In a recent cohort study, the Crataegus-based preparation Cralonin was compared and found almost equivalent to usual ACE inhibitor/diuretic treatments for mild cardiac insufficiency on all parameters except for blood pressure reduction. Differences between treatments were not significant.

Benefits of Cralonin

- Adjuvant therapeutic agent, in conjunction with administration of glycoside preparations
- Well tolerated by patients
- Suitable for long-term therapy
- Applicable to various cardiac conditions
- Regulatory effect on blood pressure

1 Schröder D, Weiser M, Klein P. Efficacy of a homeopathic Crataegus preparation compared with usual therapy for mild (NYHA II) cardiac insufficiency: results of an observational cohort study. The European Journal of Heart Failure 2003;5:319-326.
Practical Protocols
- Homotoxicology and the cardiovascular system
  Taking it to heart.......................................................... 4
- Hypertension in practice............................................... 6

Medical Studies
- Efficacy of a homeopathic Crataegus preparation compared
  with usual therapy for mild (NYHA II) cardiac insufficiency:
  results of an observational cohort study.......................... 7

Medical Summaries
- Results of the treatment of pregnant women with
  neurocirculatory asthenia (NCA) with the antihomotoxic
  preparations Cralonin® and Nervoheel®............................... 13

In Your Practice
- Cralonin: More than a treatment for cardiac failure.......... 14

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Cardiovascular disease belongs to the so-called “big five” lifestyle diseases which are reaching epidemic proportions in the Western world. The others are the metabolic syndrome, type II diabetes, dementia of the Alzheimer’s type (DAT), hyperlipidemia and cancer.

In all of these diseases a common etiological thread is emerging. Diets high in refined carbohydrates and saturated fat, modern malnutrition which results in the deficiency of vital co-factors to regulatory processes, an increase in the environmental toxins surrounding us, lack of movement and mounting psychological stress are all implicated as factors contributing to the development of these diseases.

Modern research also shows cardiovascular diseases as being multifactorial, with components of immune disturbance, neuroendocrine abnormalities and endothelial damage. The relationship between unscavenged free radicals and the development of atherosclerosis and coronary artery disease, including the other lifestyle diseases, is now well established.

According to the theory of Homotoxicology, all chronic diseases indicate regulation disturbance, enzyme damage or dysfunction and in certain cases, such as dedifferentiation, possibly damage to DNA structures. The approach to chronic dysregulation diseases should thus be multifaceted and especially include vigorous prevention programs.

CAM (Complementary and Alternative Medicine) modalities and especially Homotoxicology, recognize the gradual evolution of these diseases, and through tools such as the six-phase table of disease, classify the degree of dysregulation and formulate a treatment plan accordingly. The patient’s individual tendency towards certain disease patterns is also considered in many CAM modalities. Mainstream medicine is starting to approach some of these issues by employing nutritional supplementation such as Co-enzyme Q10, but it is only when regulation is approached in a holistic fashion that true prevention and possible regression of the condition can occur.

Homotoxicology offers several possibilities to treat cardiovascular disease in such a fashion. Detoxification should be included in the treatment of all cardiovascular related diseases. Several environmental toxins such as lead, carbon disulfide, asbestos, arsenic, ozone, cadmium, vinyl chloride fluorocarbons, Freon and pesticides have been shown to have an effect on the cardiovascular system.

Possible mechanisms that could cause cardiovascular diseases include damage to the endothelial barrier in the vascular system, activation of leukocytes and platelets, initiation of plaque formation, stimulation of the inflammatory response, kidney-related hypertension as well as direct damage to the cardiac and blood vessel tissues (Taylor 1996). The detoxification of the connective tissue will thus play an important role to rid the body of harmful substances stored in this compartment, while the support of kidney detoxification with products like Berberis-Homaccord® and Solidago compositum® (especially the latter), will not only support the renal excretory function, but also protect the kidney from damage in hypertension and toxic exposure, as mentioned above. Lastly, stimulation of the liver’s detoxification with Nux vomica-Homaccord® helps with the elimination of these substances, thereby also sparing the vital phase II enzymes, like glutathione and cysteine (two powerful free radical scavengers), leaving them free to deal with oxidants.

