Finding the sweet spot in managing diabetes with coronary artery disease and chronic kidney disease

Pharmacotherapy pearls with a focus on sodium-glucose cotransporter-2 inhibitors

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In the past decade, the availability of newer glucose-lowering medications has offered more options for achieving glycemic targets in adults living with type 2 diabetes mellitus (T2DM). However, with more options comes the challenge of considering the clinical benefits, harms, and practical issues associated with each agent. This article aims to delve into the evidence and clinical pearls that can assist in the selection of optimal therapy for an adult with T2DM and diabetic complications.

Case description

Michael, a 48-year-old man diagnosed with T2DM 10 years ago, attends the clinic for a review of his diabetes and coronary artery disease (CAD). He has been treated with metformin and gliclazide since his T2DM diagnosis, with the addition of insulin glargine last year. He was diagnosed with CAD 4 months ago when he presented with an episode of angina. This was treated with coronary angioplasty and insertion of a drug-eluting stent in his left anterior descending artery. Since that intervention, Michael has improved his diet and exercises daily, resulting in some weight loss and improved glycemic control. Recent home fasting blood glucose levels have been between 6.2 and 10.0 mmol/L. He reports no symptoms of hypoglycemia.

Other medical conditions include proliferative diabetic retinopathy treated with laser therapy 18 months ago, diabetic nephropathy (estimated glomerular filtration rate [eGFR] of 40 to 50 mL/min in the past year), mild sensory neuropathy in his feet, hypertension, and hyperlipidemia. He is an ex-smoker, having quit 5 years ago; he denies alcohol or other recreational drug use.

Current medications include 1000 mg of metformin twice daily; 60 mg of modified-release gliclazide twice daily; 22 units of insulin glargine at bedtime; 10 mg of amlodipine daily; 8 mg of perindopril daily; 10 mg of rosuvastatin daily; 81 mg of acetylsalicylic acid daily; 90 mg of ticagrelor twice daily; and 1 tablet of a multivitamin daily.

Recent laboratory test results include a hemoglobin A_{1c} (HbA_{1c}) of 8.5%; a fasting glucose level of 7.9 mmol/L; a sodium level of 141 mmol/L; a potassium level of 5.0 mmol/L; a serum creatinine level of 168 µmol/L; an eGFR of 41 mL/min; a urine albumin-to-creatinine ratio of 613.6 mg/mmol; total cholesterol level of 3.69 mmol/L; a triglyceride level of 3.16 mmol/L; a high-density lipoprotein level of 0.83 mmol/L; a low-density lipoprotein level of 1.42 mmol/L; and a non–high-density lipoprotein level of 2.86 mmol/L. Thyroid-stimulating hormone, aspartate aminotransferase, and alanine aminotransferase levels and complete blood count were normal.

Physical examination findings included weight of 93.4 kg and a body mass index of 28.8 kg/m^2. Findings of the general examination were unremarkable, with no signs of heart failure. His heart rate was 73 beats/min and regular, with normal heart sounds; his blood pressure (BP) was 144/93 mm Hg. Diabetic foot examination findings were normal.

Summary: Michael is a 48-year-old man with a 10-year history of T2DM. His glycemic control remains suboptimal despite slight improvement with lifestyle modifications. He has substantial diabetic complications with proliferative retinopathy, stage 3 chronic kidney disease (CKD), and CAD with recent angioplasty intervention.

Bringing evidence to practice

Optimizing Michael's glycemic control. There are several reasons to consider medication changes to improve glycemic control for Michael. Reduced renal function necessitates reassessment of his current agents, as well as consideration of other antihyperglycemic medications that might offer cardiorenal benefits. Because he is relatively young, functionally independent, and cognitively aware, a target HbA_{1c} of 7% or less is recommended to slow the progression of microvascular complications.[1] Thus, the following options could be considered.

