



Heralding a new era in kidney disease research and treatment: The CREDENCE trial



A landmark clinical trial transformed the status quo in diabetic kidney disease research by identifying the first new treatment in almost 20 years. Building on The George Institute's long history of research in diabetes, researchers showed a class of diabetes medication - SGLT2 inhibitors - reduces the risk of cardiovascular disease and prevents kidney failure in people with type 2 diabetes. Their work has ushered in a new era of research that led to changes in treatment guidelines and transformed practice worldwide. As a result, many millions of lives and billions of dollars in healthcare costs will be saved by averting heart disease, kidney failure and other health complications of diabetes.

Today, around half a billion people have diabetes, and at least one in three will go on to develop chronic kidney disease. People who have both diabetes and kidney disease are at high risk of kidney failure, heart attack, stroke, and death. Diabetes is the leading cause of kidney failure and the most common reason for needing dialysis worldwide. By 2030 it is estimated that over five million people worldwide will receive dialysis, yet at least half of the people with kidney failure in the world today will die because they cannot afford it.

While it is widely accepted that chronic kidney disease, diabetes and cardiovascular disease commonly occur together, share similar risk factors such as obesity and high blood pressure, and have similar treatment strategies, less than 20 years ago this was not common knowledge.

Against all odds

In the early 2000s, the field of nephrology was in a dire state with no new treatments for kidney disease on the horizon, reflects kidney specialist, Scientia Professor Vlado Perkovic, Dean of Medicine & Health, UNSW Sydney, and former Executive Director of The George Institute Australia.

"The number of people with diabetes was surging and dialysis units were filling up fast with kidney failure patients," said Professor Perkovic. "While there were various new drugs to help people with diabetes, they

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Professor Vlado Perkovic

were not slowing the progression of kidney disease and the risk of developing kidney failure remained high for these patients."

Fast facts: Diabetes & kidney disease

- Globally one in ten adults have chronic kidney disease and each year 1.2 million deaths are attributable to the disease.
- It's estimated that kidney disease will be the fifth leading cause of death by 2040 unless action is taken.
- Around 500 million people globally have diabetes – this is expected to increase by 25% by 2030 and 51% by 2045.
- Diabetes is the leading cause of kidney failure - up to 40% of those with diabetes go on to develop chronic kidney disease.
- Dialysis has been the mainstay of treatment for kidney failure for over 70 years, and over 5.4 million people worldwide are expected to need it by 2030, compared to 2.6 million people in 2010.
- More than half of people with kidney failure around the world are thought to die because they cannot afford dialysis.



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Around that time, data from a major George Institute diabetes study hinted at a potential link between treating diabetes and tackling kidney disease, sparking a quest for funding to run a clinical trial to test this theory.

“Back then, people didn’t think kidney disease was a big enough problem to investigate and it wasn’t appreciated what a big issue it is for people with diabetes,” explains Professor Perkovic. “Nobody thought a diabetes treatment might work for kidney disease. It was a challenging time to convince big pharmaceutical companies to spend hundreds of millions of dollars to conduct research to address a question that was not perceived to be important enough.”

In 2008, a class of diabetes medication designed to lower glucose levels in people with type 2 diabetes, sodium-glucose co-transporter-2 (SGLT2) inhibitors, were in advanced development. George Institute research underway at the time, funded by pharmaceutical company Janssen, was looking at whether the SGLT2 inhibitor canagliflozin could prevent cardiovascular disease in people with diabetes. Early data showed promise that the drug was protective against kidney damage.

Five years and dozens of conversations with pharmaceutical companies later, these findings helped convince Janssen to fund a new clinical trial into the effects of canagliflozin on kidney disease in people with diabetes.

New hope for many millions of people with diabetes

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial commenced in 2014, and in April 2019 - a year earlier than expected - the results were published in the *New England Journal of Medicine*. Presented at the 2019 International Society of Nephrology World Congress, the findings attracted global media attention and praise from the research community.

Finally, the field of nephrology had something to celebrate.

“This was the home run we were hoping for but not banking on.”

Professor Vlado Perkovic

Involving 4,401 patients with diabetes and kidney disease from 34 countries, CREDENCE showed that canagliflozin not only protects people with diabetes from developing kidney failure, but it also protects them from heart disease, heart failure and other cardiovascular complications. The number of people who developed kidney failure or died from either kidney failure or cardiovascular disease was reduced by 30%; the risk of hospitalisation for heart failure was reduced by 39%; and the risk of heart attack, stroke and death from cardiovascular disease was reduced by about 20%. The study also found the treatment helps people who already have reduced kidney function and are at particularly high risk of developing kidney failure.

