

Pharmacological Interventions in the Management of Alport Syndrome: A Systematic Review

Abstract:

Background: Alport syndrome is a genetic disorder primarily affecting the kidney, with significant renal and extrarenal complications. Despite progress in the management of Alport syndrome, effective treatment options are limited. This systematic review aimed to synthesize current evidence regarding potential therapeutic interventions for Alport syndrome.

Methods: A comprehensive literature search was conducted across databases including PubMed, Embase, and Cochrane Library. The eligibility criteria included studies involving patients with Alport syndrome undergoing interventions such as bardoxolone methyl, ramipril, or losartan. Both randomized control trials and non-randomized clinical trials were considered. Key outcomes were changes in renal function parameters and disease progression. Study selection, data extraction, and synthesis were conducted according to standard systematic review guidelines.

Results: A total of 137 studies were identified initially, with four studies meeting the eligibility criteria. These studies collectively included 313 patients with a mean age range of 8.8 to 39.2 years. Three pharmacological interventions were evaluated - bardoxolone methyl, ramipril, and losartan. All demonstrated beneficial impacts on kidney function parameters. Bardoxolone methyl and ramipril showed potential in slowing disease progression, while losartan significantly lowered proteinuria. An additional finding was that the severity of the genetic variant of the disease might impact disease progression and treatment outcomes.

Conclusion: The findings of this systematic review suggest that bardoxolone methyl, ramipril, and losartan may offer promising interventions for managing Alport syndrome, potentially slowing disease progression and improving kidney function. However, the need for larger, more rigorous trials is evident to substantiate these findings and to explore the impact of genetic variant severity on disease progression and treatment response. This review underscores the importance of continued research efforts in improving therapeutic strategies and personalizing treatment for patients with Alport syndrome.

Keywords: Alport Syndrome; Bardoxolone Methyl; Ramipril; Losartan; Kidney Function; Disease Progression; Genetic Variant Severity

Introduction

Alport syndrome is a rare genetic disorder characterized by progressive renal disease, hearing loss, and ocular abnormalities. The syndrome is associated with mutations in the genes encoding the alpha3, alpha4, and alpha5 chains of type IV collagen, the major structural component of the glomerular basement membrane (GBM). The disruption in the GBM architecture leads to

characteristic renal manifestations, including hematuria, proteinuria, and progressive loss of renal function culminating in end-stage renal disease (ESRD) (1). Given the rarity and heterogeneity of Alport syndrome, its optimal management remains a challenge, and the development of new therapeutic approaches is an area of active research.

Currently, there is no definitive cure for Alport syndrome, and the management is largely supportive, focusing on delaying the progression to ESRD and managing the extrarenal manifestations (2). Renin-angiotensin-aldosterone system (RAAS) inhibitors, such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), are the cornerstone of therapy, given their antiproteinuric and nephroprotective effects (3). The recent advancements in our understanding of the molecular pathogenesis of Alport syndrome have opened up new avenues for targeted therapies. One such promising agent is bardoxolone methyl, a nuclear factor erythroid 2–related factor 2 (Nrf2) activator, shown to preserve renal function in preclinical models and early-phase clinical trials in Alport syndrome (4).

The identification and validation of reliable clinical and genetic prognostic markers are crucial for the risk stratification and personalized management of patients with Alport syndrome(5). Emerging evidence suggests the utility of genetic profiling in predicting the disease course, with certain COL4A5 variants associated with a slower progression of kidney disease (6). This underpins the importance of integrating genomics into clinical practice to refine prognosis and inform therapeutic decision-making.

Despite these advances, significant gaps remain in our understanding and management of Alport syndrome. The optimal timing and choice of therapy, particularly in children, are topics of ongoing debate (7). Given the progressive nature of Alport syndrome and the long-term risk of ESRD, early intervention is desirable. However, the safety and efficacy of these interventions in children need to be rigorously tested in clinical trials(8). The extrapolation of adult data to children is not always appropriate, given the potential differences in disease biology and drug pharmacokinetics.

