The Canadian Cardiac
Chronicle

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The future belongs to those who can see it coming.

As the 2022 clock winds down a natural proclivity is to reflect on what has transpired in the last year through the rear view mirror, while at the same time ponder the forward view through the windshield as to what lies ahead for 2023.

The FIFA World Cup has occupied global centre stage over the past few weeks. It eloquently demonstrated the delicate balance between individual achievement and the collective ambition of a team in succeeding amidst the best players from countries around the world. Creativity, fitness, resilience, endurance and passion are on full display and when these qualities come together, it is a wonderful force to witness. As E.F. Schumacher observed over a half century ago in his instructive book about sustainable development *"Small can be beautiful"*, it is inspiring to see the stellar performance of some sparsely populated countries at such a highly visible event.

It is also gratifying to see and feel us emerging from the pandemic. Returning from the COVID-induced hibernation takes time as do hibernating bears emerging from their winter caves and even the ischemic left ventricle after perfusion with coronary flow. What a welcome infusion of genuine social networking at the ESC in Barcelona and the AHA in Chicago! Handshakes, hugs and back slaps were in abundance as was the uplifting sound of laughter over dinner with friends and colleagues. Long overdue meaningful face-to-face conversations in the hallways, meeting rooms and exhibits have returned.

So too, there has been plenty of evolution at the CVC and University of Alberta in the past year. Recognizing the increasing transdisciplinary of cardiovascular science, we are pleased to have welcomed two new clinician scientists to our faculty. David Collister is a nephrologist with particular interest in chronic kidney disease and dialysis. Jason Weatherald is a respirologist with expertise in the pathogenesis and treatment of pulmonary hypertension. We are excited at the prospects of engaging their energy, talent and ideas on the investigational roads ahead.

Despite the COVID assault on clinical research, we have been part of some remarkable progress in 2022. The large, international Phase 3 AEGIS-II trial has fully enrolled over 18,000 patients to establish whether intravenous apolipoprotein A-I (CSL112) will reduce cardiovascular events in acute coronary syndrome patients. Enhancing cholesterol efflux has the potential to reduce plaque burden and stabilize plaque lesions at risk of rupture. We await with great anticipation the result as careful follow up is now in progress.

The HEART-FID trial exploring intravenous ferric carboxymaltose is also near completion and will soon inform clinical practice by clarifying the role of this long-term treatment in patients with heart failure with reduced ejection fraction and the common problem of iron deficiency.

The STREAM-II trial concluded enrollment of older patients with ST-elevation myocardial infarction (including a truly elderly cohort ≥75 years) to assess pharmaco-invasive therapy with half dose tenecteplase versus primary PCI. This trial, sponsored by the University of Leuven (Frans Van de Werf) with support from Boehringer Ingelheim, has a provisional plan to unveil the results at ACC in New Orleans in March 2023. Special thanks to Drs. Robert Welsh, Kevin Bainey and the Edmonton team for being the highest enrolling site in this international trial and to our core ECG laboratory for their careful analysis of this key trial endpoint.

As we look forward to 2023, we are highly engaged with Bayer and the Duke Clinical Research Institute (DCRI) in the OCEANIC-AF trial to evaluate a promising new oral Factor XIa (FXIa) inhibitor asundexian to prevent thrombotic events in patients with atrial fibrillation.

A second new initiative in collaboration with the DCRI and CSL Behring is the study of Clazakizumab, a genetically engineered humanized anti-interleukin 6 (IL-6) monoclonal antibody (mAb), to examine its role in patients with end stage kidney disease undergoing dialysis.

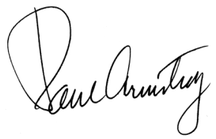
The state of global cardiovascular medicine is evolving dynamically with new potential solutions to address the many unmet needs of our patients. The men and women of the CVC are vital foundational elements of what we have accomplished

Continued on next page →

Opening Letter Continued...

this past year and where our compass is pointed. In the new era of science and medicine ahead, we can only prosper through generously spirited and strategic global collaboration. The future will require bold ideas, new tools and multidimensional paradigms that embrace diverse stakeholders.

