Effect of SGLT2 Inhibitor Dapagliflozin on Biomarkers of Tubular Injury in Patients with Acute Heart Failure: A Randomized Controlled Trial

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Research Article

Keywords: acute heart failure, acute kidney injury, biomarkers of tubular injury, SGLT2 inhibitor

Posted Date: April 2nd, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3869067/v2

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Additional Declarations: The authors declare no competing interests.
Abstract

Sodium-glucose co-transporter 2 (SGLT2) inhibitors improve cardiovascular outcomes in acute heart failure (AHF) but are associated with a transient rise in serum creatinine. The aim of this study was to assess the effect of SGLT2 inhibitor on urinary biomarkers of tubular injury in patients with AHF. Patients who hospitalized for AHF were randomized to dapagliflozin added to standard of care or control group for 28 days. The primary outcome was the change of urinary [TIMP-2] x [IGFBP7] by NephroCheck® from baseline. Out of the 32 patients who underwent randomization, 25 eligible individuals were enrolled for analysis. Compared with control group, dapagliflozin group significantly reduced urinary [TIMP-2] x [IGFBP7] after 7 days [dapagliflozin: -0.03 ± 0.11 (ng/mL)^2/1000; control: +0.4 ± 0.14 (ng/mL)^2/1000; P = 0.022] and continue this trend until the end of the study. In terms of clinical outcomes, dapagliflozin has demonstrated a trend towards decrease in acute kidney injury (AKI) events compared to the control group (33.3% vs 46.2%; P = 0.513). The changes in serum creatinine, and adverse events showed no differences in either group. In conclusion, initiation of SGLT2 inhibitors in patients with AHF significantly decrease the urinary AKI risk markers TIMP-2 and IGFBP7, that supported protective effect of SGLT2 inhibitor on renal tubular injury.

Trial registration number: The study was registered with the Thai Clinical Trials Registry TCTR20221003002.

INTRODUCTION

Acute kidney injury (AKI) in acute heart failure (AHF) or cardiorenal syndrome type 1 is common and associated with poor prognosis (1-3). Current treatment options for AHF mainly focus on relieving symptoms and reducing fluid overload, which can have potentially harmful effects on kidney function. Consequently, there is a need for the development of novel and inventive therapies aimed at improving both cardiovascular and kidney outcomes in individuals with AHF.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have emerged as a disease-modifying therapy to reduce cardiovascular events and prevent the progression of chronic kidney disease (CKD) (4-14). The rapid growth of clinical trials on SGLT2 inhibitors has expanded the approved clinical indications for these agents. The recent clinical trials (15-18) have shown that SGLT2 inhibitor have reduced the risk of cardiovascular death in the setting of AHF. Additionally, it was observed that the occurrence of AKI within the first 3 months might be less common in the SGLT2 inhibitor group compared to the placebo group in clinically stable patients hospitalized for AHF (18).

Several hypotheses have been postulated to explain the mechanism by which SGLT2 inhibitors prevent AKI, as it cannot be attributed to a reduction in glomerular pressure. A previous animal study showed that SGLT2 inhibitors can improve renal cortical oxygen tension, which might help to improve tubular cell integrity (19). Furthermore, SGLT2 inhibitors have the potential to enhance the expression of hypoxia-inducible factor 1 (HIF1) resulting in an augmentation of erythropoietin production (20).
Despite the growing evidence of benefits, physicians are still hesitant to prescribe SGLT2 inhibitors to AHF patients during their hospitalization primarily due to the transient rise in serum creatinine (21). Nevertheless, there are limitations associated with employing serum creatinine as a diagnostic tool for detecting AKI in the context of AHF due to its delayed response as a marker of tubular injury (22). Moreover, increase serum creatinine level in AKI does not always indicate renal tubular cell injury. As a result, many tubular injury biological markers have been used for the early detection of AKI in this setting. Of these, the use of tissue inhibitor of metalloproteinases-2 [TIMP-2] and insulin-like growth factor-binding protein 7 [IGFBP-7] is one of the most evidence-based (23). Several studies demonstrated that using urinary [TIMP-2] x [IGFBP-7] can accurately predict AKI in patients hospitalized for AHF when using cut-off point more than 0.3 (ng/ml)$^2$/1000 (24).

