ORIGINAL ARTICLE

Severity of arterial and/or arteriolar sclerosis in IgA nephropathy and the effects of renin–angiotensin system inhibitors on its prognosis

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Abstract

IgA nephropathy (IgAN) patients often suffer from arterial and/or arteriolar sclerosis (AAS); however, it is unclear whether these features are associated with a poor prognosis. This retrospective cohort study aimed to analyse the prognosis of IgAN patients with AAS and assess whether treatment with renin–angiotensin system inhibitors (RASI) improved their survival. The study included 678 IgAN patients, who were grouped into AAS0 ($n = 340$; AAS absent) and AAS1 ($n = 338$; AAS present) groups. Each patient's clinical, laboratory, and histological backgrounds and 20-year renal prognosis were analysed. In the AAS1 group, the impact of RASI initiated during the follow-up period on the renal prognosis was also evaluated after adjustments for background characteristics. IgAN patients with AAS had significantly higher age, blood pressure, body mass index, total cholesterol, uric acid levels, and proteinuria than patients without AAS; they also had more severe histological findings, decreased renal function, and lower survival rates than those without AAS (64.0 versus 84.7%, $p < 0.001$). Multivariate Cox regression analysis incorporating clinical and histological findings and treatments revealed AAS as an independent factor for disease progression (hazard ratio: 2.23, $p = 0.010$). Participants in the AAS1 group treated with RASI during follow-up had a significantly higher renal survival rate than those who were not (75.5 versus 44.3%, $p = 0.013$). In conclusion, AAS was found to be associated with serious clinical, laboratory, and histological findings and poor prognosis. RASI initiated during the follow-up period was found to improve renal prognosis.

Keywords: IgA nephropathy; arterial and/or arteriolar sclerosis; arterial intimal thickening; arteriolar hyaline; renin–angiotensin system inhibitors; renal prognosis

Introduction

The Oxford classification is the first universal histological classification system developed by the International IgAN Network and the International Renal Pathology Society [1–3]. This classification system has driven the progression of histological IgA nephropathy (IgAN) evaluation by appraising the following five lesions: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C). These pathological lesions were selected due to their reproducibility among pathologists, their correlation with clinical outcomes, and the correlations between them. The features

of intrarenal arterial and/or arteriolar sclerosis (AAS), such as arterial intimal thickening (AIT) in the interlobular artery and/or arteriolar hyaline (AH) in the arterioles, were not included in the Oxford classification because AH showed poor reproducibility (intraclass correlation coefficients < 0.4) and the presence of the most severe level of AAS was not statistically associated with a decreased survival from end-stage renal disease (ESRD) or a 50% drop in the glomerular filtration rate (GFR) [1,2]. A number of previously reported studies have evaluated the Oxford classification [4] and, as a result, it has become popular among nephrologists. Moreover, the Oxford classification revealed pathological features and associations between therapies, such as

immunosuppressive treatments and renin–angiotensin system (RAS) inhibitors (RASI). No interactions were detected between RASI and any of the five selected pathological features but the relationship between RASI and AAS has not been demonstrated clearly [1].

However, it is known that AAS are associated with older age [5], dyslipidaemia [6], hypertension [5,7,8], hyperuricaemia [6,7], higher levels of proteinuria [5–7], poor renal function [5,7], and other severe renal chronic lesions, such as glomerular sclerosis and tubulointerstitial damage [7]. Moreover, several recent studies have reported a relationship between AAS and renal survival [5], interstitial blood flow and hypoxia [9], nocturnal blood pressure [10], and C3 deposition, which result in unfavourable outcomes [11]. These results suggest that AAS may be an independent risk factor for IgAN. Additionally, it is known that AAS induces ischaemic glomerulopathy, increases the activity of RAS, and causes glomerular hypertension and hyperfiltration [12]. A previous report has indicated that RASI are effective in IgAN [13]; however, whether AAS are risk factors for progression in IgAN, and the interactions between RASI and AAS in IgAN, remain unclear in the current literature. Thus, this study aimed to evaluate the relationship between AAS, renal prognosis, and other clinical, laboratory, and histological factors, and to analyse whether RASI is an effective therapy for IgAN patients with AAS.

