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https://reachmd.com/programs/cme/no-patient-with-ckd-left-behind-emerging-ckd-therapies-in-t1d/36524/

Released: 01/16/2026
Valid until: 01/16/2027
Time needed to complete: 30 minutes

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No Patient with CKD Left Behind! Emerging CKD Therapies in T1D

Announcer:
Welcome to CE on ReachMD. This activity, titled “No Patient with CKD Left Behind! Emerging CKD Therapies in Type 1 Diabetes” is provided by Medcon International.

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Dr. Pratley:
We've made tremendous progress in the last few years improving the care for people with type 1 diabetes as it pertains to glucose control, but there's still a large unmet need in terms of preventing progression to chronic kidney disease and cardiovascular disease.

Now, recent clinical trials have given us new hope to address this unmet need in patients with type 1 diabetes, and hopefully we can move on and these patients won't feel left behind in the future.

This is CE on Reach MD, and I'm Dr. Richard Pratley.

Dr. Cherney:
Hello, I'm David Cherney. I'm a nephrologist at the University of Toronto.

Dr. Heerspink:
Hello, everyone. My name is Hiddo Heerspink, a clinical trialist at the University of Groningen, Netherlands.

Dr. Pratley:
Well, let's start off with the first question I have, and that’s what is the importance of early and proactive screening for CKD in type 1 diabetes? Why do we need to do it? When should we be doing it? And how do we do it?

So, David, maybe you can start with what we should be doing in terms of our patients who are in front of us in our clinic to adequately screen them.

Dr. Cherney:
Yeah, so there are a couple of important components, and of course, there are the clinical things that we do in practice, including looking at all the other risk factors for CKD progression, including control of blood pressure, a lifestyle optimization, glycemic control. But from a kidney-specific perspective, it's really important to remember to measure both eGFR and UACR. And in people with type 1 diabetes, that's typically started and needs to be done 5 years after the time of diagnosis. And that's because it's so unusual to have any significant kidney disease prior to that time.

And that's different than people with type 2 diabetes, where we should be screening patients from the time of diagnosis. And that's because there's often a long, clinically silent period that precedes the onset of kidney disease, and so it's important to screen as soon as patients are diagnosed with type 2 diabetes.

But in type 1, it's after 5 years of diabetes duration. Always remember the ACR and the eGFR, because one can be abnormal without the other. And if both are abnormal, that means there is even greater risk, both from a kidney disease progression perspective and also in terms of cardiovascular disease.

Dr. Heerspink:
And that latter part is indeed important, David, and you said it very well. And albuminuria, eGFR, when they are both—eGFR elevated, albuminuria increased—they increase not only the risk of kidney disease progression, but that cardiovascular component is so important. So we are screening for chronic kidney disease but directly capturing the cardiovascular risk as well.

Dr. Pratley:
So the how is pretty easy. It's an eGFR, part of our blood panels, and it's a urine test for the albumin-to-creatinine ratio. Yet there's still gaps.

In my practice, I see many patients who come to me who haven't had the urinary screening. David, why is that, and how can we do better?

Dr. Cherney:
Yeah, so I think there are a lot of reasons, and it's a very complicated issue. We've known that both GFR and albuminuria are crucial components of good diabetes care for decades, and yet it's still underutilized in many clinical settings. And I think there are reasons that are relevant to physicians not ordering it and not thinking necessarily that there is anything that can be done about albuminuria. Perhaps there may be issues around the patient and doing a blood test but maybe forgetting or not going to do the urine test at the time that the blood test is collected and then just putting it by the wayside and not doing those urine tests in the future. And then there are systems issues. In some places, it may be harder to get access to a urine ACR test. It may not have been checked off on the requisition, even though it was intended to be done. So there may be systems issues that are relevant too, not just in one country versus the other, but in other countries where it's not part of what's covered by public healthcare systems.

So there are lots of complicated issues that are involved. But importantly, those barriers all have to be overcome because it's so incredibly important to do.

Dr. Heerspink:
We are doing it for many years in the Netherlands. We started by screening all the inhabitants of our city, already, in 1996. And I'm always surprised because it's so easy. All you need is a bit of urine. It's much easier than a venipuncture. And I think that part of the problem is that we have different ways how to collect the urine. We talk about different ways how to measure the albumin or total protein. And I think that we've made ourselves also—

Dr. Cherney:
I'm very much agreed.

