Supplemental Material

PRospective Evaluation of natriuretic peptide-based reFERral of chronic heart failure patients in primary care (PREFER): A real-world study

This supplementary online-only material provides additional methods and results that support and extend information presented in the main manuscript.

Hobbs FDR, *et al. Open Heart* 2021; 8:e001630. doi: 10.1136/openhrt-2021-001630

Inclusion criteria

1. Willing and able to provide written informed consent and accept study procedures and time schedule.
2. Age ≥18 years.
3. Patients with chronic heart failure (HF; the diagnosis must have been made or confirmed by a cardiologist and/or hospital physician at any time in the patient's medical history).
4. Patients with reduced ejection fraction (≤40%), as confirmed at any time point in the patient's medical history.

Exclusion criteria

1. Use of investigational drugs either within 5 half-lives of enrolment, or within 30 days, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. Major surgery in the last 3 months prior to baseline or planned major surgery or cardiac intervention during the study.
3. Cancer or other significant comorbidities implying that the patient's condition is unstable.
4. Comorbidities that can be associated with elevated natriuretic peptide (NP) levels: renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m² calculated according to Modification of Diet in Renal Disease formula), recent (less than 3 months) cerebral trauma or recent (less than 3 months) cerebrovascular incident, novel diagnosis, or acute exacerbation of chronic obstructive pulmonary disease within the last 3 months.
5. Patients who are primarily managed and regularly followed up by a cardiologist for their HF.
6. Highly frail patients whose estimated lifespan due to comorbidities is less than 6 months, by the judgement of the investigator.

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Supplementary information on cardiologist's advice

The cardiologist's advice was analysed within the follow-up set and then documented. The following analyses were performed:

- Analysis on therapy level:
    - Information on the incidence of HF treatment with advice from the cardiologist was displayed by preferred name and type of advice given by the cardiologist
- Analyses on patient level:
    - Frequency of cardiologist's advice on patient level was provided, using the following categories:
        - No change: Cardiologist's advice for at least one HF treatment was 'No change' no other advice was given by the cardiologist.
        - Treatment intensification: Cardiologist's advice for at least one HF treatment was "Dose increase" or "New prescription" and no advice for "Dose reduction" or "Discontinuation" was given.
        - Treatment reduction: Cardiologist's advice for at least one HF treatment was "Dose reduction" or "Discontinuation" and no advice for "Dose increase" or "New prescription" was given.
        - Treatment adaption: Cardiologist's advice for at least one HF treatment was "Dose reduction" or "Discontinuation" and for at least one other HF treatment the advice was "Dose increase" or "New prescription".
    - Information on implementation of treatment changes by cardiologist on patient level was displayed, defined for all patients for whom the cardiologist's advice on patient level was "Treatment intensification", "Treatment reduction", or "Treatment adaption" as follows:
        - Yes: All recommended HF treatment changes for a patient were implemented by the cardiologist.

- No: No recommended HF treatment changes for a patient were implemented by the cardiologist.
- Partially: At least one recommended HF treatment change was implemented by the cardiologist and one other recommended HF treatment change was not implemented by the cardiologist.

- Acceptance of cardiologist's advice on patient level was provided, defined for all patients for whom the cardiologist's advice on patient level was "Treatment intensification", "Treatment reduction", or "Treatment adaption" as follows:
  - All changes implemented: Acceptance of all advice from cardiologist regarding change.
  - No changes implemented: Non-acceptance of all cardiologist's change advice.
  - Changes partially implemented: Acceptance of at least one and non-acceptance of at least one cardiologist's change advice.

