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ORIGINAL ARTICLE

Initiation of renin–angiotensin system inhibitors and first complete remission in patients with primary nephrotic syndrome: a nationwide cohort study

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Abstract

Background Evidence on renin–angiotensin system inhibitors (RASis) effect in reducing urinary protein levels in patients with nephrotic syndrome is insufficient. We determined whether RASis can induce complete remission (CR) in patients on immunosuppressive therapy.

Methods This cohort study included 84 adults (median age, 65 years; males, 57%) with primary nephrotic syndrome (excluding minimal change disease) not receiving RASis during enrollment in the Japanese Nephrotic Syndrome Cohort Study from January 2009 to December 2010, and were followed up for 5 years. Exposure and outcome were RASi initiation and first CR, respectively. Marginal structural models and Poisson regression were used to account for time-varying covariates and estimate causal effects of RASis on CR.

Results Overall, 51 (61%), 73 (87%), and 55 (66%) patients had membranous nephropathy, were prescribed immunosuppressive agents at baseline (1-month post-renal biopsy and/or at start of immunosuppressive therapy), and were prescribed RASis during the study period, respectively. Sixty-five patients experienced first CR (incidence rate, 5.05/100 person-months). RASi use was associated with a higher (adjusted incidence rate ratio [aIRR] 2.27, 95% confidence interval [CI] 1.06–4.84), and lower (aIRR: 0.17, 95% CI 0.04–0.68) first CR in patients with membranous nephropathy and other pathologies, respectively.

Conclusion RASis are beneficial as adjuvant therapy for inducing remission in patients with membranous nephropathy.

Keywords Renin–angiotensin system · Nephrotic syndrome · Membranous nephropathy · Glomerular disease

Introduction

Prolonged proteinuria in nephrotic syndrome is a risk factor for the progression of chronic kidney disease. Induction therapy with corticosteroids and/or immunosuppressive agents, tailored according to pathological type is the mainstay of treatment for achieving complete remission (CR).

In the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, renin–angiotensin blockade using renin–angiotensin system inhibitors (RASis), such as angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), is recommended as a first-line supportive therapy to reduce proteinuria for virtually all pathological types [1]. Moreover, an anti-proteinuric effect of RASis in nephrotic syndrome was expected by Japanese nephrologists [2]. According to recent data from the Japanese Nephrotic Syndrome Cohort Study (JNSCS), approximately 60% and 35% of patients with membranous nephropathy (MN) and focal segmental glomerulosclerosis (FSGS) were prescribed new RASi within 2 months after diagnosis or initiation of immunosuppressive therapy, respectively, including normotensive patients [3]. However, there is still insufficient evidence on the effect of RASis in reducing urinary protein levels in patients with

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nephrotic syndrome, especially with regard to achieving CR.

ARBs reduce urinary protein levels in patients with nephrotic syndrome in several randomized trials [4–6]. However, these studies did not examine CR as a study endpoint, and had a limited duration of only 12 months. In addition, there are no studies examining MN alone. One observational study conducted among patients receiving conservative therapy for MN with nephrotic syndrome demonstrated that RASis are associated with a greater likelihood of remission [7]. However, the effectiveness of adding a RASi as adjuvant therapy in patients with nephrotic syndrome who are treated with corticosteroids and/or immunosuppressive drugs has not yet been demonstrated [8, 9]. Despite the fact that the aforementioned KDIGO guidelines state that supportive therapy including RASis is the first-line therapy [1], the Japanese practice guidelines for nephrotic syndrome in 2017 state that corticosteroids monotherapy is preferred over supportive therapy for MN [10].

Therefore, this study analyzed the association between new RASi use and the incidence of first CR in patients with primary nephrotic syndrome who were registered in the JNSCS, a nationwide cohort study, using a trial emulation approach. Using a new user design with a marginal structural model [11–14] will ensure a better understanding of the likelihood of achieving first CR where all study subjects are new RASi users.

