Review of the top 5 cardiology studies of 2021-22

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Introduction

It remains challenging for pharmacists who practise in community-based or primary care settings to stay up to date with the annual torrent of medical literature, particularly in the discipline of cardiology. Here we present a brief synopsis of the "top 5" cardiology-related studies that were published in 2021-22, as identified by pharmacists who provide care to patients in community-based, primary care practices.

Methods

The methodology used was similar to previous iterations of this review.[1-5] A total of 15 cardiology-related studies potentially relevant to community-based pharmacists were identified by 2 authors (A.R.B. and R.B.). An online survey was created that included the name, citation and conclusion for each study using the University of British Columbia survey tool (Qualtrics). Respondents were invited to select up to 5 studies that they believed were most relevant to pharmacists practising in general or primary care settings. The survey link was posted on the Primary Care Pharmacy Specialty Network of the Canadian Pharmacists Association/Canadian Society of Hospital Pharmacists, which is a volunteer forum of pharmacists (currently 155) with an interest in primary care practice. The survey link was also posted on the Twitter account of the lead author (@ArdenBarry; 1982 followers). The survey was open for 4 weeks (December 5, 2022 to January 3, 2023), with 1 reminder posted on the Pharmacy Specialty Network and 3 reminders posted on Twitter.

Results

A total of 22 survey respondents provided 47 votes. The voting frequency is included in Appendix 1. Of the top 5 studies, 2 involved the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with heart failure with preserved ejection fraction (HFpEF),[6,7] 2 involved the treatment of hypertension[8,9] and the final study used a novel blinded crossover design to investigate symptomatology while taking a statin, placebo or no treatment in a cohort of patients with previous statin intolerance.[10] A summary of the numbers needed to treat for cardiovascular outcomes and all-cause death are included in Table 1.

HEART FAILURE

SGLT2 inhibitors, specifically dapagliflozin and empagliflozin, have been shown to reduce heart failure hospitalizations and cardiovascular death in patients with heart failure with reduced ejection fraction regardless of whether or not they had diabetes mellitus.[11,12] Recent randomized controlled trials (RCTs) have evaluated the use of these SGLT2 inhibitors in patients with heart failure with preserved or mildly reduced ejection fraction.

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TABLE 1 Number needed to treat for the top 5 cardiology studies of 2021-22*

Study	Intervention and control	Duration (y)	NNT	
			Primary cardiovascular composite endpoint†	All-cause death
EMPEROR-Preserved[6]	Empagliflozin 10 mg daily vs placebo in patients with HFpEF with or without DM	2.2	31	NS
DELIVER[7]	Dapagliflozin 10 mg daily vs placebo in patients with HFpEF with or without DM	2.3	33	NS
TIME[8]	Morning vs evening dosing of antihypertensive medications in adult patients with hypertension	5.2	NS	NS
STEP[9]	Systolic BP target <130 mmHg vs <150 mmHg in patients aged 60-80 years with hypertension	3.3	91	NS

BP, blood pressure; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; NNT, number needed to treat; NS, not significant.
*The SAMSON study was excluded from this table, as it did not include these outcomes.
†Refer to text for specific definition.

*EMPEROR-Preserved: Empagliflozin in heart failure with a preserved ejection fraction (*N Engl J Med *2021)*

Background: This multicentre, double-blind RCT compared empagliflozin to placebo in patients with HFpEF with or without diabetes.[6]

Patients: Eligible patients were ≥18 years of age with HFpEF, defined as a left ventricular ejection fraction (LVEF) of >40%, New York Heart Association (NYHA) class II-IV symptoms and an elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) of >300 pg/mL. Patients were excluded if they had a "disorder that would change their clinical course" independent of heart failure, such as a myocardial infarction (MI) or stroke within 90 days, decompensated heart failure, an estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2, symptomatic hypotension or a systolic blood pressure (SBP) <100 mmHg.

Intervention and control: Patients were randomized to empagliflozin 10 mg daily or placebo, in addition to usual therapy.

Outcomes: The primary outcome was a composite of cardiovascular death or hospitalization for heart failure. Secondary outcomes included change in eGFR and death from any cause.

