefradil within the first 3 months. Mortality rates were similar during the remainder of the study. Although the difficulty in identifying sudden death is acknowledged, the independent committee established to classify all events found its occurrence slightly more frequent with mibefradil.

Subgroup analysis revealed increased risk in patients with atrial fibrillation and in those concomitantly treated with antiarrhythmics, drugs associated with torsade de pointes, and amiodarone. Indeed, concomitant mibefradil and amiodarone may be in large part responsible for the negative trend of the study. As with all post hoc analyses, results must be interpreted with caution. However, 1 mechanism for the negative effect of atrial fibrillation may be the confluence of negative



**Figure 4.** Kaplan-Meier survival distribution by time to death (any reason) or clinical cutoff in placebo and mibefradil groups stratified by comedication with amiodarone. Dotted line indicates placebo without amiodarone (n=1015); solid line, mibefradil without amiodarone (n=1069); long dashed/dotted line, placebo with amiodarone (n=280); and short dashed line, mibefradil with amiodarone (n=226).

chronotropic effects precipitating bradyarrhythmias, although other proarrhythmic actions cannot be excluded.

Other drug-drug interactions may have contributed to the tendency for higher mortality early in the study. Many antiarrhythmics undergo metabolic elimination via hepatic cytochrome P-450 enzymes that are potently inhibited by mibefradil.<sup>23,24</sup> Because antiarrhythmics have a concentration-related arrhythmogenic potential, coadministration of these drugs with mibefradil may have led to toxic plasma concentrations. The resulting increased proarrhythmic risk may have been further enhanced by the bradycardic effect of mibefradil. Although speculative, the negative trend in this study may therefore be the result of a multiplicity of detrimental drug-drug interactions.

Hypotheses for the lack of long-term benefits of calcium antagonists in patients with symptomatic CHF include negative inotropy, reflex increases in neurohormones and cytokines, and underlying differences between ischemic and nonischemic disease.<sup>3,4</sup> These mechanisms fail to explain the lack of efficacy for mibefradil in this study. The beneficial effects of mibefradil on survival in a rat postinfarction model<sup>14</sup> and on hemodynamics and LV hypertrophy without impairment of myocardial contractility in patients with LV dysfunction<sup>15,16</sup> remain intriguing. This raises the question of whether mibefradil as monotherapy may have beneficial effects on LV remodeling and survival when not confounded by polypharmacy. The evolving knowledge of the role of T-type calcium channels in neuroendocrine, vascular, and myocardial physiology and pathophysiology may suggest a future role for T-channel blockade in postinfarction remodeling and CHF therapy in general.

In conclusion, this trial demonstrated the tolerance of mibefradil in patients with moderate to severe heart failure. The nonsignificant trend toward increased mortality was confined to the first 3 months of the study and was secondary to the occurrence of sudden death. The interaction of mibefradil with other negative chronotropic agents and the interference of mibefradil with the biotransformation of a variety of drugs may have played significant roles, particularly in a patient population with multiple comorbidities requiring concurrent medical therapies.

## Appendix

The following participated in the MACH-1 study.

### Steering Committee

T. Barry Levine (chairman), Peter J.L.M. Bernink, Abraham Caspi, Uri Elkayam, Edward M. Geltman, Barry Greenberg, William J. McKenna, and Susan Ammon. Independent Safety and Data Monitoring Advisory Committee: C. Richard Conti (chairman), Paul G. Hugenholz, Bertram Pitt, Philip Poole-Wilson, and Manfred Olschewski (biostatistician). Critical Events Committee: Sidney Goldstein (chairman), Alexander Battler, Martial G. Bourassa, Craig M. Pratt, and Ernst E. van der Wall.

### MACH-1 Investigators

Belgium: Guy R. Heyndrickx. Canada: Vicky Bernstein, Richard F. Davies, Eleanor Elstein, W. Peter Klinke, William Kostuk, Jos F. Lopez, Claude Maranda, Henry F. Mizgala, Gordon W. Moe, Paul H. Tanser, Chris Thompson, Wayne Warnica, and Michel White. Denmark: Ole Göttsche and Knud Skagen. France: Jean-Jacques Quarante and Faiez Zannad. Germany: Dagobert Fell, Eckart Fleck, and Gerold Prager. Israel: Edward Abinader, Shimon Braun, Abraham Caspi, Aziz Darausha, Daniel David, A. André Keren, Yehezkiel Kishon, Basil Lewis, Alon Marmor, Mohammed Omary, Leonardo H. Reisin, A. Nathan Roguin, Tiberio Rosenfeld, Zvi Schlesinger, Samuel Sclarovsky, Dan Tzivoni, and Izhar Zahavi. Italy: Salvatore Caponetto, Antonello Gavazzi. The Netherlands: Peter J.L.M. Bernink, Simon H.J.G. Braat, Willem G. de Voogt, Nicolaas J. Holwerda, Herman R. Michels, Loet H.J. van Kempen, Dirk J. van Veldhuisen, and Adrie J.A.M. Withagen. Sweden: Christer Höglund, Thomas Mooe, Olof Nyqvist, Jan Östergren, and Karl Swedberg. Switzerland: Wolfgang Kiowski and Tiziano Moccetti. United Kingdom: Stephen G. Ball, G. Brigden, Andrew J.S. Coats, Henry J. Dargie, Graham J. Davies, B. Gould, R.A. Greenbaum, Peter J.B. Hubner, I. Hutton, Avijit Lahiri, William J. McKenna, John David Stephens, and Robert D.S. Watson. United States: William T. Abraham, John W. Allen, Richard Bauer, Geetha Bhat, Neville Bittar, Douglas Blank, Dean Bramlet, Carol M. Buchter, Peter E. Carson, Douglas Chapman, Kanu Chatterjee, Michael P. Cinquegrani, James A. Conrad, Douglas L. Dawley, Linda Deere, Vincent DeQuattro, Robert Di Bianco, Uri Elkayam, John Farnham, Robert Feldman, Paul E. Fenster, Haralambos Gavras, Edward M. Geltman, Jalal K. Ghali, Mihai Gheorghide, Thomas D. Giles, Susan P. Graham, John J. Gregory, Steven Herman, Ray Hersberger, Robert E. Hobbs, Ronald P. Karlsberg, Richard Kay, Nicolas Z. Kerin, Edward S. Kersh, Marvin A. Konstam, David Korn, T. Barry Levine, Chang-Seng Liang, George I. Litman, Francisco R. Maislos, James R. Margolis, Barry M. Massie, Edward K. Massin, Frank A. McGrew, Prabodh M. Mehta, Alan B. Miller, Pramod K. Mohanty, Maria-Teresa Olivari, Suzanne Oparil, Carl Oshrain, Carl Pepine, Gregory E. Peterson, Ileana L. Piña, Marc R. Pritzker, Hillel S. Ribner, Donald Schmidt, Douglas D. Schocken, John S. Schroeder, Ralph Shabetai, Yoseph Shalev, L. Kent Smith, Eric Spivack, Stephen A. Stowers, Martin J. Sullivan, Udho Thadani, Gerald C. Timmis, David E. Tolman, Guillermo Torre, Irwin Weinstein, Harold J. Willens, and John R. Wilson.

### Coordinating Center, F. Hoffmann-La Roche

Aline Andre-Frey, Gabriele Bieska, Martin Harsch, Corine Martin, Norbert Neumann, and Elisabeth Smith.

### Acknowledgment

This work was supported by a grant from Hoffmann-La Roche, Ltd.

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