

Title: Eligibility for Pharmacological Therapies in Heart Failure with Reduced Ejection Fraction: Implications of the New CKD-EPI Creatinine Equation for Estimating Glomerular Filtration Rate

SUPPLEMENTARY MATERIAL

Table S1. Characteristics of included clinical trials

Trial	Creatinine/eGFR exclusion criteria	Age Mean (SD)	Female sex N (%)	Black race N (%)	S-creatinine mg/dL Mean (SD)
Overall N=43,138*		64.3 (11.3)	9,580 (22.2)	2,521 (5.8)	1.2 (0.4)
CIBIS-II N=2,632*	S-creatinine \geq 3.4 mg/dL (\geq 300 μ mol/L)	60.9 (10.5)	511 (19.4)	7 (0.3)	1.2 (0.3)
MERIT-HF N=3,965*	None	63.3 (9.7)	895 (22.6)	206 (5.2)	1.2 (0.4)
RALES N=1,658*	S-creatinine >2.5 mg/dL (221 μ mol/L)	65.2 (11.9)	444 (26.8)	120 (7.2)	1.2 (0.4)
BEST N=2,642*	S-creatinine >2.5 mg/dL (221 μ mol/L)	60.1 (12.4)	576 (21.8)	625 (23.7)	1.2 (0.4)
Val-HeFT N=5,003*	S-creatinine >2.5 mg/dL (221 μ mol/L)	62.7 (11.1)	1,003 (20.0)	344 (6.9)	1.3 (0.3)
CHARM-Added N=929*	S-creatinine >3 mg/dL ($>$ 265 μ mol/L)	63.7 (11.7)	213 (22.9)	111 (11.9)	1.2 (0.4)
CHARM-Alternative N=660*	S-creatinine >3 mg/dL ($>$ 265 μ mol/L)	65.9 (11.5)	212 (32.1)	68 (10.3)	1.2 (0.5)
SCD-HeFT N=2,500*	S-creatinine >2.5 mg/dL (221 μ mol/L)	59.0 (11.9)	582 (23.3)	423 (16.9)	1.2 (0.7)
CORONA N=5,011*	S-creatinine >2.5 mg/dL (221 μ mol/L)	72.7 (7.1)	1,180 (23.5)	13 (0.3)	1.3 (0.3)
EMPHASIS-HF N=2,725*	eGFR <30 ml/min/1.73 m ²	68.6 (7.6)	608 (22.3)	67 (2.5)	1.1 (0.3)
PARADIGM-HF N=8,399*	eGFR <30 mL/min/1.73 m ²	63.8 (11.4)	1,832 (21.8)	428 (5.1)	1.1 (0.3)
ATMOSPHERE N=7,014*	eGFR <35 mL/min/1.73 m ²	63.2 (11.8)	1,524 (21.7)	109 (1.6)	1.0 (0.3)

*Patients with missing creatinine measurements were excluded.

CIBIS-II, The Cardiac Insufficiency Bisoprolol Study II.

MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.

RALES, The Randomized Aldactone Evaluation Study.

BEST: The Beta-Blocker Evaluation of Survival Trial.

Val-HeFT, The Valsartan Heart Failure Trial.

CHARM-Added, Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity-Added.

CHARM-Alternative, Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity-Alternative

SCD-HeFT, The Sudden Cardiac Death in Heart Failure Trial.

CORONA, The Controlled Rosuvastatin Multinational Trial in Heart Failure.

EMPHASIS-HF, The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure.

PARADIGM-HF, The Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial.

ATMOSPHERE, The Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure.

eGFR, estimated glomerular filtration rate.

