New developments in the management of heart failure: a review of the literature in 2002

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ABSTRACT

In 2002, several studies were directed at new developments in the management of heart failure. In the COPERNICUS study, the previously reported benefits of the β-adrenoreceptor blocker carvedilol regarding morbidity and mortality in patients with mild-to-moderate heart failure were also found in patients with severe heart failure. Carvedilol not only improves survival but when given in addition to conventional therapy, ameliorates the severity of heart failure and reduces the risk of clinical deterioration, hospitalisation and other serious adverse events.
The diagnostic value of B-type natriuretic peptide (BNP) in patients with congestive heart failure has been a topic of study for the past five years. Many questions still need to be answered but the results of a study by Maisel *et al*. show that BNP is not only of diagnostic value but is also important for prognosis and evaluation of therapy.
A substudy of the Val-HeFT study focussed on the effects of the angiotensin receptor blocker valsartan on BPN and noradrenaline levels. Valsartan significantly reduced the combined endpoint of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure, if added to prescribed therapy. However, in a post-hoc observation an adverse effect on mortality and morbidity was seen in the subgroup receiving valsartan, an ACE inhibitor and a β-blocker, which raised concern about the potential safety of this specific combination.
And finally, interesting work by Abraham *et al*. on cardiac resynchronisation through atrial-synchronised biventricular pacing clearly shows that this therapy can produce a significant clinical improvement in patients with moderate-to-severe congestive heart failure and intraventricular conduction delay.

INTRODUCTION

This review aims to highlight the most relevant publications on congestive heart failure published in 2002. Unfortunately, there were no real landmark studies in this particular year. Nonetheless, some substudies of previously published large trials have raised important issues. Furthermore, other publications are also of interest.

BETA-ADRENORECEPTOR ANTAGONIST AND HEART FAILURE

The first study concerns the effect of carvedilol on the morbidity of patients with severe chronic heart failure. The results of COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival Study) were published by Packer *et al.*[1]

Background

In the past few years, knowledge on the value of β-adrenoreceptor-blocking agents in patients with mild to moderately severe congestive heart failure has considerably increased (*table 1*). However, the effect of β-adrenoreceptor-blocking agents in patients with severe congestive heart failure is less obvious. In May 2001, Packer *et al.* published the effects of carvedilol on survival in severe chronic heart failure in the *New England Journal of Medicine*.[1] They reported the results in 2289 patients with symptoms of heart failure at rest or on minimal exertion. The patients were clinically euvolaemic and had ejection fractions of less than 25%. In a double-blind fashion the patients were randomly assigned to placebo or to treatment with carvedilol for a mean period of 10.4 months, during which standard therapy for heart failure was continued. A total of 1133 patients received the placebo regimen, while 1156 patients were treated with carvedilol. Patients who required intensive care, had marked fluid retention or were receiving intravenous vasodilators or positive inotropic drugs were excluded from the study. In the placebo group there were 190 deaths, while in the carvedilol group there were 130 deaths. This meant a difference of 35% in the decrease in mortality in favour of the carvedilol-treated patients (p=0.0014). For the combined endpoint death or hospitalisation there was a difference of 24% in favour of the patients treated with carvedilol. The favourable effects on both endpoints were seen consistently in all subgroups. This made the authors come to the following conclusion: the previously reported benefits of carvedilol with regard to morbidity and mortality in patients with mild-to-moderate heart failure were also found in patients with severe heart failure.

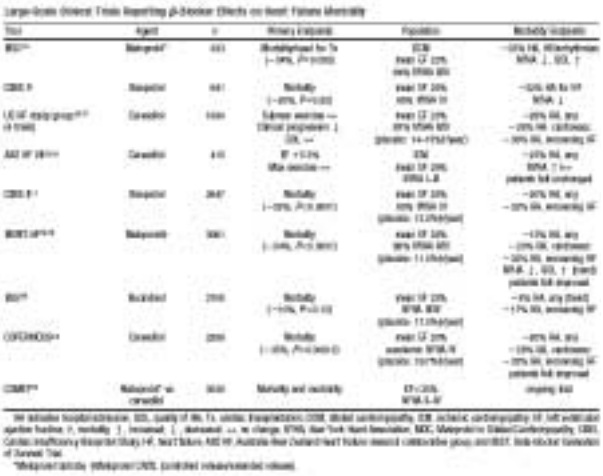
These results warranted the publication of the secondary endpoints, especially looking at differences in morbidity.[2] The secondary endpoints in the same patient population were:

- combined risk of death or hospitalisation for any reason;
- combined risk of death or hospitalisation for a cardiovascular reason;
- combined risk of death or hospitalisation for heart failure;
- the patient global quality-of-life assessment.

Carvedilol reduced the combined risk of death or hospitalisation for a cardiovascular reason by 27% (p=0.00002) (*figure 1*) and the combined risk of death or hospitalisation for heart failure by 31% (p=0.000004) (*figure 2*). Patients in the carvedilol group also spent 27% fewer days in the hospital for any reason (p=0.0005) and 40% fewer days in the hospital for heart failure (p<0.0001) (*figure 3*). These differences were the result of both decreases in the number of hospitalisations and a shorter duration of each admission. In the carvedilol group more patients felt

Table 1

Large-scale clinical trials reporting β-blocker effect on heart failure morbidity[7]