The forthcoming holiday season is a welcome opportunity to reflect and be thankful for the great people we are privileged to work with in our own locale, across the breadth of Canada and around the world village. Please also leave a space in your thoughts and pocketbooks for the many deserving charitable causes that deserve both your immediate and long term help. In the days ahead, I hope you find time to restore your spirit and energy mitigated by what has transpired in our lives since March of 2020. On behalf of all of us here at the CVC, we send you our very best wishes for a Happy Christmas, Hanukkah and all other celebrations. We are optimistic that the future belongs to those who embrace the challenges ahead…especially if we invent their solutions.



Dr. Paul W. Armstrong
CVC Founding Director

In This Issue:

CLINICAL TRIALS

POSIBIL-6

The CVC is pleased to announce a collaborative partnership with the Duke Clinical Research Institute and CSL Behring on an upcoming Ph2b – Ph3 trial, which will enroll patients with end stage kidney disease (ESKD). With academic leadership from **Dr. David Collister** (CVC Associate Faculty) and **Dr. Shaun Goodman** (CVC Co-Director), along with our Clinical Operations Team, the CVC will provide strategic leadership and site management across Canada.

We look forward to sharing addition details over the coming months. For questions, please contact CVC Clinical Trials Project Lead, Melisa Spaling, at 780-429-4011 (ext. 6) or mspaling@ualberta.ca.

POSIBIL6 ESKD

HEART-FID

Our trial, to investigate the efficacy and safety of Injectafer® as treatment for heart failure with iron deficiency, is quickly approaching completion. By the end of this month, all end of study visits will be wrapped up. What an achievement! All of our sites have put forth a tremendous effort scheduling and completing the last participant visits, entering the remaining data points, and cleaning up data. Thank you for all the remarkable work you are doing for this trial!

End of Study Data Reminders

- The date of drug discontinuation should be the date of the last dose and not the date of data entry.
- Ensure the PI has access to the eCRF and has completed the required training so eCRF pages can be reviewed and signed off in a timely manner.
- Once a participant has completed their final visit, no additional data will be collected for events that occur after that visit.
- Source documents will continue to be collected and uploaded for reported events until database lock.

Final Visits and Close-Out Visits

All sites have now been approached by a CRA to schedule a final visit or close-out visit. Select sites will have a pre-database lock final visit where the CRA will conduct on-site close-out activities, but your site will remain open and ethics approval will remain in place until after database lock. The CVC team will continue to work with your site to collect any remaining outstanding items and we will let you know once your site is officially closed. Other sites will continue to have routine monitoring visits through the final participant visits phase and will have a traditional post-database lock close-out visit on-site. All sites should keep the trial open with their REB until instructed by the CVC to close the trial. As always, if you have any questions about these upcoming visits, please contact the CVC.

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 LEARN MORE

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 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.

We did it! The enrollment phase of AEGIS-II is complete after reaching the final sample size of 18,200 patients. Canadian contributions were significant and we were able to exceed our enrollment projections. Despite the challenges brought on by COVID-19, the sites and study team persevered and were able to achieve this incredibly important milestone.
Congratulations!

We now move on to the next phase – retention and data cleaning.

A few reminders as our focus shifts to this new phase of AEGIS-II:

- Review the Patient Contact Information Form at each visit to ensure that you have current contact information for the patient and you have alternate ways to reach the patient if needed (ie. family, friends, primary care physician, pharmacy).
- Keep patients informed on what is new in AEGIS-II, disease education, and the importance of maintaining regular contact with the study team until the end of their participation.
- If a patient misses a visit, notify the CVC right away.
- The end of study visit should be done directly with the patient and within the protocol specific time window – if these requirements are not met, the visit may need to be redone.
- Enter visit data into the eCRF and resolve queries as soon as possible. The expected time window is 2 days.

