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► **To cite this version:**

Subodh Verma, Nitish K. Dhingra, Javed Butler, Stefan D. Anker, João Pedro Ferreira, et al.. Empagliflozin in Black Versus White Patients With Heart Failure: Analysis of EMPEROR-Pooled. *Circulation*, 2023, 147 (1), pp.101-104. 10.1161/CIRCULATIONAHA.122.062644 . hal-04023200v2

**HAL Id: hal-04023200**

**<https://hal.univ-lorraine.fr/hal-04023200v2>**

Submitted on 10 Mar 2023

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3  
4 **Research Letter**

5 **Empagliflozin in Black Versus White Patients with Heart Failure:**

6 **Analysis of EMPEROR-Pooled**

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17 Lorraine, Inserm, Centre d'Investigations Cliniques, - Plurithématique 14-33, and Inserm U1116,  
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24 Cardiovascular and Medical Sciences, University of Glasgow, Scotland, UK; <sup>11</sup>Boehringer  
25 Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; <sup>12</sup>Boehringer Ingelheim International  
26 GmbH, Ingelheim, Germany; <sup>13</sup>First Department of Medicine, Faculty of Medicine Mannheim,  
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34 [Running Title: EMPEROR-Pooled Black vs. White Analysis](#)

1           There are disparities in both rates and outcomes of heart failure (HF) between Black and  
2 White patients, and there remain important questions about the generalizability of conventional  
3 HF therapies, including ACE inhibitors and beta-blockers, to Black patients. While analyses from  
4 DAPA-HF and EMPEROR-Reduced have demonstrated a consistent benefit of SGLT2 inhibitors  
5 in Black patients, these data were limited to heart failure with a reduced ejection fraction (HFrEF)  
6 and included a small number of Black patients<sup>1,2</sup>. Herein, we studied the safety and efficacy of  
7 empagliflozin according to Black vs. White race in the Americas across the spectrum of EF in the  
8 pooled dataset from both EMPEROR trials (N=9718).

9           Ethics approval was obtained by each trial centre and informed consent was received from  
10 every participant. 478 Black patients and 3024 White patients were included. Black patients were  
11 more likely to be female (45.0% vs. 36.8%) and younger ( $64.4 \pm 11.7$  vs.  $69.0 \pm 10.8$  years).  
12 Compared to White patients, Black patients had a lower ejection fraction ( $39.0 \pm 15.9$  vs.  
13  $42.9 \pm 15.8\%$ ), higher rates of non-ischemic HF etiologies (69.7% vs. 58.9%), higher eGFR  
14 ( $68.0 \pm 25.4$  vs.  $60.4 \pm 20.9$  ml/min/1.73m<sup>2</sup>), lower rates of atrial fibrillation (25.1% vs. 37.6%), and  
15 similar rates of diabetes mellitus. Baseline NYHA class and NT proBNP levels [median 1338 vs.  
16 1320 pg/mL] were comparable, although Kansas City Cardiomyopathy Questionnaire (KCCQ)  
17 clinical ( $64.12 \pm 24.07$  vs.  $67.14 \pm 22.55$ ) and overall ( $61.93 \pm 24.04$  vs.  $64.78 \pm 22.87$ ) summary  
18 scores were lower amongst Black patients at baseline. Black and White patients had similar  
19 durations of HF ( $5.7 \pm 6.5$  years vs.  $5.4 \pm 6.0$  years) as well as rates of HHF in the preceding 12  
20 months (22.6% vs. 22.2%). Rates of concomitant hydralazine and nitrate use were higher in Black  
21 patients (8.4% vs. 2.8%), as were rates of loop/high ceiling diuretics (76.8% vs. 71.1%) and RAAS  
22 inhibitors (ACE/ARB/ARNI) (87.9% vs. 84.2%). Rates of beta blocker (93.1% vs. 90.3%) and

1 MRA (53.1% vs. 51.3%) were comparable. A higher percentage of Black patients had an  
2 implantable cardioverter-defibrillator (14.4% vs. 9.4%).

3 Black patients randomized to placebo had higher risk of the primary outcome [HR 1.49  
4 (95% CI 1.14 – 1.94), P=0.004] (Figure 1) as well as time to first HHF [1.55 (1.14-2.10), P=0.005],  
5 time to first event of the extended composite outcome of CV death, HHF equivalent event, or  
6 diuretic intensification [1.40 (1.13-1.74), P=0.002], and total HHF [1.44 (1.01-2.06), P=0.046]  
7 compared with White patients.