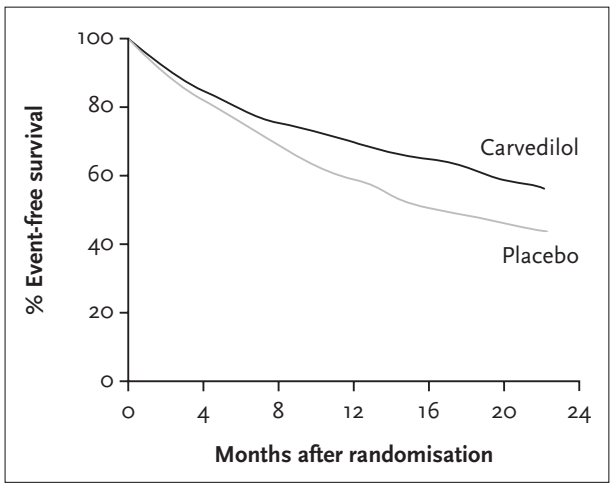


Figure 1

Kaplan-Meier analysis of time to death of hospitalisation for a protocol-specified cardiovascular reason in all patients randomised to placebo or carvedilol[1]

The 27% lower risk in the carvedilol group was highly significant (p=0.00002).

some improvement and fewer patients felt worse than in the placebo group after six months of treatment. Carvedilol-treated patients also experienced less serious adverse events (p=0.002). Serious adverse events were worsening of heart failure, sudden death, cardiogenic shock or ventricular tachycardia. With these data the investigators show that not only in mild to moderately severe congestive heart failure but also in severe heart failure carvedilol not only improves survival but also, when given in addition to conventional therapy, ameliorates the severity of heart failure and reduces the risk of clinical deterioration, hospitalisation and other serious adverse

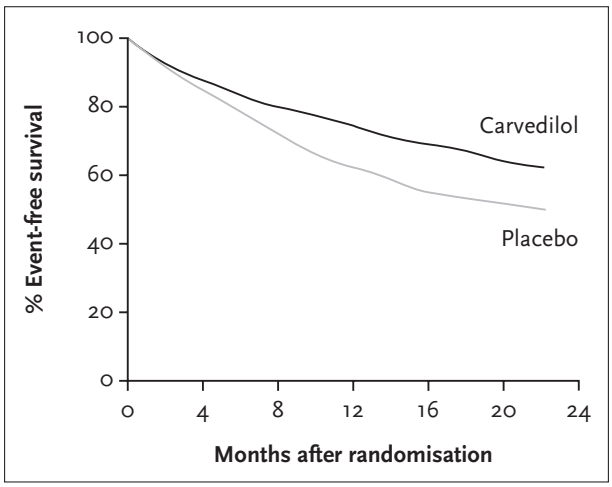


Figure 2

Kaplan-Meier analysis of time to death of hospitalisation for heart failure in all patients randomised to placebo or carvedilol[1]

The 31% lower risk in the carvedilol group was highly significant (p=0.000004).

events (*figure 4*). Whether the use of carvedilol, being a combined β1-, β2- and α-adrenoreceptor antagonists, should be advocated above the use of β1-selective compounds (bisoprolol and metropolol) is at this moment uncertain.

Table 1 gives a rough comparison of the data from different trials on β-adrenoreceptor antagonists and heart failure. Only head-to-head comparison of these drugs in a double-blind prospective study can answer this question.

B-TYPE NATRIURETIC PEPTIDE AND THE DIAGNOSIS OF HEART FAILURE

The next important article published in 2002, entitled Rapid Measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure, was by Maisel *et al.*[3]

Background

The prevalence of symptomatic heart failure in the general population in Europe varies from 0.4 to 2%. So in many patients with complaints of dyspnoea, congestive heart failure is the main cause of the symtoms. The sensitivity of diagnostic tools based on symptoms and findings during physical examination is low. It is known that B-type natriuretic peptide (BNP) is released from the cardiac ventricles in response to increased wall tension. Taking this fact into account the investigators conducted a prospective study in 1586 patients, who came to the emergency department with acute dyspnoea and whose BNP was measured with a bedside assay. The purpose of this study was to investigate whether the determination of