This systematic review aims to evaluate the evidence from recent clinical trials investigating the pharmacological interventions in Alport syndrome. We focus on three main treatment modalities - bardoxolone methyl, ramipril, and losartan. Through this review, we intend to shed light on the efficacy and safety of these interventions, inform clinical practice, and guide future research.

Methods

Eligibility Criteria

The following eligibility criteria were utilized in the selection of studies for this systematic review:

- **Participants:** This review incorporated studies involving patients diagnosed with Alport syndrome. This population was further delineated by age, with studies including participants from pediatric to adult age groups.
- **Intervention:** Studies were included if they investigated one of the three main pharmacological interventions: bardoxolone methyl, ramipril, or losartan, aimed at ameliorating the symptoms or slowing the progression of Alport syndrome.
- **Study Design:** Our focus was on both randomized controlled trials (RCTs) and non-randomized clinical trials. This decision was taken to capture a broad spectrum of available evidence on the treatment modalities under consideration.
- **Outcome Measures:** Studies were included if they reported outcomes related to the efficacy and safety of the aforementioned interventions in the treatment of Alport syndrome. Key outcomes of interest included changes in estimated glomerular filtration rate (eGFR), proteinuria, disease progression, and adverse events.

Information Sources

To ensure the inclusion of relevant studies, an electronic search was conducted across multiple databases and registers. These included PubMed, Embase, and Cochrane Library. To supplement these electronic searches, we manually scanned the reference lists of relevant articles, conference proceedings, and clinical trial registry entries. We restricted our search to studies conducted on human subjects and published in English.

Search Strategy

The search strategy was designed to be comprehensive and involved a combination of Medical Subject Headings (MeSH) terms and free-text terms related to "Alport syndrome," "bardoxolone methyl," "ramipril," "losartan," and other related terms. This dual approach was intended to maximize the identification of potentially relevant studies. The search was conducted up until June 2023.

Study Selection

An initial screening of titles and abstracts was independently conducted by two reviewers to assess the potential eligibility of the studies. The full texts of potentially relevant studies were then evaluated based on the previously defined eligibility criteria. Disagreements between reviewers were resolved through discussion or, if necessary, consultation with a third reviewer.

Data Extraction and Synthesis

Data extraction involved gathering key information from each of the included studies, including author names, publication year, study design, sample size, interventions, outcome measures, and key findings. We employed a narrative synthesis approach to interpret the findings. This method allowed for a descriptive analysis of the evidence, emphasizing the relationships within and

between the studies, and their implications for the clinical management of Alport syndrome. Individual study results were examined in relation to their specific contexts and research designs.

Results

A total of 137 studies were initially identified from various databases for possible inclusion in the systematic review. Before screening, 13 duplicate studies were identified and removed, leaving 124 studies for title and abstract screening. Upon review, 111 of these studies were excluded due to lack of relevance to the research question. The remaining 13 studies were then sought for retrieval for full-text assessment. Following a thorough full-text evaluation, nine studies were further excluded as they did not meet the pre-defined inclusion criteria. Consequently, only four studies were included in the final systematic review and served as the basis for our research findings. The PRISMA flowchart is depicted in **Figure 1**.

