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Czech and Slovak Spirapril Intervention Study (CASSIS)

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CASSIS is a randomized, double blind, placebo- and active controlled 12-week multicentric study with spirapril in patients with congestive heart failure of NYHA class II–IV. The patients were randomized to one of five treatment arms: placebo (48 pts.), spirapril 1.5 mg (48 pts.), spirapril 3 mg (53 pts.), spirapril 6 mg (51 pts.) and enalapril 5/10 mg (48 pts.).

Spirapril treatment (pooled spirapril groups) induced during these twelve weeks a significant reduction in total mortality when compared to placebo patients and a trend for reduction of serious cardiovascular adverse events as well as duration of hospitalization. These effects and improvement in lung congestion appeared to be dose-dependent.

After the double blind period of twelve weeks the study was opened and patients were studied during a further 92 weeks (ie, for a total of 104 weeks equal two years). The second year of follow-up has been analysed. The improvement of NYHA functional classification at the end of the double-blind study with spirapril continued during the second year. The excellent tolerability of spirapril was surprising; hypotension, deterioration of renal function and cough were very rare. The incidence of cough was 0.6 %. Thus spirapril might be an effective alternative to enalapril in the treatment of patients with congestive heart failure. *J Clin Basic Cardiol 2000; 3: 7–10.*

Key words: cardiac failure, ACE inhibitors, spirapril, mortality

Spirapril is a carboxyl-bearing ACE inhibitor; it is a prodrug, the active form being spiraprilat [1, 2]. Spirapril shows a balanced hepatic and renal excretion, which enables once daily treatment even in patients with impaired renal function [3, 4]. Spirapril also lacks the first dose effect. ACE inhibitors are the drugs of choice in the treatment of congestive heart failure, because they are able to decrease both cardiovascular and total mortality [5, 6].

The aim of the CASSIS study was to gain experience about the efficacy, safety and tolerability of the drug in the therapy of congestive heart failure. The detailed results were presented elsewhere [7]. In this article we intend to inform about the most important results of the main study as well as the results of the follow-up.

Methods

CASSIS was a randomized, double blind, placebo- and active-controlled multicentric, prospective study over 12 weeks in patients with chronic congestive heart failure. 18 centres from the Czech Republic and the Slovak Republic participated in this study. After a placebo run-in period of 1–4 weeks, patients were randomized to the following treatment groups: placebo (48 patients), spirapril 1.5 mg (48 patients), spirapril 3 mg (53 patients), spirapril 6 mg (51 patients) and enalapril 5/10 mg (48 patients).

The main inclusion criteria were: congestive heart failure (CHF) due to coronary heart disease (CHD) or dilated cardiomyopathy, the ability to perform an exercise tolerance test for at least 2 min, but not more than 14 min and either a left ventricular ejection fraction ≤ 40 % or a cardiothoracic ratio greater than 0.55.

Exclusion criteria were: other causes of CHF, a history of acute myocardial infarction within the previous month, uncontrolled hypertension, unstable angina pectoris, history of clinically relevant arrhythmias, systolic blood pressure < 90 mmHg, uncontrolled diabetes mellitus, clinically relevant renal, hepatic, gastrointestinal, neurological or haematological diseases, a serum creatinine level > 180 μmol/l and a history of hypersensitivity to ACE inhibitors.

Non-allowed medications included: inotropic agents other than digitalis, agents with vasodilating properties. The use of nitrates and calcium channel blockers was permitted in patients with angina. The patients were instructed not to take this medication on the day of a scheduled visit. Patients randomised to enalapril started with the dose of 5 mg and in week 3 the dose was increased to 10 mg.

Exercise test was performed on a programmable, electronically braked bicycle ergometer (Ergometrics 900 Ergoline) starting with a workload of 25 W and increasing by 10 W every 2 min. Before switching to a new stage, blood pressure, heart rate and ECG were recorded automatically. The test was performed twice in the sitting position; if the difference between the two measurements was more than 90 sec. during the placebo phase and double during the double-blind phase the test had to be repeated.

