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Effect of Integrated, Person-Centred Palliative Advanced Home and Heart Failure Care on NT-proBNP Levels: A Substudy of the PREFER Study

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Abstract

Objective: In 2012, we initiated a new person-centred model, integrated **P**alliative advanced home ca**RE** and heart **F**ailur**E** ca**R**e (PREFER), to integrate specialised palliative home care with heart failure care. Natriuretic peptide-guided treatment is valuable for younger patients (age < 75 years), but its usefulness in palliative care is uncertain. We explored whether patients in PREFER reduced mean level of N-terminal pro B-type natriuretic peptide (NT-proBNP) more than the control group. **Design:** A pre-specified, exploratory substudy, analysed within the prospective, randomised PREFER study, which had an open, non-blinded design. **Participants:** Patients in palliative care with chronic heart failure, New York Heart Association class III-IV were randomly assigned to an intervention (n = 36; 26 males, 10 females, mean age: 81.9 years) or control group (n = 36; 25 males, 11 females, mean age: 76.5 years). The intervention group received the PREFER intervention for 6 months. The control group received care as usual at a primary health care centre or heart failure clinic at the hospital. NT-proBNP was measured at the start and end of study. **Results:** Plasma levels of NT-proBNP differed significantly between groups at baseline. By the end of the study, no significant difference was found between the groups. The mean value for NT-proBNP decreased by 35% in the PREFER group but was not statistically significant (P = 0.074); NT-proBNP increased 4% in the control group. **Conclusions:** We found no statistically significant reductions of NT-proBNP levels neither between nor within the PREFER and the control group at the end of the study.

Keywords

Chronic Heart Failure, Palliative Care, Integrated Care, NT-proBNP, Elderly

1. Introduction

Patients with chronic heart failure (CHF) have symptoms as severe and distressing as those of patients with cancer, but do not have equal access to palliative care [1]. The course of CHF is unpredictable, complicating the choice of a specific point for introducing palliative care into general heart failure management [2]. In addition, patients with CHF often require frequent hospitalizations and readmissions, suggesting insufficient management that may be attributable to the frequency of concomitant chronic diseases [1] [3] [4].

In recent years, several groups have sought to characterise the impact of CHF on symptom burden, quality of life, morbidity and mortality [1] [5] [6]. Others have examined how to improve and individualize CHF treatment, including evaluation of natriuretic peptide (NP)-guided treatment of heart failure [7] [8] [9] [10] [11]. NP-guided treatment seems to be valuable for younger patients (age < 75 years) with reduced mortality and morbidity, but study results for older patients (age ≥ 75) are contradictory [8] [9] [10] [12] [13]. The plasma concentration of NP can be used in initial diagnostic testing and elevated NPs help identify those who have a worse prognosis and may require further cardiac investigations and/or treatment. Serial NP measurements may guide drug treatment for patients with CHF [14] [15], but the role of these measurements in palliative care has not been evaluated.

In 2012, a new model became available that integrated specialized palliative home care with heart failure care. The person-centred **P**alliative advanced home ca**RE** and heart **F**ailur**E** ca**R**e (PREFER) model reduced readmissions, length of stay, and symptoms and improved quality of life [16]. In addition, patients [17] and relatives [18] experienced increased security compared to traditional care. Person-centred integrated care of patients also is associated with increased evidence-based drug treatment, especially mineral corticoid receptor antagonists [19]. Given these findings, we hypothesised that patients receiving the PREFER model of treatment would have greater reductions of N-terminal pro B-type NP (NT-proBNP) levels than those receiving usual care.

2. Aim

Our aim was to explore whether the integrated heart failure and palliative homecare in the PREFER group led to a greater reduction of NT-proBNP levels compared to the usual care group.

3. Patients and Methods

From January 2011 to October 2012, a total of 72 patients with CHF, were diag-

nosed according to the ESC guidelines [3]. Patients in the PREFER study were randomized in an open non-blinded design with envelopes in blocks of 20 to the intervention group (n = 36) or to usual care (n = 36). The design and results have been described and presented elsewhere [16]. The present study was a pre-specified explorative substudy, analyzed within the prospective randomized PREFER study.

