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The Treatment of Chronic Heart Failure by Drugs

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In thirteen placebo controlled studies with reduction of total mortality there was no strict correlation between the improvement of symptoms and morbidity and the reduction of mortality. Either the reduction of mortality or the improvement of symptoms or morbidity are reliable endpoints for each other. Only spironolactone in the RALES-study showed a consistency for improving symptoms and morbidity and reduction of mortality. However, the minimal challenge for the treatment of the life threatening disease chronic heart failure is the improvement of symptoms and morbidity without reduction of life expectancy. Spironolactone, enalapril and bisoprolol can be recommended for the improvement of all three endpoints, whilst for carvedilol there is only evidence for the reduction of morbidity and mortality, for metoprolol and the combination of hydralazine and isosorbiddinitrate for the reduction of mortality and digoxin for the reduction of morbidity. For amlodipine there is no proof of the improvement of symptoms, morbidity and mortality. *J Clin Basic Cardiol* 2000; 3: 163–6.

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Studies done in the USA [1] and Scotland [2] have shown that there has been a progressive and dramatic increase in the prevalence of heart failure as a hospital diagnosis during the past 30–40 years and there seems to be sufficient evidence to suggest that there is a true increase in the disorder. The reasons are multifactorial, but two of the major factors appear to be general ageing of the population in developed countries and increased survival after myocardial infarction. Chronic heart failure therefore is a growing challenge for the treatment of this disorder. The treatment of chronic heart failure will be mainly carried out by drugs. It is expected that the treatment of chronic heart failure improve not only mortality but also morbidity and symptoms of heart failure. Therefore, in the following trials with improvement of mortality, the influence of drug therapy on the symptoms and morbidity will be examined.

Results (Table 1)

There are thirteen placebo controlled studies [3–16] with a reduction of total mortality by drug treatment of chronic heart failure. Different agents were used and the number of patients and duration of therapy differed. The changes in the symptoms were tested by the vital status, New York classification and six-minute walk test, the morbidity by the hospitalization rate, incidence and worsening of heart failure and cardiovascular events, the mortality by the relative and absolute risk reduction of total mortality.

V-HeFT-I-study [6, 7]

459 men with chronic heart failure and a left ventricular ejection rate below 45 % were treated either with hydralazine + isosorbiddinitrate or placebo in addition to digoxin and diuretics.

There were no data on symptomatology and morbidity. The total mortality in the verum group was with 38.7 %, marginally significant lower than in the placebo group with 44 %. The relative and absolute risk reduction amounted to 12 % respectively 5.3 %.

CONSENSUS(-I)-study [8]

In only 253 patients with chronic heart failure NYHA IV the additional application of enalapril lead to a significant lower total mortality with 26 % compared with placebo (44 %) after only six months. The study was discontinued prematurely.

The relative and absolute risk was reduced about 41 % respectively 18 %. The stage according to NYHA improved about 42 % in the enalapril and about 22 % in the placebo group. The difference was significant. There were no data for morbidity.

SOLVD-T-study [15]

There was a significant reduction of the risk for mortality about 11 % respectively 4.5 % in 2569 patients with chronic heart failure NYHA II and III treated additionally with enalapril or placebo for about 3½ years. The stage of the alive patients improved not significantly according to NYHA and the rate of hospitalization was significantly lower in the group of enalapril compared with the patients in the placebo group.

SOLVD-P-study [16]

In this study with 4228 patients with chronic heart failure NYHA I and II there was relative and absolute risk reduction for mortality about 6 % respectively 1 % in the enalapril and placebo group after about three years of therapy. The risk reduction was not significant. The incidence of chronic heart failure and the rate of hospitalization decreased significantly in the patients with enalapril compared with the placebo patients.

CIBIS(-I)-study [4]

The additional application of either bisoprolol or placebo to 641 patients with heart failure NYHA III and IV for 1.9 years showed no significant reduction of the relative and absolute mortality risk (16.6 %/20.9 %). Only in a subgroup of non-ischaemic cardiomyopathies was there a significantly lower mortality rate in the bisoprolol group compared with the placebo group (9.4 %/20.0 %). The NYHA-class improved significantly by one stage in 21 % respectively 15 % in the bisoprolol and placebo group and cardiovascular events occurred more often in the patients with placebo.

PRAISE-study [12]

The total mortality was not significant lower in the amlodipine group than in the placebo group (33.3 %/38.3 %). 1153 patients with chronic heart failure NYHA III or IV were included in the study and treated for more than one year. Only in patients with non-ischaemic cardiomyopathy was there a significant risk reduction between the two treatment groups. The

symptoms according to the classification of NYHA and the non-fatal cardiovascular events occurred similarly in the amlodipine group compared to patients with placebo.

