

Supplemental Material

Table S1: List of candidate predictor variables

<u>Demographics</u>	<u>Medical history</u>	<u>Laboratory measures</u>
Age	Timing of most recent heart failure hospitalisation	NT-proBNP
Sex	Time since heart failure diagnosis	High-sensitivity cardiac Troponin-T
Smoking	History of atrial fibrillation	Total Bilirubin
Body mass index	History of hypertension	Uric acid
Heart rate	Prior myocardial infarction	Albumin
Diastolic blood pressure	LBBB	Potassium
Systolic blood pressured	Peripheral edema	Neutrophils
LVEF	Volume overload	LDL-C
NYHA class	Rales	Urea nitrogen
Ischemic vs non-ischemic HF	COPD	Lymphocytes
Diabetes status (including assessment of insulin dependence)	KCCQ overall summary score	Haemoglobin
		eGFR
		Albuminuria (urinary albumin-to-creatinine

		ratio)
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Legend: LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

Note: Volume overload was a “yes/no tickbox” variable in the CRF, assessing whether the patient had or not volume overload in the investigator’s opinion.

Table S2: EMPEROR-Preserved risk model for cardiovascular mortality

	Hazard ratio (95% CI)	Chi- squared statistic	Coefficient (SE)*	P-value
Log hs-cTnT [ng/L]	1.45 (1.27, 1.66)	29.2	0.37 (0.07)	<.0001
Log NT-proBNP [pg/mL]	1.49 (1.34,1.66)	51.1	0.40 (0.06)	<.0001
History of COPD	1.74 (1.39,2.17)	23.7	0.55 (0.11)	<.0001
Baseline Albumin (per 0.1 decrease below 4.5) [g/dL]	1.07 (1.03, 1.10)	17.0	0.07 (0.02)	<.0001
NYHA class III/IV	1.33 (1.08,1.64)	7.3	0.29 (0.11)	<.0001
Age				0.0402
<65 years	1.00 (reference)			
65 to <75 years	1.30 (0.98, 1.73)	3.3	0.26 (0.15)	
>=75 years	1.43 (1.09, 1.89)	6.4	0.36 (0.14)	
LVEF				<.0001
>=50 %	1.00 (reference)			
<50 %	1.50 (1.24, 1.81)	17.8	0.41 (0.10)	
Use of Insulin in DM patients				0.0026
Non DM	1.00 (reference)			
DM + insulin	1.43 (1.11, 1.83)	7.9	0.36 (0.13)	

DM + no insulin	0.91 (0.73, 1.13)	0.8	-0.09 (0.11)
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*Coefficient (SE) are the log hazard ratio and its standard error

An estimate of each individual's 2-year risk can be calculated as follows: $1 - [0.9994^{\exp(0.37 \times \log \text{hs-cTnT} + 0.40 \times \log \text{NT-proBNP} + 0.29 \times \text{NYHA class} + 0.55 \times \text{COPD} + 0.07 \times ((4.5 - \text{Albumin})/0.1) + 0.26 \times \text{Age1} + 0.36 \times \text{Age2} + 0.41 \times \text{LVEF} + 0.36 \times \text{DM (insulin)} - 0.09 \times \text{DM (without insulin)})]$, where 'Age1' and 'Age2' are indicator variables for whether patient's age is 65 to <75 or ≥ 75 years old, respectively. NYHA is an indicator variable for whether the patient's NYHA class is III or IV. COPD is indicator variables for whether the patient has COPD. LVEF is an indicator variable for whether patient has LVEF <50%. DM (insulin) and DM (without insulin) are indicator variables for whether patient has diabetes and use of insulin at baseline or has diabetes without use of insulin. CI, confidence interval; HF, heart failure; HHF, hospitalization for heart failure; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

C-statistic (95%CI) : 0.718 (0.694,0.741)

Table S3: Risk models for the primary endpoint and for all-cause death both extended to also include UACR* and KCCQ-OSS⁺

