Review of the top nephrology studies of 2020-2023

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Introduction

Chronic kidney disease (CKD) affects approximately 4 million Canadians.[1] It is predicted to be the fifth global cause of death by 2040.[2] In Canadian primary care practices, the prevalence of CKD is 72 per 1000 individuals.[3] Since 2020, important practice changes have been made in medication management for individuals with CKD.[4-7] Given the widespread presence of CKD, pharmacists should stay up to date with the nephrology literature. This paper aims to provide summaries of the top nephrology trials from 2020 to 2023 deemed to be of greatest importance for pharmacists caring for those with CKD, identified by Canadian pharmacists working in nephology or its related specialty areas.

Methods

Two investigators (J.W., J.P.) conducted a literature search in August 2023 to identify relevant nephrology studies published between December 2020 and July 2023. Five investigators reached consensus for the top 14 studies considered to have the highest potential practice implications for pharmacists in this population.[8-21] Studies with the same medication of interest or outcomes were grouped together. An online survey was developed through Surveys Nova Scotia and included the name, study description and uniform resource locator (Appendix 1, available in the Supplementary Materials). The survey link was disseminated to pharmacists with specialized knowledge in nephrology in all provinces through the Renal Pharmacist Network, provincial renal programs posts and emails. These pharmacists were asked to rank the selected studies or study groupings based on relevance (from 1 [most relevant] to 8 [least relevant]) for pharmacists practising in all settings. The survey remained open from August 8 to 31, 2023. The top 5 studies or groupings were summarized.

Results

Seventy-two nephrology pharmacists completed the online survey, with responses from all provinces. Seventy-three percent of responders had >10 years of nephrology experience. Voting frequency for candidate studies are included in Appendix 1. The 5 top-ranked studies (n = 3) or groupings (n = 2) included sodium-glucose cotransporter-2 inhibitors (SGLT2i) in CKD patients with or without type 2 diabetes (T2DM), finerenone in those with CKD and T2DM, renin angiotensin system inhibitor (RASI) with angiotensin-converting enzyme inhibitors (ACEi) in advanced CKD, anticoagulation with apixaban for atrial fibrillation (AF) in hemodialysis (HD) and sick day medication management recommendations for people with diabetes, CKD and cardiovascular (CV) disease.[8-16] A summary of indications for patients with chronic kidney disease are outlined in Table 1.

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SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS IN CKD WITH OR WITHOUT T2DM

Dapagliflozin in patients with chronic kidney disease (N Engl J Med 2020)[8]

Background: DAPA-CKD was a multicentre randomized controlled trial (RCT) that compared dapagliflozin to placebo in patients with CKD and albuminuria, with or without T2DM.

Patients: Eligible patients had CKD, estimated glomerular filtration rate (eGFR) ≥25 to ≤75 mL/min/1.73 m^2 and urine albumin-to-creatinine ratio (UACR) ≥22.6 to <565 mg/mmol. Both groups received ACEi or angiotensin receptor blocker (ARB) at maximum tolerated dose. Exclusion criteria included type 1 diabetes, polycystic kidney disease, lupus nephritis, antineutrophil cytoplasmic antibody vasculitis and immunosuppressant treatment for kidney disease within 6 months before enrollment.

Intervention and control: Patients were randomized to dapagliflozin 10 mg daily or placebo.

Outcomes: The primary outcome was a composite of a ≥50% sustained decline in eGFR, onset of kidney failure or death from CV or kidney causes. Secondary outcomes included death from any cause.

Results: The study included 4304 patients (mean age 62 years, 67% male, 68% T2DM). The trial was stopped early, with a median follow-up of 2.4 years. Ninety-eight percent of patients received an ACEi or ARB. Dapagliflozin significantly reduced the primary outcome (9.2% vs 14.5%; hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.51-0.72; $p < 0.001$; number needed to treat [NNT] 19), which was primarily driven by preservation of eGFR. Death from any cause demonstrated a 31% relative risk reduction (HR, 0.69; CI, 0.52-0.88; $p = 0.004$; NNT 48).