Materials and methods

Study design and setting

We conducted a retrospective cohort study using data from the JNSCS. The JNSCS protocol has been described in detail elsewhere [15]. Briefly, we included JNSCS-enrolled patients who were diagnosed with primary nephrotic syndrome via kidney biopsy between January 2009 and December 2010 across 54 facilities and followed up for 5 years. Nephrotic syndrome was defined as a urinary protein level of ≥ 3.5 g/day and a serum albumin level of < 3.0 g/dL.

The participant registration date for the JNSCS protocol was set as the date of immunosuppressive therapy initiation, excluding patients who were never treated with immunosuppressive therapy. The registration date for the latter patients was set as the date of renal biopsy (Visit 0 in Fig. 1). Data were collected at registration and at follow-up visits 1, 2, 6, 12, 24, 36, 48, and 60 months after registration (Visits 1 to 8 in Fig. 1). Medical personnel at each facility obtained the data from chart reviews.

Participants

In this study, patients diagnosed with primary nephrotic syndrome as per the above definition and with indicative renal pathology were eligible. However, patients with minimal change disease (MCD) were excluded because they were expected to respond immediately to immunosuppression [1]. Moreover, patients who were already on RASis at Visit 0 were excluded because we aimed to target only new RASi users to avoid bias from the inclusion of chronic users [11]. Hence, the start of the follow-up period (the study baseline) was set as Visit 1 (Fig. 1). Therefore, patients who were censored at Visit 1 were excluded.

Exposure

The exposure was new RASi use, as indicated by the presence of new RASi prescriptions in the patient's medical charts. This metric was evaluated separately at each patient visit. A RASi was defined as ACEi or ARB use. We assumed that once a RASi was prescribed for the enrolled patients, they remained on the RASi at all subsequent visits until the end of follow-up. This definition rendered any estimate of treatment effectiveness conservative (i.e., analogous to an intention-to-treat analysis in an unblinded randomized controlled trial) [14, 16]. The visit at which RASi use was first confirmed was defined as the visit of RASi initiation.

Outcome

The outcome of interest was first CR, defined according to daily urinary protein levels of < 0.3 g/day during the study follow-up period (from Visit 1). Participants were censored at the time of loss to follow-up, at the start of kidney replacement therapy (KRT), at the time of death, or at the end of follow-up, whichever came first.

Potential confounding factors

The potential confounding factors were as follows: demographic variables (age at Visit 1, sex, and pathology type); systolic blood pressure (SBP) at Visit 0; laboratory data (serum creatinine, serum albumin, and urine protein-to-creatinine ratio) at each study visit; and medication status (antihypertensive drugs other than RASis, corticosteroids, and immunosuppressive agents other than corticosteroids) at each study visit. Laboratory data and the patients' medication status at each visit were considered potential time-dependent confounding factors. These are affected by previous RASi use; they also affect subsequent RASi use and the achievement of CR [16]. Due to the small number