Dr. Heerspink:
Let's take it simple, and let's try to harmonize all these different methods of how to do it, but let's do it.

Dr. Pratley:
So we need to be proactive. The screening is easy. It's a blood test. It's a urine test. It doesn't have to be fasting. And it's also cheap. So there's really no reason why we shouldn't be doing this.

The importance of this, of course, is that we're not only looking at a risk factor for kidney disease, but it's also a very powerful risk factor for cardiovascular disease. So we can think about, with the entire cardiometabolic continuum in our patients with type 1 diabetes, they are at higher risk for kidney disease, but especially at higher risk for cardiovascular disease. We need to know that, and this is one way

to tell that.

So let's go on now to explore some of the unique aspects and unmet needs of CKD in patients with type 1 diabetes. And, Hiddo, I know that you've thought about this for a while and have been advocating for years that we need to do better. So tell me about your perspective.

Dr. Heerspink:
Yeah, when I look at the development of new therapies for patients with diabetes, I see that over the last 10 years, many clinical trials have been done in patients with type 2 diabetes, and new therapies have emerged. We have SGLT2 inhibitors, GLP-1 receptor agonists, endothelin receptor antagonists, mineralocorticoid receptor antagonists. And then, when we look at type 1 diabetes and chronic kidney disease, only 2 clinical trials in the last 35 years. It's really, really sad that this happened. And I feel that we have to do something about it.

Dr. Pratley:
Yeah. Completely agree. So, David, anything that you want to add to that perspective?

Dr. Cherney:
Yeah, a couple of thoughts. So even though patients with type 1 diabetes are, broadly speaking, being excluded from any of these trials for the reasons that we've discussed, including the fact that it's a much more rare condition and it is harder to study in some ways, it's nevertheless important to emphasize that many of the mechanisms that are linked with progression of CKD in type 1 diabetes and type 2 diabetes are very similar.

So a couple of examples of that, if we just talk about the medication classes that we're using. So ACEs and ARBs have been shown to be beneficial in people with type 1 and type 2 diabetes in similar kinds of ways. And activation of the hormones that RAS blockers—those hormones that are activated and then blocked with RAS blockers, that blockade and that protective effect is very similar in type 1 and type 2.

For additional medications like SGLT2 inhibitors, which are sort of the second class that have been approved in type 2 diabetes, similarly, many of the mechanisms that have been shown to be of benefit in type 2 diabetes extend to people with type 1. The effects on GFR dipping, the reflection of a reduction in glomerular pressure, the reduction in albuminuria that's been shown, effects on volume that are probably so important for reducing the risk of heart failure, blood pressure reduction effects, reducing uric acid. All of these links that have been made with reducing risk in people with type 2 are also seen in people with type 1 diabetes with SGLT2 inhibitors.

And then for the nonsteroidal MRAs, similarly, activation of the mineralocorticoid receptor is broadly seen in a variety of conditions, including with hyperglycemia, which is seen in type 2 and type 1, and of course, in chronic kidney disease and heart failure and atherosclerosis and hypertension. All of these factors that tie type 1 and type 2 diabetes together. So many of the pathophysiologies are similar, and hence it's reasonable to anticipate that many of the benefits will also be seen.

Hiddo, what do you think?

Dr. Heerspink:
Yeah, no, and I completely agree, and we tend to think in boxes. Type 1 diabetes, type 2 diabetes, and then the nondiabetic CKD, we also tend to think in boxes. IgA nephropathy study, FSGS study. But when you listen to David, why should we separate type 1 diabetes and type 2 diabetes studies if the drug works through similar mechanisms and if the pathophysiology related to chronic kidney disease is the same?

So I think we can change that, and we should study diabetes if we think that the drug is safe in both type 1 and type 2 diabetes.

Dr. Cherney:
And similarly thinking maybe about CKD in general rather than thinking about it in these boxes, which is such an important point.

