β Blocker treatment and other prognostic variables in patients with clinical evidence of heart failure after acute myocardial infarction: evidence from the AIRE study

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Abstract

***Objectives*—To examine clinical outcomes associated with optional β blockade in a population of patients with evidence of heart failure after myocardial infarction.**

***Design and patients*—Data from the acute infarction ramipril efficacy (AIRE) study were analysed retrospectively. At baseline 22.3% of the patients were receiving a β blocker. To minimise confounding, β blocker and diuretic treatments, presence of clinical signs of heart failure, left ventricular ejection fraction, and 16 other baseline clinical variables were simultaneously entered in a multivariate Cox regression model. In addition, the same analysis was repeated separately within a high and a low risk group of patients, as defined according to the need for diuretic treatment.**

***Results*—β Blocker treatment was an independent predictor of reduced risk of total mortality (hazard ratio 0.66, 95% confidence interval (CI) 0.48 to 0.90) and progression to severe heart failure (0.58, 95% CI 0.40 to 0.83) for the entire study population. There were similar findings in high risk patients requiring diuretics (0.59, 95% CI 0.40 to 0.86; and 0.58, 95% CI 0.38 to 0.89).**

***Conclusions*—β Blocker treatment is associated with improved outcomes in patients with clinical evidence of mild to moderate heart failure after myocardial infarction. Most importantly, high risk patients with persistent heart failure appear to benefit at least as much as lower risk patients with transient heart failure.**

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Keywords: myocardial infarction; heart failure; left ventricular dysfunction; β blockers

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Thrombolytic agents, aspirin, and β adrenoceptor blockers form the cornerstone of early pharmacological treatment after acute myocardial infarction.[1] There is overwhelming evidence that administration of β blockers decreases short and long term mortality after myocardial infarction and prevents reinfarction and the occurrence of tachyarrhythmias.[2–4] Since the beneficial effects of β blocker treatment were established in postmyocardial infarction trials conducted in the previous decade, there is some uncertainty as to the current value of these agents following routine use of aspirin, thrombolytic, and angiotensin converting enzyme (ACE) inhibitor treatments.[1 5]

A meta-analysis of studies of long term β blocker treatment after myocardial infarction before the routine use of thrombolytic treatment showed a 23% relative reduction of overall mortality and a 27% reduction in the rate of reinfarction when these drugs were prescribed.[2] Despite these persuasive data, many studies of current practice indicate that β blockers are inadequately used.[6–9] Recent studies of β blockade after myocardial infarction indicate that only 48% to 58% of patients who have no contraindications to their use actually receive β blockers.[7 8]

Clinical evidence of congestive heart failure after acute myocardial infarction has been considered by many to be a contraindication to β adrenergic blockade and was an exclusion criterion in the major relevant trials.[10 11] It is estimated that even in the post-thrombolytic era some 32% of postmyocardial infarction patients have clinical evidence of heart failure, requiring treatment with a diuretic.[12] Therefore it is not surprising that evidence of heart failure and use of diuretic agents are the most frequent reasons for not prescribing β lockers after myocardial infarction.[7]

The use of β blockers in survivors of myocardial infarction with evidence of congestive heart failure represents a therapeutic paradox for the clinician. Although β blockers are seen as "cardioprotective" in that they reduce mortality and prevent reinfarction, they appear to be contraindicated in this high risk group of patients. Yet left ventricular dysfunction is the strongest single predictor of prognosis after myocardial infarction, so any treatment that can further reduce mortality in this group of patients would be of particular value.[13]

Results from randomised trials specifically designed to test the role of β blockade in patients with heart failure after myocardial infarction are not currently available nor are they likely to be for some years.

We therefore conducted a retrospective analysis of optionally prescribed β blocker treatment in the AIRE study, in which patients with clinical evidence of congestive heart failure after myocardial infarction were randomly allocated to receive placebo or the ACE inhibitor ramipril. We wished to examine the mortality and morbidity outcomes and modes of death with respect to β blocker use and relate these to evidence of impaired ventricular

function. In contrast to all previous retrospectively analysed studies, the AIRE study population was comprised exclusively of patients with prospectively defined and identified clinical evidence of heart failure after myocardial infarction. Therefore an analysis of the clinical outcomes associated with the empirical use of β blockers in this population was considered to be of both clinical and scientific interest.