Chelation and orthomolecular therapy in this context could be powerful adjuvants to the homotoxicological treatment.
Many natural substances have been used through the ages to treat cardiovascular diseases. In fact, nature has provided many botanicals now commonly used to treat conditions such as arrhythmias with digitalis (from foxglove or *Digitalis purpurea*) and hypertension with reserpine (from *Rauwolfia*). *Crataegus* has been used as a heart tonic for years and is one of the main ingredients found in Cralonin. *Crataegus* has many interesting properties due to its flavonoid and procyanidin content.

Data from a reference controlled cohort study showed Cralonin as being as efficient in treating NYHA Class II heart failure as conventional drugs. *Crataegus* has many other attractive properties and therapeutic applications, such as lipid protective properties and possibly even an effect on nitric oxide (NO)-mediated hypotensive action, which is discussed under basic therapy concepts. The latter is especially pertinent as most modern drugs developed to treat hypertension will stimulate NO which in turn, will stimulate endothelial relaxation. Nitric oxide is a free radical, but on its own, not an oxidant. When it combines with superoxide, another free radical, peroxynitrite is formed, which is a very dangerous oxidant. Procyanidins hypothetically can regenerate NO and thus decrease the peroxynitrite content. Peroxynitrite is also formed in diabetic patients with the resultant tissue damage.

History has taught us that we need the plant as a whole and if we extract certain active ingredients in the laboratory, we may interfere with some protective effects of others. *Rauwolfia* is such a case; reserpine, an alkaloid extracted from *Rauwolfia*, is used effectively as an antihypertensive medication, but has side effects such as Parkinsonism, which is not seen with the use of the whole plant in dilution. It is thus safer to use the diluted form (providing a botanical dose of D3 or 3X) of the whole plant.

Lastly, the Fall 2003 issue of the Journal published a summary regarding the ability of homeopathically processed Ubichinon to stimulate the proliferation of endothelial cells in vitro. For years, in Homotoxicology, we have incorporated catalysts, especially Ubichinon compositum, in the treatment of cardiovascular disease, with good empirical success. It is one example where known effects of homeopathic preparations are being researched and we are ever moving towards this understanding of how such products work on a patho-physiological basis. We are indeed working in an exciting field. The unique homotoxicological way of looking at disease, combined with the low toxicity of the medications lends itself toward the treatment of our modern scourges, one of them being diseases of the cardiovascular system.
Hypertension affects approximately 50 million individuals in the United States and about 1 billion people worldwide. The diagnosis is made on the proper measurement of the blood pressure, during two or more separate visits, while the patient is seated and calm.

In Homotoxicology, hypertension is seen as a state of dysregulation and is classified into the impregnation phase. In treating hypertension, we treat not only the high blood pressure and the possible end organ damage (such as kidney, heart and eye disease) but also the dysregulation syndrome. Apart from the detoxification mentioned previously, special attention is also given to the neuroendocrine system, the cellular respiration and the antioxidant status.

The decision of whether the biological therapy is sufficient should be determined individually, keeping in mind that Stage II hypertensive patients are probably not candidates for antihomotoxic therapy alone. In practice though, even in these patients, the biotherapeutic program can work drug sparingly, and reduce a patient to a Stage I or even a pre-hypertensive state.

The following guidelines apply (National Heart, Lung and Blood Institute 2003):

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>&lt; 120 mm Hg</td>
<td>&lt; 80 mm Hg</td>
</tr>
<tr>
<td><strong>Pre-hypertension</strong></td>
<td>120-139 mm Hg</td>
<td>80-89 mm Hg</td>
</tr>
<tr>
<td><strong>Stage I hypertension</strong></td>
<td>140-159 mm Hg</td>
<td>90-99 mm Hg</td>
</tr>
<tr>
<td><strong>Stage II hypertension</strong></td>
<td>&gt; 160 mm Hg</td>
<td>&gt; 100 mm Hg</td>
</tr>
</tbody>
</table>

The importance of **CRALONIN** as a long-term remedy is important to highlight.

The patient should be followed up regularly (every 4 weeks) and should not be allowed to remain in stage I too long. Hence, if there is no improvement, consider conventional therapy, but continue biological therapy as adjuvant and reassess at regular intervals.
Efficacy of a homeopathic *Crataegus* preparation compared with usual therapy for mild (NYHA II) cardiac insufficiency: results of an observational cohort study

(Reprint from The European Journal of Heart Failure 5 (2003) 319-326)

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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.