“The definitive trial result was a major medical breakthrough - we now have a very effective way to reduce this risk using a once daily pill,” said Professor Perkovic, lead author of the study.

The CREDENCE results:

- 30% drop in kidney failure
- Heart failure reduced by over 30%
- Major cardiovascular events down by about 20%



Professor Perkovic said there were a series of moments that made the CREDENCE trial a truly rewarding journey to be part of.

“The first magical moment was when the data monitoring committee suggested we stop the study early because the early results were so compelling,” he said. “A long period of excitement followed as people suspected something really positive was coming. This

culminated in another magical moment when we presented the results to an almost full auditorium and received a loud and lengthy standing ovation - the first I'm aware of that happening at a kidney conference. This was the home run we were hoping for but not banking on," said Professor Perkovic.

Robert Shepherd @robertshepherd

At long last, patients with #diabetic kidney disease have a new drug that improves their chance of survival. #SGLT2 #CREDESCENCE Congratulations to all the patients, investigators and industry people involved. Massive applause from the audience at #isnwcs for this announcement!

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Professor Perkovic delivered the CREDESCENCE results at the 2019 International Society of Nephrology World Congress

Co-author of several publications from the study, Dr Brendon Neuen, a kidney specialist registrar at Royal North Shore Hospital in Sydney, and a research fellow at The George Institute, says the extent of the benefits of the drug on kidney and cardiovascular outcomes were previously unheard of.

"This work has been life-changing for so many of our patients, but also for me as a clinician and researcher."

Dr Brendon Neuen

"The study reinvigorated the whole field of nephrology – it defied every single expectation along the way and set the standard for the next generation of kidney clinical trials," said Dr Neuen. "This work has been life-changing for so many of our patients, but also for me as a clinician and researcher."

Throwing a lifeline to hundreds of millions of people at risk of kidney failure, CREDESCENCE showed in a single trial how to prevent the need for dialysis, says Professor Meg

Jardine, Director of the NHMRC Clinical Trials Centre, and co-author of the study.

"This is a once-in-a-generation development for the global field of nephrology," said Professor Jardine.

Fast-tracked into standard practice

Because SGLT2 inhibitors could already be prescribed to people with diabetes, the CREDESCENCE results were soon followed by changes in guidelines and regulatory approvals, making the drug the standard of care for diabetic kidney disease.

"This is a once-in-a-generation development for the global field of nephrology,"

Professor Meg Jardine

An estimated 30 million Americans have chronic kidney disease, with most unaware they have it. Immediately after the CREDESCENCE results were announced, the US National Kidney Foundation signaled the significance of the findings, issuing an unprecedented statement declaring: "If this supplemental indication is approved by the Food and Drug Administration (FDA), it would be the first new treatment for diabetic kidney disease in decades."

National Kidney Foundation @nkf

BREAKING NEWS for patients with diabetic #kidneydisease! Data published in @NEJM shows that INVOKANA (Canagliflozin) can help patients diagnosed with type 2 #diabetes and #kidneydisease reduce the risk of end stage renal disease and cardiovascular events.

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Separately, Janssen submitted an application to the FDA for the use of canagliflozin to treat patients with chronic kidney disease and type 2 diabetes, which was approved within months.

A new era in research

CREDESCENCE quickly led to exponential growth in research around the world to see whether other SGLT2 inhibitors had the same impact and explore their potential benefits among patients without diabetes who are at risk of kidney or heart disease.

In 2019, researchers at The George Institute published a paper in *Lancet Diabetes and Endocrinology* examining data from four studies involving almost 40,000 participants to assess three of the most used SGLT2 inhibitors - canagliflozin, empagliflozin, and dapagliflozin. The results not only reaffirmed the CREDESCENCE findings but suggested all three SGLT2 inhibitors can reduce the risk of needing dialysis, kidney transplantation or death due to kidney disease in people with diabetes, opening up even more treatment options for patients.



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In an accompanying editorial in the journal, Professor Richard Gilbert from the University of Toronto said: "After years of stagnation, we are now on the brink of a new paradigm in the prevention and treatment of kidney disease in people with type 2 diabetes."

