Original Article

Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction

A Nationwide Cohort Study

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***Background*—**The pathogenic role of ischemic heart disease (IHD) in heart failure (HF) with reduced ejection fraction (HFrEF; EF <40%) is well established, but its pathogenic and prognostic significance in HF with midrange (HFmrEF; EF 40%–50%) and preserved EF (HFpEF; EF ≥50%) has been much less explored.

***Methods and Results*—**We evaluated 42 987 patients from the Swedish Heart Failure Registry with respect to baseline IHD, outcomes (IHD, HF, cardiovascular events, and all-cause death), and EF change during a median follow-up of 2.2 years. Overall, 23% had HFpEF (52% IHD), 21% had HFmrEF (61% IHD), and 55% had HFrEF (60% IHD). After multivariable adjustment, associations with baseline IHD were similar for HFmrEF and HFrEF and lower in HFpEF (risk ratio, 0.91 [0.89–0.93] versus HFmrEF and risk ratio, 0.90 [0.88–0.92] versus HFrEF). The adjusted risk of IHD events was similar for HFmrEF versus HFrEF and lower in HFpEF (hazard ratio, 0.89 [0.84–0.95] versus HFmrEF and hazard ratio, 0.84 [0.80–0.90] versus HFrEF). After adjustment, prevalent IHD was associated with increased risk of IHD events and all other outcomes in all EF categories except all-cause mortality in HFpEF. Those with IHD, particularly new IHD events, were also more likely to change to a lower EF category and less likely to change to a higher EF category over time.

***Conclusions*—**HFmrEF resembled HFrEF rather than HFpEF with regard to both a higher prevalence of IHD and a greater risk of new IHD events. Established IHD was an important prognostic factor across all HF types. **(*Circ Heart Fail*. 2017;10:e003875. DOI: 10.1161/CIRCHEARTFAILURE.117.003875.)**

Key Words: acute coronary syndrome ■ heart failure ■ outcomes ■ prevalence ■ registry

The classification of heart failure (HF) into HF with reduced ejection fraction (HFrEF; EF <40%) versus HF with preserved ejection fraction (HFpEF; EF ≥50%) leaves a significant proportion of patients with HF in the EF gap of 40% to 49%. These patients were specifically identified in recent international HF guidelines as having HF with midrange EF (HFmrEF), and for whom large gaps in knowledge exist.[1–4]

See Clinical Perspective

Ischemic heart disease (IHD) is a major underlying pathogenic factor in HF, increasing the risk of HF 8-fold and with a population-attributable risk of 65% in men and 48% in women.[5] However, with an aging population and increasingly effective treatment of the acute coronary syndrome resulting in less extensive myocardial damage and chronic remodeling, the impact of IHD on HF and its subtypes is evolving. This was further underscored by recent evidence pointing to a temporal shift in the mix of type of HF post-IHD events, increasingly favoring HFmrEF and HFpEF compared with HFrEF.[6] However, crucial gaps in evidence include scarce and highly variable data on IHD prevalence in HFmrEF and HFpEF[2,7–14]; a poor understanding of how different HF types affect ischemic outcomes[15,16]; and uncertainty about the role of established IHD in determining the risk of new ischemic events and other outcomes and longitudinal changes in EF in HFmrEF and HFpEF versus HFrEF.[7,9,17–19]

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We used the Swedish Heart Failure Registry (SwedeHF) to assess the independent association between (1) HF type (HFpEF versus HFmrEF versus HFrEF) and prevalent IHD; (2) HF type and new IHD events; (3) prevalent IHD and the risk of new ischemic and other events in HFpEF, HFmrEF, and HFrEF separately; and finally (4) concurrent prevalent and incident IHD and longitudinal EF changes across the different HF types.

Methods

Study Setting and Baseline Characteristics

SwedeHF has been previously described.[20] The protocol, case report form, and annual reports are available at http://www.SwedeHF.se. Both inpatients and outpatients from HF specialty clinics are included based on the only inclusion criterion of clinician-judged HF. There are no exclusion criteria apart from lack of HF. Approximately 80 variables are recorded at hospital discharge or clinic visit and are subsequently entered into a database managed by Uppsala Clinical Research Center (Uppsala, Sweden; www.ucr.uu.se).

SwedeHF provided the study population and baseline characteristics. Index date was defined as date of outpatient visit or hospital discharge, and the eligible inclusion interval was May 11, 2000 (start of SwedeHF), to December 31, 2012 (date of last baseline and follow-up data for this study). Patients who died during hospitalization and patients with missing EF and repeat registrations were excluded from the main analysis (Figure 1). As an exception, for the descriptive data on longitudinal EF, repeat registrations were included (see below). Additional baseline comorbidity was provided by *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes (Table I in the Data Supplement) from the National Patient Registry managed by The National Board of Health and Welfare (www.sos.se).[21] All diagnoses were considered if present from January 1, 1997 (when use of *ICD-10* codes began in Sweden), and up to and including the index date, except cancer, musculoskeletal disease, and psychiatric illness, considered active only if present in the past 3 years before index date.[13] Baseline socioeconomic variables were obtained from Statistics Sweden (www.scb.se).[22]

