

## Supplementary Material

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### **Clinical trajectory and risk-stratification for heart failure with preserved ejection fraction in a real-world cohort of patients with suspected coronary artery disease**

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## Supplementary Tables / Figures

Table S1. Baseline characteristics of patients with isolated HFpEF and stratification according to H<sub>2</sub>FPEF Score in the cohort of isolated HFpEF.

Variables	All Patients with isolated HFpEF n=499	H <sub>2</sub> FPEF Low-Risk n=109	H <sub>2</sub> FPEF Intermediate-Risk n=280	H <sub>2</sub> FPEF High-Risk n=110	p-value
<b>Patient Characteristics</b>					
Age, years	65 ± 10	58 ± 10	67 ± 9	69 ± 7	<0.01
Female sex, n. (%)	246 (49%)	54 (50%)	148 (53%)	44 (40%)	0.07
NYHA class, n. (%)	NYHA II: 466 (93.4%) NYHA III: 32 (6.4%) NYHA IV: 1 (0.2%)	NYHA II: 109 (100%) NYHA III: 0 (0%) NYHA IV: 0 (0%)	NYHA II: 267 (95.4%) NYHA III: 12 (4.2%) NYHA IV: 1 (0.4%)	NYHA II: 90 (81.8%) NYHA III: 20 (18.2%) NYHA IV: 0 (0%)	<0.01
Chest pain, n. (%)	207 (41%)	62 (57%)	108 (39%)	37 (34%)	<0.01
BMI, kg/m <sup>2</sup>	31 ± 5	28 ± 4	32 ± 5	32 ± 5	<0.01
Obesity, n. (%)	254 (51%)	19 (17%)	165 (59%)	70 (64%)	<0.01
Diabetes, n. (%)	182 (36%)	19 (17%)	105 (38%)	58 (53%)	<0.01
Arterial hypertension, n. (%)	302 (61%)	61 (56%)	177 (63%)	64 (58%)	0.36
Smoking, n. (%)	106 (21%)	22 (20%)	50 (18%)	34 (31%)	0.87
Hx CAD intervention, n. (%)	18 (4%)	2 (2%)	11 (4%)	5 (5%)	0.51
Atrial fibrillation, n. (%)	148 (30%)	0 (0%)	38 (14%)	110 (100%)	<0.01
<b>Laboratory Values</b>					
eGFR, ml/min/1.73m <sup>2</sup>	68 ± 25	74 ± 24	66 ± 25	65 ± 24	<0.01
eGFR <30, n. (%)	19 (4%)	0 (0%)	11 (4%)	8 (7%)	0.02
NT-proBNP, ng/l	262 (172 - 510)	200 (155 - 323)	251 (177 - 490)	480 (230 - 1276)	<0.01
CRP, mg/l	2.3 (1.2-5)	1.8 (1-4)	2.5 (1.3-5)	2.8 (1.4-6.3)	<0.01
Troponin T, pg/ml	10.3 (6 - 12)	7.5 (4.5 - 10.8)	10.5 (6.0 - 11.8)	10.8 (8.6 - 14.4)	<0.01
<b>Echocardiographic Parameters</b>					
LV-EF, %	61 ± 7	60 ± 6	62 ± 6	61 ± 7	0.21
E/e'	10.5 ± 3.7	8 ± 2.7	10.75 ± 3.3	12.3 ± 3.3	<0.01
LV-EDV index, ml/m <sup>2</sup>	51 ± 18	54 ± 18	50 ± 17	49 ± 18	0.05
LV-Mass index, g/m <sup>2</sup>	138.5 ± 40	137 ± 23	138 ± 40	140 ± 39	0.86
LA diameter index, mm/m <sup>2</sup>	24 ± 3.7	23.72 ± 3.7	24 ± 3.5	26 ± 4	<0.01
TR Vmax, m/s	2.5 ± 0.7	2.32 ± 0.4	2.52 ± 0.9	2.57 ± 0.4	0.02
Moderate valvular disease, n. (%)	45 (9%)	4 (4%)	23 (8%)	18 (16%)	<0.01
<b>Events during follow-up</b>					
HF rehospitalization, n. (%)	88 (18%)	8 (7%)	41 (15%)	39 (35%)	<0.01
Average number of rehospitalizations, n.	0.46 ± 1.2	0.2 ± 0.5	0.4 ± 1.17	0.9 ± 1.4	<0.01
All-cause mortality, n. (%)	57 (11%)	4 (4%)	31 (11%)	22 (20%)	<0.01
NYHA Class = New York Heart Association Class (1-4), BMI = body mass index, CAD = coronary artery disease, HF = heart failure, Hx = history, FU = follow-up, eGFR = estimated glomerular filtration rate, LV-EF = left ventricular ejection fraction, LV-EDV = left ventricular enddiastolic volume, LA = left atrial, TR Vmax = peak velocity of tricuspid valve regurgitation in CW Doppler, TAPSE = tricuspid annular plane systolic excursion. Percentages equal or greater 0.5 were rounded to the larger integer.					