Dr. Pratley:
I think it's so ironic that the very first kidney disease prevention study we did was in type 1 diabetes with captopril. And this was, what,

almost 30 years ago. And since then, there's been almost nothing happening. I can understand why patients with type 1 diabetes would feel left out when they see all this wonderful data that's coming out in type 2 diabetes with drugs decreasing progression of kidney disease, decreasing cardiovascular disease. And, hey, what about me?

So we need to change that conversation for sure. And I think, David, you outlined reasons that we need to think more broadly and include our patients with type 1 diabetes so they're not left behind so we can address some of their huge unmet needs.

Dr. Heerspink:
And on that note, I recall a patient, his name is Uros, and he mentioned to me that he was indeed feeling left behind as an individual living with type 1 diabetes. Maybe we can listen to him.

Uros:
Yeah, thank you.So people with type 1 diabetes face similar complications as people with type 2.Although the incidence rates obviously may differ, we have a feeling of being left behind in some of these areas where novel treatment is given and developed mainly for people with type 2.But unfortunately, even with our high incidence rates, we are not given the same treatment.And I think that really needs to change.

We are aware of the complications. We are aware that we are constantly reminded by our healthcare professional team that we must do everything that we can in our blood glucose management to avoid these complications. But then, if those complications do arise, then we are faced with a very bad moment that we do not get the access to the best therapies that exist.

Dr. Heerspink:
And yes, I have good news for him. We presented here at ASN Kidney Week in Houston the results of the FINE-ONE clinical trial, which is the first clinical trial that was seeking an indication for kidney protection in type 1 diabetes. And the trial enrolled 242 participants with type 1 diabetes and chronic kidney disease; 120 was assigned to the nonsteroidal mineralocorticoid receptor antagonist finerenone, and the other 122 to placebo. They were followed for 6 months, and we looked at the effect on albuminuria.

And why did we assess the effects on albuminuria? Why did we not look at GFR decline or kidney outcomes? Because, as David already mentioned, clinical trials in type 1 diabetes per se are very difficult to conduct if you need a trial of 5,000 or 6,000 patients. So we used albuminuria as the surrogate outcome to translate the evidence of kidney protection with finerenone, which is already demonstrated in type 2 diabetes, to translate that evidence to type 1 diabetes.

So in doing so, we used albuminuria as the surrogate outcome for kidney protection.

Dr. Pratley:
So, Hiddo, this idea of using a surrogate is sort of new in the field. And what's the basis for being able to use that and do a trial that is not as long term, doesn't look at the hard outcomes, and still derive information that could drive practice?

Dr. Heerspink:
You can only do that in certain conditions. First of all, the population should be relatively low, which is the case for type 1 diabetes and chronic kidney disease. There must be a high unmet need, which is the case for type 1 diabetes and chronic kidney disease. But perhaps most importantly, the drug that you study must reduce the kidney outcome as observed in another population, and in this case, the effect of the drug should be explained by the surrogate.

And we did those calculations for finerenone, and it turned out that the benefit of finerenone in type 2 diabetes on kidney outcomes was explained for 87% by the reduction in albuminuria. So you have a high confidence that if you can reduce albuminuria with finerenone, you will also reduce the risk of future kidney outcomes with finerenone.

Dr. Pratley:
So is that going to be enough for, say, the FDA?

Dr. Heerspink:
Yes. This was actually, this design and this idea came actually from the FDA and came from the regulators, and they suggested that we

use albuminuria.

Dr. Pratley:
Ah. So that's really a great concept that we're able to now pivot from this wealth of data we have in type 2 diabetes, leverage that, and do a study that will also help patients with type 1 diabetes. So maybe now, patients with type 1 diabetes won't feel so left behind.

Dr. Heerspink:
Well, let's take a look at the data and let's take a look at the results of the trial. Because in FINE-ONE, the clinical trial with finerenone in type 1 diabetes, we indeed demonstrated a 25% reduction in albuminuria compared to placebo. And we know from these big studies that a 25% reduction in albuminuria gives you more than 98% confidence that the drug will also reduce the clinical outcome.

Most importantly, when you talk about efficacy, you should balance that with safety. Finerenone in this population was extremely safe. There was no difference in adverse events or serious adverse events.

There was an increase in hyperkalemia with finerenone, which is expected, because you target the renin-angiotensin system. But the clinical impact of these adverse events are slow because most of the patients continued their medication. There were hardly any serious hyperkalemia-related serious adverse events. And of course, none of these hyperkalemia events led to death.

