JAMA Cardiology | Brief Report

Association of Dapagliflozin Use With Clinical Outcomes and the Introduction of Uric Acid–Lowering Therapy and Colchicine in Patients With Heart Failure With and Without Gout

A Patient-Level Pooled Meta-analysis of DAPA-HF and DELIVER

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IMPORTANCE Gout is common in patients with heart failure (HF), and sodium-glucose cotransporter 2 inhibitors, a foundational treatment for HF, reduce uric acid levels.

OBJECTIVE To examine the reported prevalence of gout at baseline, the association between gout and clinical outcomes, and the effect of dapagliflozin in patients with and without gout and the introduction of new uric acid–lowering therapy and colchicine.

DESIGN, SETTING, AND PARTICIPANTS This post hoc analysis used data from 2 phase 3 randomized clinical trials conducted in 26 countries, DAPA-HF (left ventricular ejection fraction [LVEF] ≤40%) and DELIVER (LVEF >40%). Patients with New York Heart Association functional class II through IV and elevated levels of N-terminal pro–B-type natriuretic peptide were eligible. Data were analyzed between September 2022 and December 2022.

INTERVENTION Addition of once-daily 10 mg of dapagliflozin or placebo to guideline-recommended therapy.

MAIN OUTCOMES AND MEASURES The primary outcome was the composite of worsening HF or cardiovascular death.

RESULTS Among 11 005 patients for whom gout history was available, 1117 patients (10.1%) had a history of gout. The prevalence of gout was 10.3% (488 of 4747 patients) and 10.1% (629 of 6258 patients) in those with an LVEF up to 40% and greater than 40%, respectively. Patients with gout were more often men (897 of 1117 [80.3%]) than those without (6252 of 9888 [63.2%]). The mean (SD) age was similar between groups, 69.6 (9.8) years for patients with gout and 69.3 (10.6) years for those without. Patients with a history of gout had a higher body mass index, more comorbidity, and lower estimated glomerular filtration rate and were more often treated with a loop diuretic. The primary outcome occurred at a rate of 14.7 per 100 person-years (95% CI, 13.0-16.5) in participants with gout compared with 10.5 per 100 person-years (95% CI, 10.1-11.0) in those without (adjusted hazard ratio [HR], 1.15; 95% CI, 1.01-1.31). A history of gout was also associated with a higher risk of the other outcomes examined. Compared with placebo, dapagliflozin reduced the risk of the primary end point to the same extent in patients with (HR, 0.84; 95% CI, 0.66-1.06) and without a history of gout (HR, 0.79; 95% CI, 0.71-0.87; *P* = .66 for interaction). The effect of dapagliflozin use with other outcomes was consistent in participants with and without gout. Initiation of uric acid–lowering therapy (HR, 0.43; 95% CI, 0.34-0.53) and colchicine (HR, 0.54; 95% CI, 0.37-0.80) was reduced by dapagliflozin compared with placebo.

CONCLUSIONS AND RELEVANCE This post hoc analysis of 2 trials found that gout was common in HF and associated with worse outcomes. The benefit of dapagliflozin was consistent in patients with and without gout. Dapagliflozin reduced the initiation of new treatments for hyperuricemia and gout.

TRIAL REGISTRATION ClinicalTrials.gov Identifiers: NCT03036124 and NCT03619213

JAMA Cardiol. 2023;8(4):386-393. doi:10.1001/jamacardio.2022.5608
Published online February 22, 2023.

Supplemental content

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Gout is a common comorbidity in patients with heart failure (HF), and it is associated with adverse clinical outcomes, including hospitalization for HF.[1-5] There is a consensus that the treatment of gout is suboptimal, with up to 70% of patients having recurring flares.[6-8] Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a foundational treatment for HF, reduce uric acid levels and may therefore reduce the incidence of gout.[9-11]

We examined the association between gout and clinical outcomes and the effect of dapagliflozin in patients with and without gout and the introduction of new uric acid–lowering therapy and colchicine (as a proxy for gout flares) across the range of ejection fraction in 2 recent clinical trials in HF. Both trials randomized participants to receive treatment with the SGLT2 inhibitor dapagliflozin or placebo and recently pooled their data.[12,13]

Key Points

Question What are the effects of dapagliflozin in patients with heart failure (HF) with and without gout and on the introduction of new uric acid–lowering therapy and colchicine?

