

# SGLT2-Inhibition in Patients With Alport Syndrome



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**Introduction:** Large-scale trials showed positive outcomes of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in adults with chronic kidney disease (CKD). Whether the use of SGLT2i is safe and effective in patients with the common hereditary CKD Alport syndrome (AS) has not yet been investigated specifically in larger cohorts.

**Methods:** This observational, multicenter, international study (NCT02378805) assessed 112 patients with AS after start of SGLT2i. The study's primary end point was change of albuminuria in albumin/g creatinine from the start of therapy.

**Results:** Compared to randomized trials investigating the effect of SGLT2i in CKD, the adult patients in this study were younger (aged  $38 \pm 14$  years) and had a better estimated glomerular filtration rate (eGFR,  $63 \pm 35$  ml/min per  $1.73$  m<sup>2</sup>;  $n = 98$ ). Maximum follow-up was 32 months. Compared to baseline, at the first 3 follow-up visits (months 1 to 3, 4 to 8, and 9 to 15) after initiation of SGLT2i therapy, a significant reduction of albuminuria in mg albumin/g creatinine ( $>30\%$ ) was observed. Mean loss of eGFR was  $9 \pm 12$  ml/min per  $1.73$  m<sup>2</sup> almost 1 year after initiation of SGLT2i therapy ( $n = 35$ ). At a total of 71 patient-years at risk, 0.24 adverse events (AEs) per patient-year on SGLT2i were reported.

**Conclusion:** This study indicates that, additive to renin-angiotensin system (RAS)-inhibition (RASi), SGLT2i have the potential to reduce the amount of albuminuria in patients with AS. Future studies are needed to investigate the long-term effects of SGLT2i on CKD progression in patients with AS to assess whether the observed reduction in albuminuria translates to a delay in kidney failure (KF).

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Slowing progression of CKD has highest priority in nephrology. Recent randomized clinical trials (RCTs) demonstrated the nephroprotective effect of SGLT2i in CKD for adult patients.<sup>1–5</sup> The hereditary type 4 collagen disease, AS, is the most common monogenetic glomerular kidney disease.<sup>6–8</sup> Patients living with AS may develop CKD early in life. The disruption of type 4 collagen structure in AS leads to a dysfunction of the basement membrane filtration barrier of the glomeruli with initial microhematuria, microalbuminuria and, with disease progression, overt proteinuria, finally progressing to KF, and can be accompanied by hearing loss and ocular lesions.<sup>9–12</sup> The majority of patients with AS have an X-linked (COL4A5 gene) inheritance, and up to 30% have an autosomal (COL4A3 or COL4A4 genes) inheritance.<sup>13–15</sup> If started early, therapy with inhibitors of the RAS can delay renal failure by years; however, many patients still reach KF at a relatively young age. Therefore, new therapy options are needed.

SGLT2i have been approved for adults with any kind of CKD in many countries, which is why SGLT2i are also prescribed increasingly for patients with AS.<sup>16</sup> In previous RCTs, the nephroprotective effects of SGLT2i were examined primarily in patients with diabetic kidney disease or other more common causes of nondiabetic CKD. Whether the use of SGLT2i is safe and effective in patients with AS (and thus a different pathogenesis than other CKDs) has not yet been investigated specifically in larger cohorts.<sup>17–20</sup> Therefore, this international, multicenter, observational, noninterventional study investigated potential side effects of SGLT2i in patients with AS and possible nephroprotective effects using the change in albuminuria and eGFR as surrogate parameter for CKD progression.<sup>21</sup>

## METHODS

### Study Population

This multicenter, observational study included a total of 112 patients with AS, who started therapy with SGLT2i. Patients from 9 countries and 21 study sites were recruited from 2021 to 2023. The presentation of this study's design at the International Workshop on Alport Syndrome 2021 led to the recruitment of potential study sites.<sup>22</sup> Some patients were followed-up retrospectively ( $n = 99$ ) and others prospectively ( $n = 13$ ). The diagnosis of AS was confirmed genetically

or by kidney biopsy (patient or affected relative). Patients living with X-linked, autosomal recessive or autosomal dominant AS were included. Patients were not included if they received kidney transplantation, were on dialysis, or did not wish to contribute. Data were pseudonymized at the study site or, in the UK, by the National Registry of Rare Kidney Diseases (for which all patients provided written informed consent with ethical approval provided by NHS Southwest-Central Bristol Research Ethics Committee (14/SW/1088)). The registry and data storage, in conformity with Good Clinical Practice guidelines, were approved by the Ethics Committee of the University Medical Center Göttingen as part of the European Alport Therapy Registry (AZ 10/11/06; renewed version in 2014 and 2020; [ClinicalTrials.gov](https://clinicaltrials.gov) identifier NCT 02378805).

### Intervention and Outcome Measures

This noninterventional study explored the intra-individual treatment effects of SGLT2i (in most patients on top of RASi). A standardized questionnaire was used as case report form to obtain data on demographic parameters, medication, blood and urine test results, as well as possible side effects. The study protocol and case report form were approved by the local ethics committee and are provided in the [Supplementary Material](#). Exchange of pseudonymized data was secured by individual contracts (data processing and cooperation agreements) between the participating centers. All investigators who contributed data vouch for the completeness and accuracy of the data set and analyses, and for the fidelity of the study to the protocol. The decision to submit the manuscript for publication was made by all the authors.