Methods

PATIENTS

The design, outcome definitions, and results of the AIRE study have been published elsewhere.[14–16] Briefly, this was a multinational, randomised, double blind, placebo controlled, parallel group study. Patients were eligible for inclusion if they had a definite acute myocardial infarction and clinical evidence of transient or persistent heart failure (S3 gallop and/or radiographic and/or clinical evidence of pulmonary venous congestion) at any time from hospital admission to randomisation. Exclusion criteria were recognised contraindications to ACE inhibitor treatment, severe heart failure (usually New York Heart Association (NYHA) class IV), heart failure of primary valvar or congenital aetiology, and unstable angina. Overall, 1014 patients were randomised to ramipril and 992 to placebo, starting from day 2 to day 9 after the index myocardial infarct (day 0). Follow up was for a minimum of six months and an average of 15 months.

Decisions as to whether to prescribe β blocker or diuretic treatment (as with all other than trial ramipril or placebo treatments) were made by attending physicians, based on clinical judgment. It was expected that the intensity and persistence of clinical evidence of left ventricular dysfunction—along with other factors such as local medical practice—would have affected decision making. To minimise bias, comprehensive multivariate analysis methods were applied to examine associations between β blocker treatment at randomisation and subsequent clinical outcomes.

Diuretic treatment at randomisation was used as an indicator of either transient/mild (low risk) or persistent/more severe (high risk) heart failure. Postmyocardial infarction patients requiring diuretic treatment have more severe clinical heart failure, larger infarcts, and lower left ventricular ejection fractions, and hence are at greater risk of death.[17] Moreover, the need for diuretic treatment in an already high risk population with clinical evidence of heart failure is associated with a further twofold increase in early mortality.[18] Retrospective data from other studies suggest that high risk postinfarction patients have the most to gain in absolute terms from β blockade. Therefore to test this concept the use of β blockade was examined separately in high risk/persistent heart failure and low risk/transient heart failure groups.

Table 1 Patient characteristics and treatments according to diuretic use at randomisation

Variable	*Not on diuretic (n = 798)*	*On diuretic (n = 1188)*	*p Value*
Mean (SD) age (years)	62.8 (11.4)	66.6 (10.0)	<0.001
Digitalis	48 (6.0)	195 (16.4)	<0.001
β Blocker	213 (26.7)	230 (19.4)	<0.001
Thrombolysis	500 (62.7)	642 (54.0)	<0.001
Nitrates	412 (62.7)	697 (58.7)	0.002
Multiple clinical signs of heart failure	375 (47.5)	634 (53.5)	0.01
Radiographic	393 (49.7)	635 (53.6)	0.09
Rales	661 (83.6)	1043 (88.1)	0.005
S3 gallop	189 (23.9)	293 (24.7)	0.66
Past medical history			
Myocardial infarction	155 (19.4)	293 (24.7)	0.006
Heart failure	53 (6.6)	110 (9.3)	0.04
Arrhythmia	41 (5.2)	81 (6.8)	0.13
Angina	268 (33.6)	440 (37.0)	0.13
Hypertension	220 (27.6)	334 (28.1)	0.79
Diabetes mellitus	95 (11.9)	145 (12.2)	0.84
Sex (male)	608 (76.2)	853 (71.8)	0.03
Mean (SD) LVEF (%)	38 (14.3)	40 (15.0)	0.09
Ramipril	418 (52.4)	586 (49.3)	0.19
Aspirin	628 (78.7)	915 (77.0)	0.38
Calcium antagonists	121 (15.0)	196 (16.5)	0.43
Location of infarct			
Anterior	462 (57.9)	689 (58.0)	0.96
Inferior	305 (38.2)	434 (36.5)	0.45
ECG classification: Q wave	491 (63.8)	715 (63.2)	0.81

Values in parentheses are percentages unless otherwise stated.
LVEF, left ventricular ejection fraction.

END POINTS

We studied the association between β blocker use and total mortality, severe/resistant heart failure occurrence, and mode of death during the entire study follow up:

Severe/resistant heart failure (SRHF) was prospectively defined as clinical judgment of severe heart failure (usually NYHA class IV)—that is, unresponsive to non-ACE-inhibitor treatment. Onset was usually the date at which open label ACE inhibitor treatment was started.

Details of the definitions and classification of mode of death in the AIRE study have been described elsewhere.[16] Two modes of death were examined in the current analysis. Sudden cardiac death included sudden collapse, death from an identified arrhythmia, cardiac arrest in the absence of pre-existing circulatory failure, and unwitnessed deaths. Death from circulatory failure included shock (that is, hypotension insufficient to maintain clinically adequate cerebral perfusion for more than 15 minutes before cessation of cardiac activity) and pulmonary oedema. In addition, two routes to death were defined, depending on whether SRHF preceded death.

STATISTICAL ANALYSIS

Baseline characteristics of different patient groups were compared by use of two sample *t* test for continuous variables and χ^2 tests for categorical variables.

