THE EFFECT OF DAPAGLIFLOZIN ON ANEMIA IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION: AN ANALYSIS OF DAPA-HF

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BACKGROUND

- In DAPA-HF, compared to placebo, the sodium-glucose cotransporter 2 (SGLT-2) inhibitor, dapagliflozin, reduced the risk of cardiovascular death or worsening heart failure in patients with heart failure with reduced ejection fraction (HFrEF).
- Anemia is common in heart failure and associated with worse outcomes.
- In this *post-hoc* analysis of DAPA-HF, we investigated the effect of dapagliflozin on outcomes according to anemia status at baseline. We also examined the effect of dapagliflozin on hematocrit over time and correction of anemia.

METHODS

- Key inclusion criteria: 1) NYHA class II-IV, 2) LVEF ≤ 40%, 3) elevated plasma NT-proBNP concentration ≥600 pg/mL (≥400 pg/mL if hospitalized for HF within the previous 12 months). Patients with atrial fibrillation or atrial flutter were required to have a NT-proBNP level ≥900 pg/mL, irrespective of history of HF hospitalization.
- Key exclusion criteria: 1) systolic BP <90 mmHg, 2) eGFR <30 ml/min/1.73m^2.
- Primary endpoint: composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death, whichever occurred first.
- 4744 patients randomized to receive either dapagliflozin (10mg daily) or placebo in addition to recommended therapy.
- Overall, dapagliflozin reduced the primary endpoint by 26% (HR 0.74, 95% CI 0.65-0.85;p=0.00001).
- Hematocrit was measured at baseline, as well as 14 days, 2 months and 4 months after randomization, and 4-monthly thereafter. Hemoglobin was measured at baseline but not after randomization. All measurements were performed in a central laboratory.
- Anemia was defined at baseline as a hematocrit <39% in men and <36% in women (WHO criteria).
- Correction of anemia after randomization was defined as two consecutive hematocrit measurements above these thresholds at any time during follow-up.

Statistical analysis

- The effect of dapagliflozin compared to placebo on outcomes was examined by anemia status at baseline using a Cox proportional-hazards model with treatment and history of HF hospitalization as factors and stratified by baseline diabetes status.
- The relationship between anemia at baseline and subsequent outcomes was examined by similar means with further adjustment performed for age, heart rate, systolic blood pressure, body mass index, ischemic etiology of heart failure, left ventricular ejection fraction, NYHA functional classification, NT-proBNP, atrial fibrillation, and estimated glomerular filtration rate.
- Changes in hematocrit were analyzed using a mixed model for repeated measurements (adjusted for baseline value, visit, randomized treatment and interaction of treatment, and visit with a random intercept and slope per patient) and are presented by subgroup as least square means difference with 95% confidence intervals.
- Analyses were performed using STATA v16.1 and SAS v9.4
- P value <0.05 considered statistically significant

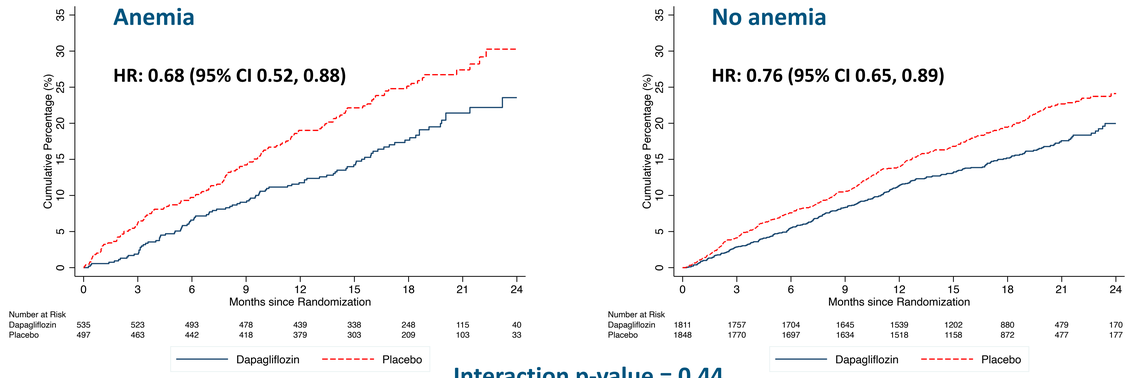
Conflicts of interest: The DAPA-HF trial was funded by AstraZeneca.

