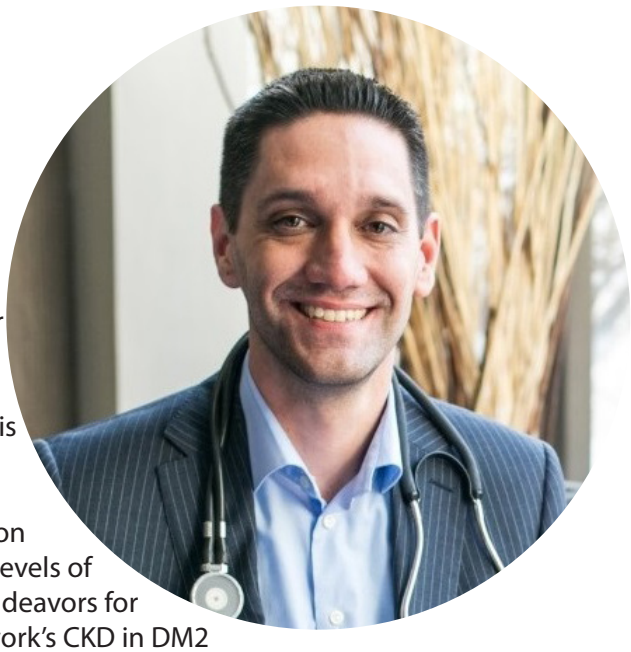
ABOUT THE AUTHOR



Louis Girard, MD, MBT, FRCPC

Dr. Louis Girard joined the Division of Nephrology at the University of Calgary in July of 2010. He is a Nephrologist and Clinical Professor of Medicine. Within the Division of Nephrology, Dr. Girard focuses on clinical immunology and infectious diseases in chronic kidney disease patients. He is the medical director of the Glomerulonephritis Clinic and Apheresis. He is heavily involved in clinical trials. He has several peer-reviewed publications, including in the New England Journal of Medicine. Dr. Girard has a strong commitment to education and has won numerous awards for his teaching contributions at all levels of medical training. He has been faculty on numerous national CME endeavors for Diabetes and is the co-chair for the Medicine Strategic Clinical Network's CKD in DM2 subcomittee.

Affiliations:
Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

MODERN MANAGEMENT OF CHRONIC KIDNEY DISEASE IN T2DM: A PRACTICAL OVERVIEW FOR PRIMARY CARE PROVIDERS

Introduction

The development of chronic kidney disease (CKD) in patients with T2DM (CKD in T2DM) is a common and major comorbidity. Not only is it associated with progressive kidney disease and end-stage kidney disease (ESKD), it is also associated with very high risk for major adverse cardiovascular events (MACE) and heart failure (HF) events.[1,2] CKD in T2DM is extremely costly from a health economic perspective; however, most importantly, it results in significant reductions in patient quality of life and survival.[3] For several decades, there has been a lack of new therapeutic options to address residual cardiorenal risk. The traditional pillars of therapy include glycemic control with a HbA1C target of 6.5%, blood pressure control with a blood pressure target of less than 130 mmHg, and the use of renin angiotensin aldosterone inhibitors (RAASi).[4] Recently, several options have emerged that can address residual kidney and cardiovascular risk in these patients, thereby providing organ protection. Importantly, these therapies are grounded in the foundation of solid randomized, controlled clinical trials and are now prevalent in the guidelines that inform the management of CKD in T2DM.[4,5] The novel pillars for kidney and cardiovascular protection include sodium glucose luminal transported 2 inhibitors (SGLT2i) and finerenone, a non-steroidal mineralocorticoid receptor antagonist (nsMRA).[4,5] This article highlights practical considerations of these pillars for primary care providers with a focus on kidney protection.

