JACC Vol. 29, No. 2
February 1997:229–36

CLINICAL STUDIES

MYOCARDIAL INFARCTION

Additive Beneficial Effects of Beta-Blockers to Angiotensin-Converting Enzyme Inhibitors in the Survival and Ventricular Enlargement (SAVE) Study

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Objectives. **This study assessed whether treatment with a beta-adrenergic blocking agent in addition to the use of the angiotensin-converting enzyme (ACE) inhibitor captopril decreases cardiovascular mortality and morbidity in patients with asymptomatic left ventricular dysfunction after myocardial infarction (MI) and whether the presence of neurohumoral activation at the time of hospital discharge predicts the effects of beta-blocker treatment in these patients.**

Background. **Both beta-blockers and ACE inhibitors have been shown to have beneficial effects in patients with left ventricular dysfunction but no overt heart failure after MI. These patients often have persistent neurohumoral activation at the time of hospital discharge, and one would expect that patients with activation of the sympathetic nervous system derive the most benefit from treatment with beta-blockers. However, beta-blockers are underutilized in this high risk group of patients, and it is unknown whether their beneficial effects are additive to those of ACE inhibitors.**

Methods. **We performed a retrospective analysis of data from the Survival and Ventricular Enlargement (SAVE) study and its neurohumoral substudy. The relations between beta-blocker use at the time of randomization and neurohumoral activation and the subsequent development of cardiovascular events were analyzed by use of Cox proportional hazards models controlling for covariates.**

Results. **After adjustment for baseline imbalances, beta-blocker use was associated with a significant reduction in risk of cardiovascular death (30%, 95% confidence interval [CI] 12% to 44%) and development of heart failure (21%, 95% CI 3% to 36%), but the reduction in recurrent MI (11%, 95% CI 13% to 31%) was not significant. These reductions were independent of the use of captopril. Beta-blockers were not found to have a greater effect in patients with neurohumoral activation at the time of hospital discharge.**

Conclusions. **The beneficial effects of beta-blocker use at the time of hospital discharge in patients with asymptomatic left ventricular dysfunction after MI appear to be additive to those of captopril and other interventions known to improve prognosis. Neurohumoral activation at the time of hospital discharge fails to identify those patients who will derive the greatest benefit from treatment with beta-blockers.**

(J Am Coll Cardiol 1997;29:229–36)

The Survival and Ventricular Enlargement (SAVE) study (1) demonstrated that long-term therapy with the angiotensin-converting enzyme (ACE) inhibitor captopril decreased mortality and morbidity among survivors of myocardial infarction (MI) who had left ventricular dysfunction in the absence of overt heart failure. Because neurohumoral activation occurs in a significant proportion of these patients at the time of hospital discharge (2), and because blockade of the renin-angiotensin-aldosterone system is one of the mechanisms of action of ACE inhibitors, it can be hypothesized that blockade of the sympathetic nervous system with beta-adrenergic blocking agents would be beneficial as well in this patient population. However, although the use of beta-blockers as secondary prevention is of proven value in the population of postinfarction patients at large (3), these agents are still relatively underutilized (4,5). In particular, their prescription in patients with impaired left ventricular function is too infrequent, probably because of fear of precipitating or aggravating heart failure. This hesitation to treat with beta-blockers persists and this despite evidence that these high risk postinfarction patients have the most to gain in absolute terms from such treatment (6–9). Indeed, left ventricular dysfunction has been found (5,10) to be a predictor of

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Manuscript received June 28, 1996; revised manuscript received October 15, 1996, accepted October 18, 1996.

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0735-1097/97/$17.00
PII SI0735-1097(96)00489-5

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CI = confidence interval
MI = myocardial infarction
SAVE = Survival and Ventricular Enlargement study

failure to prescribe beta-blockers. Furthermore, it is unclear whether these agents confer an additional benefit to the patient with asymptomatic left ventricular dysfunction who is already taking an ACE inhibitor.

In a previous analysis of the SAVE neurohumoral data (11), we demonstrated that neurohumoral activation at the time of hospital discharge after MI was associated with a higher risk of subsequent cardiovascular events (11). In particular, activation of the adrenergic system, as reflected by increased plasma norepinephrine values, was associated with a poor prognosis. Intuitively, one would expect those patients with elevated plasma norepinephrine levels to benefit the most from beta-blocker therapy, but there are no data that support this supposition.

Therefore, we conducted a retrospective analysis of data from the SAVE study to address two questions concerning survivors of MI with left ventricular dysfunction in the absence of overt heart failure: 1) Does treatment with a beta-blocker have a beneficial effect on cardiovascular mortality and morbidity in addition to and independently of the use of captopril? 2) Is there a relation between neurohumoral activation at the time of hospital discharge and the subsequent effect of beta-blockers?

Methods

Patients. The SAVE study enrolled 2,231 patients, of whom 534 participated in a substudy to evaluate the degree and prognostic significance of neurohumoral activation at the time of hospital discharge after MI. The methods and results of the main study and the neurohumoral substudy were reported previously (1,2,11,12). Briefly, only patients with a left ventricular ejection fraction ≤40% by radionuclide ventriculography and without overt heart failure or heart failure requiring vasodilator therapy were recruited and randomized to captopril or placebo therapy commencing 3 to 16 days after MI. Exclusion criteria were contraindications to the use of an ACE inhibitor; concurrent medical problems, such as renal insufficiency (creatinine >2.5 mg/dl), severe valvular disease, refractory hypertension, malignancy or other conditions thought to limit survival; geographic problems; or inability or unwillingness to give informed consent. Patients with ischemic symptoms or markedly positive exercise test results were also excluded unless cardiac catheterization and appropriate revascularization procedures were conducted before randomization. The average length of follow-up (±SD) for the surviving patients was 42 ± 10 months in the total SAVE population and 38 ± 7 months in the group constituting the neurohumoral substudy.

