



# Efficacy and Safety of ACE Inhibitor and Angiotensin Receptor Blocker Therapies in Primary Focal Segmental Glomerulosclerosis Treatment: A Systematic Review and Meta-Analysis

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**Rationale and Objective:** Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy (renin-angiotensin-aldosterone system [RAAS] inhibitor) to control proteinuria in primary and genetic focal segmental glomerulosclerosis (FSGS) follows guidelines based on other proteinuria-related kidney diseases. There is no consensus on the efficacy and safety of RAAS inhibitor therapies in primary and genetic FSGS. This systematic review assessed the effects of RAAS inhibitor therapy on kidney outcomes in these patients.

**Study Design:** Systematic review of randomized controlled trials, interventional nonrandomized studies, observational studies, and retrospective studies.

**Setting & Study Populations:** Patients with primary and genetic FSGS.

**Selection Criteria for Studies:** PubMed, Cochrane Library, and Embase.

**Data Extraction:** 2 investigators independently screened studies and extracted data.

**Analytical Approach:** Results were summarized as the ratio of means (ROM) between baseline and follow-up measurements or as the hazard ratio using random-effects models.

**Results:** 30 publications were selected; 5 were controlled trials (4 randomized controlled trials). 8

assessed RAAS inhibitor monotherapy, while the rest studied RAAS inhibitors in combination with other drugs, mainly immunosuppressants. On average, a 32% proteinuria reduction (ROM, 0.68; 95% CI, 0.47-0.98) and no change in creatinine clearance (ROM, 0.95; 95% CI, 0.77-1.16) from baseline to the last reported follow-up was observed in patients treated with RAAS inhibitor monotherapy. When a RAAS inhibitor was combined with other drugs, a 72% proteinuria reduction was observed from baseline to the last reported follow-up (ROM, 0.24; 95% CI, 0.08-0.75). The published data did not allow for the assessment of the effects of RAAS inhibitor monotherapy on estimated glomerular filtration rate and end-stage kidney disease risks.

**Limitations:** Large study heterogeneity in design, patient populations, and treatment regimens. No access to individual patient-level data.

**Conclusions:** This review supports the tendency to observe a proteinuria reduction with RAAS inhibitors in patients with primary FSGS. RAAS inhibitor monotherapy was associated with maintained kidney function, as shown by no change in creatinine clearance. Strong evidence to quantify the effects of RAAS inhibitor monotherapy on end-stage kidney disease and glomerular filtration rate was lacking. Larger, well-designed clinical trials are needed to better understand the effects of RAAS inhibitors on primary FSGS.

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Primary focal segmental glomerulosclerosis (FSGS) is a rare condition that causes kidney scarring and leads to chronic kidney failure. The disease incidence is increasing and, in the United States, nearly 50% of patients with primary FSGS and nephrotic-range proteinuria resistant to treatment will reach chronic kidney failure within 5-10 years of diagnosis.<sup>1</sup> Treatment with corticosteroids or other immunosuppressive agents targets the reduction of proteinuria, a key predictor of kidney survival in patients with primary FSGS. However, the use of immunosuppressive or immunomodulating agents is associated with therapy-limiting side effects, and many patients with FSGS fail to achieve a significant reduction in proteinuria despite treatment with these drugs.<sup>2-5</sup> Therefore, supportive management, including the inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker

(ARB) therapies (ACE inhibitor/ARBs), the control of blood pressure, and dietary salt restriction, is routinely recommended for patients with FSGS with persistent proteinuria, based on evidence from other proteinuria-related kidney diseases.<sup>2</sup> However, the effects of ACE inhibitor/ARBs on kidney outcomes, such as proteinuria, glomerular filtration rate (GFR), and kidney survival, in patients with primary FSGS remains unclear. Thus, this systematic literature review aimed to assess the benefits and risks of ACE inhibitor/ARB therapies in the available literature on kidney outcomes in patients with primary FSGS.

## METHODS

### Search Strategies

The MEDLINE (PubMed), Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register

**PLAIN-LANGUAGE SUMMARY**

Primary focal segmental glomerulosclerosis (FSGS) causes kidney damage and can lead to kidney failure. This systematic review examined the treatment of primary FSGS with renin-angiotensin-aldosterone system (RAAS) inhibitors, which include angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapies, in 30 publications (8 studies examined RAAS inhibitor treatment alone; the remaining studies examined RAAS inhibitors in combination with other drugs). Treatment of FSGS targets the reduction of protein in urine to protect long-term kidney health. On average, protein in urine was reduced by one-third when RAAS inhibitor treatment was used alone and by more than two-thirds when RAAS inhibitor treatment was combined with other drugs. Larger clinical trials that compare RAAS inhibitor treatment alone and with other treatments are needed to better understand RAAS inhibitor effects in primary FSGS clinical outcomes.

of Controlled Trials, Database of Abstracts of Reviews of Effects), and Embase databases were searched on April 5, 2019. A population, intervention or comparator, and outcomes strategy was used to construct the systematic literature search protocol, and the keywords and respective syntax used in each database search are presented in [Tables S1-S3](#). Studies not retrieved using the systemic literature search protocol, or published after the date of the systematic search, were manually searched to identify additional relevant studies.

**Study Selection**

Exploratory searches found a small number of randomized controlled trials (RCTs) investigating the clinical efficacy of ACE inhibitor/ARBs in treating primary or idiopathic FSGS that have been published thus far. For this reason, various study designs and types of publications were included in this systematic review, such as RCTs, interventional non-RCTs (ie, single-arm clinical trials and nonrandomized comparative studies), observational studies, retrospective studies, and registries. Additionally, studies were included if they reported the treatment of patients with primary or idiopathic FSGS with ACE inhibitor/ARB monotherapy or ACE inhibitor/ARBs in combination with other therapeutic agents, and as a single arm or in comparison with non-RAAS inhibitor agents, placebo, or no treatment. The other inclusion criteria were: (1) reporting any of the efficacy outcomes of proteinuria (as daily total proteinuria or the urinary protein-creatinine ratio), kidney function (estimated GFR [eGFR] or creatinine clearance [CrCl]), and kidney survival (defined as reaching end-stage kidney disease [ESKD], kidney failure, doubling of creatinine, or author reported), and adverse events; (2) human studies,

with the full text available; and (3) publication in the English language. No time limit was applied in this search. Studies were excluded if they were focused on secondary FSGS, or if they focused on patients with FSGS recurrence after transplant and the patients received immunosuppressive therapy composed of rituximab or monoclonal antibodies. Preclinical studies, economic evaluations, editorials, notes, comments or letters, narratives, articles without abstracts or nonsystematic literature reviews, case reports, or case series were also excluded.

