Impact of glucagon like peptide-1 receptor agonist and sodium glucose cotransporter 2 inhibitors on type 2 diabetes patients with renal impairment

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Abstract
Introduction: Diabetes mellitus is a progressive disease with cardiovascular complications. We evaluated the impact of a glucagon like peptide-1 (GLP-1) receptor agonist and sodium glucose cotransporter 2 (SGLT-2) inhibitors dapagliflozin and empagliflozin on renal and cardiac function in type 2 diabetes patients with renal impairment.

Materials and methods: A total of 156 patients referred with suboptimal glycemic control were assigned to Group G (GLP-1): n = 72 or Group S (SGLT-2 inhibitor)—dapagliflozin (n = 52) or empagliflozin (n = 32). Renal function was assessed every 3 months for 36 months. Cardiovascular parameters were evaluated every 12 months for 36 months.

Results: Compared with baseline, HbA1c and systolic blood pressure significantly decreased in both groups (p < 0.05). The estimated glomerular filtration rate decreased, but without significance. Albuminuria decreased significantly in both groups and then subsequently increased after 30 months in Group S. Diastolic cardiac function, assessed by E/e′ or left atrial volume index, decreased only in Group G at 36 months.

Conclusions: The GLP-1 receptor agonist and SGLT-2 inhibitors were effective for glycemic and blood pressure control and for maintaining renal function. The GLP-1 receptor agonist improved diastolic function at 36 months.

Keywords
GLP-1 receptor agonist, SGLT-2 inhibitor, eGFR, albuminuria, cardiac diastolic function

Introduction
DM is a progressive multifactorial disease associated with cardiovascular complications. There are many risk factors of atherosclerosis in DM patients including hyperglycemia, insulin resistance, hypertension, dyslipidemia, obesity, impaired renal function, and albuminuria. Among these, the two most important factors are insulin resistance and hyperglycemia. In recent times, GLP-1RA and SGLT-2 inhibitors have been thought to be beneficial for hypoglycemic or hyperglycemic episodes. Furthermore, both agents have the effects of reducing body weight improved insulin resistance, and may have beneficial effects for atherosclerosis. Aside from improvement of glycemic and blood pressure control, GLP-1RA or SGLT-2 inhibitor therapy has been reported to preserve renal function and reduce the risk of cardiovascular events. In addition, the reduction of interstitial volume induced by SGLT-2 inhibitors could be particularly beneficial with respect to heart failure outcome. Nevertheless, in most studies, the dose of these agents used was larger than the dosage that pertains in Japan. Further, Lorenzi et al. reported that liraglutide was superior to SGLT-2 inhibitors with regard to glycemic control or body weight, and Kalliopi et al. state that SGLT-2 inhibitors and GLP-1RA have similar effects on cardiovascular events. Therefore, in the present study, we investigated the efficacy of a GLP-1RA and SGLT-2 inhibitors on cardiac and renal function in type 2 diabetes patients with renal impairment, specifically focusing on cardiac diastolic function using...
Japanese standard doses. Further, we compared the data with other studies.

**Materials and methods**

This prospective cohort study enrolled 188 type 2 diabetes patients with renal impairment (eGFR $\geq$30 ml/min/1.73 m² and $<40$ ml/min/1.73 m², albuminuria $<1000$ mg/gCr). Glycemic control of all patients was not optimal, such that several episodes of hypoglycemia and hyperglycemia occurred, requiring antidiabetic agents to be switched or added to GLP-1RA (Group G) or SGLT-2 inhibitors (Group S) regimen. The reasons for treatment discontinuation were as follows: (Table 1)

- Uncontrolled glycemia (hyperglycemia)—22 (30.6%) in Group G, 30 (35.7%) in Group S
- Polypharmacy (poor medical adherence)—20 (27.8%) in Group G, 30 (35.7%) in Group S
- Overcontrolled glycemia (hypoglycemia)—30 (41.6%) in Group G, 24 (28.6%) in Group S

