Variability in drug response: towards more personalized diabetes care
Petrykiv, Sergei
Chapter 4

The albuminuria lowering response to dapagliflozin is variable and reproducible between individual patients

Sergei Petrykiv
Gozewijn Laverman
Dick de Zeeuw
Hiddo Lambers Heerspink
Abstract

Objective: Albuminuria reduction is essential for renal and cardiovascular protection. We characterized the efficacy of dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, on albuminuria. Secondly, we assessed whether the albuminuria lowering effect varies between patients, and whether this variability in response is reproducible.

Research Design and methods: A double-blind, randomized, placebo controlled crossover trial was conducted. Patients with type 2 diabetes and albumin:creatinine ratio >100 mg/g on a stable dose of an Angiotensin Converting Enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) were enrolled. Patients were assigned to 6-weeks treatment periods with dapagliflozin 10 mg/d or placebo in random order, separated by 6-weeks wash-out periods. After the two treatment periods, half of all patients were re-exposed to 6 weeks dapagliflozin 10 mg/d. Primary outcome was the change in 24-hour urinary albumin excretion rate (24h UAE). To assess the reproducibility in the individual albuminuria response, responses from the first and second exposure to dapagliflozin were correlated.

Results: Thirty-three patients (age 61 years; female gender 24.2%; median 24h UAE 470 mg/24hr) completed the study. Dapagliflozin compared to placebo reduced 24h UAE by 36.2% (95%CI 22.9 to 47.2; p<0.001). Systolic blood pressure fell by 5.2 mmHg (95%CI 0.5 – 10.0) and eGFR by 5.3 (95%CI 2.7 to 8.0). All effects were reversible directly after treatment discontinuation. In a subgroup of 15 patients who were exposed twice to dapagliflozin, 24h UAE responses showed a large variation between individuals: first exposure (range -76% to +52%) and second exposure (-90% to +95%), and first and second individual response significantly correlated (r=0.69 [95%CI 0.27 – 0.89]; p<0.004).

Conclusion: Dapagliflozin significantly reduces albuminuria when given as adjunct to ACEis or ARBs. The albuminuria response to dapagliflozin markedly varies between patients. This variation is not a random phenomenon, but reproducible upon re-exposure. These data support personalized therapy approaches to optimize diabetic nephropathy care.

Introduction

The Sodium glucose co-transporter 2 (SGLT2), located in the proximal tubule of the kidney, is an effective transporter system which is responsible for reabsorption of glucose and sodium. Dapagliflozin is an SGLT2 inhibitor which reversely inhibits the SGLT-2 transporter. This leads to enhanced glucose and sodium excretion and
reductions in HbA1c, plasma volume, body weight and blood pressure.[1-3] Post-hoc analyses from various clinical trials have suggested that SGLT2-inhibitors decrease albuminuria.[4-7] Long-term renoprotective effects have also been suggested based on secondary outcomes from large clinical trials.[8] Potential renoprotective effects are thought to involve various pathways including natriuretic and diuretic effects as well as restoration of tubulo-glomerular feedback and correcting glomerular hyperfiltration.[9, 10] However, dedicated prospective randomized trials characterizing the albuminuria lowering and renoprotective effects of SGLT2-inhibitors are lacking. Previous studies have shown that individual patients show a wide variability in their albuminuria response to many drugs.[11] Since it is also known that albuminuria fluctuates from day to day,[11, 12] the between individual drug response variability could reflect a true variation in drug response or random fluctuations in albuminuria. Prospective clinical trials to address this issue are lacking.

We conducted a randomized controlled cross-over study to, firstly, prospectively determine the albuminuria lowering effects of the SGLT2 inhibitor dapagliflozin. Secondly, we assessed the between-patient variability in albuminuria response during dapagliflozin, and assessed whether the individual albuminuria response to dapagliflozin is reproducible at second exposure.

### Research Design and Methods

#### Trial design

We conducted a prospective, randomized, double-blind, placebo-controlled cross-over clinical trial. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen, the Netherlands (METc 2014/111). The study was registered with the Netherlands Trial Register (NTR 4439) and complied with the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent before any specific study procedure commenced.

