

Diltiazem Increases Late-Onset Congestive Heart Failure in Postinfarction Patients With Early Reduction in Ejection Fraction

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The Multicenter Diltiazem Postinfarction Trial (MDPIT) reported no consistent diltiazem effect on new or worsened congestive heart failure (CHF) during 12–52 months' follow-up after acute myocardial infarction. This was puzzling in light of the observation that patients with findings suggesting left ventricular dysfunction (LVD) at baseline on diltiazem had more cardiac events (cardiac mortality or recurrent nonfatal infarction) than such patients on placebo. We hypothesized that diltiazem increased the frequency of late CHF as well as of cardiac events, but only in patients predisposed by LVD. Using the same characterizing variables as the primary MDPIT analysis, we found that patients with pulmonary congestion, anterolateral Q wave infarction, or reduced ejection fraction (EF) at baseline were more likely to have CHF during follow-up than those without these markers of LVD. CHF was particularly frequent in the patients with LVD who were randomized to diltiazem. Among those with a baseline EF of less than 0.40, late CHF appeared in 12% (39/326) receiving placebo and 21% (61/297) receiving diltiazem ($p=0.004$). Life table analysis in patients with an EF of less than 0.40 confirmed more frequent late CHF in those taking diltiazem ($p=0.0017$). In addition, the diltiazem-associated rise in the frequency of late CHF was progressively greater with increasingly severe decrements in baseline EF. This diltiazem effect was absent in patients with pulmonary congestion at baseline but an EF of 0.40 or more, suggesting a unique association between diltiazem-related late CHF and systolic LVD. Diltiazem-associated enhancement of CHF in patients with an EF of less than 0.40 was evident among those who took concomitant β -blockers and among those who did not. We conclude that postinfarction patients with reduced EF are at particular risk for subsequent CHF when treated with diltiazem. This problem, along with the greater occurrence of cardiac events in patients with LVD, indicates a need for caution when giving diltiazem to patients with postinfarction LVD. (*Circulation* 1991;83:52–60)

Diltiazem is effective in suppressing myocardial ischemia in patients with coronary artery disease.^{1–4} However, diltiazem and other calcium channel blockers can augment hemodynamic abnormalities in patients with congestive heart failure (CHF).^{5–9} These contrary actions would explain the findings of the Multicenter Diltiazem

Postinfarction Trial (MDPIT): during long-term follow-up, diltiazem reduced the frequency of first

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recurrent cardiac events (i.e., cardiac mortality or nonfatal reinfarction) in postinfarction patients with preserved left ventricular function but increased the

article (see Reference 10).

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frequency of such events in those with impaired left ventricular function evident soon after infarction.^{10,11} However, diltiazem did not consistently precipitate symptomatic CHF in the MDPIT patients: new or worsened CHF had a similar incidence whether patients were assigned to diltiazem (7.7%) or to placebo (7.0%).¹⁰ Since the adverse influence of diltiazem on first recurrent cardiac events was confined to groups with left ventricular dysfunction, we hypothesized that a diltiazem-associated increase in the frequency of new CHF would also be found exclusively in these groups. Because of the limited number of patients with left ventricular dysfunction (about 20% of the total MDPIT population), important diltiazem-induced augmentation of CHF in these groups would be diluted and rendered undetectable when the entire study population is considered. In a detailed secondary analysis of the MDPIT data, we evaluated the influence of study drug assignment on the occurrence of new or worsened CHF in patient groups defined by left ventricular function at initial (baseline) assessment.

Methods

General Study Procedures

MDPIT was a randomized, double-blind, placebo-controlled trial of diltiazem in 2,466 postinfarction patients followed up for 12–52 (mean 25) months to a common termination date, June 30, 1987. A full description of the MDPIT policies and procedures has been published.¹⁰ In brief, patients from 38 collaborating hospitals were enrolled and assigned to start diltiazem (240 mg/day) or placebo 3–15 days after a documented acute myocardial infarction, while still hospitalized. Patients were excluded from study enrollment if they had symptomatic hypotension, bradycardia, or complicating diseases. Patients with CHF unassociated with these conditions, however, were not excluded. The randomization procedure for assignment of study drug included blocking within each hospital on the number of days from infarction to randomization (≤ 5 or > 5 days), current use of β -blockers (yes or no), and New York Heart Association functional class (I or \geq II) 1 month before the current hospitalization.

