

## Supplementary Material

Supplementary Table 1. Patients' characteristics by erythrocytosis status

Characteristic	No Erythrocytosis	Erythrocytosis	P-value
N.	5859 (97.9)	127 (2.1)	-
Age, yrs	72.1 ± 9.5	66.9 ± 9.4	<0.001
Women	2655 (45.3)	20 (15.8)	<0.001
Ethnicity			0.78
White	4442 (75.8)	98 (77.2)	
Asian	807 (13.8)	17 (13.4)	
Black	255 (4.4)	3 (2.4)	
Indian	190 (3.2)	3 (3.2)	
Other	165 (2.8)	5 (3.9)	
Region			0.40
Asia	672 (11.5)	14 (11.0)	
East Europe	1846 (31.5)	39 (30.7)	
Latin America	1482 (25.3)	33 (26.0)	
North America	709 (12.1)	10 (7.9)	
West Europe	784 (13.4)	18 (14.2)	
Other	366 (6.3)	13 (10.2)	
Hypertension	5308 (90.6)	114 (89.8)	0.75
Diabetes status			0.079
Pre-diabetes	1946 (33.2)	33 (26.0)	
Diabetes	2874 (49.1)	63 (49.6)	
HFH prev. 12mo	1443 (24.6)	25 (19.7)	0.20
AFib/Flutter	3062 (52.3)	72 (56.7)	0.33
PAD	549 (9.4)	11 (8.7)	0.79
Smoker (current)	412 (7.0)	24 (19.1)	<0.001
COPD	770 (13.1)	25 (20.0)	0.032
Ischemic HF	2072 (35.4)	44 (34.7)	0.68
SBP, mmHg	131.9 ± 15.6	130.9 ± 15.8	0.49
DBP, mmHg	75.6 ± 10.6	80.3 ± 10.2	<0.001
Heart rate, bpm	70.3 ± 11.9	74.3 ± 11.9	<0.001
BMI, Kg/m <sup>2</sup>	29.8 ± 5.9	31.6 ± 5.7	<0.001
Hemoglobin, g/dL	13.2 ± 1.5	17.2 ± 0.8	<0.001
Hematocrit, %	40.7 ± 4.5	52.6 ± 3.1	<0.001
eGFR, ml/min/1.73m <sup>2</sup>	60.5 ± 19.8	65.6 ± 18.4	0.004
eGFR category			0.20
≥90	454 (7.8)	14 (11.0)	
60 to <90	2469 (42.2)	61 (48.0)	
45 to <60	1534 (26.2)	30 (23.6)	
30 to <45	1095 (18.7)	19 (15.0)	
<30	306 (5.2)	2 (2.4)	
UACR, mg/g*	20 (8-70)	36 (13-170)	0.001
UACR category			0.056
<30	3412 (58.5)	61 (48.0)	
30 to ≤300	1811 (31.0)	48 (37.8)	
>300	611 (10.5)	18 (14.2)	
NYHA class			0.28

II	4786 (81.7)	99 (78.0)	
III/IV	1073 (18.3)	28 (22.1)	
Per. edema	1508 (25.7)	30 (23.6)	0.79
Pul. rales	308 (5.2)	13 (10.2)	0.046
LVEF, %	54.4 ± 8.8	52.6 ± 8.1	0.028
LVEF group			0.33
<50	1934 (33.0)	48 (37.8)	
50 to <60	2013 (34.4)	45 (35.4)	
≥60	1912 (32.6)	34 (26.8)	
Sodium, mmol/L	140.9 ± 2.7	140.9 ± 3.0	0.93
Potassium, mmol/L	4.5 ± 0.5	4.5 ± 0.5	0.30
NT-pro BNP, pg/mL*	974 (500-1737)	991 (467-1623)	0.69
hsTnT, ng/L*	18 (12-27)	20 (13-28)	0.14
ACEi/ARB	4595 (78.4)	108 (85.0)	0.072
Loop diuretic	3965 (67.7)	87 (68.5)	0.84
ARNi	131 (2.2)	3 (2.4)	0.92
Thiazide	1214 (20.7)	25 (19.7)	0.78
MRA	2199 (37.5)	45 (35.4)	0.63
Beta-blocker	5050 (86.2)	115 (90.6)	0.16
Anti-platelet agent	5130 (87.6)	108 (85.0)	0.39
Anticoagulant	2847 (48.6)	64 (50.4)	0.69
NSAIDs	2682 (45.8)	52 (40.9)	0.28
KCCQ-CSS	70.4 ± 21.1	72.8 ± 21.3	0.20

Legend: HFH, heart failure hospitalization; AFib, atrial fibrillation; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; NT-pro BNP, N-terminal pro brain natriuretic peptide; hs-TnT, high sensitivity troponin T; ARNi, angiotensin-receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score.

Results presented as absolute number (%), mean ± standard deviation, or \* median percentile (25-75)

Baseline hemoglobin levels were missing in 2 patients.