#### Study population

Patients aged between 18 and 75 years with a first morning void albumin:creatinine ratio (UACR) ≥100 mg/g and <3500 mg/g, eGFR ≥ 45 ml/min/1.73m², HbA1c between 55 and 100 mmol/mol (7.2 and 11.3 %), and who were on stable doses of Angiotensin-Converting-Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB) for more than 4 weeks were recruited from the outpatient clinic of the Department of Internal Medicine Ziekenhuis-Groep Twente, Almelo/Hengelo, the Netherlands. Key exclusion criteria were systolic/diastolic blood pressure > 180/110 mmHg, cardiovascular event
during the past 6 months, and current use of pioglitazone, GLP-1 analogues, DDP-IV-inhibitors and SGLT-2 inhibitors.

**Intervention and randomization**
Patients were randomly allocated to one of the two treatment orders generated by an independent pharmacist using a computer software tool prior to the inclusion of the first patient. The study employed a double-blind design. There was no difference in appearance between the medications for each sequence/treatment group. In each phase, medication for each treatment group was supplied in identical bottles, labelled appropriately so as to maintain the study blind. All Study personnel and patients remained blinded to the sequence allocation.

**Procedures**
The study consisted of a screening visit and a run-in period of 4 weeks for those subjects who were not on a stable dose of ACEi or ARB or glucose lowering medication. Eligible patients then proceeded to the randomization visit. The study employed three consecutive cross-over treatment periods of 6 weeks each, in which patients were treated with dapagliflozin 10 mg per day or placebo, with wash-out periods of 6 weeks in between. Accordingly, fifteen randomly selected patients were exposed to dapagliflozin 10 mg per day during two treatment periods. Study medication was dispensed at the beginning of each treatment period. Patients were instructed to take the tablet in the morning. All efforts were done to keep the use and dosage of all concomitant medication stable during follow-up.

**Measurements**
Patients collected 24-hour urine samples at the beginning and end of each treatment period to assess urinary albumin concentration. In addition, three consecutive first morning void urine samples were also collected at the beginning and end of each treatment period to determine the urinary albumin to creatinine ratio. Blood samples were taken in fasting condition at the beginning and end of each treatment to assess glucose, HbA1c, and lipid profile. eGFR was calculated from the MDRD equation using serum creatinine concentration measured at the beginning and end of each treatment period.[13] Systolic and diastolic blood pressure was recorded as the mean of three consecutive blood pressure readings. Blood pressure measurements were performed with a calibrated sphygmomanometer in a seated position after at least 10 minutes of rest with a time interval of two minutes between readings.

**Endpoints**
The primary endpoint was the percentage change in 24-hour urinary albumin excretion (24h UAE). Secondary endpoints included the correlation between the 24h UAE
response to dapagliflozin during the first and second treatment period. Additional secondary endpoints included change from baseline in first morning void UACR of three consecutive first morning void urine samples, plasma glucose, HbA1c, body weight, systolic blood pressure, and eGFR. Data on reported adverse events and serious adverse events were collected during the trial.

**Statistical analyses**
A sample size of 32 patients completing the protocol was estimated to provide 80% power to detect a 25% reduction in 24h UAE between the dapagliflozin and placebo group assuming a standard deviation of 0.7 in log transformed 24h UAE. To account for potential loss to follow-up we enrolled 34 patients. Efficacy analyses were conducted on the modified intention to treat population comprising all individuals who completed the study. The primary analysis was a mixed effects repeated measures analysis. The model included sequence, period, treatment and subject as factors and baseline 24h UAE as a covariate. Albuminuria was log transformed before entering the data in the repeated measures model. The between group geometric mean change in 24h UAE was derived by 100*(exp[least square mean change]-1), and the same transformation was applied to the 95% confidence limits. For secondary end point analyses, the same repeated measures model as was used as for the primary analysis with the exception that baseline 24h UAE was removed as covariate and the analyses were adjusted for the baseline parameter of interest. Comparisons of changes in 24h UAE between the first and second exposure to dapagliflozin were performed using Deming linear regression which accounts for errors in observations in both the x-value and y-value. A Fisher’s z’ transformation was performed to calculate the 95% confidence interval of the correlation. Exposing fifteen patients twice to dapagliflozin provided 80% power to detect a correlation between first and second exposure of 0.65. All statistical analyses were performed with SAS software version 8.2 (SAS Institute, Inc., Cary, NC, USA). All statistical tests were two-sided, with a statistical significance level of 5%.
Results

Between September 2014 and February 2016, 46 patients were screened of whom 34 were randomized. One patient was hospitalized during the study, discontinued study medication, and was excluded from the primary analysis (Figure 1).

