

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

Gianluigi Savarese^{a,*}, Camilla Settergren^a, Benedikt Schrage^a, Tonje Thorvaldsen^a, Ida Löfman^a, Ulrik Sartipy^{b,c}, Linda Mellbin^a, Andrea Meyers^d, Soulmaz Fazeli Farsani^e, Martina Brueckmann^{e,f}, Kimberly G. Brodovicz^d, Ola Vedin^{g,h}, Folkert W. Asselbergs^{i,j,k}, Ulf Dahlström^{l,m}, Francesco Cosentino^a, 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 Faculty of Medicine Mannheim at the University of Heidelberg, Mannheim, Germany

^g Affiliation is Boehringer Ingelheim AB, Sweden

^h Department of Medical Sciences, Uppsala University, Uppsala, Sweden

ⁱ Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

^j Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom

^k Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom

^l Department of Cardiology, Linköping University, Linköping, Sweden

^m Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

ARTICLE INFO

Article history:

Received 31 March 2020

Received in revised form 17 April 2020

Accepted 24 April 2020

Available online 30 April 2020

Keywords:

Type 2 diabetes mellitus

Chronic kidney disease

Atrial fibrillation

Heart failure

Ejection fraction

Trial design

ABSTRACT

Background: Comorbidities may differently affect treatment response and cause-specific outcomes in heart failure (HF) with preserved (HFpEF) 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. HFpEF had higher prevalence of CKD and AF, HFmrEF 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 HFpEF. CKD increased CV events somewhat more than non-CV events and less so in HFpEF. AF increased CV events considerably more than non-CV events and more so in HFpEF and HFmrEF.

Conclusion: HFpEF is distinguished from HFmrEF and HFrEF 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.

© 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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].

* Corresponding author at: Division of Cardiology, Department of Medicine, Karolinska Institutet, SE-17176 Stockholm, Sweden.

E-mail address: gianluigi.savarese@ki.se (G. Savarese).

