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Efficacy and Safety of ACE Inhibitors and ARB Therapies in Primary FSGS Treatment: A Systematic Review and Meta-analysis

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Background

Primary focal segmental glomerulosclerosis (primary FSGS) is a rare disease that attacks the kidney's filtering units (glomeruli) causing serious scarring and leading to permanent kidney damage and even failure (end-stage renal disease [ESRD]). Disease incidence is increasing, and in the United States, nearly 50% of patients with primary FSGS and nephrotic-range proteinuria resistant to treatment will require renal replacement therapy within 5–10 years of diagnosis (Korbet, 2012). Regardless of the clinical form of FSGS, a conservative management including the use of Renin Angiotensin System inhibition (RASi) with angiotensin-converting enzyme inhibitors (ACEi) and/or angiotensin-receptor blockers (ARB), optimal blood pressure control, and dietary salt restriction is recommended for patients with persistent proteinuria. However, this recommendation is based on evidence from other proteinuria-related kidney diseases (KDIGO, 2012), and thus the effect of ACEi/ARB on renal outcomes such as proteinuria, GFR, and renal survival in primary FSGS patients remains unclear.

Aims and Objectives

This systematic literature review (SLR) aims to assess the benefits and risks of ACEi/ARB therapies on renal outcomes in primary FSGS patients.

Methods

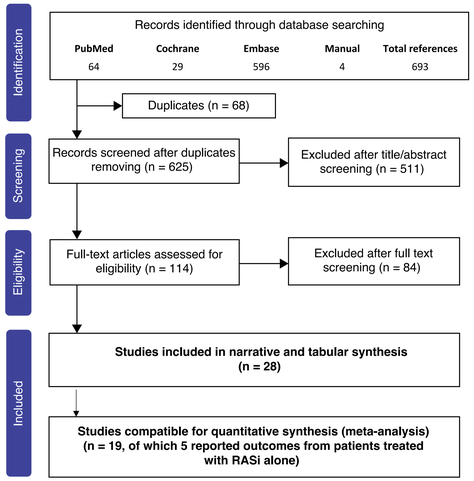
- English language, human studies were searched on April 5, 2019 using the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials databases, and relevant publications not detected with the SLR protocol were hand-searched to complement this investigation
- Various cohort study designs and type of publications reporting the treatment of primary or idiopathic FSGS patients with ACEi/ARB and assessing any relevant renal function outcome (proteinuria, renal function, or renal survival) or adverse events were selected in this SLR
- 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 random effect model was used to compute: the estimated summary ratio of means (ROM) between last follow-up timepoint and baseline and the estimated summary mean difference (MD) between mean values at the last follow-up and baseline.

Results and Findings

Study selection and characteristics

- A PRISMA chart presented in **Figure 1** displays the selection process of the articles included in this SLR
- The 30 publications deemed relevant for inclusion corresponded to 28 independent studies, with the majority consisting of real-world studies (n=23 studies) and only 5 controlled studies
- All studies were conducted in primary or idiopathic FSGS patients, or reported specific results for this target population
- Patients with nephrotic syndrome were included in 21 studies and the majority comprised more than 50% of nephrotic patients (n= 17 studies). In 6 studies, the nephrotic state of the patient was not mentioned, and one study considered only non-nephrotic patients.
- Studies often reported the use of ACEi, ARB, or both in combination with other drugs (n=23 studies), mainly immunosuppressants (n=16 studies). Only 8 studies assessed ACEi/ARB treatment as monotherapy.
- A considerable heterogeneity was found among the studies due to different baseline characteristics, patient populations, study designs, treatment regimens, investigated drugs, and time interval between baseline and follow-up time measurements

Figure 1. Flowchart describing the study selection process

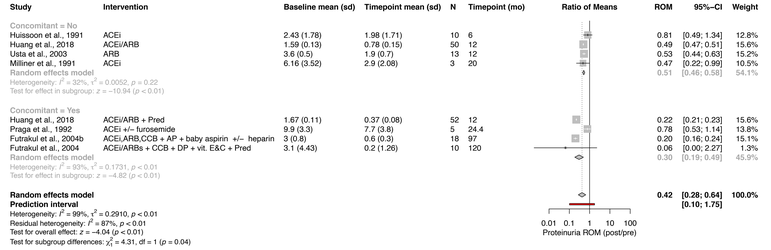


Number of studies identified, screened, assessed for eligibility, and included for narrative (tabular) or quantitative (meta-analysis) synthesis.

Effect on proteinuria

- A total of 12 studies assessed daily proteinuria after treatment with ACEi/ARB, of which 7 reported data compatible with the computing of a ROM meta-analysis for daily proteinuria

Figure 2. Change in daily proteinuria outcome in patients treated with ACEi/ARB



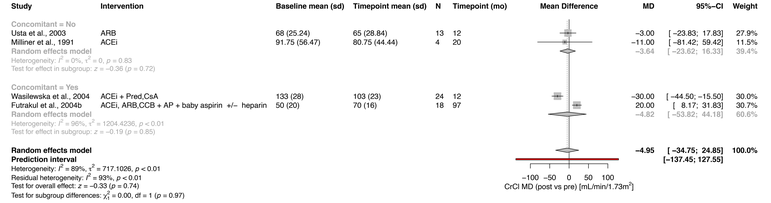
Change in daily proteinuria are expressed as ratio of means (response ratio) between last timepoint reported and baseline measurements. ROM, ratio of means; 95% CI, 95% confidence interval; N, number of patients in sample group; ACEi, angiotensin-converting enzyme (ACE) inhibitors; ARB, angiotensin-receptor blockers; Pred, prednisone; CCB, calcium channel blocker; DP, dipyridamole. Summary effect of all studies, regardless of the type of ACEi/ARB therapy is highlighted in bold. Summary effect of the concomitant and non-concomitant treatment subgroups is highlighted in grey.