The patients taking part in the neurohumoral substudy consented to have additional blood samples drawn before their randomization (mean 12 days after MI), to measure plasma renin activity and plasma concentrations of norepinephrine, atrial natriuretic peptide, arginine vasopressin, epinephrine, aldosterone and dopamine. An indwelling venous cannula was inserted on the morning after an overnight fast, and the patient had to rest in the supine position for 30 min before blood sampling. The samples were centrifuged at 4°C, frozen at −80°C and sent monthly to the central laboratory (Hôpital du Sacré-Coeur de Montréal) packed in dry ice. All sample transfers between peripheral and central laboratories took <24 h. Samples that were delayed, hemolyzed or thawed were not measured. Previously described neurohormone assays (13,14) were used. To minimize the loss of activity, ANP levels were measured as soon as the samples were received (15). Activation of a neurohormone was considered present when the plasma activity or level was equal to or higher than the mean plus 1.96 times the standard deviation of 38 age-matched control subjects without known disease and not taking medication (57 ± 7 years; 14 women) (2). Blood samples from these control subjects were obtained and handled in a manner identical to that used for the SAVE patients.

End points. The end points studied were 1-year cardiovascular mortality, total cardiovascular mortality, severe heart failure, recurrent MI and the combined end point of total cardiovascular mortality or severe heart failure or recurrent MI, whichever occurred first. An independent committee assessed and classified deaths as to whether they resulted from cardiovascular disease. *Severe heart failure* was defined as heart failure requiring hospital admission for management or clinical deterioration requiring the use of open label ACE inhibition. *Recurrent MI* was defined as a clinical MI by the participating center or for fatal events by the mortality committee.

Data analysis. Information about beta-blocker use was systematically obtained as part of the recruitment and follow-up procedure of the SAVE study. Use of a beta-blocker was optional and was left to the discretion of the treating physician. Neither type nor dose of beta-blocker nor indication for its use was recorded. Analysis was carried out on an intention to treat basis: Depending on whether patients were taking a beta-blocker at randomization, they were categorized into the group using a beta-blocker or the group not using a beta-blocker regardless of the patient's postbaseline beta-blocker exposure.

Baseline characteristics of different patient categories were compared by use of the two-sample *t* test for continuous variables and chi-square tests for categoric variables.

Cox proportional hazard models were used to analyze the relations between beta-blocker use and subsequent end points in the entire SAVE population as well as in the neurohumoral subgroup. Relative risk (more precisely, relative hazard), 95% confidence intervals and Wald chi-square and p values were derived from the regression coefficients of the independent

Table 1. Baseline Characteristics

	Entire SAVE Population (n = 2,231)			Neurohumoral Subgroup (n = 534)			
	No BBs (n = 1,442)	BBs (n = 789)	p Value*	No BBs (n = 352)	BBs (n = 182)	p Value*	p Value†
Age (yr)	60 ± 10	58 ± 11	<0.001	61 ± 11	59 ± 10	NS	0.039
Male gender	82	83	NS	83	79	NS	NS
Previous MI	37	32	0.016	35	34	NS	NS
Diabetes	23	21	NS	20	20	NS	NS
Hypertension	35	42	0.003	26	38	0.006	<0.001
LVEF	30 ± 7	32 ± 6	<0.001	30 ± 7	33 ± 6	<0.001	NS
Thrombolysis	33	38	0.015	32	33	NS	NS
Captopril	50	50	NS	51	49	NS	NS
Aspirin or warfarin	75	80	0.018	74	85	0.003	NS
Highest serum CK (U/liter)	2,598 ± 2,462	2,594 ± 2,168	NS	2,590 ± 2,275	2,547 ± 1,911	NS	NS
Revascularization before randomization	25	21	0.016	13	13	NS	<0.001

*No beta-blockers (BBs) versus beta-blockers. †Neurohumoral subgroup versus remainder of SAVE population. Data presented are mean value ± SD or percent of patients. CK = creatine kinase; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SAVE = Survival and Ventricular Enlargement study.

variables. First, a univariate analysis was performed with beta-blocker use as the only independent variable. Then, nine major independent variables (age, gender, history of previous MI, diabetes mellitus, hypertension, left ventricular ejection fraction, use of thrombolytic therapy, use of aspirin or warfarin, and randomization to captopril) were added to the model, and a multivariate analysis was conducted.

To compare the effect of beta-blockers on the development of end points in patients with and without activation of a particular neurohormone, the neurohumoral subgroup was stratified according to the absence or presence of neurohumoral activation. Within each stratum, the score statistic of a univariate Cox model with beta-blocker use as the independent variable was used to assess differences in event-free survival between patients receiving beta-blockers and those not receiving these agents for each type of end point. Survival curves were generated by the Kaplan-Meier method. To determine whether neurohumoral activation modifies the relation between beta-blocker use and subsequent end points, a multivariate Cox model was used in the neurohumoral subgroup as a whole, with beta-blocker use, dichotomized neurohormone level (activation or not) and an interaction term as independent variables. The *interaction term* was defined as the product of the other two independent variables.

All statistical analyses were performed using the SAS and the BMDP software packages. The reported probability values are two-tailed, and a significance level of 0.05 was used.

