Comorbidities and cause-specific outcomes in heart failure across the ejection fraction spectrum: A blueprint for clinical trial design

Gianluigi Savarese a,b, Camilla Settergren a, Benedikt Schrage a, Tonje Thorvaldsen a, Ida Löfman a, Ulrik Sartipy b,c, Linda Mellbin a, Andrea Meyers d, Soulmaz Fazeli Farsanie e, Martina Brueckmanne f, Francesco Cosentinoa, Lars H. Lund a

a Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
b Department of Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden
c Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
d Boehringer Ingelheim Pharmaceuticals, Ridgefield, United States of America
e Boehringer Ingelheim International GmbH, Ingelheim Am Rhein, Germany
f Boehringer Ingelheim Pharmaceuticals, Ridgefield, United States of America
g Afeld, United States of America
h Department of Medical and Health Sciences, Linköping University, Linköping, Sweden
i Department of Cardiology, Linköping University, Linköping, Sweden
j Department of Medical Sciences, Uppsala University, Uppsala, Sweden
k Afeld, United States of America
l Department of Medical Sciences, Linköping University, Linköping, Sweden

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ABSTRACT

Background: Comorbidities may differently affect treatment response and cause-specific outcomes in heart failure (HF) with preserved (HFrEF) vs. mid-range/mildly-reduced (HFmrEF) vs. reduced (HFrEF) ejection fraction (EF), complicating trial design. In patients with HF, we performed a comprehensive analysis of type 2 diabetes (T2DM), atrial fibrillation (AF) chronic kidney disease (CKD), and cause-specific outcomes.

Methods and results: Of 42,583 patients from the Swedish HF registry (23% HFpEF, 21% HFmrEF, 56% HFrEF), 24% had T2DM, 51% CKD, 56% AF, and 8% all three comorbidities. HFrEF had higher prevalence of CKD and AF, HFrEF had intermediate prevalence of AF, and prevalence of T2DM was similar across the EF spectrum. Patients with T2DM, AF and/or CKD were more likely to have also other comorbidities and more severe HF. Risk of cardiovascular (CV) events was highest in HFrEF vs. HFpEF and HFmrEF; non-CV risk was highest in HFpEF vs. HFmrEF vs. HFrEF. T2DM increased CV and non-CV events similarly but less so in HFrEF. CKD increased CV events somewhat more than non-CV events and less so in HFrEF. AF increased CV events considerably more than non-CV events and more so in HFrEF and HFmrEF.

Conclusion: HFrEF is distinguished from HFmrEF and HFpEF by more comorbidities, non-CV events, but lower effect of T2DM and CKD on events. CV events are most frequent in HFrEF. To enrich for CV vs. non-CV events, trialists should not exclude patients with lower EF, AF and/or CKD, who report higher CV risk.

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1. Introduction

Heart failure (HF) is a clinical syndrome characterized by severe morbidity and mortality [1]. Its prevalence is overall 2–3% in Western countries and is expected to exponentially rise due to the ageing of the global population [1].

Ejection fraction (EF) is currently used for diagnostic, prognostic, therapeutic and trial inclusion purposes in HF. According to EF, HF is classified as with reduced (HFrEF), mid-range (HFmrEF) and preserved (HFpEF) EF [2]. The individual EF subtypes are characterized by a different distribution of comorbidities, which may play distinct prognostic roles across the EF spectrum [3].

Type 2 diabetes mellitus (T2DM), atrial fibrillation (AF) and chronic kidney disease (CKD) are three major comorbidities in patients with HF [4–6]. Granular data on T2DM, AF and CKD, their interplay and association with cause-specific outcomes in HF across the EF spectrum are...
limited. A comprehensive and detailed characterization of HF according to EF, comorbidities and outcomes may improve phenotyping, prognostication, diagnosis and clinical management, and importantly, facilitate interventional trial design planning in HF. In this setting information on comorbidities and cause-specific outcomes is critical for setting up eligibility criteria, assessing feasibility of enrolment, and estimating cardiovascular (CV) and competing event rates.

Therefore, the aim of this study was to comprehensively assess patient characteristics, cause-specific outcomes and prognostic predictors according to EF strata and concomitant T2DM, AF and CKD, in a large and unselected HF cohort.

2. Methods

2.1. Study protocol and setting

The Swedish HF Registry (SwedeHF) was previously described [7]. The only inclusion criterion is clinician-judged HF. Approximately 80 variables are recorded at the discharge from hospital (i.e. for inpatients) or clinical visit date (i.e. for outpatients). The registry includes HF patients regardless of EF, with HFrEF defined as EF ≤ 40%, HfmrEF as EF 40–49%, and HFpEF as EF ≥ 50% [2].