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 HFpEF, 21% HFmrEF and 56% HFrEF. 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). HFpEF had greater prevalence of AF (64%) and CKD (56%). HFmrEF and HFrEF had lower prevalence of CKD (48% and 46%, respectively), HFmrEF had intermediate prevalence of AF (58%), which was lowest in HFrEF (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 HFrEF, 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 HFrEF (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		P	Chronic kidney disease		P	Atrial fibrillation		P
	No N = 32,375 (76%)	Yes N = 10,208 (24%)		No N = 21,815 (49%)	Yes N = 20,768 (51%)		No N = 18,827 (44%)	Yes N = 23,756 (56%)	
Demographics/organizational									
Sex*			<0.001			<0.001			0.49
Male	20,201 (62%)	6654 (65%)		14,969 (69%)	11,886 (57%)		11,839 (63%)	15,016 (63%)	
Female	12,174 (38%)	3554 (35%)		6846 (31%)	8882 (43%)		6988 (37%)	8740 (37%)	
Age, yrs*	74 (12)	73 (10)	0.040	69 (13)	79 (9)	<0.001	71 (13)	76 (10)	<0.001
Specialty*			0.026			<0.001			0.44
Internal medicine/geriatrics	13,933 (46%)	4543 (47%)		9134 (44%)	9342 (48%)		8118 (46%)	10,358 (46%)	
Cardiology	16,660 (54%)	5156 (53%)		11,541 (56%)	10,275 (52%)		9669 (54%)	12,147 (54%)	
Caregiver*			<0.001			<0.001			<0.001
Inpatient	17,971 (56%)	6487 (64%)		11,131 (51%)	13,327 (64%)		9836 (52%)	14,622 (62%)	
Outpatient	14,404 (44%)	3721 (36%)		10,684 (49%)	7441 (36%)		8991 (48%)	9134 (38%)	
Follow-up referral specialty*			<0.001			<0.001			<0.001
Specialty care	19,126 (63%)	5654 (59%)		14,561 (71%)	10,219 (53%)		11,848 (67%)	12,932 (58%)	
Primary care/Other	11,341 (37%)	3882 (41%)		6068 (29%)	9155 (47%)		5953 (33%)	9270 (42%)	
Follow-up at nurse-led HF clinic*	18,175 (60%)	5963 (63%)	<0.001	9406 (46%)	6409 (33%)	<0.001	7716 (43%)	8099 (36%)	<0.001
HF type*			0.22			<0.001			<0.001
HFpEF	7424 (23%)	2425 (24%)		4370 (20%)	5479 (26%)		3552 (19%)	6297 (27%)	
HFmrEF	6985 (22%)	2166 (21%)		4736 (22%)	4415 (21%)		3808 (20%)	5343 (22%)	
HFrEF	17,966 (55%)	5617 (55%)		12,709 (58%)	10,874 (52%)		11,467 (61%)	12,116 (51%)	
Clinical									
Duration of HF*			<0.001			<0.001			<0.001
<6 months	16,909 (53%)	4310 (42%)		12,808 (59%)	8411 (41%)		10,615 (57%)	10,604 (45%)	
≥6 months	15,241 (47%)	5846 (58%)		8859 (41%)	12,228 (59%)		8087 (43%)	13,000 (55%)	
NYHA class*			<0.001			<0.001			<0.001
I	3010 (13%)	606 (8%)		2518 (15%)	1098 (8%)		1950 (14%)	1666 (10%)	
II	11,465 (48%)	2998 (42%)		8393 (51%)	6070 (42%)		6768 (49%)	7695 (45%)	
III	8432 (36%)	3187 (44%)		5057 (31%)	6562 (45%)		4695 (34%)	6924 (41%)	
IV	818 (3%)	388 (5%)		414 (3%)	792 (5%)		493 (4%)	713 (4%)	
BMI, kg/m ² *	26 (5)	29 (6)	<0.001	27 (6)	27 (5)	<0.001	27 (5)	27 (5)	0.064
Systolic BP, mmHg	127 (21)	130 (21)	<0.001	127 (21)	128 (22)	0.007	129 (22)	127 (21)	<0.001
Diastolic BP, mmHg	74 (12)	73 (12)	<0.001	75 (12)	72 (12)	<0.001	73 (12)	74 (12)	<0.001
Mean arterial BP, mmHg*	91 (13)	92 (13)	0.034	92 (13)	91 (13)	<0.001	92 (14)	91 (13)	0.85
Heart rate, bpm*	74 (16)	74 (15)	0.006	74 (16)	74 (15)	0.75	71 (14)	76 (17)	<0.001
Laboratory									
eGFR, ml/min/1.73 m ²	62 (46, 80)	56 (39, 75)	<0.001	78 (68, 89)	44 (34, 52)	<0.001	65 (47, 84)	58 (42, 74)	<0.001
