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A randomised double blind placebo controlled clinical trial of a standardised extract of fresh Crataegus berries (Crataegisan®) in the treatment of patients with congestive heart failure NYHA II

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Summary

A placebo controlled, randomised, parallel group, multicentre trial conducted in accordance with the guidelines of Good Clinical Practice (GCP) shows the efficacy and safety of a standardised extract of fresh berries of *Crataegus oxyacantha* L. and monogyna Jacq. (Crataegisan®) in patients with cardiac failure NYHA class II.
A total of 143 patients (72 men, 71 women, mean age of 64.8 (8.0 years) were recruited and treated with 3 times 30 drops of the extract (n = 69) or placebo (n = 74) for 8 weeks. The primary variable for the evaluation of efficacy was the change in exercise tolerance determined with bicycle exercise testing, secondary variables included the blood pressure-heart rate product (BHP). Subjective cardiac symptoms at rest and at higher levels of exertion were assessed by the patient on a categorical rating scale. An overall assessment of efficacy at the final visit was provided by the patient and the investigator.
In the ITT population there was a significant increase in exercise tolerance in both groups between visit 1 and visit 3. The difference between the treatment groups was 8.3 watts in favour of the standardised extract of fresh Crataegus berries (p = 0.045). The result is confirmed in the PP population (p = 0.047). Changes in BHP at 50 watts and at comparable maximum load were in favour of Crataegus extract but the results are not statistically significant. The subjective assessment of cardiac symptoms at rest and at higher levels of exertion did not change significantly and the patient and investigator overall assessment of efficacy were similar for the two groups.
The medication was well tolerated and had a high level of patient acceptability.
The significant improvement, due to the fact that dyspnoea and fatigue do not occur until a significantly higher wattage has been reached in the bicycle exercise testing allows the conclusion that the recruited NYHA II patients may expect an improvement in their heart failure condition under long term therapy with the standardised extract of fresh Crataegus berries.

Key words: crataegus extract, crataegus berries, hawthorn, congestive heart failure, exercise tolerance, randomised double-blind placebo controlled trial

Introduction

Heart failure is the inability of the heart to supply the body with the required blood volume and occurs in about 1% of the population, with an increasing morbidity rate in the elderly. The most common causes are ischaemic heart disease and hypertension. Left ventricular systolic dysfunction is the most common finding in patients with heart failure. Symptoms include dyspnoea and fatigue and the New York Heart Association

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(NYHA) has recognised four stages of the disease (class I, II, III, IV). An early start of a long-term therapy is recommended already for the milder forms of heart failure (NYHA classes I and II) to stop further deterioration in cardiac output and to improve the medium-term prognosis of these patients. However, classes I and II often remain untreated due to side effects of standard therapies. The reported excellent safety of Crataegus extracts suggests its use for early treatment and in prevention of decreasing cardiac performance.

Hawthorn (*Crataegus oxyacantha*) has a long history as a medical substance. The active ingredients are thought to be oligomeric procyanidines and flavonoids. Preclinical trials of hawthorn preparations have demonstrated a positive inotropic effect on human heart muscle in addition to a reduction in stimulus threshold and a coronary vasodilative action (Ammon et al. 1981). Only in few studies objective and clinical relevant parameters like exercise tolerance were tested. Primary outcome in older studies were subjective scores of cardiac symptoms.

Several placebo controlled clinical studies have demonstrated the efficacy of extracts of flowers and leaves of hawthorn in the treatment of cardiac insufficiency of NYHA Class II and with higher doses even III (WHO Monograph, 1998; Zapfe, 2001). In a recent placebo-controlled, randomised double-blind study the efficacy of a standardised extract of fresh Crataegus berries (Rob 10) on exercise tolerance and quality of life has been shown (Rietbrock et al. 2001). Earlier, an observational study in 44 patients using an extract of fresh Crataegus berries (Crataegisan®) showed a clinically significant improvement in symptoms in 86% of patients and a very good tolerability (Degenring, 1996). The current study is a controlled, randomised trial to evaluate the efficacy and safety of Crataegisan® in heart failure to be conducted in accordance with the guidelines of Good Clinical Practice (GCP).