Glycemic Management

Tight glycemic control has been shown to reduce the progression of microvascular complications and, in particular, diabetic nephropathy (DN).[6] In certain long-term outcome studies of DN, tight glycemic control has also been shown to reduce ESKD.[6] Glycemic control targets, typically supporting a HbA1C target of 6.5% for reduction in the progression of nephropathy, continue to form a central pillar of the major diabetes guidelines.[4] It is important to note that in the earlier studies of tight glycemic control, the benefits were offset by the risk of hypoglycemia.[6] However, tight glycemic control may not carry the same risk with modern therapies, as many of these carry a much lower risk of hypoglycemia.[7]

SGLT2i's are effective agents in reducing blood glucose in patients with estimated glomerular filtration rates (eGFR) > 60 mL/min. Additional benefits include modest blood pressure reduction (3-4 mmHg) and modest weight loss (1.5-2.0 kg). It is important to note that the site of action of SGLT2i is in the proximal tubular lumen of the nephrons and delivery to this site is dependent on kidney filtration. As a practical consideration, because their mechanism of action is dependent on kidney filtration, the efficacy of SGLT2i blood glucose lowering diminishes with diminishing eGFR. In patients with an eGFR > 60 mL/min, an HbA1C reduction of approximately 0.8% is expected. When the eGFR declines below 45 mL/min, reductions of 0.25% or less have been demonstrated. Interestingly, the organ-protective properties of these agents remain, despite the loss of glycemic lowering efficacy.[8-10]

While glucagon like peptide 1 receptor agonists (GLP-1RA) are not thoroughly reviewed in this article, as they have not yet been shown to demonstrate hard kidney outcome reduction, they are agents to prioritize in this group of patients for several reasons.[5] GLP-1RA are extremely effective anti-hyperglycemic therapies. Additionally, they have a significant impact on weight loss (5%-10% of body weight), they do not require dose adjustment in patients with CKD, and they reduce MACE in this group of patients.[11]

Renin Angiotensin Aldosterone Inhibitor (RAASi) Agents for CKD in T2DM

To place the effect of SGLT2i's in context, reviewing the comparative effect of standard of care agents is a useful exercise. Prior to the emergence of SGLT2i's, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) represented the stand of care in CKD in T2DM and in non-diabetic albuminuric CKD.[4,5] Randomized trial data in these patient populations demonstrate an expected GFR protection of 0.75-1.0 mL/min/year. The outcome of reduction of progression of kidney function decline by 0.75 mL/min/year is a recognized benchmark that serves as a surrogate for predicting a reduction in ESKD.[12,13] ACEi's and ARBs remain a pillar of care in patients with albuminuric CKD.[4,5]

SGLT2i's: Kidney Outcomes for CKD in T2DM

Three landmark primary kidney outcome trials have been conducted on the SGLT2i's that are pertinent to medications that can be accessed in Canada. It is important to note that in these three trials, patients were required to be on an ACEi or ARB (unless intolerant or contraindicated) and this resulted in 97% or greater utilization of these medications. Ten additional randomized trials have been conducted in which kidney outcomes were reported as secondary outcomes. A meta-analysis of these trials reveals a relative risk reduction in the composite outcome of kidney disease progression (> 50% decline in eGFR, ESKD or renal death) of 38% (RR 0.62; 0.56-0.68) in favour of SGLT2i use for patients with T2DM.14 Due to their mechanism of action, an initial decline in eGFR of up to 30% is expected; this should not be a cause for concern.[15] From a safety perspective, the meta-analysis demonstrated a 21% (HR 0.79; 0.72-0.88) relative risk reduction in the incidence of acute kidney injury (AKI), demonstrating a protective effect of SGLT2i's for this outcome. Ketoacidosis was a rare event in patients with T2DM but does occur more frequently (HR 2.19; 1.49-3.04). In addition, lower limb amputation occurred more frequently in patients on an SGLT2i (HR 1.15; 1.02-1.30); however, this was driven by the results of one cardiovascular outcome trial (CVOT) and was not seen in the other trials.[14] There is an increased risk of genital mycotic infections (GMI) in patients with T2DM who receive treatment with an SGLT2i.[14]

GFR slope has become an important outcome in clinical trials. It is a measure of decline in GFR over the course of a year. It is assumed that by slowing the rate of decline in GFR, the hard outcome of ESKD will be delayed.[16] When examining the outcome of GFR slope, the CREDENCE trial, which included solely patients with T2DM, demonstrated a 2.74 mL/min/year benefit of canagliflozin vs ACEi or ARB alone.[8] Similarly, the DAPA-CKD trial, which included patients with and without T2DM, demonstrated a 1.92 mL/min/year protection in favour of dapagliflozin.[9] In the most recent primary kidney trial, EMPA-KIDNEY enrolled patients with and without T2DM. Patients with an eGFR of 20-45 mL/min did not require albuminuria to be enrolled in the trial, which was a requirement in the other two trials. In this trial, there was a 1.37 mL/min/year slope difference in favour of empagliflozin. Based on trial data, an SGLT2i can be initiated at an eGFR > 20 mL/min and continued until the patient develops ESKD or another contraindication.[10] The above data clearly establish SGLT2i's as a standard of care for kidney protection in patients with CKD in T2DM.[5]