Potassium, mEq/l	4.1 (3.9, 4.4)	4.2 (3.9, 4.5)	0.001	4.1 (3.9, 4.4)	4.2 (3.9, 4.5)	<0.001	4.2 (3.9, 4.4)	4.1 (3.8, 4.4)	<0.001
Hemoglobin, g/l	133 (17)	129 (17)	<0.001	136 (17)	128 (17)	<0.001	132 (17)	132 (18)	0.019
NT-proBNP, pg/ml*	2570 (1110, 5707)	2688 (1200, 5990)	0.098	1898 (824, 4130)	3820 (1740, 8295)	<0.001	2060 (747, 5357)	3000 (1486, 6070)	<0.001
Treatments									
ACEi or ARB*	27,064 (84%)	8720 (86%)	<0.001	19,564 (90%)	16,220 (79%)	<0.001	16,269 (87%)	19,515 (83%)	<0.001
Mineralocorticoid receptor antagonist*	9054 (28%)	3382 (33%)	<0.001	6245 (29%)	6191 (30%)	0.007	5104 (27%)	7332 (31%)	<0.001
Digoxin*	5726 (18%)	1662 (16%)	<0.001	4010 (18%)	3378 (16%)	<0.001	677 (4%)	6711 (28%)	<0.001
Diuretic*	24,934 (77%)	8946 (88%)	<0.001	15,326 (71%)	18,554 (90%)	<0.001	13,781 (74%)	20,099 (85%)	<0.001
Nitrate*	4677 (15%)	2346 (23%)	<0.001	2381 (11%)	4642 (23%)	<0.001	3133 (17%)	3890 (16%)	0.51
Platelet inhibitor*	15,660 (49%)	5947 (59%)	<0.001	10,672 (49%)	10,935 (53%)	<0.001	12,668 (68%)	8939 (38%)	<0.001
Oral anticoagulant*	12,818 (40%)	3669 (36%)	<0.001	8434 (39%)	8053 (39%)	0.85	2269 (12%)	14,218 (60%)	<0.001
Statins*	13,162 (41%)	6240 (61%)	<0.001	10,039 (46%)	9363 (45%)	0.054	9904 (53%)	9498 (40%)	<0.001
Beta blocker*	27,787 (86%)	8943 (88%)	<0.001	18,910 (87%)	17,820 (86%)	0.004	16,004 (85%)	20,726 (88%)	<0.001
HF device*			0.003			<0.001			<0.001
No ICD or CRT	30,878 (96.0%)	9661 (95.5%)		20,791 (96.0%)	19,748 (95.7%)		17,986 (96.2%)	22,553 (95.6%)	
CRT-P	383 (1.2%)	136 (1.3%)		201 (0.9%)	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 (1.1%)	
ICD	598 (1.9%)	180 (1.8%)		430 (2.0%)	348 (1.7%)		339 (1.8%)	439 (1.9%)	
Comorbidities									
Smoking*			<0.001			<0.001			<0.001
Never	11,125 (44%)	3198 (41%)		6985 (39%)	7338 (48%)		6046 (40%)	8277 (46%)	
Previous	10,684 (42%)	3703 (47%)		7740 (43%)	6647 (44%)		6689 (44%)	7698 (43%)	
Current	3441 (14%)	993 (13%)		3140 (18%)	1294 (8%)		2549 (17%)	1885 (11%)	
Hypertension*	17,917 (55%)	7685 (75%)	<0.001	11,601 (53%)	14,001 (67%)	<0.001	10,781 (57%)	14,821 (62%)	<0.001
T2DM*	0 (0%)	10,208 (100%)	<0.001	4489 (21%)	5719 (28%)	<0.001	4762 (25%)	5446 (23%)	<0.001
Ischemic heart disease*	15,995 (51%)	6673 (67%)	<0.001	10,208 (49%)	12,460 (62%)	<0.001	11,042 (61%)	11,626 (51%)	<0.001
Coronary revascularization*	8764 (27%)	4038 (40%)	<0.001	6253 (29%)	6549 (32%)	<0.001	6450 (34%)	6352 (27%)	<0.001
Peripheral artery disease*	2827 (9%)	1456 (14%)	<0.001	1576 (7%)	2707 (13%)	<0.001	1845 (10%)	2438 (10%)	0.11
Stroke/TIA*	5184 (16%)	2011 (20%)	<0.001	2916 (13%)	4279 (21%)	<0.001	2531 (13%)	4664 (20%)	<0.001
AF*	18,310 (57%)	5446 (53%)	<0.001	10,941 (50%)	12,815 (62%)	<0.001	0 (0%)	23,756 (100%)	<0.001
CKD*	15,049 (46%)	5719 (56%)	<0.001	0 (0%)	20,768 (100%)	<0.001	7953 (42%)	12,815 (54%)	<0.001
Anemia*	10,301 (32%)	4348 (43%)	<0.001	5551 (25%)	9098 (44%)	<0.001	6228 (33%)	8421 (35%)	<0.001
Valvular disease*	8613 (27%)	2317 (23%)	<0.001	4759 (22%)	6171 (30%)	<0.001	3959 (22%)	6971 (30%)	<0.001
Valvular intervention*	2090 (7%)	602 (6%)	0.054	1283 (6%)	1409 (7%)	<0.001	714 (4%)	1978 (8%)	<0.001
Major bleeding*	6195 (19%)	2324 (23%)	<0.001	3439 (16%)	5080 (24%)	<0.001	3156 (17%)	5363 (23%)	<0.001