Blood sampling of NTproBNP at baseline and at six months (end of study) took place from fasting patients who had rested for 20 minutes, 3600 rates per minutes. After 5 minutes, the samples were centrifuged for 10 minutes at 4˚C and then stored frozen at −70˚C. NT-proBNP was analysed at our local laboratory using a clinically available immunoassay, Roche Elecsys (Roche Diagnostics) [20].

3.1. Statistical Analysis

The results are presented as mean ± standard deviation or number (percent). Baseline and end-of-study values of NT-proBNP were not normally distributed and thereby log-transformed. The difference in NT-proBNP levels between baseline and study end is presented as both a numerical and a categorised difference. Compared to levels at baseline, lower levels of NT-proBNP at the end of the study were defined as "improved" and higher levels as "impaired", respectively.

Differences between the PREFER and control groups were evaluated with Chi^2 test for categories or Student t-tests for normally distributed or logarithmic data. Within-group analysis was analysed with paired sample t-tests. We used univariate and multivariate logistic regression analyses or linear regression analysis to test associations of independent variable and outcome (difference between baseline and end of study) of NT-proBNP. For multivariate analysis, we adjusted for predetermined variables (age, sex, weight, renal function). $P < 0.05$ was considered to indicate significance. For all statistical analyses, IBM SPSS Statistics 22.0 was used.

3.2. Ethics

All study participants gave oral and written informed consent. The study is based on the principles of the Helsinki Declaration. It is approved by the Regional Ethics Examination Board at Umeå University (dnr. 2010-294-31M), and the main PREFER study is registered at http://www.clinicaltrials.gov (reg no. NCT0130481).

4. Results

Seventy-two patients in palliative care with CHF, New York Heart Association class III-IV were randomly assigned to an intervention (n = 36; 26 males, 10 females, mean age: 81.9 years) or control group (n = 36; 25 males, 11 females, mean age: 76.5 years). At six months eight patients had died in the PREFER group and four in the control group. At baseline, only mean age differed signifi-

cantly between the PREFER and control group. Baseline characteristics are shown in Table 1.

Baseline values and differences in NT-proBNP levels between baseline and the end of the study are shown in Table 2. Plasma NT-proBNP levels differed significantly between groups at baseline but not at the end of the study. Of note, the mean value of NT-proBNP decreased from 11,893 to 7764 ng/L (35% decrease) in the PREFER group, although this decrease was not statistically significant (P = 0.074). NT-proBNP increased from 5407 to 5608 ng/L (4% increase) in the control group (Figure 1).

Table 1. Baseline characteristics.

Variable	PREFEER n = 36	Control n = 36	P
Age	81.9 ± 7.2	76.6 ± 10.2	0.01
Gender			
Female	10 (27.8)	11 (30.6)	0.80
Male	26 (72.2)	25 (69.4)	0.80
Marital status			
Single	14 (39.0)	14 (39.0)	1.00
Married/Cohabiting	22 (61.0)	22 (61.0)	1.00
Smoking			
Never	13 (36.1)	14 (38.9)	0.81
Former	21 (58.3)	17 (47.2)	0.35
Actual/unknown	2 (5.6)	5 (13.8)	0.23
Alcohol			
Never	15 (41.7)	13 (36.1)	0.09
Regular use	16 (44.4)	17 (47.2)	0.41
Unknown	5 (13.9)	6 (16.7)	0.26
History of primary cardiovascular disease for CHF	26 (77.2)	26 (77.2)	1.00
Hypertension	9 (25.0)	9 (25.0)	1.00
Ischemic Heart disease	13 (36.1)	13 (36.1)	1.00
Valve disease	1 (2.8)	1 (2.8)	1.00
Other (e.g., cardiomyopathy)	3 (8.4)	3 (8.4)	1.00
Unknown	10 (28.0)	10 (28.0)	1.00
Other illness in health history			
History of atrial fibrillation/flutter	23 (63.9)	22 (61.1)	0.81
History of pulmonary disorder	15 (41.7)	18 (50.0)	0.48
History of stroke	14 (38.9)	12 (33.3)	0.56
Renal disorder	10 (27.8)	11 (30.6)	0.57
Depression	6 (16.7)	12 (33.3)	0.30
Diabetes	13 (19.4)	8 (16.6)	0.07
History of malignancy	6 (16.7)	2 (5.6)	0.13
New York Heart Association class			

