Future Rare Diseases

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifrd20

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To cite this article: David Pitcher, Jonathan Barratt, Bruce Hendry, Alister Humphreys & Alex Mercer (2025) A plain language summary of a study of long-term outcomes in patients with IgA nephropathy from the UK National Registry of Rare Kidney Diseases (RaDaR), Future Rare Diseases, 5:1, 2439237, DOI: 10.1080/23995270.2024.2439237

To link to this article: https://doi.org/10.1080/23995270.2024.2439237

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Published online: 28 Jan 2025.

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Plain Language Summary of Publication

Future Rare Diseases

A plain language summary of a study of long-term outcomes in patients with IgA nephropathy from the UK National Registry of Rare Kidney Diseases (RaDaR)

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First draft submitted: 17 May 2024; Accepted for publication: 4 December 2024

Where can I find the original article on which this summary is based?

The original article titled 'Long-Term Outcomes in IgA Nephropathy', was published in the *Clinical Journal of the American Society of Nephrology* in June 2023. You can read the original article for free at: https://journals.lww.com/cjasn/Fulltext/2023/06000/Long_Term_Outcomes_in_IgA_Nephropathy.9

Summary

What is this summary about?

This study that looked at people with a rare type of lifelong kidney disease called **immunoglobulin** A (IgA) nephropathy. It is caused by the buildup of **antibodies** from the immune system in the kidneys, which leads to inflammation and permanent damage. IgA **nephropathy** typically gets worse over time, and the damage reduces the kidneys' ability to selectively filter waste products from the blood to be removed in the urine. This results in high levels of protein in the urine (called **proteinuria**) and a gradual worsening of kidney function that can eventually cause the kidneys to stop working altogether (called kidney failure). One way that doctors can check how well people's kidneys are working is by testing a sample of their urine for proteinuria.

How to say (download PDF and double click sound icon to play sound)…

- **Antibody:** AN-ti-baa-dee
- **Glomerular:** glo-mer-yew-ler
- **Immunoglobulin:** im-yew-no-GLOB-yuh-len
- **Nephropathy:** NEH-fruh-pa-thee
- **Proteinuria:** Proh-tee-NYUR-ee-uh

Antibody: A protein produced in the body to help fight infections.
Immunoglobulin: A certain type of antibody.
Nephropathy: A term for diseases of the kidney.
Proteinuria: High levels of protein in the urine.

What happened in this study?

Researchers looked at information from medical records of people with IgA nephropathy to see how the level of proteinuria was related to the likelihood of kidney disease getting worse over time (loss of kidney function) and the lifelong risk of kidney failure.

What were the main results?

This study found that people with IgA nephropathy were diagnosed at an average age of 41 years. It also found that for many people, the time from IgA nephropathy diagnosis to developing kidney failure (meaning they needed dialysis or a kidney transplant) was around 11 and a half years, and almost all people with IgA nephropathy are at risk of developing kidney failure in their lifetime. People with lower levels of proteinuria had a slower worsening of kidney disease and a better chance of their kidneys continuing to function in the long term compared with those with higher levels of proteinuria. Finally, this study showed that reducing proteinuria levels in people with IgA nephropathy could lead to slower progression of kidney disease and a lower chance of kidney failure.

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What do the results mean?
This study indicates that starting treatment to lower proteinuria early after diagnosis may be important for people living with IgA nephropathy, as this might prevent irreversible kidney damage and delay the time to kidney failure.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research.

The results of this study may differ from those of other studies. Healthcare professionals should make treatment decisions based on all available evidence and not on the results of a single study.

Who sponsored this study?

This study was **sponsored** by Travere Therapeutics, Inc.

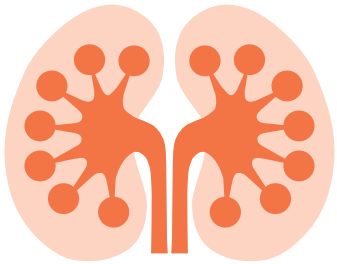
Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information from the study.

Who is this article for?

The aim of this summary is to help people living with IgA nephropathy, their families, and caregivers better understand the long-term outcomes of their disease. This summary may also be helpful for healthcare professionals managing patients with IgA nephropathy, patient advocates, and support groups.

