Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND

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Aims

Differences in clinical characteristics and outcome of patients with established heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) are well established. Data on epidemiology and prediction of new onset HFrEF compared with HFpEF, have not been described.

Methods and results

In 8592 subjects of the Prevention of Renal and Vascular End-stage Disease (PREVEND), a community-based, middle-aged cohort study, we performed cause-specific hazard analyses to study the predictive value of risk factors and established cardiovascular biomarkers on new onset HFrEF vs. HFpEF (left ventricular ejection fraction ≤40 and ≥50%, respectively). A P-value for competing risk (Pcr) < 0.10 between HFrEF and HFpEF was considered statistically significant. All potential new onset heart failure cases were reviewed and adjudicated to HFrEF or HFpEF by an independent committee. During a median follow-up of 11.5 years, 374 (4.4%) subjects were diagnosed with heart failure, of which 125 (34%) with HFpEF and 241 (66%) with HFrEF. The average time to diagnosis of new onset HFrEF was 6.6 ± 3.6 years; it was 8.3 ± 3.3 years for HFpEF (Pcr, 0.001). Male gender was associated with new onset HFrEF, whereas female gender with new onset HFpEF (Pcr < 0.001). Higher age and increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) increased the risk for both HFpEF and HFrEF, although for age this was stronger for HFpEF (Pcr = 0.018), whereas NT-proBNP was stronger associated with risk for HFrEF (Pcr = 0.083). Current smokers, increased highly sensitive troponin T, and previous myocardial infarction conferred a significantly increased risk for HFrEF, but not for HFpEF (Pcr = 0.093, 0.091, and 0.061, respectively). Conversely, a history of atrial fibrillation, increased urinary albumin excretion (UAE), and cystatin C were significantly more associated with the risk for HFpEF, but not for HFrEF (Pcr < 0.001, 0.061, and 0.033, respectively). The presence of obesity at baseline was associated with comparable prognostic information for both HFpEF and HFrEF.

Conclusion

Higher age, UAE, cystatin C, and history of atrial fibrillation are strong risk factors for new onset HFpEF. This underscores differential pathophysiological mechanisms for both subtypes of heart failure.

Keywords

New onset heart failure • HFpEF • HFrEF • Epidemiology

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† F.P.B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All co-authors have contributed significantly to the manuscript, regarding interpretation of the data and revising it for important intellectual content.

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Introduction

Heart failure is a progressive syndrome with high morbidity and mortality despite recent improvements of its treatment.1,2 Owing to the ageing population, it is expected that the incidence and prevalence of heart failure will increase exponentially in the next decade.3 Preventing new onset heart failure is increasingly important and requires knowledge of its risk factors.4,5 Several studies have established risk factors for new onset heart failure, including higher age, hypertension, and the presence of ischaemic heart disease.6–8 Initially, studies aimed at identifying risk factors were based on a heart failure diagnosis on signs and symptoms only.3,9 More recently, the diagnosis of heart failure was defined by reduced left ventricular ejection fraction (LVEF), with or without symptoms.7,9 We now recognize two subtypes of heart failure: heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HfP EF). Data on the incidence of new onset HfP EF and its risk factors in population-based cohorts are scarce and studies directly comparing new onset HfP EF vs. HFrEF are lacking.

In a community-based cohort, we identified all cases of new onset heart failure during 11 years of follow-up and adjudicated them as either HFrEF or HfP EF. Using available clinical and biochemical baseline characteristics, we identified risk factors for new onset HfP EF and HFrEF.

Methods

Study population

The study was performed using the data of the PREVEND (Prevention of Renal and Vascular End-stage Disease) cohort study, which has been described elsewhere.10,11 In summary, from 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years (n = 85 421) were asked to send in a first morning urine sample and complete a short questionnaire on demographics and cardiovascular disease history, and 40 856 subjects responded (47.8%). All subjects with urinary albumin excretion (UAE) > 10 mg/L (n = 7786) in their morning urine as well as a randomly selected control group with a UAE < 10 mg/L (n = 3395) were invited to an outpatient clinic for a detailed assessment of cardiovascular and renal risk factors, including filling in questionnaires, measuring anthropometrics, and blood and urine sampling. After excluding subjects with insulin-dependent diabetes mellitus, pregnant women, and subjects unable or unwilling to participate, a total of 8592 subjects completed the screening programme. The PREVEND study was approved by the institutional medical Ethics Committee and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Definitions