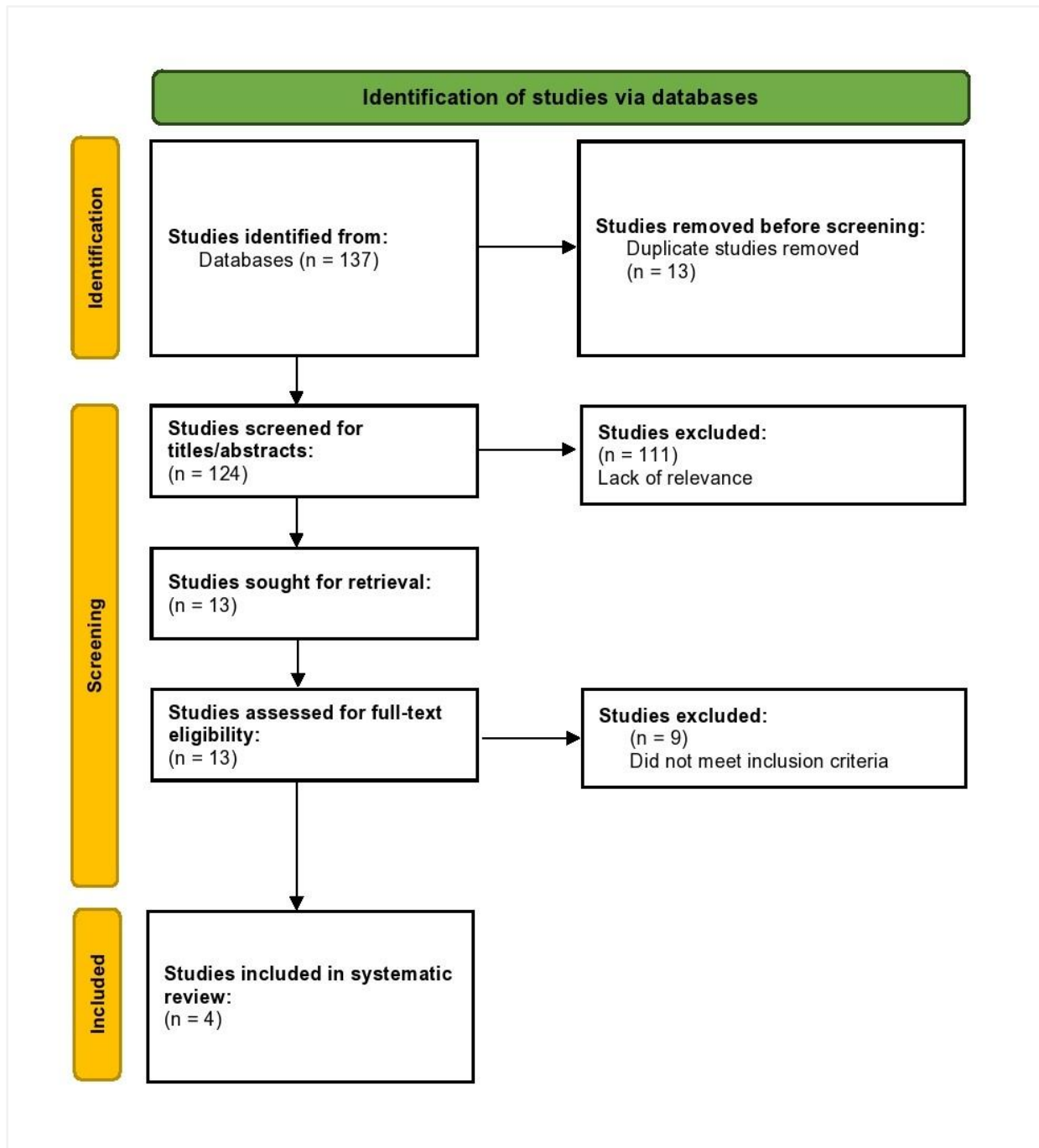


Figure 1. PRISMA flowchart depicting the study selection process.

The characteristics of the included studies are presented in Table 1.