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-variates [15,16]. 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;i: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-variates 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-variates 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-variates. 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-variates that are used to calculate PS, division into five strata will eliminate approximately 90% of the bias of each of the co-variates [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-variates) 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-variates: 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-variates based on interval data and the Cochran-Mantel-Haenszel test for co-variates with dichotomous values. Prior to stratification, treatment groups differed significantly on five co-variates; however, there were no statistically significant differences after adjustment for PS.
To compare treatment groups for non-inferiority of Cralonin vs ACE inhibitors/diuretics, the adjusted differences (reduction Cralonin - 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 Cralonin. 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 comparisons: small between-treatment difference (0.2 * standard deviation, SD) and medium difference (0.5 * SD) [210].

### Table 1: Stratification of subjects according to PS

<table>
<thead>
<tr>
<th>Group</th>
<th>Cralonin (mean PS=0.66)</th>
<th>ACE inhibitor (mean PS=0.37)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>PS&lt;0.3</td>
<td>11</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td>0.3&lt;PS&lt;0.55</td>
<td>15</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>0.55&lt;PS&lt;0.7</td>
<td>28</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>0.7&lt;PS</td>
<td>56</td>
<td>16</td>
<td>72</td>
</tr>
<tr>
<td>Total</td>
<td>110</td>
<td>102</td>
<td>212</td>
</tr>
</tbody>
</table>

### 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 Cralonin 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 Cralonin drops tid and 102 received standard therapy for mild cardiac insufficiency, consisting of ACE inhibitor/diuretics. Most patients in the Cralonin 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, clazapril, 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 Cralonin 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 Cralonin group) and earlier therapy was more common in the control group (64.7% vs 26.4% in the Cralonin 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 Cralonin 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 Cralonin 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. Cralonin 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 Cralonin group than in the control population (walk test, Cralonin mean improvement 0.8, control 0.6; staircase test, Cralonin 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 Cralonin 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,
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%).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cralonin</th>
<th>Control</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± S.D.</td>
<td>(n)</td>
<td>mean ± S.D.</td>
<td>(n)</td>
</tr>
<tr>
<td>Pretreated (%)</td>
<td>26.4</td>
<td>(110)</td>
<td>64.7</td>
<td>(102)</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>48.2</td>
<td>(110)</td>
<td>49.0</td>
<td>(102)</td>
</tr>
<tr>
<td>Vitium cordis (%)</td>
<td>1.8</td>
<td>(110)</td>
<td>1.0</td>
<td>(102)</td>
</tr>
<tr>
<td>Nocturnal urinations (%)</td>
<td>81.8</td>
<td>(110)</td>
<td>87.3</td>
<td>(102)</td>
</tr>
<tr>
<td>Cardiac myopathy (%)</td>
<td>10.9</td>
<td>(110)</td>
<td>5.9</td>
<td>(102)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>54.5</td>
<td>(110)</td>
<td>72.5</td>
<td>(102)</td>
</tr>
<tr>
<td>Risk factors present (e.g., obesity, smoking, diabetes mellitus) (%)</td>
<td>84.5</td>
<td>(110)</td>
<td>85.3</td>
<td>(102)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cralonin</th>
<th>Control</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean ± S.D.</td>
<td>(n)</td>
<td>mean ± S.D.</td>
<td>(n)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>68.5 ±7.85</td>
<td>(110)</td>
<td>65.6 ±9.06</td>
<td>(101)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.3 ±11.91</td>
<td>(109)</td>
<td>76.5 ±12.74</td>
<td>(101)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>29.1</td>
<td>(109)</td>
<td>47.1</td>
<td>(103)</td>
</tr>
<tr>
<td>• Female</td>
<td>70.9</td>
<td>(109)</td>
<td>52.9</td>
<td>(103)</td>
</tr>
</tbody>
</table>

* 0.05 > P > 0.01; ** P < 0.01; ns = P > 0.05.
1. Measured on a scale of 0-3 where 0 = no difficulties and 3 = major difficulties.
2. Distance the patient is able to walk on level ground without fatigue; 1 = <300 m, 2 = 300-500 m, 3 = 500-900 m, 4 = 900-1,000 m, 5 = 1,000 m in about 15 minutes, 6 = further than 1,000 m (in > 15 minutes).
3. Number of stairs the patient is able to walk without fatigue; 1 = <5 steps, 2 = 5-10 steps, 3 = 11-15, 4 = 16-20, 5 = 21-25, 6 = 26-30, 7 = > 30 steps.
4. min⁻¹ mmHg/100.