US-Carvedilol-study [11]

The relative and absolute risk for total mortality was significantly lower in the patients who were treated with carvedilol rather than placebo (59 %/4.6 %). 1094 patients with chronic heart failure NYHA II–IV were treated for 6.5 months. The study was stopped early. There was no improvement in the six-minute walk test, but the hospitalization rate was significantly lower in the enalapril group compared with the placebo patients (14.1 %/19.6 %).

ANZ-study [3]

In the Australian-New Zealand-study 415 patients with chronic heart failure NYHA-stage II–IV were treated additional with carvedilol respectively placebo for 19 months on average.

The relative and absolute risk for total mortality decreased about 24 % respectively 3 %. The difference was not significant between the treatment groups (9.6 %/12.6 %).

The NYHA stage improved during 6 and 12 months (11 %/13.5 % respectively 12.6 %/13.5 %). The differences were not significant. Worsening of chronic heart failure was not significantly different in the two treatment groups (39.4 %/36.2 %).

DIG-study [9]

The additional application of digoxin respectively placebo in 6800 patients with chronic heart failure NYHA I–IV and sinus rhythm lead to no significant reduction of the risk for total mortality during the treatment phase of 37 months (34.8 %/35.1 %). There was no improvement of symptoms according to the stage of NYHA classification, but worsening of chronic heart failure was significantly less frequent in the digoxin group compared with the placebo patients.

Table 1. Symptomatology, morbidity and mortality in the different studies (m. = males, f. = females, CHF = chronic heart failure, Hosp. = Hospitalization, RRR = relative risk reduction, ARR = absolute risk reduction) (* = significant)

Study (year) (stage)	Number patients (mean age)	Drug (mean duration of therapy)	Symptomatology (verum/placebo)	Morbidity (verum/placebo)	Mortality RRR (ARR)
V-HeFT-I (1996) (LVEF < 45 %)	459 m (58.3/58.5 years)	Hydralazine + Isosorbid- dinitrate (2.3 years)	—	—	12 %* (5.3 %)
CONSENSUS (1987) (NYHA IV)	253 m. & f. (71/70 years)	Enalapril (6 months)	NYHA 42/22 %*	—	41 %* (18.0 %)
SOLVD-T (1991) (NYHA II and III)	2569 m. & f. (60.7/61 years)	Enalapril (41.4 months)	Vital status: 0: 52.3/42.7 % 1: 7.4/9.6 % 2: 2.4/3.7 % 3: 1.2/2.1 % ≥ 4: 1.6/2.2 %	Hospitalization: 1×: 25.8/36.6 %* ≥ 2×: 12.2/18.2*	11 %* (4.5 %)
SOLVD-P (1992) (NYHA I and II)	4228 m. & f. (59.1/59.1 years)	Enalapril (37.4 months)	—	CHF: 20.7/30.2 %* Hosp. 1×: 8.7/12.9 %* Hosp. > 1×: 2.7/4.8 %*	6 % (1.0 %)
CIBIS-I (1994) (NYHA III and IV)	641 m. & f. (50.1/59.2 years)	Bisoprolol (1.9 years)	NYHA I- Improvement: 21/15 %*	Cardiovascular events: 57.2/75.7 %*	21 % (4.3 %)
PRAISE (1996) (NYHA III or IV)	1153 m. & f. (64.7/64.7 years)	Amlodipine (13.8 months)	NYHA III: 80.9/80.4 % IV: 19.1/19.4 %	Cardiovascular events (nonfatal): 10.9/9.3 %	13 % (5.0)
US-Carvedilol (1996) (NYHA II–IV)	1094 m. & f. (57.9/58.1 years)	Carvedilol (6.5 months)	Six-minute walk: < 396 m: 49.6/50.75 % ≥ 396 m: 50.4/49.2 %	Hospitalization: ≥ 1×: 14.1/19.6 %*	59 %* (4.6 %)
ANZ (1997) (NYHA II–IV)	415 m. & f. (67 years)	Carvedilol (19.0 months)	NYHA improved: 6 months: 11/13.5 % 12 months: 12.6/13.5 %	Worsening CHF: 39.4/36.2 %	24 % (3.0 %)
DIG (1997) (NYHA I–IV)	6800 m. & f. (63.4/63.5 years)	Digoxin (37.0 months)	NYHA I or II: 67.0/67.5 % III or IV: 32.9/32.5 %	Worsening CHF: 26.8/34.7 %*	1 % (0.3 %)
CIBIS-II (1999) (NYHA III and IV)	2647 m. & f. (60.0/61.0)	Bisoprolol (1.3 years)	NYHA: III: 83.3/83.0 % IV: 16.7/17.0 %	Hospitalization for worsening CHF: 12/18 %*	32 %* (5.5 %)
MERIT-HF (1999) (NYHA II–IV)	3991 m. & f. (63.9/63.7 years)	Metoprolol CR/XL (1.0 years)	—	—	32 %* (3.5 %)
RALES (1999) (NYHA III and IV)	1663 m. & f. (65.0/65.0 years)	Spironolactone (24.0 months)	NYHA improved: 41/33 %*	Hospitalization (cardiac causes): 31.6/39.95 %*	25 %* (4.7 %)
RESOLVD-II (2000) (NYHA I–IV)	426 m. & f. (62.0/61.0 years)	Metoprolol CR (24 weeks)	Six-minute walk: 397/396 m (mean)	Hospitalization CHF: 7.9/3.3 %*	54 % (4.7 %)