What is IgA nephropathy

Immunoglobulin A (IgA) nephropathy is a rare type of lifelong kidney disease.



The kidneys are responsible for many functions in the body

- Filtration of blood
- Removal of toxins and waste products from the blood via urine
- Regulation of:
  - » Amount of fluids
  - » Electrolytes (salts)
  - » Blood pressure

IgA is an antibody made by the body. Its main role is to fight infections throughout the body.

In IgA nephropathy, IgA builds up in the tiny filters of the kidneys (called glomeruli), causing inflammation, damage, and scarring in the kidneys. This makes it harder for the kidneys to properly filter and remove waste and extra fluid from the bloodstream so that they can be removed out of the body through the urine.

When the kidneys are damaged, too much protein can leak into the urine (this is called proteinuria). Proteinuria is both a sign that the kidneys are not functioning properly, as well as a cause of additional kidney damage, which can make IgA nephropathy worse over time.

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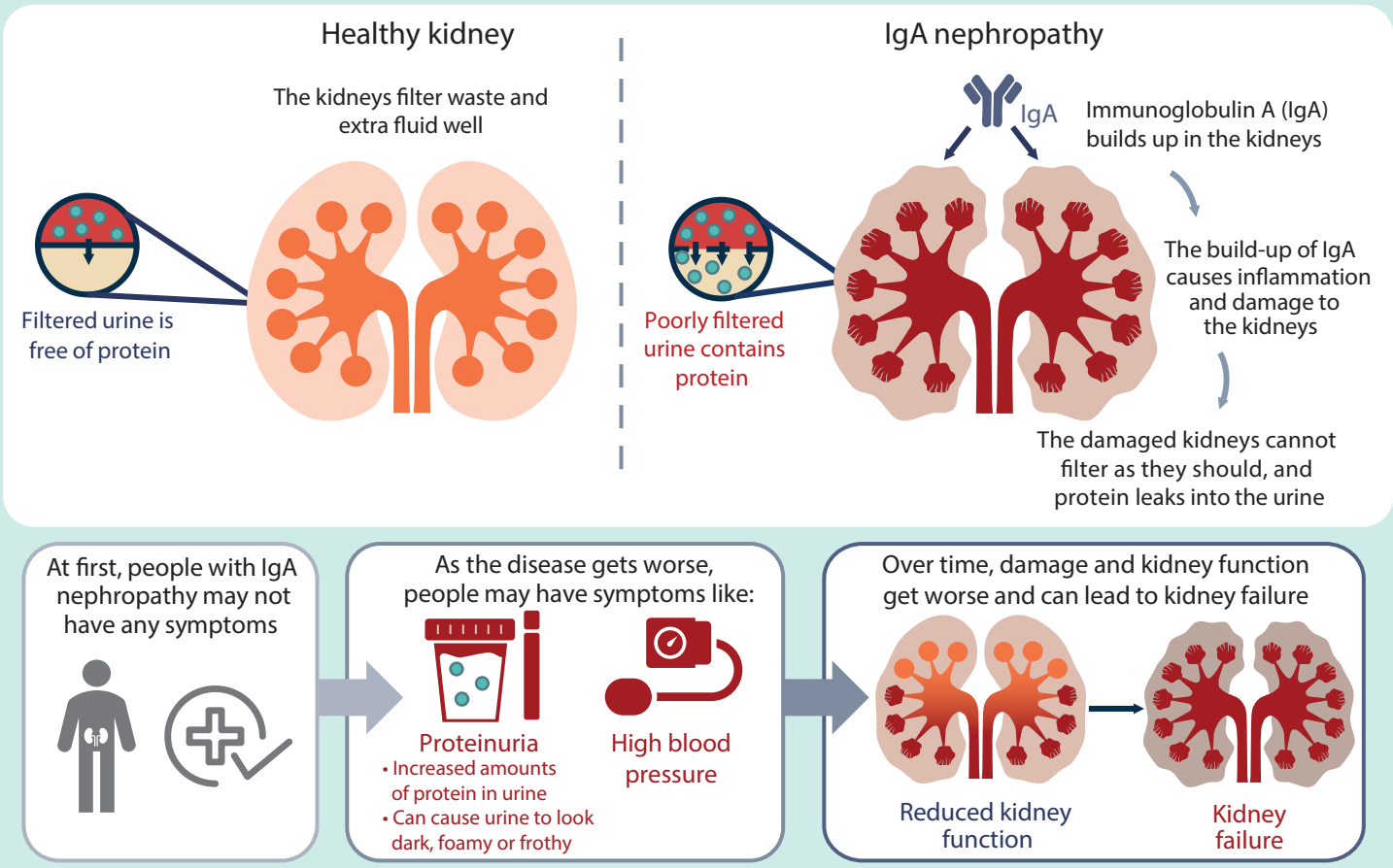
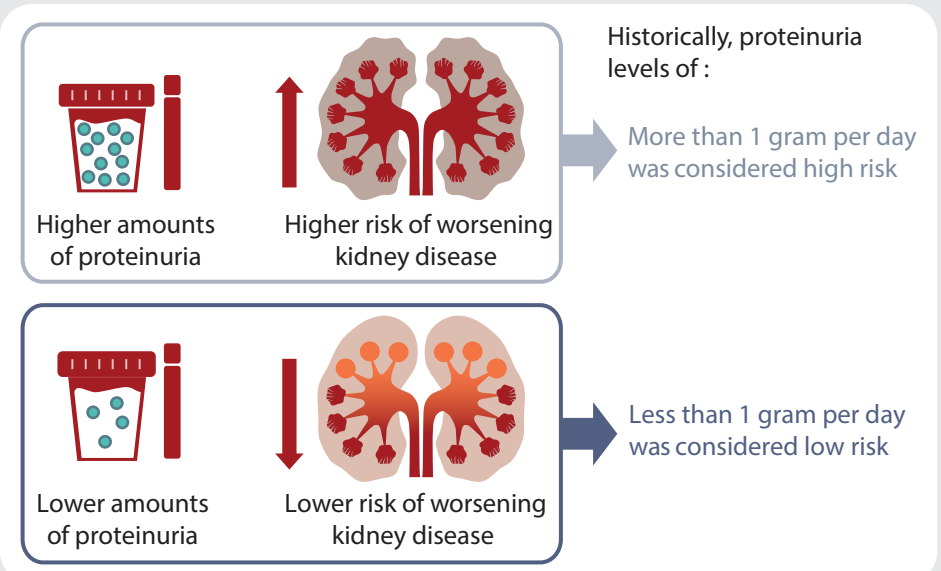