Thank you to all of the AEGIS-II sites in Canada for your dedication over the last 4.5 years – we definitely "finished strong" as per the AEGIS-II mantra, and the CVC team is extremely proud of this achievement!

If you are interested in further information regarding this trial, please contact Clinical Trials Project Lead, Lyndsey Garritty, at 1-800-707-9098 (ext. 4) or lyndsey.garritty@ualberta.ca.

AEGIS-II 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.

We are entering the final stretch of enrollment for this trial! The updated study timeline was recently shared with sites.

Event reporting is key. In preparation for upcoming patient visits, don't forget to: (1) review the EMR ahead of time, if available. (2) Scan for any encounters (ER visits; Hospitalizations) and make a note to ask about these. (3) During scheduled visits, ask probing questions to ensure no hospitalizations are missed (SAEs, Endpoints). (4) be sure to watch the helpful video resource that was circulated in November on conducting patient interviews. Send the CVC a copy of your site's attestation.

CVC sites have randomized over **300** participants into the trial thus far! Great job, Canada! Congratulations to the following 9 sites who randomized at least **2 patients** between October 1st and November 30th:

1. **Dr. Udell & Libby Leung-Kalman**
2. **Dr. Cantor & Kim Robbins**
3. **Dr. Jedrzkiewicz & Adic Perez**
4. **Dr. Rodes & Karine Maheux**
5. **Dr. Daneault & Julie Caron**
6. **Dr. Burstein & Areti Apatsidou**
7. **Dr. Abuzeid & Brigita Zile**
8. **Dr. Dehghani & Neha Mehta**
9. **Dr. Mansour & Caroline Vallieres**

Thanks to all the study coordinators for their ongoing data cleaning efforts. Your commitment and diligence is appreciated!

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

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SONOSTEMI-LYSIS

The **SONO**thrombolysis in patients with an **ST**-segment **E**levation **M**yocardial Infarction with fibrino**LYSIS** trial is a single-centre project taking place at the University of Alberta Hospital / Mazankowski Alberta Heart Institute.

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 further information about the SONOSTEMI-LYSIS study, please contact the Clinical Trial Project Lead, Karin Kushniruk, at 1-800-707- 9098, (ext. 7) or karin.kushniruk@ualberta.ca.

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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.

CONGRATULATIONS to all on completing their final 24-month visits, we are thrilled to have reached this last-patient-last-visit milestone! We now turn our attention to secondary analyses and look forward to sharing some results in 2023. We also continue to focus on the long term follow up sub-study so to those sites participating, keep up the great work!

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

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ABBREVIATE

De-**A**doption **β**eta-**B**lockers in patients with stable ischemic heart disease without **RE**duced L**V** ejection fraction, ongoing **I**schemia, or **A**rrhythmias: a pragma**T**ic randomiz**E**d trial with blinded endpoints is a multi-centre vanguard project taking place within Alberta. We are in the final stages of startup and anticipate enrollment to commence in the very near future.

Patients with stable coronary artery disease are often prescribed many medications at the same time (called polypharmacy) and these patients may experience drug interactions or negative drug related side effects. With the introduction of newer medications and treatments, it is not well known whether older drugs, such as beta-blockers, are still an effective and safe option for treating heart disease. Some evidence suggests beta-blockers should be continued, whereas other evidence suggests beta-blockers might cause unnecessary harm.

The study investigators hope to find out whether continuation or discontinuation of beta-blockers will affect long term cardiovascular outcomes, including death, heart attack, hospitalization for cardiac arrest, unstable angina requiring urgent revascularization (i.e., angioplasty and stenting), and heart failure. The study investigators will also examine how beta-blockers continuation or discontinuation affects several quality-of-life measures.