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits, using an automatic Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or self-reported use of antihypertensive medication. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m²), and obesity was defined as a BMI > 30 kg/m². Hypercholesterolaemia was defined as total serum cholesterol > 6.5 mmol/L (251 mg/dL) or a serum cholesterol ≥ 5.0 mmol/L (193 mg/dL) if a history of myocardial infarction (MI) was present or when lipid-lowering medication was used. Type 2 diabetes was defined as a fasting plasma glucose > 7.0 mmol/L (126 mg/dL), a non-fasting plasma glucose > 11.1 mmol/L, or use of anti-diabetic drugs. Urinary albumin excretion was calculated as the average value from two consecutive 24 h urine collections. The glomerular filtration rate (eGFR) was estimated using the simplified modification of diet in renal disease formula.12 Smoking was defined as current nicotine use or quit smoking within the previous year. History of MI was defined as participant-reported hospitalization for at least 3 days as a result of this condition. Standard 12-lead electrocardiograms were recorded using the computer program Modular ECG Analysis System,13 and AF was defined according to Minnesota codes 8.3.1 and 8.3.3.

Assays

At baseline, EDTA plasma samples were drawn from all participants for biomarker assessment. Aliquots of these samples were stored immediately after collection at −80°C until analyses. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and highly sensitive C-reactive protein (hs-C-reactive protein) were measured as described in detail elsewhere.14,15 Highly sensitive troponin T (hs-TnT) was measured using modular analytics serum work areas, with < 10% coefficient of variation at the 99th percentile of the reference range (Roche Diagnostics). Urinary albumin concentration was determined by nephelometry, with a threshold of 2.3 mg/L and intra- and interassay coefficients variation of 2.2 and 2.6%, respectively (BNII, Dade Behring Diagnostica, Marburg, Germany).

Heart failure and cardiovascular events

Follow-up for the present investigation was defined as the time between the baseline visit to the outpatient department and the date of new onset heart failure, or 1 January 2010. Subjects were censored at the date they moved to an unknown destination or at the last date of the follow-up (1 January 2010), whatever date came first. Information on dates and causes of death for every participant was obtained from Statistics Netherlands16 and coded according to the 10th revision of the International Classification of Diseases.

The patient population of PREVEND, from the city of Groningen, has a low migration rate16 and is covered by two main hospitals in the region. Patient files were checked in both hospitals for the presence of heart failure at baseline and for new onset heart failure, by recording signs, symptoms, and objective evidence of heart failure. Permission to access hospital records was granted by the local Ethics Committees of both hospitals. Using criteria in accordance with the Heart Failure Guidelines of the European Society of Cardiology (ESC),17,18 586 individual cases were identified as suspected heart failure, as shown in Figure 1. An endpoint adjudication committee of seven independent experts in the field of heart failure evaluated all cases suspected for the diagnosis of new onset heart failure. Each case was validated by two different experts by reviewing anonymized clinical charts, hospitalization, and physician office records in order to ascertain the incidence of heart failure. In case of consensus, patients were classified as ‘definite new onset heart failure’, ‘definite no new onset heart failure’, or ‘definite heart failure, with date of onset before time of recruitment in PREVEND’. In case of difference of opinion about an individual case, the committee made a joint decision. Based on LVEF at the time of diagnosis, heart failure was classified as HFrEF or HfP EF (LVEF ≤ 40 or ≥ 50%, respectively). The cut-offs were chosen due to the lack of consensus in the most recent ESC guidelines for diagnosis of new onset heart failure.17,18 Subjects in the grey area, with an LVEF of 41–49% (n = 8), were excluded from...
the analyses to prevent blending and dilution of differential epidemiological profiles. The aetiology and the date of onset of heart failure were also derived from clinical charts. Data on LVEF were available in 98.4% of cases with new onset heart failure. In six cases, diagnosis was confirmed through joint decision, because of insufficient data on LVEF.