Table S1: **Study objectives**

Primary objectives
To assess if NT-proBNP measurement-guided cardiologist referral of patients with chronic HF, who are currently judged by their PCP as being clinically stable[a], leads to optimisation of HF treatment, defined as adherence[b] to level I-A treatment recommendations of the current[c] ESC guidelines for the treatment of HF.
Secondary objectives
To describe the baseline demographic and clinical characteristics, as well as pharmacological and device treatment, of patients with chronic HF managed in the primary care setting (in the total population of enrolled patients and also further characterised by European country and patient characteristics).
To assess, in clinically stable patients, the impact of patients' key baseline characteristics on cardiologists' and PCPs' prescription practice for HF treatment, and adherence of these treatment choices to the recommendations of the current ESC guidelines.
To describe the blood levels of NT-proBNP in patients with chronic HF managed in the primary care setting.
To describe the proportion of patients with chronic HF managed in the primary care setting who are considered as being clinically stable according to the above definition.
To describe local prescription practice of cardiologists for the treatment of clinically stable patients with chronic HF and NT-proBNP levels ≥600 pg/mL.
To describe local prescription practice and decision making of PCPs for the treatment of clinically stable patients with chronic HF and NT-proBNP levels ≥600 pg/mL.

To characterise how treatment optimisation, defined as prescription of treatment regimens adherent to the recommendations of the ESC guidelines, affects NT-proBNP levels in clinically stable patients with chronic HF and baseline NT-proBNP levels ≥600 pg/mL.
To assess baseline health-related QoL in patients with chronic HF and describe the temporal course of QoL after specialist referral in clinically stable patients with chronic HF patients with NT-proBNP ≥600 pg/mL, by means of the EuroQoL EQ-5D questionnaire and the KCCQ.

[a]Patients whose PCP did not consider it necessary to amend the ongoing HFrEF treatment during baseline visit and whose HFrEF treatment had not changed in the 3 months prior to the baseline visit.

[b]Prescription of all HF-specific drugs with level I-A recommendation for a given patient's clinical status at a dose ≥50% of the recommended daily dose.

[c]As recommended by the ESC guidelines available at the time of patient recruitment.

ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCP, primary care physician; QoL, quality of life.

Table S2: **Analysis sets by country (all patients)**

Countries	Number of investigators	Average number of patients recruited (min, max)	Inclusion in final analysis, n (%)	Enlisted Set, n (%)	Follow-up Set, n (%)
Russia	12	18.8 (4, 40)	226 (16)	226 (16)	173 (20.1)
Belgium	45	4.6 (1, 14)	201 (14.2)	201 (14.2)	114 (13.2)
Croatia	18	9.4 (1, 23)	169 (11.9)	169 (11.9)	95 (11.0)
Slovenia	17	7.2 (1, 16)	122 (8.6)	122 (8.6)	72 (8.4)
Poland	24	5.0 (1, 13)	120 (8.5)	120 (8.5)	74 (8.6)
Lithuania	7	14.7 (4, 43)	103 (7.3)	103 (7.3)	65 (7.5)
Hungary	15	6.2 (1, 16)	4 (6.9)	4 (6.9)	58 (6.7)
France	25	3.6 (1, 9)	89 (6.3)	89 (6.3)	54 (6.3)
Spain	20	3.8 (1, 11)	76 (5.4)	76 (5.4)	30 (3.5)
Norway	11	5.3 (2, 11)	58 (4.1)	58 (4.1)	33 (3.8)
Cyprus	2	18.0 (10, 26)	36 (2.5)	36 (2.5)	20 (2.3)
Latvia	6	5.7 (3, 9)	34 (2.4)	34 (2.4)	22 (2.6)
Malta	3	8.7 (1, 20)	26 (1.8)	26 (1.8)	17 (2)
Estonia	5	3.6 (2, 5)	18 (1.3)	18 (1.3)	16 (1.9)

Denmark	2	9.5 (9, 10)	19 (1.3)	19 (1.3)	4 (0.5)
Portugal	7	1.9 (1, 4)	13 (0.9)	13 (0.9)	6 (0.7)
Israel	1	7.0 (NA)	7 (0.5)	7 (0.5)	4 (0.5)
Italy	3	1.3 (1, 2)	4 (0.3)	4 (0.3)	4 (0.5)

Table S3: **Comorbid diseases at baseline (>4% of patients in the follow-up set)**

