TWO ROADS DIVERGED IN A YELLOW WOOD, AND SORRY I COULD NOT TRAVEL BOTH AND BE ONE TRAVELER, LONG I STOOD AND LOOKED DOWN ONE AS FAR AS I COULD TO WHERE IT BENT IN THE UNDERGROWTH; THEN TOOK THE OTHER, AS JUST AS FAIR, AND HAVING PERHAPS THE BETTER CLAIM, BECAUSE IT WAS GRASSY AND WANTED WEAR; THOUGH AS FOR THAT THE PASSING THERE HAD WORN THEM REALLY ABOUT THE SAME, AND BOTH THAT MORNING EQUALLY LAY IN LEAVES NO STEP HAD TRODDEN BLACK. OH, I KEPT THE FIRST FOR ANOTHER DAY! YET KNOWING HOW WAY LEADS ON TO WAY, I DOUBTED IF I SHOULD EVER COME BACK. I SHALL BE TELLING THIS WITH A SIGH SOMEWHERE AGES AND AGES HENCE: TWO ROADS DIVERGED IN A WOOD, AND I—I TOOK THE ONE LESS TRAVELED BY, AND THAT HAS MADE ALL THE DIFFERENCE.

The Canadian VIGOUR Centre

FORGING NEW PATHS

2014 Annual Report

Message from the Founding Director

What does poetry offer an academic research organization dedicated to enhancing cardiovascular health? Perhaps John Burnside's reflections help us with the answer in his definition of poetry's value "It is, in its subtle yet powerful way, a discipline for re-engaging with a world we take too much for granted".

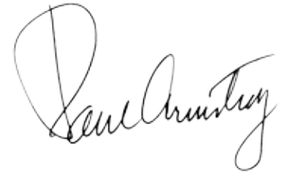
And thus for me the inspired choice that emerges from Robert Frost's famous poem "the Road Not Taken" is highly relevant to our CVC vision and mission that commits us to be pathfinders and explore less travelled roads. As is the case with our primary service mandate in the care and treatment of our patients, we must balance risk in our research and educational adventures in order to advance our objectives as a learning organization aiming to be continuously innovative.

Within this year's annual report you will find a rich synopsis of the work of our wonderful CVC team dedicated to advancing cardiovascular health. The enthusiasm of our trainees, their scholarly output and progress will be evident. So too will be the key role that mentoring plays in attracting trainees and junior faculty and enriching their career development. Within the presentations and publications summary the spectrum of population health, clinical registries and clinical trials is well represented by the work of our dedicated faculty. Our clinical operations group, biostatistical team, ECG core laboratory, monitors, finance and administration group collaborate to provide a full range of talents that are crucial to our success. Our distinguished speaker program brings the best of the outside world to our doorstep and our faculty reciprocates by presenting our work elsewhere. Importantly in the spring of 2014 we received key visitors from our two key academic partners, Stanford University and the Duke Clinical Research Institute (DCRI). Eric Peterson (DCRI Director) and Lisa Berdan (Director of Global Megatrials) proceeded on from their CVC visit to Banff to participate in a new CVC venture ably led by Tracy Temple and detailed herein: the Research Colloquium was a unique experience and resounding success greatly appreciated by investigator and coordinator attendees from our clinical research sites and sponsors. It deserves to be part of our future.

In 2014 we took a road less travelled with a small biotechnology company called Regado. This approach used a novel anticoagulant or aptamer that employs an entirely new technology. It involved single stranded nucleic acids that target specific binding sites which in this case interfere with normal blood clotting. Because the aptamer platform is associated with a mirror image protein that specifically binds to the active agent it provides the unique potential to not only rapidly turn on, but also rapidly reverse the therapeutic effect. This pharmacology was especially well suited to study in the cardiac catherization laboratory in patients undergoing percutaneous angioplasty where rapid onset and off set of anticoagulation is very desirable. We were making good progress in this trial towards our target of over 12000 patient and had recruited over 3000 patients (over 10% of these from Canada) when the Data and Safety Monitoring Board signaled the need to cease enrollment because of serious allergic reactions in a small but significant proportion of study patients. This unexpected and unfortunate outcome was a cogent reminder of the uncertainties associated with novel research. We do not yet understand why this allergy occurred but it is imperative that we learn more in order to ensure that we can pursue related lines of new treatment and avoid unnecessary hazards. This is part of the uncertainty in travelling new paths while searching for innovative solutions to the unmet needs of our patients.

In September of 2014 I was both surprised and honored to receive the University Cup for "outstanding distinction in scholarly research, teaching and service to the U of A and to the greater community". In reflecting on this award I was especially conscious of some overarching themes that framed this event for me; the privilege of working in an academic- university based health care system that provides the freedom to pursue creative ideas; the opportunity to fulfill my social contract to the broader community of tax payers that have funded my education and career; the collaborative spirit of many outstanding colleagues and the support of our splendid CVC team who have been so pivotal in the work we have together accomplished.

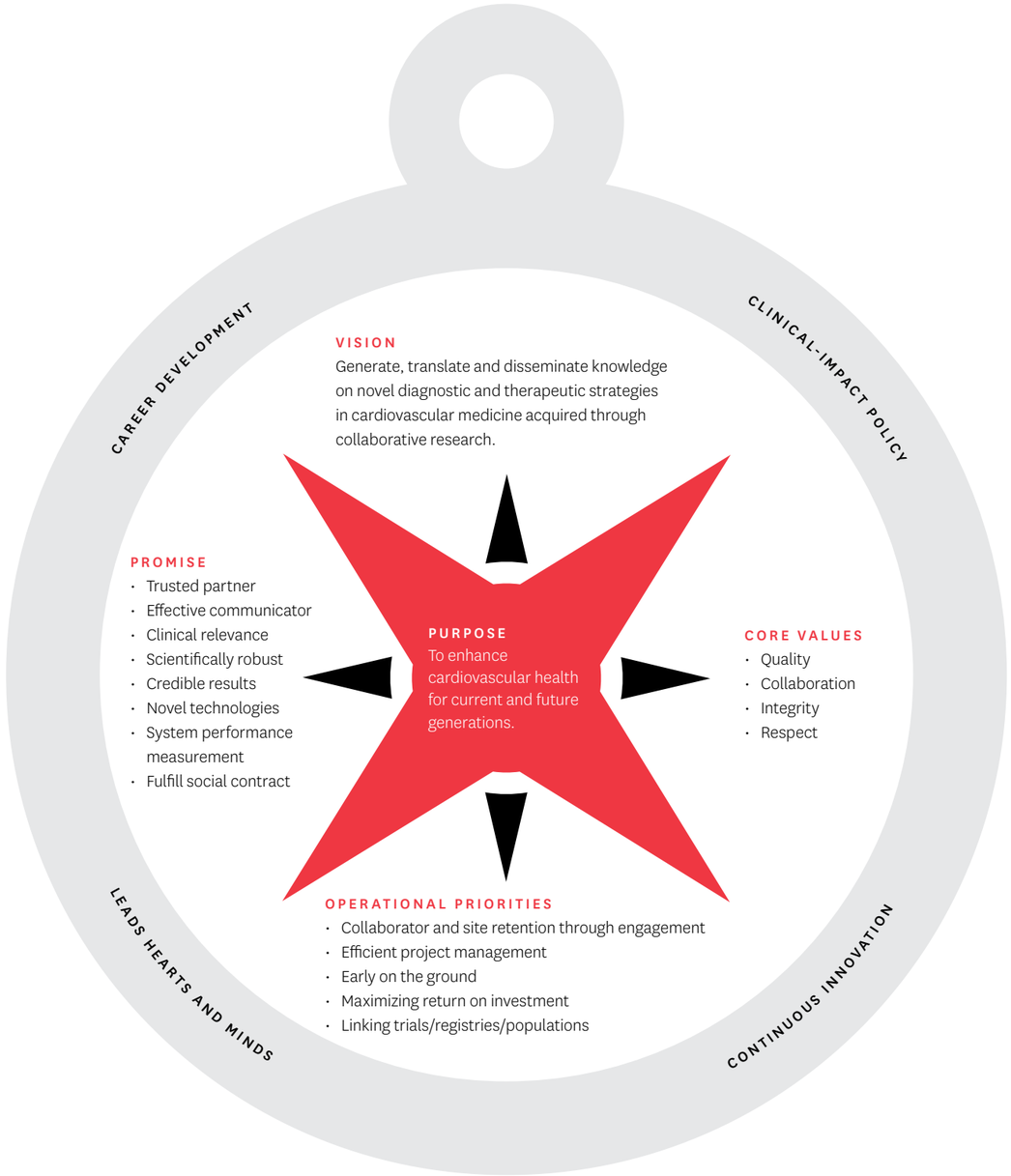
I hope you take time to peruse our 2014 annual report to better understand who we are, what we do and how we are progressing in pursuit of our mission. Constructive feedback from our key stakeholders is always appreciated as we strive to be better in the days ahead on the road less travelled.



TWO ROADS DIVERGED IN A WOOD, AND I—
I TOOK THE ONE LESS TRAVELLED BY,
AND THAT HAS MADE ALL THE DIFFERENCE.

—ROBERT FROST

Compass



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 conductive to personal growth and development that is aligned with our overall mission.

EXCELLENCE IS NEVER AN ACCIDENT.

IT IS ALWAYS THE RESULT OF HIGH INTENTION,

SINCERE EFFORT,

AND INTELLIGENT EXECUTION;

IT REPRESENTS THE WISE CHOICE OF MANY ALTERNATIVES -

CHOICE, NOT CHANCE,

DETERMINES YOUR DESTINY.

—ARISTOTLE

HOW DOES YOUR KNOWLEDGE STAND TODAY?

WHAT MUST YOU EXPECT TO FORGET?

WHAT REMAINS FOR YOU TO LEARN?

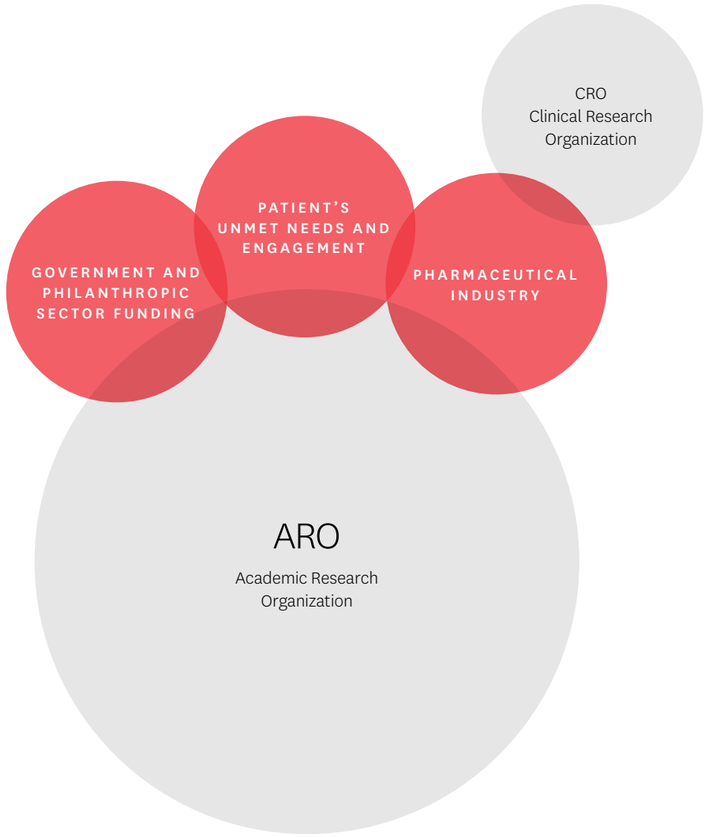
—OLIVER WENDALL HOLMES

Value Proposition of an ARO

An academic research organization (ARO) possesses scholarly values of inquiry and truth and shares knowledge in an ethical framework. Dedicated to enhancing public health, it values discovery, novel approaches and methodologies over profit.

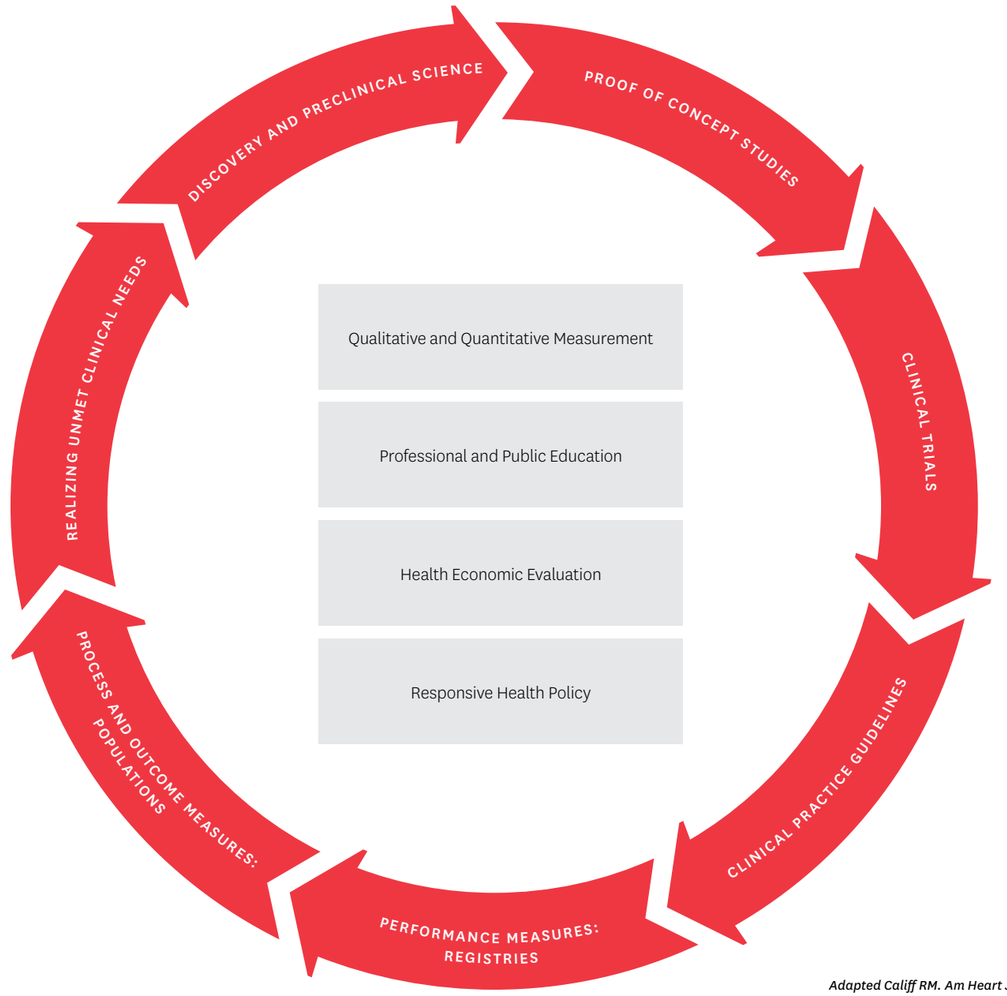
Intent upon maximizing the return on research investment, an ARO strives to exceed the operational efficiencies of a clinical research organization (CRO), and intentionally seeks funding from diverse sources beyond industry. An ARO is almost always embedded in a University and therefore reserves their right to publish their insights with objectivity.

An ARO functions on a not for profit basis, and reinvests all sources of capital, both financial and intellectual, into the education of the next generation of health professionals, and thereby aims to fulfill its social contract to promote the public good.