Baseline was defined as the start of therapy with SGLT2i. The study's primary end point was change of albuminuria in mg/g creatinine 6 months after baseline. If albuminuria was not available, proteinuria was analyzed.<sup>23</sup> Considering the different local standards of measurement, percentage changes from baseline were calculated for overall comparison in patients with overt proteinuria. Additional analyses were performed approximately 3 months after baseline, 1 year after baseline and, if available, at individual's longest follow-up (up to 32 month). Additional analysis included demographic parameters, change of body mass index (BMI), blood pressure, and renal function (eGFR).

Patients younger than 18 years ( $n = 10$ ) were analyzed separately. In children, the CKiD U25 formula could not be used because cystatin c was not available; therefore, the Schwartz formula was used to calculate eGFR.

### Statistical Methods

Statistical comparisons were not formally powered or prespecified. Continuous variables were presented as mean and SD or as median and interquartile range (IQR), categorical variables as frequencies (percentages). For intraindividual comparison of continuous outcomes, a paired  $t$  test was used. To study subgroups, comparison of means between groups was conducted with the unpaired  $t$  test. If equal variances were not assumed, the Welch test was used for group comparison. Pearson's correlation was performed to assess correlations. Probability values ( $P$  values)  $< 0.05$  were considered statistically significant. Data analyses were performed with IBM SPSS Statistics (version 28 for MacOS, IBM Corporation, Armonk, NY).

## RESULTS

The duration of therapy in this observational study with SGLT2i in 112 patients with AS added up to a total of 82 patient-years on SGLT2i. Mean follow-up time was  $9 \pm 7$  month. At baseline, mean age was  $36 \pm 15$  years, mean eGFR was  $68 \pm 38$  ml/min per  $1.73 \text{ m}^2$  ( $n = 108$ ) and mean albuminuria was  $1689 \pm 1455$  mg/g creatinine ( $n = 53$ ). Most patients were treated with dapagliflozin (107/112; 96%) and 5 patients were treated with empagliflozin (4%).

## ADULT PATIENTS

### Baseline Characteristics at Initiation of SGLT2i Therapy

In Table 1, we show baseline characteristics from the 102 adult patients with AS. The mean age at baseline was  $38 \pm 14$  years. Most patients were Caucasian (80%) and most patients (63/96; 66%) were male. Diagnosis of AS was confirmed by biopsy in 16 patients (17%), by genetic testing in 51 patients (53%), and by both biopsy and genetic testing in 29 patients (30%) ( $n = 96$ ). In 6 patients, it was not reported how diagnosis was secured. The mode of inheritance was reported in 88 patients (86%). In these patients, 58 patients had X-linked AS (66%), 29 patients had autosomal AS (including autosomal dominant and autosomal recessive AS) (33%), and 1 patient had AS with digenic heterozygous variants in the COL4A3 and COL4A5 genes (1%). Most adult patients (95/102; 93%) were treated with RASi. Of those, 45 patients (47%) were treated with angiotensin-converting enzyme inhibitors, 42 patients (44%) were treated with angiotensin receptor

**Table 1.** Demographic and clinical characteristics of the 102 adult patients with AS at baseline

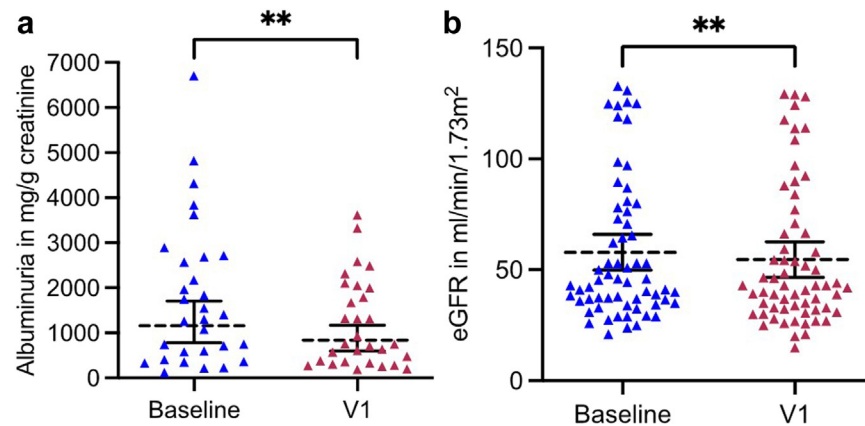
Characteristics	<i>n</i>	Result
Age (yrs)	102	$38 \pm 14$
Male no. (%)	96	63 (66)
Ethnicity	88	
Caucasian		68 (80)
Asian		16 (19)
Hispanic		1 (1)
Country (%)	102	
Belgium		6 (6)
China		3 (3)
France		6 (6)
Germany		39 (38)
Lithuania		8 (8)
South Korea		9 (9)
Switzerland		2 (2)
UK		22 (22)
USA		7 (7)
Mode of inheritance (%)	88	
X-linked		58 (66)
Autosomal		29 (33)
Digen		1 (1)
RASi	102	95 (93)
ACEi		45 (47)
ARB		42 (44)
ACEi + ARB		8 (8)
BMI ( $\text{kg}/\text{m}^2$ )	77	$27 \pm 6$
Systolic/diastolic blood pressure (mm Hg)	82	$127 \pm 16 / 78 \pm 11$
Albumin (g/dl)	69	$3.8 \pm 0.5$
Creatinine (mg/dl)	101	$1.6 \pm 0.7$
eGFR (ml/min per $1.73 \text{ m}^2$ )	98	$63 \pm 35$
Albuminuria (mg/g creatinine)	51	$1699 \pm 1472$
Proteinuria (mg/g creatinine)	36	$1805 \pm 1326$