Methods

Study design

The study is a double-blind, placebo controlled, randomised, parallel group, multicentre trial in patients with cardiac failure of NYHA Class II. At visit 1 (Day 0), patients who had given written informed consent to entry were checked for eligibility. Demographic details, medical history, cardiac symptoms and concomitant medication were recorded. An echocardiogram was performed, if one had not been done within the previous four weeks.

Exercise tolerance was determined by bicycle ergometry. The test was started with a load of 25 watts and this was increased by 25 watts every two minutes until subjective or objective discontinuation criteria occurred (Table 1). An electrocardiogram (ECG) was performed and blood pressure and pulse determined at rest and at the end of each watt setting. The maximum depression of the ST segment (lead I or V_6) after a load of 50 watts was documented, as were any symptoms experienced by the patient during the test.

Patients attended for follow-up at one and two months (visits 2 and 3) after the first visit. Changes in concomitant medication, adverse events and subjective cardiac symptoms were recorded. The exercise tolerance test was repeated. At visit 3 the overall efficacy of the treatment was assessed by the investigator and patient, and tolerability and acceptability of treatment were assessed by the patient.

Randomisation to active or placebo medication was at visit 1 by means of a computer-generated randomisation list in which the medication was distributed in blocks of four. Patients were allocated to the lowest available study number. The Clinical Trial Supplies of the CRO dispersed the study medication to the investigators. They received for each patient a sealed cartonbox containing two bottles of the study medication which they dispensed at visits 1 and 2. The returned medication at visits 2 and 3 was weighed. Compliance was checked by establishing the volume remaining in the bottle. The randomisation list was kept locked at the study coordinator of the sponsor.

Patients

Patients were recruited from 12 centres (10 internists and 2 general practitioners) in Germany. They were between 44 and 79 years of age (median value: 65 years, mean value: 64.8 years) with NYHA class II heart failure diagnosed at least three months previously and able to undergo a bicycle exercise test. Ejection fraction on echocardiography was at least 45% with no subsequent changes in clinical condition. Concomitant medications were not allowed during the study and within 4 weeks before the study. Pregnant females and those of childbearing age not using adequate contraception were excluded as were patients with a history of drug or alcohol abuse, psychiatric illness or those having

Table 1. Exercise test discontinuation criteria.

Fatigue
Dyspnoea
Angina pectoris
Heart rate of more than 200 less age
ST depression more than 4 mm (1 mm = 0.1 mV)
Drop in systolic blood pressure of more than 15 mm Hg compared to previous wattage
Patient request

taken part in a clinical trial within the previous 30 days. Patients with anaemia, thyroid disease, obstructive diseases of the respiratory tract, malignant tumour or hepatic or renal insufficiency were not eligible.

A number of cardiac pathologies were excluded and some concomitant medications were not permitted within the previous four weeks (Table 2).

Treatment

The active study medication was an ethanolic (49% V/V) extract (DER 1:3.2) of fresh *Crataegus oxyacantha* L. et monogyna Jacq. (Crataegisan®, Bioforce). A dose of 0.75 ml (30 drops) diluted in water was to be taken orally half an hour before meals, three times daily. This resulted in a daily dose of the active oligomeric procyanidines of at least 6.4 mg or total phenolic compounds of at least 12.7 mg. The placebo medication was coloured drops containing no Crataegus. The active and placebo medications were identical in appearance, odour and taste. Treatment was scheduled to continue for 56 (±7) days.

Study measurements

• *Efficacy:* Exercise tolerance testing is an important diagnostic and prognostic tool for assessing patients with suspected or known ischiemic heart disease. It is among the cardiologically approved methods for evaluation of efficacy of cardiac medications (Schmidt et al. 1994).

Exercise tolerance was defined as the maximum wattage that was sustained for 2 minutes during bicycle exercise testing. If the wattage at which the exercise test was discontinued was sustained for at least 1 minute, the exercise tolerance was the previous wattage level plus 12.5 watts. The primary variable for the evaluation of efficacy was the change in exercise tolerance between baseline (visit 1) and the final visit (visit 3).