Cycle of Quality

As a learning organization committed to enhancing the health of current and future generations through research, 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. Am Heart J 2008

2014 Metrics

322
Number of monitoring visits that occured in Canada.

133
Number of Principal Investigators participating in CVC managed trials.

52
Number of publications that CVC's body of research produced.

10
Number of industry and grant funded projects currently underway.

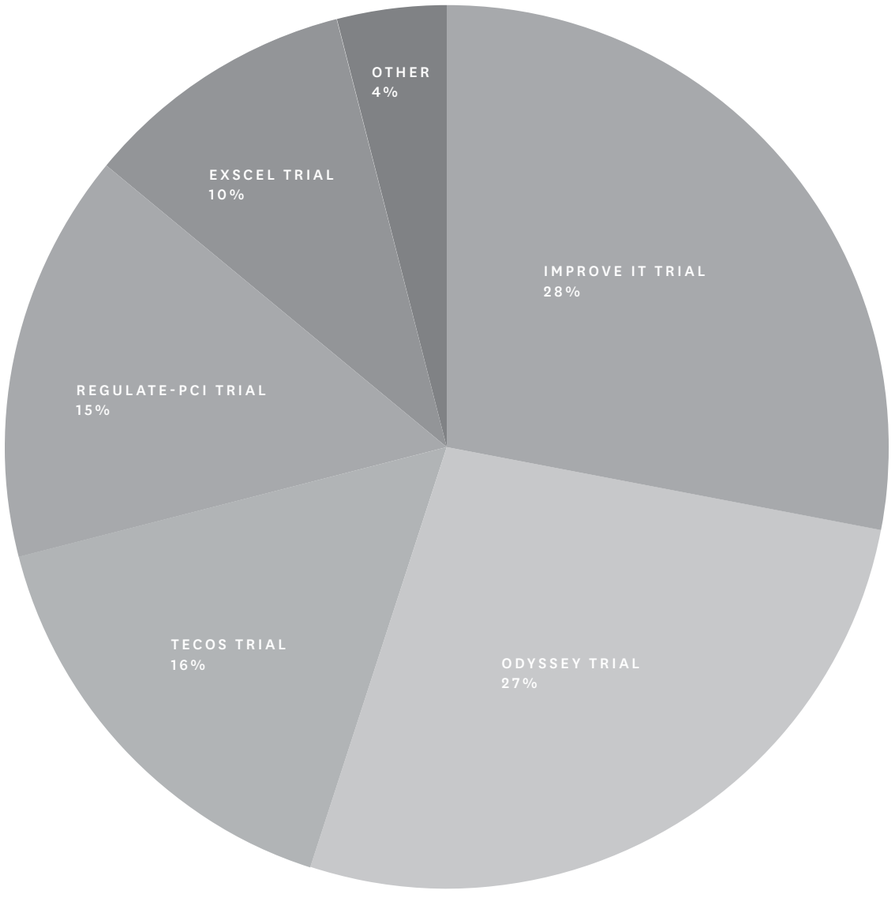
500,000+
Size of data repository reflecting health of Albertans with cardiovascular disease.

5,498
Number of ECGs analyzed by CVC.

144
Number of global users accessing CVC's online collaborative platform.

Financial Summary

REVENUES FROM INDUSTRY-SPONSORED CLINICAL TRIALS AND EXPENSE RECOVERY
January 1, 2014 - December 31, 2014



Grants

PROJECT	SPONSOR(S)	GRANT HOLDERS	TERM	TOTAL GRANTED (CAD)
Providing Rapid Out of Hospital Acute Cardiovascular Treatment (PROACT-4)	Heart and Stroke Foundation Mazankowski Alberta Heart Institute University Hospital Foundation	Justin Ezekowitz (PI) Paul Armstrong Padma Kaul Robert Welsh	2014-2017	$233,000
SODIUM HF	Canadian Institutes of Health Research	Justin Ezekowitz	2013-2017	$698,301
Team Grant: Alberta Heart Failure Etiology and Analysis Research Team (Alberta-HEART)	Alberta Innovates-Health Solutions	Jason Dyck (PI) Todd Anderson (PI) Finlay McAlister Justin Ezekowitz Padma Kaul	2009-2014	$5,000,000
Canadian Health Outcomes, Performance and Efficiency (CanHOPE) - project for analysis of AMI and stroke care data for policy making	Heart and Stroke Foundation	Arto Ohinmaa (PI) Scott Klarenbach Padma Kaul Philip Jacobs	2013-2014	$109,450
Gestational Diabetes Mellitus (GDM) in Alberta	Canadian Institutes of Health Research	Padma Kaul (PI)	2014-2017	$278,139

Featured Publications

Original Article

Use of Renin–Angiotensin System Blockers in Acute Coronary Syndromes

Findings From Get With the Guidelines-Coronary Artery Disease Program

Kevin R. Bainey, MD, MSC; Paul W. Armstrong, MD; Gregg C. Fonarow, MD; Christopher P. Cannon, MD; Adrian F. Hernandez, MD; Eric D. Peterson, MD, MPH; W. Frank Peacock, MD; Warren K. Laskey, MD; Xin Zhao, MS; Lee H. Schwamm, MD; Deepak L. Bhatt, MD, MPH

Background—Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) initiated after myocardial infarction (MI) reduce mortality and are American College of Cardiology/American Heart Association guideline recommended. Yet the extent to which ACEI/ARB therapy is applied in patients with acute coronary syndrome at hospital discharge is unclear.

Methods and Results—We performed an observational analysis of 80 241 patients admitted with an acute coronary syndrome and discharged home from 311 US hospitals participating in the Get With the Guidelines-Coronary Artery Disease Program from January 2005 to December 2009. Among the 60 847 patients with an American College of Cardiology/American Heart Association class I indication (left ventricular dysfunction or medical history of heart failure, hypertension, diabetes mellitus, or chronic kidney disease), 49 682 (81.7%) received ACEI/ARB with an increase in the rate of treatment over the study period (76.7%–84.6%; adjusted odds ratio, 1.17; 95% confidence interval, 1.10–1.24; $P<0.001$, per calendar year). In-hospital coronary artery bypass grafting and renal insufficiency were independently associated with lower use (adjusted odds ratio, 0.55; 95% confidence interval, 0.48–0.63 and adjusted odds ratio, 0.58; 95% confidence interval, 0.52–0.64, respectively).

Conclusions—Results from this large US national registry suggest that 1 in 5 eligible patients hospitalized for acute coronary syndrome failed to receive American College of Cardiology/American Heart Association class I guideline-recommended ACEI/ARB therapy, and the use varies by patient factors. In particular, the low likelihood of ACEI/ARB after coronary artery bypass grafting surgery or in patients with renal insufficiency raises concern. These findings highlight an unmet need in this population and provide an incentive for additional quality improvement efforts. **(*Circ Cardiovasc Qual Outcomes*. 2014;7:227-235.)**

Key Words: acute coronary syndrome ■ angiotensin-converting enzyme inhibitors ■ angiotensin receptor blockers

The use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) initiated early after myocardial infarction (MI) has been widely established to prevent ventricular remodeling, decrease the risk of heart failure, and improve overall survival in landmark clinical trials.[1–13] As such, the American College of Cardiology/American Heart Association (ACC/AHA) strongly recommend that an ACEI or ARB be started and continued indefinitely in all patients recovering from an acute coronary syndrome (ACS) with left ventricular (LV) ejection fraction ≤40% and for those with hypertension, diabetes mellitus, or chronic kidney disease (class 1, level A). Among lower risk patients (ie, absence of LV dysfunction, hypertension, or diabetes mellitus), the use of ACEI or ARB is reasonable and should be initiated (class II, Level of Evidence A).[14,15] Yet older data suggest only a minority of patients receive renin–angiotensin system blockers at hospital discharge.[16] Contemporary use of ACEI or ARB in ACS is largely unknown. Accordingly,

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This article was handled independently by Nilay D. Shah, PhD, as Guest Editor. The editors had no role in the evaluation of the manuscript or in the decision about its acceptance.

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***Circ Cardiovasc Qual Outcomes* is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/CIRCOUTCOMES.113.000422**

Circulation
Cardiovascular Quality and Outcomes
Journal of the American Heart Association

USE OF RENIN–ANGIOTENSIN SYSTEM BLOCKERS IN ACUTE CORONARY SYNDROMES

Findings From Get With the Guidelines-Coronary Artery Disease Program

In another look at applying best evidence to patient care in the U.S. Kevin Bainey studied 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. He and his colleagues analyzed a large cohort of patients admitted with an acute coronary syndrome and discharged home from hospitals participating in the Get With the Guidelines-Coronary Artery Disease Program. Approximately one in five eligible patients failed to receive American College of Cardiology/ American Heart Association class I guideline recommended ACEI/ARB therapy. Interestingly, in-hospital coronary artery bypass grafting and renal insufficiency were independently associated with lower use of ACEI/ARB therapy and the also concluded that additional quality improvement efforts focused on this therapy was warranted. This work originated from Dr. Bainey's training in Boston and was subsequently undertaken during his faculty appointment at the University of Alberta and CVC.

British Cardiovascular Society

ABORTED MYOCARDIAL INFARCTION IN ST-ELEVATION MYOCARDIAL INFARCTION: INSIGHTS FROM THE STRATEGIC REPERFUSION EARLY AFTER MYOCARDIAL INFARCTION TRIAL

Dr. Neda Dianati Maleki a trainee working in our core ECG laboratory, ably assisted by Gray Zheng and Dr. Cindy Westherhout examined how often heart attacks could essentially be avoided (so called "aborted MIs") according to the use of pharmacoinvasive strategy vs. percutaneous coronary intervention (PCI) in the STREAM [Strategic Reperfusion Early After Myocardial Infarction] trial.

The key messages published in the journal Heart were:

1. Aborted MI has been known to occur when reperfusion therapy in ST elevation MI is begun early and be associated with improved outcomes in observational cohorts.
2. This report was the first prospective randomized trial to study the frequency and outcomes of aborted MI with pharmacoinvasive versus primary PCI treatment early after symptom onset. It shows that there are significantly more aborted MIs with the pharmacoinvasive approach.
3. This study emphasizes the advantage of a pharmacoinvasive approach in STEMI patients who cannot undergo primary PCI within one hour of symptom onset

Dr. Malecki, a medical graduate from Iran, is now pursuing further training in New York with the intention of becoming an academic cardiologist and hopes to pursue her career in Canada.

ORIGINAL ARTICLE

Aborted myocardial infarction in ST-elevation myocardial infarction: insights from the STrategic Reperfusion Early After Myocardial infarction trial

Neda Dianati Maleki,[1] Frans Van de Werf,[2] Patrick Goldstein,[3] Jennifer A Adgey,[4] Yves Lambert,[5] Vitaly Sulimov,[6] Fernando Rosell-Ortiz,[7] Anthony H Gershlick,[8] Yinggan Zheng,[1] Cynthia M Westerhout,[1] Paul W Armstrong[1]

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ABSTRACT

Background We evaluated the prespecified endpoint, aborted myocardial infarction (AbMI), according to the use of a pharmacoinvasive (PI) strategy versus primary percutaneous coronary intervention (PCI) in 1754 patients randomised within 3 h of symptom onset in the STrategic Reperfusion Early After Myocardial infarction (STREAM) trial.

Methods Based on sequential ECG's and biomarkers, AbMI was defined as ST-elevation resolution ≥50% (90 min posttenecteplase (TNK) in the PI arm or 30 min postprimary PCI) with minimal biomarker rise.

Results In the PI arm 11.1% (n=99) had AbMI versus 6.9% (n=59) in primary PCI arm (p<0.01). In a multivariable model, AbMI patients overall had less baseline ΣST-deviation, fewer baseline Q-waves and shorter total ischaemic times. PI AbMI patients had faster time to TNK (90 vs 100 min, p=0.015): total ischaemic time was 100 min longer in primary PCI AbMI patients and no difference in ischaemic time existed between AbMI and non-AbMI patients within this group. Although no significant interaction between treatment and AbMI on the composite endpoint of death/shock/congestive heart failure/recurrent MI occurred (p=0.292), PI AbMI patients had a lower incidence in this endpoint than non-AbMI patients (5.1 vs 12%, p=0.038); this was not evident in primary PCI patients. Forty-five patients (ie, 2.5%) had masquerading MI with minimal biomarker elevation and no evolution in baseline ST-elevation.

Conclusions A PI strategy of early fibrinolysis more frequently aborts MI than primary PCI. Such PI patients had more favourable outcomes as compared with non-AbMIs. Diligent review of ECG evolution in STEMI distinguishes AbMI from infarct masquerade.

Clinical Trials.gov ID NCT00623623.

CrossMark

To cite: Dianati Maleki N, Van de Werf F, Goldstein P, *et al*. *Heart* 2014;**100**:1543–1549.

INTRODUCTION

Aborted myocardial infarction (AbMI) during acute ST-elevation myocardial infarction (STEMI) has been defined by ≥50% resolution in ST-segment elevation coupled with no or minimal subsequent rise in cardiac biomarkers and deemed to be an indicator of successful reperfusion therapy.[1 2] This entity was originally identified in the context of prehospital fibrinolysis and is known to be time sensitive.[3 4] Subsequently, AbMI has been shown to be associated with smaller infarct sizes, better ventricular function and improved outcomes than those without AbMI, thereby leading to the call for prospective validation of its prognostic relevance and the suggestion that it might constitute a novel and useful efficacy endpoint when assessing treatment interventions in STEMI.[4–7]

While prior studies in patients with myocardial infarction (MI) have examined the frequency of AbMI both after fibrinolysis[1–4] and primary percutaneous coronary intervention (PCI),[5 6] no direct prospective comparison of the incidence of AbMI between these two reperfusion strategies has ever been performed. Accordingly, we provide the first report from a prespecified comparison within the STrategic Reperfusion Early After Myocardial Infarction (STREAM) study of AbMI in patients with STEMI who were randomised to either a pharmacoinvasive (PI) strategy of fibrinolysis followed by rescue/scheduled catheterisation or primary PCI.[8] This endpoint was specifically identified of interest in STREAM because of the trial's unique focus on prehospital enrolment and requirement for a symptom onset to randomisation time of less than 3 h. Our objectives were to (i) compare the incidence of AbMI in the two treatment groups of the STREAM trial, (ii) examine the relationship between AbMI and the clinical outcomes according to assigned study treatment and (iii) evaluate the relationship between AbMI and clinical outcomes, irrespective of study treatment assignment.

METHODS

STREAM was a randomised multicentre trial to compare a PI strategy versus primary PCI in STEMI. The specific entry criteria and treatment strategies of STREAM trial have been published previously.[9] Briefly, STEMI patients >18 years, presenting within 3 h from symptom onset were randomised to either (i) a strategy of fibrinolysis with tenecteplase (TNK) followed by scheduled or rescue PCI, based on achievement or failure to achieve at least 50% ST resolution in the single worst lead at baseline (PI) or (ii) primary PCI administered according to local standards (Primary PCI). STEMI was defined by ≥2 mV ST-elevation in two contiguous leads of the baseline ECG. Creatinine kinase (CK), creatinine kinase MB isoenzyme (CK-MB) and troponin levels were collected as multiples exceeding the upper limit of normal (ULN) at baseline, 8–12 h and 24 h after randomisation.