Table S2. Baseline characteristics of patients with isolated HFpEF and stratification according to H<sub>2</sub>FPEF Score in the cohort of HFpEF with overlapping conditions.

Variables	All Patients HFpEF with overlapping conditions n=555	H <sub>2</sub> FPEF Low-Risk n=130	H <sub>2</sub> FPEF Intermediate-Risk n=323	H <sub>2</sub> FPEF High-Risk n=102	P-value
<b>Patient Characteristics</b>					
Age, years	67 ± 10	58.7 ± 11	68 ± 6	71 ± 4	<0.01
Female sex, n. (%)	175 (32%)	30 (23%)	108 (33%)	37 (36%)	0.05
NYHA class, n. (%)	NYHA II: 511 (92%) NYHA III: 36 (6%) NYHA IV: 8 (2%)	NYHA II: 124 (95%) NYHA III: 3 (2.5%) NYHA IV: 3 (2.5%)	NYHA II: 301 (93%) NYHA III: 19 (6%) NYHA IV: 3 (1%)	NYHA II: 86 (84%) NYHA III: 14 (14%) NYHA IV: 2 (2%)	<0.01
Chest pain, n. (%)	238 (43%)	90 (69%)	104 (32%)	44 (43%)	<0.01
BMI, kg/m <sup>2</sup>	30 ± 5	27.5 ± 3.9	30.1 ± 4.6	30.7 ± 4.8	<0.01
Obesity, n. (%)	233 (42%)	16 (12%)	159 (49%)	58 (57%)	<0.01
Diabetes, n. (%)	189 (34%)	24 (18%)	112 (35%)	53 (52%)	<0.01
Arterial hypertension, n. (%)	354 (64%)	78 (60%)	207 (64%)	69 (68%)	0.48
Smoking, n. (%)	262 (47%)	62 (48%)	157 (49%)	43 (42%)	0.52
Hx CAD intervention, n. (%)	151 (27%)	24 (18%)	96 (30%)	31 (30%)	0.04
Atrial fibrillation, n. (%)	131 (24%)	0 (0%)	29 (9%)	102 (100%)	<0.01
<b>Laboratory Values</b>					
eGFR, ml/min/1.73m <sup>2</sup>	64 ± 24	76 ± 29	60.5 ± 22	60.5 ± 21.7	<0.01
eGFR <30, n. (%)	32 (6%)	5 (4%)	22 (7%)	5 (5%)	0.43
NT-proBNP, ng/l	288 (183 - 572)	232 (171 - 375)	283 (183 - 542)	454 (230 - 1011)	<0.01
CRP, mg/l	2.5 (1.2-5.2)	2.1 (0.9-4.7)	2.5 (1.2-5)	3.0 (1.6-5.4)	0.08
Troponin T, pg/ml	10.8 (7.2 - 12)	8.8 (5.7 - 10.8)	10.8 (7.8 - 11.7)	10.8 (8.5 - 14)	<0.01
<b>Echocardiographic Parameters</b>					
LV-EF, %	61 ± 6.6	60 ± 6	61 ± 6.8	61.5 ± 6.9	0.57
E/e'	10 ± 3.3	8 ± 1.9	10.6 ± 2.8	12.3 ± 3.7	<0.01
LV-EDV index, ml/m <sup>2</sup>	54.4 ± 18	60.7 ± 18.7	53 ± 17	50.7 ± 17.8	<0.01
LV-Mass index, g/m <sup>2</sup>	138 ± 40	143 ± 40.6	136.4 ± 38.9	136.7 ± 37.9	0.25
LA diameter index, mm/m <sup>2</sup>	24 ± 3.7	24 ± 3.1	23.3 ± 3.4	25 ± 3.4	<0.01
TR Vmax, m/s	2.5 ± 0.4	2.3 ± 0.3	2.4 ± 0.4	2.6 ± 0.4	<0.01
Moderate valvular disease, n. (%)	75 (14%)	9 (7%)	41 (13%)	25 (25%)	<0.01
<b>Events during follow-up</b>					
HF rehospitalization, n. (%)	140 (25%)	18 (14%)	78 (24%)	44 (43%)	<0.01
Average number of rehospitalizations, n.	1.78 ± 1.8	1.25 ± 1.6	1.77 ± 1.8	2.5 ± 2.0	<0.01
All-cause mortality, n. (%)	62 (11%)	8 (6%)	33 (10%)	21 (21%)	<0.01
NYHA Class = New York Heart Association Class (1-4), BMI = body mass index, CAD = coronary artery disease, HF = heart failure, Hx = history, FU = follow-up, eGFR = estimated glomerular filtration rate, LV-EF = left ventricular ejection fraction, LV-EDV = left ventricular enddiastolic volume, LA = left atrial, TR Vmax = peak velocity of tricuspid valve regurgitation in CW Doppler, TAPSE = tricuspid annular plane systolic excursion. Percentages equal or greater 0.5 were rounded to the larger integer.					