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; Dige, digenic heterozygous; eGFR, estimated glomerular filtration rate; RASi, inhibitors of the renin-angiotensin system. Values are mean  $\pm$  SD or  $n$  (%) as appropriate.

blockers, and 8 patients (8%) were treated with both. Hearing loss was reported in 15 patients (16%;  $n = 93$ ). Most frequent comorbidities were hypercholesterolemia (36/89; 40%), high blood pressure (33/88; 38%), hyperuricemia (25/88; 28%), and vitamin D deficiency (17/88; 19%). The mean BMI was  $27 \pm 6 \text{ kg}/\text{m}^2$  ( $n = 77$ ), 19 patients were obese (19/77; 25%). Mean eGFR was  $63 \pm 35$  ml/min per  $1.73 \text{ m}^2$  ( $n = 98$ ) and mean albuminuria was  $1699 \pm 1472$  mg/g creatinine ( $n = 51$ ).

### First Follow-Up After 1 to 3 Month(s) (V1)

At a mean time on SGLT2i therapy of  $2 \pm 1$  months, 67 of the 102 patients (66%) had their first follow-up after initiation of treatment. The mean age in these patients was  $38 \pm 16$  years ( $n = 66$ ). Albuminuria was measured in 30 patients and significantly decreased from  $1797 \pm 1600$  mg/g creatinine to  $1197 \pm 978$  mg/g creatinine ( $P = 0.002$ ) (Figure 1a). Proteinuria was measured in 17 patients and decreased from  $1101 \pm 1119$  to  $766 \pm 857$  mg/l ( $P = 0.067$ ). Serum creatinine significantly



**Figure 1.** Albuminuria and eGFR at V1 (months 1–3). (a) Albuminuria before initiation of SGLT2i therapy (baseline; blue) and after a mean follow-up of  $2 \pm 1$  months (V1; red) of SGLT2i therapy ( $P = 0.002$ ,  $n = 30$ ; geometric mean with 95% CI). (b) eGFR before initiation of SGLT2i therapy (baseline; blue) and after mean follow-up of  $2 \pm 1$  months (V1, red) ( $P = 0.004$ ,  $n = 62$ ; mean with 95% CI). CI, confidence interval; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

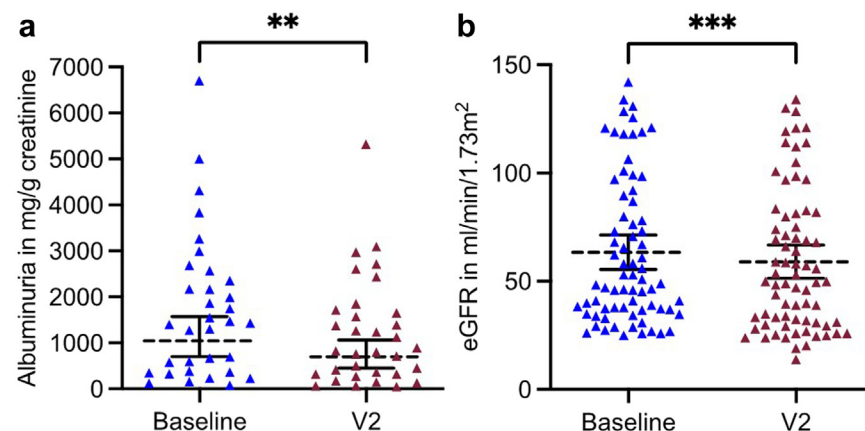
increased from  $1.7 \pm 0.7$  to  $1.8 \pm 0.8$  mg/dl ( $n = 64$ ;  $P < 0.001$ ) and, correspondingly eGFR decreased from  $58 \pm 32$  to  $55 \pm 32$  ml/min per  $1.73 \text{ m}^2$  ( $n = 62$ ;  $P = 0.004$ ) (Figure 1b). Systolic blood pressure was lower ( $126 \pm 15$  vs.  $123 \pm 20$  mm Hg;  $P = 0.147$ ), whereas diastolic blood pressure remained similar ( $77 \pm 10$  vs.  $78 \pm 11$  mm Hg;  $P = 0.438$ ) ( $n = 55$ ).

### Second Follow-Up After 4 to 8 Months (V2)

At a mean time on SGLT2i therapy of  $6 \pm 1$  months, 74 of 102 patients (73%) had a follow-up (V2): albuminuria decreased significantly ( $1727 \pm 1564$  vs.  $1203 \pm 1165$  mg/g creatinine;  $n = 33$ ;  $P = 0.01$ ) (Figure 2a) and proteinuria decreased from  $1191 \pm 1206$  to  $749 \pm 613$  mg/l ( $n = 15$ ;  $P = 0.098$ ). Serum creatinine increased significantly from  $1.6 \pm 0.7$  to  $1.7 \pm 0.9$  mg/dl ( $n = 73$ ;  $P < 0.001$ ), and corresponding eGFR decreased from  $63 \pm 34$  to  $59 \pm 33$  ml/min per  $1.73 \text{ m}^2$  ( $n = 72$ ;  $P < 0.001$ ) (Figure 2b). Systolic blood pressure was significantly