ELSEVIER CrossMark

Canadian Journal of Cardiology 30 (2014) 1208–1215

Clinical Research

Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 (PROACT-3)

Justin A. Ezekowitz, MBBCh, MSc,[a,b] Robert C. Welsh, MD,[a,b] Courtney Gubbels, BA,[a] Neil Brass, MD,[c] Michael Chan, MD,[c] William Keeble, BMBS, DM,[d] Fadi Khadour, MD,[e] Thomas L. Koshy, PhD,[f] Darren Knapp, EMT-A,[g] Sanjay Sharma, MD,[h] Sunil Sookram, MD,[i] Wayne Tymchak, MD,[a,b] Dale Weiss,[g] Cynthia M. Westerhout, PhD,[a] and Paul W. Armstrong, MD[a]

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[b] *Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada*
[c] *Royal Alexandra Hospital, Edmonton, Alberta, Canada*
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[e] *Sturgeon Community Hospital and Health Centre, Edmonton, Alberta, Canada*
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[i] *University of Alberta Hospital, Edmonton, Alberta, Canada*

ABSTRACT

Background: The outcomes of acute cardiovascular symptom presentations are potentially modifiable with the use of biomarkers to accelerate accurate diagnosis. This randomized trial tested troponin and B-type natriuretic peptide before hospital guidance in patients with acute cardiovascular symptoms.

Methods: Patients with either chest pain or shortness of breath were randomized to usual care or biomarkers analyzed using a point-of-care device in the ambulance. The primary end point was time to final disposition (discharge from the emergency department or admission to hospital). The trial was stopped prematurely because of less than expected enrollment of patients of interest and no difference in the primary end point.

RÉSUMÉ

Introduction : Les résultats concernant le tableau clinique de la maladie cardiovasculaire en phase aiguë sont potentiellement modifiables par l'utilisation de biomarqueurs pour poser rapidement un diagnostic précis. Cet essai aléatoire a testé la troponine et le propeptide natriurétique de type B avant d'orienter vers l'hôpital les patients ayant un tableau clinique de maladie cardiovasculaire en phase aiguë.

Méthodes : Les patients souffrant de douleurs thoraciques ou d'essoufflement ont été répartis au hasard pour recevoir les soins habituels ou selon les biomarqueurs analysés à l'aide d'un dispositif au chevet du patient disponible dans l'ambulance. Le critère de jugement principal a été le moment de la destination finale (congé du service des urgences ou admission à l'hôpital). L'essai a été interrompu

Acute cardiovascular disease constitutes a major resource-intensive public health challenge. Symptoms compatible with acute cardiovascular disease comprise a high proportion of patient assessments in the emergency department (ED), leading to costly investigations and hospital admissions to "rule out" acute cardiovascular disease.[1-5] Most are ultimately discovered to have noncardiac causes for their symptoms.[2,4]

In ST-elevation myocardial infarction, diagnosis before hospital arrival, triage, and treatment improves time to treatment and enhances patient outcomes[6,7] but this has yet to be translated to other acute cardiovascular conditions: acute coronary syndrome (ACS) or acute heart failure (AHF). Whether disposition of patients with suspected AHF or ACS can be improved by using blood tests before hospital arrival like troponin or B-type natriuretic peptide (BNP) is uncertain.

Received for publication January 20, 2014. Accepted April 14, 2014.

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See page 1214 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2014.04.012

CJC Canadian Journal of Cardiology Journal canadien de cardiologie

PROVIDING RAPID OUT OF HOSPITAL ACUTE CARDIOVASCULAR TREATMENT 3 (PROACT-3)

A few areas in medicine require quick thinking, swift decisions and the informed action. Paramedics take this action in the ambulance when seeing patients with chest pain or shortness of breath, and in the PROACT-3 trial, they and their ER colleagues had additional early troponin and BNP data to guide their decisions. In this trial, lead author Justin Ezekowitz along with a truly pan-Edmonton collaborative group representing all five hospitals, emergency departments and emergency medicine and our VIGOUR centre, did not demonstrate that we could shorten the overall time in the ER by using these earlier biomarkers, but has allowed us an instructive look at what happens in forward thinking health systems: work collaboratively, test new ideas, study results and reboot with a modified plan. All of this was possible with team work importantly facilitated by funding from the University Hospital Foundation, Heart and Stroke Foundation of Canada and our industry partner Alere.

Canadian Journal of Cardiology
Journal canadien de cardiologie

INCREASED UPTAKE OF GUIDELINE-RECOMMENDED ORAL ANTIPLATELET THERAPY: INSIGHTS FROM THE CANADIAN ACUTE CORONARY SYNDROME REFLECTIVE

In this multiauthored report anchored by CVC Co-Director Shaun Goodman together with 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 new anti-platelet agents in over 3000 patients assessed in 83 Canadian hospitals and found relative underuse of the newer agents shown to produce clinical benefit. This observation showing the treatment gap highlights some of the challenges in translating research discovery into the "real world" and signals the need to overcome barriers to implementing guideline based therapy.

ELSEVIER CrossMark

Canadian Journal of Cardiology 30 (2014) 1725–1731

Training/Practice
Health Policy and Promotion

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

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ABSTRACT
Current guideline-based recommendations for oral dual-antiplatelet therapy in an acute coronary syndrome (ACS) include the use of newer adenosine diphosphate receptor inhibitor (ADPri) regimens and agents. The Canadian ACS Reflective Program is a multicenter observational quality-enhancement project that compared the use of

RÉSUMÉ
Les recommandations basées sur les lignes directrices actuelles pour la bithérapie antiplaquettaire orale dans le syndrome coronarien aigu (SCA) incluent l'utilisation de nouveaux schémas posologiques et agents pharmacologiques à base d'inhibiteur du récepteur à l'adénosine diphosphate (ADPri). Le Canadian ACS Reflective Program

Current guideline-based recommendations from the Canadian Cardiovascular Society (CCS) for oral dual-antiplatelet therapy (acetylsalicylic acid [ASA] + adenosine diphosphate receptor inhibitor [ADPri] in an acute coronary syndrome [ACS]) includes the use of newer more potent regimens such as double-dose clopidogrel (eg, 600 mg loading dose followed by 150 mg daily for 6 days) and newer agents such as prasugrel (in patients undergoing percutaneous coronary intervention [PCI]), and ticagrelor.[1] There are several challenges to the optimal and appropriate use of oral antiplatelet therapies. These include uncertainties

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Which risk score best predicts perioperative outcomes in nonvalvular atrial fibrillation patients undergoing noncardiac surgery?

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Background Patients with nonvalvular atrial fibrillation (NVAF) are at increased risk for adverse events after noncardiac surgery. The Revised Cardiac Index (RCI) is commonly used to predict perioperative events; however, the prognostic utility of NVAF risk scores ($CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2) has not been evaluated in patients undergoing noncardiac surgery.

Methods Using a population-based data set of NVAF patients (n = 32,160) who underwent major or minor noncardiac surgery between April 1, 1999, and November 30, 2009, in Alberta, Canada, we examined the incremental prognostic value of the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores over the RCI using continuous net reclassification improvement (NRI). The primary composite outcome was 30-day mortality, stroke, transient ischemic attack, or systemic embolism.

Results The median age was 73 years, 55.1% were male, 6.6% had a previous thromboembolism, 17% of patients underwent major surgery, and the median risk scores were as follows: RCI = 1, $CHADS_2$ = 1, CHA_2DS_2-VASc = 3, and R_2CHADS_2 = 2. The incidence of our 30-day composite was 4.2% (mortality 3.3%; stroke, transient ischemic attack, or systemic embolism 1.2%); and c indices were 0.65 for the RCI, 0.67 for the $CHADS_2$ (NRI 14.3%, $P < .001$), 0.67 for CHA_2DS_2-VASc (NRI 10.7%, $P < .001$), and 0.68 for R_2CHADS_2 (NRI 11.4%, $P < .001$). The $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores were also all significantly better than the RCI for mortality risk prediction (NRI 12.3%, 8.4%, and 13.3%, respectively; all Ps < .01).

Conclusions In NVAF patients undergoing noncardiac surgery, the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores all improved the prediction of major perioperative events including mortality compared to the RCI. (Am Heart J 2014;168:60-67.e5.)

The prevalence of nonvalvular atrial fibrillation and flutter (NVAF) in the general population is increasing.[1] Accordingly, more patients with NVAF will require preoperative risk stratification before noncardiac surgery. Clinical perioperative risk prediction models[2–7] and guidelines[8,9] for perioperative risk assessment do not include NVAF as an independent risk factor for adverse perioperative outcomes; however, some risk models have found that nonsinus rhythms or premature atrial contractions were independently associated with perioperative cardiac events.[2,5,6,7] Importantly, postoperative AF is a well-recognized adverse prognostic marker in noncardiac surgery[10–12]; and a recent study has reported that preoperative NVAF was independently associated with higher 30-day perioperative mortality and readmission rates.[13]

The $CHADS_2$ and CHA_2DS_2-VASc scores are clinical prediction models endorsed by major clinical societies to assess thromboembolic risk in patients with NVAF, and the R_2CHADS_2 index has recently been shown to further improve thromboembolic discrimination in a clinical trial population.[9,14–17] The application of these models has been extended to nonembolic outcomes including the prediction of postcardioversion mortality,[18] AF recurrence after ablation,[19] mortality in patients paced for sick sinus syndrome,[20] and the risk of AF after cardiothoracic surgery.[21] Whether the $CHADS_2$, CHA_2DS_2-VASc, or R_2CHADS_2 scores are associated with 30-day perioperative outcomes in patients with nonvalvular AF undergoing major or minor noncardiac surgery and whether these scores can improve preoperative risk prediction compared to the Revised Cardiac Index (RCI, the currently recommended preoperative risk score for noncardiac surgery)[8,9] remain unclear.

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WHICH RISK SCORE BEST PREDICTS PERIOPERATIVE OUTCOMES IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS UNDERGOING NONCARDIAC SURGERY?

The power of lateral thinking is evident when a cardiologist also becomes and ICU physician and looks for new ways to risk stratify patients undergoing non-cardiac surgery. Sean van Diepen evaluated a common clinical question (what is the risk for a perioperative event in this patient?) with another common tool – the atrial fibrillation risk scores (e.g. CHADS2). Interestingly, the most commonly used risk score, the Revised Cardiac Index, performed poorly at predicting perioperative events, and the common stroke risk scores including CHADS2, CHADS2VASc and R2CHADS2 improved on this prediction.

This stands as a good example of applying common and simple tools from one area in medicine to aid in patient care in another by thinking laterally.

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MORTALITY OUTCOMES AMONG STATUS ABORIGINALS AND WHITES WITH HEART FAILURE

In this analysis of patients in Alberta with heart failure, cardiology trainee Kristin Lyons, CVC biostatisticians and three CVC faculty (Kaul, Ezekowitz and McAlister) collaborated to explore the similarities and differences of Aboriginal and non-Aboriginal patients. Not surprising to clinicians who may be familiar with in-hospital care of patients with heart failure, the Aboriginal patients were younger (by a full decade) and had higher rates of diabetes than their counterpart non-aboriginal patients with heart failure. Importantly, this younger aged cohort of Aboriginal patients had a higher risk of mortality over the next one and five years – even after adjusting for the increased healthcare resource use, access to care and other clinical variables. This analysis draws out the importance of ensuring equitable access and quality of care to those most vulnerable to poor health outcomes. Dr. Lyons is continuing her heart failure research and clinical training pursuits with another former trainee, Ali Nsair, at UCLA in California, with plans to return to Alberta in 2016.

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Clinical Research

Mortality Outcomes Among Status Aboriginals and Whites With Heart Failure

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ABSTRACT

Background: Aboriginals have more cardiovascular risk factors than do non-Aboriginals that predispose them to the development of heart failure (HF). Whether long-term mortality outcomes and health care use differ between Aboriginals and whites with HF is unknown.

Methods: The population consisted of all Albertans aged ≥ 20 years with an incident HF hospitalization between 2000 and 2008. Aboriginal status is recorded in the Alberta Health Care Insurance Registry and white ethnicity was determined using previously validated surname analysis algorithms. Cox and logistic regression was used to examine mortality outcomes after adjustment for key variables.

Results: Compared with whites (n = 42,288), status aboriginal patients with HF (n = 1158) were significantly younger (mean age, 62.6 vs 75.4 years; $P < 0.0001$) and had higher rates of diabetes (45% vs 29%; $P < 0.0001$) and chronic obstructive pulmonary disease (40% vs 36%; $P < 0.0001$) but lower rates of most other comorbidities.

RÉSUMÉ

Introduction : Les Autochtones présentent plus de facteurs de risque cardiovasculaire les prédisposant à l'apparition de l'insuffisance cardiaque (IC) que les non-Autochtones. On ignore si les effets à long terme sur la mortalité et l'utilisation des soins de santé diffèrent entre les Autochtones et les Blancs souffrant d'IC.

Méthodes : La population comptait tous les Albertains âgés de ≥ 20 ans ayant nécessité une première hospitalisation en raison d'une IC entre 2000 et 2008. Les Autochtones sont enregistrés au Regime d'assurance-maladie de l'Alberta, et l'origine ethnique blanche était déterminée en utilisant précédemment les algorithmes de validation de l'analyse du nom de famille. La régression logistique et le modèle de Cox étaient utilisés pour examiner les effets sur la mortalité après l'ajustement des variables principales.

Résultats : Comparativement aux patients blancs (n = 42 288), les patients autochtones ayant une IC (n = 1158) étaient beaucoup plus

Heart failure (HF) is a common condition with a lifetime risk of 20% in individuals ≥ 40 years.[1] It is associated with significant morbidity and mortality and is the leading cause of acute care hospitalizations, with an estimated annual cost of inpatient management in Canada of more than CAD$1 billion.[2] Current evidence suggests that ethnicity modulates HF incidence and outcomes,[3–9] and previous studies have shown that Aboriginal populations have a higher prevalence of HF and HF deaths than do non-Aboriginal populations.[10–13]

According to the 2006 Canadian census, Canada's Aboriginal population includes ~ 1.2 million First Nations, Métis, and Inuit peoples.[14] At almost 4% of the national population, Canada has the second largest proportional Aboriginal population in the world.[14] Life expectancy for Canadian Aboriginal men and women is 7.4 and 5.2 years less than for non-Aboriginal Canadian men and women, respectively.[14] Aboriginal Canadians have higher rates of HF risk factors—including obesity, hypertension, diabetes mellitus, cardiovascular disease, and atherosclerosis—when compared with non-Aboriginal Canadians.[10,15–17] To our knowledge, no previous study has examined the differences in clinical characteristics and mortality outcomes among Aboriginal and non-Aboriginals already diagnosed with HF.

Accordingly, we used population-based health care databases to examine mortality outcomes in status Aboriginal and white patients after an incident hospitalization for HF and whether these outcomes are modulated by differences in demographic, comorbid, and socioeconomic factors. We also examined the differences in health care resource use between status Aboriginals and whites in the year before and the year after an incident HF hospitalization.

