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LETTER TO THE EDITOR
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The effect of dapagliflozin in Chinese elderly patients with heart failure

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Clinical guidelines typically classify heart failure (HF) into three categories based on left ventricular ejection fraction (LVEF): reduced (HFrEF), mildly reduced (HFmrEF), and preserved (HFpEF).[1] Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been demonstrated to lower cardiovascular mortality and HF events. The EMPEROR trials indicated similar efficacy and safety for SGLT2 inhibitors compared to placebo in outpatients with HFrEF as well as HFmrEF and HFpEF.[2] A meta-analysis showed that dapagliflozin decreased the risk of cardiovascular death and hospital admissions for HF across the LVEF spectrum.[3] However, a comprehensive evaluation of dapagliflozin's efficacy and safety across the baseline LVEF spectrum in Chinese patients with HF is still lacking.[4] Therefore, this study aims to investigate the efficacy and safety of dapagliflozin across the full range of LVEF in Chinese patients.

This single-center cohort clinical trial was conducted at Northern Jiangsu People's Hospital from April 2022 to January 2024. Informed consent was signed by all participants in accordance with the Ethics Committee of Northern Jiangsu People's Hospital (No.2024ky239), Jiangsu, China. The treatment group received dapagliflozin 10 mg once daily in addition to standard HF treatments, while the control group received only standard HF treatments. Patients were monitored for twelve months, during which their clinical symptoms were assessed, and both clinical examinations and echocardiographic evaluations were conducted. The study flowchart was shown in Figure 1. Measurements of LVEF, left atrium (LA), left ventricular (LV), Left ventricular diastolic diameter (LVDd) and left ventricular systolic diameter (LVSd) were taken.

A total of 212 elderly patients participated in this study. The demographical and clinical characteristics of all study patients are summarized in Table 1. No significant differences were observed between the two groups in baseline characteristics ($P > 0.05$). After 12 months of follow-up, 100 patients can be calculated in the dapagliflozin group. Ninety patients can be calculated in the control group. Table 2 compares the means of NT-proBNP, 6-minute walk distance (6MWD), LVEF, LA, LVSd, LVDd, fractional shortening (FS), systolic blood pressure (SBP), and diastolic blood pressure (DBP) between the dapagliflozin and control groups. At twelve months post-treatment, LA, LVSd, LVDd, NT-proBNP, SBP, and DBP were significantly lower in both groups compared to

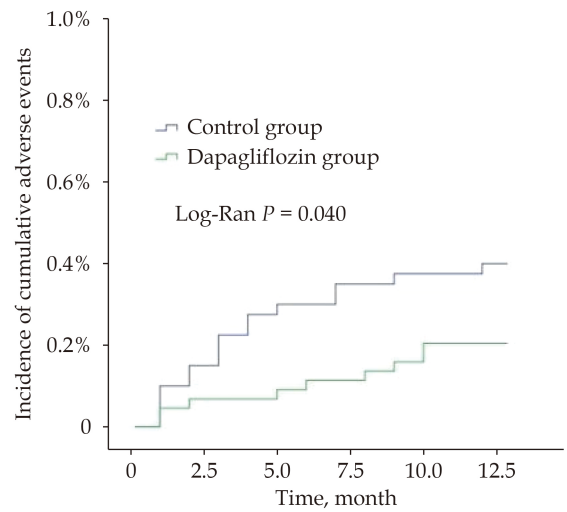

Figure 1 The study flowchart of the patients.

Table 1 The baseline characteristics of the participants in the two groups.