- Encourage diabetes self-management. Given the recent change to his health status, Michael could benefit from individualized diabetes self-management education. This includes goal setting and support for the many facets of diabetes care such as nutrition, physical activity, medication adherence, and psychosocial stress management.[2]
- Maintain metformin therapy but adjust the dose to ensure safe use in the context of CKD. Metformin remains the first-line treatment for T2DM owing to its low risk of hypoglycemia and weight gain,[3] established glycemic-lowering efficacy, low cost, and positive long-term safety record. Metformin was the earliest

antihyperglycemic agent to show cardiovascular (CV) and mortality benefits in an obese population,[4] with mortality benefits persisting after 20 years of follow-up.[5] As outlined in **Table 1**, the metformin dose should be adjusted in patients with decreased but stable renal function, minimizing the risk of adverse events and lactic acidosis related to the accumulation of metformin.[6,7]

- Explore the additional pharmacotherapy options listed in **Table 2** by comparing the potential for lowering HbA_{1c}, hypoglycemia risk, effects on weight, and available evidence for CV and renal benefits of each antihyperglycemic medication.[8-14]

For patients with T2DM, CAD, CKD, or a combination thereof, Canadian, American, and European clinical practice guidelines recommend selecting glucose-lowering medications that have demonstrated CV and renal benefits in cardiovascular outcome trials (CVOTs).[6,7,15] **Table 3** summarizes the CVOTs of medications in the sodium-glucose cotransporter-2 (SGLT2) inhibitor and glucagonlike peptide 1 (GLP1) agonist classes that have demonstrated positive CV evidence in patients with established cardiovascular disease (CVD).[8-13] In the SGLT2 inhibitor class, empagliflozin and canagliflozin reduced major adverse CV events, with empagliflozin additionally decreasing all-cause mortality over 3.1 years.[8,9] (A trial summary of the EMPA-REG [Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes] trial is available from **CFPlus.***) Dapagliflozin showed noninferiority (not superiority) when compared with placebo for major adverse CV events.[10] However, this CVOT had the largest proportion of patients (59%) without established CVD at baseline.[10]

In the GLP1 agonist class, liraglutide, semaglutide, and dulaglutide reduced major adverse CV events when added to standard care.[11-13] Additionally, liraglutide decreased all-cause mortality over the course of 3.8 years.[11] In the CVOTs where SGLT2 inhibitors and GLP1 agonists were added to standard care, the mean HbA_{1c} difference was minimal, suggesting that CV benefits might be independent of glucose lowering. Review of the dipeptidyl peptidase 4 inhibitor CVOTs shows a "cardioneutral" class effect without the same CV-benefit evidence as the GLP1 agonist and SGLT2 inhibitor classes.[16-20] There is also a concern signaling increased hospitalization for heart failure with saxagliptin and alogliptin.[17,20] (The full RxFiles CVOTs Chart and the RxFiles Outcomes Comparison Summary Table are available from **CFPlus.***)

Back to our case

You explain to Michael that his metformin dose should be decreased to 500 mg twice daily because of his reduced renal function. You inform him that another medication or increased insulin might be required to reach an HbA_{1c} level of 7% or lower, as this might slow the progression of his microvascular complications. In view of his CAD, your preference is to select one of the 5 antihyperglycemic medications that have demonstrated CV benefit, rather than increasing insulin therapy. Before discussing your recommendation with Michael, you decide to ascertain whether any of these medications have beneficial evidence related to diabetic nephropathy.

Table 1. Metformin dosing adjustment for renal function

RENAL FUNCTION	SUGGESTED MAXIMUM METFORMIN DOSE, mg/d	INTERVAL FOR MONITORING RENAL FUNCTION
eGFR, mL/min		
• ≥ 60	≤ 2550	Every 6-12 mo
• 45-59	≤ 2000	Every 3-6 mo
• 30-44	≤ 1000	Every 3 mo
• < 30	NA*	NA*
Dialysis		
• Peritoneal dialysis	250	NA
• Hemodialysis	500 (after dialysis)	NA

eGFR—estimated glomerular filtration rate, NA—not applicable.
*Diabetes Canada[6] and American Diabetes Association[7] guidelines suggest avoiding metformin if eGFR is < 30 mL/min owing to risk of lactic acidosis. However, given the outcome benefits and the rare risk of lactic acidosis, it is sometimes used cautiously (eg, 500 mg/d) in individuals with stable renal function between eGFR of 15 and 30 mL/min. Consider nephrology consultation.

