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ORIGINAL RESEARCH ARTICLE

# Real-world clinical diagnostics of heart failure patients with reduced or preserved ejection fraction

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## Abstract

**Aims** The study aimed at investigating the use of guideline-recommended diagnostic tools and medication in patients with heart failure (HF) in specialty care in Southwest Finland. We also compared the characteristics of the diagnosed and undiagnosed patients as well as laboratory tests, procedures, and treatments in everyday clinical practice.

**Methods and results** Patients diagnosed with HF, cardiomyopathy, or hypertension-induced heart disease ($n$ = 20 878, primary cohort) or not diagnosed with HF but having a record of elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) (>125 ng/L, $n$ = 24 321, secondary cohort) were included in the study from the specialty care patient register of the Hospital District of Southwest Finland during the years 2005–2017. Among patients with an International Classification of Diseases, Tenth Revision (ICD-10) code for HF, only 50% had ejection fraction (EF) data to be found by data mining from the electronic health records. Of these patients, 39% ($n$ = 4042) had EF $\leq$ 40% [HF with reduced EF (HFrEF)] and 61% ($n$ = 6347) had EF $>$ 40%. Elevated NT-proBNP together with EF $>$ 40% narrowed down the number to 4590 patients, a population defined as HF with preserved EF (HFpEF) patients. HFpEF patients were further stratified into HF with mildly reduced EF (HFmrEF; EF 41–50%, $n$ = 1468) and EF $>$ 50% patients ($n$ = 3122) to compare clinical characteristics. NT-proBNP was higher within the HFrEF patients vs. HFpEF {4580 [inter-quartile range (IQR): 2065–9765] vs. 2900 [2065–9765] ng/L, $P < 0.001$}. Baseline co-morbidities differed between HFpEF and HFrEF groups. Further, HFpEF patients had more procedures and lab tests taken prior to diagnosis than had HFrEF patients. HFmrEF patients were found to resemble more HFrEF than EF $>$ 50% patients. In 70% ($n$ = 17 156) of patients in the secondary cohort, the NT-proBNP concentrations were >300 ng/L, median was 1090 (IQR 551–2558) ng/L and EF 58.4 ± 12.1% ($n$ with EF available = 6845). Reduced EF was present in 6.8% of patients lacking HF diagnosis.

**Conclusions** Half of the patients with ICD-10 code for HF did not have EF data available after a visit at specialty care. In particular, the diagnosis of HFpEF seems challenging, reflected as an increase in procedures and laboratory test preceding diagnosis compared with those in HFrEF patients. Also, a large proportion of patients did not have HF diagnosis, yet they presented elevated NT-proBNP concentrations and clinical characteristics resembling those of HFpEF patients.

**Keywords** Heart failure; Diagnosis; HFpEF; HFrEF; Real-world evidence

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## Introduction

Heart failure (HF) has a typical clinical manifestation of dyspnoea, ankle swelling, and fatigue resulting from an abnormal cardiac structure and function.[1] The prevalence of HF is increasing worldwide, and HF is associated with a substantial health care burden, as well as morbidity and mortality.[1–4] Thus, a correct and timely diagnosis of patients with HF would be important to achieve optimal care.

Echocardiography is the most commonly used and widely available diagnostic tool in patients with suspected HF to establish the diagnosis. It provides immediate information on chamber volumes, systolic and diastolic ventricular function, wall thickness, valve function, and pulmonary hypertension.[1,5–7] The diagnosis of HF emphasizes also the initial

assessment of N-terminal pro-brain natriuretic peptide (NT-proBNP), with a negative cut-off value of 125 ng/L in non-acute patients and 300 ng/L in acute patients presenting symptoms and clinical features of HF.[1,8]

Treatment of HF with reduced ejection fraction (HFrEF) with angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), or angiotensin receptor–neprilysin inhibitor (ARNI) and mineralocorticoid receptor antagonist (MRA) have been shown to reduce mortality and hospitalizations, but there is a lack of similar evidence in HF with preserved EF (HFpEF).[9] Specific treatment guidelines for HFpEF do not exist, and the care mainly focuses on treating hypertension, volume overload, and co-morbidities and symptoms. However, some benefit on HFpEF outcomes may be indicated with MRA treatment,[9,10] and at least population with EF $>$ 57% may benefit from treatment with ARNI.[11]

HF is surrounded by many uncertainties, such as delayed or lack of diagnosis. These uncertainties are present especially among patients with HFpEF, and new treatments are under investigation for this patient group. Research is needed to better characterize HF and its clinical diagnosis, in order to increase the understanding of diagnostics, and to accelerate the progress of new treatments. In this study, we investigated the current HF diagnosis praxis and utilization of recommended diagnostic tools, as well as medication patterns in patients with HFpEF, HFrEF, and elevated NT-proBNP.

# Methods

Patients were included to this retrospective, register-based study during the years 2005–2017 from the specialty care electronic patient register of the Hospital District of Southwest Finland. The study was approved by the Turku University Hospital administration (permission number 118/2018) and was conducted in accordance with the Declaration of Helsinki.[12] Inclusion criteria were one of the following: International Classification of Diseases, Tenth Revision (ICD-10) codes as any diagnosis: HF (I50), cardiomyopathies (I42.0, I42.6, I42.8, and I42.9), hypertension-induced heart disease (I11.0, I13.0, and I13.2), and EF data and NT-proBNP $>$ 125 ng/L for patients with EF $>$ 40% (primary cohort); or NT-proBNP concentration $>$ 125 ng/L (secondary cohort).