Parameter	Enlisted set N=1415	Follow-up set N=861
Hypertension	1047 (74.2)	652 (75.8)
Dyslipidaemia	868 (61.6)	505 (58.8)
History of myocardial infarction	619 (43.9)	381 (44.4)
Atrial fibrillation	575 (40.8)	450 (52.3)
Obesity (BMI ≥30 kg/m^2)	509 (36.1)	265 (30.8)
Stable angina pectoris	443 (31.4)	291 (33.8)
Type 2 diabetes mellitus	421 (29.9)	271 (31.5)
COPD	184 (13.0)	120 (14.0)
Renal disease (other)	160 (11.3)	121 (14.1)
Depression	142 (10.1)	75 (8.7)
Renal disease (due to hypertension)	135 (9.6)	94 (10.9)
Tachyarrhythmia	134 (9.5)	85 (9.9)
Peripheral vascular disease	131 (9.3)	95 (11.1)
Prior stroke	127 (9.0)	85 (9.9)
Carotid artery stenosis	118 (8.4)	88 (10.2)
Anaemia	114 (8.1)	74 (8.6)
Hypothyroidism	101 (7.2)	68 (7.9)
Previous/current malignant disease	96 (6.8)	58 (6.8)
Renal disease (due to diabetes)	82 (5.8)	62 (7.2)
Osteoporosis	69 (4.9)	47 (5.5)
Asthma	61 (4.3)	41 (4.8)
Peripheral neuropathy (any aetiology)	61 (4.3)	35 (4.1)
Prior transient ischaemic attack	60 (4.3)	44 (5.1)
Sleep apnoea	60 (4.3)	31 (3.6)
Steatohepatitis	60 (4.3)	34 (4.0)

Data are presented as n (%).

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table S4: **HF-related use of medical resources at baseline**

Parameter	Enlisted set N=1415	Follow-up set N=861
Medical resources used, n (%)		
Hospitalised due to HF	383 (27.1)	262 (30.4)
ED without hospitalisation	91 (6.4)	67 (7.8)
HF outpatient clinic or cardiologist	628 (44.4)	363 (42.2)
Hospitalisations due to HF		
N	379	261
Mean (SD)	1.4 (1.0)	1.4 (1.1)
Median (range)	1 (1–12)	1 (1–12)
ED visits without hospitalisation		
N	89	65
Mean (SD)	1.2 (0.5)	1.2 (0.5)
Median (range)	1 (1–3)	1 (1–3)
Number of HF outpatient clinic or cardiologist visits		
N	618	358
Mean (SD)	2.1 (2.7)	1.9 (1.6)
Median (range)	1 (1–50)	1 (1–11)

ED, emergency department; HF, heart failure; SD, standard deviation.

Table S5: LVEF in enrolled patients at visits 1, 2, and 3

LVEF	**N**	**Mean (SD)**
LVEF (%) at visit 1	582	33.8 (8.1)
LVEF (%) at visit 2	210	39.2 (13.6)
LVEF (%) at visit 3	46	37.7 (13.9)

LVEF, left ventricular ejection fraction; SD, standard deviation.

Table S6: Adherence to ESC guidelines (by region)

	Drug type		Drug type and dose	
Visit type	**Western EU**	**Eastern EU**	**Western EU**	**Eastern EU**
Baseline visit, n (%)	15 (8.9)	44 (10.6)	6 (3.6)	10 (2.4)
Post-referral visit, n (%)	13 (9.9)	44 (11.6)	6 (4.6)	11 (2.9)
Final visit, n (%)	8 (9.2)	36 (12.0)	4 (4.6)	10 (3.3)
Post-referral visit (patients non-adherent at baseline visit), n (%)	3 (2.6)	12 (3.5)	1 (0.8)	3 (0.8)
Post-referral visit (patients adherent at baseline), n (%)	10 (71.4)	32 (82.1)	5 (83.3)	8 (88.9)

Data presented are n (%).

