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## ► To cite this version:

Jawad H Butt, Carly Adamson, Kieran F Docherty, Muthiah Vaduganathan, Scott D Solomon, et al.. Eligibility for pharmacological therapies in heart failure with reduced ejection fraction: implications of the new Chronic Kidney Disease Epidemiology Collaboration creatinine equation for estimating glomerular filtration rate. *European Journal of Heart Failure*, 2022, 24 (5), pp.861-866. 10.1002/ejhf.2460 . hal-03797312

**HAL Id: hal-03797312**

**<https://hal.univ-lorraine.fr/hal-03797312>**

Submitted on 4 Oct 2022

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# Eligibility for pharmacological therapies in heart failure with reduced ejection fraction: implications of the new Chronic Kidney Disease Epidemiology Collaboration creatinine equation for estimating glomerular filtration rate

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Received 31 January 2022; revised 24 December 2021; accepted 18 February 2022; online publish-ahead-of-print 8 March 2022

## Aims

The new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating glomerular filtration rate (eGFR), based on serum creatinine, that does not incorporate race may reclassify individuals, irrespective of race, from one eGFR category to another, with implications for eligibility for treatments in patients with heart failure and reduced ejection fraction (HFrEF).

## Methods and results

A total of 43 138 ambulatory patients with HFrEF from 12 clinical trials were included (mean age 64.3 years; 9580 [22.2%] women). Mean eGFR was 67 (standard deviation [SD] 21) ml/min/1.73 m<sup>2</sup> and 70 (SD 21) ml/min/1.73 m<sup>2</sup> using the original and new CKD-EPI equations, respectively (mean difference 3.20 ml/min/1.73 m<sup>2</sup>, 95% confidence interval [CI] 3.17–3.23,  $p < 0.001$ ). Of the 935 patients with chronic kidney disease (CKD) stages 4 or 5, identified using the original equation, 309 (33.0%) were reclassified to CKD stages 1–3 (eGFR  $\geq 30$  ml/min/1.73 m<sup>2</sup>) with the new equation. However, the opposite was observed among the 2521 Black patients (5.8%) included, with a reduction in mean eGFR from 75 to 68 ml/min/1.73 m<sup>2</sup> using the original and new equations, respectively (mean difference 6.94 ml/min/1.73 m<sup>2</sup>, [95% CI 6.82–7.06],  $p < 0.001$ ). The number of Black patients with an eGFR  $< 30$  ml/min/1.73 m<sup>2</sup> increased from 49 (1.9%) using the original equation to 71 (2.8%) with the new equation.

## Conclusions

The new CKD-EPI creatinine equation reclassified CKD stage in a large proportion of patients with HFrEF enrolled in clinical trials. As eGFR is an essential determinant of eligibility for several key pharmacological therapies in HFrEF, this reclassification could result in a substantial change in the proportion of patients considered eligible for such therapies and reduce the proportion of eligible Black patients.

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## Introduction

The current guideline-recommended equation for estimating glomerular filtration rate (eGFR) based on serum creatinine, developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), incorporates age, sex, and race.<sup>1</sup> However, there has been concern that inclusion of race, a social construct (and not a solely biological property), may contribute to existing disparities in health care.<sup>2</sup> Consequently, some institutions in the United States have omitted the racial coefficient when calculating eGFR, thereby assigning the value for non-Black individuals to Black individuals.<sup>2</sup> The accuracy of this approach as compared with measured GFR has not been evaluated, and CKD-EPI has therefore developed a new equation for estimating GFR based on serum creatinine, incorporating age and sex, but not race.<sup>3</sup> Both Black and non-Black people could be reclassified from one eGFR category using the original CKD-EPI equation to another using the new equation. Therefore, the use of the new equation for GFR estimation may have important implications regarding eligibility for treatments such as a renin–angiotensin system (RAS) blocker, angiotensin receptor–neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist (MRA), non-vitamin K oral anticoagulants (NOAC), and sodium–glucose cotransporter-2 inhibitor (SGLT2i) in patients with heart failure with reduced ejection fraction (HFrEF).<sup>4</sup> We compared the new CKD-EPI equation based on serum creatinine with the original equation (incorporating race) and examined changes in eGFR and chronic kidney disease (CKD) stage in a large cohort of ambulatory patients with HFrEF enrolled in clinical trials.