Index date was the first date when the patient fulfilled any of the inclusion criteria, and patients were followed up from that date onwards until 31 December 2017 or death. For each patient, data on left ventricular EF (LVEF) was extracted through text mining. In accordance with the first Finnish national HF guideline from 2017, LVEF of 40% was used as cut-off value for HFrEF and HFpEF.[8] Utilization of electrocardiogram (ECG) was assessed from procedure codes and noted as performed/not performed. Co-morbidities were assessed from diagnosis codes (ICD-10) given at specialty care at baseline. Patients were divided into subgroups as presented in *Figure 1*. Shortly, patients included with an ICD-10 diagnosis presenting with reduced LVEF ($\leq$ 40%) were classified as HFrEF. The remaining patients with an available EF (EF $>$ 40%), and elevated NT-proBNP were defined as HFpEF patients in this study. Moreover, those lacking the inclusion diagnoses, but presenting with elevated NT-proBNP, were included into the secondary cohort. The secondary cohort was formed to be able to compare the clinical characteristics of patients who have elevated NT-proBNP value but have not been diagnosed with HF by ICD code with those of patients who have been diagnosed with HF by I50 code (primary cohort).

## Medication

Electronic prescriptions have been used comprehensively in the Hospital District of Southwest Finland since 2010. Thus, all medication-related analyses were restricted to the subpopulation of HF patients, with an index date of 1 January 2010 or later. A predefined set of drugs prescribed at the hospital for inpatient care or prescribed from the hospital for outpatient care [Anatomic Therapeutic Chemical (ATC) codes: C01*, C03A*, C03B*, C03C*, C03DA*, C03DB*, C03E*, C03X*, C07*, C09A*, C09B*, C09C*, and C09D*] was assessed at 6 months, 2 years, and 5 years after index. For the analysis of ACE-Is or ARBs, beta-blockers (BBs), and diuretics, ATC codes were pooled to an upper level. For the analysis of treatment combinations, drug prescriptions were required to have overlapping dates in the electronic prescription register of the hospital.

## Statistical analyses

For continuous variables, mean values and standard deviation (SD) were reported (or median and 25% and 75% quartiles for skewed variables). For categorical variables, the number of patients and proportion was reported. Differences between groups were tested using non-parametric Kruskal–Wallis test (continuous variables) or $\chi^2$ test (categorical variables), where appropriate.

# Results

A total of 45 199 patients with a specialty care visit at the Hospital District of Southwest Finland were identified as potential HF patients. Out of these, 46% ($n$ = 20 878) were included to the primary cohort on the basis of the pre-selected ICD-10 codes (diagnostic code for HF) and 54% ($n$ = 24 321) to the secondary study cohort on the basis of an elevated NT-proBNP ($>$125 ng/L) (*Figure 1*). In the primary cohort, HF (I50) was the inclusion code for 92.3% of patients,

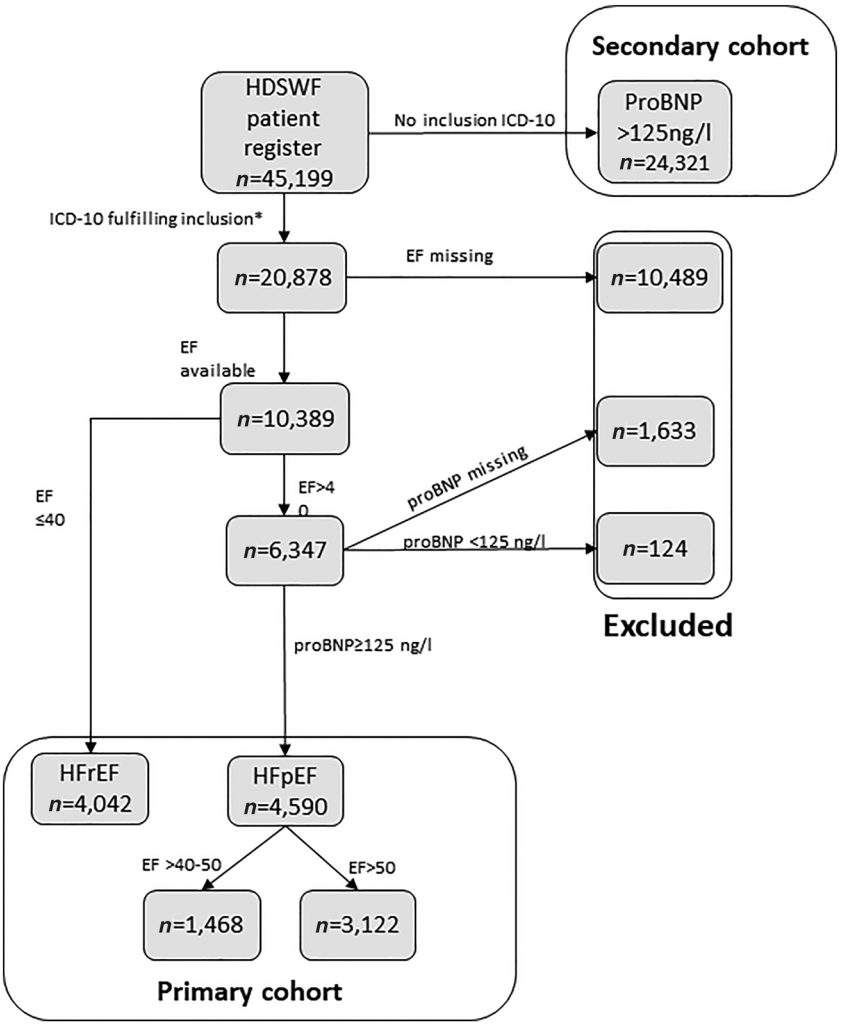


**Figure 1** Study cohort formation. Patients in the primary cohort had one of the inclusion International Classification of Diseases, Tenth Revision (ICD-10) codes as any diagnosis (*I42.0, I42.6, I42.8, I42.9, I11.0, I13.0, I13.2, and I50), left ventricular ejection fraction (EF) ≤ 40% or EF > 40% and elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) (>125 ng/L) at index. Heart failure with preserved EF (HFpEF) patients were further stratified into EF 41–50% or >50%. Patients lacking the above-mentioned ICD-10 codes but presenting elevated NT-proBNP (>125 ng/L) were included to the secondary cohort.

and 7.6% were included based on other ICD-10 codes (cardiomyopathy: I42.0, I42.6, I42.8, and I42.9; hypertension-induced heart disease: I11.0, I13.0, and I13.2).

