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RESEARCH ARTICLE

Renal and blood pressure effects of dapagliflozin in recently hospitalized patients with heart failure with mildly reduced or preserved ejection fraction: Insights from the DELIVER trial

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Aims

Patients recently hospitalized for heart failure (HF) often have unstable haemodynamics and experience worsening renal failure, and are at elevated risk for recurrent HF events. In DELIVER, dapagliflozin reduced HF events or cardiovascular death including among patients who were hospitalized or recently hospitalized.

Methods and results

We examined the effects of dapagliflozin versus placebo on estimated glomerular filtration rate (eGFR) slope (acute and chronic), 1-month change in systolic blood pressure, and the occurrence of serious hypovolaemic or renal adverse events in patients with and without HF hospitalization within 30 days of randomization. The 654 (90 randomized during hospitalization, 147 1–7 days post-discharge and 417 8–30 days post-discharge) recently hospitalized patients had lower baseline eGFR compared with those without recent HF hospitalization (median [interquartile range] 55 [43, 71] vs. 60 [47, 75] ml/min/1.73 m^2). Dapagliflozin consistently reduced the risk of all-cause ($p_{interaction} = 0.20$), cardiac-related ($p_{interaction} = 0.75$), and HF-specific ($p_{interaction} = 0.90$) hospitalizations, irrespective of recent HF hospitalization. In those recently hospitalized, acute placebo-corrected eGFR reductions with dapagliflozin were modest and similar to patients without recent hospitalization (−2.0 [−4.1, +0.1] vs. −3.4 [−3.9, −2.9] ml/min/1.73 m^2, $p_{interaction} = 0.12$). Dapagliflozin's effect to slow chronic eGFR decline was similar regardless of recent hospitalization ($p_{interaction} = 0.57$). Dapagliflozin had a minimal effect on 1-month systolic blood pressure and to a similar degree in patients with and without recent hospitalization (−1.3 vs.−1.8 mmHg, $p_{interaction} = 0.64$). There was no treatment-related excess in renal or hypovolaemic serious adverse events, irrespective of recent HF hospitalization.

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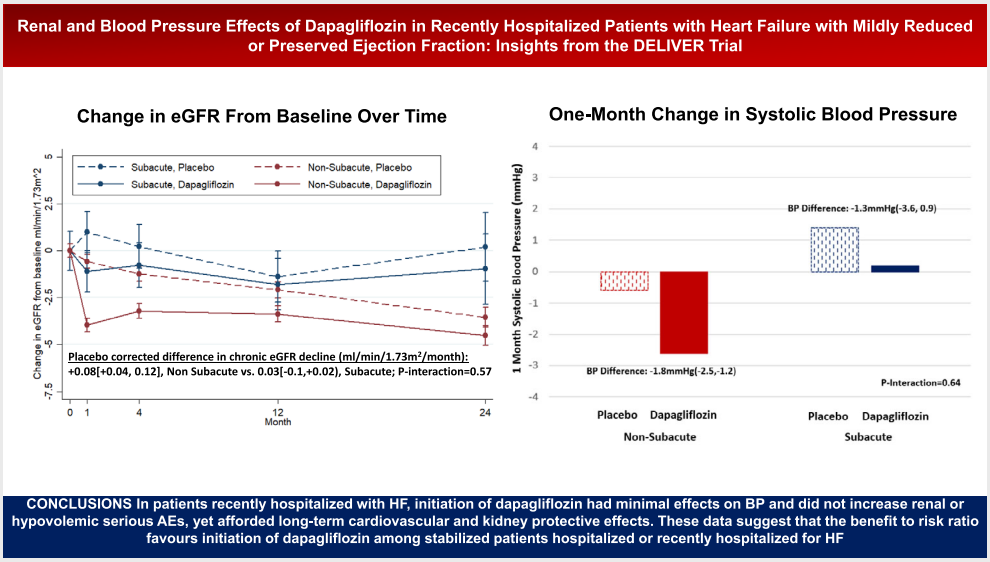
Conclusion In patients recently hospitalized with HF, initiation of dapagliflozin had minimal effects on blood pressure and did not increase renal or hypovolaemic serious adverse events, yet afforded long-term cardiovascular and kidney protective effects. These data suggest that the benefit to risk ratio favours initiation of dapagliflozin among stabilized patients hospitalized or recently hospitalized for HF.
Clinical Trial Registration: ClinicalTrials.gov NCT03619213.