Results

Patient characteristics. Table 1 shows the baseline characteristics of the entire SAVE population as well as of the 534 patients in the neurohumoral substudy. The neurohumoral substudy patients did not differ from the rest of the SAVE population with respect to male/female ratio; history of MI or diabetes; left ventricular ejection fraction; use of thrombolysis and captopril; use of warfarin or aspirin; and peak creatine kinase level. However, the patients in the neurohumoral substudy, were slightly older, less often had hypertension and underwent less revascularization procedures before randomization. The proportion of patients receiving beta-blocker therapy in the neurohumoral subgroup and the proportion in the remainder of the population were comparable (34% and 36% respectively, p = NS). Both in the entire SAVE population and in the neurohumoral subgroup, patients using beta-blockers had a higher incidence of hypertension and a higher left ventricular ejection fraction and were more often treated with aspirin or warfarin. Furthermore, in the entire SAVE population, but not in the neurohumoral subgroup, patients taking beta-blockers were younger, were less likely to have had a previous MI, received thrombolytic agents more frequently and underwent less revascularization procedures before randomization. In the neurohumoral subgroup, neurohormone

Table 2. Neurohumoral Variables*

	No BBs	BBs
Plasma renin activity (ng/ml per liter) (n = 506)	3.12 ± 4.0	2.60 ± 3.0
% activated	22	21
Plasma NE (pg/ml) (n = 506)	297 ± 189	300 ± 198
% activated	24	23
Plasma ANP (pg/ml) (n = 508)	77 ± 79	73 ± 69
% activated	66	66
Plasma AVP (pg/ml) (n = 506)	2.1 ± 8.1	1.4 ± 2.5
% activated	30	27
Plasma epinephrine (pg/ml) (n = 505)	36.1 ± 30.3	36.3 ± 23.4
% activated	9	9
Plasma aldosterone (ng/dl) (n = 504)	27.7 ± 30.8	25.5 ± 20.1
% activated	27	25
Plasma dopamine (pg/ml) (n = 496)	27.7 ± 25.0	27.9 ± 23.5
% activated	26	26

*p = NS for all comparisons. Data presented are mean values ± SD or percent of patients. Activated = a value 1.96 SD above the mean level in age-matched control subjects; ANP = atrial natriuretic peptide; AVP = arginine vasopressin; BBs = beta-blockers; NE = norepinephrine.

Table 3. Univariate Cox Proportional Hazards Analysis of Relations Between Beta-Blocker Use at Baseline and Individual End Points

	Entire SAVE Population					Neurohumoral Subgroup				
	No BBs (n = 1,442)	BBs (n = 789)	Wald Chi-Square	p Value	RR (95% CI)	No BBs (n = 352)	BBs (n = 182)	Wald Chi-Square	p Value	RR (95% CI)
1-yr CV mortality	11.9	7.1	12.36	<0.001	0.58 (0.43–0.79)	11.1	5.5	4.26	0.039	0.48 (0.24–0.96)
Total CV mortality	22.1	13.1	25.43	<0.001	0.57 (0.45–0.71)	19.0	10.4	6.55	0.011	0.51 (0.31–0.86)
Severe HF	22.6	16.5	14.24	<0.001	0.68 (0.55–0.83)	19.0	12.6	4.25	0.039	0.61 (0.38–0.98)
Recurrent MI	14.3	12.3	2.68	NS	0.82 (0.64–1.04)	11.7	9.9	0.62	NS	0.80 (0.46–1.39)
CV mortality or severe HF or recurrent MI	39.7	29.8	18.17	<0.001	0.72 (0.62–0.84)	32.4	26.9	2.25	NS	0.77 (0.55–1.08)

CI = confidence interval; CV = cardiovascular; HF = heart failure; RR = relative risk; other abbreviations as in Table 1.

levels and the proportion of patients with activation of a specific neurohormone were similar for patients using beta-blockers and those not using beta-blockers (Table 2).

Effects of beta-blocker use on end points. The univariate relations between beta-blocker use and subsequent end points are shown in Table 3. In the entire SAVE population, the use of beta-blockers was significantly associated with lower 1-year cardiovascular mortality, total cardiovascular mortality, occurrence of severe heart failure and occurrence of the combined end point. Although patients using beta-blockers had a lower risk of developing a recurrent MI, this risk reduction did not reach statistical significance. Although a qualitatively and quantitatively similar reduction in risk associated with beta-blocker use was noted in the neurohumoral subgroup, because of the smaller number of patients and thus wider confidence intervals, only the reductions of 1-year cardiovascular mortality, total cardiovascular mortality and development of severe heart failure were statistically significant.

More important, when the use of beta-blockers was considered along with age, gender, history of previous MI, hypertension, diabetes mellitus, left ventricular ejection fraction, use of thrombolysis, randomization to captopril and use of aspirin or warfarin in multivariate analyses (Table 4) in the total SAVE population, the influence of beta-blocker use at randomization remained significant. However, the reductions in relative risk associated with the use of beta-blockers were smaller, suggesting that beta-blocker effectiveness may be associated with covariates and that imbalances existed in the use of beta-blockers. In the neurohumoral subpopulation, despite being qualitatively and quantitatively similar to those observed in the total SAVE population, the reductions in risk associated with the use of beta-blockers were not statistically significant, perhaps because of the small number of events in proportion to the number of independent variables used in the multivariate analyses.

