Review of the top 5 cardiology studies of 2015-16

Arden R. Barry, BSc, BSc(Pharm), PharmD, ACPR; Hazal E. Babadagli, BScPharm, PharmD; Jade E. Basaraba, BScPharm, ACPR; Rosaleen Boswell, BScPharm, ACPR; June W. Chen, BScPharm, ACPR; Mohamed A. Omar, BScPharm, PhD; Dylan M. Pollmann, BScPharm; Jian Song Zhou, BScPharm, ACPR; Margaret L. Ackman, BSc(Pharm), PharmD, ACPR, FCSHP

Countless trials are published each year in the field of cardiology. Since many are not relevant to pharmacists in primary care practice, staying informed of current literature is challenging. This article presents the top 5 recently published cardiology-related studies deemed relevant to primary care pharmacists (with 1 honourable mention).

Methods

The study selection process for this review used a similar methodology to previous publications.[1,2] A list of 19 potentially relevant cardiology-associated studies published in 2015-16 was created through discussions with hospital-based pharmacists practising in cardiology.[3-21] This list (with accompanying citations and abstracts) was used to create an online survey that was emailed to the 382 pharmacists subscribed to the Primary Care Pharmacy Specialty Network of the Canadian Pharmacists Association/Canadian Society of Hospital Pharmacists. Respondents were asked to select up to a maximum of 5 cardiology studies relevant to their practice. The survey was open for 2 weeks with 2 reminder emails.

Results

Twenty-three pharmacists responded. A full list of the studies and voting frequency is included in Appendix 1, available in the online version of the article. Due to its relevance to primary care practice, the sixth-ranked study was also included as an honourable mention, as it evaluated a pharmacist-led intervention aimed at reducing cardiovascular risk in community-dwelling patients. The 3 trials receiving the most votes focused on the cardiovascular safety of chronic therapies, and 2 addressed the management of common cardiovascular risk factors. The numbers needed to treat to reduce the risk of an adverse cardiovascular event or death from any cause are included in Table 1.

HYPERTENSION

SPRINT: A randomized trial of intensive versus standard blood-pressure control (*N Engl J Med* 2015)

Background: Hypertension is a well-known cardiovascular risk factor, but the most appropriate blood pressure (BP) targets are controversial.[3] The objective of this multicentre, open-label, randomized controlled trial (RCT) was to determine whether intensive systolic blood pressure (SBP) control would improve cardiovascular outcomes compared to standard SBP control in patients at high risk for cardiovascular disease (CVD).

Patients: Included were patients ≥50 years of age with SBP of 130-180 mmHg and at increased cardiovascular risk, defined as ≥1 of the following: CVD, Framingham Risk Score (FRS) ≥15%, estimated glomerular filtration rate (eGFR) 20-59 mL/minute or age ≥75 years. Patients with diabetes, previous stroke, recent cardiovascular event/procedure or a left ventricular ejection fraction <35%, as well as nursing home residents, were excluded.

Intervention and control: Patients were randomized to an intensive SBP target (<120 mmHg) or standard SBP target (135-139 mmHg). A treatment

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TABLE 1 Numbers needed to treat for top 5 studies of 2015-16

Study	Intervention	Duration, y	Number needed to treat	
			CV composite*	All-cause death
SPRINT[3]	Intensive versus standard BP control in patients with or at risk of CVD	3.3	63	84
EMPA-REG OUTCOME[7]	Empagliflozin versus placebo in patients with CVD	3.1	63	39
LEADER[8]	Liraglutide versus placebo in patients with or at risk of CVD	3.8	53	72
IMPROVE-IT[9]	Ezetimibe versus placebo, in addition to simvastatin, in patients with a recent ACS	7.0	50	NS
PRECISION[10]	Celecoxib versus ibuprofen or naproxen in patients with arthritis	2.8	NI	NI

ACS, acute coronary syndrome; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; NI, noninferior; NS, not significant.
*The cardiovascular composite varied among trials but included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke plus/minus unstable angina, heart failure or coronary revascularization.

algorithm was used to guide clinicians in achieving the target BP, which encouraged use of drug classes with strong evidence for cardiovascular risk reduction.