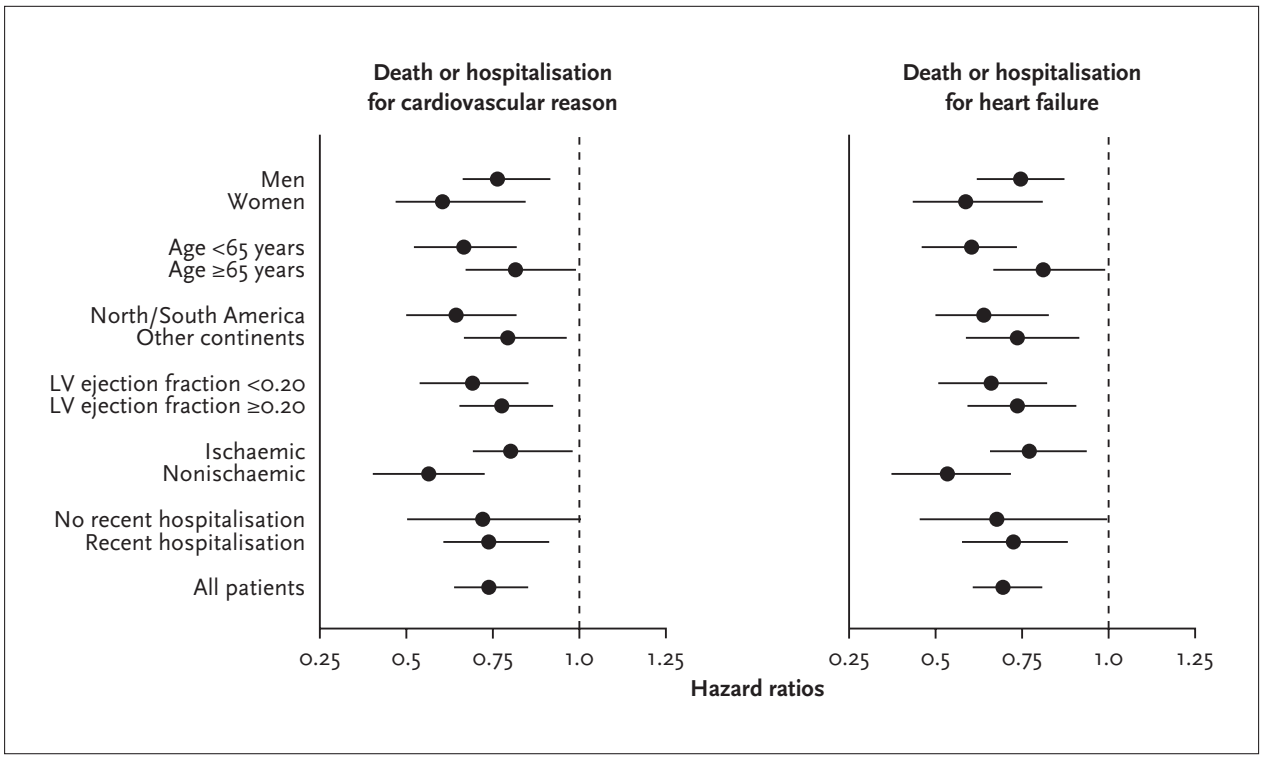


Figure 3

Hazard ratios (and 95% CI) for death from any cause in subgroups defined according to baseline characteristics[1]

LVEF = left ventricular ejection fraction. Recent hospitalisation refers to hospitalisation for heart failure within the year before enrollment.

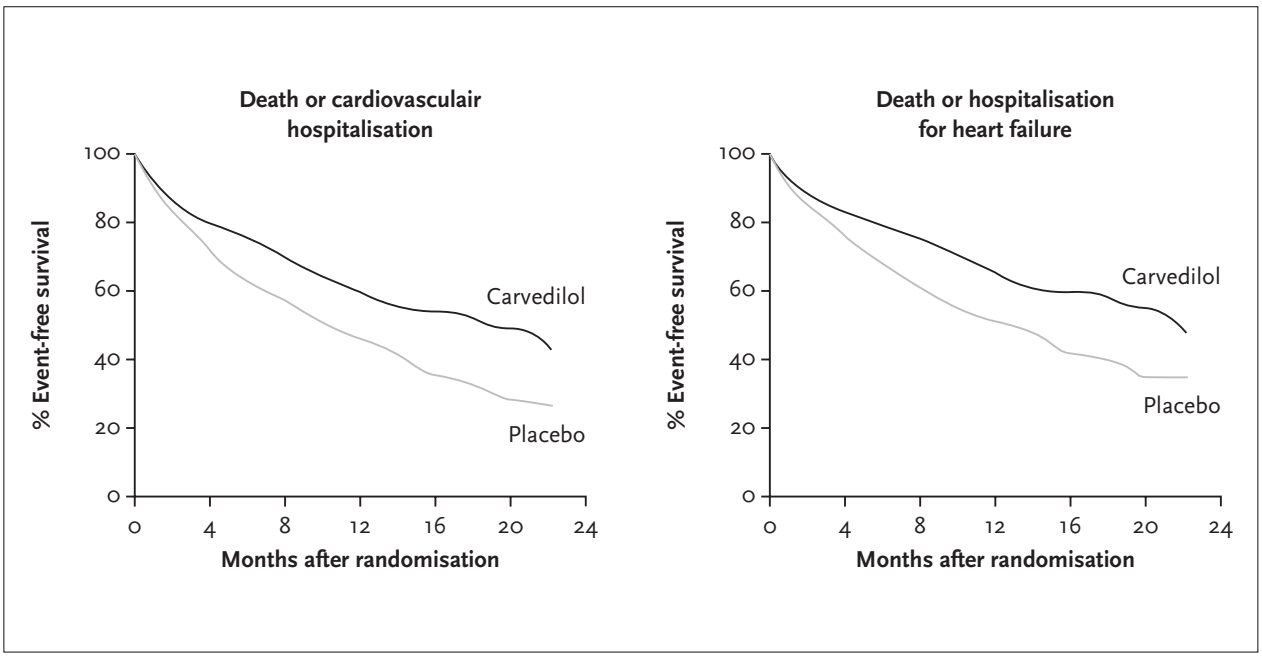


Figure 4

Kaplan-Meier analysis of time to death or cardiovascular hospitalisation (left panel) or death or hospitalisation for heart failure (right panel) in the 624 patients randomised to placebo or carvedilol who had recent or recurrent decompensation or a very depressed ejection fraction (≤15%)[2]

In both analyses, carvedilol reduced the risk of a major clinical event by 33% (both p=0.002).

BNP could improve the accuracy of the diagnosis in patients with acute dyspnoea. Furthermore, they tried to determine reliable cut-off values of BNP for the diagnosis congestive heart failure. The clinical diagnosis of congestive heart failure was made by two independent cardiologists who were blinded for the results of the BNP assay.