Bringing evidence to practice

Limited evidence for GLP1 agonists in CKD. Positive exploratory findings of secondary analysis of CVOT data signal a possible nephroprotective class effect.[11-13,21] However, nephroprotection as a primary end point has not been studied for the GLP1 agonist class of medications.

Nephroprotective outcomes of SGLT2 inhibitors. There is stronger evidence of benefit for SGLT2 inhibitor use in CKD. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have the ability to slow the progression of diabetic nephropathy by reducing glomerular hypertension.[22] The SGLT2 inhibitors appear to complement this nephroprotective state by further reducing intraglomerular pressure, a mechanism independent of glucose levels.[23]

The nephroprotective class effect is supported by the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE), as well as by secondary analysis of 3 large SGLT2 inhibitor CVOTs.[8-10,23,24] The CREDENCE trial is the first published trial studying renal benefits of SGLT2 inhibitors as a primary outcome.[23] It produced strong evidence for adults with T2DM and stage 2 or 3 CKD; 100 mg of canagliflozin once daily added to nephroprotective renin-angiotensin-aldosterone system inhibitors reduced the primary composite outcome of end-stage kidney disease over

***The EMPA-REG trial summary, the full RxFiles Cardiovascular Outcome Trials Chart, the RxFiles Outcomes Comparison Summary Table, the CREDENCE trial summary,** and **the RxFiles adapted SADMANS Patient Handout** are available at **www.cfp.ca.** Go to the full text of the article online and click on the **CFPlus** tab.

Table 2. Comparison of noninsulin medications in type 2 diabetes mellitus

MEDICATION	DECLINE IN HbA_{1c}, %	HYPOGLYCEMIA RISK	EFFECT ON WEIGHT	EVIDENCE OF BENEFIT*	
				CV	RENAL
Metformin	1.0-1.5	Minimal†	Neutral or decreased	++	-
Sulfonylureas	1.0-1.5	Moderate‡	Increase of 1.5-2.5 kg	-	-
DPP4 inhibitors	0.5-0.7	Minimal†	Neutral	-	-
SGLT2 inhibitors	0.5-0.8	Minimal†	Decrease of 2.0-3.0 kg	++	++
GLP1 agonists	1.0-1.5	Minimal†	Decrease of 1.5-3.0 kg	++§	+
Thiazolidinediones	1.0	Minimal†	Increase of 2.5-5.0 kg	-	-
Repaglinide	1.0-1.5	Moderate	Increase of 0.7-1.8 kg	-	-
Acarbose	0.5-0.8	Minimal†	Neutral	+	-

CV—cardiovascular, DPP4—dipeptidyl peptidase 4, GLP1—glucagonlike peptide 1, HbA_{1c}—hemoglobin A_{1c}, SGLT2—sodium-glucose cotransporter-2.
*Based on available randomized controlled trial evidence; the quality and degree of evidence and type of benefit vary for each agent within a class; refer to **Table 3** for more detail.[8-13] For evidence of benefit, + represents some evidence from randomized controlled trials but not as a primary outcome or in a specific type 2 diabetes population; ++ represents evidence from randomized controlled trials as a primary outcome in type 2 diabetes or a consistent class effect in meta-analysis; - represents a lack of evidence of benefit or neutral outcomes.
†Negligible as monotherapy.
‡Gliclazide has the least chance of causing hypoglycemia compared with glyburide and glimepiride. Gliclazide is therefore preferred in older adults according to the Beers criteria.[14]
§CV benefit demonstrated only for liraglutide, semaglutide, and dulaglutide.

