**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Message from the Founding Director</td>
</tr>
<tr>
<td>6</td>
<td>Compass</td>
</tr>
<tr>
<td>7</td>
<td>Vision, Mission, and Core Values</td>
</tr>
<tr>
<td>8</td>
<td>The Value of an ARO</td>
</tr>
<tr>
<td>10</td>
<td>Cycle of Quality</td>
</tr>
<tr>
<td>12</td>
<td>Collaborators</td>
</tr>
<tr>
<td>14</td>
<td>A Decade of Discovery: 2010-2019</td>
</tr>
<tr>
<td>36</td>
<td>A Decade of Data: Facts and Figures</td>
</tr>
<tr>
<td>38</td>
<td>Introducing New Co-Director Dr. Padma Kaul</td>
</tr>
<tr>
<td>40</td>
<td>Featured Publications</td>
</tr>
<tr>
<td>44</td>
<td>The Next Generation of Health Researchers</td>
</tr>
<tr>
<td>50</td>
<td>Collaborative Outreach</td>
</tr>
<tr>
<td>58</td>
<td>Services and Activities</td>
</tr>
<tr>
<td>60</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>66</td>
<td>ECG Core Laboratory</td>
</tr>
<tr>
<td>68</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>70</td>
<td>Population Health and Economic Outcomes</td>
</tr>
<tr>
<td>72</td>
<td>Business Operations and Research Administration</td>
</tr>
<tr>
<td>74</td>
<td>Faculty</td>
</tr>
<tr>
<td>82</td>
<td>Acknowledgements</td>
</tr>
</tbody>
</table>

“I WAS TAUGHT THAT THE WAY OF PROGRESS IS NEITHER SWIFT NOR EASY.”

- MARIE CURIE
I am delighted to welcome you to our 2019 CVC annual report. This reflection on the past decade has been titled as one featuring discovery.

The 10-year horizon between 2010 and 2019 affords one a long view. It also underscores the crucial role of having a clear vision and staying the course set on the compass, whose parameters are well described herein. When we set that course in 2010, we knew it would be subject to change but we were unclear what would modulate those changes. The evolution in the health care environment over the past decade has been truly stunning. Cloning the human genome and the gene editing capabilities afforded by CRISPR are at one end of this evolution, while advances in health information technology, mobile health, telemedicine, and new understanding of the social determinants and systems of care populate the other. We also have entered a welcomed era where part of health care personalization is patient engagement with new focus on quality of life. This requires new planning and the use of different metrics. A few selected comments follow on the CVC’s progress.

In a pivotal “connecting the dots” study, Dr. Kevin Bainey, along with Yinggan Zheng, Dr. Cynthia Westerhout and other colleagues, showed how effective the pharmacoinvasive approach is in the management of ST-elevation myocardial infarction. He studied over 3,000 such patients in the greater Edmonton region using data from the Vital Heart Response Registry created by Dr. Robert Walsh. Aligned with ECG insights from our ECG core laboratory and 1-year population outcomes, Dr. Bainey showed how the application of research from our clinical trial work led to the Edmonton region having the lowest mortality in the country. This is a great demonstration of Goethe’s maxim: “Knowing is not enough; we must do.”

An advance in genetics led to the development of monoclonal antibodies to PCSK9, a receptor that when blocked leads to reductions in low-density lipoprotein (LDL) cholesterol. Dr. Shaun Goodman played a leadership role in the ODYSSEY-OUTCOMES study, which used a strategy of a twice-monthly injectable drug called alirocumab. They found dramatic reductions in cholesterol with a welcome concomitant decrease in cardiac events thus opening a key new path for prevention.

The CVC recently had the privilege of playing a lead role assessing a novel small molecule drug named veniciguat that targets a unique intracellular pathway thought to be deficient in heart failure. Bringing to fruition this 5,050 patient trial, which was conducted in 43 countries over the past 3 years, was a substantial endeavor. Along with our academic partners at the Duke Clinical Research Institute and industry sponsors Bayer and Merck, it was a great and true team collaboration. I am proud of how well our CVC team performed and the excellent work performed by Tracy Temple and Dr. Justin Ezekowitz. Importantly, the trial met its primary endpoint and we can look forward to having a new therapy to address unmet needs for our patients with advanced heart failure in the future. An additional benefit of this project is the rich data set we now can access thanks to Dr. Westerhout’s leadership. This is leading to key new insights and rich academic offerings that will help us better understand and care for patients with high-risk heart failure. Our team is privileged to work with thought leaders around the world to help bring their hard work to fruition based on the informative learnings from this collaboration.

Over the past decade, our analysts have matured and begun to master understanding large data sets. Machine learning and artificial intelligence have facilitated more adroit and timely access to our rich population health data in Alberta. We are more aware of how well the evidence garnered from clinical trials and incorporated into care guidelines is actually being applied. Learning the consequences of this precept is fundamental to guiding health policy and designing future research. As our research portfolio became more balanced with a greater focus on population health and real world evidence, it was clear that appointing Dr. Padma Kaul as a new Co-Director was an obvious and important addition to strengthen our leadership team.

This 2019 annual report is entitled A Decade of Discovery. How does one define discovery? There are over 40 suggested synonyms for this word but I hope readers of this report will focus on the verbs detect, reveal, unearth and originate. Within this year’s report, I am confident you will discover all of these at work.

Notwithstanding the extraordinary changes we have witnessed in the past decade, I believe the CVC mission remains a shining north star to guide us… "Knowing is not enough; we must apply. Willing to master understanding large data sets. Machine learning and artificial intelligence have facilitated more adroit and timely access to our rich population health data in Alberta. We are more aware of how well the evidence garnered from clinical trials and incorporated into care guidelines is actually being applied. Learning the consequences of this precept is fundamental to guiding health policy and designing future research. As our research portfolio became more balanced with a greater focus on population health and real world evidence, it was clear that appointing Dr. Padma Kaul as a new Co-Director was an obvious and important addition to strengthen our leadership team.

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Notwithstanding the extraordinary changes we have witnessed in the past decade, I believe the CVC mission remains a shining north star to guide us. Generating, translating and disseminating knowledge on novel diagnostic and therapeutic strategies in cardiovascular medicine acquired through global collaborative research.

It will be for others to judge whether we have succeeded and to what extent our work has energized careers, affected the thoughts and actions of others, and influenced health care policy.
VISION, MISSION, AND CORE VALUES

VISION
Generate, translate, and disseminate knowledge on novel diagnostic and therapeutic strategies in cardiovascular medicine acquired through collaborative research to enhance the health of the citizens of Alberta, Canada, and the world.

MISSION
Aligned with the University of Alberta and the Mazankowski Alberta Heart Institute (MAHI), our mission is to:
- Design, conduct, analyze, and disseminate findings arising from novel clinical research.
- Interrogate clinical trial, registry, and population health data to evaluate outcomes, identify unmet needs, and inform future basic and clinical research directions.
- Identify, inspire, and nurture the next generation of health researchers and professionals.

CORE VALUES
Quality
Aspire to the highest standard of work while respecting a balanced life perspective. Attract, mentor, and retain high quality colleagues and collaborators with similar core values.

Collaboration
Promote and support an outstanding team that integrates a diversity of knowledge, experience, ideas, and skills supportive of our mission/vision.

Integrity
Perform our roles in an ethical framework, which enhances our reputation as honest, trustworthy, and responsible.

Respect
Create an innovative, engaging, and inclusive work environment, appreciative of individual differences and contributions. Our workplace will be conducive to personal growth and development that is aligned with our overall mission.
THE VALUE OF AN ARO

AS AN ACADEMIC RESEARCH ORGANIZATION (ARO), THE CVC:

- Is committed to the scholarly value of scientific inquiry and truth, and believes knowledge should be shared openly in an ethical research environment.
- Is dedicated to enhancing public health and values discovery, novel approaches, and methodologies over profit.
- Strives to exceed the operational efficiencies of a clinical research organization (CRO), and intentionally seeks funding from diverse sources beyond industry.
- Is connected with a university, and therefore, reserves the right to publish all insights with objectivity.
- Functions as a not-for-profit and reinvests all sources of capital, both financial and intellectual, into the education of the next generation of health professionals, thereby aiming to fulfill our social contract to promote the public good.
As a learning organization committed to enhancing the health of current and future generations through research, the CVC relentlessly pursues the generation, translation, and dissemination of new knowledge addressing unmet clinical needs. This culture of learning embraces the cycle of quality that begins with health science discovery, followed by its application to human disease using careful quantitative and qualitative measures. For discovery to have an impact, its efficacy must be first examined in controlled populations. Subsequently, the effectiveness needs to be evaluated through performance measures in carefully crafted patient registries acquired in selected disease states. To complete this cyclical process, there must be successful dissemination of new knowledge into clinical practice resulting in meaningful differences in health outcomes at the population level. Health economic evaluation, demonstrable return on investment, and responsive health policy enrich the success and timeliness of this journey. Professional and public education are seminal components of the process occurring in parallel. The inevitable destination of this construct is a new appreciation for the unmet needs of the population and re-entry into the cycle to continue the quest for improvement in clinical and/or health system outcomes.

*Adapted Califf RM Heart 2008*
COLLABORATORS

The CVC has forged strong partnerships with a number of institutions and centres around the world in the pursuit of novel research directions and the advancement of cardiovascular research. The CVC takes great pride in our relationships with these collaborators, who are internationally recognized leaders in the advancement of cardiovascular research.

The map illustrates the CVC’s worldwide network of collaborators.
This year’s theme - A Decade of Discovery - celebrates the pathway forged by the CVC, both as it relates to our organization’s history and future vision. The following timeline outlines the innovative and expansive research projects undertaken by the CVC over the past ten years, and highlights some of the key contributions of our faculty, staff, and trainees. This reflection on the last decade demonstrates both the CVC’s dedication to discovery and the continuing pursuit of the vision that has steadfastly guided our organization throughout the years.
Clinical research could be a challenging and even intimidating experience for the beginner, I was fully supported and intellectually encouraged by Drs. Paul Armstrong and Cynthia Westerhout, which made my first taste of cardiovascular research exciting and very stimulating. The CVC is an excellent media for planting the seeds of future researchers; the educational, professional and interpersonal atmosphere is the ultimate necessity for the motivation of trainees to continue on their research efforts and complete great projects.

— Olga Toleva, MD
Cardiology Trainee in 2010

The ASCEND-HF, IMPROVE-IT, and TRACER clinical trials completed patient enrollment in 2010. Total enrollment in Canada for the three trials was 2,155 patients. Dr. Paul Armstrong served as a thought leader for all three trials, and the CVC also undertook trial management within Canada.

Predicting Chronic Left Ventricular Dysfunction 90 Days After ST-Segment Elevation Myocardial Infarction: An Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) Substudy.

(Am Heart J. 2010;160:272-278)

Dr. Justin Ezekowitz and his fellow co-authors determined predictors of 90-day left ventricular function following acute ST-segment elevation myocardial infarction (STEMI) using variables from clinical presentation, biomarker testing, and cardiovascular magnetic resonance imaging. Their findings demonstrated a clear link between infarct size, microvascular obstruction, and NT-proBNP in predicting subsequent left ventricular infarct size, microvascular obstruction, and NT-proBNP.

The study found that compared to clopidogrel therapy, intravenous and oral eptifibatide therapy did not significantly increase TIMI major or minor bleeding, but was associated with higher rates of bleeding requiring medical attention.

There were a total of 652 patients randomized from 5 countries. Canada contributed 132 of the patients in this trial from 12 sites across the country. Dr. Robert Welsh acted as the co-principal investigator and chair for this study and was actively involved in protocol development and guidance throughout. The CVC undertook trial management within Canada.

Electrocardiographic Identification of the Culprit Coronary Artery in Inferior Wall ST-Elevation Myocardial Infarction.

