The Canadian Cardiac
Chronicle

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"April.... hath put a spirit of youth in everything."
- William Shakespeare, Sonnet XCVIII

As it goes in the far north, the polar bears emerge from their den in spring to begin their journey across the melting sheets of ice, to forage for food, and raise their young. They follow this pattern to ensure they get the nutrition they need and prepare for the next winter - planning ahead is important, particularly in areas of scarce resources.

This year we have followed a very similar pattern as humans. For many of us it's been a long winter by climate, and societally - we have been continually hunkering down and limited in our ability to collaborate and spend time with others in the same space. That time is beginning to pass along for many as COVID-19 becomes endemic, and we remain cautious yet optimistic about the future. Many of you actively working in a healthcare environment will also be following much stricter protocols because of the exposure risk to patients, yourselves, as well as your family and friends. However, as we have emerged from our metaphorical den this year, many of us remain hopeful and forward-looking. This reset is how we function -taking the best from the past and reinventing for the future is met with anticipation and it will take time to get it 'right'. For example, how we do trials, how we engage patients, how we balance life and work and enhance work-from-home and collaboration.

Unlike the polar bear, we have been active over this winter and into spring with all of the research-based activities that have been underway for some time, and those that are starting soon. We've been active in continuing efforts in ongoing trials, planning for upcoming trials, and analyzing data to answer secondary research questions from already published trials and established registries. Some of these secondary analyses will serve as fodder for the next trial, provide a new lens on existing published data, or stimulate us to ask yet another scientific question.

The SODIUM-HF trial was born of one such important unanswered question from clinical practice: for patients with heart failure, does recommending a low sodium diet make a difference in clinical outcomes? Funded by CIHR, the UHF, and with support from the HRCNZ, the CVC operationalized this pragmatic trial that required sites to think differently as to how they enroll patients and who was part of the research team, let alone conducting a trial that was a strategy-based trial and involved many aspects new to patients and the research team alike. This culminated in the results being presented at the American College of Cardiology in Washington D.C. in April 2022 and published in *The Lancet* simultaneously - the collective efforts of over 800 patients, 26 sites across 6 countries, and countless hours of the clinical research teams on the ground. The results of the trial provide a mixed answer to the question: lower sodium in the diet did not reduce the number of clinical events but did improve quality of life. This mixed picture requires clarity and we will strive to answer these questions with the wealth of data available and new information to be collected.

Clinical research is at yet another cross-road with opportunities to continue best practices and to adopt new ones, including new methods of designing and delivering trials utilizing advanced data science techniques. So, like the polar bear who makes the most of all seasons outdoors, we look forward to getting outdoors more, and seeing family, friends, and colleagues in-person.

Dr. Justin Ezekowitz
CVC Co-Director

CLINICAL TRIALS

In This Issue:

AEGIS-II

AEGIS-II is a large, international, multicentre Phase 3 trial of infusing an intravenous formulation of apolipoprotein A-I (CSL112) to reduce cardiovascular events in acute coronary syndrome patients. CSL112, an intravenous formulation of apoA-I, enhances cholesterol efflux capacity, and therefore has the potential to reduce plaque burden, stabilize plaque lesions at risk of rupture and decrease the high rate of early recurrent events.

In the first few months of 2022 we experienced another wave of COVID-19 challenges, however, along with the melting snow March brought us the highest enrolling month in Canada in 12 months! Meeting this target was very exciting and once again reassured us that our site teams are extremely resilient and have not given up.

A rejuvenation meeting took place in April and we are thankful that many of our sites were able to attend. It was wonderful to see our AEGIS-II colleagues in person once again. One of the main discussion points of the meeting was enrollment, and the global study team is requesting that all AEGIS-II sites do their best to randomize 1 patient per month over the next 6 months as we focus on a strong finish to the enrollment phase of the study. We need our Canadian sites to rise to the challenge!