Materials and methods

Study population and design

In this retrospective cohort study, 1,147 patients with IgAN diagnosed by renal biopsy at the Tokyo Women's Medical University between 1974 and 2015 were included. The exclusion criteria were: renal biopsy specimen containing fewer than eight glomeruli; renal biopsy specimen that was not analysed for AAS; the presence of other systemic diseases such as systemic lupus erythematosus, liver cirrhosis, and IgA vasculitis; and a history of prior observation for less than 1 year after undergoing renal biopsy (unless ESRD occurred within 1 year). To analyse the relationship between AAS and renal prognosis, AAS was evaluated in 678 IgAN patients. The patients were classified into two groups: those with AAS (AAS1: $n = 338$) and those without AAS (AAS0: $n = 340$). The clinical, laboratory, and histological findings, along with the treatments and renal prognosis, were analysed and compared between the groups. Additionally, risk factors associated with progression were analysed using univariate and multivariate Cox regression analyses. IgAN patients classified as AAS1 underwent evaluation of the impact of RASI initiated during the follow-up period. Accordingly, appropriate adjustments were made for comparing the clinical and histological findings and treatment between the RASI (+) groups and the RASI (−) groups (controls). Renal prognosis was also evaluated (Figure 1).

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Tokyo Women's Medical University (reference #5104-R). Written informed consent to obtain a renal biopsy was obtained from all the participants. All patients were able to access information about this study (aim, plan, study participants, and duration) via the institutional webpage, and they were provided with the opportunity to ask questions and discuss the details and results of this study with us.

Diagnosis of IgAN and histological evaluation of the renal biopsy specimens

IgAN was diagnosed according to the presence of mesangial proliferative changes by light microscopy, mesangial IgA deposition by immunofluorescence, and/or mesangial electron-dense deposits by electron microscopy. Histological findings were graded according to the Oxford classification [1–3]. AAS was recognised as the presence of AIT and/or AH. To reduce sampling errors, AH was considered as the presence of any level of hyalinosis in the arterioles and AIT was considered as the presence of any level of intimal thickness, although they were scored as absent, mild, moderate, and severe based on the Oxford classification. All histological findings were obtained from pathology reports, some of which were repeatedly reviewed by the pathologist for confirmation of the findings.

Clinical and laboratory data

Each patient's sex, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded. Laboratory data, which included the estimated GFR (eGFR), uric acid (UA), total cholesterol (T-Cho), triglyceride (TG), urinary protein excretion (U-Prot), and urinary red blood cells (U-RBC), were evaluated at the time of renal biopsy as baseline data. The eGFR was calculated using the Isotope Dilution Mass
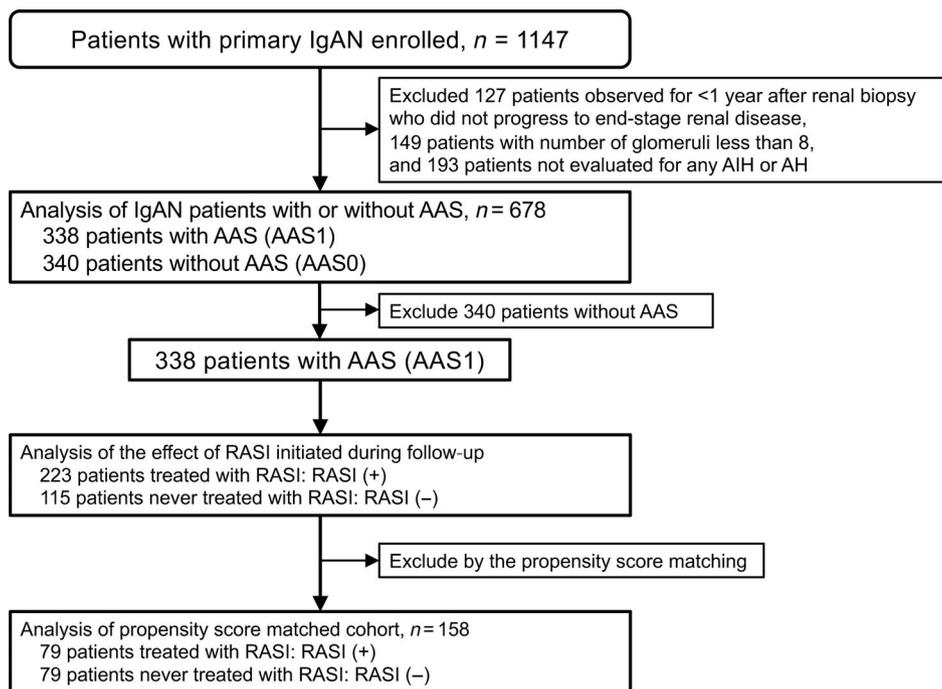
Figure 1. Algorithm of the study's design.