2.6 years.[23] These findings were realized despite modest reductions in HbA_{1c}, weight, and BP. (The CREDENCE trial summary is available from **CFPlus**.*) Other renal outcome trials with empagliflozin and dapagliflozin are ongoing; the results will provide more definitive evidence regarding an SGLT2 inhibitor renal class effect.

Back to our case

You discuss the potential benefits of adding 10 mg of empagliflozin once daily to Michael's regimen. This includes evidence for reducing CV complications and mortality, a hypothesized nephroprotective effect, BP-lowering potential, and weight reduction. It might also aid in decreasing his blood glucose levels, although this benefit might be minimal because of his reduced renal function. Additionally, some Canadian provincial plans provide coverage for adults with T2DM and established CVD, and a combination pill of

Table 3. Summary of cardiovascular outcome trials of SGLT2 inhibitors and GLP1 agonists that demonstrated beneficial clinical outcomes

STUDY, DATE • DURATION • NO. OF PARTICIPANTS	POPULATION BASELINE	GLYCEMIC INTERVENTION	FINAL HbA_{1c} DIFFERENCE	PRIMARY OUTCOME: 3-POINT MACE*	SECONDARY OUTCOME: ALL-CAUSE MORTALITY
SGLT2 inhibitors					
Zinman et al, 2015[8] • About 3.1 y • N = 7020	Established CVD (100%) • Mean 10-y history of T2DM • Mean HbA_{1c} = 8.0% • Mean eGFR = 74 mL/min • eGFR < 60 mL/min (26%)	Oral empagliflozin 10 mg or 25 mg once daily vs placebo	Mean decrease of 0.24% vs placebo	Superiority: • HR = 0.86 (95% CI 0.74-0.99) • NNT = 63 over 3.1 y	Superiority: • HR = 0.68 (95% CI 0.57-0.82) • NNT = 39 over 3.1 y
Neal et al, 2017[9] • About 3.6 y • N = 10 142	Established CVD (66%) Risk factors for CVD (34%)† • Mean 13.5-y history of T2DM • Mean HbA_{1c} = 8.2% • Mean eGFR = 77 mL/min • eGFR < 60 mL/min (20%)	Oral canagliflozin 100 mg or 300 mg once daily vs placebo	Mean decrease of 0.58% vs placebo	Superiority: • HR = 0.86 (95% CI 0.75-0.97) • NNT = about 220/y	Non-significant: • HR = 0.87 (95% CI 0.74-1.01)
Wiviott et al, 2019[10] • About 4.2 y • N = 17 160	Established CVD (41%) Risk factors for CVD (59%)† • Mean 11-y history of T2DM • Mean HbA_{1c} = 8.3% • Mean eGFR = 85 mL/min • eGFR < 60 mL/min (7%)	Oral dapagliflozin 10 mg once daily vs placebo	Mean decrease of 0.42% vs placebo	Noninferior to placebo: • HR = 0.93 (95% CI 0.84-1.03)	Non-significant: • HR = 0.93 (95% CI 0.82-1.04)
GLP1 agonists					
Marso et al, 2016[11] • About 3.8 y • N = 9340	Established CVD or CKD (81%)‡ Risk factors for CVD (19%)† • Mean 13-y history of T2DM • Mean HbA_{1c} = 8.7% • eGFR < 60 mL/min (23%)	SC liraglutide 1.8 mg once daily vs placebo	Mean decrease of 0.40% vs placebo	Superiority: • HR = 0.87 (95% CI 0.78-0.97) • NNT = 53 over 3.8 y	Superiority: • HR = 0.85 (95% CI 0.74-0.97) • NNT = 72 over 3.8 y
Marso et al, 2016[12] • About 2.1 y • N = 3297	Established CVD or CKD (83%)‡ Risk factors for CVD (17%)† • Mean 14-y history of T2DM • Mean HbA_{1c} = 8.7% • eGFR < 60 mL/min (29%)	SC semaglutide 0.5 mg or 1.0 mg once weekly vs placebo	Mean HbA_{1c} of 7.6% (0.5 mg) and 7.3% (1 mg) vs 8.3% (placebo)	Superiority: • HR = 0.74 (95% CI 0.58-0.95) • NNT = 44 over 2.1 y	Non-significant: • HR = 1.05 (95% CI 0.74-1.50)
Gerstein et al, 2019[13] • About 5.4 y • N = 9901	Established CVD (32%) Risk factors for CVD (68%)† • Mean 10-y history of T2DM • Mean HbA_1 = 7.2% • Mean eGFR = 75 mL/min • eGFR < 60 mL/min (22%)	SC dulaglutide 1.5 mg once weekly vs placebo	Mean decrease of 0.60% vs placebo	Superiority: • HR = 0.88 (95% CI 0.79-0.99) • NNT = 72 over 5.4 y	Non-significant: • HR = 0.90 (95% CI 0.80-1.01)