In the primary cohort, 49.8% ($n$ = 10 389) of patients had an EF measurement available from the electronic medical records (EMRs). Of these, EF was reduced in 39% (EF ≤ 40%, $n$ = 4042) and preserved EF in 61% of patients (EF > 40%, $n$ = 6347) (*Figure 1*). To further define these as HFpEF patients in this study, NT-proBNP concentration > 125 ng/L was required. This excluded an additional 28% of the patients, leading to a final HFpEF cohort of 4590 patients (*Figure 1*). Patients who could be defined as HFrEF or HFpEF patients according to the above-mentioned criteria formed the primary cohort of this study. Within the patients with HFpEF/HFrEF, 72% had echocardiography marked by procedure coding, and for the rest, EF value was found as unstructured data. The frequency of marked echocardiography procedure codes increased in the primary cohort from 64% in year 2005 to >83% in 2017.

The primary cohort was further characterized by assessing NT-proBNP concentrations. As described previously in the literature,[1,13] we also found that the median NT-proBNP was higher in the HFrEF vs. HFpEF patients {4580 [inter-quartile range (IQR): 2065–9765] vs. 2900 [2065–9765] ng/L, $P < 0.001$, *Table 1*}. In 95.6% of HFpEF and 97.9% of HFrEF patients, NT-proBNP was >300 ng/L. The distribution of NT-proBNP values is presented in *Figure 2*.

HFpEF was more frequent in women (HFpEF vs. HFrEF: 52% vs. 37%, $P < 0.001$), and HFpEF patients were on average 4 years older at diagnosis than HFrEF patients (*Table 1*). Within the HFpEF group, those with mildly reduced EF (41–50%, $n$ = 1468) displayed more similarities to HFrEF, than

**Table 1** Baseline characteristics of patients in the primary cohort (±6 months from diagnosis) and secondary cohort

| Variable | Primary cohort | | | | | | Secondary cohort |
|---|---|---|---|---|---|---|---|
| | HFpEF (EF > 40) | HFrEF (EF < 40) | $P^a$ | EF 41–50 | EF > 50 | $P^b$ | High BNP |
| *n* | 4590 | 4042 | — | 1468 | 3122 | — | 24 321 |
| Female, *n* (%) | 2381 (51.9%) | 1242 (30.7%) | <0.001 | 626 (42.6%) | 1755 (56.2%) | <0.001 | 12 366 (50.8%) |
| Age, years | 74.88 (11.2) | 70.76 (12.2) | <0.001 | 74.21 (11.6) | 75.2 (11) | 0.005 | 71.87 (12.9) |
| EF, mean (SD) | 57.53 (9.9) {0%} | 31.29 (7) {0%} | 0 | 46.56 (2.8) | 62.7 (7.5) | 0 | 59.81 (11.5) {60.1%} |
| NT-proBNP (ng/L) | 2900 [1280–6230] {0%} | 4580 [2065–9765] {23.3%} | <0.001 | 3470 [1510–7515] {0%} | 2700 [1200–5785] {0%} | <0.001 | 617 [262–1710] {0%} |
| NT-proBNP < 125 ng/L, *n* (%) | 0 (0%) | 30 (0.7%) | — | 0 (0%) | 0 (0%) | — | 0 (0%) |
| NT-proBNP < 300 ng/L, *n* (%) | 204 (4.4%) | 85 (2.1%) | — | 46 (3.1%) | 158 (5.1%) | — | 7165 (29.5%) |
| Haemoglobin (mg/L) | 125 [110–139] {0.4%} | 134 [119–147] {1.6%} | <0.001 | 127 [113–141] {0.6%} | 123 [109–137] {0.3%} | <0.001 | 130 [116–142] {3.8%} |
| Potassium (mmol/L) | 4.1 [3.8–4.5] {0.3%} | 4.1 [3.8–4.4] {1%} | 0.001 | 4.1 [3.8–4.4] {0.6%} | 4.1 [3.8–4.5] {0.2%} | 0.285 | 4 [3.8–4.3] {4.8%} |
| C-reactive protein (mg/L) | 10 [4–33] {3.5%} | 10 [4–28] {8.7%} | 0.019 | 10 [4–28.5] {4.7%} | 10 [4–35] {2.9%} | 0.101 | 10 [2–50] {9.8%} |
| Creatinine (μmol/L) | 88 [71–115] {0.3%} | 92 [76–115] {1%} | <0.001 | 91 [74–117] {0.3%} | 86 [70–114] {0.2%} | <0.001 | 81 [67–100] {3.7%} |
| CKD-EPI eGFR (mL/min/1.73 $m^2$) | 63.71 [45.5–81.4] {0.3%} | 66.57 [48.9–83.4] {1%} | <0.001 | 62.65 [46.3–79.7] {0.3%} | 64.2 [44.9–82.1] {0.2%} | 0.409 | 72.88 [55–87.5] {3.7%} |
| CKD1 (eGFR > 90) | 604 (13.2%) | 654 (16.2%) | <0.001 | 181 (12.3%) | 423 (13.5%) | 0.313 | 4864 (20%) |
| CKD2 (eGFR 60–90) | 1951 (42.5%) | 1753 (43.4%) | | 622 (42.4%) | 1329 (42.6%) | | 11 168 (45.9%) |
| CKD3 (eGFR < 60–30) | 1575 (34.3%) | 1303 (32.2%) | | 528 (36%) | 1047 (33.5%) | | 5915 (24.3%) |
| CKD5 (eGFR 30–15) | 349 (7.6%) | 218 (5.4%) | | 106 (7.2%) | 243 (7.8%) | | 938 (3.9%) |
| CKD5 (eGFR < 15) | 99 (2.2%) | 73 (1.8%) | | 26 (1.8%) | 73 (2.3%) | | 546 (2.2%) |
| CKD missing, *n* (%) | 12 (0.3%) | 41 (1%) | | 5 (0.3%) | 7 (0.2%) | | 890 (3.7%) |
| ECG procedure code, *n* (%) | 2191 (47.7%) | 1941 (48%) | 0.807 | 744 (50.7%) | 1447 (46.3%) | 0.007 | 8311 (34.2%) |
| ECHO procedure code, *n* (%) | 3311 (72.1%) | 2871 (71%) | 0.266 | 1054 (71.8%) | 2257 (72.3%) | 0.754 | 8168 (33.6%) |