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

Results: In total, 9361 patients were enrolled (mean age 68 years, 64% male). The trial was stopped prematurely after 3.3 years due to observed benefit with intensive treatment. A mean SBP of 121 mmHg was achieved in the intensive group and 135 mmHg in the standard group. The primary outcome was reduced by 1.6% (5.2% vs 6.8%; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.64-0.89). Death from any cause was also lower with intensive treatment (3.3% vs 4.5%; HR, 0.73; 95% CI, 0.60-0.90). However, intensive treatment required use of more antihypertensive medications (mean of approximately 3 and 2 for the intensive and standard groups, respectively). Compared to the standard group, intensive treatment resulted in significantly more hypotension, syncope, electrolyte abnormalities and acute kidney injury.

Implications for practice: This trial demonstrated that, in patients at high cardiovascular risk, targeting a SBP of <120 mmHg resulted in a significant reduction in cardiovascular events and mortality, but with a higher risk of hypotension, electrolyte derangements and renal impairment. As the trial was stopped early, the long-term safety of intensive SBP control is unknown. Overall, intensive SBP control could be considered for select high-risk patients and is recommended by the 2017 Hypertension Canada guidelines based on the SPRINT criteria.[22] However, these patients need to be monitored frequently for adverse effects. Pharmacists in primary care are ideally situated to both achieve intensive BP control and monitor for adverse effects.

DIABETES MELLITUS

In 2008, the US Food and Drug Administration (FDA) mandated that manufacturers of new antidiabetic drugs provide evidence of cardiovascular safety,[23] which resulted from an analysis demonstrating rosiglitazone significantly increased the risk of myocardial infarction (MI).[24] Thus, multiple double-blind, placebo-controlled trials have recently been published evaluating the cardiovascular safety of new antihyperglycemic agents compared to placebo in patients at high cardiovascular risk. Cardiovascular safety was defined as an upper 95% CI of <1.3 (i.e., the new drug could have up to a 30% higher rate of cardiovascular events given the worst-case scenario). If the drug met the criteria for noninferiority, a test for superiority could be performed.

The Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS) trial enrolled 14,735 patients with established CVD (coronary artery disease [CAD], cerebrovascular disease or peripheral arterial disease) and type 2 diabetes who were randomized to sitagliptin 100 mg daily or placebo.[4] Sitagliptin was noninferior (but not superior) to placebo for the primary composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina (UA) (9.6% vs 9.6%; HR, 0.98; 95% CI, 0.88-1.09). In the Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome (ELIXA) trial, 6068 patients with a recent ACS were randomized to lixisenatide 20 mcg subcutaneously daily or placebo.[5] Lixisenatide was noninferior to placebo for the same primary composite outcome used in the TECOS trial (13.4% vs 13.2%; HR, 1.02; 95% CI, 0.89-1.17). For the Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6) trial, eligible patients had established CVD, chronic kidney disease (CKD), HF or were ≥60 years of age with ≥1 cardiovascular risk factor.[6] A total of 3297 patients were randomized to semaglutide 0.5-1 mg subcutaneously or placebo once weekly. Semaglutide significantly reduced the primary composite endpoint of cardiovascular death, nonfatal MI or nonfatal stroke compared to placebo (6.6% vs 8.9%; HR, 0.74; 95% CI, 0.58-0.95), which was primarily driven by a reduction in nonfatal stroke.

Despite generally positive results, the studies described above were not selected in the top 5. This is likely because sitagliptin and lixisenatide failed to demonstrate superiority over placebo and semaglutide is currently not available in Canada. However, these trials, as well as the 2 included below, highlight the differences in cardiovascular effect between currently available antidiabetic agents and emphasize the importance of considering these data when selecting antihyperglycemic therapy for patients with type 2 diabetes.

EMPA-REG OUTCOME: Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes (*N Engl J Med* 2015)

Background: The objective of this multicentre, double-blind RCT was to compare empagliflozin, a sodium-glucose co-transporter 2 inhibitor, to placebo in adults with type 2 diabetes at high cardiovascular risk.[7]

Patients: Included were patients ≥18 years of age with type 2 diabetes, established CVD and an eGFR ≥30 mL/minute. Patients were excluded if they had planned cardiac surgery or coronary angioplasty within 3 months or had an ACS, stroke or transient ischemic attack within 2 months of recruitment.

Intervention and control: Patients were initiated on empagliflozin 10 mg or 25 mg daily or matching placebo in addition to standard care.