**Data Extraction**

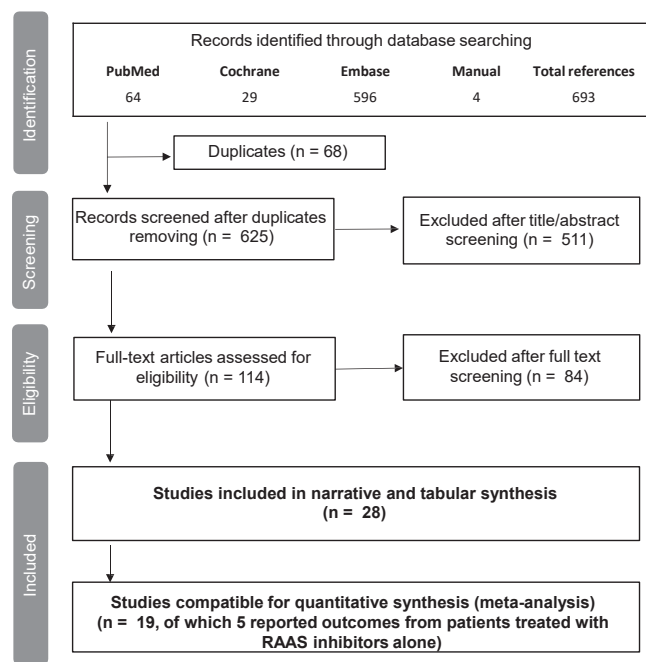
Studies were independently screened by 2 investigators (BM and MF) who subsequently extracted pertinent data and analyzed the results. Any discrepancies in study selection and data collection between the 2 authors were resolved by discussion with a third author (NP). Daily proteinuria measurements were extracted if reported in g/d or if the conversion to this unit of measurement was possible. Kidney function was represented as eGFR or CrCl, according to the data provided by the authors of the included studies. Kidney survival outcomes were separately extracted as the kidney survival rate, rate of patients reaching ESKD, hazard ratio of reaching ESKD with exposure versus no exposure to ACE inhibitor/ARB, or time to ESKD. Treatment-related changes at baseline and during the follow-up periods were reported as mean values and standard deviations (SDs) unless otherwise specified. Whenever the variation was represented as the standard error of the mean (SEM), the SD was calculated using the formula:  $SEM \times \text{square root of sample size}$ .

**Quality Assessment**

The risk of bias in the RCTs was assessed independently by 2 authors (BM and MF) using the risk-of-bias checklist developed by the Cochrane Renal Group for RCTs. Discrepancies were resolved by discussion with a third author (AZ). The items assessed in the checklist were allocation concealment, blinding of investigators, participants, outcome assessors, and data analysts, intention-to-treat analysis, and completeness to follow-up. Each item was answered with yes, no, or unclear, in combination with a narrative response and an overall assessment of the risk of bias.

**Statistical Analyses**

Meta-analyses were performed with R (v. 3.6.0), using the `dplyr` (0.8.3), `meta` (4.9.5), and `metaphor` (2.1.0) packages. The ratio of mean (ROM) values at the last time point reported and of mean values at baseline, as well as their 95% confidence intervals (CIs), were calculated for the included studies and transformed into an estimated summary ROM. The ROM was computed using the last time point available for each study. Similarly, the mean difference between mean values at the last time point reported and of mean values at baseline, as well as their 95% CIs, were calculated for the included studies and pooled into an



**Figure 1.** Flowchart describing the study selection process, with the number of studies identified, screened, assessed for eligibility, and included for narrative (tabular) or quantitative (meta-analysis) synthesis. Abbreviation: RAAS, renin-angiotensin-aldosterone system.

estimated summary mean difference (MD). The standardized mean difference was computed between treatment and control arms using the last time point reported for both arms. Summary effects of the ROM, MD, standardized MD, and hazard ratio were computed using the random-effects model to account for heterogeneity or between-study variation.

## RESULTS

### Study Selection and Characteristics of the Studies

The Preferred Reporting Items for Systematic Reviews and Meta-analyses chart presented in Fig 1 displays the selection process of the articles. The systematic literature search retrieved 689 articles from the selected databases, and 4 additional articles were captured by a manual search. A total of 625 publications were screened after the removal of duplicates, in accordance with the inclusion and exclusion criteria. After title and abstract screening, 114 articles were considered for a full-text assessment. A total of 30 publications, corresponding to 28 studies, were deemed relevant for inclusion according to the inclusion and exclusion criteria. From the 28 included studies, 19 were eligible for quantitative assessment synthesis through a meta-analysis, of which 5 reported outcomes from patients treated with ACE inhibitor/ARBs alone.

The majority of the publications which were included corresponded to real-world studies (23 studies), and only 5 studies were controlled trials. A risk-of-bias assessment

was performed for the RCTs (4 studies). Overall, only 1 RCT was considered to have internal validity; therefore, the variation between the different treatment groups is attributable to the intervention in question, and not to other forms of biases.<sup>6</sup> It was not possible to exclude biases for the remaining 3 studies, as a risk of selection, performance, or detection bias was observed (Table S4).<sup>7-9</sup> All studies were conducted in patients with primary or idiopathic FSGS or reported results for this target population. An equal number of studies were performed in children and young adults compared with adults (12 studies in each age group). Two studies were performed in mixed-aged populations; and in 2 other studies, the age group of the patients was not specified. Patients with nephrotic syndrome were included in 21 studies, and the majority comprised more than 50% of nephrotic patients (17 studies). In 6 studies, the nephrotic state of the patient was not specified, and 1 study considered only nonnephrotic patients.

Most studies reported the use of ACE inhibitor/ARBs in combination with other drugs (23 studies), mainly immunosuppressants (16 studies). Various types of immunosuppressive or immunomodulatory drugs were used in combination with ACE inhibitor/ARBs, including corticosteroids, calcineurin inhibitors, and alkylating agents, among others. Non-immunosuppressive treatments (eg, other antihypertensive agents, diuretics, statins, antiplatelet drugs) were also used in combination with ACE inhibitor/ARBs (7 studies), although to a lesser extent. Only 8 studies assessed the use of ACE inhibitor/ARBs as the only type of pharmacological intervention.

Considerable heterogeneity was found among the studies because of different baseline characteristics, patient populations, study designs, treatment regimens, investigated drugs, and time intervals between measurements of the last reported time point and baseline. The characteristics of the included studies are shown in Table 1.

