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The effect of *Crataegus oxycantha* special extract WS 1442 on clinical progression in patients with mild to moderate symptoms of heart failure[☆]

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Abstract

Aim: To examine whether hawthorn (*Crataegus* Special Extract WS 1442 {CSE}) inhibits progression in heart failure (HF) patients.

Methods: We performed a retrospective analysis of data from the HERB CHF study in which patients with mild to moderate HF were randomised to either CSE 900 mg or placebo for 6 months. The primary outcome was time to progression of HF (HF death, hospitalisation, or sustained increase in diuretics) as assessed by log-rank tests and by Cox modelling.

Results: Progression of HF occurred in 46.6% of the CSE and 43.3% of the placebo groups (OR 1.14, 95% CI=0.56, 2.35; $p=0.86$). Patients receiving CSE were 3.9 times (95% CI=1.1–13.7; $p=0.035$) more likely to experience HF progression at baseline. In adjusted analysis, the risk of having early HF progression in the CSE group increased to 6.4 (95% CI=1.5, 26.5; $p=0.011$). In patients with LVEF $\leq 35\%$, those taking CSE were at significantly greater risk (3.2, 95% CI=1.3, 8.3; $p=0.02$) than the placebo group.

Conclusions: CSE does not reduce heart failure progression in patients who have HF. CSE appears to increase the early risk of HF progression.

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Keywords: Hawthorn; Heart failure progression; *Crataegus* Special Extract WS 1442; *Crataegus oxycantha*

1. Introduction

The pharmacological treatment of heart failure (HF) has seen tremendous advances in recent years. In appropriate patients, the addition of β -adrenergic and aldosterone antagonists, and the combination of hydralazine and nitrates

have each substantially improved the quality of life and reduced symptoms of HF, the risk of death and the rate of HF progression. Nevertheless, even with contemporary evidence based treatment regimens, progression of HF is inexorable. As the prevalence of heart failure continues to increase, there is a pressing need for new agents that could positively affect HF progression.

Inflammatory signalling and oxidative stress appear to be involved in transcriptional regulatory pathways that lead to progression of HF [1]. Elevated aldosterone levels, which have been suggested as having a significant role in left ventricular remodelling, stimulate reactive oxygen species (ROS) in the myocyte [2]. Thus, inflammatory signalling may be one of the mechanisms through which activation of the sympathetic nervous system causes left ventricular remodelling. As the neurohormonal system is triggered early in HF disease

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progression, drugs with anti-inflammatory effects may, in theory, reduce the risk of clinical progression.

Crataegus oxycantha, or hawthorn berries, leaves and flowers and their extracts have been used for cardiac and circulatory disorders since the first century AD [3]. *C. oxycantha* demonstrates numerous properties that may be beneficial in HF progression, including antioxidant activities [4–9] and anti-inflammatory effects [10–12]. A recent meta-analysis of clinical trials concluded that *C. oxycantha* may be a safe and effective treatment for HF [13].

Although most previous trials of *C. oxycantha* have reported modest improvements in exercise capacity, quality of life (QOL) and HF-related symptoms [13], none of these studies have examined the effect of *C. oxycantha* on HF progression. Consequently, we performed a secondary data analysis of a randomised, double-blind, placebo-controlled trial of *Crataegus* Special Extract WS1442 in patients with mild to moderate symptomatic HF (HERB CHF), to examine the effect of *Crataegus* Special Extract WS 1442 versus placebo on clinical measures of HF progression.

2. Methods

We retrospectively analyzed baseline, three and six month data from 120 HF patients who had completed a six month randomised, double-blind, placebo-controlled drug trial, HERB CHF, in which treatment with *Crataegus* Special Extract WS 1442 was found to have a neutral effect on clinical outcomes in patients with New York Heart Association (NYHA) classes II–IV symptoms [14].