Results

The final diagnosis of this study was dyspnoea due to congestive heart failure in 744 patients (47%), dyspnoea due to noncardiac causes in 72 patients with a history of left ventricular dysfunction (5%) and no finding of congestive heart failure in 770 patients (49%) (*figure 5*). BNP levels in themselves were more accurate than any historical or physical finding or other laboratory values in identifying congestive heart failure as the cause of dyspnoea in this type of patient. The diagnostic accuracy of BNP at the cut-off point of 100 pg/ml was 83.4%. The negative predictive value of BNP at levels of less than 50 pg/ml was 69% (*figure 6*). In a multiple logistic regression analysis, measurements of BNP added significant independent predictive power to other clinical variables in models predicting whether patients had congestive heart failure or not. In the past five years, important progress has been made on the value of BNP in patients with congestive heart failure, but many questions still need to be elucidated. In this respect this study is of special importance. It is

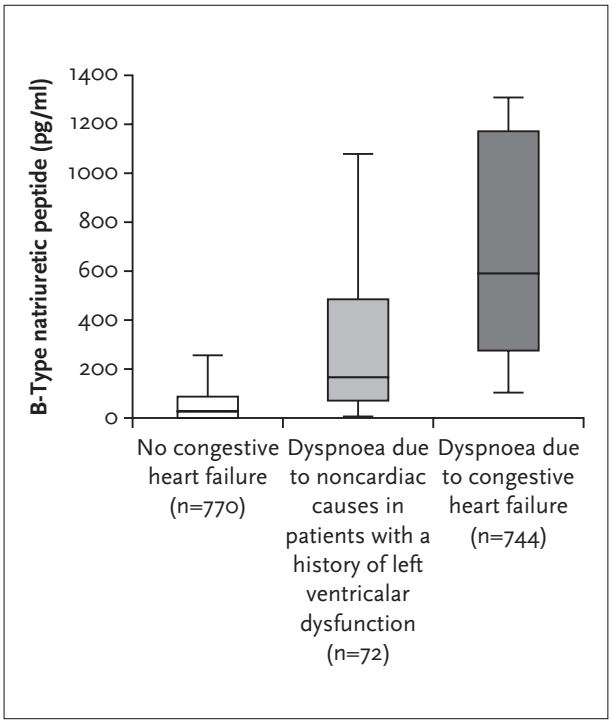
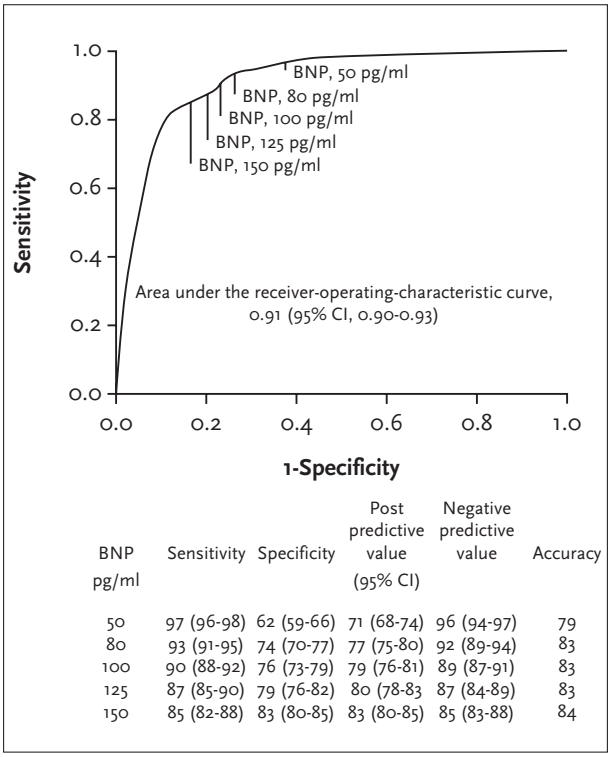


Figure 5

Box plots showing median levels of B-type natriuretic peptide measured in the emergency department in three groups of patients[3]

Boxes show interquartile ranges and I bars represent highest and lowest values.



BNP pg/ml	Sensitivity	Specificity	Post predictive value (95% CI)	Negative predictive value	Accuracy
50	97 (96-98)	62 (59-66)	71 (68-74)	96 (94-97)	79
80	93 (91-95)	74 (70-77)	77 (75-80)	92 (89-94)	83
100	90 (88-92)	76 (73-79)	79 (76-81)	89 (87-91)	83
125	87 (85-90)	79 (76-82)	80 (78-83	87 (84-89)	83
150	85 (82-88)	83 (80-85)	83 (80-85)	85 (83-88)	84

Figure 6
Receiver operating characteristic curve for various cut-off levels of B-type natriuretic peptide (BNP) in differentiating between dyspnoea due to congestive heart failure and dyspnoea due to other causes[3]

becoming more and more evident that the determination of BNP levels in patients with complaints of dyspnoea is not only of diagnostic value but is also important with regard to prognosis and evaluation of therapy.

ANGIOTENSIN II RECEPTOR ANTAGONIST, HEART FAILURE AND NEUROHUMORAL PARAMETERS

Background

In 2002, Cohn *et al.* published the results of the Valsartan Heart Failure Trial (Val-HeFT).[4]
A further analysis of these results, focussed on the effects of valsartan on BNP and noradrenaline level, was published in *Circulation*.
Val-HeFT was a randomised trial of the angiotensin receptor-blocker valsartan in chronic heart failure. The rationale of this study was based on the important role of angiotensin II in the progression of congestive heart failure and on the recent insight that angiotensin II is still produced in patients on ACE inhibitors. Up to now, it was not known whether addition of an angiotensin II receptor blocker is useful in patients with congestive heart failure treated with currently recommended drugs,