In this study, we investigated the protective effect of SGLT2 inhibitor on tubular injury biomarkers (urinary [TIMP-2] x [IGFBP-7]) in patients hospitalized for AHF. The primary objective of this study was to compare the change of urinary [TIMP-2] x [IGFBP-7] in SGLT2 inhibitor add on to standard of care with standard of care alone. The incident of AKI, change from baseline serum creatinine, length of stays, cumulative urine output, and adverse events were also assessed.

**MATERIAL AND METHODS**

**Study design**

We conducted a randomized prospective open-label controlled trial of patients hospitalized for AHF in Bhumibol Adulyadej Hospital, Directorate of Medical Services, Royal Thai Air Force. The study protocol was approved by the Institutional Review Board of Bhumibol Adulyadej Hospital with approval number 46/65 and was registered in the Thai Clinical Trials Registry (TCTR) with registration number TCTR20221003002. This study was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki and its later amendments. The investigators informed patients or their surrogates concerning the study orally and written informed consent was given before entry into the study.

Inclusion criteria were aged $\geq$ 18 years, presence of AHF requiring hospital admission as well as serum level of N-terminal pro-brain natriuretic peptide (NT-proBNP) $\geq$ 1600 pg/ml or $\geq$ 2000 pg/ml in patients with atrial fibrillation regardless of ejection fraction or diabetes status. Key exclusion criteria were: patients with type 1 diabetes, history of diabetic ketoacidosis or ketosis, estimated glomerular filtration rate by the CKD Epidemiology Collaboration [eGFR (CKD-EPI)] < 30 ml/min/1.73m$^2$, patients with cardiogenic shock, septic shock or systolic blood pressure < 100 mmHg, patients with intravenous vasopressor, vasodilators or inotropic drugs within 6 hours, planned for percutaneous coronary intervention therapy, acidemia (blood pH < 7.2), and liver failure. In terms of calculating the sample size, the following assumptions were considered: power 0.8, alpha 0.05, and standard deviation of urinary [TIMP-2] x [IGFBP-7] of 0.47 (ng/ml)$^2$/1000. From these assumptions, a total sample size of 22
would enable the detection of a 0.6 (ng/ml)$^2$/1000 difference in the change from baseline of urinary [TIMP-2] x [IGFBP-7] based on Thiele K, et al. (25).

**Primary and secondary outcomes**

The primary outcome of this study is the change from baseline of urinary [TIMP-2] x [IGFBP-7]. Statistical analysis was based on detecting a difference in urinary [TIMP-2] x [IGFBP-7] change from baseline between the dapagliflozin group and controls. The secondary outcome is the incidence of AKI by KDIGO creatinine criteria, the change from baseline creatinine, length of stays, cumulative urine output, and adverse events.

**Trial procedures**

Patients were randomized into 2 groups using a random block of 4 allocation method to receive either dapagliflozin 10 mg on top of standard of care within 24 hours after enrollment (dapagliflozin group) or standard of care alone (control group). Baseline information including demographic data, comorbidities and current medication were recorded. Laboratory investigations were performed at baseline and 1 day, 2 days, 3 days, 7 days, 14 days, and 28 days following treatment initiation as shown in Figure 1. The urine sample was collected then centrifuged and frozen at -80 °C and then urinary [TIMP-2] x [IGFBP-7] was performed by NephroCheck® using the VITROS 5600 Integrated System (Astute Medical, San Diego, CA, USA) at baseline, on day 7, and on day 28. The outcome including length of stay, cumulative urine output, adverse events including the gastrointestinal system, urinary tract infection, electrolyte imbalance, discontinuation of treatment and date of death were collected. All patients received treatment in accordance with the ESC guidelines for the diagnosis and treatment of acute heart failure (26).

**Relevant Definition**

Kidney disease improving global outcome (KDIGO) serum creatinine criteria were used to classify AKI status (27). The baseline serum creatinine was the first creatinine recorded on the day of enrolment. AHF refers to heart failure that occurs suddenly or a stable condition that then becomes worse within a short period of time, according to the criteria of the European Society of Cardiology guidelines (ESC) (26).