Table S2. Estimated glomerular filtration rate according to the original and new Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine and cystatin in the overall population.

eGFR ⁺	2012 CKD-EPI* N=1,922	2021 CKD-EPI** N=1,922	2021 CKD-EPI compared to 2012 CKD-EPI		
			Increase in eGFR	No change in eGFR	Decrease in eGFR
Overall, N (%)					
≥90 (CKD stage 1)	213 (11.1)	301 (15.7)	0/213 (0.0)	213/213 (100)	0/213 (0.0)
60-89 (CKD stage 2)	870 (45.3)	914 (47.6)	88/870 (10.1)	782/870 (89.9)	0/870 (0.0)
<60 (CKD stages 3-5)	839 (43.7)	707 (36.8)	238/839 (28.4)	601/839 (71.6)	0/839 (0.0)
Breakdown of CKD stages 3-5, N (%)					
45-59 (CKD stage 3a)	473 (24.6)	433 (22.5)	132/473 (27.9)	341/473 (72.1)	0/473 (0.0)
30-44 (CKD stage 3b)	320 (16.6)	242 (12.6)	92/320 (28.8)	228/320 (71.3)	0/320 (0.0)
<30 (CKD stages 4+5)	46 (2.4)	32 (1.7)	14/46 (30.4)	32/46 (69.6)	0/46 (0.0)

*2012 CKD-EPI with race: $135 * \min_1(\text{CREAT}/A, 1)^B * \max_1(\text{CREAT}/A, 1)^{-0.601} * \min_2(\text{CYS}/0.8, 1)^{-0.375} * \max_2(\text{CYS}/0.8, 1)^{0.711} * 0.995^{\text{AGE}} * C * D$

Min₁, minimum of CREAT/A or 1; max₁, maximum of CREAT/A or 1; CREAT, creatinine in mg/dL; A: 0.9 for men, 0.7 for women; B: -0.207 for men, -0.248 for women; Min₂, minimum of CYS/0.8 or 1; max₂, maximum of CYS/0.8 or 1; CYS, cystatin C in mg/dL; C: 1 for men, 0.969 for women; D: 1 for non-Black, 1.080 for Black.

**2021 CKD-EPI without race: $135 * \min(\text{CREAT}/A, 1)^B * \max(\text{CREAT}/A, 1)^{-0.544} * \min_2(\text{CYS}/0.8, 1)^{-0.323} * \max_2(\text{CYS}/0.8, 1)^{0.778} * 0.9961^{\text{AGE}} * C$

Min₁, minimum of CREAT/A or 1; max₁, maximum of CREAT/A or 1; CREAT, creatinine in mg/dL; A: 0.9 for men, 0.7 for women; B: -0.144 for men, -0.219 for women; Min₂, minimum of CYS/0.8 or 1; max₂, maximum of CYS/0.8 or 1; CYS, cystatin C in mg/dL; C: 1 for men, 0.963 for women.