(Can J Cardiol. 2010;26:293-296)

This collaboration between CVC trainee Dr. Mohammed Almansori, cardiology fellow (2010), CVC faculty Drs. Padma Kaul and Paul Armstrong, and Dr. Yuling Fu, ECG Core Lab Director (2010), demonstrated the usefulness of the electrocardiogram (ECG) in identifying right coronary artery (RCA) involvement in inferior wall myocardial infarction before angiography. In this study, a simple algorithm was generated from a large cohort of patients and it was determined to be a potentially useful tool in identifying RCA involvement at the bedside.

Dr. Padma Kaul was appointed Director of Health Outcomes at the CVC.

Dr. Padma Kaul received a Canadian Institute of Health Research grant for her project “Tracking Gender Differences in Acute Coronary Syndromes: At the First Point of Care and Beyond.” This project examined sex differences in the presentation, treatment and outcomes of patients with acute coronary syndromes. As part of the project, Dr. Kaul examined why women with heart attacks delay seeking medical attention and the consequences resulting from this delay.

The Academy brings together Canada’s top-ranked scientists to make a positive impact on the urgent health concerns of Canadians.

Dr. Finlay McAlister was elected to the Canadian Academy of Health Sciences, in recognition of sustained research excellence in health. The Academy brought together Canada’s top-ranked scientists to make a positive impact on the urgent health concerns of Canadians.

The INNOVATE-PCI study was presented on August 30, 2010 at the European Society of Cardiology Congress Hotline Session in Stockholm, Sweden. The study evaluated the safety, efficacy, and tolerability of eptifibatide in patients undergoing nonurgent percutaneous coronary intervention. The study found that compared to clopidogrel therapy, intravenous and oral eptifibatide therapy did not significantly increase TIMI major or minor bleeding, but was associated with higher rates of bleeding requiring medical attention.

Dr. Finlay McAlister was awarded a Canadian Institute of Health Research grant for the project “Evaluating the Impact of a Province Wide Disease Management Program on Heart Failure Outcomes in Alberta.” Between February 2008 and October 2008, the Alberta Government spent $11.8 million on an integrated strategy to improve care for cardiac patients in Alberta ($3.8 million of which was earmarked for improving heart failure care) – this program was titled the Alberta Cardiac Access Collaborative (ACAC). Dr. McAlister’s grant evaluated the impact of the ACAC on heart failure care in Alberta.

Dr. Robert Welsh became the Director and Founder of the Peripheral Chest Pain Program at the Mazankowski Alberta Heart Institute.
The TRACER study evaluated the safety and efficacy of adding a new thrombin receptor antagonist (vorapaxar) to the standard of care for a minimum of one year in patients with non-ST-segment elevation acute coronary syndrome.

The trial results were presented at the American Heart Association Scientific Sessions in Orlando, Florida in November, 2011 as a late breaking clinical trial, and were simultaneously published in the New England Journal of Medicine. The results showed that in patients with acute coronary syndromes, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite endpoint but significantly increased the risk of major bleeding, including intracranial hemorrhage.

Dr. Paul Armstrong served as a member of the study executive committee, and the CVC undertook trial management within Canada.

The ARISTOTLE Trial sought to determine if apixaban, an investigational anticoagulant is as effective as standard therapy (warfarin) in preventing stroke and systemic embolism in subjects with atrial fibrillation and risk factors for stroke.

The study results were presented in August 2011 at the European Society of Cardiology Congress in Paris, France, and were simultaneously published in the New England Journal of Medicine. In this study of a population of 15,000 high-risk patients with atrial fibrillation, it was found that apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Dr. Justin Ezekowitz was a principal investigator and a member of the steering committee for the trial.
The CVC ECG Laboratory provides useful insight into our organization’s conduct of clinical trials and care of patients. Arising from PLATO, a platelet inhibition and patient outcomes trial, this ECG substudy of over 6,000 patients demonstrated that the extent of deviation of the ST-segment on the baseline ECG was independently associated with one year vascular death and recurrent myocardial infarction.

Dr. Finlay McAlister was appointed the Capital Health Research Chair in Cardiovascular Outcomes.

Dr. Shaun Goodman, based out of St. Michael’s Hospital in Toronto, Ontario, was appointed a member of the CVC faculty.

Dr. Justin Ezekowitz was appointed an Associate Professor in the Division of Cardiology, Department of Medicine at the University of Alberta.

Launched in 2012 and led by Dr. Robert Welsh, the RemCon-STEMI study tested the impact of remote ischemic conditioning in acute ST-elevation myocardial infarction (STEMI). Following acute STEMI, patients may have significant myocardial damage and subsequent heart failure. Remote ischemic condition is a process whereby repetitive intermittent limb ischemia is used to decrease the magnitude of myocardial damage caused by coronary artery occlusion and the subsequent reperfusion injury in STEMI patients.

Dr. Justin Ezekowitz undertook a substudy of the ASCEND-HF trial, which included 400 patients from 37 participating institutions in Canada and the United States. By carefully monitoring characterizing changes in shortness of breath with spirometry (an established measurement of lung and airway function used in patients with respiratory disease), Drs. Ezekowitz, Paul Armstrong, and co-authors established the clinical utility of this method, thereby setting an important new platform for future studies of acute heart failure.

Dr. Neda Dianati Maleki joined the CVC in 2012 and worked under the guidance of Dr. Paul Armstrong in the ECG Core Laboratory on the STREAM clinical trial and PROACT projects.


Q waves have been shown to be a stronger prognostic marker than time from symptom onset to percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction. Dr. Padma Kaul and co-authors examined whether the relative importance of these two measurements is modulated by patient gender. It was determined that baseline Q wave is a better marker of risk of 90-day mortality than time from symptom onset to PCI, overall, and especially in women.

Dr. Justin Ezekowitz was awarded a grant from the University Hospital Foundation for the SODIUM-HF pilot trial. An increasing number of people are being diagnosed with heart failure in Canada. Patients with heart failure are recommended to reduce the amount of salt in their diet, but the total amount of salt that patients with heart failure should consume per day is not clear. The SODIUM-HF Trial was proposed to address this challenge.
The Alberta COAPT study was launched in 2013. The study, which is still ongoing, examines Albertans diagnosed with acute cardiac syndromes (ACS) for whom three years of follow-up data is available, focusing on patients undergoing cardiac catheterization during the index hospitalization. Alberta COAPT data have been used for several research projects, including:

- Evaluating short- (30-day) and long-term (1-year) clinical outcomes for patients with ACS, including death, myocardial infarction, repeated revascularization, and repeat hospitalization and associated treatments (medical management versus percutaneous coronary intervention versus coronary artery bypass grafting).
- Analyzing medication efficacy.
- Analyzing costs associated with each therapeutic strategy.

CVC faculty involvement includes Drs. Robert Welsh, Kevin Bainey, Paul Armstrong, and Padma Kaul.

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Dr. Paul Armstrong was awarded both the University Cup and the Margolese National Heart Disorders Prize in 2014. The University Cup is a capstone award from the University of Alberta for outstanding contributions in teaching, research, and service. The Margolese National Heart Disorders Prize is awarded by the University of British Columbia annually to a Canadian who has made outstanding contributions to the treatment, amelioration, or cure of heart disease.

**2014 Use of Renin–Angiotensin System Blockers in Acute Coronary Syndromes: Findings from Get With The Guidelines-Coronary Artery Disease Program.**

*(Circ Cardiovasc Qual Outcomes. 2014;7:227-235)*

In this paper, Drs. Kevin Bainey and Paul Armstrong, along with their co-authors, examined the role of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), both of which are known to improve survival after an acute coronary syndrome (ACS). Results from this large US national registry suggest that 1 in 5 eligible patients hospitalized for ACS failed to receive American College of Cardiology/American Heart Association class I guideline-recommended ACEI/ARB therapy, and the use varies by patient factors. These findings highlighted an unmet need in this population and provided an incentive for additional quality improvement efforts. This work originated from Dr. Bainey’s training in Boston and was subsequently undertaken during his faculty appointment at the University of Alberta and the CVC.

The results of the IMPROVE-IT trial were presented in November 2014 at the American Heart Association meeting as a late breaking clinical trial. The IMPROVE-IT trial represents the first time that adding a non-statin lipid modifying agent to patients’ secondary prevention regimen not only resulted in even lower low-density lipoprotein (LDL) cholesterol levels, but led to a significant reduction in subsequent cardiovascular events.

The team at the CVC undertook trial management in Canada for IMPROVE-IT, and Dr. Paul Armstrong was both a member of the steering committee and a national leader for the study.

**Increased Uptake of Guideline-Recommended Oral Antiplatelet Therapy: Insights from the Canadian Acute Coronary Syndrome Reflective.**

*(Can J Cardiol. 2014;30:1725-1731)*

In this multi-authored report anchored by CVC Co-Director Dr. Shaun Goodman and faculty member Dr. Robert Welsh, the value of collaboration with front-line Canadian internists, cardiologists, pharmacists, nurses, and other allied health care providers is evident. This study tracked the uptake of new guideline based recommendations on the use of novel anti-platelet agents in over 3,000 patients assessed in 83 Canadian hospitals, and found relative underuse of the newer agents shown to produce clinical benefit. This treatment gap highlighted some of the challenges in translating research discovery into the “real world” and signalled the need to overcome barriers to implementing guideline based therapy.

**Increased Uptake of Guideline-Recommended Oral Antiplatelet Therapy: Insights from the Canadian Acute Coronary Syndrome Reflective.**

*(Can J Cardiol. 2014;30:1725-1731)*

In this multi-authored report anchored by CVC Co-Director Dr. Shaun Goodman and faculty member Dr. Robert Welsh, the value of collaboration with front-line Canadian internists, cardiologists, pharmacists, nurses, and other allied health care providers is evident. This study tracked the uptake of new guideline based recommendations on the use of novel anti-platelet agents in over 3,000 patients assessed in 83 Canadian hospitals, and found relative underuse of the newer agents shown to produce clinical benefit. This treatment gap highlighted some of the challenges in translating research discovery into the “real world” and signalled the need to overcome barriers to implementing guideline based therapy.

"Dr. Armstrong has been a great mentor. He has taught me how to separate noise from signal, think tangentially yet not lose focus and has moulded me into an all-round clinician, steps that I would be proud to emulate in the future." – Jay Shavadia, MD

Cardiology Fellow in 2014
Dr. Padma Kaul received the American Diabetes Association (ADA) Vivian Fonseca Scholar Award for her abstract “Ethnic Differences in Gestational Diabetes Mellitus: A Population-Level Analysis.” (first author, Rose Yeung, MD), which was submitted to the 2015 ADA Scientific Sessions. This award recognizes diabetes research focused on the South Asian, Asian American, Native Hawaiian, and Pacific Islander populations and research by a scientist from these areas of the world.

Dr. Robert Welsh was appointed the Alberta Health Services Zone Clinical Department Head for Cardiac Sciences in the Edmonton Zone.

Dr. Kevin Bainey was appointed Co-Director of the Alberta Acute Coronary Syndrome Group for the Cardiovascular Health and Stroke Strategic Clinical Network at Alberta Health Services.

Dr. Sean van Diepen was appointed Co-Director of the Coronary Intensive Care Unit at the University of Alberta Hospital.

Dr. Finlay McAlister was awarded the Killam Annual Professorship by the University of Alberta, recognizing his outstanding scholarship and significant academic contributions to both the University of Alberta and the Canadian research community.

It’s a great honour but it’s not an individual honour: it’s recognizing the people I work with both clinically and in research. I have great colleagues and collaborators and any award of this type is a recognition of the entire team. Nobody does this work in a vacuum.

– Finlay McAlister, MD, MSc

TECOS was a large pragmatic international study designed to assess the impact of sitagliptin versus placebos on cardiovascular events. This intervention was added to usual diabetes care and undertaken in nearly 15,000 patients with type 2 diabetes who already had an established cardiovascular disease. The results were presented in June 2015 at the American Diabetes Association meeting, and were simultaneously published in the New England Journal of Medicine. The study showed sitagliptin did not aggravate heart failure or other ischemic endpoints over the three years of follow up care as had been suggested previously with a number of diabetes drugs, including one within the class of Dipeptidyl Peptidase-4 Inhibitors where sitagliptin resides.