Role of neurohumoral activation. Table 5 shows the effects of beta-blockers on cardiovascular events in the neurohumoral subgroup according to the absence or presence of neurohumoral activation. For the most part, beta-blockers were not found to have a greater effect in patients with neurohumoral activation. On the contrary, with the exception of atrial natriuretic peptide, beta-blockers appeared to have less or even no effect in the presence of neurohumoral activation and to be most effective in patients without neurohumoral activation, as illustrated in Figure 1 for norepinephrine. Table 6 shows that a statistically significant interaction between the use of beta-blockers and neurohumoral activation could be found only in the relations between total cardiovascular mortality and activation of norepinephrine and aldosterone. In both cases the regression coefficient of the interaction term has a positive sign, meaning that neurohumoral activation reduces the efficacy of beta-blockers.

Discussion

The present study demonstrates that, irrespective of randomization to captopril, survivors of MI who have asymptomatic left ventricular dysfunction and who are taking a beta-

Table 4. Multivariate Cox Proportional Hazards Analysis of Relations Between Beta-Blocker Use at Baseline and Individual End Points

	Entire SAVE Population			Neurohumoral Subgroup		
	Wald Chi-Square	p Value	RR (95% CI)	Wald Chi-Square	p Value	RR (95% CI)
1-yr CV mortality	3.78	0.052	0.74 (0.54–1.00)	0.89	NS	0.71 (0.34–1.46)
Total CV mortality	9.35	0.002	0.70 (0.56–0.88)	1.35	NS	0.73 (0.43–1.24)
Severe HF	5.09	0.024	0.79 (0.64–0.97)	3.22	NS	0.63 (0.38–1.04)
Recurrent MI	0.96	NS	0.89 (0.69–1.13)	0.10	NS	0.91 (0.51–1.62)
CV mortality or severe HF or recurrent MI	6.12	0.013	0.82 (0.71–0.96)	1.06	NS	0.83 (0.59–1.18)

Abbreviations as in Tables 1 and 3.

Table 5. Effects of Beta-Blockers According to Absence or Presence of Neurohumoral Activation in the Neurohumoral Subgroup*