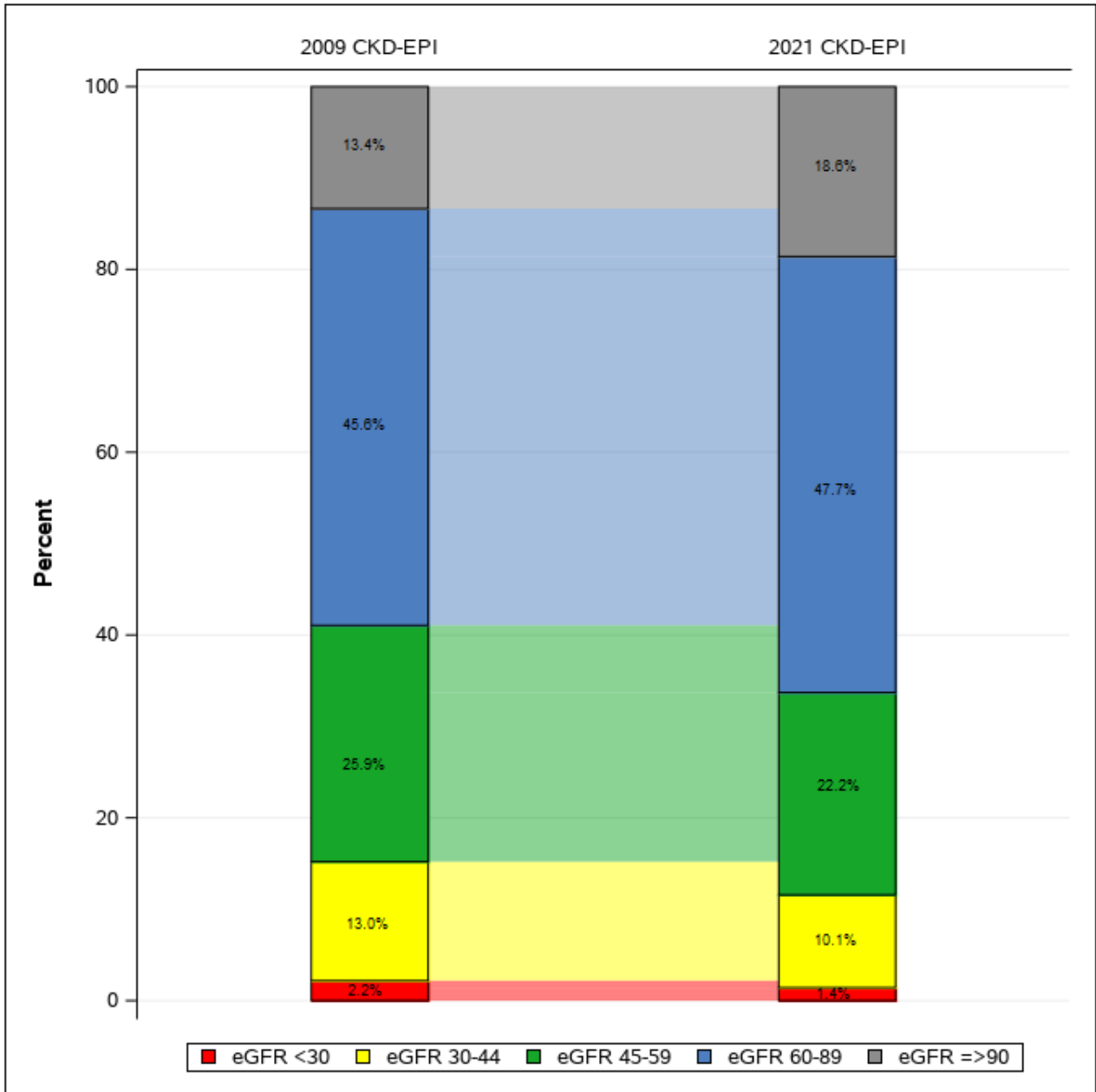
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

⁺mL/min/1.73 m²

Only a subset of patients enrolled in the PARADIGM-HF trial with an available cystatin measurement at randomization were included in this analysis.

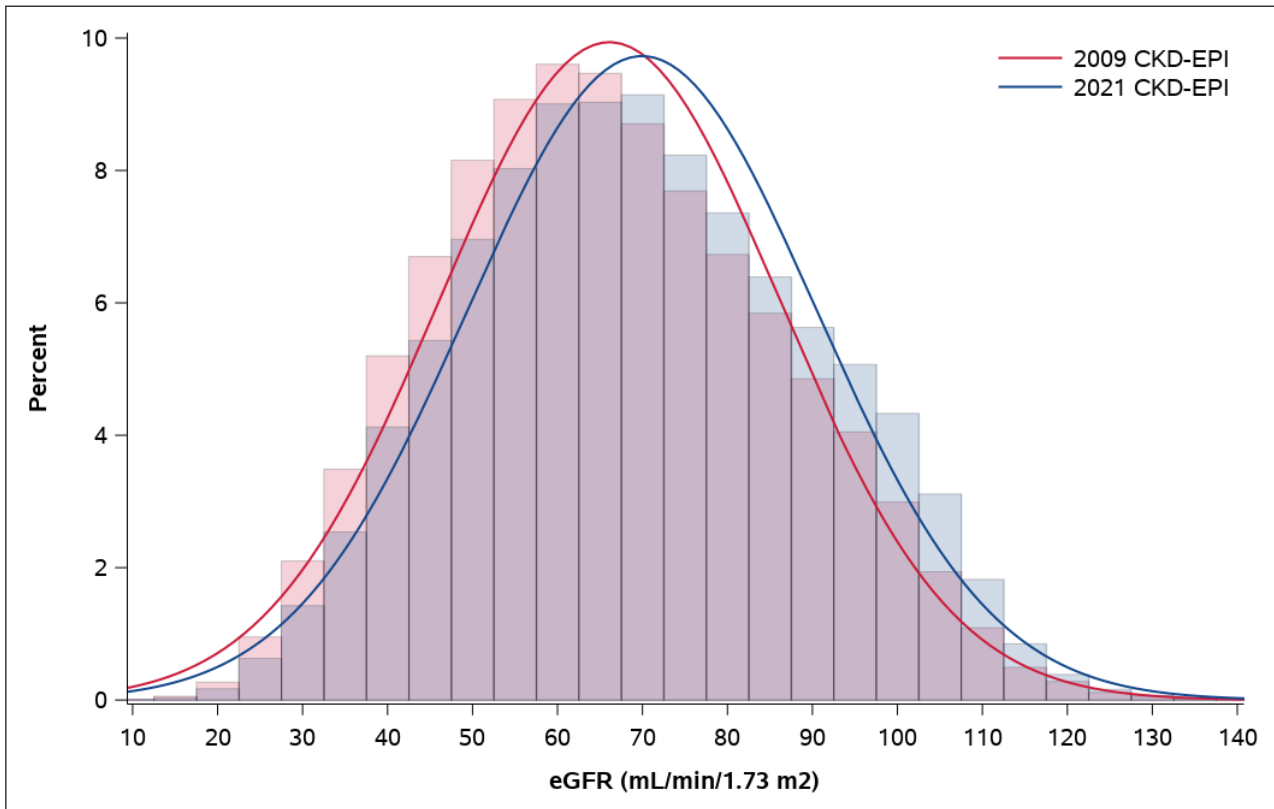
Figure S1. Estimated glomerular filtration rate according to the original and new Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine according to race

