Review of the top 5 cardiology studies of 2019-20

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Introduction

Numerous studies are published annually in the discipline of cardiology, making it difficult to stay up to date. Additionally, 2020 was a tumultuous year, with the added need to closely follow the rapidly evolving literature with the COVID-19 pandemic. Notwithstanding, our patients still have chronic medical issues that require ongoing management. We hope this article aids in keeping pharmacists informed of relevant trials in the field of cardiology. This article presents a brief synopsis of the top 5 cardiology-based studies (plus 1 additional study) from 2019-20 identified as being most relevant to primary care practice.

Methods

The methodology was similar to previous publications, with the addition of using social media to increase survey uptake.[1-4] In brief, 19 cardiology studies published in 2019 and 2020 were identified by a group of hospital-based pharmacists practising in cardiology. An online survey that listed these studies, with accompanying abstracts and citations, was posted on the Primary Care Pharmacy Specialty Network (PSN) of the Canadian Pharmacists Association/Canadian Society of Hospital Pharmacists (95 members) and Cardiology PSN of the Canadian Society of Hospital Pharmacists (304 members). These voluntary groups support communication and networking among pharmacists practising in primary care and cardiology, respectively. In addition, the survey link was posted on Twitter by the lead author (A.R.B.; 1736 followers) to increase the response rate. The survey instructed pharmacist respondents to select up to a maximum of 5 cardiology studies that they perceived to be applicable to primary care. The survey was open for 2 weeks (November 23 to December 6, 2020), with 1 PSN reminder each and 4 reminders on Twitter.

Results

There were 46 respondents. Voting frequency for each study is included in Appendix 1 (available online). The 2 randomized controlled trials (RCTs) that received the most votes involved the novel use of sodium glucose co-transporter 2 (SGLT2) inhibitors in patients with heart failure (HF) with reduced ejection fraction (HFrEF), with or without type 2 diabetes mellitus.[5,6] One study, which tied for the fourth highest number of votes, examined sacubitril/valsartan for HF with preserved ejection fraction (HFpEF).[7] Two studies involved patients with atrial fibrillation (AF) who either experienced an acute coronary syndrome (ACS) or underwent percutaneous coronary intervention (PCI) or had stable coronary artery disease (CAD).[8,9] Finally, a sixth study, which evaluated an innovative omega-3 fatty acid preparation to reduce cardiovascular events in patients at high cardiovascular risk, was included because it was tied for the fourth highest number of votes.[10] The numbers needed to treat to reduce the risk of an adverse cardiovascular event or death from any cause are included in Table 1.

DOI:10.1177/17151635211029328

The SGLT2 inhibitors have been shown to reduce HF hospitalizations in patients with type 2 diabetes, although as a secondary outcome.[11,12] Two recent RCTs evaluated the benefit of SGLT2 inhibitors (dapagliflozin and empagliflozin) specifically in patients with HFrEF, irrespective of having diabetes.

DAPA-HF: Dapagliflozin in patients with heart failure and reduced ejection fraction (N Engl J Med *2019*)

Background: This multicentre, double-blind RCT determined whether dapagliflozin, when compared to placebo, reduced cardiovascular death or worsening HF in patients with HFrEF with or without diabetes.[5]

Patients: Patients aged ≥18 years with 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) were included. Patients were excluded if they had an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, symptomatic hypotension or a systolic blood pressure (SBP) <95 mmHg.

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

Outcomes: The primary outcome was a composite of worsening HF (unplanned hospitalization or urgent visit requiring intravenous therapy) and cardiovascular death. Secondary outcomes included a composite of hospitalization due to HF and cardiovascular death and death from any cause.

Results: A total of 4744 patients were randomized (mean age 66 years, 77% male, 70% white, mean LVEF 31%) and followed for a median of 18 months. Less than half of the patients (45%) had diabetes. There was high use of guideline-directed medical therapy at baseline. Compared to placebo, dapagliflozin reduced the primary composite endpoint (16.3% vs 21.2%; hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.65-0.85; number needed to treat [NNT] 21). The effect of dapagliflozin was consistent between the subgroups of patients with and without diabetes. Dapagliflozin also reduced the secondary endpoints of cardiovascular death and HF hospitalization (NNT 21) and all-cause death (NNT 44). Adverse events (e.g., volume depletion, adverse renal events, fractures, amputations, diabetic ketoacidosis) were not significantly different between groups.