Table 1. Baseline characteristics of IgAN patients with AAS0 and AAS1.

	All patients	AAS0	AAS1	*P* value
Clinical findings				
Age (years)	31.0 (25.0–42.0)	27.0 (23.0–32.0)	40.0 (30.0–49.0)	<0.001
Sex (male/female)	274/404	128/212	146/192	0.141
BMI (kg/m^2)	21.4 (19.6–23.6)	20.8 (19.2–22.4)	21.8 (20.1–24.5)	<0.001
SBP (mmHg)	120.0 (110.0–130.0)	116.0 (107.0–125.0)	123.0 (113.5–137.0)	<0.001
DBP (mmHg)	74.0 (66.0–83.0)	71.0 (64.0–80.0)	78.0 (69.0–86.0)	<0.001
MAP (mmHg)	89.3 (81.3–98.7)	86.3 (78.8–93.3)	92.7 (84.0–101.7)	<0.001
Laboratory findings				
eGFR (ml/min.1.73 m^2)	75.6 (59.0–94.1)	84.2 (68.0–103.3)	66.3 (51.1–81.4)	<0.001
UA (mg/dl)	5.5 (4.6–6.8)	5.2 (4.2–6.4)	5.9 (4.8–7.2)	<0.001
T-Cho (mg/dl)	193.0 (169.0–225.5)	184.0 (162.2–207.5)	205.0 (179.0–240.0)	<0.001
TG (mg/dl)	100.0 (73.0–143.0)	89.5 (66.8–122.5)	108.0 (79.0–165.5)	<0.001
U-Prot (g/day)	0.65 (0.29–1.34)	0.5 (0.22–1.09)	0.78 (0.37–1.67)	<0.001
U-RBC (counts/HPF)				<0.001
(<5, 5–25, 26–49, 50–99, ≥100)	70, 296, 112, 82, 115	24, 130, 57, 49, 79	46, 166, 55, 33, 36	
Histological findings, *n*				
M0/M1	340/338	180/160	170/168	0.491
E0/E1	365/313	186/154	179/159	0.648
S0/S1	177/501	109/231	68/270	<0.001
T0/T1/T2	505/134/39	293/36/11	212/98/28	<0.001
C0/C1/C2	335/309/33	177/145/17	158/164/16	0.321
AIT0/AIT1	415/263	340/0	75/263	–
AH0/AH1	379/299	340/0	39/299	–

HPF, high-power field.

Spectrometry adjusted Modification of Diet in Renal Disease (IDMS-MDRD) study equation for Japanese individuals (eGFR $= 194 \times$ S-Cr$^{-1.094} \times$ age$^{-0.287} \times$ 0.739 [if female]) [14]. The time taken to progress to ESRD, which was defined as requiring dialysis or renal transplantation, was considered the endpoint. Risk

factors associated with the progression to ESRD were also evaluated.