The patients were divided into two groups according to baseline the antidiabetic agent: Group G ($n=88$; 0.9 mg/day of liraglutide); Group S ($n=100$): 5 mg/day of dapagliflozin ($n=63$) and 10 mg/day of empagliflozin ($n=37$). Demographic and clinical variables were collected for all patients. Blood glucose, glycosylated hemoglobin (HbA1c), serum creatinine, uric acid, β₂-microglobulin, HDL- and LDL-cholesterol, and albuminuria were analyzed at baseline and every 3 months for 36 months at outpatient visit. Blood pressure and body weight were also checked. The eGFR values were calculated according to the Japanese Society of Nephrology guidelines. Albuminuria was indicated by the ratio of urinary albumin (mg/dL) to urinary creatinine (g/dL). Echocardiography, ankle brachial pressure index (ABI), and cardio-ankle vascular index (CAVI) were examined every 12 months for 36 months. As for echocardiography, 2-dimensional echocardiography was performed at

| Table 1. Patient characteristics at baseline. |
|-----------------------------------------------|
|                                  | Group G | Group S | $p$ value |
|-----------------------------------------------|
| $N$                                      | 72      | 84      | 0.881     |
| Age (year)                               | 66.1 ± 8.2 | 65.3 ± 11.4 | 0.959     |
| Male/Female (n)                          | 36/26   | 45/29   | 0.652     |
| DM vintage (year)                        | 11.8 ± 8.8 | 11.2 ± 4.7  | 0.718     |
| BW (kg)                                  | 65.6 [58.7, 84.7] | 66.3 [57.5, 77.9] | 0.235     |

| Medication for glycemic control (%)        | Pre/Post | Pre/Post |
|-----------------------------------------------|---------|---------|
| Insulin                                    | 48.6    | 23.6    | 52.4    | 22.6    | 0.188/0.375 |
| SU                                         | 44.4    | 0.0     | 36.9    | 0.0     | 0.330/0.999 |
| Glinide                                    | 30.6    | 0.0     | 29.8    | 0.0     | 0.914/0.999 |
| αGI                                        | 12.5    | 0.0     | 15.5    | 0.0     | 0.594/0.999 |
| DPP-inhibitor                              | 36.1    | 0.0     | 32.1    | 0.0     | 0.602/0.999 |
| GLP-1 RA                                   | 0.0     | 100.0   | 4.8     | 0.0     | 0.001/0.001 |
| SGLT-2 inhibitor                           | 4.2     | 0.0     | 0.0     | 100.0   | 0.858/0.001 |
| BG                                         | 8.3     | 8.3     | 10.7    | 8.3     | 0.615/0.999 |
| Oral anti-diabetic agents (n)              | 3.7 ± 2.7 | 3.6 ± 2.6 | 0.447 |
| Reason for treatment discontinuation (%)   |         |         |         | 0.115   |
| Uncontrolled glycemia (hyperglycemia)      | 22 (30.6) | 30 (35.7) | 0.44 |
| Polypharmacy (poor medical adherence)      | 20 (27.8) | 30 (35.7) | 0.858 |
| Over controlled glycemia (hypoglycemia)    | 30 (41.6) | 24 (28.6) | 0.44 |

| Medication for underline disease (%)       |         |         |         |
|---------------------------------------------|---------|---------|---------|
| ARB                                        | 77.8    | 78.6    | 0.940   |
| CCB                                        | 66.7    | 64.3    | 0.886   |
| β blocker                                  | 13.9    | 15.5    | 0.958   |
| Statin                                     | 52.8    | 58.3    | 0.486   |
| Diuretics                                  | 31.9    | 35.7    | 0.620   |
| Total oral tablets (n)                     | 11.8 ± 4.0 | 10.9 ± 4.3 | 0.178 |

Data are expressed as mean ± standard deviation, or median and IQR. SU: sulfonyl urea; αGI: alpha glucosidase inhibitor; BG: biguanide; ARB: angiotensin II receptor inhibitor; CCB: calcium channel blocker.
baseline and every year for 3 years using a standard imaging transducer (Vivid7; GE, Fairfield, Connecticut, USA) with a linear probe frequency of 5 MHz. The data was examined and checked afterwards by five or six echo cardiologists. ABI and CAVI were evaluated using a Form Exceed (Omron Colin Co., Tokyo, Japan). The average data of ABI and CAVI for both sides were also evaluated in this study. Patients who did not comply with this protocol because of transfer to another clinic, discontinuation of anti-diabetic agents, or modification of anti-diabetic regimen were withdrawn from the study protocol.

Study endpoints

Primary endpoints included the rate of new onset renal replacement therapy and new onset cardiovascular events including myocardial infarction, stroke, and admission due to heart failure. Secondary endpoints included a ≥30% decline in eGFR or ≥30% increase in albuminuria, left ventricular mass index (LVMI), and ratio of early diastolic transmural flow velocity to peak early diastolic mitral annular velocity (E/e’).