Table S3. Logistic Regression for HF-hospitalization in cohort of patients with HFpEF and overlapping conditions at presentation.

	Logistic Regression Model (univariate)				Logistic Regression Model (multivariable)			
	95.0% CI for EXP(B)				95.0% CI for EXP(B)			
	EXP(B)	Lower	Upper	p-value	EXP(B)	Lower	Upper	p-value
Male sex	0.99	0.65	1.50	0.98	1.12	0.72	1.73	0.63
lnNTproBNP	1.07	0.85	1.34	0.55	1.22	0.88	1.69	0.23
NYHA-class	0.59	0.30	1.20	0.15	0.42	0.15	1.16	0.10
H <sub>2</sub> FPEF high-risk	2.82	1.79	4.33	<0.01	2.70	1.65	4.41	<0.01
H <sub>2</sub> FPEF high risk = H <sub>2</sub> FPEF score equal or greater than 6 as binary variable, lnNT-pro-BNP = natural logarithm of the NT-pro-BNP at baseline, NYHA-Class = New York Heart association class (1-4), EXP(B) is considered equivalent to odds ratio. Hosmer and Lemeshow Test p =0.44, Cox & Snell R Square p=0.05, Nagelkerke R Square p= 0.73, Age, Afib, BMI and E/e' were not inputted due to significant co-linearity with H <sub>2</sub> FPEF score.								

Table S4. Logistic Regression for HF-hospitalization in cohort of patients with isolated HFpEF

	Logistic Regression Model (univariate)				Logistic Regression Model (multivariable)			
	EXP(B)	95.0% CI for EXP(B)		p-value	EXP(B)	95.0% CI for EXP(B)		p-value
		Lower	Upper			Lower	Upper	
Male Sex	0.78	0.49	1.24	0.30	1.09	0.67	1.79	0.72
lnNTproBNP	0.97	0.72	1.29	0.84	0.95	0.78	1.02	0.13
NYHA-Class	1.00	0.41	2.42	0.99	0.61	0.28	1.31	0.96
H <sub>2</sub> FPEF high-risk	3.81	2.33	6.24	<0.01	5.19	2.95	9.10	<0.01

H<sub>2</sub>FPEF high risk = H<sub>2</sub>FPEF score equal or greater than 6 as binary variable, lnNT-pro-BNP = natural logarithm of the NT-pro-BNP at baseline, NYHA-Class = New York Heart association class (1-4), EXP(B) is considered equivalent to odds ratio. Hosmer and Lemeshow Test p =0.12, Cox & Snell R Square p=0.07, Nagelkerke R Square p= 0.11, Age, Afib, BMI and E/e' were not inputted due to significant co-linearity with H<sub>2</sub>FPEF score.

Figure S1. Classification of the overall cohort with detailed reason of hospitalization for the subgroup of HFpEF with overlapping conditions.