A. Primary Endpoint Model

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
Log NT-proBNP [pg/mL]	1.53 (1.42, 1.66)	113.4	0.43 (0.04)	<.0001
Log hs-cTnT [ng/L]	1.51 (1.38, 1.67)	71.0	0.41 (0.05)	<.0001
Time since most recent HHF				
>6 months	1.00 (reference)			<.0001
3-6 months	1.64 (1.30, 2.07)	17.1	0.49 (0.12)	
<3 months	1.94 (1.63, 2.30)	56.1	0.66 (0.09)	
NYHA class III/IV	1.45 (1.25, 1.69)	23.6	0.37 (0.07)	<.0001
History of COPD	1.69 (1.44, 1.99)	41.9	0.52 (0.08)	<.0001
Use of Insulin in DM patients				
Non DM	1.00 (reference)			<.0001

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
DM + no insulin	1.07 (0.92, 1.24)	0.7	0.07 (0.08)	
DM + insulin	1.35 (1.12, 1.62)	10.0	0.30 (0.09)	
Baseline haemoglobin				<.0001
>=12 [g/dL]	1.00 (reference)			
<12 [g/dL]	1.35 (1.17, 1.57)	16.2	0.30 (0.08)	
Time since HF diagnosis				
3 months-1 year	1.00 (reference)			0.0002
>=1 year	1.38 (1.17, 1.63)	15.0	0.32 (0.08)	
KCCQ-OSS (per 10 increase)	0.92 (0.89, 0.95))	26.8	-0.08 (0.02)	<.0001
Baseline UACR				<.0001
<30 [mg/g]	1.00 (reference)			
30 to <=300[mg/g]	1.39 (1.19, 1.61)	18.3	0.33 (0.08)	
>300 [mg/g]	1.62 (1.33, 1.97)	22.9	0.48 (0.10)	
Randomized to Empagliflozin	0.75 (0.66, 0.86)	18.6	-0.29 (0.07)	<.0001

*Coefficient (SE) are the log hazard ratio and its standard error

c-statistic 0.756 (0.741,0.772)

B. All-Cause Death Model

	Hazard ratio (95% CI)	Chi- squared statistic	Coefficient (SE)*	P-value
Log hs-cTnT [ng/L]	1.48 (1.34,1.64)	58.6	0.39 (0.05)	<.0001
Log NT-proBNP [pg/mL]	1.35 (1.25,1.47)	51.7	0.30 (0.04)	<.0001
History of COPD	1.71 (1.45, 2.02)	40.2	0.54 (0.08)	<.0001
Baseline Albumin (per 0.1 decrease below 4.5) [g/dL]	1.07 (1.04, 1.09)	28.7	0.07 (0.01)	<.0001
LVEF				<.0001
>=50 %	1.00 (reference)			
<50 %	1.39 (1.21, 1.60)	21.1	0.33 (0.07)	
Age				<.0001
<65 years	1.00 (reference)			
65 to <75 years	1.25 (1.01, 1.56)	4.1	0.22 (0.11)	
>=75 years	1.62 (1.32, 2.00)	20.6	0.48 (0.11)	
NYHA class III/IV	1.24 (1.06,1.46)	6.9	0.22 (0.08)	0.009
Use of Insulin in DM patients				0.023
Non DM	1.00 (reference)			

DM + no insulin	0.99 (0.85, 1.16)	0.02	-0.01 (0.08)	
DM + insulin	1.28 (1.05, 1.56)	6.2	0.25 (0.10)	
KCCQ-OSS (per 10 increase)	0.94 (0.91, 0.97)	13.0	-0.06 (0.02)	0.0003
Baseline UACR				0.0009
<30 [mg/g]	1.00 (reference)			
30 to <=300[mg/g]	1.32 (1.13, 1.54)	12.4	0.28 (0.08)	
>300 [mg/g]	1.35 (1.25, 1.47)	7.1	0.30 (0.11)	

* Coefficient (SE) are the log hazard ratio and its standard error

c-statistic 0.721 (0.704,0.739)

**for UACR a good model fit was achieved for 3 categories <30, 30-300 and ≥300 mg/g

†for KCCQ-OSS hazard ratios are expressed per 10 point increase [Tomoko can you please see to this in Table S3 and S4B]

Table S4: The EMPEROR-Preserved risk model for predicting incidence of heart failure hospitalization