SGLT2i's: Additional Outcomes for CKD in T2DM

Patients with CKD in T2DM are at high risk of MACE, HF events and mortality. In the meta-analysis discussed above, SGLT2i's were associated with a 23% reduction in the combined outcome of CV death or hospitalization for HF (HHF [hypertensive heart failure] HR 0.77; 0.73-0.81) and a reduction in CV death alone (HR 0.86; 0.80-0.92). Furthermore, a 12% reduction in all-cause mortality was reported (HR 0.88; 0.84-.93).[14] Although it is beyond the scope of this paper, significant benefits have also been shown in reductions in HF events in patients with and without established HF.

SGLT2i's: Non-diabetic CKD

Patients with non-diabetic CKD have been studied in some of the primary kidney trials and in other trials, such as those investigating HF. When comparing the sub-analysis from these trials of patients with and without T2DM, the beneficial kidney outcomes are seen in both groups and statistically, the positive outcome results are the same as positive outcome results of the overall trial. Meta-analysis demonstrates a 31% relative risk reduction in the primary kidney outcome (HR 0.69; 0.57-0.82) with a similar 34% reduction in AKI (HR 0.66; 0.54-0.61). From a CV perspective in patients without T2DM, similar benefits were seen in the reduction of the composite outcome of CV death or HHF and CV death alone, as in patients with T2DM. The safety profile is favourable for SGLT2i's in patients with T2DM and appears to be even more favourable in those without T2DM. There are no concerns over limb amputation, hypoglycemia, ketoacidosis, or GMI. This data establishes SGLT2i's as a new standard of care in patients without T2DM, particularly for those with albuminuria.[14,17] GFR slope analysis from the EMPA-KIDNEY trial also demonstrates benefit in patients with normoalbuminuria and an eGFR of 20-45 mL/min; however, this is a lower risk group with a higher number needed to treat (NNT).[10]

Finerenone: Outcomes for CKD in T2DM

The newest guideline-based pillar for kidney protection is finerenone.[5] It is important to understand that this is a novel class of medications known as nsMRA and should not be viewed as interchangeable with steroidal MRAs. Finerenone has been studied in two large randomized, controlled trials (FIGARO and FIDELIO) which were designed to be studied together. The pooled analysis of these two trials is FIDELITY which represents 13,026 patients with T2DM, a GFR > 25 mL/min and optimized RAASi. Patients with a potassium of 4.8 mEq/L or less were eligible, while on optimal RAASi therapy. When compared with placebo, finerenone demonstrated a 23% reduction (HR 0.77; 0.67-0.86) in the primary composite kidney outcome and a 20% reduction (HR 0.80; 0.64-0.99) in ESKD alone. Additionally, there was significant 14% reduction in MACE in favour of finerenone (HR 0.86; 0.78-0.95). There was also a reduction in HHF; however, formal phase 3 trials in patients with established HF have yet to be completed. Finerenone was also safe with the main consideration being a small, but higher rate of discontinuation due to hyperkalemia compared with placebo (1.7% vs 0.6%).[18] Therefore, this represents a novel, guideline-based organ protective therapy that primary care providers should add to their therapeutic armamentarium.[5]

Conclusion

SGLT2i's are a foundational therapy in the reduction and prevention of kidney disease, as well as CV outcomes in patients with and without T2DM.The medical community needs to broadly implement this class of medication at their organ-protective dose in patients with CKD, as has occurred with statins in the past. There is no other singular class of CKD medication that has been shown to have comparable efficacy in so many domains. Additionally, these medications are safe, with the adverse events in patients with T2DM being predictable, and almost non-existent in those without T2DM. Access to these medication remains disparate across Canada. It is incumbent on public payors to facilitate broad access to SGLT2i's. A recent Canadian study suggests that when accounting for kidney outcomes, SGLT2i's are also beneficial from a health economics perspective.[19] Finerenone has been approved in Canada. It has demonstrated extremely robust kidney and CV protection data in patients with CKD in T2DM. These classes of medications, including GLP-1RA, should be used systematically and in combination by primary care providers to optimally address residual organ risk in patients with CKD in T2DM.