Statistical analysis

Data are expressed as mean $\pm$ standard deviation for normally distributed data and median and inter-quartile range for skewed data and were analysed using JMP® Pro 15.0.0 (SAS Institute Inc., Cary, NC, USA). The unpaired Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for skewed data were used to compare the clinical findings between patients treated with immunosuppressants and those who were not. The chi-square test was used to compare the sex distribution, the number of patients of each U-RBC grade at the time of renal biopsy, the Oxford classification, the prevalence of AAS, and immunosuppressive therapy, including corticosteroid therapy, tonsillectomy, and RASI use, between the groups. The cumulative renal survival rate until ESRD was analysed by the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate Cox regression analyses were used to evaluate the risk of deterioration to ESRD, which was expressed as a hazard ratio with 95% confidence intervals. Propensity score matching was conducted to adjust for differences in the clinical and histological findings and treatments between the RASI (+) and RASI (−) groups. A logistic regression model was used to estimate the propensity score between both groups. Matching was conducted using 1-1-digit matching (the nearest neighbour matching method). In all analyses, $p < 0.05$ was considered to be statistically significant.

Results

Comparison of the baseline characteristics between IgAN patients with or without AAS

Table 1 demonstrates a comparison of the clinical, laboratory, and histological findings and treatments between the AAS0 and AAS1 groups. The median age, BMI, SBP, DBP, and MAP were significantly higher in the AAS1 group than in the AAS0 group ($p < 0.001$). Renal function, hyperuricaemia, and dyslipidaemia were significantly more severe and the U-Prot was significantly higher in the AAS1 group than in the AAS0 group ($p < 0.001$). The histological findings demonstrated that the incidence of the S1, T1, and T2 lesions was significantly higher in the AAS1

group than in the AAS0 group ($p < 0.001$). The numbers of M, E, and C lesions were similar between the two groups.

The 20-year renal survival rate and risk factors for ESRD in IgAN patients with or without AAS

The renal survival rate was significantly higher in the AAS0 group than in the AAS1 group (84.7 versus 64.0%, $p < 0.001$; Figure 2). In univariate Cox regression analysis, the presence of AAS was found to be a significant risk factor for the progression to ESRD (Table 2, crude). In multivariate Cox regression analysis, we selected some histological, laboratory, and clinical findings that showed significant differences between the AAS1 and AAS0 groups in Table 1 and in the univariate Cox regression analysis (data not shown); multivariate analysis also revealed that the presence of AAS and other histological findings (S and T scores in the Oxford classification) were significant risk factors for progression to ESRD (Table 2,
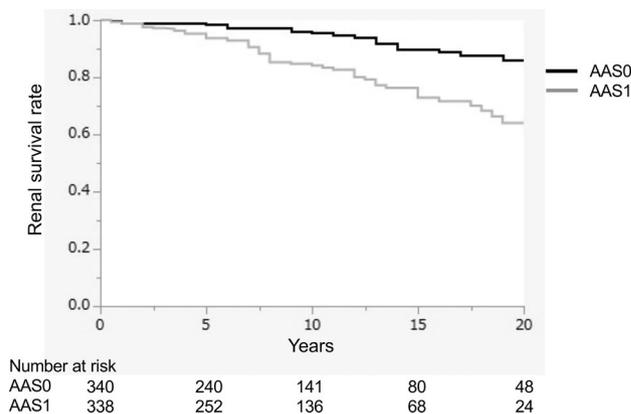

Figure 2. Renal survival rates in IgAN patients according to the absence or presence of AAS. Renal survival rate until ESRD was reached (AAS0: 84.7%, AAS1: 64.0%; $p < 0.001$).

Table 2. Univariate and multivariate Cox regression analyses of the presence of AAS as a risk factor in IgAN patients.

AAS1	HR	95% CI	P value
Crude	3.01	1.85–5.26	<0.001
Model 1	2.07	1.20–3.58	0.009
Model 2	1.72	0.96–3.08	0.067
Model 3	2.23	1.21–4.09	0.010

Model 1: adjusted for S and T scores in Oxford classification. Model-2: model 1 + age, BMI, MAP, eGFR, and U-Prot. Model 3: model 2 + immunosuppressants, tonsillectomy, and RASI.
CI, confidence interval; HR, hazard ratio.

model 1) and that AAS, along with clinical and laboratory findings, histological findings, and treatments (immunosuppressants, tonsillectomy, and RASI), were significant risk factors for progression to ESRD (Table 2, model 3); however, it was not significant with clinical and laboratory findings (age, BMI, MAP, eGFR, and U-Prot) and histological findings (Table 2, model 2).