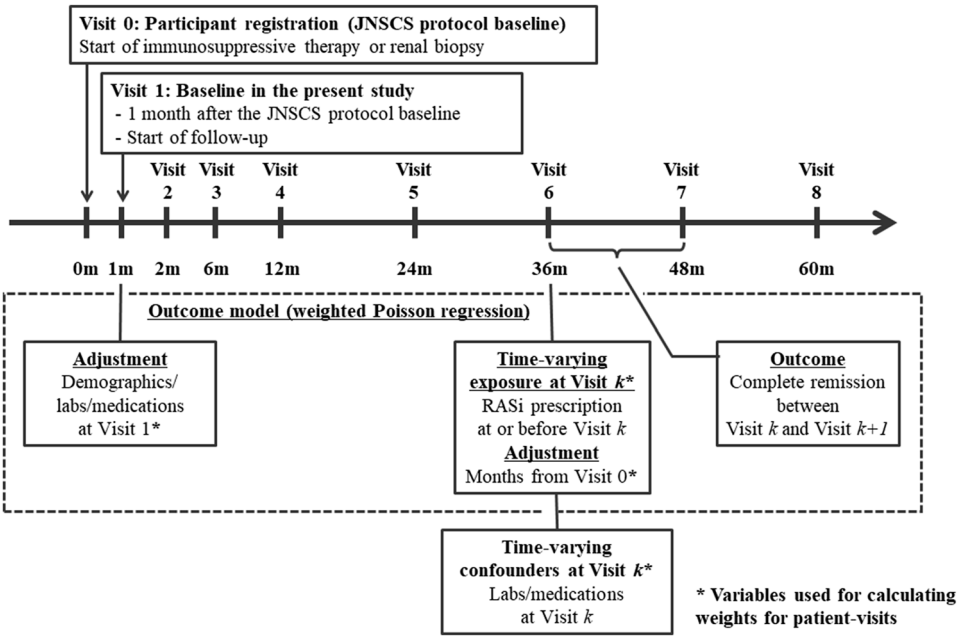

Fig. 1 Timeline of the Japanese Nephrotic Syndrome Cohort Study (JNSCS) protocol and the conceptualization of marginal structural models in the present study. According to the JNSCS protocol, the registration date (Visit 0) was defined as the date of immunosuppressive therapy initiation, with the exception of patients who were never treated with immunosuppressive therapy; the registration date for the latter patients was set as the date of renal biopsy. Post-registration data were collected at pre-specified time intervals, from 1 month (Visit 1) to a maximum of 60 months after registration (Visit 8). For the present study, Visit 1 was defined as the start of follow-up (i.e., the study baseline). The outcome (first complete remission [CR]) was modeled using a weighted Poisson regression model for repeated measures (indicated by a dashed box). The solid boxes in the dashed box represent an example of the outcome model between Visits 6 and 7. For each patient visit, the incidence of first CR between Visit k and Visit $k+1$ was modeled based on the exposure of interest (RASi prescription) at Visit k, with adjustment of time-invariant demographics and laboratory and medication variables at Visit 1 (the baseline of the present study) as well as time trends. Patient-visit weights were calculated using time-varying RASi prescription, laboratory, and medication data from Visit 1 to Visit k (marked with asterisks [*]) as described in the text. The lack of independence of the intra-individual observations was addressed via cluster-robust variance estimation. The differences in the intervals between each study visit were represented by an offset term in the outcome model

of enrolled patients with pathology types other than MN, patients were categorized based on the pathology type into two groups: MN and other pathologies (e.g., FSGS). SBP at Visit 0 was used as the baseline blood pressure variable (i.e., it was substituted as the Visit 1 variable), as this variable was not measured after Visit 1 according to the JNSCS protocol.

Statistical analyses

All analyses were performed according to pathology type category (MN or other pathologies) due to the possibility of effect modification (i.e., such that the effect of RASi treatment would differ depending on the pathology type of the enrolled patients).

Descriptive analyses

Continuous variables are expressed as medians and interquartile ranges (IQRs), while categorical variables are expressed as numbers and percentages. We also estimated the crude incidence of first CR using a previously published cumulative incidence function [17–19], with the incidence of KRT and death treated as competing risks instead of being censored.

Primary analysis: marginal structural model

We used marginal structural models to account for time-varying covariates appropriately and to estimate the causal effects of RASi on first CR [12–14, 16]. Two steps were required to implement this model. First, we estimated each participant's probability based on their own RASi history and calculated their inverse probability of treatment weight (IPTW). Second, the effect measure (incidence rate ratio [IRRs]) was estimated in a Poisson regression model weighted by the respective IPTWs [14, 16]. Since we were evaluating a single event, for the first CR, the Poisson distribution was considered acceptable [14, 20, 21]. IRRs are interpreted as the ratio between two incident rates (i.e., the ratio of the rate of first CR that would be expected if all

participants were treated with RASis and the rate that would be expected if none received it). The respective effects of RASis with regard to MN as well as other pathologies were derived by estimating the IRR in the outcome model using the overall weights for each group separately. Full explanations of primary analyses are included in Online Resource 1 (Supplementary Text).