Figure 1: Trial profile.

The baseline demographics, clinical and biochemical characteristics of the 33 patients comprising the efficacy population are shown in Table 1. Adherence to study medication was excellent with 97.5% (standard deviation 5.0) of all doses being taken. Adherence was more than 90% in all patients.
Table 1: Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 (9)</td>
</tr>
<tr>
<td>Sex (female/male) (n)</td>
<td>8/25</td>
</tr>
<tr>
<td>Caucasian (n,%)</td>
<td>30 (91)</td>
</tr>
<tr>
<td>Smoking (n,%)</td>
<td>9 (27.3)</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>57 (9.5)</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>142 (15)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>77 (5.9)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>96 (22)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>31 (5.5)</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73m2)</td>
<td>72 (21)</td>
</tr>
<tr>
<td>Cardiovascular disease history (n,%)</td>
<td>10 (30.3)</td>
</tr>
<tr>
<td>UAER (mg/24h)</td>
<td>470 [191 – 997]</td>
</tr>
<tr>
<td>UACRa (mg/mmol)</td>
<td>31 [13 – 68]</td>
</tr>
</tbody>
</table>

Medication

- Metformin use, n (%) 30 (90.9)
- Sulfonylurea use, n (%) 9 (27.3)
- Insulin use, n (%) 21 (63.6)
- Antihypertensive medication use, n (%) 33(100)
  - ACEi 16 (48.5)
  - ARB 16 (48.5)
  - B-blocker 16 (48.5)
  - Ca – channel blockers 14 (42.4)
  - Diuretics 26 (78.8)

Data are given mean (SD) and a geometric mean (25th to 75th Percentile)

† Cardiovascular disease history defined as a history of coronary artery disease or peripheral vascular disease

Effects on albuminuria

Patients had a geometric mean 24h UAE of 470 (95%CI 334 to 662) mg/24hr at baseline, which was reduced to 331 (95%CI 303 to 362) mg/24hr after 6 weeks treatment with dapagliflozin. During 6 weeks treatment with placebo albuminuria increased to 519 mg/g (95%CI 475 to 567). Accordingly, the repeated measures model showed that dapagliflozin compared to placebo significantly decreased albuminuria by 36.2% (95% CI 22.9 to 47.2; Figure 2A; P<0.001). The individual albuminuria response to dapagliflozin varied markedly between individuals (range -84% to +94%). During dapagliflozin treatment 84% and 65% of patients achieved a ≥0% and ≥30% reduction in 24h UAE (both P<0.01 versus placebo). Dapagliflozin decreased first morning void UACR by 29.7% (95%CI 16.8 to 40.7%; Figure 2B) compared to placebo (P<0.001). Six weeks after the end of the dapagliflozin treatment period the change in 24h UAE from baseline was 0.5% (95%CI -20.4 to 26.8), indicating that the anti-albuminuric response was completely reversible after six weeks of dapagliflozin discontinuation.
**Effects on eGFR, HbA1c, blood pressure, and body weight**

Baseline eGFR was 72 ml/min/1.73 m². eGFR fell during dapagliflozin treatment by 4.8 ml/min/1.73 m² (95% CI –6.7, –3.0) and increased by 0.9 ml/min/1.73 m² (95% CI -1.5 to 3.3) during placebo treatment (P<0.001 versus dapagliflozin; Figure 2F). eGFR change 6 weeks after dapagliflozin discontinuation was -1.3 ml/min/1.73m² (95%CI -4.6 to +1.5), indicating that eGFR returned to baseline values. After six weeks dapagliflozin treatment changes in HbA1c and SBP relative to placebo were -2.5 mmol/mol (95% CI –4.7, –0.3; P=0.026) and –5.2 mmHg (95% CI -10.0 to -0.5; p=0.032), respectively (Figure 2C,E). The corresponding change in body weight was -0.4 kg (95% CI –1.0 to 0.1; P =0.095; Figure 2D).