Findings In this post hoc analysis of 2 phase 3 clinical trials that included 11 005 patients with HF, dapagliflozin reduced the risk of clinical outcomes to the same extent in patients with and without gout. Dapagliflozin reduced the initiation of a uric acid–lowering agent by 57% and treatment with colchicine by 46%.

Meaning The benefits of dapagliflozin were consistent irrespective of gout, and dapagliflozin use was associated with a reduction in the initiation of new treatments for hyperuricemia and gout.

Methods

DAPA-HF and DELIVER were randomized, double-blind, clinical trials including patients with symptomatic HF and elevated natriuretic peptide levels that compared the efficacy and safety of dapagliflozin, 10 mg once daily, with placebo.[12,13] The principal difference between the trials was the left ventricular ejection fraction (LVEF) enrollment criterion (≤40% in DAPA-HF, >40% in DELIVER). The trial protocols were approved by the ethics committee at each participating institution, and all patients provided written informed consent. Both trials were reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Data on history of gout were investigator-reported and retrieved from the trial case report forms. The primary outcome was the composite of worsening HF or cardiovascular death. The definition of cardiovascular death included deaths of undetermined causes. Among patients who were not treated with a uric acid–lowering agent or colchicine at baseline, we examined the initiation of these drugs.

Time-to-event data and total events were evaluated with Cox proportional hazards models and semiparametric proportional rates models, respectively, and models were stratified according to diabetes status and trial and adjusted for treatment and history of HF hospitalization (except for all-cause death). The change in Kansas City Cardiomyopathy Questionnaire total symptom score from baseline to 8 months was analyzed using mixed-effect models for repeated measurements, adjusted for baseline value, treatment assignment, interaction of treatment and visit, and trial. All analyses were conducted using Stata version 17.0 between September 2022 and December 2022.

Results

Of the 11 007 patients randomized in DAPA-HF and DELIVER, 2 were excluded because of missing history of gout at baseline. A total of 1117 patients (10.1%) had a history of gout at baseline (10.3% [488 of 4747 patients] and 10.1% [629 of 6258 patients] in those with a LVEF ≤40% and >40%, respectively).

Patients with gout were more often men (897 of 1117 patients were men [80.3%] vs 6252 of 9888 [63.2%] in the group without gout). The mean (SD) age was similar between groups, 69.6 (9.8) years for patients with gout and 69.3 (10.6) years for those without. Patients with gout had more comorbidities and more severe HF compared with those without gout (**Table 1**). They were more frequently treated with a loop diuretic but less often treated with a mineralocorticoid receptor antagonist or a thiazide diuretic.

After adjustment for prognostic variables, patients with gout had a significantly higher risk of all clinical outcomes, except cardiovascular death, all-cause death, and the composite of total HF hospitalizations and cardiovascular death, where the risks were numerically but not significantly higher (eTable 1 in Supplement 1). These associations were not modified by LVEF (eFigure in Supplement 1).

Compared with placebo, dapagliflozin reduced the risk of worsening HF or cardiovascular death to the same extent in patients with (HR, 0.84; 95% CI, 0.66-1.06) and without gout (HR, 0.79; 95% CI, 0.71-0.87), with no interaction between gout and treatment effect (P = .66 for interaction). The effect of dapagliflozin was also consistent regardless of gout for all secondary clinical outcomes (**Table 2**).

During a median follow-up of 22 months, 370 of 9556 patients (3.9%) with no use of uric acid–lowering therapy at baseline initiated this therapy. Compared with placebo, dapagliflozin use was associated with a reduced risk of initiating a uric acid–lowering agent (HR, 0.43; 95% CI, 0.34-0.53). The association of dapagliflozin with the initiation of this therapy was not modified by history of gout (P = .73 for interaction) or LVEF (P = .65 for interaction) (**Figure** and eTables 2 and 3 in Supplement 1).

During follow-up, 113 of 10 926 patients (1.0%) with no use of colchicine at baseline initiated this therapy. The rate of initiation of colchicine was 3.9 per 1000 person-years (95% CI, 2.9-5.3) and 7.2 per 1000 person-years (95% CI, 5.7-9.0) in the dapagliflozin and placebo groups, respectively. Dapagliflozin use, compared with placebo, was associated with a reduced risk of initiating colchicine (HR, 0.54; 95% CI, 0.37-0.80), and the association was not modified by history of gout (P = .76 for interaction) or LVEF (P = .06 for interaction) (Figure and eTables 2 and 3 in Supplement 1).