**Statistical Analysis**

The study used IBM SPSS Statistics Version 22 (Chicago, IL, USA) program for data analysis and data processing. The categorical data were reported as the number with a percentage. The continuous data were reported as mean ± standard deviation (SD), mean ± standard error (SE), or median (interquartile range, IQR) as appropriate. Fisher's exact test or Chi-square test were used for categorical variable and student's *t*-test or Mann Whitney U test for continuous variable. We used a P value < 0.05 as statistically significant.
RESULTS

Baseline characteristics

The enrollment period took place from August 2022 to January 2023. Out of the initial 32 patients who underwent randomization, seven were subsequently excluded from the study due to incomplete biochemical data in the first week, comprising 5 cases discharged and 2 case died. Consequently, 25 eligible patients were enrolled for analysis (12 dapagliflozin, 13 control). The mean age was 67.1 ± 15.1 years, 48.5% were male, the mean ejection fraction was 42.1 ± 16.5% and the median NT-proBNP was 5,359 pg/ml (interquartile range 3,496 – 10,843). Other underlying diseases and medications at baseline were balanced between treatment groups as shown in Table 1.

Effect of dapagliflozin on tubular injury markers

The mean ± standard error (SE) of urinary [TIMP-2] x [IGFBP-7] in the dapagliflozin and control group were 0.223 ± 0.165 vs 0.073 ± 0.048 (P = 0.340) at the enrollment. Compared with control group, dapagliflozin group significantly reduced urinary [TIMP-2] x [IGFBP7] after 7 days [dapagliflozin: -0.03 ± 0.11 (ng/mL)^2/1000; control: +0.4 ± 0.14 (ng/mL)^2/1000; P = 0.022]. After a 28-day follow-up period, 7 patients (3 in the dapagliflozin, 4 in the control group) were discharged home and 2 patients died (1 from each group), leaving a total of 16 patients with complete data available. The mean change in urinary [TIMP-2] x [IGFBP-7] in dapagliflozin group tended to be decreased compared to controls. [dapagliflozin: -0.09 ± 0.28 (ng/mL)^2/1000; control: +0.67 ± 0.32 (ng/mL)^2/1000; P = 0.096] (Figure 2). Furthermore, we conducted additional analysis using a threshold of 0.3 (ng/ml)^2/1000, a value that showed a strong association with AKI. We observed a trend where the number of patients with urinary [TIMP-2] x [IGFBP-7] levels exceeding 0.3 was slightly lower in the dapagliflozin group, although this difference did not reach statistically significance (25.0% vs 53.8%, P = 0.288). (Table 2)

Effect of dapagliflozin on secondary outcomes

Incidence of AKI by serum creatinine from KDIGO criteria in the dapagliflozin and control group was 33.3% and 46.2%, respectively (P = 0.513). All cases of AKI were KDIGO stage 1 (Table 2). Further analyses showed no difference between the dapagliflozin and control group for the change from baseline serum creatinine, length of stay, and adverse events. (Table 2 and Figure 3). The cumulative urine output during the first 3 days was not statistically different between both groups (8,587 ± 1,346 vs 8,060 ± 1,090 ml; P=0.420). (Figure 4). However, dapagliflozin group demonstrated a trend towards lower cumulative furosemide dose compared with control group. [61.94 ± 10.37 vs 104.62 ± 21.92 mg/day; P=0.100].

DISCUSSION

This study demonstrated that initiation of dapagliflozin significantly decrease urine [TIMP-2] x [IGFBP7] during the first week, that supported the protective effect of SGLT2 inhibitor on renal tubular injury. The results are consistent with study from Thiele K, et al. that showed the reduction of urine [TIMP-2] x
[IGFBP7] after initiation of empagliflozin in AHF patients for 3 days (25). Thus, we may conclude that SGLT2 inhibitor can improve tubular cell injury in patients hospitalized for acute heart failure since urinary [TIMP-2] x [IGFBP-7] is the biomarker of cell cycle arrest during the early phase of tubular damage.

The proximal tubule accounts for the highest oxygen consumption in the kidney because the substantial energy demand associated with the reabsorption of electrolytes and organic solutes within this tubular segment. Moreover, tubular hypoxia is a crucial factor in the pathophysiology of acute tubular necrosis (28). It disrupts normal kidney function, triggers cellular damage and inflammation, and ultimately leads to AKI. Administration of SGLT2 inhibitors could abolish this effect. A previous studies demonstrated that SGLT2 inhibition in type 2 diabetes patients improved renal cortical oxygen tension, potentially benefitting the tubular cell integrity (29). These results were collaborated by meta-analysis, which found that SGLT-2 inhibitor was associated with a reduced risk of AKI in various settings (30,31).