Dr. Paul Armstrong served as a member of the executive committee and the CVC undertook trial management within Canada.

CICU

Dr. Justin Ezekowitz was awarded a grant from the Heart and Stroke Foundation of Canada for the HiLo-HF study. Supplemental oxygen (O₂) therapy is a routine treatment in the management of many patients with dyspnea, including those with acute heart failure (AHF). This study investigated the effect of O₂ titrated to a high versus low pulse oximetry target in patients hospitalized with AHF.

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Applying Novel Methods to Assess Clinical Outcomes: Insights From the TRILOGY ACS Trial. (Eur Heart J. 2015;36:385-392a)

Several methods provide new insights into understanding clinical trial composite endpoints, using both conventional and novel methods. In this paper, the TRILOGY ACS trial was used as a contemporary example to prospectively compare these methods side by side.

The study authors, including Drs. Paul Armstrong, Shaun Goodman, and Cynthia Westerhout, considered the relative efficiency of various methods for assessing clinical trial events comprising the composite endpoint. The methods accounting for all events, in particular those incorporating their clinical relevance, appear most advantageous and may be useful in interpreting future trials. This clinical and statistical advantage is especially evident with long-term follow-up where multiple non-fatal events are more common.

The University of Alberta’s Department of Medicine hosted the Paul Armstrong Symposium, an academic celebration and gala dinner to honour Dr. Paul Armstrong’s 35 years of exemplary care, discovery, and mentorship as a cardiologist. The symposium featured presentations from four internationally renowned cardiologists: Drs. Frans Van de Werf, Robert Califf, Eric Peterson, and Robert Harrington, whose professional lives were inextricably linked to Dr. Armstrong.

2015
Failure Exacerbation: The Importance of Early Follow-Up After a Heart Failure Exacerbation.

Youngson, explored whether longer follow-up within 14 days, the authors, Drs. Finlay McAlister, Padma Kaul, Justin Ezekowitz, and CVC collaborator Erik Kaul, examined whether longer follow-up within 14 days, and physician continuity would influence outcomes within 30 days of a heart failure exacerbation. They concluded that outpatient follow-up within 14 days is associated with better outcomes, and outcomes are best if such follow-up is done by a physician familiar with the patient. This work is a great example of how accessing data from the rich Alberta population database informs how well clinical practice adheres to guidelines, and what lessons can be learned to improve patterns and systems of care in the future.

Temporal and Provilional Variation in Ambulance Use Among Patients Who Present to Acute Care Hospitals With ST-Elevation Myocardial Infarction.

Drs. Padma Kaul, Robert Welsh, Paul Armstrong, and Anamaria Savu examined the temporal and provincial variation in ambulance use among patients who presented to Canadian acute care hospitals with ST-segment elevation myocardial infarction. Hospital data from the Canadian Institutes of Health Information were queried in all provinces (except Quebec) from 2007 to 2013. The proportion of patients who presented by ambulance increased from 60% to 68%. The authors found that substantial variation in its use across the provinces existed, with Alberta recording the highest percentage of ambulance use in 2012.

Do Stable Non-ST-Segment Elevation Acute Coronary Syndromes Require Admission to Coronary Care Units?

The CVC has undertaken study management in Canada and our ECG core laboratory carries out ECG assessments and adjudication for STREAM-2. Additionally, Dr. Paul Armstrong is the study chair and Dr. Robert Welsh is the Canadian principal investigator for the study. The STREAM study demonstrated that a pharmacoinvasive strategy was at least as effective as primary PCI (pPCI) in patients presenting early with ST-elevation myocardial infarction (STEMI). The STREAM-2 study was launched in 2016 as a response to the finding that reduced intracranial hemorrhage in elderly patients occurred after halving the dose of tenecteplase. This ongoing study will provide new insights aimed at establishing an effective and safer pharmacoinvasive treatment for the growing population of older STEMI patients who cannot undergo timely pPCI.

The CVC launched a new logo, which was designed by a student from the University of Alberta’s Department of Art & Design. The logo reflects both the CVC’s proud history and bold future vision, and also embodies the shape of a heart, an image that is central to the organization’s objectives and identity. The heart is in turn formed by three distinct parts – the letters C, V, and C.
In this paper, Drs. Cynthia Westerhout and Paul Armstrong provided new insights and a rationale for how future clinical trials could be better composed. They proposed that this could maximize trial efficiency and anticipated that the emerging big data revolution may provide an even broader scope of outcomes than ever before. Additionally, they suggested that leading associations of healthcare professionals, patient engagement groups, journal editors, and regulatory agencies collaborate to establish more uniformly accepted calibration of clinical endpoint definitions, and their relative significance, by weighting them in a more meaningful sense.

The CONNECT AF+PCI study was launched in 2017. Patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention have traditionally been treated with “triple therapy” including aspirin, P2Y12 receptor inhibitor, and oral anticoagulant. This ongoing research initiative was launched in order to report the translation of this emerging data in contemporary Canadian practice and identify opportunities for optimization of antithrombotic and bleeding risk in such patients. CVC faculty members Drs. Shaun Goodman (study chair), Robert Welsh (steering committee member), and Kevin Baney (co-author) are involved in the study.

The LEVO-CTS trial results were presented in March 2017 at the American College of Cardiology Annual Scientific Sessions in Washington, DC, and were simultaneously published in the New England Journal of Medicine. The study reported no statistically significant differences in the co-primary composite outcomes of death, renal replacement therapy, peri-operative myocardial infarction, or the use of mechanical assist devices; or death or mechanical assist device use. Lewis and her colleagues, however, increased cardiac output; reduced the incidence of post-operative low cardiac output syndrome, and the use of inotropes beyond 24 hours without an increase in pre-specified safety endpoints or post-operative adverse events. Taken together, this is the first trial of an inotropic therapy in the cardiac surgical population to demonstrate hemodynamic efficacy and safety. The CVC undertook trial management in Canada, and Drs. Shaun Goodman and Sean van Diepen both served as members of the Canadian leadership team. Dr. Justin Ezekowitz was appointed a member of the College of New Scholars, Artists, and Scientists by the Royal Society of Canada. Those named to the College represent the emerging generation of scholarly, scientific, and artistic leadership in Canada.

Dr. Padma Kaul was awarded a Canadian Institute of Health Research grant for her project “Impact of Maternal Diabetes Status on Neonatal and Early Childhood Outcomes.” Due to increasing maternal age and obesity, diabetes during pregnancy is becoming a serious healthcare challenge. This ongoing project uses population health data to assess the health impacts of pre-existing (type 1 or type 2) and gestational diabetes. It describes the relative risks of the different diabetes types, as well as the types of treatments used and their links to adverse pregnancy and neonatal health outcomes. This work builds on Dr. Kaul’s previous research in the area of gestational diabetes epidemiology and outcomes. Dr. Justin Ezekowitz and Padma Kaul were both appointed as Professors in the Division of Cardiology, Department of Medicine at the University of Alberta.
MINOCA is a known clinical conundrum with limited investigation. In this paper, Drs. Kevin Bainey, Robert Welsh, Wendimagegn Alemayehu, Cynthia Westerhout, Paul Armstrong, Padma Kaul, and co-authors analyzed patients who have myocardial infarction, yet they have little or no evidence of coronary arterial narrowing. This population, previously thought to have a benign prognosis, in fact turns out to have impaired 5-year outcomes as it relates to both cardiac mortality and recurrent myocardial infarction.

Dr. Padma Kaul was featured in the cover story for Momentum Magazine, a publication from the University of Alberta’s Faculty of Medicine & Dentistry. The article, “Big Data Opens Door to Big Possibilities in Health Care,” examines the promise of big data to revolutionize everything from prevention to diagnosis to treatment.

Dr. Finlay McAlister gave the Canadian Society of Internal Medicine (CSIM) and the Royal College of Physicians and Surgeons of Canada Osler Lecture at the 2018 annual CSIM meeting. His presentation, entitled “Precision Medicine and the General Internist,” explored the potential benefits and limits of precision medicine in the practice of general internal medicine.

Dr. Paul Armstrong was named an Officer of the Order of Canada, Canada’s highest civilian honour, for his “contributions to the advancement of cardiology, notably for his pioneering research in acute cardiac care, and for his leadership in health care institutions.” (photo credit: Sgt Johanie Maheu, Rideau Hall © OSGG, 2018)

Dr. Justin Ezekowitz was awarded a grant from the University Hospital Foundation for the FEAST-HF trial. FEAST-HF is a single-centre clinical trial in ambulatory patients with chronic heart failure (HF) that evaluates whether dietary supplementation with acacia gum reduces HF-related biomarkers NT-proBNP and ST2 and how the gut microbiome responds to dietary supplementation with acacia gum.

Dr. Sean van Diepen received the Best Paper of the Year Award from the University of Alberta’s Department of Critical Care Medicine for his publication “Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association.” This award is given to a physician member within the department for the best published peer-reviewed paper.


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The ODYSSEY OUTCOMES trial results were presented as a late-breaking clinical trial at the American College of Cardiology Scientific Sessions in Orlando, Florida in March 2018, and subsequently published in November 2018 in the New England Journal of Medicine.

ODYSSEY OUTCOMES is a landmark research study proving that a new cholesterol-lowering agent - a monoclonal antibody called alirocumab - improves outcomes among patients who have had a previous acute cardiac event and who were already receiving high-dose conventional statin therapy. Importantly, this new agent is administered as an injection under the skin once every two weeks. Dr. Shaun Goodman was a member of the executive committee, and the CVC undertook trial management within Canada.

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Dr. Sean McMurtry and Roopinder Sandhu were appointed associate faculty members at the CVC.

My first exposure to the CVC was working with Dr. Paul Armstrong as a cardiology resident. He is an inspiring figure who has built the strong and productive research enterprise that is the CVC.

– M. Sean McMurtry, MD, PhD

The area of clinical research that interests me the most is arrhythmia (atrial fibrillation and syncope) health outcomes research. This research aligns itself well with the CVC’s strengths of conducting clinical trials, and population health and economic research.

– Roopinder Sandhu, MD, MPH


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Dr. Paul Armstrong presented the Paul Dudley White International Lecture at the American Heart Association Scientific Sessions in Philadelphia, Pennsylvania in November 2019. His presentation on “Enhancing Cardiovascular Care: Global Collaboration is How it Happens,” was followed by a Fireside Chat with Drs. Christopher Granger, Frans Van de Werf, Padma Kaul, and Cynthia Westerhout.

In this article Dr. Sean McMurtry and co-authors describe an initiative led by the Canadian Cardiovascular Society to determine the feasibility and outcomes of a structured process for considering sex in a clinical practice guideline (CPG) for the management of ST-segment elevation myocardial infarction (STEMI).

The authors concluded that incorporating a systematic appraisal of sex evidence as part of CPG development is straightforward and feasible. Major challenges with the published literature on CPG development is straightforward and feasible.

The results of the VICTORIA trial were presented in March 2020 as a late breaking clinical trial at the American College of Cardiology/World Congress of Cardiology Scientific Sessions and simultaneously published in the New England Journal of Medicine.

In this article, Drs. Paul Armstrong, Justin Ezekowitz, Cynthia Westerhout, and co-authors described the distinguishing features of the VICTORIA trial patient population. Patients suffering from heart failure with reduced ejection fraction (HFrEF) experience further worsening of their heart failure (HF) despite receiving best contemporary standard of care. VICTORIA was designed to capture a HF population at increased risk for mortality and rehospitalization that represents a major continuing therapeutic challenge.

This publication was recognized as one of the top downloaded papers of 2018-2019 by the European Journal of Heart Failure.