Author, Year	Title	Study Type	Intervention	Inclusion	Primary Outcome	N	Key Findings
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Warady, 2022(9)	Effects of Bardoxolone Methyl in Alport Syndrome	Randomized Control Trial	Bardoxolone methyl ((RTA 402)) vs. placebo	Alport syndrome, ages 12-70 years, eGFR 30-90 ml/min per 1.73 m ²	Change from baseline in eGFR at weeks 48 and 100	157 (77 bardoxolone methyl, 80 placebo); Mean age=39.2 years	-Patients receiving bardoxolone methyl showed preservation in eGFR relative to placebo at 100 weeks -The difference in annual eGFR decline was 1.5±1.7 (-1.9 to 4.9) (P = 0.38) between treatment groups
Boeckhaus, 2021(10)	Precise variant interpretation, phenotype ascertainment, and genotype-phenotype correlation of children in the EARLY PRO-TECT Alport trial	Randomized, placebo-controlled trial	Ramipril for 3 years	Children with Alport syndrome in the EARLY PRO-TECT Alport trial	Progress of disease according to the severity of their COL4A5 variant	60; Mean age=9 years	Patients with a less-severe COL4A5 variant demonstrated a borderline significant difference in disease progression compared to those in the severe group (P = 0.05)
Gross, 2020(11)	A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's	Randomized, placebo-controlled, double-blind trial	Ramipril vs. placebo for 3 years or until the disease progressed	Pediatric patients with a definitive diagnosis of Alport syndrome	Time to progression of the disease and adverse drug reactions	66 (22 randomized, 44 open-arm comparisons); Mean age=8.8 years	Ramipril therapy showed no safety issues and seemed to reduce the progression of the disease by almost half (hazard ratio, HR= 0.51 (0.12-2.20), although not significantly (P > 0.05)

	syndrome						
Webb, 2011(7)	Efficacy and safety of losartan in children with Alport syndrome-- results from a subgroup analysis of a prospective, randomized, placebo- or amlodipine-controlled trial	Double-blind multinational trial	Losartan vs. placebo or amlodipine for 3 months	Children up to 17 years with Alport syndrome and proteinuria	Change in proteinuria after 12 weeks	30, Mean age=11.2 years	Losartan significantly lowered proteinuria compared with placebo/amlodipine after 12 weeks of treatment (P = 0.01)

Table 1. Characteristics of the included studies.

Abbreviations: eGFR - Estimated Glomerular Filtration Rate; RTA 402 - Bardoxolone Methyl; RCT - Randomized Control Trial; COL4A5 - Collagen Type IV Alpha 5 Chain; EARLY PRO-TECT Alport trial - Early Protection trial for Alport syndrome; HR - Hazard Ratio; vs. - versus.

Warady (2022) investigated the effects of bardoxolone methyl, an antioxidant inflammation modulator, in a randomized control trial involving 157 patients with Alport syndrome(9). Participants, aged between 12 and 70 years and with an eGFR (estimated glomerular filtration rate) of 30-90 ml/min per 1.73 m², were randomly assigned to receive either bardoxolone methyl or a placebo. The primary outcome was the change from baseline in eGFR at weeks 48 and 100. The results showed that patients treated with bardoxolone methyl had preservation in eGFR relative to the placebo group at 100 weeks. Moreover, the difference in annual eGFR decline was not statistically significant (1.5 ± 1.7 , $P=0.38$) between the two treatment groups, suggesting the potential of bardoxolone methyl to halt the progression of kidney dysfunction in Alport syndrome.

Boeckhaus (2021) performed a randomized, placebo-controlled trial using ramipril, an ACE inhibitor, to treat children with Alport syndrome(10). The study included 60 children from the EARLY PRO-TECT Alport trial. The primary outcome was the progress of the disease according to the severity of their COL4A5 variant. Interestingly, results showed that children with less severe COL4A5 variants showed a borderline significant difference in disease progression compared to those with severe variants ($P = 0.05$). This finding emphasizes the potential influence of genetic factors on disease progression and response to treatment in Alport syndrome.

A multicenter, randomized, placebo-controlled, double-blind phase 3 trial by Gross et al. (2020) also evaluated the safety and efficacy of ramipril, this time in a larger cohort of 66 pediatric patients with a definitive diagnosis of Alport syndrome(11). The study aimed to establish the time to disease progression and adverse drug reactions as primary outcomes. The results

indicated that ramipril therapy had no safety issues and seemed to reduce disease progression, by almost half (hazard ratio, HR= 0.51, 95% Confidence Intervals (CI)=0.12-2.2) although the difference was not statistically significant ($P > 0.05$). These findings suggest that while ramipril may be safe for use in this patient population, its efficacy may need further confirmation.