Hazard ratios, 95% confidence intervals (CI), and p values of the tested variables were derived from univariate and multivariate Cox proportional hazard analyses. To minimise any confounding, all available baseline variables were simultaneously[19] entered into a Cox proportional hazards multivariate analysis (β blocker, diuretic, digoxin, nitrate, aspirin, and calcium antagonist treatments at randomisation; allocation to ramipril; thrombolytic treatment for the index myocardial infarction; presence of inspiratory rales, S3 gallop and radiographic evidence of pulmonary venous congestion at any time from hospital admission to randomisation; left ventricular ejection

Table 2 Mortality and severe/resistant heart failure (SRHF) outcomes by baseline clinical features in 1986 patients

	Total mortality hazard ratios (95% CI)	*SRHF hazard ratios (95% CI)*
Past medical history of heart failure	1.76 (1.31 to 2.38)	2.17 (1.57 to 3.01)
p Value	< 0.001	< 0.001
Past medical history of diabetes mellitus	1.60 (1.23 to 2.10)	1.25 (0.92 to 1.71)
p Value	< 0.001	0.16
S3 gallop	1.46 (1.16 to 1.85)	1.72 (1.33 to 2.22)
p Value	0.016	< 0.001
Left ventricular ejection fraction < 39%	1.42 (0.93 to 2.18)	1.41 (0.90 to 2.23)
p Value	0.10	0.14
Digoxin	1.41 (1.07 to 1.86)	1.19 (0.87 to 1.63)
p Value	0.014	0.28
Diuretics	1.37 (1.08 to 1.73)	1.50 (1.16 to 1.96)
p Value	0.009	0.024
Past medical history of angina	1.34 (1.06 to 1.68)	1.18 (0.91 to 1.53)
p Value	0.013	0.22
Anterior myocardial infarction	1.28 (1.03 to 1.61)	1.11 (0.35 to 3.53)
p Value	0.029	0.83
Radiographic evidence of heart failure	1.22 (0.98 to 1.51)	1.27 (1.00 to 1.62)
p Value	0.078	0.048
Past medical history of myocardial infarction	1.08 (0.85 to 1.39)	1.46 (1.12 to 1.91)
p Value	0.55	0.005
Age (per 1 year)	1.03 (1.02 to 1.04)	1.02 (1.01 to 1.04)
p Value	< 0.001	< 0.001
Ramipril	0.80 (0.65 to 0.99)	0.82 (0.65 to 1.04)
p Value	0.041	0.09
Thrombolysis	0.68 (0.55 to 0.85)	0.75 (0.59 to 0.96)
p Value	< 0.001	0.02
β Blockers	0.66 (0.48 to 0.90)	0.58 (0.40 to 0.83)
p Value	0.008	0.003

Hazard ratios derived by multivariate analysis with either total mortality or severe/resistant heart failure as an end point in the entire AIRE study population. Covariates were included in this table if $p \leq 0.1$ for at least one analysis and were ordered by size of hazard ratio for total mortality analysis.

fraction; age; sex; previous medical history of heart failure, myocardial infarction, diabetes mellitus, angina, and hypertension; ECG classification of the index myocardial infarction as to its location and Q wave development). Measurements of left ventricular ejection fraction using multiple methods were available in a cohort of 557 patients (28%) and were entered into the analysis as a categorical variable using the mean (39%) as a cut off point, with a separate value for non-available measurements.

The same multivariate Cox proportional hazard model was applied to examine subgroups of patients who were either receiving (persistent heart failure) or not receiving (transient heart failure) diuretic treatment at the time of randomisation.

All p values are two tailed, and a significance level of 0.05 was used. Statistical analyses were performed using the SPSS version 6.1.

Table 3 Baseline characteristics and treatments according to β blocker use at randomisation

	Not on β blocker (n = 1543)	*On β blocker (n = 443)*	*p Value*
Mean (SD) age (years)	65.7 (10.6)	63.1 (11.1)	<0.001
Diuretic	958 (62.1)	230 (51.9)	<0.001
Multiple clinical signs of HF	827 (53.6)	182 (41.1)	<0.001
Radiographic	829 (53.7)	199 (44.9)	0.001
Rales	1345 (87.2)	359 (81.0)	0.002
S3 gallop	394 (25.5)	88 (19.9)	0.016
Digitalis	213 (13.8)	30 (6.8)	<0.001
Calcium antagonist	273 (17.7)	44 (9.9)	<0.001
Aspirin	1166 (75.6)	377 (85.1)	<0.001
Mean (SD) LVEF (%)	38.5 (14.8)	40.3 (13.7)	0.17
Location of infarct			
Anterior	870 (54.6)	281 (63.4)	0.008
Inferior	587 (38.0)	152 (34.3)	0.15
Thrombolysis	863 (55.9)	279 (63.0)	0.009
Past medical history			
Angina	565 (36.2)	143 (32.3)	0.12
Arrhythmia	101 (6.6)	21 (4.8)	0.17
Heart failure	132 (8.5)	31 (7.0)	0.29
Diabetes mellitus	190 (12.3)	50 (11.3)	0.56
Myocardial infarction	352 (22.8)	96 (21.7)	0.61
Hypertension	427 (27.7)	127 (28.7)	0.68
ECG classification: Q wave	942 (61.0)	264 (59.6)	0.18
Ramipril	768 (49.8)	236 (53.3)	0.20
Sex (male)	1126 (73.0)	335 (75.6)	0.25
Nitrates	856 (55.5)	253 (57.1)	0.54