EMPEROR-Reduced: Cardiovascular and renal outcomes with empagliflozin in heart failure (N Engl J Med *2020*)

Background: Similar to DAPA-HF, this multicentre, double-blind RCT compared empagliflozin vs placebo in patients with HFrEF with or without diabetes.[6]

Patients: Eligible patients were ≥18 years of age with HFrEF (LVEF ≤40%, NYHA class II-IV symptoms and an elevated NT-proBNP). Patients were excluded if they had had a cardiovascular event (e.g., myocardial infarction [MI] or stroke) in <90 days, decompensated HF, eGFR <20 mL/min/1.73m^2, symptomatic hypotension or 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 HF. Death from any cause was also a prespecified endpoint.

Results: In total, 3730 patients (mean age 67 years, 76% male, 70% white, mean LVEF 27%) were included. Median follow-up was 16 months. Approximately 50% of patients had diabetes at baseline, with high use of guideline-directed medical therapy. Empagliflozin reduced the primary composite outcome (19.4% vs 24.7%; HR, 0.75; 95% CI, 0.65-0.86; NNT 19) vs placebo, which was primarily driven by a reduction in HF hospitalization (NNT 20). As with the DAPA-HF trial, the primary endpoint was reduced by a similar degree in patients regardless of their diabetes status. Death from any cause was not significantly different between groups. With respect to safety, there was a higher rate of genital infections with empagliflozin (number needed to harm [NNH] 91), with no significant difference in other adverse events.

Implication for practice: The DAPA-HF and EMPEROR-Reduced trials demonstrated that in patients with HFrEF—with or without diabetes—the addition of dapagliflozin or empagliflozin to standard care reduced HF hospitalizations and cardiovascular death with an impressive NNT of about 20; however, only dapagliflozin reduced all-cause death. Furthermore, these agents were not associated with an increased incidence in adverse events (except genital infections with empagliflozin). Consequently, the 2020 Canadian Cardiovascular Society HF guidelines now recommend SGLT2 inhibitor therapy for patients with HFrEF (LVEF ≤40%) regardless of whether they have diabetes.[13] Of note, currently only dapagliflozin has received Health Canada approval for use in patients with HFrEF regardless of diabetes status.

PARAGON-HF: Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction (N Engl J Med *2019*)

Background: The PARADIGM-HF trial demonstrated that sacubitril/valsartan reduced the rate of HF hospitalizations and cardiovascular death when compared to enalapril in patients with HFrEF.[14] Unfortunately, many pharmacotherapeutic interventions have not demonstrated a significant reduction in morbidity or mortality in patients with HFpEF.[15] The objective of this multicentre, randomized, double-blind, active-comparator trial was to determine the effect of sacubitril/valsartan in patients with HFpEF.[7]

TABLE 1 Numbers needed to treat for the top 5 cardiology studies of 2019-20*

Study	Intervention	Duration (y)	NNT	
			Primary cardiovascular composite endpoint†	All-cause death
DAPA-HF[5]	Dapagliflozin 10 mg daily in patients with HFrEF with or without DM	1.5	21	44
EMEROR-Reduced[6]	Empagliflozin 10 mg daily in patients with HFrEF with or without DM	1.3	19	NS
PARAGON-HF[7]	Sacubitril/valsartan 97/103 mg twice daily in patients with HFpEF	2.9	NS	NS
AFIRE[9]	Rivaroxaban 15 mg daily ± ASA or a $P2Y_{12}$ inhibitor in patients with AF and stable CAD	2.0	35	35
REDUCE-IT[10]	Icosapent ethyl 2 g twice daily in patients with (or at risk of) CVD and hypertriglyceridemia	4.9	21	NS

AF, atrial fibrillation; ASA, acetylsalicylic acid; CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; NS, not significant.
*The AUGUSTUS trial was excluded from the table, as the primary outcome was bleeding.
†Refer to text for specific definition.

Patients: Included were patients aged ≥50 years with LVEF ≥45% and NYHA class II-IV symptoms. Additional criteria included an elevated natriuretic peptide level, evidence of structural heart disease and recent diuretic use. Patients were excluded if they had a prior documented LVEF of <40%, recent (<3 months) ACS or PCI, symptomatic hypotension or SBP <110 mmHg, or eGFR <30 mL/min/1.73 m^2.