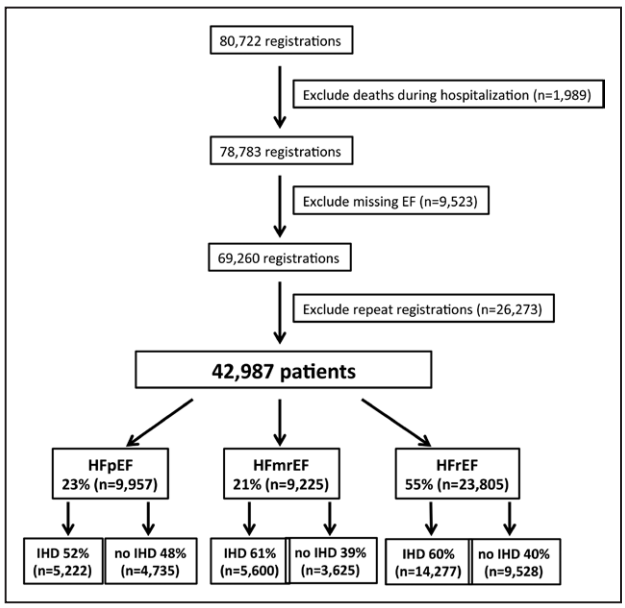

Figure 1. Patient inclusion flow chart. EF indicates ejection fraction; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and IHD, ischemic heart disease.

Ejection Fraction

In SwedeHF, EF is reported in intervals of <30%, 30% to 39%, 40% to 49%, and ≥50%. In the present analysis, HFpEF was defined as EF ≥50%, HFmrEF as ≥40% to 49%, and HFrEF as ≤39% according to the 2016 European Society of Cardiology HF Guidelines.[1]

Outcomes

The primary outcome was time to a fatal or nonfatal IHD event (with censoring at non-IHD death). Secondary outcomes were time to fatal or nonfatal HF event (with censoring at non-HF death), fatal or nonfatal cardiovascular event (with censoring at noncardiovascular death), and all-cause mortality.

Definitions of Baseline IHD and Outcomes

Details on which *ICD-10* codes and other variables were used to define baseline IHD, cause-specific outcomes, and baseline variables included in multivariable models are provided in Table I in the Data Supplement. Baseline IHD was established based on either documented IHD in SwedeHF or an *ICD-10* diagnosis in any position corresponding to IHD or revascularization before the index event in the National Patient Registry (but no earlier than January 1, 1997). New IHD events, HF, and cardiovascular events included both nonfatal and fatal events after the index date and were based on *ICD-10* codes from the National Patient Registry in main position (main or contributory position for revascularization) or Cause of Death Registry, as the underlying cause of death (ie, not mode of death). Validation studies of *ICD-10* discharge diagnoses in the National Patient Registry have demonstrated a positive predictive value of 95% to 100% for ischemic outcomes[23] and 95% for HF[24] when using corresponding ICD codes as a primary diagnosis, which was also done in the present study. Ascertainment of cause of death is based on death certificates and has been shown to be less reliable.[25]

Statistics

Descriptive Data

Descriptive data were compared for IHD versus no IHD within each EF group with the χ^2 or Kruskal–Wallis test and are displayed as percentages or median and interquartile range for categorical and continuous variables, respectively.

Associations Between HF Type, Baseline IHD, and Outcomes

All multivariable models included 39 to 40 baseline covariates, depending on whether baseline IHD was used as a covariate. To avoid bias because of data not missing completely at random, multiple imputation (n=10) using predictive mean matching was performed for the baseline variables with missing data, using the same 40 variables, including the outcome, IHD, although not imputed itself because it contained no missing values. Imputation corrections to the resulting SEs were performed.

Multivariable generalized estimating equations with a Poisson distribution and a log link with robust variance[26] were used to estimate risk ratios for associations between HF type and baseline IHD, with IHD as the dependent variable.

Event rates for new IHD events, HF, cardiovascular events, and all-cause death were presented by HF type and by IHD yes versus no within each HF type as number of events/total number of patients and incidence/1000 patient-years including 95% Poisson confidence intervals (CIs) for incidence.

Cumulative incidence was calculated and presented as Kaplan–Meier curves, 1 for each of the 4 outcomes, stratified for EF and baseline IHD.

Uni- and multivariable Cox proportional hazards models were used to determine associations between HF type and new IHD events. Associations between baseline IHD and all outcomes within each HF type were also assessed by Cox regression. The proportional hazards assumption was tested for the multivariable model for the 4 separate

outcomes (not divided by IHD) by plotting the scaled Schoenfeld residuals and formally testing for correlation between the scaled Schoenfeld residuals and survival [cox.zph (survival) in R]. Variables with detected problems were stratified for in the models. All the continuous variables were modeled using restricted cubic splines with 4 degrees of freedom.

Longitudinal Change in EF Category

Patients with at least one echocardiogram in addition to baseline were categorized by type of change in HF type between the baseline and subsequent echocardiogram (improved, unchanged, or worsened) according to baseline IHD status and by occurrence of interim IHD events. For those who had ≥2 additional echocardiograms, the one closest to 2 years after the baseline echo was included. An interim IHD event was defined as an IHD event at any point in between the serial echocardiograms. Improved EF was defined as HFrEF changing to either HFmrEF or HFpEF and HFmrEF changing to HFpEF. Worsened EF was defined as HFpEF changing to either HFmrEF or HFrEF and HFmrEF changing to HFrEF.

A 2-tailed P value of <0.05 was considered statistically significant. All statistical analyses were performed in R version 3.3.2 (Vienna, Austria).