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The relationship between left ventricular ejection fraction and mortality in patients with acute heart failure: insights from the ASCEND-HF Trial

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Aim	Acute decompensated heart failure (ADHF) is associated with significant morbidity and mortality but the relationship between LVEF and outcomes is unclear. We explored the association between LVEF and 30 and 180 day mortality in 7007 ADHF patients enrolled in the Acute Studies of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial.
Methods and results	We explored the association between LVEF and 30 and 180 day mortality in 7007 ADHF patients enrolled in the Acute Studies of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial. LVEF was analysed both as a continuous variable and according to three categories: < 40% (LowEF), 40–50% [intermediate EF (IntEF)], and > 50% [preserved ejection fraction (PresEF)]. Of the patients in the trial, 4474 (78.7%) had LowEF, 674 (11.9%) had IntEF, and 539 (9.5%) had PresEF. The unadjusted 30 and 180 day mortality was similar for LowEF (3.7%, 12.3%), IntEF (3.4%, 13.1%), and PresEF (4.3%, 14.1%), respectively ($P > 0.05$). After multivariable adjustment, the hazard ratio (HR) for 180 day mortality remained similar for the LowEF [HR 0.96, 95% confidence interval (CI) 0.75–1.24; $P = 0.77$] and IntEF (0.91, 95% CI 0.66–1.3; $P = 0.58$) compared to PresEF patients. By contrast, when LVEF was evaluated as a continuous measure, it exhibited a U-shaped pattern with mortality. After matching for age and sex, the mortality risk attributed to LVEF was attenuated, as the LVEF increased as a continuous variable over 35%. However, in patients with EF < 35%, the mortality risk continue to increase as the LVEF declined.
Conclusions	Among patients with ADHF, the unadjusted mortality rates are similar across LVEF strata. However, after accounting for key patient variables, the mortality risk increases as EF falls below 35%. These data will be useful in planning future studies of ADHF.
Clinical Trial Registration	www.clinicaltrials.gov identifier: NCT00475852
Keywords	Acute heart failure • Ejection fraction • Clinical trial • Outcomes

Introduction

Acute decompensated heart failure (ADHF) is a common condition with high morbidity and mortality, as defined by readmission rates of 29% at 60–90 days and 1 year mortality rates of 20–30% in observational cohorts.[1–4] As the population continues to age, the incidence of ADHF will provide a commensurate burden to the health care system, thereby constituting a key unmet need and priority for future study.

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EUROPEAN SOCIETY OF CARDIOLOGY

THE RELATIONSHIP BETWEEN LEFT VENTRICULAR EJECTION FRACTION AND MORTALITY IN PATIENTS WITH ACUTE HEART FAILURE: INSIGHTS FROM THE ASCEND-HF TRIAL

Randomized clinical trials often have more data beyond the primary hypothesis that is tested in the main trial. In the case of the global mega-trial in acute heart failure, ASCEND-HF, we have asked and answered many questions (~20 manuscripts and counting). In this analysis, Mustafa Toma, a former cardiology trainee at the University of Alberta and now faculty and staff cardiologist at UBC/St. Paul's Hospital in Vancouver, B.C., evaluated the relationship between ejection fraction and clinical outcomes. Two clinically important findings were identified: first, after adjustment for key patient information, there is little additional difference in risk if the ejection fraction is near or well above 35%; however, if the ejection fraction is <35%, the risk for death increases as the ejection declines. Risk stratification is never simple in patients with heart failure, so this does highlight that differences exist even within a group of patients with a 'low EF'. Mustafa has also continued his academic involvement in the HF trials arena – now as an investigator at St. Paul's hospital as part of three trials CVC is leading: BLAST-AHF, the NIH-sponsored GUIDE-IT trial, and the CIHR-sponsored SODIUM-HF trial.

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WHERE IS THE WISDOM

WE HAVE LOST IN KNOWLEDGE?

WHERE IS THE KNOWLEDGE

WE HAVE LOST IN INFORMATION?

—T.S. ELLIOT

Trainees:
The Next Generation of Health Researchers

The CVC continues its enthusiastic commitment to fostering a research environment conducive to disciplined academic inquiry and novel approaches to clinical questions and methodologies. We are pleased to offer research opportunities across a full spectrum of experience, education and backgrounds. CVC has provided research opportunities for undergraduates, medical students, and postdoctoral fellows from across Canada and from around the world. The hallmark of an academic research organization, CVC's mission remains steadfast in its dedicated efforts to inspire and nurture the next generation of health researchers.

In the following section, several of our young researchers discuss their research projects and reflect upon their experience collaborating with the CVC faculty.

ELOISA COLIN RAMIREZ

Postdoctoral Fellow

Please tell us a little about your research

I began to collaborate with the CVC as a Postdoctoral Fellow in February 2012 as part of the research team working on the SODIUM-HF trial, under the supervision of Dr. Justin Ezekowitz. The SODIUM-HF study is a randomized control trial on sodium restriction in patients with chronic heart failure (HF). Sodium restriction has been broadly recommended as part of the self-care strategies in heart failure yet is based on little high-quality evidence. The pilot SODIUM-HF trial evaluated the effects of sodium restriction in 38 patients with chronic HF. 19 patients were prescribed a low sodium containing diet (1500 mg/day) and 19 a moderate sodium containing diet (2300 mg/day). Results of this pilot were recently published in the American Heart Journal. Currently, the SODIUM-HF trial is being conducted. This ongoing multicenter trial is expected to provide definitive results on the effects of sodium restriction in HF patients and develop evidence-based guidelines for sodium restriction in this patient population.

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?

Undoubtedly, CVC is a place to learn from internationally-recognized leaders in clinical research. Dr. Ezekowitz was a terrific supervisor who put all his effort into creating a learning environment based on respect and trust. He always provided support, guidance and motivation when things seemed to be unclear and I started to lose perspective. I also had the opportunity to work with Drs. Armstrong and McAlister, whose ability to share their knowledge and provide significant and positive feedback encouraged learning and academic growth. Without any hesitation, this has been a life changing experience. I feel so fortunate to have been given the opportunity to be part of this team.

RABIA KASHUR

MSc Student, Medicine

Please tell us a little about your research

I am currently a master's student with Dr. Robert Welsh. My thesis project is about examining ethics issues of Cardiology research in ACS trials. Also as part of the many opportunities offered by the CVC to its trainees, I am involved in the PROACT-3 ECG substudy where we are analysing EMS and In-hospital ECG data and trying to identify the correlation between those dynamic changes and adjudicated diagnoses, cardiac biomarkers, timing intervals from symptoms onset and study end points/outcomes. The study's objective is to recognize key variables in EMS/In-hospital ECGs in conjunction with cardiac biomarkers to help triage patients with symptoms suspecting acute cardiovascular disease and identify high risk groups among them.

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?

It's a pleasure and a great opportunity to be part of the CVC, where you receive support with unlimited resources, and can collaborate within a close-knit team from diverse professional backgrounds. Working with the CVC faculty under their mentorship feels like having a storm of ideas but you don't know which one to pursue. Once the ideas are presented, you are steered to find the proper way. I consider myself among the luckiest to work under the mentorship of prominent stars in the field of ACS and heart failure. They have taught me to challenge my abilities and have encouraged me to strive to the best of my capacity and true potential.

NARIMAN SEPEHRVAND

PhD Candidate, Experimental Medicine

Please tell us a little about your research

Like all other CVC members, I am working on research projects related to cardiovascular diseases. I had the chance to work on the data we had at the CVC from the PROACT-3 trial which was the first trial to study the efficacy of pre-hospital biomarker testing in CV diseases. Receiving great mentorship from Dr. Ezekowitz and Dr. Armstrong, in collaboration with the CVC biostatistical team, we have succeeded in accomplishing a sub-study addressing the issue of the comparison between the performance of site versus adjudication committee in clinical trials. We have developed two potential population-based projects which use administrative health data for answering specific cardiovascular health-related questions. Besides the above-mentioned studies, we have determined a couple of study questions to address as different parts of my PhD thesis which is about the diagnosis and management of patients with acute heart failure. These studies will cover a broad range of study designs from observational studies to clinical trials, from primary research to secondary researches (e.g. systematic review and meta-analysis).

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?

The training I have received at the CVC about current cardiology research is really priceless. All of the CVC faculty are internationally known experts, and it is great to have the chance to learn from their experiences in research, clinical practice and health policy issues. Their solid history of mentoring students facilitates the learning process for the trainee.

During 2014, I received wonderful mentorship from Dr. Ezekowitz. His commitment to making a difference in the field of medicine is very prominent. I learned a lot from him about which questions are worthwhile, and how to seek through a potential research project for those that are not.

ISMAIL RAED RASLAN
MSc Student, Experimental Medicine

Please tell us a little about your research
CCU beds account for 5-10% of all hospital beds and up to 35% of hospital costs in North America. Identifying patients who will require a higher level of care at the time of emergency department triage may help reduce unnecessary CCU admissions and reduce health care costs. However, little is known about which patients admitted to hospital with acute decompensated heart failure (ADHF), who do not immediately require critical care therapies, are at risk for in-hospital major adverse cardiovascular events and could potentially benefit from an admission to a higher intensity unit. The purpose of our study is to develop a point-of-care clinical prediction model to help appropriately triage patients with ADHF admissions to CCU or hospital ward beds.

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?
It was a sincere pleasure and delight to work with the faculty at the CVC. Even before I came I felt very welcomed. They are very knowledgeable, humble, understanding and always very supportive. I'm very thankful to my mentors from the CVC; their knowledge, experience and support is at the core of my progress. Their continuous support and feedback is the fuel that drives my research.

PAUL BROWN
PhD Candidate, Medicine

Please tell us a little about your research
My research, under the guidance of Dr. Ezekowitz, compares and evaluates measures of treatment response in studies of acute heart failure; basically considering whether we are making the most of our data: how best to analyse and present the data, or increase statistical efficiency.

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?
[To describe their mentorship as] valuable is an understatement. The questions I investigate are posed by my supervisor, Dr Ezekowitz, and along the way my thinking is constantly calibrated and kept in check by our discussions. Thus I am brought up to speed (with what seems an endless literature) and can contribute far sooner than I otherwise could. There is always another interesting study waiting for me; I have the sense that I could never tire of the work.

ABHINAV SHARMA
MSc Student, Translational Medicine

Please tell us a little about your research
My research is primarily focused on the interaction between diabetes and heart failure. Using clinical registries and data from randomized clinical trials I will evaluate outcomes, prognostication models, and biomarker analysis.

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?
It has opened the doors to a worldwide network of researchers, collaborators, and future colleagues. My supervisor Dr. Justin Ezekowitz is a wonderful mentor. He is always accessible, whether for a few minutes conversation or a two hour discussion. He has provided me with excellent connections globally, phenomenal advice, and superb clinical and research advice.

2014 Highlights:
3rd place at the Canadian Cardiovascular Society-Bayer Resident Vascular Award at CCS 2014

PISHOY GOUDA
MB BCh BAO Candidate

Please tell us a little about your research
Acute heart failure (AHF) is a heterogeneous group of disorders presenting to the emergency department (ED) with acute shortness of breath or other symptoms that are broadly linked to left/right ventricular dysfunction. AHF carries a significant risk for death or morbidity such as re-hospitalization in the next 30 days (10% mortality, 25% re-hospitalization rate). Clinical decision-making on these patients incorporates current and past medical history, physical examination, chest x-ray and blood tests. Patients attending an ED will also have an electrocardiogram (ECG) to evaluate for an arrhythmia or myocardial ischemia. While much is known about the prognostic implications of an abnormal ECG in patients with chronic HF, little is known about whether these findings in patients with AHF symptoms are related to short-term adverse outcomes. The objective of my research was to describe ECG findings in a well characterized AHF population, describe the prognostic implications of abnormal ECG findings and describe their pre-hospital care.

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?
Over the past 3 years, I have been extremely fortunate to be able to work with several members of the CVC team. In short, I have found them extremely supportive, welcoming and helpful to a junior researcher such as myself.

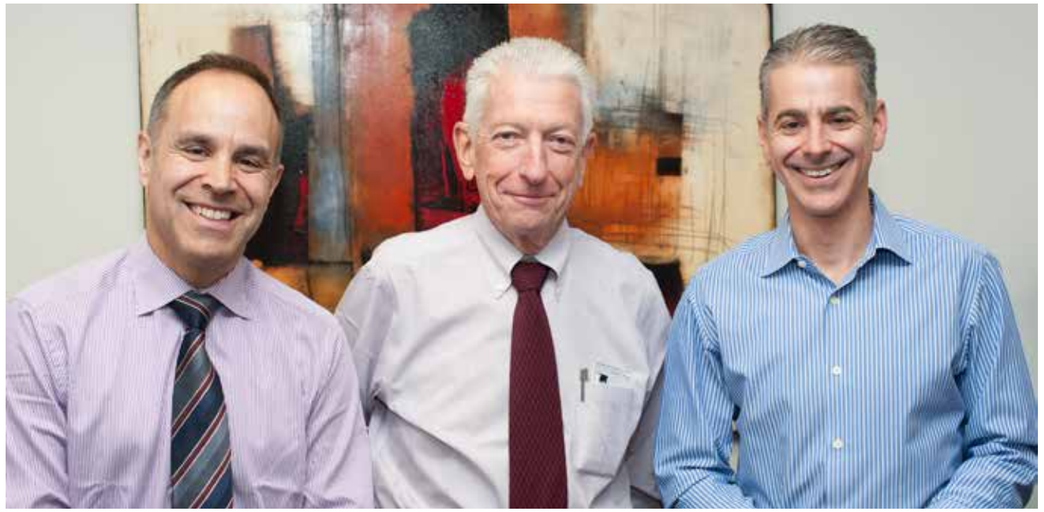
Three years ago Dr. Ezekowitz provided me with my first opportunity to gain some research experience. That same summer, more than half my classmates also did some sort of research but our experiences could not have been more different. Medical students often feel like research is a chore, an application box ticking exercise. My experience was quite the opposite. Rather I became excited by the prospect of asking new questions and figuring out how to find the answers to those questions. Dr. Ezekowitz played a big role in this. Rather than handing me the answers, he helped me figure them out myself. Instead of giving me tasks, he pointed me in the general direction and gave me guidance. In short, without his mentorship, I do not think I would have developed such a great interest in research.

JAY SHAVADIA
Cardiology Fellow

Please tell us a little about your research
My research proposal looked at the development of shock and heart failure vis-a-vis the infarct size in the two reperfusion strategies tested in the STREAM trial.

How would you describe your experience working with the CVC faculty, and how has their mentorship been valuable to you?
Collaborating with CVC faculty on this project has certainly been an 'eye-opener' into research methodology and data analysis. Sitting in the CVC boardroom rehearsing an oral presentation initially felt like a daunting task, but at the end of it all, the confidence to stand to colleagues in major meetings has been fulfilling. 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 all-round clinician, steps that I would be proud to emulate in the future.

2014 Highlights:
Best Clinical Presentation Award, Cardiac Sciences Day 2014



Conversations about Mentoring

"TELL ME AND I FORGET, TEACH ME AND I MAY REMEMBER, INVOLVE ME AND I LEARN."
— BENJAMIN FRANKLIN

As both an academic research organization and a university centre, the CVC is committed to providing excellent mentorship opportunities to the next generation of health researchers and professionals. In the section below, Drs. Armstrong, Ezekowitz and Goodman provide some insights into the importance of mentoring.

HOW HAS THE MENTORING YOU RECEIVED IMPACTED YOUR RESEARCH AND CAREER?

Justin Ezekowitz: Simply put: I would not have been successful without mentorship. For me, mentorship has been more than career advice. I received the highest quality mentoring that one can receive. It has had an impact on my research by direct feedback as well as connected me internally and externally with my collaborators with whom I currently work. I have projects where I have expanded my opportunities because of the mentorship I received, which has forced me to think carefully about the science that I am conducting. I had the opportunity to work in a research team and learn how to instruct others and be instructed as well. Being aware of my limitations as well as my strengths within the research environment makes me a better researcher as well as a better physician. Additionally, learning how to focus on the project while remaining nimble and innovative, and being open to criticism as well as defending my work has of course led to better manuscripts, projects and grants.