Results: In total, 5988 patients (mean age 72 years, 55% male, 76% white, 49% diabetes) were included. The mean LVEF was 54%, and the mean eGFR was 61 mL/min/1.73 m^2. Median follow-up was 26 months. Empagliflozin significantly reduced the primary outcome (13.8% vs 17.1%; hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.69-0.90; number needed to treat [NNT] 31) compared with placebo, which was primarily driven by a reduction in hospitalization for heart failure (NNT 32). Patients in the empagliflozin group also had a lower decrease in eGFR over the follow-up period (mean slope change per year −1.3 vs −2.6 mL/min/1.73 m^2). Cardiovascular and all-cause death were not significantly different between groups. As with the EMPEROR-Reduced trial, the primary endpoint was reduced by a similar degree in patients regardless of their diabetes status.[12] With respect to safety, the empagliflozin group had a higher rate of genital infections (number needed to harm [NNH] 67), urinary tract infections (NNH 56) and hypotension (NNH 56), with no significant difference in other adverse events.

*DELIVER: Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction (*N Engl J Med *2022)*

Background: Similar to the EMPEROR-Preserved trial, this multicentre RCT evaluated dapagliflozin, as compared with placebo in a double-blind fashion, in HFpEF patients with or without diabetes.[7]

Patients: Patients ≥40 years of age with an LVEF >40%, NYHA class II-IV symptoms, evidence of structural heart disease (e.g., left ventricular hypertrophy) and an NT-proBNP level ≥300 pg/mL were included. Exclusion criteria included an eGFR <25 mL/min/1.73 m^2, type 1 diabetes or SBP <95 mmHg.

Intervention and control: Patients were randomized to dapagliflozin 10 mg daily or placebo, in addition to usual therapy.

Outcomes: The primary outcome was a composite of worsening heart failure (unplanned hospitalization or urgent visit) or cardiovascular death. All-cause death was included as a secondary outcome.

Results: A total of 6263 patients were randomized (mean age 72 years, 56% male, 71% white, 45% diabetes) and followed for a median of 2.3 years. The mean LVEF was 54%. Compared with placebo, dapagliflozin significantly reduced the primary outcome (16.4% vs 19.5%; HR, 0.82; 95% CI, 0.73-0.92; NNT 33). As with the EMPEROR-Preserved trial, the reduction in the primary outcome was predominantly driven by a reduction in heart failure hospitalization (NNT 36). There was no significant difference in cardiovascular death or all-cause death. The effect of dapagliflozin on the primary outcome was similar in patients with or without diabetes, which was consistent with the DAPA-HF trial.[11] The rate of serious adverse events was similar between dapagliflozin and placebo. The rates of genital and urinary tract infections were not reported.

Implication for practice: The EMPEROR-Preserved and DELIVER trials demonstrated that both dapagliflozin and empagliflozin reduced the risk of cardiovascular death and heart failure hospitalization in patients with HFpEF with a similar NNT of about 30. In both trials, the primary composite endpoint was driven by a reduction in heart failure hospitalizations (not cardiovascular death). Furthermore, these agents were not associated with an increased incidence of serious adverse events, although patients should be monitored for urinary tract or genital infections as well as hypotension. Based on the totality of the evidence to date, SGLT2 inhibitors have demonstrated a consistent benefit across the full range of heart failure irrespective of the patient's LVEF. Consequently, the 2022 American College of Cardiology/American Heart Association heart failure guidelines now recommend SGLT2 inhibitor therapy for patients with heart failure with mildly reduced ejection fraction (LVEF 41%-49%) and HFpEF (LVEF $\geq$ 50%), regardless of whether they have diabetes, to decrease heart failure hospitalizations and cardiovascular mortality.[13] Of note, the most recent Canadian Cardiovascular Society heart failure guidelines were published prior to this evidence. Based on the results of the EMPEROR-Preserved trial, empagliflozin is currently the only SGLT2 inhibitor that has received official Health Canada approval for use in patients with HFpEF regardless of diabetes status, yet dapagliflozin is also commonly used in practice. Canagliflozin has not been studied in a large-scale, cardiovascular outcome–driven RCT of patients with HFpEF.

HYPERTENSION

TIME: Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (Lancet *2022)*

Background: The objective of this prospective, open-label RCT was to determine if evening dosing of usual antihypertensive therapy, as compared with morning dosing, would reduce major adverse cardiovascular events in patients with hypertension.[8]

Patients: Included were patients aged ≥18 years with hypertension taking at least 1 antihypertensive medication daily. Patients taking antihypertensive medications more than once daily or those working regular overnight shifts were excluded. The study was conducted in the United Kingdom.

Intervention and control: Patients were randomized to take their usual antihypertensive medications in the morning (between 6:00 am and 10:00 am) or in the evening (between 8:00 pm and midnight).

Outcomes: The primary outcome was a composite of vascular death or hospitalization for a nonfatal MI or nonfatal stroke. Secondary outcomes included the individual components of the primary outcome, all-cause death and heart failure death or hospitalization, as well as adherence and prespecified adverse events based on patient self-report.