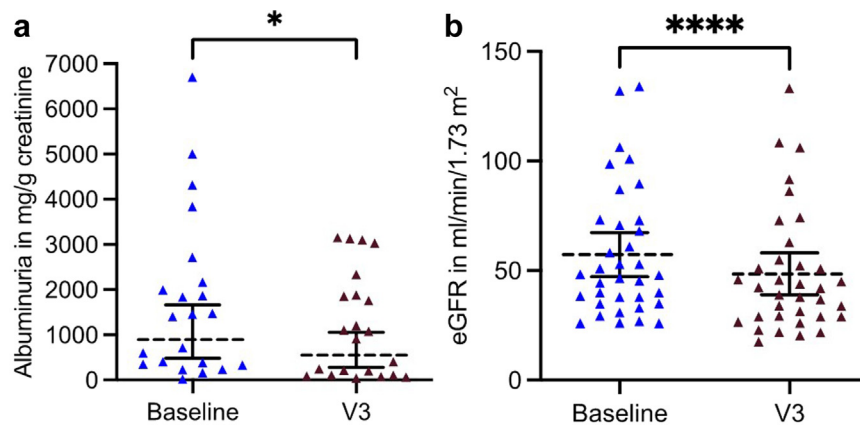
lower at V2 ( $128 \pm 14$  vs.  $124 \pm 13$  mm Hg;  $n = 51$ ;  $P = 0.029$ ), whereas diastolic blood pressure remained similar ( $79 \pm 12$  vs.  $78 \pm 11$  mm Hg;  $n = 51$ ;  $P = 0.369$ ). BMI also remained similar ( $27 \pm 7$  vs.  $27 \pm 7$  kg/m<sup>2</sup>;  $n = 35$ ;  $P = 0.6$ ).

The median reduction in proteinuria or albuminuria was similar in male patients ( $n = 34$ ) and female patients ( $n = 17$ ) (26%, IQR: 68 vs. 34%, IQR: 81;  $P = 0.795$ ). A nonsignificant trend toward a higher median reduction of proteinuria or albuminuria was observed in patients with autosomal AS (41%, IQR: 105;  $n = 17$ ) than in patients with X-linked AS (27%, IQR: 61;  $n = 29$ ) ( $P = 0.531$ ). Furthermore, a nonsignificant trend toward a higher reduction of albuminuria was observed in patients receiving angiotensin receptor blockers ( $712 \pm 876$  mg/g creatinine;  $n = 16$ ) than in patients treated with angiotensin-converting enzyme inhibitors ( $338 \pm 833$  mg/g creatinine;  $n = 14$ ) ( $P = 0.243$ ).



**Figure 2.** Albuminuria and eGFR at V2 (months 4–8). (a) Albuminuria before initiation of SGLT2i therapy (baseline; blue) and after a mean follow-up of  $6 \pm 1$  months (V2; red) ( $P = 0.01$ ,  $n = 33$ , geometric mean with 95% CI). (b) eGFR before initiation of SGLT2i therapy (baseline, blue) and after a mean follow-up of  $6 \pm 1$  months (V2; red) ( $P < 0.001$ ,  $n = 72$ , mean with 95% CI). CI, confidence interval; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2 inhibitors.





**Figure 3.** Albuminuria and eGFR at V3 (months 9–15). (a) Albuminuria before initiation of SGLT2i therapy (baseline; blue) and after a mean follow-up of  $12 \pm 2$  months (V3; dark red) ( $P = 0.032$ ,  $n = 22$ , geometric mean with 95% CI). (b) eGFR before initiation of SGLT2i therapy (baseline; blue) and after a mean follow-up of  $12 \pm 2$  months (V3; dark red) ( $P < 0.001$ ,  $n = 35$ , mean with 95% CI). CI, confidence interval; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

### Third Follow-Up After 9 to 15 Months (V3)

At a mean time on SGLT2i therapy of  $12 \pm 2$  months, 38 of the 102 patients (37%) had a follow-up (V3): albuminuria was still significantly lower compared to baseline ( $1737 \pm 1796$  vs.  $1189 \pm 1158$  mg/g creatinine ( $n = 22$ ;  $P = 0.032$ ) (Figure 3a). Serum-creatinine increased significantly from  $1.6 \pm 0.6$  to  $2 \pm 0.8$  mg/dl ( $n = 34$ ;  $P < 0.001$ ); and correspondingly, eGFR decreased from  $57 \pm 30$  to  $49 \pm 28$  ml/min per  $1.73 \text{ m}^2$  ( $n = 35$ ;  $P < 0.001$ ) (Figure 3b). Mean loss of eGFR was  $9 \pm 12$  ml/min per  $1.73 \text{ m}^2$  almost 1 year after baseline ( $n = 35$ ) and a significant negative correlation between the amount of albuminuria at baseline and the change in eGFR was observed ( $r = -0.82$ ,  $P < 0.01$ ;  $n = 20$ ) (Figure 4). BMI ( $27 \pm 6$  vs.  $27 \pm 6$  kg/m<sup>2</sup>;  $n = 22$ ;  $P = 0.62$ ) and blood pressure were almost similar

(systolic blood pressure:  $127 \pm 13$  vs.  $126 \pm 16$  mm Hg;  $n = 26$ ;  $P = 0.827$ ; diastolic blood pressure:  $82 \pm 12$  vs.  $81 \pm 11$  mm Hg;  $n = 26$ ;  $P = 0.705$ ).