Shaun Goodman: The role model aspect of working with Paul Armstrong and some of my other mentors has been particularly important. Watching them in action, specifically in terms of how they conduct themselves, interact with research staff, and seeing how hard they work is a constant reminder that the time, energy, and wisdom they are investing in you is not necessarily intended to be returned to the mentor, but to be paid forward to the next generation. It is critical to see in action the investment they make and the obligation you have to give back. You also have a responsibility to step up to the plate and ensure you follow through on the things they have enhanced or facilitated for you.

Paul Armstrong: The quote that sticks with me is from Alfred, Lord Tennyson's Ulysses –"I am a part of all that I have met." As I reflect on my mentors and how they inspired me to shoot for the stars and do things I didn't even think I was even capable of, I think of how their inspiration was transformative. You learn things from walking in someone's footsteps that are not teachable or learnable in any other way.

I remember it as though it were yesterday, for the first time telling a young woman she was now a widow. My mentors in those early days of being a physician demonstrated how to deal with these tragedies and interact with human beings. They also taught me how to evaluate patients, how to do a cardiac catheterization, how to present, how to write, how to ask for help when you are out of your depth, and to recognize someone is there to help you out.

You also learn different things from different people. Warren Hawthorne taught me skills nobody else could with cardiac catheterization for instance. I can remember like it was yesterday at Massachusetts General Hospital trying to cross an aortic valve retrograde and I could not do it and asked for his help. He came into the case and said "Paul, listen to the music of the catheter – tap, tap, tap –and think about putting a pencil through a straw." That was in 1969 and I have never forgotten it.

WHAT INSPIRED YOU TO TAKE AN INTEREST IN MENTORING?

Shaun Goodman: In the context of the mentor/mentee relationship you hopefully see that it is about both give and take. As a mentee you can see when the experience has been beneficial or rewarding to the mentor. Being a mentor is about giving back but also seeing the value and the reward of influencing another human being and helping them to be not only a better physician but a better person. A big piece for me is the connections. I would not be able to do the things I do clinically or research-wise without the connections built with other individuals, including experts in the field, colleagues, and international collaborators. Having been the beneficiary of this, and now having my own independent relationships, it is important for me to now be able to provide those connections to others. This is about personally giving back, but also recognizing that I am in a fantastic position to facilitate and enhance the experience of the next generation. I want people to have the experience I had and lead the next generation of clinical trials.

Justin Ezekowitz: I have been very lucky with my mentors as I have been in clinical medicine and research. Over the years, my mentors have provided me with the tremendous opportunity to grow as a person as well as a clinician scientist. My success in a large way is due to my mentors and specifically the mentee-mentor relationship that developed. It's clear to me that this is an important feature for training the next-generation of clinician scientists and for me this is an important goal. I've had the opportunity to work with some of the 'mentors of the mentors' and recognize the importance of lifelong mentorship. Mentorship should start early and continue, perhaps never stop. This has inspired me to ensure I continue the tradition of ensuring high quality mentorship, and also reminded me that all of us benefit from continued mentorship, be it formal or informal.

Paul Armstrong: Shaun's comment reminded me of something we do as mentors: we write letters of support, we make phone calls on their behalf, and we act on behalf of young people who show promise and are trying to establish their careers. We do this because we experienced this process first hand and being an advocate for the next generation is critically important. I remember walking into an interview at Massachusetts General Hospital Harvard Medical School with Charlie Sanders, the Director of the Cath. Lab, who had worked with one of my mentor's Peter Morrin from Queen's University. In the interview he said to me "If Peter Morrin says you're a good man, you're a good man." I was given a job offer and this was because someone made a phone call.

There was a young man I mentored who after a summer working at John Hopkins Hospital came by my office to visit and say thank you. I was fairly young in my career at that point and to have someone come back and say thank you was very meaningful to me. None of us say thank you enough –we all try, but often forget.

Since we have grown up in an academic environment, we are constantly in a position to teach; there are always younger people behind us, and the teaching piece is an important aspect of mentoring. It comes down to the fact that it is our responsibility to pass on our knowledge and give back to the youth.

There comes a time for all of us when we feel a vicarious joy for the success of those we mentor. It was Willis Hurst, a real giant in Cardiology, who once said to me "Always remember when your young people are in the sunshine you should be in the shadows."

WHAT CRITERIA SHOULD A PERSON USE TO EVALUATE SOMEONE THEY ARE CONSIDERING AS A POTENTIAL MENTOR?

Justin Ezekowitz: The criteria are not easily quantified in a numeric sense. The characteristics to look for in a mentor are often those she/he would look for in a colleague or a teacher. The classical teaching is that one should look for someone who will be a friend, an advisor, a teacher and a role model so those are the key features. The key attributes of anybody who will be a mentor are that of mutual respect, trustworthiness, accessibility, and their level of accomplishment. Simply put, a long list of grants and publications is a good starting point, but mentors are more than the parts of a CV! Prior successful mentorship is also helpful – a prior mentee's success will often predict future mentee-mentor success.

Shaun Goodman: It is a delicate balance that is both an evolution and work-in-progress. For instance, in the beginning there needs to be an alignment in terms of goals and objectives. Later, after challenging the mentee to decide upon their direction and goals and giving them the assistance they need to move in the right direction, the best mentors allow their mentees to develop their own agenda. At the end of the day a successful mentor must be comfortable in allowing the mentee to act independently and make their own decisions. It is similar to a relationship between a parent and child in the sense that you have invested in them, given them skills, and shared your expertise and wisdom, and then following a period of time they need to be able to choose their own direction and you need to be able to step back, which indirectly is actually support for the individual.

Paul Armstrong: Personal integrity and a relationship of trust are both critical, especially when the mentee is in an evolutionary stage of their research. The sense that the information and knowledge they share will be kept in confidence I think is a key element.

The best mentors understand who you are as a person as well as where you are in your career and what you want to do –this balance which is different for all of us and changes over time is critically important. There is never a lack of need for mentoring. I've always had people ahead of me that I could talk to about opportunities I have been given and their opinions and experiences. In that way, I think mentoring is a lifelong process that has different requirements at different stages.

Beyond 2000

In October 2014, CVC hosted our 20th anniversary of the New Concepts in Acute Coronary Syndrome: Beyond 2000, held in Vancouver, BC in conjunction with the Canadian Cardiovascular Congress and supported by an unrestricted educational grants from AstraZeneca. As has been our tradition with this symposium, we were pleased to have partnered with the Mazankowski Alberta Heart Institute and the University of Alberta in undertaking this venture which probes new avenues in acute coronary syndromes and also address the role of novel technologies amidst the brave new information age in which we work.

This year's program addressed highlight key advances that have transformed the pathophysiology, management and prevention of acute coronary syndromes. Special emphasis was placed on key lessons learned that have informed the best current evidence-based therapy. New insights into the care of ST elevation myocardial infarction was provided that are relevant to the Canadian practitioner. A discussion on how to make informed choices amidst a surfeit of currently available (or soon to be available) antiplatelet and anticoagulant agents will occur. The program was specifically focus on the concept of residual risk and the need to account for the special challenges imposed by diabetes and dyslipidemia. Furthermore a strategy to overcome the risk-treatment paradox was presented. As is traditionally the case, the impact of recent and evolving clinical trials relating to the ever-changing face of ACS was undertaken.

To ensure the high quality presentations and video dialogues with key speakers is preserved from this legacy event; we have established a web site: www.Beyond2000.org that is now available for your viewing under the "Continuing Conversation" banner.

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The CVC Clinical Trials Colloquium – Banff, Alberta – March 2014

Seeking out more efficient ways to run clinical trials in Canada, in late 2013 we commenced planning for the first annual CVC Clinical Trials Research Colloquium held in Banff, AB on March 9, 2014 in conjunction with the ACC Rockies Meeting. The intent of this meeting was to bring together 10 – 12 key Canadian sites, have them complete a detailed survey on all aspects of clinical trials at their site and then bring them together in Banff where we could look at the compiled data from the survey and discuss strategies to enhance start up and overall efficiencies of clinical trials in Canada.

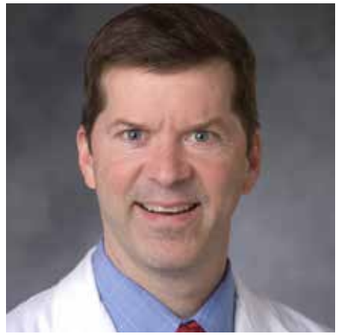
The interactive session which included 11 investigators and 12 study coordinators representing 13 sites from across the country along with sponsor and ARO representation provided a unique opportunity for open discussion around the many challenges facing clinical trials in Canada, including cost of doing research, impediments to start up, contract issues and the future of clinical research in Canada. This open discussion not only presented the opportunity to express the challenges but openly bring forth solutions. With a 100% response rate on the 75 question survey distributed prior to the colloquium, we were able to ascertain meaningful information from 16 of our investigative sites. The key findings were shared in the June 2014 issue of our Canadian Cardiac Chronicle and detailed report cards were also provided to all sites who participated in the survey. The primary impediments to quick start up surrounded contracts and ethics reviews, however, it was interesting to see that while the average time to start-up was two-six months, many of the sites had broken the barrier and were able to produce a quick start up in under two months. We saw a similar result with time to enrollment following activation where the average was two-four weeks but most sites had shown that their quickest recruitment post activation was done in under two weeks. As noted previously, additional highlights are available in the June 2014 issue of the Canadian Cardiac Chronicle.

Thanks to an unrestricted grant from our sponsors Amgen Canada Inc., AstraZeneca Canada Inc., Merck & Co., Inc., and Sanofi Canada it was possible to move forward with this unique event. The response to the inaugural 2014 CVC Clinical Trials Colloquium from investigators, study coordinators and the supporting sponsors was very positive, highlighting this as a unique opportunity to share experiences from across the country in an effort to improve and streamline the overall process of conducting clinical trials in Canada. The positive response to the colloquium has resulted in an expansion for 2015 which will not only include the main Colloquium session but also a closed Study Coordinator workshop and an open Clinical Research Workshop linked into the ACC Rockies Meeting. Highlights from the 2nd Annual Clinical Trials Colloquium will again be featured in the CVC Canadian Cardiac Chronicle.

Distinguished Visitors

In 2014, the faculty of the CVC had the privilege of hosting five outstanding, internationally renowned academics continuing a program generously sponsored by an unrestricted educational grant from AstraZeneca.

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. They provide a welcome window on 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 educational/research mission.



DR. G. MICHAEL FELKER
Associate Professor Division of Cardiology, Chief Heart Failure Section at Duke University School of Medicine
Director of the Heart Center Clinical Research Unit and Director of Heart Failure Research, Duke Clinical Research Institute

March 12, 2014
- Cardiology Divisional Rounds: "New Therapies for Acute Heart Failure"
- Research Rounds: "Biomarker Guided Therapy for Heart Failure"

Michael Felker gave us the key information on why biomarker trials succeed or fail, and how this is intimately related to the biomarker being tested as well as the patient population selected and clinical trial design. He 'guided' us through the design of his collaborative project [GUIDE-IT] that involves CVC as a Canadian lead for the National Institutes of Health funded research project. His insightful CCU rounds also provided for an excellent training experience for the cardiology trainees, which will continue through our CVC-DCRI collaborative training environment.

DR. ROBERT HARRINGTON
Interventional Cardiologist
Professor of Medicine
Chairman of the Department of Medicine, Stanford University

April 16, 2014
- Cardiology Divisional Rounds: "The Evolution of How we Think about NSTE ACS: From Rule Out MI to Acute Coronary Syndrome"
- Research Rounds: "New Thinking about Therapeutic Drug Development"

Robert Harrington provided his perspective not only on the future of cardiovascular clinical trials but also presented on our own research in progress and potential directions for future collaborations. Dr. Harrington - previously Director of the Duke Clinical Research Institute- moved to Stanford University in 2012 and was subsequently joined by Ken Mahaffey from DCRI. Together they are aiming to develop clinical research and we have worked towards a new academic research collaboration facilitating both North/South and East/West connectivity. This exciting opportunity will unquestionably enrich our opportunities, capacity and creativity as the clinical research agenda environment evolves in the times ahead.

DR. MICHAEL E. FARKOUH
Professor of Medicine, University of Toronto
Peter Munk Chair in Multinational Clinical Trials, University Health Network
Director, Heart & Stroke Richard Lewar Centre of Excellence, University of Toronto

October 29, 2014
- Cardiology Divisional Rounds: "Medical and Revascularization Strategies in Diabetic Patients with Coronary Artery Disease"
- Research Rounds: "The TAILOR-PCI Trial - Clinical Implementation of Clopidogrel Pharmacogenetics"

Michael Farkouh's presentation during the Cardiology Divisional Rounds provided an instructive overview on the role of medical treatment and revascularization strategies in diabetic patients with coronary artery disease informed by his leadership in the FREEDOM trial. In his research rounds he presented novel work relating to clinical implementation of clopidogrel pharmacogenetics. New opportunities for east-west collaboration emerged from this visit and are being facilitated by CVC Co-Director Shaun Goodman.

DR. ADRIAAN VOORS
Professor of Cardiology
Director of the Heart Clinic and Director of the Department of Echocardiography
University Medical Center, Groningen, Netherlands.

November 19, 2014
- Cardiology Divisional Rounds: "Diuretic response and renal function in patients hospitalize for Acute Heart Failure"
- Research Rounds: "Individualized responses to chronic heart failure treatment"

Adriaan Voors, leading expert in biomarkers, heart failure and lead investigator of acute HF trials, reminded us about the importance of the clinical evaluation and how it plays a role even in the clinical trial environment. The research rounds explored the massive wealth of data – 'omics particularly – that is soon to play a role in HF. He laid the groundwork for future exchange for trainees, introduced new ideas that are already underway and also increase collaboration between Europe and Canada and specifically the Netherlands.

DR. ROXANA MEHRAN
Professor of Medicine (Cardiology) and Health Evidence and Policy
Director of Interventional Cardiovascular Research and Clinical Trials
The Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai

December 9 & 10, 2014
- Research Rounds: "Clinical Research in Crisis: What is the future?"
- Cardiology Divisional Rounds: "DAPT Duration after stenting: Is Shorter better or is Longer Safer?"

Roxana Mehran provided insights into the contemporary challenges of clinical research and the current thinking around the vexing challenges of optimal duration of dual antiplatelet therapy after coronary stenting. Dr.Mehran is an outstanding role model for women in cardiovascular medicine and during her visit we provided a "women only" opportunity for trainees and staff to gain her insights into career development and success.

"MORE THAN MANY AREAS OF SCIENCE, CLINICAL RESEARCH REQUIRES A TEAM OF COLLABORATORS TO BE ABLE TO SUCCESSFULLY ASK AND ANSWER QUESTIONS. OVER THE LAST TWENTY-FIVE YEARS, I HAVE BEEN VERY FORTUNATE TO HAVE A RESEARCH RELATIONSHIP AND PERSONAL FRIENDSHIPS WITH THE INVESTIGATORS AND STAFF OF CVC.

WHEN I SERVED AS DCRI DIRECTOR FROM 2006-2012, I CONSIDER NO COLLABORATIVE RELATIONSHIP MORE VALUED THAN THE ONE BETWEEN DCRI AND CVC. IN MANY WAYS, IT WAS AKIN TO THE "SPECIAL RELATIONSHIP" DESCRIBED BETWEEN THE US AND THE UK, A RELATIONSHIP BORNE OF A COMMON SET OF BELIEFS AND VALUES.