### Effect on Proteinuria

A total of 12 studies assessed daily proteinuria after treatment with ACE inhibitor/ARBs, of which 7 studies reported data that were compatible with the computing of a ROM meta-analysis for daily proteinuria (eg, reported outcomes included both the mean and the variance, expressed as SD or SEM).

In patients treated with ACE inhibitor/ARBs, alone or in combination with other therapies, daily total proteinuria decreased by more than 50% from baseline to the last reported time point (ROM, 0.42; 95% CI, 0.28-0.64; Fig 2). Nevertheless, as none of the studies were designed to assess the effect of ACE inhibitor/ARBs alone, the observed reduction cannot be attributed solely to this intervention (Fig 2). There were insufficient studies to clearly determine the relationship between the length of follow-up and reduction in proteinuria from baseline (Fig S1).

**Table 1.** Description and General Characteristics of the Studies Included in the Systematic Literature Review

Study, Country	Study Type	Study Arm Or Cohort (N)	Baseline Characteristics							Follow-Up Period and Tx Duration	Clinical Outcomes Reported For Patients With FSGS	
			General Patient Characteristics				Proteinuria Levels, g/day	UPCR, g/g	eGFR, ml/min /1.73 m <sup>2</sup>			CrCl, ml/min/1.73 m <sup>2</sup>
			Disease	Age, y	% Of Nephrotic							
Bagchi et al, <sup>12</sup> India	Retrospective	ACEi/ARB + IS [Pred +/- CNI] (116) <sup>a</sup>	primary FSGS	≥18	100	5.1 ± 2.6	-	96.9 ± 35.1	-	Follow-up: 23.6 mo (range, 6–65.1 mo)	Kidney survival or progression to ESKD; Time to ESKD; Safety Events; HR	
Bagga et al, <sup>7</sup> India	Prospective, randomized, crossover	Arm 1: LD then HD ACEi [enalapril] + IS [Pred] (11, 4 FSGS) <sup>a</sup> Arm 2: HD then LD ACEi [enalapril] + IS [Pred] (14, 5 FSGS) <sup>a</sup>	SRNS, several GN	<18	1	-	-	-	-	Follow-up: up to 20 wk	Biomarkers; BP	
Chandar et al, <sup>16</sup> United States	Retrospective	ACEi/ARB [enalapril, candesartan, losartan] (17, 7 FSGS) <sup>a</sup>	several GN	<21	0.59	-	3.6 ± 4.6 mg/mg	147 ± 45	-	Follow-up: up to 30 mo	Proteinuria and other biomarkers; eGFR; BP	
Crenshaw et al, <sup>17</sup> United States	Retrospective	ACEi [enalapril] + steroids +/- CCB +/- diuretics (40) <sup>a</sup>	primary FSGS	>18	0.7	6.32 ± 1.1	-	-	80.2 ± 9.5 ml/min	Follow-up: 31.7 ± 4.5 mo	Kidney survival or progression to ESKD; Time to ESKD; HR	
Delucchi et al, <sup>18</sup> Chile	Retrospective	ACEi + Pred (13, 4 FSGS) <sup>a</sup>	SRNS, several GN	<18	1	7.4 ± 2.6 g/m <sup>2</sup> per day	-	-	-	Follow-up; Tx duration 48 mo; mean: 48 mo (range, 24–84 mo)	Proteinuria	
Ferder et al, <sup>19</sup> Argentina	Prospective	ACEi/ARB [enalapril] + diuretics [furosemide] (14, 3 FSGS) <sup>a</sup>	primary GN	>18	Not specified	-	-	-	-	Follow-up; Tx duration at least 30 mo; 30 mo	BP	
Ferder et al, <sup>20</sup> Argentina	Prospective	ACEi/ARB [enalapril] + diuretics [furosemide] (10, 1 FSGS) <sup>a</sup>	primary GN	>18	Not specified	5	-	-	37 ml/min	Follow-up; Tx duration 9 mo; 9 mo	Proteinuria and other biomarkers; CrCl; BP	
Futrakul et al, <sup>21</sup> Thailand	Retrospective	ACEi [cilazapril or enalapril] or ARBs + CCB [isradipine] + AP [DP] + vit. E & C (24, 8 idiopathic FSGS) <sup>a</sup>	Idiopathic NS several GN + CKD	Not specified	62.5% of all pts, 100% of FSGS pts	-	-	-	44.8 ± 67.9	Not specified	CrCl	
Futrakul et al, <sup>22</sup> Thailand	Retrospective	ACEi [cilazapril or enalapril] or ARBs + CCB [isradipine] + AP [DP] +	NS idiopathic FSGS	Not specified	1	3.1 ± 4.4	-	35 ± 53.8	34 ± 37.9	Follow-up: ≥10 y	Proteinuria; eGFR and CrCl	

(Continued)

**Table 1 (Cont'd).** Description and General Characteristics of the Studies Included in the Systematic Literature Review