For this analysis, SwedeHF was linked with the Cause of Death Registry and the National Patient Registry. From the Cause of Death Registry we obtained the date of death and the underlying cause rather than immediate mode of death. The Patient Registry provided additional baseline comorbidities and the outcomes including, all-cause, CV, non-CV, and HF hospitalization. Socioeconomic data were obtained by Statistics Sweden. Variables description is reported in Supplementary Table 1.

Establishment of SwedeHF and this analysis with linking of the above-mentioned registries was approved by a multisite ethics committee. Individual patient consent was not required, but patients in Sweden are informed of entry into national registries and have the opportunity to opt out.

2.2. Patients

Patients enrolled in SwedeHF between 11th May 2000 and 31st December 2012 without missing data for EF and for the comorbidities of interest (i.e. T2DM, AF, CKD) and with follow-up ≥ 1 day (i.e. excluding patients who died during the hospital admission/visit linked to the first SwedeHF registration) were considered eligible for the current study. End of follow-up was 31st December 2012.

2.3. Statistical methods

2.3.1. Baseline characteristics

Baseline characteristics were compared in patients with vs. without AF (permanent, persistent or paroxysmal) and/or CKD (estimated glomerular filtration rate < 60 ml/min/1.73 m² calculated by Chronic Kidney Disease Epidemiology Collaboration formula) and/or T2DM, and across patients with different combinations of these comorbidities within each HF phenotype by t-test or ANOVA, Wilcoxon rank-sum test or Kruskal Wallis tests for continuous variables and by chi-square test for categorical variables.

2.3.2. Outcome analysis

Primary outcome was the composite of CV death and first HF hospitalization. Secondary outcomes were first events of 1) HF hospitalization, 2) all-cause hospitalization, 3) CV events (death or hospitalization) and 4) non-CV events (death or hospitalization). Outcomes were censored at death or end of follow-up. Unadjusted survival was estimated by Kaplan Meier method whereas univariable and multivariable Cox regression models (including the variables labelled with * in Table 1) were fitted to calculate hazard ratios (HR) with 95% confidence interval (CI). In considering the impact of a comorbidity in trial design, the unadjusted role of that comorbidity is relevant, but when considering the independent additive role of that comorbidity, the adjusted role is relevant. Therefore, we present both unadjusted and adjusted hazard ratios. Multivariable Cox regression models were also performed to identify the independent predictors of the primary outcome occurrence in patients with the comorbidities of interest. Interactions between potential predictors and EF group were also assessed, and when statistically significant, HRs were reported separately for the different EF subtypes.

For fitting multivariable models, we performed multiple imputation (MI) (10 completed datasets generated) within each EF strata to handle missing data in baseline characteristics (variables labelled with * in Table 1 were included in the models).

A p-value < 0.05 was considered as statistically significant for all the analyses. Statistical analyses were performed by Stata 14.2 (StataCorp LLC, College Station, Texas, USA).

3. Results

Out of 80,772 registrations in SwedeHF between 11th May 2000 and 31st December 2012 from 51,060 patients, a total of 42,583 patients fulfilled the inclusion/exclusion criteria for this study and thus were included in the analyses (Supplementary Fig. 1). Of those, 23% had HFrEF, 21% HfmrEF and 56% HFpEF. Mean age was 74 ± 12 years and 37% were females.

Overall, 56% of patients had AF, 51% CKD, 24% T2DM, and 8% had all three comorbidities, with AF and CKD being the most likely to coexist (22% of the population). HFrEF had greater prevalence of AF (64%) and CKD (56%). HfmrEF and HFpEF had lower prevalence of CKD (48% and 46%, respectively). HfmrEF had intermediate prevalence of AF (58%), which was lowest in HFpEF (51%). All three EF groups had similar prevalence of T2DM (25% in HFpEF, 24% in HfmrEF and 24% in HFrEF) (Fig. 1).