SINCE MOVING TO STANFORD, I SEE THE TREMENDOUS POSSIBILITIES IN EXTENDING THAT DCRI-CVC COLLABORATION TO OUR CAMPUS HERE IN PALO ALTO. ON A MORE PERSONAL LEVEL, I HAVE NO WISER FRIEND, COLLEAGUE AND MENTOR THAN MY TRUSTED COLLABORATOR, PAUL ARMSTRONG."

— Robert Harrington
Arthur L. Bloomfield Professor of Medicine, Chair, Department of Medicine, Stanford University

Duke Clinical Research Institute – March 2014 Visit

For well over a decade, we have had an outstanding collaboration and master clinical research agreement with the Duke Clinical Research Institute (DCRI). This partnership has facilitated the development of a strong academic thought leadership, focused on the enhancement of patient care and health care systems through the generation, translation and dissemination of new knowledge. This partnering has facilitated the sharing of clinical trial data and the incorporation of innovative high quality research across the full investigative spectrum. It has also provided training and mentoring of young clinician scientists, many of whom have trained at the DCRI and then returned to centres in Canada, including the University of Toronto, the University of Alberta, and elsewhere.

In March of 2014 we were delighted to host a visit from Eric Peterson, Director of the Duke Clinical Research Institute and Lisa Berdan, Director of Global Mega-Trials at Duke Clinical Research Institute: this was a pivotal opportunity to advance our ARO collaboration and review current and future joint projects. These colleagues then joined us at the Research Colloquium and ACC Rockies meeting. As part of the ACC Rockies Distinguished Professor program Dr. Peterson provided an insightful presentation at the University of Alberta entitled "Cardiovascular Care in 2020: Impact of Current Cardiovascular Trials on Future Patient Care" highlighting the key role of research on clinical practice.

"THE CANADIAN VIGOUR CENTER IS ONE OF OUR OLDEST AND STRONGEST COLLABORATORS. OUR ORGANIZATIONS SHARE THE SAME VALUES AND MOTIVATIONS, THAT BEING A DESIRE TO CARRY OUT IMPORTANT, HIGH QUALITY, AND INNOVATIVE RESEARCH THAT IMPACTS PATIENT CARE."
— Eric Peterson, Director,
Duke Clinical Research Institute

Canadian Cardiac Chronicle

CVC is pleased to publish The Canadian Cardiac Chronicle, our newsletter that shares current trial information and upcoming projects that may be of interest to our site network.

The Chronicle also lists current publications by the CVC faculty, resulting from the projects and trials data we manage.

Posted on our website at www.vigour.ualberta.ca, the Chronicle is distributed to over 500 recipients, including our investigative sites, sponsors and international collaborators.


The Canadian Cardiac Chronicle
Volume 18, No. 2 Summer 2014

By the time this special issue of the Chronicle reaches your desk and/or computer screen, the summer solstice will be in your neighbourhood and ours. It is extraordinary to reflect that the tilt of our planet is then most inclined toward the sun (a tilt that maximizes at 23º 26'). As a result, the land of the midnight sun in the Arctic Circle at 66º56'N is in full illumination. For those of us living a bit south of the Arctic Circle at 53º27'N in Edmonton Alberta, we will celebrate over 17 hours of daylight as compared to the approximate 7.5 hours we have on December 21st. Stimulated by the increasing illumination this time of year brings, we are energized to provide you this edition of the Chronicle, chock-full of interesting and new information about CVC. There are four matters that I think are worthy of special note:

1. In March of this year, in conjunction with the ACC Rockies educational event chaired by Robert Welsh, we held a Clinical Trials Colloquium. Our purpose was to generate dialogue on the key issues that affect our clinical trial activities in Canada, and then to examine how best to overcome any impediments to pursuing our pathway to discovering better cardiovascular health. It was a remarkable meeting, with great representation from across the country that resulted in vigorous participation and good ideas and suggestions as summarized elsewhere in the Chronicle. We are most grateful for the sponsorship of Amgen, AstraZeneca, Merck Canada and Sanofi-aventis in support of this endeavour. Special thanks to Tracy Temple for her organizational leadership of the event and to Justin Ezekowitz, Shaun Goodman and Lisa Berdan for their collaboration in developing this inaugural program.

2. The second matter relates to our growing academic partnerships with our friends and colleagues south of the border. For well over a decade, we have had an outstanding collaboration and master clinical research agreement with the Duke Clinical Research Institute. This partnership has facilitated the development of a strong academic thought leadership, focused on the enhancement of patient care and health care systems through the generation, translation and dissemination

In This issue:

of new knowledge. This partnering has facilitated the sharing of clinical trial data and the incorporation of innovative high quality research across the full investigative spectrum. It has also provided training and mentoring of young clinician scientists, many of whom have trained at the Duke Clinical Research Institute and then returned to centres in Canada, including the University of Toronto, the University of Alberta, and elsewhere.

Two years ago, the then Duke Clinical Research Institute Director Robert Harrington, moved to Stanford University and assumed the Chair of Medicine; subsequently he was joined by Ken Mahaffey from DCRI. As a result, over the past year, we have worked towards a new academic research collaboration facilitating both North/South and East/West connectivity. This exciting opportunity will unquestionably enrich our opportunities, capacity and creativity as the clinical research agenda environment evolves in the times ahead. Visible evidence of this collaboration is provided within this issue of the Chronicle. We were delighted to host a visit from Eric Peterson, Director of Duke Clinical Research Institute and Lisa Berdan, Director of Global Mega-Trials at Duke Clinical Research Institute in March who then joined us subsequently at the Research Colloquium and ACC Rockies meeting. In the subsequent month, we were pleased to welcome Robert Harrington, The Arthur L. Bloomfield Professor of Medicine, Chairman, Department of Medicine at Stanford and gain his perspective not only on the future of cardiovascular clinical trials but also to present our own research

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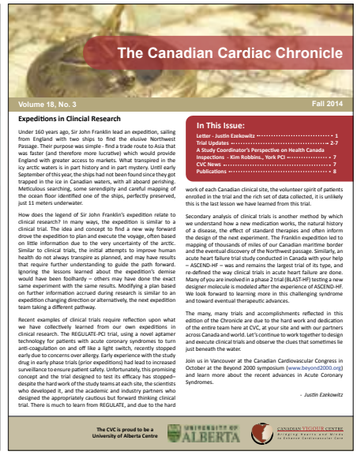
The Canadian Cardiac Chronicle
Volume 18, No. 3 Fall 2014

Expeditions in Clincial Research

Under 160 years ago, Sir John Franklin lead an expedition, sailing from England with two ships to find the elusive Northwest Passage. Their purpose was simple - find a trade route to Asia that was faster (and therefore more lucrative) which would provide England with greater access to markets. What transpired in the icy arctic waters is in part history and in part mystery. Until early September of this year, the ships had not been found since they got trapped in the ice in Canadian waters, with all aboard perishing. Meticulous searching, some serendipity and careful mapping of the ocean floor identified one of the ships, perfectly preserved, just 11 meters underwater.

How does the legend of Sir John Franklin's expedition relate to clinical research? In many ways, the expedition is similar to a clinical trial. The idea and concept to find a new way forward drove the expedition to plan and execute the voyage, often based on little information due to the very uncertainty of the arctic. Similar to clinical trials, the initial attempts to improve human health do not always transpire as planned, and may have results that require further understanding to guide the path forward. Ignoring the lessons learned about the expedition's demise would have been foolhardy – others may have done the exact same experiment with the same results. Modifying a plan based on further information accrued during research is similar to an expedition changing direction or alternatively, the next expedition team taking a different pathway.

Recent examples of clinical trials require reflection upon what we have collectively learned from our own expeditions in clinical research. The REGULATE-PCI trial, using a novel aptamer technology for patients with acute coronary syndromes to turn anti-coagulation on and off like a light switch, recently stopped early due to concerns over allergy. Early experience with the study drug in early phase trials (prior expeditions) had lead to increased surveillance to ensure patient safety. Unfortunately, this promising concept and the trial designed to test its efficacy has stopped– despite the hard work of the study teams at each site, the scientists who developed it, and the academic and industry partners who designed the appropriately cautious but forward thinking clinical trial. There is much to learn from REGULATE, and due to the hard

In This Issue:

work of each Canadian clinical site, the volunteer spirit of patients enrolled in the trial and the rich set of data collected, it is unlikely this is the last lesson we have learned from this trial.

Secondary analysis of clinical trials is another method by which we understand how a new medication works, the natural history of a disease, the effect of standard therapies and often inform the design of the next experiment. The Franklin expedition led to mapping of thousands of miles of our Canadian maritime border and the eventual discovery of the Northwest passage. Similarly, an acute heart failure trial study conducted in Canada with your help – ASCEND-HF – was and remains the largest trial of its type, and re-defined the way clinical trials in acute heart failure are done. Many of you are involved in a phase 2 trial (BLAST-HF) testing a new designer molecule is modeled after the experience of ASCEND-HF. We look forward to learning more in this challenging syndrome and toward eventual therapeutic advances.

The many, many trials and accomplishments reflected in this edition of the Chronicle are due to the hard work and dedication of the entire team here at CVC, at your site and with our partners across Canada and world. Let's continue to work together to design and execute clinical trials and observe the clues that sometimes lie just beneath the water.

Join us in Vancouver at the Canadian Cardiovascular Congress in October at the Beyond 2000 symposium (www.beyond2000.org) and learn more about the recent advances in Acute Coronary Syndromes.

- Justin Ezekowitz

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The Canadian Cardiac Chronicle
Volume 18, No. 1 Spring 2014

Sometimes you just need to talk to people.

So we did just that on Sunday, March 9th during a CVC sponsored clinical research colloquium held in Banff, Alberta in conjunction with the annual ACC Rockies Meeting. For some time we have been reflecting on the challenges facing our valued clinical research partners across Canada as it relates to continued participation in clinical trials. Last autumn we finally decided it was time to do some direct listening and learning. The concept was simple, namely to foster an open communication between our own academic research organization (CVC) and key community practicing site principal investigators and site coordinators. The aim was to generate productive dialogue that resulted in identification of key issues that restrict clinical trial involvement in Canada and develop strategies to overcome them. Once this concept was hatched and Tracy Temple agreed to organize it, I knew we were on the right track! We were fortunate to be able to generate both enthusiasm and unrestricted educational grant support from Amgen, Astra Zeneca, Merck and Sanofi-aventis that allowed us to hold the event this past month.

We had an ambitious set of goals (i) review major impediments to timely/efficient participation in clinical trials at the site level, ii) identify common issues that can be addressed collectively, iii) understand how best to add value to clinical trial experience at site level, iv) enhance our research and performing sites (quality/quantity) and V) explore the potential for more common standard operating procedures (SOPs) in order to enhance Canada's position in CV trials/research.

Because we reckoned there were differing trial "cultures" and correspondingly different needs for acute trials (e.g. acute coronary syndromes and heart failure) versus those involving secondary prevention (e.g. post ACS, diabetes and dyslipidemia) we decided to invite a spectrum of colleagues that represented those areas of research and also our geographic diversity.

In This Issue:

Key members of the CVC clinical trials coordinating team participated in this half day interactive session with both academic and community site principal investigators and coordinators in the presence of industrial medical representatives. All participants were required to complete a pre-meeting web-based survey that identified catalysts and barriers to the conduct of clinical trials in Canada. In conjunction with key, selected and brief presentations; the survey results were collated and presented at the half day interactive session. There was ample time for vigorous and open discussion and we committed to summarizing the discussion in a white paper that will accompany the next edition of the Chronicle. Although a formal evaluation is still in progress, the immediate feedback from both our invitees and sponsors was enthusiastically positive about the event. Specific action items emerged aimed at accelerating trial "startup times", avoiding duplication and rationalizing SUSAR reporting. Each invitee is about to receive the overall survey result as well to be able to reflect on their views in this context.

We look forward to sharing more learnings from this informative and rewarding networking event and engaging our other valued collaborators in the future. Stay tuned..

With kind regards,

Paul W. Armstrong

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The Canadian Cardiac Chronicle
Volume 18, No. 4 Winter 2014

Canadian Clinical Trial Performance: Embarking on an ODYSSEY to further IMPROVE-IT

I recently returned from the cold and windy city of Chicago– to the cold and windy city of Toronto– where I attended the 2014 American Heart Association Scientific Sessions. During my flight home, I read an article in the *Wall Street Journal* highlighting the long-awaited results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). Nine years after this important global randomized clinical trial started, the preliminary findings from 18,144 post-acute coronary syndrome patients had finally been presented from the Late Breaking Clinical Trials podium and were now in the public domain.

The journal headline described the addition of ezetimibe to simvastatin therapy as showing a "...modest benefit in reducing heart attacks..." However, the subtitle of the article more appropriately captured the spirit of this enormous undertaking by physicians, study coordinators, and academic research organizations: *"Trial Marks a Milestone in Battle to Fight Cardiovascular Disease by Lowering Cholesterol"*. Indeed, 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 LDL cholesterol levels, but led to a significant reduction in subsequent cardiovascular events.

Canadian contribution to this trial was substantial– we were the 3rd highest enrolling country (of 39) in the world with 1,106 patients from 64 sites! The IMPROVE-IT trial, consistent with the vision of the Canadian VIGOUR Centre (CVC) *"...to generate, translate and disseminate knowledge on novel... therapeutics strategies in cardiovascular medicine acquired through collaborative research to enhance the health of the citizens of...Canada, and the world"* embodied our core values of quality, collaboration, integrity, and respect. Indeed, one measure of the outstanding Canadian effort was the fact that only 5 patients (<1%) were lost to follow-up at sites collaborating with the CVC. This is a remarkably low rate in the context of a trial that identified >5,300 primary endpoints during almost 100,000 total patient-years of follow-up.

In This Issue:

Of course, to get to the finish line, one has to first enrol the "right" patient from the start. Even after careful identification of potentially eligible patients, recruitment requires a discussion with the patient (and often their family member[s]) as part of the informed consent process, including the importance of maintaining study drug and regular follow-up assessments. As in most trials like IMPROVE-IT, participants are analyzed according to their allocated treatment (i.e., intention-to-treat) even if they temporarily or permanently discontinue study drug. The potential treatment effect may be diluted or even nullified if we aren't able to keep our patients on the assigned study drug. This critical issue was brought to the forefront midway through the trial when negative publicity regarding ezetimibe required the IMPROVE-IT leadership to provide compelling arguments that the study needed to continue. We still didn't have the answer to whether ezetimibe could improve clinical outcomes. Indeed, continued enrolment and adherence to study drug treatment in the trial was both ethical and vital. However, despite the global challenge of keeping patients on study drug, particularly in such a long-term trial with negative press, Canada's rate of study drug continuation was above the trial average, representing yet another indication of the high quality of Canadian investigator and coordinator engagement in order to maintain high intensity patient participation.

In addition to demonstrating the safety and efficacy of ezetimibe, the IMPROVE-IT investigators were able to reaffirm the LDL hypothesis—that lowering LDL (even with a non-statin agent) prevented cardiovascular events. Furthermore, the axiom that "even lower is better" was confirmed: patients on statin therapy alone achieved mean LDL cholesterol levels

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WHISTLER, CANADA

Kevin Bainey

- Invited Lectureship: Do We Need to Select for TAVI? - December 2014

VANCOUVER, CANADA

Paul Armstrong

- Presentation: Data and safety monitoring boards for clinical trials: Opening the kimono. 2014 Margolese Prize, University of British Columbia, St. Paul's Hospital - November 2014

Sean Van Diepen

- 2014 Canadian Cardiovascular Congress – October 2014
  - Optimal care of the post arrest patient revisited: the evolution of the therapeutic hypothermia and other contemporary technologies in the cardiac arrest management.
  - Evolution of Critical Care Cardiology: What Lies Ahead.