Baseline Assessment

Chest roentgenograms were obtained for 2,399 patients (97% of enrollees) while in the coronary care unit and interpreted by staff radiologists at each collaborating hospital. Trained study coordinators coded their written reports according to a four-level scale for severity of pulmonary congestion. For this report, these data were dichotomized into a two-level variable: any pulmonary congestion (PC) versus none (no PC). Enrollment electrocardiograms from 2,464 patients were coded by the Electrocardiogram Reading Center using the recently developed Manhattan criteria.¹² Patients with left bundle branch block or paced rhythm were excluded. Anterolateral Q wave

infarction (ALQMI) was coded for patients with 0.04-second Q waves in leads I, VL, or V_1 through V_6 plus accompanying acute ST and T wave alterations. Radionuclide ejection fraction (EF) was assessed prior to discharge in 2,159 patients (88% of enrollees); in 1,066 patients (43% of enrollees) EF was measured before initiating the study drug. For this analysis, the continuous EF data were dichotomized according to the same (prespecified) criteria used in the primary data analysis: 0.40 or more and less than 0.40.¹⁰

Follow-up

After discharge, patients were evaluated every 3 months for 1 year and then every 4 months until trial completion. At each evaluation the center investigator and study coordinator took a medical history and performed a physical examination according to prespecified guidelines. All medications were recorded at each evaluation; use of agents other than the study drug was at the discretion of each patient's managing physician. New or worsened CHF was tallied as an adverse experience. The decision that an adverse experience had occurred was based on the clinical judgment of the center investigator. When an adverse experience was identified, appropriate documentation was submitted to the Food and Drug Administration and to the MDPIT Data Coordinating Center. Adverse experiences were cataloged for MDPIT coding purposes but were not required to satisfy specific clinical or laboratory criteria. Investigator identification of CHF was based on the presence of symptoms or signs of left ventricular dysfunction, such as orthopnea or bibasilar pulmonary rales. Unaccompanied edema was not regarded as indicative of CHF. Only alterations in clinical status were reported as adverse experiences; stable problems did not lead to repeated reports of an adverse experience.

Data Analysis

The primary end points for MDPIT were 1) first recurrent cardiac event (as defined above) and 2) cardiac mortality. Initial analysis related these end points to the assigned treatment and examined potential interactions between assigned treatment and 12 prespecified baseline variables.¹⁰ Bidirectional interaction was evident for three variables: in patients taking diltiazem, the presence of PC ($p < 0.01$), ALQMI, or EF less than 0.40 at baseline was associated with an increased incidence of first recurrent cardiac events relative to those taking placebo (hazard ratio 1.13–1.41) and the absence of each variable was associated with a reduced incidence of these events (hazard ratio 0.73–0.77). In the present analysis these three baseline variables were related to the occurrence of new or worsened CHF during follow-up (termed "late CHF").

For the present analysis patients were judged to have late CHF based upon one or more reports of this problem during follow-up. All such reports were utilized regardless of whether the center investigator considered the adverse experience to be drug-re-

TABLE 1. Effects of Baseline Left Ventricular Functional Parameters and Treatment Assignment on Congestive Heart Failure During Long-term Follow-up

Baseline assessment	Occurrence of CHF during follow-up			
	Placebo		Diltiazem	
	%	No. (CHF/total)	%	No. (CHF/total)
Pulmonary congestion in CCU				
Present	14.9	37/248	17.4	42/242
Absent	4.5	43/959	5.6	53/950
Acute anterolateral Q wave MI				
Yes	8.8	34/387	13.4*	52/388
No	5.6	47/846	5.2	44/843
Predischarge ejection fraction				
<0.40	12.0	39/326	20.5†	61/297
≥0.40	4.2	32/758	4.0	31/778

CHF, congestive heart failure; CCU, coronary care unit; MI, myocardial infarction.

* $p=0.041$ ($\chi^2=4.2$), † $p=0.004$ ($\chi^2=8.5$) different from placebo.

lated. As in the primary analysis, treatment group reflected the initial assignment—the “intention-to-treat” principle. Initially, the effects of treatment assignment were tested in subsets of patients with or without PC, ALQMI, or EF less than 0.40 using standard χ^2 methods. The observation of statistical significance ($p=0.004$) in the group with EF less than 0.40 justified more detailed statistical analysis of relations between EF and CHF. Life table analysis¹³ was performed using the computer program BMDP-1L; all other statistical data processing employed SAS-90 software.

The current article is based on the summary analytic data base (version 2.0) released April 16, 1988. This data base differs slightly from the one released November 1, 1987, which was used in the primary article.¹⁰ The updated data base resulted from ongoing quality control procedures and the late receipt (after November 1, 1987) of a small amount of study data. Changes in the data base involved less than 0.15% of the baseline and follow-up data, and the changes were made without knowledge of trial medication assignment or end point events. Results of the analyses using the updated data base were only negligibly different from the findings reported in the primary article. Specifically, the hazard ratios for primary end points and the occurrence rates for CHF were unchanged from those initially reported when recalculated using data base version 2.0. The hazard ratios in subgroups defined by left ventricular dysfunction (PC, ALQMI or EF less than 0.40) were each changed by less than 4%.