Graphical Abstract



AE, adverse event; BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure.

Keywords Acute heart failure • SGLT2 inhibitor • Renal function • Blood pressure

Background

Sodium–glucose cotransporter 2 (SGLT2) inhibitors improve clinical outcomes in patients with both acute decompensated and chronic heart failure (HF).[1,2] The DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial allowed enrolment of patients during or closely following hospitalization and demonstrated consistent clinical benefits among patients with and without a history of recent HF hospitalization.[3] Treatment with dapagliflozin relative to placebo resulted in 22% (hazard ratio [HR] 0.78; 95% confidence interval [CI] 0.60–1.03) and 18% (HR 0.82; 95% CI 0.72–0.94) reductions in the primary composite outcome in patients with and without recent hospitalization respectively ($p_{interaction} = 0.71$).[3]

The peri-hospitalization period is characterized by increased risk for recurrent clinical events, and some patients might experience worsening renal function and/or hypotension.[4] SGLT2 inhibitors are associated with an early decline in estimated glomerular filtration rate (eGFR) which does not portend adverse outcomes in patients with chronic HF[5,6] and slows eGFR decline in long-term follow-up. In the overall DELIVER trial population, dapagliflozin modestly reduced systolic blood pressure by 1.8 mmHg compared to placebo.[7] How the renal and haemodynamic effects of SGLT2 inhibitors may differ according to the setting of initiation (whether recently hospitalized or in the chronic phase of illness) in patients with HF with mildly reduced or preserved ejection fraction has not been well characterized. SGLT2 inhibitors have been shown to be beneficial and well tolerated when initiated in patients during or shortly following hospitalization for HF.[2,8] However, the proportion of patients with mildly reduced or preserved ejection fraction included in these trials was limited.

In-hospital optimization of guideline-directed medical therapy represents a class I recommendation in the latest US and European guidelines.[9–11] Deferring initiation is associated with increased risk of rehospitalization and mortality early after discharge as well as long-term failure to initiate therapy.[12,13] However, concern for

causing hypotension or worsening renal function may prevent initiation of HF therapy in the peri-hospitalization period. The objectives of this study were to evaluate the effects of dapagliflozin versus placebo on acute and chronic eGFR slope, early blood pressure changes, and on serious renal and hypovolaemic adverse events.

Methods

Study design

The trial design and primary study results have been reported previously.[1] In brief, DELIVER was a double-blind, randomized controlled trial which assessed the effect of dapagliflozin 10 mg once daily versus placebo in patients aged >40 years with symptomatic HF (New York Heart Association class II–IV) and left ventricular ejection fraction >40%. DELIVER included hospitalized patients who were clinically stable (off intravenous HF therapies for ≥24 h prior to randomization) or within 30 days of discharge from HF hospitalization. The study protocol was approved by the ethics committees at each study site and written informed consent was provided by participants.

Statistical analysis

The baseline characteristics of patients with and without recent HF hospitalization have been reported previously.[3] Treatment effects on total (first and recurrent) all-cause hospitalization and cardiac-related hospitalizations were assessed using semiparametric proportional rates methods of Lin *et al.*[14] The treatment effect of dapagliflozin versus placebo on changes in eGFR over time in patients with and without recent HF hospitalization was assessed with repeated measures mixed-effects models using data that were available at baseline, 1, 4, 12, 24, and 36 months. The slope of change in eGFR in each treatment arm was compared from baseline to 1 month (acute slope), month 1 to end of follow up (chronic slope) and from baseline to end of follow-up (total slope). Treatment, time, and the interaction between treatment assignment and time were included as fixed effects. The placebo-corrected change in systolic blood pressure from baseline to 1-month follow-up was assessed using linear regression. Interaction testing was performed to assess for differences in treatment effect on 1-month blood pressure changes in patients with and without recent HF hospitalization.