The VITALITY-HFpEF trial was designed to capture a HF population at increased risk for mortality and rehospitalization that represents a major continuing therapeutic challenge. This study will examine the uncertainties that exist regarding the current real world management and outcomes of patients with chronic atherosclerotic vascular disease.
A DECADE OF DATA


34

CLINICAL TRIALS MANAGED BY THE CVC

1,030+

PUBLICATIONS PRODUCED BY THE CVC

7,400+

PATIENTS ENROLLED BY THE CVC IN CLINICAL TRIALS

75,000+

ECGs ANALYZED BY THE CVC ECG CORE LABORATORY

2.5 M

CANADIANS REPRESENTED IN THE CVC’S DATA REPOSITORY
INTRODUCING NEW CO-DIRECTOR
DR. PADMA KAUL

Dr. Padma Kaul is an epidemiologist and health services researcher who examines issues related to access, outcomes, and costs of cardiovascular disease. Her research portfolio includes projects focused on diabetes and heart disease at every life-stage. In 2019, Dr. Kaul took on a new role at the CVC as a Co-Director. In the following interview, she speaks about her time at the CVC, research initiatives, and future goals for the organization.

Q: You originally joined the CVC in 1998. How has your time with the organization influenced your research and professional experiences?

It is pretty incredible how time has flown! When I joined the CVC, I was a PhD student and the research group consisted of Dr. Paul Armstrong, and two other people. Today, the CVC’s research core consists of nine PhD-level biostatisticians, epidemiologists, research associates, and data scientists, and five Masters-level statisticians and analysts, and also supports the research portfolios of ten faculty members. The CVC has broadened beyond an organization focused primarily on clinical trials to one that also examines real world evidence from clinical registries and population-health administrative data. This broader mandate has been the single most overarching element of my career. First as Director, Health Outcomes (from 2011 – 2019) and now as the Co-Director of the CVC, I have worked closely with our colleagues in Alberta Health and Alberta Health Services (AHS), to develop longitudinal population-level cohorts of patients with cardiovascular disease, tracking them across multiple health care settings. These data have been a tremendous resource for our faculty who have used them to examine the epidemiology of heart disease and to address important questions related to access to care, health outcomes among vulnerable populations, and health care costs. Importantly, they have the potential to influence the path of future clinical investigation.

Q: What are your top priorities as a Co-Director? Are there any specific initiatives or projects that you would like to carry out?

The CVC has identified the following strategic directions for the next five years: 1) clinical trials, 2) population health and real world evidence, 3) data science, and 4) patient engagement, knowledge translation, and dissemination. Although I intend to support activities in all our strategic areas of interest, my top priorities as Co-Director will be around population health and data science. I am keen to work with our colleagues in AHS, particularly the AHS Cardiovascular Health and Stroke Strategic Clinical Network (CvHS SCN) to understand how the CVC can continue to provide evidence addressing cardiovascular issues where high geographic variability, controversy, or cost reside.

The volume of health data, especially as we attempt to incorporate electronic medical record data, has brought us into the realm of “big-data,” i.e., data that are considered too large or complex to be processed using traditional data processing tools. Big-data analytics and employing artificial intelligence techniques such as machine-learning in the analysis of health data has now become a major priority for the CVC. Accordingly, we have assembled an excellent team of computer scientists, led by Dr. Sunil Kalamady. Our team is working closely on several projects with the University of Alberta’s computer science faculty and we are looking forward to future collaborations with our international colleagues.

Q: The 2019 annual report celebrates a decade of discovery. Is there a specific highlight from the past ten years that is particularly meaningful to you?

The development of the Alberta pregnancy-birth cohort has been my baby (pun intended). The cohort, which includes data on all women who have had live births in Alberta since 1999, was developed to support our research into the epidemiology and outcomes of gestational diabetes mellitus (GDM). GDM is glucose intolerance first recognized during pregnancy and, although it is generally a temporary condition and resolves post-partum, it is an established risk factor for the subsequent development of type 2 diabetes, not only for the mother but also for the child. This unique integrated database includes detailed information on the mother, including demographics, clinical and obstetrical outcomes, and laboratory data such as glucose, creatinine, and cholesterol; as well as on the child, including birth weight, neonatal intensive care unit (NICU) stay, and mortality.

The longitudinal aspect of the cohort has allowed us to examine the long-term impact of pregnancy factors on chronic disease development in both the mother and the child. For example, we have recently received funding from the Canadian Institute of Health Research to examine the association between GDM and preeclampsia during pregnancy and the long-term development of cardiovascular disease in the mother. This project will bring together pregnancy-birth cohorts from Alberta and Denmark. Similarly, as part of a peer-reviewed grant from Novo-Nordisk Canada and the University Hospital Foundation, we are using the Alberta pregnancy-birth cohort to examine the social and clinical determinants of childhood obesity in Alberta.

Q: What do you hope to see the CVC accomplish in the next decade?

It is amazing to see what our faculty, staff, and trainees have accomplished in the last decade. I hope that the CVC maintains its trajectory as an internationally-recognized organization known for generating excellent cardiovascular research. I also hope that we will fulfill our social contract by providing evidence that is relevant to health care decision/policy makers, thus completing the cycle of quality and developing a learning health care system in Alberta.
Pharmacoinvasive Strategy Versus Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction in Clinical Practice: Insights from the Vital Heart Response Registry.


This is an important observational analysis from our STEMI network (Vital Heart Response) which supports prevailing evidence and confirms our use of a selective pharmacoinvasive strategy. – Kevin R. Bainey, MD

Recent clinical trial data support a pharmacoinvasive strategy as an alternative to primary percutaneous coronary intervention (pPCI) in ST-segment elevation myocardial infarction (STEMI). In this article, the authors compared electrocardiogram (ECG) core-lab assessments of reperfusion and clinical outcomes of patients receiving pharmacoinvasive reperfusion versus pPCI in patients with STEMI followed in a large comprehensive Canadian registry.

The research concludes that, in a large comprehensive STEMI network registry based in an integrated prehospital and community dual reperfusion program, a selective pharmacoinvasive strategy was associated with improved ST resolution after PCI with enhanced clinical outcome within 1 year follow-up. Evidence and confirms our use of a selective pharmacoinvasive strategy. – Kevin R. Bainey, MD

Frequency, Predictors, and Prognosis of Ejection Fraction Improvement in Heart Failure: An Echocardiogram-based Registry Study.

Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA.


The issue of HFrEEF is an important emerging issue and we need more research to determine which of these patients should stay on therapy life long and whom it could be safe to down-tate therapy in. – Finlay A. McAlister, MD

There is emerging interest in identifying the natural history and prognosis for heart failure (HF) patients exhibiting improvements in their left ventricular ejection fraction (LVEF) with treatment (HFrEEF). Cohort-studies and secondary analyses of randomized trials suggest that 10–20% of HF patients with LVEF <40% demonstrate improvement in LVEF. However, currently published studies on HFrEEF are subject to selection bias as they included only randomized trial participants or patients from selected specialty referral practices. The authors designed this retrospective cohort study to examine a broader spectrum of HF patients to establish the prevalence, predictors, and prognosis of patients with HFrEEF in contemporary clinical practice.

The research concludes that although HFrEEF is more common in women, those without ischaemic heart disease, and those with narrower QRS complexes at baseline, more work is needed to narrow the classification and develop a treatment strategy that targets these patients.

Effects of Alirocumab on Cardiovascular Events After Coronary Bypass Surgery.


I had the honour of leading this subgroup analysis as an Executive Steering Committee member. In addition, as the National Leader, with outstanding project leadership from the CVC team, we were able to support 38 Canadian centers throughout the 5-year course of this trial, facilitating the enrolment of 361 patients. Thus, the key findings from this paper – patients with prior CABG are at particularly high risk for important clinical events (including mortality) and the addition of alirocumab to maximally tolerated statin therapy substantially reduced the likelihood of having these adverse outcomes – are directly applicable to Canadian ACS patients. – Shaun G. Goodman, MD

Patients with acute coronary syndrome (ACS) and history of coronary artery bypass grafting (CABG) are at high risk for recurrent cardiovascular (CV) events and death. This study sought to determine the clinical benefit of adding alirocumab to statins in ACS patients with prior CABG in a pre-specified analysis of ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab). Among patients with recent ACS and elevated atherogenic lipoproteins despite intensive statin therapy, alirocumab was associated with large absolute reductions in major CV events and death in those with CABG preceding the ACS event.

Sex and Prognostic Significance of Self-Reported Frailty in Non–ST-Segment Elevation Acute Coronary Syndromes: Insights from the TRILOGY ACS Trial.


Hamlet’s assertion, ‘Frailty, thy name is woman!’ appears to no longer be true in the 21st century, at least not from the women’s point of view! Although women in our study were older and had higher rates of comorbidities, self-reported prevalence of frailty and its symptoms were similar between the two sexes. – Padma Kaul, PhD

The effect of sex on self-reported frailty in acute coronary syndromes (ACS) is unclear. In this article the authors examined the prevalence of self-reported frailty and its association with all-cause death among men and women. Self-reported frailty was collected at baseline for all patients aged ≥65 years in the TRILOGY ACS trial. Patients were asked to report unintentional weight loss; decreased grip strength; increased fatigue/lethargy or declining endurance; reduced normal walking speed over short distances; or decline in typical physical activity level.

The prevalence of self-reported frailty and its symptoms are similar among men and women presenting with ACS. Frailty increased with age among men only, and the association between frailty and all-cause mortality was more pronounced among men compared with women. Patient-reported frailty may be a useful marker to identify elderly patients with ACS at high risk of mortality.
High vs. Low Oxygen Therapy in Patients with Acute Heart Failure: HiLo-HF Pilot Trial.

Sepehrvand N, Alemayehu W, Rowe BH, McAlister FA, van Diepen S, Stickland M, Ezekowitz JA.


HiLo-HF was the first RCT to explore the effects of oxygen therapy in acute heart failure. As a pilot trial, it provided us with important lessons about how to address this question in the HF setting in future trials. – Nariman Sepehrvand, MD, PhD

Supplemental oxygen (O₂) therapy is a routine treatment in the management of many patients with dyspnea, including those with acute heart failure (AHF). In this pilot, open-label randomized controlled trial (RCT), the authors investigated the effect of O₂ titrated to high vs. low pulse oximetry targets in patients hospitalized with AHF. This RCT found no differences in the primary or secondary outcomes for patients randomized to high vs. low SpO₂ targets. Further RCTs with larger sample sizes are warranted to determine the efficacy and safety of O₂ therapy in patients with AHF.

Associations Between β-blocker Therapy and Cardiovascular Outcomes in Patients with Diabetes and Established Cardiovascular Disease.


With the emergence of newer drug classes demonstrating CV risk reduction in patients with diabetes, we should be thinking about the incremental secondary prevention role of some of the traditionally established standard of care. – Jay S. Shavadia, MD

This collaborative work was completed as part of Dr. Jay Shavadia’s Master’s of Science degree at Duke Clinical Research Institute. Type 2 diabetes (T2D) almost universally associates with clinical or subclinical accelerated atherosclerosis; consequently, of fundamental importance in patients with T2D is the optimization of secondary prevention pharmacotherapies. β-blockers have historically been integral to cardiovascular (CV) risk modification, and while the evidence for their use is most robust in patients with prior myocardial infarction (MI) and systolic heart failure (HF), high-quality evidence also exists to support broader indications for β-blocker therapy in patients with T2D.

In this article, the authors evaluated patients with T2D and established atherosclerotic cardiovascular disease (ASCVD) enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) to examine the association between β-blocker use at randomization (baseline) and within-trial CV outcomes.

In this comparative safety and effectiveness analysis, β-blockers appear to be utilized frequently in patients with T2D and ASCVD, yet there was no association between use of β-blockers and increased risk of severe hypoglycemic events, nor a decrease in risk of major adverse CV events, including in patients with prior MI or HF, supporting a randomized examination of chronic β-blocker therapy in this patient population.
THE NEXT GENERATION OF HEALTH RESEARCHERS

The foundation of the CVC mission is to enhance cardiovascular health for current and future generations, thereby fulfilling its societal contract. As a learning organization, one of the CVC’s central tenets is to engage the next generation of health professionals in a research culture that embraces curiosity, welcomes new ideas, and seeks to address key unanswered questions that are likely to alter the minds and actions of all those involved in health care delivery.