Study, Country	Study Type	Study Arm Or Cohort (N)	Baseline Characteristics							Follow-Up Period and Tx Duration	Clinical Outcomes Reported For Patients With FSGS	
			General Patient Characteristics				Proteinuria Levels, g/day	UPCR, g/g	eGFR, ml/min /1.73 m <sup>2</sup>			CrCl, ml/min/1.73 m <sup>2</sup>
			Disease	Age, y	% Of Nephrotic							
Futrakul et al, <sup>23</sup> Thailand	Prospective trial	vit. E & C + IS [Pred] (10) <sup>a</sup> Arm 1: IS [Pred, CYC] + AH [reserpine, hydralazine or prazosin] (11) Arm 2: ACEi [enalapril], ARB [losartan], CCB [isradipine] + AP [dipyridamole] + baby aspirin +/- AP [heparin] (18) <sup>a</sup>	NS FSGS	19 ± 2 20 ± 3	1	3.2 ± 0.7 <sup>b</sup> 3 ± 0.8 <sup>b</sup>	-	60 ± 21 <sup>b</sup> 51 ± 23 <sup>b</sup>	47 ± 25 <sup>b</sup> 50 ± 19 <sup>b</sup>	Follow-up 77 ± 24 <sup>b</sup> mo 97 ± 33 <sup>b</sup> mo	Proteinuria; eGFR and CrCl; Time to ESKD; Mortality/Survival	
Gellermann et al, <sup>13</sup> Germany	Uncontrolled retrospective	IS [MP, Pred, CsA, MMF] +/- ACEi/ARB +/- diuretics (23) <sup>a</sup>	primary SRNS with FSGS	<18	1	-	-	-	(n = 16) 106.2 ± 26.3	Follow-up; MMF Tx duration 7.0 y (range, 1.7-16.5 y); 3.6 y (range, 0.8-10 y)	eGFR; Safety events	
Gipson et al, <sup>4</sup> United States	Retrospective	IS [CS, CNI, CYC, MMF] +/- ACEi/ARB +/- lipid lowering agents (60) <sup>a</sup>	primary FSGS	<21	Not specified	5.6 (range, 1.0-24.0)	-	90.2 (range, 14.2-175)	-	Follow-up: 33 mo (range, 3-233 mo)	Kidney survival or progression to ESKD; Time to ESKD; Mortality/Survival; HR	
Gipson et al, <sup>8</sup> United States	Open-label, randomized controlled trial	Arm 1: MMF/DEX +/- ACEi/ARB (lisinopril or losartan) +/- additional AH (66) <sup>a</sup> Arm 2: CsA +/- ACEi/ARB (lisinopril or losartan) +/- additional AH (72) <sup>a</sup>	SR primary FSGS	2-40	Not specified	-	-	-	-	Follow-up: 78 wk	BP; Kidney survival or progression to ESKD; Time to ESKD; Mortality/Survival; Safety events; HR	
Greenwood et al, <sup>24</sup> Australia	Retrospective	ACEi/ARB or diuretics + immunosuppressants [prednisolone] (98) <sup>a</sup>	primary and secondary FSGS	>18	0.51	-	-	-	-	Follow-up: 4.32 HR y (range, 0-17)		
Hogg et al, <sup>25</sup> United States	Post hoc analysis of Gipson et al <sup>8</sup>	Arm 1: MMF/DEX +/- ACEi/ARB (lisinopril or losartan) +/- additional AH (20) Arm 2: CsA +/- ACEi/ARB (lisinopril or losartan) +/- additional AH (22) <sup>a</sup>	SR primary FSGS	7-34	Not specified	3.6 (10th-90th percentile: 1.1-9.6) 2.7 (10th-90th percentile: 1.1-5.1)	-	122.6 ± 50.7 126.8 ± 50.5	-	Follow-up; Tx duration 78 wk; CsA or MMF or DEX: 52 wk ACEi or ARB; 78 wk	Proteinuria; eGFR	
Hori et al, <sup>26</sup> Japan	Retrospective	ACEi [captopril or enalapril or	primary FSGS	<18	0.67	-	-	-	-	Follow-up: 6.9 ± 5.0 y	Odds ratio	

(Continued)

**Table 1 (Cont'd).** Description and General Characteristics of the Studies Included in the Systematic Literature Review

Study, Country	Study Type	Study Arm Or Cohort (N)	Baseline Characteristics							Follow-Up Period and Tx Duration	Clinical Outcomes Reported For Patients With FSGS	
			General Patient Characteristics				Proteinuria Levels, g/day	UPCR, g/g	eGFR, ml/min /1.73 m <sup>2</sup>			CrCl, ml/min/1.73 m <sup>2</sup>
			Disease	Age, y	% Of Nephrotic							
Huang et al, <sup>11</sup> China	Prospective, open-label, controlled trial	benazepril +/- IS [CYC, CsA, MP] (43) <sup>a</sup> Arm 1: ACEi/ARB + IS [Pred] (52) Arm 2: ACEi/ARB (50) <sup>a</sup>	primary FSGS	>18	0	1.67 (range, 1.04-3.26) 1.58 (range, 1.09-3.43)	-	72.94 ± 28.52 ml/min; 71.33 ± 30.82 ml/min	-	Follow-up: 36 mo (range, 12-101 mo); 37.5 mo (range, 12-117 mo)	Proteinuria and other biomarkers; Kidney survival or progression to ESKD; Time to ESKD; HR	
Huissoon et al, <sup>27</sup> Ireland	Pilot uncontrolled study	ACEi [captopril] (13, 11 FSGS) <sup>a</sup>	FSGS and IgAN	≥18	Not specified	2.4 ± 1.8	-	76.0 ± 26.4 ml/min	-	Follow-up: 6 mo	Proteinuria; eGFR	
Kangovi et al, <sup>28</sup> United States	Retrospective	Arm 1: ACEi/ARB (35) <sup>a</sup> Arm 2: IS +/- ACEi/ARB (32)	primary FSGS	<21	Not specified	-	4.5 ± 6.3 mg/mg 14.4 ± 11.5 mg/mg	100.8 ± 43.1 132.9 ± 56.1	-	Follow-up; Initial Tx duration: 53.9 ± 28.9 70.2 ± 49.5; 80.5 mo 11.0 mo	Kidney survival/ progression to ESKD; Time to ESKD; HR	
Milliner et al, <sup>10</sup> United States	Prospective	ACEi [enalapril] (6, 4 FSGS) <sup>a</sup>	SRNS, several GN	<18	1	6.9 ± 4.9	25.2 ± 20.1 mg/mg	-	88.3 ± 44.5	Follow-up: up to 20 mo	Proteinuria and other biomarkers; CrCl; BP	
Montané et al, <sup>14</sup> United States	Prospective	IS [MP +/- Pred +MMF] +/- diuretics +/- ACEi/ARB [enalapril, captopril, candesartan, losartan] (9) <sup>a</sup>	SRNS FSGS	≤24	1	-	13 ± 6 mg/mg	118 ± 35	-	Tx duration: 36 ± 11 mo	Proteinuria and other biomarkers; eGFR; BP; Safety events	
Praga et al, <sup>29</sup> Spain	Prospective	ACEi [captopril] +/- diuretics [furosemide] (46, 5 FSGS) <sup>a</sup>	several GN	>18	1	9.9 ± 3.3	-	-	-	Follow-up; Captopril Tx duration: 24.4 ± 7.6 mo; >12 mo	Proteinuria	
Praga et al, <sup>30</sup> Spain	Retrospective	Arm 1: ACEi in obese FSGS <sup>b</sup> (15) <sup>a</sup> Arm 2: IS +/- ACEi in idiopathic FSGS (15)	primary FSGS	≥15	0.4	3.1 ± 2 6.5 ± 2.4	-	-	91 ± 44 ml/min; 80 ± 32 ml/min	Follow-up: 82 ± 57 mo (range, 36-204 mo); 64 ± 38 mo (range, 30-190 mo)	Proteinuria and other biomarkers; CrCl; Kidney survival or progression to ESKD; Time to ESKD	
Ren et al, <sup>31</sup> China	Retrospective	Arm 1: ACEi/ARB alone (79) <sup>a</sup> Arm 2: GC alone (75) Arm 3: GC combined with other IS (62)	primary FSGS	>18	0.446	0.88 ± 0.1 2.6 ± 1.8 3.1 ± 0.5	-	67.3 ± 10.9 ml/min; 84.7 ± 8.9 ml/min; 86.3 ± 7.4 ml/min	-	Follow-up: 26 mo (range, 3-104 mo); 8 mo (range, 2-26 mo); 12 mo	Kidney survival or progression to ESKD; Time to ESKD	
	Prospective		SRNS	<18	0.875			239.2 ± 48.4	201.9 ± 45.1			