A. Using Variables in the Primary Endpoint Risk Model*

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
Log NT-proBNP [pg/mL]	1.63 (1.48, 1.79)	100.6	0.49 (0.05)	<.0001
Log hs-cTnT [ng/L]	1.77 (1.58, 1.99)	98.9	0.57(0.06)	<.0001
Time since most recent HHF				
>6 months	1.00 (reference)			<.0001
3-6 months	2.22 (1.70, 2.89)	34.2	0.80 (0.14)	
<3 months	2.76 (2.28, 3.36)	105.1	1.02 (0.10)	
NYHA class III/IV	1.93 (1.63, 2.28)	58.1	0.66 (0.09)	<.0001
History of COPD	1.79 (1.48, 2.17)	36.3	0.58 (0.10)	<.0001
Baseline haemoglobin				
>=12 [g/dL]	1.00 (reference)			<.0001
<12 [g/dL]	1.62 (1.36, 1.92)	29.9	0.48 (0.09)	
Time since HF diagnosis				
3 months-1 year	1.00 (reference)			<.0001
>=1 year	1.56 (1.27, 1.91)	18.4	0.44(0.10)	

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
Randomized to				
Empagliflozin	0.68 (0.58, 0.80)	22.6	-0.39 (0.08)	<.0001

*Coefficient (SE) are the log hazard ratio and its standard error

An estimate of each individual's 2-year risk can be calculated as follows: $1 - [0.99973^{\exp (0.57 \times \log \text{hs-cTnT} + 0.49 \times \log \text{NT-proBNP} + 0.66 \times \text{NYHA class} + 0.80 \times \text{recent HHF1} + 1.02 \times \text{recent HHF2} + 0.58 \times \text{COPD} + 0.44 \times \text{HF diagnosis} + 0.48 \times \text{haemoglobin} - 0.39 \times \text{Empagliflozin})}]$, where 'recent HHF1' and 'recent HHF2' are indicator variables for whether the most recent HHF was within 3–6 months or <3 months, respectively. NYHA is an indicator variable for whether the patient's NYHA class is III or IV. COPD and empagliflozin are indicator variables for whether the patient has COPD or is to be treated with empagliflozin, respectively. HF diagnosis is indicator variable for whether time since HF diagnosis is ≥ 1 year. Haemoglobin is an indicator variable for whether baseline haemoglobin is < 12 g/dL. CI, confidence interval; HF, heart failure; HHF, hospitalization for heart failure; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SE, standard error.

c-statistic: 0.787 (0.769,0.805)

B. Also Including UACR and KCCQ-OSS

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
Log NT-proBNP [pg/mL]	1.56 (1.42, 1.72)	83.2	0.44 (0.05)	<.0001
Log hs-cTnT [ng/L]	1.65 (1.47, 1.85)	71.5	0.50 (0.06)	<.0001
Time since most recent HHF				
>6 months	1.00 (reference)			<.0001
3-6 months	2.12 (1.61, 2.78)	29.3	0.75 (0.14)	
<3 months	2.72 (2.24, 3.31)	100.9	1.00 (0.10)	
NYHA class III/IV	1.66 (1.39, 1.99)	30.6	0.51 (0.09)	<.0001
History of COPD	1.79 (1.48, 2.17)	35.1	0.58 (0.10)	<.0001
Baseline haemoglobin				
>=12 [g/dL]	1.00 (reference)			<.0001
<12 [g/dL]	1.52 (1.28, 1.81)	21.9	0.42 (0.09)	
Time since HF diagnosis				
3 months-1 year	1.00 (reference)			<.0001
>=1 year	1.54 (1.25, 1.89)	16.9	0.43 (0.10)	
KCCQ-OSS	0.92 (0.89, 0.96)	16.6	-0.01 (0.02)	<.0001
Baseline UACR				
<30 [mg/g]	1.00 (reference)			<.0001

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
30 to <=300[mg/g]	1.36 (1.13, 1.64)	10.4	0.31 (0.09)	
>300 [mg/g]	1.78 (1.42, 2.24)	24.7	0.58 (0.12)	
Randomized to				
Empagliflozin	0.67 (0.57, 0.79)	23.7	-0.40 (0.08)	<.0001

c-statistic: 0.793 (0.775,0.811)

