

Efficacy of a homeopathic *Crataegus* preparation compared with usual therapy for mild (NYHA II) cardiac insufficiency: results of an observational cohort study

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ABSTRACT

Objectives: To compare the efficacy of the homeopathic *Crataegus* preparation Cralonin for non-inferiority to standard treatment for mild cardiac insufficiency.

Methods: Multicentre non-randomized cohort study in patients 50-75 years suffering from NYHA class II. Patients received Cralonin (n = 110) or ACE inhibitor/diuretics (n = 102) for 8 weeks. To adjust for confounding by baseline factors, populations were stratified according to propensity score. After adjusting, there were no statistically significant differences between treatment groups. Treatment efficacy was assessed on 15 variables. A stringent non-inferiority criterion for the upper limit of the 97.5% one-sided confidence interval of the treatment difference was set to 0.2 * the standard deviation.

Results: Both treatment regimens improved scores on most variables studied, with the greatest effect on double product after exercise (average score reduction 15.4% with Cralonin vs 16.0% for the control group). Stringent non-inferiority of Cralonin was demonstrated on 7 variables. Medium-stringent (0.5 * the standard deviation) non-inferiority was indicated by 13 variables (exceptions: systolic blood pressure (BP) during exercise and diastolic BP at rest; for these, differences between treatments were not significant). Both treatments were well tolerated.

Conclusion: The *Crataegus*-based preparation Cralonin is non-inferior to usual ACE-inhibitor/diuretics treatment for mild cardiac insufficiency on all parameters except BP reduction.



Keywords: Cralonin, Cardiac insufficiency, Homeopathy, Double product

Abbreviations	
AE	Adverse event
BP	Blood pressure
DBP	Diastolic blood pressure
DP	Double product
HR	Heart rate
NYHA	New York Heart Association
PS	Propensity score
QOL	Quality of life
SBP	Systolic blood pressure
SD	Standard deviation
SEM	Standard error of mean
tid	tris in diem, thrice daily

1. INTRODUCTION

Complementary medicine is widely used in the developed world^[1,2]. In particular, the use of and belief in the principles of homeopathy are widespread both in the US and in Europe^[3-8]. However, the issue of whether there are real benefits from homeopathic treatment has not been conclusively resolved to date. Several reviews and meta-analyses of clinical trials agree that there seem to be benefits over placebo generally, but that more rigorous and systematic research is warranted^[9,11]. However, many of the trials conducted to date have been of low quality and a general increase in the standards of trials would be beneficial to practitioners and patients alike.

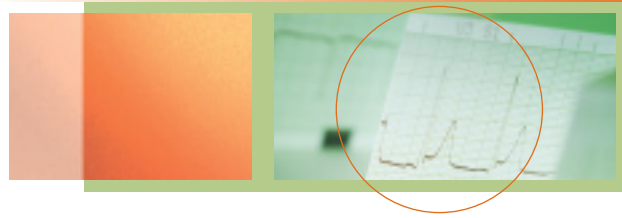
The current study evaluates the efficacy of the homeopathic preparation Cralonin in mild cardiac insufficiency, NYHA class II. The preparation is based on extracts from *Crataegus* (hawthorn) and *Spigelia anthelmia* (Pink root). Cralonin is registered in Germany as a homeopathic preparation (Registration No. 9054.00.00) and has a long and well-documented history of use for mild cardiac insufficiency^[12,13]. Preparation and administration of Cralonin follow the rules of homeopathy.

The study was designed to disprove inferiority of a Cralonin preparation to ACE inhibitor/diuretics therapy. Focus was on clinical symptoms as observed by the practicing physician and the patients themselves, not on underlying cardiac parameters.

In the case of Cralonin, there is a real risk that the subset of patients, who are willing to be randomized to treatments as widely different as an established mainstream therapy and a homeopathic medication, exhibit important differences from the target population^[14]. Also, homeopathic remedies are prescribed to a very wide range of patients and treatment is highly individualized, with the possibility of altering medication during the treatment regimen. For these reasons, the study used a non-randomized approach and applied the established methodology of propensity-score (PS) analysis to construct matched strata that balance observed co-variables^[15,18]. This allowed inclusion of a broad range of populations in both the Cralonin and control groups. A multivariate analysis was not carried out as this method is not applicable to the demonstration of non-inferiority using one-sided confidence intervals.