Supplementary Table 2. Outcome association by erythrocytosis status in the placebo group

<b>Outcome</b>	<b>No Erythrocytosis</b> N =2905	<b>Erythrocytosis</b> N =84	<b>HR (95%CI)*</b>	<b>P-value</b>
CVD or HFH	499 (17.2) IR =8.7	12 (15.2) IR =7.7	0.90 (0.51-1.61)	0.73
HFH	348 (12.0) IR =6.1	4 (5.1) IR =2.6	0.44 (0.16-1.18)	0.10
CVD	235 (8.1) IR =3.8	9 (11.4) IR =5.6	1.50 (0.77-2.95)	0.23
MI	38 (1.3) IR =0.6	2 (2.5) IR =1.3	1.79 (0.43-7.50)	0.43
Stroke	81 (2.8) IR =1.3	3 (3.8) IR =1.9	1.46 (0.45-4.67)	0.53
3P-MACE	319 (11.0) IR =5.3	12 (15.2) IR =7.8	1.44 (0.80-2.58)	0.22
DVT/PTE	33 (1.1) IR =0.5	0	-	-
Kidney EP	111 (3.8) IR =1.8	1 (1.2) IR =0.6	0.38 (0.05-2.76)	0.34
ACM	412 (14.2) IR =6.7	15 (19.0) IR =9.3	1.38 (0.83-2.35)	0.21

Legend: CVD, cardiovascular death; HFH, heart failure hospitalization; MI, myocardial infarction; 3P-MACE, composite endpoint of myocardial infarction, stroke or cardiovascular death; DVT/PTE, deep venous thrombosis or pulmonary embolism; Kidney EP, composite endpoint of sustained eGFR drop  $\geq 40\%$  from baseline, end-stage renal disease, dialysis, or death related to kidney dysfunction; ACM, all-cause mortality; IR, incidence rate per 100 person-years; HR, hazard ratio; CI, confidence interval.

\*Model adjusted on age, sex, region, diabetes status, ejection fraction, and eGFR.

Supplementary Table 3. Time-updated associations of erythrocytosis with outcomes

<b>Outcome</b>	<b>HR (95%CI)</b>	<b>P-value</b>
Stroke	1.01 (0.50-2.05)	0.97
MI	1.22 (0.48-3.06)	0.68
CVD	1.13 (0.73-1.77)	0.58
3P-MACE	1.03 (0.70-1.50)	0.88
DVT/PTE	0.41 (0.06-2.96)	0.38

Legend: MI, myocardial infarction; CVD, cardiovascular death; 3P-MACE, composite endpoint of myocardial infarction, stroke or cardiovascular death; DVT/PTE, deep venous thrombosis or pulmonary embolism.

Supplementary Table 4. Effect of empagliflozin by erythrocytosis status

<b>Outcome/Anemia status</b>	<b>Placebo n/N (%)</b>	<b>Empagliflozin n/N (%)</b>	<b>Empa. vs Pbo. HR (95%CI)</b>	<b>InteractionP</b>
CVD or HFH				
No Erythrocytosis	499/2910 (17.2)	403/2949 (13.7)	0.78 (0.68-0.89)	0.069
Erythrocytosis	12/79 (15.2)	12/48 (25.0)	1.65 (0.74-3.68)	
3P-MACE				
No Erythrocytosis	319/2910 (11.0)	311/2949 (10.6)	0.97 (0.83-1.14)	0.94
Erythrocytosis	12/79 (15.2)	8/48 (16.7)	1.00 (0.41-2.44)	
ACM				
No Erythrocytosis	412/2910 (14.2)	414/2949 (14.0)	0.99 (0.87-1.14)	0.64
Erythrocytosis	15/79 (19.0)	8/48 (16.7)	0.81 (0.34-1.92)	

Legend: CVD, cardiovascular death; HFH, heart failure hospitalization; 3P-MACE, composite endpoint of myocardial infarction, stroke or cardiovascular death; Kidney EP, composite endpoint of sustained eGFR drop  $\geq 40\%$  from baseline, end-stage renal disease, dialysis, or death related to kidney dysfunction; ACM, all-cause mortality; HR, hazard ration; CI, confidence interval.

Note: Individual components of the primary outcome and kidney EP not reported due to less than 10 events per treatment group.

Supplementary Table 5. Effect of empagliflozin on hemoglobin levels across CKD categories

eGFR categories	Placebo Hb (SE) g/dL	Empagliflozin Hb (SE) g/dL	Difference (SE) P-value
≥90 ml/min	13.27 (0.05)	13.82 (0.05)	0.55 (0.07) P <0.001
60-89 ml/min	13.26 (0.02)	13.84 (0.02)	0.58 (0.03) P <0.001
45-59 ml/min	13.17 (0.03)	13.77 (0.03)	0.60 (0.04) P <0.001
30-44 ml/min	13.18 (0.03)	13.66 (0.03)	0.48 (0.04) P <0.001
<30 ml/min	12.91 (0.06)	13.57 (0.06)	0.66 (0.09) P <0.001

Legend: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; Hb, hemoglobin; SE, standard error.