3.1. Clinical phenotypes according to EF and comorbidities

As shown in Table 1 and Supplementary Tables 2–4, patients with T2DM and/or AF and/or CKD were more likely to suffer from other comorbidities (i.e. hypertension, anemia, stroke/TIA), to be inpatients, have more severe HF (i.e. higher New York heart association [NYHA] class, N-terminal pro-B-type natriuretic peptide [NT-proBNP] levels and use of diuretics, longer HF duration), but paradoxically less likely to be followed-up in specialty vs. primary care and in nurse-led HF clinic. Patients with CKD were also more likely to suffer from AF and T2DM and vice versa, whereas those with T2DM were less likely to have AF and vice versa. These differences were overall observed in patients with vs. without comorbidities in all the EF strata. Regardless of EF, history of ischemic heart disease was more likely in CKD and/or T2DM, but less in AF. There was no difference in sex distribution in patients with vs. without AF (except for HFpEF, with females less likely to have AF), but more patients with CKD were female and more patients with T2DM male. In all EF phenotypes, patients with CKD and/or AF were older, whereas those with T2DM were younger.

Regardless of EF, body mass index (BMI) was higher in T2DM but lower in CKD. Use of renin-angiotensin-system inhibitors (RASi) was lower in those with vs. without CKD and/or AF but higher in T2DM.

When comparing patients with isolated CKD vs. AF vs. T2DM, those with CKD were more likely female, older and with characteristics linked with more severe HF. Patients with T2DM were more likely to be male, younger, had higher BMI and lower NT-proBNP, and more hypertension and ischemic heart disease. These profiles were consistent across the EF spectrum, although patients with T2DM vs. those with AF or CKD were more likely to have HFpEF (Supplementary Tables 5–11).
Table 1
Baseline characteristics in patients with vs. without type 2 diabetes mellitus, chronic kidney disease and atrial fibrillation.

| Type 2 Diabetes mellitus | Chronic kidney disease | Atrial fibrillation |
|--------------------------|------------------------|---------------------|
| **N**                    | **Yes**                | **N**               | **Yes**     | **N**               | **Yes**     |
| 32,375 (76%)             | 10,208 (24%)           | 21,815 (49%)        | 20,768 (51%)| 18,827 (44%)        | 23,756 (56%)|

Demographics/organizational

| Valvular disease          | Age, yrs | Systolic BP, mmHg | Potassium, mEq/l | Hemoglobin, g/l | Heart rate, bpm | Mean arterial BP, mmHg | NYHA class |
|---------------------------|----------|-------------------|------------------|-----------------|-----------------|------------------------|------------|
| Male                      | 20,201 (62%) | 14,969 (69%)       | 4.1 (3.9, 4.4)   | 133 (17)        | 75 (12)        | 127 (21)               | 16,660 (54%)|
| Female                    | 12,174 (38%) | 11,886 (57%)       | 4.2 (3.9, 4.5)   | 129 (17)        | 73 (9)         | 128 (22)               | 5,156 (54%) |

Age, yrs

| <60 years                  | 74 (12) | 69 (13) | 70 (9) | 71 (13) | 76 (10) | <0.001   | 0.49      |
| ≥60 years                  | 0.026   | 0.001   | 0.44   |         |         |          |           |

Smoking

| No ICD or CRT             | 39,607 (96%) | 16,200 (95%) | 20,791 (94%) | 19,748 (95%) | 17,786 (96%) | 22,553 (96%) |
| CRT-P                     | 383 (1.2%)  | 316 (1.3%)  | 301 (1.0%)  | 318 (1.5%)  | 167 (0.9%)  | 352 (1.5%)   |
| CRT-D                     | 314 (1.0%)  | 140 (1.4%)  | 230 (1.1%)  | 224 (1.1%)  | 202 (1.1%)  | 252 (1.3%)   |
| ICD                       | 598 (1.9%)  | 180 (1.8%)  | 430 (2.0%)  | 438 (1.7%)  | 339 (1.8%)  | 439 (1.9%)   |

Smoking*

| No ICD or CRT             | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001   |
| CRT-P                     |       |       |       |       |       |          |
| CRT-D                     |       |       |       |       |       |          |
| ICD                       |       |       |       |       |       |          |

Comorbidities

| Smoker*                   | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001   |
| Never                     |       |       |       |       |       |          |
| Previous                  |       |       |       |       |       |          |
| Hypertension*             |       |       |       |       |       |          |
| T2DM*                     |       |       |       |       |       |          |
| Ischemic heart disease    |       |       |       |       |       |          |
| Coronary revascularization|       |       |       |       |       |          |
| Peripheral artery disease |       |       |       |       |       |          |
| Stroke/TIA                |       |       |       |       |       |          |
| AF*                       |       |       |       |       |       |          |
| CKD*                      |       |       |       |       |       |          |
| Anemia*                   |       |       |       |       |       |          |
| Valvular disease*         |       |       |       |       |       |          |
| Valvular intervention*    |       |       |       |       |       |          |