Secondary variables included the blood pressure-heart rate product (BHP), calculated as (systolic BP × heart rate/100) at 50 watts and at the maximum wattage attained by the patient at visit 1 and visit 3. BHP has been used as parameter in older studies and therefore, has been included here. The reduction of BHP shows a linear proportionality to the reduction of myocardial oxygen consumption.

Subjective cardiac symptoms at rest (sensations of pressure/constriction, palpitations, nervousness, stabbing pain, quick pulse, feelings of unrest) and at higher levels of exertion (fatigue, dyspnoea, cough, anginal symptoms, palpitations) were assessed by the patient on a categorical rating scale as none, mild, moderate or severe. With milder degrees of severity such as NYHA class II, symptoms at rest are usually not heart specific, however, should not be left out of account.

An overall assessment of efficacy at the final visit was provided by the patient and the investigator.

• *Safety:* Safety was assessed by the recording of all adverse events during the study, patient and investigator evaluation of tolerability and patient evaluation of acceptability of the treatment. There were no safety outcomes defined in advance.

Statistical analysis and Sample size

The individual and summary evaluations of patient data were performed with SAS, version 6.12. Test analyses were carried out with TESTIMATE, version 5.2. The main criterion for the assessment of efficacy was the change in exercise tolerance from baseline (visit 1) to visit 3 in the intention to treat (ITT) population (all patients randomised). Comparison between the active and placebo groups was by the two-way U-test (Mann-Whitney Rank sum Test). Primary analysis was performed on the ITT – population, missing values of the main criterion were replaced by the last observation carried forward (LOCF) – method.

The statistical analysis was carried out without stratification because the number of patients in most of the centres was therefore too small.

Sample size calculations were based on an estimated difference in the relative reduction of exercise tolerance between active and placebo of 0.10 and a standard deviation of 0.16. Sixty one patients were required in each group to have a 90% power of detecting a significant difference between active and placebo medication at the 5% level, using two-tailed tests. Assuming a withdrawal rate of 12% a total of 140 patients were required.

Table 2. Study exclusion criteria.

Excluded cardiac pathology	Excluded medication
Blood pressure of 180/100 mmHg or more	Cardiac glycosides, calcium antagonists
Myocardial infarction within the previous 6 months	ACE inhibitors
Angina pectoris at rest	Sympathomimetics
Myocarditis	Anti-arrhythmics
Atrial fibrillation	Vasodilators
Valvular defect	Diuretics
Ejection fraction < 45% or significant ventricular dysfunction	Long-acting nitrates
Ventricular extrasystoles, class IVb or V according to Lown	Beta blockers
2nd or 3rd degree AV block	Calcium antagonists
Left or right bundle-branch block	

Results

A total of 143 patients were recruited by 12 centres. Two centres recruited more than 25 patients, four centres between twelve and sixteen patients and six centres one to seven patients. These 143 patients comprise the ITT population. Three patients withdrew from treatment at their own request (2 from verum, 1 from placebo) and 140 patients completed the study. There were 23 patients with protocol violations (12 violations in the verum and 16 in the placebo group), mainly due to medication compliance being less than 70%, and these were excluded from the analysis of the per protocol (PP) population (Fig. 1).

The two groups were similar in terms of demographics and baseline clinical signs (Table 3). Exercise tolerance and subjective cardiac symptoms at rest and at higher levels of exertion were also similar. The mean percentage treatment compliance was over 90% in both treatment groups.