Western EU: Norway, Denmark, Belgium, France, Spain, Portugal, Italy, Malta.

Eastern EU: Russia, Hungary, Poland, Lithuania, Latvia, Estonia, Cyprus, Croatia, Slovenia, Israel.

ESC, European Society of Cardiology; EU, European Union.

Table S7: **Adherence to ESC guidelines[a] (supportive analyses)**

Adherence to ESC guidelines	Baseline visit				Post-referral visit		Final visit	
	Enlisted set (n=1415)		Follow-up set (n=861)		Follow-up set (n=753)		Follow-up set (n=573)	
	Level 1[b]	Level 2[c]	Level 1[b]	Level 2[c]	Level 1[b]	Level 2[c]	Level 1[b]	Level 2[c]
Without considering HF[d]	156 (17.1)	-	84 (14.4)	-	78 (15.3)	-	55 (14.2)	-
Missing LVEF defined as LVEF >35%[e]	176 (12.4)	67 (4.7)	94 (10.9)	32 (3.7)	85 (11.3)	28 (3.7)	65 (11.3)	24 (4.2)
Only assessing ACEI/ARB and β-blockers[f]	195 (21.4)	62 (6.8)	111 (19.1)	33 (5.7)	107 (21.0)	33 (6.5)	80 (20.7)	26 (6.7)

Data are presented as n (%) and mean (SD).

[a]As recommended by the ESC guidelines available at the time of patient recruitment.

[b]Treatment with an ACEI or sacubitril/valsartan or an ARB (only HF treatment), in combination with a β-blocker and an MRA for patients with an LVEF ≤35% at baseline visit. Treatment with an ACEI (only HF treatment) or sacubitril/valsartan or an ARB, in combination with a β-blocker but without an MRA for patients with an LVEF >35% at baseline visit.

[c]Guideline adherence with respect to drug types and dosage of all respective guideline-defined drugs ≥50% of the recommended target dose.

[d]Patients treated with drugs lacking HFrEF indication/evidence (target dose in HFrEF unknown).

[e]The missing values for LVEF at baseline were replaced by '>35'; therefore, the respective patients could be included in the analysis.

[f]Sensitivity analysis with adherence to ESC guideline recommendations in patients with LVED and without considering intake of one MRA.

ACEI, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

Table S8: **Vital signs and eGFR by visit (follow-up set)**

Parameter	Baseline visit	Post-referral visit	Final visit
Heart rate (bpm), mean ± SD (N)	72.6 ± 11.6 (858)	72.0 ± 10.6 (749)	71.9 ± 10.9 (571)
Systolic blood pressure (mmHg), mean ± SD (N)	126.8 ± 17.2 (861)	124.8 ± 15.7 (750)	124.3 ± 15.5 (571)
<100 mmHg, % (n/N)	3.5 (30/861)	3.3 (28/861)	3.3 (28/861)
Diastolic blood pressure	75.3 ± 11.0 (861)	74.5 ± 9.9 (750)	74.2 ± 9.2 (571)
Plasma potassium[a] % (n/N)			
≤5.5 mmol/L	95.3 (696/730)	92.0 (219/238)	95.7 (177/185)
>5.5 mmol/L	4.7 (34/730)	8.0 (19/238)	4.3 (8/185)
eGFR according to MDRD (mL/min) , mean ± SD (N)	66.5 ± 29.6 (774)	57.6 ± 28.8 (245)	60.5 ± 28.9 (178)
<30 mL/min/m^2, % (n/N)	5.2 (40/774)	15.1 (36/239)	13.6 (24/176)
≥30 mL/min/m^2, % (n/N)	94.8 (734/774)	84.9 (203/239)	86.4 (152/176)

bpm, beats per minute; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SD, standard deviation.

Table S9: **Rates of adverse events**

Parameter	**Follow-up set (N=861)**
Any adverse event	256 (29.7)
Any serious adverse event	114 (13.2)
Any fatal event[a]	30 (3.5)

Data presented are n (%).

[a]N=852.