Table 1 (continued)

	Type 2 Diabetes mellitus		P	Chronic kidney disease		P	Atrial fibrillation		P
	No N = 32,375 (76%)	Yes N = 10,208 (24%)		No N = 21,815 (49%)	Yes N = 20,768 (51%)		No N = 18,827 (44%)	Yes N = 23,756 (56%)	
Liver disease*	466 (1%)	236 (2%)	<0.001	362 (2%)	340 (2%)	0.86	291 (2%)	411 (2%)	0.14
Cancer in the last 3 years*	4403 (14%)	1233 (12%)	<0.001	2430 (11%)	3206 (15%)	<0.001	2254 (12%)	3382 (14%)	<0.001
Chronic obstructive pulmonary disease*	5493 (17%)	2010 (20%)	<0.001	3595 (16%)	3908 (19%)	<0.001	3263 (17%)	4240 (18%)	0.16
Socioeconomical									
Family type*			0.74			<0.001			0.44
Living alone	16,616 (51%)	5224 (51%)		10,629 (49%)	11,211 (54%)		9613 (51%)	12,227 (52%)	
Married/cohabitating	15,687 (49%)	4969 (49%)		11,124 (51%)	9532 (46%)		9168 (49%)	11,488 (48%)	
Education*			<0.001			<0.001			<0.001
Compulsory school	15,397 (48%)	5348 (53%)		9564 (44%)	11,181 (55%)		8823 (47%)	11,922 (51%)	
Secondary school	11,826 (37%)	3564 (35%)		8592 (40%)	6798 (33%)		7171 (39%)	8219 (35%)	
University	4787 (15%)	1171 (12%)		3429 (16%)	2529 (12%)		2602 (14%)	3356 (14%)	
Income (Above/equal to median)*	16,572 (51%)	4651 (46%)	<0.001	12,225 (56%)	8998 (43%)	<0.001	9472 (51%)	11,751 (50%)	0.067
Number of children (>2)*	10,011 (31%)	3374 (33%)	<0.001	6698 (31%)	6687 (32%)	<0.001	5834 (31%)	7551 (32%)	0.078

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; HFpEF: 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.

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; HFpEF 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 HFpEF 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; HFpEF had the highest risk of all-cause hospitalization and non-CV events; HFmrEF was intermediate between HFpEF 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 HFpEF 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.