Even though people might not have symptoms at first, frothy and/or dark urine as well as high blood pressure can be early signs of IgA nephropathy, and people with these symptoms should have their urine tested to check if they have proteinuria or blood present. While proteinuria might be a sign of IgA nephropathy, doctors can only know for certain by examining a piece of tissue (a biopsy) from the patient's kidney, because proteinuria can have other causes.

Why is knowing the level of proteinuria important?

Proteinuria is known to be a risk factor for worsening kidney disease. The level of proteinuria can help doctors predict which people are at higher risk for their IgA nephropathy getting worse over time.

For many years, doctors thought that a proteinuria level at or below 1 gram per day meant that a person with IgA nephropathy was not at high risk of their kidney disease worsening so much that they would need dialysis or a kidney transplant in the near future. A key reason that this study was done was to better understand the risks of worsening kidney disease and eventually needing dialysis or a kidney transplant for people with IgA nephropathy with any level of proteinuria, including those at or below 1 gram per day.



Why was this study carried out?

This study was carried out to help researchers understand more about the likelihood of kidney disease getting worse over time in people living with IgA nephropathy. They looked at how the level of proteinuria is related to worsening kidney function over time and the risk of permanent kidney failure in the future.

Proteinuria, kidney function, and kidney failure

In people with a lifelong kidney disease such as IgA nephropathy, doctors use blood and/or urine tests to check how well the kidneys are working (also called kidney function) and how much kidney function remains. There are 2 laboratory values (also called lab values) that doctors use to see how well a person's kidneys are working:

- Proteinuria, or elevated levels of protein in the urine, which can be a sign of kidney damage
- A higher proteinuria level can mean that there is more kidney damage
- **Estimated glomerular filtration rate** (also called eGFR) is a measure of how well the kidneys are working to filter waste in the body
- As kidney disease gets worse, the kidneys do not filter waste as well, and eGFR gets lower
  - » An eGFR lower than 60 mL/min/1.73 m^2 for 3 months or more suggests that the kidneys are injured
  - » An eGFR lower than 15 mL/min/1.73 m^2 is considered kidney failure
- Kidney failure is when the kidneys have stopped working well enough to filter the body's waste on their own, and dialysis or a kidney transplant is needed

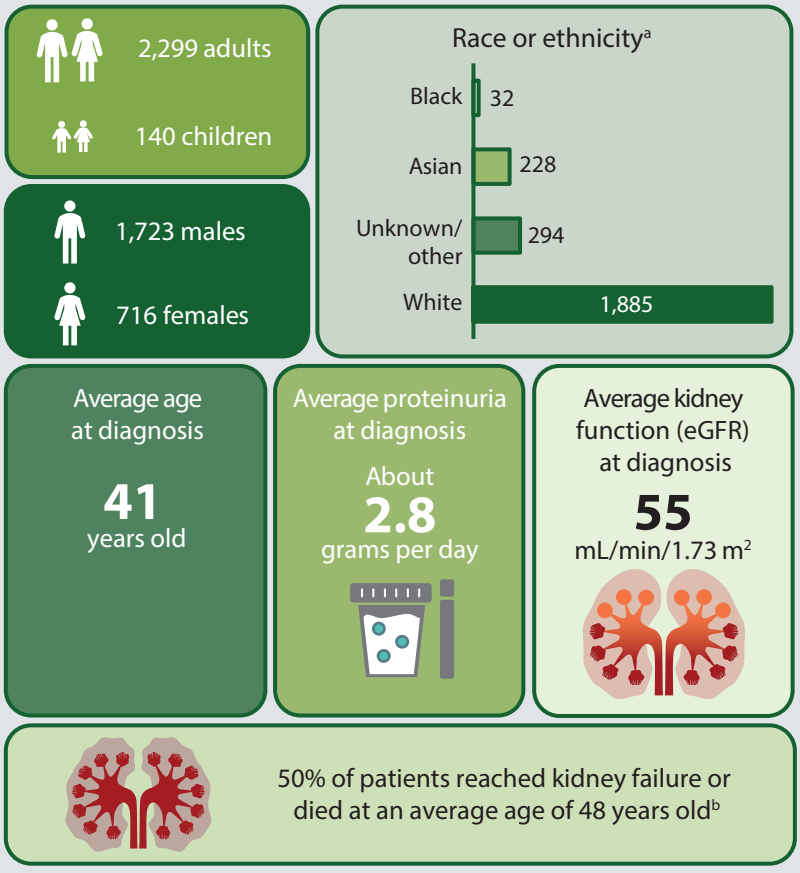
Estimated glomerular filtration rate: Measures how well the kidneys are functioning; often abbreviated as 'eGFR'. The unit of measurement for estimating eGFR is 'mL/min/1.73 m^2'.

Who took part in this study?

This study was carried out in the United Kingdom (UK) and included a total of 2,439 people living with IgA nephropathy who took part in the UK Registry of Rare Kidney Diseases (also known as RaDaR).

[a]Participants were mostly White in this study as it was based on a UK registry, where the population is predominantly White.

[b]During the time that patients were observed in this study, half reached kidney failure or died at an average age of 48 years. This, however, does not indicate a 50% chance of any given patient reaching kidney failure or dying, due to the many different factors contributing to individual outcomes over time. The risks of disease progression based on proteinuria are detailed in the rest of this summary.