CKD—chronic kidney disease, CVD—cardiovascular disease, eGFR—estimated glomerular filtration rate, GLP1—glucagonlike peptide 1, HbA_{1c}—hemoglobin A_{1c}, HR—hazard ratio, MACE—major adverse cardiovascular events, MI—myocardial infarction, NNT—number needed to treat, SC—subcutaneous, SGLT2—sodium-glucose cotransporter-2, T2DM—type 2 diabetes mellitus.
*Composite of cardiovascular death, nonfatal MI, or nonfatal stroke.
†Risk factors for CVD inclusion criteria were specific to each study.
‡Inclusion criteria for the study were both established CVD or CKD of stage 3 or greater in the baseline population.

empagliflozin and metformin is available to lessen his pill burden once he is stabilized on this regimen.

Monitoring parameters when initiating an SGLT2 inhibitor

When initiating SGLT2 inhibitor therapy, it is common for patients to experience increased urinary volume and frequency owing to the medication's mode of action. Glycosuria with associated increased urinary excretion of water might cause intravascular volume depletion and hypotension if an individual has inadequate fluid intake. Further, SGLT2 inhibitors cause an early reduction in eGFR—on average about 5 mL/min but it might reduce further. This initial reduction in kidney function generally stabilizes within 1 to 3 months.[25] **Box 1** outlines parameters for BP and renal monitoring as well as important patient education related to SGLT2 inhibitor use.[6,7]

Back to our case

You inform Michael that with the addition of empagliflozin he should expect to urinate more frequently and suggest he take this medication in the morning to minimize nocturia. You emphasize the importance of adequate hydration with water and monitoring for symptoms of hypotension. You also recommend daily home BP monitoring.

Follow-up with Michael after 1 month of empagliflozin

The addition of empagliflozin to metformin, gliclazide, and insulin glargine appears to be lowering his blood glucose level with no symptoms of hypoglycemia. Polyuria has become less prominent in the past week as glucose levels have improved. His only concern is increasing symptoms of postural hypotension, with home BP readings between 100/79 mm Hg and 90/64 mm Hg in the past week. Results of renal and electrolyte blood tests performed 2 weeks after starting empagliflozin are acceptable, with the serum creatinine level increased to 183 µmol/L from 168 µmol/L at baseline, and eGFR decreased to 39 mL/min from 41 mL/min. Findings of the clinical examination at this visit include a heart rate of 78 beats/min and BP of 115/70 mm Hg with postural drop to 96/60 mm Hg.