2. METHODS

This was a multicentre, non-randomized cohort study assessing the non-inferiority of Cralonin to ACE/diuretics therapy. The study was carried out in 27 centers in Germany between July 1 and December 31, 2000. A total of 216 patients were enrolled. All patients were informed about the background and purpose of the study, which was conducted in full compliance with the principles of the Declaration of Helsinki (Br Med J 1964;ii:177) and in accordance with the German "Recommendations for the planning, performance, and evaluation of postmarketing clinical studies" (Bundesanzeiger Federal Gazette) No. 229 of December 12, 1998.



2.1. Inclusion criteria

Men or women aged 50-75 years, with diagnosed mild cardiac insufficiency NYHA class II, necessitating therapy but not currently undergoing treatment with either Cralonin drops or ACE inhibitor/diuretics. Patients were outpatients, with or without (stable) hypertension (systolic blood pressure (SBP) > 140 mm Hg, diastolic blood pressure (DBP) > 90 mm Hg).

2.2. Exclusion criteria

Unstable coronary heart disease, concomitant cardiac therapy different from study medication and intolerance toward any of the study treatments. Patients currently on either treatment therapy were also excluded. However, earlier therapy with either study drug was not a criterion for exclusion.

2.3. Study design

As only patients currently not receiving therapy were included, there was no washout period. Patients received either Cralonin drops (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany) thrice daily (tid) or ACE inhibitor/diuretics treatment. The dosage for each patient was at the administering practitioner's discretion. The Cralonin preparation consists of pro 100 ml: *Crataegus* Ø (mother tincture), 70 ml; *Spigelia anthelmia* D2/2X, 1 ml; *Kalium carbonicum* D3/3X, 1 ml; ethanol 45% (v/v).

Each patient was followed-up for 8 weeks, with data collected at baseline, at week 4 and at the end of the study. Treatment efficacy was evaluated on heart rate (HR), blood pressure (BP), double product (DP; evaluated on a bicycle ergometric test and defined as HR*BP/100 where HR is heart rate in bpm and BP blood pressure in mm Hg), fatigue, listlessness, dyspnea under strain, pretibial edema, rapid exhaustion, frequency of nocturnal urinations and exercise tolerance (distance walked and number of stairs ascended without fatigue).

2.4. Measurements

DP was measured at rest and after a 2-minute exercise at 50 W. Fatigue, listlessness, performance reduction, dyspnea under strain and pretibial edema were evaluated on a scale from 0-3, where 0 = no difficulties and 3 = major difficulties. The walking test assessed the distance the patient was able to walk on level ground without fatigue on a scale from 1-6, where 1 = < 100 m; 2 = 100-300 m; 3 = 300-500 m; 4 = 500-900 m; 5 = 1000 m (in about 15 minutes); 6 = further than 1,000 m (in > 15 minutes). The staircase test evaluated the number of stairs the patient was able to walk without fatigue on a scale from 1 to 7, where 1 = < 5 steps; 2 = 5-10 steps; 3 = 11-15 steps; 4 = 16-20 steps; 5 = 21-25 steps; 6 = 26-30 and 7 = > 30 steps. Global treatment results were assessed by the practitioner on a scale ranging from very good, good, moderate, no effects to negative development. Tolerability was assessed by recording adverse events (AEs) and by the practitioner's assessment of global tolerability (very good, good, moderate or low). Compliance was assessed by the practitioner as very good, good, moderate or low.