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

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PRESSURE CABG

PRotocolized vs p**E**rsonalized blood pre**SSU**re pe**R**i-operative param**E**ters in **C**oronary **A**rtery **B**ypass **G**rafting Surgery: The PRESSURE CABG Cardiac Surgery Trial is a single-centre project taking place at the University of Alberta Hospital / Mazankowski Alberta Heart Institute. Congratulations to **Dr. Sean van Diepen** and his team for a successful start to recruitment earlier this year!

Current medical care includes many strategies to treat and prevent low blood pressure during heart surgery. These include aiming to control blood pressure within a prescribed range (i.e., one size fits all), or, a more personalized range (i.e., based on the patient's baseline blood pressure prior to surgery). Both ways of managing blood pressure are within the current standard treatment, however, there are few high-quality studies that have explored whether prescribed or personalized blood pressure ranges are better for patients. This study aims to find out whether *prescribed* or *personalized* blood pressure management is better for preventing acute kidney injury, stroke, or delirium as well as which strategy is better for patients overall.

If you are interested in further information about the PRESSURE-CABG 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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STREAM 2

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, completed enrollment this past September with our Canadian team being the top enrolling site. Congrats! We look forward to sharing the results of the trial in the coming months!

Data from the last participants has been entered, including all 30-day follow-up visit data, and data pages have been signed by the PI for all participants. Thanks to the Canadian team for getting data entered and cleaned! Please continue your dedicated data efforts by entering the last follow-up visit for each participant when appropriate. As the trial is winding down, this is a good time to review your regulatory study files to ensure you have all documents ready for archiving. A close-out visit will be planned with your site once all participant follow-ups are completed.

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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OCEANIC-AF

The OCEANIC-AF trial will enroll patients with atrial fibrillation and investigate the safety and efficacy of asundexian, an investigational oral Factor XIa (FXIa) inhibitor.

Thank you to all sites for your ongoing commitment to the OCEANIC-AF trial. We recognize the hard work and dedication it takes to work through the start-up phase; thank you for moving the start-up pieces along as efficiently as possible. Both the CVC and Bayer Canada look forward to seeing the first patient enrolled in Canada and celebrating the first enrollment at each of your sites!

CVC will resume open session calls with **Dr. Shaun Goodman and Dr. Roopinder Sandhu** in early 2023; please stay tuned for further details.

For questions, please contact Clinical Trials Project Lead, Melisa Spaling, at 780-429-4011 (ext. 6) or mspaling@ualberta.ca.

OCEANIC AF

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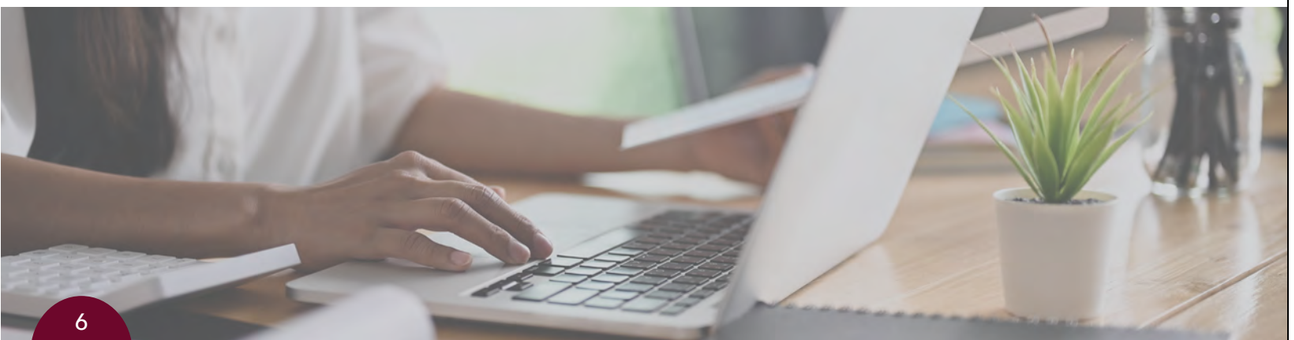
Quality: The Importance of Training