Around the world:

- In Australia, 1.7 million people have diabetes and around two-thirds also have cardiovascular disease, chronic kidney disease or both. Treating end-stage kidney disease costs AUD\$12 billion annually.
- It is estimated China's economy will lose US\$558 billion over the next decade due to death and disability attributable to chronic cardiovascular and renal disease.
- In England, kidney disease costs the health system more than breast, lung, colon, and skin cancer combined.
- In India, around 70 million people have diabetes, the fastest growing chronic condition, and up to 40% will go on to develop kidney disease. Over 1.4 million people die annually because they cannot afford dialysis.
- In the US, 37 million people have chronic kidney disease and one in three people are at risk of developing chronic kidney disease. It's estimated around 90% aren't aware they have the disease.

"If implemented, evidence from SGLT2 inhibitors research will transform the management of chronic kidney disease in the coming years."

Professor Hiddo Heerspink

In January 2020, a separate study published in the *Journal of the American Heart Association* showed the SGLT2 inhibitor drug class provides cardiovascular benefit for all patients with diabetes. Lead author Associate Professor Clare Arnott, Co-Director of the Better Treatments Program at The George Institute, and a cardiologist at Royal Prince Alfred Hospital in Sydney, says the consistency in findings reinforces the tremendous cardiovascular protection of SGLT2 inhibitors.

"Cardiovascular disease is the leading cause of death in people with diabetes," said Associate Professor Arnott. "This body of research proves we now have a whole class of drug in our treatment arsenal that could significantly reduce cardiovascular and kidney complications from diabetes."

"As more SGLT2 inhibitor treatment options become available, we hope fewer patients will go on to require more invasive and costly interventions and need to be hospitalised," she said.

In October 2020, an international clinical trial involving 4,304 people, Dapagliflozin and Protection of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD), published in the *New England Journal of Medicine*, showed another SGLT2 inhibitor, dapagliflozin, had significant benefits for people with chronic kidney disease, regardless of whether they had diabetes or not. Led by Professor Hiddo Heerspink, Co-Director of the Better Treatments Program at The George Institute, DAPA-CKD showed the drug reduced the risk of kidney failure by approximately 40%, hospitalisation for heart failure or cardiovascular death by almost a third, and significantly prolonged survival in people with chronic kidney disease. Like CREDENCE, the trial

was also stopped early at the recommendation of the independent data monitoring committee because the evidence was so convincing.

“Crucially, DAPA-CKD demonstrated for the first time that SGLT2 inhibitors can also protect patients without diabetes from the risk of chronic kidney disease, paving the way for this drug to offer even more people life-saving benefits,” said Professor Heerspink.

Based on DAPA-CKD data, for the first time the use of dapagliflozin was approved to treat chronic kidney disease patients with and without diabetes by the FDA in April 2021 and in the European Union in August 2021, as well as approvals in Australia, Japan and the United Kingdom.

Defining best practice in treatment

Today, the use of SGLT2 inhibitors continues to be studied among large numbers of people, with up to 100,000 having participated in related clinical trials to date, new publications coming out monthly and clinical guidelines being updated regularly.

Almost all major international treatment guidelines for diabetes, cardiovascular disease and kidney disease now recommend that SGLT2 inhibitors are prescribed for people with chronic kidney disease (with or without diabetes), heart failure, or for those with diabetes who are at high risk of cardiovascular disease.

“The overlap between kidney disease, cardiovascular disease and diabetes is now widely recognised, as is the need to consider this when treating patients,” said Professor Heerspink. “If implemented, evidence from SGLT2 inhibitors research will transform the management of chronic kidney disease in the coming years.”

Saving lives and healthcare costs

A 2021 report published by The George Institute found that making SGLT2 inhibitors more widely available in Australia alone would save a significant number of lives and reduce costs to society. Specifically, an AUD\$1 billion government investment over 10 years in SGLT2 inhibitor treatments would return almost AUD\$5 billion in benefits to society. The report estimated such an investment would prevent 4,284 people from suffering acute kidney injury, 8,744 from developing kidney failure and avert 4,148 heart attacks and 7,450 deaths over 10 years. Furthermore, these findings are a conservative estimate given the evidence is now clear that this class of drug also has tremendous benefits for people without diabetes who have heart failure and/or chronic kidney disease.