Results: In total, 21,104 patients were included (mean age 65 years, 43% female, 91% white). Approximately 13% had cardiovascular disease (CVD), and 13% had diabetes. The median follow-up was 5.2 years. About 12% of the patients withdrew from the study, of whom most were in the evening dosing group (63% vs 37% in the morning dosing group). The primary outcome was not significantly different between groups (3.4% in the evening dosing group vs 3.7% in the morning dosing group; HR, 0.95; 95% CI, 0.83-1.10). There were also no significant differences between groups for the individual components of the primary outcome. Furthermore, all-cause death and heart failure death or hospitalization were not significantly different between groups. More patients in the evening dosing group reported nonadherence to their dosing schedule (39% vs 23% in the morning dosing group, $p < 0.0001$) but also reported fewer overall adverse events (69% vs 71% in the morning dosing group, $p = 0.04$). For example, dizziness or lightheadedness and falls were significantly less common in the evening dosing group (37% vs 40% and 21% vs 22%, respectively), while excessive visits to the toilet during the day or night were more common in the evening dosing group (40% vs 36%). Throughout the trial, the evening dosing group had a small but significantly lower self-reported difference in morning blood pressure (−1.8/−0.4 mmHg) but significantly higher self-reported difference in evening blood pressure (1.1/0.9 mmHg) when compared with the morning dosing group.

Implication for practice: This study demonstrated that in patients with hypertension, taking their usual antihypertensive medications in the evening, as opposed to the morning, did not lower the risk of adverse cardiovascular outcomes. The 2020

Hypertension Canada guidelines recommend tailoring antihypertensive medication therapy to fit patients' daily habits to improve adherence, which is unlikely to change based on the results of this trial.[14] Interestingly, these results contradict the results of the controversial Hygia Chronotherapy trial, which is currently under investigation by the editors of the *European Heart Journal*, who recommend "to interpret the major results and conclusions [of this trial] with caution until further notice."[15]

STEP: Trial of intensive blood-pressure control in older patients with hypertension (N Engl J Med *2021*)

Background: Hypertension is a common cardiovascular risk factor among older patients, but the most appropriate blood pressure target is debatable.[14,16] The objective of this multicentre, open-label RCT was to determine whether an intensive SBP target, versus a standard SBP target, would reduce cardiovascular outcomes in older adults.[9]

Patients: Included were patients aged 60 to 80 years with an SBP of 140 to 190 mmHg, who were recruited from 42 centres in China. Patients with a previous ischemic or hemorrhagic stroke, recent cardiovascular event or procedure, NYHA class III-IV heart failure symptoms or severe cognitive impairment were excluded.

Intervention and control: Patients were randomized to an intensive SBP target (110-129 mmHg) or standard SBP target (130-149 mmHg). A standardized treatment algorithm was used to guide clinicians in achieving the target blood pressure, with amlodipine or olmesartan used as the first-line agent.

Outcomes: The primary outcome was a composite of stroke (ischemic or hemorrhagic), acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation or death from cardiovascular causes. Secondary outcomes included the individual components of the primary outcome and death from any cause.

Results: A total of 8511 patients were enrolled (mean age 66 years, 24% aged 70-80 years, 47% male). Nineteen percent of patients had a history of diabetes, and 6% had a history of CVD. The trial was stopped early after 3.3 years due to observed benefit with intensive treatment. A mean SBP of 127 mmHg was achieved in the intensive group versus 136 mmHg in the standard group throughout the follow-up period. The primary outcome was significantly reduced in the intensive SBP target group by an absolute risk reduction of 1.1% (3.5% vs 4.6%; HR, 0.74; 95% CI, 0.60-0.92; NNT 91). With respect to the individual outcomes, stroke, acute coronary syndrome and acute decompensated heart failure were all significantly lower with intensive treatment. However, all-cause death was not significantly different between groups. Intensive treatment required the use of more antihypertensive medications compared with the standard group (mean of 1.9 vs 1.5 medications, respectively). Compared with the standard treatment group, intensive treatment resulted in more hypotension (NNH 125), with no significant differences observed in other adverse events.

Implication for practice: This trial demonstrated that in older Chinese patients without a history of stroke, targeting an SBP of <130 mmHg, as compared with <150 mmHg, reduced cardiovascular events but increased the risk of hypotension. These findings are comparable to a subgroup analysis of the landmark SPRINT trial, which demonstrated that an intensive SBP target of <120 mmHg versus <140 mmHg lowered the risk of cardiovascular events in patients aged ≥75 years with hypertension.[17] As the STEP trial was halted prematurely, similar to the SPRINT trial, the long-term safety of intensive SBP control in older patients remains unclear. Overall, intensive blood pressure control may be considered for select older patients with hypertension. An SBP of <120 mmHg is endorsed by the 2020 Hypertension Canada guidelines based on the SPRINT trial criteria.[14] However, an SBP target of <130 mmHg may be considered in some patients who meet the STEP trial criteria.