Table 3. Comparison of baseline characteristics between RASI (−) and RASI (+) groups in the IgAN patients in the AAS1 group.

	Before propensity score matching			After propensity score matching		
	RASI (−) group ($n = 115$)	RASI (+) group ($n = 223$)	P value	RASI (−) group ($n = 79$)	RASI (+) group ($n = 79$)	P value
Clinical findings						
Age (years)	33.0 (27.0–43.0)	42.0 (33.0–51.0)	<0.001	37.0 (29.0–47.0)	37.0 (30.0–46.0)	0.872
Sex (male/female)	40/75	106/117	0.024	35/44	31/48	0.519
BMI (kg/m^2)	21.1 (19.3–23.2)	22.3 (20.5–25.4)	<0.001	21.6 (20.0–23.4)	21.7 (19.9–24.3)	0.870
SBP (mmHg)	118.0 (109.0–128.0)	126.0 (117.0–140.0)	<0.001	120.0 (110.0–131.0)	120.0 (112.0–133.0)	0.734
DBP (mmHg)	72.0 (66.0–84.0)	80.0 (71.0–88.0)	<0.001	74.0 (68.0–87.0)	76.0 (68.0–82.0)	0.355
MAP (mmHg)	87.3 (80.0–97.0)	95.8 (87.7–104.3)	<0.001	90.5 (82.3–100.3)	90.7 (83.3–99.0)	0.777
Laboratory findings						
eGFR (ml/min.1.73 m^2)	75.4 (55.3–86.8)	63.8 (49.9–78.1)	0.003	66.4 (53.4–81.0)	72.8 (49.9–91.9)	0.674
T-Cho (mg/dl)	201.8 (170.0–248.0)	205.5 (183.1–235.5)	0.617	210.0 (168.0–250.0)	200.0 (177.5–240.5)	0.986
TG (mg/dl)	97.5 (72.5–157.0)	114.0 (82.0–169.0)	0.057	116.0 (78.5–166.5)	105.5 (79.0–159.0)	0.630
U-Prot (g/day)	0.5 (0.28–1.77)	0.94 (0.48–1.67)	0.009	0.62 (0.27–1.73)	0.75 (0.31–2.15)	0.640
U-RBC (counts/HPF) (<5, 5–25, 26–49, 50–99, ≥100)	11, 52, 20, 17, 15	35, 114, 35, 16, 21	0.090	9, 37, 12, 13, 8	13, 41, 11, 6, 7	0.451
Histological findings, n						
M0/M1	57/58	113/110	0.847	35/44	44/35	0.152
E0/E1	58/57	121/102	0.504	39/40	43/36	0.524
S0/S1	30/85	38/185	0.053	19/60	13/66	0.234
T0/T1/T2	87/18/10	125/80/18	<0.001	57/15/7	756/20/3	0.306
C0/C1/C2	47/63/5	111/101/11	0.252	33/43/3	43/32/4	0.214
AIT0/AIT1	30/85	45/178	0.220	12/67	10/69	0.646
AH0/AH1	19/96	20/203	0.044	20/59	16/63	0.448
Treatment, n						
Immunosuppressants (−/+)	43/72	84/139	0.960	36/46	26/53	0.249
Tonsillectomy (−/+)	74/41	150/73	0.592	55/24	48/31	0.242
RASI (−/+)	115/−	−/223	−	79/−	−/79	−