Results

Effects of Baseline Variables on Late CHF

The primary MDPIT analysis showed that PC, ALQMI, or EF less than 0.40 at baseline was predictive of an increased frequency of cardiac death or nonfatal reinfarction during long-term follow-up of patients assigned to take placebo.¹⁰ The same was true for late CHF: placebo-treated patients with baseline PC had a 3.3-fold increase, those with

ALQMI a 1.6-fold increase, and those with EF less than 0.40 a 2.8-fold increase in the occurrence of late CHF relative to patients lacking the corresponding baseline abnormality (Table 1). Thus, EF separated postinfarction patients into groups with high and low likelihoods of CHF during long-term follow-up. However, the routinely evaluated radiographic assessment of PC at baseline was also very effective in achieving this separation.

Diltiazem treatment had no influence on the occurrence of late CHF in any of the subsets with normal baseline variables (Table 1). In contrast, assignment to diltiazem appeared to increase the occurrence of late CHF in groups with PC, ALQMI, or EF less than 0.40. Although this was only a tendency for PC, the effect of diltiazem treatment was borderline significant ($p=0.041$) for ALQMI and highly significant ($p=0.004$) for EF less than 0.40. This effect of diltiazem did not bear an ordinal relation to the occurrence of late CHF in the absence of diltiazem: the group with the greatest diltiazem-related change (patients with EF less than 0.40) exhibited neither the highest nor the lowest occurrence of late CHF when its members received placebo.

To examine the interaction of EF, PC, and diltiazem, we separately assessed the occurrence of late CHF in patient subsets defined by baseline EF and PC as well as treatment status (Figure 1). Among placebo-treated patients with EF of 0.40 or more, those with PC much more frequently had late CHF (11.4%) than those without PC (3.0%) ($p<0.005$). When EF was 0.40 or more, diltiazem treatment did not increase the frequency of late CHF in either those with or those without PC. By contrast, when EF was less than 0.40, diltiazem-treated patients more frequently had late CHF than corresponding patients treated with placebo when PC was present and when PC was absent. Thus, in the MDPIT patients, the diltiazem-related increment in the frequency of late CHF seemed to be associated with reduced EF rather than with the presence of PC at baseline. Patients with only a reduction in EF (and no PC) comprised the subgroup

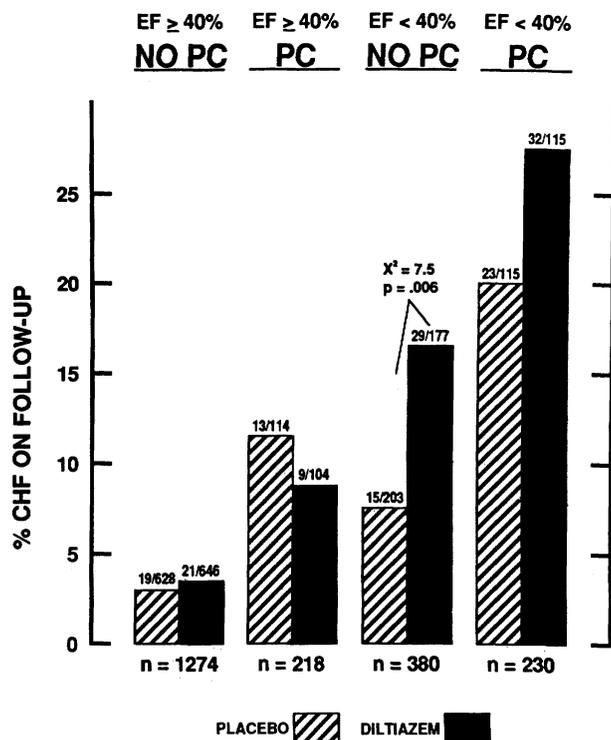


FIGURE 1. Percent of patients with new or worsened congestive heart failure (CHF) during long-term follow-up is shown for four groups defined by presence or absence of reduced ejection fraction ($EF < 0.40$) and pulmonary congestion (PC) at approximately the time of study enrollment. Paired bars demonstrate occurrence of late CHF in placebo- and diltiazem-treated subsets. Number of patients with CHF (numerator) and total number in each subset (denominator) are displayed above each bar. Number of patients in given group is indicated below corresponding pair of bars. Results are shown for 2,102 individuals with baseline evaluation of both EF and PC. Diltiazem-associated increase in late CHF was seen in both groups with $EF < 0.40$. In group with $EF < 0.40$ and no PC, increase was significant ($\chi^2 = 7.5$, $p = 0.006$); in those with $EF < 0.40$ and PC, increase was not significant ($\chi^2 = 1.9$, $p = 0.18$). Diltiazem-associated increase in late CHF was not found in either group with $EF \geq 0.40$.

with the largest diltiazem-associated difference in the occurrence of late CHF: 16.4% for diltiazem versus 7.4% for placebo ($p = 0.006$).