## Methods

We pooled individual patient-level data from 12 HFrEF trials (online supplementary Table S1). Patients were included if they had a creatinine measurement at randomization. Race was patient-reported. eGFR values were calculated using the 2009 and 2021 CKD-EPI creatinine equations.<sup>3</sup> Based on the calculated eGFR values, patients were categorized into the following CKD stages according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification<sup>1</sup>: <30 ml/min/1.73 m<sup>2</sup> (stages 4–5); 30–44 ml/min/1.73 m<sup>2</sup> (stage 3b); 45–59 ml/min/1.73 m<sup>2</sup> (stage 3a); 60–89 ml/min/1.73 m<sup>2</sup> (stage 2), and ≥90 ml/min/1.73 m<sup>2</sup> (stage 1). The proportion of patients in each CKD stage were compared between the 2009 and 2021 equations. In addition to examining this in the overall population, we did the same analyses in non-Black and Black patients. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

In a subset of 1922 patients in one of the trials included (PARADIGM-HF), a cystatin C measurement at randomization was available. For this subset of patients, eGFR values were also calculated using the 2012 and 2021 CKD-EPI equations, incorporating both creatinine and cystatin C measurements.<sup>3</sup>

## Results

We analysed data from 43 138 patients with HFrEF. Overall, mean age was 64.3 years, 22.2% were women, and 5.8% were Black (online supplementary Table S1). Mean eGFR was 67 (standard deviation [SD] 21) ml/min/1.73 m<sup>2</sup> and 70 (SD 21) ml/min/1.73 m<sup>2</sup>

using the 2009 and 2021 CKD-EPI equations, respectively (mean difference 3.20 ml/min/1.73 m<sup>2</sup>, 95% confidence interval [CI] 3.17–3.23;  $p < 0.001$ ).

Overall, 935 (2.2%) patients were in CKD stages 4 or 5 (eGFR <30 ml/min/1.73 m<sup>2</sup>) calculated using the 2009 equation versus 648 (1.5%) patients with eGFR calculated using the 2021 equation ( $p < 0.001$ ). In other words, 309 (33.0%) patients with CKD stages 4 or 5 were reclassified to CKD stages 1–3 (eGFR ≥30 ml/min/1.73 m<sup>2</sup>) with the 2021 equation (Table 1, Figure 1).

In total, 17 431 (40.4%) patients were in CKD stages 3–5 (eGFR <60 ml/min/1.73 m<sup>2</sup>) using the 2009 equation versus 14 681 (34.0%) patients using the 2021 equation ( $p < 0.001$ ). Of the 17 431 patients in CKD stages 3–5 (according to the 2009 equation), 2983 (17.1%) were reclassified to CKD stages 1–2 (eGFR ≥60 ml/min/1.73 m<sup>2</sup>) using the 2021 equation (Table 1, Figure 1).

Among the 40 617 non-Black patients included in the combined dataset, there was an increase in mean eGFR from 66 (SD 20) ml/min/1.73 m<sup>2</sup> to 70 (SD 21) ml/min/1.73 m<sup>2</sup> using the 2009 and 2021 equations, respectively (mean difference –3.83 ml/min/1.73 m<sup>2</sup>, 95% CI –3.84 to –3.82,  $p < 0.001$ ). The number of patients with an eGFR <30 ml/min/1.73 m<sup>2</sup> was 886 (2.2%) calculated using the 2009 equation and 577 (1.4%) with the 2021 equation (Table 2, online supplementary Figure S1).