TABLE 1: BASELINE CHARACTERISTICS

	No anemia	Anemia	p-value
	N=3,659	N=1,032	
Age – yr	65.4±11.0	69.8±9.7	<0.001
Sex - no (%)			<0.001
Female	893 (24.4)	200 (19.4)	
Male	2,766 (75.6)	832 (80.6)	
NYHA functional classification – no. (%)			0.13
II	2,440 (66.7)	718 (69.6)	
III	1,182 (32.3)	308 (29.8)	
IV	37 (1.0)	6 (0.6)	
Heart rate – beats/min	71.7±11.7	70.6±11.4	0.008
Systolic Blood Pressure – mmHg	122.3±16.2	120.2±16.5	<0.001
Left ventricular ejection fraction – %	31.0±6.9	31.5±6.6	0.036
Median NT-proBNP (IQR) – pg/ml	1351 (821-2442)	1840 (1043-3315)	<0.001
Median KCCQ-TSS (IQR)	77.1 (58.3-91.7)	78.1 (60.4-91.7)	0.39
Hemoglobin (g/L)	140.6±13.4	117.7±12.2	<0.001
Principal cause of heart failure – no. (%)			0.033
Ischemic	2,031 (55.5)	619 (60.0)	
Non-ischemic	1,331 (36.4)	333 (32.3)	
Unknown	297 (8.1)	80 (7.8)	
Medical history – no. (%)			
Hospitalization for heart failure	1,702 (46.5)	510 (49.4)	0.099
Atrial fibrillation	1,408 (38.5)	391 (37.9)	0.73
Type 2 diabetes*	1,433 (39.2)	526 (51.0)	<0.001
Prior MI	1,598 (43.7)	476 (46.1)	0.16
Prior PCI	1,229 (33.6)	384 (37.2)	0.031
Prior CABG	559 (15.3)	231 (22.4)	<0.001
Estimated GFR – ml/min/1.73 m^2	67.6±19.2	59.3±18.6	<0.001
Device therapy – no (%)			
Implantable cardioverter-defibrillator†	945 (25.8)	285 (27.6)	0.25
Cardiac-resynchronization therapy‡	263 (7.2)	90 (8.7)	0.099
Heart failure medication at randomization visit – no (%)			
Diuretic	3,070 (83.9)	893 (86.5)	0.039
ACE-inhibitor or ARB	3,072 (84.0)	829 (80.3)	0.006
Sacubitril-valsartan	385 (10.5)	123 (11.9)	0.20
Beta-blocker	3,519 (96.2)	989 (95.8)	0.62
Mineralocorticoid receptor antagonist	2,653 (72.5)	687 (66.6)	<0.001
Digitalis	706 (19.3)	158 (15.3)	0.004
Antiplatelet	1,947 (53.2)	610 (59.1)	<0.001
Anticoagulant	1,531 (41.8)	416 (40.3)	0.38

Data presented as mean ± standard deviation unless otherwise indicated.

FIGURE 1 – EFFECT OF DAPAGLIFLOZIN ON THE PRIMARY ENDPOINT BY BASELINE ANEMIA STATUS



Interaction p-value = 0.44

RESULTS

- Of the 4744 patients randomized in DAPA-HF, 4691 had a hematocrit available at baseline and 1032 of these participants were anemic (22.0%).

Baseline characteristics

- The baseline characteristics of patients according to their anemia status are shown in **Table 1**.
- Compared to those who were not anemic, patients who were anemic were older, more likely to be male and had a lower mean systolic blood pressure, higher NT-proBNP level, and worse kidney function. A history of coronary heart disease, diabetes and prior heart failure hospitalization was more common among patients with anemia, compared to those without anemia. NYHA functional class and KCCQ-Total Symptom Score (TSS) did not differ significantly between those with and without anemia.

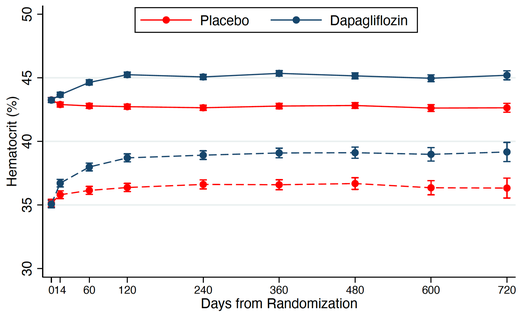
Cardiovascular outcomes according to anemia status at baseline

- The cumulative incidence of the primary composite outcome by anemia status and randomized treatment is shown in **Figure 1**.
- In unadjusted analyses, the risk of the primary composite outcome, its individual components and all-cause mortality was higher in patients with anemia compared to those without.
- After adjustment, only worsening heart failure and not death remained significantly higher in anemic patients compared to those without anemia.

Effect of dapagliflozin on cardiovascular outcomes

- The beneficial effect of dapagliflozin, compared with placebo, on the primary endpoint was consistent in patients with (HR 0.68; 95%CI 0.52, 0.88) and without (HR 0.76; 95%CI 0.65,0.89) anemia (interaction p=0.44) – **Figure 1**.
- Similar findings were found for the individual components of the primary outcome and all-cause mortality.

FIGURE 2 – EFFECT OF DAPAGLIFLOZIN ON HEMATOCRIT



Solid lines represent patients without anemia and the dashed lines represent those with anemia at baseline.

Effect of dapagliflozin on hematocrit

- Change in hematocrit from baseline by anemia status is shown in **Figure 2.** The mean placebo-corrected increase at 8 months was 2.38 (95%CI 1.93, 2.83)% in participants with anemia and 2.44 (95%CI 2.21, 2.67)% in those without anemia (interaction p=0.88).
- The proportion of patients who were anemic at baseline and experienced a persistent rise in hematocrit into the non-anemic range was 62.2% in the dapagliflozin group and 41.1% in the placebo group, giving an odds ratio for anemia correction of 2.37 (95%CI 1.84, 3.04); p<0.001.
- Patients with correction of anemia had a lower risk of the primary outcome than those in which anemia persisted (HR 0.43; 95%CI 0.23, 0.58).

CONCLUSIONS

- Patients with anemia had worse outcomes in DAPA-HF. Dapagliflozin corrected anemia more often than placebo and improved outcomes, irrespective of anemia status at baseline.