Statistical analysis

For variables with normal distribution, data are presented as mean ± SD, while data for asymmetrically distributed valuables are expressed as median and IQR. A p value <0.05 was considered significant. Data were compared using unpaired t-tests (if the variables showed a normal distribution) or Mann–Whitney tests (if distribution asymmetrical). Frequencies of cardiovascular events, ≥30% GFR decline, ACR, LVMI, LA VI, E/e’, and CAVI increase were analyzed using the χ² test. Using linear regression analysis, we evaluated the relation between glycemic control and cardiovascular events. All statistical analyses were performed using SPSS version 23 for Windows (SPSS, Inc., Chicago, IL, USA).

Ethics

All patients provided written informed consent prior to participation. The study protocol was approved by the ethics committees at Konan-Kosei Hospital and was conducted in adherence to the ethical principles of the Declaration of Helsinki and the Japanese Ministry of Health, Labor and Welfare. The reporting of the study is in accordance with the STROBE statement, along with references to the STROBE statement, and the broader EQUATOR guidelines.

Results

During this study, 32 patients did not comply with the protocol. Nine (three in Group G, six in Group S) were transferred to another clinic, 10 (eight in Group G, two in Group S) withdrew because of economic problems, and 13 (five in Group G, eight in Group S) added other anti-diabetic agent(s). Therefore, the data of 156 type 2 diabetes patients were analyzed: Group G (n = 72), liraglutide 0.9 mg/day and Group S (n = 84) comprising dapagliflozin 5 mg/day (n = 52) and empagliflozin 10 mg/day (n = 32).

At baseline, mean age was 66.1 ± 8.2 versus 65.3 ± 11.4 years for Group G and Group S, respectively (p = 0.959). DM duration was 11.8 ± 8.8 versus 11.2 ± 4.7 years (p = 0.718), total oral pill count was 11.8 ± 4.0 versus 10.9 ± 4.3 tablets (p = 0.178), and total oral antidiabetic count was 3.7 ± 2.7 versus 3.6 ± 2.6 tablets (p = 0.447) for Group G and Group S, respectively. There were no differences in the characteristics between the two groups (Table 1).

Compared with baseline, HbA1c and systolic blood pressure significantly decreased in both groups (p < 0.05 after 6–21 months). Albuminuria was significantly decreased after the initiation of both Group G and Group S (p < 0.05 at 6–21 months and p < 0.01 at 24–36 month in both groups), but there was a non-significant decrease in eGFR in both groups (Table 2, Figure 1). No severe hypoglycemic episode (blood glucose <50 mg/dL or unconsciousness) occurred. Average mild hypoglycemic episode rate (blood glucose <70 mg/dL and ≥50 mg/dL) occurred 0.083 times/year/person in Group G and 0.060 times/year/person in Group S (p = 0.791). Moreover, all patients with hypoglycemic episodes had insulin treatment.

As shown in Table 3, there were no patients with new renal replacement therapy in either group. Cerebrovascular infarction and peripheral artery disease (PAD) were more frequent in Group G than in Group S (p = 0.015, 6.9% and 19.0% had a ≥30% increase in LAVI (p = 0.027), 5.6% and 15.5% had a ≥30% increase in E/e’ (p = 0.047). However, the other parameters were not significant, with a ≥30% increase in albuminuria occurring in 9.7% in Group G and 6.0% in Group S (p = 0.378), respectively, and a ≥30% increase in LVMI occurring in 16.7% in Group G and 26.2% in Group S (p = 0.151), respectively (Table 3).

Cardiac systolic function indicated by ejection fraction and diastolic function indicated by E/e’ or left atrial dimension were stable or improved only in Group G. Moreover, arterial stiffness assessed by CAVI remained stable in Group G (Figure 2).

Discussion

In the present study, we evaluated the effect of a GLP-1RA and SGLT-2 inhibitors on renal and cardiac function. Our
Table 2. Change in clinical parameters.