Intervention and control: Patients in the intervention group received sacubitril/valsartan titrated to the target dose of 97/103 mg twice daily, while the comparator group received valsartan titrated to the target dose of 160 mg twice daily.

Outcomes: The primary outcome was a composite of total hospitalizations for HF and death from cardiovascular causes. Secondary outcomes included all-cause death, a composite of adverse renal outcomes (decrease in eGFR of ≥50%, end-stage renal disease or death due to renal failure) and quality of life (based on change in the Kansas City Cardiomyopathy Questionnaire [KCCQ] score).

Results: A total of 4796 patients were included (mean age 73 years, 52% women, 81% white, mean LVEF 58%), with a median follow-up of 35 months. There was no significant difference in the primary outcome between groups (894 events vs 1009 events; rate ratio, 0.87; 95% CI, 0.75-1.01). The individual components of the primary outcome, as well as death from any cause, were not significantly different between groups. However, in exploratory analyses, patients in the sacubitril/valsartan group had a lower rate of adverse renal outcomes (1.4% vs 2.7%; HR, 0.50; 95% CI, 0.33-0.77; NNT 77). Additionally, more patients in the sacubitril/valsartan group experienced a clinically meaningful improvement in KCCQ score at 8 months. Prespecified subgroup analyses suggested that sacubitril/valsartan might benefit women and patients with LVEF ≤57%. Patients in the sacubitril/valsartan group were more likely to develop hypotension with SBP <100 mmHg (NNH 20) or angioedema (NNH 250) and were less likely to have a serum creatinine ≥177 μmol/L (NNT 35) or serum potassium >5.5 mmol/L (NNT 48).

Implication for practice: The PARAGON-HF trial did not show a significant benefit in reducing HF hospitalizations and cardiovascular death with sacubitril/valsartan vs valsartan in HFpEF patients. These results do not support the use of sacubitril/valsartan in patients with HFpEF, which is consistent with recommendations from the 2020 Canadian Cardiovascular Society HF guidelines.[13] However, the observed improvement in renal outcomes and HF symptoms, as well as the benefit noted in the subgroups of women and patients with a moderately reduced LVEF (45%-57%), may help guide future research.

ATRIAL FIBRILLATION

*AUGUSTUS: Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation (*N Engl J Med *2019)*

Background: The objective of this noninferiority RCT was to assess bleeding outcomes in patients with AF who had a recent ACS or PCI with planned treatment with a $P2Y_{12}$ inhibitor.[8]

Patients: Included were patients aged ≥18 years with AF on an oral anticoagulant with a recent ACS or PCI and planned use of a $P2Y_{12}$ inhibitor for ≥6 months. Excluded were those with severe renal dysfunction, history of an intracranial hemorrhage, recent/planned coronary artery bypass grafting or a bleeding disorder.

Intervention and control: Under a 2×2 factorial design, patients were randomized to open-label apixaban or a vitamin K antagonist (VKA) and double-blind acetylsalicylic acid (ASA) or placebo. All patients received a $P2Y_{12}$ inhibitor, the choice of which was at the discretion of the prescriber. Regimens compared were 1) apixaban + $P2Y_{12}$ inhibitor + placebo; 2) VKA + $P2Y_{12}$ inhibitor + placebo; 3) apixaban + $P2Y_{12}$ inhibitor + ASA; and 4) VKA + $P2Y_{12}$ inhibitor + ASA.

Outcomes: The primary outcome was major or clinically relevant nonmajor bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH). Secondary outcomes included the composite of death and hospitalization, and composite of death and ischemic events (e.g., MI, stroke, stent thrombosis or urgent revascularization).