2.5. Statistical methods

As this was a non-randomized cohort study, the principal investigator had no control over the treatment assignment and there might have been large differences in observed co-variables between the treatment groups. Hence, the direct comparison of treatment effects might be confounded by a number of baseline characteristics. A means to adjust for treatment differences between co-variables and to reduce bias is using a propensity score (PS), as described by Rosenbaum^[16]. PS is a description of the conditional probability of receiving treatment given the observed co-variables. As shown by Rosenbaum and Rubin, PS is a balancing score and is applicable to observational studies to reduce bias, allowing for the application of standard statistical methods^[15]. Patients with approximately the same PS value are similar in observed covariates independently of whether they are treated with test treatment or control treatment and treatment effects can be expected to be largely unbiased by confounding parameters. It has been calculated that, as PS balances all co-variables that are used to calculate PS, division into five strata will eliminate approximately 90% of the bias of each of the co-variables^[15,19].

PS was estimated for each patient using logistic regression (i.e. the logarithm of the odds for the probability of receiving Cralonin, $\log(p/(1-p))$, will be seen as linear function of observed co-variables) and patients were divided into four strata according to PS scores. A breakdown of the groups is shown in Table 1. After calculation of treatment effects within each PS stratum, overall treatment effect was calculated by weighted means of the stratum effects as described by Fleiss^[17].

All observed variables were used as underlying co-variables: weight, age, fatigue, listlessness, performance on walking test and staircase test, HR, duration of illness, dyspnea under strain, DP, SBP and DBP, pretibial edema and reduced overall performance.

Treatment groups were compared after adjustment for PS using a two-way ANOVA model for co-variables based on interval data and the Cochran-Mantel-Haenszel test for co-variables with dichotomous values. Prior to stratification, treatment groups differed significantly on five co-variables; however, there were no statistically significant differences after adjustment for PS.

To compare treatment groups for non-inferiority of Cralolin vs ACE inhibitors/diuretics, the adjusted differences (reduction Cralolin - reduction ACE inhibitors/diuretics) between treatments were calculated with 97.5% one-sided confidence intervals. Except for the walk test and staircase test, negative treatment differences indicated superiority of Cralolin. The upper limits of the confidence intervals can be interpreted as boundaries for assessing non-inferiority and were compared with two commonly used “benchmarks” for inter-group differences: small between-treatment difference (0.2 * standard deviation, SD) and medium difference (0.5 * SD) [20].

Table 1: Stratification of subjects according to PS

Group	Cralolin (mean PS=0.66)		ACE inhibitor (mean PS=0.37)		Total	
	N	%	N	%	N	%
PS<0.3	11	10.00	52	50.98	63	29.72
0.3<PS<0.55	15	13.64	24	23.53	39	18.40
0.55<PS<0.7	28	25.45	10	9.80	38	17.92
0.7<PS	56	50.91	16	15.69	72	33.96
Total	110	100.00	102	100.00	212	100.00

3. RESULTS

3.1. Patients

A total of 216 outpatients were enrolled in the study. Four patients were excluded as they were already receiving one of the study medications, and the final analysis was carried out on 212 patients: 110 in the Cralolin group and 102 in the ACE inhibitor/diuretics group. As shown in Table 2, the main reasons for cardiac insufficiency were coronary heart disease, cardiomyopathy, vitium cordis and hypertension.

Of the study population, 110 received Cralolin drops tid and 102 received standard therapy for mild cardiac insufficiency, consisting of ACE inhibitor/diuretics. Most patients in the Cralolin group (80.0%) received the standard dosage of 20 drops tid; 15.4% received 10 drops tid. The control medication was given as monotherapy or combination therapy, at the discretion of the prescribing practitioner. Of the patients in the control group, 52.0% received ACE inhibitors (benazepril, captopril, cilazapril, fosinopril, lisinopril, perindopril or ramipril), 6.9% diuretics (hydrochlorothiazide, furosemide, torasemide, indapamide or triamteren) and 41.2% a combination of both. ACE inhibitors/diuretics were given at doses commonly used in clinical practice; however, doses varied between individuals. Mean treatment period in the Cralolin group was 66.5 days, ranging from 33 to 132 days. The control group was treated for a mean of 65.2 days (32-157 days).

Unadjusted baseline demographic data were comparable for both groups for age and weight, but there was a difference in sex distribution between groups (Table 3). After adjusting for PS, however, differences were no longer statistically significant (Table 3).