### Statistical analysis

By design, the PREVEND study overselected subjects with an elevated UAE (>10 mg/L). It should be clear that this is not a random sample of a general population, where all elementary units have an equal probability of being selected. Statistical formulas to calculate population parameter estimates should be used to account for the likelihood of selection. A design-based analysis was performed to overcome this overselction of subjects with elevated UAE. This statistical weighting method allows conclusions to be generalized to the general population. Baseline continuous data are reported as mean (standard deviation) for normal data. NT-proBNP, hs-TnT, UAE, cystatin C, serum triglycerides, and hs-C-reactive protein showed a log-linear functional shape with the response variable and were transformed to a 2-log scale and reported as median (inter-quartile range). This means that risk estimates should be interpreted as the relative risk if values were doubled (e.g. 1 to 2 mg/L or 10 to 20 mg/24 h). We fitted Cox proportional hazards models to the data and Schoenfeld residuals were calculated to assess whether proportionality assumptions were satisfied. For multivariate regression analysis, we imported variables which reached significance ($P < 0.10$) in univariate analysis. Two competing endpoints were distinguished: HFrEF and HfPEF. All variables from the multivariate analyses were explored using cause-specific hazard analyses, which allowed us to compare the effects of explanatory variables on either HFrEF or HfPEF. To control for the type I error in the cause-specific hazard analysis (effect-by-covariate), and increasing power for the analysis, a $P$-value for competing risk ($P_c$) between HFrEF and HfPEF of $<0.10$ is considered statistically significant. Results are summarized as hazard (risk) ratios, with 95% confidence intervals based on robust standard error estimates. A value of $P < 0.05$ (two-sided) was used as the nominal level of statistical significance. Individual relative hazards were estimated by post-estimation, based on the multivariate cause-specific cox proportional hazard analysis. To define the proportion of usable subject pairs in which outcome and prediction are concordant, we calculated the Harrell $C$-coefficient, for the model for HfPEF and the model for HFrEF. Time to first event was estimated using cumulative incident curves, for total new onset heart failure and both subtypes, and adjusted for mortality during the follow-up. All analyses were performed using StataC (version 11.0 software for Windows).

### Results

During a median follow-up of 11.5 years (range 10.8–11.9), 374 individuals (4.4%) were diagnosed with new onset heart failure, of whom 125 (34%) were classified as HfPEF and 241 (66%) as HFrEF. The average time to diagnosis of new onset heart failure was 7.2 ($\pm$3.6) years; for HFrEF, this was 6.6 ($\pm$3.6) years, and 8.3 ($\pm$3.3) years for HfPEF ($P < 0.001$). Figure 2 shows the cumulative incidence of new onset heart failure and separately for HFrEF and HfPEF. Five-year all-cause mortality was higher for subjects diagnosed with new onset HFrEF, compared with new onset HfPEF ($P = 0.038$), as depicted in Figure 3. Baseline characteristics are presented in Table 1 for subjects without heart failure during the follow-up and for subjects with new onset heart failure during the follow-up. At baseline, subjects who developed heart failure during the follow-up were older, more likely male, had
higher BMI, blood pressure, and heart rate, worse renal function and more likely to have CV risk factors: i.e. hypertension, diabetes, and hypercholesterolaemia (Table 1). Glucose, total cholesterol, UAE, NT-proBNP, hs-TnT, cystatin C, and hs-C-reactive protein were also higher at baseline for subjects with new onset heart failure (all \( P < 0.001 \)). Table 1 also shows baseline characteristics of subjects with new onset HFrEF and HFpEF. Subjects with HFrEF during the follow-up were more likely male, more smokers, and had higher levels of creatinine, NT-proBNP, and hs-TnT at baseline. During the follow-up period, there were 169 MIs. In 25.4% of subjects, this was followed by new onset HFrEF and HFpEF. In multivariate analysis, age, male gender, previous MI, atrial fibrillation, diabetes mellitus, and hypercholesterolaemia was significantly associated with new onset heart failure. Particular strong predictors for HFpEF were older age, female gender, atrial fibrillation, higher cystatin C, and UAE. In contrast, male gender, previous MI, smoking, hs-TnT, and NT-proBNP were significant predictors specifically for HFrEF. This underscores differential pathophysiological mechanisms for both subtypes of heart failure.