Results: In total, 4614 patients (median age 71 years, 71% male, 92% white, median CHA_2DS_2-VASc score 4, median HAS-BLED score 3) were included and followed for 6 months. Most patients (93%) were receiving clopidogrel. Apixaban was superior to VKA for a reduction in the primary bleeding outcome (10.5% vs 14.7%; HR, 0.69; 95% CI, 0.58-0.81; NNT 24). Conversely, patients randomized to ASA had a significantly higher rate of bleeding compared to placebo (16.1% vs 9.0%; HR, 1.89; 95% CI, 1.59-2.24; NNH 14). The primary bleeding endpoint was highest in the VKA + $P2Y_{12}$ inhibitor + ASA group (18.7%) and lowest in the apixaban + $P2Y_{12}$ inhibitor + placebo group (7.3%). For the secondary outcomes, the NNT to prevent 1 death or hospitalization with apixaban vs VKA was 26, whereas this outcome was not significantly different between the ASA and placebo groups. The composite of death and ischemic events was not significantly different between apixaban and VKA.

Implications for practice: This trial demonstrated that in AF patients with a recent ACS or PCI, who were concomitantly treated with a $P2Y_{12}$ inhibitor, apixaban reduced the risk of clinically relevant bleeding compared to VKA at 6 months, whereas adding ASA to an oral anticoagulant and $P2Y_{12}$ inhibitor increased the risk of bleeding vs placebo. There was no significant difference in death or ischemic events with apixaban compared to a VKA, although the trial was not designed or powered to assess individual ischemic outcomes. Based on these results, the combination of a $P2Y_{12}$ inhibitor (primarily clopidogrel) plus apixaban (i.e., without ASA) should be considered for this population to reduce the risk of bleeding and is recommended by the 2020 Canadian Cardiovascular Society AF guidelines.[16]

*AFIRE: Antithrombotic therapy for atrial fibrillation with stable coronary disease (*N Engl J Med *2019)*

Background: This multicentre, open-label, blinded endpoint noninferiority RCT evaluated the efficacy and safety of rivaroxaban monotherapy compared to rivaroxaban plus an antiplatelet agent in patients with AF and stable CAD.[9]

Patients: Enrolled were patients in Japan ≥20 years of age with AF ($CHADS_2$ score ≥1) and stable CAD, defined as a history of coronary artery bypass grafting or PCI ≥1 year prior to enrollment, or coronary stenosis ≥50% not requiring revascularization. Excluded were patients with a history of stent thrombosis or uncontrolled hypertension.

Intervention and control: Patients were randomized to rivaroxaban monotherapy (15 mg daily or 10 mg daily if their creatinine clearance was 15-49 mL/min, which are the standard doses in Japan) or combination therapy with rivaroxaban at those doses plus ASA or a $P2Y_{12}$ inhibitor (at the prescriber's discretion).

Outcomes: The primary efficacy outcome was a composite of cardiovascular events (ischemic or hemorrhagic stroke, systemic embolism, MI and unstable angina requiring revascularization) or death from any cause. The primary safety outcome was major bleeding, based on ISTH criteria. Secondary outcomes included the individual components of the primary endpoint and any bleeding.

Results: A total of 2215 patients were included in the modified intention-to-treat analysis (mean age 74 years, 79% male, median CHA_2DS_2-VASc score 4, median HAS-BLED score 2). The majority of patients had a history of PCI (71%), and ASA was the most commonly prescribed antiplatelet agent (70%) in the combination group. After noninferiority was established for the efficacy endpoint and superiority for safety, a superiority analysis (not prespecified) was conducted for the efficacy endpoints. Rivaroxaban monotherapy was superior to combination therapy for the primary efficacy endpoint (8.0% vs 10.9%; HR, 0.72; 95% CI, 0.55-0.95; NNT 35). This was driven by lower all-cause mortality with monotherapy (NNT 35), which led to the study being terminated early after a median follow-up of 24 months. The primary safety endpoint was also lower with rivaroxaban monotherapy (3.2% vs 5.2%; HR, 0.59;

95% CI, 0.39-0.89; NNT 50). Any bleeding events were also lower with rivaroxaban monotherapy (NNT 13).