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Table 1. Baseline Characteristics According to History of Gout

	No. (%)		
	No history of gout (n = 9888)	History of gout (n = 1117)	*P* value
Age, mean (SD), y	69.3 (10.6)	69.6 (9.8)	.37
Age group			.76
<75 y	6523 (66.0)	742 (66.4)	
≥75 y	3365 (34.0)	375 (33.6)	
Sex			<.001
Women	3636 (36.8)	220 (19.7)	
Men	6252 (63.2)	897 (80.3)	
Race[a]			<.001
Asian	2106 (21.3)	284 (25.4)	
Black or African American	331 (3.3)	54 (4.8)	
White	7000 (70.8)	770 (68.9)	
Other	451 (4.6)	9 (0.8)	
Geographic region			<.001
Europe and Saudi Arabia	4606 (46.6)	551 (49.3)	
North America	1297 (13.1)	231 (20.7)	
South America	1937 (19.6)	61 (5.5)	
Asia Pacific	2048 (20.7)	274 (24.5)	
Physiological measures			
Systolic blood pressure, mean (SD), mm Hg	125.5 (16.1)	124.9 (15.8)	.25
Heart rate, mean (SD), bpm	71.5 (11.7)	71.7 (11.9)	.63
BMI, mean (SD)[b]	29.0 (6.1)	30.4 (6.4)	<.001
BMI group			<.001
<18.5	132 (1.3)	9 (0.8)	
18.5-24.9	2399 (24.3)	205 (18.4)	
25.0-29.9	3445 (34.9)	349 (31.2)	
30-34.9	2292 (23.2)	294 (26.3)	
≥35.0	1612 (16.3)	260 (23.3)	
NT-proBNP, median (IQR), pg/mL	1164 (694-2093)	1320 (784-2333)	<.001
Atrial fibrillation/flutter on ECG			
Yes	1528 (1026-2463)	1693 (1066-2721)	.01
No	958 (562-1820)	1016 (605-2041)	.03
Uric acid, mean (SD), mg/dL[c]	6.1 (1.7)	6.3 (2.0)	.08
Hemoglobin A_{1c}, mean (SD), %	6.5 (1.4)	6.5 (1.2)	.46
Creatinine, mean (SD), μmol/L	101.6 (29.7)	118.8 (35.6)	<.001
eGFR, mean (SD), mL/min/1.73 m^2	63.8 (19.3)	56.5 (18.9)	<.001
eGFR group			<.001
≥60 mL/min/1.73 m^2	5557 (56.2)	450 (40.3)	
<60 mL/min/1.73 m^2	4328 (43.8)	667 (59.7)	
Duration of HF			<.001
0-3 mo	645 (6.5)	73 (6.5)	
3-6 mo	893 (9.0)	92 (8.2)	
6-12 mo	1300 (13.2)	95 (8.5)	
1-2 y	1549 (15.7)	132 (11.8)	
2-5 y	2385 (24.1)	289 (25.9)	
>5 y	3111 (31.5)	436 (39.0)	
LVEF, mean (SD), %	44.2 (13.9)	44.3 (14.2)	.87
LVEF category			.03
≤40%	4259 (43.1)	488 (43.7)	
41%-49%	1930 (19.5)	183 (16.4)	
≥50%	3699 (37.4)	446 (39.9)	

(continued)

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Table 1. Baseline Characteristics According to History of Gout (continued)