2.1. Study population

Patients aged 18 years and older who had been diagnosed with HF (NYHA functional classes II–III) for ≥ 3 months with a left ventricular ejection fraction (LVEF) $\leq 40\%$ (by radionuclide ventriculography, contrast left ventriculography or echocardiography, assessed during usual clinical care within the 12 months prior to randomisation) were recruited from the University of Michigan Health System cardiology clinics, and from the surrounding community by local newspaper advertisements. Patients were eligible to participate if they were receiving indicated standard therapy (if not contraindicated or intolerant) defined as a diuretic, an ACE inhibitor or an angiotensin receptor blocker (ARB) and a β -blocker. Patients with NYHA class III symptoms were also required to receive spironolactone. Doses of these drugs had to be stable for ≥ 3 months, except for diuretics, for which ≥ 1 month of stability was required.

Patients were ineligible if they had haemodynamically severe uncorrected primary valvular disease; active myocarditis; hypertrophic cardiomyopathy; restrictive cardiomyopathy; myocardial infarction, stroke, unstable angina, coronary artery bypass graft surgery, valvular surgery, cardiac resynchronization therapy or angioplasty ≤ 3 months before randomisation. In addition, patients with symptomatic

or sustained ventricular tachycardia not controlled by antiarrhythmic drugs or an implantable cardioverter–defibrillator; any condition other than HF that would be expected to limit exercise (e.g., angina, peripheral vascular disease, pulmonary disease, arthritis or an orthopaedic problem severe enough to limit exercise); nursing mothers, pregnant women and those planning a pregnancy during the study period, were also excluded. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study was approved by the University of Michigan Medical School Institutional Review Board and was overseen by an independent Data Safety Monitoring Board. All participants provided written informed consent.

2.2. Study procedures

Screening occurred at the end of a HF clinic visit. Interested patients were asked to undertake a 6-minute walk test. Patients who walked between 150 and 450 m were invited to attend for a baseline visit within the following two weeks. Written informed consent was obtained at the beginning of the baseline visit. If participants were found to be clinically stable and euvolaemic at the baseline visit, they were asked to perform another 6-minute walk test. Those who walked between 150 and 450 m were randomised and all others were deemed ineligible. Eligible patients also had their LVEFs assessed at the baseline visit by radionuclide ventriculography.

2.3. Intervention

Eligible patients were randomly assigned to receive either *C. oxycantha* extract, *Crataegus* Special Extract WS 1442 (*Crataegutt forte*[®], Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany), 450 mg twice daily, or a matching placebo. This dose was chosen based on the manufacturer's recommendations and on doses used in previous clinical studies using this extract. Each tablet contained 450 mg dry extract of *C. oxycantha* leaves with flowers [4–6.6:1 extraction solvent: ethanol 45%] standardized to 84.3 mg of oligomeric proanthocyanidins (OPCs). The entire study was conducted using a single batch of *Crataegus* Special Extract WS 1442 to optimize product consistency. Content of OPCs in the study medication were independently verified using appropriate high performance liquid chromatography methods (Integrated Biomolecule; Tucson, AZ). The OPC content at the end of the study was 84.06 mg/tablet. Placebo tablets contained lactose, and were coloured to match the placebo tablets. Participants were told to take the study medication twice per day with water and to bring all unused tablets to each study visit. Patients were seen at the study clinic three months and six months after the baseline visit.

2.4. Statistical analysis

Baseline characteristics are reported by treatment group using means and standard deviations (SD) for continuous

variables, and counts and percentages for categorical variables. The primary outcome for this analysis, progression of HF, was defined as (1) death due to HF, (2) hospitalisation due to HF, or (3) sustained increase in diuretic dose for HF. An increase in diuretic dose was defined as an increase of at least 50% from baseline at either the three month or six month visit. The three parts of the primary endpoint were considered in hierarchical order, where HF death took precedence over HF hospitalisation and HF hospitalisation had precedence over increased diuretic dose. Consequently, patients with more than one endpoint were only counted once.