Baseline values for efficacy variables were similar between groups (Table 2), with a few exceptions: more patients in the control group were hypertensive (defined as SBP > 140 mm Hg, DBP > 90 mm Hg) at baseline (72.5% vs 54.5% in the Cralolin group) and earlier therapy was more common in the control group (64.7% vs 26.4% in the Cralolin group). These unadjusted differences were significant on chi-square test. However, after adjusting for PS the differences were not shown to be significant (Cochran-Mantel-Haenszel test controlling for stratum). The most common earlier therapies in the Cralolin group were nitrates (10.0%) calcium-channel blockers (7.3%) and diuretics (6.4%). In the control group, most common earlier therapies were ACE inhibitors (37.3%) diuretics (24.5%) and calcium-channel blockers (8.8%).

Baseline BP, HR and performance test scores did not differ significantly between treatments (Table 2), but overall performance was more reduced in the control group, which also tended to have a higher rate of pretibial edema than the Cralolin group.

3.2. Treatment effects

Both treatments had beneficial effects on most variables studied. Changes in BP, HR and DP are shown in Figure 1. Marked improvements with both treatments were seen in DP after exercise. Cralolin reduced average scores by 15.4% (from 183.4 ±39.37 min⁻¹ mm Hg/100 before treatment to 155.2 ±37.6 min⁻¹ mm Hg/100) after 8 weeks, compared with a reduction of 16.0% (from 194.6 ±43.25 to 163.4 ±36.92) in the control group.

Benefits from treatment were also seen in both groups on most other criteria. On walk tests and staircase tests, there was a trend towards better scores in the Cralolin group than in the control population (walk test, Cralolin mean improvement 0.8, control 0.6; staircase test, Cralolin mean improvement 1.3, control 1.0). The average number of nocturnal urinations likewise was reduced to a similar extent in both groups, from 2.0 to 1.2. Both treatments reduced fatigue, listlessness and dyspnea under strain. Score reductions for these criteria were 0.3 to 1.0 point in both groups, from baseline values in the mild-to-moderate range (1-2). Pretibial edema (baseline scores 0.8 and 1.0, i.e., “mild”) was reduced by a mean of 0.6 points by both treatments.

3.3. Between-treatment differences at end of study

Figure 2 summarizes adjusted differences in outcomes between the Cralolin and control groups for the 15 criteria evaluated. The non-equivalence hypothesis for a variable was considered disproved if the upper limits of confidence intervals for treatment differences fell within one of two limits: a stringent limit of 0.2 * SD and a medium limit of 0.5 * SD. Using the stringent limit, non-inferiority was demonstrated on 7 out of 15 variables. If the medium difference interval of 0.5 * SD was used,

Table 2: Baseline criteria with significance levels before and after PS adjustment

Variable	Cralonin		Control		Unadjusted (test result)	Adjusted (test result)
	mean ± S.D.	(n)	mean ± S.D.	(n)		
Pretreated (%)	26.4	(110)	64.7	(102)	**	ns
Coronary heart disease (%)	48.2	(110)	49.0	(102)	ns	ns
Vitium cordis (%)	1.8	(110)	1.0	(102)	ns	ns
Nocturnal urinations (%)	81.8	(110)	87.3	(102)	ns	ns
Cardiac myopathy (%)	10.9	(110)	5.9	(102)	ns	ns
Hypertension (%)	54.5	(110)	72.5	(102)	**	ns
Risk factors present (e.g. obesity, smoking, diabetes mellitus) (%)	84.5	(110)	85.3	(102)	ns	ns
HR (bpm)	78.84 ± 8.888	(105)	78.06 ± 10.71	(100)	ns	ns
Fatigue ^a	1.81 ± 0.669	(104)	1.82 ± 0.737	(102)	ns	ns
Listlessness ^a	1.59 ± 0.719	(104)	1.61 ± 0.810	(102)	ns	ns
Duration of illness (yrs)	3.02 ± 1.521	(109)	3.14 ± 1.485	(99)	ns	ns
SBP (mm Hg)	146.9 ± 16.24	(109)	150.2 ± 16.04	(100)	ns	ns
DBP (mmHg)	86.43 ± 8.985	(109)	88.04 ± 10.36	(100)	ns	ns
Pretibial edema ^a	0.82 ± 0.769	(105)	1.01 ± 0.850	(102)	ns	ns
Walk test ^b	3.95 ± 1.245	(106)	3.81 ± 1.376	(101)	ns	ns
Staircase test ^c	3.95 ± 1.298	(110)	3.90 ± 1.432	(102)	ns	ns
Dyspnea under strain ^a	1.74 ± 0.724	(104)	1.83 ± 0.772	(102)	ns	ns
Reduced overall performance ^a	1.68 ± 0.624	(108)	1.88 ± 0.708	(102)	*	ns
Increase in DP ^d	70.01 ± 33.57	(104)	74.87 ± 39.97	(100)	ns	ns
Nocturnal urinations (n/night)	2.0 ± 0.86	(88)	2.0 ± 0.77	(89)	ns	ns