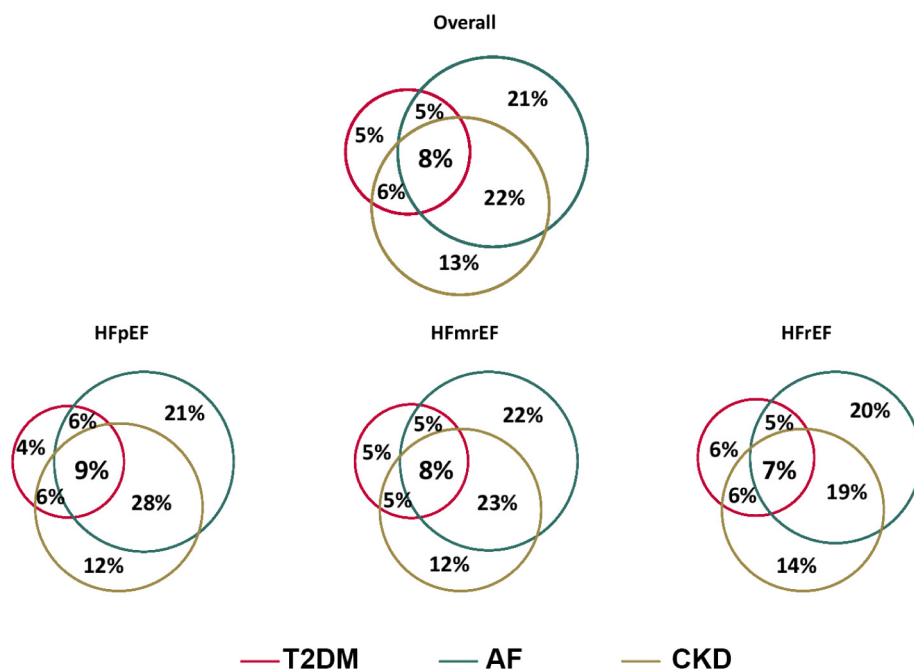


Fig. 1. Venn diagram showing the interrelationship among type 2 diabetes mellitus, chronic kidney disease and atrial fibrillation. Abbreviations: HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; HFrEF: heart failure with reduced ejection fraction; T2DM: type 2 diabetes mellitus; AF: atrial fibrillation; CKD: chronic kidney disease.

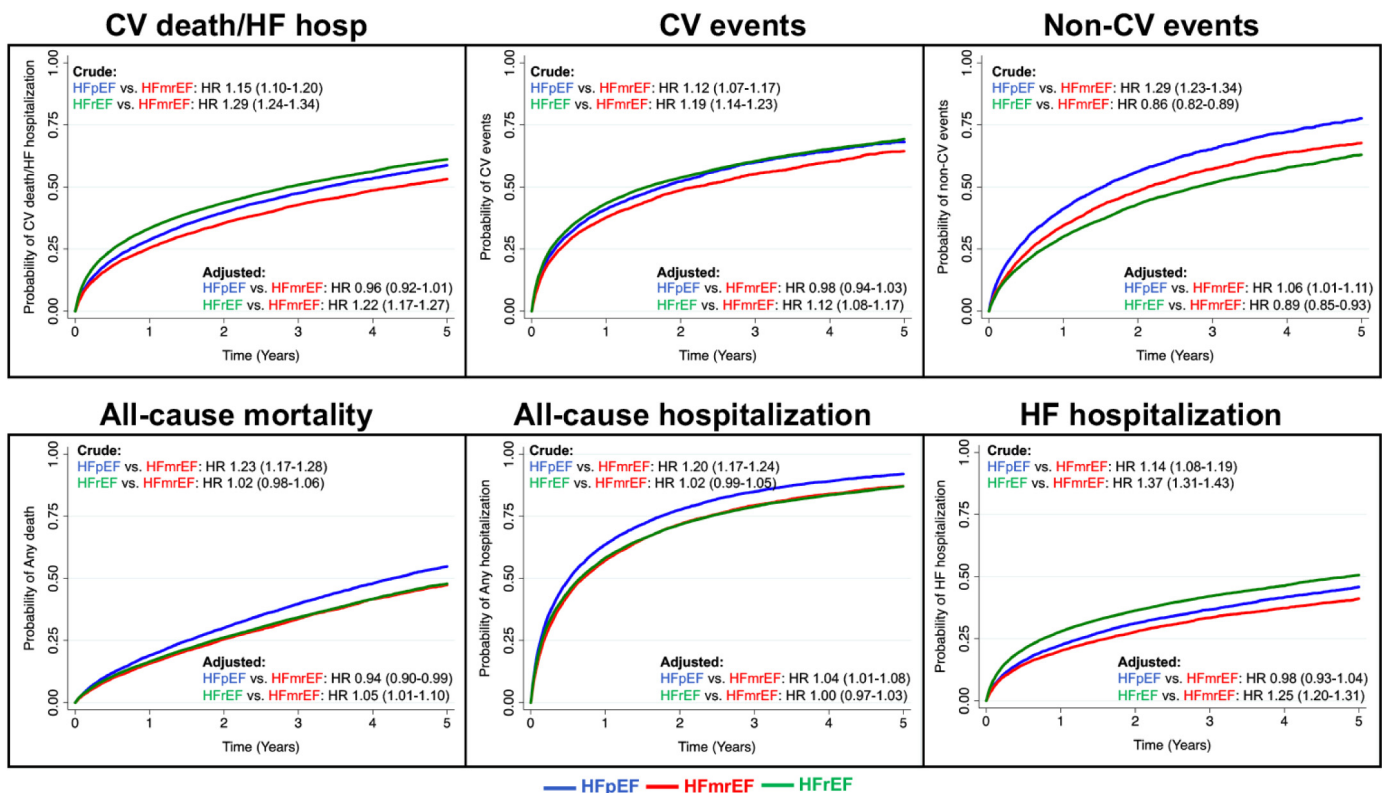


Fig. 2. Kaplan Meier curves for all the outcomes in heart failure with preserved vs. mid-range vs. reduced ejection fraction.