The CVC recognizes that a research experience can be life changing, whether during a summer studentship, an elective experience in clinical medicine, or through dedicated graduate or postdoctoral training. Whatever we provide to our trainees is inevitably returned to us bearing interest: this return on investment provides fresh and unbiased thinking, challenges to accepted dogma, and is formulated with an energetic and enthusiastic willingness to learn.

Irrespective of an individual trainee’s career plans, exposure to research galvanizes the development of a more critical mind that can then be applied to the unending search for better health solutions. An attitude of lifelong learning, coupled with a continuing commitment to remain engaged in the process of research—irrespective of individual career destinations—is our aspiration for research trainees.

In the following section, three of our trainees reflect upon their research highlights and experience collaborating with the CVC in 2019.
Briefly describe your educational background, and if applicable, what program you are currently enrolled in.

I have approached my education with the goal of training myself to be able to conduct impactful research towards ameliorating complex human diseases. I started with a BSc and MSc in medical biotechnology, which I then followed up with an MSc in computer science. Later, I finished my PhD in neuropsychiatry at the National Institute of Mental Health and Neurosciences in India, where I studied correlates of structural and functional brain abnormalities in schizophrenia. Prior to joining the CVC, I carried out my postdoctoral research on developing successful diagnostic and prognostic models for psychiatric disorders using functional magnetic resonance imaging (MRI) at the Alberta Machine Intelligence Institute and in the departments of Psychiatry and Computing Science at the University of Alberta.

What are your research highlights from your time at the CVC?

I have been working on a research project aimed at developing machine learning models to predict readmissions among heart failure patients. In parallel, I have been working on learning models to predict low birth weight using descriptors of mothers in Alberta. I have also started laying some groundwork towards implementing deep learning methods for identifying clinical diagnoses and outcomes from electrocardiogram (ECG) recordings.

What have you learned from working with your mentor(s) at the CVC?

I am grateful to have received the most gracious welcome into the world of cardiovascular research by my mentors and colleagues at the CVC. I am very appreciative of the amount of time and effort that Drs. Justin Ezekowitz and Padma Kaul took to provide guidance, encouragement, and academic support. I have witnessed from my interactions with them, as well as with Dr. Paul Armstrong and Ms. Karen Mellor, is the strength and the beauty of compassionate leadership. I deeply admire and aspire to learn their ability to passionately own a vision and drive it with integrity and humility.

How has your time at the CVC impacted your research or career goals? Are there any specific insights or lessons you will take forward with you?

The CVC has positively impacted my research goals by providing a collaborative and nourishing research environment. It has been a wonderful opportunity for me to explore some of the open scientific questions in the cardiovascular domain, as well as to become familiar with pragmatic challenges for data science research with large-scale population level data. The centre's dedication, enthusiasm, and insight into the core research problems is contagiously inspiring, and pushes me to relentlessly pursue my goal of advancing options for personalized treatment in complex medical disorders through application of machine learning.

How has your time at the CVC impacted your research or career goals? Are there any specific insights or lessons you will take forward with you?

I have enjoyed my time at the CVC and I am sure that the knowledge I gained about statistics during this period will be very important for my clinical practice. I would love to split my time between research and clinical practice, particularly since research is crucial to improving medicine.

My educational background is based in medicine and specifically on clinical practice. I completed my medical degree at the University of Milan, and I am currently a resident in Internal Medicine at the San Paolo Hospital in Milan.

What are your research highlights from your time at the CVC?

During the time I spent at the CVC, I was involved with several epidemiological projects using International Classification of Diseases (ICD) codes. In particular, I worked on three projects that were focused on:

- The incidence of pulmonary embolism in patients with syncope and unspecific chest pain
- Frailty and atrial fibrillation
- High users of health systems among patients with syncope

What have you learned from working with your mentor(s) at the CVC?

With the support of my supervisor, Dr. Padma Kaul, and all the statistical staff at the CVC (particular thanks to Dr. Douglas Dover), I have learned a lot about how to write proposals and work on epidemiological studies using ICD codes. The collaboration that occurs between clinical doctors in medicine and statistics is fundamental.
Briefly describe your educational background, and if applicable, what program you are currently enrolled in.

I completed a BSc in Statistics at the University of Birjand and a MSc in Biostatistics at the Hamadan University of Medical Sciences in Iran. The results of my master thesis were published in the Iranian Journal of Public Health and presented at the International Society of Clinical Biostatistics (ISCB) conference. After graduation, I began my career as a statistical research consultant at the Birjand University of Medical Sciences, where I collaborated with various research centers and participated in developing grant proposals for research projects on a variety of topics. I was involved in project management, training staff to complete data collection, entry, and analysis. As a team, we were successful in publishing in several peer-reviewed journals and presented the results at various scientific conferences.

In September 2017, I was admitted to the PhD program in epidemiology, here at the University of Alberta.

What are your research highlights from your time at the CVC?

I have had the opportunity to work on a few projects since joining the CVC as a trainee in September 2018. During my first year, I worked under the supervision of Dr. Padma Kaul on a project to update the latest birth weight percentiles for infants who were born in Alberta. Currently this project is close to submission. I also had the opportunity to collaborate with Drs. Livn Moore and Padma Kaul on an ongoing project investigating the maternal and obstetrical characteristics of infants who were born to mothers receiving infertility treatment with artificial reproductive technologies. Moreover, the CVC has introduced me to other cardiovascular researchers. For example, my work with Dr. Paolo Raggi on myocardial blood flow and the response to vasodilator nuclear stress testing with dipyridamole in patients with end stage renal disease was recently published in the Journal of Nephrology (J Nephrol. 2020. doi: 10.1007/s40620-020-00736-x).

Overall, I have had many highlights working at the CVC. It has been a valuable experience participating in the process of forming a clinical research question, working with Canadian administrative data, having meetings with biostatisticians and clinicians, and preparing manuscripts for submission.

What have you learned from working with your mentor(s) at the CVC?

Working with the large group of experts at the CVC, I have had the opportunity to improve my skills in medical research, data analysis, interpretation, and teamwork. I am extremely grateful for the time that the CVC biostatisticians and research associates took out of their schedule to mentor and coach me throughout my learning process at the CVC.

How has your time at the CVC impacted your research or career goals? Are there any specific insights or lessons you will take forward with you?

When I joined the CVC, I was intimidated by the high caliber of each researcher, however, I was excited to learn and embark on a new experience. Over the last year and half, I have met and become friends with many of my colleagues at the CVC and I want to thank them all for an amazing learning experience and for the friendships that have been built.

My experience as a trainee at the CVC has taught me that I need to be patient in research, think outside the box, listen carefully, and respect dedication and collaboration. Participating in different research projects and weekly meetings at the CVC improved my skills in working with administrative data, performing advanced statistical methods, and understanding the importance of medical research in clinical practice. I think my main take-away from my time at the CVC would be the understanding of the relationship between profound medical research and the development of an evidence-based intervention. As I continue with my studies as a PhD student in the epidemiology program at the School of Public Health, I am committed to improving my research skills and to working on more projects impacting public health and quality of care.
B2K 2019 Symposium  
Saturday, October 26th  
Montréal, Québec

B2K19 SYMPOSIUM

Montreal provided a superb backdrop for the 25th annual B2K symposium, which was held on October 26, 2019, in conjunction with the Canadian Cardiovascular Congress (CCC). B2K continues to be one of the most highly attended sessions at the Congress each year. The CVC was extremely gratified to have over 300 healthcare professionals attend the symposia, and are pleased at the overwhelmingly positive feedback we have received about the merit of the program and its speakers.

B2K 2019: New Concepts in Acute Coronary Syndromes, Atrial Fibrillation, Heart Failure, and Diabetes was co-chaired by Drs. Justin Ezekowitz and Shaun Goodman, and their planning committee colleagues were Drs. Heather Ross, Robert Welsh, and David Bewick. 2019 marked the silver anniversary of the B2K symposium. This quarter-of-a-century milestone was celebrated through the unveiling of a new logo and the inaugural Paul W. Armstrong B2K keynote presentation.

The CVC and B2K gratefully acknowledge our sponsors, AstraZeneca, Bayer, BMS/Pfizer Alliance, Boehringer-Ingelheim Eli Lilly Alliance, Novartis, and Sanofi, without whom this annual symposium would not be possible.

More information about B2K can be found at thecvc.ca/beyond-2000.
Given the small critical mass of clinical cardiovascular (CV) disease researchers who are spread across the country and vying for limited research funding in an increasingly competitive funding environment, there is an imperative to share and combine efforts. Thus in 2018, with the support and leadership of the CVC, we established the Canadian Cardiovascular Research Collaboratory (C\(^3\)), a virtual, clinical research network aiming to blend two fundamental elements - "collaboration" and the clinical "laboratory." With over 40 national members participating in five strategic working groups (Prevention, Coronary Artery Disease, Heart Failure, Interventions/ Surgery, and Population Health), the C\(^3\) has provided novel opportunities to identify and study important unanswered questions, and address unmet CV health care needs that would be challenging for a single center to definitively evaluate. As part of an overarching aim to stimulate the growth of CV research in Canada by inspiring, nurturing, engaging, connecting, and mentoring the next generation of talented and committed CV researchers, the C\(^3\) welcomed a number of cardiologists who have more recently joined Canadian university faculties. In addition to two face-to-face meetings in Montreal in 2019, including one prior to the annual Canadian Cardiovascular Congress, the working groups continue to have bimonthly teleconferences during which they undertake environmental scans of research directions and discuss key unmet health care needs and unanswered questions that would benefit from a trans-Canada systematic study. To date, several projects have been submitted for peer-reviewed funding. The rationale, objectives, and organizational structure of the C\(^3\) have been published in the Canadian Journal of Cardiology. (Can J Cardiol. 2020;50828-282X(19)31446-1).
CLINICAL TRIALS COLLOQUIUM

On March 10th, 2019, the CVC welcomed 17 sites from six provinces to participate in the sixth annual CVC Clinical Trials Colloquium in Banff, Alberta. Primary objectives included:

1. Enhancing best practices in conducting clinical trials, through an open forum of discussions, breakouts, and sharing;

2. Looking at trial designs, research infrastructure, cost effectiveness, and privacy challenges within the current clinical trial environment and thinking about how we can continue to adapt and enhance trials within a changing research environment;

3. Learning from our patients and strategizing on successful ways to engage them in clinical trials conduct;

4. Developing tools and methods to connect our research community/network; and

5. Sharing and gaining knowledge from past and current trials experiences in order to achieve success in all aspects – from start-up through to closeout – including quality and training.

Led by CVC Associate Director of Clinical Trials, Tracy Temple, and CVC Co-Directors, Drs. Shaun Goodman and Justin Ezekowitz, the Colloquium provides a unique opportunity to exchange clinical trial research insights, ask important questions, and collaborate on solutions through open discussion.

We were pleased to welcome back our colleagues from Duke Clinical Research Institute, Ty Rorick, Associate Director of Mega Trials, and Lisa Berdan, Director of Mega Trials. Lisa Berdan and Drs. Goodman and Ezekowitz reviewed some of the biggest challenges faced by those conducting clinical trials, and facilitated a lively ‘cost and compensation’ debate to explore considerations and challenges in determining adequate trial budgets and fair compensation. In what was perhaps one of our most meaningful Colloquium sessions to date, we welcomed Mr. Ginter Hilbrecht, a clinical trial research participant. Through his experience both as a research participant and a representative of a study patient advisory board, Mr. Hilbrecht provided a valuable first-hand account of the research participant’s experience. From the participant perspective, we explored how to improve all aspects of trial design and conduct, including increasing recruitment, minimizing participant burden, keeping participants engaged, and ultimately optimizing public awareness and perception of clinical research. Our colleague, Dr. Scott Garrison, then shared his experience as a family physician. He provided insight into some of the barriers faced when implementing traditional trial designs within the family practice setting, and the importance of involving community general practitioners in clinical trials. Dr. Garrison shared his innovative work to streamline recruitment and foster patient engagement in pragmatic clinical trials. Ty Rorick invited us to consider the pros and cons of accreditation, while noting site vs. institution requirements, country vs. global implications, and if implemented, whether this should be mandatory or voluntary. Closely related to accreditation, we examined the often daunting amount of training required in today’s research climate, as well as the overlap that inevitably occurs across various trials and sponsors. We had a round-table deliberation about defining the minimum training requirements in order for sites to participate in clinical trials.