	No. (%)		
	No history of gout (n = 9888)	History of gout (n = 1117)	*P* value
NYHA class			.67
I	1 (0.0)	0	
II	7095 (71.8)	819 (73.3)	
III	2738 (27.7)	291 (26.1)	
IV	54 (0.5)	7 (0.6)	
KCCQ, mean (SD)			
TSS	71.5 (22.0)	72.4 (22.4)	.22
CSS	69.4 (20.8)	70.5 (20.7)	.12
OSS	67.2 (20.5)	68.6 (20.4)	.04
Medical history			
Time from last HF hospitalization			<.001
None prior	5656 (57.2)	561 (50.2)	
0-3 mo	1225 (12.4)	145 (13.0)	
3-6 mo	647 (6.5)	70 (6.3)	
6-12 mo	769 (7.8)	78 (7.0)	
>1 y	1591 (16.1)	263 (23.5)	
Atrial fibrillation	4614 (46.7)	669 (59.9)	<.001
Stroke	926 (9.4)	137 (12.3)	.002
Myocardial infarction	3399 (34.4)	332 (29.7)	.002
Hypertension	8092 (81.8)	982 (87.9)	<.001
Type 2 diabetes	4218 (42.7)	571 (51.1)	<.001
Treatment			
ACE inhibitor	4484 (45.3)	471 (42.2)	.04
ARB	3261 (33.0)	317 (28.4)	.002
ACE inhibitor/ARB	7709 (78.0)	784 (70.2)	<.001
ARNI	709 (7.2)	100 (9.0)	.03
β-Blocker	8744 (88.4)	990 (88.6)	.84
MRA	5488 (55.5)	548 (49.1)	<.001
Any loop diuretic	7701 (77.9)	933 (83.5)	<.001
Furosemide	5769 (58.4)	678 (60.7)	.13
Dose, mean (SD), mg/d	46.1 (43.4)	51.4 (44.5)	.003
Bumetanide	208 (2.1)	53 (4.7)	<.001
Dose, mean (SD), mg/d	2.6 (4.1)	2.4 (1.7)	.77
Torasemide	1675 (16.9)	187 (16.7)	.86
Dose, mean (SD), mg/d	12.6 (15.8)	22.9 (27.5)	<.001
Azosemide	191 (1.9)	44 (3.9)	<.001
Dose, mean (SD), mg/d	36.0 (18.5)	36.6 (17.6)	.86
Thiazide	1051 (10.6)	93 (8.3)	.02
Digoxin	1044 (10.6)	139 (12.4)	.05
Statin	6485 (65.6)	730 (65.4)	.88
Antiplatelet	4765 (48.2)	457 (40.9)	<.001
Anticoagulant	4695 (47.5)	656 (58.7)	<.001
CRT-P/CRT-D	382 (3.9)	72 (6.4)	<.001
ICD/CRT-D	1216 (12.3)	194 (17.4)	<.001
Uric acid–lowering therapy	767 (7.8)	682 (61.1)	<.001
Uric acid production–inhibiting therapy[d]	743 (7.5)	666 (59.6)	<.001
Uric acid–excreting therapy[e]	25 (0.3)	18 (1.6)	<.001
Colchicine	13 (0.1)	66 (5.9)	<.001
Uric acid–lowering therapy or colchicine	776 (7.8)	712 (63.7)	<.001

Abbreviations:
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ATC, Anatomical Therapeutic Chemical; BMI, body mass index; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; CSS, clinical summary score; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FI, frailty index; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; OSS, overall summary score; TSS, total symptom score.

[a] Race was captured on a dedicated demographics case report form and included the following categories: Asian, Black or African American, White, or other race designation (including Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native).

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Only available in 3119 patients enrolled in DAPA-HF.

[d] ATC code: M04AA. Drugs used in the trials were allopurinol, febuxostat, or topiroxostat.

[e] ATC code: M04AB. Drugs used in the trials were benzbromarone or probenecid.

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Table 2. Effects of Dapagliflozin Compared With Placebo and Outcomes According to History of Gout