### Longest Follow-Up About 2 Years After Initiation of SGLT2i Therapy (V4)

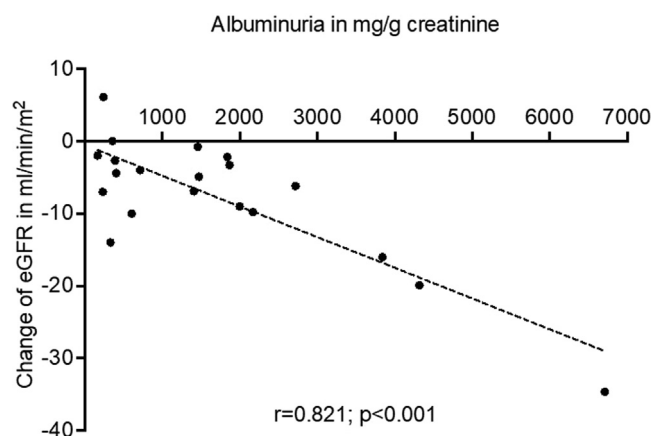
In 13 patients, data on a longer follow-up were available (mean follow-up:  $24 \pm 6$  month). Albuminuria was still lower compared to baseline ( $2127 \pm 1666$  vs.  $1903 \pm 1371$  mg/g creatinine;  $n = 7$ ;  $P = 0.524$ ). Serum-creatinine increased significantly from  $1.3 \pm 0.6$  to  $1.5 \pm 0.7$  mg/dl ( $n = 11$ ;  $P = 0.04$ ), and corresponding eGFR decreased from  $75 \pm 46$  to  $67 \pm 42$  ml/min per  $1.73 \text{ m}^2$  ( $n = 11$ ;  $P = 0.05$ ).

### Serum Albumin as Surrogate Marker of Loss of Urine Proteins

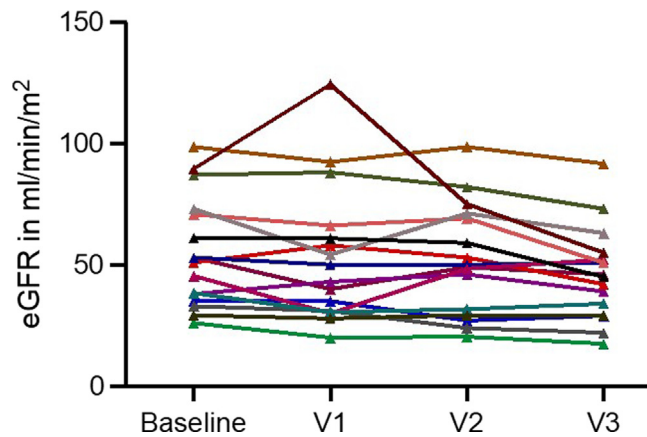
At a mean follow-up of  $12 \pm 2$  months after initiation of SGLT2i therapy, serum albumin increased significantly from  $3.7 \pm 0.7$  to  $4.0 \pm 0.4$  g/dl ( $n = 18$ ;  $P = 0.019$ ). The change in serum albumin in patients with hypoalbuminemia at baseline was calculated and a relevant increase was observed: serum albumin increased from  $3.1 \pm 0.4$  to  $3.4 \pm 0.3$  mg/dl after a mean follow-up of  $9 \pm 7$  months after baseline ( $n = 17$ ;  $P = 0.06$ ). Out of 17 patients with hypoalbuminemia at baseline, 8 (47%) recovered to serum albumin levels within the normal range at follow-up.

### Course of eGFR

A total of 16 patients had a follow-up at every single predefined visit. In these patients, a similar decrease of eGFR compared to the overall cohort was observed ( $55.1 \pm 22.8$  ml/min per  $1.73 \text{ m}^2$  to  $46.3 \pm 19$  ml/min per  $1.73 \text{ m}^2$ ;  $P = 0.02$ ) (Figure 5).



**Figure 4.** Correlation between amount of albuminuria at baseline and the change in eGFR after initiation of SGLT2i. Pearson's correlation between amount of albuminuria at baseline and absolute change in eGFR at a mean follow-up of  $11 \pm 2$  months ( $r = 0.821$ ;  $P < 0.01$ ;  $n = 20$ ). eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2 inhibitors.



**Figure 5.** Change in eGFR over time after initiation of SGLT2i therapy. eGFR at baseline, V1 (months 1–3), V2 (months 4–8) and V3 (months 9–15) in 16 patients, who completed every visit from V1 to V3. eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

### Genotype-Phenotype Correlation

To investigate a possible influence of the genotype, male patients with X-linked AS were divided into 2 groups depending on their pathogenic variant causing AS. Out of 28 patients, 17 (61%) had missense variants and 11 (39%) had nonmissense variants (defining a faster progression of their CKD). At baseline, patients with missense variants were older ( $35 \pm 12$  years;  $n = 16$  vs.  $27 \pm 9$  years;  $n = 11$ ), had a significant lower eGFR  $63 \pm 33$  ( $n = 16$ ) versus  $92 \pm 32$  ml/min per  $1.73 \text{ m}^2$  ( $n = 11$ ) and a higher median amount of albuminuria of 1865 (IQR: 2442;  $n = 11$ ) versus 750 (IQR: 763;  $n = 5$ ) mg/g creatinine. Of note, despite the higher amount of albuminuria at baseline, at V2 after a mean follow-up of 6 months, a significantly higher loss of eGFR was observed in patients with non-missense variants ( $13 \pm 9$  ml/min per  $1.73 \text{ m}^2$ ;  $n = 16$ ) than in patients with missense variants ( $4 \pm 9$  ml/min per  $1.73 \text{ m}^2$ ;  $n = 11$ ) ( $P = 0.023$ ). In parallel, median amount of albuminuria decreased in patients with missense variants from 1865 (IQR: 2442) to 775 (IQR: 1615) mg/g creatinine, whereas median amount of albuminuria increased in patients with nonmissense variants to 1086 (IQR: 450) mg/g creatinine.