**Associations of clinical and biochemical characteristics with heart failure with preserved ejection fraction and heart failure with reduced ejection fraction**

Table 2 summarizes the results of the Cox proportional hazard analysis and the cause-specific hazard analysis. Adjusted for age and gender, the presence or absence of obesity, hypertension, previous MI, atrial fibrillation, diabetes mellitus, and hypercholesterolaemia was significantly associated with new onset heart failure. Also, higher levels of UAE, hs-C-reactive protein, cystatin C, NT-proBNP, and hs-TnT were associated with higher risk for new onset heart failure. In multivariate analysis, age, male gender, obesity, previous MI, increased NT-proBNP, and hs-TnT remained associated with an increased risk for new onset heart failure. Presence of diabetes and hypercholesterolaemia at baseline showed a trend for increased risk for new onset heart failure when multivariately adjusted (\( P = 0.056 \) and 0.096, respectively). The Harrell C-coefficient for the model with total new onset heart failure was 0.87 (95% CI 0.84−0.90).

Cause-specific hazard analyses were performed to analyse possible competing risk between the two endpoints (HFrEF and HFpEF). There was a highly significant interaction between HFrEF and HFpEF for gender, indicating that male gender is associated with new onset HFrEF, whereas female gender is associated with new onset HFpEF (\( P _ { cr } < 0.001 \)). Higher age and increased NT-proBNP predicted both new onset HFrEF and HFpEF, although for age this was significantly stronger for HFrEF (\( P _ { cr } = 0.018 \)), whereas for NT-proBNP, this was significantly stronger for HFpEF (\( P _ { cr } = 0.083 \)). In addition, smokers, an increased hs-TnT, and subjects with previous MI had a significantly increased risk for HFrEF, but not for HFpEF (\( P _ { cr } = 0.086 \), \( P _ { cr } = 0.091 \), \( P _ { cr } = 0.058 \), respectively). History of atrial fibrillation, increased UAE, and cystatin C were significantly more associated with the risk for HFpEF, but not for HFrEF. The presence of obesity at baseline was associated with comparable prognostic information for both HFpEF and HFrEF. Furthermore, the additional value of subjects categorized to values of hs-TnT below the detection limit (\( n = 4728 \)) was not significant in the cause-specific hazard model for HFrEF, nor for HFpEF (\( P _ { cr } = 0.493 \)).

The proportionality assumptions in the model were satisfied (chi-squared test 36.05; \( P = 0.141 \)). For both HFrEF and HFpEF, two separate models were created, consisting of the significant variables from the above cause-specific Cox proportional hazard analysis. The model for HFpEF had a Harrell C-coefficient of 0.90 (95% CI 0.87–0.92) and the model for HFrEF a Harrell C-coefficient of 0.88 (95% CI 0.84–0.91).

**Discussion**

The present study reports on detailed epidemiological data on the comparison of new onset HFpEF vs. HFrEF. Using a population-based cohort, we report a total incidence of new onset heart failure of 4.4% after 11.4 years of follow-up. The presence of obesity was a common risk factor for incidence of both subtypes of heart failure. Particular strong predictors for HFpEF were older age, female gender, atrial fibrillation, higher cystatin C, and UAE. In contrast, male gender, previous MI, smoking, hs-TnT, and NT-proBNP were significant predictors specifically for HFrEF. This underscores differential pathophysiological mechanisms for both subtypes of heart failure.

