# Adult Treatment Overview: Medications

*The following information was prepared by Alport Syndrome Foundation with the guidance of Medical Advisory Committee members Dr. Caitlin Carter and Dr. James Simon, as well as Prof. Neil Turner (University of Edinburgh). This document is intended for those with a confirmed Alport syndrome diagnosis currently in kidney disease stages 1–4 (eGFR of 15–90+) and receiving care in the United States. It contains information on commonly prescribed medications, their potential side effects, and lists questions to ask your nephrologist during checkups.*

**Important Treatment Terminology**

The following medication classes are frequently referenced in this document:
ACE: Angiotensin-converting-enzyme inhibitor (ex. lisinopril, enalapril, ramipril)
ARB: Angiotensin II receptor blocker (ex. losartan)
SGLT-2: Sodium-glucose Cotransporter-2 inhibitor (ex. dapagliflozin [Farxiga])

## Frequently Asked Questions

### I was just diagnosed with Alport syndrome. How soon should I begin treatment?

For X-linked males and autosomal recessive patients, it is important to begin an ACE or ARB medication after receiving a confirmed Alport diagnosis and then attain the highest tolerated dose. For X-linked females and those with autosomal dominant Alport, the decision of when to begin treatment is more nuanced and based on various factors such as the presence of protein in the urine or high blood pressure. There is good-quality data showing that renin-angiotensin-aldosterone system (RAAS) inhibition (via ACEs and ARBs) alters the course of disease progression in Alport syndrome, especially when started early.

### What are the common medications used to treat Alport syndrome, and how do these medications differ?

Many physicians in the Alport community have a preference for prescribing an ACE inhibitor first, but there is a low threshold for switching to an ARB if the patient experiences side effects. For young patients, and young females in particular who tend to have naturally lower blood pressures, lisinopril (an ACE) is preferred because it comes in very low dosage options. Some data suggest that ACEs may be slightly more beneficial than ARBs in adults, and there is more data on ACE inhibitors for Alport treatment overall. However, the majority of Alport patients tend to be on ARBs (up to two-thirds) because they are often tolerated better than ACE inhibitors.

An additional type of medication, SGLT-2 inhibitors, have been shown to decrease the risk of kidney failure, heart attacks, and death in patients with diabetes. More recently, research has shown that this class of medication also protects kidneys in chronic kidney disease (CKD) patients without diabetes. One of these medications, dapagliflozin (Farxiga), is now FDA approved for use in patients with CKD without diabetes who are at increased risk for progressing to kidney failure. These medications reduce urine protein as well. While they have not been studied specifically in patients with Alport syndrome, they are increasingly being used in addition to ACEs/ARBs to help reduce the risk of kidney failure.

### What is the relationship between my kidney and cardiovascular health management?

CKD, whatever the cause, increases the risk for cardiovascular disease, including heart attacks, congestive heart failure, and strokes. It is important for your medical team to address other cardiovascular risk factors, such as cholesterol, high blood pressure, and smoking when managing your kidney dysfunction. ACEs/ARBs and SGLT-2 inhibitors have a doubly beneficial role in this case. While they have been shown to delay kidney disease progression, they also have a beneficial effect on the entire cardiovascular system, leading to overall better health and outcomes.

### What are common side effects associated with Alport syndrome treatment medications?

ACE inhibitors sometimes cause a persistent, dry cough. If this is experienced due to the ACE inhibitor, you can talk with your nephrologist about switching to an ARB.

Some of the more common side effects with both ACE inhibitors and ARBs include dizziness, fainting, and fatigue. These are often due to low blood pressure, so it is important to check blood pressure readings regularly. Hyperkalemia (higher than normal blood potassium level) is another side effect to watch for. This is more common at later stages of CKD (stages 4–5 or a GFR < 30 mL/min) but can be seen at higher GFRs, especially if you are also taking other medications that raise the potassium level (ex. spironolactone). How often to monitor your potassium level depends on your GFR and whether you have had abnormal levels in the past. This should be discussed with your nephrologist.