a) Non-Black patients: Changes in eGFR categories



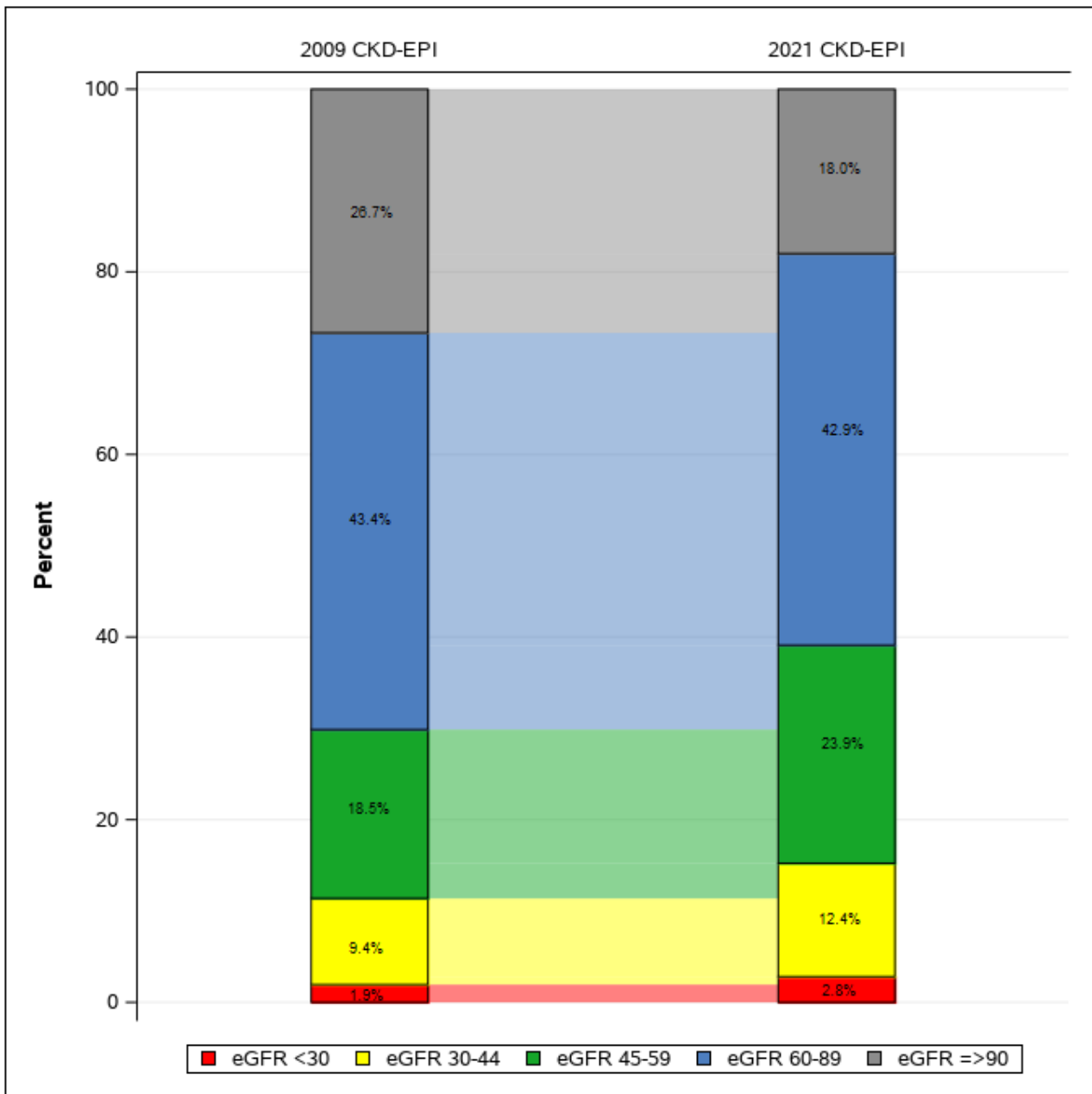
Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