We closed our day with a novel brainstorming session on building a stronger research network and community. We learned more about the methods our sites currently use to stay connected to their research communities, which include live conferences, trial-specific meetings, social media, and various professional research organizations, all ranging from local to international in scope. Our discussion helped identify both the unmet needs experienced by our sites, as well as an initial determination of which methods and tools might be valuable to develop in the future.

The contributions of investigators, coordinators, and sponsors make the Colloquium an engaging and unique opportunity. Our goal remains to share lessons learned while continually optimizing the execution and outcomes of clinical trials in Canada.

A sincere thank you to our sponsors Amgen, AstraZeneca, BMS-Pfizer Alliance, Boehringer-Ingelheim, CSL Behring, Novartis, and Sanofi for their support.
In 2019, the faculty of the CVC had the privilege of hosting two outstanding, internationally renowned academics. The Distinguished Visitor Series is a continuing program generously sponsored by unrestricted educational grants from Bayer.

These visits are a highlight of our CVC academic year and allow for one-on-one faculty time and teaching of our cardiology and research trainees. The speakers provide a welcome look through the window at the global state of cardiovascular medicine as it relates to career choices for trainees and potential future directions for meaningful research. They constitute a seminal part of our education and research mission.

Robert Giugliano, MD, MScMD, FACC, FAHA,
Senior Investigator, TIMI Study Group
Staff Physician, Cardiovascular Division, Brigham and Women's Hospital
Associate Professor of Medicine, Harvard Medical School

March 8, 2019

- Department of Medicine Grand Rounds: "How Low Should You Target LDL-C?"
- Cardiology Research Rounds: "Antithrombotic Therapy in Patients with Atrial Fibrillation - Who to Treat and Which Agents?"

Dr. Robert Giugliano is a world-leading cardiologist and clinical trialist with expertise in numerous areas, including cholesterol lowering in patients with atherosclerotic cardiovascular disease and antithrombotic therapy in stroke prevention in patients with atrial fibrillation (AF). His visit to the University of Alberta began with an outstanding update on the secondary prevention of patients with elevated levels of low-density lipoprotein cholesterol (LDL-C). Using examples of contemporary large randomized clinical trials, including the IMPROVE-IT ACS study (led in Canada by the CVC) and the FOURIER and ODYSSEY OUTCOMES (led in Canada by the CVC) studies, Dr. Giugliano highlighted the benefits and safety of intensive LDL-C lowering in high-risk patients. His second presentation provided comprehensive insights regarding oral anticoagulant therapy directed towards the prevention of stroke in AF patients. In addition, his helpful feedback shared during a CVC research-in-progress session was well received and capped off an extremely successful distinguished visitor event.

David Morrow, MD, MPH
Director, TIMI Biomarker Program, TIMI Study Group
Director, Samuel A. Levine Cardiac Intensive Care Unit, Director, Critical Care Cardiology Fellowship Pathway, Section Head, Critical Care Cardiology, Brigham and Women's Hospital
Professor of Medicine, Harvard Medical School

September 18, 2019

- Cardiology Divisional Rounds: "High Sensitivity Cardiac Troponin: Friend or Foe?"
- Cardiology Research Rounds: "A New Registry for Critical Care Cardiology: If You Build It, Will They Come?"

Dr. David Morrow is world leader in high sensitivity troponin testing and in critical care cardiology. He began his visit presenting Cardiology Grand Rounds on the data supporting the use of high sensitivity troponin testing and his own insights from his experience with the roll out at the Brigham and Women’s Hospital. The topic was particularly timely as the Edmonton Zone prepares its own transition to high sensitivity testing, and the talk was well attended by members of the Cardiology, Emergency Medicine, Laboratory Medicine, and Internal Medicine divisions. His second presentation provided a scientific and operational overview of the successes and challenges of developing a critical care cardiology registry and plans to leverage the registry for future pragmatic trials.
SERVICES AND ACTIVITIES

The Canadian VIGOUR Centre provides a wide range of services supporting worldwide improvements in health outcomes, and has an exemplary track record supporting cardiovascular, population, and economic-health outcomes research. Our organization has led or participated in clinical trials that have had seminal impacts on outcomes for patients with cardiovascular disease, and has developed clinical data registries informing on prognostic models, treatment guidelines, and outcomes.

BIOSTATISTICS
- Consultation on design of research protocols/studies
- Statistical analysis plans, database specifications, and data management
- Data analysis using SAS and R
- Generation of statistical tables, figures, listings, and interpretation of findings
- Execution of advanced statistical methods

CLINICAL TRIALS
- Project, site, and data management
- Negotiation and oversight of site contracts and payments
- Site/investigator selection and recruitment
- Investigative site start-up and training
- Communication/collaboration with all trial-related stakeholders
- Site regulatory compliance, data collection, and query resolution
- Clinical monitoring and adverse-event reporting
- Creation and dissemination of newsletters and trial-related communications

CLINICAL DATA REGISTRIES
- Generate and manage clinical data registries containing data on patients that are critical for informing treatment guidelines, prognostic models, and describing temporal trends in therapies and outcomes.

CORE LABORATORIES

ECG Core Laboratory
- ECG reading/analysis; collecting and tracking of ECG tracings
- Pathophysiological, prognosis, and outcomes assessments
- Data management (collection, entry, and quality control)
- Informing trial design
- Monitoring protocol adherence
- ECG-based admissibility criteria (for clinical trials and registries)

Food Record Core Laboratory
- Receiving, tracking, and analyzing Food Records in Food Processor, a powerful nutrition analysis software
- Initiating and following up on Food Record queries
- Entering Food Record data (from Food Processor) into REDCap for site access and use

THOUGHT LEADERSHIP
- Expert advice on cardiovascular disease, treatment guidelines, and population health
- Promoting research characterized by quality, scholarship, and integrity
- Defining unmet clinical needs for patients with, and those at risk of developing, cardiovascular disease
- Aligning cardiovascular research with these unmet needs
- Enhancing return-on-investment in cardiovascular research
- Trial architecture, development, data acquisition, integration, analysis, and dissemination in peer-reviewed publications
- Creation of novel sub-studies aimed at mechanistically informing primary clinical trial results
- Mentoring junior faculty, medical trainees, students, and allied health professionals

POPULATION AND ECONOMIC HEALTH OUTCOMES
- Analyzing healthcare administrative databases (CIHI, Alberta Health, etc.)
- Linking health outcomes to urban/rural residence, socioeconomic group, etc.
- Comparing cost-effectiveness of treatment options
- Collection of resource utilization and cost data
- Clinical registry development
CLINICAL TRIALS

With over 20 years of experience in clinical trial operations for phase II/III/IV, registries, and investigator-initiated studies, our team brings the knowledge and skills needed to deliver a high quality and well-executed trial from study start-up to closeout. Having worked with over 460 Canadian site investigators, which are representative of more than 230 institutions across Canada, we not only have the knowledge and expertise to understand their capabilities, but have also developed ongoing collaborations and relationships with them. This relationship enables us to approach the best sites who can deliver the right patients for the study. As an academic research organization, all of our clinical trials include the involvement of at least one of our faculty members who, as practicing physicians, are able to relate to the role of the investigator and site.

We have a very experienced, diverse, knowledgeable, and personable clinical trials team comprised of a senior project manager, a quality assurance and regulatory compliance lead, clinical trial project leads, regulatory specialists, a monitoring lead, regionally based monitors, and administrative support. At a senior project management level, we work directly with the study leadership and sponsor to coordinate all efforts related to the study executive and steering committees. Our clinical trial project leads and regulatory specialists are responsible for ensuring all operational aspects of the study run smoothly. They work closely with our sites to strive for rapid and efficient start-up, high recruitment and retention of patients that meet the study criteria, data entry that is accurate and well-maintained, and delivery on timelines as laid out from study start-up to study completion. As the primary contact for the Canadian sites, the clinical trial project leads have their fingers on the pulse of all aspects of the trial, which enables them to maintain a good understanding of the overall functioning of the study while closely monitoring trends and issues across Canada.

Our team is adaptable and flexible, recognizing the differing requirements for each project. In addition to routine on-site monitoring, our monitors, as well as our in-house teams, have experience implementing and working with both risk-based, and central and/or remote monitoring approaches. The CVC monitors conduct source document verification, drug accountability, and other required monitoring-related tasks, while also utilizing visits as a teaching opportunity to share lessons learned and ideas from other sites. The advice and suggestions are beneficial to the daily work of site personnel, and also help to ensure sites are audit prepared.

The CVC is a strong advocate of continuing education for our staff, and in addition to being ICH/GCP trained, many of our team members also hold or are working toward the Certified Clinical Research Professionals (CCRP) designation with the Society of Clinical Research Associates (SOCRA), or the Certified Clinical Research Associates (CCRA) designation with the Association of Clinical Research Professionals (ACRP). We maintain a strong focus on training and quality, and encourage our teams to share their knowledge, lessons learned, and expertise on an ongoing basis in their work with sites and sponsors to help build more efficient and cost effective clinical trials in Canada.

Our team also works collaboratively to produce the Canadian Cardiac Chronicle, a newsletter published three times a year that provides information on the CVC’s current trials, upcoming projects, and events and information that might be of interest to our site network. The chronicle is distributed to approximately 850 people in 11 countries, and can also be found on our website (www.thecvc.ca). Our clinical trials team works hard to establish and maintain strong relationships with our sites, sponsors, and partners to deliver pragmatic, efficient, cost effective, and high quality clinical trials. In addition to the relationships we have built, we also attribute our success in the management of clinical trials to the hands on, collaborative team approach we provide to our sites, sponsors, and partners.

References:
1 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP)
CLINICAL TRIALS AND REGISTRIES

AEGIS-II

**Study Title:** A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Investigate the Efficacy and Safety of CSL112 in Subjects with Acute Coronary Syndrome

**Sponsor:** CSL Behring LLC

**Anticipated Timeline:** August 2017 - June 2022

**Study Purpose:** The primary objective of this study is to evaluate the efficacy of CSL112 on reducing the risk of major adverse cardiac event (MACE) (cardiovascular death, myocardial infarction, or stroke) from the time of randomization through 90 days in subjects with acute coronary syndrome (diagnosed with ST-elevation myocardial infarction (STEMI) or non-STEMI).

**Trial Status:** Recruiting

FEAST-HF

**Study Title:** The Need for Fiber Addition in Symptomatic Heart Failure

**Sponsor:** University of Alberta Hospital Foundation, Weston Family Microbiome Initiative

**Anticipated Timeline:** July 2018 - September 2021

**Study Purpose:** To assess whether dietary supplementation with acacia gum reduces heart failure related biomarkers (NT-proBNP and ST2) and how the gut microbiome responds to dietary supplementation with acacia gum in patients with heart failure.

**Trial Status:** Recruiting

HEART-FID

**Study Title:** A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Injectafer® (Ferric Carboxymaltose) as Treatment for Heart Failure with Iron Deficiency

**Sponsor:** American Regent, Inc.

**Anticipated Timeline:** February 2017 - June 2022

**Study Purpose:** The primary objective of this study is to determine the efficacy and safety of iron therapy using intravenous ferric carboxymaltose (FCM), relative to placebo, in the treatment of participants in heart failure with iron deficiency and with a reduced ejection fraction.

**Trial Status:** Recruiting

HILO-HF REGISTRY

**Study Title:** High Versus Low SpO2 Oxygen Therapy in Patients with Acute Heart Failure - Registry

**Sponsor:** Heart and Stroke Foundation, Alberta Innovates Health Solutions

**Anticipated Timeline:** November 2016 - July 2019

**Study Purpose:** The primary objective of this registry is to determine the usual oxygen saturation levels in patients presenting to the emergency department with symptoms suggestive of acute heart failure, routine practice of oxygen therapy in those patients, and whether the use of high versus low level of supplemental oxygen is associated with worse clinical outcomes.