Smoker*                   | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001   |

Never                     |       |       |       |       |       |          |
| Previous                  |       |       |       |       |       |          |
| Hypertension*             |       |       |       |       |       |          |
| T2DM*                     |       |       |       |       |       |          |
| Ischemic heart disease    |       |       |       |       |       |          |
| Coronary revascularization|       |       |       |       |       |          |
| Peripheral artery disease |       |       |       |       |       |          |
| Stroke/TIA                |       |       |       |       |       |          |
| AF*                       |       |       |       |       |       |          |
| CKD*                      |       |       |       |       |       |          |
| Anemia*                   |       |       |       |       |       |          |
| Valvular disease*         |       |       |       |       |       |          |
| Valvular intervention*    |       |       |       |       |       |          |
3.2. Outcomes

3.2.1. Patients with vs. without T2DM and/or AF and/or CKD

Figs. 2–3, Supplementary Tables 12–15 and Supplementary Figs. 2–3 present results on six outcomes over a median follow-up of 2.22 (interquartile range: 0.88–4.08) years according to the three EF groups and three comorbidities.

The key outcomes findings are summarized as follows: 1) HFrEF had highest crude risk of all CV and HF events; HFrEF had highest crude risk of all-cause mortality, all-cause hospitalization and non-CV events; HFmrEF had lowest crude risk of all CV and HF events, but it was intermediate between HFrEF and HFrEF for the crude risk of non-CV events and similar to HFrEF for all-cause hospitalization and mortality; 2) HFrEF had the highest adjusted risk of CV and HF events and of all-cause death; HFrEF had the highest risk of all-cause hospitalization and non-CV events; HFmrEF was intermediate between HFrEF and HFrEF for the adjusted risk of CV and non-CV events, all-cause death and HF hospitalization, similar to HFrEF for all-cause hospitalization and to HFrEF for HF hospitalization; 3) in all EF subtypes, T2DM, AF and CKD were associated with greater risk of all outcomes, and this risk was lower after multivariable adjustment.

Table 1 (continued)

|                               | Type 2 Diabetes mellitus | P       | Chronic kidney disease | P       | Atrial fibrillation | P       |
|-------------------------------|--------------------------|---------|------------------------|---------|--------------------|---------|
|                               | No: N = 22,375(76%)      |         | No: N = 21,815(49%)    |         | No: N = 18,827(44%) |         |
|                               | Yes: N = 10,208(24%)     |         | Yes: N = 20,768(51%)   |         | Yes: N = 23,756(56%) |         |
| Liver disease                 | <0.001                   |         | <0.001                 | <0.001  | <0.001             | <0.001  |
| Cancer in the last 3 years    | 466(1%) 236(2%)          |         | 362(2%) 340(2%)        |         | 291(2%) 411(2%)    |         |
| Chronic obstructive pulmonary disease | 4403(14%) 1233(12%) | <0.001  | 2430(11%) 3206(15%)    | <0.001  | 2254(12%) 3382(14%) | <0.001  |
| Age, body mass index, blood pressure and hemoglobin are reported as mean (standard deviation), estimated glomerular filtration rate, N-terminal pro-B-type natriuretic peptide and potassium are reported as median (interquartile range).
| HF: heart failure; HFrEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); NT-proBNP: N-terminal pro-B-type natriuretic peptide; ACEi: angiotensin converting enzyme inhibitor; ARB: aldosterone receptor blocker; ICD: implantable cardioverter-defibrillator; CRT: cardiac resynchronization therapy; CRT-P: CRT-Pacemaker; CRT-D: CRT-Defibrillator; T2DM: type 2 diabetes mellitus; TIA: transient ischemic attack; AF: atrial fibrillation; CKD: chronic kidney disease.

* Variables included in multivariable models, and in multiple imputation models (together with the primary outcome). Continuous variables have been categorized as shown in Fig. 3.

Fig. 1. Venn diagram showing the interrelationship among type 2 diabetes mellitus, chronic kidney disease and atrial fibrillation. Abbreviations: HF: heart failure; HFrEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; T2DM: type 2 diabetes mellitus; AF: atrial fibrillation; CKD: chronic kidney disease.
T2DM similarly increased CV events and non-CV events but did so generally less in HFpEF, except for the increase in HF hospitalization which was similar in all three EF groups (Fig. 3; Supplementary Tables 14–15).