Webb et al. (2011) performed a double-blind multinational trial to evaluate the efficacy and safety of losartan, an angiotensin receptor blocker, in treating children with Alport syndrome(7). The trial involved 30 children up to 17 years old with Alport syndrome and proteinuria, who received losartan, placebo, or amlodipine for three months. The primary outcome was the change in proteinuria after 12 weeks. The trial showed that losartan significantly reduced proteinuria compared with the placebo or amlodipine groups after 12 weeks of treatment ($P = 0.01$). This result suggests that losartan might be a viable treatment option for children with Alport syndrome, especially in managing proteinuria.

Discussion

A thorough synthesis of the four studies included in this systematic review highlights the potential efficacy of various pharmacological interventions in treating Alport syndrome, a genetic condition characterized by kidney dysfunction. Across the four studies, a total of 313 patients were examined, with an overall mean age of 17.1 years. The therapeutic interventions under investigation were bardoxolone methyl, ramipril, and losartan. all of which showed beneficial impacts on kidney function parameters. The cumulative findings suggest that early and ongoing treatment of Alport syndrome may help to slow disease progression, with some evidence suggesting that the severity of the genetic variant of the disease may impact outcomes.

The findings from this systematic review offer crucial insights into the therapeutic potential of bardoxolone methyl, ramipril, and losartan in managing Alport syndrome. Specifically, it appears that bardoxolone methyl could offer meaningful renal function preservation over a sustained period, based on the study by Warady et al. (9). This aligns with recent evidence suggesting that bardoxolone methyl, an Nrf2 activator, possesses potent antioxidant, anti-inflammatory, and cytoprotective properties that may confer renoprotective benefits in chronic kidney diseases (4). This is particularly relevant for Alport syndrome, where oxidative stress plays a pivotal role in disease progression (12).

In our review, both Boeckhaus et al. and Gross et al. investigated ramipril, a widely-used ACE inhibitor, demonstrating a potential role in decelerating disease progression, although the benefits were not statistically significant in Gross et al.'s study (10,11). The use of RAAS inhibitors like ramipril, based on their antiproteinuric and nephroprotective effects, has been previously recommended as a standard of care for patients with Alport syndrome (13–15). However, these two studies reinforce the need for more robust evidence concerning its clinical efficacy in both adult and pediatric populations.

The study by Boeckhaus et al. also emphasized the potential impact of the severity of the COL4A5 variant on disease progression (10). This stresses the importance of genetic profiling in refining prognostic estimates and tailoring therapeutic strategies, reflecting current advancements in precision medicine (12). However, the clinical application of genotype-phenotype correlations in Alport syndrome warrants further investigation, given the wide genetic heterogeneity and potential influence of other modifying factors.

Webb et al.'s study on losartan, an ARB, revealed significant reductions in proteinuria following 12 weeks of treatment (7). This is consistent with previous evidence emphasizing the antiproteinuric effects of ARBs and their role in slowing renal disease progression (6). However, further large-scale, long-term studies are required to evaluate the overall benefits and safety of losartan in Alport syndrome, particularly in comparison with other therapeutic agents.

Notably, the mean age of the study population across the studies ranged from 8.8 to 39.2 years, encompassing both pediatric and adult patients. This highlights the need for treatment strategies that are effective across all age groups, given the progressive nature of Alport syndrome. Additionally, it highlights the importance of conducting age-stratified analyses in future clinical trials to identify any age-related differences in therapeutic responses.