Data presented as frequency in population (%), mean (SD), or median [25th–75th quartile]. Additionally, the per cent with missing data {%} is presented.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ECG, electrocardiography; ECHO, echocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.
[a]*P*-value for HFpEF vs. HFrEF.
[b]*P*-value for HFmrEF (EF 41–50) vs. EF > 50.

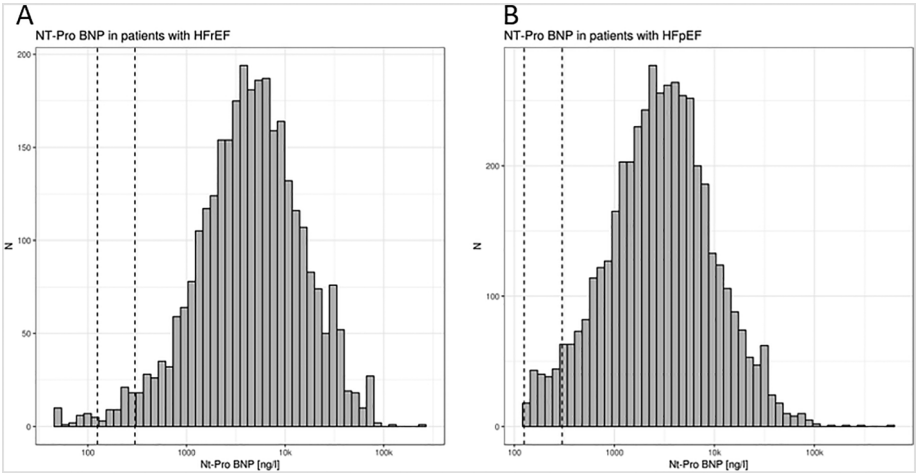


**Figure 2** Distribution of N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations (ng/L) in the primary cohort stratified by ejection fraction data to heart failure with reduced (A) or preserved ejection fraction (B). Dashed lines represent NT-proBNP 125 and 300 ng/L cut-offs.

did those with EF > 50% (*n* = 3122) by presenting higher concentrations of NT-proBNP and lower female prevalence (*Table 1*).

The secondary cohort consisted of patients who did not have an ICD-10 HF diagnosis but had elevated NT-proBNP. In the secondary cohort, the mean age was 71.9 ± 12.9, and the median NT-proBNP 617 (IQR: 262–1710) ng/L and EF 59.8 ± 11.5% (*n* with EF available = 9706). In 71% (*n* = 17 156) of the secondary cohort patients, NT-proBNP was >300 ng/L, mean age 73.6 ± 12.5, median NT-proBNP 1090 (551–2558) ng/L and EF 58.4 ± 12.1% (*n* with EF available = 6845). EF ≤ 40% was noted in 498 (5.1%) and 464 (6.8%) patients with NT-proBNP > 125 and >300 ng/L, respectively. Within both NT-proBNP cut-off values (>125/>300 ng/L), 51/50% of patients were female (*Table 1*).

We also shortly characterized the patient population that had ICD-10 code for HF but no EF value available (*n* = 10 489, *Table* S1). Briefly, the mean age of this population was 82 years, they were mostly women (61.3%), and the NT-proBNP value measured from 51.3% of the patients was on average 3470 ng/L.

Taken together, HFrEF and HFpEF patients differed from each other with HFpEF patients having lower NT-proBNP concentrations, being younger, and more often female. HFmrEF patients seemed to resemble more HFrEF than did HFpEF patients. It is notable that the secondary cohort had >6000 patients resembling validated HFpEF patients by their clinical characteristics but not having a diagnosis for HF.