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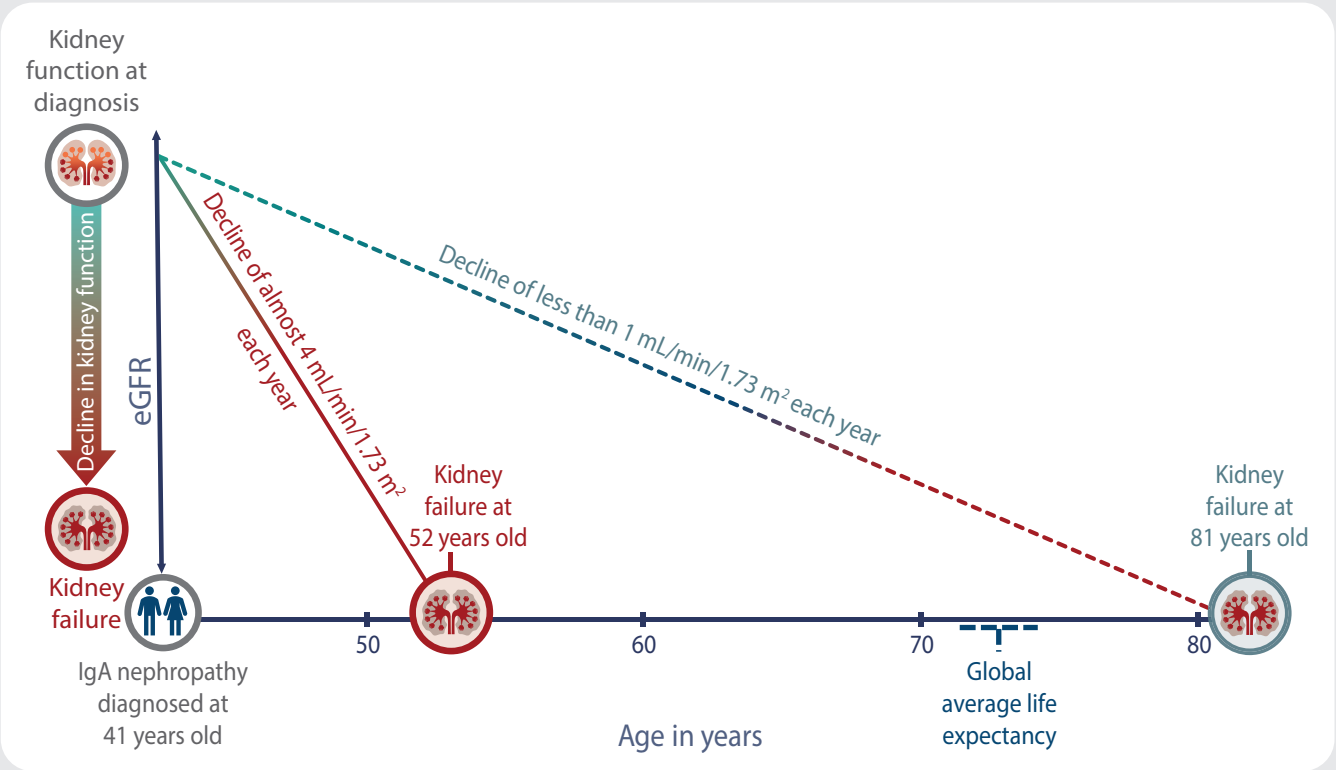
How was this study carried out?

Researchers looked at what happened to people living with IgA nephropathy by examining their medical records to determine how well their kidneys work and how proteinuria levels were related to kidney function and kidney survival over time. Information in the medical records was reviewed starting from each patient's diagnosis of IgA nephropathy. For the group of people included in this study, medical records were available for a median time of about 6 years from their diagnosis. A median time of 6 years means that half the people had medical records available for longer than 6 years from diagnosis, and half the people had medical records available for less than 6 years from diagnosis. The medical records of the people included in this study were used with their permission. This kind of study is known as a 'retrospective cohort study'.

What is a retrospective cohort study?

- A retrospective cohort study is a study in which researchers look back in time to answer a medical question. In this type of study, the medical records of groups of individuals who have similar medical traits are compared to observe particular outcomes. In this study, researchers looked at the outcomes of kidney function and and kidney survival, meaning no kidney failure or death, over time in a group of people with IgA nephropathy.

What were the overall results of this study?