**Incidence of heart failure**

In this population-based cohort study, we identified 374 patients with a certain diagnosis of new onset heart failure. For this, we used the Heart Failure Guidelines from the ESC, and each suspected case was validated by an expert committee. To prevent blending and dilution of epidemiological profiles between HFrEF and HFpEF, we excluded eight subjects in the so-called grey area of LVEF 41–49%. In sub-analyses with strict cut-off values of 40 or 50%, results are similar to the current analyses. However, the current paper aims to identify differential epidemiological risk profiles in contrast to evaluating the ideal cut-off for LVEF. By excluding subjects in the grey area of LVEF 41–49%, we present subjects with true new onset HFrEF and HFpEF. In contrast to other epidemiological studies of new onset heart failure, there was no pre-selection during the screening process, with all 8952 subjects of PREVEND being individually evaluated for suspected heart failure. Through this method, we achieved a very limited under-reporting of new onset heart failure in our cohort and no false positives. Also, data on LVEF were available for almost all cases (98.4%).
to accomplish accurate adjudication to HFrEF or HfP EF. Compared with other cohorts with new onset heart failure in the community, the incidence rate of heart failure cases is slightly higher, especially given the young mean age of subjects at baseline (49 ± 12 years) in PREVEND. For example, Smith et al.22 and Vela-
gleti et al.22 report an incidence rate of 2.2% during 14 years of follow-up (mean age at baseline 58 years) and 3.4% during 9.4 years of follow-up (mean age at baseline 59 years). However, the incidence of HfP EF compared with HFrEF (34 vs. 66%, respective-
ly) is slightly lower, compared with other community-based studies.2,23 It is most likely that the lower average age at baseline in the current study is responsible for this relatively low proportion of subjects with new onset HfP EF. The incidence of HfP EF is presumed to increase during prolonged follow-up. Despite lower age at baseline, through our thorough screening methods for identifying new onset heart failure we achieved accurate and true incidence rate for new onset heart failure in a population-based middle-aged cohort.

### Clinical characteristics of new onset heart failure

Few studies have presented data on new onset heart failure in the community, and especially studies regarding separate data for

### Table 1 Baseline characteristics of subjects without heart failure during the follow-up and of subjects with new onset heart failure during the follow-up a

<table>
<thead>
<tr>
<th></th>
<th>No HF n = 8195</th>
<th>HFrEF n = 374</th>
<th>P-value</th>
<th>HfP EF n = 241</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 12</td>
<td>62 ± 10</td>
<td>&lt;0.001</td>
<td>62 ± 10</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Males (%)</td>
<td>49.2</td>
<td>64.4</td>
<td>&lt;0.001</td>
<td>73.4</td>
<td>48.0</td>
</tr>
<tr>
<td>Caucasians (%)</td>
<td>95.4</td>
<td>97.3</td>
<td>0.187</td>
<td>97.5</td>
<td>97.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 4</td>
<td>28 ± 5</td>
<td>&lt;0.001</td>
<td>28 ± 4</td>
<td>29 ± 5</td>
</tr>
<tr>
<td>&gt;30 (%)</td>
<td>14.9</td>
<td>30.2</td>
<td>&lt;0.001</td>
<td>29.1</td>
<td>32.0</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>128 ± 20</td>
<td>147 ± 23</td>
<td>&lt;0.001</td>
<td>145 ± 22</td>
<td>149 ± 25</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>74 ± 10</td>
<td>80 ± 10</td>
<td>&lt;0.001</td>
<td>80 ± 10</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>69 ± 10</td>
<td>70 ± 12</td>
<td>0.070</td>
<td>70 ± 12</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>Baseline medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking or quit &lt;1 year (%)</td>
<td>38.0</td>
<td>38.2</td>
<td>0.928</td>
<td>43.5</td>
<td>28.8</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>5.1</td>
<td>25.6</td>
<td>&lt;0.001</td>
<td>28.8</td>
<td>19.5</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>30.1</td>
<td>71.1</td>
<td>&lt;0.001</td>
<td>68.1</td>
<td>75.8</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>25.5</td>
<td>47.0</td>
<td>&lt;0.001</td>
<td>48.3</td>
<td>42.2</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>3.4</td>
<td>12.3</td>
<td>&lt;0.001</td>
<td>12.0</td>
<td>12.2</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>1.0</td>
<td>4.6</td>
<td>&lt;0.001</td>
<td>4.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.9 ± 1.1</td>
<td>5.5 ± 1.9</td>
<td>&lt;0.001</td>
<td>5.4 ± 1.7</td>
<td>5.6 ± 2.1</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.6 ± 1.1</td>
<td>6.0 ± 1.0</td>
<td>&lt;0.001</td>
<td>6.0 ± 1.0</td>
<td>6.0 ± 1.0</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.33 ± 0.40</td>
<td>1.22 ± 0.36</td>
<td>&lt;0.001</td>
<td>1.20 ± 0.36</td>
<td>1.27 ± 0.35</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.15 (0.84–1.67)</td>
<td>1.39 (1.00–1.93)</td>
<td>&lt;0.001</td>
<td>1.41 (0.97–2.03)</td>
<td>1.36 (1.01–1.78)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>82 (73–92)</td>
<td>87 (76–99)</td>
<td>&lt;0.001</td>
<td>90 (80–102)</td>
<td>81 (72–97)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>81 ± 15</td>
<td>75 ± 16</td>
<td>&lt;0.001</td>
<td>75 ± 14</td>
<td>75 ± 18</td>
</tr>
<tr>
<td>&lt;60 (%)</td>
<td>6.0</td>
<td>12.7</td>
<td>&lt;0.001</td>
<td>12.9</td>
<td>12.9</td>
</tr>
<tr>
<td>Cystatine C (mg/L)</td>
<td>0.77 (0.69–0.87)</td>
<td>0.89 (0.79–1.03)</td>
<td>&lt;0.001</td>
<td>0.91 (0.79–1.05)</td>
<td>0.88 (0.77–1.04)</td>
</tr>
<tr>
<td>UAE (mg/24 h)</td>
<td>9.2 (6.3–16.9)</td>
<td>19.4 (9.3–52.2)</td>
<td>&lt;0.001</td>
<td>19.2 (9.3–50.8)</td>
<td>20.4 (9.9–57.8)</td>
</tr>
<tr>
<td>hs-C-reactive protein (mg/L)</td>
<td>1.24 (0.54–2.88)</td>
<td>2.47 (1.18–4.83)</td>
<td>&lt;0.001</td>
<td>2.48 (1.24–4.83)</td>
<td>2.05 (0.88–4.46)</td>
</tr>
<tr>
<td>NT-proBNP (ng/L)</td>
<td>36 (16–70)</td>
<td>104 (43–285)</td>
<td>&lt;0.001</td>
<td>121 (45–358)</td>
<td>86 (37–172)</td>
</tr>
<tr>
<td>hs-TnT (ng/L)</td>
<td>2.5 (2.5–4.0)</td>
<td>7.0 (4.0–10.0)</td>
<td>&lt;0.001</td>
<td>7.0 (4.0–11.0)</td>
<td>5.0 (3.0–9.0)</td>
</tr>
</tbody>
</table>