## Co-morbidities

At baseline, differences in the co-morbidities/co-diagnoses at specialty care were evident between HFpEF and HFrEF patients (*Table 2*). Of the 15 most common diagnoses, ischaemic heart disease and myocardial infarction were more commonly diagnosed in patients with HFrEF ($P < 0.001$), whereas HFpEF patients were more frequently diagnosed with, for example, essential hypertension, atrial fibrillation and flutter, pneumonia, and abnormalities of breathing ($P < 0.001$, *Table 2*). Within HFpEF, patients with EF 41–50% vs. EF > 50% were less frequently diagnosed with essential hypertension, but more often with chronic ischaemic heart disease and acute myocardial infarction (*Table 2*). In the secondary cohort, the most common co-morbidities were essential hypertension, atrial fibrillation, and chronic ischaemic heart disease, but these were less prevalent than in HFrEF or HFpEF cohorts. Approximately five per cent of the patients had any type of a cardiac pacemaker at the baseline (*Table* S2). The type of the cardiac pacemaker could not be specified from the structured patient records. The presence of a cardiac pacemaker or the adjustment and management of cardiac pacemaker in the baseline did not differ between HFrEF and HFpEF patients or between EF 41–50% patients and EF > 50% patients (*Table* S2). In the end of the follow-up, it was more common for the HFrEF patients to have a pacemaker than for the HFpEF patients (16.9% vs. 11.2%, $P < 0.001$) and also for the EF 41–50% patients to have a pacemaker compared with EF > 50% patients (14.2% vs. 11.2%, $P = 0.005$) (*Table* S2). A larger proportion of HFrEF patients also had adjustment and management performed to the pacemaker compared with that of HFpEF patients (11.9% vs. 7.4%, $P < 0.001$) (*Table* S2). In the secondary cohort, 1.9% of the patients had a cardiac pacemaker in the baseline, and this proportion increased to 5.1% by the end of the follow-up (*Table* S2).

## Pre-diagnostic assessment

The most common procedure within the 6 months preceding diagnosis was ECG, performed in 37.4% of patients in the

**Table 2** Baseline diagnoses given at specialty care to the primary cohort stratified by ejection fraction to heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, and heart failure with mildly reduced ejection fraction and to the secondary cohort

| | | Primary cohort | | | | | | | Secondary cohort |
|---|---|---|---|---|---|---|---|---|---|
| ICD10 | Description | All | HFpEF (%) | HFrEF (%) | $P^a$ | HFmrEF (%) | EF > 50 (%) | $P^b$ | High BNP (%) |
| I50 | Heart failure | 92.9 | 96.1 | 89.4 | <0.001 | 94.8 | 96.7 | 0.002 | 0.0 |
| I10 | Essential (primary) hypertension | 48.1 | 55.4 | 39.8 | <0.001 | 49.8 | 58.1 | <0.001 | 39.4 |
| I48 | Atrial fibrillation and flutter | 45.3 | 49.9 | 40.1 | <0.001 | 50.2 | 49.7 | 0.780 | 23.0 |
| I25 | Chronic ischaemic heart disease | 33.0 | 29.5 | 37.0 | <0.001 | 36.3 | 26.4 | <0.001 | 17.1 |
| E11 | Non-insulin-dependent diabetes mellitus | 25.0 | 25.9 | 23.9 | 0.032 | 26.2 | 25.8 | 0.816 | 14.5 |
| I21 | Acute myocardial infarction | 22.2 | 19.0 | 26.0 | <0.001 | 24.2 | 16.5 | <0.001 | 13.6 |
| H25 | Senile cataract | 17.5 | 21.8 | 12.7 | <0.001 | 20.7 | 22.4 | 0.221 | 16.5 |
| J18 | Pneumonia, organism unspecified | 17.5 | 20.3 | 14.3 | <0.001 | 16.5 | 22.0 | <0.001 | 15.0 |
| Z01 | Other special examinations and investigations of persons without complaint or reported diagnosis | 17.2 | 21.1 | 12.6 | <0.001 | 19.6 | 21.8 | 0.092 | 20.8 |
| E78 | Disorders of lipoprotein metabolism and other lipidaemias | 15.4 | 16.4 | 14.3 | 0.006 | 16.6 | 16.4 | 0.862 | 13.2 |
| R06 | Abnormalities of breathing | 13.8 | 16.6 | 10.7 | <0.001 | 14.0 | 17.8 | 0.002 | 10.5 |
| Z95 | Presence of cardiac and vascular implants and grafts | 12.9 | 12.9 | 13.0 | 0.875 | 14.1 | 12.3 | 0.099 | 5.7 |
| Z03 | Medical observation and evaluation for suspected diseases and conditions | 11.8 | 14.5 | 8.7 | <0.001 | 13.4 | 15.1 | 0.138 | 14.6 |
| I35 | Non-rheumatic aortic valve disorders | 11.0 | 14.1 | 7.6 | <0.001 | 12.2 | 14.9 | 0.015 | 5.0 |
| I20 | Angina pectoris | 10.8 | 11.7 | 9.7 | 0.004 | 12.8 | 11.2 | 0.121 | 8.7 |

[a]*P*-value for HFpEF vs. HFrEF.
[b]*P*-value for EF 41–50% vs. EF > 50%.

primary cohort (*Table* S3). Many procedures were more common in HFpEF than in HFrEF, for example, thorax X-ray (30 vs. 23%, $P < 0.001$) and extensive ultrasound examination of the heart (21 vs. 18%, $P < 0.001$, *Table* S3). In other procedures, the differences in frequency between HFpEF and HFrEF, as well as between EF 41–50% and EF > 50%, were minor. In addition to NT-proBNP concentration measurements being more frequent in HFpEF vs. HFrEF (72 vs. 54%, $P < 0.001$), other common laboratory tests, for example, creatinine, blood counts, and C-reactive protein, showed the same pattern (*Table* S4).