Table S5: Incidence rates per 100 patient years (and 95% CIs) of 1) the primary outcome and 2) all-cause death for patients simultaneously grouped in thirds of NT-pro BNP and hs-cTnT

	Level of hs-cTnT		
Level of NT-pro BNP	Bottom third <=13.85 ng/L	Middle third >13.85 and <=22.70 ng/L	Top third >22.70 ng/L
<u>Primary outcome</u>			
Bottom third (<=636.00 pg/mL)	N=914 Events=43 Rate=2.2 (1.6-2.9)	N=661 Events=56 Rate=4.0 (3.0-5.1)	N=422 Events=60 Rate=7.1 (5.4-9.0)
Middle third (>636.00 and <=1428.50 pg/mL)	N=652 Events=57 Rate=4.0 (3.1-5.2)	N=722 Events=109 Rate=7.5 (6.2-9.0)	N=621 Events=124 Rate=10.6 (8.8-12.6)
Top third (>1428.50 pg/mL)	N=430 Events=61 Rate=6.9 (5.3- 8.7)	N=617 Events=108 Rate=9.0 (7.4-10.8)	N=949 Events=308 Rate=19.2 (17.1- 21.4)
<u>All-cause death</u>			
Bottom third (<=636.00 pg/mL)	N=914 Deaths=47 Rate=2.3 (1.7-3.0)	N=661 Deaths=59 Rate=4.1 (3.1- 5.2)	N=422 Deaths=60 Rate=6.6 (5.0-8.4)

Middle third	N=652	N=722	N=621
(>636.00 and <=1428.50 pg/mL)	Deaths=46 Rate=3.2 (2.3-4.2)	Deaths=89 Rate=5.7 (4.6-7.0)	Deaths=130 Rate=10.1 (8.4-11.9)
Top third	N=430	N=617	N=949
(>1428.50 pg/mL)	Deaths=51 Rate=5.4 (4.0- 7.0)	Deaths=97 Rate=7.4 (6.0-8.9)	Deaths=270 Rate=14.4 (12.7- 16.2)

Table S6: The EMPEROR-Preserved risk model for the Primary Outcome (HF hospitalization or CV death) in LVEF \geq 50 vs. 40-49%

LVEF \geq 50%

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
Log hs-cTnT [ng/L]	1.62 (1.44, 1.83)	65.0	0.48 (0.06)	<.0001
Log NT-proBNP [pg/mL]	1.61 (1.46, 1.77)	89.2	0.48 (0.05)	<.0001
NYHA class III/IV	1.70 (1.42, 2.03)	34.7	0.53 (0.09)	<.0001
Time since most recent HHF				
>6 months	1.00 (reference)			<.0001
3-6 months	1.74 (1.29, 2.35)	13.0	0.55 (0.15)	
<3 months	2.10 (1.70, 2.59)	47.0	0.74 (0.11)	
History of COPD	1.59 (1.31, 1.94)	21.3	0.46 (0.10)	<.0001
Use of Insulin in DM patients				
Non DM	1.00 (reference)			<.0001
DM + insulin	1.84 (1.50, 2.26)	33.7	0.61 (0.11)	

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
DM + no insulin	0.97 (0.80, 1.18)	0.07	-0.03 (0.10)	
Time since HF diagnosis				
3 months-1 year	1.00 (reference)			0.0008
>=1 year	1.43 (1.16, 1.76)	11.2	0.36 (0.11)	
Baseline haemoglobin				
>=12 [g/dL]	1.00 (reference)			0.0004
<12 [g/dL]	1.38 (1.16, 1.65)	12.6	0.32 (0.09)	
Randomised to Empagliflozin	0.77 (0.66, 0.91)	9.7	-0.26 (0.08)	0.0019

C-statistic (95%CI) : 0.759 (0.740, 0.778)

Table S7: The EMPEROR-Preserved risk model for all-cause mortality in LVEF \geq 50 vs. 40-49%