HF, heart failure; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; hs-C-reactive protein; highly sensitive C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-TnT, highly sensitive troponin T; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion.

aContinuous variables are presented as mean ± standard deviation and compared with the use of Student’s t-test, in case of normal distribution. In case of skewed distribution, continuous variables are presented as median (inter-quartile range) and compared using the Kruskall–Wallis test. Binary categorical variables were compared using standard chi-squared tests.

bMean time to diagnosis = 7.2 (± 3.6) years.
HFrEF and HFpEF are lacking. Next to a multimarker strategy for the prediction of new onset heart failure, these studies have reported on specific risk factors for overall new onset heart failure, for example age, NT-proBNP, diabetes, and urinary albumin-creatinine ratio. Data on HFrEF and HFpEF are available separately from the Rochester Epidemiology Project and the Framingham Heart Study. However, the Rochester Epidemiology Project has few cases of new onset heart failure with known LVEF (n = 137) and no biochemical data. It was shown that female sex and age ≥ 90 years were associated with HFrEF, whereas left bundle-branch block and MI pattern on the ECG were associated with age and hypercholesterolaemia was however, unlike other studies, not associated with increased risk for new onset heart failure. This could be caused by the definitions utilized in PREVEND, where subjects were also classified as such if treated for the disease. However, a proxy of hypertension, UAE, was significantly associated with new onset HFpEF. Also, hypertension is a major risk factor for atrial fibrillation, another predictor of HFpEF. We add to previous published data, when regarding HFpEF and HFrEF and the existence of different risk profiles, many years before symptoms of heart failure become manifest.

We confirm earlier findings of significant risk factors for new onset heart failure, namely higher age, obesity, previous MI, NT-proBNP, and hs-TnT. The presence of hypertension, diabetes, and hypercholesterolaemia was however, unlike other studies, not associated with increased risk for new onset heart failure. This could be caused by the definitions utilized in PREVEND, where subjects were also classified as such if treated for the disease. However, a proxy of hypertension, UAE, was significantly associated with new onset HFpEF. Also, hypertension is a major risk factor for atrial fibrillation, another predictor of HFpEF. We add to previous published data, when regarding HFpEF and HFrEF and the existence of different risk profiles, many years before symptoms of heart failure become manifest.