Among the 2521 Black patients included in the combined dataset, a different pattern was observed, with a reduction in mean eGFR from 75 (SD 25) ml/min/1.73 m<sup>2</sup> to 68 (SD 22) ml/min/1.73 m<sup>2</sup> using the 2009 and 2021 equations, respectively (mean difference 6.94 ml/min/1.73 m<sup>2</sup>, 95% CI 6.82–7.06,  $p < 0.001$ ). The number of patients with an eGFR <30 ml/min/1.73 m<sup>2</sup> was 49 (1.9%) calculated using the 2009 equation and 71 (2.8%) with the 2021 equation (Table 3, online supplementary Figure S1).

Among the 1922 patients (56 Black patients) with an available creatinine and cystatin C measurement, there was an increase in mean eGFR from 64 (SD 20) ml/min/1.73 m<sup>2</sup> to 68 (SD 21) ml/min/1.73 m<sup>2</sup> using the 2012 and 2021 equations (incorporating both creatinine and cystatin C measurements), respectively (mean difference –3.99 ml/min/1.73 m<sup>2</sup>, 95% CI –4.07 to –3.92,  $p < 0.001$ ). The number of patients with an eGFR <30 ml/min/1.73 m<sup>2</sup> was 46 (2.4%) calculated using the 2012 equation and 32 (1.7%) with the 2021 equation. In total, 14 (30.4%) patients with CKD stages 4 or 5 were reclassified to CKD stages 1–3 (eGFR ≥30 ml/min/1.73 m<sup>2</sup>) with the 2021 equation (online supplementary Table S2 and Figure S2).

## Discussion

In this large HFrEF dataset, the new CKD-EPI equation, based on creatinine, that does not incorporate race, leads to a large decrease in the overall proportion of patients categorized by the original CKD-EPI equation as having a severe reduction in eGFR (CKD stages 4 and 5) and more modest, but still substantial, reductions in the proportions of patients originally classified as CKD stages 3a and 3b. This was also the case when the CKD-EPI equation

**Table 1** Estimated glomerular filtration rate according to the original and new Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine in the overall population

eGFR <sup>a</sup>	2009 CKD-EPI <sup>b</sup> (n = 43 138)	2021 CKD-EPI <sup>c</sup> (n = 43 138)	2021 vs. 2009 CKD-EPI		
			Increase in eGFR	No change in eGFR	Decrease in eGFR
Overall, n (%)					
≥90 (CKD stage 1)	6097 (14.1)	8004 (18.6)	0/6097 (0.0)	5878/6097 (96.4)	219/6097 (3.6)
60–89 (CKD stage 2)	19 610 (45.5)	20 453 (47.4)	2126/19 610 (10.8)	17 251/19 610 (88.0)	233/19 610 (1.2)
<60 (CKD stages 3–5)	17 431 (40.4)	14 681 (34.0)	4771/17 431 (27.4)	12 541/17 431 (71.9)	119/17 431 (0.7)
Breakdown of CKD stages 3–5, n (%)					
45–59 (CKD stage 3a)	10 967 (25.4)	9599 (22.3)	2983/10 967 (27.2)	7887/10 967 (71.9)	97/10 967 (0.9)
30–44 (CKD stage 3b)	5529 (12.8)	4434 (10.3)	1479/5529 (26.7)	4028/5529 (72.9)	22/5529 (0.4)
<30 (CKD stages 4+5)	935 (2.2)	648 (1.5)	309/935 (33.0)	626/935 (67.0)	0/935 (0.0)

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

Min, minimum of CREAT/A or 1; max, maximum of CREAT/A or 1; CREAT, creatinine in mg/dl; A: 0.9 for men, 0.7 for women; B: –0.411 for men, –0.329 for women; C: 1 for men, 1.018 for women; D: 1 for non-Black, 1.159 for Black.

Min, minimum of CREAT/A or 1; max, maximum of CREAT/A or 1; CREAT, creatinine in mg/dl; A: 0.9 for men, 0.7 for women; B: –0.302 for men, –0.241 for women; C: 1 for men, 1.012 for women.

<sup>a</sup>ml/min/1.73 m<sup>2</sup>.