Numbers in parentheses are percentages unless otherwise stated.
HF, heart failure; LVEF, left ventricular ejection fraction.

Results

DIURETIC USE AND ASSOCIATIONS WITH CLINICAL OUTCOMES

Analysis of the clinical characteristics and concomitant treatments at baseline showed that patients requiring diuretics at randomisation were significantly older and were more likely to be female. They more often had a previous medical history of heart failure and myocardial infarction and they were less likely to have received thrombolytic treatment for the index myocardial infarction. They were more likely to have multiple clinical signs of heart failure and to be receiving concomitant digitalis and nitrate treatment. Finally, as expected the use of β blockers in these patients was less common (table 1).

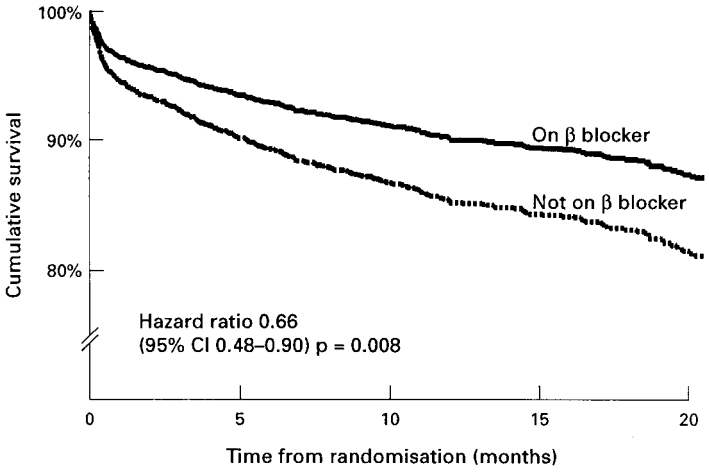
In a cohort of 557 patients from the AIRE study, the average left ventricular ejection fraction was 39% and there was a trend towards a lower left ventricular ejection fraction in those who required diuretic treatment. The need for diuretic treatment after acute myocardial infarction is associated with lower left ventricular ejection fraction.[17] Presumably, the relation between diuretic use and a lower left ventricular ejection fraction was attenuated in the AIRE study by the fact that all the patients had clinical evidence of left ventricular dysfunction.

Univariate analysis revealed that diuretic use at randomisation was associated with a highly significant increased risk for all cause mortality (hazard ratio 1.7, 95% CI 1.36 to 2.12, $p < 0.001$) and SRHF (hazard ratio 1.83, 95% CI 1.42 to 2.34, $p < 0.001$). Furthermore, when the use of diuretics was considered along with the use of β blockers, the presence of clinical signs of heart failure, the left ventricular ejection fraction, and 16 other baseline clinical characteristics in a multivariate analysis, the need for diuretic treatment at randomisation remained an independent and highly significant predictor of increased mortality and SRHF incidence (table 2). Patients on diuretics at randomisation were more likely to need open label ACE inhibitor treatment during the follow up period (15.3% *v* 10.9%, $p = 0.005$).

Circulatory failure deaths were significantly more common in patients treated with diuretics (hazard ratio 1.54, 95% CI 1.03 to 2.32, $p = 0.037$) and appeared to account for most of the increased total mortality risk in this group.