LVEF \geq 50%

	Hazard ratio (95% CI)	Chi-squared statistic	Coefficient (SE)*	P-value
Log hs-cTnT [ng/L]	1.58 (1.40,1.78)	53.8	0.46 (0.06)	<.0001
Log NT-proBNP [pg/mL]	1.46 (1.31,1.62)	50.5	0.38 (0.05)	<.0001
History of COPD	1.52 (1.23,1.87)	15.1	0.42 (0.11)	0.0001
Baseline Albumin (per 0.1 decrease below 4.5) [g/dL]	1.07 (1.04, 1.10)	19.5	0.07 (0.01)	<.0001
NYHA class III/IV	1.34 (1.10,1.62)	8.4	0.29 (0.10)	0.0037
Age				0.0002
<65 years	1.00 (reference)			
65 to <75 years	1.27 (0.94, 1.72)	2.5	0.24 (0.15)	
\geq 75 years	1.70 (1.28, 2.24)	13.6	0.53 (0.14)	
Use of Insulin in DM patients				0.0003
Non DM	1.00 (reference)			
DM + insulin	1.56 (1.23, 1.96)	13.9	0.44 (0.12)	
DM + no insulin	0.99 (0.81, 1.22)	0.01	-0.01 (0.11)	

C-statistic (95%CI) : 0.723 (0.701, 0.745)

LVEF40-49%

	Hazard ratio (95% CI)	Chi- squared statistic	Coefficient (SE)*	P-value
Log hs-cTnT [ng/L]	1.39 (1.18,1.64)	19.5	0.33 (0.07)	0.0001
Log NT-proBNP [pg/mL]	1.34 (1.18,1.52)	14.9	0.29 (0.08)	<.0001
History of COPD	2.05 (1.57,2.67)	28.0	0.72 (0.14)	<.0001
Baseline Albumin (per 0.1 decrease below 4.5) [g/dL]	1.09 (1.05, 1.14)	20.4	0.09 (0.02)	<.0001
NYHA class III/IV	1.49 (1.16,1.90)	10.0	0.40 (0.13)	0.0016
Age				0.0297
<65 years	1.00 (reference)			
65 to <75 years	1.15 (0.84, 1.57)	0.8	0.14 (0.16)	
>=75 years	1.46 (1.07, 1.98)	5.8	0.38 (0.16)	
Use of Insulin in DM patients				0.4830
Non DM	1.00 (reference)			
DM + insulin	1.22 (0.88, 1.68)	1.5	0.20 (0.16)	

DM + no insulin

1.06 (0.84, 1.35) 0.2

0.06 (0.12)

C-statistic (95%CI) : 0.701 (0.670, 0.732)

Table S8: Comparison of the baseline characteristics of the patients enrolled in EMPEROR-Preserved and subset of PARAGON

Characteristic	EMPEROR-Preserved (n=5988)	Subset of PARAGON-HF Used for validation (n=1,251)	Other PARAGON-HF patients (n=3545)
Age, yr	71.9 ± 9.4	73.6 ± 8.0	72.4 ± 8.6
Female sex, n. (%)	2676 (44.7)	643 (51.4)	1,836 (51.8)
NYHA III/IV, n. (%)	1101 (18.4)	270 (21.6)	681 (19.2)
LVEF, % , mean±SD	54.3 ± 8.8	57.2 ± 7.5	57.6 ± 8.0
Time since most recent HFH, n. (%)			
<3 months	549 (9.2)	105 (8.4)	548 (15.5)
>3 to 6 months	393 (6.6)	142 (11.4)	608 (17.2)
>6 months	5046 (84.3)	1,004 (80.3)	2,386 (67.4)
Time since HF diagnosis, n. (%)			
3 months-1 year	1512 (25.3)	500 (40.0)	1,480 (41.8)
>1 year	4476 (74.7)	751 (60.0)	2,058 (58.2)
History of COPD, n. (%)	795 (13.3)	209 (16.7)	461 (13.0)
Diabetes mellitus, n. (%)	2938 (49.1)	521 (41.6)	1,543 (43.5)
Use of Insulin in diabetic patients, n. (%)	861 (14.4)	164 (13.1)	493 (13.9)
Haemoglobin, g/dL, mean±SD	13.3 ± 1.6	13.5 ± 1.5	13.5 (1.6)
Albumin, g/dL, mean±SD	4.4 ± 0.3	4.2 ± 0.3	4.2 (0.3)
NT-proBNP, pg/mL*	974 (499 – 1731)	945 (505 – 1553)	892 (451-1644)
hs-cTnT, ng/L *	17.7 (11.6 – 26.9)	16.0 (11.0 – 24.0)	N/A

Legend: NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HFH, heart failure hospitalization; COPD, Chronic obstructive pulmonary disease; NT-proBNP, N-terminal pro brain natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T.