<sup>b</sup>2009 CKD-EPI with race:  $141 * \min(\text{CREAT}/A, 1)^B * \max(\text{CREAT}/A, 1)^{-1.209} * 0.993^{\text{AGE}} * C * D$ .

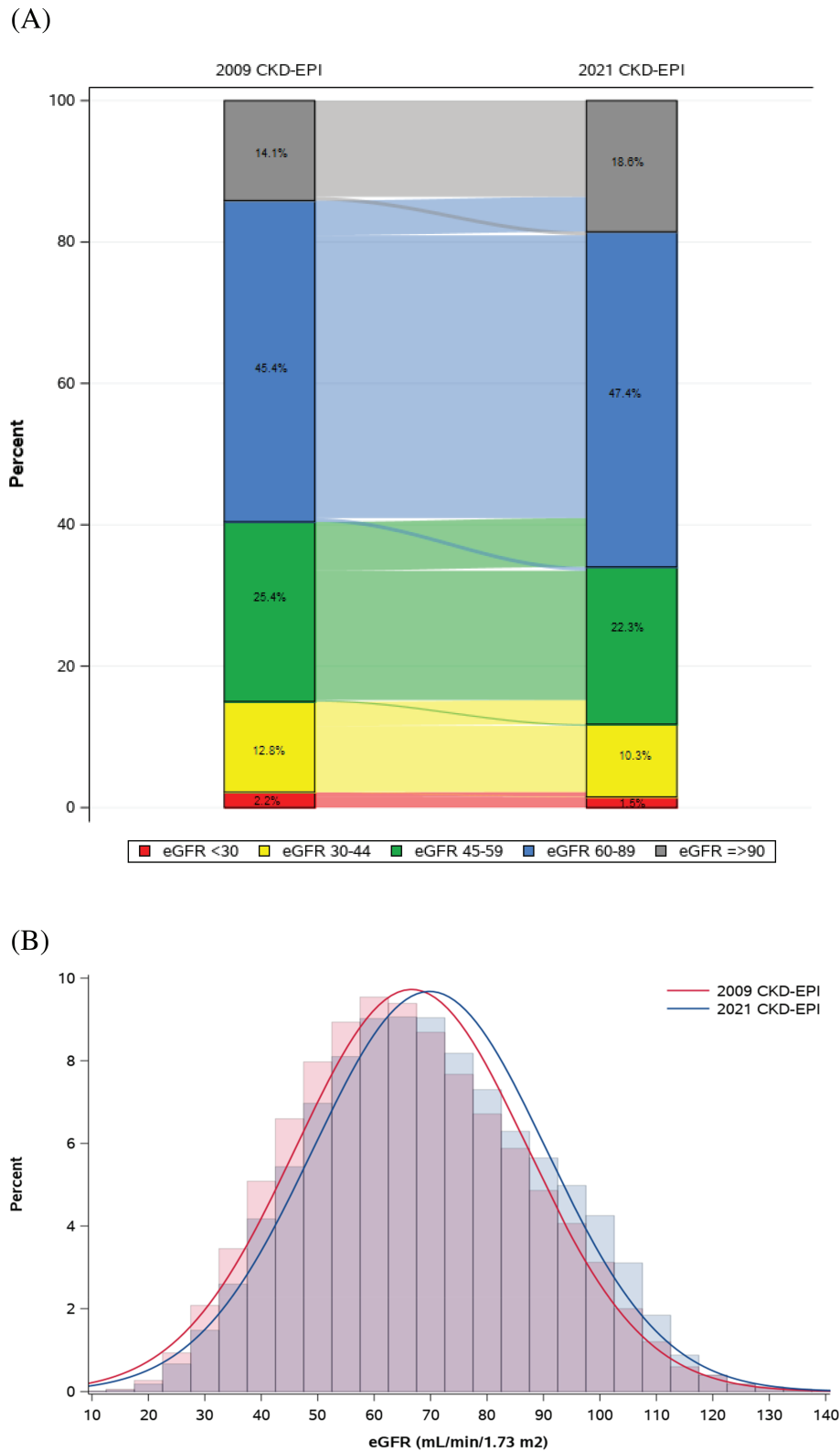
<sup>c</sup>2021 CKD-EPI without race:  $142 * \min(\text{CREAT}/A, 1)^B * \max(\text{CREAT}/A, 1)^{-1.200} * 0.9938^{\text{AGE}} * C$ .