Ethics

Establishment of SwedeHF and this specific analysis with linking of numerous registries were approved by a multisite ethics committee and conform to the Declaration of Helsinki. In SwedeHF, individual patient consent is not required, but patients are informed of registration in national registries and allowed to opt out.

Results

Baseline Characteristics

Between May 11, 2000, and December 31, 2012, a total of 80 772 registrations were entered into the registry. After exclusion of patients who died during hospitalization and those with missing EF and repeat registrations, 42 987 patients remained for the analysis, of which 23.2% had HFpEF, 21.4% had HFmrEF, and 55.4% had HFrEF (Figure 1).

Baseline characteristics according to presence of IHD within each EF group are presented in Table 1. The prevalence of IHD was similar in HFmrEF (60.7%) and HFrEF (60.0%) and higher than in HFpEF (52.4%). Among IHD patients, previous myocardial infarction was more common in HFmrEF (68%) and in HFrEF (71%) than in HFpEF (56%). Compared with HFpEF, a larger proportion of IHD patients with HFmrEF and HFrEF had undergone revascularization, whereas IHD patients with HFpEF had more angina pectoris. Compared with those without IHD, patients with IHD in all EF categories were older; were more frequently men; and had more cardiovascular risk factors, comorbidities, more HF symptoms, and higher levels of NT-proBNP (N-terminal pro-B-type natriuretic peptide).

Associations Between HF Type and Baseline IHD

Crude and adjusted associations between HF type and prevalence of baseline IHD are shown in Figure 2. Before and after multivariable adjustment, HFpEF was associated with a lower prevalence of IHD compared with both HFmrEF (adjusted risk ratio, 0.91; 95% CI, 0.89–0.93) and HFrEF (risk ratio, 0.90; 95% CI, 0.88–0.92), whereas no difference was observed between HFmrEF and HFrEF (risk ratio, 1.00 95%; CI, 0.98–1.01).

Event Rates According to HF Type and Baseline IHD Status

Event rates for patients with and without baseline IHD in the 3 HF categories are shown in Table II in the Data Supplement. The cumulative incidence for all outcomes according to HF type and IHD status is depicted in Figure 3A through 3D. During a median follow-up of 2.2 years, there were 9629 new nonfatal or fatal IHD events, 16 005 nonfatal or fatal HF events, 26 734 nonfatal or fatal cardiovascular events, and 16 866 all-cause death events.

Associations Between HF Type and New IHD Events

We also explored differences in risk of new IHD events between HF types after full adjustment, including presence of baseline IHD, thus illuminating a more isolated relationship between ejection fraction category and incident IHD. After full adjustment, the risk of new IHD events was lower in HFpEF than in both HFmrEF (HFpEF versus HFmrEF hazard ratio, 0.89; 95% CI, 0.84–0.95) and HFrEF (HFpEF versus HFrEF hazard ratio, 0.84; 95% CI, 0.80–0.90) but only marginally lower in HFmrEF than in HFrEF (hazard ratio, 0.95; 95% CI, 0.90–1.00).

Associations Between Baseline IHD and Outcomes

Crude and adjusted associations between baseline IHD and risk of events are shown in Table 2. In all 3 EF categories, prevalent IHD was independently associated with increased risk of all 4 outcomes, except all-cause mortality in HFpEF. The strongest associations were observed for new IHD events, for which the risk was increased >3-fold among HFrEF patients with IHD versus no IHD at baseline and more than doubled among HFmrEF and HFpEF patients with IHD versus no IHD at baseline. The risk of HF associated with baseline IHD was slightly and similarly increased within all EF categories, whereas the risk increases for cardiovascular events and all-cause mortality seemed somewhat greater in HFrEF than in HFmrEF and HFpEF.

Longitudinal EF Change According to HF Type, Baseline IHD, and New IHD Events

A total of 4678 patients (18% HFpEF, 19% HFmrEF, and 63% HFrEF at baseline) had longitudinal EF data. A minimum of 1 day and a maximum of 5386 days had elapsed between included echocardiograms. More than one third of HFpEF and HFmrEF patients experienced worsening EF during follow-up, whereas approximately one fourth of HFmrEF and HFrEF patients improved their EF (Figure 4). Patients with IHD in general, and new IHD events in particular, were more likely to experience worsening EF and less likely to experience improvement in EF, over time (Figure 5).

Discussion

In this comprehensive analysis from a large, well-characterized, and generalizable HF population, we found that prevalent IHD and new IHD events were more common in HFmrEF and HFrEF