CKD had a greater effect on all-cause mortality than T2DM and AF, but less so in HFpEF. CKD increased CV and non-CV risk again less in HFpEF, except for HF hospitalization, where the risk increase was greatest in HFmrEF (Fig. 3; Supplementary Tables 14–15).

AF increased CV risk but had minimal effect on non-CV risk, and the CV risk increase appeared greatest in HFmrEF. (Fig. 3; Supplementary Tables 14–15).

3.2.2. Patients with combinations of AF, CKD and T2DM

A higher number of concomitant comorbidities was associated with greater risk of all the outcomes regardless of EF (Supplementary Figs. 4–5; Supplementary Tables 16–17), and in particular, with higher risk of outcomes in HFrEF vs. HFmrEF vs. HFpEF.

3.2.3. Predictors

Independent predictors of the higher risk of the primary outcome were consistent across the different comorbidities. Important predictors were male sex, older age, care in cardiology departments, lower EF, more severe HF, higher comorbidity burden, lower educational level and living alone vs. cohabitating (Supplementary Fig. 6; Supplementary Table 18). Relevant statistically significant interactions with EF regardless of concomitant CKD or AF or T2DM were observed for sex and age (both with lowest HRs in HFrEF), for ischemic heart disease in patients with CKD and or AF (with higher HRs in HFpEF vs. HFmrEF vs. HFrEF), and for CKD in patients with AF and T2DM (with highest HRs in HFmrEF and HFrEF) (Supplementary Table 19).

4. Discussion

In a large and unselected HF cohort, we performed comprehensive and detailed assessments of T2DM, CKD and AF, and analyzed their associations with cause-specific outcomes in the three HF subtypes defined by ejection fraction - HFrEF, HFmrEF and HFpEF.

The extensive results presented in multiple tables and figures and further described in a large supplement will be useful as comprehensive and quantitative reference material for epidemiologists, investigators or trialists seeking detailed outcome events data on particular combinations of HF subtypes with certain comorbidities.

Overall, several findings were consistent with those observed in isolation in smaller data sets and/or studies assessing single comorbidities or outcomes: HFpEF had more comorbidity and greater non-CV risk, and HFrEF had greater CV risk. However, several findings were more nuanced: HFrEF had distinctly greater risk of non-CV events, all-cause mortality, and all-cause hospitalization, but the risk of CV events was actually nearly as high in HFpEF as in HFrEF. Therefore, the common perception that HFpEF has low CV risk may rather reflect greater non-CV risk. CKD was distinctly more common in HFpEF and similar in HFmrEF and HFrEF; AF was most common in HFpEF and intermediate in HFmrEF; T2DM had similar prevalence regardless of EF. The consequence of CKD, T2DM and AF (i.e. risk increase due to the comorbidity), however, was distinctly lower in HFrEF.

4.1.1. Prevalence of AF, CKD and T2DM in HF

In our non-selective HF population, 56% had AF and 51% CKD, which is higher than in previous studies and may be reflective of a more contemporary and unselected HF population than in trials and of lower likelihood of underdiagnoses than in claims data analyses [8–12]. Patients with HFrEF had higher prevalence of AF and CKD vs. HFmrEF/HFrEF, which is consistent with the overall higher comorbidity burden in HFrEF vs. HFmrEF/HFrEF [3,13]. Previous studies showed similar prevalence in HFrEF and HFmrEF for CKD and AF, whereas we observed HFmrEF being more similar to HFrEF in CKD prevalence and intermediate between HFrEF and HFmrEF in AF prevalence [14,15]. CKD and AF are age-related comorbidities [4,5]. Differences in age distribution across the EF spectrum in ours vs. previous analyses may explain these discrepancies in prevalences [14,15]. We also show that T2DM had a

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**Fig. 2.** Kaplan Meier curves for all the outcomes in heart failure with preserved vs. mid-range vs. reduced ejection fraction.
prevalence of 24% in the overall population, with a similar distribution across the EF spectrum, which is consistent with previous analyses of both trial and registry cohorts [15].

Notably, we observed that the prevalence of combined CKD and AF was 22%, which was higher than the proportion with only CKD or T2DM and, unexpectedly, those with concomitant CKD and T2DM. Atrial remodeling caused by high atrial pressure due to CKD may contribute to explain this finding [16]. T2DM was more likely observed in combination with AF or CKD or with both than as a stand-alone comorbidity. Indeed, diabetes is characterized by an enhanced inflammation status which may play a role in the generation, maintenance and perpetuation of AF [17], but also DM is the leading cause of kidney failure [18].