incorporating both creatinine and cystatin C measurements was used. Reclassification in this way has a potentially major implication. Approximately one-third of patients generally considered ineligible for treatment with a RAS blocker, ARNI, MRA, or SGLT2i would become eligible and fewer patients would need dose reduction or discontinuation of a NOAC.<sup>5</sup> However, the opposite result was observed for Black patients, with a generally lower eGFR estimated using the new, as compared to the original, CKD-EPI equation. Patel and colleagues recently reported a similar finding when they re-estimated CKD-EPI-based eGFR by removing the race coefficient.<sup>6</sup> The potential implication of this is reduced eligibility of the aforementioned treatments in Black patients.

Although trials with RAS blockers excluded patients based on creatinine level, in practice an eGFR threshold of 30 ml/min/1.73 m<sup>2</sup> is often applied when these drugs are used in contemporary practice. The 2021 European Society of Cardiology guidelines on the management of heart failure recommended this eGFR threshold for both RAS blockers and sacubitril/valsartan.<sup>4</sup> However, the 2021 update of the American College of Cardiology expert consensus document for optimization of heart failure treatment stated that an eGFR <30 ml/min/1.73 m<sup>2</sup> was not a contraindication for sacubitril/valsartan, although caution should be taken when initiating this therapy in patients with severe renal impairment.<sup>7</sup> Regulatory labelling and guidance on eGFR thresholds for SGLT2i has evolved with the publication of new trials and differs between jurisdictions, although some agents in this class may be used in patients with an eGFR as low as 20 ml/min/1.73 m<sup>2</sup>. However, 'real-world' evidence suggests that RAS blockers and MRAs are underused even in patients with an eGFR <60 ml/min/1.73 m<sup>2</sup>. In a recent analysis of recommended therapies prescribed at discharge among more than 365 000 hospitalized patients enrolled in the Get With the Guidelines Heart Failure registry, the proportions of patients not receiving a RAS blocker or ARNI were 62%, 50%, and

21% respectively, among those with an eGFR of <30, 30–44, and 45–60 ml/min/1.73 m<sup>2</sup>, respectively; the corresponding figures for an MRA were 86%, 74%, and 65%.<sup>6</sup> A similar picture was observed in the outpatient Change the Management of Patients with Heart Failure (CHAMP-HF) registry.<sup>8</sup> This is despite clear evidence that patients with an eGFR <60 ml/min/1.73 m<sup>2</sup> are at much higher risk of non-fatal and fatal outcomes, compared to patients without CKD.<sup>9–11</sup> More importantly, all the treatments mentioned are equally effective and generally well-tolerated in patients with an eGFR <60 ml/min/1.73 m<sup>2</sup>. As a result, the absolute risk reduction in patients with CKD is large. Consequently, the CKD stage reclassification by the new CKD-EPI equation could have considerable benefits at a population level by increasing treatment eligibility, although not among Black patients. The new CKD-EPI equations incorporating both creatinine and cystatin C gave a closer estimate to measured eGFR than creatinine only-based equations and had smaller differences in bias between race groups and, potentially, could be valuable in patients with a 'borderline' eGFR, in terms of treatment eligibility.<sup>3</sup>

One major limitation of this analysis is that we used data from clinical trials, many of which excluded patients with severe CKD and, consequently, we had few patients with an eGFR <30 ml/min/1.73 m<sup>2</sup> (2.2% of the population) and even fewer with an eGFR <15 ml/min/1.73 m<sup>2</sup> (0.04% of the population). Therefore, we do not know how patients with a very low eGFR might be reclassified, although the new formula results in a general shift to the right in the frequency-distribution curve for eGFR. However, the opposite seemed to be the case in the relatively small number of Black patients in our study (5.8% of the study population). In addition, although the new CKD-EPI equation reclassified a large proportion of patients with HFrEF to less severe CKD stages, it has not yet been studied whether GFR estimated with the new CKD-EPI equation correlates with measured GFR in these patients.