Left ventricular ejection fraction was estimated by two-dimensional echocardiography. Cardiothoracic ratio was assessed by chest X-ray and analysed centrally in one centre by two clinicians blinded to the randomization. Lung congestion was evaluated according to Spinar et al. [8].

Statistical evaluation

Changes from baseline were analysed using the paired t-test and Wilcoxon signed rank sum test. Inter-group comparisons were performed as overall tests using analysis of covariance and the Mann-Whitney rank sum test, and categorical data were analysed using the χ^2-test and Fisher's two-tailed exact test. For exploration purposes, baseline and outcome parameters were analysed using a multiple linear correlation matrix.

Follow-up of the randomized study

After the end of the 12-week double-blind CASSIS study the study was opened and all patients could continue treatment for a further 92 weeks with spirapril on a voluntary basis. The results of the second year (last 52 weeks) of the follow-up are presented. 190 patients were included in this open study. During the study 86 patients were treated with 3 mg spirapril for the total time of 291 days and 92 patients with 6 mg spirapril for a total time of 301 days. Only 12 patients were treated with 12 mg spirapril for a total time of 263 days.

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Results of the randomized study

275 patients had been screened, 248 patients were randomised. The main reason for exclusion before the beginning of the study was higher duration of exercise test. The majority of patients were in an advanced stage of congestive heart failure, 56 % being in stage III and 19 % in stage IV of the NYHA functional classification. Only 25 % of the group had stage II NYHA functional classification. Table 1 demonstrates the characteristics of the total group of patients.

96 % of the group were treated with diuretics and 91 % with digoxin. No significant difference existed in concomitant treatment between the groups. Minor differences included: less frequent nitrate treatment in the placebo group than in the group treated with 1.5 mg of spirapril, less frequent antiplatelet treatment in the placebo group, more frequent antiplatelet treatment in the group treated with 6 mg spirapril. Calcium channel blockers were more frequently used in the group treated with 1.5 mg spirapril.

Efficacy of spirapril: mortality and drop-outs during the twelve-weeks study

Treatment was interrupted by 22 patients (drop-outs), from these 13 patients died either by sudden death or progressive heart failure. One patient treated with enalapril died due to a traffic accident and a further patient, also treated with enalapril, died 8 weeks after the interruption of treatment due to a progression of heart failure.

Total and cardiovascular mortality of patients treated with ACE-inhibitors were significantly lower than the mortality of placebo treated patients ($p = 0.023$). The mortality of all patients treated with spirapril was also significantly lower than the mortality of the placebo group ($p = 0.025$). Mortality of the patients treated with spirapril 3 mg was also significantly lower than the mortality of the placebo group ($p = 0.01$). All statistical evaluations were performed according to Fisher's test (Table 2).

The number of major cardiovascular events and the frequency and duration of hospitalization were significantly lower in the group of patients treated with spirapril when compared to placebo or even when compared to the enalapril treated group.

The number of patients, for whom a dose increase of spirapril was necessary or to whom new drugs had to be prescribed, was lower when compared to the placebo group or to the enalapril treated group.

Exercise tests

The mean duration of exercise test at baseline was 8 minutes and mean load was 65 W. The duration of exercise test increased significantly in all groups of patients. The absolute and relative changes were greatest in the group treated with 6 mg of spirapril and in the group treated with enalapril. Further analysis has disclosed that pre-existing angina, angina during the baseline exercise tolerance test, or the concomitant use of calcium channel blockers showed a significant negative correlation with the exercise duration, ie, patients with these cofactors showed no or even a negative response to ACE inhibitor treatment, whereas patients without these factors improved.

Left ventricular ejection fraction increased significantly in all groups treated with ACE inhibitors when compared to placebo. However, no significant difference could be observed between individual groups. Data of chest X-ray are in contrast to the changes of left ventricular ejection fraction. Only in patients on spirapril the mean relative heart size was reduced versus baseline. In the blinded, centralized analysis of the chest X-rays significantly more improvement in lung congestion was observed with 6 mg spirapril than with placebo.