(Continued)

**Table 1 (Cont'd).** Description and General Characteristics of the Studies Included in the Systematic Literature Review

Study, Country	Study Type	Study Arm Or Cohort (N)	Baseline Characteristics							Follow-Up Period and Tx Duration	Clinical Outcomes Reported For Patients With FSGS
			General Patient Characteristics			Proteinuria Levels, g/day	UPCR, g/g	eGFR, ml/min /1.73 m <sup>2</sup>	CrCl, ml/min/1.73 m <sup>2</sup>		
Disease	Age, y	% Of Nephrotic									
Supavekin et al, <sup>32</sup> Thailand		ACEi [enalapril] + ARB [losartan] + IS [prednisolone] (8, 7 FSGS) <sup>a</sup>				139.6 ± 45.6, 182.8 ± 59.6 mg/m <sup>2</sup> /h	9.6 ± 2.3 spot UPCR			Follow-up (visit 10): 32 wk	Proteinuria and other biomarkers <sup>c</sup> ; eGFR and CrCl <sup>c</sup> ; BP <sup>c</sup>
Trachtman et al, <sup>6</sup> United States, EU	Ph2 double blind, RCT	Arm 1: sparsentan, all doses +/- diuretics +/- IS (73) Arm 2: ARB (irbesartan) +/- diuretics +/- IS (36)	primary FSGS	US: 45; 8-75; EU: 39 18-75	45; 39	-	3.12 (range, 0.9-10.7); 3.61 (range, 0.4-18.7)	74.5 ± 44.7 74.4 ± 37.3	-	Follow-up; Tx duration 8 wk; 8 wk	Proteinuria and other biomarkers; eGFR; BP; safety events
Trachtman et al, <sup>9</sup> United States, Canada	Phase I/II open-label RCT	Arm 1: SCT (ACEi + ARB [lisinopril + losartan] + atorvastatin) (7) Arm 2: SCT + IS (adalimumab) (7) Arm 3: SCT + galactose (7)	resistant primary FSGS	14.7 (IQR: 13.0-20.8)	Not specified	-	8.8 ± 4.7 5.1 ± 4.6 12.2 ± 16.8	179.1 ± 59.5 121.3 ± 96.3 108.1 ± 56.5	-	Follow-up: 1.63 y (range, 1.27-1.74 y)	Proteinuria; eGFR; Safety events
Troyanov et al, <sup>5</sup> Canada	Retrospective	ACEi/ARB + IS [CS, CsA, others] (281)	NS primary FSGS	>18	1	4.7 (range, 0.2-98.3)	-	-	73 ± 31	Follow-up: 64 mo (range, 12-346 mo)	CrCl; BP; Kidney survival or progression to ESKD; Time to ESKD; Survival/mortality; HR
Usta et al, <sup>33</sup> Turkey	Prospective	Arm 1: ARB [losartan] (13) Arm 2: Control [not specified] (10)	Resistant to immunosuppressive therapy primary FSGS	Arm 1: 32 ± 10; Arm 2: 32 ± 13	38.4; 40	3.6 ± 0.5 3.4 ± 0.4	-	-	68 ± 7 mL/min; 70 ± 4 mL/min	Follow-up: 12 mo	Proteinuria and other biomarkers; CrCl; BP
Wasilewska et al, <sup>34</sup> Poland	Prospective	Arm 1: ACEi (enalapril) + IS [Pred, CsA] (24) Arm 2: control healthy children (20)	SDNS - FSGS	<18	1	32 ± 19 mg/kg per 24 h	-	-	133 ± 28	Follow-up: 12 mo	Proteinuria and other biomarkers; CrCl

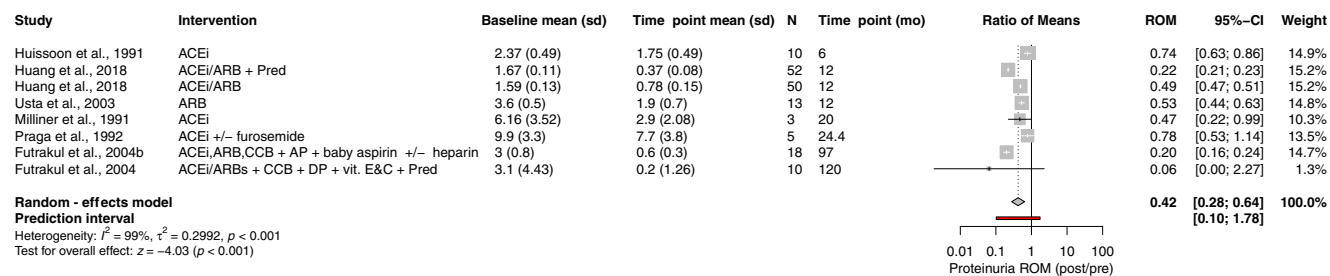
*Note:* The report by Praga et al<sup>30</sup> about the use of ACEi as monotherapy for the initial 24 months of study follow-up, for which we extracted proteinuria results. Later, some patients required antidiabetics as concomitant Tx to ACEi, which is the reason the results for CrCl and kidney survival are not considered as outcomes of RAAS inhibitor monotherapy treatment. Unless specified otherwise, data are reported as mean ± SD or median (95% CI, IQR, or range). Units of measure are noted in table cells when different from the overall column.

Abbreviations: +/-, some patients within the cohort may not have received the referred medication; ACEi, angiotensin-converting enzyme inhibitors; ACEi/ARB, treatment with an angiotensin-converting enzyme inhibitor alone, an angiotensin receptor blocker alone, or a combination of the 2; AH, antihypertensives; AP, antiplatelets; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blockers or inhibitors; CI, confidence interval; CKD, chronic kidney disease; CNI, calcineurin inhibitors; CrCl, creatinine clearance; CS, corticosteroids; CsA, cyclosporine or cyclosporine A; CYC, cyclophosphamide; DEX, dexamethasone; DP, dipyrindamole; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; EU, European Union; FSGS, focal segmental glomerulosclerosis; GC, glucocorticoids; GN, glomerulonephropathy; HD, high dose; HR, hazard ratio; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; IS, immunosuppressants; LD, low dose; MMF, mycophenolate mofetil; MP, methylprednisone; NS, nephrotic syndrome; Pred, prednisone or prednisolone; RAAS, renin-angiotensin-aldosterone system; SCT, standard conservative therapy; SDNS, steroid dependent nephrotic syndrome; SD, standard deviation; SEM, standard error of the mean; SRNS, steroid resistant nephrotic syndrome; Tx, treatment; UPCR, urinary protein-creatinine ratio

<sup>a</sup>Study arm or cohort of interest (for which outcomes were reported).