Variable	Dapagliflozin (*n* = 116)	Control (*n* = 96)	*P*-value
Age, yrs	69.60 ± 5.13	71.45 ± 6.70	0.815
Men	69 (59.48%)	52 (54.17%)	0.160
BMI	24.87 ± 4.70	24.83 ± 4.33	0.564
SBP	131.26 ± 20.32	130.23 ± 21.21	0.765
DBP	78.31 ± 14.21	77.75 ± 13.75	0.702
6MWD	272.75 ± 84.52	281.84 ± 88.60	0.872
Current smoking	30 (25.86%)	30 (31.25%)	0.089
NYHA functional class			
II	15 (12.93%)	16 (16.67%)	0.128
III	57 (49.14%)	51 (53.13%)	0.554
IV	44 (37.93%)	35 (36.46%)	0.559
Medical history			
Atrial fibrillation/flutter	49 (42.24%)	55 (57.29%)	0.892
Type 2 diabetes mellitus	47 (40.52%)	38 (39.59%)	0.542
Hypertension	66 (56.90%)	53 (55.21%)	0.632
Stroke	14 (12.07%)	14 (14.58%)	0.285
Coronary artery disease	51 (43.97%)	41 (42.71%)	0.713
Hyperlipidaemia	7 (6.03%)	5 (5.21%)	0.606
COPD	9 (7.76%)	9 (9.38%)	0.404
History of PCI	11 (9.48%)	7 (7.29%)	0.255
Treatment			
Anticoagulants	48 (41.38%)	54 (56.25%)	0.501
Loop diuretic agents	96 (82.76%)	77 (80.21%)	0.344
MRA	97 (83.62%)	75 (78.13%)	0.216
Beta-blocker	83 (71.55%)	71 (73.96%)	0.434
ACEi/ARB/ARNi	89 (76.72%)	79 (82.29%)	0.474
radiofrequency ablation	3 (2.59%)	2 (2.08%)	0.633
Laboratory data			
eGFR, mL/min per 1.73 m^2, median (IQR)	61.92 (43.63, 84.58)	58.43 (40.49,78.43)	0.724
Haemoglobin, g/L	132.27 ± 20.18	127.46 ± 23.70	0.184
ALT, median (IQR)	19.00 (13.00, 29.00)	22.00 (13.25, 32.50)	0.890
AST, median (IQR)	23.00 (19.00, 32.00)	24.60 (18.45, 37.00)	0.569
CK-MB, median (IQR)	2.15 (1.16, 3.31)	2.02 (0.92, 2.75)	0.477
PLT,	177.53 ± 63.48	174.40 ± 64.76	0.925
HbA1c, %	6.93 ± 1.89	6.83 ± 1.02	0.053
HDL-C	1.10 ± 0.31	1.10 ± 0.35	0.247
TG, median (IQR)	1.20 (0.96, 1.48)	1.10 (0.75, 1.53)	0.556
CHO	3.76 ± 1.05	3.62 ± 1.01	0.690
LDL-C	2.28 ± 0.88	2.22 ± 0.80	0.224
LP(a), median (IQR)	190.55 (92.35, 349.28)	153.45 (101.95, 259.25)	0.577

Data are presented as mean ± SD *n* (%) or median (IQR). ACEI: angiotensin-converting-enzyme inhibitors; ARB: angiotensin receptor blocker; BMI: body mass index; CABG: coronary artery bypass surgery; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HF: heart failure; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; MRA: mineralocorticoid receptor antagonists; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SBP: systolic blood pressure.

Table 2 Outcomes of the two groups.

Variable	Dapagliflozin		Control	
	Baseline	12-month	Baseline	12-month
NT-proBNP	2017.00 (989.00, 3864.00)	1240.00 (454.00, 2900.00)[a]	1690.00 (828.00, 3323.25)	980.00 (371.00, 2795.00)[a]
6MWD	278.00 (192.00, 326.00)	304.00 (228.75, 339.00)[a]	342.00 (304.00, 378.00)	333.50 (300.75, 392.50)[a]
LVEF, %	42.72 ± 11.26	47.99 ± 12.45[a,b]	44.12 ± 12.86	46.48 ± 9.92[a]
LA	42.00 ± 6.78	40.96 ± 7.05[a]	42.53 ± 8.86	41.53 ± 8.46[a]
LVSd	44.39 ± 9.98	40.91 ± 9.61[a]	42.65 ± 11.10	40.88 ± 10.73[a]
LVDd	55.63 ± 10.43	54.16 ± 8.45	54.66 ± 9.31	54.61 ± 9.22
FS	21.25 ± 6.56	24.34 ± 7.03[a]	22.47 ± 7.37	24.54 ± 7.44[a]
SBP	133.05 ± 18.25	117.24 ± 13.66[a]	128.41 ± 18.59	120.85 ± 12.78[a]
DBP	79.33 ± 13.34	70.63 ± 8.10[a]	77.18 ± 13.76	71.73 ± 9.06[a]