Outcome[a]	No history of gout (n = 9888)		History of gout (n = 1117)		*P* value for interaction
	Placebo (n = 4899)	Dapagliflozin (n = 4989)	Placebo (n = 603)	Dapagliflozin (n = 514)	
Worsening HF or cardiovascular death					
Events, No. (%)	1007 (20.6)	833 (16.7)	159 (26.4)	121 (23.5)	.66
Event rate per 100 person-years (95% CI)	11.8 (11.1 to 12.6)	9.3 (8.7 to 10.0)	15.7 (13.4 to 18.3)	13.5 (11.3 to 16.1)	
HR (95% CI)[b]	0.79 (0.71 to 0.87)		0.84 (0.66 to 1.06)		
HF hospitalization or cardiovascular death					
Events, No. (%)	976 (19.9)	795 (15.9)	152 (25.2)	118 (23.0)	.47
Event rate per 100 person-years (95% CI)	11.4 (10.7 to 12.1)	8.9 (8.3 to 9.5)	14.8 (12.7 to 17.4)	13.1 (10.9 to 15.6)	
HR (95% CI)[b]	0.78 (0.71 to 0.85)		0.86 (0.67 to 1.09)		
Worsening HF					
Events, No. (%)	658 (13.4)	524 (10.5)	122 (20.2)	81 (15.8)	.78
Event rate per 100 person-years (95% CI)	7.7 (7.1 to 8.3)	5.9 (5.4 to 6.4)	12.0 (10.1 to 14.4)	9.0 (7.3 to 11.2)	
HR (95% CI)[b]	0.76 (0.68 to 0.85)		0.73 (0.55 to 0.97)		
HF hospitalization					
Events, No. (%)	623 (12.7)	483 (9.7)	113 (18.7)	77 (15.0)	.95
Event rate per 100 person-years (95% CI)	7.3 (6.7 to 7.8)	5.4 (4.9 to 5.9)	11.0 (9.2 to 13.3)	8.5 (6.8 to 10.7)	
HR (95% CI)[b]	0.74 (0.66 to 0.83)		0.75 (0.56 to 1.00)		
Cardiovascular death					
Events, No. (%)	536 (10.9)	457 (9.2)	71 (11.8)	68 (13.2)	.13
Event rate per 100 person-years (95% CI)	5.8 (5.4 to 6.3)	4.9 (4.4 to 5.3)	6.3 (5.0 to 8.0)	7.1 (5.6 to 8.9)	
HR (95% CI)[b]	0.83 (0.74 to 0.94)		1.09 (0.78 to 1.52)		
All-cause death					
No. of events (%)	751 (15.3)	680 (13.6)	104 (17.2)	93 (18.1)	.31
Event rate per 100 person-years (95% CI)	8.2 (7.6 to 8.8)	7.2 (6.7 to 7.8)	9.2 (7.6 to 11.2)	9.6 (7.9 to 11.8)	
HR (95% CI)[b]	0.88 (0.80 to 0.98)		1.03 (0.78 to 1.36)		
Total HF hospitalizations and cardiovascular death					
No. of events	1532	1196	251	177	.70
RR (95% CI)[b]	0.76 (0.68 to 0.85)		0.81 (0.62 to 1.05)		
KCCQ-TSS					.24
Change from baseline to 8 mo (95% CI)[c]	4.7 (4.1 to 5.2)	7.2 (6.7 to 7.7)	3.7 (2.2 to 5.2)	5.7 (4.1 to 7.3)	
Placebo-corrected change at 8 mo (95% CI)[c]	2.5 (1.8 to 3.2)		2.0 (−0.2 to 4.2)		

Abbreviations: HF, heart failure; HR, hazard ratio; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; RR, rate ratio.

[a] Cardiovascular death includes undetermined deaths.

[b] Models were stratified by diabetes status and trial and adjusted for a history of HF hospitalization (except in the analysis of all-cause death).

[c] Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 4 and 8), randomized treatment, interaction of treatment and visit, and trial.

Discussion

In a pooled analysis of data from DAPA-HF and DELIVER including more than 11 000 patients with HF with reduced, mildly reduced, and preserved ejection fraction, a history of gout was common and associated with worse outcomes. The beneficial effects of dapagliflozin on clinical events were consistent in patients with and without gout. Dapagliflozin reduced the initiation of a uric acid–lowering agent by 57% and treatment with colchicine by 46%.

In a secondary analysis of EMPEROR-Reduced, there was a significant interaction between the levels of uric acid and the effect of empagliflozin on mortality, with a beneficial effect of this treatment in individuals with higher uric acid levels but not in those with lower levels.[9] The explanation for this unexpected finding is not clear, and it may have resulted from chance. In the present study, the benefits of dapagliflozin on clinical outcomes, including mortality, were not modified by the presence of gout. These data underline the substantial and clinically important benefits of dapagliflozin in HF, irrespective of gout status.

In EMPEROR-Reduced, empagliflozin use was associated with a decreased risk of clinically relevant hyperuricemic events (defined as a composite of episodes of acute gout, episodes of gouty arthritis, and the initiation of uric acid–lowering therapy) by 32% and initiation of uric acid–lowering therapy by 31%.[9] The present analysis confirms and extends these findings by demonstrating the same clinical benefit of dapagliflozin in a much larger and more diverse cohort of patients with HF across the spectrum of LVEF. It is uncertain whether the greater reductions in this analysis, compared with those of EMPEROR-Reduced, reflect the play of chance or a true difference between dapagliflozin and empagliflozin.