*Median (percentile 25 to 75).

Figure S1: Cumulative incidence of the primary outcome by risk tertile and by randomized treatment

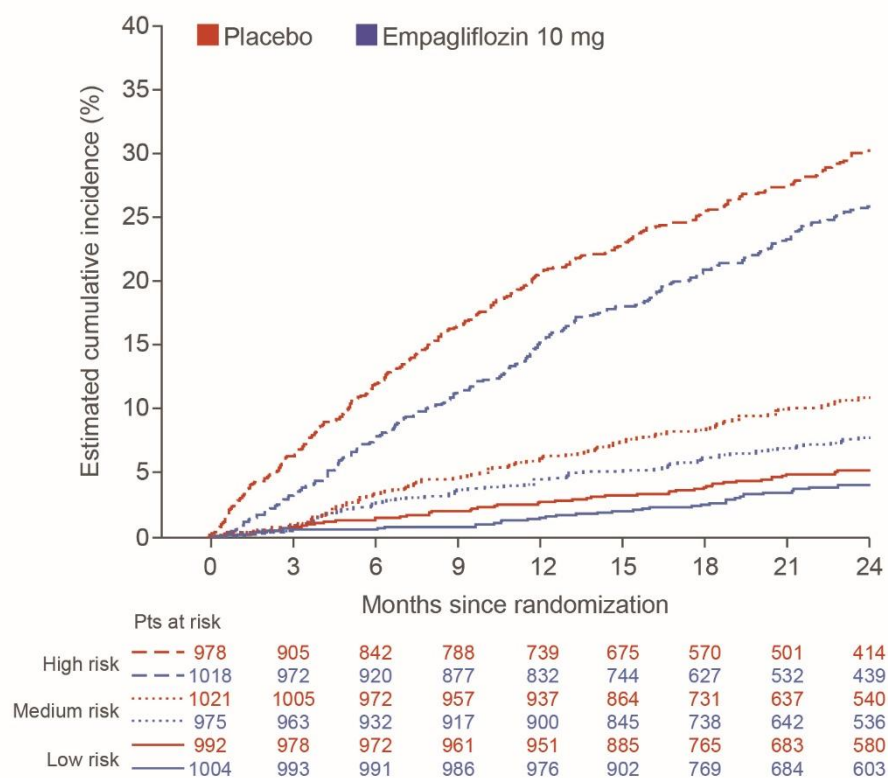


Figure S2: Observed vs predicted 2 year incidence of HF hospitalization by tenths of the risk score distribution in EMPEROR-Preserved

