Bart J. Kramers, MD, PhD, graduated with a degree in medicine from the Rijksuniversity Groningen in 2016. In 2017, he enrolled in the PhD program to study autosomal dominant polycystic kidney disease (ADPKD) at the ADPKD expertise center of Professor Ron Gansevoort. There, he mainly studied the vasopressin V2 receptor antagonist tolvaptan and its aquaretic side effects in experimental and clinical studies. He is currently working as a resident of internal medicine and continues to be involved in ADPKD research.

RM: Can you introduce yourself to the CJASN audience?

BK: Yes, thank you, my name Bart Kramers. I am from Groningen, The Netherlands, where I just finished my PhD that focused on polycystic kidney disease. I specifically studied treatment with vasopressin V2 receptor antagonist tolvaptan and its side effects. Currently, I am a resident in the field of internal medicine.

RM: What sparked your interest in research in treatment of PKD broadly?

BK: During my medicine studies, I really developed an interest in research in general. I always found nephrology fascinating, and after graduating, I came in contact with a PhD student in Ron Gansevoort’s ADPKD research group. She told me that they were looking for a new PhD student to help with the clinical studies in the lab. At that point, in 2017, tolvaptan had just become available in The Netherlands as the first effective pharmacological treatment for ADPKD. I was immediately fascinated. I thought it was interesting to study the first and only effective treatment for ADPKD and to hopefully make a small contribution to the field. I also found the side effects of tolvaptan highly interesting as it causes a form of nephrogenic diabetes insipidus by blocking the vasopressin V2 receptor and, as a result, polyuria.

RM: What specific gap in knowledge were you hoping you could bridge with your work?

BK: Tolvaptan is the first effective pharmacological treatment in ADPKD. This drug slows down kidney function decline in ADPKD and can postpone the need for kidney replacement therapy. Unfortunately, as a side effect, tolvaptan causes polyuria of on average 7 liters per day. Because of this, some patients find treatment with this drug intolerable.
We wanted to test whether there were additional medicines that one could prescribe alongside tolvaptan in order to diminish the polyuria. We hypothesized that potentially hydrochlorothiazide and/or metformin could be useful in this regard. Hydrochlorothiazide has been used as a treatment to reduce polyuria in nephrogenic diabetes insipidus of other origins. And metformin has been successfully used to decrease polyuria in animal studies for tolvaptan.

RM: So, what did you find?

BK: In a double-blind cross-over RCT of 13 tolvaptan-treated ADPKD patients, we found that both hydrochlorothiazide and metformin could reduce polyuria. Hydrochlorothiazide reduced daily urine production from 6.9 to 5.1 liters per day, and metformin from 6.9 to 5.4 liters per day. Because the combination of tolvaptan and hydrochlorothiazide seemed more favorable in effects and had less adverse effects in the short-term clinical study, we also investigated this combination in a long-term animal experiment. In that study, we found similar effects on polyuria. With regard to ADPKD disease progression, we found that the combined tolvaptan-hydrochlorothiazide treatment was superior to no treatment, and superior or equal to tolvaptan monotherapy, depending on the used marker.

RM: Just taking a step back: how does your work fit into that larger body of work regarding tolvaptan polycystic kidney disease and its treatment?

BK: Because of these findings, patients may be able to benefit from the tolvaptan-hydrochlorothiazide combination in the future, and more patients might be able to tolerate tolvaptan treatment. This is important as effective treatment could delay dialysis or kidney transplantation. The combination of metformin and tolvaptan also remains very interesting, especially because metformin monotherapy is also being studied in large clinical trials as a potential effective treatment to slow down disease progression in ADPKD. If metformin turns out to be effective in this regard, the combination with tolvaptan could be doubly beneficial.

RM: Fascinating! That makes quite a lot of sense. Your work is quite a meaningful advance in our knowledge. What is the next step for your research? And more broadly, where should the field be going?

BK: We are setting up a larger, long-term RCT, called the HYDRO-PROTECT trial. In this trial, tolvaptan-treated ADPKD patients will be randomized to tolvaptan+hydrochlorothiazide or tolvaptan+placebo. In this trial, we want to confirm the effects on polyuria—we will especially study the effects of these treatments on eGFR decline to test whether the combination with hydrochlorothiazide is equal or may even be superior to tolvaptan alone.

With regard to the field, I think it remains very relevant to study whether there are additional medicines that could slow down ADPKD disease progression. I know that a lot of research is being done in that regard.
RM: Thank you, this is very important work. Congratulations again! What words of advice or wisdom do you have for people that are contemplating or just starting their research training with a focus on kidney diseases?

BK: As someone who has only just started doing research in this field myself, I fear that I still have a lot of wisdom to gain before I can share it with others. But my advice to someone contemplating research in nephrology would be to go for it! The kidney is extremely interesting, and every research idea could lead to that breakthrough that helps many patients!

Finally, I want to thank you, Dr. Mehrotra, and the CJASN editorial board very much for this prize. It is truly an honor. It was also great to participate in this podcast. Thank you!