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 HFrfEF 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 HFrfEF), for ischemic heart disease in patients with CKD and or AF (with higher HRs in HFrfEF vs. HFmrEF vs. HFpEF), and for CKD in patients with AF and T2DM (with highest HRs in HFmrEF and HFpEF) (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 - HFpEF, HFmrEF and HFrfEF.

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 HFrfEF had greater CV risk. However, several findings were more nuanced: HFpEF 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 HFrfEF. 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 HFrfEF; 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 HFpEF.

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 HFpEF had higher prevalence of AF and CKD vs. HFmrEF/HFrEF, which is consistent with the overall higher comorbidity burden in HFpEF vs. HFmrEF/HFrEF [3,13]. Previous studies showed similar prevalence in HFpEF and HFmrEF for CKD and AF, whereas we observed HFmrEF being more similar to HFrEF in CKD prevalence and intermediate between HFpEF and HFrEF 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

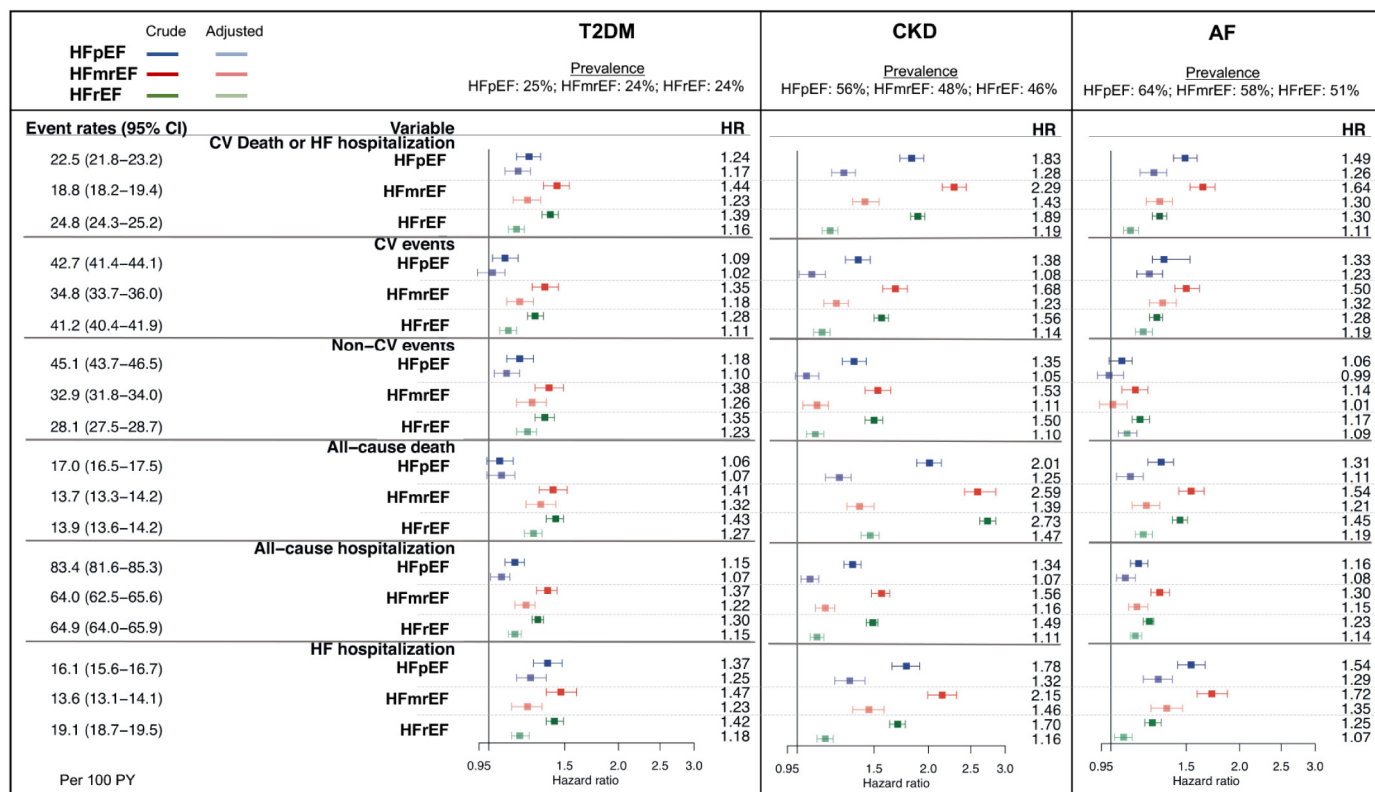


Fig. 3. (Take-home figure). Risk of outcomes in patients with type 2 diabetes mellitus, chronic kidney disease and atrial fibrillation. Abbreviations: as in Fig. 1 + HR: hazard ratio; CI: confidence interval; PY: patient-years.

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 HFrEF, and highest risk of non-CV events in HFpEF, which is consistent with HFrEF 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 HFrEF, 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 HFrEF vs. HFmrEF vs. HFpEF. Consistently, AF affected overall mortality and hospitalization more in HFmrEF and HFrEF 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 