A very rare but potentially serious reaction called angioedema (swelling of the face, tongue, and/or lips) can occur with ACEs and ARBs. This can be a medical emergency. If this occurs, you should go directly to the emergency room. Antihistamines and steroids may be recommended.

SGLT-2 inhibitors can lead to increased urine volume, as sodium and sugar pull water with them into the urine, which can lead to dehydration in rare cases. The most serious potential side effects of taking SGLT-2 inhibitors include the risk of ketoacidosis (high levels of blood acids called ketones), especially in patients with diabetes, as well as urinary tract and genital fungal infections.

### When should a change in medication dosage or type be considered?

Changes in medication type or dosage can be discussed if:

- Blood pressure is not adequately controlled on current medication/dosage;
- The patient is experiencing side effects and isn't tolerating medication/dosage well;
- Lab results (estimated glomerular filtration rate [eGFR], urine albumin-creatinine ratio [UACR], urine protein creatinine ratio [UPCR]) are trending in the wrong direction.

### Is it common for adult patients to be on "combination therapy" (ACE + ARB)?

No, usually one or the other is used. However, the combination of an ACE or ARB with an SGLT-2 inhibitor is becoming increasingly common. Potassium-sparing diuretics might be added in some high-risk patients (ex. those with severe mutations, hypokalemia [low potassium level in the bloodstream], difficult to control high blood pressure, or persistent proteinuria).

## Tips for Optimal Care

### Pausing or discontinuing Alport treatment

The decision to skip or stop taking a medication should be individualized for each person. It is important to remember that Alport treatment medications prevent progression of kidney disease, so for people at high risk of kidney disease progression, it may not be a good idea to skip them at all to minimize interruptions in treatment. For others, it may be safe to skip them for a period of time. If you are thinking about stopping any prescribed medication, you should discuss the risks and benefits with your physician first.

You should discuss skipping/avoiding Alport medications with your nephrologist if:

- **You are actively trying to get pregnant or are currently pregnant or breastfeeding**. ACE, ARB, and SGLT-2 inhibitors are not recommended if you are planning to become pregnant. It is important to avoid unplanned pregnancies while on these medications. They should be stopped at least 3 months before becoming pregnant. If an unplanned pregnancy occurs, they should be stopped as soon as you find out you are pregnant. If breastfeeding, there are ACE inhibitors that do not transfer into breast milk to a significant degree and are considered safe to use. While breastfeeding, you should discuss all medications that you take with your child's pediatrician to be sure that they are safe for your baby. Those with Alport syndrome should talk with their doctors (OBGYN and nephrologist) about their specific medical situation before (if possible) and as soon as they become pregnant. Your doctors can work together to make sure you are on the right medications for you and your baby.

- **You are sick/vomiting/at risk of dehydration**. ACEs, ARBs, and SGLT-2 inhibitors are considered "sick day" medications, meaning you should skip taking them if you are significantly ill, such as being unable to keep fluids down. Taking SGLT-2s in this situation can increase the risk of a ketoacidosis and coma, even in nondiabetics. Continuing to take any of these medications in the setting of dehydration can lead to worsening kidney function. If you are severely ill or dehydrated, consider not taking these medications, monitoring your blood pressure closely, and speaking to a healthcare professional if your blood pressure drops significantly.

- **You forget or skip a dose of medication**. Ideally, you take your medication at the same time every time. If you do miss a dose, take the next regular dose on schedule. Do not double up to make up for the missed dose. However, this depends on your blood pressure, how sensitive you are to the medications, and how long it's been after the dose has been missed. If it has been less than half-way between your missed dose and your next dose (ex. 12 hours for once-daily dosing), you can probably take the dose you missed. If you are getting closer to the time of the next regularly scheduled dose, just wait and take the next scheduled dose. You should not take more than your prescribed dose on any single day.