The frequency of any renal related adverse event and subcategories of renal adverse events (including acute kidney injury, chronic kidney disease, end-stage renal disease, oliguria, pre-renal failure, renal failure, renal impairment, and renal injury) was compared between treatment groups among patients with and without a history of recent HF hospitalization in the safety population.

All analyses were conducted using STATA 17 (Stata Corp., College Station, TX, USA). A *p*-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

In DELIVER, of the total 6263 patients who were randomized, 654 (10.4%) had experienced a recent HF hospitalization (i.e. randomized during or within 30 days of hospitalization). Of these patients, 90 (14%) were randomized during hospitalization, 147 (22%) 1–7 days post-discharge, and 417 (64%) 8–30 days post-randomization. Patients who were recently hospitalized had a lower baseline starting eGFR relative to those without recent HF hospitalization (median [interquartile range] 55 [43, 71] vs. 60 [47, 75] ml/min/1.73 m^2 and mean 58 ± 19 vs. 61 ± 19 ml/min/1.73 m^2; online supplementary *Figure S1*). A significantly higher proportion of patients who were recently hospitalized were on triple HF therapy (beta-blocker, mineralocorticoid receptor antagonist, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor) at baseline (29.9% vs. 23.8%, $p < 0.001$). Patients who were randomized during hospitalization had a higher median N-terminal pro-B-type natriuretic peptide concentration ($p < 0.001$) and higher rates of dyslipidaemia ($p = 0.006$) but were otherwise similar to patients randomized early post-discharge (online supplementary *Table S1*). Event rates of the primary composite outcome were similarly elevated among those randomized during hospitalization and those randomized early after hospital discharge (online supplementary *Table S1*).

Treatment effect on all-cause and cause-specific hospitalizations

As previously reported, dapagliflozin significantly reduced the risk of first HF hospitalization regardless of recent HF hospitalization ($p_{interaction} = 0.90$).[3] In this analysis, dapagliflozin consistently reduced the risk of total all-cause hospitalizations in patients with recent HF hospitalization (rate ratio [RR] 0.77; 95% CI 0.60–1.00) or without recent HF hospitalization (RR 0.92; 95% CI 0.84–1.01; $p_{interaction} = 0.20$). Similarly, dapagliflozin consistently reduced the risk of total cardiac-related hospitalizations in patients with recent HF hospitalization (RR 0.80; 95% CI 0.57–1.13) and without recent HF hospitalization (RR 0.85; 95% CI 0.74–0.97; $p_{interaction} = 0.75$; *Figure 1*).

Estimated glomerular filtration rate over time

Treatment with dapagliflozin resulted in an acute reduction in eGFR, from baseline to 1 month of follow up, of −1.0 (−2.4, +0.4) ml/min/1.73 m^2 in patients with recent HF hospitalization, and of −4.0 (−4.3, −3.6) ml/min/1.73 m^2 in patients without recent HF hospitalization (*Figure 2*). Overall, the acute placebo-corrected declines in eGFR were modest and similar between patients with (−2.0 [−4.1, +0.1] ml/min/1.73 m^2) and without (−3.4 [−3.9, −2.9] ml/min/1.73 m^2) recent HF hospitalization ($p_{interaction} = 0.12$; *Figure 2*). Treatment with dapagliflozin relative to placebo resulted in similar attenuation of eGFR decline from month 1 to 24 months of follow-up in patients with (+0.03 [−0.1, +0.2] ml/min/1.73 m^2) and without (+0.08 [+0.04, +0.12] ml/min/1.73 m^2) recent HF hospitalization ($p_{interaction} = 0.57$; *Figure 2*). The effect of dapagliflozin treatment on total slope from baseline to end of follow-up was also similar in patients with (+0.02 [−0.12, +0.16] ml/min/1.73 m^2) and without (+0.04 [+0.01, +0.07] ml/min/1.73 m^2) recent HF hospitalization ($p_{interaction} = 0.66$).