A reminder that enrolling the right patient is extremely important for the integrity of the study. Once a patient is randomized to AEGIS-II they are part of the intent-to-treat population. We want all patients to complete the infusions as per protocol and continue with follow-up visits until the end of the study. One way to ensure that this happens is to provide the patient with a thorough consenting process, which may include:

- Involving the family or caregivers to confirm their willingness to support the patient during participation.
- Taking your time and providing ample opportunity for questions.
- Ensuring the patient is fully aware of the time commitments involved.
- The PI could speak with the patient about the background, safety, and importance of the study.
- Obtaining alternate contacts in the event you cannot reach the patient (ie. primary physician, pharmacy, family members).

If you are interested in further information regarding AEGIS-II, please contact the Clinical Trials Project Lead, Lyndsey Garritty at 1-800-707-9098 or lyndsey.garritty@ualberta.ca

AEGIS-II LEARN MORE

SODIUM-HF

SODIUM-HF is a multicenter, randomized, open-label **S**tudy **o**f **D**ietary **I**ntervention **U**nder 100 **M**MOL in **H**eart **F**ailure.

Once again, we are thrilled to announce that primary analysis results are now available for review. Our sincerest thanks and gratitude to each and every site who helped us reach this exciting milestone – we could not have done this without everyone's stellar contribution!

With the Year 2 follow-up visits still underway, we wish to encourage the remaining sites to finish strong. Final analysis is planned for 2023, so keep up the great work on those 18-month and 24-month visits!

Reminder:

We **cannot** have any **LTFU** patients in this trial. Every patient counts, so please keep searching for all LTFU patients until database lock. Your continued diligence in this regard is much appreciated.

For sites participating in the long-term follow-up sub-study, about 95% of eligible patients have been approached thus far - amazing!

For general study updates and news, visit sodiumhftrial.com or follow us on Twitter @sodiumhf.

If you have questions about the SODIUM-HF trial, please contact the Clinical Trials Project Lead, Karin Kushniruk at 1-800-707-9098, ext. 7 or karin.kushniruk@ualberta.ca.

SODIUM-HF 100 LEARN MORE

EMPACT-MI

EMPACT-MI is a streamlined, multicentre, randomised, parallel group, double-blind placebo-controlled superiority trial to evaluate the effect of **EMPA**gliflozin on hospitalisation for heart failure and mortality in patients with a**C**u**T**e **M**yocardial **I**nfarction.

A huge thank you to all of the study coordinators for their diligent data cleaning efforts for the second data snapshot that took place over the Easter weekend. It was another impressive accomplishment after a peak of over 350 queries due to the recent database update. Great job!

Each month, Canada is meeting our enrollment target. Our sites have randomized over 220 participants into the trial thus far. Canada currently ranks 6th out of 22 countries and our average enrollment rate of 0.7 pts/month/site exceeds expectations. Keep up the great work!

Congratulations go out to our top three enrolling sites: **Dr. Har and Milada Pajevic**, who is the reigning Top Recruiting site in North America, **Dr. Burstein and Tim Wong**, and **Dr. Daneault and Julie Caron**. You have all set the bar high!

For questions about EMPACT-MI, please contact Jodi Parrotta, Clinical Trials Project Lead/QA-Regulatory Compliance Lead at 1-800-707-9098, ext. 3 or Jodi.Parrotta@ualberta.ca.

EMPACT-MI LEARN MORE

HEART-FID

Our essential trial, to investigate the efficacy and safety of Injectafer® as treatment for heart failure with iron deficiency, is in the final stretch. Thanks for your continued efforts to keep HEART-FID front and center in the minds of your team and your participants. Many thanks to you, your team, and your participants for ensuring our study is successful!

Data

We are currently in our 60/60/60 data campaign. Our focus is – no open queries greater than 60 days, no overdue visits greater than 60 days, and no missing forms greater than 60 days. Keeping your data clean will help prepare for the next DSMB data cut coming soon. It will also assist in preparing for close out. Please continue to review your data for overdue visits and open queries on a routine basis. Some data pages can get a bit tricky. Please refer to the latest eCRF instruction manual (version 6) to help guide you through the data entry pages. Also, please feel free to reach out to the CVC if you have any questions on how to enter a particularly complicated visit or event.