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

This study assesses the efficacy and tolerability of the homeopathic preparation Cralonin in patients with mild cardiac insufficiency, NYHA class II. Cralonin 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 Cralonin. 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 Cralonin [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-variates 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-variates. 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-variates but, unlike random assignment of treatment, it cannot balance co-variates 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-variates 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 [24].

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.
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. Whereas Cralonin has an excellent tolerability profile, documented through long use and in an observational study in 2,178 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 show into improved performance [27], as was indeed seen in our study in staircase and walk tests. Similar improved performance scores 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.

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 2,178 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.

**REFERENCES**


Results of the treatment of pregnant women with neurocirculatory asthenia (NCA) with the antihomotoxic preparations Cralonin® and Nervoheel®

Reprint from Biologicheskaya Terapia, Ukraine, #4, 2002, p.26. - Podolsky V.V., Teslyuk R.S. Institute of pediatrics, obstetrics and gynecology of AMS of Ukraine, Kyiv

SUMMARY:

The objective of the study was to establish the clinical efficacy of antihomotoxic preparations in pregnant women suffering from NCA.

METHODOLOGY:

N = 60: 30 test subjects and 30 controls.
The test group consisted of 11 women with the hypertensive form of NCA, 9 with the hypotonic form and 10 with the cardiac form.
The age group of the patients ranged from 18-35 years.
17 patients were primipara and 13 were multipara.
The duration of the disease was from 1-7 years.
The control group was made up of 30 controls.

The test group received NERVOHEEL® and CRALONIN® according to the following scheme:

NERVOHEEL: 1 tablet three times daily sublingually, 15 min before meals, for 2 weeks
CRALONIN: 20 drops 3 times daily on the tongue, 15 min before meals, for 2 weeks.

The control group received standard therapy.

The diagnosis and state of regulation were determined by clinical examination.
Both groups had typical symptoms of anxiety, psychomotor lability, cardiac complaints, chest pain and decreased or increased blood pressure.

RESULTS:

Metabolic acidosis was noticeably decreased in the test group in deference to the control group. Cardiotocography of the fetus showed an increase in the amplitude and acceleration of fetal heart and a reduction in the deceleration episodes (p < 0.001). The same rate of change was not seen in the control group.

CONCLUSION:

Nervoheel and Cralonin may be applied in pregnant women with NCA. Exacerbations of the condition may be treated through all terms of pregnancy as no adverse effects of the preparations are known.

*Free translation
Cralonin® is a homeopathic complex preparation with two plants and one mineral ingredient. *Crataegus* is contained in a mother tincture, *Spigelia anthelmia* at a D2 or 2X potency and *Kalium carbonicum*, a mineral, at a D3 or 3X potency. Of these ingredients, *Crataegus* has been the most studied for its effects on the cardiovascular system. The *Crataegus* in this case is made from the fresh, ripe fruit of *Crataegus laevigata* and *Crataegus monogyna* Jacq. emend. Lindm.

Hawthorn has been extensively used as a cardiac tonic throughout history. It is thought that most of its therapeutic properties come from the flavonoids and procyanidins. Both of these have different actions. The flavonoids act as powerful antioxidants, also in the respiratory chain where most of the free radicals are formed. In this respect, the action is similar to that of Co-enzyme Q10. Although the fruit of *Crataegus* has less flavonoids than the flower and stems, only the experiments done with extracts of the fruit show significant results.

The cardiovascular effects are believed to be the result of positive inotropic (contractile) activity by improving left ventricular function and ejection fraction, the ability to increase the integrity of the blood vessel wall, to improve coronary blood flow and to increase oxygen utilization.

*Crataegus* has an effect on the vascular tone, and has been shown in a randomized double-blind study to be effective in treating mild essential hypertension. An important incidental finding in this study was that the group taking *Crataegus* had a notable trend towards the reduction of anxiety. Another study has shown this effect to be mediated by the procyanidins, possibly via an endothelium dependent nitric oxide-mediated relaxation and an increase in the cyclic GMP (guanine monophosphatase). These effects were not produced by the flavonoids.