Table 1. Selected Baseline Characteristics

	HFpEF (23.2%; N=9957)			HFmrEF (21.4%; N=9225)			HFrEF (55.4%; N=23 805)		
	No IHD (47.6%; n=4735)	IHD (52.4%; n=5222)	*P* Value	No IHD (39.3%; n=3625)	IHD (60.7%; n=5600)	*P* Value	No IHD (40.0%; n=9528)	IHD (60.0%; n=14 277)	*P* Value
Age, %	79 (71–85)	80 (73–85)	<0.001	75 (65–82)	77 (69–83)	<0.001	69 (59–79)	76 (68–82)	<0.001
Female sex, %	57	52	<0.001	45	36	<0.001	32	27	<0.001
Previous myocardial infarction, %	0	56	<0.001	0	68	<0.001	0	71	<0.001
Angina pectoris, %	0	61	<0.001	0	56	<0.001	0	51	<0.001
Previous revascularization, %	0	53	<0.001	0	69	<0.001	0	66	<0.001
Smoking, %			<0.001			<0.001			<0.001
Current	10	9		13	11		18	14	
Never	54	48		49	42		43	37	
Previous	36	43		38	47		39	49	
Body mass index, kg/m^2	27 (23–31)	27 (24–31)	0.25	26 (23–31)	26 (24–30)	0.79	26 (23–30)	26 (23–29)	0.059
Hypertension, %	66	75	<0.001	57	67	<0.001	47	59	<0.001
Atrial fibrillation/ flutter, %	66	60	<0.001	67	52	<0.001	54	48	<0.001
Diabetes mellitus, %	23	33	<0.001	19	32	<0.001	18	33	<0.001
Valvular heart disease, %	33	32	0.22	25	24	0.27	21	24	<0.001
Peripheral artery disease, %	6	14	<0.001	6	13	<0.001	5	13	<0.001
Previous stroke/ TIA, %	16	23	<0.001	14	19	<0.001	11	19	<0.001
Creatinine clearance	56 (40–79)	51 (36–70)	<0.001	63 (44–90)	57 (40–80)	<0.001	71 (50–98)	56 (39–78)	<0.001
NT-proBNP, pg/mL	1937 (910–4064)	2103 (910–4698)	0.039	2020 (871–4440)	2310 (997–5471)	0.001	2793 (1243–6116)	3463 (1468–7851)	<0.001
Hemoglobin, g/L	129 (116–141)	126 (115–138)	<0.001	134 (122–146)	131 (119–142)	<0.001	140 (128–150)	132 (120–144)	<0.001
Heart rate	73 (64–84)	70 (62–80)	<0.001	72 (64–84)	70 (60–80)	<0.001	75 (64–86)	70 (62–80)	<0.001
Systolic blood pressure, mm Hg	130 (120–145)	130 (120–150)	0.001	130 (115–143)	130 (118–140)	0.70	120 (110–140)	120 (110–140)	0.004
NYHA, %			<0.001			<0.001			<0.001
I	18	14		16	14		11	8	
II	46	44		55	52		50	42	
III	33	38		27	31		36	45	
IV	3	4		2	3		3	6	
ACE-i/ARB, %	71	72	0.30	83	83	0.78	92	89	<0.001
β-Blocker, %	75	82	<0.001	82	88	<0.001	90	90	0.32
Aldosterone antagonist, %	28	25	<0.001	24	23	0.40	32	33	0.38
Statin, %	22	54	<0.001	22	65	<0.001	23	64	<0.001
Platelet inhibitor, %	32	60	<0.001	30	67	<0.001	30	67	<0.001

Numbers are median (25th–75th percentile) or percentages. ACE-i indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and TIA, transitory ischemic attack.

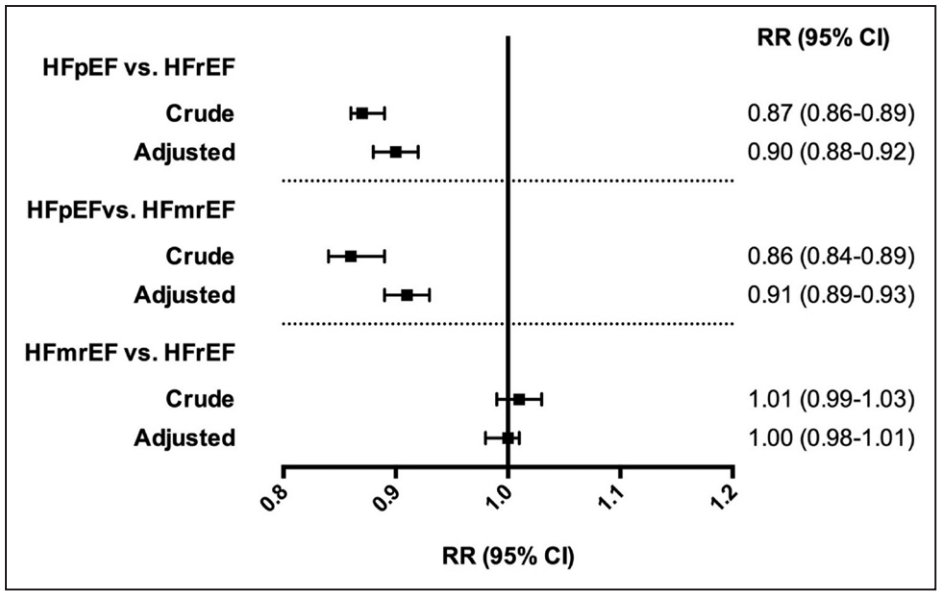

Figure 2. Associations between heart failure (HF) type and baseline ischemic heart disease (IHD). Adjusted includes age, sex, index year, clinic type, caregiver type, HF duration, smoking status, body mass index, alcohol consumption, hypertension, atrial fibrillation/flutter, diabetes mellitus, lung disease, creatinine clearance, NT-proBNP (N-terminal pro-B-type natriuretic peptide), hemoglobin, heart rate, systolic blood pressure, pulse pressure, New York Heart Association class, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blockers, aldosterone antagonist, diuretics, digoxin, statin, anticoagulants, platelet inhibitors, planned follow-up, income, education, civil status, peripheral artery disease, previous stroke/transitory ischemic attack, musculoskeletal disease, cancer, psychiatric disease, follow-up specialty, and follow-up HF nurse. CI indicates confidence interval; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and RR, risk ratio.

than HFpEF. Prevalent IHD was associated with increased risk of new IHD events, HF hospitalization, and cardiovascular events in all HF types, as well as all-cause mortality in HFmrEF and HFrEF. Furthermore, patients with new IHD events were more likely to transition to a lower EF category over time.