CLINICAL SIGNS OF HEART FAILURE AND ASSOCIATIONS WITH CLINICAL OUTCOMES

Among the subset of patients in whom the left ventricular ejection fraction was determined, individuals with multiple (> 1) clinical signs of heart failure (S3 gallop, inspiratory rales, radiographic evidence of pulmonary venous



Numbers at risk

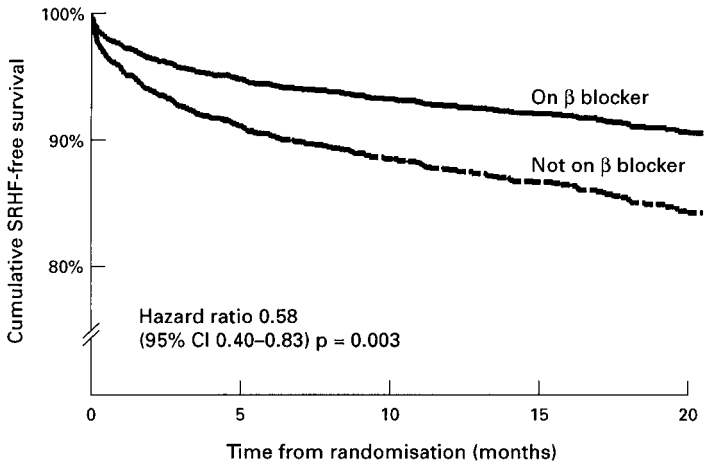
On β blocker	443	407	315	205	76
Not on β blocker	1543	1334	1064	729	384

Figure 1 Cumulative survival curves according to β blocker treatment at randomisation (derived from the multivariate Cox regression analysis). CI, confidence interval.

congestion) had a significantly lower mean left ventricular ejection fraction (mean (SD), 36.6 (13.4)% *v* 43 (15.8)%, p < 0.001).

Univariate analysis showed that the presence of multiple clinical signs of heart failure was a highly significant predictor of the risk of increased mortality (hazard ratio 1.41, 95% CI 1.15 to 1.72, p = 0.009) and SRHF (hazard ratio 1.57, 95% CI 1.25 to 1.97, p < 0.001). In the multivariate analysis, S3 gallop was the only independent heart failure sign predictive of mortality risk and SRHF incidence in the entire study population and in both groups of patients with transient and persistent heart failure (table 2). Radiographic evidence of heart failure was an independent predictor of SRHF occurrence and was associated with a trend towards increased mortality risk in the entire study population. The presence of inspiratory rales did not appear to predict either of these outcomes in any of the groups.

These data suggest that the inclusion of the clinical correlates of left ventricular function into multivariate analysis permits baseline risk adjustment and stratification over and above that denoted by diuretic use, left ventricular ejection fraction, and all the other variables used.



Numbers at risk

On β blocker	443	409	324	214	77
Not on β blocker	1543	1359	1105	758	402

Figure 2 Cumulative severe/resistant heart failure (SRHF)-free survival according to β blocker treatment at randomisation (derived from the multivariate Cox regression analysis). CI, confidence interval.

β BLOCKER USE AND BASELINE CHARACTERISTICS

Analysis of the clinical characteristics and concomitant treatments at baseline revealed that the 443 patients receiving β blockers were significantly younger and more likely to have received thrombolytic treatment. Not surprisingly, β blockers were prescribed less often when there was evidence of pronounced left ventricular dysfunction with multiple clinical signs of heart failure or the need for diuretic treatment. All three clinical criteria of heart failure were significant negative predictors of β blocker prescription. Patients on β blockers were less likely to be receiving digitalis and calcium antagonists and more likely to be taking aspirin at randomisation (table 3).

In the patients in whom the left ventricular ejection fraction was determined, β blocker treatment did not appear to be associated with a significantly greater mean left ventricular ejection fraction.

OUTCOMES WITH RESPECT TO β BLOCKER USE

Mortality and SRHF incidence analysis

Univariate analysis showed that β blocker use was associated with a lower all cause mortality risk (52 deaths (11.7%) in the β blocker group, 340 deaths (22%) in those not on β blocker treatment; hazard ratio 0.53, 95% CI 0.40 to 0.72, p < 0.001) and a lower risk of SRHF development (41 events (9.2%) in the β blocker group, 280 events (18.1%) in those not on β blocker treatment; hazard ratio 0.49, 95% CI 0.35 to 0.68, p < 0.001). Importantly, when β blocker treatment was considered along with 21 other covariates in a multivariate analysis, it remained an independent and highly significant predictor of reduced total mortality (hazard ratio 0.66, 95% CI 0.48 to 0.90, p = 0.008) and SRHF occurrence (hazard ratio 0.58, 95% CI 0.40 to 0.83, p = 0.003) (table 2, figs 1 and 2). Though confidence intervals were wide, the reductions in the relative risk associated with the β blocker use appeared smaller in the multivariate analysis, indicating that efficacy may have been partially influenced by covariates. However, despite attenuation of the univariate analysis estimate of risk, the association between β blocker treatment and improved outcomes was still highly significant and the most sizeable (by hazard ratio ranking) of all the other beneficial postmyocardial infarction treatments.