Outcomes: The primary outcome was a composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke. Secondary outcomes included a composite of the primary outcome plus hospitalization for UA, as well as death from cardiovascular causes, all-cause death and hospitalizations for HF.

Results: A total of 7028 patients (median age 63 years, 71% male) were included and followed for 3.1 years. There was a statistically significant reduction in the primary composite outcome (10.5% vs 12.1%; HR, 0.86; 95% CI, 0.74-0.99) but not in the secondary composite outcome. Patients in the empagliflozin group had a significantly lower risk of death from any cause and from cardiovascular causes, as well as hospitalizations for HF. With respect to safety, the rates of hypoglycemia and acute kidney injury were similar between groups. There was an increase in genital infections with empagliflozin compared to placebo (6.4% vs 1.8%; $p < 0.001$).

LEADER: Liraglutide and cardiovascular outcomes in type 2 diabetes (*N Engl J Med* 2016)

Background: This multicentre, double-blind RCT was designed to evaluate liraglutide versus placebo in patients with type 2 diabetes at high cardiovascular risk.[8]

Patients: Eligible patients were ≥50 years of age with ≥1 cardiovascular condition (e.g., CAD, cerebrovascular disease, peripheral vascular disease, CKD, HF) or ≥60 years of age with ≥1 cardiovascular risk factor (e.g., microalbuminuria/proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction or low ankle-brachial index) and glycated hemoglobin (A1c) of ≥7%. Patients were excluded if they were using an incretin agent, pramlintide or rapid-acting insulin or experienced an acute coronary or cerebrovascular event within 14 days before screening.

Intervention and control: Patients were randomized to liraglutide 1.8 mg (or maximum tolerated dose) subcutaneously daily or placebo in addition to existing therapy.

Outcomes: The primary composite outcome was the occurrence of death from cardiovascular causes, nonfatal MI or nonfatal stroke. Prespecified exploratory outcomes included an expanded cardiovascular composite that included coronary revascularization or hospitalization for UA or HF and death from any cause.

Results: In total, 9340 patients (mean age 64 years, 64% male) were randomized with a follow-up of 3.8 years. Approximately 80% of patients had established CVD with a mean A1c of 8.7%. Compared to placebo, the addition of liraglutide to standard care significantly reduced the primary composite outcome (13.0% vs 14.9%; HR, 0.87; 95% CI, 0.78-0.97), as well as cardiovascular death and all-cause death. Liraglutide also significantly reduced the expanded composite cardiovascular outcome. There was no statistically significant difference in nonfatal MI or nonfatal stroke. More patients in the liraglutide group discontinued the study medication due to adverse events, mainly driven by gastrointestinal events.

Implications for practice: Both the EMPA-REG OUTCOME and LEADER trials demonstrated that in patients with type 2 diabetes at high risk of CVD, the addition of empagliflozin or liraglutide to standard therapy reduced the risk of cardiovascular events, as well as all-cause and cardiovascular mortality. As such, the Canadian Diabetes Association's 2016 clinical practice guidelines interim update now recommends empagliflozin or liraglutide for patients with clinical CVD in whom glycemic targets are not met with existing antihyperglycemic therapy.[25] However, other factors should be considered, such as the patient's comorbidities and preferences (e.g., oral versus subcutaneous administration), drug adverse effect profile and cost.

ACUTE CORONARY SYNDROMES

IMPROVE-IT: Ezetimibe added to statin therapy after acute coronary syndromes (*N Engl J Med* 2015)

Background: Although intensive statin therapy has demonstrated benefit as secondary prevention, there remains interest in further reducing cardiovascular risk with combination therapy. This multicentre, double-blind RCT evaluated the effect of adding ezetimibe to simvastatin on the rate of cardiovascular events in patients with a recent ACS.[9]

Patients: Included were clinically stable patients ≥50 years of age who experienced an ACS within the preceding 10 days and had a low-density lipoprotein cholesterol (LDL-C) level of 1.3-2.6 mmol/L (if they were receiving chronic lipid-lowering therapy) or 1.3-3.2 mmol/L (if they were not on therapy). Exclusion criteria were patients on chronic lipid-lowering therapy more potent than simvastatin 40 mg daily, active liver disease, creatinine clearance <30 mL/minute or planned coronary artery bypass graft surgery for the ACS event.