* 0.05 > P > 0.01; ** P < 0.01; ns = P > 0.05.

^a Measured on a scale of 0-3 where 0 = no difficulties and 3 = major difficulties.

^b Distance the patient is able to walk on level ground without fatigue;

^c 1 = <100 m, 2 = 100-300 m, 3 = 300-500 m, 4 = 500-900 m, 5 = 1,000 m in about 15 minutes, 6 = further than 1,000 m (in > 15 minutes).

^d Number of stairs the patient is able to walk without fatigue; 1 = <5 steps, 2 = 5-10 steps, 3 = 11-15, 4 = 16-10, 5 = 21-25, 6 = 26-30, 7 = > 30 steps.

^e min⁻¹ mmHg/100.

Table 3: Baseline demographics with test results before and after PS adjustment

Variable	Cralonin		Control		Unadjusted (test result)	Adjusted (test result)
	mean ± S.D.	(n)	mean ± S.D.	(n)		
Age (yrs)	68.5 ± 7.85	(110)	65.6 ± 9.06	(101)	ns	ns
Weight (kg)	76.3 ± 11.91	(109)	76.5 ± 12.74	(101)	ns	ns
Sex (%)						
• Male	29.1		47.1		*	ns
• Female	70.9		52.9		*	ns

* P < 0.01; ns = P > 0.05.

non-inferiority was inferred on 13 of 15 variables. Intervals crossed the 0.5 * SD boundary only for the criteria SBP during exercise and DBP at rest. However, the differences between treatments were not significant in these cases.

Global assessments of treatment results were somewhat more favorable to Cralonin, with 28.2% judging the results as “very good” (15.7% in the control group) and with similar percentages judging the results as “good” (58.2% for Cralonin, 52.0% for ACE inhibitors/diuretics; p = 0.002 for the overall comparison between treatments).

Both treatments were very well tolerated, but the percentage of patients with tolerability evaluated as “very good” was significantly higher for Cralonin than for the control medication (82.7% vs 46.1%, p < 0.0001). AEs occurred in one patient in each treatment group. With Cralonin there was one case of pressure in the heart region and with ACE inhibitors one case of dry cough needing medical attention. Both AEs were considered possibly treatment-related, but none led to discontinuation of the study.

Compliance with treatment was good in both groups. Patients receiving Cralonin demonstrated a greater degree of compliance than the control group. Compliance with Cralonin was judged by practitioners as “very good” in 57.3% of patients (37.3% in the control group, p = 0.007 for the differences between groups) and “good” in 40% (control group 55.9%).