HPF, high-power field; RASI (−) group, RASI never treated during the follow-up period; RASI (+) group, RASI initiated during the follow-up period.
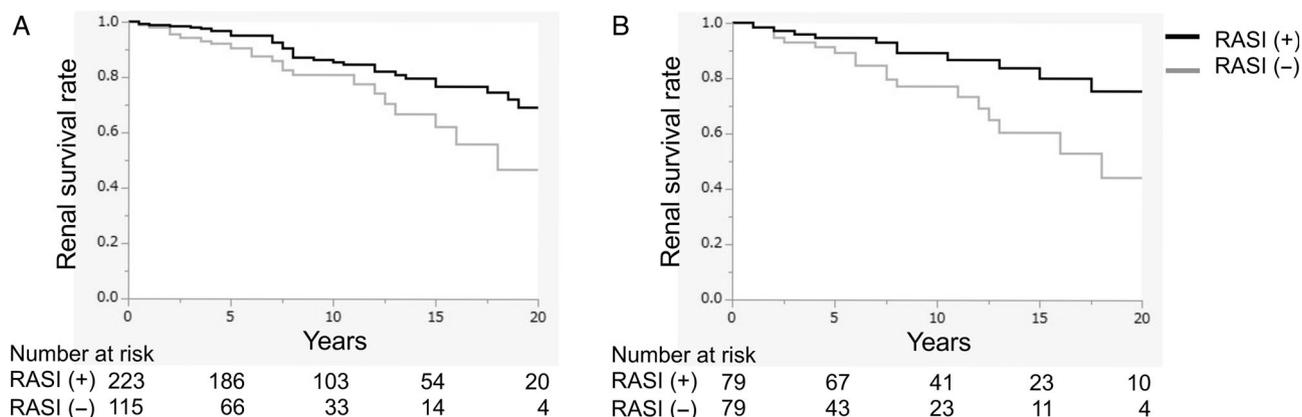

Figure 3. Renal survival rates in patients with IgAN according to whether they received RASI during the follow-up period. Renal survival rates until ESRD in IgAN patients with AAS1 (A) before propensity score matching (RASI (+): 69.4%, RASI (−): 46.7%; $p = 0.019$) and (B) after propensity score matching (RASI (+): 75.5%, RASI (−): 44.3%; $p = 0.013$) are shown.

Comparison of the baseline characteristics and renal survival rate between IgAN patients with AAS who were treated with RASI initiated during the follow-up period and those who were not

In the AAS1 group, 338 IgAN patients were classified into the RASI (+) group ($n = 223$; RASI initiated during the follow-up period) and the RASI (−) group ($n = 115$; control group). The RASI (+) group was found to have more severe clinical, laboratory, and histological findings than the RASI (−) group (Table 3, left). Other treatments, such as immunosuppressants and tonsillectomy, were similar between the two groups; however, despite more severe disease, the 20-year renal survival rate was significantly higher in the RASI (+) group than in the RASI (−) group (69.4 versus 46.7%, $p = 0.019$; Figure 3A). After adjusting for background characteristics using propensity score matching with a logistic regression model for significantly different factors, such as age, sex, BMI, MAP, eGFR, U-Prot, and T-score (calliper a: 0.20, calliper c: 0.23), the baseline characteristics were found to be similar between the two groups (Table 3, right); however, the 20-year renal survival rate was significantly higher in the RASI (+) group than in the RASI (−) group (75.5 versus 44.3%, $p = 0.013$; Figure 3B). Univariate and multivariate Cox regression analyses revealed RASI as an independent factor that appeared to slow the disease progression in the AAS1 group (see supplementary material, Table S1).

Discussion

This study evaluated whether AAS was an independent risk factor for IgAN and whether RASI prevented progression in IgAN patients with AAS. Initially, we confirmed that IgAN patients with AAS had a higher age, BP, T-Cho, TG, and UA, which were also associated with systemic atherosclerosis. Moreover, AAS was found to be associated with lower renal function; higher concentrations of U-Prot; and S1, T1, and T2 lesions by the Oxford classification. Kaplan–Meier analysis, the log-rank test, and univariate and multivariate Cox regression analyses demonstrated that the presence of AAS was a significant risk factor for progression of the disease. These results indicate that AAS results from several clinical factors related to systemic atherosclerosis and chronic histological findings and that it is important to control these risk factors to prevent the progression of IgAN. The presence of AAS induces microvascular narrowing, which subsequently causes glomerular ischaemia and the