Implications for practice: The AFIRE trial demonstrated that in patients with AF and stable CAD, rivaroxaban monotherapy resulted in a lower risk of cardiovascular events and all-cause death and major bleeding when compared to rivaroxaban plus an antiplatelet agent. Accordingly, the 2020 Canadian Cardiovascular Society AF guidelines recommend using oral anticoagulation alone in patients with AF (age ≥65 years or $CHADS_2$ score ≥1) and stable CAD.[16] Use of rivaroxaban 15 mg daily has been compared to warfarin in Japanese patients with AF but not in other populations.[17] Therefore, when applying these results to non-Japanese patients, rivaroxaban 20 mg daily (or 15 mg daily if the patient's creatinine clearance is 15-49 mL/min) should be recommended.[18]

CARDIOVASCULAR RISK REDUCTION

REDUCE-IT: Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia (N Engl J Med 2019)

Background: Elevated triglycerides have been associated with an increased cardiovascular risk; however, triglyceride-lowering medications, particularly over-the-counter omega-3 fatty acid supplements, have not shown a consistent clinical benefit.[19,20] This multicentre, double-blind RCT evaluated the effect of adding icosapent ethyl, a purified ethyl ester formulation of eicosapentaenoic acid, to statin therapy in patients with high cardiovascular risk and elevated triglycerides.[10]

Patients: Patients aged ≥45 years with cardiovascular disease (CVD) or aged ≥50 years with diabetes and ≥1 additional cardiovascular risk factor were included. Eligible patients were taking a statin for ≥4 weeks and had a fasting triglyceride level of 1.52-5.63 mmol/L and low-density lipoprotein cholesterol level of 1.06-2.59 mmol/L. Exclusion criteria included severe HF, active severe liver disease, glycated hemoglobin >10%, planned coronary intervention or surgery, history of pancreatitis, or hypersensitivity to fish or shellfish.

Intervention and control: Patients were randomized to icosapent ethyl 2 g twice daily or mineral oil-containing placebo.

Outcomes: The primary composite endpoint consisted of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization and unstable angina. Key secondary endpoints included the individual components of the primary outcome and all-cause death.

Results: In total, 8179 patients (median age 64 years, 71% male, 90% white) were included. At baseline, 71% of patients had CVD and 58% had diabetes. Median baseline triglyceride level was 2.44 mmol/L and low-density lipoprotein cholesterol level was 1.94 mmol/L. Median follow-up was 4.9 years. Compared to placebo, icosapent ethyl significantly reduced the primary endpoint (17.2% vs 22.0%; HR, 0.75; 95% CI, 0.68-0.83; NNT 21). Cardiovascular death was significantly reduced with icosapent ethyl (NNT 112), but not all-cause death. The benefit with icosapent ethyl was consistent regardless of baseline or achieved triglyceride levels. Rates of AF and peripheral edema were significantly higher in the icosapent ethyl group (NNH 72 and 67, respectively). The rate of serious bleeding events was similar between groups, while the incidence of gastrointestinal disorders was frequent but was actually lower with icosapent ethyl (33.0% vs 35.1%; $p = 0.04$).

Implications for practice: Addition of icosapent ethyl to statin therapy reduced cardiovascular events, including cardiovascular death, in patients with (or at high risk of) CVD and elevated triglyceride levels. However, cost is currently a barrier to access. It should be noted that icosapent ethyl is a unique preparation that is not equivalent to over-the-counter products. Interestingly, another recently published RCT (STRENGTH) demonstrated that a high-dose omega-3 carboxylic acid supplement did not demonstrate a cardiovascular benefit in statin-treated patients at risk of CVD with hypertriglyceridemia and a low high-density lipoprotein cholesterol level.[21] ■

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Author contributions: *A. R. Barry co-initiated the project, drafted the list of relevant studies, designed and conducted the survey, co-wrote the introduction, methods and results, supervised the manuscript writing, reviewed each draft and revised the final manuscript. H. E. Babadagli and B. V. Nguyen wrote the summary of the AFIRE trial, R. Boswell and C. L. McMillan wrote the summary of the AUGUSTUS trial, J. W. Chen and E. L. Dawson wrote the summary of the REDUCE-IT trial, D. G. Lopaschuk and J. S. Zhou wrote the summary of the DAPA-HF and EMPEROR-Reduced trials and M. A. Omar and D. M. Pollmann wrote the summary of the PARAGON-HF trial. All contributed to and reviewed the list of relevant studies, reviewed each draft and revised the final manuscript. M. L. Ackman co-initiated the project, contributed to and reviewed the list of relevant studies, co-wrote the introduction, methods and results, supervised the manuscript writing, reviewed each draft and revised the final manuscript.*

Funding: *This review was unfunded.*

Statement of conflicting interests: *The authors have no financial or other conflicts of interest related to this work.*

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