CALGARY, CANADA

Justin Ezekowitz

- Poster and Rapid Fire oral presentation: Determinants of Early Readmission After Heart Failure Hospitalization. Cardiovascular Institute Research Day, Libin Cardiovascular Institute - April 2014

TORONTO, CANADA

Paul Armstrong

- Key Note: ACS Update: Cardiovascular medicine 2014: Lessons learned and roads untraveled reflections from a clinician investigator. Cardiology for the Practitioner - Cardiology Day, St. Michael's Hospital – April 2014

Justin Ezekowitz

- Cardiology Rounds: Natriuretic Peptide-Guided Therapy: Fact, Finished or Future? St. Michael's Hospital - January 2014
- Acute Heart Failure: Risk and Outcomes Heart & Stroke/Richard Lewar Centre of Excellence, University of Toronto - January 2014

OTTAWA, CANADA

Shaun Goodman

- Is There Still A Role for Coronary Revascularization in Improving Outcomes in CAD in the Era of New Medical Therapies for ISCHEMIA? - 17th International Toronto Ottawa Heart Summit - June 2014

NEW YORK, USA

Paul Armstrong

- Invited Speaker: State-of-the-Art Lecture: Reperfusion and STEMI. 2014 Case Studies from the Heart of Manhattan course - April 2014

MONTREAL, CANADA

Justin Ezekowitz

- PRO: CRT should be recommended for patients with HF and Atrial Fibrillation. Canadian Heart Failure Society Heart Failure Update 2014 – May 2014

KINGSTON, CANADA

Paul Armstrong

- Invited Lectureship: ST elevation myocardial infarction 2014: Lessons learned and roads untraveled. Macdonald Lectureship, Queen's University - June 2014

WASHINGTON DC, USA

Paul Armstrong

- ACC Co-Chair Special Session: Late Breaking Clinical Sessions Deep Dive. The American College of Cardiology 63rd Annual Scientific Session – March 2014

Robert Welsh

- Transcatheter Cardiovascular Therapeutics (TCT 2014) – September 2014
  - Didactic Symposia: Clinical Trial Design and Interpretation, Part 1
  - Partnership Session: Montreal Live in Partnership with TCT: Clinical Update on Bioresorable Scaffold Technology and Structural Heart Procedures.
  - International Session: Management of Multivessel CAD. (Presented by the Scottish Cardiac Society Working Group on Interventional Cardiology and the Canadian Association of Interventional Cardiology (CAIC-ACCI)).

BARCELONA, SPAIN

2014 European Society of Cardiology Annual Congress - August 2014

Paul Armstrong

- Chairperson: STEMI Satellite Symposium: STEMI 2014: Aligning optimal care to time, place and person.
- Presentation: STREAM: new insights on reperfusion choices.
- Presentation: Pharmaco-invasive vs. primary PCI.

Justin Ezekowitz

- State of the Art - Rethinking Current Heart Failure Therapies: Colin-Ramirez E, McAlister F, Zheng Y, Sharma S, Armstrong PW, Ezekowitz JA. The SODIUM-HF (Study Of Dietary Intervention Under 100 MMOL in Heart Failure) pilot results.

Shaun Goodman

- Panel Discussion: New frontiers in cholesterol management in high CV risk patients
- Presentation: How might PCSK9 inhibition change this debate?

BERLIN, GERMANY

Robert Welsh

- Thrombosis Research Global Science Forum - November 2014
  - Plenary Session 1: PIONEER AF-PCI
  - November 2014 Hot Table Sessions: Interaction of Atrial Fibrillation and Acute Coronary Syndromes.

RIYADH, SAUDI ARABIA

Robert Welsh

- Saudi Heart Association Meeting – February 2014
  - Presentation: Advances in Anti-Platelet Therapy and the Clinical Implications of Recent Trials.
  - Chairperson: Interventional Cardiology, Women in Innovations (SCAI).
  - Presentation: Implementation the Fibrinolysis Pharmaco-Invasive Strategy for STEMI Patients When Primary PCI is not Practical.

SYDNEY, AUSTRALIA

Robert Welsh

- Innovations in Cardiovascular Care: Tran-catheter Aortic Valve Implantation and From guidelines to practice: DAPT in ACS. St Vincents Hospital, Darlinghurst
- Advances in Antiplatelet Therapy and the Clinical Implications of Recent Trials - May 2014

Crossing Borders

Reflecting the CVC's global reach and network of collaborators, this map highlights some of the key international lectures and presentations that were delivered by CVC faculty members in 2014. The CVC's insights and impact are enhanced by these pursuits of knowledge translation and dissemination.

ARO Services

CVC SERVICES AND ACTIVITIES

The Canadian VIGOUR Centre is recognized as a thought leader and valuable partner in cardiovascular research across all regions of Canada and amongst key centres around the world. Its track record of conducting, delivering and health outcomes is strongly influenced by clinical practice and health care.

POPULATION AND ECONOMIC HEALTH OUTCOMES RESEARCH

- Collection of resource utilization and cost data
- Development of economic models
- Cost-effectiveness analyses
- Clinical Registry development

BIOSTATISTICS

- Design of research protocols and studies
- Development of statistical analysis plans and database specifications
- Data management
- Programming expertise in SAS and R
- Generation of statistical tables, figures, listings and interpretation of findings
- Consultation and execution of advanced statistical methods
- Development and application of novel statistical methods

ECG CORE LAB

- Informing trial design
- Monitoring protocol adherence
- Guiding mechanistic insights
- Prognosis and outcomes assessment

CLINICAL TRIALS

- Investigator selection, qualification and recruitment
- Investigative site start-up and training
- Ensuring site regulatory compliance
- Project, Site, Data management
- In-house and onsite clinical monitoring (including bilingual services)

THOUGHT LEADERSHIP

- Provide expert advice and promotion of cardiovascular research characterized by quality, scholarship and integrity
- Defined unmet needs for patients with and those at risk of cardiovascular disease
- Align new cardiovascular research with these unmet needs
- Seek cost effective solutions and enhance return on investment in research
- Trial architecture, development, data acquisition, integration, analysis, presentation and peer-review publication
- Creation of novel sub studies aimed at mechanistically informing primary clinical trial results
- Mentoring junior faculty, medical trainees, students and allied health professionals

CLINICAL REGISTRIES

Vital Heart Response (VHR): R Welsh

- CQI
- Regional Collaboration
- Trials within registries e.g. PROACT
- Model for others

Acute Heart Failure (AHF): J Ezekowitz

- CIHR: inquiry regarding outcomes/ biomarkers
- Novel Interventions/trials

KNOWLEDGE WHICH IS UNABLE TO SUPPORT ACTION IS NOT GENUINE -

AND HOW UNSURE IS ACTIVITY WITHOUT UNDERSTANDING!

—RUDOLPH VIRCHOW

Clinical Trials

TRACY TEMPLE
RN, BScN - Assistant Director, Clinical Trials

HALINA NAWROCKI
RN- Lead Clinical Research Associate

AMANDA CARAPELLUCCI
BSc- Clinical Trials Project Lead

COURTNEY GUBBELS
BA-Clinical Trials Project Lead

JODI PARROTTA
MA - Clinical Trials Project Lead

LYNDSEY GARRITTY
BA - Clinical Trials Project Lead

As a key component to our organization, the clinical trials we are involved in provide us with valuable data to help support and influence change within clinical practice and the care of patients. In 2014 we were involved in five Phase III studies, two Phase II studies, and three grant funded studies. Initial planning and negotiations for additional projects are currently underway. With a network of over 200 sites across Canada, we had more than 130 investigators from our site network involved in at least one clinical trial this year. A total of 903 patients were enrolled in Canada from six recruiting trials this year and to date the sites working with us have enrolled a total of 20,490 Canadian patients, contributing to the 306,015 patients recruited globally from the 53 Phase II and III trials we have been involved in.

With close to 15 years of experience in clinical research and a background in cardiovascular nursing our Clinical Trials team continues to be led by Assistant Director of Clinical Trials, Tracy Temple. The highly dedicated and well trained team with varying clinical research experience includes five in house Clinical Trial Project Leads, two regulatory and site management support staff and one administrative support person. Based regionally across the country our monitoring team includes Lead Clinical Research Associate, Halina Nawrocki, a team of seven monitors and one report reviewer. In addition to our team being ICH/GCP trained, many also hold the CCRP designation with SoCRA or the CCRA designation with ACRP. Responsible for ensuring all operational aspects of the study run smoothly our Clinical Trial Project Leads and support staff work closely with our sites to strive for quick 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 pulse on 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 Clinical Trial Project Leads

MELISA SPALING
M Ed. - Clinical Trials Project Lead

KALLI BELSECK
BA - Regulatory Specialist

PAULA PRIEST
Project Coordinator

DEVON BLANCHETTE
Administrative Assistant

maintain a close working relationship with the Canadian National Coordinator(s) and/or Operational Lead ensuring they are kept up to date on the operational aspects of the study in Canada and utilize their expertise and support throughout the study.

In addition to conducting source document verification, drug accountability and other required monitoring related tasks, the CVC monitors use their visits as a teaching opportunity to share lessons learned and ideas from other sites which is beneficial in their daily work as well as ensuring they are audit prepared. With an extensive background in monitoring and having been involved in many audits and inspections throughout her career with CVC, Halina Nawrocki has helped prepare many of our sites for their upcoming inspections as well as shared lessons learned with our team and sites. With the ongoing support and expertise of our project and monitoring team and well prepared sites, all CVC monitored sites who underwent inspections in 2014 received compliant ratings.

Overall our Clinical Trials team strives to build relationships with sites, sponsors and partners across Canada and globally, enhance efficiency in our processes, achieve the highest level of quality, and deliver a strong Canadian contribution in each clinical trial.

Clinical Trials

ODYSSEY OUTCOMES

Protocol #: EFC11570
Sponsor: Sanofi-aventis Recherche & Développement
Drug: Alirocumab (SAR236553/REGN727)
Anticipated Timeline: June 2012 - March 2018
Trial Status: Actively enrolling

A randomized, double blind, placebo-controlled, parallel-group study to evaluate the effect of Alirocumab SAR236553/REGN727 on the occurrence of cardiovascular events in patients who have already recently experienced an acute coronary syndrome.

232/18,000
(Canada/Global)
Patient enrollment target

153/9,154
(Canada/Global)
Patient enrollment achieved to date

36/1,241
(Canada/Global)
Number of sites participating

IMPROVE IT

IMProved **R**eduction of **O**utcomes:**V**ytorin **E**fficacy **I**nternational **T**rial

Protocol #: P04103
Sponsor: Merck & Co. Inc.
Drug: Vytorin
Anticipated Timeline: March 2005 - December 2014
Trial Status: Database locked and closing out sites

A multicenter, double-blind, randomized study to establish the clinical benefit and safety of Vytorin (ezetimibe/simvastatin Tablet) vs. simvastatin monotherapy in high-risk patients presenting with acute coronary syndrome.

500*/18,000
(Canada (CVC) /Global)
Patient enrollment target

602/18,142 COMPLETED
(Canada/Global)
Patient enrollment achieved

36/1,159
(Canada/Global)
Number of sites participating

* Note that the 500 for Canada is based on original projections and sample size and does not reflect modified sample size.

AEGIS-I

Protocol #: CSLCT-HDL-12-77
Sponsor: CSL Behring LLC
Drug: CSL112
Anticipated Timeline: Aug/2013-Dec/2015
Trial Status: Study Start up, Safety Lead in Actively enrolling

A Phase 2b, multicenter, randomized, placebo-controlled, dose-ranging study to investigate the safety and toleability of multiple does administration of CS112 in subjects with acute myocardial infarction.

40/1,200
(Canada/Global)
Patient enrollment target

0/0
(Canada/Global)
Patient enrollment achieved to date

10/290
(Canada/Global)
Number of sites participating

BLAST-HF

Protocol #: CP027
Sponsor: Trevena Inc.
Drug: TRV027
Anticipated Timeline: March 2014 - December 2015
Trial Status: Actively enrolling

Randomized, double-blind, placebo-controlled, dose ranging study to explore the efficacy of TRV027 in patients hospitalized for acute decompensated heart failure.

15/500
(Canada/Global)
Patient enrollment target

0/252
(Canada/Global)
Patient enrollment achieved to date

3/80
(Canada/Global)
Number of sites participating

GUIDE-IT

GUIDing **E**vidence Based Therapy Using Biomarker **I**ntensified **T**reatment in Heart Failure

Protocol #: Pro00033097
Sponsor: Duke Clinical Research Institute & Roche
Drug: N/A
Anticipated Timeline: December 2012 - June 2017
Trial Status: Actively enrolling

Determine the efficacy of a strategy of biomarker-guided therapy compared with usual care in high risk patients with left ventricular systolic dysfunction.

120/1,100
(Canada/Global)
Patient enrollment target

59/500
(Canada/Global)
Patient enrollment achieved to date

6/37
(Canada/Global)
Number of sites participating

REGULATE-PCI

Protocol #: REG1-CLIN310
Sponsor: Regado Biosciences Inc.
Drug: REG1 Anticoagulation System (pegnivacogin & anivamersen)
Anticipated Timeline: July 2013 - September 2016
Trial Status: Closed early

Randomized, open-label, multi-center, active-controlled, parallel group study to determine the efficacy and safety of the REG1 Anticoagulation System Compared to Bivalirudin in Patients Undergoing Percutaneous Coronary Intervention.

405/13,200
(Canada/Global)
Patient enrollment target

288/3,234
(Canada/Global)
Patient enrollment achieved

16/325
(Canada/Global)
Number of sites participating

PROACT

Providing **R**apid **O**ut of Hospital **A**cute **C**ardiovascular **T**reatment

Protocol #: N/A
Sponsor: University Hospital Foundation & Mazankowski Alberta Heart Institute
Drug: N/A
Anticipated Timeline: October 2011 - Jan 2015
Trial Status: Actively enrolling

Determine if early diagnosis and risk stratification acquired through pre-hospital clinical assessment, 12-lead electrocardiogram and point of care biomarkers will facilitate enhanced triage and treatment in patients with presumed non-ST elevation acute coronary syndromes (NSTEMI).

600 - CANADA ONLY
(Canada/Global)
Patient enrollment target

572 - CANADA ONLY
(Canada/Global)
Patient enrollment achieved to date

LOCAL EDMONTON ONLY
(Canada/Global)
Number of sites participating

SODIUM-HF

Study **O**f **D**ietary **I**ntervention **U**nder 100 **M**MOL in **H**eart **F**ailure

Protocol #: MOP130275
Sponsor: CIHR grant
Drug: N/A
Anticipated Timeline: December 2013-December 2017
Trial Status: Actively enrolling

Multicenter clinical trial in ambulatory patients with chronic HF to evaluate the efficacy of a low sodium containing diet on a composite clinical outcome composed of of all-cause mortality, cardiovascular hospitalizations and cardiovascular emergency department visits.