activation of RAS [6]. Similarly, AAS induces glomerular hypertension and the impairment of renal autoregulation. All these factors induce systemic hypertension, subsequent glomerular hypertension, and hypertrophy of the remaining glomeruli, which results in glomerulosclerosis, tubulointerstitial damage, renal dysfunction, and proteinuria [15]. Therefore, it was hypothesised that RASI might prevent the progression to ESRD in IgAN patients with AAS. We suspected that RASI initiated at any time during the follow-up period might affect IgAN with AAS and prevent progression to ESRD because AAS are generally considered to cause irreversible chronic lesions. Then, we analysed the effects of RASI initiated during the follow-up period. The results revealed that IgAN patients in the AAS1 group treated with RASI were older, had a higher BP, and suffered from more severe renal dysfunction and tubulointerstitial damage than patients who were not treated with RASI. Despite this, treatment with RASI was found to significantly improve renal survival in IgAN patients with AAS. As expected, after adjusting for background characteristics in both groups, RASI was found to significantly improve renal survival in IgAN patients with AAS. Moreover, in IgAN patients without AAS, the reno-protective effects of RASI were not observed (see supplementary material, Figure S1). All these results support our hypothesis that AAS are risk factors for progression of IgAN, and that RASI is effective in IgAN patients with AAS, which is consistent with the findings of previous studies that reported that AAS induces glomerular ischaemia, increases RAS activity, and impairs autoregulation [7,11]. Previous reports also support our hypothesis that the reno-protective effects of RASI include the suppression of glomerular hyperfiltration and glomerular hypertension, which are caused by the activation of RAS and increase in angiotensin II, thereby resulting in vasoconstriction, modification of the glomerular basement membrane, suppression of nephrin, induction of profibrogenic and proinflammatory cytokines, induction of chemokines, injury to podocytes, generation of reactive oxygen species, activation of nuclear factor-kappa B, and stimulation of fibroblast proliferation [12,16]. RASI-induced suppression of RAS activation also reduces glomerular permeability and proteinuria and prevents a progressive decline in renal function. AAS was found to induce glomerulosclerosis and related lesions but our results differ from the original Oxford classification [1,2] and a previous report [17]; there are very few reports that describe the beneficial effects of RASI on IgAN patients with arteriolar lesions. Kaneko *et al* reported that AH was associated with renal prognosis

on univariate and multivariate analyses, considering other MEST-C scores, but not with clinical findings or RASI [5]. Zhang *et al* reported that AAS was associated with renal prognosis on univariate analysis, and that RASI prevented ESRD in patients with vascular lesions, including AAS and acute arterial lesions, such as arteriolar endothelial swelling, inflammatory cell infiltration, and thrombosis [18]. These previous reports support the hypothesis and results of this investigation.

Our study has limitations. First, it is a single-centre cohort study undertaken in Japan. AAS are significantly related to obesity, hypertension, dyslipidaemia, and hyperuricaemia, the rates of which vary significantly between countries due to different cultures, lifestyles, and dietary habits. Therefore, this study should be repeated internationally to obtain a global perspective. Second, this study is a retrospective analysis. Although patient characteristics were similar after propensity score matching, large randomised controlled trials are needed to generate more robust data.

In conclusion, our results suggest that AAS are associated with clinical and histological factors that cause disease progression in patients with IgAN. AAS may be an indicator of poor renal prognosis; however, treatment with RASI, initiated at any time during the follow-up period, may effectively slow the rate of patient decline.

Acknowledgement

Author contributions statement

NS, TM, YM and KK conceived the experiments and analysed the data. NS, YM and TM carried out the experiments. All authors were involved in writing the paper and had final approval of the submitted and published versions.

Data availability statement

The clinical data, study protocol, and statistical analysis plan that support this research are available from the corresponding author, TM, upon reasonable request, and with restrictions on information that could compromise the privacy of the patients.

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SUPPLEMENTARY MATERIAL ONLINE

Figure S1. Renal survival rate in IgAN patients treated with or without RASI in the AAS0 group

Table S1. Independent risk factors associated with disease progression identified using univariate and multivariate Cox regression analyses in IgAN patients with AAS