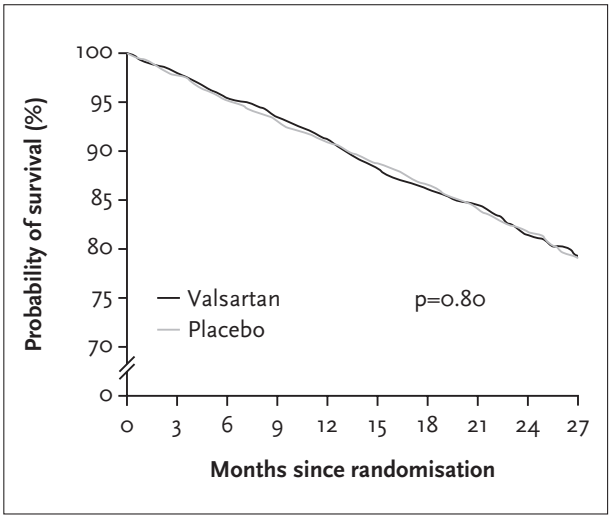


Figure 7
Kaplan-Meier analysis of the probability of survival[4]

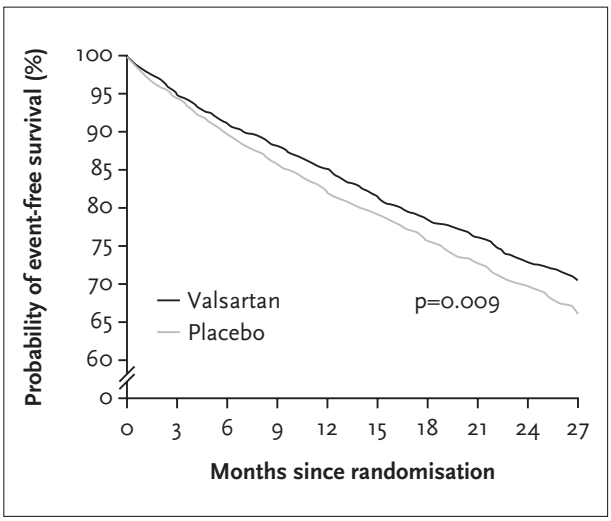


Figure 8
Kaplan-Meier analysis of the probability of freedom from the combined endpoint (death any cause, cardiac arrest with resuscitation, hospitalisation for worsening heart failure or therapy with intravenous inotropes or vasodilators)[4]

especially ACE inhibitors. In the Val-HeFT a total of 5010 patients with heart failure of New York Heart Association (NYHA) class II, III or IV were randomly assigned to receive 160 mg of valsartan or placebo twice daily on top of their normal medication (diuretic, digoxin, β-blockers, ACE inhibitors). The primary outcomes were mortality and the combined endpoint of mortality and morbidity defined as the incidence of cardiac arrest with resuscitation, hospitalisation for heart failure and receipt of intravenous inotropics or vasodilator therapy for at least four hours. The main results showed an overall mortality that was similar in the two groups (*figure 7*).

The incidence of the combined endpoint, however, was 13.2% lower with valsartan than with placebo, (*figure 8*) predominantly because of a lower number of patients hospitalised for heart failure: 455 (18.2%) in the placebo group and 346 (13.8%) in the valsartan group (p<0.001). Treatment with valsartan resulted in a significant improvement in NYHA class, ejection fraction and signs and symptoms of heart failure as well as in quality of life as compared with placebo (p<0.001). The authors concluded that valsartan significantly reduced the combined endpoint of mortality and morbidity, and improved clinical signs and symptoms in patients with heart failure if added to prescribed therapy. However, in the post-hoc observation an adverse effect on mortality and morbidity was seen in the subgroup receiving valsartan, an ACE inhibitor and a β-blocker, which raised concern about the potential safety of this specific combination (three is a crowd!) (*figure 9*).
In a substudy of Val-HeFT, changes in circulating BNP and norepinephrine (NE) were studied, knowing that the levels of these neurohormones are strongly related to the severity and the prognosis of heart failure.[5] The long-term effects of an angiotensin receptor blocker on BNP and NE in heart failure patients were not known.

Methods and results

Both BNP and NE were measured in 4284 patients, randomised to valsartan or placebo at baseline and at 4, 12 and 24 months after randomisation. BNP and NE concentrations were similar at baseline in the two groups and were decreased by valsartan, starting at four months, and remained decreased for up to 24 months (*figure 10*). BNP increased over time in the placebo group. Concomitant therapy with both ACE inhibitors and β-blockers significantly reduced the effect of valsartan on BNP but not on NE (*figures 11* and *12*).
This study shows for the first time that an angiotensin receptor blocker decreases two major markers of the severity of heart failure. The effects on BNP and NE can be seen within four months and last for at least 24 months. As such, the benefit of valsartan in heart failure, which was consistent across all variables analysed with the exception of mortality (combined endpoint of morbidity and mortality, quality of life, clinical signs, NYHA class, left ventricular ejection fraction, and left ventricular diameter) can now be extended to BNP and NE levels. However, the exact clinical meaning of these findings still has to be elucidated.

CARDIAC RESYNCHRONISATION IN CHRONIC HEART FAILURE

In June of 2002, Abraham *et al.* published an interesting study on the results of cardiac resynchronisation in chronic heart failure.[6]
The rationale of this study was that previous studies have suggested that cardiac resynchronisation achieved through