In keeping with these findings, patients on β blockers at randomisation were less likely to need open label ACE inhibitor treatment during the follow up period (10% *v* 14.6%, p = 0.012).

To evaluate the soundness of these findings we conducted a series of sensitivity analyses.

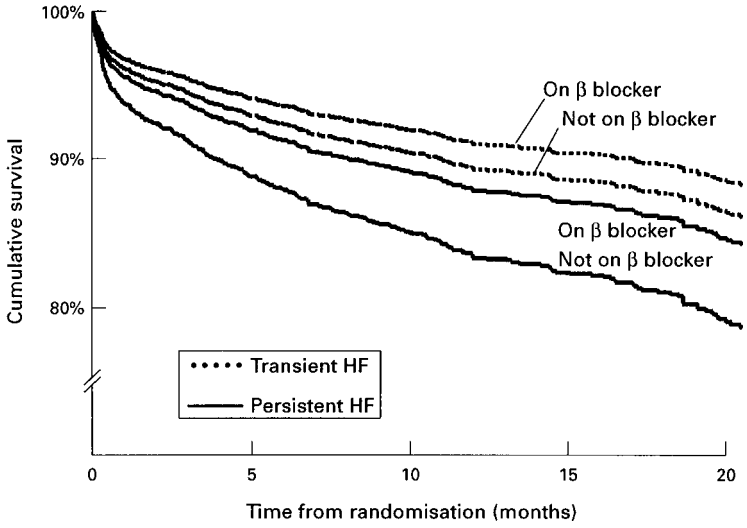


Figure 3 Cumulative survival curves according to β blocker treatment in the transient heart failure (HF) group (hazard ratio 0.78, 95% confidence interval (CI) 0.45 to 1.33, p = 0.36) and the persistent HF group (hazard ratio 0.59, 95% CI 0.40 to 0.86, p = 0.007) (derived from the multivariate Cox regression analysis).

For a more precise correction for the degree of left ventricular dysfunction, the left ventricular ejection fraction was entered as a continuous variable in our multivariate analysis model. As a result, less than one third of the study population was examined and inevitably the power of the analysis fell considerably. Although no longer statistically significant, the degree of lowering of the relative risks of total mortality (hazard ratio 0.67, 95% CI 0.34 to 1.33, p = 0.25) and SRHF (hazard ratio 0.54, 95% CI 0.24 to 1.20, p = 0.12) remained essentially unchanged.

When multivariate analysis of all cause mortality was conducted only in the high risk, persistent heart failure group, β blocker treatment was still associated with a significant decrease in risk (hazard ratio 0.59, 95% CI 0.40 to 0.86, p = 0.007). In the lower risk, transient heart failure group, β blocker treatment was associated with a mortality benefit, though statistical significance was not demonstrated (hazard ratio 0.78, 95% CI 0.45 to 1.33, p = 0.36) (fig 3). In a similar way, β blocker use was associated with a lower SRHF occurrence risk in both the persistent and transient heart failure groups (hazard ratios 0.58, 95% CI 0.38 to 0.89, p = 0.012; and 0.56, 95% CI 0.28 to 1.11, p = 0.096), though in the latter group this association was not significant (fig 4).

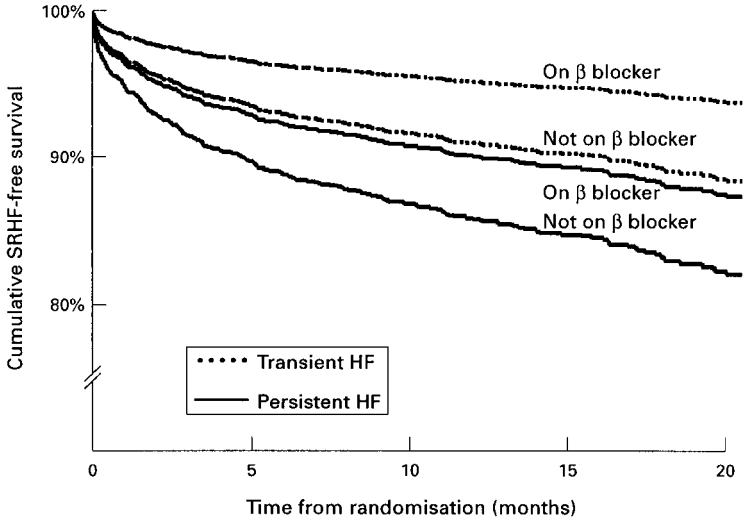


Figure 4 Cumulative severe/resistant heart failure (SRHF)-free survival curves according to β blocker treatment in the transient HF group (hazard ratio 0.56, 95% confidence interval (CI) 0.28 to 1.11, p = 0.096) and the persistent HF group (hazard ratio 0.58, 95% CI 0.38 to 0.89, p = 0.012) (derived from the multivariate Cox regression analysis).