CIBIS-II-study [5]

Bisoprolol lead in comparison to placebo to reduction of the risk of total mortality about 32 % relatively and absolutely about 5.5 % in 2647 patients with chronic heart failure NYHA III and IV after 1.3 year treatment on average. There was no change in the NYHA stage between the treatment groups. Hospitalization for worsening of heart failure was significantly less often in the bisoprolol group compared with the patients receiving placebo (12 %/18 %).

MERIT-HF-study [10]

The total mortality rate was significantly lowered by the additional treatment with metoprolol CR/XL compared to placebo with a relative and absolute risk reduction of 32 % respectively 5.5 % in 3991 patients with chronic heart failure NYHA II–IV during a treatment phase of one year. There were no data on symptoms and morbidity.

RALES-study [13]

The additional application of spironolactone respectively placebo in 1663 patients with chronic heart failure NYHA III or IV over a treatment period of two years reduced the relative and absolute risk for total mortality about 25 % respectively 11.4 %. An improvement of the NYHA stage occurred in 41 % respectively 33 % in the spironolactone and placebo group. The differences were significant between the treatment groups.

The hospitalization rate was significantly reduced in the spironolactone group compared with the placebo group (31.6 %/39.6 %).

RESOLVD-II-study [14]

426 patients with chronic heart failure NYHA I–IV were treated with metoprolol CR or placebo for 24 weeks. The relative and absolute risk for mortality was reduced not significantly about 54 % respectively 4.7 % by metoprolol CR.

There were no differences in the six-minute walk test (mean 397 m/396 m) between the treatment groups. The hospitalization rate for chronic heart failure was significantly higher in the metoprolol CR group compared with the placebo group (7.9 %/3.3 %).

Discussion

In the thirteen placebo controlled studies with reduction of the total mortality there was also an improvement of the symptoms in five studies and of the morbidity in seven studies. In three studies there were no data for symptoms and morbidity. Therefore in 50 % and 70 % of the studies with mortality reduction there was an improvement of symptoms and morbidity.

Significant reduction of mortality occurred in seven studies, significant improvements of symptoms in three studies and of morbidity in seven studies. Only in one study [13] was there a uniform significant reduction of mortality and improvement of symptoms and morbidity. In this study spironolactone was the study medication. An unitary incidence of a significant reduction of mortality and improvement of symptoms occurred in only two studies [8, 13], in which enalapril and spironolactone were used.

A significant reduction of mortality and morbidity resulted in four studies [5, 11, 13, 15] with enalapril, carvedilol, bisoprolol and spironolactone. In the SOLVD-P- [16] and the DIG-study [9] with enalapril there was a significant reduction in morbidity, but not in mortality, and in the CIBIS-I-study [4] with bisoprolol there were significant improvements of symptoms and morbidity, but not in mortality.

In the RESOLVD II-study [14] morbidity increased significantly and mortality decreased non-significantly.

In summary there is no strict correlation between the reduction of mortality and the improvement of symptoms and morbidity. The reasons for this defective correlation can be different effects of the drugs but also the different stages or aetiology of chronic heart failure.

It is well known that the improvement of symptoms and morbidity is not absolutely a surrogate endpoint for mortality but vice versa mortality is not unconditionally an endpoint for symptoms and morbidity. Although the reduction of mortality is a condition for treating a life threatening disease like chronic heart failure, the improvement of symptoms and morbidity requires an additional examination.

The minimal challenge for treatment of symptoms and morbidity of chronic heart failure is not to reduce life expectancy. Only in the RALES-study [13] spironolactone improved symptoms and morbidity significantly with a real reduction of mortality. Spironolactone therefore can be seen as an ideal agent for the treatment of chronic heart failure. But in the RALES-study there was a high mortality in the placebo group (45.9 %), which could have an impact on the results and therefore can not be generalized for all patients with chronic heart failure. Also the mechanism for the surprisingly good results are unclear. With the other drugs there was no consistent influence on symptoms, morbidity and mortality.

Conclusion

Keeping in mind the risk in terms of reducing life expectancy, the differing drugs can be recommended in the following manner:

- spironolactone, enalapril and bisoprolol for the improvement of symptoms and reduction of morbidity and mortality;
- carvedilol for the reduction of morbidity and mortality;
- metoprolol and a combination of hydralazine and isosorbiddinitrate for the reduction of mortality;
- digoxin for the improvement of morbidity.

Amlodipine showed no significant improvement of symptoms, morbidity or mortality.

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