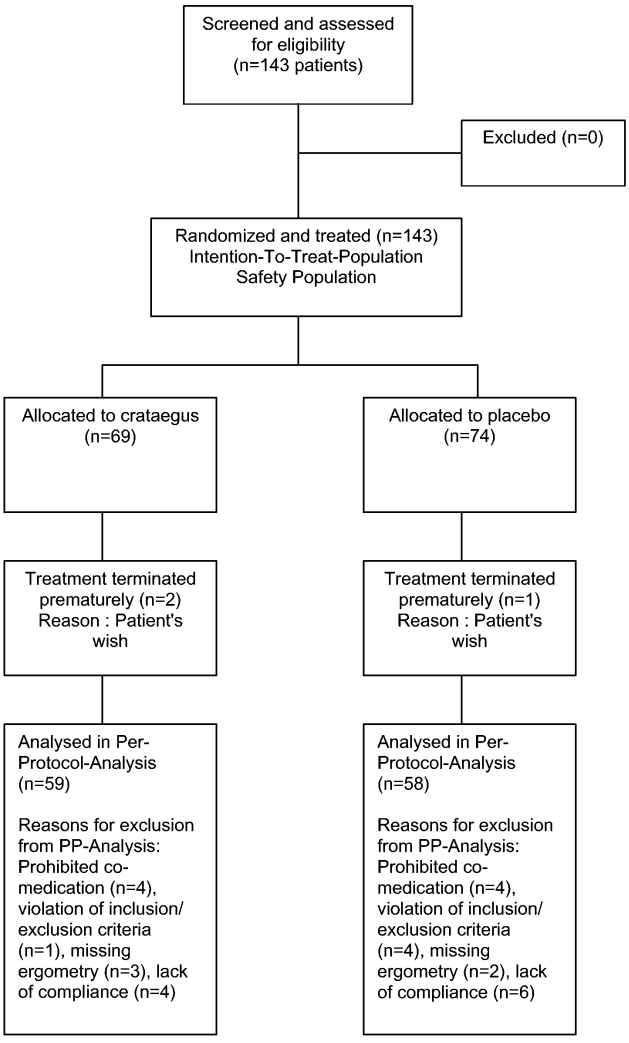

Fig. 1. Flow diagram of the clinical trial.

Efficacy

In the ITT population there was an increase in exercise tolerance in both groups between visit 1 and visit 3 (Table 4, Fig. 2). The difference between the treatment groups was 8.3 watts in favour of Crataegisan® and this was statistically significant (Mann-Whitney statistic 0.596, 95% confidence interval –16.3 to –0.3, p = 0.045). The result is confirmed in the PP population where there was a treatment difference of 9.5 watts in favour of Crataegisan® (p = 0.047).

There were no statistically significant differences between the two groups for changes in blood pressure heart rate product (BHP) at a load of 50 watts or at the maximum load achieved or in depression of the ST segment on ECG (Table 5).

The subjective assessment of cardiac symptoms at rest and at higher levels of exertion did not change significantly. A detailed listing of the symptoms at exertion is given in Table 6.

The patient and investigator overall assessment of efficacy was similar for the two groups. 72.4% of the patients considered the preparation to have an average to good efficacy (placebo 62.2%).

Safety

Nine patients in the Crataegisan® group and 11 patients in the placebo group reported adverse events. These were gastrointestinal, musculoskeletal, respiratory, urinary, vascular and psychiatric disorders of mild to mod-

Table 3. Patients baseline characteristics as number. Height, weight and ejection fraction expressed as mean value (SD).

	Crataegisan® (n = 69)	Placebo (n = 74)
Male	35	37
Female	34	37
Height as m	1.7 (0.1)	1.7 (0.1)
Weight as kg	78.5 (13.8)	75.0 (12.1)
Smoker	16	19
Ejection Fraction as %	56.5 (10.8)	56.0 (9.8)
Ventricular Dysfunction: Yes	1	2
No	68	72
Basal rales	4	8
Hepatomegaly	7	4
Leg edema	19	18
Congestion of jugular veins	7	9

erate severity. All were assessed by the treating physicians as being unlikely related to the study medication. The tolerability of both the study medication and placebo were assessed as 'good' by 98.6% of patients. A similar number of patients in the two groups would take the medication again (82.6% active, 87.8% placebo).