Intervention and control: On a background of simvastatin 40 mg daily, patients were randomized to ezetimibe 10 mg daily or matching placebo.

Outcomes: The primary efficacy endpoint was a composite of cardiovascular death, nonfatal MI, UA requiring hospitalization, coronary revascularization (≥30 days after randomization) or nonfatal stroke. Additional efficacy endpoints included MI, stroke, cardiovascular death and all-cause death. Safety outcomes included elevation in liver enzymes and creatine kinase, myopathy, rhabdomyolysis, gallbladder-related adverse events and cancer.

Results: A total of 18,144 patients (mean age 64 years, 76% male) were randomized and followed for a median of 6 years. At the time of the index event, the mean LDL-C level was 2.4 mmol/L and 34% were taking a statin. Compared to placebo, the addition of ezetimibe to simvastatin significantly reduced the primary endpoint at 7 years (32.7% vs 34.7%; HR, 0.94; 95% CI, 0.89-0.99), as well as the rate of any MI (13.1% vs 14.8%; HR, 0.87; 95% CI, 0.80-0.95) and ischemic stroke (3.4% vs 4.1%; HR, 0.79; 95% CI, 0.67-0.94). There was no significant difference in the rates of death from cardiovascular causes or any cause. The mean LDL-C level at 1 year was lower in the ezetimibe-simvastatin group (1.4 mmol/L vs 1.8 mmol/L; $p < 0.001$). Adverse events were not significantly different between groups.

Implications for practice: This study demonstrated that the addition of ezetimibe to a moderate-dose statin further reduced cardiovascular events and incrementally lowered LDL-C in patients with a recent ACS without increasing adverse events. Ezetimibe is the first nonstatin to

demonstrate a cardiovascular benefit, which supports the LDL-C hypothesis. However, the clinical effect was modest, with a number needed to treat of 50 over 7 years. The 2016 Canadian Cardiovascular Society dyslipidemia guidelines now recommend ezetimibe as first-line add-on therapy for patients who are unable to achieve their lipid target with maximally tolerated statin therapy.[26]

CARDIOVASCULAR SAFETY

PRECISION: Cardiovascular safety of celecoxib, naproxen or ibuprofen for arthritis (*N Engl J Med* 2016)

Background: Previous studies demonstrated an increased cardiovascular risk associated with cyclooxygenase-2 (COX-2) inhibitors, resulting in the withdrawal of all COX-2 inhibitors from the market, save for celecoxib. Subsequently, the FDA required the manufacturer of celecoxib to conduct a cardiovascular safety trial comparing it to traditional nonsteroidal anti-inflammatory drugs (NSAIDs).[27] This multicentre, double-blind, parallel group RCT compared celecoxib to naproxen and ibuprofen with respect to cardiovascular outcomes in the treatment of patients with arthritis.[10] The margin for noninferiority was an upper 97.5% CI of ≤1.4 for cardiovascular events for the on-treatment population.

Patients: Enrolled were adult patients with NSAID-dependent chronic pain secondary to arthritis (both rheumatoid and osteoarthritis) and established or at risk of CVD.

Intervention and control: Patients were randomized 1:1:1 to celecoxib 100-200 mg twice daily (limited to 200 mg daily for patients with osteoarthritis), ibuprofen 600-800 mg 3 times daily or naproxen 375-500 mg twice daily, with matching placebo.

Outcomes: The primary composite outcome was death from cardiovascular causes, nonfatal MI or nonfatal stroke. The composite of clinically significant gastrointestinal events was a secondary outcome.

Results: A total of 24,222 patients were randomized (mean age 63 years, 64% female, 90% osteoarthritis). Only 23% had established CVD, but 46% were taking low-dose acetylsalicylic acid at baseline. Mean duration of follow-up was 34 months. In the on-treatment analysis, the primary outcome occurred in 1.7% of patients in the celecoxib group, 1.8% in the naproxen group and 1.9% in the ibuprofen group. The HR for celecoxib versus naproxen was 0.90 (95% CI, 0.71-1.15; $p < 0.001$ for noninferiority) and versus ibuprofen was 0.81 (95% CI, 0.65-1.02; $p < 0.001$ for noninferiority). The rate of clinically significant gastrointestinal events was lower with celecoxib compared to naproxen (0.3% vs 0.7%; HR, 0.51; 95% CI, 0.32-0.81) and ibuprofen (0.3% vs 0.7%; HR 0.43; 95% CI, 0.27-0.68).