This study also demonstrated that SGLT2 inhibitor is safe for early administration in patients hospitalized for AHF. Although dapagliflozin initiation in AHF initially leads to a transient increase in serum creatinine, but this effect stabilizes overtime. Furthermore, dapagliflozin has demonstrated the capacity to improve renal function within the first few weeks in most patients. These findings align with sub-study of EMPA-RESPONSE-AHF (21) and EMPULSE study (18). Furthermore, analysis from EMPULSE study showing that patients who received SGLT2 inhibitor (7.7%) had less AKI than the placebo group (12.1%) during the total study period of 3 months, although there was no statistical analysis for this outcome in EMPULSE (18).

In terms of secondary outcomes, both groups did not show a statistically significant in cumulative urine output, but dapagliflozin group demonstrated a tendency for reduced cumulative furosemide dose. The length of stay and adverse events such as urinary tract infection, hepatitis and electrolyte imbalance were not different in both groups. Taking all the data together, we can conclude that SGLT2 inhibitors are safe for early administration in hospitalized patients with AHF.

This study also had certain limitations that should be considered. Firstly, it involved a small sample size, and some patients who had enrolled were lost to follow-up after discharge from the hospital. Thus, the power of this study must be a point of concern. Secondly, the lack of blinding among participants in this study could potentially impact the integrity of the trial protocol. Finally, our study did not possess sufficient power to detect a statistically significant difference in AKI events between the two treatment groups. Therefore, A larger prospective study should be conducted to investigate the potential benefits of this on clinical outcomes.

**CONCLUSION**

Initiation of SGLT2 inhibitors in patients with AHF significantly decrease the urinary AKI risk markers TIMP-2 and IGFBP7, that supported protective effect of SGLT2 inhibitor on renal tubular injury.
References


Declarations

ACKNOWLEDGEMENT

The authors would like to thank all the nurses, the cardiology team, medical and emergency physician residents, medical staffs and laboratory staffs in Bhumibol Adulyadej Hospital, Directorate of Medical Services, Royal Thai Air Force and Ms. Sasipha Tachaboon, laboratory staff in Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital.

AUTHOR CONTRIBUTIONS

P.G. and J.W. have contributed equally to this work. P.G. conceived the study and was in charge of overall direction and planning. All authors contributed to the trial design and protocol. J.W. was the principal investigators. P.G. analyzed the data. All authors contributed to the interpretation of the results. P.G. and J.W. prepared the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version for submission.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author (P.G.).

FUNDING

This study was supported by a grant from the kidney foundation of Thailand and Bhumibol Adulyadej Hospital Research Center.

COMPETING INTERESTS

All authors declare that there are no competing financial or other conflicts of interest in relation to this study.
### Tables

**Table 1.** Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Dapagliflozin (n = 12)</th>
<th>Control (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>67.0 ± 17.4</td>
<td>67.2 ± 13.4</td>
<td>0.970</td>
</tr>
<tr>
<td>Male (%)</td>
<td>7(58.3)</td>
<td>7(53.8)</td>
<td>0.821</td>
</tr>
<tr>
<td>Cr, mg/dl, mean ± SD</td>
<td>1.18 ± 0.32</td>
<td>1.16 ± 0.42</td>
<td>0.886</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m², mean ± SD</td>
<td>61.3 ± 20.7</td>
<td>64.9 ± 24.4</td>
<td>0.698</td>
</tr>
<tr>
<td>EF, %, mean ± SD</td>
<td>42.4 ± 17.0</td>
<td>41.8 ± 16.7</td>
<td>0.924</td>
</tr>
<tr>
<td>Type of AHF (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New onset</td>
<td>5(41.7)</td>
<td>9(69.2)</td>
<td>0.238</td>
</tr>
<tr>
<td>ADHF</td>
<td>7(58.3)</td>
<td>4(30.8)</td>
<td>0.238</td>
</tr>
<tr>
<td>NT-proBNP, pg/ml (IQR)</td>
<td>8,048.5 (3,471, 15,760)</td>
<td>4,802 (3,537, 9,273)</td>
<td>0.550</td>
</tr>
<tr>
<td>Acute respiratory Failure (%)</td>
<td>0(0)</td>
<td>2(15.4)</td>
<td>0.497</td>
</tr>
</tbody>
</table>