Empagliflozin in patients with chronic kidney disease (N Engl J Med 2023)[9]

Background: EMPA-KIDNEY was a multicentre RCT that evaluated empagliflozin versus placebo in individuals with CKD with and without albuminuria or T2DM.

Patients: Eligible patients had CKD and eGFR of 20 to 44 mL/min/1.73 m^2 *or* eGFR 45 to 89 mL/min/1.73 m^2 with UACR ≥22.6 mg/mmol and were prescribed a clinically appropriate dose of ACEi or ARB. Exclusion criteria were consistent with the DAPA-CKD trial.

Intervention and control: Patients were randomized to empagliflozin 10 mg daily or placebo.

Outcomes: The primary outcome was a composite outcome of kidney disease progression or CV death. The key secondary outcomes were hospitalization for heart failure or CV death, all-cause hospitalizations and death from any cause.

Results: The study included 6609 patients (mean age 64 years, 77% male, 46% T2DM). The trial was stopped early with a median follow-up of 2 years. Eighty-five percent received an ACEi or ARB. Empagliflozin significantly reduced the primary outcome (13.1% vs 16.9%; HR, 0.72; 95% CI, 0.64-0.82; $p <$ 0.001; NNT 26). Fewer all-cause hospitalizations occurred in the empagliflozin group, but no significant effect on hospitalization was found for heart failure or CV death or death from any cause.

Implications for practice for SGLT2i: In individuals with T2DM and CKD with eGFR >20 mL/min/1.73 m^2, treatment with an SGLT2i can be initiated as part of the standard of care along with an ACEi or ARB and blood pressure (BP) and glycemic control. Although the use of SGLT2i was recommended, it is noteworthy that there is moderate evidence for SGLT2i in adults without diabetes with eGFR ≥20 to 44 mL/min/1.73 m^2 and UACR <22.6 mg/mmol.[7] An initial eGFR dip is expected with SGLT2i. If >30% eGFR decrease occurs, a review of other prerenal causes is needed (e.g., illness, diuretics).[4] If tolerated, SGLT2i should be continued until dialysis or kidney transplant. Routine monitoring of eGFR or electrolytes is recommended in the presence of volume status concerns. No increased risk of hypoglycemia or urinary tract infection was observed. The study found an increased risk of mild mycotic genital infections in men and women, which can be treated with topical agents.[7]

FINERENONE IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND TYPE 2 DIABETES

Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes (N Engl J Med 2020)[10]

Background: FIDELIO-DKD was a multicentre, double-blind RCT that compared finerenone to placebo in those with CKD and T2DM.

Patients: Eligible patients had CKD, eGFR 25 to <60 mL/min/1.73 m^2 and UACR 3.4 to <33.9 mg/mmol and diabetic retinopathy *or* eGFR 25 to <75 mL/min/1.73 m^2 and UACR 33.9 to 565 mg/mmol. Patients were receiving maximally tolerated RASI, and serum potassium was ≤4.8 mmol/L.

Intervention and control: Patients were randomized to finerenone 10 mg or 20 mg daily or placebo. Initial dose of finerenone was 10 mg for eGFR 25 to <60 mL/min/1.73 m^2 and 20 mg for eGFR ≥60 mL/min/1.73 m^2. Doses were increased from 10 to 20 mg after 1 month and if potassium was ≤4.8 mmol/L.

Outcomes: The primary outcome was a composite of time to kidney failure, a sustained decrease from baseline of ≥40% in eGFR from baseline or death from kidney causes. The secondary outcome was a composite of time to death from CV causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure.