|                          | Baseline | 12 months | 24 months | 36 months |
|--------------------------|----------|-----------|-----------|-----------|
| HbA1c (%)                | Group G  | 7.14 ± 1.28 | 6.67 ± 0.99* | 6.61 ± 0.82* | 6.51 ± 0.74* |
|                          | Group S  | 7.33 ± 0.73 | 7.08 ± 0.71* | 7.03 ± 0.93† | 7.05 ± 1.02† |
| BMI (kg/m²)              | Group G  | 26.8 ± 5.6** | 25.3 ± 4.7** | 25.1 ± 4.7** | 25.1 ± 4.7** |
|                          | Group S  | 26.3 ± 3.7  | 25.4 ± 3.6** | 25.2 ± 3.8** | 25.3 ± 4.0** |
| Hb (g/dL)                | Group G  | 12.7 ± 1.6  | 12.5 ± 1.8  | 12.5 ± 1.5  | 12.4 ± 1.6  |
|                          | Group S  | 13.1 ± 1.0  | 13.6 ± 1.2**† | 13.8 ± 1.3**† | 13.7 ± 1.2**† |
| Uric acid (mg/dL)        | Group G  | 6.2 ± 1.7   | 6.0 ± 1.5   | 6.1 ± 1.6   | 5.7 ± 1.5   |
|                          | Group S  | 6.0 ± 1.6   | 5.3 ± 1.6**† | 5.2 ± 1.5**† | 5.2 ± 1.4**† |
| HDL-C (mg/dL)            | Group G  | 44.9 ± 13.5  | 49.7 ± 16.0** | 49.1 ± 15.4** | 50.5 ± 13.8** |
|                          | Group S  | 44.8 ± 13.4  | 49.2 ± 15.6** | 49.6 ± 15.6** | 50.2 ± 14.2** |
| LDL-C (mg/dL)            | Group G  | 105.5 ± 28.7 | 98.5 ± 30.1** | 95.1 ± 23.9* | 96.2 ± 24.7* |
|                          | Group S  | 103.1 ± 32.8 | 100.0 ± 30.6 | 103.2 ± 34.0 | 105.0 ± 27.0 |
| CRP (mg/dL)              | Group G  | 0.16 ± 0.11  | 0.07 ± 0.07** | 0.05 ± 0.05** | 0.05 ± 0.05** |
|                          | Group S  | 0.14 ± 0.14  | 0.09 ± 0.09** | 0.08 ± 0.09** | 0.07 ± 0.10** |
| eGFR (mL/min/1.73 m²)    | Group G  | 47.2 ± 10.0  | 45.7 ± 8.8   | 44.8 ± 9.2   | 44.2 ± 9.8   |
|                          | Group S  | 47.8 ± 9.5   | 46.0 ± 11.1  | 45.8 ± 10.9  | 44.9 ± 11.9  |
| ACR (mg/gCr)             | Group G  | 284.7 ± 246.5 | 166.5 ± 155.7** | 151.8 ± 115.8** | 147.9 ± 113.8** |
|                          | Group S  | 263.8 ± 215.2 | 179.1 ± 207.2** | 201.5 ± 198.1* | 199.4 ± 159.2† |
| β2 MG (mg/L)             | Group G  | 4.43 ± 2.53  | 4.10 ± 2.29** | 4.16 ± 2.30** | 4.23 ± 2.31** |
|                          | Group S  | 2.56 ± 3.56† | 2.62 ± 1.32† | 2.73 ± 1.48† | 2.82 ± 1.60† |
| BNP (pg/mL)              | Group G  | 58.5 ± 37.0  | 35.0 ± 30.4** | 34.1 ± 23.8** | 28.5 ± 23.1** |
|                          | Group S  | 58.8 ± 86.6  | 32.2 ± 39.6** | 32.1 ± 39.7** | 31.7 ± 36.7** |
| Systolic blood pressure (mmHg) | Group G  | 140.9 ± 14.0 | 132.0 ± 16.2* | 130.3 ± 15.4** | 130.3 ± 11.0** |
|                          | Group S  | 136.2 ± 15.9 | 127.3 ± 114.1* | 128.2 ± 13.0** | 130.7 ± 10.7** |
| Diastolic blood pressure (mmHg) | Group G  | 87.1 ± 7.0   | 79.0 ± 8.5* | 80.5 ± 12.7* | 76.2 ± 6.1** |
|                          | Group S  | 73.0 ± 11.4† | 71.5 ± 10.3**† | 73.7 ± 8.1† | 76.2 ± 10.7 |

Data are expressed as mean ± standard deviation. BMI: body mass index; Hb: hemoglobin; CRP: C-reactive protein; β2MG: β2 microglobulin; BNP: brain natriuretic peptide.

*p < 0.05, **p < 0.01 versus at baseline, †p < 0.05 versus Group G.

Data revealed no difference between the groups in regards the impact on renal function including eGFRs and albuminuria. These data were consistent with other studies although our study was conducted using Japanese standard doses.