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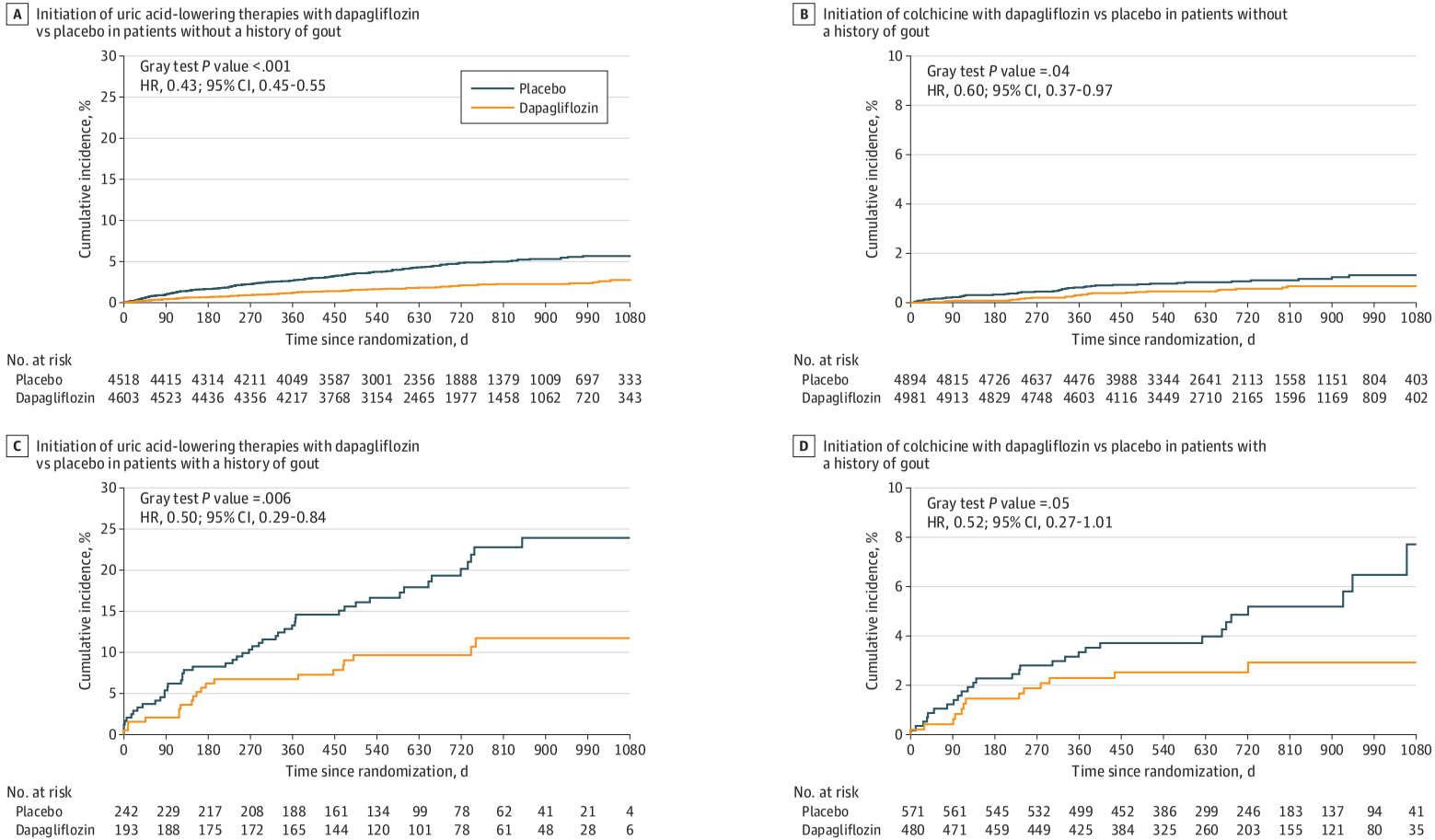
Figure. Initiation of Uric Acid–Lowering Therapies or Colchicine With Dapagliflozin vs Placebo During Follow-up



Panels A and C show the cumulative incidence of initiation of uric acid–lowering therapies with dapagliflozin vs placebo during follow-up in patients without and with a history of gout, respectively. Panels B and D show the cumulative incidence of initiation of colchicine with dapagliflozin vs placebo during follow-up in patients without and with a history of gout, respectively. Patients without use of these therapies at randomization were included in this analysis. HR indicates hazard ratio.

Although it is difficult to compare across trials and in different medical conditions, a recent meta-analysis also suggested a greater reduction in uric acid levels with dapagliflozin and luseogliflozin than with other SGLT2 inhibitors in individuals with type 2 diabetes.[11] These observations warrant further investigation.