STATIN THERAPY

SAMSON: Side effect patterns in a crossover trial of statin, placebo and no treatment (J Am Coll Cardiol *2021*)

Background: Statins are often discontinued in practice due to adverse effects, despite RCT evidence demonstrating no significant increase in adverse effects with statin therapy when compared with placebo.[18,19] This was a randomized, double-blind, crossover N-of-1 trial of patients who had discontinued all statins because of intolerable adverse effects.[10]

Patients: Patients aged ≥18 years with an indication for statin therapy, but who had stopped taking 1 or more statins because of intolerable adverse effects that arose within 2 weeks of treatment initiation and who had no intention of restarting, were enrolled. Patients were recruited from across the United Kingdom. Excluded were patients with a history of chronic pain or severe mental illness, concomitant fibrate therapy (or other medications that interact with statins) or high-risk adverse effects to statin therapy (specifically, rhabdomyolysis, myositis, elevation in creatine kinase greater than 5 times the upper limit of normal, elevation in alanine aminotransferase or aspartate aminotransferase greater than 3 times the upper limit of normal or anaphylaxis).

Intervention and control: Patients were randomized to take a statin, placebo or no treatment. Patients received 12 × 1-month medication bottles that were taken according to a random sequence. Four bottles contained atorvastatin 20 mg tablets, 4 bottles contained placebo tablets and 4 bottles were

empty. For the bottles that contained tablets, patients were instructed to take 1 tablet daily. Patients were asked to report a symptom intensity score daily on a smartphone application, ranging from 0 (no symptoms) to 100 (worst imaginable symptoms). If symptoms were unacceptably severe, patients could discontinue the tablets for that month and start the next bottle, as per their schedule. For missing data and data for days after stopping tablets, multiple imputation was used so as not to underestimate the symptom burden from the tablets.

Outcomes: The primary endpoint was the ratio of the symptom intensity score induced by placebo (minus the symptom intensity score with no tablets) divided by the symptom intensity score with atorvastatin (minus the symptom intensity score with no tablets), which was termed the *nocebo ratio*. The nocebo effect, which is essentially the opposite of the placebo effect, refers to the belief that a medication will cause harm. The symptom intensity scores of individual patients were pooled before calculating the nocebo ratio due to extreme or indeterminable ratios.

Results: A total of 60 patients (mean age 66 years, 42% female) were randomized, and 49 (82%) completed the full 12-month protocol. Most participants (77%) were prescribed a statin for primary prevention, and the mean baseline low-density lipoprotein cholesterol level was 4.16 mmol/L. At baseline, patients had trialed a median of 2 different statins with a median duration of treatment of 1.1 years. The most common symptoms resulting in statin discontinuation prior to enrollment were muscle aches, fatigue or tiredness and cramps. During the follow-up period, the mean symptom intensity score was 8 during the no-tablet months (95% CI, 4.7-11.3), 15.4 during the placebo months (95% CI, 12.1-18.7, $p < 0.001$ vs no-tablet months) and 16.3 during the statin months (95% CI, 13-19.6, $p < 0.001$ vs no-tablet months). There was no significant difference in the mean symptom intensity score between placebo and atorvastatin ($p = 0.39$). The nocebo ratio was 0.90, which means that 90% of the symptoms induced by atorvastatin were also induced by placebo. There was no significant difference between atorvastatin and placebo in the frequency of discontinuing tablets (odds ratio [OR], 1.48; 95% CI, 0.85-2.62), intensity of symptom onset (OR, 1.02; 95% CI, 0.98-1.06) or magnitude of symptom offset (OR, 1.01; 95% CI, 0.98-1.05). Six months after completing the trial, 30 of the 60 participants (50%) successfully restarted statin therapy.

Implication for practice: In patients who previously discontinued statins due to intolerable adverse effects, 90% of the symptoms attributed to the statin were also present when the patient was taking placebo in a blinded fashion. Significantly more patients experienced symptoms when they were taking a tablet (statin or placebo) versus no tablet and were just as likely to stop taking a placebo tablet due to adverse effects as they were a statin tablet. In conclusion, in patients who had abandoned statin therapy because of intolerable symptoms, most of those symptoms were likely due to the nocebo effect, and half of those patients were able to successfully rechallenge taking a statin. Pharmacists should discuss the benefits of restarting a statin in those patients with "statin intolerance." ■

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