Our primary outcome, proportion of patients with clinical progression of HF, was analyzed using Cochran–Mantel–Haenszel techniques to calculate relative risks (RR) and 95% confidence intervals (CI). Time to progression by treatment group was determined by construction of Kaplan–Meier survival estimates and tested using the log-rank test. To test for the effect of potentially important prognostic determinants (baseline age, sex, HF aetiology, serum creatinine, NYHA functional class, serum sodium, peak oxygen consumption, LVEF, mean blood pressure, Heart Failure Survival Score [15], β -blocker and ACE inhibitor use as well as time by treatment interaction) we used Cox modelling, with backward stepwise regression to determine the most parsimonious models. An α of ≤ 0.05 was considered significant.

With a sample size of 60 per group and a 43% event rate in the placebo group, we have 84% power to detect a hazard ratio of 2.0 or greater, assuming $\alpha=0.05$ and two-sided log-rank test. For the subgroup LVEF of 35% and below, with a sample size of approximately 34 per group and a 43% event rate in the placebo group, we have 81% power to detect a hazard ratio of 2.6 or greater.

3. Results

3.1. Socio-demographic and clinical characteristics

The socio-demographic and clinical characteristics of participants by treatment group are shown in Table 1. There were no differences between treatment groups for any demographic or clinical characteristics. However, despite the entry requirement of an LVEF $\leq 40\%$ measured during a clinically-indicated study within the previous 12 months (see above), the baseline radionuclide ventriculogram performed after study randomisation detected an LVEF $>40\%$ in 38 of the study participants. Since the baseline assessment of LVEF occurred after randomisation, we were not able to exclude these patients.

3.2. Patient flow

Of the 120 patients who were randomised into the HERB CHF trial, 60 were assigned to placebo and 60 to *Crataegus* Special Extract WS 1442. One hundred and eleven patients

Table 1
Socio-demographic and clinical characteristics of the study population by treatment group

Characteristics	Placebo, (n=60)	Hawthorn, (n=60)
	n (%) or mean (\pm SD)	n (%) or mean (\pm SD)
Sex		
Men	44 (73)	46 (77)
Women	16 (27)	14 (23)
Age	57.8 (± 9.0)	54.4 (± 12.6)
Race		
White	50 (83)	45 (75)
Blood pressure, mm Hg		
Systolic	113 (± 19)	109 (± 15)
Diastolic	66 (± 10)	66 (± 10)
Heart rate, bpm	71 \pm 11	68 \pm 11
NYHA class		
II	33 (55)	30 (50)
III	27 (45)	30 (50)
LVEF, %	34.8 (± 14.5)	36.2 (± 15.1)
LVEF $\leq 40\%$	44 (73)	38 (63)
Six-minute walk test, m	374.0 (± 52.4)	358.2 (± 59.2)
Peak oxygen consumption, mL/kg/min	14.6 (± 3.8)	14.7 (± 3.5)
Medications		
ACE inhibitor	46 (77)	48 (80)
ARB	11 (18)	9 (15)
ACE inhibitor or ARB	57 (95)	57 (95)
Beta blocker	52 (87)	54 (90)
Digoxin	49 (82)	47 (78)
Loop diuretic	57 (95)	55 (92)
Spironolactone	39 (65)	39 (65)
Thiazide diuretic	10 (17)	11 (18)

completed all six months of the study. In the placebo group three patients did not complete the study; one died due to HF, one had severe pneumonia and one had a United Network for Organ Sharing (UNOS) status 1 heart transplant. In the *Crataegus* Special Extract WS 1442 group six patients did not complete the study: three patients died, one due to aplastic anaemia and two due to HF; of the other three patients: one patient developed Grave's disease; one developed thymomas and one had a UNOS status 1 heart transplant.