The reduction in the initiation of anti-gout medication with dapagliflozin most likely reflects the uric acid–lowering effect of SGLT2 inhibitors, but the mechanism for this is unknown. Whatever the reason, the reduction in the need for initiation of anti-gout medication represents a meaningful additional clinical benefit of dapagliflozin in patients with HF. In addition, avoiding anti-gout medication is desirable because of drug intolerance; drug interactions with HF therapies, including angiotensin-converting enzyme inhibitors and furosemide; risks of serious adverse events, such as hypersensitivity reactions; and less polypharmacy, which could improve patient adherence to lifesaving HF therapies.[14,15]

Limitations

This study has several limitations. The analyses were not prespecified. Serum uric acid was not measured in DELIVER. Colchicine may be used for medical conditions other than gout flares, eg, pericarditis. Only serious adverse events and selected adverse events were collected in DAPA-HF and DELIVER; consequently, we did not have information on the occurrence of gout flares and had to use prescription of colchicine as a proxy, which may have underestimated the true incidence. A small proportion of patients without a history of gout were receiving uric acid–reducing therapy at baseline, potentially representing patient misclassification, although asymptomatic hyperuricemia is treated in some patients in some countries.

Conclusions

In this post hoc analysis of 2 phase 3 clinical trials, the beneficial effect of dapagliflozin use with clinical outcomes was consistent among patients with HF irrespective of gout status. Dapagliflozin reduced the initiation of medications used to reduce urate level or to treat gout flares, representing a meaningful additional clinical benefit of dapagliflozin in patients with HF.

ARTICLE INFORMATION

Accepted for Publication: December 19, 2022.

Published Online: February 22, 2023. doi:10.1001/jamacardio.2022.5608

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Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Butt, Claggett, Jhund.
Obtained funding: Petersson, Solomon.
Administrative, technical, or material support: Butt, Shah.
Supervision: Langkilde, Kosiborod, Køber, Martinez, Ponikowski, Shah, Jhund, Solomon, McMurray.
Other: Ponikowski.
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Conflict of Interest Disclosures: Dr Butt reported advisory board honoraria from Bayer, travel grants from AstraZeneca, and consultant honoraria from Novartis outside the submitted work. Dr Docherty reported personal fees and payment from AstraZeneca to his institution for his involvement in the DAPA-HF and DELIVER trials during the conduct of the study and grants from Boehringer Ingelheim to his institution and advisory board fees from Us2.ai outside the submitted work. Dr Claggett reported consulting fees from Boehringer Ingelheim, Cardurion, Corvia, Cytokinetics, Intellia, and Novartis outside the submitted work. Dr Desai reported grants to his institution and consulting fees from AstraZeneca during the conduct of the study; grants to his institution from Abbott, Alnylam, Bayer, and Novartis outside the submitted work; and consulting fees from Abbott, Alnylam, Amgen, Avidity Biopha, Axon Therapeutics, Bayer, Biofourmis, Boston Scientific, Boehringer Ingelheim, Corvidia, Cytokinetics, DalCor Pharma, Merck, New Amsterdam, Novo Nordisk, Novartis, Parexel, Medpace, Regeneron, Relypsa, Roche, Veristat, Verily, and Zydus outside the submitted work. Dr Petersson reported being an employee and shareholder of AstraZeneca during the conduct of the study. Dr Langkilde reported being an employee and shareholder of AstraZeneca during the conduct of the study. Dr de Boer reported grants to his institution from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals, Ionis Pharmaceuticals, Novo Nordisk, and Roche and speaker fees from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche outside the submitted work. Dr Hernandez reported research support from American Regent, AstraZeneca, Boehringer Ingelheim, Merck, Novartis, and Verily and having served as a consultant or on the advisory board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Myokardia, Merck, Novartis, and Vifor. Dr Inzucchi reported having served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion and having given lectures sponsored by AstraZeneca and Boehringer Ingelheim. Dr Kosiborod reported research grant support from AstraZeneca and Boehringer Ingelheim; having served as a consultant or on an advisory board for Amgen, Alnylam, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck, Novo Nordisk, Pharmacosmos, Sanofi, and Vifor Pharma; having received other research support from AstraZeneca; and having received honorarium from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Dr Køber reported speakers honorarium from Novo Nordisk, Novartis, AstraZeneca, and Boehringer Ingelheim outside the submitted work. Dr Lam reported being supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; receiving research support from AstraZeneca, Bayer, Boston Scientific, and Roche Diagnostics; having served as a consultant or on the advisory board/steering committee/executive committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio,