Missing values were imputed according to the medians of the variables at the same visit for continuous variables and based on the last observation carried forward technique for dichotomous variables. Statistical significance was set at a P value of < 0.05. All analyses were performed using STATA version 17 (Stata MP, College Station, TX, USA).

Results

Descriptive statistics

Among the 374 patients registered in the JNSCS database, 84 with primary nephrotic syndrome were eligible (Fig. 2). Of the 84 patients, 51 (61%) had MN and 33 (39%) had other pathologies. In the order of prevalence, sixteen had FSGS, eight had IgA nephropathy, four had membranoproliferative glomerulonephritis, three had mesangial proliferative glomerulonephritis, and two had endocapillary proliferative glomerulonephritis.

The patients' medical and demographic characteristics are shown in Table 1. The median age at baseline was 65 years, and 48 (57%) patients were male. The median urinary protein level was 6.6 g/g Cr at the time of registration in the JNSCS (Visit 0) and 2.7 g/g Cr at the study baseline (Visit 1) when 73 (87%) had already started to receive immunosuppressive agents. Regarding the immunosuppressive agents prescribed at Visit 1, 73 (87%) patients were prescribed corticosteroids, 28 (33%) received calcineurin inhibitors, and 7 (8%) were prescribed other immunosuppressive agents.

Throughout the study period, RASis were newly prescribed to 55 (66%) patients; 34 (62%) of these patients had an SBP of < 140 mmHg at Visit 0. At Visit 1, the urine protein level was higher among RASis ever users than among RASis never users; this difference was especially evident in MN (Online Resource 1, Table S2). Non-RASis antihypertensive drugs were prescribed to 28 (33%) patients at Visit 1.

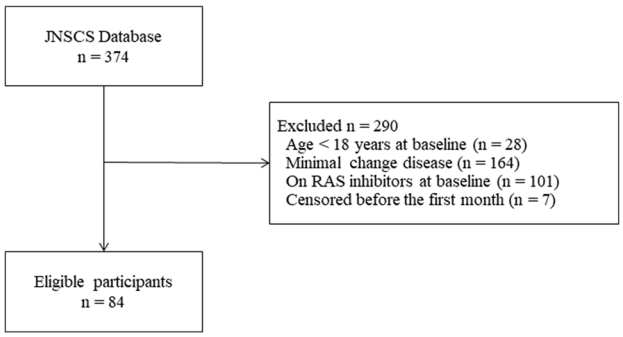

Fig. 2 Study flow diagram. *RAS* renin–angiotensin system

Incidence of first CR

During a median follow-up of 9.0 (IQR: 3.3–18.1) months (Table 1), 65 first CRs were observed, yielding an incidence rate of 5.05 per 100 person-months (Table 2). The incidence of first CR was similar for MN and other pathologies (4.67 and 5.82 per 100 person-months, respectively). Among the nineteen patients who did not achieve any CR, two died, three started receiving KRT, nine were lost to follow-up, and five were censored due to the administrative end of the study.

The cumulative incidence of first CR was 36% (95% confidence interval [CI] 26–47%) at 6 months; 57% (95% CI 45–67%) at 12 months; and 84% (95% CI 73–90%) at 60 months (Fig. 3). The cumulative incidence of first CR in MN was 29% (95% CI 17–42%) at 6 months; 56% (95% CI 41%-69%) at 12 months; and 86% (95% CI 71–93%) at 60 months. The cumulative incidence of first CR for other pathologies was 48% (95% CI 30–64%) at 6 months; 58% (95% CI 38–73%) at 12 months; and 81% (95% CI 62–91%) at 60 months.

Association between new RASi use and first CR

Pathological characteristics modified the effectiveness of RASis with regard to first CR (Table 3). New RASi use was associated with a higher incidence of first CR (adjusted IRR 2.27, 95% CI 1.06–4.84) among patients with MN, and a lower incidence of first CR in patients with other pathological types (adjusted IRR 0.17, 95% CI 0.04–0.68). The median time from the visit of RASi initiation to the first incidence of CR was 9.1 (IQR: 5.0–14.4) months for MN and 5.4 (IQR: 1.3–17.0) months for other pathological types (Online Resource1, Table S2).