Results: The study included 5734 patients (mean age 65 years, 70% male, 4.6% receiving SGLT2i). Finerenone reduced the risk of the primary composite kidney outcome (HR, 0.82; 95% CI, 0.73-0.93; p = 0.001; NNT 29) and the secondary composite CV outcome (HR, 0.86; 95% CI, 0.75-0.99; p = 0.026; NNT 55) compared with placebo during a median follow-up of 2.6 years. Hyperkalemia adverse events were twice as frequent with finerenone compared with placebo (18.3% and 9%, respectively).

Cardiovascular events with finerenone in kidney disease and type 2 diabetes (N Engl J Med *2021*)[11]

Background: FIGARO-DKD was the same study design as FIDELIO-DKD.

Patients: Eligible patients had CKD, eGFR 25 to 90 mL/min/1.73 m^2 and UACR 3.4 to <33.9 mg/mmol *or* eGFR ≥60 and UACR 33.9 to 565 mg/mmol. Patients were receiving maximally tolerated RASI and serum potassium was ≤4.8 mmol/L.

Intervention and control: Patients were randomized to finerenone 10 mg or 20 mg daily or placebo. The initial finerenone dose and dose titration were the same as in FIDELIO-DKD.

Outcomes: The primary and secondary outcomes were the secondary and primary outcomes in FIDELIO-DKD.

Results: The study included 7437 patients (mean age 64 years, 69% male, 8.4% receiving SGLT2i). Finerenone reduced the risk of the primary composite CV outcome by 13% (HR, 0.87; 95% CI, 0.76-0.98; p = 0.03; NNT 47) compared with placebo, which was driven by a lower rate of hospitalization for heart failure during a median follow-up of 3.4 years. Finerenone reduced the risk of secondary kidney outcomes by 13% (HR, 0.87; 95% CI, 0.76-1.01; p = 0.069) but was not statistically significant.

Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis (Eur Heart J *2022*)[12]

Background: FIDELITY was a prespecified pooled efficacy and safety analysis of FIDELIO-DKD and FIGARO-DKD.

Patients: As per FIDELIO-DKD and FIGARO-DKD.

Intervention and control: As per FIDELIO-DKD and FIGARO-DKD.

Outcomes: The primary outcome was a CV composite of time to death from CV causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure and a composite of time to kidney failure, a sustained ≥57% decrease in eGFR from baseline over ≥4 weeks or death from kidney causes.

Results: The study included 13,025 patients (mean age 65 years, 70% male, 6.7% receiving SGLT2i). Finerenone reduced the risk of both the primary composite CV outcome (HR, 0.86; 95% CI, 0.78-0.95; p = 0.0018; NNT 46) and the composite kidney outcome (HR, 0.77; 95% CI, 0.67-0.88; p = 0.0002; NNT 60) compared with placebo, with a median follow-up of 3 years. The safety profile of finerenone compared with placebo was similar among studies. Hyperkalemia with finerenone was the most common adverse event, which led to permanent treatment discontinuation compared with placebo (FIDELIO-DKD 2.3% vs 0.9%; FIGARO-DKD 1.2% vs 0.4%; FIDELITY 1.7% vs 0.6%, respectively).

Implications for practice: Finerenone reduced the risk of CV and kidney events in patients with T2DM and CKD across a broad range of albuminuria and kidney stages. Finerenone should be considered to further reduce the risk of CV and CKD progression in those with T2DM and CKD with an eGFR ≥25 mL/min/1.73 m^2, normal potassium and UACR ≥3 mg/mmol, despite taking maximum tolerated doses of ACEi or ARB with or without SGLT2i. When initiating finerenone, providers should check serum potassium in 2 to 4 weeks and regularly thereafter. Its use requires careful monitoring of serum potassium and eGFR, and dose adjustment or discontinuation may be necessary in some patients.

RENIN-ANGIOTENSIN SYSTEM INHIBITION IN ADVANCED CKD

Renin-angiotensin system inhibition in advanced CKD: STOP-ACEi (N Engl J Med *2022*)[13]

Background: STOP-ACEi was a multicentre, randomized open-label trial that assessed whether discontinuation of RASI would increase or stabilize the eGFR over a 3-year follow-up period.