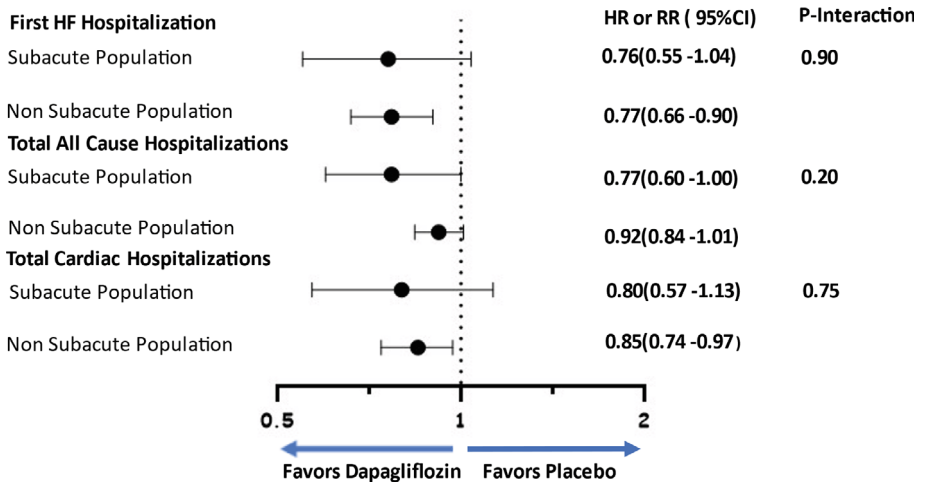
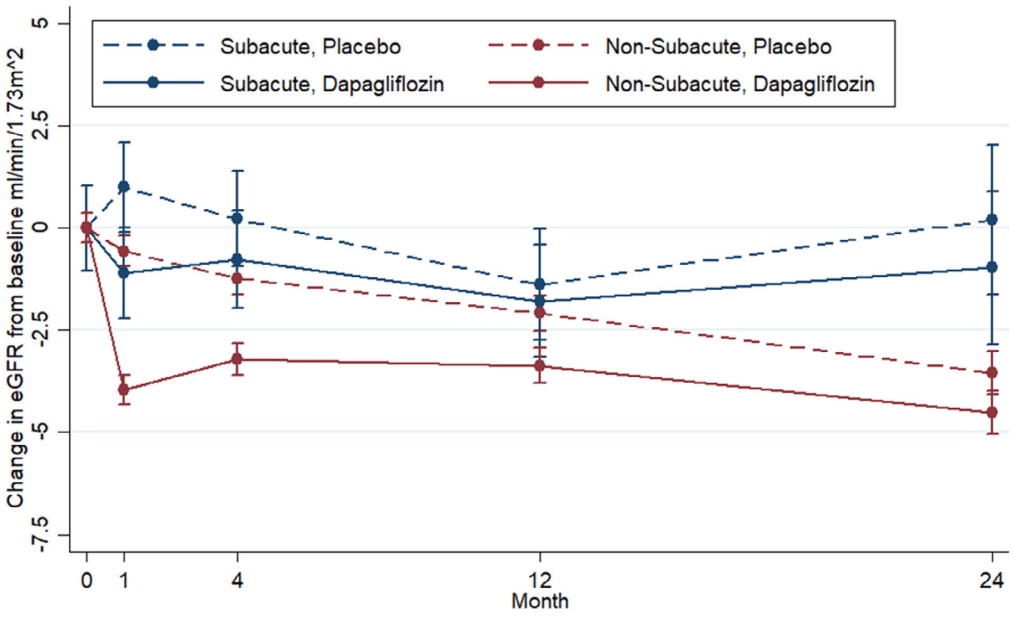


Figure 1 Effects of dapagliflozin on all-cause and cause-specific hospitalizations according to recent heart failure (HF) hospitalization status. CI, confidence interval; HR, hazard ratio; RR, rate ratio.