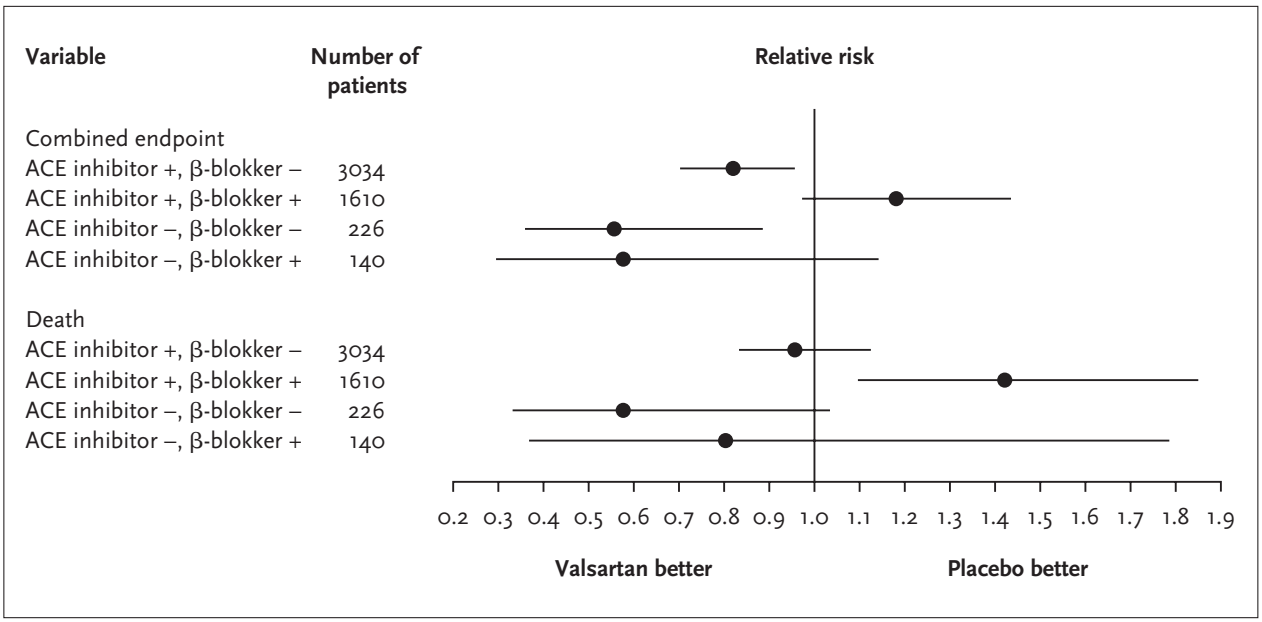


Figure 9

Relative risks and 95% CI for the combined endpoint (death any cause, cardiac arrest with resuscitation, hospitalisation for worsening heart failure or therapy with intravenous inotropes or vasodilators), according to the background therapy at baseline, as calculated by means of a Cox regression model[4]

ACE = angiotensin-converting enzyme + the use of the drug and non-use.

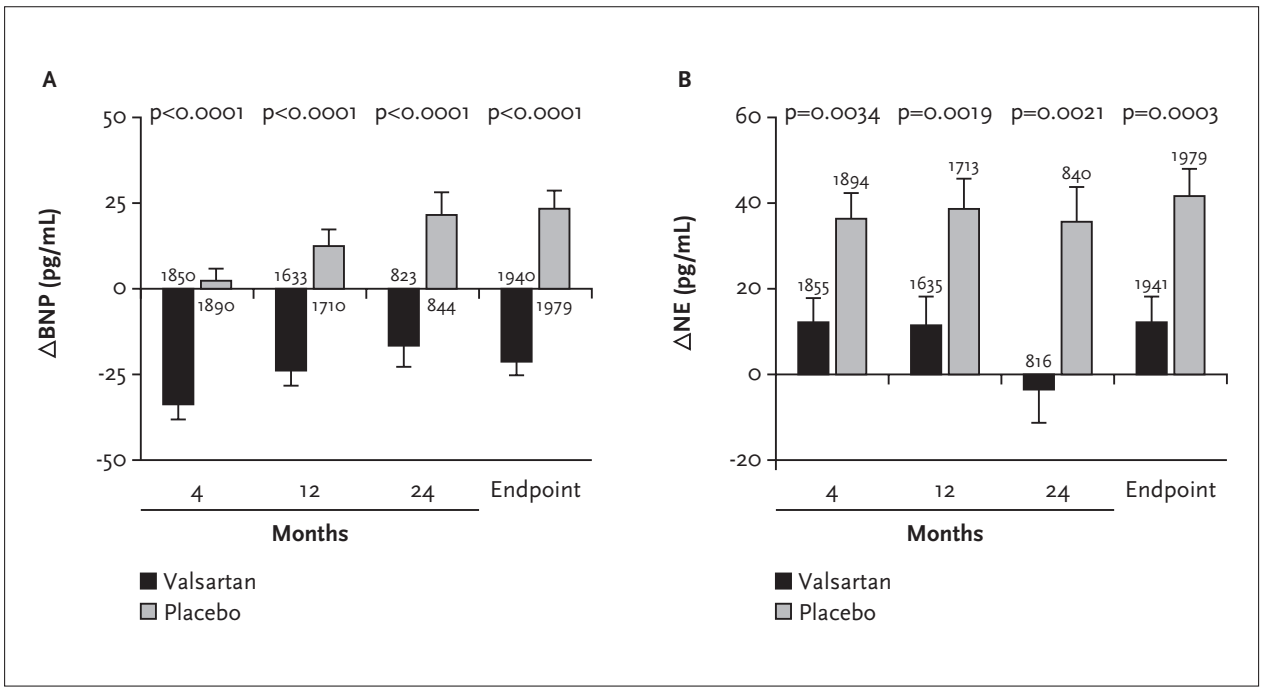


Figure 10

Change from randomisation in plasma concentrations of (a) BNP and (b) NE at 4, 12 and 24 months and at endpoint[5]

Data are presented as least-squares mean ± SEM, with probability values for between-treatment comparison of means. Number of patients in group are shown in bar.