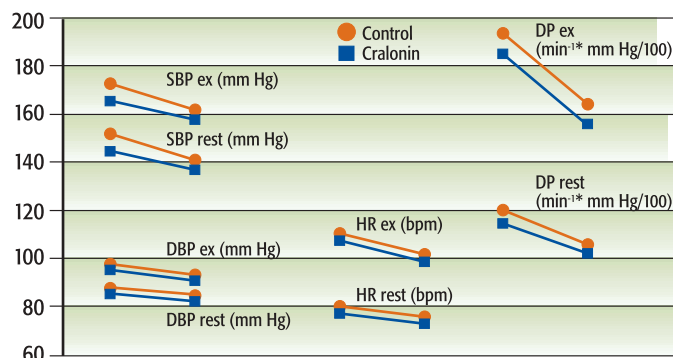


Fig. 1: Changes in BP, HR and DP values (± S.E.M.) at rest and after exercise (ex) from baseline to end of study for Cralonin (squares) and control groups (circles). S.E.M. values are greater than 2 only for the DP scores.

4. DISCUSSION

This study assesses the efficacy and tolerability of the homeopathic preparation Cralolin in patients with mild cardiac insufficiency, NYHA class II. Cralolin treatment was shown to be non-inferior to standard ACE-inhibitor/diuretics therapy on 13 out of 15 variables, the exceptions being SBP during exercise and DBP at rest. For staircase test and HR increase under exercise, the treatment effects tended towards superiority of Cralolin. As assessments were made at three 4-week intervals, it seems highly unlikely that the differences between the beginning and end of the study were due to a training effect.

In contrast to earlier reports on the efficacy of Cralolin^[12,13], the current study is a direct comparison with standard treatment with ACE inhibitors/diuretics on effects on symptoms relevant to the patients' overall status.

The results may be considered controversial, as this is a trial of a homeopathic combination preparation. However, as reviews of clinical trials in homeopathy have concluded, homeopathy can and should be evaluated using the same standards as with allopathic treatments^[10,11]. The present study fulfills criteria identified by Benson *et al.*^[21]: for observational studies able to yield valuable data, studies shall assess differences between two treatments or between a treatment and no treatment, treatments shall be implemented by physicians and the study must include a control group.

The current study attempts to capture the actual practice by leaving the individualization of treatment regimens to the respective practitioners. The makeup of populations willing to be randomized to homeopathic or standard treatments can be expected to differ from the general population. Additionally, randomized studies often exclude a significant proportion, between 9 and 51% of screened patients^[22]. For these reasons, we decided to forgo the randomized trial in favor of a non-randomized cohort study.

In non-randomized studies co-variables must be balanced by statistical methods, if treated and control groups are to be comparable in the sense of having similar distribution of co-variables. We used PS adjustments^[15,23] to construct matched strata that balance observed co-variables. Before adjustment, the baseline variables hypertension, female sex and history of previous treatment differed between treatment groups. However after PS adjustment, these differences were no longer statistically significant.

Recent surveys have challenged the perception that non-randomized studies tend to report greater effects from treatments than randomized trials. Benson *et al.* compared observational studies with randomized clinical trials in 136 cases and 19 treatment areas and found very good agreement between results. Specifically, cardiological studies showed agreement between randomized and observational results in six out of seven cases^[21]. Similarly, the UK Health Technology Assessment Group^[24] evaluated studies of 18 treatments, surgical, pharmaceutical and organizational, and concluded that there was no systematic bias in observational studies. Concato *et al.* came to similar conclusions in an analysis of five clinical topics and 99 reports, 44 of which were related to hypertension and coronary heart disease^[25].

As has been pointed out^[18], PS adjustment adequately balances observed co-variables but, unlike random assignment of treatment, it cannot balance co-variables that were not observed. However, surveys by Britton *et al.* and Benson *et al.*^[21,24] indicate that this risk is not significantly higher in observational studies than in standard randomized clinical trials. Given the large number of co-variables included in our analysis, it appears unlikely that the risk of bias is larger than the risk of unintentional bias (e.g., non-random allocation of treatment) frequently present, even in randomized trials^[26].

One consequence of our study design was that the composition of the control medication was not homogenous. Half of the control population, (52.0%) received ACE inhibitors as monotherapy and 41.2% received a combination of ACE inhibitors/diuretics. This reflects the fact that the individual therapy was decided by the prescribing practitioner. This could be seen as a weakness, as outcomes in the control group might have been slightly different with standardized treatment. However, the composition of the control group reflects the treatment situation for cardiac insufficiency in general practice and the results in the control group arguably reflect the outcome of individually optimized treatments.