### Children

In Table 2, we show the baseline characteristics and follow-up data from the 10 children in this study. All the children were treated with an angiotensin-converting enzyme inhibitor. Hearing loss was reported in 3 patients (30%). One patient had also hypercholesterolemia and vitamin D deficiency. In 1 patient, hyperglycemia was reported.

At baseline, mean age was  $15 \pm 3$  (range: 9–17) years, mean BMI was  $21 \pm 4 \text{ kg/m}^2$ . The mean longest

**Table 2.** Baseline characteristics and follow-up data after a mean follow-up of  $4 \pm 5$  months in 10 children

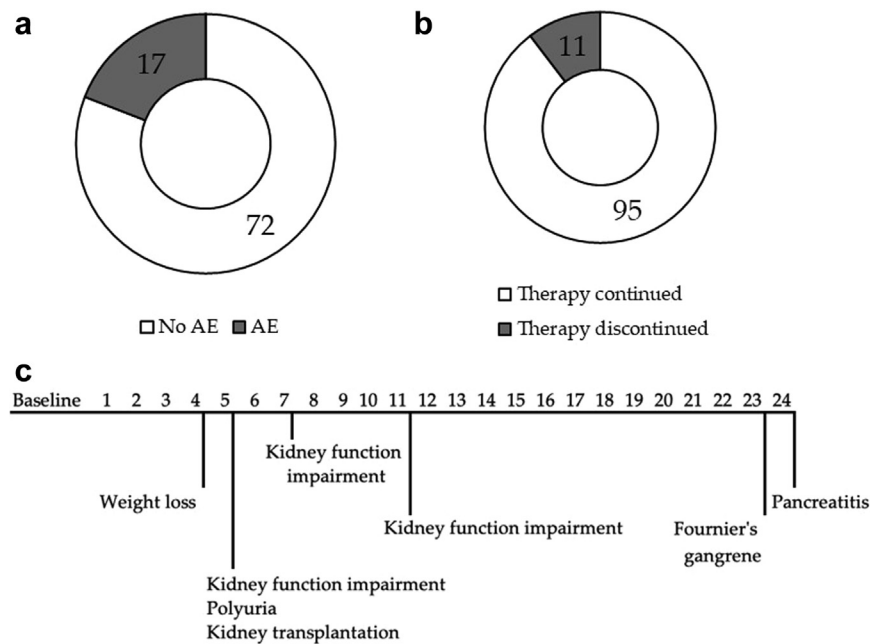
Characteristics	N	Baseline	Follow-up
Age (yrs)	10	$15 \pm 3$	
Male no. (%)	5	5 (50)	
Mode of inheritance (%)	10		
X-linked		9 (10)	
Autosomal		1 (10)	
BMI ( $\text{kg/m}^2$ )	10	$21 \pm 4$	
Systolic/diastolic blood pressure (mm Hg)	8	$116 \pm 13 / 72 \pm 11$	$117 \pm 13 / 71 \pm 13$
Creatinine (mg/dl)	10	$0.8 \pm 0.3$	$0.9 \pm 0.3$
eGFR (ml/min per $1.73 \text{ m}^2$ )	10	$119 \pm 32$	$107 \pm 36$
Proteinuria (mg/dl)	8	$114 \pm 94$	$122 \pm 110$
Albuminuria (mg/g creatinine)	2	$1426 \pm 1247$	$641 \pm 190$

BMI, body mass index; eGFR, estimated glomerular filtration rate. Values are mean  $\pm$  SD or  $n$  (%) as appropriate.

follow-up time was  $4 \pm 5$  months. Serum-creatinine increased from  $0.8 \pm 0.3$  to  $0.9 \pm 0.3$  mg/dl and eGFR decreased from  $119 \pm 32$  to  $107 \pm 34$  ml/min ( $n = 10$ ). In most patients, proteinuria was measured in mg/dl ( $n = 8$ ) and increased slightly ( $114 \pm 94$  vs.  $122 \pm 110$  mg/dl). Interestingly, in the 2 patients with already overt proteinuria, in which albuminuria was measured, albuminuria decreased from  $1426 \pm 1247$  to  $641 \pm 190$  mg/g creatinine. Blood pressure remained similar ( $116 \pm 13 / 72 \pm 11$  vs.  $117 \pm 13 / 71 \pm 13$  mm Hg;  $n = 8$ ).