**Co-morbidities**

| Type 2 Diabetes (%)                          | 5(41.7)                | 4(30.8)          | 0.888   |
| Hypertension (%)                             | 9(75.0)                | 8(61.5)          | 0.471   |
| Dyslipidemia (%)                             | 6(50.0)                | 7(53.8)          | 0.848   |
| History of Heart Failure (%)                 | 3(25.0)                | 3(23.1)          | 1.000   |
| History of IHD (%)                           | 5(41.7)                | 4(30.8)          | 0.881   |
| History of CVA (%)                           | 1(8.3)                 | 1(7.7)           | 1.000   |
| Atrial Fibrillation (%)                      | 1(8.3)                 | 2(15.4)          | 1.000   |
| Valvular Heart Disease (%)                   | 3(18.8)                | 2(15.4)          | 0.920   |
| Chronic kidney Disease (%)                   | 5(41.8)                | 7(53.8)          | 0.858   |

**Medications**

| ACEIs or ARBs or ARNi (%)                    | 3(25.0)                | 7(53.8)          | 0.288   |
| Calcium channel blocker (%)                  | 2(16.7)                | 5(38.5)          | 0.443   |
| Beta blocker (%)                             | 6(50.0)                | 5(38.5)          | 0.561   |
| Furosemide (%)                               | 4(33.3)                | 4(30.8)          | 1.000   |
| Thiazide (%)                                 | 0(0)                   | 1(7.7)           | 1.000   |
| MRA (%)                                      | 2(16.7)                | 2(15.4)          | 1.000   |
| Statin (%)                                   | 5(41.7)                | 5(38.5)          | 0.870   |
ADHF, acute decompensated heart failure; AHF, acute heart failure; ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ARNi, angiotensin receptor – neprilysin inhibitor; Cr, serum creatinine; CVA, cerebrovascular disease; eGFR, estimated glomerular filtration rate; EF, ejection fraction; IHD, ischemic heart disease; NT-proBNP, Serum N-terminal pro B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist.

Table 2: Secondary outcomes and adverse events

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Dapagliflozin (n = 12)</th>
<th>Control (n = 13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI by creatinine criteria (%)</td>
<td>4(33.3)</td>
<td>6(46.2)</td>
<td>0.513</td>
</tr>
<tr>
<td>AKI stage I</td>
<td>4(33.3)</td>
<td>6(46.2)</td>
<td>0.513</td>
</tr>
<tr>
<td>AKI stage II</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>AKI stage III</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Predicted AKI by urinary [TIMP-2] x [IGFBP-7] criteria* (%)</td>
<td>3(25)</td>
<td>7(53.8)</td>
<td>0.288</td>
</tr>
<tr>
<td>Mean Urine Output (first 3 days), ml, mean ± SE</td>
<td>2,237.0 ± 876.1</td>
<td>1,855.9 ± 473.5</td>
<td>0.184</td>
</tr>
<tr>
<td>Length of stay, days, median (IQR)</td>
<td>4(3-4)</td>
<td>5(3-11)</td>
<td>0.141</td>
</tr>
<tr>
<td>28-day mortality (%)</td>
<td>1(8.3)</td>
<td>1(7.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Revisit in 28-day (%)</td>
<td>1(8.3)</td>
<td>1(7.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Adverse Events (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>1(8.3)</td>
<td>2(15.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8(66.7)</td>
<td>8(53.8)</td>
<td>0.839</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>6(50.0)</td>
<td>4(30.8)</td>
<td>0.622</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1(7.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2(16.7)</td>
<td>2(15.4)</td>
<td>0.656</td>
</tr>
</tbody>
</table>

*Predicted AKI by urinary [TIMP-2] x [IGFBP-7] criteria using a threshold of 0.3 (ng/ml)^2 / 100

Figures
Figure 1

Protocol and timeline of the study

Figure 2

Urinary [TIMP-2] x [IGFBP7] (ng/mL)²/1000

P = 0.022

P = 0.096
Effects of dapagliflozin on urinary [TIMP-2] x [IGFBP-7] in patients with acute heart failure treated with dapagliflozin (n = 12, orange line) or control (n = 13, blue line). Data are shown as mean urinary [TIMP-2] x [IGFBP-7] at baseline, after 7, and 28 days. p-value compared changes from baseline between both groups.

Figure 3

Effects of dapagliflozin on serum creatinine in patients with acute heart failure treated with dapagliflozin (n = 12, orange line) or control (n = 13, blue line). Data are shown as mean serum creatinine at baseline, after 1, 2, 3, 7, 14, and 28 days. p-value compared changes from baseline between both groups.
Figure 4

The mean of cumulative urine output during the first 3 days in patients with acute heart failure treated with dapagliflozin (n = 12, orange line) or control (n = 13, blue line). p-value compared the cumulative urine output at day 3.

P = 0.420