Continued

III	28 (77.8)	23 (63.9)	0.34
IV	8 (22.2)	11 (30.6)	0.34
Blood pressure baseline			
Systolic mmHg	124 ± 25.8	120 ± 19.9	0.42
Diastolic mmHg	70 ± 12.5	74 ± 9.7	0.12
Systolic function, % ejection fraction			
Preserved, 40% - 49%	13 (36.1)	12 (33.3)	0.80
Reduced, 30% - 39%	16 (44.4)	21 (58.3)	0.36
Reduced, <30%	7 (19.4)	3 (8.3)	0.17
Creatinine > 130 mmol/L	12 (33.3)	12 (33.3)	1.00
Glomerular filtration rate < 60 mL/min	25 (69.4)	22 (61.1)	0.46
Anemia < 120 g/L	19 (52.7)	15 (41.7)	0.29
Dyspnea			
None	1 (2.8)	2 (5.6)	0.56
Mild	8 (22.2)	6 (16.6)	0.55
Moderate	23 (63.9)	22 (61.1)	0.81
Severe	4 (11.1)	6 (16.7)	0.50
Fatigue			
None/missing	3 (8.3)	4 (11.1)	0.69
Mild	10 (27.8)	7 (19.4)	0.41
Moderate	16 (44.4)	15 (41.7)	0.81
Severe	7 (19.4)	10 (27.8)	0.41
Treatment			
Renin-angiotensin system blockade	32 (86.1)	33 (91.7)	0.69
Beta-blocker	30 (83.3)	31 (86.1)	0.74
Mineralocorticoid receptor antagonist	10 (27.8)	13 (36.1)	0.45
Loop diuretics	32 (88.9)	30 (83.3)	0.50
Digitalis	8 (22.2)	5 (13.9)	0.36
Nitrates	12 (33.3)	11 (30.6)	0.80
Statins	12 (33.3)	18 (50.0)	0.15
Anticoagulants	17 (47.2)	17 (47.2)	1.00
Acetylsalicylic acid/platelet inhibitors	21 (58.3)	15 (41.7)	0.16
Number of other drug treatments, median	5	6	0.73
Devices, procedures			
Cardiac resynchronisation therapy	3 (8.3)	4 (10.1)	0.35
Pacemaker	4 (11.1)	5 (13.9)	0.72
Valve operations	4 (11.1)	3 (8.3)	0.69
History of coronary artery bypass graft/percutaneous coronary intervention	17 (47.2)	13 (36.1)	0.34

The variables are presented as number, (%) or mean ± standard deviation. Classification of dyspnea and fatigue were performed according to the Swedish HF registry.

Table 2. NT-proBNP levels.

Plasma NT-proBNP levels, ng/L	PREFER	Control	P
Baseline, mean ± SD	11,893 ± 15,416 N = 36	5407 ± 5280 N = 36	0.021
End of study, mean ± SD	7764 ± 10086 N = 28	5608 ± 6398 N = 32	0.330
Mean ± SD of differences (baseline to end of study)	1332 ± 7243	−634 ± 4735	0.210
Logarithmic baseline, mean ± SD	3.80 ± 0.52	3.56 ± 0.42	0.028
Logarithmic end of study, mean ± SD	3.63 ± 0.48	3.52 ± 0.47	0.350
Mean ± SD differences (Log baseline vs log end of study)	0.12 ± 0.33	0.0053 ± 0.30	0.180
Categorised difference:	N = 28	N = 32	
Improved NT-proBNP	20	16	0.091
Impaired NT-proBNP	8	16	0.091

The variables are presented as number or mean ± standard deviation (SD).