## Medication

Differences were observed in the level of medication use between HFrEF and HFpEF patients, in both inpatient and outpatient care. ACE-I or ARBs combined with BB for inpatient care were prescribed more frequently to HFrEF, than to HFpEF patients, at 6 months, 2 years, and 5 years after diagnosis (*Figure 3*A and B). During the first 6 months after the index date, 43% of HFpEF and 62% of HFrEF ($P < 0.001$) had received ACE-I/ARB in combination with BB at the hospital. Outpatient prescriptions of ACE-I/ARB and BB from the hospital were also less frequent in HFpEF vs. HFrEF (14% vs. 32%, $P < 0.001$) during the first 6 months after index date.

The same patterns were evident when assessing patients prescribed with diuretics on top of ACE-I/ARB and BB, where the frequency of both inpatient and outpatient prescriptions increased over time in both HFpEF and HFrEF patients (*Figure 3*A and B). Outpatient prescriptions of MRA were more frequent in HFrEF vs. HFpEF at 6 months (19.8 vs. 7.2%, $P < 0.001$), 2 years (23.2 vs. 9.4%, $P < 0.001$), and 5 years (24.6 vs. 10.8%, $P < 0.001$) after the index date. Inpatient prescriptions of MRA were similarly more common in HFrEF than HFpEF (6 months 30.3% vs. 14.5%; 2 years 35.0% vs. 19.4%; 5 years 37.7% vs. 22.4%, $P < 0.001$ for all time points).

HF medication (ACE-I/ARB, BB, and diuretics) prescribed in or from the hospital for inpatient or outpatient setting for the primary cohort (HFpEF and HFrEF patients) differed significantly from those prescribed to the patients having an ICD-10 code for HF but no EF data available (primary cohort vs. missing EF group, $P < 0.001$ for all drug combinations at all time points). Differences were also evident when comparing the primary and secondary cohorts (primary cohort vs. high NT-proBNP group, $P < 0.001$ for all drug combinations in all time points) in all time points assessed (*Figure 3*C and D).

# Discussion

In this study, the real-world diagnostic patterns and characteristics of patients with HFpEF/HFrEF and elevated NT-proBNP were investigated. The population catchment of the utilized medical record is 480 000 persons, which is ~9%

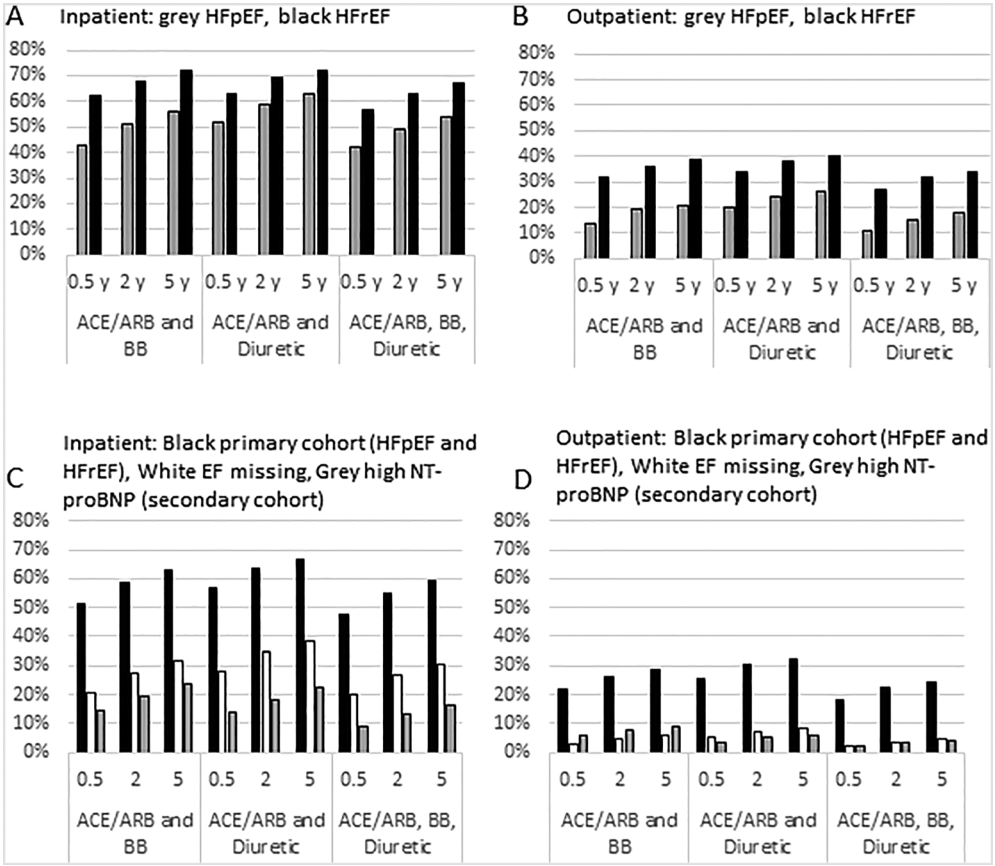


**Figure 3** Inpatient (A) and outpatient (B) medication of angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) in combination with beta-blocker (BB) or diuretic, or their combination in patients with heart failure with preserved ejection fraction (HFpEF) (grey bars) and HF with reduced EF (HFrEF) (black bars) at 0.5, 2, and 5 years after diagnosis. Significance indicated between HFpEF and HFrEF groups, $*P < 0.001$. Inpatient (C) and outpatient (D) medication of ACE-I or ARB in combination with BB or diuretic, or their combination in patients in the primary cohort (HFrEF and HFpEF patients, black bars), patients with ICD code for HF but no EF data available (white bars), and patients with high NT-proBNP but no International Classification of Diseases, Tenth Revision (ICD-10) code for HF (secondary cohort, grey bars) at 0.5, 2, and 5 years after diagnosis. All differences between HFpEF and HFrEF groups in (A) and (B), $P < 0.001$; all differences between primary cohort and EF missing group in (C) and (D) $P < 0.001$; all differences between the primary and secondary cohorts in (C) and (D) $P < 0.001$.

of the entire Finnish population. Thus, these results may be considered representative to the Finnish population.