Baseline EF data were obtained before the initiation of study drug in 1,066 patients and 1–6 days after the initiation of study drug in 1,093 patients. These results were pooled for the analyses just presented. To assess the effects of timing of the EF determination, comparisons were repeated with these two patient groups kept separate (Table 2). Patients with EF of 0.40 or more had infrequent occurrence of late CHF, regardless of treatment group or timing of the EF determination. A diltiazem-related increase in the occurrence of CHF during follow-up was particularly evident in patients with EF less than 0.40 assessed before the initiation of study drug ($p = 0.005$ versus placebo). However, an increased occurrence

TABLE 2. Effects of Magnitude and Timing of Determination of Baseline Ejection Fraction and Treatment Assignment on Congestive Heart Failure During Long-term Follow-up

Timing	Occurrence of CHF during follow-up			
	Placebo		Diltiazem	
	%	No. (CHF/total)	%	No. (CHF/total)
EF ≥ 0.40				
Pre Rx	4.2	16/378	3.3	12/362
Post Rx	4.2	16/380	4.6	19/416
EF < 0.40				
Pre Rx	9.1	16/176	20.0*	30/150
Post Rx	15.3	23/150	21.1	31/147

CHF, congestive heart failure; EF, ejection fraction at baseline; Rx, initiation of therapy with study drug.

* $p = 0.005$ ($\chi^2 = 8.0$) different from placebo.

of late CHF was also observed in diltiazem-treated patients with baseline EF less than 0.40 determined after the study drug was started. The homogeneity of diltiazem's influence provided justification for the pooling of data from patients with early and late determination of baseline EF.

Detailed Analyses of Baseline EF and Late CHF

The relation between baseline EF and late CHF was further explored by comparing placebo- and diltiazem-treated subsets within each of four EF categories (Figure 2). The occurrence of late CHF was low (3.9% overall) in patients with normal baseline EF (≥ 0.45) and not different in subsets treated with placebo or diltiazem. Progressively more severe impairment of baseline EF was associated with progressively greater occurrence of late CHF. Although this increase was evident for both placebo- and diltiazem-treated subsets, patients receiving diltiazem had a more rapid rise. Thus, the more severe the reduction in baseline EF, the greater the increment in diltiazem-associated occurrence of late CHF relative to placebo. This was evident in the ratio of percentages with CHF in each treatment category (Figure 2). These ratios increased with declining baseline EF, reaching a maximum of 1.78 (i.e., a 78% greater occurrence of late CHF) associated with diltiazem treatment in the lowest EF category (< 0.25).

The association between diltiazem treatment and increased occurrence of late CHF in patients with reduced EF was further substantiated by life table analysis of patients with EF less than 0.40 (Figure 3). Patients receiving placebo had a relatively high rate of CHF occurrence during the first 60 days after randomization, with a gradual shift to a lesser rate that remained stable for the balance of the study. Patients receiving diltiazem had an initial rate of CHF occurrence that was substantially greater than the initial rate for patients receiving placebo. The curves for placebo- and diltiazem-treated patients were roughly parallel for the remainder of the study, suggesting that later occurrence rates were similar in the two treatment subsets. The curves for the two