Biomarkers

Biomarkers provide important information on disease aetiology and clinical risk. In the current analyses, we did not use a biochemical data for new onset heart failure compared with healthy subjects with no diagnosis of heart failure during the follow-up. With a mean time from baseline to new onset heart failure of 7.2 years in our cohort, our data add unique information on the incidence and the risk factors of both HFpEF and HFrEF and the existence of different risk profiles, many years before symptoms of heart failure become manifest.

Table 2  Cox regression: cause-specific hazard (risk) ratios

|                        | Adjusted for age and sex | Mutually adjusted* | HFrEF | HFpEF | **P**
|------------------------|--------------------------|--------------------|-------|-------|------
| Age (per 10 years)     | –                        | 1.81 (1.47–2.24)   | <0.001| 1.61 (1.24–2.09)| 2.53 (1.93–3.30)| 0.018
| Males                  | –                        | 1.48 (1.03–2.13)   | 0.035 | 2.43 (1.49–3.95)| 0.56 (0.31–1.01)| <0.001
| Obesity                | 1.93 (1.37–2.73)         | 1.62 (1.10–2.37)   | 0.014 | –     | –    | 0.750
| Heart rate (per 5 b.p.m.) | 1.05 (0.98–1.13)      | 0.155              | –     | –     | –    | 0.288
| Hypertension           | 1.99 (1.37–2.89)         | 1.17 (0.77–1.77)   | 0.458 | –     | –    | 0.974
| Myocardial infarction  | 3.45 (2.38–4.99)         | <0.001             | 2.27 (1.54–3.34)| <0.001| 2.77 (1.73–4.43)| 1.25 (0.64–2.45)| 0.058
| Smoking or quit smoking <1 year | 1.31 (0.96–1.79) | 0.087              | 1.24 (0.87–1.77)| 0.228 | 1.51 (0.96–2.36)| 0.80 (0.46–1.41)| 0.086
| Atrial fibrillation    | 2.64 (1.23–5.66)         | 0.013              | 1.10 (0.55–2.19)| 0.787 | 0.42 (0.19–0.93)| 3.79 (1.64–8.77)| <0.001
| Diabetes mellitus      | 2.41 (1.51–3.85)         | <0.001             | 1.66 (0.99–2.78)| 0.056 | –    | –    | 0.713
| Hypercholesterolaemia (mmol/L) | 1.65 (1.21–2.26) | 0.002              | 1.34 (0.95–1.88)| 0.096 | –    | –    | 0.001
| Log Creatinine (per doubling) | 1.00 (0.84–1.20) | 0.973              | –     | –     | –    | 0.001
| eGFR >60 mL/min/kg     | 1.07 (0.66–1.74)         | 0.782              | –     | –     | –    | 0.001
| Log Cystatin C (per doubling) | 1.43 (1.23–1.68) | <0.001             | 1.08 (0.94–1.24)| 0.295 | 0.98 (0.86–1.11)| 1.45 (1.03–2.04)| 0.033
| Log UAE (per doubling) | 1.35 (1.22–1.50)         | <0.001             | 1.01 (0.91–1.14)| 0.798 | 0.96 (0.84–1.09)| 1.21 (0.98–1.48)| 0.061
| Log hs-C-reactive protein (per doubling) | 1.41 (1.17–1.70) | <0.001             | 1.14 (0.92–1.41)| 0.228 | –    | –    | 0.230
| Log NT-proBNP (per doubling) | 2.11 (1.79–2.49) | <0.001             | 1.68 (1.39–2.04)| <0.001| 1.85 (1.42–2.41)| 1.35 (1.06–1.72)| 0.082
| Log hs-TnT (per doubling) | 1.67 (1.51–1.86) | <0.001             | 1.33 (1.17–1.52)| <0.001| 1.38 (1.18–1.60)| 1.10 (0.90–1.36)| 0.091

Univariate and multivariate endpoint: total incident HF. All variables from multivariate regression are tested for competing risk between HFrEF and HFpEF.

Obesity, body mass index >30 kg/m²; HDL-cholesterol, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; hs-C-reactive protein, highly sensitive C-reactive protein; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; hs-TnT, highly sensitive troponin T.