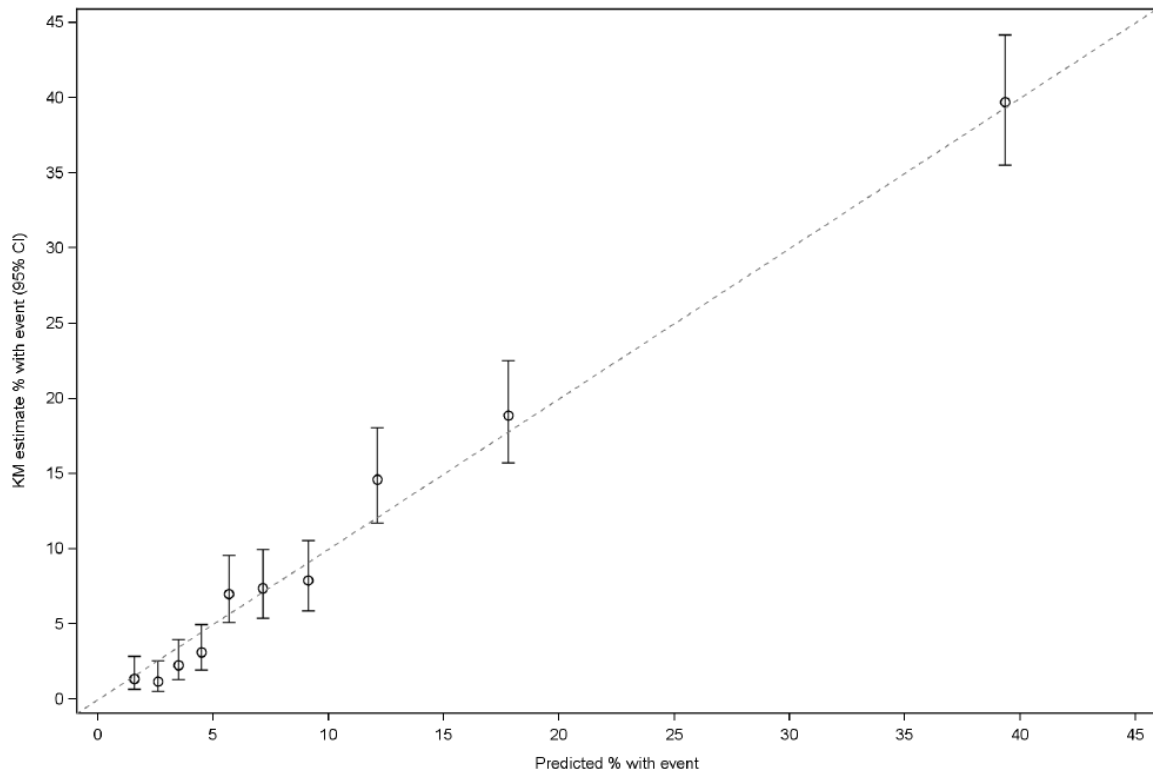


Figure S3: Distributions of the five quantitative risk factors in the risk model for all-cause death