b) Non-Black patients: Histogram and frequency distribution curves



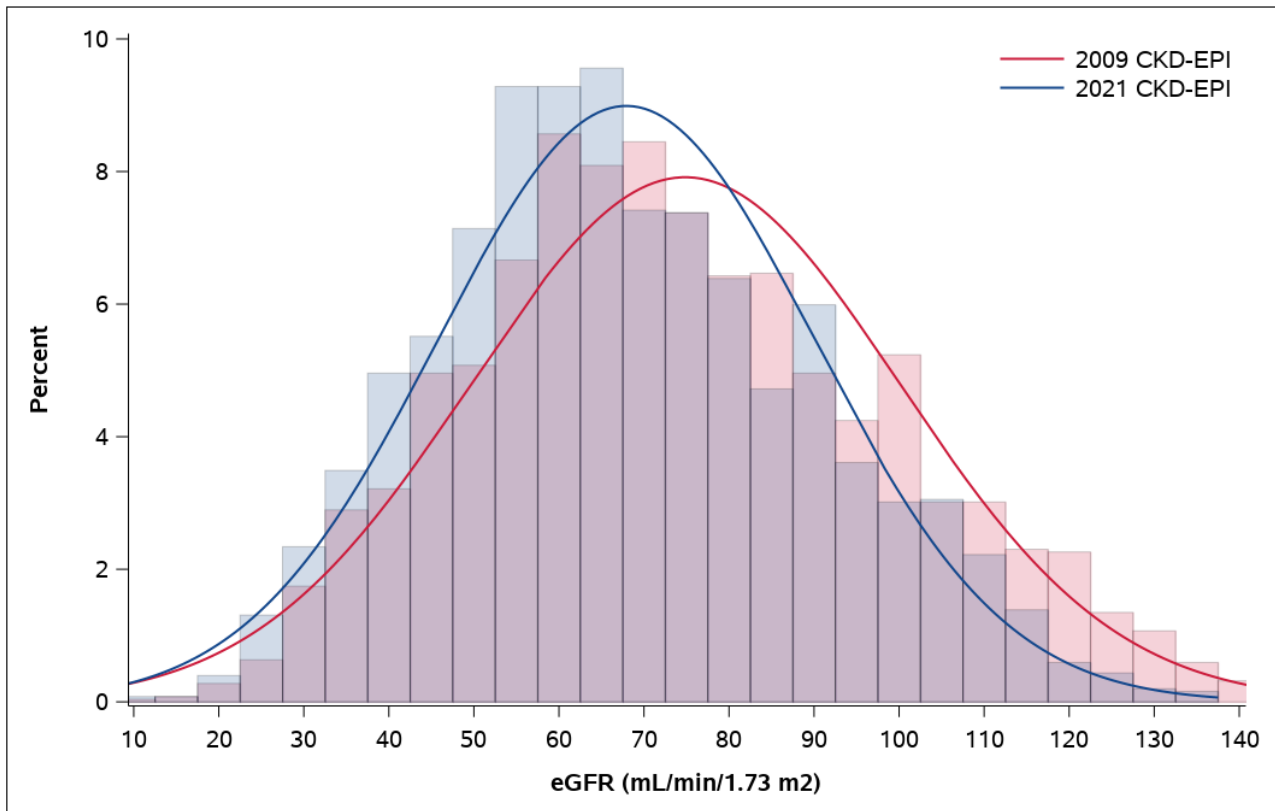
Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