Patients: Adults with CKD stage 4 and 5 (eGFR ≤30 mL/min/1.73 m^2) were eligible if they were not receiving dialysis, had not undergone kidney transplant, had a decrease in eGFR of >2 mL/min/1.73 m^2 per year in the previous 2 years and were receiving RASI for >6 months. Those with uncontrolled hypertension (e.g., BP >160/90 mmHg), a history of myocardial infarction or stroke within the last 3 months were excluded.

Intervention and control: Patients were randomized to discontinue or continue RASI. In the group that discontinued RASI, guideline-recommended antihypertensives could be used to control BP.

Outcomes: Primary outcome was eGFR at 3 years. Main secondary outcomes were development of end-stage kidney disease (ESKD) or initiation of renal replacement therapy (RRT); a composite of a decrease of >50% in eGFR, development of ESKD or initiation of RRT; and hospitalization for any cause, CV events and death.

Results: At 3 years, 411 patients (median age 63 years, 68% male, 15% non-white, baseline eGFR 18 mL/min/1.73 m^2, urine protein-creatinine ratio 115 mg/mmol, potassium 5 mmol/L, diabetes 37% and ≥3 antihypertensives 58%) were enrolled. There was no difference in the primary outcome. The least-square mean eGFR was 12.6 ± 0.7 mL/min/1.73 m^2 in the discontinuation group and 13.4 ± 0.6 mL/min/1.73 m^2 in the continuation group (difference, −0.7; 95% CI, −2.5 to 1.0; p = 0.42). No heterogeneity in specified subgroups was observed. The secondary outcome of ESKD or initiation of RRT occurred in 63% and 56% of patients in the discontinuation and continuation groups, respectively (adjusted HR, 1.28; 95% CI, 0.99-1.65). The secondary composite outcome occurred in 140 (68%) patients in the discontinuation group and 127 (62%) patients in the continuation group (adjusted RR, 1.07; 95% CI, 0.94-1.22). Numbers of hospitalizations for any cause (414 vs 413), CV events (108 vs 88) or death (20 vs 22) were similar in the discontinuation and continuation groups, respectively.

Implications for practice: The STOP-ACEi study provides evidence that discontinuation of RASI in patients with advanced CKD does not lead to meaningful improvements in eGFR. The study population included few non-white patients, diabetic patients or those with heart failure, and it was unclear whether patients were concurrently receiving potassium binders, as hyperkalemia was reported in 4 and 2 patients in the discontinuation and continuation arms, respectively. Importantly, very few were receiving SGLT2i, which is now CKD standard of care. STOP-ACEi was not powered to examine the effect on CV events or mortality. The decision to continue or discontinue should be individualized based on level of proteinuria, BP, tolerability, serum potassium and cardiovascular risk.

ANTICOAGULATION WITH APIXABAN FOR ATRIAL FIBRILLATION IN HEMODIALYSIS

***Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial* (Circulation 2022)**[14]

Background: RENAL-AF was a prospective, randomized open-label, blinded outcome evaluation (PROBE) of apixaban versus warfarin in HD patients with AF.

Patients: Eligibility included those with paroxysmal, persistent or permanent AF documented by electrocardiogram (ECG), as well as a CHA_2DS_2-VASc score ≥2 and treatment with HD ≥3 months. Key exclusion criteria were moderate to severe mitral stenosis, ongoing need for aspirin >100 mg daily, aspirin with $P2Y_{12}$ antagonist therapy, or anticoagulation for any reason other than AF.

Intervention and control: Patients were randomized to apixaban 5 mg twice daily (2.5 mg twice daily for age ≥80 years or weight ≤60 kg) or dose-adjusted warfarin (international normalized ratio [INR], 2.0-3.0).