**Trial Status:** Close-Out

MAP-AHF

**Study Title:** MRI Assessment of Pulmonary Edema in Acute Heart Failure

**Sponsor:** Canadian Institute of Health Research

**Anticipated Timeline:** December 2019 - June 2024

**Study Purpose:** The purpose of this research study is to measure the lung water in patients hospitalized for heart failure, to determine the change in lung water over the course of hospitalization and treatment, and to find out if lung water levels can predict if patients are higher or lower risk for returning to the hospital or dying from heart failure.

**Trial Status:** Recruiting

PRESSURE CABG

**Study Title:** Protocolized vs Personalized Blood Pressure Peri-operative Parameters in Coronary Artery Bypass Grafting Surgery: The PRESSURE CABG Cardiac Surgery Trial

**Sponsor:** Canadian VIGOUR Centre

**Anticipated Timeline:** July 2019 - April 30, 2021

**Study Purpose:** To determine the clinical outcomes of personalized peri-operative Mean Arterial Blood Pressure (MAP) vs protocolized MAP targets.

**Trial Status:** Start-Up

SODIUM-HF

**Study Title:** Study Of Dietary Intervention Under 100 MMOL in Heart Failure

**Sponsor:** Canadian Institutes of Health Research, University Hospital Foundation

**Anticipated Timeline:** December 2013 - 2022

**Study Purpose:** To evaluate the long-term effects of a low sodium containing diet on a composite clinical outcome composed of all-cause mortality, cardiovascular hospitalizations or cardiovascular emergency department visits in patients with heart failure.

**Trial Status:** Recruiting
### SONOSTEMI-LYSIS

**Study Title:** Sonothrombolysis in Patients with an ST-segment  Elevation Myocardial Infarction With fibrinolysis Trial  
**Sponsor:** Canadian VIGOUR Centre  
**Anticipated Timeline:** July 2019 - September 2022  
**Study Purpose:** This study will assess the safety and feasibility of sonothrombolysis in the acute management of ST-elevation myocardial infarction (STEMI) undergoing reperfusion therapy with systemic fibrinolysis as part of a pharmacoinvasive approach.  
**Trial Status:** Start-Up

### STREAM-II

**Study Title:** Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction  
**Sponsor:** Leuven Research & Development (URD) at University of Leuven, Belgium  
**Anticipated Timeline:** September 2016 - June 2022  
**Study Purpose:** In patients ≥ 60yrs with acute ST-elevation myocardial infarction randomized within three hours of onset of symptoms, the efficacy and safety of a strategy of early fibrinolytic treatment with half-dose tenecteplase and additional antiplatelet therapy with a loading dose of 300 mg clopidogrel, aspirin and coupled with antithrombin therapy followed by catheterisation within 6-24 hours or rescue coronary intervention as required, will be compared to a strategy of primary percutaneous coronary intervention with a P2Y12 antagonist and antithrombin treatment according to local standards.  
**Trial Status:** Recruiting

### VICTORIA

**Study Title:** Vericiguat Global Study in Subjects with Heart Failure with Reduced EjectionFraction Registry  
**Sponsor:** Merck, Bayer  
**Anticipated Timeline:** March 2017 - June 2019  
**Study Purpose:** To assess the safety and efficacy of vericiguat in reducing physical limitations in patients with heart failure and preserved ejection fraction.  
**Trial Status:** Close-Out

### VICTORIA-HF REGISTRY

**Study Title:** Vericiguat Global Study in Subjects with Heart Failure with Reduced EjectionFraction Registry  
**Sponsor:** Merck, Bayer  
**Anticipated Timeline:** February 2018 - June 2020  
**Study Purpose:** The main objective of the study is to describe the baseline characteristics, practice patterns and in-hospital clinical outcomes of patients hospitalized for chronic heart failure with reduced ejection fraction at select North American sites.  
**Trial Status:** Close-Out

### VITALITY-HFPEF

**Study Title:** A Randomized Parallel-group, Placebo-controlled, Double-blind, Multi-center Trial to Evaluate the Efficacy and Safety of the Oral sGC Stimulator Vericiguat to Improve Physical Functioning in Activities of Daily Living in Patients with Heart Failure and Preserved Ejection Fraction [VITALITY-HFpEF]  
**Sponsor:** Bayer, Merck  
**Anticipated Timeline:** May 2016 - December 2020  
**Study Purpose:** Randomized parallel-group, placebo-controlled, double-blind, event-driven, multi-centre pivotal phase III clinical outcome trial of efficacy and safety of the oral sGC stimulator vericiguat in subjects with heart failure with reduced ejection fraction.  
**Trial Status:** Close-Out

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**CVC TRIAL PATIENT POPULATION**

- **Acute Coronary Syndrome:** 17%  
- **Acute Heart Failure:** 8%  
- **Heart Failure:** 50%  
- **ST-Elevation Myocardial Infarction:** 8%  
- **Coronary Artery Bypass:** 17%
The aim of our ECG Core Laboratory is to translate research results into clinically relevant applications. Using the electrocardiogram (ECG) – a venerable but powerful biomarker – we can generate an improved understanding of the pathophysiologic processes involved in acute coronary syndromes, thereby enabling not only prediction of outcomes, but also assessing effectiveness of treatment. These insights serve to further stimulate cardiovascular scientific research.

The ECG Core Laboratory’s key project in 2019 was the Vital Heart Response (VHR) study. The VHR-1 and VHR-2 projects, led by Dr. Robert Welsh, are a regional initiative that aims to implement timely evidence-based reperfusion strategies to maximize the outcome of patients with ST-segment elevation myocardial infarction (STEMI) utilizing a pre-hospital approach. VHR has enrolled over 3,000 patients and the Core Laboratory has completed analysis of over 4,000 ECGs done by our ECG reader, Eric Ly. The use of VHR registry-acquired ECGs and the biostatistical analyses performed by Yinggan (Gray) Zheng provide unique insights and often validation from “real world” patients as it relates to the original findings from our clinical trials. Recently, our findings from the VHR registry were published in Circulation: Cardiovascular Interventions, which found improved ST-segment resolution with a pharmacoinvasive approach compared to primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction leading towards enhanced myocardial perfusion and improved clinical outcomes. We are now exploring the ECG outcomes of elderly VHR patients receiving ½ dose tenecteplase (TNK) as part of a pharmacoinvasive strategy.

Another important project underway in 2019 was the STREAM-2 (Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction) study. STREAM-2 will build upon the important foundation laid by the first STREAM study in which the ECG Core Laboratory played a critical role. As in the first study, STREAM-2 ECGs will be analyzed for ST deviation (to determine area at risk) and resolution (as a marker of myocardial reperfusion) and QRS Score (for infarct size) in patients experiencing acute myocardial infarction. The Core Laboratory provides central adjudication for patients with rescue PCI to determine whether the clinical indications for the procedure were met. The objectives of this study are to compare the efficacy and safety of a pharmacoinvasive reperfusion strategy with primary PCI in elderly STEMI patients, and to compare the incidence of intracranial hemorrhage (ICH) and non-ICH major systemic bleeding in these elderly STEMI patients who receive pre-hospital clopidogrel as an adjunct to half-dose TNK.

The ECG Core Laboratory continues its mandate of conducting quality analyses using clinical research data. To date, ECGs from over 75,000 patients enrolled in studies around the world have been analyzed. This provides an excellent database for additional sub-studies, analyses, and ‘big-data’ research using an artificial intelligence machine learning (AIML) approach. Our aim in 2020 is to utilize AIML technology to help predict 30-day death in patients with acute myocardial infarction. This information could prove to be clinically useful in stratifying patients who may benefit from further preventative strategies.

References:
As active collaborators in discovery, CVC Biostatistics works with clinical investigators to develop research questions, design studies, refine measurements, plan and analyze data, and translate findings into knowledge and action. Our team has extensive experience in working with both population-based data and randomized clinical trials, and with data generated at all levels: locally, nationally, and internationally. We are also dedicated to advancing statistical methodology in clinical research.

The following are a few highlights of our activities in 2019.

Investigating novel therapies is an exciting aspect of the discovery cycle. The VICTORIA trial which tested the efficacy of vericiguat in patients with heart failure with reduced ejection fraction concluded in 2019 and will present its primary results in early 2020. Prior to database lock, Cynthia M. Westerhoud, PhD and others worked to characterize over 5000 patients enrolled worldwide and put this cohort into context with other contemporary heart failure trials.¹ There will be numerous opportunities to learn more about the pathophysiology, treatment and prognosis; many of which the CVC Biostatistics will be involved in over the coming years.

The translation of findings from clinical trials into ‘real world’ populations is important to the mission of the CVC. This year, Yinggan (Gray) Zheng, MA MEd led a study in its design and analysis of the treatment for ST-elevation myocardial infarction in the Vital Heart Response registry based in the Edmonton zone.² When delay to primary percutaneous coronary intervention exists, a pharmacoinvasive strategy was associated with improved ST-segment resolution and improved clinical outcomes within one year, which was demonstrated earlier in the globally conducted STREAM trial. As the current study was observational (rather than a randomized clinical trial), bias for the treatment was a concern and was accounted for using inverse probability weighting.

Pragmatic clinical trials also aim to bridge the gap between randomized clinical trials (RCTs) and observational studies, especially for comparative effectiveness. In JAMA Cardiology, Wendimagen Ghidey Alemayehu, PhD and coauthors examined the trends in the explanatory or pragmatic natures of contemporary heart failure trials.³ They revealed the extent to pragmatism or explanatory nature. They identified the need and opportunities to increase this trajectory to further support practice guidelines and evaluate the broader application of studied interventions.

Large-scale databases offer excellent opportunities for discovery in the health of many. Using the national level data from the Canadian Institute of Health Information, Sunjidatul Islam, MBBS, MSc and Douglas C. Dover, PhD began exploring temporal trends and provincial differences in population rates of incident atrial fibrillation/atrial flutter (AF/AFL) hospitalizations, as well as contemporary trends for quality indicators related to stroke, major bleeding, and heart failure in patients with AF/AFL in Canada.

Revelations in the earlier stages of life, such as maternal and childhood health, have also been explored by CVC Biostatistics. Anamaria Saux, PhD has examined the relationship of glucose and pregnancy outcomes in patients with gestational diabetes, using a large population-based cohort in Alberta. The rates of large-for-gestational-age and hypertensive disorders of pregnancy were significantly higher in pregnancies with elevated fasting plasma glucose than in those with elevated post-load glucose levels.⁴ Extending beyond pregnancy, Sunjidatul Islam, MBBS, MSc began developing a model to predict excess weight status of children at preschool age using maternal demographic characteristics, pregnancy related factors and childhood factors from birth to 2 years of age.

CVC Biostatistics is also committed to methods-based research. Douglas C. Dover, PhD furthered his ongoing interest in health equity measurement.⁵ He synthesized current knowledge on social determinants of health and health service utilization into a single, comprehensive framework – the Health Equity Measurement Framework (HEMF), which provides guidance when considering how social determinants affect health and for the modelling and measurement of health equity. These findings present an opportunity to systematically measure equity in cardiovascular and other health outcomes with the goal of reducing health inequities.

At the 2019 meeting of the Statistical Society of Canada, Wendimagen Ghidey Alemayehu, PhD presented his work on the statistical modeling of the temporal change of biomarkers on clinical outcomes in patients with cardiovascular disease.⁶ Using simulations and applications to actual data, the proposed integrated modeling approach estimates the association between the underlying temporal change and the outcome, and results in more consistent and efficient estimates.

References:
The CVC is actively involved in examining population-level issues related to access, delivery, treatment, and outcomes of heart disease in Alberta and Canada. Healthcare administrative databases have become a cornerstone in the process of assessing performance and providing feedback to improve quality of health care delivery at a population level.