Treatment-by-CKD interaction P-value =0.99.

Supplementary Table 6. Association between hemoglobin changes and health status

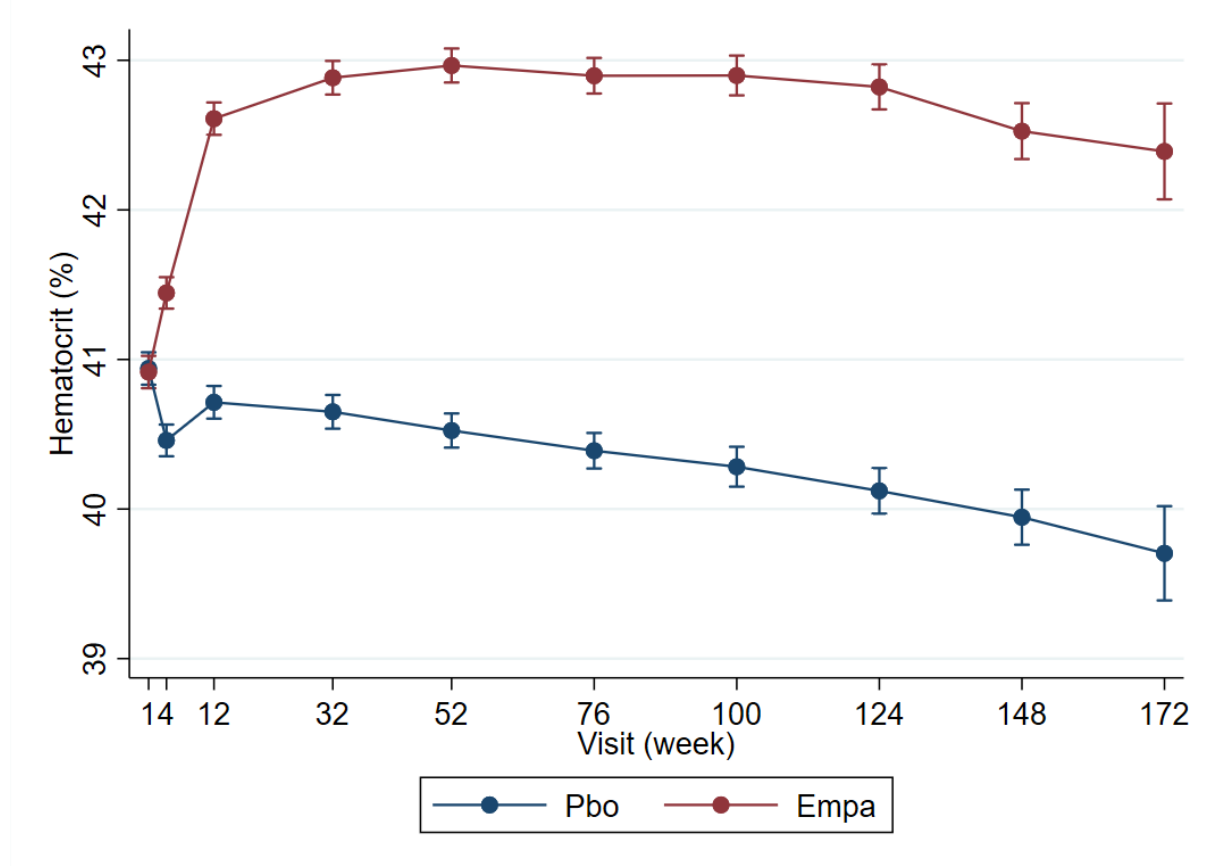
KCCQ-CSS change	Hemoglobin change (g/dL)*	
	Placebo OR (95%CI) P-value	Empagliflozin OR (95%CI) P-value
≥5pt increase	1.07 (0.99-1.16) P =0.10	1.12 (1.03-1.21) P =0.003
≥5pt decrease	0.94 (0.85-1.03) P =0.20	0.89 (0.81-0.98) P =0.013
Correlation	0.03	0.05

Legend: KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score.

\*Hemoglobin change from baseline to week 12 (with similar results found with changes from baseline to week 52).



Supplementary Figure 1. Effect of empagliflozin on hematocrit levels over time



Legend: Empa., empagliflozin; Pbo., placebo; SE, standard error.

Notes: Throughout the follow-up, the average (standard error) hematocrit level in the placebo group was 40.45 (0.04) % and 42.40 (0.04) % in the empagliflozin group, with a between-group (empagliflozin vs placebo) difference of 1.94 (0.06) %, joint P-value <0.001. Regarding specific time-points, at baseline the between-group difference was 0.03 (0.08) %, at week 12 was 1.95 (0.08) %, at week 52 was 2.49 (0.09) %, and at week 100 was 2.65 (0.10) %.