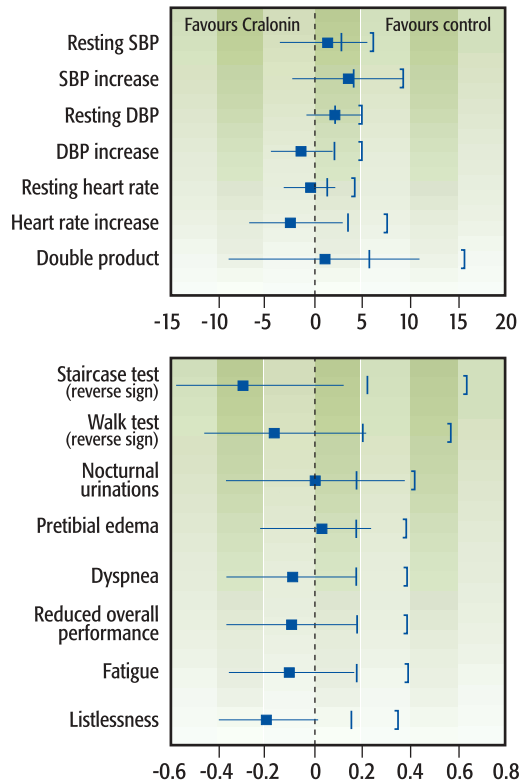


Fig. 2: Adjusted differences between treatments (Cralolin vs ACE inhibitor/diuretic therapy) with 97.5% one-sided confidence intervals. Vertical bars, non-inferiority limit 0.2 X pooled S.D.; brackets, non-inferiority limit 0.5 X S.D. Note that for uniformity the values for walk and staircase tests are transformed by the factor -1 (reversed sign), as in the original tests, positive values favor Cralolin.

Another possible weakness is that the data was collected by the attending physician, which may allow for observational bias. This would be expected to be a greater problem with endpoints such as fatigue and listlessness, where evaluations are subjective to a degree. However, endpoints such as DP and HR, which are less susceptible to subjective influence, were very similar to the other endpoints in showing no significant differences between Cralonin and the control group (Figure 2), which supports the limited conclusions drawn.

A decrease in DP indicates improved oxygen transport and lesser risk of cardiac complications. This is expected to translate into improved performance^[27], as was indeed seen in our study in staircase and walk tests. Similar improved performance scores have been reported from other studies with *Crataegus*-based therapy^[28]. As moderate exercise is recognized as being beneficial in heart failure^[29], increasing performance would be expected to lead to increased exercise and a positive feedback loop.

There are advantages with Cralonin that speak for the preparation as an alternative to ACE inhibitors/diuretics in mild cardiac insufficiency. Whereas Cralonin has an excellent tolerability profile, documented through long use and in an observational study in 2178 patients^[12], ACE inhibitors and diuretics are associated with unwanted effects: cough in the case of ACE inhibitors^[30] and reduced quality of life (QOL) with many diuretics^[31,32]. Subjective reports on Cralonin from patients show favorable effects on QOL and effects such as reduced nocturnal urination would improve a patient's perceived QOL.

A good tolerability profile is particularly relevant in the case of cardiac insufficiency. Patients with only mild symptoms are unlikely to adhere to a regimen with noticeable side effects, whereas more severely afflicted patients are usually prescribed multiple drug regimens, where compatibility can be an issue. The compatibility of Cralonin with currently recommended medications indicates that the preparation can be safely added to existing drug regimens.

It would be extremely difficult to prove the superiority of a homeopathic preparation in an indication such as heart failure in the current treatment milieu, as it would be unethical to withhold effective treatment from patients in randomized clinical trials. A large, controlled study on *Crataegus* in patients with heart failure class NYHA II-III has recently been announced^[33]. However, as this trial does not use a homeopathic preparation, the results may not be applicable to this study. Based on the indications of non-inferiority, and the well-established safety and tolerability record of Cralonin, a controlled trial where Cralonin is added to patients' usual therapy would seem both desirable and ethically defensible.

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