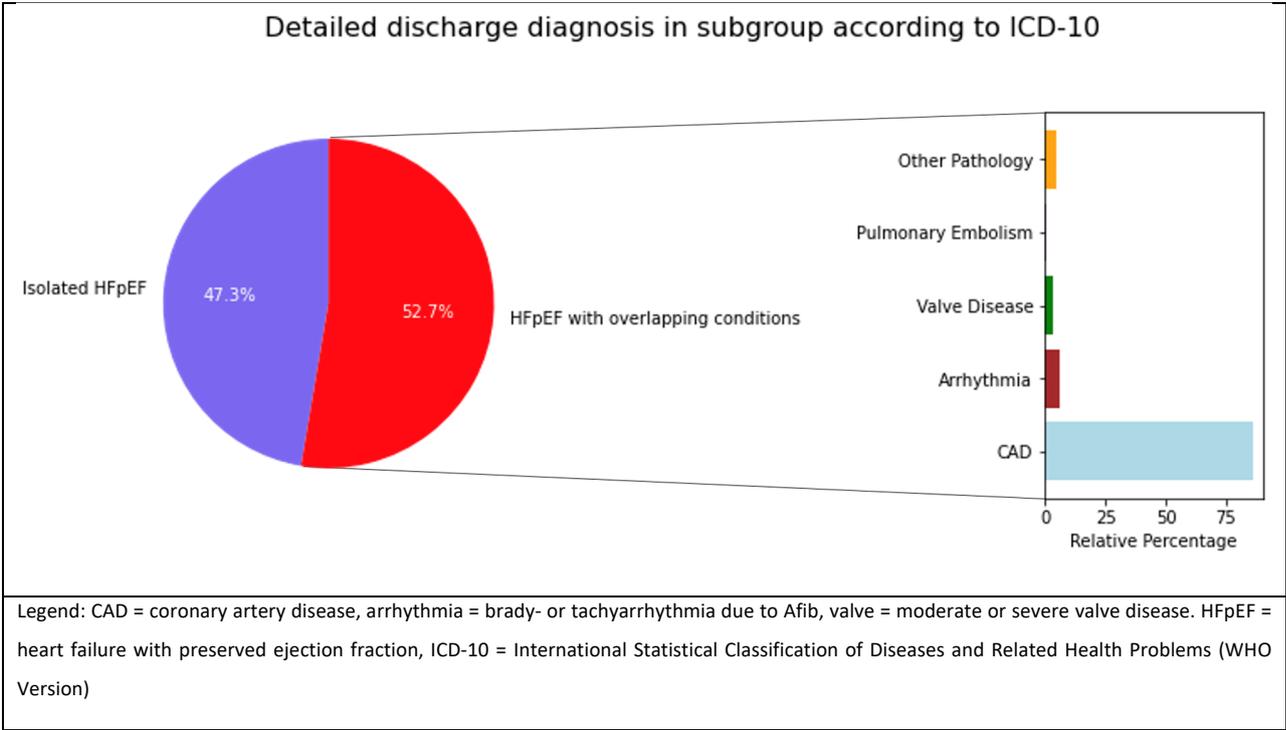


Figure S2. Detailed reasons of first rehospitalization.