- In patients treated with ACEi/ARB, alone or in combination with other therapies, daily proteinuria decreased by more than 50% from baseline to last follow-up (ROM, 0.42; 95% CI, 0.28 to 0.64) (**Figure 2**). Nevertheless, as none of the studies were designed to assess the effect of ACEi/ARB, the observed reduction cannot be certainly attributed to an individual effect of these drugs.
- Due to the heterogeneity of the subgroups in terms of length of follow-up, we could not reliably compare the effect observed in patients treated with ACEi/ARB alone versus patients treated with ACEi/ARB in concomitance with other therapies (**Figure 2**)

Effect on renal function

- 16 studies reported the mean glomerular filtration rate between various follow-up and baseline measurements, as either eGFR (n=9 studies) or creatinine clearance (CrCl, n=10 studies) or both (n=3 studies). Only 4 studies were eligible for a meta-analysis, of these, 2 assessed CrCl in patients treated with ACEi/ARB monotherapy and 2 assessed patients treated with a combination of ACEi/ARB with immunossupressive or non-immunosuppressive therapies

Figure 3. Change in CrCl in patients treated with ACEi/ARB



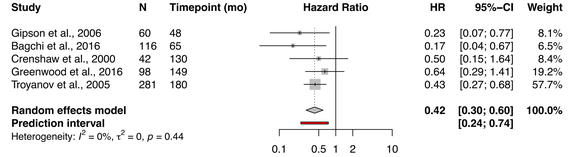
Change in CrCl is expressed as mean difference between last timepoint reported and baseline measurements. MD, mean difference, 95% CI, 95% confidence interval; N, number of patients in sample group; ACEi, angiotensin-converting enzyme (ACE) inhibitors; ARB, angiotensin-receptor blockers; Pred, prednisone; CCB, calcium channel blocker; CsA, cyclosporine A; AP, antiplatelets. Summary effect of all studies, regardless of the type of IS therapy is highlighted in bold. Summary effect of all studies, regardless of the type of ACEi/ARB therapy is highlighted in bold. Summary effect of the concomitant and non-concomitant treatment subgroups is highlighted in grey.

- Only 4 studies could be pooled in a meta-analysis, which suggested no significant change in CrCl from baseline to variable follow-up timepoints (12 to 97 months), regardless if ACEi/ARB were used alone or concomitantly with other type of therapies (**Figure 3**)
- However, results of this meta-analysis must be taken with caution as the limited amount of data and their considerable degree of variability, notably in terms of length of follow-up and baseline CrCl values, represent a big limitation in this analysis

Effect on renal survival

- 7 studies investigated renal survival in patients treated with ACEi/ARB as the risk of reaching ESRD or renal failure rate. Of these, 5 studies reported the relationship between ACEi/ARB treatment and the progression of the disease using an analysis of hazard ratios (HR).
- None of the included studies evaluated the effect of ACEi/ARB as monotherapy, which hinders the determination of the individual effect of ACEi/ARB on the progression to renal failure

Figure 4. Effect of ACEi/ARB treatment on the risk of reaching ESRD (or surrogate endpoint) assessed using the univariate hazard ratio



Univariate HR of ESRD or surrogate endpoint for exposure to ACEi/ARBs as a risk factor

Risk of reaching ESRD (or surrogate endpoint) is expressed as hazard ratio of using versus not using ACEi/ARB. ACEi, angiotensin-converting enzyme (ACE) inhibitors; ARB, angiotensin-receptor blockers; ESRD, end-stage renal disease; HR, hazard ratio; 95% CI, 95% confidence interval; N, number of patients in the study.

- A meta-analysis of these studies suggests a trend towards a reduced risk (~58%) to reach ESRD with the use of ACEi/ARB therapies in combination with other treatments (**Figure 4**). However, the high level of variability between studies in terms of study design, patient populations and treatment regimens are a strong limitation of this analysis.

Effect on safety and tolerability

- Out of the 30 publications retrieved in this SLR, only 7 studies reported adverse effects of ACEi/ARB monotherapy or of the combination of ACEi/ARB with other therapies. Adverse events reported included hypertension, hypotension, infections, hyperkalemia, pain, and edema.
- Huang et al. (2018) was the only controlled study reporting adverse events related to the use of ACEi/ARB as monotherapy, and it showed that only 2 patients had hypotension, and none suffered from hyperkalemia
- 2 cohort studies (Bagchi et al., 2016; Gellermann et al., 2012) stated adverse effects associated only to the use of immunosuppressants (tacrolimus, mycophenolate mofetil, cyclosporine A)
- The remaining 5 studies (Gipson et al., 2011; Huang et al., 2018; Montane et al., 2003; Trachtman et al., 2018; Trachtman et al., 2015) stated that infections (urinary tract and respiratory), hospitalization, edema, and pain were the main adverse effects observed in patients treated with ACEi/ARB in combination with other therapies (immunosuppressive or non-immunosuppressive)

Conclusions

- This SLR suggests a tendency to a reduction in proteinuria levels in patients treated with ACEi/ARB alone or in combination with other treatments
- The absence of a strong level of evidence, due to a high degree of heterogeneity among the few available studies and lack of controlled trials, precludes the quantification of ACEi/ARB monotherapy effect on proteinuria as well as on renal function and long-term renal survival in primary FSGS patients
- This SLR stresses the need for larger and better designed clinical trials to accurately determine the clinical benefit of ACEi/ARB in primary FSGS

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