4.1.2. Comorbidity associated patient characteristics

The presence of T2DM, CKD or AF was associated with patient characteristics linked with more severe HF, overall higher comorbidity burden, but less specialist care and higher use of diuretics. Consistently, this patient profile was even more distinct when more comorbidities coexisted. Patients with comorbidities may be referred to primary care to foster a more appropriate management of their comorbidities. This may result in underuse of HF-specific treatments [19], and may also limit the enrollment of patients with multiple comorbidities in HF randomized controlled trials, leading to selection bias, with lower comorbidity status in trials vs. real-world cohorts and less generalizability of trial results.

4.1.3. Interplay between EF, comorbidities and outcomes

As in previous analyses, we observed highest crude and adjusted risk of CV events in HFpEF, and highest risk of non-CV events in HfPEF, which is consistent with HfPEF having greater CV risk profile and HfPEF characterized by higher age, more females and comorbidities [3,20]. However, CV risk in HfPEF was nearly as high as in HfPEF, suggesting that the common perception of lower CV risk in HfPEF may instead be a reflection of higher competing non-CV risk.

Consistent with more severe HF in the presence of CKD and/or T2DM and/or AF, each comorbidity affected mortality/morbidity regardless of EF. Higher comorbidity burden was associated with higher risk of outcomes in HfPEF vs. HfMfEF vs. HfPEF. Consistently, AF affected overall mortality and hospitalization more in HfMfEF and HfPEF vs. HfPEF. Our findings highlight that although CKD and AF are more common in HfPEF, they may represent two among many other comorbidities contributing to HfPEF pathophysiology and driving its development and progression over time (i.e. risk factors), while they may be more likely linked with HF severity in HfMfEF and HfPEF (i.e. risk markers). The stronger interaction between T2DM and ischemic heart disease in HfPEF and HfMfEF vs. HfPEF may explain the higher T2DM-associated risk of CV events and overall mortality in HfMfEF and HfPEF vs. HfPEF [21]. Although, as shown in our and previous analyses, HfPEF carried the highest risk of non-CV events [20], surprisingly AF, CKD and/or T2DM affected non-CV risk more in HfMfEF and HfPEF, which may be explained by higher impact of these three comorbidities on non-CV risk when the overall comorbidity burden is lower, as it is in HfMfEF/ HfPEF vs. HfPEF.

4.1.4. Limitations

We analyzed several outcomes but due to the explanatory nature of our analyses, we did not adjust for multiplicity. We did not consider competing risk in our survival analyses, which could have led to estimates of cumulative incidence and predicted risk biased upwards [22]. Around 15% of the SwedeHF population was excluded due to missing EF, which might increase the chances of a selection bias. We defined the HF phenotype based on the EF at the registration, but due to the limited availability of longitudinal data on EF in SwedeHF, we could not assess whether EF had changed at the time of the clinical events. Although we assessed and adjusted for use of several HF/CV treatments, we could not investigate procedures such as mechanical circulatory support, heart transplantation and AF ablation. Since SwedeHF has incomplete coverage (54%), with most patients enrolled in secondary care, this
may affect prevalence estimates and limit generalizability. Additionally, lifestyle and geographic factors influence the comorbidity burden and thus generalizability of our analyses of a national registry to other countries may be limited. Finally, due to the lack of a systematic screening, T2DM prevalence may be underestimated.

5. Conclusions

We found that the risk of CV events was nearly as high in HfP EF as in HFrEF and therefore, the common perception that HfP EF has low CV risk may rather reflect greater non-CV risk. We also confirmed that HfP EF had more comorbidity and greater non-CV risk, while HFrEF had greater CV risk. CKD was linked to HfP EF, AF was gradually more common with higher EF, and T2DM was similarly prevalent regardless of EF. However, the consequence of CKD, T2DM and AF (i.e. the respective contribution to risk) was distinctly lower in HfP EF. These findings highlight that if trialists wish to enrich for CV vs. non-CV events, they should not exclude patients with lower EF, AF and/or CKD.

Author statement

GS: conceptualization, methodology, analysis, writing – original draft, supervision.
LHL: conceptualization, writing - review & editing.
CS and BS: writing – original draft.
TT, IL, SFF, MB, KGB, OV, FWA, UD, FC: writing – review & editing.

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Declaration of competing interest

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CS, BS, TT, IL, US, LB, FC, FA: None related with the current study. AM, SFF, MB, KGB and OV are employed by Boehringer Ingelheim.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.04.068.

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