<sup>b</sup>Not specified whether data show the SD or SEM.

<sup>c</sup>Clinical outcomes were reported for the general GN population and not for the FSGS-specific patients.



**Figure 2.** Change in daily proteinuria outcomes in patients treated with ACEi/ARBs. Changes in daily proteinuria are expressed as the ROM (response ratio) between measurements from the last reported time point and baseline. Summary effects of all studies, regardless of the type of therapy, are highlighted in bold. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AP, antiplatelets; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; DP, dipyridamole; Pred, prednisone; ROM, ratio of means; SD, standard deviation.

In concordance with the observations made on daily proteinuria, studies reporting urinary protein-creatinine ratio values (3 studies) after treatment with ACE inhibitor/ARBs also demonstrated a reduction in this outcome (ROM, 0.52; 95% CI, 0.30-0.90; follow-ups, 6-24 months; Fig S2). Only 1 study reported urinary protein-creatinine ratio measurements in patients treated with ACE inhibitor alone, while the remaining 2 studies were in patients treated with ACE inhibitor/ARBs in combination with immunosuppressive or nonimmunosuppressive therapies.<sup>10</sup> Similarly, the lack of controlled studies precluded the possibility of attributing the observed reduction to an effect of ACE inhibitor/ARBs alone.

Only 1 controlled study prospectively assessed the effects of ACE inhibitor/ARBs combined with immunosuppressive therapies versus ACE inhibitor/ARBs alone (prednisone + ACE inhibitor/ARBs vs ACE inhibitor/ARBs), and the result showed that adding immunosuppressants to ACE inhibitor/ARBs led to a stronger reduction in daily proteinuria than the treatment with ACE inhibitor/ARBs alone (MD, -0.41 g/d; 95% CI, -0.46 to -0.36; Fig 3).<sup>11</sup>

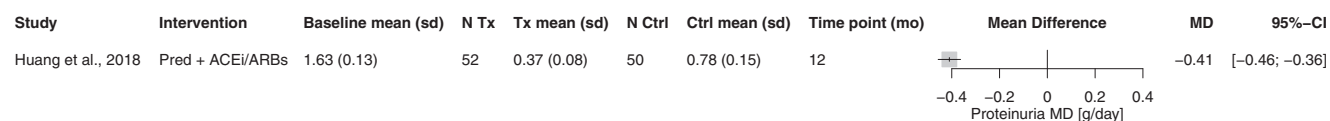
### Effect on Kidney Function

Sixteen studies reported the mean GFRs between various follow-up and baseline measurements, as either the eGFR (9 studies), CrCl (10 studies), or both (3 studies).

Four studies reporting CrCl results could be pooled in a meta-analysis, of which 2 studies measured CrCl in patients treated with ACE inhibitor/ARB monotherapy and 2 in patients treated with a combination of ACE inhibitor/ARB and immunosuppressive or nonimmunosuppressive

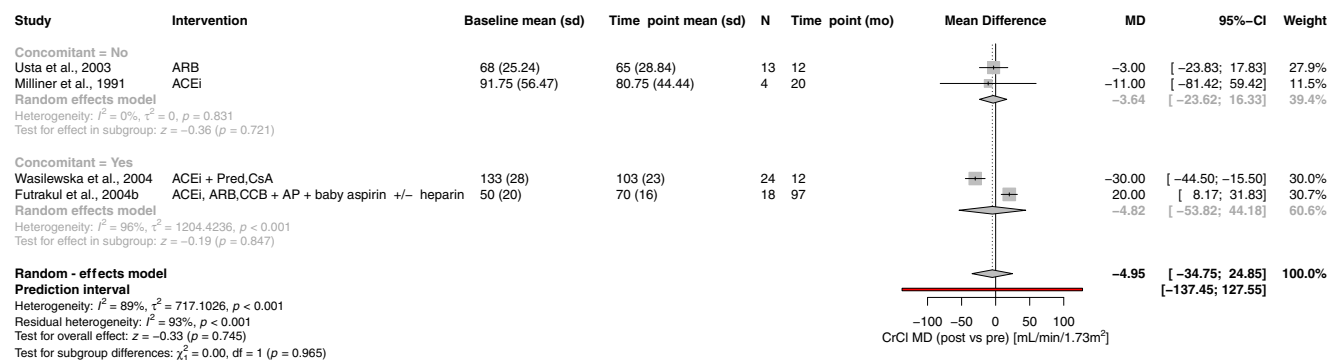
therapies. The summary effects of these 4 studies suggested no significant change in CrCl from baseline to the last reported time point (12-97 months), regardless of whether ACE inhibitor/ARBs were used alone or in combination with other types of therapy (MD, -4.95 ml/min/1.73 m<sup>2</sup>; 95% CI, -34.75 to 24.85; P = 0.97; Fig 4). However, the results of this meta-analysis must be interpreted with caution because of the limited amount of data and the considerable degree of variability, notably in terms of length of follow-up and baseline CrCl values.

The eGFR values reported in 4 studies were compatible with a meta-analysis, but none of the studies evaluated the effects of ACE inhibitor/ARBs alone. One open-label RCT assessed the effects of standard conservative therapy (an ACE inhibitor [lisinopril], an ARB [losartan], and a statin [atorvastatin]) alone or in combination with an immunosuppressant (adalimumab) or galactose.<sup>9</sup> The remaining 3 studies assessed the effects of ACE inhibitor/ARBs in combination with immunosuppressive and nonimmunosuppressive therapies. No significant change in eGFR between baseline and the last reported time point (6.5-24 months) was demonstrated (MD, -0.32 ml/min/1.73 m<sup>2</sup>; 95% CI, -23.80 to 23.17; P = 0.98; Fig 5). Stratification by the length of follow-up or time point did not show a correlation between the length of follow-up or time point and the change in eGFR from baseline (Fig S3). As observed for CrCl, the considerable data variability and the absence of studies on patients treated only with ACE inhibitor/ARBs hinders the association of the observed effect directly with the use of these drugs.