Discussion

In this study, new RASi use was associated with first CR in patients with MN. Most of these patients received corticosteroid or immunosuppressive therapy. In contrast, an inverse association was observed in patients with other pathological types other than MCD.

The effectiveness of RASis for first CR in this study is consistent with previous findings, especially in nephrotic patients with MN. More specifically, urinary protein levels in patients with MN are reportedly associated with elevated intrarenal renin–angiotensin system (RAS) activity [22],

Table 1 Characteristics of patients according to the pathological classification ($N=84$)

	Pathological classification		Total
	MN	Other	
	$n=51$	$n=33$	$n=84$
Demographics			
Age, years	67 [57, 77]	61 [42, 72]	65 [52, 74]
Male sex	27 (53%)	21 (64%)	48 (57%)
Pathological classification			
MN	51 (100%)	0 (0%)	51 (61%)
FSGS	0 (0%)	16 (48%)	16 (19%)
Other	0 (0%)	17 (52%)	17 (20%)
Serum creatinine, mg/dL[a]			
Visit 0	0.90 [0.70, 1.27]	1.16 [0.89, 1.65]	1.00 [0.74, 1.47]
Visit 1	0.98 [0.74, 1.13] (missing, $n=1$)	1.16 [0.85, 1.49]	1.00 [0.79, 1.43] (missing, $n=1$)
Serum albumin, mg/dL			
Visit 0	1.9 [1.5, 2.3]	2.2 [1.6, 2.7]	2.0 [1.5, 2.5]
Visit 1	2.3 [2.0, 2.7] (missing, $n=2$)	2.8 [2.2, 3.1]	2.4 [2.1, 3.1] (missing, $n=2$)
Urine protein, g/g Cr			
Visit 0	6.2 [4.6, 10.6] (missing, $n=10$)	7.2 [5.0, 9.3] (missing, $n=5$)	6.6 [4.6, 10.6] (missing, $n=15$)
Visit 1	4.1 [1.3, 5.6] (missing, $n=12$)	2.3 [1.1, 5.0] (missing, $n=8$)	2.7 [1.3, 5.5] (missing, $n=20$)
Immunosuppressive agents			
Steroids, Visit 0	0 (0%)	0 (0%)	0 (0%)
Steroids, Visit 1	45 (90%) (missing, $n=1$)	28 (84%)	73 (88%) (missing, $n=1$)
Steroids, ever use	46 (90%)	28 (85%)	74 (88%)
Calcineurin inhibitors, Visit 0	0 (0%)	0 (0%)	0 (0%)
Calcineurin inhibitors, Visit 1	20 (40%) (missing, $n=1$)	8 (24%)	28 (34%) (missing, $n=1$)
Calcineurin inhibitors, ever use	28 (55%)	10 (30%)	38 (45%)
Other, Visit 0	0 (0%)	0 (0%)	0 (0%)
Other, Visit 1	6 (12%) (missing, $n=1$)	1 (3%)	7 (8%) (missing, $n=1$)
Other, ever use	9 (18%)	1 (3%)	10 (12%)
Antidiabetic agents			
Visit 0	0 (0%)	0 (0%)	0 (0%)
Visit 1	9 (18%) (missing, $n=1$)	4 (12%)	13 (16%) (missing, $n=1$)
SBP, mmHg	130 [117, 140] (missing, $n=1$)	139 [120, 148]	131 [119, 142] (missing, $n=1$)
Hypertension (≥ 140 mmHg, Visit 0)	13 (26%) (missing, $n=1$)	16 (49%)	29 (35%) (missing, $n=1$)
Antihypertensive agents other than RASi			
Visit 0	15 (29%)	9 (27%)	24 (29%)
Visit 1	17 (34%) (missing, $n=1$)	11 (33%)	28 (34%) (missing, $n=1$)
RASi, ever use[b]	38 (75%)	17 (52%)	55 (66%)
Follow-up time, months	10.8 [4.7, 18.4]	6.0 [2.2, 17.7]	9.0 [3.3, 18.1]
First complete remission	40 (78%)	25 (76%)	65 (77%)