**Albuminuria response after re-exposure**

To assess whether the individual response to dapagliflozin is reproducible upon re-exposure we exposed fifteen patients twice to 6-weeks of dapagliflozin 10 mg. The baseline characteristics of these 15 patients are shown in supplement table 1. In this subgroup, the 24h UAE change during the first exposure was -41% (range -76 to +52) and during the second exposure -27% (range -90 to +95; p=0.18 vs first period; Figure 3). A statistically significant correlation was observed in the UAER response during the first and second exposure (r=0.69; [95% CI 0.27 – 0.89] p=0.004) indicating that 48% of the between individual variance in UAER response during the second exposure could be explained by the first exposure (Figure 3). Adjustment of changes in 24-hour sodium, potassium, phosphate excretion, (as proxies for changes in dietary intake) between the first and second treatment increased the explained variance (R²) of the 24h UAE response during the second exposure to 69%. One patient used a non-steroidal anti-inflammatory drug during the first treatment period. Excluding this patient from the analysis did not change the result. Significant correlations in response between the first and second exposure were also observed for systolic blood pressure (r=0.67; R²=0.45 [95% CI 0.24 – 0.88]; P =0.006).

**Predictors of individual albuminuria response**

Various baseline parameters were analyzed to assess if these predict the individual response to dapagliflozin. The placebo corrected reduction in 24h UAE was consistent in patients with microalbuminuria, 46.3% (95%CI 26.4 to 60.8)) and macroalbuminuria, 29.9% (11.4 to 44.6; P for interaction= 0.173). Similarly, 24h UAE response was consistent in patients with eGFR <60 ml/min/1.73m2, 36.6% (15.1 to 52.6), and ≥60 ml/min/1.73m2, 36.0% (17.9 to 50.1; P for interaction= 0.961). The albuminuria response was also not determined by baseline age, gender, HbA1c, systolic blood pressure, or 24-hr sodium or potassium excretion. The change in systolic blood pressure, HbA1c, fasting plasma glucose did not correlate with the change in 24h UAE during dapagliflozin except eGFR which showed a modest association with 24h UAE (r=0.34; P=0.06).
Figure 2: A: Primary endpoint: Percentage change in 24-hour urinary albumin excretion rate from baseline. B-F: Secondary endpoints: B: Percentage change in first morning void albumin:creatinine ratio from baseline; C: Change in systolic blood pressure; D: Change in body weight; E: Change in HbA1c; F: Change in eGFR.
Figure 3: A: Change in 24-hour urinary albumin excretion over time during dapagliflozin and placebo treatment among 15 patients who received dapagliflozin during two treatment periods; B: Individual changes in albuminuria during dapagliflozin and placebo treatment; C: Correlation between albuminuria changes during the first and second dapagliflozin treatment period.
Safety
Overall, dapagliflozin was well tolerated. Three patients experienced a urinary tract infection during dapagliflozin versus one patient during placebo treatment. Hypoglycemia was reported by two patients during dapagliflozin treatment. None of these events led to drug discontinuation. Serious adverse events occurred in four patients. Three of these events occurred during dapagliflozin and one during placebo treatment.