Albuminuria was improved in patients with microalbuminuria, and eGFR was sustained in both groups. Moreover, although there was no difference in systolic function, GLP-1RA prevented left ventricular or atrial hypertrophy and dilated dysfunction over the 3 years. SGLT-2 inhibitors also prevented left ventricular hypertrophy and dilated dysfunction, but dilated dysfunction returned at 3 years. In addition, GLP-1RA may have beneficial effects for cerebral infarction or PAD, and SGLT-2 inhibitors for heart failure. Our data were similar to that of other study.9 Hypoglycemic episodes may increase the risk of cardiovascular events. Nevertheless, there were no differences in the frequencies of hypoglycemic episodes in this study; therefore, hypoglycemia might not have influenced differences in those events between groups. There were also differences in HbA1c values 24 months after the initiation of new antidiabetic agents. Nevertheless, linear regression analysis revealed that these differences had little influence on cardiovascular outcomes. This is because both hyperglycemic and hypoglycemic attacks and many other factors may affect these outcomes.

Cardiac inflammation is reported to be one of the mechanisms leading to diabetic cardiomyopathy in diabetic patients.9 Further, oxidative stress plays an important role in the pathogenesis of cardiac hypertrophy and remodeling.10,11 Risks of atherosclerosis beyond glucose control include blood pressure, weight, visceral adiposity, hyperinsulinemia, arterial stiffness, albuminuria, uric acid, and oxidative stress.12 Liraglutide or SGLT-2 inhibitors are reported to induce natriuresis, diuresis and decreased blood glucose and blood pressure; therefore, they promote the maintenance of renal function.13-16 Throughout the study period, antihypertensive drugs were not changed in any participant. Both SGLT-2 inhibitors and liraglutide reduced systolic blood pressure similarly, and patients in both groups had reduced body weight. Moreover, anti-oxidative action ameliorates vascular constriction. These actions may reduce blood pressure. Reduced blood pressure improves glomerular filtration pressure and, therefore, reduces albuminuria. Moreover, hyperglycemia can increase glomerular filtration rate. Therefore, reducing hyperglycemia might also reduce albuminuria.
In this study, natriuresis was not evaluated. However, in another study that we conducted among in-patients with renal impairment (eGFR < 60 and $\geq 30\text{ mL/min/1.73 m}^2$), 32 patients with GLP-1RA and 33 patients with SGLT-2 inhibitor receiving the same diet (not published) showed 168.6 $\pm$ 58.7 at baseline, 200.1 $\pm$ 54.1 on day 1 after 0.9 mg/day ($p = 0.0267$ vs baseline), and 201.7 $\pm$ 62.2 mEq/day on day 7 after 0.9 mg/day use ($p = 0.0297$ vs baseline) of natriuresis in GLP-1RA group. Otherwise, with respect to SGLT-2, 187.7 $\pm$ 46.3 at baseline, 212.6 $\pm$ 42.5 on day 1 after SGLT-2 inhibitor use ($p = 0.0243$ vs baseline), and 190.4 $\pm$ 49.6 mEq/day on day 7 after SGLT-2 inhibitor use ($p = 0.0518$ vs baseline) of natriuresis were found. Moreover, in the early phase, SGLT-2 inhibitors induced natriuresis up to 1.40-fold, but after 1 month, there was no increase in natriuresis.17 However, liraglutide increased sodium excretion in up to 21 days of treatment.18

Liraglutide and SGLT-2 inhibitors may reduce oxidative stress and inflammatory states.19 SGLT-2 inhibitors decrease reabsorption of sodium at the proximal tubules. This reduces oxygen consumption and may preserve renal function in mice.20 Further, GLP-1 RA may induce natriuresis, thereby also preserving renal function. In addition, both GLP-1 RA and SGLT-2 inhibitors might improve inflammatory status and oxidative stress independent of glucose-lowering effects.21 Anti-inflammatory and anti-oxidative effects may explain how liraglutide appears to improve endothelial function and NO production.21

Metabolic abnormalities, poor glycemic control, hypertension, and ischemic changes are associated with cardiac dysfunction.22,23 Liraglutide and SGLT-2 inhibitors were reported to improve cardiac diastolic dysfunction.24,25 Strong and sustained glycemic control by liraglutide may reduce albuminuria and improve cardiac function, reflected by BNP, LVMI, LAD, and E/e’.24 Also, both drugs induce less hypoglycemic attacks and decreased glycemic fluctuation.26,27