Associations Between HF Type and Prevalent IHD: HFmrEF Resembles HFrEF

The separation of patients with an EF ≥40% into HFmrEF and HFpEF resulted in approximately a quarter of the registry population in each group, ultimately rendering a lower HFpEF prevalence than observed in many previous studies, which in itself could have important implications for the interpretation of previous trial and registry data in HFpEF. In accordance with previous registry and clinical trial data,[12,14,15,27,28] the crude IHD prevalence in the SwedeHF cohort was similar between HFmrEF and HFrEF but higher than that in HFpEF. In this respect, our findings are largely confirmatory, but whether these similarities in prevalence are determined by covariance of confounders has not been previously determined. The fact that multivariable adjustment did not meaningfully alter the association suggests that there is a direct IHD-EF link. Our findings, therefore, further strengthens the notion of HFmrEF, representing a phenotypic subset of HFrEF with IHD that is equally prevalent but possibly less extensive or associated with smaller myocardial infarctions, potentially as a result of earlier revascularization and less resulting remodeling.[29]

Associations Between HF Type and Incident IHD: HFmrEF Is Intermediate

There is a distinct lack of information in the literature on long-term cause-specific outcomes in all 3 EF groups, particularly with respect to new ischemic events. Current evidence is conflicting and emanates from a small community cohort in which HFrEF patients did not have an increased risk of myocardial infarction,[16] whereas data from a highly selected randomized controlled trial population demonstrated a linearly increased risk of myocardial infarction with decreasing EF <45%.[15] Our observation that HFmrEF and HFrEF had an elevated risk of ischemic events compared with HFpEF, therefore, provides important confirmatory evidence of the relationship between EF and ischemic outcomes and novel information on this topic from a highly generalizable setting. The finding is particularly noteworthy as it was independent of prevalent IHD, and although the lower risk in HFmrEF versus HFrEF was statistically significant, it was numerically small. The reason why HFmrEF and HFrEF without known IHD would have greater risk of incident IHD events than HFpEF is unclear and suggests that there may be significant underdetection of subclinical IHD in HFmrEF and HFrEF at presentation. HFrEF has and HFmrEF may have a greater risk of sudden cardiac death, which may be because of underlying coronary events,[30] and HFpEF patients may be at greater competing risk of non-IHD events and deaths.[31]

Association Between Prevalent IHD and New Ischemic and Other Events: Greater With Lower EF

The prognostic impact of IHD has been extensively studied in HFrEF, but less and with inconsistent findings in HFpEF and, to our knowledge, not at all in HFmrEF. In HFpEF, 2 studies have demonstrated worse survival among patients with IHD versus those without IHD,[7,9] whereas evidence from combined HFpEF and HFrEF populations have shown