Box 1. A few practical tips for patient education and monitoring of blood pressure and renal function after SGLT2 inhibitor initiation

BP:
- Educate on the importance of adequate hydration and when to hold medication (see **Box 2** for "sick day" management[6])
- Counsel patient on the risk of postural hypotension and how to recognize this
- Suggest home BP monitoring
- Expect a mean reduction in BP of about 5/2 mm Hg
- Consider discontinuing or lowering the dose of diuretics or other antihypertensives if BP is low at initiation of SGLT2 inhibitor, or if patient develops hypotension

Renal function:
- Perform renal function and electrolyte blood tests at baseline and within 2-4 wk of initiation, watching for increased SCr and hyperkalemia
- Reassess patients with >30% increase in SCr levels over baseline. Some increase in SCr is expected, but an increase of >30% warrants reassessment and possible discontinuation of SGLT2 inhibitor or diuretics
- Expect an early mean reduction in eGFR of about 5 mL/min, which generally stabilizes within 1-3 mo
- Continue monitoring as indicated based on initial effect on SCr levels, severity of pre-existing diabetic kidney disease, and presence of other medications that affect kidney function
- Be vigilant when combining renal-affecting medications that increase the risk of acute kidney injury (eg, diuretics, NSAIDs, SGLT2 inhibitors, ACEIs, ARBs)

ACEI—angiotensin-converting enzyme inhibitor, ARB—angiotensin receptor blocker, BP—blood pressure, eGFR—estimated glomerular filtration rate, NSAID—nonsteroidal anti-inflammatory drug, SCr—serum creatinine, SGLT2—sodium-glucose cotransporter-2.

Back to our case

Because of the excessive drop in BP, amlodipine is decreased to 5 mg once daily. You recommend ongoing home BP monitoring, with clinical follow-up in 2 weeks. Measurement of his renal and electrolyte levels will be repeated in 2 weeks to ensure that serum creatinine does not increase more than 30% from baseline, which is indicative of acute kidney injury and warrants discontinuation of the SGLT2 inhibitor.

Although Michael has not experienced any symptoms of hypoglycemia, you remind him how to recognize and treat them. He is at increased risk of hypoglycemia because of the cumulative effect of taking basal insulin and a high-dose sulfonylurea, and having stage 3 CKD. If his renal function continues to decline, or if he experiences hypoglycemia, the initial step would be to discontinue or reduce the dose of gliclazide. In the next few months, insulin therapy should be reviewed based on HbA_{1c} levels, as well as fasting, preprandial, and postprandial blood glucose levels.

Further management and counseling for patients taking SGLT2 inhibitors

Given the potential BP-lowering effects of SGLT2 inhibitors, it is important to continue monitoring BP and to reduce antihypertensive therapy as indicated. This is particularly important in older adults who are taking diuretics and have an increased risk of falls and fractures. Additional patient counseling is also required for recognition and management of other potential adverse events associated with this class of medication, including genital fungal skin infections and diabetic ketoacidosis.

Several medications used in adults with diabetes might cause or contribute to acute kidney injury.[26,27] It is recommended that health care providers discuss the "sick day" management of medications (the SADMANS acronym) listed in **Box 2**.[6] These medications should be temporarily held during acute illness, when a patient has reduced fluid intake or is dehydrated, or when he or she has an acute decline in renal function.[3] This will prevent

Box 2. "Sick day" management using SADMANS

Sulfonylureas, other secretagogues
Angiotensin-converting enzyme inhibitors
Diuretics, direct renin inhibitors
Metformin
Angiotensin receptor blockers
Nonsteroidal anti-inflammatory drugs
Sodium-glucose cotransporter-2 inhibitors

Acronym from Diabetes Canada.[6]

the accumulation of metformin and secretagogues, as well as decrease the risk of acute kidney injury associated with the remaining medications on the SADMANS list. A patient information tool can assist caregivers in educating patients on this important topic. (The RxFiles adapted SADMANS Patient Handout is available from **CFPlus.***)

Conclusion

There are many pharmacotherapeutic options available for achieving glycemic control in adults living with T2DM, with some options providing additional benefits such as CV and renal protection. Considering the clinical benefits, harms, and practical issues associated with each agent might help guide and individualize therapy decisions for optimizing patient care.

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