**Figure 3.** Comparison of immunosuppressive treatment versus nonimmunosuppressive treatment on daily proteinuria. The treatment effect is expressed as the MD between the intervention and control arms at the last reported time point (Pred + ACEi/ARBs vs ACEi/ARBs alone). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; MD, mean difference; Pred, prednisone; SD, standard deviation.





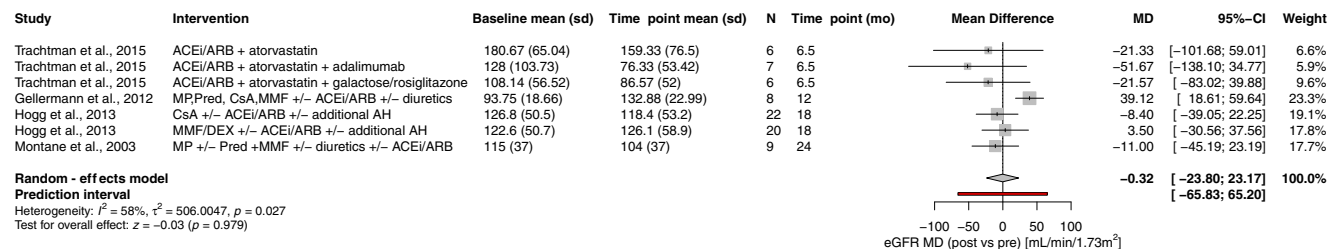
**Figure 4.** Change in CrCl in patients treated with ACEi/ARB. The change in CrCl is expressed as the MD between measurements at the last reported time point and baseline. The summary effects of all studies, regardless of the type of therapy, are highlighted in bold. The summary effects of the concomitant and nonconcomitant treatment subgroups are highlighted in gray. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AP, antiplatelets; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; CrCl, creatinine clearance; CsA, cyclosporine A; MD, mean difference; Pred, prednisone; SD, standard deviation.

### Effect on Kidney Survival

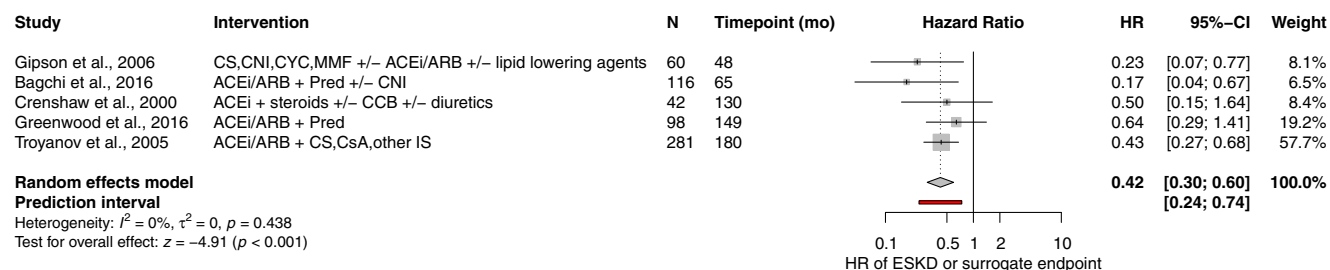
Seven studies investigated kidney survival in patients treated with ACE inhibitor/ARBs as the risk of reaching ESKD or another surrogate end point defined by the investigators. Of these, 5 studies reported the hazard ratio of reaching ESKD or kidney failure under the use of ACE inhibitor/ARB (treatment with ACE inhibitor/ARB vs no treatment). No study evaluated the effect of ACE inhibitor/ARBs in monotherapy, which hindered the assessment of the individual effects of ACE inhibitor/ARBs on the progression to kidney failure. A meta-analysis of these studies suggests a trend toward a 58% reduction of the risk of reaching ESKD or kidney failure with the use of ACE inhibitor/ARB therapies when used in combination with other treatments (hazard ratio, 0.42; 95% CI, 0.30-0.60;  $P < 0.001$ ; Fig 6). However, it is important to note that the selection bias commonly occurring in retrospective studies may be a confounding factor contributing to the strong long-term benefit observed. Also, the high level of heterogeneity between studies in terms of study design, patient populations, and treatment regimens is a strong limitation of this analysis.

### Safety and Tolerability

Out of the 30 publications retrieved, only 7 studies reported adverse effects of ACE inhibitor/ARB monotherapy or of the combination of ACE inhibitor/ARBs with other treatments. The study by Huang et al<sup>11</sup> was the only controlled study reporting adverse events related to the use of ACE inhibitor/ARB monotherapy, and it showed that only 2 patients had hypotension and none developed hyperkalemia. In the same study, when patients were given prednisone plus ACE inhibitor/ARBs, 3 patients developed infections, 3 had elevated serum glucose, and 2 had skin acne. Two cohort studies stated adverse effects associated only with the use of immunosuppressive drugs (tacrolimus, mycophenolate mofetil, and cyclosporine A).<sup>12,13</sup> The remaining 5 studies reported that infections (urinary tract and respiratory), hospitalization, edema, and pain were the main adverse effects observed in patients treated with ACE inhibitor/ARBs in combination with other therapies (immunosuppressive or nonimmunosuppressive).<sup>6,8,9,11,14</sup> Hyperkalemia was documented only in 1 study, in which patients were



**Figure 5.** Changes in eGFRs in patients treated with ACEi/ARB. Changes in eGFR are expressed as the MD between measurements at the last reported time point and baseline. Summary effects of all studies, regardless of the type of therapy, are highlighted in bold. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACEi/ARB, treatment with an ACEi alone, an ARB alone, or a combination of the 2; AH, antihypertensives; ARB, angiotensin receptor blocker; CI, confidence interval; CsA, cyclosporine A; DEX, dexamethasone; eGFR, estimated glomerular filtration rate; MD, mean difference; MMF, mycophenolate mofetil; MP, methylprednisolone; Pred, prednisone; SD, standard deviation.



**Figure 6.** Effects of ACEi/ARB treatment on the risks of reaching ESKD or kidney failure (or a surrogate end point), assessed using the univariate HR. Reductions in the risks of reaching ESKD or kidney failure (or a surrogate end point) under ACEi/ARB medication were reported as a univariate HR (results of the Kaplan-Meier analyses; exposure to ACEi/ARBs was considered as a single predictor in each study). In all studies, patients received complex interventions with various concomitant therapies, which are summarized in the second column of the figure. Not all patients were exposed to ACEi/ARBs. Summary effects of all studies, regardless of the type of therapy, are highlighted in bold. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACEi/ARB, treatment with an ACEi alone, an ARB alone, or a combination of the 2; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; CI, confidence interval; CNI, calcineurin inhibitors; CS, corticosteroids; CsA, cyclosporine A; CYC, cyclophosphamide; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; IS, immunosuppressants; MMF, mycophenolate mofetil; Pred, prednisone.

treated either with mycophenolate mofetil/dexamethasone plus ACE inhibitor/ARB and other hypertensives, or cyclosporine A with ACE inhibitor/ARB and other hypertensives.<sup>8</sup> At 52 weeks, 3 patients in the mycophenolate mofetil/dexamethasone group and 9 patients in the cyclosporine A group developed hyperkalemia.