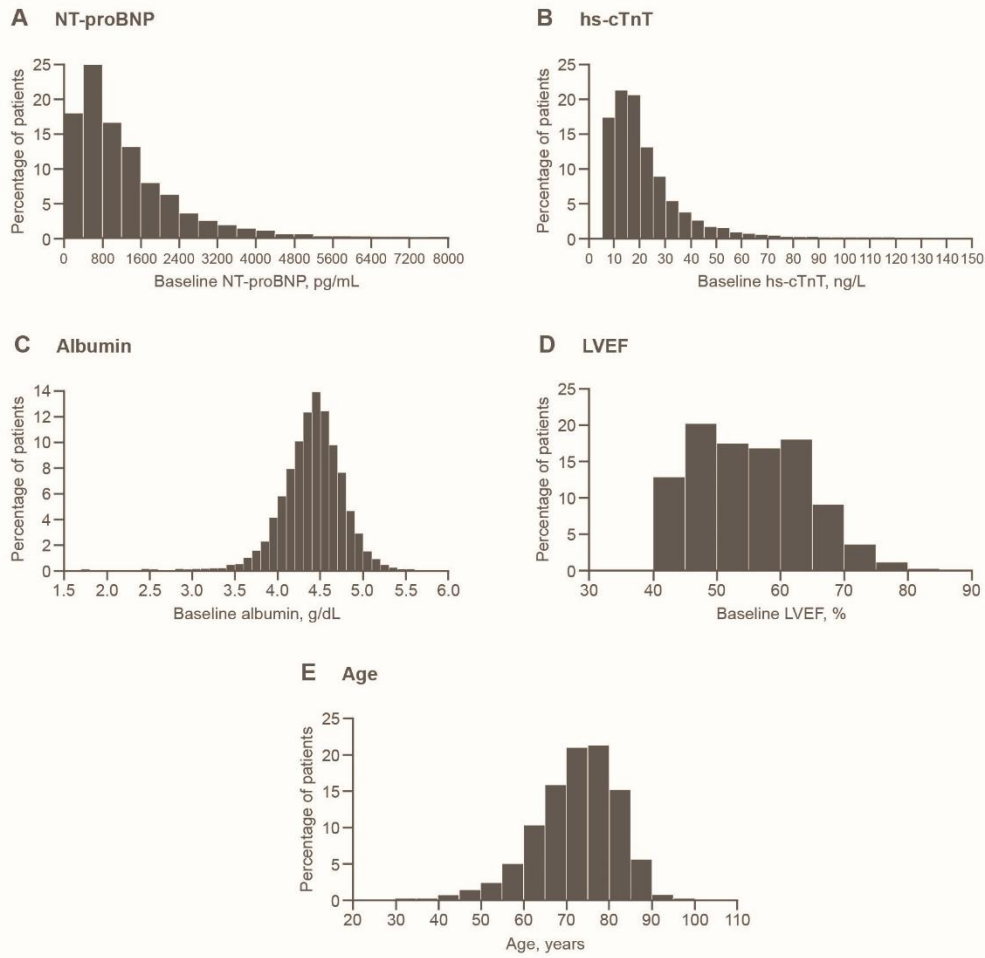
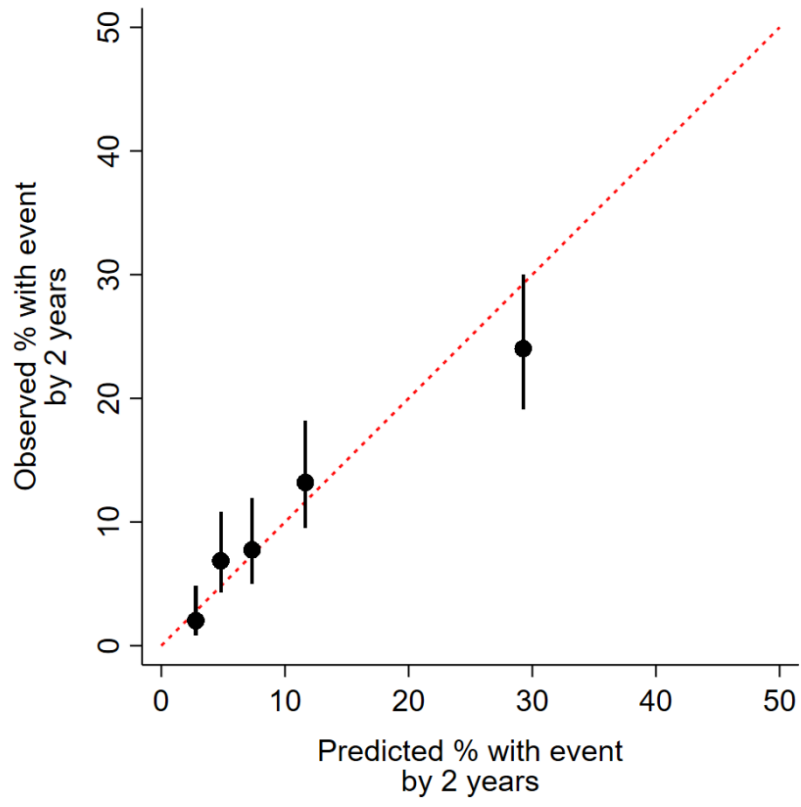


Figure S4: Observed vs predicted 2 year incidence of HF hospitalization by fifths of the risk score distribution in PARAGON-HF



Patient characteristics	Enter patient values in this column		
NT-proBNP (pg/mL)	1200		
High-sensitivity cardiac troponin-T (ng/L)	499		
Time since most recent heart failure hospitalisation (select item from drop-down menu)	3-6 months		
Time since heart failure diagnosis (select item from drop-down menu)	>=1year		
Haemoglobin (select item from drop-down menu)	>=12 g/dL		
Patient's NYHA class (select item from drop-down menu)	III or IV		
History of COPD (select item from drop-down menu)	No		
Is patient on SGLT2 inhibitor? (select item from drop-down menu)	No		
Use of Insulin in DM patients (select item from drop-down menu)	Non diabetic		
Albumin (g/dL)	4.3		
Age (select item from drop-down menu)	65 to <75 years		
LVEF (select item from drop-down menu)	<50%		
RESULTS			
	Patients 2 year risk of outcome	Assessment of risk	Decile of risk within the EMPEROR-Reduced study population
Heart failure hospitalisation or CV death	77.1%	Very high risk	90-100%
All-cause death	42.5%	Very high risk	90-100%
Cardiovascular death	26.4%	Very high risk	90-100%