Compared with before treatment, [a]$P < 0.05$; comparison with control group, [b]$P < 0.05$. DBP: diastolic blood pressure; FS: left ventricular shortening fraction; LA: left atrium; LVDd: left ventricular diastolic diameter; LVSd: left ventricular systolic diameter; SBP: systolic blood pressure; 6MWD: 6-minute walk distance.

baseline, while 6MWD scores, LVEF, and FS were significantly higher ($P < 0.05$). Additionally, LVEF in the dapagliflozin group was significantly better than in the control group at twelve months, with a statistically significant difference ($P < 0.05$).

The results related to endpoint outcome and adverse events in the two groups of patients during the twelve months of follow-up are listed in Table 3. However, there were no significant differences between both groups in the adverse events of major hypoglycemic event, major hypotensive event, urinary tract infection and impaired liver and kidney function. The incidence of cumulative adverse events showed that 9 (9.00%) of 100 patients in the Dapagliflozin group had adverse events, while 16 (17.78%) of 90 patients in the control group had adverse events. The incidence of cumulative adverse events in the two groups is shown in the Kaplan-Meier curve to be lower in the dapagliflozin group than in the control group and the log-rank test showed there was a significant difference between the two groups ($P = 0.040$). The results are shown in Figure 2.

The study demonstrated that a twelve-month treatment with dapagliflozin significantly increased LVEF in the dapagliflozin group compared to the control group. Moreover, dapagliflozin notably reduced adverse events rates for HF compared to the control group, regardless of LVEF. These findings collectively endorse the early in-hospital initiation of dapagliflozin in HF patients irrespective of their LVEF. Singh *et al.* examined the impact of dapagliflozin on LV remodeling in diabetic patients with and without HFrEF, finding no effect on LVESV or other LV remodeling parameters. However, dapagliflozin treatment was associated with a decrease in diastolic blood pressure and reduced need for loop diuretics compared to placebo.[5] In contrast, our study found no significant decrease in blood pressure with dapagliflozin treatment compared to the control group. The dapagliflozin group showed significantly LVEF elevated

Table 3 Endpoint outcomes and adverse events in the two groups of patients.

Outcomes	Dapagliflozin (100)	Control (90)	Hazard ratio (95% CI)	*P*-value
Hospitalisation	1 (1.00%)	6 (6.67%)	4.429 (3.393–5.464)	0.666
Urgent HF Visit	2 (2.00%)	4 (4.44%)	3.667 (1.664–5.670)	0.804
death	1 (1.00%)	3 (3.33%)	2.594 (0.000–9.334)	0.896
Any major hypoglycemic event	0	0	-	1.000
Any major Hypotensive event	2 (2.00%)	1 (1.11%)	3.333 (1.605–5.062)	0.157
Urinary tract infection	1 (1.00%)	1 (1.11%)	1.500 (0.520–2.480)	0.317
Impaired Liver and kidney function	2 (2.00%)	1 (1.11%)	1.667 (1.013–2.320)	0.480
Cumulative adverse events	9 (9.00%)	16 (17.78%)	10.524 (9.621–11.427)	0.040