Correspondence:
Dr. Louis Girard
Email: lgirard@ucalgary.ca

Financial Disclosures:
CME/Advisory Board Honoraria: AstraZeneca, Bayer, BI/Lily and Janssen.

References

1. *Hahr AJ, Molitch ME. Management of diabetes mellitus in patients with CKD: Core Curriculum 2022. Am J Kidney Dis. 2022 May;79(5):728-736.*

2. *Birkeland KI, Bodegard J, Eriksson JW, Norhammar A, Haller H, Linssen GCM. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: A large multinational cohort study. Diabetes ObesMetab. 2020Sep;22(9):1607-1618.*

3. *Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020 Feb 29;395(10225):709-733.*

4. *Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.*

5. *de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and kidney disease: improving global outcomes (KDIGO). Diabetes Care. 2022 Dec 1;45(12):3075-3090.*

6. *Zoungas S, Arima H, Gerstein HC, Holman RR, Woodward M, Reaven P, et al. Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol. 2017 Jun;5(6):431-437.*

7. *Zhao JZ, Weinhandl ED, Carlson AM, St Peter WL. Hypoglycemia risk with SGLT2 inhibitors or glucagon-like peptide 1 receptor agonists versus sulfonylureas among Medicare insured adults with CKD in the United States. Kidney Med. 2022 Jun 26;4(8):100510.*

8. *Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM. CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306.*

9. *Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446.*

10. *The EMPA-KIDNEY Collaborative Group. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023 Jan 12;388(2):117-127.*

11. *Yoshiji S, Minamino H, Tanaka D, Yamane S, Harada N, Inagaki N. Effects of glucagon-like peptide-1 receptor agonists on cardiovascular and renal outcomes: A meta-analysis and meta-regression analysis. Diabetes Obes Metab. 2022 Jun;24(6):1029-1037.*

12. *Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, et al. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet. 2015 May 23;385(9982):2047-56.*

13. *Collier W, Inker LA, Haaland B, Appel GB, Badve SV, Caravaca-Fontán F, et al.Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)*. Evaluation of variation in the performance of GFR slope as a surrogate end point for kidney failure in clinical trials that differ by severity of CKD. Clin J Am Soc Nephrol. 2023 Feb 1;18(2):183-192.*

14. *Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022 Nov 19;400(10365):1788-1801.*

15. *Lytvyn Y, Kimura K, Peter N, Lai V, Tse J, Cham L, et al. Renal and vascular effects of combined SGLT2 and angiotensin-converting enzyme inhibition. Circulation. 2022 Aug 9;146(6):450-462.*

16. *Collier W, Inker LA, Haaland B, Appel GB, Badve SV, Caravaca-Fontán F, et al.Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)*. Evaluation of variation in the performance of GFR slope as a surrogate end point for kidney failure in clinical trials that differ by severity of CKD. Clin J Am Soc Nephrol. 2023 Feb 1;18(2):183-192.*

17. *Mancini GBJ, O'Meara E, Zieroth S, Bernier M, Cheng AYY, Cherney DZI, et al. 2022 Canadian Cardiovascular Society Guideline for Use of GLP-1 Receptor Agonists and SGLT2 Inhibitors for Cardiorenal Risk Reduction in Adults. Can J Cardiol. 2022 Aug;38(8):1153-1167.*

18. *Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, et al. FIDELIO-DKD and FIGARO-DKD investigators. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. Eur Heart J. 2022 Feb 10;43(6):474-484.*

19. *Yi TW, Atiquzzaman M, Zheng Y, Smyth B, Jardine M, Levin A. Findings of sodium-glucose cotransporter-2 inhibitor kidney outcome trials applied to a Canadian chronic kidney disease population: a retrospective cohort study. Can J Kidney Health Dis. 2022 Dec 20;9:20543581221145068.*