8 In the pooled analysis, there was a concordant efficacy of empagliflozin on the primary  
9 outcome in Black versus White patients [0.56 (0.38 – 0.81) vs. 0.80 (0.68 – 0.95),  $P_{\text{interaction}}=0.083$ ]  
10 (Figure 1). In the HFrEF population specifically, this difference reached statistical significance  
11 [0.44 (0.27 – 0.73) vs. 0.84 (0.66-1.06),  $P_{\text{interaction}}=0.022$ ]. This trend was driven by a larger  
12 treatment benefit amongst Black patients on time to first HHF in EMPEROR-Pooled [0.44 (0.28  
13 – 0.70) vs. 0.73 (0.60-0.90),  $P_{\text{interaction}} = 0.052$ ], an effect modification which was again particularly  
14 noted in the HFrEF population [0.35 (0.20 – 0.63) vs. 0.79 (0.60 – 1.05),  $P_{\text{interaction}} = 0.014$ ], but  
15 not in the HFpEF population. This also extended to total HHF, specifically with HFrEF [Black:  
16 0.36 (0.18-0.75) vs. White: 0.87 (0.63-1.20),  $P_{\text{interaction}}=0.030$ ]. Black patients with HFrEF (but not  
17 HFpEF) had an amplified benefit of empagliflozin on the extended composite outcome [0.49 (0.32-  
18 0.74) vs. 0.86 (0.71-1.05),  $P_{\text{interaction}}=0.015$ ], as well as on KCCQ clinical summary scores at 52  
19 weeks [vs. placebo: 6.71 (1.47-11.96) vs. 0.77 (-1.57-3.12),  $P_{\text{interaction}} = 0.043$ ] compared with  
20 White patients.

21 A sensitivity analysis was conducted with covariates limited to only treatment and race.  
22 The results were comparable for the primary outcome [Black: 0.54 (0.37-0.79) vs. White: 0.80

1 (0.68-0.94),  $P_{\text{interaction}} = 0.063$ ], time to first HHF [0.42 (0.27-0.67) vs. 0.72 (0.59-0.89),  $P_{\text{interaction}} =$   
2 0.037], total HHF [0.50 (0.29-0.88) vs. 0.86 (0.68-1.10),  $P_{\text{interaction}} = 0.084$ ], and time to CV death  
3 [0.75 (0.42-1.32) vs. 1.03 (0.81-1.30),  $P_{\text{interaction}} = 0.305$ ].

4 Adverse events (AEs) and serious AEs were comparable for empagliflozin vs. placebo in  
5 Black and White patients [AEs: (Black: Placebo – 88.3%, Empagliflozin – 85.4%; White: Placebo  
6 – 83.6%, Empagliflozin – 82.9%); serious AEs: Black: Placebo – 61.5%, Empagliflozin – 53.1%;  
7 White: Placebo – 51.2%, Empagliflozin 48.2%)], however, the placebo incidence of adverse events  
8 was higher in Black patients. Empagliflozin’s safety profile with respect to-rates of hypotension,  
9 symptomatic hypotension, volume depletion, genital infections, acute kidney injury, and  
10 hypoglycemia was also comparable between populations.

11 Study data will be stored at the Vivli - Center for Global Clinical Research Data and access  
12 pertinent to the development of publications may be requested after the necessary regulatory  
13 activities are complete, and other criteria are met.

14 In summary, Black vs. White patients were at higher risk of HF events in EMPEROR  
15 Pooled. However, the efficacy and safety profile of empagliflozin is similar in Black and White  
16 patients with HF when assessed irrespective of EF, with a suggestion of potential enhanced  
17 efficacy in Black versus White patients particularly with HFrEF. Black patients may be  
18 predisposed to greater fluid retention and hence may derive more benefit from empagliflozin’s  
19 decongestive properties.<sup>3,4</sup> Our findings are limited by the relatively small number of Black  
20 patients and could be confounded by differences in baseline characteristics; hence this finding  
21 remains hypothesis generating. Efforts to recruit more Black patients in future trials are needed<sup>5</sup>.

1 **Acknowledgements**

2 The author(s) meet criteria for authorship as recommended by the International Committee of  
3 Medical Journal Editors (ICMJE) and were fully responsible for all content and editorial decisions,  
4 and were involved at all stages of publication development.