Conclusion
In this prospective randomized controlled trial the albuminuria lowering effect of the SGLT2 inhibitor dapagliflozin was assessed in patients with type 2 diabetes and residual albuminuria. Dapagliflozin 10mg/d lowered 24-hour urinary albumin excretion on average by 36% with a large variation between individuals. The individual albuminuria lowering response was reproducible when patients were re-exposed to dapagliflozin 10 mg/d supporting the notion that the individual anti-albuminuric response is a true response to dapagliflozin and can be adequately quantified in a clinical trial setting. Previous post-hoc analyses of clinical trials have indicated that SGLT2 inhibitors appear to decrease albuminuria. All these trials were primarily designed to assess effects of SGLT2 inhibitors on HbA1c or blood pressure.[4-7] To the best of our knowledge this is the first dedicated prospective randomized controlled trial which demonstrates and confirms the albuminuria lowering efficacy of the SGLT2 inhibitor dapagliflozin. In this trial both 24-hour urine samples and three consecutive first morning void urine samples were collected to precisely characterize the albuminuria lowering effect of dapagliflozin, whereas previous trials only used single random urine samples, a less precise measure to assess albuminuria lowering effects.[12] The magnitude of the albuminuria lowering effect was similar to that previously described in post-hoc analyses. For example, in patients with type 2 diabetes and micro- or macroalbuminuria dapagliflozin and empagliflozin decreased albumin:creatinine ratio by approximately 30%.[4, 6] Similar magnitudes of effect were reported with canagliflozin in a subgroup of patients with type 2 diabetes and micro- or macroalbuminuria.[14]
A large between individual variability in 24h UAE changes was observed after six weeks exposure to dapagliflozin. The finding that the individual response at re-exposure was reproducible for the individual indicates that the large between patient heterogeneity in albuminuria response is a true pharmacological variation in response to dapagliflozin and can be adequately quantified in a clinical trial setting. Given that the change in albuminuria is a strong predictor of future risk changes for renal and cardiovascular
disease, these data suggest that some patients achieve a large benefit while others, with no reduction in albuminuria, comprising approximately 20% to 30% of the population, are less likely to benefit. We explored several physical and biochemical parameters as predictors of response but could not identify any. Future analyses are required to identify biomarkers of response to dapagliflozin to tailor and optimize therapy. We had not expected that the individual 24h UAE response to dapagliflozin at second exposure would be completely reproducible to the first dapagliflozin response since it is known that the biological day-to-day variation in albuminuria is high.[12] In addition, many factors, which could be different during the first and second period, may have influenced the reproducibility in response to dapagliflozin, including variation in dietary patterns, differences in disease activity, or changes in concomitant medication. Indeed, when we adjusted the analyses for differences in sodium, potassium and phosphate excretion, as proxy for differences in dietary intake, the albuminuria correlation between first and second exposure increased. This suggests that despite the careful provision of dietary advices, changes in dietary patterns have influenced the reproducibility in response. We also explored changes in concomitant medication during the first and second dapagliflozin period as potential explanation for the incomplete correlation but these were markedly stable throughout the study. Changes in metabolic parameters including HbA1c, fasting plasma glucose and body weight were not the primary focus of this study. In particular, in line with the duration of the active treatment period, there was only a modest, but statistically significant, reduction in HbA1c. Interestingly, despite the small reduction in HbA1c, a large reduction in albuminuria was present indicating that the reduction in albuminuria is independent of glycemic control. This finding is in accordance with a previous post-hoc analysis from a large randomized controlled trial demonstrating that long-term effects of the SGLT2 inhibitor canagliflozin on renal function is independent of its glycemic effects. [14] What could be the mechanism of the albuminuria lowering effect? As observed in the current study, previous trials have shown acute but modest decline in eGFR within three to six weeks of treatment initiation. The acute decline in eGFR is followed by a period of stable renal function, and is reversible after drug discontinuation. This pattern is reminiscent of ACEi and ARBs and suggest a reduction in glomerular pressure and renal hyperfiltration which is associated with long-term renoprotection.[16] Such a mechanism could also explain the reduction in albuminuria independent of changes in metabolic control, and the association we found between changes in eGFR and 24h UAE during dapagliflozin. The difference between SGLT2 inhibitors and ACEIs or ARBs is that the reduction in intraglomerular pressure induced by ACEIs and ARBs is mediated through efferent vasodilation whereas SGLT2 inhibitors are thought to induce afferent vasoconstriction.[10] The hypothesis that SGLT2 inhibition reduces intraglomerular
pressure is supported by data in patients with type 1 diabetes demonstrating that the SGLT2 inhibitor empagliflozin reduces calculated glomerular pressure and afferent arterial tone.[17]

An alternative mechanism that may contribute to the albuminuria lowering effects may be related to decreases in circulating volume and natriuretic effects. Dapagliflozin has been shown to decrease plasma volume and to increase hematocrit to a similar extent as hydrochlorothiazide.[3] Previous studies have shown that optimizing extracellular volume through dietary sodium restriction or diuretic use decreases albuminuria allegedly through potentiating the effects of ACEIs or ARBs.[17] As patients in the current study were already receiving ACEIs and ARBs, a sustained reduction in effective circulating volume induced by dapagliflozin may have potentiated ACEIs and ARBs effects. In support of this proposed mechanism is the finding from the EMPAREG trial demonstrating that the renoprotective effects of the SGLT2 inhibitor empagliflozin tended to be larger among patients already using ACEIs or ARBs.[18]