Regulatory

As you know, there is a new ICF Addendum. Once you receive the draft ICF Addendum, please add in your site-specific details as quickly as possible. It will be important to have a quick turn around so that participants still on study drug will have an opportunity to review and sign the ICF Addendum at their next on-site visit.

Retention

Our goal is to keep all participants in the trial and on study drug if possible. Please continue to keep the lines of communication open between your site and your participants. Keeping participants informed about the approaching end of the study will help them understand our timelines and be ready for study closure when it occurs. For participants currently off study drug, you might want to bring up the possibility of reintroducing study drug for the final visits. Participants are always able to come back on study drug if they have previously discontinued. If you are changing the status of a participant, remember to change their status in the eCRF and in the IXRS. Please contact the CVC if you need assistance in changing a participant's status in either study system.

If you are interested in further information regarding this trial, please contact Clinical Trials Project Lead Courtney Gubbels at 1-800-707-9098, ext 2 or courtney.gubbels@ualberta.ca.

HEART-FID

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STREAM-2

If the enrollment pace keeps up, our trial designed to determine efficacy and safety of early fibrinolytic treatment, with half-dose tenecteplase and additional antiplatelet and antithrombin therapy, in subjects with acute ST-elevation myocardial infarction, could complete enrollment in late summer or early fall. We encourage our Canadian team to keep up their amazing recruitment rate. Great work everyone!

Entering adverse events and serious adverse events can get complicated. In this trial, depending on the event, there may be two ways to document an SAE. Please always refer to the detailed flow diagram in the protocol. Also, feel free to contact the CVC for assistance on data entry or for any other study related issue.

If you are interested in further information regarding this trial, please contact Clinical Trials Project Lead Courtney Gubbels at 1-800-707-9098, ext. 2 or courtney.gubbels@ualberta.ca.

Stream-2
Strategic Reperfusion Early After Myocardial Infarction

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SONOSTEMI-LYSIS

The **SONO**thrombolysis in patients with an **ST**-segment **E**levation **M**yocardial **I**nfarction with fibrino**LYSIS** (SONOSTEMI-LYSIS) trial is a single-centre project taking place at the University of Alberta Hospital/Mazankowski Alberta Heart Institute. Congratulations to Dr. Kevin Bainey and his team for enrolling several more patients over the last quarter!

While prompt reperfusion therapy has been shown to reduce mortality, infarct size and improve left ventricular function in patients with STEMI, reperfusion itself may result in adverse events such as reperfusion injury. In patients with STEMI receiving fibrinolysis therapy, this study will explore whether the addition of *sonothrombolysis* (i.e., high mechanical index impulses during diagnostic ultrasound) to standard care results in enhanced myocardial perfusion, improved left ventricular function, and better clinical outcomes.

If you are interested in finding further information about the SONOSTEMI-LYSIS study, please contact the Clinical Trials Project Lead, Karin Kushniruk, at 1-800-707-9098, ext. 7 or karin.kushniruk@ualberta.ca.

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FEAST-HF

Got Fiber?

Recent attention has been focused on the role of the gut microbiome in human disease, including its significant role in the pathogenesis of heart failure. Several small studies have shown an interplay between the microbiome and heart failure, and that the gut microbiome can be modulated by dietary interventions, such as the addition of dietary fiber. The FEAST-HF trial is exploring if modification of the microbiome can mitigate the symptoms of patients with heart failure, and whether new avenues for treatment and future research for patients with heart failure will be revealed.

Recruitment closed earlier this year and we wish to express our sincerest thanks to all sites for their hard work throughout the trial. The study is currently in the analysis phase and we look forward to sharing some results in the near future.

If you are interested in further information about the FEAST-HF trial, please contact the Clinical Trials Project Lead, Karin Kushniruk, at 1-800-707-9098, ext. 7 or karin.kushniruk@ualberta.ca.