In the all cause mortality multivariate analysis, all the suspected interactions between variables were tested. The only significant interaction found was that between diuretic treatment and left ventricular ejection fraction (χ^2 = 10.3 on 1 degree of freedom, p = 0.004), indicating that the poor outcome associated with diuretic treatment most probably reflects the lower left ventricular ejection fraction among patients in need of this treatment.

Mode of death analysis

In the entire AIRE population, multivariate analysis showed that β blocker treatment was independently associated with a significantly lower risk of sudden death (hazard ratio 0.61, 95% CI 0.40 to 0.93, p = 0.02) and death not preceded by SRHF (hazard ratio 0.61, 95% CI 0.37 to 1.00, p = 0.047). A trend towards lower risk of death from circulatory failure (hazard ratio 0.65, 95% CI 0.38 to 1.09, p = 0.1) and death preceded by SRHF (hazard ratio 0.69, 95% CI 0.46 to 1.03, p= 0.066) was also observed in patients treated with β blockers.

Discussion

This retrospective analysis of the optional use of β blocker treatment in the AIRE study indicates that β blockade in patients with acute myocardial infarction and clinical evidence of heart failure is associated with improved outcomes. However, as patients were not randomly allocated to β blocker treatment, the results should be treated cautiously. To correct for lack of randomisation we applied the principles of covariate adjustment[20] to account for differences in all available clinical and historical variables. Further supporting the validity of these findings is their consistency with the data from other postmyocardial infarction trials, though again these were not prospectively designed to address this issue.

The large number of events in the AIRE study (392 deaths and 321 SRHF occurrences) means that suggested criteria for overfitting data were not violated. All the outcomes associated with β blocker treatment were evaluated for adherence to the assumption of proportional hazards and in all cases the criteria of proportionality were fulfilled.

As discussed previously, the use of β blocker treatment in the AIRE study is anticipated to have been heavily biased by the clinical and laboratory estimation of the degree of the left ventricular dysfunction. Therefore the need for diuretic treatment and the clinical signs of heart failure present at any time before randomisation served as clinical correlates of left ventricular function,[17 21–25] permitting the necessary adjustments. The importance of simple clinical criteria is emphasised by the fact

that for any given level of ejection fraction clinical evidence of heart failure is still an independent prognostic predictor, which more than doubles mortality in a postinfarct population.[23 24] Furthermore, information on left ventricular ejection fraction was available for an appreciable number of patients, and was accordingly used in the multivariate analysis, allowing additional adjustment.

Clinical outcomes with respect to β blocker treatment were examined separately in high and lower risk groups of patients, using identical methods. These groups were defined according to whether patients were receiving diuretic treatment at baseline. Multivariate analysis showed β blocker treatment to be a significant independent predictor of decreased risk of all cause mortality only in the high risk group of patients. In the lower risk patients with transient evidence of heart failure, β blocker treatment was not a significant independent predictor of total mortality risk, probably as a result of the lower number of deaths observed. However, when the response to β blockade in the two subgroups was compared formally, there was no statistically significant difference between them. Similar trends were observed in the multivariate analysis of the SRHF occurrence with respect to β blocker treatment. Once more, β blocker treatment at baseline was an independent predictor of reduced progress to SRHF in the group with persistent heart failure.

It appears that when β blocker treatment was used in a high risk patient, the mortality and SRHF risks were significantly reduced, being similar to those of lower risk individuals.

Among the clinical signs of heart failure, the presence of S3 gallop was the strongest predictor of increased total mortality, SRHF occurrence, and failure to prescribe β blockers. At the other end of the spectrum, the presence of inspiratory crackles did not appear to predict any of the clinical outcomes examined but was predictive of failure to prescribe β blockers.

Concerning mode of death, we observed that β blocker treatment was associated with a significantly lower risk of sudden death in the AIRE study population. The route to death without preceding SRHF was also less common in the β blocker treated patients. These findings are in keeping with the results of other studies showing β blockade to be particularly effective in reducing sudden death in high risk patients with evidence of heart failure.[25–27] Moreover, β blocker treatment was also associated with a trend towards lower risk of death from circulatory failure and death preceded by SRHF, alleviating fears to the contrary in patients with clinical evidence of heart failure after myocardial infarction.