## Diagnosis

Among the 20 878 patients included to the study with a diagnosis code, the majority were diagnosed with HF, whereas cardiomyopathy or hypertension-induced heart disease were inclusion codes for <10% of patients. EF is the cornerstone of guideline-recommended diagnostic tools for supporting HF diagnosis.[8] Nevertheless, based on these data, EF data were available for only 50% of the patients with an ICD-10 HF diagnosis. The average age of patients with a diagnosis code for HF but no EF data available was 82 years. For many of these patients, the more precise diagnostic measurements might not have changed the treatment decisions, and this might have guided the clinical decision for not to perform echocardiographic assessment. Also, it needs to be noted that in this study, the EF value was searched from the electronic patient journals, and we cannot overrule the possibility that some of the patients might have had echocardiographic data, but we have not been able to find it.

Interestingly, half of the patients with an ICD-10 code for HF and no EF value available also lacked NT-proBNP measurement. This might indicate that the diagnosis was given with symptoms and signs of HF but no further diagnostic measurements performed. According to the current guidelines,[1,8,9] NT-proBNP should be used as a rule-out method in HF diagnostics. However, 26% of patients having ICD-10 code for HF and EF > 40% were excluded from the primary cohort because no NT-proBNP measurement was

available. For HFrEF diagnosis, the clinical practice in diagnostics is more straightforward; a diagnosis can be given to a patient with signs and symptoms of HF and EF $\leq$ 40% without NT-proBNP rule-out. In this study, 23.3% of HFrEF patients did not have NT-proBNP measurement to be found in their records.

Furthermore, a substantial proportion of patients with elevated NT-proBNP, characteristically resembling HFpEF patients, did not have an HF diagnosis.

The current guidelines[1,8,9] give a working algorithm to diagnose HF after the discovery of clinical signs and symptoms of HF. By following these algorithms, the correct diagnosis would most probably be achieved in a majority of patients. However, it needs to be noted that with a large patient population and sparse resources, clinical judgement needs to be performed in everyday practice in whether confirming the diagnosis with echocardiography and laboratory measurements in addition to clinical signs and symptoms would change the treatment of the patient.

Differentiation of patients with HFpEF and HFrEF based on LVEF is important owing to different underlying aetiologies, demographics, co-morbidities, and response to therapies.[1,10] An increase in echocardiography procedure codes was observed during the follow-up, likely explained by an increase in availability associated with the centralized treatment of these patients at the hospital's heart centre from 2013 onwards. Of those with EF available, 39% presented with HFrEF and 61% with HFpEF. Based on these data, a more systematic follow-up of patients and recording of the current treatment guidelines in the EMR could benefit the diagnosis.

In addition to serving diagnostics, NT-proBNP concentrations are emerging with prognostic value including all-cause and cardiovascular mortality and morbidity.[9] NT-proBNP levels are typically lower in HFpEF than HFrEF patients,[1,13] also seen in this study with a median NT-proBNP of 2900 ng/L in HFpEF vs. 4580 ng/L in HFrEF. High NT-proBNP levels have been shown to increase the risk of mortality in both HFrEF and HFpEF patients independent of LVEF.[4,13] In a previous publication on the same population, 5 year mortality was shown to be 55% for both HFpEF and HFrEF patients, even though the effect of NT-proBNP on mortality was not assessed.[14]

In 2013, American College of Cardiology/American Heart Association Guidelines for the Management of Heart Failure distributed HFrEF and HFpEF patients to have EF of $\leq$40% and $\geq$50%, respectively.[15] Also, a patient population with intermediate EF of 41–49% and with improved EF of >40% (HFpEF patients who previously were HFrEF) was determined. Even though it is stated that the patients in the intermediate EF group resemble those in HFpEF by their characteristics, treatment patterns, and outcomes, they also state that these patients are often treated with guideline-directed medical therapy similar to that used in HFrEF patients. A similar EF group, HFmrEF (EF 40–49%), was introduced in the ESC guidelines in 2016.[1] Neither of the guidelines offer specific treatment guidance for patients with EF between 40% and 50%. A recent study with HFpEF patients found that patients with EF 45–57% may benefit from medical therapy with sacubitril/valsartan, compared with patients with EF > 57%,[11] which might indicate that these patients do differ from HFpEF patients in their response to pharmacotherapy. In this study, we found that within the HFpEF group, HFmrEF patients (EF 41–50%) differed from those with EF > 50%, by higher NT-proBNP concentrations and a co-morbidity profile more resembling that of HFrEF patients (i.e. an increased frequency of chronic ischaemic heart disease and acute myocardial infarction). A larger proportion of HFmrEF patients had a cardiac pacemaker compared with those with EF > 50%, resembling more the HFrEF patients who also had more pacemakers implanted compared with EF > 50% patients. However, whether HFmrEF patients with EF 41–50% progress to HFrEF or improve to EF > 50% remains a question for further studies.