Outcomes: The primary safety outcome was major and clinically relevant nonmajor bleeding (CRNB) on the basis of the International Society of Thrombosis and Haemostasis definitions. Secondary outcomes included stroke and mortality.

Results: The study included 154 patients (median age 68 years, 64% male, CHA_2DS_2-VASc score 4, time in therapeutic range [TTR] 44% for warfarin group). The primary safety outcome at 1 year occurred in 32% and 26% of patients in the apixaban and warfarin groups, respectively (HR, 1.20; 95% CI, 0.63-2.30). HD access site bleeding accounted for the majority of CRNB. There were 9 (11%) and 7 (10%) major bleeding events in the apixaban and warfarin groups, respectively. The 1-year rates for stroke and systemic embolism were 3% (apixaban) and 3.3% (warfarin). Mortality was underpowered but occurred in 26% (21/82) in the apixaban arm and 18% (13/72) in the warfarin arm.

***A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis* (Circulation 2023)**[15]

Background: AXADIA-AFNET 8 was a PROBE of apixaban versus the vitamin K antagonist (VKA) phenprocoumon in HD patients with AF.

Patients: Eligibility included AF documented on ≥2 ECGs on different days, an increased risk of stroke risk estimated by CHA_2DS_2-VASc score ≥2 and treatment with HD >3 months. Key exclusion criteria included stroke within 3 months of enrollment, moderate or severe aortic or mitral stenosis, conditions other than AF requiring anticoagulation, planned AF or flutter ablation or need for chronic aspirin therapy.

Intervention and control: Patients were randomized to apixaban 2.5 mg twice daily or dose-adjusted phenprocoumon (INR, 2.0-3.0).

TABLE 1 Key study messages with chronic kidney disease management

CKD with or without T2DM (N Engl J Med 2020, 2023)[8,9]
SGLT2i if eGFR >20 mL/min/1.73 m^2. Once initiated, continue until dialysis or kidney transplantation.
CKD with T2DM (N Engl J Med 2020, 2021, 2022)[10,11,12]
Finerenone if eGFR ≥25 mL/min/1.73 m^2, normal potassium and UACR ≥3 mg/mmol, despite taking maximally tolerated ACEi or ARB with or without SGLT2i.
ACEi in CKD with eGFR <30 mL/min/1.73 m^2 (N Engl J Med 2022)[13]
Continuation or discontinuation of ACEi should be individualized based on level of proteinuria, BP, tolerability, serum potassium and cardiovascular risk.
Anticoagulation in HD with AF (Circulation 2022, 2023)[14,15]
Apixaban considered an alternative to warfarin particularly when contraindications are present (e.g., history of calciphylaxis, labile INR values). Apixaban 2.5 mg twice-daily dosing strategy in those ≥80 years and ≤60 kg. Ideal dosing strategy requires further investigation. Consider interacting drugs that can potentiate the effect of apixaban.
Sick day medication guidance for people with diabetes, kidney or cardiovascular disease (Am J Kid Dis 2023)[16]
Triggers for SDMG include volume depletion (vomiting or diarrhea, anorexia or nausea, new lightheadedness or weakness, lower weight or urine output, increased thirst). Hold medications that increase risk for acute kidney injury (SGLT2i, ACEi or ARB, etc.) until patient returns to normal eating or drinking.

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis; INR, international normalized ratio; SDMG, sick day medication guidance; SGLT2i, sodium-glucose cotransporter-2 inhibitors; T2DM, type 2 diabetes mellitus; UACR, urine albumin-to-creatinine ratio.

Outcomes: The primary safety composite outcome was time of first event of major bleeding, CRNB or all-cause death. The primary efficacy composite outcome included ischemic stroke, all-cause death and myocardial infarction.