Such improved glycemic control may reduce oxidative stress and inflammation, which aside from glycemic control reduces atherosclerosis in patients taking GLP-1 RA and SGLT-2 inhibitors. In this study, the percentage of patients with cerebral infarction was lower with the GLP-1 RA than with SGLT-2 inhibitors, though not significantly. This finding was consistent with other reports related to GLP-1 RA and SGLT-2 inhibitors including LEADER and EMPA-REG OUTCOME trials.21,28 There were more patients with congestive heart failure with GLP-1 RA. GLP-1 RA might prevent atherosclerosis more than SGLT-2 inhibitors. However, SGLT-2 inhibitors might
have more intensive diuretic action. They may increase hemoglobin levels and blood viscosity. These effects may have more positive effects on heart failure than GLP-1 RA and negative effects on cerebral infarction.

Reduction in body weight improves insulin resistance. The strong and sustained blood pressure reduction, glycemic control, diuresis, and natriuresis may have reduced albuminuria and improved cardiac function, including BNP, LVMI, LAVI, and E/e'. Nevertheless, intensive anti-atherosclerotic factors might sustain improved diastolic dysfunction in the GLP-1 RA. The stronger glycemic control shown in this study might have important effects in renal function or atherosclerotic findings. Further investigation is therefore required.

There were some limitations to the study. This was a prospective study but with a small sample size. In addition, no randomization was performed, with the possibility of other differences between the two groups apart from the variables shown in Table 1. There were differences in HbA1c values 24 months after the initiation of new agents. However, in linear regression analysis, the relations between HbA1c (average throughout the period) and cardiovascular events were not significant (data not shown). Further, there were some participants who withdrew. Thirteen participants who were given other antidiabetic agents because of poor glycemic control discontinued the study, but there was no difference between the groups. In this trial, 5 mg of dapagliflozin, 10 mg of empagliflozin, and 0.9 mg of liraglutide were prescribed to the participants.

The findings of the study are not the same as others using larger doses of agents, as in other countries. It is thought that larger doses of these agents, as used in most countries outside Japan, might have more beneficial cardiovascular protective effects. In the future, we would like to investigate using high dose agents.

**Figure 2.** Changes in echocardiography and atherosclerosis: (a) ejection fraction, (b) left ventricular mass index, (c) E/e', (d) left atrial volume index, (e) ankle brachial index, and (f) cardio-ankle velocity index.

Data are expressed as mean ± standard deviation.

*p < 0.05. **p < 0.01 versus at baseline. †p < 0.05 versus Group G.
Further randomized prospective trials with larger samples and high dose agents are needed to more fully understand the actions of these drugs on renal and cardiac function.

**Conclusion**

Use of liraglutide and SGLT-2 inhibitors in type 2 diabetes patients with renal impairment have similar effects on renal function, including eGFR, albuminuria, and left ventricular and atrial volume. However, liraglutide may provide more beneficial effects on arterial stiffness than SGLT-2 inhibitors.

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**Table 3. Study endpoint data.**

| Primary endpoint; n (%/year) | Group G | Group S | p value |
|-----------------------------|---------|---------|---------|
| Renal replacement therapy   | 0 (0.0) | 0 (0.0) | 0.999   |
| Death                       | 0 (0.0) | 0 (0.0) | 0.999   |
| Myocardial infarction       | 2 (0.8) | 2 (0.8) | 0.332   |
| Admission due to heart failure | 12 (16.7) | 22 (26.2) | 0.015 |
| Stroke                      | 11 (1.3) | 11 (1.3) | 1.000   |
| PAD                         | 4 (1.6) | 2 (0.8) | 0.102   |

| Secondary endpoint; n (%) | Group G | Group S | p value |
|---------------------------|---------|---------|---------|
| ≥30% eGFR decline         | 7 (9.7) | 22 (26.2) | 0.015 |
| ≥30% ACR worsening        | 7 (9.7) | 5 (6.0) | 0.378 |
| ≥30% LVMI worsening       | 12 (16.7) | 22 (26.2) | 0.151 |
| ≥30% LAVI worsening       | 5 (6.9) | 16 (19.0) | 0.027 |
| ≥30% E/e’ worsening       | 4 (5.6) | 13 (15.5) | 0.047 |
| ≥30% CAVI worsening       | 0 (0.0) | 0 (0.0) | 0.999 |

Data are expressed as number and frequency of event (%).
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