### Safety

Data on AEs were reported in 89 patients (79%). At a total of 71 patient-years at risk (mean time on therapy was  $10 \pm 7$  months), 0.24 AEs per patient-year on SGLT2i were reported. In 72 patients (81%), there were no AEs reported (Figure 6a). The AEs in the remaining 17 patients (18%) included impairment of kidney function ( $n = 7$ , in 1 patient during a severe infection with SARS-CoV-2), headache ( $n = 2$ ), hypovolemia ( $n = 1$ ), 1 bone fracture (bike accident), genital infection in 1 female, and 1 patient reported an unwanted loss of weight. A 33-year-old female was hospitalized because of an acute necrotizing pancreatitis 2 years after therapy with SGLT2i was started. A 33-year-old male with X-linked AS received a kidney transplantation 5 months after SGLT2i was started. One 44-year-old male with compound heterozygous autosomal AS and an eGFR of  $27 \text{ ml/min per } 1.73 \text{ m}^2$  when SGLT2i was started, reached KF 9 months later. Ketoacidosis or major hypoglycemic events were not reported. The most severe AE was observed in a male without diabetes, who developed Fournier's gangrene after 23 months of treatment with SGLT2i.<sup>24</sup> In brief, this life-threatening situation developed within hours, requiring emergency wound debridement. During his stay on the intensive care unit, the patient developed an acute on chronic kidney injury AKIN III; however,



**Figure 6.** Frequency of adverse events and discontinuation of SGLT2i therapy. (a) Number of patients with observed adverse events (AEs) (white) and patients without observed AEs (dark grey) ( $n = 89$ ). (b) Number of patients without (therapy continued; white) and with discontinuation of therapy with SGLT2i (therapy discontinued; dark grey) ( $n = 106$ ). (c) Time to discontinuation of SGLT2i therapy in months. The reason for discontinuation in 1 patient after 7 months was not reported. SGLT2i, sodium-glucose cotransporter-2 inhibitors.

kidney function recovered to baseline. The patient slowly recovered with sequelae.

Data on discontinuation of therapy were available in 106 patients (95%). Therapy was discontinued in 9 patients (8%) (Figure 6b). Mean time to discontinuation of therapy was  $10 \pm 8$  months (Figure 6c). Therapy was discontinued due to increase of creatinine ( $n = 1$ ) or polyuria ( $n = 1$ ). In 2 patients, SGLT2i was discontinued due to impairment of kidney function and was restarted after infusion therapy. The patient with unwanted weight loss decided to pause therapy for a few months and restarted therapy with SGLT2i. Therapy was stopped permanently in the patient with the Fournier's gangrene and the patient with acute necrotizing pancreatitis. In 1 patient, the reason for discontinuation was not reported. In the 10 children of our study, there were no AEs observed and the treatment with SGLT2i was not discontinued.

## DISCUSSION

This worldwide, observational study investigated a cohort of patients, including 10 children, with AS, who started therapy with SGLT2i. The primary end point was change of albuminuria after 6 months on therapy. The primary mechanism by which SGLT2is are considered to be nephroprotective is afferent vasoconstriction and reduction in intraglomerular pressure due the tubuloglomerular feedback via the macula densa.<sup>25,26</sup> A marker of this reduction is a decrease in

the amount of albuminuria, which is largely independent of concomitant changes in metabolic parameters or eGFR.<sup>27</sup> Notably, a 25% decrease in albuminuria has been reported to provide confidence that an intervention would result in a clinical benefit.<sup>28</sup> In the adult patients of this study, at the first 3 follow-up visits after initiation of SGLT2i therapy, a consistent and significant reduction of albuminuria by  $>30\%$  was observed. This can be interpreted as a promising signal that the reduction of albuminuria in these patients might result in clinical benefit at longer follow-up. Importantly, this study showed a significant correlation between the amount of albuminuria at baseline and the later change of eGFR in patients with AS. Patients with truncating gene variants causing AS are less responsive to RASi therapy.<sup>29</sup> This study indicates that patients with AS with nonmissense variants might also be less responsive to SGLT2i therapy than patients with missense variants, because a significant higher loss of eGFR was observed in patients with AS with nonmissense variants in this study. Therefore, future studies investigating SGLT2i in AS should consider stratifying by genotype.

At baseline, a relevant number of patients had a hypoalbuminemia. In agreement with the decrease of albuminuria after start of SGLT2i therapy, 47% of the patients with hypoalbuminemia at baseline recovered to a normal serum albumin at follow-up. One can speculate that the positive effect of SGLT2i therapy on lowering albuminuria contributed to the increase in

serum albumin though regression to the mean over the cause of this study cannot be ruled out. Therefore, SGLT2i might be considered as an additional treatment option in patients with AS and hypoalbuminemia due to nephrotic range albuminuria.

Approximately 1 year after baseline, a significant decrease in the eGFR of  $-9 \pm 12$  ml/min per  $1.73 \text{ m}^2$  per year was observed. SGLT2i can cause an acute transient decrease in eGFR through a reduction in glomerular pressure.<sup>30</sup> For that reason, the decrease in eGFR observed in this study is thought to be, in part, triggered by the initiation of SGLT2i therapy. However, the change in eGFR in this study appears to be higher than in previously described changes in eGFR in other glomerular diseases. eGFR changed by  $-3.7$  and  $-3.5$  ml/min per  $1.73 \text{ m}^2$  per year in patients with focal segmental glomerulosclerosis and IgA nephropathy.<sup>31,32</sup> Due to the observational nature of this study, the change in eGFR is not placebo-controlled. This limitation should be acknowledged; however, patients with AS need to be recognized as a high-risk group for fast CKD progression.<sup>33</sup>