HFmrEF and HFrEF (i.e. risk markers). The stronger interaction between T2DM and ischemic heart disease in HFrEF and HFmrEF vs. HFpEF may explain the higher T2DM-associated risk of CV events and overall mortality in HFmrEF and HFrEF 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 HFmrEF and HFrEF, 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 HFmrEF/HFrEF 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 HFpEF as in HFrEF and therefore, the common perception that HFpEF has low CV risk may rather reflect greater non-CV risk. We also confirmed that HFpEF had more comorbidity and greater non-CV risk, while HFrEF had greater CV risk. CKD was linked to HFpEF, 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 HFpEF. 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.

Funding

This study received support from Boehringer Ingelheim and the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking BigData@Heart grant (no. 116074).

Declaration of competing interest

GS reports grants and personal fees from Vifor, non-financial support from Boehringer Ingelheim, personal fees from Societa' Prodotti Antibiotici, grants from MSD, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, personal fees from GENESIS, personal fees from Medtronic, personal fees from Cytokinetics, outside the submitted work.

LHL reports grants and personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Merck, personal fees from Sanofi, grants and personal fees from Vifor-Fresenius, grants and personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, grants and personal fees from Novartis, personal fees from Pharmacosmos, personal fees from Abbott, grants and personal fees from Mundipharma, personal fees from Medscape, outside the submitted work.

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>.