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NEWS & UPDATES

Health Canada Updates to Record Retention Period

Did you know that Health Canada has reduced the requirement for Record Retention from 25 years to 15 years? This regulatory change to both the ***Food and Drug Regulations*** and ***Natural Health Products Regulations*** came into effect on February 11, 2022 and applies to new and ongoing clinical trials. The shorter period addresses the issues of cost and administrative burden that the 25-year requirement placed on sponsors. The new retention period is also better aligned with those of other international regulatory authorities. As a result, Canada will be a more favourable location for conducting clinical trials. Health Canada will be updating their policies, guidance documents, and other documents accordingly.

What does this mean for you?

Sites should check whether their clinical trial agreement (contract) and/or ICF references the old retention period, and consider whether a CTA amendment and/or an ICF update is required to ensure alignment with the current regulations.

For any quality-related questions, please contact Jodi Parrotta, Clinical Trials Project Lead/QA-Regulatory Compliance Lead/ Clinical Research Associate at 1-800-707-9098, ext. 3 or Jodi.Parrotta@ualberta.ca.

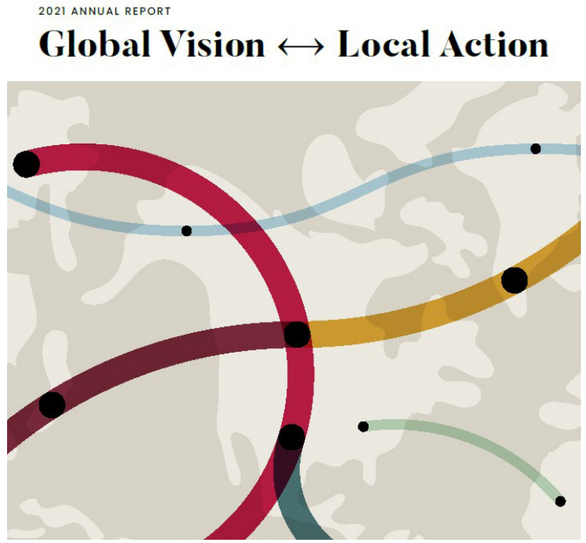
2021 CVC Annual Report

The 2021 CVC annual report is coming soon!

This year's theme, ***Global Vision ↔ Local Action***, highlights a variety of the CVC's activities that have started at a global or national scale and have subsequently translated into local initiatives. The theme also reflects our organization's aim to bring people from different places together in the collective pursuit of improving cardiovascular care and patient outcomes around the world.

We greatly appreciate the interest and support of the many friends and collaborators who make it possible for us to succeed.

In the coming days you will receive a link to the digital report by email. The report will also be available on our website in the following location: https://thecvc.ca/about-us/annual-report/



FEATURED PUBLICATIONS

Prevalence of CVD in High-Cost HealthCare Service Users

Dr. Padma Kaul and co-authors (including **Nathan Klassen, Drs. Douglas Dover, Nariman Sepehrvand, Roopinder Sandhu, Sean van Diepen, Kevin Bainey, Sean McMurtry, Robert Welsh, Justin Ezekowitz, Shaun Goodman, Paul Armstrong, and Finlay McAlister** from the CVC) recently published the article, Prevalence of Cardiovascular Disease in a Population-Based Cohort of High-Cost Healthcare Services Users in *CJC Open*.

A small proportion of patients account for a large proportion of healthcare costs. There are limited data on the prevalence of cardiovascular disease (CVD) and multimorbidity in contemporary cohorts of these high-cost users (HCUs) in Canada. In a cohort of complex HCUs between 2011-2012 and 2014-2015 in Alberta, Canada this study compared health expenditures among HCUs with and without CVD.

Almost a third of the HCUs were hospitalized with a primary diagnosis of CVD, and an additional half were hospitalized with a secondary diagnosis of CVD, leading to a prevalence of CVD of over 75%. Healthcare costs among HCUs with CVD accounted for $7.7 billion of the total $9.7 billion for all HCUs in Alberta during the 4-year time period. Hospitalization costs accounted for 80% of healthcare expenditures among HCUs with CVD, and costs of physician services, ambulatory care, and drugs accounted for the remaining 20% of total healthcare costs. Frailty and multi-morbidity were major drivers of both costs and mortality among HCUs with CVD.