Dr. Pratley:
I think you raise an important point, and this is something that's a little bit different in our T1D population. David mentioned that the mechanisms for the other medications, like SGLT2 inhibitors, should apply in type 1 diabetes as well. But it's not necessarily the same risk and benefit ratio because we've seen that patients with T1D are at higher risk for DKA with the SGLT2 inhibitors. And this is in contrast to that. We've seen that the safety profile with finerenone very much matched what we saw in patients with type 2 diabetes. And I think that's reassuring as well.

And it allows us maybe to go forward with more confidence, while other medications, like the SGLT2 inhibitors, are conceivably even GLP-1 receptor agonists. I think we'd have to do more to really mitigate that risk that we see.

Dr. Cherney:
Yeah, so in terms of using medications and repurposing them and thinking about using them in other populations that have not been included in the large outcome trials, it's really important to think about why. And with the SGLT2 inhibitors, of course, there were no outcome trials to date. There's one that's ongoing called SUGAR-N-SALT, but there have been no outcome trials to date because of exactly this issue of balance of risk and benefit, because although there is an effect with SGLT2 inhibitors on reducing hyperglycemia, there is a risk of DKA that is also increased. And so the real, compelling reason to do a trial in people with type 1 diabetes and kidney disease with an SGLT2 inhibitor is to take advantage of that big benefit that they may have: a significant reduction in cardiorenal risk. Hopefully the DKA risk will be the same or lower, but it's necessary to do that trial in that population to show that good risk-to-benefit profile.

And in contrast, exactly like you say, with the results FINE-ONE, there isn't that same concern about differences in risk. The risk is exactly what we would anticipate with a medication that, as a nephrologist, I use every day in my practice. We use finerenone in people with type 2 diabetes, in people with albuminuria all the time. So we have a very good feel of hyperkalemia, how to manage it, how to avoid it in the first place, how to combine medications so that we lower the potassium and avoid increases in potassium. And we would do the same kind of approach in people with type 1 diabetes based on our experience in people with type 2 diabetes, recognizing that the effects on all of these parameters that we're now using as markers of efficacy, especially albuminuria, that the benefits are essentially the same.

So same benefits, same low risks. It becomes a very easy decision-making process in practice.

Dr. Pratley:
And that gives me a lot of hope that we're going to be able to get this into practice, helping patients with T1D and CKD much quicker. We won't have to wait for the next trial and that way to mitigate the risk, for DKA, for example.

Dr. Cherney:

And that's one of the big benefits of having a repurposing trial, is that the drug is already available. We just have to figure out now how to get it into clinical practice and improve uptake for people with type 1 diabetes, pending all of the logistics around payment and approvals and all those other aspects that are also, of course, important.

Dr. Heerspink:
No, and that's why I'm very happy for Uros, that we have something. And as you say, David, I think that this is an incentive for more clinical trials following the example of FINE-ONE.

Dr. Pratley:
I really see this as kind of a pivot point in the care of patients with T1D and cardiovascular kidney complications. I think it does give us new hope for the future, not just because we now have finerenone, but also because hopefully other companies will see the potential benefit of pursuing this pathway and see that it is indeed possible to do.

Dr. Cherney:
And to do trials that are feasible within a relatively brief time frame and trials that are feasible in terms of the sample size that we can actually accomplish in the setting of type 1 diabetes, which as Dr. Heerspink mentioned, is a relatively rare condition, and CKD in type 1 is a rare version of a rare condition. So we have to make sure we design trials appropriately to answer those questions.

Dr. Pratley:
I hope it also encourages people to participate in trials, because as a trialist, we can't do this without patients who are affected by the disease cooperating with us, participating in trials, and being our partners as we seek to find new therapies.

Dr. Cherney:
Very, very important points.

Dr. Pratley:
Hiddo, anything else on FINE-ONE?

Dr. Heerspink:
No, I think it's a fantastic trial and you will see much more, I think, in the next couple of months. We are still analyzing the data. The study was just published, too, just finished 2 weeks ago. So we are at the start of a new era for type 1 diabetes and CKD.