	Neurohumoral Activation Absent					Neurohumoral Activation Present				
	No BBs	BBs	RR (95% CI)	Score Statistic	p Value†	No BBs	BBs	RR (95% CI)	Score Statistic	p Value†
1-yr CV mortality										
Renin	27/262 (10.3%)	5/134 (3.7%)	0.35 (0.13–0.91)	5.083	0.024	11/75 (14.7%)	5/35 (14.3%)	0.96 (0.33–2.75)	0.007	NS
NE	27/258 (10.5%)	4/128 (3.1%)	0.29 (0.10–0.82)	6.184	0.013	10/81 (12.4%)	5/39 (12.8%)	1.04 (0.35–3.04)	0.005	NS
ANP	5/116 (4.3%)	3/58 (5.2%)	1.20 (0.29–5.03)	0.063	NS	33/223 (14.8%)	7/111 (6.3%)	0.41 (0.18–0.92)	5.021	0.025
AVP	22/235 (9.4%)	7/124 (5.7%)	0.59 (0.25–1.39)	1.472	NS	15/102 (14.7%)	3/45 (6.7%)	0.43 (0.12–1.49)	1.883	NS
Epinephrine	31/306 (10.1%)	8/152 (5.3%)	0.51 (0.23–1.10)	3.048	0.081	6/32 (18.8%)	1/15 (6.7%)	0.34 (0.04–2.84)	1.083	NS
Aldosterone	24/247 (9.7%)	4/125 (3.2%)	0.32 (0.11–0.91)	5.063	0.024	14/90 (15.6%)	6/42 (14.3%)	0.93 (0.36–2.42)	0.023	NS
Dopamine	25/246 (10.2%)	4/122 (3.3%)	0.31 (0.11–0.90)	5.212	0.022	12/85 (14.1%)	4/43 (9.3%)	0.65 (0.21–2.02)	0.563	NS
Total CV mortality										
Renin	42/262 (16%)	11/134 (8.2%)	0.49 (0.25–0.94)	4.767	0.029	22/75 (29.3%)	7/35 (20%)	0.66 (0.28–1.55)	0.921	NS
NE	46/258 (17.8%)	8/128 (6.3%)	0.32 (0.15–0.69)	9.627	0.002	18/81 (22.2%)	9/39 (23.1%)	1.08 (0.48–2.41)	0.032	NS
ANP	9/116 (7.8%)	4/58 (6.9%)	0.89 (0.27–2.88)	0.04	NS	56/223 (25.1%)	14/111 (12.6%)	0.46 (0.26–0.83)	6.951	0.008
AVP	38/235 (16.2%)	11/124 (8.9%)	0.53 (0.27–1.04)	3.512	0.061	25/102 (24.5%)	7/45 (15.6%)	0.59 (0.26–1.37)	1.529	NS
Epinephrine	55/306 (18%)	16/152 (10.5%)	0.56 (0.32–0.97)	4.378	0.036	9/32 (28.1%)	1/15 (6.7%)	0.23 (0.03–1.85)	2.249	NS
Aldosterone	43/247 (17.4%)	8/125 (6.4%)	0.34 (0.16–0.72)	8.732	0.003	22/90 (24.4%)	10/42 (23.8%)	1.02 (0.48–2.17)	0.003	NS
Dopamine	43/246 (17.5%)	10/122 (8.2%)	0.44 (0.22–0.87)	5.935	0.015	20/85 (23.5%)	6/43 (14%)	0.56 (0.23–1.40)	1.584	NS
Severe HF										
Renin	41/262 (15.7%)	17/134 (12.7%)	0.74 (0.42–1.30)	1.133	NS	24/75 (32%)	6/35 (17.1%)	0.48 (0.20–1.17)	2.735	0.098
NE	43/258 (16.7%)	14/128 (10.9%)	0.59 (0.32–1.07)	3.075	0.079	21/81 (25.9%)	9/39 (23.1%)	0.85 (0.39–1.87)	0.155	NS
ANP	13/116 (11.2%)	4/58 (6.9%)	0.58 (0.19–1.79)	0.908	NS	52/223 (23.3%)	19/111 (17.1%)	0.65 (0.38–1.09)	2.672	NS
AVP	39/235 (16.6%)	15/124 (12.1%)	0.67 (0.37–1.22)	1.754	NS	25/102 (24.5%)	8/45 (17.8%)	0.65 (0.29–1.45)	1.118	NS
Epinephrine	57/306 (18.6%)	18/152 (11.8%)	0.57 (0.34–0.97)	4.409	0.036	7/32 (21.9%)	5/15 (33.3%)	1.40 (0.45–4.43)	0.34	NS
Aldosterone	41/247 (16.6%)	14/125 (11.2%)	0.59 (0.32–1.09)	2.881	0.090	24/90 (26.7%)	9/42 (21.4%)	0.79 (0.37–1.71)	0.353	NS
Dopamine	46/246 (18.7%)	18/122 (14.8%)	0.71 (0.41–1.22)	1.558	NS	15/85 (17.7%)	5/43 (11.6%)	0.62 (0.23–1.71)	0.863	NS
Recurrent MI										
Renin	27/262 (10.3%)	16/134 (11.9%)	1.11 (0.60–2.07)	0.109	NS	12/75 (16%)	2/35 (6%)	0.33 (0.07–1.48)	2.328	NS
NE	28/258 (10.9%)	14/128 (10.9%)	0.96 (0.50–1.81)	0.02	NS	10/81 (12.4%)	4/39 (10.3%)	0.80 (0.25–2.55)	0.147	NS
ANP	19/116 (16.4%)	5/58 (8.6%)	0.51 (0.19–1.37)	1.864	NS	20/223 (9%)	13/111 (11.7%)	1.26 (0.62–2.53)	0.411	NS
AVP	20/235 (8.5%)	11/124 (8.9%)	1.02 (0.49–2.13)	0.003	NS	19/102 (18.6%)	7/45 (15.6%)	0.77 (0.32–1.82)	0.366	NS
Epinephrine	31/306 (10.1%)	18/152 (11.8%)	1.13 (0.63–2.01)	0.163	NS	7/32 (21.9%)	0/15 (0%)	0.00 (0.00–∞)	3.408	0.065
Aldosterone	26/247 (10.5%)	13/125 (10.41%)	0.93 (0.48–1.82)	0.041	NS	13/90 (14.4%)	5/42 (11.9%)	0.80 (0.28–2.24)	0.184	NS
Dopamine	25/246 (10.2%)	17/122 (13.9%)	1.32 (0.72–2.45)	0.802	NS	11/85 (12.9%)	1/43 (2.3%)	0.16 (0.02–1.24)	4.049	0.044
CV mortality or severe HF or recurrent MI										
Renin	74/262 (28.2%)	36/134 (26.9%)	0.91 (0.61–1.35)	0.238	NS	36/75 (48%)	12/35 (34.3%)	0.63 (0.33–1.21)	1.948	NS
NE	78/258 (30.2%)	30/128 (23.4%)	0.72 (0.47–1.10)	2.287	NS	32/81 (39.5%)	17/39 (43.6%)	1.05 (0.58–1.89)	0.022	NS
ANP	29/116 (25%)	10/58 (17.2%)	0.67 (0.33–1.37)	1.1217	NS	82/223 (36.8%)	38/111 (34.2%)	0.87 (0.59–1.27)	0.536	NS
AVP	64/235 (27.2%)	32/124 (25.8%)	0.91 (0.59–1.39)	0.199	NS	45/102 (44.1%)	16/45 (35.6%)	0.73 (0.41–1.28)	1.215	NS
Epinephrine	97/306 (31.7%)	42/152 (27.6%)	0.82 (0.57–1.17)	1.197	NS	13/32 (40.6%)	5/15 (33.3%)	0.78 (0.28–2.19)	0.226	NS
Aldosterone	71/247 (28.7%)	31/125 (24.8%)	0.80 (0.52–1.21)	1.118	NS	40/90 (44.4%)	17/42 (40.5%)	0.88 (0.50–1.55)	0.212	NS
Dopamine	77/246 (31.3%)	35/122 (28.7%)	0.86 (0.58–1.29)	0.534	NS	30/85 (35.3%)	1/43 (25.6%)	0.67 (0.33–1.33)	1.347	NS

*Relative risks, score statistics and p values calculated from univariate Cox models. †Beta-blockers (BBs) versus no beta-blockers. Data presented are number (%) of patients, unless otherwise indicated. Other abbreviations as in Tables 1 to 3.

blocker at the time of hospital discharge have a better prognosis than those who are not using one of these agents. This association between beta-blocker use and better prognosis is independent of nine other factors known to influence prognosis after MI. In addition, neurohumoral activation does not clearly identify patients who would derive the most benefit from treatment with a beta-blocker. Indeed, in this analysis, patients with elevated plasma norepinephrine levels appeared to derive little or no benefit from treatment with beta-blockers, the benefits of beta-blockers being limited to those without activation of plasma norepinephrine.