Continuous variables are presented as the median and interquartile range [q25, q75]. Visit 0: the participant registration date according to the Japanese Nephrotic Syndrome Cohort Study (JNSCS) protocol (i.e., the date of immunosuppressive therapy initiation, with the exception of patients who were never treated with immunosuppressive therapy; for these patients, the registration date was set as the date of renal biopsy). Visit 1 occurred 1 month after Visit 0

FSGS focal segmental glomerulosclerosis; *MN* membranous nephropathy; *RASi* renin–angiotensin system inhibitor; *SBP* systolic blood pressure

[a]Conversion factor for serum creatinine: mg/dL to μmol/L, × 88.4

[b]No patients were prescribed RASis at the start of the original cohort

Table 2 Incidence of first complete remission according to pathologic subtype

Population	Patients, *n*	Time at risk, months	Incidence rate per 100 person-months (95% confidence interval)
MN	51	857	4.67 (3.43–6.37)
Others[a]	33	430	5.82 (3.93–8.61)

MN membranous nephropathy

[a]The "others" category included sixteen patients with focal segmental glomerulosclerosis, eight with immunoglobulin A (IgA) nephropathy, four with membranoproliferative glomerulonephritis, three with mesangial proliferative glomerulonephritis, and two with endocapillary proliferative glomerulonephritis

which provides the biological underpinnings for the inhibition of RAS activity by RASis with regard to inducing disease remission. The strength of the effectiveness of CR in patients with MN in this study is similar to that of the previously reported association between RASi administration and spontaneous remission in nephrotic MN under conservative therapy (hazard ratio 2.36) [7]. This concordance supports the potential benefit of RASi therapy with regard to CR in patients with nephrotic MN, regardless of concomitant corticosteroid or immunosuppressive therapy use. Further research is warranted to understand whether the mechanism of CR by RASis is attributable to improvement in renal damage associated with immune complex deposition, improvement in intraglomerular pressure, or other effects beyond blood pressure lowering. On one hand, since RASis administration may lead to a decline in renal function in nephrotic syndrome during severe hypoalbuminemia, nephrologists should prescribe RASis after weighing the potential harms. Indeed, the time point with the lowest serum albumin level in the study population was Visit 0, and RASis had not yet been prescribed at that time.

RASi therapy was associated with a lower likelihood of first CR in patients with other pathologies in this study. The inverse association between RASi use and first CR in this group may be due to confounding by indication. Examples of unmeasured confounding leading to an apparent inverse association include practice patterns (e.g., RASis being prescribed along with high doses of immunosuppressive agents to achieve remission [23] or RASis being prescribed for histologically severe cases with poor responsiveness

Table 3 Associations between RASi initiation and first complete remission using marginal structural models

Population	Adjusted IRR (95% CI)	*P* value
MN (51 patients, 185 observations)	2.27 (1.06–4.84)	0.035
Others (33 patients, 106 observations)[a]	0.17 (0.04–0.68)	0.012

The marginal structural model approach was used herein. To estimate the effectiveness of RASis, pooled Poisson regression models were fitted using stabilized weights and cluster-robust variance estimation. The visit interval was used as an offset term

IRR incidence rate ratio; *MN* membranous nephropathy; *RASi* renin–angiotensin system inhibitor

[a]The "others" category included 16 patients with focal segmental glomerulosclerosis, eight with IgA nephropathy, four with membranoproliferative glomerulonephritis, three with mesangial proliferative glomerulonephritis, and two with endocapillary proliferative glomerulonephritis