SGLT2is are, irrespective of hypertension status, associated with a slight reduction in blood pressure mediated through natriuresis, reduction in arterial stiffness, and improvement in endothelial function.<sup>34-37</sup> In this study, systolic blood pressure was significantly lower at V2 ( $128 \pm 14$  vs.  $124 \pm 13$  mm Hg). However, this difference was not observed after a longer follow-up, possibly due to the small number of patients remaining at that time point. The slight decrease of blood pressure might contribute to the nephroprotective effect of SGLT2is. Reducing glomerular filtration pressure can alleviate proteinuria and subsequent renal tubular and interstitial damage.<sup>6,11,38</sup> Therefore, preventing angiotensin 2-mediated constriction of the efferent arteriole by RASi is the cornerstone of antiproteinuric therapy to reduce podocyte injury in AS.<sup>39,40</sup> SGLT2i are expected to have an additive effect on the glomerulus via afferent arteriole constriction. Therefore, combining RASi with SGLT2i in patients with albuminuria due to glomerular disease is anticipated to enhance KF-free timespan.<sup>41</sup> Although the precise mechanisms underlying preservation of kidney function by SGLT2i are not fully understood, other proposed pathways include inflammation and fibrosis suppression as well as a reduction in renal ischemia.<sup>42,43</sup>

Therapy with SGLT2i was overall well-tolerated with a relatively low rate of discontinuation of therapy or reported AEs. AEs related to hypovolemia, which were reported to be more common in patients treated with SGLT2i, was observed in 1 patient.<sup>44</sup> Ketoacidosis or severe hypoglycemia were not

observed; however, 2 severe AEs (acute necrotizing pancreatitis and Fournier's gangrene) occurred. Due to the relevant loss of eGFR and severe AEs observed in this study (though a relationship between SGLT2i and these events is uncertain), a cautious approach is currently recommended when administering SGLT2 inhibitors to patients with AS. Furthermore, this underscores the importance of generating further high-level evidence for efficacy and safety when SGLT2i are prescribed in rare disease such as AS, at early stages of CKD or in young patients, especially children, because these groups were not well-represented in the previous RCTs. Therefore, the multicenter, randomized, double-blind, placebo-controlled, trial DOUBLE PRO-TECT Alport trial (NCT05944016) will assess safety and efficacy of the SGLT2i dapagliflozin in children and young adults with AS. Eligible patients will be 2:1 randomly assigned to 48 weeks of treatment with dapagliflozin or placebo. The primary end point will be change in urine albumin-to-creatinine ratio and, as a key secondary outcome, eGFR change will be analyzed.<sup>45</sup>

This study had limitations that warrant cautious interpretation of the results. Due to the observational nature of this study, the timing of urine albumin-to-creatinine ratio and eGFR assessments after treatment initiation were not standardized and changes in eGFR and urine albumin-to-creatinine ratio were not placebo-controlled. The retrospective design also limits the ability to comprehensively assess the safety profile of SGLT2i in patients with AS. Although the lack of a control arm limits the generalizability of the study findings, including one might have posed challenges in interpretation. Patients in a control arm would likely have a more stable disease course compared to those who opted for a new treatment option. This inherent selection bias would have complicated the analysis of treatment effects. Therefore, the study design focused on intraindividual changes in eGFR and urine albumin-to-creatinine ratio to assess treatment response. Conversely, this approach introduces a potential selection bias of its own, with a possible overrepresentation of patients with a higher risk of CKD progression. Furthermore, only a small number of children and adolescents could be included in the study, the observation period for these patients was relatively short, and due to the unavailability of cystatin C, the CKiD U25 formula could not be used. In addition, for 6 patients, the method used to confirm the diagnosis was not provided.

Despite these limitations, this study provides first evidence for a possible nephroprotective effect of SGLT2i in patients with AS by including a substantial number of patients with AS, considering the rarity of



the disease and the recent approval of SGLT2i for CKD; and formed the scientific basis for the current RCT with SGLT2i in children and young adults with AS, DOUBLE PRO-TECT Alport.

## CONCLUSION

In conclusion, this study indicates that, additive to RASi, SGLT2i have the potential to reduce the amount of albuminuria in patients with AS. This study successfully formed the scientific basis for the current RCT with SGLT2i in children and young adults with AS, DOUBLE PRO-TECT Alport. Future studies are needed to investigate the long-term effects of SGLT2i on CKD progression in patients with AS to assess whether the observed reduction in albuminuria translates to a delay in KF.

## DISCLOSURE

JB, OG, TF, and JS are members of the steering committee of the DOUBLE PRO-TECT Alport trial. OG received advisory fees from AstraZeneca, his employer received advisory fees from Boehringer Ingelheim. MH has received speaker fees from AstraZeneca. All the other authors declared no conflicting interests.

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## DATA AVAILABILITY STATEMENT

After deidentification, individual participant data that underlie the results reported in this article will be shared to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. The full study protocol is provided in the [Supplementary Material](#). Requests should be sent to the corresponding author.

## AUTHOR CONTRIBUTIONS

JB wrote the first draft of the article and contributed to data analysis, data interpretation, content and design of all figures, discussion of the results and manuscript. OG contributed as initiator and head principal investigator of the trial, had access to and assessed the final data and critically revised the manuscript. TF critically revised the manuscript and contributed to data analysis, data interpretation, and discussion of the results and the

manuscript. DPG, JS, JD, YZ, CB, ANT, MH, JAS, SS, HGK, AC-K, VG, KC, BK, JF, UW, MC, MS, R-UM, PT, BH, MZ, BK, and JH contributed to data collection, data interpretation, and discussion of the results and the manuscript. All authors edited and approved the final version of the article.

## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

STROBE Checklist.

Guard Alport study protocol.

Questionnaire.

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