Tackling barriers to access

If made more widely available, SGLT2 inhibitors have the potential to become one of the most impactful new treatments in decades, particularly in low- and middle-income countries where the prevalence of diabetes, kidney disease and cardiovascular disease is greatest.

“We are in a unique position to have such strong evidence that these drugs reduce death from a range of chronic conditions, but the challenge now is how to get them to the people most likely to benefit,” said Associate Professor Arnott.

“While it’s understood that SGLT2 inhibitors are the optimal care, the number of patients who actually receive guideline-based care for kidney disease is appalling,” she said.

In October 2021, in a global milestone, SGLT2 inhibitors were added to the World Health Organization (WHO) List of Essential Medications, highlighting the drug’s life-saving cardiovascular and kidney benefits. Because SGLT2 inhibitors are still patented and high-priced, the WHO and the Medicines Patent Pool, a United Nations-backed organisation, are working with patent-owners to make these drugs affordable in low- and middle-income countries.

In tandem, George Institute researchers and colleagues are investigating how to overcome treatment barriers so that SGLT2 inhibitors can be easily accessible to the many millions of people who can benefit, no matter where they live.

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Associate Professor Clare Arnott

“We urgently need to bridge the knowledge gap across all levels of clinical practice and get better at identifying people with diabetes and kidney disease, conducting regular check-ups for people over 50, and ensuring those at high risk receive treatment sooner rather than later,” says Professor Perkovic. “As we grapple with overstretched health systems and see chronic conditions growing in epidemic proportions, we need to be smarter at how we prevent and treat disease.”

Until the CREDENCE trial, for almost two decades there were no new treatments to protect kidney function in people with diabetes. Reinvigorating a stagnant area of research and practice, CREDENCE spurred a global community of researchers and clinicians to run a whole new series of clinical trials to find better treatments for kidney disease. CREDENCE and the wave of new research it triggered, not only changed traditional ways of treating diabetes, cardiovascular disease, and kidney disease, it led to SGLT2 inhibitors being recognised as the standard of care for diabetic kidney disease. If translated into practice, hundreds of millions of people globally will benefit from improved health outcomes and countless lives will be saved.



A patient receiving peritoneal dialysis at home

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Project:

CREDENCE

Research leads:

Dr Brendon Neuen, Associate Professor Clare Arnott, Professor Hiddo Heerspink, Professor Meg Jardine, and Professor Vlado Perkovic.

Project Cycle:

2014–2019

Partners and supporters:

The CREDENCE trial was funded by Janssen, which manufactures canagliflozin, and was led by an independent, academic-led Steering Committee.

About The George Institute for Global Health:

The George Institute for Global Health is focused on generating robust evidence to create better treatments, better care and healthier societies. This means not only generating evidence to determine what works, and doesn't work, but also which health service or treatment is value for money and where the cost of healthcare can be reduced. Paramount to our work is finding new ways to fund healthcare so health systems can become more sustainable, as well as operate more equitably.

About the PRISM Initiative:

Through interviews with investigators and research partners, project staff and peers in the research community, the Project & Research Impact Story Mapping (PRISM) Initiative examines key research milestones of The George Institute and explores the impact of its projects on health sectors and systems, government policies, communities and more. Join us as we explore key research achievements of the past 20 years, examine how conventional thinking was challenged, who benefitted and what led the research to be transformed into practice.

To read more PRISM impact case studies, visit www.georgeinstitute.org/case-studies-and-examples

CREDENCE at a glance:

- Involved 4,401 patients from 34 countries.
- Treating people with diabetes with SGLT2 inhibitor, canagliflozin, showed:
 - A 30% drop in kidney failure
 - Reduced heart failure by over 30%
 - Major cardiovascular events down by about 20%
- Within months of the results, the US Food and Drug Administration approved the use of canagliflozin to treat patients with chronic kidney disease and type 2 diabetes, becoming the first drug approved in nearly 20 years to slow diabetic kidney disease.
- SGLT2 inhibitors were added to the World Health Organization List of Essential Medications, highlighting the cardiovascular and kidney benefits.
- Since CREDENCE, up to 100,000 people have participated in SGLT2 inhibitor-related clinical trials, including the landmark DAPA-CKD trial.
- Today, almost all major international treatment guidelines for diabetes, cardiovascular disease and kidney disease recommend that SGLT2 inhibitors are prescribed for people with chronic kidney disease (with or without diabetes), heart failure, or for those with diabetes who are at high risk of cardiovascular disease.