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Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, EchoNous, Eli Lilly, Impulse Dynamics, Intellia Therapeutics, Ionis Pharmaceutical, Darma, Us2.ai, Janssen Research & Development, Medscape, Merck, Novartis, Novo Nordisk, Prosciento, Radcliffe Group, Redcardio, ReCor Medical, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics, and WebMD; serving as the cofounder and non-executive director of Us2.ai; and having a patent pending (PCT/SG2016/050217, Method for diagnosis and prognosis of chronic heart failure) and a patent issued (US patent No. 10,702,247, Automated clinical workflow that recognizes and analyses 2-dimensional and Doppler echo images for cardiac measurements and the diagnosis, prediction and prognosis of heart disease). Dr Martinez reported personal fees from AstraZeneca during the conduct of the study. Dr Ponikowski reported compensation for consultant services from Amgen, AstraZeneca, Boehringer Ingelheim, Servier, and Vifor Pharma and compensation for other services from Abbott Vascular, AstraZeneca, Bayer, Berlin Chemie, Bristol Myers Squibb, Cibiem, Pfizer, MSD, Novartis, Respicardia, and RenalGuardSolution. Dr Sabatine reported grants to his institution and consulting fees from AstraZeneca during the conduct of the study; reported grants to his institution and/or consulting fees from Abbott, Althera, Amgen, Anthos Therapeutics, Bayer, Beren Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, CVS Caremark, DalCor, Daiichi-Sankyo, Dr. Reddy's Laboratories, Eisai, Fibrogen, IFM Therapeutics, Intarcia, Ionis, Medicines Company, MedImmune, Merck, Moderna, Novartis, Novo Nordisk, Pfizer, Quark Pharmaceuticals, and Silence Therapeutics outside the submitted work; and being a member of the TIMI Study Group, which has also received institutional research grant support through ARCA Biopharma, Janssen Research and Development, Pfizer, Regeneron Pharmaceuticals, Roche, Siemens Healthcare Diagnostics, Softcell Medical, and Zora Biosciences. Dr Shah reported personal or institutional research support for DELIVER from AstraZeneca during the conduct of the study. Dr Vaduganathan reported research grant support or having served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Chiesi, Cytokinetics, Lexicon Pharmaceuticals, Novo Nordisk, Relypsa, and Tricog; speaker engagements with Novartis and Roche Diagnostics; and participating on clinical end point committees for studies sponsored by Galmed, Impulse Dynamics, Novartis, and Occlutech. Dr Jhund reported grants to his institution and personal fees from AstraZeneca during the conduct of the study; grants and/or personal fees from Novartis, Boehringer Ingelheim, Bayer, Cytokinetics, Novo Nordisk, Analog Devices, Alkem Metablomics, Sun Pharmaceuticals, and Roche Diagnostics outside the submitted work; and being a director at Global Clinical Trial Partners. Dr Solomon reported having received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Neurotronik, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Theracos, and Us2.ai; and having consulted for Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellPro-Thera, Moderna, American Regent, Sarepta, Lexicon, Anacardio, Akros, and Puretech Health outside the submitted work. Dr McMurray reported payments through Glasgow University from work on clinical trials, consulting, and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardurion, Cytokinetics, DalCor, GSK, Ionis, KBP Biosciences, Novartis, Pfizer, and Theracos; reported personal lecture and other fees from Corpus, Abbott, Alkem Metabolics, Eris Lifesciences, Hikma, Ionis Pharmaceuticals, Lupin, Sun Pharmaceuticals, Medscape/Heart.org, ProAdWise Communications, Radcliffe Cardiology, and Servier; and reported being a director at Global Clinical Trial Partners. No other disclosures were reported.

Funding/Support: The DAPA-HF and DELIVER trials were funded by AstraZeneca. Dr McMurray is supported by a British Heart Foundation Centre of Research Excellence grant (RE/18/6/34217).

Role of the Funder/Sponsor: The DAPA-HF and DELIVER trials were designed by the academic members of the executive committee in collaboration with representatives from AstraZeneca. AstraZeneca was involved in the overall design and conduct of the trials and collection, management, and interpretation of the data but had no role in the statistical analysis of this secondary analysis, drafting and preparation of the manuscript, or decision to submit the manuscript for publication. Coauthors who are employees of AstraZeneca reviewed and approved the manuscript in accordance with authorship guidelines.

Data Sharing Statement: See Supplement 2.

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