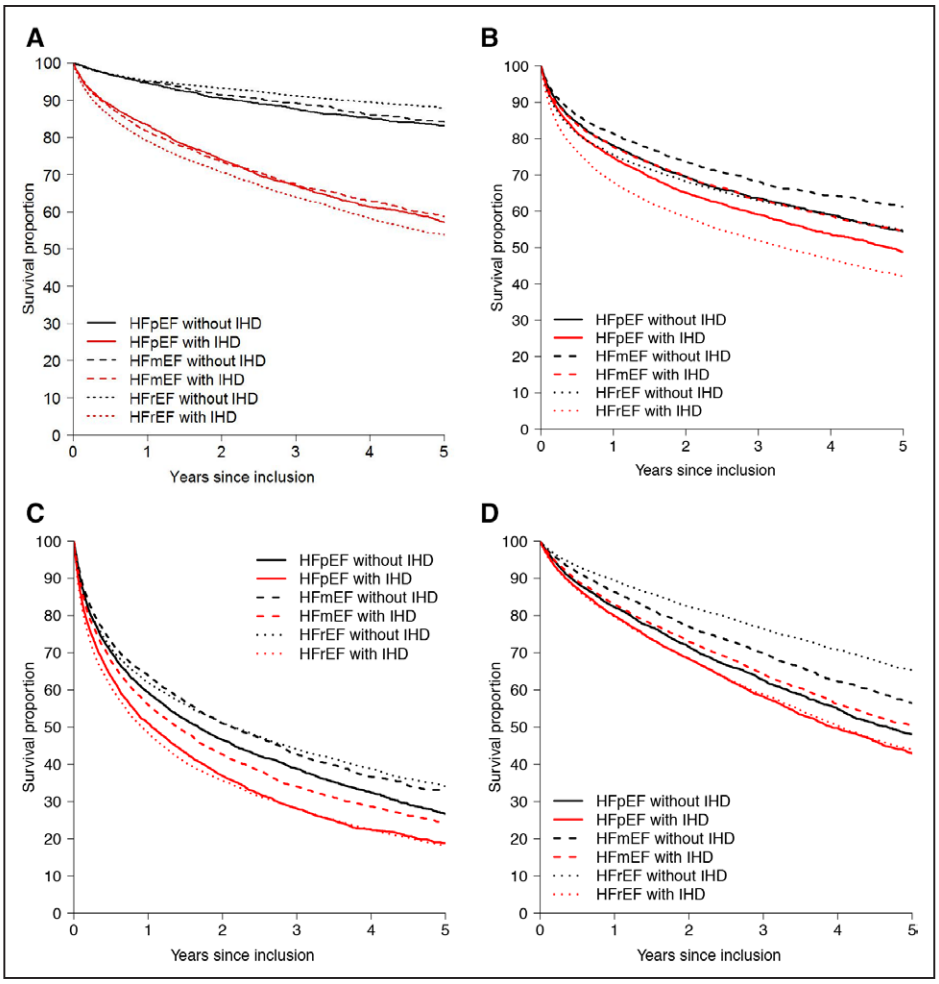

Figure 3. Cumulative incidence of (**A**) nonfatal and fatal ischemic heart disease (IHD), (**B**) nonfatal and fatal heart failure (HF), (**C**) nonfatal and fatal cardiovascular events, and (**D**) all-cause death. HFmEF indicates heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

IHD to have an impact on ischemic outcomes alone,[18] having no prognostic impact at all,[31] or only in HFrEF and not in HFpEF.[17,19]

In contrast, in this comprehensively adjusted analysis, the presence of IHD was strongly associated with an increased risk of new IHD events. This risk increase was evident in all EF categories but greater in HFrEF than in HFmrEF and HFpEF. Although confirmatory of earlier data in HFrEF, this information points to the importance of prevalent IHD in determining the risk of new IHD events also in HFpEF and HFmrEF, among whom this relationship has been previously undecided but should clearly not be underestimated. This is further underscored by evidence from HF studies evaluating IHD-specific therapies. For instance, in HFrEF, revascularization improves long-term outcomes.[32] Moreover, in generalizable settings, statins have been associated with favorable outcome in both HFrEF[33] and HFpEF,[34] although not confirmed in randomized trials.[35]

Not only did baseline IHD increase the risk of subsequent IHD events but also that of HF and cardiovascular events and all-cause death. The only outcome for which baseline IHD did not increase the risk was all-cause death in HFpEF, possibly because of a larger proportion of noncardiovascular deaths in HFpEF. Overall, the data suggest that detection of IHD is important in patients with HF and that future randomized studies of IHD interventions in all HF categories are indeed warranted. This is perhaps most pressing in IHD patients with HFpEF and HFmrEF who in our study were subject to less IHD therapies, such as revascularization, antiplatelet agents, and statins than in HFrEF. Finally, even HF therapies not primarily aimed at IHD, which seemingly lack efficacy in HFpEF and lack evidence in HFmrEF, may be of value in a subset of patients with IHD as suggested by a subgroup analysis from the Perindopril in Elderly People with Chronic Heart Failure trial.[36]

IHD and Longitudinal Changes in EF

A comprehensive delineation of IHD in different HF types warrants attention to temporal changes in EF for several reasons. Previous data from smaller cohorts have suggested that a significant proportion of HFmrEF may be in transition between HFpEF and HFrEF and that IHD could be an important mediator of EF deterioration.[9,37] Furthermore, a recent study suggested that HF patients with recovery of EF (≤40%–>40%) had a better prognosis than both HFrEF and HFpEF patients without EF change.[38] Our study, the largest to date to assess longitudinal EF change and first to do so in all

Table 2. Risk of New Nonfatal and Fatal IHD, Heart Failure, and CV Events and All-Cause Death According to Baseline IHD Status and HF Type

Outcome	Model	HFpEF		HFmrEF		HFrEF	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
IHD	N	1957		2049		5623	
	Crude	3.09 (2.79–3.42)	<0.001	3.27 (2.92–3.66)	<0.001	4.83 (4.48–5.20)	<0.001
	+all	2.34 (2.10–2.62)	<0.001	2.43 (2.14–2.75)	<0.001	3.13 (2.87–3.40)	<0.001
Heart failure	N	3446		2951		9608	
	Crude	1.18 (1.10–1.26)	<0.001	1.21 (1.12–1.30)	<0.001	1.41 (1.35–1.47)	<0.001
	+all	1.09 (1.01–1.17)	0.031	1.13 (1.03–1.23)	0.007	1.12 (1.07–1.18)	<0.001
CV events	N	6210		5489		15035	
	Crude	1.29 (1.23–1.36)	<0.001	1.26 (1.19–1.33)	<0.001	1.55 (1.50–1.60)	<0.001
	+all	1.19 (1.12–1.26)	<0.001	1.18 (1.11–1.26)	<0.001	1.27 (1.22–1.32)	<0.001
All-cause death	N	7100		3471		9134	
	Crude	1.16 (1.09–1.23)	<0.001	1.23 (1.15–1.32)	<0.001	1.95 (1.86–2.04)	<0.001
	+all	1.03 (0.97–1.11)	0.33	1.09 (1.01–1.18)	0.031	1.27 (1.21–1.34)	<0.001

All includes adjustment for age, sex, index year, clinic type, caregiver type, HF duration, smoking, body mass index, alcohol consumption, hypertension, atrial fibrillation/flutter, diabetes mellitus, lung disease, creatinine clearance, NT-proBNP, hemoglobin, heart rate, systolic blood pressure, pulse pressure, NYHA class, ACE-i/ARB, β-blockers, aldosterone antagonist, diuretics, digoxin, statin, anticoagulants, platelet inhibitors, follow-up level, income, education, civil status, peripheral artery disease, previous stroke/TIA, musculoskeletal disease, cancer, psychiatric disease, follow-up specialty, and follow-up HF nurse. ACE-i indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio for baseline IHD present vs absent; IHD, ischemic heart disease; N, number of patients with events; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and TIA, transitory ischemic attack.