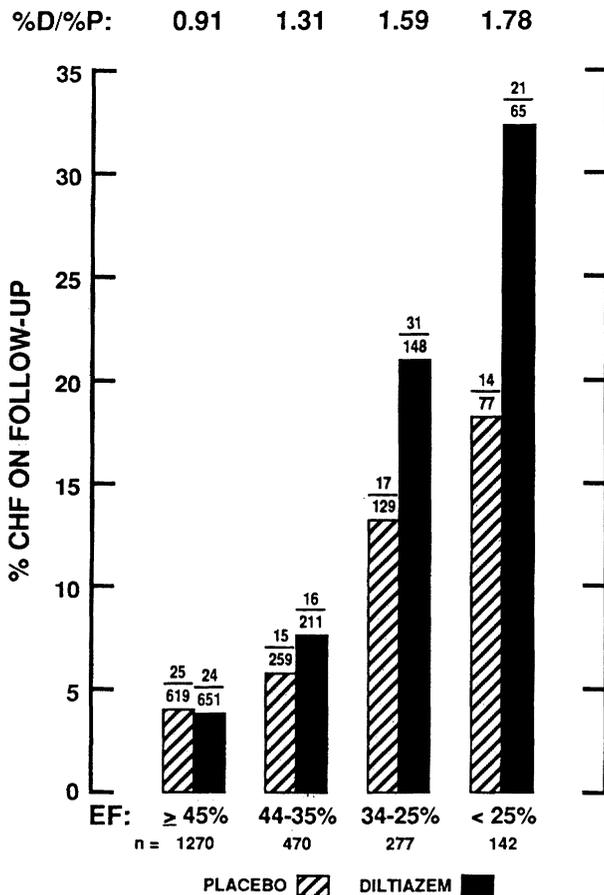


FIGURE 2. Percent of patients with new or worsened congestive heart failure (CHF) during long-term follow-up is shown for four groups defined solely by baseline ejection fraction (EF): ≥ 0.45 , 0.44–0.35, 0.34–0.25, and < 0.25 . Paired bars demonstrate occurrence of late CHF in placebo- and diltiazem-treated subsets. Number of patients with CHF (numerator) and total number in each subset (denominator) are displayed above each bar. At top of figure, value for each group shows percent of patients with late CHF among those given diltiazem (D) divided by percent of patients with late CHF among those given placebo (P). Data are shown for 2,159 patients with baseline measurement of EF. Diltiazem-associated increase in late CHF is progressively larger as baseline EF is reduced.

treatment subsets were significantly different ($p=0.0017$ by Tarone–Ware test). Similar life table comparison of treatment subsets in patients with baseline EF less than 0.40 used two other end points: 1) cardiac death and 2) cardiac death or late CHF. In either case, diltiazem-treated patients tended to have greater initial and subsequent rates of occurrence of adverse outcome. However, the difference between treatment subsets was significant ($p=0.028$ by Tarone–Ware test) only for the combined end point cardiac death or late CHF.

Covariate Effects

More frequent occurrence of late CHF in diltiazem-treated patients with low baseline EF may

reflect a spurious association of diltiazem therapy with recognized predictors of adverse outcome in postinfarction patients. Twelve baseline variables of particular relevance¹⁰ were assessed in placebo- and diltiazem-treated subsets of patients with EF less than 0.40 (Table 3). The frequency of abnormality of each variable did not differ in the two treatment subsets. Thus, the observed influence of diltiazem is not attributable to imbalance of one or more of these variables.

Concomitant use of β -blockers was examined because of the potential additivity of negatively inotropic drug action with that of diltiazem in predisposed patients. Patients were grouped based on β -blocker usage at study enrollment since detailed analysis revealed little change in β -blocker status during follow-up: 12 months after enrollment 76% of patients (1,601/2,096) had not changed with respect to use or nonuse of β -blockers. Groups taking β -blockers had less frequent late CHF than corresponding groups not taking β -blockers (Figure 4), an outcome that may reflect selection bias (β -blockers were not randomly allocated) as well as a drug effect. Occurrence of late CHF was compared in placebo- and diltiazem-treated patients within groups defined by β -blocker use and baseline EF (Figure 4). Diltiazem treatment was associated with an increased frequency of late CHF in both patient groups having EF less than 0.40—those not using β -blockers (ratio of percentages with late CHF [diltiazem/placebo]=1.80) as well as those using β -blockers (ratio of percentages=1.54). The connection with diltiazem was stronger and significant ($p=0.008$) in patients with EF less than 0.40 not using β -blockers. In patients with EF less than 0.40 who used β -blockers, the diltiazem-associated increase was not significant ($p=0.22$). Diltiazem treatment was not associated with an increased frequency of late CHF in patients with EF of 0.40 or more, independent of β -blocker usage.

Clinical Events in Patients With Late CHF

New or worsened CHF during follow-up was reported as “a potentially serious cardiovascular complication” by the local center investigator in 157 of 177 instances (89%). Study medication was discontinued during 45% (80) of these episodes. Only 13 of the episodes (7%) occurred within 1 week of a cardiac event (recurrent nonfatal myocardial infarction or cardiac death). Of the patients experiencing new or worsened CHF, 69 (39%) eventually developed cardiac events and 52 (29%) had cardiac deaths. These rates are 3.4-fold and 2.5-fold greater, respectively, than corresponding rates for patients without CHF. Cardiac mortality occurred in 34 (35%) of 96 patients with late CHF assigned to diltiazem treatment and in 18 (22%) of 81 patients with late CHF assigned to placebo ($p=0.055$).