A key component of quality is training. Per GCP E6 (R2) 2.8, *"Each individual involved in conducting a trial should be qualified by education, training, and experience to perform their respective task(s)".* Sites should be able to readily produce (for a monitor or for an auditor/inspector) training records for everyone listed on the delegation log. Such training should reflect the tasks they are delegated (e.g., medical license for confirming eligibility; and CRF training for data entry), and in regards to the protocol (and any amendment) in general. The delegation log should be maintained and kept as current and complete as possible. Ensure that staff who have left the study have been end-dated on the Log. In a recent Health Canada inspection, one observation highlighted that the PI should initial and date their delegation of duties on the date they are delegated to the person (which should be **only when** all training has been completed [not before]).

Sites should also be able to produce records regarding training on their local SOPs. Suggested SOPs include: AE reporting; drug accountability/storage/destruction; 15 year record retention; consent process; training. Sites should review SOPs at regular intervals to make sure their SOPs reflect what they are actually doing. It would be an audit finding to NOT be following one's SOPs.



NEWS & UPDATES

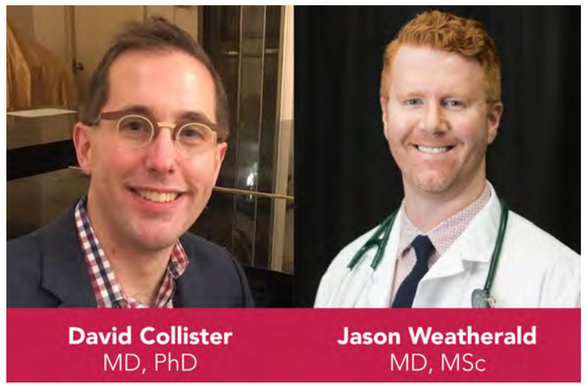
CVC Colloquium

Thank you to all of the attendees and speakers who took part in the 2022 CVC virtual colloquium sessions. The presentations during our sessions on "Regulatory Inspections and Audits" and "Research Potpourri" were very informative and sparked interesting discussion and questions.

We would like to remind everyone to save the date for an upcoming session in the New Year, which will take place on **February 2, 2023 (9am PT/10am MT/11am CT/12pm AT)**. The topic for this one hour session is "Tips and Strategies for a Quick and Efficient Startup." Stay tuned for registration details and additional information on session presenters!

If you have any questions regarding the CVC Clinical Trials Colloquium, please do not hesitate to reach out to Tracy Temple at tracy.temple@ualberta.ca.

Introducing New Associate Faculty



The CVC is pleased to announce the addition of two new associate faculty members.

Dr. David Collister is a nephrologist at the University of Alberta Hospital and an Assistant Professor in the Department of Medicine at the University of Alberta. His research focuses on randomized controlled trials and prospective observational studies in chronic kidney disease and dialysis, precision medicine approaches to uremic symptoms and cognition, and the intersection of kidney disease with gender-diverse populations.

Dr. Jason Weatherald is a pulmonologist at the University of Alberta Hospital and Mazankowski Alberta Heart Institute, and an Associate Professor in the Department of Medicine at the University of Alberta. His research interests include risk assessment in pulmonary arterial hypertension, use of clinical registries and real-world data for patient-oriented research, and use of adaptive trial designs for the investigation of right heart failure interventions.

FEATURED PUBLICATIONS

Canadian Mother-Child Cohort Active Surveillance Initiative

The Canadian Mother-Child Cohort Active Surveillance Initiative (CAMCCO): Comparisons between Quebec, Manitoba, Saskatchewan, and Alberta was recently published in *PLOS ONE*. CVC co-authors on this publication include **Dr. Padma Kaul** and **Dr. Anamaria Savu**. We asked Dr. Savu a few questions to better understand the results of this research.

What are the key findings from this research?