3 HF categories, demonstrated that a substantial proportion of both HFpEF and HFmrEF patients worsened over time, that is, to a lower EF category. This could, to some extent, reflect selection bias but was nevertheless similar to previous data from the Olmsted cohort.[37] Furthermore, we could confirm a correlation between IHD, particularly between new IHD events and worsening EF in all HF types, which should further reinforce research efforts into the possibly beneficial effects of revascularization in HFmrEF and HFpEF.[9]

Limitations

As with all observational studies, causality cannot be inferred from our study, and a possibility of residual confounding remains. There were missing data, and the registry setting may limit accuracy of reported data compared with a clinical trial setting, limiting internal validity. However, we used multiple imputation for missing data, limiting bias attributable to some patients undergoing less rigorous examinations or data registration data, which together with the large sample size provides for external validity and generalizability. HF diagnosis in SwedeHF was clinician judged, and although median NT-proBNP levels were generally high across HF categories, 1937 to 2103, 2020 to 2310, and 2793 to 3463 in HpEF, HFmrEF, and HFrEF respectively, we cannot rule out an element of misclassification with some patients possibly having symptoms resulting from comorbidities and not HF. Moreover, there is also a possibility of misclassification of HFpEF and HFmrEF according to the recently published European Society of Cardiology guidelines[1] as we lacked echo information other than EF. Ascertainment of cause-specific outcomes from *ICD-10* codes in the National Patient Registry has been previously shown to have a high accuracy.[23,24] However, for cause of death, accuracy is considerably lower,[25] which warrants some caution when interpreting the present findings. Elucidating effects of revascularization would have added further value to the presented findings. However, because baseline revascularization is subject to significant selection bias, resulting findings would likely be biased and difficult to interpret. The proportion of patients with worsening EF may be exaggerated compared with a general HF population because of selection bias, as new cardiac events are likely to produce repeat

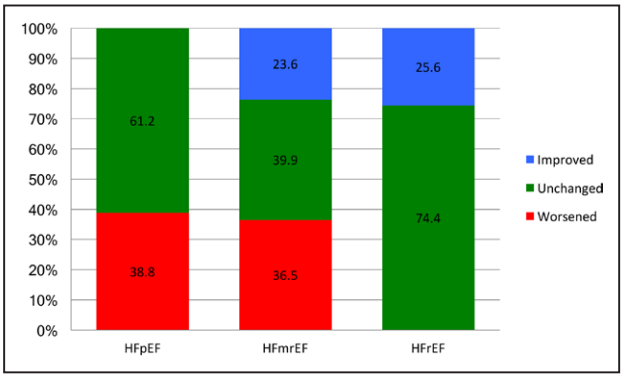

Figure 4. Proportion of patients with improved, unchanged, or worsened ejection fraction (EF) category during follow-up. Improved EF indicates heart failure with reduced ejection fraction (HFrEF) to either heart failure with midrange ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) and HFmrEF to HFpEF. Worsened EF indicates HFpEF to either HFmrEF or HFrEF and HFmrEF to HFrEF.

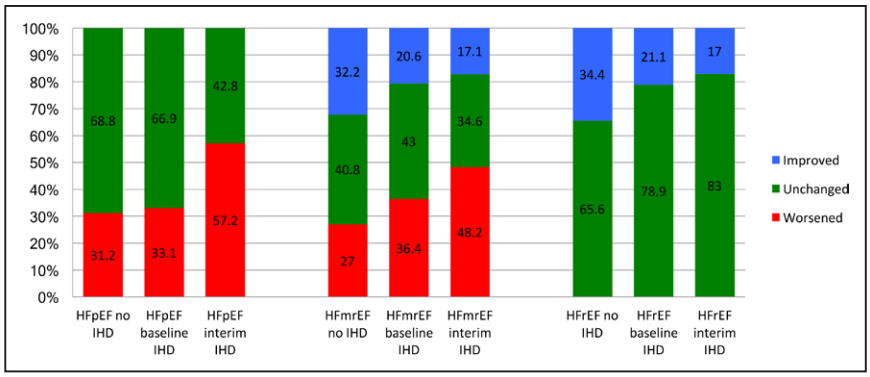

Figure 5. Proportion of patients with improved, unchanged, or worsened ejection fraction (EF) over time according to baseline heart failure (HF) type, baseline ischemic heart disease (IHD) status, and interim IHD events. Improved EF indicates heart failure with reduced ejection fraction (HFrEF) to either heart failure with mid-range ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) and HFmrEF to HFpEF. Worsened EF indicates HFpEF to either HFmrEF or HFrEF and HFmrEF to HFrEF.

echocardiograms. We cannot rule out the possibility that some of the recorded EF changes are not attributable to real change but subject to error caused by bias and interpretation variability between examiners. Multiple tests were performed, and because no adjustment for multiple comparisons was made, it should be noted that if the null hypothesis is true, the probability of making a type I error increases with the number of statistical tests performed. Therefore, some care should be taken when interpreting the results.