Beta-blockers and subsequent mortality and morbidity. This study demonstrates that the long-term use of beta-blockers in patients who have had a MI and who have left ventricular dysfunction is associated with a decrease in cardiovascular mortality and a decrease in the incidence of severe heart failure. These reductions in risk are independent of other known risk factors for these same end points. Several large, randomized, placebo-controlled trials (3) performed in the late 1970s to mid-1980s showed that long-term treatment with beta-blockers reduces mortality by ~25% in patients who sustained a MI. In these trials the relative mortality reduction

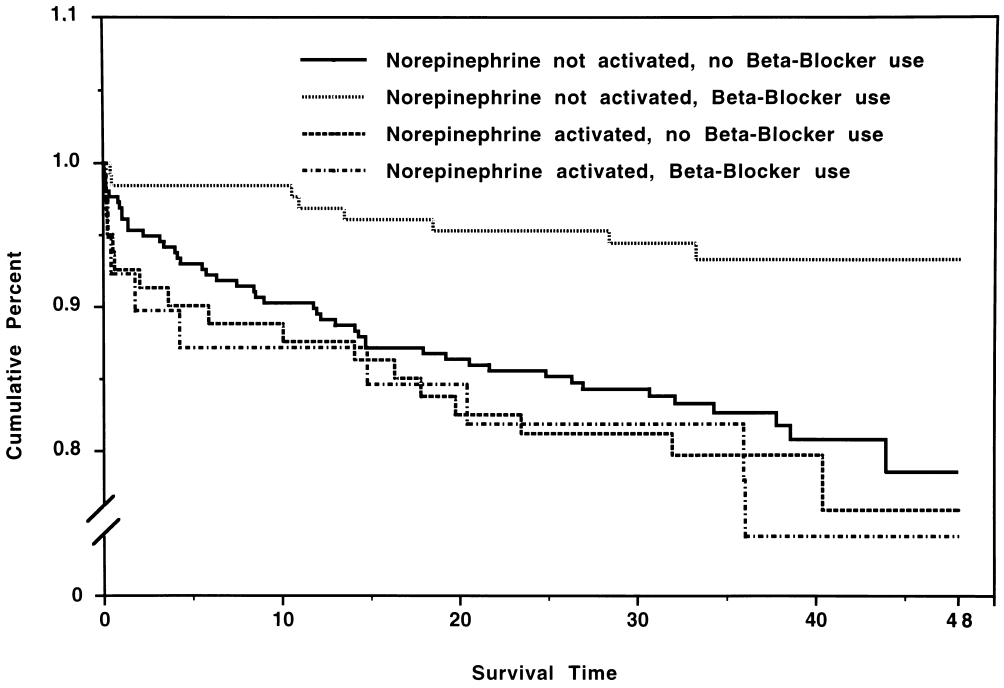

Figure 1. Survival curves as a function of activation of norepinephrine and use of beta-blockers.

in patients with left ventricular dysfunction was comparable to that observed in the global population (6–9). Consequently, because of their higher than average mortality, the survival benefit of long-term beta-blocker treatment in absolute numbers is even more impressive in these high risk patients. Indeed, a report of the American College of Cardiology/American Heart Association Task Force (16) considered long-term beta-blockade in "all but low risk patients who do not have a clear contraindication to beta-blockade" to be a class I recommendation, and it is very unlikely that other randomized trials of long-term beta-blockade specifically targeted to high risk postinfarction patients will ever be performed in the future. However, since the introduction of beta-blockers, numerous other interventions that improve survival after MI have become standard practice. Whether the beneficial effects of long-term treatment with beta-blockers are additive to the benefits of these newer interventions or have become less important has, to our knowledge, never been studied before the present analysis.

In the SAVE study, a substantial proportion of the patients were treated with thrombolytic agents, aspirin or warfarin or had a revascularization procedure before randomization to be eligible, and 50% by design were using captopril. Despite these interventions, an analysis using a multivariate model to adjust for possible differences in important prognostic variables between patients taking and not taking beta-blockers indicates that beta-blocker treatment was associated with a 26% reduction in 1-year cardiovascular mortality and a 30% reduction in cardiovascular mortality over the length of the study. These results are consistent with the findings of the randomized trials and suggest that long-term beta-blocker treatment improves survival in postinfarction patients with asymptomatic left ventricular dysfunction in addition to, and independent of, more recently proven beneficial interventions, including ACE inhibition, and remains a valuable tool in current postinfarction care.

We found that the use of beta-blockers was associated with a 21% lower risk of developing severe heart failure. However, because this was not a prospective, randomized study and because variables increasing the risk of developing heart failure may have been missed despite our best efforts, it is difficult to be certain whether the observed risk reduction was the result of beta-blocker treatment or of patient selection. This is particularly true when one considers that previous prospective, randomized studies of beta-blocker use in postinfarction patients have not demonstrated this type of beneficial effect (3). Nevertheless, this observation could help to alleviate the fear of increasing the risk of heart failure when prescribing beta-blockers to postinfarction patients with asymptomatic left ventricular dysfunction.