The Canadian Mother Child Cohort (CAMCCO) infrastructure that consists of 4 pregnancies-birth cohorts from 4 Canadian provinces can be reliably used to study medication use in pregnancy and adverse pregnancy outcomes. Almost two-thirds of women took medications during pregnancy, the majority of these medications being antibiotics. Most of these medications were taken during organogenesis. Adverse pregnancy outcomes, such as prematurity, low birth weight (LBW), or congenital malformations in the infant differ across the 4 provinces. Prematurity rates ranged from 5.9 to 6.8% across the 4 provinces. LBW ranged between 4.0 and 5.2% across the 4 provinces. Major malformations increased over time in Quebec, Saskatchewan, and Alberta, but decreased in Manitoba. Alberta had the highest prematurity and LBW rates, and congenital malformations.

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

Medication use during pregnancy has to be carefully evaluated, weighing benefits against side effects. CAMCCO is a reliable Mother-Child infrastructure to perform research and obtain evidence-based findings.

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

CAMCCO infrastructure can be used to quantify the benefits/risks of medication use during pregnancy for mothers and children in a timely and harmonized manner, providing health policy-makers important evidence on the treatment of maternal conditions during and after gestation.

Risk Factors Associated with LCOS Following Cardiac Surgery

Predictors and Associated Clinical Outcomes of Low Cardiac Output Syndrome Following Cardiac Surgery: Insights from the LEVO-CTS Trial was recently published in the *European Heart Journal: Acute Cardiovascular Care*. CVC co-authors on this publication include **Yinggan (Gray) Zheng**, **Dr. Sean van Diepen**, **Dr. Cindy Westerhout**, and **Dr. Shaun Goodman**. Dr. van Diepen shares some insights on this research below.

What are the key findings from this research?

In a North American randomized trial, we observed that in high-risk cardiac surgical patients with reduced preoperative left ventricular ejection fraction (LVEF), low cardiac output syndrome (LCOS) was common occurring in 22% of patients. The risk factors for LCOS were age, prior heart failure, and peripheral vascular disease, while protective associations included isolated coronary artery bypass and Levosimendan use. Finally, LCOS was independently associated with 90-day mortality (adjusted HR 5.04, 95% CI: 2.66–9.55).

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

Our findings suggest that Levosimendan may help reduce the incidence of LCOS in high-risk cardiac surgical patients, but it should be acknowledged that this outcome was not the primary focus of the randomized trial.

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

Further research could focus on validating the role of prophylactic Levosimendan in high-risk cardiac surgery patients with reduced LVEF and identifying other lower risk cardiac surgical populations who may benefit from prophylactic Levosimendan. In addition, whether prevention of LCOS can improve patient morbidity and mortality remains unclear.

Sequential Evaluation of NT-proBNP in HF

Dr. Paul Armstrong and co-authors (including **Yinggan (Gray) Zheng**, **Cindy Westerhout**, and **Justin Ezekowitz** from the CVC) recently published their article, Sequential Evaluation of NT-proBNP in Heart Failure: Insights Into Clinical Outcomes and Efficacy of Vericiguat in the *Journal of the American College of Cardiology: Heart Failure*. Dr. Armstrong shares some insights on this research below.

What are the key findings from this research?

We found a strong relationship between changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the subsequent occurrence of cardiovascular death and heart failure hospitalization in patients with worsening heart failure with reduced ejection fraction (HFrEF). Patients treated with vericiguat compared with placebo had significantly greater declines and lesser increments in sequential measures of NT-proBNP.

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

These changes appear related to the clinical benefit of vericiguat therapy.

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

Further studies to define more precisely which patients with heart failure gain the most benefit from vericiguat when it is added to foundational therapy.

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

The CVC offices will be closed from December 26, 2022 to January 2, 2023

Should any urgent issues arise, we ask that you call the designated helpline for your study.

The CVC's main voicemail will be checked daily throughout the closure to address any important study-related issues, and staff email will be checked intermittently.

Any urgent requests can be sent to tracy.temple@ualberta.ca, or call 780-952-2140.

About the Chronicle

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