Uros:
My name is Uros, and I've been living with type 1 diabetes for the past 16 years. I'm optimistic to see data which shows a new treatment option is on the horizon for people living with type 1 diabetes and chronic kidney disease, a patient group which has been long left behind.

Now, work needs to be done to make this treatment option available and accessible to millions of people living with type 1 diabetes and chronic kidney disease.

Dr. Pratley:
We don't want to leave behind patients with just CKD. So let's see a video of a patient with CKD, feeling left behind.

John:
Hi. My name is John, and I have chronic kidney disease, or CKD. CKD is a disease that other people don't necessarily know you have, but it's significant just the same. I worry about how I'm doing, about my test results, and about my long-term prognosis. And to be honest, with all the fuss and notoriety about advances in treatment for patients with diabetes, I feel a little jealous. And that makes me feel a little left behind.

Dr. Heerspink:
Yeah, and I think we should also keep an eye on the future. We talked about type 2 diabetes, we talked about type 1 diabetes, we talked about thinking in boxes and actually talking about drugs that are actually applicable, probably, to many patients with chronic kidney disease, not only related to diabetes. And from that perspective, the FINE-CKD clinical trial is a very interesting clinical trial as well,

because this is not a clinical trial with finerenone in people with chronic kidney disease, but now without diabetes. So we're moving ahead to the next step to people without diabetes.

Dr. Pratley:
I think David made the point that in type 1 and type 2 diabetes, the pathophysiologic mechanisms are largely shared. But we also know that in patients that don't have diabetes, there are many similarities as well. I think the example of that was our SGLT2 inhibitor studies, where we found that there was this big benefit in patients with type 2 diabetes. But we also found that that benefit was independent of glucose lowering. And when we did the trials, we saw that the benefit was equally apparent in patients who didn't have diabetes. So we're talking about a whole different mechanism. It's not glucose lowering. And I think we can kind of extrapolate to finerenone there. We're not talking about a diabetes-specific mechanism so much.

What do you think?

Dr. Heerspink:
No, I agree. And the FINE-CKD trial is a clinical trial in more than 1,500 patients with chronic kidney disease to test that hypothesis that finerenone is also effective in slowing the progression of chronic kidney disease in people without diabetes. So the trial is set up not with albuminuria as the endpoint, but now with the change in GFR over time, which is basically an intermediate endpoint because it is always connected directly to kidney failure. If you can slow the progression towards kidney failure, dialysis, you slow GFR decline, so it's directly connected. And that's why it's chosen as the endpoint in that clinical trial.

It's a larger trial than the FINE-ONE trial we just talked about, and the follow-up is also much longer. Patients are followed for a minimum of 32 months. And the first patient enrolled has been in the trial now for more than 4 years. So we have an extensive safety database, a very large efficacy database, and we hope that results will become available early next year.

We look forward to it because it's a clinical trial, not only in patients with a certain type of kidney disease, it has enrolled people with IgA nephropathy, with FSGS, hypertensive nephropathy. So there are different types, clinical phenotypes, enrolled in the population to further broaden, hopefully, the indication of finerenone to patients without diabetes.

Dr. Cherney:
And like the other mechanisms that you mentioned around the similarities of SGLT2 inhibitors that are glucose independent, the effects of finerenone are independent of glucose, of course, but also have a very broad, ubiquitous effect on many of the mechanisms that are linked with CKD progression. There is likely a bit of a hemodynamic effect, so reducing glomerular pressure with finerenone. We see a little dip in GFR after starting finerenone and after stopping it with a washout, the GFR tends to rebound, so this all suggests intrarenal hemodynamic effect.

And then, there are also studies suggesting that there is an effect on attenuating inflammatory and fibrotic mechanisms. And that's really important because pro-inflammatory and pro-fibrotic pathways are also ubiquitous across type 1, type 2, nondiabetic CKD, all these different etiologies where the mineralocorticoid receptor is over-activated, leading to inflammation and fibrosis if we block it. That likely has a benefit across these different diverse causes of chronic kidney disease. So the mechanisms tie it all together. And that's why we expect to see the benefits not only in FIGARO and FIDELIO, also the benefits that we saw in FINE-ONE, and hopefully the benefits that we'll see in FINE-CKD.