**Figure 1** Estimated glomerular filtration rate (eGFR) according to the original and new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on creatinine. (A) Changes in eGFR categories. (B) Histogram and frequency distribution curves.

**Table 2** Estimated glomerular filtration rate according to the original and new Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine in non-Black patients only

eGFR <sup>a</sup>	2009 CKD-EPI <sup>b</sup> (n = 40 617)	2021 CKD-EPI <sup>c</sup> (n = 40 617)	2021 vs. 2009 CKD-EPI		
			Increase in eGFR	No change in eGFR	Decrease in eGFR
Overall, n (%)					
≥90 (CKD stage 1)	5424 (13.4)	7550 (18.6)	0/5424 (0.0)	5424/5424 (100)	0/5424 (0.0)
60–89 (CKD stage 2)	18 515 (45.6)	19 372 (47.7)	2126/18 515 (11.5)	16 389/18 515 (88.5)	0/18 515 (0.0)
<60 (CKD stages 3–5)	16 678 (41.1)	13 695 (33.7)	4771/16 678 (28.6)	11 907/16 678 (71.4)	0/16 678 (0.0)
Breakdown of CKD stages 3–5, n (%)					
45–59 (CKD stage 3a)	10 501 (25.9)	8997 (22.2)	2983/10 501 (28.4)	7518/10 501 (71.6)	0/10 501 (0.0)
30–44 (CKD stage 3b)	5291 (13.0)	4121 (10.1)	1479/5291 (28.0)	3812/5291 (72.0)	0/5291 (0.0)
<30 (CKD stages 4+5)	886 (2.2)	577 (1.4)	309/886 (34.9)	577/886 (65.1)	0/886 (0.0)

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

Min, minimum of CREAT/A or 1; max, maximum of CREAT/A or 1; CREAT, creatinine in mg/dl; A: 0.9 for men, 0.7 for women; B: –0.411 for men, –0.329 for women; C: 1 for men, 1.018 for women; D: 1 for non-Black, 1.159 for Black.

Min, minimum of CREAT/A or 1; max, maximum of CREAT/A or 1; CREAT, creatinine in mg/dl; A: 0.9 for men, 0.7 for women; B: –0.302 for men, –0.241 for women; C: 1 for men, 1.012 for women.

<sup>a</sup>ml/min/1.73 m<sup>2</sup>.

<sup>b</sup>2009 CKD-EPI with race:  $141 * \min(\text{CREAT}/A, 1)^B * \max(\text{CREAT}/A, 1)^{-1.209} * 0.993^{\text{AGE}} * C * D$ .

<sup>c</sup>2021 CKD-EPI without race:  $142 * \min(\text{CREAT}/A, 1)^B * \max(\text{CREAT}/A, 1)^{-1.200} * 0.9938^{\text{AGE}} * C$ .

**Table 3** Estimated glomerular filtration rate according to the original and new Chronic Kidney Disease Epidemiology Collaboration equation based on creatinine in Black patients only

eGFR <sup>a</sup>	2009 CKD-EPI <sup>b</sup> (n = 2521)	2021 CKD-EPI <sup>c</sup> (n = 2521)	2021 vs. 2009 CKD-EPI		
			Increase in eGFR	No change in eGFR	Decrease in eGFR
Overall, n (%)					
≥90 (CKD stage 1)	673 (26.7)	454 (18.0)	0/673 (0.0)	454/673 (67.5)	219/673 (32.5)
60–89 (CKD stage 2)	1095 (43.4)	1081 (42.9)	0/1095 (0.0)	862/1095 (78.7)	233/1095 (21.3)
<60 (CKD stages 3–5)	753 (29.9)	986 (39.1)	0/753 (0.0)	634/753 (84.2)	119/753 (15.8)
Breakdown of CKD stages 3–5, n (%)					
45–59 (CKD stage 3a)	466 (18.5)	602 (23.9)	0/466 (0.0)	369/466 (79.2)	97/466 (20.8)
30–44 (CKD stage 3b)	238 (9.4)	313 (12.4)	0/238 (0.0)	216/238 (90.8)	22/238 (9.2)
<30 (CKD stages 4+5)	49 (1.9)	71 (2.8)	0/49 (0.0)	49/49 (100)	0/49 (0.0)