In the present study the reduction in risk of recurrent MI associated with the use of beta-blockers was small (18%) and not statistically significant. This risk reduction was even smaller (11%) when other risk factors were accounted for in a multivariate analysis. These results are at odds with previous prospective, randomized studies (3) in which the use of beta-blockers resulted in a significant decrease (~25%) in the rate of recurrent MI. The smaller risk reduction observed in the SAVE study may be the result of the fact that patients in SAVE received other medications that reduce the reinfarction rate but had not yet been used in earlier prospective random-

Table 6. Cox Proportional Hazards Analysis of Interaction Between Beta-Blocker Use and Neurohumoral Activation

	RR of Interaction (95% CI)	Regression Coeff of Interaction	Wald Chi-Square	p Value
1-yr CV mortality				
Renin	2.72 (0.65–11.28)	0.9993	1.89	NS
NE	3.60 (0.79–16.48)	1.2806	2.79	NS
ANP	0.34 (0.07–1.76)	−1.0808	1.65	NS
AVP	0.72 (0.16–3.22)	−0.3342	0.19	NS
Epinephrine	0.64 (0.07–6.12)	−0.4436	0.15	NS
Aldosterone	2.94 (0.71–12.23)	1.0775	2.19	NS
Dopamine	2.08 (0.44–9.77)	0.7314	0.86	NS
Total CV mortality				
Renin	1.38 (0.47–4.07)	0.3249	0.35	NS
NE	3.18 (1.06–9.52)	1.1556	4.26	0.039
ANP	0.53 (0.14–1.97)	−0.6392	0.91	NS
AVP	1.12 (0.38–3.27)	0.1108	0.04	NS
Epinephrine	0.39 (0.05–3.35)	−0.9323	0.73	NS
Aldosterone	2.95 (1.02–8.53)	1.0803	3.97	0.046
Dopamine	1.27 (0.41–3.98)	0.2392	0.17	NS
Severe HF				
Renin	0.64 (0.22–1.84)	−0.4503	0.69	NS
NE	1.47 (0.55–3.94)	0.3835	0.58	NS
ANP	1.10 (0.32–3.79)	0.0945	0.02	NS
AVP	0.98 (0.36–2.65)	−0.0192	0.00	NS
Epinephrine	2.49 (0.70–8.82)	0.9122	2.00	NS
Aldosterone	1.32 (0.50–3.50)	0.2762	0.31	NS
Dopamine	0.86 (0.27–2.72)	−0.1484	0.06	NS
Recurrent MI				
Renin	0.30 (0.06–1.53)	−1.1978	2.1	NS
NE	0.86 (0.23–3.22)	−0.1549	0.05	NS
ANP	2.51 (0.75–8.41)	0.9204	2.22	NS
AVP	0.75 (0.24–2.35)	−0.2817	0.24	NS
Epinephrine	0.00 (0.00–∞)	−11.005	0.01	NS
Aldosterone	0.85 (0.25–2.91)	−0.1602	0.07	NS
Dopamine	0.13 (0.01–1.08)	−2.0623	3.57	NS

Coeff = coefficient; other abbreviations as in Tables 2 and 3.

ized studies. Also, to be eligible for the SAVE study, 27% of the patients had to undergo revascularization procedures before randomization because of recurrent ischemia or positive exercise test results. These interventions may have reduced the effect of beta-blocker treatment on the risk of recurrent MI and might explain these discrepant results. Furthermore, because recurrent MI was the least frequent end point with the smallest difference in incidence between patients taking and not taking beta-blockers, the sample size may have been too small for the observed difference to reach statistical significance.

When comparing our results with those of past large, randomized trials (3), it must be kept in mind that the evidence for the beneficial effects and tolerability of beta-blockers in survivors of MI who have left ventricular dysfunction is derived from post hoc subgroup analysis (6,7) or meta-analysis (8,9) of the trial data. Several of these trials included varying numbers of patients with a history of compensated or mild congestive heart failure or with symptoms and signs suggesting left ventricular dysfunction, but left ventricular function was never directly measured. In contrast, the SAVE population was made up exclusively of postinfarction patients satisfying a uniform and objective definition of left ventricular dysfunction (ejection fraction ≤40% by radionuclide angiography). However, in the present retrospective analysis, patients were not randomized to beta-blocker use, and some form of selection bias that could not be accounted for in our multivariate analysis cannot be ruled out.

Role of neurohumoral activation. Neurohumoral activation has been shown to be an independent predictor of mortality in the SAVE population (11), in other studies of postinfarction patients (17) and in studies of patients with chronic congestive heart failure (18,19). Among patients with chronic congestive heart failure, those who have the most marked neurohumoral activation appear to derive the greatest survival benefit from treatment with ACE inhibitors (19,20).

In the SAVE neurohumoral substudy, captopril was associated with the same relative benefit regardless of the absence or presence of neurohumoral activation, but because patients with neurohumoral activation were at greater absolute risk, they experienced the greatest benefit in absolute terms (11). In the same SAVE population, neurohumoral activation appeared to be of little use in identifying patients who would benefit the most from long-term treatment with a beta-blocker. Furthermore, when an interaction between the use of beta-blockers and activation of norepinephrine and aldosterone was found, it was a negative one. This observation indicates that in these instances neurohumoral activation was associated with less beneficial effects of beta-blockers. The reasons for these surprising findings are not clear and may be due to one or more of the following factors:

1. The dose of beta-blocker used in the present study was not recorded, and thus it is possible that the dose of beta-blocker used was inadequate to block the deleterious effects of norepinephrine in patients with activation of the sympathetic nervous system. This is particularly true when one considers that the plasma norepinephrine concentration is an imperfect measure of adrenergic activity and may underestimate cardiac sympathetic activation, which is known to be pronounced in patients with severe left ventricular dysfunction (21).

2. A single determination of neurohumoral activity done at rest during the first weeks after MI is an imperfect reflection of long-term neurohumoral activation after MI and may inadequately reflect the dynamic nature of neurohumoral disturbances in these patients (22). For example, patients who develop progressive left ventricular dilation are known to be at higher risk of developing heart failure (23) and thus of increasing neurohumoral activation, whereas those without ventricular dilation may have an attenuation of neurohumoral activation.