Dr. Pratley:
Yeah. So, Hiddo, you started this by saying we need to keep an eye on the future, so I'm going to have you guys put on your crystal balls. David, you mentioned inflammation and fibrosis. This is not just the kidney; it's the heart as well. And then, type 2 diabetes and FIGARO, FIDELIO, and the FIDELIO analysis.

It wasn't just kidney disease prevention. It was heart failure; it was cardiovascular disease. Do we think that this might extend into T1D and the patients without diabetes?

Dr. Cherney:
Yeah. So and not only were there benefits in FIGARO and FIDELIO, also the FINE-ARTS trial and people with heart failure and preserved ejection fraction, where there were benefits, especially in reducing the risk of hospitalization for heart failure or maybe

through some hemodynamic benefits. Possibly, through some of the anti-inflammatory, anti-cardiac remodeling benefits that MRAs can have. And similar to what we have discussed around mechanisms that extend across different etiologies, I think it's reasonable to hypothesize that those mechanisms will extend from the kidney over to the heart and could have cardiovascular benefits in people with type 1 diabetes, too.

The trouble is the FINE-ONE trial is simply not designed to do that. It's not a heart failure cohort. It's very hard to study heart failure outcomes in a non-heart failure cohort because the risk is just so low. So that is not the way we'll answer that question, perhaps in dedicated trials, perhaps in real-world studies in the future. So there may be ways of looking at this, but I think your point's very important, and the benefits may extend from the kidney to the heart.

Dr. Pratley:
Hiddo, what's your crystal ball say?

Dr. Heerspink:
Same. The same. Completely the same. I think that finerenone, by reducing albuminuria, slowing the progression of GFR, it will also translate into cardiovascular protection. But it is difficult to demonstrate in a 240-patient study of unresolved patients.

Dr. Pratley:
Yeah, of course.

Well, this is a pretty exciting time for not only patients with type 1 diabetes but patients with chronic kidney disease in general. We heard at the ASN some really inspiring talks to open the whole session about how far kidney disease management has come. And now, we've transitioned away from just taking care of patients with end-stage kidney disease on dialysis to actually preventing the initiation of kidney disease. It's an exciting time and it really will have a big impact on health.

Any last-minute thoughts, David? Final take-home message?

Dr. Cherney:
So final take-home message is implementation. So the question now is where do we go with this? And will we be able to access these medications for our patients? And as a nephrologist who takes care, uniquely, of patients with diabetes—type 1 and type 2, that's all I do in my clinical practice in terms of ambulatory care—it's very, very disheartening to have nothing new to offer a patient when you've seen—I've some seen my patients for a decade sometimes, and nothing to offer them over that period of time. And so this is very encouraging because it’s hopefully bringing us closer in terms of management of type 1 to what we currently do in type 2 diabetes. And the treatment of type 2 diabetes is both rewarding clinically and patients do really, really well. And I think we have to make it our mission to try to translate, as much as we can, the therapies that we have at our disposal that are safe and that we can show are also effective for people with type 1 diabetes so that we can try and help them in the same way that we help type 2.

So I think that's the take-home message. The translation is going to be challenging, but it's certainly within our grasp now.

Dr. Pratley:
And what I would say in addition to what you said is, it is not up to the David Cherneys of the world to prescribe finerenone.

Dr. Cherney:
Yes.

Dr. Pratley:
Endocrinologists, primary care docs, who are taking care of patients with T1D and type 2 diabetes on the front line, should be picking up that baton.

Dr. Cherney:
Not only should, they're going to have to because there aren't enough nephrologists out there.

Dr. Heerspink:

It's their responsibility, and I believe that the FINE-ONE trial gives new hope to patients with type 1 diabetes and chronic kidney disease. I'm very pleased with the results.

Let's move forward with this. Let's keep this momentum for other patients and let's use it as an example that, indeed, we don't leave patients behind. And let's look for patients, also, with chronic kidney disease in the future.

Dr. Pratley:
Right. Well, that was great. That's all the time we have today, so I want to thank our audience for tuning in and say thank you. Thank you to David Cherney and Dr. Hiddo Heerspink for this great conversation. It was really great speaking with you today.

Dr. Heerspink:
Thank you very much, Rich. It was a great session.

Dr. Cherney:
Yeah, great to be here. Thanks so much.

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