Safety

The overall incidence of adverse effects was slightly lower than in the placebo group. Only few adverse events were considered by the investigators to be related to study medication: symptomatic hypotension was observed in two patients with spirapril 1.5 mg and one patient with 6 mg spirapril. Cough was surprisingly rare. Cough as adverse effect was observed only in one patient with 3 mg spirapril and one patient with enalapril. Further two cases of anaemia with enalapril and two cases of hyperpotassaemia with enalapril were reported. Table 3 demonstrates the incidence of adverse events.

Hospitalization and the number of days spent in the hospital were markedly lower especially in the 6 mg spirapril group compared to the placebo and enalapril group.

Results of the follow-up study (second year)

The total mortality data during the follow-up of the CASSIS study are presented in Table 4. The Kaplan-Meier analysis of the probability of survival showed that the 3-months interval total mortality remained constant during the 2 years of the study and was about 4 %. The mortality was similar in both groups treated either with 3 mg or 6 mg spirapril. The treatment with spirapril induced an improvement of the NYHA classification after three months, which remained also present at the end of the second year of the follow-up (Table 5).

The frequency of adverse effects due to spirapril during the second year of observation was also suprisingly low (Table 6).

No changes in haematocrit, haemoglobin, erythrocyte, leucocyte and platelet counts were reported. Neither changes in liver enzymes (ALAT, ASAT, GMT, ALP) and bilirubine levels were reported. Most adverse effects were related to the diuretic treatment (increase in uric acid level (10.1 %), deterioration of diabetes mellitus (1.8 %), hyperglycaemia (3.4 %) and increase in total cholesterol (3.0 %) or triglycerides (2.4 %) levels.

Table 1. Characteristics of the patients included into the CASSIS study

Characteristics	Mean (SD)
Gender = male	83 %
Age, yrs	57.5 ± 10
NYHA class II/III/IV	25 %/56 %/19 %
LV ejection fraction	28 ± 8 %
Cardiothoracic ratio	0.57 ± 0.06
Heart rate	82 ± 12 beats/min.
Systolic blood pressure	124 ± 16 mmHg
Diastolic blood pressure	80 ± 9 mmHg

Table 2. Total mortality during the twelve-weeks study

	Number of patients	3-month mortality
Placebo	48	12.5 %
Enalapril	48	4.2 %
All spirapril groups	152	3.3 %

Table 3. The frequency of adverse events, deaths and hospitalization during the twelve-weeks study

	Placebo	Spirapril			Enalapril
	(n=48)	1.5 mg (n=48)	3 mg (n=53)	6 mg (n=51)	5/10 mg (n=48)
Serious adv. event	22	17	14	10	23
– death	6	2	0	3	2
– sudden death	4	2	0	2	1
– hospitalization	11	8	7	4	12
Hypotension	1	2	0	1	0
Cough	0	0	1	0	1

Discussion

Several survival studies have demonstrated that ACE inhibitors can decrease cardiovascular and total mortality in patients with congestive heart failure not only in NYHA class IV [5], but also in NYHA class II or III [6]. ACE inhibitors are also able to prevent progression of the asymptomatic left ventricular systolic dysfunction into manifest congestive heart failure [6]. The treatment with ACE inhibitors can also improve the prognosis of patients with acute myocardial infarction with asymptomatic left ventricular systolic dysfunction [9–11]. A less marked short-term effect on total mortality was demonstrated when ACE inhibitors were given to all patients with acute myocardial infarction [12, 13]. ACE inhibitors prevent the progression of left ventricular systolic dysfunction. They may lead to a decrease in the incidence of myocardial infarction and unstable angina pectoris [14–16].