Implications for practice: This trial showed that moderate-dose celecoxib was noninferior to naproxen or ibuprofen with regard to cardiovascular safety. The high study drug discontinuation rate (69%) and low event rate, however, limit the statistical power of the analysis. Furthermore, the relatively low daily dose of celecoxib (mean 209 mg) may have provided a safety advantage compared to the higher daily doses of naproxen (mean 852 mg) and ibuprofen (mean 2045 mg).[28,29] In contrast to the other COX-2 inhibitor data, this study provides some reassurance regarding the relative cardiovascular safety of celecoxib in the long-term treatment of arthritis pain, as compared to traditional NSAIDs.

CARDIOVASCULAR RISK REDUCTION

Honourable mention: Effectiveness of community pharmacist prescribing and care on cardiovascular risk reduction: randomized controlled RxEACH trial (*J Am Coll Cardiol* 2016)

Background: With expanded scope of practice for pharmacists, there is a need to examine if these new authorities improve patient health outcomes. The purpose of this open-label RCT was to evaluate the effectiveness of a community pharmacy-based intervention to reduce cardiovascular risk.[11]

Patients: Included were adults at high risk of cardiovascular events (defined as ≥1 of the following: diabetes, CKD, established atherosclerotic vascular disease or FRS >20%) with ≥1 uncontrolled cardiovascular risk factor (elevated BP, LDL-C, A1c or current smoker).

Intervention and control: The intervention group received pharmacist-led physical and laboratory assessment, cardiovascular risk score calculation, patient education and guideline-based treatment recommendations (including adapting and/or prescribing medications) as needed for hypertension, dyslipidemia, glycemic control or smoking cessation. Patients received follow-up every month for 3 months. The control group received usual community pharmacist care.

Outcomes: The primary outcome was the difference in estimated cardiovascular risk between the intervention and usual care groups, which was measured by 3 validated risk engines. Secondary outcomes included change in the individual cardiovascular risk factors.

Results: In total, 723 patients (mean age 62 years, 58% male) from 56 community pharmacies in Alberta were enrolled. Seventy-nine percent had diabetes, 40% CKD and 30% established atherosclerotic vascular disease. The most common risk factor leading to study entry was uncontrolled A1c (79%) followed by uncontrolled BP (72%). At 3 months, the estimated cardiovascular risk decreased in the intervention group, as compared to usual care, by 21% (absolute difference of 5.4%; 95% CI, 4.2-6.6; $p < 0.001$). Additionally, there were significant reductions in all individual risk factors in the intervention group (SBP −9.4 mmHg, diastolic BP −2.9 mmHg, LDL-C −0.2 mmol/L, A1c −0.92% and 20.2% fewer smokers). There were no adverse events reported during the trial.

Implications for practice: Compared to usual care, community pharmacist-based interventions resulted in a significant reduction in CVD risk in patients with ≥1 uncontrolled cardiovascular risk factor. Past trials have shown improvement in individual cardiovascular risk factors with pharmacist-led interventions, but this was the first trial to target multiple risk factors at once. This study provides evidence that community pharmacists could have a large impact on reducing CVD burden if these interventions were widely adopted. It also highlights the merit of a broader scope of practice for pharmacists, including additional prescribing authority and ability to order laboratory tests.

Conclusion

The top 5 cardiology studies of 2015-16 focus on the prevention of adverse cardiovascular events in patients with established, or at risk of, cardiovascular disease. These trials represent an important opportunity for community-based practitioners to improve clinical outcomes and estimate cardiovascular risk. The majority of these trial results have changed national guidelines, which reinforces their potential to positively impact the health of Canadians. In addition, the novel RxEACH trial provides evidence that pharmacists with an expanded scope of practice can implement these results to improve the cardiovascular risk profile of their patients. ■

From Lower Mainland Pharmacy Services (Barry), Chilliwack General Hospital, Chilliwack, and the Faculty of Pharmaceutical Sciences (Barry), University of British Columbia, Vancouver, British Columbia; and the Mazankowski Alberta Heart Institute, Pharmacy Services (Babadagli, Basaraba, Boswell, Chen, Omar, Pollmann, Zhou, Ackman), Alberta Health Services, Edmonton, Alberta. Contact arden.barry@ubc.ca.

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