c) Black patients: Changes in eGFR categories



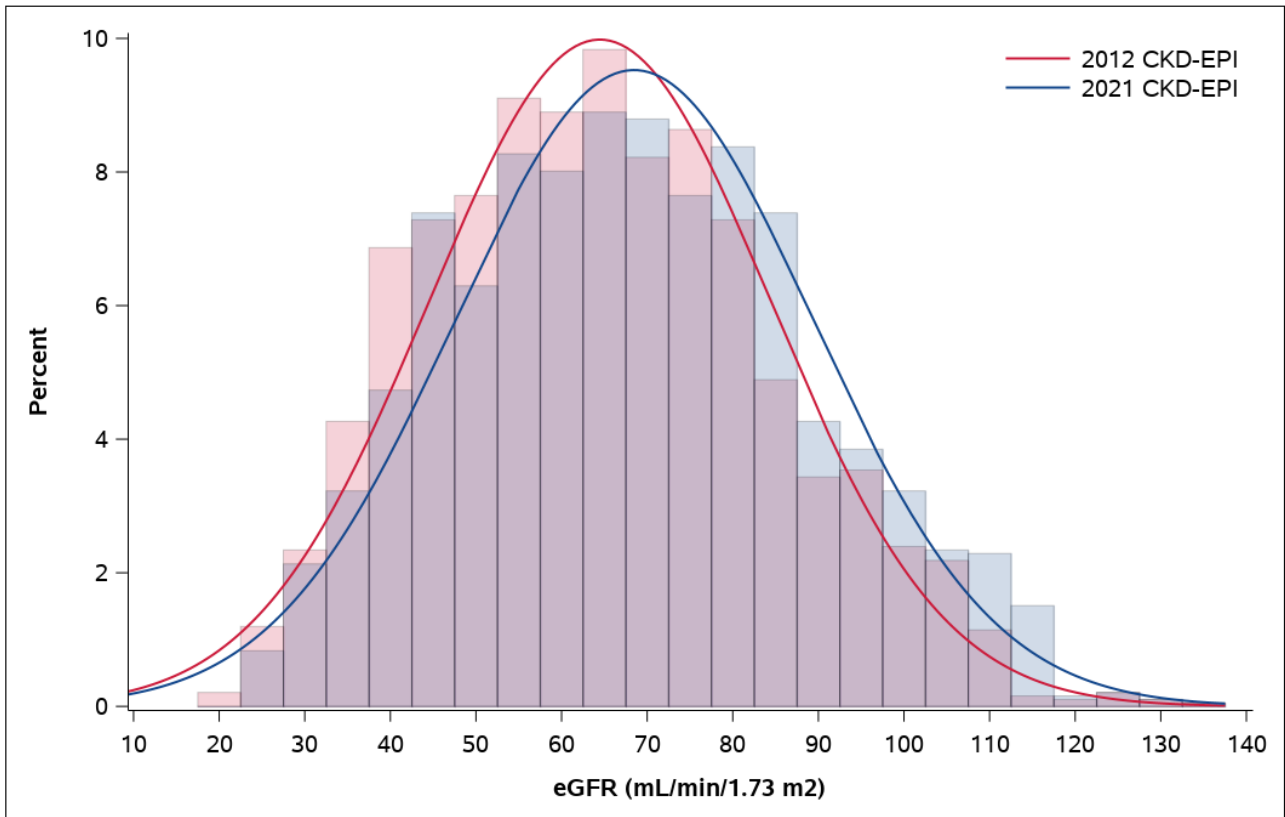
Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

d) Black patients: Histogram and frequency distribution curves



Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

Figure S2. Histogram and frequency distribution curves of the estimated glomerular filtration rate according to the original and new Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine and cystatin in the overall population.



*Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.
Only a subset of patients enrolled in the PARADIGM-HF trial with an available cystatin measurement at randomization were included in this analysis.*