	Non Subacute Population			Subacute Population			P-Int
	Placebo	Dapagliflozin	Difference	Placebo	Dapagliflozin	Difference	
Acute Slope (1 month)	-0.6 (-0.9,-0.2)	-4.0(-4.3,-3.6)	-3.4(-3.9,-2.9)	+1.0(-0.5,+2.6)	-1.0(-2.4,+0.4)	-2.0(-4.1,+0.1)	0.12
Chronic Slope (>1month)	-0.11(-0.1,0.08)	-0.03(-0.05,0.0)	+0.08(+0.04,+0.12)	+0.01(-0.1,+0.1)	-0.06(-0.04,+0.2)	+0.03(-0.1,+0.2)	0.57
Total Slope	-0.14(-0.15, 0.12)	-0.09(-0.10,-0.07)	+0.04(+0.01,+0.07)	-0.03(-0.11, 0.04)	-0.003(-0.07,+0.08)	+0.02(-0.12,+0.16)	0.66

Figure 2 Change in estimated glomerular filtration rate (eGFR) from baseline over time according to treatment assignment in patients with and without recent heart failure hospitalization.

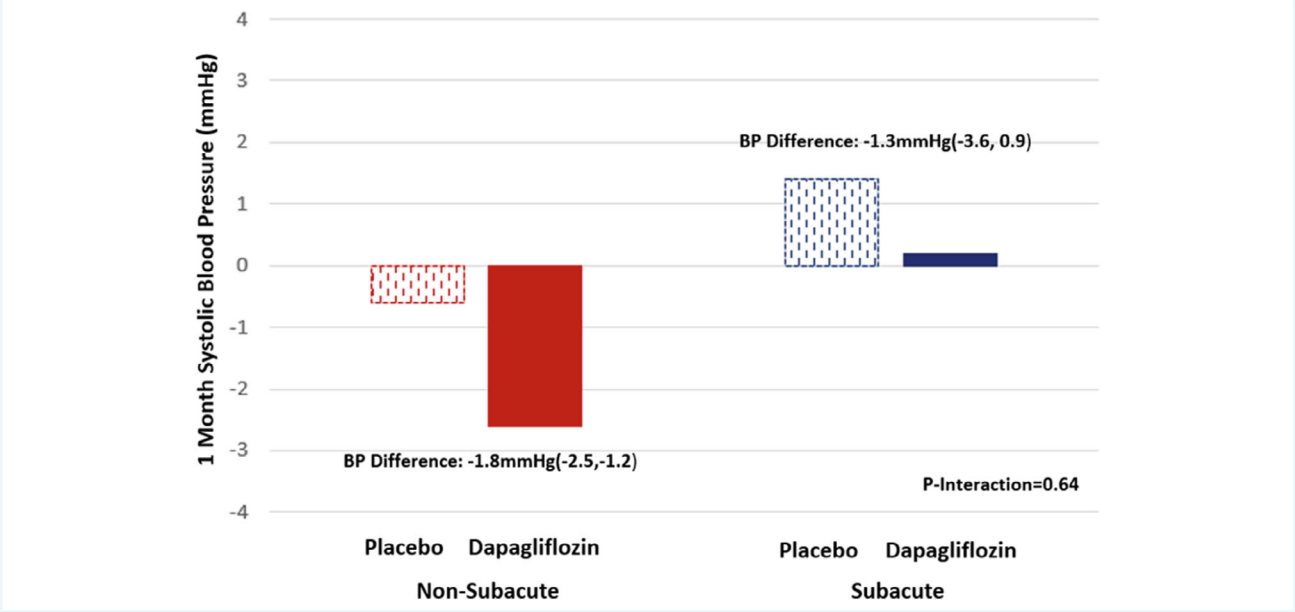


Figure 3 One-month change in systolic blood pressure (BP) according to treatment in patients with and without recent heart failure hospitalization.