5 **Funding**

6 The EMPEROR studies were sponsored by the Boehringer Ingelheim and Eli Lilly and Company  
7 Diabetes Alliance.

8

9 **Author COI disclosures**

10 **S.V.** holds a tier 1 Canada Research Chair in cardiovascular surgery; and reports receiving  
11 research grants and honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim,  
12 Bristol-Myers Squibb, Eli Lilly, HLS Therapeutics, Janssen, Novartis, Novo Nordisk, PhaseBio,  
13 and Pfizer; and receiving honoraria from Sanofi, Sun Pharmaceuticals, and the Toronto  
14 Knowledge Translation Working Group. He is a member of the scientific excellence committee  
15 of the EMPEROR-Reduced trial and served as a national lead investigator of the DAPA-HF and  
16 EMPEROR-Reduced trials. He is the President of the Canadian Medical and Surgical  
17 Knowledge Translation Research Group, a federally incorporated not-for-profit physician  
18 organisation. **N.K.D.** declares no competing interests. **J.B.** reports personal fees from Boehringer  
19 Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, Cardior,  
20 CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold,  
21 Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave

1 and Vifor, outside the submitted work. **S.D.A.** reports grants and personal fees from Vifor Int.  
2 and Abbott Vascular, and personal fees from Astra-Zeneca, Bayer, Brahms, Boehringer  
3 Ingelheim, Cardiac Dimensions, Novartis, Occlutech, Servier, and Vifor Int. Personal fees from  
4 Boehringer Ingelheim during the conduct of the study. **J.P.F.** reports personal fees from  
5 Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer  
6 Ingelheim, outside the submitted work. **G.F.** reports personal fees from Boehringer Ingelheim,  
7 during the conduct of the study; personal fees from Medtronic, Vifor, Servier, Novartis, Bayer,  
8 Amgen and Boehringer Ingelheim, outside the submitted work. **J.L.J.** a Trustee of the American  
9 College of Cardiology, a Board member of Imbria Pharmaceuticals, has received grant support  
10 from Applied Therapeutics, Innolife, Novartis Pharmaceuticals and Abbott Diagnostics,  
11 consulting income from Abbott, Janssen, Novartis, and Roche Diagnostics, and participates in  
12 clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer,  
13 CVRx, Janssen, MyoKardia and Takeda. **C.S.P.L.** served on the Scientific Excellence  
14 Committee of the EMPEROR Program; has received research support from AstraZeneca, Bayer,  
15 Boston Scientific and Roche Diagnostics; has served as consultant or on the Advisory Board/  
16 Steering Committee/ Executive Committee for Actelion, Amgen, Applied Therapeutics,  
17 AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., Us2.ai,  
18 Janssen Research & Development LLC, Medscape, Merck, Novartis, Novo Nordisk, Radcliffe  
19 Group Ltd., Roche Diagnostics, Sanofi and WebMD Global LLC; and serves as co-founder &  
20 non-executive director of Us2.ai. **N.S.** has consulted for Amgen, Astrazeneca, Boehringer  
21 Ingelheim, Eli-Lilly, Hanmi Pharmaceuticals, Novo Nordisk, Novartis, Novartis, Sanofi and  
22 Pfizer and received grant support from Boehringer Ingelheim. **E.P.**, **M.N.** and **M.B.** are  
23 employees of Boehringer Ingelheim. **S.J.P.** reports personal fees from Boehringer Ingelheim,

1 during the conduct of the study; personal fees from Boehringer Ingelheim, outside the submitted  
2 work. **F.Z.** reports personal fees from Boehringer Ingelheim, during the conduct of the study;  
3 personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor  
4 Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer and,  
5 Cellprothera, other from CVCT, and Cardiorenal, outside the submitted work.

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31 **Figure 1.** Summary of major findings of White and Black patients in the Americas including (A)  
32 endpoint data in EMPEROR-Pooled according to White versus Black race and (B) cumulative  
33 incidence of the primary endpoint in both the placebo and empagliflozin groups by Black versus  
34 White race. A total of 9718 HF patients were included in EMPEROR-Pooled, a prospectively  
35 designed combined analysis of EMPEROR-Reduced and -Preserved. Patients were randomized to  
36 10mg empagliflozin or placebo in addition to existing background therapy. The primary outcome  
37 of the trials was time to first HF hospitalization (HHF) or cardiovascular (CV) death. The eGFR  
38 values presented are derived from the conventional CKD-EPI equation, which utilizes serum  
39 creatinine and corrects for age, sex, and race. Given that 92.8% (478/515) of Black patients were  
40 recruited from the Americas, we report results of EMPEROR-Pooled by Black vs. White patients  
41 specifically within the Americas. Baseline characteristics were compared between Black and