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

Min, minimum of CREAT/A or 1; max, maximum of CREAT/A or 1; CREAT, creatinine in mg/dl; A: 0.9 for men, 0.7 for women; B: –0.411 for men, –0.329 for women; C: 1 for men, 1.018 for women; D: 1 for non-Black, 1.159 for Black.

Min, minimum of CREAT/A or 1; max, maximum of CREAT/A or 1; CREAT, creatinine in mg/dl; A: 0.9 for men, 0.7 for women; B: –0.302 for men, –0.241 for women; C: 1 for men, 1.012 for women.

<sup>a</sup>ml/min/1.73 m<sup>2</sup>.

<sup>b</sup>2009 CKD-EPI with race:  $141 * \min(\text{CREAT}/A, 1)^B * \max(\text{CREAT}/A, 1)^{-1.209} * 0.993^{\text{AGE}} * C * D$ .

<sup>c</sup>2021 CKD-EPI without race:  $142 * \min(\text{CREAT}/A, 1)^B * \max(\text{CREAT}/A, 1)^{-1.200} * 0.9938^{\text{AGE}} * C$ .

Finally, all patients in our trials had HFrEF and we do not know how the new CKD-EPI equation might recategorize patients with heart failure and preserved ejection fraction.

## Conclusion

In a large ambulatory HFrEF population enrolled in clinical trials, the new CKD-EPI creatinine equation for estimating GFR, compared with the current equation, reclassified a large proportion of patients with CKD stages 4 or 5 (eGFR <30 ml/min/1.73 m<sup>2</sup>) to CKD stages 1–3. Similarly, the new equation reclassified a

substantial proportion of patients with CKD stages 3–5 (eGFR <60 ml/min/1.73 m<sup>2</sup>) to CKD stages 1–2. However, the opposite was observed for Black patients, who, on average, had a lower eGFR with the new equation. These findings may have important implications for eligibility for treatment with several key pharmacological therapies in heart failure.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Conflict of interest:** J.H.B. has served on advisory boards for Bayer, outside the submitted work. K.F.D. has received speaker's fees from AstraZeneca. M.V. has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, and Sanofi, speaker engagements with Novartis and Roche Diagnostics, and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. S.D.S. has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI and has consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, Puretech Health. I.S.A. reports personal fees and other from Novartis, during the conduct of the study; personal fees from Amgen, personal fees from ARCA, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Boston Scientific, personal fees from LivaNova, outside the submitted work. F.Z. reports personal fees from Boehringer Ingelheim, Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno pharmaceutical, Applied Therapeutics, Merck, Bayer, and Cellprothera; and other support from CVCT and Cardiorenal. L.K. has received speaker's honorarium from AstraZeneca, Novo, Novartis and Boehringer. P.S.J. has received speaker's fees, advisory board fees, or research grants from Novartis, AstraZeneca, Boehringer Ingelheim, Bayer, NovoNordisk, and Analog Devices Inc. J.J.V.M. declares payments to his employer, Glasgow University, for his work on clinical trials, consulting and other activities:

Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, Dal-Cor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, Theracos. Personal lecture fees: Abbott, Alkem Metabolics, AstraZeneca, Eris Lifesciences, Hikma, Lupin, Sun Pharmaceuticals, Medscape/Heart.Org, ProAdWise Communications, S & L Solutions Event Management Inc, Radcliffe Cardiology, Servier, the Corpus, Translational Medical Academy, Web MD and (as Director) the Global Clinical Trial Partners Ltd (GCTP). C.A. has nothing to declare.

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