## DISCUSSION

In this systematic review and meta-analysis evaluating the effects of RAAS inhibitor (ie, ACE inhibitor/ARB) therapies on primary FSGS, there was a tendency toward the reduction of proteinuria in patients with primary FSGS during treatment with RAAS inhibitors, with an approximate doubling of the proteinuria reduction when RAAS inhibitor treatment was combined with other drugs, most commonly immunosuppressants. RAAS inhibitor monotherapy was associated with maintained kidney function, as shown by no change in CrCl through the last reported follow-up of studies. The effects of RAAS inhibitor monotherapy on kidney function and survival, as indicated by changes in eGFR and ESKD risk, could not be determined because of the limitations of the available treatment studies.

FSGS does not represent a single disease entity, but rather a histologic pattern of injury arising from a heterogeneous and complex array of underlying genetic, immunologic, hemodynamic, metabolic, and infectious insults. RAAS blockade is a standard component of a comprehensive treatment strategy across the spectrum of FSGS, whether primary or secondary, nephrotic or subnephrotic. The current study identified several challenges and limitations within the existing treatment literature that has examined RAAS inhibitor therapy for primary FSGS.

First, the lack of strong evidence on the benefits of ACE inhibitor/ARB use in the context of FSGS is striking, particularly in subnephrotic patients, in whom these

treatments are typically used as monotherapy and are generally accepted as the standard of care. In light of this, the results of our analysis regarding the effects of ACE inhibitor/ARB therapy on any of the evaluated outcomes should be interpreted with caution and as a tendency rather than a true response.

Second, none of the retrieved studies included patients explicitly diagnosed with genetic FSGS. The limited use of genetic testing or commercially available tests to identify circulating factors makes it difficult to accurately identify the underlying cause of primary FSGS. Despite the best intentions of investigators to define inclusion and exclusion criteria that enable the selection of only patients with primary FSGS, the included studies are likely to have included patients with secondary disease, thereby limiting the conclusions that we can derive from the efficacy of ACE inhibitor/ARB therapy for primary FSGS.

Third, as is done in clinical practice and especially for nephrotic patients, ACE inhibitor/ARB therapy is typically given in combination with immunosuppression, including steroids. It is therefore not surprising that 23 of the 28 studies included fell into this category. The observation that the addition of immunosuppression to ACE inhibitor/ARB therapy increases proteinuria reduction is encouraging, but while it is important to note that there is an overall trend toward kidney protection, it must also be noted that the large majority of the published literature does not allow us to assess the independent effects of RAAS blockades on kidney survival in patients with FSGS. Nonetheless, a recent report showed that graded proteinuria reduction is associated with greater kidney survival in steroid-resistant FSGS.<sup>15</sup>

There are limitations in the collective studies in this systematic review and meta-analysis, and thus in the applicability of these results to clinical practice. The high heterogeneity across the available studies that examined

RAAS inhibitor treatment of primary FSGS, including heterogeneity in design, patient populations, and treatment regimens, complicates data interpretation. Patient heterogeneity resulted from the inclusion of patients with glomerular disorders other than primary FSGS in some studies, and the lack of access to patient-level data prevented the management of this heterogeneity through the exclusion of these patients. Thus, the effects of RAAS inhibitor therapies in primary FSGS may be overestimated or underestimated in these studies. Most of the assessed studies evaluated RAAS inhibitor treatment combined with other drugs, and the independent effects of the RAAS inhibitor versus the other treatments on the reduction of proteinuria in these patients cannot be distinguished. Study design heterogeneity followed from the limited available controlled trials and the resulting inclusion of nonrandomized and observational studies. Finally, the lack of a universally accepted tool for risk-of-bias assessments in nonrandomized, observational intervention studies included in systematic reviews prevented a risk-of-bias assessment in these types of studies included in the analyses of RAAS inhibitor treatment in primary FSGS.

This systematic review and meta-analysis highlights important gaps in the available evidence for the evaluation of RAAS inhibitor treatment in primary FSGS. The evidence gap is reflective of the state of the science, in that the use of RAAS inhibitors is foundational, although not specifically indicated for FSGS treatment. These gaps provide key directions for future clinical studies in patients with primary or genetic FSGS to allow robust evaluation of RAAS inhibitor monotherapy and FSGS clinical outcomes, including kidney survival. Management of heterogeneity in study designs, patient populations, and treatment regimens is needed for optimal clinical application of assessed outcomes. To help alleviate patient heterogeneity, investigators are encouraged to assess for genetic FSGS as well as circulating factors associated with primary FSGS through the use of genetic testing or commercially available tests, to guide the exclusion of patients with other glomerular diseases. Additionally, investigators are encouraged to make available patient-level data for use in meta-analyses. To manage heterogeneity in treatment regimens, the inclusion of a separate treatment arm for RAAS inhibitor monotherapy versus combined treatment or another drug will allow for the robust evaluation of the effects of RAAS inhibitor monotherapy on clinical outcomes. The inclusion of the patient-related and intervention-related approaches into RCTs will provide a larger evidence base for meta-analyses and help reduce study design heterogeneity.

In conclusion, proteinuria reduction is emerging as a useful surrogate marker for the efficacy of FSGS treatment. This suggests that any incremental reduction in proteinuria achieved by ACE inhibitor/ARB therapy has the potential for clinical benefits.

Sufficiently powered and well-controlled studies are still needed to better define the contributions of RAAS blockade to improve clinical outcomes in patients with FSGS.

## SUPPLEMENTARY MATERIAL

### Supplementary File (PDF)

**Figure S1:** Change in daily proteinuria in patients treated with ACE inhibitor/ARB, stratified by timepoint.

**Figure S2:** Change in UPCR in patients treated with ACE inhibitor/ARB.

**Figure S3:** Change in eGFR in patients treated with ACE inhibitor/ARB, stratified by timepoint.

**Table S1:** Systematic literature review protocol for PubMed search.

**Table S2:** Systematic literature review protocol for Embase search.

**Table S3:** Systematic literature review protocol for Cochrane search.

**Table S4:** Bias assessment for RCTs included in the systematic literature review.

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