The integrated system of health care delivery in Alberta, with one centralized provider and one payer, has facilitated the linking of traditional administrative claims databases (inpatient, outpatient [including emergency department], practitioner claims) with more unique data, including pharmaceutical claims and laboratory data, at the population level. The CVC is engaged in several projects that further supplement administrative data by linking it with clinical registries, clinical data repositories, or public health databases. As an example, in the ongoing Alberta Contemporary Acute Coronary Syndrome (COAPT) study, administrative data have been linked to the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry, which includes detailed demographic, clinical, and anatomical data for all patients who undergo cardiac catheterization in Alberta.

In 2019, for the first time, Drs. Finlay McAlister, Justin Ezekowitz and colleagues linked administrative health data to echocardiogram databases maintained at the Mazankowski Alberta Heart Institute (Edmonton) and the Libin Cardiovascular Institute of Alberta (Calgary). They used the linked data to examine a broad spectrum of heart failure patients to establish contemporary clinical practice. 1

Similarly, Padma Kaul and colleagues linked administrative data from the Alberta pregnancy-birth cohort to the public health child immunisation data. The latter includes data not only on immunisation status, but also on breast-feeding status at each immunisation visit and the child’s height and weight at their pre-school immunisation visit, which occurs between 4 and 6 years of age. Because of this linkage, they were able to examine the association between maternal diabetes during pregnancy, large for gestational age at birth, and breast-feeding, on being overweight or obese in early childhood in a cohort of 69,506 children. 2

In the current environment of constrained health care resources, CVC faculty members are actively identifying opportunities for potential cost savings. Heart failure is a leading cause of hospitalisation and admission to coronary and medical intensive care units (ICUs). An ICU-day costs three times more than a day in a hospital ward bed. Drs. Sean van Diepen, Justin Ezekowitz, Finlay McAlister, and Padma Kaul used national data from the Canadian Institutes of Health Information to describe the variability in the rates of admission of low-risk patients with heart failure to higher cost ICUs across the country, and estimated the potential national cost savings if all hospitals adopted low ICU admission practices. The development of standardized admission criteria for high-cost and high acuity ICU beds could reduce costs to the healthcare system. 3

Similarly, it has been suggested that reduction in the inappropriate use of noninvasive cardiac tests (NICTs) could result in potential healthcare cost savings. Dr. Kevin Bainey and co-authors used the Alberta COAPT study to evaluate the use and costs of NICTs among patients discharged within 1 year after an acute coronary syndrome (ACS) in Alberta. The authors found that the rates and costs of NICTs within the year are substantial and appear to be increasing at a pace much faster than the increase in ACS incidence and prevalence. Further investigation is warranted to examine whether the increase in NICTs is associated with clinical benefits. 4

References:
BUSINESS OPERATIONS

The business office is fundamental to the organizational and financial underpinnings of the CVC. Reviewing and negotiating contracts is one of its key tasks, along with providing expert service in the areas of managing agreements, developing and tracking metrics, and executing invoices and site payments. Dedicated to financial stewardship, the business office prudently manages revenue and expense administration. It is also committed to the progress of information systems management, strategic planning, process improvement, and the promotion of learning and development initiatives.

The business office is responsible for the development and distribution of all marketing materials aimed at creating strong brand awareness that speaks to the mission and values of the organization. Additionally, the office manages the CVC’s website and social media portfolio, and provides visual design support to our staff and faculty for a variety of projects.

Finally, the office facilitates communications between the CVC and its many institutional partners. Our dedication to upholding strong partnerships with these institutions is essential to the day-to-day operations of the CVC.

ACADEMIC RESEARCH ADMINISTRATION

The Academic Research Administrator (ARA) is involved in the development and management of investigator initiated academic research projects. The ARA coordinates and facilitates proposal development, from identifying potential funding sources, drafting proposals, and critical review of project design, through to editing and final polish. For research projects underway, the ARA manages ethics submissions, reporting to stakeholders, and knowledge translation by way of manuscript development, graphical abstract design, and data visualizations for various presentation formats.
FACULTY

The CVC Faculty are internationally recognized as Thought Leaders in their respective areas of interest, and they collectively represent a diverse field of clinical research. Our faculty are passionately dedicated to advancing the frontiers of cardiovascular science through several domains:

- **Clinical Trials** – architecture, operational management, analysis, and interpretation
- **Registry Development** – creative insights into the process of care of acute coronary syndromes and congestive heart failure
- **Large Population Databases** – informing the impact of research on practice, and pointing towards unmet needs and future directions

Our faculty plays a pivotal role in linking new knowledge to the community, understanding the implications on health outcomes, embracing the quality feedback loop, and discovering science through clinical trials registries and population outcomes. The CVC faculty is deeply engaged in identifying, nurturing, and mentoring the health professionals and leaders of tomorrow by grounding them in the discipline of cardiovascular research.
PAUL W. ARMSTRONG, MD

• Founding Director, Canadian VIGOUR Centre
• Distinguished University Professor, Division of Cardiology, University of Alberta
• Formerly Chair of the Department of Medicine, University of Alberta
• Founding Director of TORCH (Tomorrow’s Research Cardiovascular Health Professionals), a Strategic Training Program Initiative
• Founding President of the Canadian Academy of Health Sciences
• 2014 Recipient of the University Cup, the University of Alberta capstone award for outstanding contributions in teaching, research, and service
• 2014 Recipient of the Margolese National Heart Disorders Prize, awarded annually to a Canadian who has made outstanding contributions to the treatment, amelioration, or cure of heart disease
• Recognized in 2018 as an Officer of the Order of Canada, in acknowledgement of “his contributions to the advancement of cardiology, notably for his pioneering research in acute cardiac care, and for his leadership in health care institutions”
• Cited amongst the top 10 most productive authors in medical literature (Trials. 2020;21:34)

Dr. Armstrong’s research interests include:
• Development of novel methods to enhance clinical trial methodology
• Cardiovascular implications of diabetes and aging
• Pathophysiology and novel therapeutic approaches of congestive heart failure
• Diagnosis and management of acute coronary syndromes, with emphasis on timely interventions
• Cardiovascular health in populations

JUSTIN EZEKOWITZ, MBBCH, MSC

• Co-Director, Canadian VIGOUR Centre
• Professor, Division of Cardiology, University of Alberta
• Director, Cardiovascular Research, University of Alberta
• 2017 Appointed Member, Royal Society of Canada College of New Scholars, Artists and Scientists

Dr. Ezekowitz’ research interests include:
• Testing the impact of drugs, existing care, and processes of care for patients with acute and chronic heart failure
• Non-pharmalogic interventions such as dietary sodium or altering the gut microbiome, and existing tools such as biomarkers for discovery or prognosis
• Population health studies on outcomes and interventions
• Clinical trial design and endpoints

SHAUN GOODMAN, MD, MSC

• Co-Director, Canadian VIGOUR Centre
• Adjunct Professor, Department of Medicine, University of Alberta
• Associate Head, Division of Cardiology, Department of Medicine, St. Michael’s Hospital
• Heart & Stroke Foundation of Ontario (Polo) Chair and Professor, Department of Medicine, University of Toronto

Dr. Goodman’s research interests include:
Facilitating collaborative clinical trial, observational, and knowledge translation research in cardiovascular disease in Canada with a focus on:
• Diagnosis, management, and prognosis of stable coronary artery disease and acute coronary syndromes
• Secondary prevention of cardiovascular disease, including those with diabetes mellitus
• Optimal stroke prevention risk stratification and management in atrial fibrillation

PADMA KAUL, PHD

• Co-Director, Canadian VIGOUR Centre
• Professor, Department of Medicine, University of Alberta
• Adjunct Associate Professor, School of Public Health, University of Alberta

Dr. Kaul’s research interests include:
• International differences in practice patterns and outcomes
• Sex differences in treatment and outcomes of cardiovascular disease
• Long term chronic disease implications for pregnancy related complications
• Issues related to access, delivery, and costs of care at a population level
KEVIN R. BAINEY, MD MSC

- Director, ECG Core Laboratory, Canadian VIGOUR Centre
- Interventional Cardiologist, Mazankowski Alberta Heart Institute
- Associate Professor, Division of Cardiology, University of Alberta
- Director, Adult Cardiac Catheterization and Interventional Cardiology Laboratory
- Director, Interventional Cardiology Fellowship Program
- Co-Director of the ACS working group for Alberta Health Services Cardiovascular Health and Stroke Strategic Clinical Network

Dr. Bainey’s research interests include:

- Optimizing reperfusion strategies in ST-elevation myocardial infarction
- Population health outcomes in acute coronary syndromes

SEAN VAN DIEPEN, MD

- Academic Cardiologist-Intensivist, University of Alberta Hospital
- Co-Director, Coronary Intensive Care Unit, University of Alberta Hospital
- Associate Professor, Critical Care Medicine, Division of Critical Care and Division of Cardiology, University of Alberta
- Associate Editor, American Heart Journal

Dr. van Diepen’s research interests include:

- Critical care cardiology
- Cardiovascular surgical care
- Critical care resource utilization

FINLAY MCALISTER, MD, MSC

- General Internist, University of Alberta Hospital
- Professor, Division of General Internal Medicine, University of Alberta
- Lead, Alberta SPOR (Support for Patient Oriented Research) Data Platform
- Alberta Health Services Chair in Cardiovascular Outcomes Research
- Past-Chair, Outcomes Research Task Force, Canadian Hypertension Education Program
- Past-President, Canadian Society of Internal Medicine

Dr. McAlister’s research interests include:

- Outcomes research in hypertension, heart failure, perioperative care, and coronary artery disease
- Clinical epidemiology methodology with a focus on evidence-based medicine and implementation of evidence at the bedside
- Methodology of trials and systematic reviews

M. SEAN MCMURTRY, MD, PHD

- Clinician Scientist, Mazankowski Alberta Heart Institute
- Associate Professor, Division of Cardiology, University of Alberta
- Program Director, Clinical Investigator Program, University of Alberta

Dr. McMurry’s research interests include:

- Thoracic aortic disease
- Venous thromboembolism
- Sex differences in cardiovascular disease
- Coronary artery disease
ROOPINDER SANDHU, MD, MPH

- Cardiac Electrophysiologist, Division of Cardiology, University of Alberta
- Associate Professor, Division of Cardiology, University of Alberta
- Visiting Scientist, Brigham and Women’s Hospital, Boston
- Director, Edmonton Cardiac Arrhythmia Trials (ECAT) group

Dr. Sandhu’s research interests include:

- Arrhythmia health services and outcomes research
- Atrial fibrillation
- Cardiac implantable devices
- Syncope

ROBERT WELSH, MD

- Interventional Cardiologist, Mazankowski Alberta Heart Institute
- Professor, Division of Cardiology, University of Alberta
- Edmonton Zone Clinical Department Head, Cardiac Sciences
- Chair, Canadian Cardiovascular Society, PCI quality working group
- Co-Chair, Transcatheter Aortic Valve Implantation (TAVI) Program, Mazankowski Alberta Heart Institute

Dr. Welsh’s research interests include:

- Acute coronary syndromes and interventional cardiology
- Atherosclerotic cardiovascular disease
- Cardiovascular disease and diabetes
- Exercise physiology and cardiac physiology
- Pre-hospital management of ST-elevation myocardial infarction, and the interaction of pharmacological (antithrombotic and fibrinolytic) and mechanical interventions (primary and rescue angioplasty)
CVC gratefully acknowledges and thanks:

- The patients, for their willing participation in our trials and registries. They are the true heroes of clinical research and we honour their volunteer spirit.

- The CVC faculty, external advisors, and collaborators for their enriching contributions and for providing ongoing research opportunities. We look forward to providing continued support and to future collaborations in advance of our mission.

- The CVC staff and management for their outstanding dedication, professionalism, excellent contributions, and ingenuity, which enhances the quality of our research work.

- Our trainees for their commitment, ideas, and enthusiasm. You are the next generation of researchers and health care providers.

- The sponsors and granting agencies; without their generous financial support our research and educational activities would not be possible.

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