Pathophysiologic events at the time of death were not examined in the present analysis. In a recent evaluation of MDPIT data, Marcus et al¹⁴ stated, “There was no evidence that the ratio of arrhythmia to myocardial failure deaths varied for patients with

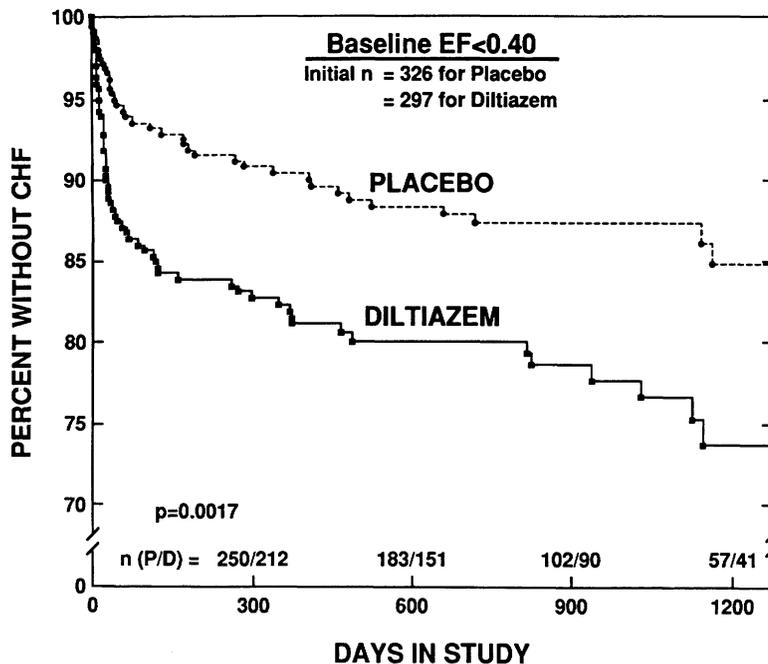


FIGURE 3. Life table analysis showing occurrence of new or worsened congestive heart failure (CHF) in postinfarction patients with ejection fraction (EF) of <0.40 at study enrollment. Percent remaining without CHF (vertical axis) is plotted against days after study enrollment (horizontal axis). Initially, 326 patients were assigned to placebo (dashed line) and 297 were assigned to diltiazem (solid line). Numbers of patients participating in follow-up on days 300, 600, 900, and 1,200 are shown (as placebo/diltiazem) above horizontal axis.

pulmonary congestion compared to those without it, and this ratio did not vary significantly between treatment groups.”

Discussion

The primary MDPIT analysis found no overall increase in the frequency of late CHF among postinfarction patients receiving diltiazem.¹⁰ The analysis also identified a diltiazem-related increment in the frequency of recurrent cardiac events in patients with early evidence of left ventricular dysfunction.^{10,11} These results were puzzling: diltiazem-induced exacerbation of impaired performance was suggested by the cardiac event data but not confirmed by the data regarding late CHF. The present, secondary analysis extends and clarifies the previous findings by showing that late CHF occurs more frequently in patients with the same markers of left ventricular dysfunction identified in the primary MDPIT analysis (Table 1). Results from the Beta-Blocker Heart Attack Trial (BHAT) generally support this association: a two-fold to threefold increase in the frequency of late CHF was noted among patients with previous myocardial infarction, history of CHF before the index infarction, enlarged cardiothoracic ratio, use of digitalis, and other clinical indicators of left ventricular dysfunction.¹⁵

More importantly, the present analysis of MDPIT data demonstrates that patients with peri-infarction left ventricular dysfunction assigned to diltiazem more frequently have new or worsened CHF during follow-up than patients assigned to placebo. This appears particularly evident for patients with reduced EF. A highly significant diltiazem-associated increment in the frequency of late CHF is seen among patients with EF less than 0.40 (Table 1). This

is further supported by the progressive rise of the diltiazem-associated increment in occurrence of late CHF with greater reduction in EF (Figure 2) and by the consistently increased incidence of late CHF in diltiazem-treated individuals observed on life table analysis of patients with EF less than 0.40 (Figure 3).

These results could reflect an imbalanced distribution of adverse characteristics in placebo- and diltiazem-treated subsets as well as diltiazem effects that promote late CHF. However, the blinded, randomized character of MDPIT drug assignment acted to balance clinical variables, supplemental pharmacologic management, and end point identification. The comparability of patients in placebo- and diltiazem-treated subsets is further substantiated by examination of relevant clinical parameters (Table 3). Features other than drug assignment that might lead to an increased frequency of late CHF were equally represented in placebo- and diltiazem-treated subsets.