3.3. Progression of heart failure

Progression of HF occurred in 46.6% (28/60) of *Crataegus* Special Extract WS1442 patients and 43.3% (26/60) of placebo patients. This reflects no difference in the incidence of the primary outcome between the groups ($p=0.86$) (Fig. 1). The odds ratio of HF progression was 1.14 (95% CI=0.56, 2.35) for *Crataegus* Special Extract WS1442 compared to placebo. Evaluating each component of the combined endpoint separately, *Crataegus* Special Extract WS1442 resulted in nominally more HF deaths

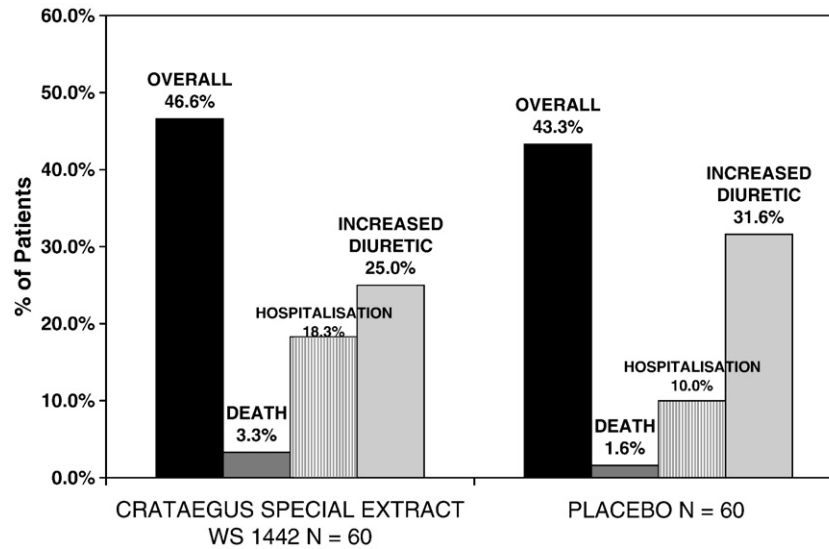


Fig. 1. Heart failure progression endpoints in the *Crataegus* Special Extract WS 1442 and placebo groups for the 120 patients in the HERB CHF trial.

(3.3%, 2/60 vs. 1.6%, 1/60) and HF hospitalisations (18.3%, 11/60 vs. 10.0%, 6/60) but less frequent need for increased diuretic (25.0%, 15/60 vs. 31.6%, 19/60) compared to placebo.

The Kaplan–Meier curve for *Crataegus* Special Extract WS1442 and placebo (Fig. 2.) showed a crossing pattern that could indicate changing hazards over time. We consequently performed a non-proportional Cox regression analysis using a time by treatment interaction that demonstrated the risk of HF progression between the two groups changed significantly through time ($p=0.047$). The non-proportional Cox

model demonstrated that patients in the *Crataegus* Special Extract WS1442 group were 3.9 times (95% CI=1.1, 13.7; $p=0.035$) more likely to experience a HF progression event at baseline than the placebo group. The hazard ratio (HR) for the *Crataegus* Special Extract WS1442 group decreased through time, so that at six months (182 days) *Crataegus* Special Extract WS1442 did not increase progression (HR=0.63, 95% CI=0.29, 1.47; $p=0.72$) compared to the placebo group. In a similar fashion, when adjusted for baseline NYHA functional class, peak oxygen consumption, LVEF, Heart Failure Survival Score, and ACE