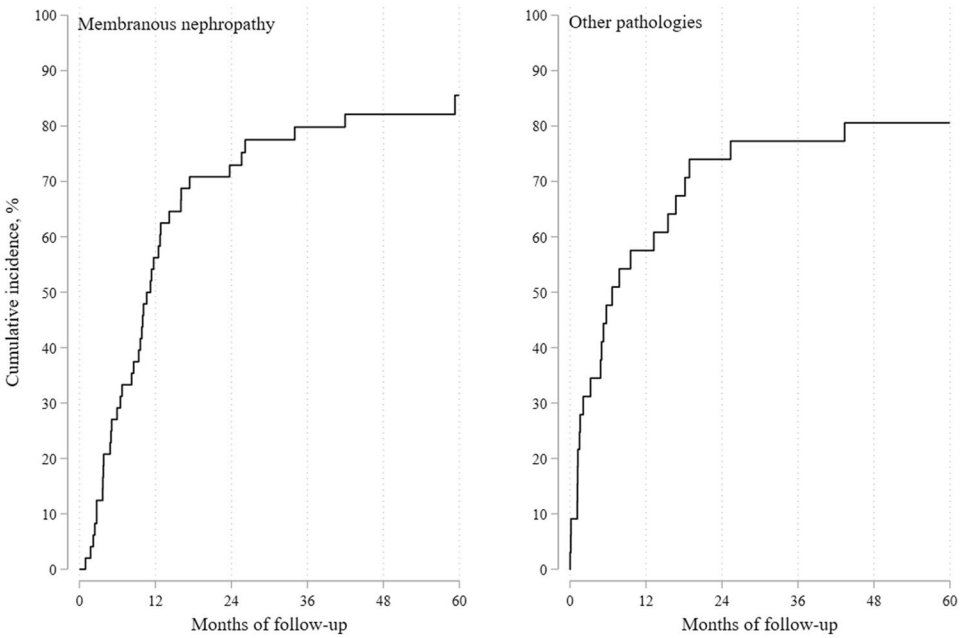

Fig. 3 Cumulative incidence estimates for first complete remission. The incidence of kidney failure requiring kidney replacement therapy and mortality were treated as competing outcomes

to immunosuppressive agents) and the fact that this study group was composed of a small number of patients presenting with various pathological types. The finding that urinary protein in patients with other pathological types treated with RASis was lower than that in MN patients treated with RASi suggests that the severity of laboratory data among the former group was mild. Nevertheless, given the inverse correlation between RASis prescription and first CR observed in patients with other pathological types, severity of the glomerular damage, which cannot be captured by laboratory data, may have confounded the effectiveness of RASis on first CR in that group. However, a previously published small-sized randomized controlled trial of FSGS that enrolled patients without nephrotic syndrome (i.e., approximately 60% of the subjects) showed a reduction in proteinuria with the use of losartan [6]. Taking into account the evidence to date, we do not believe that RASis is ineffective against pathological types other than MN, based solely on the findings of the present study. Thus, additional studies are warranted to evaluate whether the addition of RASis as an adjuvant therapy leads to first CR for pathological types other than MN with nephrotic-range proteinuria.

This study has several strengths. First, it was conducted using the JNSCS, a nationwide cohort study in which detailed, granular clinical data for patients with primary nephrotic syndrome were measured repeatedly at intervals of ≤ 1 year during a 5-year follow-up period. Second, we used a marginal structural model to quantify the effectiveness of the evaluated time-updated treatment exposure by comparing otherwise identical patients with primary nephrotic syndrome who had or had not initiated RASis. Our results can be interpreted as reflecting the average effectiveness in a real-world MN population of older adults (median age 65 years) mostly receiving steroids and calcineurin inhibitors. Contrastingly, previous studies evaluating the effectiveness of RASis on remission in MN have had substantial methodological limitations, including the omission of time-dependent confounding and suboptimal covariate selection with a forward stepwise method [7–9].