ACE inhibitors improve the clinical state of patients with congestive heart failure by several mechanisms: A vasodilatory effect leads to a decrease of the afterload due to a decrease of angiotensin II levels, decrease of the sympathetic activity and increase of bradykinin levels. The vasodilatory effect alone does not explain the positive effects of ACE inhibitors, because they are superior in influencing the survival in patients with congestive heart failure to vasodilatory treatment with the combinations of nitrates and hydralazine [17]. ACE inhibitors also decrease preload and lead to a decrease of cardiac dilatation. They decrease potassium losses due to diuretic treatment. ACE inhibitors also have a cardioprotective effect by preventing the remodeling of the left ventricular chamber and decreasing the amount of pathologically increased interstitial and perivascular collagen tissue [18].They increase the water and salt elimination due to a decrease of aldosteron and angiotensin II levels. ACE inhibitors also prevent the remodeling of the myocardium after acute myocardial infarction. Continuously increased activation of renin-angiotensin-aldosteron and sympatho-adrenergic systems is clearly negatively related to prognosis in patients with congestive heart failure [18–20]. For all these positive properties ACE inhibitors are recommended both by the US and European guidelines [21, 22] as first line drugs for congestive heart failure.

A positive effect on survival rates has been also found in the CASSIS study despite the fact that the sample size was not planned for that aim and these results should therefore be read with caution. Spirapril improved also NYHA functional classification, reduced heart size, improved X-ray signs of lung congestion and reduced also the number and duration of hospitalization.

The effect of both spirapril and enalapril on exercise tolerance was not significantly different from the placebo group, but these results could be negatively influenced by the interaction with calcium antagonists [7]. It cannot be excluded that the use of a treadmill instead of a bicycle ergometer would bring more positive results.

However, the most surprising finding of our study was the excellent tolerability of spirapril. The incidence of hypotension or deterioration of renal function was markedly low not only in the randomized study, but also during the analyzed second year of the follow-up.

Dry cough appears to be a frequent side effect for the class of the ACE inhibitors [22]. The frequence of cough is usually markedly high (10–15 %) and in 5–10 % it leads to the interruption of treatment. Markedly high incidence of cough was observed in the large SOLVD trial [6] using enalapril or TRACE trial using trandolapril [12]. In contrast, the excellent tolerability of spirapril was demonstrated by the low frequency of cough (0.6 %).

The low incidence of cough has also been observed in studies dealing with spirapril treatment of systemic hypertension. In the study of Fairhurst et al. 1994 [23], the incidence of cough was the same as in the placebo group, being 1.7 % vs 1.8 % and in the study of Guitard et al. 1994 [24] the incidence was 0 %. A similar incidence of cough of 0.88 % was also reported by Schmidt and Bachinger 1998 [25] in an open post-marketing surveillance study including 4685 patients.

In conclusion our results indicate that spirapril is an efficient ACE inhibitor in patients with congestive heart failure with excellent tolerability which surpasses some other ACE inhibitors. Thus spirapril can be considered as a well-tolerated and effective drug for long-term treatment of chronic congestive heart failure.

Table 4. Total mortality in the follow-up of the CASSIS study

Months of follow-up	Number of patients	3-months mortality*
3–6	216	4.2 %
6–9	199	2.5 %
9–12	192	7.8 %
12–15	174	4.0 %
15–18	162	4.3 %
18–21	155	5.2 %
21–24	145	3.4 %

*for the considered interval

Table 5. Improvement of functional NYHA classification during the randomized study and at the end of the follow-up of the CASSIS study

	Baseline	After 3 months	After 24 months
NYHA I	0 %	3 %	5 %
NYHA II	28 %	60 %	63 %
NYHA III	54 %	33 %	25 %
NYHA IV	18 %	4 %	7 %

Table 6. The incidence of adverse effects after two years of follow-up of the CASSIS study (n = 190)

Hypotension	0.6 %
Cough	0.6 %
Increase in urea plasma level	1.2 %
Increase in creatinine plasma level	0 %
Gastrointestinal	2.4 %
Cerebrovascular	3.0 %
Myocardial infarction	1.4 %
Neoplasma	2.4 %
Bronchopulmonary	8.9 %
Pulmonary embolism	0.6 %
Hyperpotassaemia	0.6 %
Hypopotassaemia	0.6 %

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