1 White patients using t-tests for continuous variables and chi-square tests for categorical variables.  
2 Time-to-first event analyses were performed with a Cox proportional-hazards model, adjusted for  
3 age, sex, region (North America, Latin America), diabetes status (diabetes, prediabetes, no  
4 diabetes), eGFR at baseline, left ventricular ejection fraction at baseline, and study. These analyses  
5 were performed according to the intention-to-treat principle for all randomized patients, and  
6 included data up to the end of the planned treatment period. Event rates per 100 patient years and  
7 adjusted hazard ratios (HR) are reported. Total (first and recurrent) hospitalizations for HF were  
8 evaluated accordingly with a joint frailty model that accounted for cardiovascular death, adjusted  
9 for the same covariates as the Cox model. Continuous endpoints were analyzed with the same  
10 covariates in a mixed model with repeated measures (MMRM). To assess the consistency of the  
11 treatment effects across Black and White subgroups, subgroup-by-treatment interaction terms were  
12 added to the models. Adverse events were analyzed descriptively based on patients with events  
13 occurring during the on-treatment period (including 7 days after last drug consumption by the  
14 patient).

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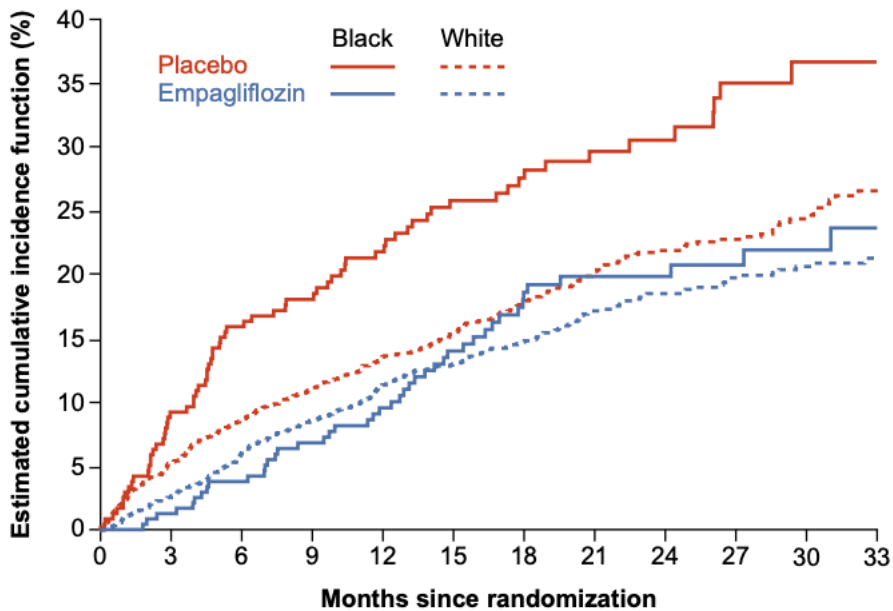
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	Empagliflozin 10 mg		Placebo		HR (95% CI)	Interaction P-value
	n/N	Events/100 py	n/N	Events/100 py		
<b>EMPEROR-Pooled</b>						
<b>Primary endpoint</b>						
White	257/1529	10.45	305/1495	13.15	0.80 (0.68, 0.95)	0.08
Black	44/239	10.99	71/239	20.83	0.56 (0.38, 0.81)	
<b>Time to first HHF</b>						
White	212/1529	6.59	162/1495	9.14	0.73 (0.60, 0.90)	0.05
Black	27/239	6.74	56/239	16.43	0.44 (0.28, 0.70)	
<b>Total HHF</b>						
White	271/1529	N/A	301/1495	N/A	0.84 (0.67, 1.06)	0.29
Black	44/239	N/A	85/239	N/A	0.61 (0.35, 1.05)	
<b>Time to CV death</b>						
White	144/1529	5.52	137/1495	5.37	1.02 (0.81, 1.29)	0.31
Black	21/239	4.96	27/239	6.65	0.75 (0.42, 1.32)	
<b>Extended composite endpoint*</b>						
White	419/1529	18.66	495/1495	23.83	0.79 (0.70, 0.90)	0.12
Black	75/239	20.98	106/239	36.06	0.61 (0.46, 0.82)	

\* CV death or HHF equiv. events or reported intensification of diuretic since last visit by race

1

**Pooled Race CI curve**



**Patients at risk**

	0	3	6	9	12	15	18	21	24	27	30	33
<b>Black</b>												
Placebo	239	216	199	178	158	131	111	85	63	49	34	26
Empagliflozin	239	235	225	206	186	159	131	110	85	63	44	38
<b>White</b>												
Placebo	1495	1407	1343	1214	1094	959	751	600	461	344	237	143
Empagliflozin	1529	1480	1414	1284	1144	1001	804	633	494	386	276	165

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