Discussion

This is to our knowledge the second randomised, double-blind, placebo controlled study carried out in compliance with the requirements of GCP to investigate the effects of an extract of Crataegus berries in patients with mild heart failure (Rietbrock et al. 2001). The daily dose of Crataegus berries extract (DER 1:3.2) of 2.25 ml corresponding to at least 6.4 mg oligomeric procyanidines per day is lower than that in other clinical studies (160–900 mg of flowers and leaves extract DER 4–7:1 per day containing 18.75% oligomeric procyanidines). However, a similar degree of improvement in the exercise tolerance was found using extracts from leaves and flowers of the plant (Eichstädt et al. 1989; Förster et al. 1984; Schmidt et al. 1994; Tauchert et al. 1994; Zapfe jun., 2001). In the majority of published studies the duration of treatment is eight weeks. Two studies of four weeks of treatment produced conflicting results, with a significant increase in exercise tolerance in only one (Bödigheimer et al. 1994; Eichstädt et al. 1989). A treatment duration of 12 weeks produced similar results to those obtained in the current study (Zapfe jun., 2001). Due to the fact that dyspnoea and fatigue do not

Table 4. Change in Exercise tolerance expressed in watt

Visit	Crataegisan® (n = 69)		Placebo (n = 74)	
	Mean (SD)	Change from Visit 1	Mean (SD)	Change from Visit 1
1 (Day 0)	67.6 (34.6)		75.7 (32.9)	
2 (Day 28)	70.5 (31.6)	2.9 (22.2)	75.7 (32.1)	0.0 (22.3)
3 (Day 56)	81.0 (29.8)	13.4 (26.0)	80.7 (32.1)	5.1 (22.4)

Table 5. Changes in other parameters of efficacy.

Visit	Crataegisan® (n = 69), Mean (SD)			Placebo (n = 74), Mean (SD)		
	BHP at 50 watts	BHP at max load	ST depression (50 watt load)	BHP at 50 watts	BHP at max load	ST depression
1 (Day 0)	167.3 (38.8)	196.9 (53.0)	0.3 (0.6)	160.4 (33.6)	194.2 (43.5)	0.3 (0.6)
2 (Day 28)	171.0 (37.3)	194.8 (51.3)		160.8 (30.1)	195.3 (44.3)	
3 (Day 56)	163.7 (32.6)	189.9 (45.3)	0.2 (0.4)	159.4 (32.8)	192.1 (40.0)	0.2 (0.5)
Visit 3–Visit1*	–5.3 (32.0)	–6.4 (36.1)	–0.1 (0.4)	–2.5 (29.7)	–2.1 (39.3)	–0.1 (0.3)
P value (Mann-Whitney-U-Test)				0.79	0.85	0.89

* Differences between visit 3 and visit 1 were calculated only from patients who completed these two visits

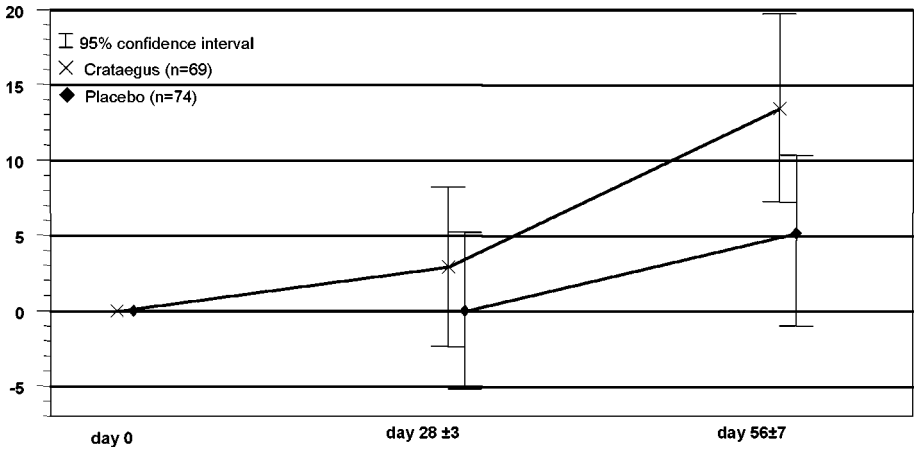

Fig. 2. Change in Exercise tolerance after 28 and 56 days of treatment with a standardised extract of fresh berries of *Crataegus oxyacantha* L and monogyna Jacq. (Crataegisan®) or placebo in the ITT population (n = 143). The difference between the groups was 8.3 watts in favour of the extract (p = 0.0453).