Results: The study included 97 patients (mean age 75 years, CHA_2DS_2-VASc score 4.5, TTR 50.7% for phenprocoumon group). The primary safety outcome occurred in 45.8% of patients receiving apixaban and 51% of patients receiving VKA, with a median follow-up of 429 and 506 days, respectively (HR, 0.93; 95% CI, 0.53-1.65). There were 5 and 6 major bleeding events with apixaban (10.4%) vs VKA (12.2%), respectively ($p = 1.0$). The primary efficacy outcome occurred in 20.8% (apixaban) and 30.6% (VKA) ($p = 0.51$) of patients.

Implications for practice: Bleeding rates were high, but no significant difference was observed between groups. There was a trend toward fewer safety events in the apixaban group in the AXATIA-AFNET 8 trial, which could be attributed to the lower apixaban dose of 2.5 mg twice daily. There was no significant difference in efficacy outcomes between groups. These trials were underpowered due to recruitment difficulties and limited follow-up duration. Apixaban may be considered an alternative to VKA for AF in HD, particularly when contraindications to VKA exist (e.g., history of calciphylaxis, labile INR values). Apixaban 2.5 mg twice-daily dosing strategy should be used in those age ≥80 years and weight ≤60 kg; however, the ideal dosing strategy for patients who do not meet these criteria requires further investigation with larger trials. Screening of medications known to interact with apixaban (e.g., inhibitors or inducers of both cytochrome P450 3A4 and P-glycoprotein) and signs of bleeding should be monitored at each HD session.

SICK DAY MEDICATION MANAGEMENT RECOMMENDATIONS FOR PEOPLE WITH DIABETES, KIDNEY OR CARDIOVASCULAR DISEASE

Consensus recommendations for sick day medication guidance for people with diabetes, kidney or cardiovascular disease: a modified Delphi process (Am J Kid Dis *2023*)[16]

Background: Sick day medication guidance (SDMG) consists of adjusting or withholding medications, during times of acute illness, that may lead to hypotension, acute kidney injury or hypoglycemia. Experts in diabetes, CKD and CVD sought to generate consensus recommendations for SDMG.

Setting and participants: International clinician experts were identified to conduct a modified Delphi process. The items for the modified Delphi process were informed by a scoping review of the SDMG literature, a qualitative needs assessment with primary care physicians, pharmacists and patients with chronic conditions of interest.

Intervention and control: Three rounds of the Delphi process were conducted virtually with stakeholders.

Outcomes: Participant opinions were measured as the percentage of agreement on recommendations for SDMG, and the threshold for consensus was defined as >75% agreement.

Results: Twenty-six clinicians from 10 health backgrounds participated from 4 countries, including Canada. Consensus was reached for 42 (91%) recommendations. These included 5 recommendations for signs and symptoms of volume depletion from acute illness that should trigger SDMG, 6 recommendations pertaining to signs and symptoms considered severe enough to prompt contact with a health care practitioner, 14 recommendations related to scenarios and strategies for patient self-management (including symptom triage and patient instructions to avoid or reverse sick day symptoms) and 16 recommendations for medication guidance on withdrawal, adjustment or resumption.

Implications for practice: SDMG consensus recommendations serve as a guide for clinicians. Volume depletion signs considered triggers to initiate SDMG include vomiting or diarrhea, anorexia or nausea, new lightheadedness or weakness, lower weight or urine output and increased thirst. Severe signs considered triggers to contact a health care practitioner include severe vomiting (>4 times in 12 hours), reduced level of consciousness or confusion, low BP (systolic BP <80 mmHg; decrease of 20 mmHg in systolic BP or 10 mmHg in diastolic BP), and presence of ketones, tachycardia and fever. RASI, diuretics, nonsteroidal inflammatory drugs, SGLT2i and metformin can be temporarily withheld, whereas insulin, sulfonylurea and/or meglitinides should be held only if blood glucose is low. Basal and bolus insulin should be increased by 10% to 20% if blood glucose is elevated. Resumption of medications within 24 to 48 hours is guided by resolution of symptoms and return to normal eating and drinking. ■

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