Based on the secondary cohort, one important finding was that there were >24 000 patients with elevated NT-proBNP, with 70% of patients presenting NT-proBNP>300 ng/L, but lacking any of the inclusion diagnosis codes as a formal diagnosis for HF. Even though NT-proBNP values on their own do not provide diagnostic standalone evidence of HF,[1,7] age in this secondary cohort was similar to that in the primary cohort, and in a large proportion, NT-proBNP is markedly above the age reference values of 486 ng/L in men and 738 ng/L in women for people > 75 years.[16] In a Swedish cohort of subjects of similar age to patients in this study, an upper limit of NT-proBNP 540 ng/L for healthy elderly was established, with a clinical decision limit of 1700 ng/L affecting cardiovascular mortality in HF patients.[17] Importantly, 6000 patients (25%) in our secondary cohort presented values > 1700 ng/L. The frequency of baseline co-diagnoses of essential hypertension was further similar between the secondary cohort and HFrEF patients (39% in both); however, atrial fibrillation, chronic ischaemic heart disease, and acute myocardial infarction were less frequent than in HFpEF or HFrEF patients. Kidney function is moreover unlikely to explain the elevation of NT-proBNP in the secondary cohort, as <6.5% of patients had an estimated glomerular filtration rate of <30 mL/min/1.73 $m^2$.[7] Moreover, 28% ($n$ = 6845) of patients in the secondary cohort seem to resemble HFpEF patients regarding age and NT-proBNP concentrations with mean EF of 58%, even if these patients did not have HF diagnosis. Additionally, >400 patients in the secondary cohort with elevated NT-proBNP and reduced EF $\leq$ 40% lacked diagnosis even if clinically representing HFrEF. Even though we cannot retrospectively suggest a clinical diagnosis for HF, these data indicate that the secondary cohort patients would likely have benefitted from echocardiography to aid with diagnosis differentiation.

### Medication

Treatment guidelines recommend the use of ACE-I/ARB, BB, and diuretics for all HFrEF patients, as well as intensification of care with MRA when symptoms remain.[8,9] Inpatient medication treatment with ACE-I/ARB and BB or diuretic or the combination was 1.2-fold to 1.4-fold more common in HFrEF patients compared with HFpEF patients. The triple medication combination (ACE-I/ARB + BB + diuretic) was prescribed for inpatient care to 57% of HFrEF patients within 6 months after the diagnosis, increasing somewhat over time. Intensification of inpatient medication with MRA was evident in 30% and 15% of HFrEF and HFpEF patients, respectively. Outpatient prescriptions from the hospital of MRA within 6 months were recorded in 20% vs. 7.2% of HFrEF and HFpEF patients, which is markedly less than in studies from the USA and Sweden with 30–40% of patients treated with MRA.[18,19] Additionally, MRA has been shown to be potentially beneficial in HFpEF patients as well.[10] Nevertheless, based on our data, the proportion of patients receiving MRA was low. Outpatient medication prescribed from the hospital followed similar patterns as inpatient medication, with HFrEF patients more frequently treated with guideline-recommended HF medication. This likely reflects the fact that clinical trials have largely shown prognostic benefit with medication only for HFrEF patients, and thus, also medication recommendations concentrate on HFrEF care.[9] However, a clear limitation of the study is that we were unable to include primary care prescriptions.

We also compared the use of ACE-I/ARB, BB, and diuretic combinations between the primary cohort (HFpEF and HFrEF patients) and patients with ICD code for HF, but no EF data are available (EF missing) as well as between the primary and secondary (high NT-proBNP) cohorts. Interestingly, the use of all medication combinations in hospital inpatient and outpatient setting was significantly lower in the EF missing group and the secondary cohort patients in all time points compared with that of the primary cohort. As we acknowledge the fact that we may have missed part of the medication information owing to the lack of primary care data, this finding might indicate that following the guideline-recommended diagnostic algorithm in placing the diagnosis might also lead to a better use of guideline-recommended pharmacotherapy. Also, it needs to be noted that the patients having ICD-10 code for HF but lacking further diagnostic confirmation with echocardiography were older, and thus, multiple co-morbidities as well as common frailty might have affected the treatment choices.

Another limitation of the study is that we were unable to assess other echocardiography measures, such as changes in structural parameters essential in HFpEF diagnostics, apart from EF. However, the validity of the HFpEF diagnosis in the primary cohort was based on HF diagnosis code in combination with elevated NT-proBNP and measured preserved EF. In addition, determining the aetiology of HF would have been of great interest in this study. However, the retrospective and registry nature of the study did not allow a reliable confirmation of the aetiology, as the information is not required in the electronic patient record. Thus, the study data are restricted to listing the co-morbidities of the patients.

## Conclusions

This study underlines that guideline-recommended diagnostic pathways are not completely implemented, as half of the patients with ICD-10 diagnosis for HF lacked echocardiography, and also a large population resembling HFpEF patients by clinical characteristics had no diagnosis. HFpEF patients, compared with HFrEF patients, had more procedures performed, more laboratory tests taken, and more co-diagnoses given, likely reflecting the difficulty of diagnosis and multiple co-morbidities. Timely diagnosis would be important for HF patients to enable the most effective treatment, as these have been shown to prevent recurrent hospitalizations and decrease mortality in HFrEF.

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## Conflict of interest

J. Huusko and T. Purmonen are employees of Novartis Finland Oy. M. Lassenius and I. Toppila are employees of Medaffcon Oy. H. Ukkonen declares that he has no conflicts of interest.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Basic characteristics of the patients with ICD-10 code for HF but no EF data available.
**Table S2.** The amount of HF patients with presence of cardiac pacemaker and the amount of HF patients with adjustment

or management procedures done to the cardiac pacemaker at the baseline and the end of the follow-up. *P* values for difference between HFrEF and HFpEF patients and patients with HFmrEF and EF $>$ 50% in the baseline and in the end of the follow-up.

**Table S3.** The 20 most common procedures performed at specialty care of the primary cohort patients within the 6 months preceding diagnosis.

**Table S4.** Frequency of the 20 most common laboratory tests taken at specialty care of the primary cohort patients within the 6 months preceding diagnosis.

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