Finally, it may be possible that SGLT2 inhibitors influence pro-inflammatory pathways. Inflammatory pathways are often activated in patients with diabetic nephropathy and may initiate and sustain disease progression.[19] Experimental studies have reported that SGLT2 inhibitors reduce markers of inflammation.[20, 21] Further studies are required to characterize the anti-inflammatory properties of SGLT2 inhibitors.

This study has limitations. First, the study used a surrogate outcome measure as primary outcome and additional studies are required to characterize the renoprotective effects of dapagliflozin on hard renal end points. In addition the study follow-up period was only 6 weeks. Whether reductions in 24h UAE persist over longer time periods could not be investigated. A post-hoc analysis from the EMPAREG trial suggested that the SGLT2i empagliflozin instantaneously reduces albuminuria and the effect persisted throughout the 4 years follow-up.[22] That trial also reported that empagliflozin reduces renal risk but the number of hard renal end points was small.[18] The renoprotective effects of SGLT2 inhibitors in patients with type 2 diabetes will be definitively tested in the CREDENCE trial (Clinical Trials.gov identifier NCT02065791). Secondly, we used dapagliflozin at 10 mg per day which is the clinically used dose. This dose is however selected based on dose-response studies using HbA1c as the primary efficacy parameter. Whether the dose-response curve for albuminuria is similar to that of HbA1c is unknown. In addition, whether patients not responding to dapagliflozin 10 mg/day would respond to a higher dose was not assessed. Finally, despite strict dietary advices not all patients adhered to a stable dietary pattern which has likely led to an underestimation of the reproducibility in individual responses during the two exposures to dapagliflozin.

In conclusion, dapagliflozin therapy markedly reduces 24-hour urinary albumin excretion in patients with type 2 diabetes with micro- or macroalbuminuria who are already treated with ACEi or ARB therapy. The reduction in albuminuria however varies
to a significant degree between individual patients. Although albuminuria fluctuates within an individual over time, the variation in albuminuria response to dapagliflozin is reproducible upon re-exposure. These data support implementation of personalized medicine approaches in clinical practice to optimally tailor therapy and maximize diabetic nephropathy care.

**Acknowledgements**

We thank all patients and research staff for their participation and assistance in this study. We thank Astra Zeneca for kindly providing study medication. The sponsor had no influence in the design, conduct, analysis, and interpretation of the study, as well as no influence in the writing of the report.
## Supplement Table: Baseline characteristics of 15 individuals exposed twice to dapagliflozin 10 mg/day

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Sex (female/male) (n)</td>
<td>2/13</td>
</tr>
<tr>
<td>Caucasian (n,%)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Smoking (n,%)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>HbA1C (mmol/mol)</td>
<td>59 (11)</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>144 (18)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>77 (6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>103 (21)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>32 (5)</td>
</tr>
<tr>
<td>Estimated GFR (ml/min/1.73m2)</td>
<td>69 (15)</td>
</tr>
<tr>
<td>Cardiovascular disease history (n,%)†</td>
<td>6 (40)</td>
</tr>
<tr>
<td>UAER (mg/24 h)</td>
<td>413 [212 – 690]</td>
</tr>
<tr>
<td>UACRa (mg/mmol)</td>
<td>23.6 [11 – 42]</td>
</tr>
</tbody>
</table>

### Medication
- Metformin use, n (%) 14 (93)
- Sulfonylurea use, n (%) 6 (40)
- Insulin use, n (%) 10 (66.7)
- Antihypertensive medication use, n (%) 15 (100)
  - ACEi 8 (52.3)
  - ARB 7 (46.7)
  - B-blocker 7 (46.7)
  - Ca – channel blockers 9 (60.0)
  - Diuretics 12 (80.0)

Data are given mean (SD) and a geometric mean (25th to 75th Percentile)

† Cardiovascular disease history defined as a history of coronary artery disease or peripheral vascular disease
References


Albuminuria lowering effects of dapagliflozin (IMPROVE-study)