A spurious increase in the occurrence of late CHF might also result from a diltiazem-mediated decrease in the frequency of cardiac deaths among patients with reduced EF. More individuals with severely impaired left ventricles kept alive in the diltiazem-treated group could increase this group's occurrence of CHF. Under these circumstances, life table analysis would show diltiazem to be better than placebo in relation to cardiac mortality and equivalent to placebo in relation to the combined end point of cardiac mortality or late CHF. In fact, the diltiazem-treated group had no better cardiac mortality and had a worsened occurrence of the combined end point. These results indicate that the diltiazem-associated increase in the frequency of CHF in patients

TABLE 3. Distribution of Baseline Variables in Patients Grouped by Baseline Ejection Fraction and Treatment Assignment

Variable	EF \geq 40%				EF <40%			
	Placebo (n=758)		Diltiazem (n=778)		Placebo (n=326)		Diltiazem (n=297)	
	No.	%	No.	%	No.	%	No.	%
NYHA class								
I	646	85	641	82	246	75	227	76
II-IV	112	15	137	18	80	25	70	24
β -blockers*								
Yes	330	44	343	44	129	40	116	39
No	428	56	435	56	197	60	181	61
Entry after MI (days)†								
\leq 5	130	17	132	17	42	13	48	16
>5	628	83	646	83	284	87	249	84
Age (yr)								
<60	380	50	403	52	160	49	132	44
\geq 60	378	50	375	48	166	51	165	56
Sex								
Female	175	23	164	21	57	17	44	15
Male	583	77	614	79	269	83	253	85
Pulmonary congestion‡								
No	628	85	646	86	203	64	177	61
Yes	114	15	104	14	115	36	115	39
Acute ALQ								
No	595	80	586	78	123	39	102	36
Yes	149	20	169	22	195	61	182	64
Acute IPQ								
No	388	52	387	51	250	79	215	76
Yes	356	48	364	49	68	21	69	24
Acute Non-Q MI								
No	505	68	537	71	263	83	251	88
Yes	239	32	218	29	55	17	33	12
Ventricular ectopics§								
<10/hr	462	88	490	88	147	71	148	74
\geq 10/hr	65	12	68	12	59	29	51	26
Blood urea nitrogen								
\leq 35 mg/dl	717	95	737	95	281	87	262	89
>35 mg/dl	40	5	36	5	43	13	34	11

ALQ, anterolateral Q wave; EF, radionuclide ejection fraction; IPQ, inferoposterior Q wave; MI, myocardial infarction; NYHA, New York Heart Association.

*Drug use at randomization.

†Days elapsed between acute myocardial infarction and study entry (randomization).

‡On radiographs taken in the coronary care unit.

§On 24-hour Holter monitoring.

with EF less than 0.40 cannot be attributed to salvage of those most predisposed to CHF.

The findings presented here must be viewed with caution since the underlying hypotheses are secondary and their investigation is retrospective. Nonetheless, the findings of this analysis and the primary article¹⁰ are consistent: diltiazem appeared to increase the occurrence of overt late CHF as well as recurrent cardiac events in patients with left ventricular dysfunction. These observations suggest that

diltiazem initiates pathophysiologic mechanisms favoring both of these complications. For example, diltiazem may enhance neuroendocrine activation in these patients, thereby accelerating left ventricular decompensation¹⁶ and augmenting the likelihood of lethal arrhythmia.¹⁷ In addition, negatively inotropic actions of diltiazem could act to increase the likelihood of late CHF in predisposed patients. The diltiazem-associated increase in the frequency of late CHF seems uniquely related to reduced EF (Table 1 and Figure 2). This increase is not seen in patients with PC and EF of 0.40 or more despite the frequent (11%) occurrence of late CHF. Diltiazem may cause particularly evident adverse effects in patients with systolic dysfunction (reduced EF). Such effects may be mitigated by favorable actions of calcium channel blockade in patients whose main difficulty is ischemia or diastolic dysfunction (PC with normal EF).

It is noteworthy that long-term diltiazem treatment appeared to increase the frequency of late CHF in postinfarction patients with left ventricular dysfunction, while a similar adverse drug action was not found in BHAT, a randomized study of propranolol.¹⁵ This may reflect differing effects of calcium channel blockers and β -blockers on neuroendocrine activation.¹⁶ However, the MDPIT data demonstrated an unequivocal diltiazem-related increase in the frequency of late CHF only in patients with EF less than 0.40, a group not defined in BHAT. The MDPIT group identified by PC, a less precise measure of left ventricular dysfunction, showed a nonsignificant trend toward a diltiazem-related increase in the frequency of late CHF (Table 1). This finding is not very different from the BHAT results regarding propranolol in the postinfarction patients at higher risk for CHF.¹⁵ Mortality data more clearly demonstrated a difference between propranolol and diltiazem in patients with left ventricular dysfunction: propranolol substantially reduced the rate of cardiac death in these patients¹⁵ while diltiazem augmented the frequency of cardiac death in a similar group.¹⁰