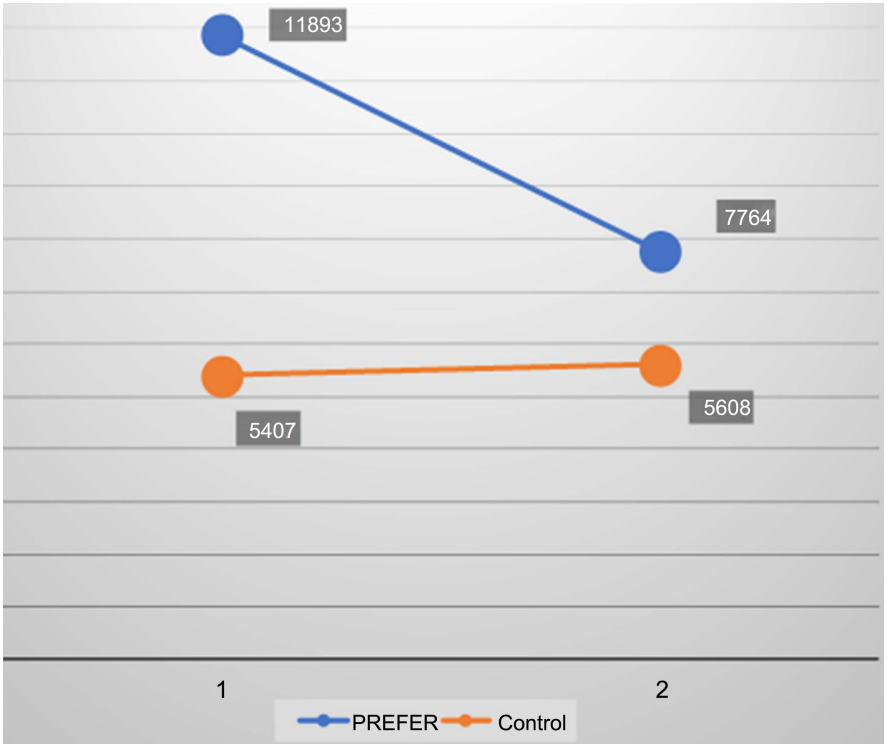

Figure 1. Changes in mean values for NT-proBNP.

Multivariate analyses with adjustments for age, sex, renal function, and weight showed no significant differences between the PREFER and control groups for changes in NT-proBNP (unadjusted, P = 0.094; adjusted, P = 0.057).

5. Discussion

The main finding of this exploratory study was that the PREFER and controls

groups did not differ significantly at the end of the study for mean levels of NT-proBNP. Therefore, the proposed null hypothesis could not be rejected.

Our results are in line with the meta-analysis of De Vecchis *et al.* [12]. They found an association of NP-guided therapy with both lower mortality and morbidity for people under age 75 years but not over age 75 years. In contrast, the PROTECT study showed that NT-proBNP-guided treatment was associated with decreased cardiovascular event rates for people over age 75 years [10]. They argued that treatment in the older age groups as in previous studies, such as TIME-CHF [8]. Or BATTLESCARRED [9], failed to lower NT-proBNP to clinically relevant, predefined levels, which could explain why an absence of positive results in the older age group. Other studies have shown significant reductions in NT-proBNP levels following medical treatment of CHF [21] [22] [23]. In the current work, we identified a numerical reduction in mean NT-proBNP value, suggesting that NT-proBNP can be lowered in this older age group. The numerical improvement with PREFER may be linked to the significant optimisation of recommended drug treatment as previously reported [19]. The marked reductions of hospitalizations found in the PREFER study [16] suggest that other components of the model, such as the team-based and person-centred care and the continuity may be of equal or of greater importance than improvements of drug treatment. Further and larger clinical studies are needed to further explore the relationship between NT-proBNP and clinical outcomes in palliative care.

6. Clinical Implications

The role of NT-proBNP measurements in the care of older patients with severe heart failure and in palliative care is still not clear. Medical treatment plays an important role, but improvements in drug treatment for elderly people with CHF require careful monitoring and consideration because the drugs have side effects that can lead to severe complications such as confusion, kidney impairment, or fall trauma with fractures. Fully optimising drug treatment requires meticulous monitoring and measuring NT-proBNP levels may become a useful tool, but this must be further examined.

7. Limitations

The study has several limitations. The PREFER substudy was a one-centre exploratory study with limited number of patients involving no power calculations for changes in NT-proBNP. For this reason, a type 2 error cannot be excluded.

Patients in the PREFER group were significantly older than those in the control group, but adjustments were made for this difference in the analyses. The intervention in the PREFER trial did not use NT-proBNP to monitor and adjust drug treatment to a certain level.

8. Conclusions

We found no significant reductions in NT-proBNP levels between or within the

PREFER and control groups for six months treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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