The researchers concluded that CVD accounts for a large proportion of healthcare costs among HCUs. Additionally, HCUs with CVD have high rates of other comorbidities that contribute substantially to healthcare costs and adverse outcomes. Further research is needed to identify and intervene earlier, in order to flatten the cost curve in these complex patients.

Vericiguat in Patients with CAD and HFrEF

Dr. Paul Armstrong and coauthors recently published the article Vericiguat in Patients with Coronary Artery Disease and Heart Failure with Reduced Ejection Fraction in the *European Journal of Heart Failure*. Dr. Armstrong shares some insights on this research below.

What are the key findings from this research?

This study of over 5,000 patients with heart failure and reduced ejection fraction (HFrEF) found that the presence of coronary artery disease (CAD) had a major impact on increasing the rates of both cardiovascular death and heart failure hospitalization in the high-risk patients in the VICTORIA trial. It also showed that vericiguat was equally well tolerated in both patients with and without CAD, and the treatment benefit was similar in both cohorts.

What are the real-world implications of these research findings?

Although the 58% of patients with CAD have worse outcomes in heart failure, the beneficial effect and safety profile of vericiguat was similar irrespective of CAD.

What should be the focus of future research on this topic?

The 3.1% absolute increase in sudden cardiac death in patients with CAD (8.6) vs. 5.5% in non-CAD patients occurred despite a much greater overall use of implantable cardiovascular devices (ICDs) in these patients. However, when ICD's were employed their use was associated with significantly less sudden death. Interestingly, the incidence of sudden death in patients without CAD was similar irrespective of the presence of an ICD. These findings also have implications both for the care of patients with HFrEF and for gauging the potential mortality outcomes in the planning of future research to address the continuing unmet needs of patients with HFrEF.

Statins and SARS-CoV-2 Infection

Dr. Finlay McAlister and coauthors (including **Drs. Shaun Goodman**, **Sean van Diepen**, and **Padma Kaul** from the CVC) recently published their article, Statins and SARS-CoV-2 Infection: Results of a Population-Based Prospective Cohort Study of 469 749 Adults From 2 Canadian Provinces in the *Journal of the American Heart Association*. Dr. McAlister shares some insights on this research below.

What are the key findings from this research?

A few small observational studies suggested that statin users had a lower risk of contracting severe COVID-19 and exhibited faster recovery times. To further investigate this hypothesis, the authors designed this study to test whether current use of statins is associated with decreased susceptibility of adults to SARS-CoV-2 infection and/or better outcomes in those with a positive SARS-CoV-2 test. Using large-scale, population-based cohorts in Alberta and Ontario, the authors measured the association between current use of statins and infection rates among adults who underwent SARS-CoV-2 testing; they also assessed the association of current statin use with outcomes in adults with laboratory-confirmed SARS-CoV-2 infection. In stark contrast to the previous observational studies, this research found that compared with statin nonusers, patients taking statins exhibit the same risk of testing positive for SARS-CoV-2 and those younger than 75 years exhibit similar outcomes within 30 days of a positive test. Patients older than 75 years with a positive SARS-CoV-2 test and who were taking statins had more emergency department visits and hospitalizations, but exhibited lower 30-day all-cause mortality risk. This is a reflection that patients who are taking statins are generally doing so for underlying conditions that predispose them to ED visits and hospitalizations and statins themselves were not independently associated with any differences in risk of contracting SARS-CoV-2 or in developing a severe case of COVID-19.

What are the real-world implications of these research findings?

While this proves that taking statins isn't beneficial for prevention of COVID-19, it at least provides reassurance that it is safe for patients to remain on statins even if they are infected with SARS-CoV-2.

What should be the focus of future research on this topic?

As our study is observational, we called for randomized trials to definitively establish whether there is any difference in COVID-19 outcomes for statin users - a small RCT has since been completed and found similar results as our observational study - no evidence of benefit or harm.

Visit the Publications Archive for a comprehensive list of CVC publications.

About the Chronicle

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