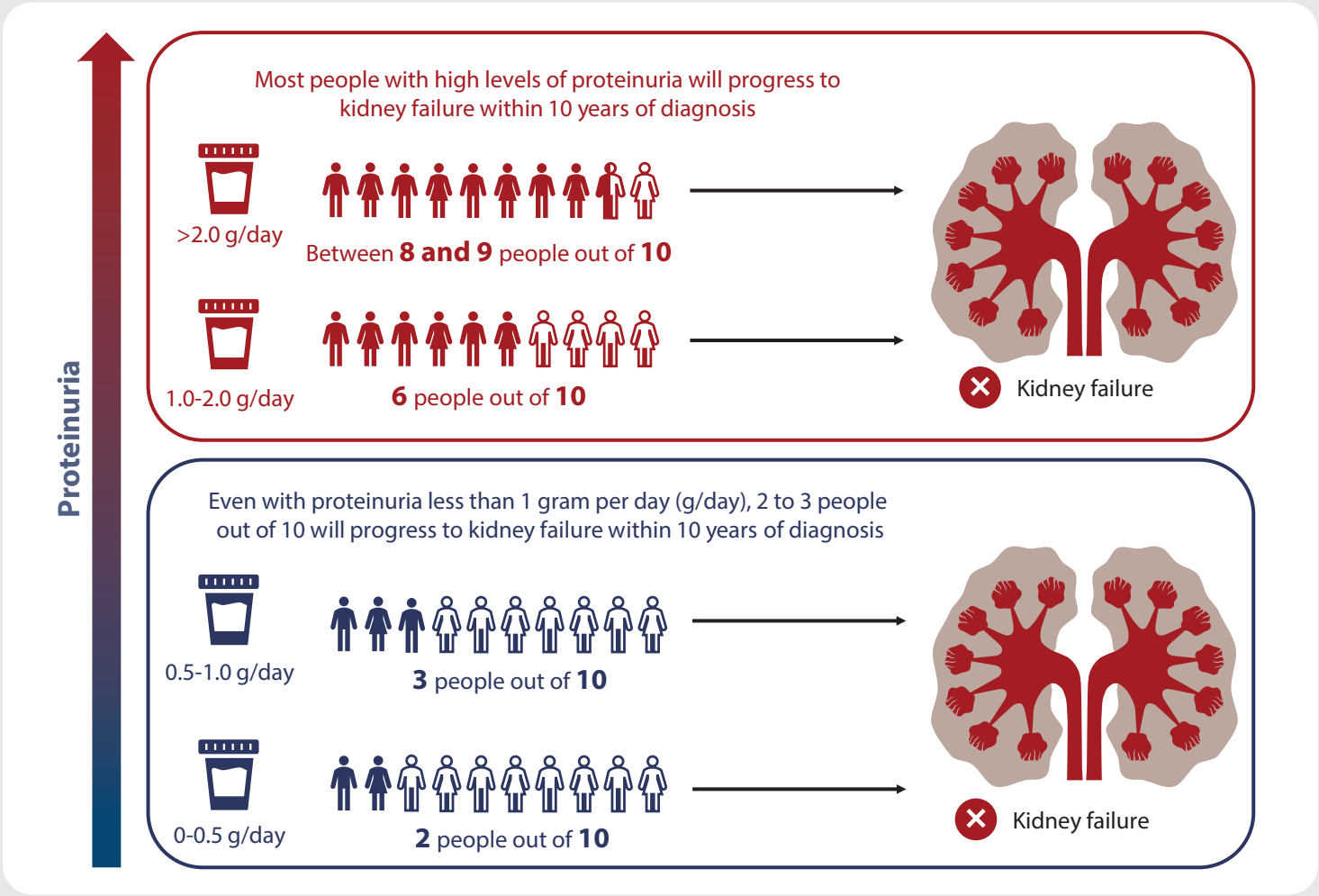
On average, a person in this study was **41 years old when they were diagnosed with IgA nephropathy**, and their kidney function (as measured by eGFR) got worse over time, which meant that their kidneys filtered less waste than they did the year before. The average eGFR at diagnosis in this study was 55 mL/min/1.73 m^2. **The loss of eGFR (worsening of kidney function) was about 4 mL/min/1.73 m^2 each year**.