*Adjusted for age, sex, and all variables from the univariate analyses with a P-value < 0.10.

**P** = P-value for competing risk: heart failure with reduced vs. preserved ejection fraction.
multimarker approach to identify subjects at risk, but we took the strongest biomarker for different pathophysiological domains: NT-proBNP, hs-TnT, hs-C-reactive protein, and cystatin C. Except for NT-proBNP, there are currently no biomarkers registered to aid in the early diagnosis of heart failure. This is especially relevant for HFrEF, where diagnosis is more difficult to make. Our data show that NT-proBNP and hs-TnT were associated with new onset HFrEF. For new onset HFrEF, however, cystatin C and NT-proBNP (although less strong than for HFrEF) were strong predictors. NT-proBNP, as a marker of myocardial wall stress, thus remains a powerful biomarker for identifying subjects at risk for either subtype of new onset heart failure. The value of hs-TnT in predicting incident heart failure has been described in older adults, but not for either HFrEF or HFrEF specifically. Our data show increased risk for new onset HFrEF, but not HFrEF, which indicates an early trend towards an ischaemic aetiology. Specifically, an increased hs-TnT could be reflecting increased risk for developing MI, which in turn increases the risk for HFrEF. A decreased kidney function, as determined by cystatin C, has been shown to be associated with left ventricular hypertrophy, vascular stiffness, and new onset heart failure. This is in accordance with our findings, which associate higher levels of cystatin C with an increased risk for developing new onset HFrEF, although there was no increased risk for new onset HFrEF. In a study by Moran et al., cystatin C was associated with both new onset HFrEF and HFrEF, although the levels of cystatin C in their cohort were much higher, probably due to the selection of older subjects. This may indicate that in asymptomatic subjects, cystatin C could be an interesting marker for early cardiovascular disease progression, especially regarding HFrEF. Highly sensitive-C-reactive protein has been associated with increased risk for cardiovascular disease in PREVEND. However, when adjusted for all CV variables, hs-C-reactive protein was not associated with a significantly increased risk for either subtype of new onset heart failure.

Clincial consequences

Multiple intervention studies have clearly shown that patients with established HFrEF benefit from ACE-inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. But to date, not a single drug has proved to reduce mortality in patients with HFrEF, nor is any drug recommended for the treatment of HFrEF in the current guidelines. Our data clearly show distinct clinical risk profiles for new onset HFrEF and HFrEF. This implies that prevention of new onset HFrEF might need a different approach when compared with the prevention of HFrEF. Apart from the treatment of hypertension, strategies to reduce an elevated UAE and prevention of permanent atrial fibrillation may help to prevent or delay new onset HFrEF. Future studies are needed to further evaluate effective preventive treatment for both different risk profiles.

Strengths and limitations

The large, community-based cohort and long follow-up, standardized biomarker and clinical parameter measurements, and the thorough validation of incident heart failure diagnosis, with little loss to the follow-up, are strengths of our study. Our study is limited by the fact that the PREVEND study subjects are predominately Caucasian and our results can therefore not be extrapolated to subjects from other ethnicities. Also, heart failure was identified retrospectively by chart review. This could have resulted in underdetection of subjects with new onset heart failure, when diagnosis is not pursued in the symptomatic patient with normal ejection fraction. Then, the PREVEND cohort was enriched for increased albumin excretion. Although we corrected for this by conducting a design-based analysis, we cannot exclude that our results are affected by the study design. However, compared with the Framingham cohort, UAE was not higher in PREVEND, and incidence of all-cause mortality and new onset heart failure is comparable with unselected general population studies. Also, the multivariable cause-specific hazard models for HFrEF and HFrEF were adjusted for study design and are therefore not affected by the enrichment for higher albuminuria levels.

Conclusions

These data show incidence rates of both new onset HFrEF and HFrEF in a community-based cohort. Moreover, a differential clinical risk profile at baseline for both subtypes of HF was found. Apart from higher age and female gender, an increased UAE, atrial fibrillation, and cystatin C emerged as new risk indicators for HFrEF. Overall, our data suggest that a differential approach is indicated in order to prevent both HFrEF and HFrEF.

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References