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4 **Research Letter**

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

6 **Analysis of EMPEROR-Pooled**

7 Subodh Verma MD, PhD¹, Nitish K. Dhingra BHSc¹, Javed Butler MD, MPH, MBA,^{2,3} Stefan D.
8 Anker MD,⁴ Joao Pedro Ferreira MD, PhD^{5,6}, Gerasimos Filippatos MD,⁷ James L. Januzzi MD,⁸
9 Carolyn S.P. Lam MBBS, PhD,⁹ Naveed Sattar MD,¹⁰ Egon Pfarr MS,¹¹ Matias Nordaby MD¹²,
10 Martina Brueckmann MD^{12,13} Stuart J. Pocock PhD¹⁴, Faiez Zannad MD, PhD⁵, and Milton Packer
11 MD^{15,16} for the EMPEROR-Pooled Trial Committees and Investigators

12 ¹Division of Cardiac Surgery, St. Michael's Hospital, University of Toronto, Toronto, Canada;
13 ²Baylor Scott and White Research Institute, Dallas, TX, USA ³Department of Medicine, University
14 of Mississippi School of Medicine, Jackson, MS, USA; ⁴Department of Cardiology (CVK), and
15 Berlin Institute of Health Center for Regenerative Therapies, German Centre for Cardiovascular
16 Research Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany; ⁵Université de
17 Lorraine, Inserm, Centre d'Investigations Cliniques, - Plurithématique 14-33, and Inserm U1116,
18 CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France ;
19 ⁶Cardiovascular Research and Development Center, Department of Surgery and Physiology,
20 Faculty of Medicine of the University of Porto, Porto, Portugal; ⁷National and Kapodistrian
21 University of Athens School of Medicine, Athens University Hospital Attikon, Athens, Greece;
22 ⁸Division of Cardiology, Harvard Medical School and Massachusetts General Hospital, Boston
23 MA; ⁹National Heart Centre Singapore, Duke-NUS Medical School, Singapore; ¹⁰Institute of
24 Cardiovascular and Medical Sciences, University of Glasgow, Scotland, UK; ¹¹Boehringer
25 Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; ¹²Boehringer Ingelheim International
26 GmbH, Ingelheim, Germany; ¹³First Department of Medicine, Faculty of Medicine Mannheim,
27 University of Heidelberg, Mannheim, Germany ¹⁴Department of Medical Statistics, London
28 School of Hygiene and Tropical Medicine, London, UK; ¹⁵Baylor Heart and Vascular Institute,
29 Baylor University Medical Center, Dallas TX USA, ¹⁶Imperial College, London UK

30 Corresponding Author: Subodh Verma MD PhD FRCSC, Professor and Cardiac Surgeon, St.
31 Michael's Hospital, University of Toronto, 30 Bond Street, Toronto, Ontario, M5B 1W8,
32 Canada.

33 TEL 416 864 5997 ; FAX 416 864 5881 Subodh.Verma@unityhealth.to

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^{1,2}. 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 ± 11.7 vs. 69.0 ± 10.8 years).
12 Compared to White patients, Black patients had a lower ejection fraction (39.0 ± 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 ± 25.4 vs. 60.4 ± 20.9 ml/min/1.73m²), 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 ± 24.07 vs. 67.14 ± 22.55) and overall (61.93 ± 24.04 vs. 64.78 ± 22.87) summary
18 scores were lower amongst Black patients at baseline. Black and White patients had similar
19 durations of HF (5.7 ± 6.5 years vs. 5.4 ± 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.^{3,4} 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 needed⁵.

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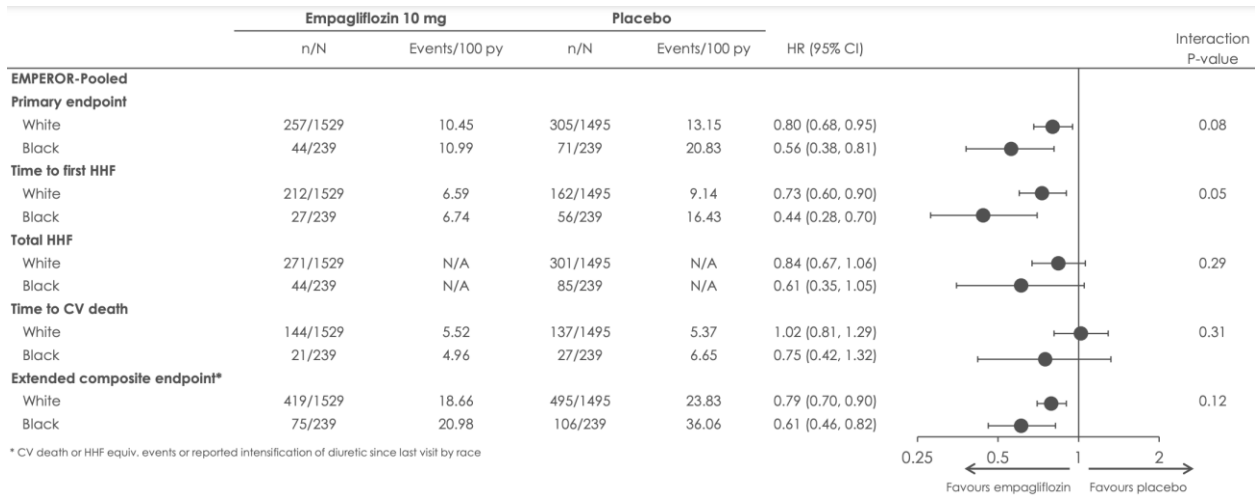
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31 **Figure 1.** Summary of major findings of White and Black patients in the Americas including (A)
32 endpoint data in EMPEROR-Pooled according to White versus Black race and (B) cumulative
33 incidence of the primary endpoint in both the placebo 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).

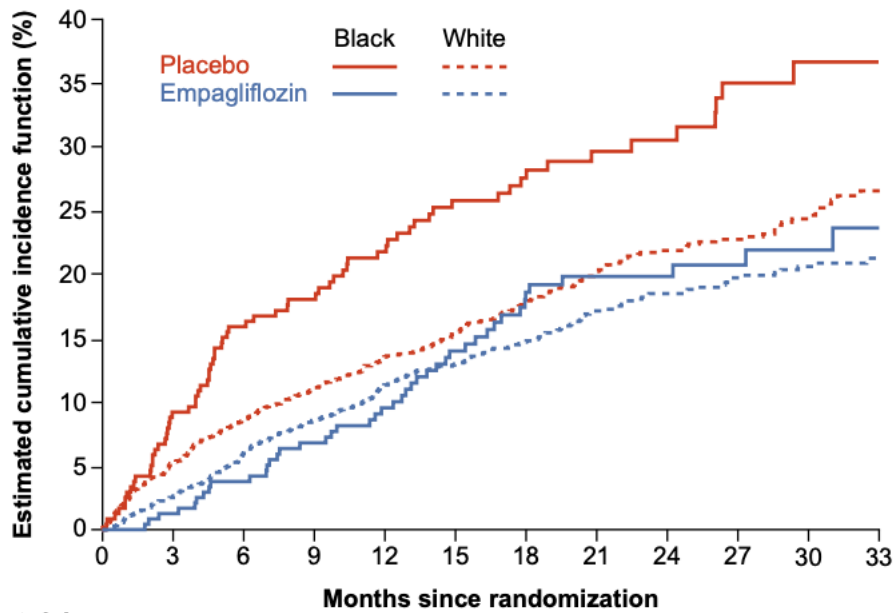
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Pooled Race CI curve



Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33
Black												
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
White												
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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