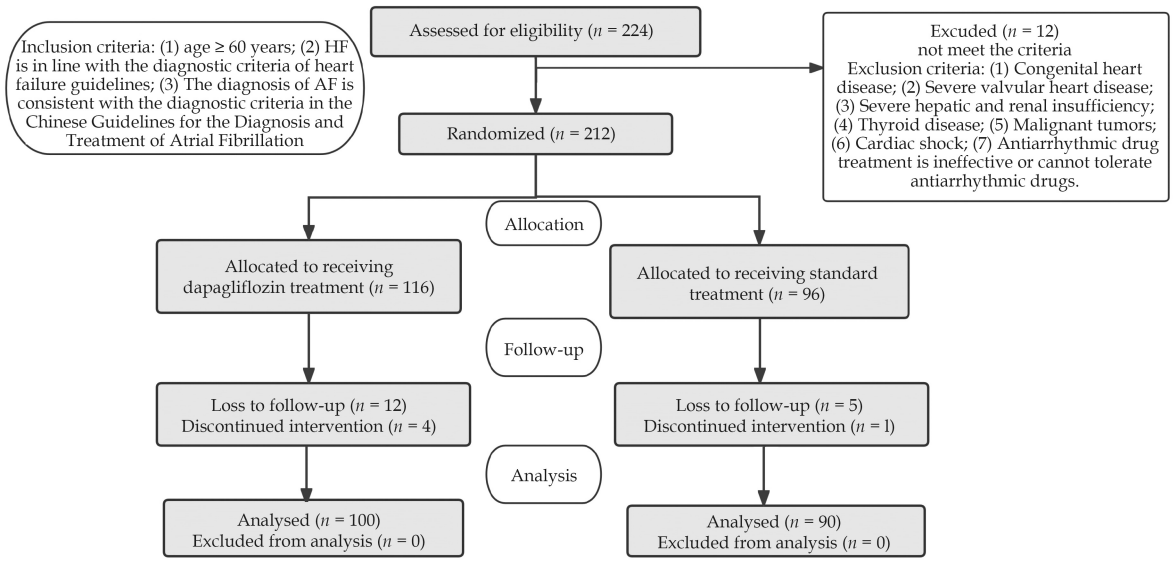

Figure 2 The incidence of cumulative adverse events in two groups.

after twelve months, while other parameters like LVDd and LVSd did not show significant decrease. The reason may be both of the groups were treated with standard medication which will be given the striking improvements in HF outcomes demonstrated in large clinical trials of SGLT2i.[6]

The significant improvement in LVEF in our study highlights the efficacy of dapagliflozin when combined with standard treatments. The benefits of dapagliflozin were consistent regardless of the baseline medication count, and adverse events (AEs) did not occur more frequently with dapagliflozin compared to the control group.[7] Accelerated implementation and up-titration of all four foundational therapies is further supported by a recent modelling study, which suggested that starting treatment sequences with SGLT2 inhibitors was associated with the shortest time to begin all four foundational therapies.[8] In this study, AEs and treatment discontinuation were not more frequent with dapagliflozin. Alongside findings from the DETERMINE trial, concerns about adding another medication, such as older age and polypharmacy, do not appear to diminish the benefit-safety ratio of dapagliflozin.[9]

The cumulative incidence of adverse events was lower in dapagliflozin group than in control group significantly. This data provides reassurance for its use, particularly in vulnerable individuals with multimorbidity and polypharmacy.[10] It indicated that beginning treatment sequences with SGLT2 inhibitors results in the shortest time to initiate all four foundational therapies. This implies that SGLT2 inhibitors can be introduced in patients with new-onset HF even before LVEF information is available and other treatments are initiated. This study had limitations. The effects of the medication were examined over twelve months and long-term effects were not assessed. LV structure was evaluated by echocardiography rather than cardiac magnetic resonance (CMR). Further studies with larger sample sizes and consideration of potential contributing factors are needed.

In conclusion, these results demonstrate that dapagliflozin effectively improves LVEF and reduces cumulative adverse events rates in HF patients across a wide range of baseline medication use, including those with polypharmacy.

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