3. Although the population of the neurohumoral substudy of SAVE is thus far the largest cohort of postinfarction patients for whom neurohumoral data are available, the possibility of low statistical power due to inadequate sample size must be considered. This is especially true because patients needed to be classified into four subgroups for the analyses

shown in Table 5. Nevertheless, our findings indicate a negative association between increased norepinephrine levels and the beneficial effects of beta-blockers. Thus, although the significance of this negative association can be questioned, it is unlikely that a positive association could be found had a greater sample size been evaluated.

4. The lack of effect of beta-blockers in patients with neurohumoral activation could also be due to differences in patient characteristics rather than differences in treatment. However, the small number of events precluded meaningful multivariate analysis to adjust for eventual differences in patient characteristics.

5. Neurohumoral activation may be a marker for severity of disease only and may be unrelated to the actual beneficial effects of beta-blockers, which relate primarily to their effects on improving excitation–contraction, calcium transport and heart rate slowing (24).

Conclusions. The present retrospective analysis of the SAVE data provides strong support for the persistent value of beta-blocker treatment in the current management of MI in addition to more recently proven beneficial measures, such as use of aspirin and ACE inhibitors, especially in the high risk group of patients with asymptomatic left ventricular dysfunction.

References

1. Pfeffer MA, Braunwald E, Moyé LA, et al, on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1992;327:669–77.
2. Rouleau JL, de Champlain J, Klein M, et al. Activation of neurohumoral systems in postinfarction left ventricular dysfunction. J Am Coll Cardiol 1993;22:390–8.
3. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335–71.
4. Rogers WJ, Bowlby LJ, Chandra NC, et al, for the Participants in the National Registry of Myocardial Infarction. Treatment of myocardial infarction in the United States (1990 to 1993): observations from the National Registry of Myocardial Infarction. Circulation 1994;90:2103–14.
5. Viskin S, Kitzis I, Lev E, et al. Treatment with beta-adrenergic blocking agents after myocardial infarction: from randomized trials to clinical practice. J Am Coll Cardiol 1995;25:1327–32.
6. Gundersen T. Influence of heart size on mortality and reinfarction in patients treated with timolol after myocardial infarction. Br Heart J 1983; 50:135–9.
7. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986;73:503–10.
8. The Beta-Blocker Pooling Project Research Group. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trials in post infarction patients. Eur Heart J 1988;9:8–16.
9. Held P. Effects of beta blockers on ventricular dysfunction after myocardial infarction: tolerability and survival effects. Am J Cardiol 1993;71:39C–44C.
10. Lichstein E, Hager WD, Gregory JJ, Fleiss JL, Rolnitzky LM, Bigger JT Jr, for the Multicenter Diltiazem Post-Infarction Research Group. Relation between beta-adrenergic blocker use, various correlates of left ventricular function and the chance of developing congestive heart failure. J Am Coll Cardiol 1990;16:1327–32.
11. Rouleau JL, Packer M, Moyé L, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. J Am Coll Cardiol 1994;24:583–91.
12. Moyé LA, Pfeffer MA, Braunwald E, for the SAVE Investigators. Rationale, design and baseline characteristics of the survival and ventricular enlargement trial. Am J Cardiol 1991;68:70D–9D.
13. Mettauer B, Rouleau JL, Bichet D, et al. Differential long-term intrarenal and neurohormonal effects of captopril and prazosin in patients with chronic congestive heart failure: importance of initial plasma renin activity. Circulation 1986;73:492–502.
14. Wilson N, Ledsome JR, Keeler R, Rankin AJ, Wade JP, Cournyea CA. Heterologous radioimmunoassay of atrial natriuretic peptide in dog and rabbit plasma. J Immunoassay 1986;7:73–96.
15. Nelesen RA, Dimsdale JE, Ziegler MG. Plasma atrial natriuretic peptide is unstable under most storage conditions. Circulation 1992;86:463–6.
16. Gunnar RM, Bourdillon PDV, Dixon DW, et al. Guidelines for the early management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular procedures. J Am Coll Cardiol 1990;16:249–92.
17. Omland T, Bonarjee VVS, Lie RT, Caidahl K. Neurohumoral measurements as indicators of long-term prognosis after acute myocardial infarction. Am J Cardiol 1995;76:230–5.
18. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819–23.
19. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L, for the CONSENSUS Trial Study Group. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. Circulation 1990;82:1730–6.
20. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A, for the V-HeFT VA Cooperative Studies Group. Plasma norepinephrine, plasma renin activity and congestive heart failure: relations to survival and the effects of therapy in V-HeFT II. Circulation 1993;87 Suppl VI:VI-40–8.
21. Meredith IT, Eisenhofer G, Lambert GW, Dewar EM, Jennings GL, Esler MD. Cardiac sympathetic nervous activity in congestive heart failure: evidence for increased neuronal norepinephrine release and preserved neuronal uptake. Circulation 1993;88:136–45.
22. Sigurdsson A, Swedberg K, Ullman B. Effects of ramipril on the neurohormonal response to exercise in patients with mild or moderate congestive heart failure. Eur Heart J 1994;15:247–54.
23. St. John Sutton M, Pfeffer MA, Plappert T, et al., for the SAVE Investigators. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction: the protective effects of captopril. Circulation 1994;89:68–75.
24. Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. Am J Cardiol 1993;71:12C–22C.