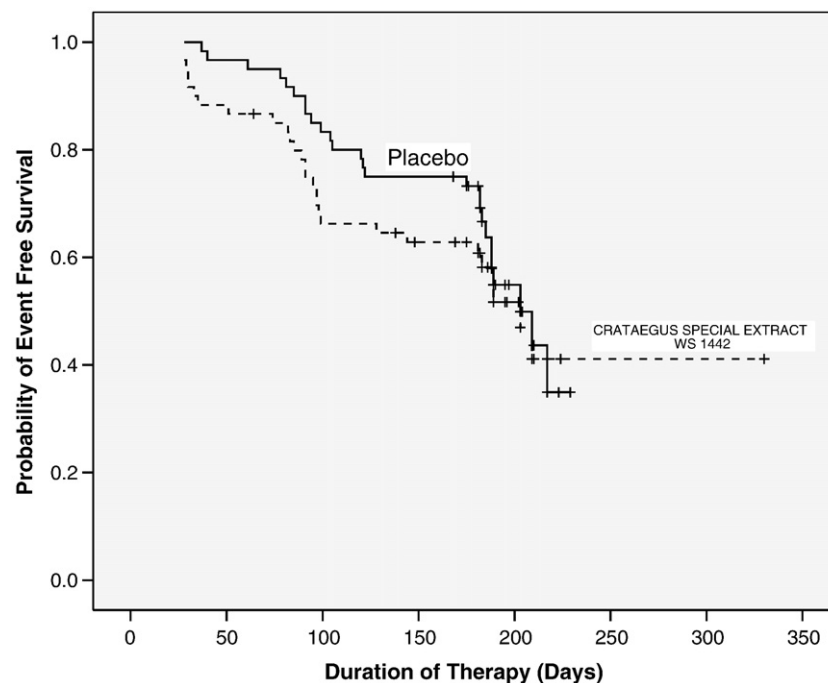


Fig. 2. Kaplan–Meier plot of the effect of *Crataegus* Special Extract WS 1442 versus placebo on progression of heart failure in patients in the HERB CHF trial. *Crataegus* Special Extract WS 1442 had no effect on the rate of heart failure progression (hazard ratio=1.14, (95% CI=0.56, 2.35).

inhibitor use, as well as the time by treatment interaction, the risk of having a HF progression event at baseline in the *Crataegus* Special Extract WS1442 group increased to HR=6.4 (95% CI=1.5, 26.5; $p=0.011$) times greater than the placebo group. At six months (182 days), after adjustment, *Crataegus* Special Extract WS1442 again no longer increased progression (HR=0.41, 95% CI=0.14, 1.18; $p=0.64$) compared to the placebo group.

We conducted the same analyses on the subgroup of 68 participants with LVEF $\leq 35\%$. Results in this subgroup of patients were similar to those observed for the whole group. Progression of HF occurred in 51.5% (17/33) of *Crataegus* Special Extract WS1442 patients and 42.9% (15/35) of placebo patients. This difference reflects a non-significant increase in the primary endpoint of 13% ($p=0.48$) in the *Crataegus* Special Extract WS1442 group. The odds ratio of HF progression was 1.42 (95% CI=0.55, 3.69; $p=0.48$) for *Crataegus* Special Extract WS1442 compared to placebo.

Kaplan–Meier analysis also demonstrated the possibility that the risk of having HF events appeared to change through time between the two groups. A non-proportional Cox regression analysis indicated that time by treatment interaction was not significant ($p=0.13$). When adjusted for baseline peak oxygen consumption, cause of HF, serum sodium, and ACE inhibitor use, the risk of having a HF progression event in the *Crataegus* Special Extract WS1442 group was HR=3.2 (95% CI=1.3, 8.3; $p=0.02$) times higher than in the placebo group.

4. Discussion

C. oxycantha in the formulation and dose administered in this study when added to optimum evidence based therapy did not decrease the risk of our primary outcome, clinical HF progression compared to placebo. There were, however, significantly more HF progression events at baseline in the *Crataegus* Special Extract WS1442 group versus the placebo group. Subgroup analysis of data from patients with LVEF $\leq 35\%$ demonstrated similar results, although more ill patients who received *Crataegus* Special Extract WS1442 were at a significantly increased risk of having a HF progression event throughout the 6 months of the study and not just at baseline.

It is unclear why patients who receive *Crataegus* Special Extract WS1442 are at greater risk at baseline or if more ill throughout the entire 6 months of the study for having a HF-related hospitalisation, death or increased diuretic use. Our results could well be due to chance, as this study was a secondary data analysis and had limited power due to the small sample size. The analysis in sicker patients, with an even smaller sample size, was even more limited and vulnerable to chance outcomes. Moreover, as other clinical trials examining *C. oxycantha* for HF have not examined the occurrence of clinical HF events through time, we are unable to determine if this is a unique conclusion of our study or a