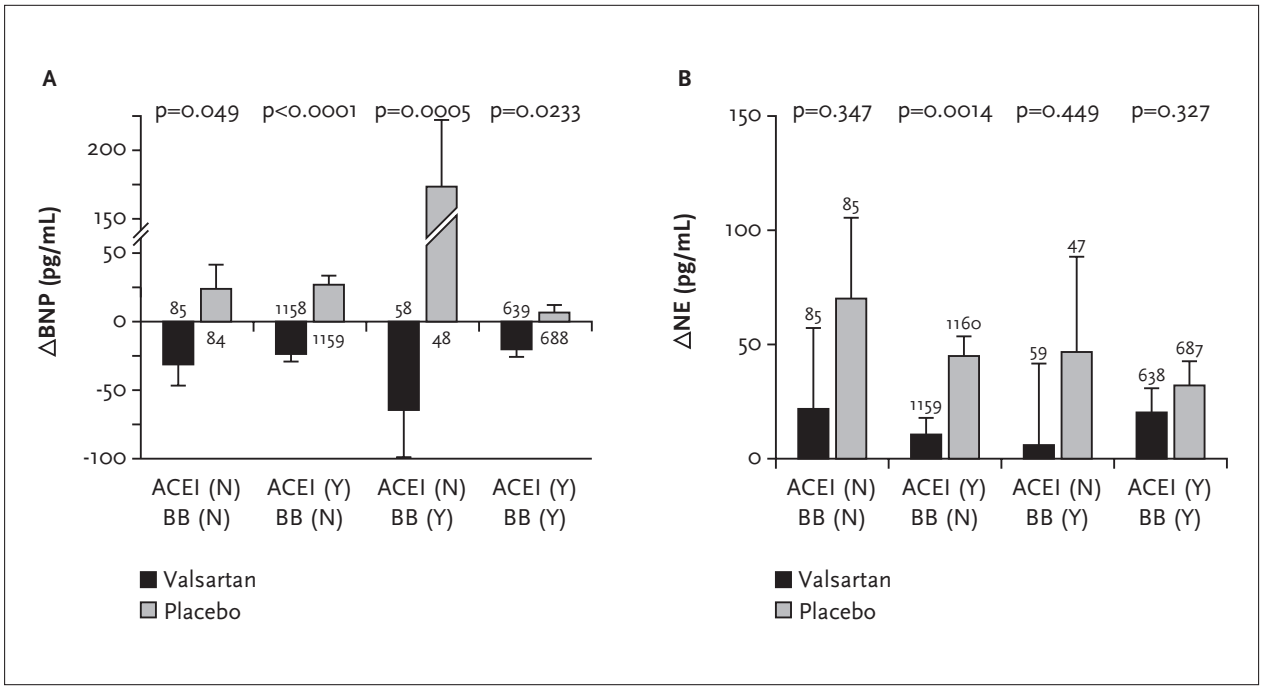


Figure 11

Effects of valsartan on changes from randomisation in plasma concentrations of (a) BNP and (b) NE at endpoint in four subgroups defined by concomitant therapy[5]

Combinations were ACEI (Y/N) and BB (Y/N). Data are presented as least-squares mean ± SEM, with probability values for between-treatment comparison of means. Treatment x 4 subgroup interaction: BNP p=0.109, NE p=0.2413.

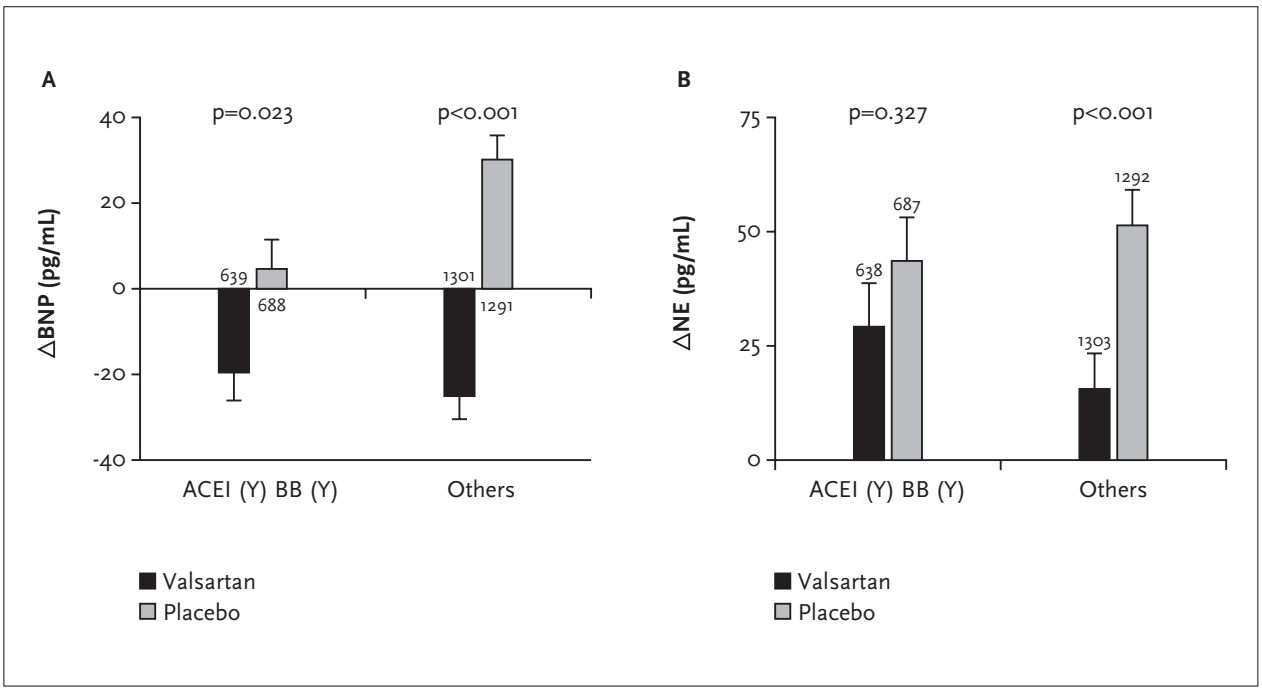


Figure 12

Effects of valsartan on changes from baseline to endpoint in (a) BNP and (b) NE by subgroups on ACE1 (Y/N) and/or BB (Y/N) at randomisation[5]