Conclusions

HFmrEF resembled HFrEF rather than HFpEF with respect to IHD as underlying cause and was intermediate with regard to risk of new ischemic events. Established IHD had an adverse impact on a majority of outcomes in all EF categories, although most prominent for new IHD events and in HFrEF. These findings are of importance to future research strategies on prevention and treatment of different HF types and IHD.

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CLINICAL PERSPECTIVE

Ischemic heart disease is a well-recognized pathogenic factor in heart failure (HF) with reduced ejection fraction (HFrEF), but its prognostic and pathogenic significance in HF with preserved ejection fraction (HFpEF) and HF with midrange ejection fraction (HFmrEF) ejection fraction is much less certain. The fact that HFmrEF and HFpEF fraction constitute an increasing proportion of post–ischemic heart disease (IHD) HF paired with the recognition of HFmrEF as a much understudied HF entity further underscores the need for more knowledge in this area. In this study consisting of 42 987 patients in the Swedish Heart Failure Registry, we could confirm previous observations of IHD being generally common in HF and that HFmrEF had an IHD prevalence more similar to HFrEF. However, we also found that baseline IHD was similarly associated between HFmrEF and HFrEF even after controlling for confounders, strengthening the hypothesis that HFmrEF constitutes a milder HFrEF phenotype. Moreover, the presence of IHD was an important determinant of prognosis across all HF groups, not only for ischemic events but also for HF and cardiovascular events. The findings suggest that IHD is an important unifying factor between HFmrEF and HFrEF and that the presence of IHD is crucial for the clinician to recognize in all HF patients, given the association with a wide range of outcomes. The results also suggest the possibility of IHD treatment being a valid treatment option not only in HFrEF but also in HFpEF and HFmrEF, although such interventions need to be studied in randomized trials.

Circulation
Heart Failure

Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study

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SUPPLEMENTAL MATERIAL

Appendix-Table 1. Definitions and registry sources for selected baseline variables and outcome variables

Variable	ICD-10 code	Registry
Outcome IHD	I20-24 (Main position). FNA, FNB, FNC, FND, FNE, FNF, FNH, FNG00-06 (Any position)	National Patient Registry
	I20-25 (except I255)	Cause of Death Registry
Outcome Heart Failure	I50, I42-I43, I255, K761, I110, I130 I132, J81 (Main position)	National Patient Registry
	I50, I42-I43, I255, K761, I110, I130, I132, J81	Cause of Death Registry
Outcome Cardiovascular Events	I00-I99, K761, G45, J81 (Main position)	National Patient Registry
	I00-I99, K761, G45, J81	Cause of Death Registry
Outcome All-cause Death		Population Registry
Baseline IHD	I20-25, Z951, Z955, FNA, FNB, FNC, FND, FNE, FNF, FNH, FNG00-06 (Any position)	National Patient Registry
		SwedeHF
Age, gender, smoking, alcohol consumption, BMI, Creatinine clearance, NT-proBNP, Hemoglobin, Latest echo, Heart rate, Systolic blood pressure, Pulse pressure, All treatments, Year of registration, Duration of HF, Type of clinic, Type of care, Follow-up specialty, Follow-up HF nurse		SwedeHF
Hypertension	I10-15	National Patient Registry
		SwedeHF

Atrial fibrillation/flutter	I48	National Patient Registry
		SwedeHF
Diabetes Mellitus	E10-14	National Patient Registry
		SwedeHF
Chronic lung disease	J4, J6-9	National Patient Registry
		SwedeHF
Peripheral artery disease	I70-73	National Patient Registry
Prior stroke/TIA	I60-64, I690-694, G45	National Patient Registry
Musculoskeletal disease	M chapter within last 3 years	National Patient Registry
Cancer	C chapter within last 3 years	National Patient Registry
Psychiatric disease	F chapter within last 3 years	National Patient Registry
Living alone, Children, Highest education		Statistics Sweden

SwedeHF, www.swedehf.se[1]; National Patient Registry[2] and Cause of Death Registry[3], www.sos.se;

Appendix-Table 2. Event and incidence rates during total follow-up time.

	HFpEF		HFmrEF		HFrEF	
Outcome	**no IHD**	**IHD**	**no IHD**	**IHD**	**no IHD**	**IHD**
IHD						
No events/No total	490/4735	1467/5222	366/3625	1683/5600	802/9528	4821/14277
Incidence/1000 py (95% CI)	42 (38-46)	134 (127-141)	39 (35-43)	129 (123-135)	29 (27-32)	151 (147-155)
Heart Failure						
No events/No total	1549/4735	1897/5222	1045/3625	1906/5600	3319/9528	6289/14277
Incidence/1000 py (95% CI)	156 (148-164)	187 (179-196)	127 (119-135)	154 (147-161)	157 (152-162)	236 (230-242)
CV						
No events/No total	2737/4735	3473/5222	1941/3625	3548/5600	5082/9528	9953/14277
Incidence/1000 py (95% CI)	360 (347-374)	491 (474-507)	304 (290-317)	392 (380-405)	295 (287-303)	503 (493-513)
All-cause death						
No events/No total	1896/4735	2365/5222	1189/3625	2282/5600	2538/9528	6596/14277
Incidence/1000 py (95% CI)	156 (149-164)	182 (175-189)	120 (113-127)	148 (142-154)	89 (86-93)	177 (173-181)

IHD,ischemic heart disease; CV, cardiovascular; py, patient years; CI, confidence interval

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