The interaction of diltiazem and β -blockers within the MDPIT data base is potentially relevant because of shared negatively inotropic influences of these drugs. A diltiazem-associated increase in the frequency of late CHF was fully manifested in patients with EF less than 0.40 who were not taking β -blockers (Figure 4). Thus, this increase did not require concomitant β -blockade, which might have offered a preconditioning negatively inotropic action or inhibition of adrenergic compensation^{18,19} in patients with reduced EF. In fact, patients in each EF category who took β -blockers had somewhat less frequent late CHF than corresponding patients not taking β -blockers. A trend toward diltiazem enhancement of late CHF was evident in patients with EF less than 0.40 who took β -blockers; β -blockade did not eliminate this diltiazem influence.

The appearance of CHF during follow-up was clinically distinctive. In most cases the onset of CHF was judged to be a serious occurrence by managing physi-

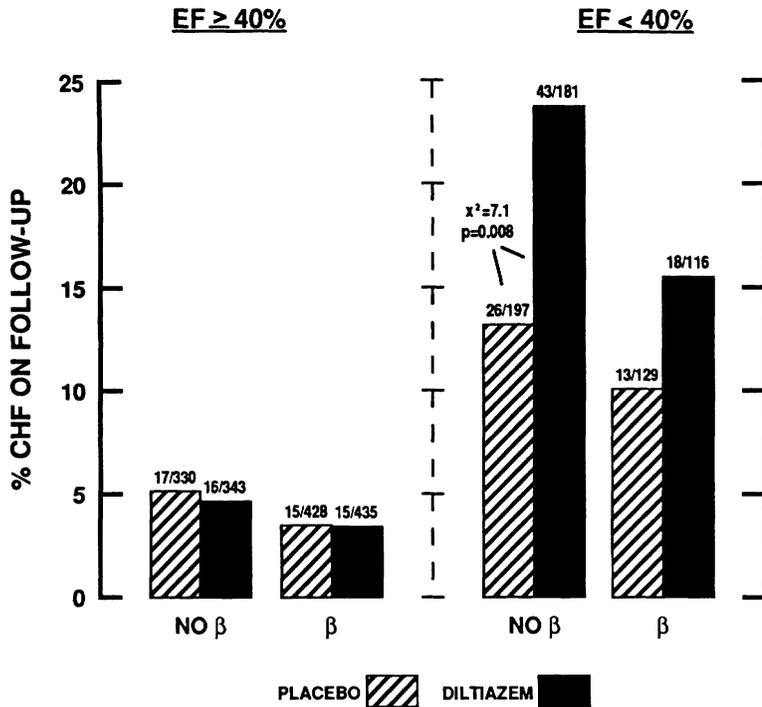


FIGURE 4. Percent of patients with new or worsened congestive heart failure (CHF) on long-term follow-up is shown for four groups defined by baseline ejection fraction (EF), dichotomized at 0.40, and use (β) or nonuse (NO β) of β -blockers. Paired bars demonstrate occurrence of late CHF in placebo- and diltiazem-treated subsets. Number of patients with CHF (numerator) and total number in each subset (denominator) are displayed above each bar. Results are shown for 2,159 individuals with baseline evaluation of EF. Diltiazem-associated increase in late occurrence of CHF was seen in both groups with EF < 0.40. In group with EF < 0.40 and NO β , increase was significant ($\chi^2=7.1$, $p=0.008$); in those with EF < 0.40 and β , increase was not significant ($\chi^2=1.6$, $p=0.22$). Diltiazem-associated increase in late CHF was not found in either group with EF ≥ 0.40 .

cians. Of the patients developing CHF, 29% later experienced cardiac death, a rate 2.5-fold greater than that in patients without CHF. The results presented here confirm that the occurrence of CHF during the months following acute myocardial infarction is substantially increased in patients with evidence of left ventricular dysfunction at the time of the acute infarction. The likelihood of late CHF is further enhanced in patients taking diltiazem. Thus, the risks of diltiazem use by patients with peri-infarction left ventricular dysfunction include not only increased frequency of cardiac events (cardiac mortality or recurrent non-fatal infarction) but also increased development of late CHF. By identifying an additional, independently assessed adverse consequence of diltiazem use, the present analysis reinforces the recommendation arising from the primary MDPIT analysis¹⁰ that diltiazem therapy should be avoided in postinfarction patients with left ventricular dysfunction. In particular, the results regarding the late appearance of CHF suggest that diltiazem use should be avoided in patients with substantially reduced EF.

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