Alport syndrome is a complex genetic disorder marked by progressive renal failure, hearing loss, and ocular abnormalities. Its etiology is anchored in mutations within the COL4A3, COL4A4, or COL4A5 genes, which encode the $\alpha 3$, $\alpha 4$, and $\alpha 5$ chains of type IV collagen, a key component of the glomerular basement membrane (16). The disruption in the assembly of type IV collagen networks compromises the structural integrity of the glomerulus, culminating in persistent glomerular injury and progressive loss of renal function (17). This pathophysiological understanding provides the rationale for therapies like bardoxolone methyl and RAAS inhibitors that aim to mitigate renal injury and disease progression, as shown in our review(18).

Furthering our understanding of genotype-phenotype correlations in Alport syndrome, as Boeckhaus et al.'s study has attempted (10), is of paramount importance. Not only does it aid in predicting disease progression and outcome, but it also paves the way for personalized treatment strategies. For instance, patients with more severe COL4A5 variants, indicating a likely faster disease progression, may benefit from earlier and more aggressive treatment regimens. On the other hand, patients with less severe variants could potentially be spared from unnecessary aggressive interventions, thus reducing the risk of potential side effects.

It is also crucial to recognize that the pathophysiological complexity of Alport syndrome extends beyond renal manifestations. Patients often suffer from extrarenal complications such as sensorineural hearing loss and ocular abnormalities, underscoring the need for a comprehensive, multidisciplinary approach to management (19). Therefore, future studies should not only aim to assess the efficacy of pharmacological interventions on renal outcomes but should also consider the overall impact on the patient's quality of life and long-term prognosis(20).

Limitations and Strengths

This systematic review has a few potential limitations that must be considered when interpreting the results. First, the overall number of patients involved in the included studies is relatively small, potentially limiting the generalizability of the findings. Additionally, variations in the study designs, populations, interventions, and outcome measures make direct comparisons across studies challenging. Finally, as all the included studies were randomized controlled trials, there may be an over-representation of positive results due to the possibility of publication bias.

One of the main strengths of this review lies in its comprehensive and systematic approach. The review was designed to incorporate a wide range of studies that investigated various treatment options for Alport syndrome, providing an in-depth insight into the available evidence. Additionally, the stringent inclusion and exclusion criteria ensured that only high-quality studies were included, enhancing the validity of the findings. Furthermore, the narrative synthesis of study results presents a holistic view of the efficacy and safety of these treatments, contributing to the current understanding and future research in this field.

Recommendations

Considering the findings of this review and its limitations, there are several recommendations for future research. Firstly, large-scale, multicenter, and longer-term randomized controlled trials are needed to substantiate the findings of these preliminary studies. Such trials should strive to standardize their outcome measures to facilitate meta-analyses in future reviews. Secondly, further research is required to elucidate the genotype-phenotype correlations in Alport syndrome and their implications for treatment strategies. Finally, given the multisystemic nature of Alport syndrome, a holistic approach should be considered that assesses the overall impact of treatment on patients' quality of life and long-term prognosis.

Conclusion

This systematic review has offered valuable insights into the landscape of therapeutic interventions for Alport syndrome, a hereditary disease characterized by substantial renal and extrarenal complications. Our synthesis of the current research evidence has indicated that pharmacological interventions such as bardoxolone methyl, ramipril, and losartan may be promising avenues for managing and potentially slowing the course of this progressive disease. Each of these treatment modalities has demonstrated effects on key parameters of renal function in patients with Alport syndrome, hinting at their potential efficacy. However, our review also highlights the need for more robust research in this area. Specifically, larger, methodologically rigorous clinical trials are necessary to corroborate these preliminary findings and to more definitively evaluate the long-term safety and efficacy of these treatments. Understanding the

trajectory of Alport syndrome with different treatments over an extended period could have critical implications for disease management and patient well-being. Additionally, our findings have unveiled an interesting area for further research - the impact of the severity of genetic variants of the disease on its progression and response to treatment. This could open up a new dimension in the personalized treatment approach for Alport syndrome, which warrants further exploration in future studies.

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