common pattern with *C. oxycantha* intake in this population. The Survival and Prognosis: Investigation of *Crataegus* Extract WS 1442 in Congestive Heart Failure (SPICE) trial has recently been completed. The SPICE trial was a randomised clinical trial in nearly 3000 HF patients with LVEF $\leq 35\%$, the primary endpoint was cardiac morbidity, non-fatal myocardial infarction and hospitalisation due to HF progression over 24 months [16]. The SPICE trial used *Crataegus* Special Extract WS1442 at the same dose as in our study and enrolled patients with similar baseline demographic and clinical characteristics [17]. However, since the SPICE trial has not yet been published, only data presented orally and in the associated abstract are currently available, allowing only limited comparisons with our study data. The SPICE trial reported similar results to our study, in that there was no significant difference in HF progression between the active and placebo groups (27.9% vs. 28.9%; $p=NS$), although clearly our trial had a higher percentage of HF progression events (46.6% vs. 43.3%) [16]. Kaplan–Meier curves have not yet been presented for the SPICE trial, consequently it is unclear if the relative risk between the active and placebo groups changed through time, and if there was an increased risk in the *Crataegus* Special Extract WS1442 group at baseline or in sicker patients.

One possible explanation for the increased risk for progression of HF at baseline in the *Crataegus* Special Extract WS1442 group and for patients with LVEF $\leq 35\%$ (in the adjusted analysis) is the possibility of herb–drug interactions. As the majority of patients with HF are on several different drugs, many interactions are theoretically possible. In particular, the flavonoids in *C. oxycantha* are chemically similar to other flavonoids that have demonstrated P-glycoprotein activity, which may lead to various drug–flavonoid interactions [18–20]. Only one study has examined possible interactions between *C. oxycantha* and a commonly administered HF medication, digoxin. This study found that *Crataegus* Special Extract WS 1442 (450 mg twice daily) did not significantly alter the pharmacokinetic parameters of digoxin [21]. Further, several flavonoids in *C. oxycantha* such as the vitexin rhamnosides have been demonstrated to have low oral absorption or undergo extensive conjugation before reaching the systemic circulation [22–23]. Both the negative study examining potential interactions with digoxin and the low level absorption of the main flavonoids present in *C. oxycantha* diminish the potential of possible *C. oxycantha*–drug interactions. It is possible that constituents other than flavonoids in *C. oxycantha* may cause herb–drug interactions, but currently there is not enough information to determine whether *C. oxycantha*–drug interaction led to the increased early risk of HF progression.

This study had several limitations. As with all secondary analyses this study was not designed *a priori* to detect HF progression events. As such, we did not have a data collection method in place to monitor changes in HF medications continuously over the six month study period. Instead we collected

information about medications taken, their dose and frequency at baseline, three and six months. At three and six months, we noted if the patient's diuretic dose was increased from their last visit. As a consequence we could have included patients who did not truly have an increased sustained diuretic dose and missed including patients with sustained increased diuretic dose. These potential misclassifications, however, should have been non-differentially spread across both groups, thus keeping the risk relationships between the two groups the same.

Another major limitation of this study is its small sample size. With 54 events in 120 patients we are able to detect relatively moderate changes in hazard ratios (2 times or greater) between the groups but not small differences. This is even more pronounced in the subgroup analyses of patients with LVEF of $\leq 35\%$ where we have 32 events in 68 patients.

We suggest that healthcare providers use caution when considering prescribing *C. oxycantha* to patients with HF. Patients already taking *C. oxycantha* should also be observed closely for any adverse events that could be temporally related to *C. oxycantha* ingestion. We make these recommendations because *Crataegus* Special Extract WS1442, at a commonly recommended dose, significantly increased the risk for progression of HF at baseline and in the more clinically compromised patients with LVEF $\leq 35\%$ in this study. Moreover, *Crataegus* Special Extract WS1442 increased risk consistently in more compromised patients with LVEF $\leq 35\%$.

In summary, *Crataegus* Special Extract WS 1442 does not reduce heart failure progression in patients who have mild to moderate HF. *Crataegus* Special Extract WS 1442 appears to increase the early risk of heart failure progression.

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