However, this study has some limitations. First, although we used data from a nationwide cohort, the sample size was relatively small because we excluded patients who had already been prescribed RASis; this was to correctly estimate the effectiveness of RASis [11]. Second, as already mentioned in the interpretation of the results for "other" pathology types, confounding by indication may be applicable in MN, with regard to corticosteroid dosage and post-baseline blood pressure. However, the strength of the true association between RASi use and CR may have been greater if these confounding factors were driving factors for RASi use given the difficulty of achieving remission. In addition, information on serum potassium, which may influence RASis prescription, was not available in the database. However, given the fact that serum potassium is unlikely to be the cause of CR, we reasonably concluded that serum potassium did not meet the criteria as a confounding factor and therefore did not need to be included in the analytical models [24]. Third, as data on RASi dosage were unavailable, only the association between RASi use and outcome could be evaluated. Further studies on RASi dosage are needed to determine the effect of RASi up-titration. Fourth, the measurement of anti-phospholipase A2 receptor (anti-PLA2R) antibody is not covered by health insurance in Japan, and related data were not collected in this cohort. The relationship between anti-PLA2R antibody positivity and RASi effectiveness requires further investigation. Fifth, because the data are from a nationwide cohort in Japan, the generalizability to other populations and countries with different practice patterns for immunosuppressive agents may be limited. Finally, the data and variables were not sufficient to establish a clinically meaningful outcome such as preserved renal function because (1) there was a small number of dialysis initiation cases and (2) the uncertainty about whether the renal function at the start of the study was baseline or decreased.

The findings of this study have important clinical implications. RASi use as an adjunctive therapy for the treatment of nephrotic patients with MN was effective in achieving first CR. Our findings endorse the recommendations of the new Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for glomerular disease: RASis should be up-titrated to the maximum, provided that renal function does not deteriorate rapidly (Practice Point 1.5.3.), especially in MN [1]. Moreover, Japanese guidelines for nephrotic syndrome suggest that patients with MN should be started with conservative therapy, such as diuretics, RASis, and antiplatelet agents, following which the addition of monotherapy with corticosteroids or combination therapy with corticosteroids and immunosuppressive agents should be considered [25]. However, this study indicates that RASis may be actively considered as an adjunctive therapy to achieve CR for patients with MN.

In conclusion, we demonstrated the effectiveness of RASi initiation in achieving first CR in MN. We also found an inverse association for "other" pathology types. Well-conducted randomized trials and larger observational studies with relevant time-dependent confounders and fine temporal granularity are required for better evidence. Thus, our findings can guide future research directions, clinical practice guidelines, and effective clinical decision-making.

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Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Conflict of interest Honoraria: Yugo Shibagaki (Astellas, Chugai Pharmaceutical, Daiichi Sankyo, Kyowa Kirin, Novartis, Otsuka Pharmaceutical, Teijin Pharma), Hirokazu Okada (Astrazeneca, Daiichi Sankyo, Kyowa Kirin, Mitsubishi Tanabe Pharm, Torii Pharmaceutical), Ichiei Narita (Astellas, Daiichi Sankyo, Otsuka Pharmaceutical, Sanofi, Sumitomo Pharma), Noriaki Kurita (GlaxoSmithKline), Research funding: Yugo Shibagaki (Kyowa Kirin, Sanwa Kagaku Kenkyusho), Hirokazu Okada (Kyowa Kirin), Subsidies or Donations: Yugo Shibagaki (Astellas, AstraZeneca, Mitshbishi Tanabe Phama, Pfizer, Teijin Pharma), Hirokazu Okada (Bayer, Chugai Pharmaceutical, Kyowa Kirin, Ono Pharmaceutical), Ichiei Narita (Astellas, Bayer, Chu-

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Ethical standards All the procedures were conducted in accordance with the ethical standards of the institutional and/or national research committees at which each component of this multicenter collaboration study was conducted (institutional review board [IRB] approval numbers: 061171, 08212, and 13134 issued by the ethics committee of Osaka University Hospital), as well as in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from participants in 53 hospitals, while one hospital used an opt-out approach, according to the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects [26].

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