References

- [1] G. Savarese, L.H. Lund, Global public health burden of heart failure, *Cardiac Failure Review*. 3 (2017) 7–11.
- [2] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, *Eur. Heart J.* 37 (2016) 2129–2200.
- [3] A.S. Koh, W.T. Tay, T.H.K. Teng, O. Vedin, L. Benson, U. Dahlstrom, et al., A comprehensive population-based characterization of heart failure with mid-range ejection fraction, *Eur. J. Heart Fail.* 19 (2017) 1624–1634.
- [4] U. Sartipy, U. Dahlstrom, M. Fu, L.H. Lund, Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction, *JACC Heart Fail.* 5 (2017) 565–574.
- [5] I. Lofman, K. Szummer, U. Dahlstrom, T. Jernberg, L.H. Lund, Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction, *Eur. J. Heart Fail.* 19 (12) (2017) 1606–1614.
- [6] I. Johansson, U. Dahlström, M. Edner, P. Näsman, L. Rydén, A. Norhammar, Type 2 diabetes and heart failure: characteristics and prognosis in preserved, mid-range and reduced ventricular function, *Diabetes and Vascular Disease Research*. 15 (2018) 494–503.
- [7] G. Savarese, P. Vasko, A. Jonsson, M. Edner, U. Dahlstrom, L.H. Lund, The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure, *Ups. J. Med. Sci.* (2018) 1–5.
- [8] L.H. Lund, B. Claggett, J. Liu, C.S. Lam, P.S. Jhund, G.M. Rosano, et al., Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum, *Eur. J. Heart Fail.* 20 (8) (2018) 1230–1239.
- [9] S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, et al., Angiotensin-Nepirylsin inhibition in heart failure with preserved ejection fraction, *N. Engl. J. Med.* 381 (2019) 1609–1620.
- [10] J.J. McMurray, M. Packer, A.S. Desai, J. Gong, M.P. Lefkowitz, A.R. Rizkala, et al., Angiotensin-nepirylsin inhibition versus enalapril in heart failure, *N. Engl. J. Med.* 371 (2014) 993–1004.
- [11] Z.J. Eapen, M.A. Greiner, G.C. Fonarow, Z. Yuan, R.M. Mills, A.F. Hernandez, et al., Associations between atrial fibrillation and early outcomes of patients with heart failure and reduced or preserved ejection fraction, *Am. Heart J.* 167 (2014) 369–375 (e2).
- [12] S. Ather, W. Chan, B. Bozkurt, D. Aguilar, K. Ramasubbu, A.A. Zachariah, et al., Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction, *J. Am. Coll. Cardiol.* 59 (2012) 998–1005.
- [13] J. Tromp, W.T. Tay, W. Ouwerkerk, T.K. Teng, J. Yap, M.R. MacDonald, et al., Multimorbidity in patients with heart failure from 11 Asian regions: a prospective cohort study using the ASIAN-HF registry, *PLoS Med.* 15 (2018) e1002541.
- [14] B.A. Steinberg, X. Zhao, P.A. Heidenreich, E.D. Peterson, D.L. Bhatt, C.P. Cannon, et al., Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes, *Circulation*. 126 (2012) 65–75.
- [15] G.C. Fonarow, W.G. Stough, W.T. Abraham, N.M. Albert, M. Gheorghiade, B.H. Greenberg, et al., Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry, *J. Am. Coll. Cardiol.* 50 (2007) 768–777.
- [16] E.L. Schiffrin, M.L. Lipman, J.F. Mann, Chronic kidney disease: effects on the cardiovascular system, *Circulation*. 116 (2007) 85–97.
- [17] M.K. Chung, D.O. Martin, D. Sprecher, O. Wazni, A. Kanderian, C.A. Carnes, et al., C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation, *Circulation*. 104 (2001) 2886–2891.
- [18] R.Z. Alicic, M.T. Rooney, K.R. Tuttle, Diabetic kidney disease: challenges, progress, and possibilities, *Clin. J. Am. Soc. Nephrol.* 12 (2017) 2032–2045.
- [19] G. Savarese, L.H. Lund, U. Dahlstrom, A. Stromberg, Nurse-led heart failure clinics are associated with reduced mortality but not heart failure hospitalization, *J. Am. Heart Assoc.* 8 (2019), e011737.
- [20] G. Savarese, N. Orsini, C. Hage, O. Vedin, F. Cosentino, G.M.C. Rosano, et al., Utilizing NT-proBNP for eligibility and enrichment in trials in HFpEF, HFmrEF, and HFrEF, *Jacc-Heart Fail.* 6 (2018) 246–256.
- [21] O. Vedin, C.S.P. Lam, A.S. Koh, L. Benson, T.H.K. Teng, W.T. Tay, et al., Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a Nationwide cohort study, *Circ Heart Fail.* 10 (2017).
- [22] H. Abdel-Qadir, J. Fang, D.S. Lee, J.V. Tu, E. Amir, P.C. Austin, et al., Importance of considering competing risks in time-to-event analyses: application to stroke risk in a retrospective cohort study of elderly patients with atrial fibrillation, *Circ Cardiovasc Qual Outcomes*. 11 (2018) e004580.