Two-group ANOVA test for interaction: ACEi (y)/BB (Y) versus others. BNP: treatment x ACEi/BB, p=0.0228; NE: treatment x ACEi/BB, p=0.2289. Data are presented as least-squares mean ± SEM. Probability values are for between-treatment comparison of means. Number of patients in group are shown in bar. BNP at baseline: ACEi (Y)/BB (Y): placebo 164 ± 8, valsartan 169 ± 8 pg/ml; others: placebo 169 ± 6, valsartsan 181 ± 6 pg/ml. NE at baseline: ACEi (Y)/BB (Y): placebo 449 ACEi (Y)/BB (Y):10, valsartan 456 ± 10 pg/ml; others placebo 461 ± 8, valsartan 449 ± 8 pg/ml. No significant differences ACEi (Y)/BB (Y) versus others or placebo versus valsartan.

atrial-synchronised biventricular pacing produces clinical benefits in patients with heart failure and an intraventricular conduction delay. In the present study, 453 patients from 45 different medical centres with moderate-to-severe congestive heart failure were investigated in a double-blind fashion. They all had an ejection fraction of 35% or less and a QRS interval on the ECG of 130 msec or more. They were randomly assigned to a cardiac-resynchronisation group (228 patients) or to a control group (225 patients). The conventional medical treatment was continued. Follow-up lasted for six months and all patients received a device. The primary endpoints were the NYHA classification, quality-of-life assessment and the distance walked in six minutes. Secondary endpoints were maximal exercise performance, left ventricular ejection fraction and left ventricular end-diastolic diameter, severity of mitral valve insufficiency and QRS interval. During the study 571 patients appeared to be eligible. Of these, 47 patients had to be excluded because implantation was not successful (43 patients), pacing appeared to be necessary (2 patients) or they developed unstable congestive heart failure (2 patients). A total of 71 patients only joined the pilot period of the study (three months). Of the remaining group of 453 patients, 225 patients were randomised to the control group and 228 patients to the paced group. The result of the study was very promising (*table 2*). In the paced group there was a significant improvement in six-minute walking distance compared with the non-paced group (p=0.005). There was also a significant improvement in functional NYHA class (p<0.001). The quality of life as well as the ejection fraction improved significantly in the paced group: p=0.001 and p<0.001 respectively. In the paced group there were also less hospitalisations. Probably the most important reason for the better results in the paced group was a reduction in the severity of the mitral valve insufficiency. This study clearly shows that cardiac resynchronisation in moderate-to-severe congestive heart failure with intraventricular conduction delay results in a significant clinical improvement. Implantation of the pacemaker was unsuccessful in only 8% of the patients, and as such this treatment modality can help the majority of this specific group of patients.

Table 2
Effect of cardiac resynchronisation on efficacy endpoints[6]

TABLE 2. EFFECT OF CARDIAC RESYNCHRONIZATION ON EFFICACY END POINTS.

END POINT*	CONTROL GROUP	CARDIAC-RESYNCHRONIZATION GROUP	P VALUE
Change in the distance walked in six minutes — m			
Median	+18	+39	0.005
95 percent confidence interval	8 to +25	+26 to +54	
No. of patients	198	214	
Change in the Minnesota Living with Heart Failure score			
Median	−9	−18	0.001
95 percent confidence interval	−12 to −5	−22 to −12	
No. of patients	192	213	
Change in the New York Heart Association functional class — no. (%)			<0.001
Improved by two or more classes	12 (6)	34 (16)	
Improved by one class	62 (32)	109 (52)	
No change	115 (59)	64 (30)	
Worsened	7 (4)	4 (2)	
Change in peak oxygen consumption — ml/kg/min			
Median	+0.2	+1.1	0.009
95 percent confidence interval	−0.2 to +0.8	+0.6 to +1.7	
No. of patients	145	158	
Change in total exercise time — sec			
Median	+19	+81	0.001
95 percent confidence interval	−1 to +47	+62 to +119	
No. of patients	146	159	
Change in patient's view of progress — no. (%)			<0.001
Markedly improved	24 (12)	80 (38)	
Moderately improved	42 (22)	46 (22)	
Slightly improved	44 (23)	40 (19)	
No change	51 (26)	26 (12)	
Slightly worse	20 (10)	11 (5)	
Moderately worse	10 (5)	5 (2)	
Markedly worse	4 (2)	1 (1)	
Absolute change in left ventricular ejection fraction — %			
Median	−0.2	+4.6	<0.001
95 percent confidence interval	−1.0 to +1.1	+3.2 to +6.4	
No. of patients	146	155	
Change in left ventricular end-diastolic dimension — mm			
Median	0.0	−2.5	<0.001
95 percent confidence interval	−1 to +2	−6 to −1	
No. of patients	98	90	
Change in area of the mitral regurgitant jet — cm^2			
Median	−0.5	−2.7	<0.001
95 percent confidence interval	−1.1 to 0.0	−4.0 to −2.1	
No. of patients	118	116	
Change in QRS duration — msec			
Median	0	−29	<0.001
95 percent confidence interval	−10 to 0	−38 to −12	
No. of patients	192	206	

*The numbers of patients with data available for each variable are listed.

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