DATA FROM OTHER STUDIES

A few of the large randomised, postmyocardial infarction, β blocker trials conducted before the routine use of thrombolytic and ACE inhibitor treatment did include small numbers of patients with compensated mild to moderate heart failure.[25 28–32] Although they were not designed to test the role of β blockade in patients with heart failure, subgroup analysis of these trials supports the policy of a more liberal use of β blocker treatment in patients with evidence of mild to moderate left ventricular dysfunction. A recent survey of all the trials which provided mortality data for subsets of patients with left ventricular dysfunction indicates that β blocker treatment was well tolerated and was associated with a 20–30% risk reduction in total mortality.[33] Noticeably, this was the same mortality reduction as was observed in the entire population. Because of the high mortality among patients with left ventricular dysfunction, the absolute gain in numbers of lives saved per 100 patients treated with β blockers is much larger than that in patients with preserved ventricular function. Our findings are consistent with data suggesting that β blocker treatment after myocardial infarction is particularly beneficial in patients with evidence of left ventricular dysfunction and other groups at higher risk.[3 25 28–30 32–35]

Lichstein *et al* carried out a retrospective analysis of non-randomised β blocker use in the multicenter diltiazem post-infarction trial (MDPIT)[36] and found that in various left ventricular ejection fraction and heart failure strata, β blocker treatment appeared to be a predictor of decreased all cause mortality and increased heart failure-free survival. However, it is unknown whether β blocker treatment would have remained a significant independent predictor of mortality had a multivariate analysis model adjusting for all these indicators of left ventricular function been performed. Similarly, Kennedy *et al* analysed the optional, non-randomised use of β blockers in the cardiac arrhythmia suppression trial (CAST).[27] They included 2611 patients with a left ventricular ejection fraction of ⩽ 40% but only 16% had a history of congestive heart failure. Multivariate analysis using a Cox regression model including 12 baseline historical and clinical characteristics showed that β blocker treatment was associated with a decrease in all cause mortality risk.

Evaluation of β blocker use in a different population from our own, in an ACE inhibition postmyocardial infarction trial (survival and ventricular enlargement study) selecting asymptomatic patients with a radionuclide left ventricular ejection fraction of ⩽ 40% has recently been reported.[37] Multivariate analysis correcting for nine baseline clinical characteristics showed that β blocker treatment at randomisation was independently associated with a lower cardiovascular mortality and occurrence of severe heart failure.

In contrast to each of the above studies, all patients in the AIRE study had clinical evidence of heart failure after myocardial infarction. In addition, the AIRE study database allowed us to address the issue of postmyocardial infarction β blocker treatment in the modern context, where aspirin, thrombolytic, and ACE inhibitor treatments are routinely used. Of particular interest is our finding that the beneficial effects of β blockers and ACE inhibitors were independent and multiplicative, both effects appearing more marked

in patients requiring concomitant diuretic treatment.

β ADRENERGIC RECEPTOR BLOCKADE IN CHRONIC HEART FAILURE AND AFTER MYOCARDIAL INFARCTION

To date, a growing body of evidence indicates that β blockers may have a role in the treatment of patients with congestive heart failure.[38–41] Three large mortality studies of β blockade in chronic heart failure are under way at present and are expected to provide a definitive answer (MERIT, BEST, and CIBIS-II).[42–44]

Although uncertainty persists, the beneficial actions of β blockers in this setting may result from antagonism of the activated neurohumoral axis, upregulation of the β adrenoceptors, and anti-ischaemic, antiarrhythmic, and favourable haemodynamic effects.[39 45 46] Most of these actions would be particularly welcome when left ventricular dysfunction develops after myocardial infarction.[47]

Whether clinical evidence of heart failure following myocardial infarction is caused by a rise in end diastolic pressure associated with ischaemia rather than "true" myocardial necrosis is of little importance, as the value of β blockade in preventing the evolution of unstable angina to myocardial infarction[48] and in reducing infarct size[49] and reinfarction rate[2] have all been shown convincingly. β Blockade should be particularly effective in eliminating any component of reversible ischaemia in this setting.

In conclusion, optional β blocker treatment after myocardial infarction in patients with clinical evidence of heart failure was associated with an independent decrease in total mortality and progression to severe heart failure. Importantly, this association remained statistically significant and substantial in the high risk group of patients who required diuretic treatment and had more marked and persistent heart failure. This is the very group of patients in whom the use of β blockers has generally been avoided by clinicians.

These results reinforce accumulating data that suggest that high risk patients with evidence of heart failure following myocardial infarction derive at least the same relative, and therefore greater absolute, benefit from β blockade as low risk patients without evidence of heart failure. Treating such patients—particularly those with more severe, overt heart failure—will require considerable care. Large scale randomised trials are needed urgently to confirm or refute these findings and establish appropriate clinical practice.

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