For a person diagnosed at age 41, if this loss of kidney function continued each year, **this person would be estimated to reach kidney failure when they were 52 years old**.

This study also estimated that for this patient to avoid kidney failure until the age of 81 (a likely life expectancy), their loss of eGFR (worsening of kidney function) would need to be slowed to less than 1 mL/min/1.73 m^2 each year.

This study also showed that the level of proteinuria was related to how quickly kidney function worsened over time and the chance of kidney failure. While any level of proteinuria was associated with risk of kidney failure, people with higher levels of proteinuria had a faster loss of kidney function and were more likely to progress to kidney failure.

The study also found that people with lower levels of proteinuria had a slower loss of kidney function and a better chance of kidney survival compared with higher levels of proteinuria. These results are similar to the findings from other research studies that included White and Asian people with IgA nephropathy. Importantly, this study found that many people with proteinuria levels historically considered 'lower risk' (proteinuria levels of less than 1 gram of protein per day) were still at risk of developing kidney failure within 10 years.



An important finding of this study was showing that lowering the level of proteinuria can help reduce the risk of kidney failure in people living with IgA nephropathy. This means that starting treatments to lower proteinuria earlier after diagnosis, regardless of proteinuria levels, may extend the time before dialysis or kidney transplant would be needed. Based on the results of this study, proteinuria levels of 0 to 0.5 grams each day is the recommended target to achieve the greatest reduction in lifetime risk of reaching kidney failure.

What do the results of this study mean?

This study showed that most people living with IgA nephropathy are at risk of developing kidney failure within their lifetime.

In this study, higher levels of proteinuria were linked to a higher risk of developing kidney failure.

Lowering proteinuria may reduce the risk of developing kidney failure in people living with IgA nephropathy, regardless of current proteinuria level.

Treatments that reduce proteinuria levels may slow down the loss of kidney function, and starting treatments earlier is important to avoid worsening of kidney disease.

Where can readers find more information on this study?

Original article: This manuscript is a plain language summary of the following original article: Pitcher D, et al. *Clin J Am Soc Nephrol.* 2023;18(6):727-738. The original article can be accessed free of charge at: https://journals.lww.com/cjasn/Fulltext/2023/06000/Long_Term_Outcomes_in_IgA_Nephropathy.9.

For more information on the UK Registry of Rare Kidney Diseases, follow the link at: https://www.ukkidney.org/rare-renal/about.

For more information on IgA nephropathy and resources for patients:

USA

- IgAN Foundation: https://igan.org/
- NephCure: https://nephcure.org/

- American Kidney Foundation: https://www.kidneyfund.org/
- National Kidney Foundation: https://www.kidney.org/
- National Organization for Rare Disorders (NORD): https://rarediseases.org/

EU

- EU IgAN Patient Community with EKPF: https://ekpf.eu/

UK

- Kidney Care UK: https://kidneycareuk.org/
- Kidney Research UK: https://www.kidneyresearchuk.org/research/patient-involvement
- Renal Patient Support Group (RPSG): https://rpsg.org.uk/rpsg-information-portal/

Acknowledgements

The authors would like to thank the National Registry of Rare Kidney Diseases (RaDaR) and the patients who participated in providing their information for use in RaDaR in order to advance the understanding of IgA nephropathy and the effect of current treatments on patient outcomes.

Author contributions

All authors were involved in the writing, reviewing, and editing of the manuscript, and approved the final version.

Disclosure statement

Jonathan Barratt reports research funding and consultancy fees from Travere Therapeutics, Inc. Alex Mercer reports consultancy fees from Travere Therapeutics, Inc. Bruce Hendry is an employee and stockholder of Travere Therapeutics, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing assistance and editorial support for this plain language summary were provided by Jordan Skinner, MChem, Ari Simenauer, PhD, and Lisa Havran, PhD, CMPP, of Nucleus Global, an Inizio company, in accordance with Good Publication Practice guidelines, and was funded by Travere Therapeutics, Inc.

Patient reviewers on this plain language summary of a publication have received honorarium from *Future Rare Diseases* for their review work but have no other relevant financial relationships to disclose.

Funding

This study was sponsored by Travere Therapeutics, Inc.