Early blood pressure trajectory

In patients with recent HF hospitalization, systolic blood pressure rose at 1 month by 1.4 mmHg in the placebo group versus 0.2 mmHg in the dapagliflozin group (placebo-corrected difference of −1.3 mmHg [−3.6, 0.9]). Among patients without recent HF hospitalization, systolic blood pressure decreased by −0.6 mmHg in the placebo group versus −2.6 mmHg in the dapagliflozin group (placebo-corrected difference of −1.8 mmHg [−2.5, −1.2]; $p_{interaction} = 0.64$; *Figure 3*).

Renal adverse events and subcategories of renal adverse events

The occurrence of any renal adverse event in follow-up was similar between treatment groups among patients with and without recent HF hospitalization ($p_{interaction} = 0.75$; online supplementary *Table S2*). Effects of dapagliflozin versus placebo on the occurrence of subcategories of renal adverse events were also similar among patients with and without recent HF hospitalization (online supplementary *Table S1*).

Discussion

In this *post hoc* analysis of the DELIVER trial, the SGLT2i dapagliflozin consistently reduced all-cause, cardiac-related, and HF-specific hospitalizations and slowed long-term eGFR decline in patients recently hospitalized with HF with mildly reduced or preserved ejection fraction. Early blood pressure reduction, acute eGFR decline, and the occurrence of renal or hypovolaemic adverse events were comparable irrespective of the setting of dapagliflozin initiation (*Graphical Abstract*).

The initial decline in eGFR observed with SGLT2 inhibitors was modest, without increased risk of acute kidney injury, regardless of the setting of initiation and is consistent with other reports in both subacute and chronic HF.[5,6,15] The observation of preserved long-term attenuation in eGFR decline in patients with recent hospitalization is consistent with similar reports in acute HF in patients with reduced ejection fraction.[15] These findings are particularly important given higher baseline rates of chronic kidney disease and risk of worsening renal function in this population.[4] Moreover, patients experiencing HF hospitalization appear to be on an accelerated trajectory of kidney disease progression, which begins well before and continues well after hospitalization.[16] Interrupting the trajectory of renal decline is therefore of specific relevance in patients with recent HF hospitalization.

The SGLT2 inhibitors appear to have minimal effects on blood pressure in HF across the spectrum of ejection fraction.[17,18] Blood pressure perturbations are common in hospitalized patients with HF and limit optimization of medical therapy owing to concerns for haemodynamic and renal complications.[4] The data presented here extend the finding of a minimal blood pressure effect to the high-risk subgroup of patients with recent HF hospitalization.

The following limitations should be acknowledged. This was not a pre-specified analysis of DELIVER and therefore the findings must be considered hypothesis generating. The sample size ($n = 654$) was relatively modest, yet at the present time, represents one of the larger cohorts of SGLT2 inhibition initiation in recently hospitalized patients. A relatively small proportion (90 patients) of the recently hospitalized cohort was randomized during hospitalization limiting conclusions about this group specifically. DAPA-ACT HF-TIMI

68 (NCT04363697) is ongoing and will evaluate the effect to dapagliflozin on clinical outcomes specifically in stabilized patients hospitalized for acute HF.[19] Collection of renal adverse events was limited and not formally adjudicated.

Conclusion

Overall, these data underscore and extend the renal and haemodynamic safety profile of SGLT2 inhibitors among patients with HF with mildly reduced or preserved ejection fraction, including in higher risk settings when initiated during or early after hospitalization. Dapagliflozin reduces all-cause, cardiac-related, and HF-specific hospitalizations and slows long-term decline in kidney function, irrespective of setting of initiation.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

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Conflict of interest: none declared.

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