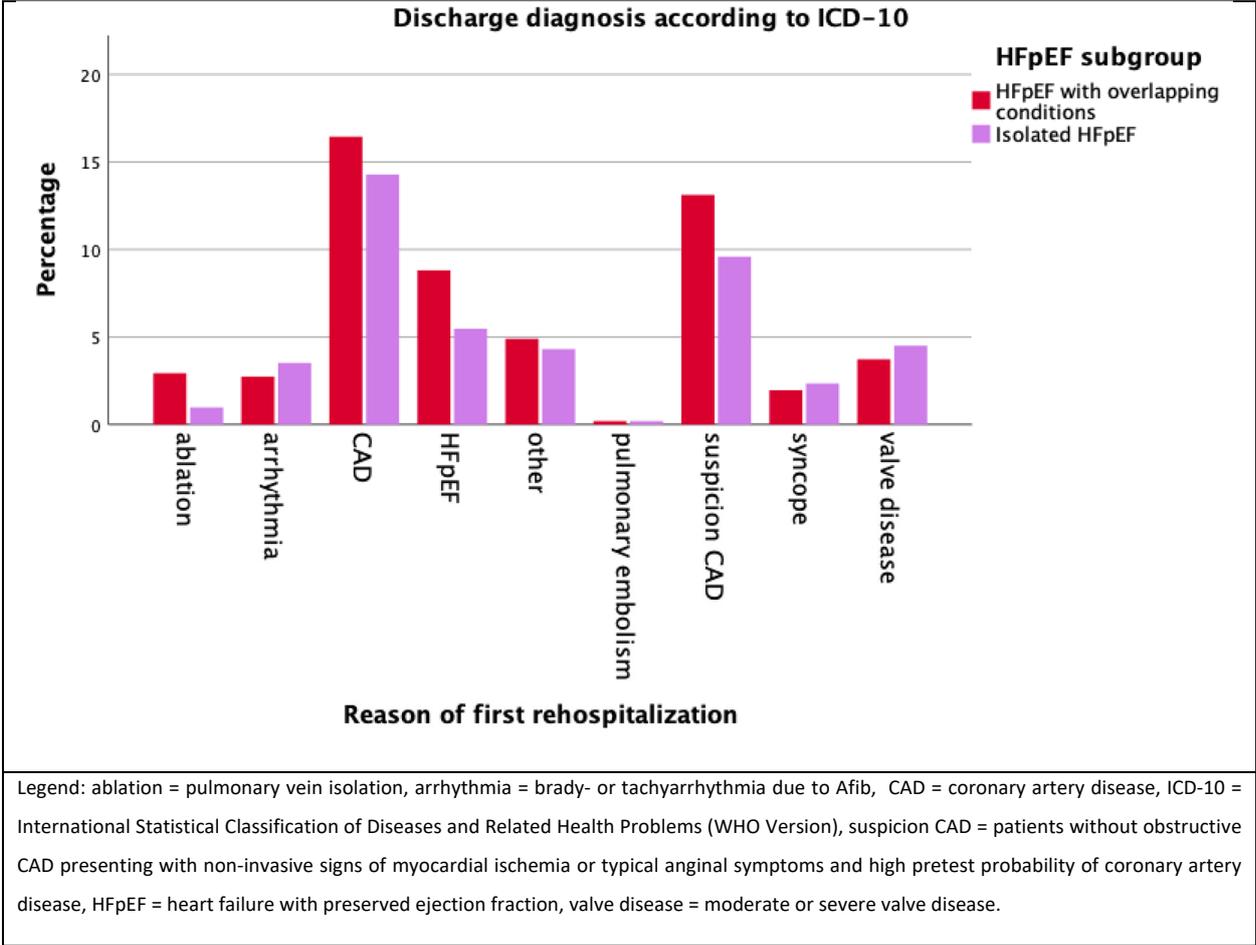


Figure S3. ROC curves for HFpEF hospitalization and death in overall cohort, CAD subgroup and Non-CAD subgroup.

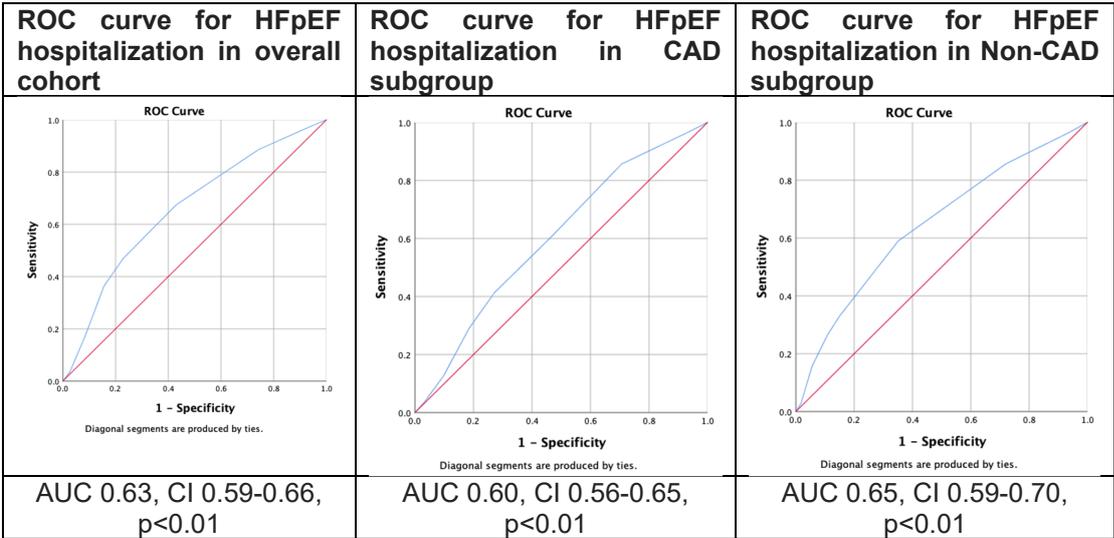


Figure S4. KM-estimates for isolated HFpEF and HFpEF with overlapping conditions in H<sub>2</sub>FpEF score high risk group.