Table 6. Subjective symptoms at higher levels of exertion on day 0 and day 56.

			Crataegisan® (n = 69)	Placebo (n = 74)	MW statistic[1] P value[2]
Decrease in physical ability, fatigability	Day 0	none	1 (1.4)	2 (2.7)	0.51
		mild	21 (30.4)	19 (25.7)	0.83
		moderate	37 (53.6)	43 (58.1)	
		severe	10 (14.5)	10 (13.5)	
	Day 56	none	12 (17.4)	16 (21.6)	0.52
		mild	40 (58.0)	33 (44.6)	0.61
		moderate	13 (18.8)	24 (32.4)	
		severe	2 (2.9)	0 (0.0)	
Shortness of breath	Day 0	none	5 (7.2)	4 (5.4)	0.44
		mild	27 (39.1)	41 (55.4)	0.18
		moderate	36 (52.2)	27 (36.5)	
		severe	1 (1.4)	2 (2.7)	
	Day 56	none	31 (44.9)	32 (43.2)	0.50
		mild	24 (34.8)	31 (41.9)	0.98
		moderate	12 (17.4)	10 (13.5)	
		severe	2 (2.9)	1 (1.4)	
Cough	Day 0	none	51 (73.9)	53 (71.6)	0.52
		mild	16 (23.2)	16 (21.6)	0.66
		moderate	2 (2.9)	3 (4.1)	
		severe	0 (0.0)	2 (2.7)	
	Day 56	none	57 (82.6)	59 (79.7)	0.52
		mild	9 (13.0)	12 (16.2)	0.49
		moderate	1 (1.4)	2 (2.7)	
		severe	2 (2.9)	1 (1.4)	
Sensations of constriction, pressure or anxiety	Day 0	none	0	0	0.49
		mild	26 (37.7)	30 (40.5)	0.86
		moderate	17 (24.6)	14 (18.9)	
		severe	2 (2.9)	4 (5.4)	
	Day 56	none	41 (59.4)	48 (64.9)	0.50
		mild	23 (33.3)	15 (20.3)	0.93
		moderate	3 (4.3)	10 (13.5)	
		severe	2 (2.9)	1 (1.4)	
Uncomfortable awareness of heart beat, racing heart	Day 0	none	10 (14.5)	18 (24.3)	0.45
		mild	36 (52.2)	35 (47.3)	0.23
		moderate	17 (24.6)	15 (20.3)	
		severe	6 (8.7)	6 (8.1)	
	Day 56	none	33 (47.8)	26 (35.1)	0.58
		mild	33 (47.8)	43 (58.1)	0.07
		moderate	1 (1.4)	4 (5.4)	
		severe	2 (2.9)	1 (1.4)	

[1] Mann-Whitney Statistic
[2] Wilcoxon-Mann-Whitney U-test

occur until a significantly higher wattage has been reached, we assume that the significant improvement in bicycle ergometry allows the conclusion that NYHA II patients may profit from long term treatment with the Crataegus berry extract. The impact of treatment and hence optimisation of heart work already in NYHA I and II patients is discussed to reduce mortality significantly (Roger et al. 1998). Further research is needed to investigate the benefit of Crataegus on patients suffering from congestive heart failure.

Changes in BHP in this study show a weak trend in favour of Crataegisan® but the results are not statistically significant. Similar results have been seen in other studies (Eichstädt et al. 1989; Leuchtgens, 1993; Tauchert et al. 1994; Zapfe jun., 2001).

The good tolerability which was to be expected for Crataegus extracts was confirmed in this clinical trial.

Overall, the current study indicates that this extract of the Crataegus berry, taken as 30 drops, three times daily for eight weeks, leads to a similar increase in exercise tolerance in patients with congestive heart failure of NYHA class II as it has been reported earlier in trials with the established extract combinations of Crataegus flowers and leaves. The medication is well tolerated and has a high level of patient acceptability.

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