### Hydration for adults while on ACE/ARB medications

It is important to stay hydrated while on ACEs and ARBs, as they can affect the kidneys' filtration force. If you become dehydrated (ex. high levels of exercise/exertion, heat exposure, illness, diarrhea/vomiting) while on these medications, kidney filtration force can significantly decline and kidney function can worsen. However, this does not mean you need to overhydrate or avoid exercise. Just try to consume normal amounts of non-caffeinated fluids and drink as needed when exercising.

### The ideal time to take medications

It's generally best to take medications when you are most likely to remember to take them and when they are best tolerated. If you are on multiple blood pressure medications, evidence suggests there is a benefit of taking at least one of them in the evening or at bedtime.

### First-line treatment for high potassium (hyperkalemia) as a result of Alport-related medication(s)

The first-line treatment for persistent high potassium is to review whether you are eating foods high in potassium and avoid them. If dietary moderation does not keep the potassium controlled, there are medications that bind potassium in your gut to prevent them from being absorbed (ex. patiromer, sodium polystyrene) or help the kidneys to excrete more potassium into the urine (diuretics). These must be taken every day to control potassium levels. However, these add to the burden of medications to take – some are expensive and they can have side effects.

Given the importance of ACEs/ARBs in delaying kidney failure in patients with Alport syndrome, if hyperkalemia develops while taking one of these medications, it is worth discussing with your nephrologist whether a potassium binder may be added so that you can remain on the ACE/ARB rather than stop the medication.

If you have hypertension that needs additional treatment, adding a diuretic with blood pressure–lowering effects like chlorthalidone might help to lower potassium. However, some other types of diuretics have the opposite effect on potassium. If your potassium gets very high, emergency treatments may be needed. This is unusual and generally only happens if you are unwell from a separate illness or have a significant change in your kidney function. High potassium is also less common in those taking an SGLT-2 inhibitor.

### Common drug interactions with ACEs and ARBs

Every medication has a long list of potential medication interactions. Most of them involve enhancing blood pressure–lowering effects, the high potassium side effect, or decreasing blood flow to the kidneys. Your doctor and the pharmacy should alert you if there are any drug interactions present in your medication regimen. If recommended, you may need extra blood tests for monitoring purposes.

### Drugs to potentially avoid

This can sometimes depend on your kidney function. If you have normal or preserved kidney function, most medications are safe. Many medications need to have their doses reduced if the kidney function declines because the kidneys clear them, not because they harm the kidneys (ex. gabapentin, colchicine). Here are a few other examples to be aware of:

- There are some antibiotics that have potential to affect kidney function and should be avoided or used with caution. Make sure any healthcare professional knows you have kidney disease before prescribing an antibiotic.
- Metformin is commonly confused as “hurting the kidneys.” In actuality, using it at very low GFRs increases the risk of a side effect known as lactic acidosis especially during times of significant illness. This is why it will usually be reduced at GFRs below 45 mL/min and stopped if the GFR drops below 30 mL/min.
- Kidney patients are often told to avoid nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs may not be completely forbidden in patients with good kidney function, as long as they are used just occasionally for short periods of time. This should be discussed with your nephrologist.

## Additional Questions to Ask Your Nephrologist

- Do any of my lab values appear out of range or concern you? Do any values perhaps warrant a change in dietary/lifestyle choices or medication type/dosage?
- When will I need to go for lab work/urine testing next? When will I next see you for a checkup? Can I contact you between visits? Your preferred contact method?
- Should I routinely check my blood pressure, and if so, at what time during the day? What do you consider a healthy blood pressure range for me?
- What factors would lead you to encourage or discourage me to consider or explore joining a clinical trial?
- Can voluntary changes to my eating schedule (intermittent fasting, etc.) alter the safety and efficacy of my current Alport treatment medication(s)?

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Additional information on Alport syndrome treatment can be found on the ASF website. In addition to information for patients and families, our website also includes numerous resources for Medical Professionals, including published research, information on our Patient Registry, and more.

Email: info@alportsyndrome.org