*Crataegus* also has an effect on lipid metabolism. Not only has it been shown to have hypolipidemic activity in animals, but also to inhibit LDL oxidation, the latter being a major patho-physiological factor in the development of arteriosclerosis. This vasodilatory and lipid protective effect makes it of course extremely attractive for use in the metabolic syndrome.

Other effects on the heart, which have been shown with *Crataegus*, include a protective effect against reperfusion arrhythmias after global ischemia. This could allow it to play a role in open heart surgery, where heart-lung machines are used and where these arrhythmias pose common problems. One could also see a role in the treatment in cases of hypothermia, where the same problems occur.

*Crataegus* probably also acts as a general cell stimulant according to feeding experiments done by Klatt at the Hamburg Zoological Institute, where changing the diet of a species of butterflies to hawthorn saved the breed from extinction. This experiment was repeated in another laboratory on the fruit fly. An interesting further property of *Crataegus* came to light when it was recently shown to have antiviral and antioxidant properties against Herpes Simplex Virus I (HSV-1).

Cralonin contains *Crataegus* in a mother tincture (undiluted) and enables extrapolation that it will have similar effects as these mentioned above. The other two ingredients in Cralonin have not been as well researched yet, but are well known from the homeopathic Materia Medica.
**SPIGELIA ANTHELMIA** (Pink root) contains a volatile alkaloid, spigelein, which is thought to be the active ingredient. In homeopathy, it is used for stabbing chest pain radiating to the left arm, also for pain in the region of the apex of the heart.

**KALIUM CARBONICUM** (Potassium carbonate) is used based on empirical homeopathic experiences. It acts primarily on the mucous membranes and the heart. It can be used for arrhythmias, valvular defects with myocardial weakness, and stabbing chest pain.

In view of the above, the application possibilities of Cralonin can be summarized in the following manner:

**FOR MYOCARDIAL WEAKNESS:** Cardiac failure (Class I-II), Sportsman’s heart, Myocarditis, Cardiomyopathy, Senile heart.

**ANGINA PECTORIS,** as baseline therapy with conventional therapy for acute attacks, or as massive dose therapy: 10 drops every 5 min (if no relief after three doses, conventional vasodilators should be taken).

**ARRHYTHMIAS** of various origins including reperfusion arrhythmias.

**Note:** Can be used adjuvantly to Digoxin as a study showed no interaction between Crataegus and Digoxin.

**HYPERTENSION:** Essential or as part of the metabolic syndrome and sympathetic outflow hypertension (has an anxiolytic effect).

**HYPERLIPIDEMIA AND ARTERIOSCLEROSIS**

**Dosage:**

**Massive initial dose therapy:** 10 drops every 15 min for 2 hours (angina: 10 drops every 5 min for 3 doses).

**In general:** 10 drops 3x/day.

**INJECTION:**

**Acute:** 1-2 ampules per day.

**In general:** 1-3 ampules per week.

**NOTE:**

The effect of Cralonin reaches its optimum for chronic conditions only after long-term use. The preparation should thus be used as a basic therapy over months, while suitable preparations for regulation, such as detoxification products, catalysts and neuroendocrine support are applied.

References available upon request.
The Detox-Kit® from Heel® combines three carefully formulated homeopathic preparations to relieve symptoms of illness caused by an unhealthy lifestyle and/or exposure to environmental toxins such as pollution and pesticides. The Detox-Kit® works by stimulating the body’s natural processes of elimination to get rid of toxins which can build up over time and negatively affect the immune system. It is made up of the following products:

**Lyphosot/Lymphomyosot (30 ml / 50 ml)**
Activates the lymphatic system in order to detoxify the connective tissue and the mesenchyme.

**Nux vomica-Homaccord (30 ml / 50 ml)**
Stimulates the gastrointestinal excretion pathways as well as the hepatic system.

**Berberis-Homaccord (30 ml / 50 ml)**
Activates the renal and biliary systems.

**Length of treatment:**
Take the Detox-Kit for 3 weeks, stop for 1 week and take another kit for 3 more weeks.

**Recommended use:**
Pour 30 drops of each preparation in a bottle of flat water (0.7 - 1.5 liters), shake lightly and drink throughout the course of the day.