1000/0
(Canada/Global)
Patient enrollment target

54/0
(Canada/Global)
Patient enrollment achieved to date

14/5
(Canada/Global)
Number of sites participating

TECOS

Trial **E**valuating **C**ardiovascular **O**utcomes with **S**itagliptin

Protocol #:	082-04
Sponsor:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Drug:	Sitagliptin
Anticipated Timeline:	August 2008 - March 2015
Trial Status:	Enrolment complete, Patient visits complete, In closeout

Randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with sitagliptin in patients with Type 2 diabetes mellitus and inadequate glycemic control.

481/14,000
(Canada/Global)
Patient enrollment target

549/14,745 COMPLETED
(Canada/Global)
Patient enrollment achieved

28/681
(Canada/Global)
Number of sites participating

EXSCEL

Exenatide **S**tudy of **C**ardiovascular **E**vent **L**owering

Protocol #:	BCB109
Sponsor:	Amylin Pharmaceuticals, LLC a subsidiary of Bristol-Myers Squibb. (Acquired by AstraZeneca in 2014.)
Drug:	Exenatide
Anticipated Timeline:	May 2009 - December 2017
Trial Status:	Actively enrolling

A randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus.

500/14,000
(Canada/Global)
Patient enrollment target

488/12,889
(Canada/Global)
Patient enrollment achieved to date

28/633
(Canada/Global)
Number of sites participating

Canadian Clinical Trial Performance: Hard to IMPROVE-IT!

— SHAUN GOODMAN

The long-awaited results of the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) arrived in Chicago at the American Heart Association meeting in November, 2014. Nine years after this important global randomized clinical trial started, the preliminary findings from 18,144 post-acute coronary syndrome patients had finally been presented from the Late Breaking Clinical Trials podium and were now in the public domain.

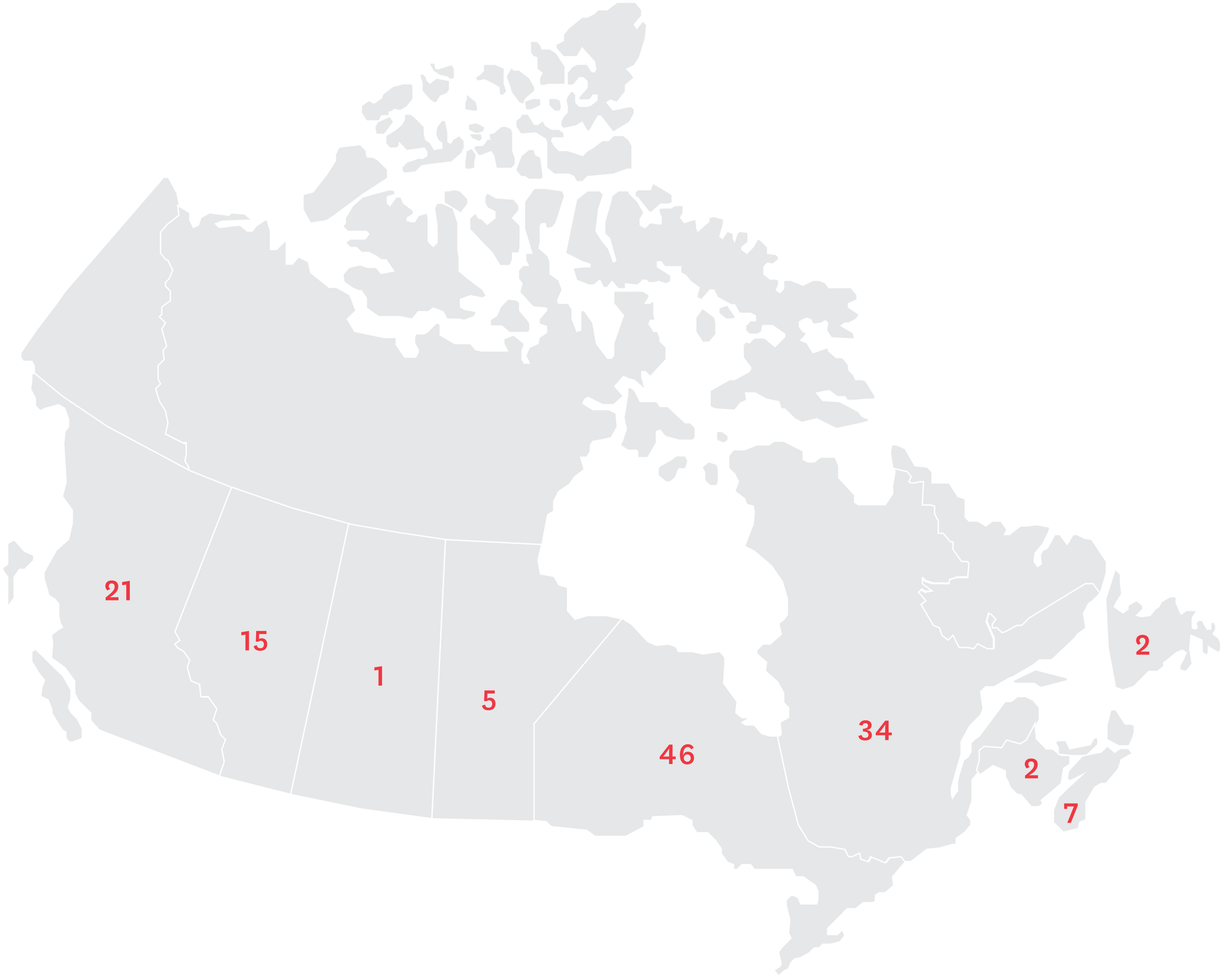
The Wall Street Journal headline described the addition of ezetimibe to simvastatin therapy as showing a "…modest benefit in reducing heart attacks…". However, the subtitle of the article more appropriately captured the spirit of this enormous undertaking by physicians, study coordinators, and academic research organizations: "Trial Marks a Milestone in Battle to Fight Cardiovascular Disease by Lowering Cholesterol". Indeed, 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 LDL cholesterol levels, but led to a significant reduction in subsequent cardiovascular events.

Canadian contribution to this trial was substantial—we were the third highest enrolling country (of 39) in the world with 1,106 patients from 64 sites! The IMPROVE-IT trial, consistent with the vision of the Canadian VIGOUR Centre (CVC) "… to generate, translate and disseminate knowledge on novel…therapeutics strategies in cardiovascular medicine acquired through collaborative research to enhance the health of the citizens of…Canada, and the world" embodied our core values of quality, collaboration, integrity, and respect. Indeed, one measure of the outstanding Canadian effort was the fact that only five patients (<1%) were lost to follow-up at sites collaborating with the CVC. This is a remarkably low rate in the context of a trial that identified >5,300 primary endpoints during almost 100,000 total patient-years of follow-up.

The abovementioned outstanding Canadian participation and performance, together with the unique findings of benefit in the IMPROVE-IT study, are extremely encouraging. The CVC looks forward to continued collaboration with Canadian investigators and coordinators in ongoing and future studies aimed at translating these types of benefits realized in randomized clinical outcome trials and ultimately into routine clinical practice for our patients.

Active Principal Investigators

CVC has an extensive site network across Canada of principal investigators (PIs) who actively participate in CVC managed clinical drug trials, to meet patient enrollment targets. This map represents the locations of 133 principal investigators who were participating in nine (9) of the active clinical trials either coordinated by the CVC, or monitored by the CVC, in 2014. Nearly 50% of these sites have participated in more than one CVC managed clinical trial. In 2014, 322 visits were carried out at these sites by the CVC monitoring team, to ensure adherence to trial protocols and patient safety.



ECG Core Lab

PUSHPA JAGASIA
MD - Senior ECG Reader

The aim of our ECG Core Laboratory is to translate research results into clinically relevant applications. Using the ECG – a venerable but powerful biomarker- we can generate an improved understanding of the pathophysiologic processes involved in acute coronary syndromes (ACS), thereby enabling not only prediction of outcomes but also assessing effectiveness of treatment. These insights serve to further stimulate cardiovascular scientific research. Hence in 2014 one of our featured publications (Aborted MI by Malecki et al) arose from the CVC ECG Core Laboratory.

Other key projects the ECG Core Lab is involved in include the Vital Heart Response and PROACT4 projects.

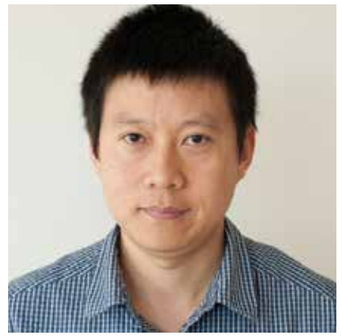
The Vital Heart Response (VHR) project led by Dr. Robert Welsh is a regional initiative that aims to implement timely evidence-based reperfusion strategies to maximize the outcome of patients with ST-segment elevation myocardial infarction (STEMI). The VHR project has enrolled 3,578 patients and the Core Lab has completed analysis of 1,992 patients (5,498 ECGs).

In 2014, the ECG Core Lab was involved in PROACT4, the fourth stage of the PROACT project. A key component of this project is timely recognition of acute cardiovascular patient presentations and how best to provide rapid early diagnosis and more efficient patient care. In 2014, 382 patients (405 ECGs) were analyzed and this data will be analyzed in concert with acute biomarkers from patients with acute chest pain as well as those with shortness of breath and presumed heart failure.

The ECG Core Lab at the CVC continued its mandate of conducting quality analyses using clinical research data in 2014. The Core Lab has accumulated a wealth of experience in its readers and continues to mentor and serve as valuable training ground for the next generation of talented researchers. To date ECGs from over 73,300 patients enrolled in studies around the world have been analyzed. This provides an excellent database for additional sub-studies, analyses and research.

Biostatistics

CYNTHIA WESTERHOUT
PhD - Assistant Director, Biostatistics and, Senior Research Associate



YINGGAN (GRAY) ZHENG
MA, M ED. - Senior Biostatistician

The CVC houses databases from over 27 clinical trials, which provide a rich cache of patient characteristics, ECGs, treatment and outcomes. The CVC also has access to population based data for over 500,000 Albertan patients seeking cardiovascular medical care between the fiscal years 1999/2000 and 2009/2010 and Canadian Institute of Health Information data on over 4,400,000 cardiac-related acute care hospitalizations in Canada (not including Quebec), between the fiscal year 2002 and fiscal year 2013 as well as those participating in the following registries or studies:

- AHF-EM Retrospective Cohorts
- Alberta Heart Registry
- ASCEND-HF Registry
- PROACT Retrospective Cohorts
- Vital Heart Response Registry

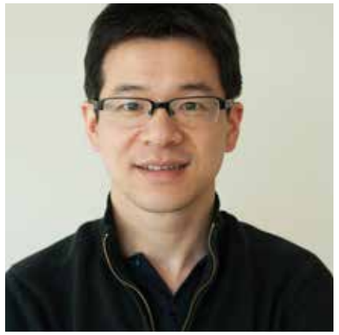
The CVC Biostatistics group works with clinician investigators to conduct innovative clinical research in cardiovascular medicine in collaboration with local, national, and international researchers. This research focuses on the assessment of patient, environmental and process-of-care factors and their association with outcomes in patients with acute coronary syndromes (ACS), acute and chronic heart failure, cardiac arrest, arrhythmias, syncope and diabetes. Areas of interest include: international and regional differences, incidence/prevalence and temporal trends, time to treatment, use of pharmacologic and mechanic interventions, resource allocation and utilization, and gender/sex and age differences in relation to clinical outcomes. Services provided by CVC's biostatistics team include data management, development of statistical analysis plans and database specifications, programming expertise in SAS and R, generation of statistical tables, figures and listings and interpretation of findings, and consultation and execution of advanced statistical methods.

In 2014, the Biostatistics group participated in numerous studies based on clinical trial or population-based data, utilizing a variety of statistical techniques. These ranged from survival analysis to a novel analysis of composite endpoints in ACS trials. The latter has garnered increased interest from various stakeholders and remains a key area of research. In keeping with the CVC mandate, members of the biostatistics team contribute to mentoring the next generation of cardiovascular researchers. They work closely with medical students, residents and other junior researchers to explain the statistical techniques used and their interpretation.

Population Health and Economic Outcomes

PADMA KAUL
PhD - Director, Outcomes Research

ANAMARIA SAVU
PhD - Biostatistician



WEI LUI
MSc - Data Analyst

In the last decade over half a million Albertans have been diagnosed with heart disease, which accounts for the second highest number of deaths in the province annually. Ongoing technological advances in the treatment of acute coronary syndromes and heart failure make it essential to examine whether the use of these expensive drugs and devices is equitable and to assess their impact on current and future costs of cardiac care in Alberta.

The CVC Outcomes Group (led by Drs. Kaul, Ezekowitz and McAlister) has been actively involved in using health care administrative data to examine issues related to access, delivery, treatment, and outcomes of heart disease in Alberta and Canada. 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. Using administrative data received from Alberta Health and Wellness (AHW), the Canadian Institutes of Health Information (CIHI) and the Alberta Health Services Data Integration, Management and Reporting (DIMR) system, the CVC Outcomes group has developed integrated longitudinal databases linking inpatient, outpatient (including emergency department), physician office, pharmaceutical claims, registry, vital statistics and census data for all Alberta residents with heart failure, acute coronary syndromes, nonacute ischemic heart disease, cardiac arrhythmias and congenital heart disease between 1999 and 2010 in Alberta. The CIHI data have been used to compare practice patterns and outcomes in Alberta with those in other Canadian provinces.

Our extensive portfolio of research projects based on these data includes examining the following: socioeconomic and urban/rural differences in access to treatment and outcomes; outcomes among vulnerable populations such as women, the elderly, and ethnic minorities; the association of risk factors and use of evidence-based therapies on long-term outcomes; impact of alternative levels of care; resource utilization and costs of care; validity and reliability of disease coding; and novel methods to risk stratify patients.

A major goal of the CVC Outcomes group is to identify, inspire, and train junior faculty and students in the analysis of linked administrative healthcare databases. Trainees and junior faculty continue to feature prominently in our population health projects and manuscripts.

Business Office and Administration

SHAFFIN KHERANI
BSc, MBA - Assistant Director, Operations

CARLA PRICE
BSc - Business and Research Administrator

ELLEN PYEAR
MA - Business and Operations Assistant

OKSANA GRANT
Business and Operations Assistant

YVONNE REGNIER
Executive Assistant to Dr. Paul Armstrong / Dr. Justin Ezekowitz

The business office is fundamental to the organizational and financial underpinnings of the CVC. Reviewing and negotiating contracts is one of its key tasks, alongside 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 creation and distribution of all marketing materials aimed at creating strong brand awareness that speaks to the mission and values of this organization. Finally, the office facilitates communications between the CVC and many institutional partners, which include, but are not limited to, Duke Clinical Research Institute (DCRI), Alberta Health Services (AHS), and Northern Alberta Clinical Trials and Research Centre (NACTRC). Our dedication to upholding strong partnerships with these institutions is essential to the day-to-day operations of the CVC.

Faculty

Our CVC Faculty are internationally recognized as Thought Leaders in their respective areas of interest.

They represent a unique and dynamic integration of clinical research. The approach begins by addressing unmet clinical needs through conducting rigorous clinical investigation and clinical trials of novel diagnostic and therapeutic interventions in selected areas of cardiovascular medicine. It extends from that pivot to the knowledge gained through detailed registries of all patients in areas of particular interest and relevance to public health, namely Acute Coronary Syndromes and Heart Failure. Our group has been especially keen to explore better ways of analyzing the responses of patients to interventions by modeling their outcomes over time, taking account of the relative value patients put on differing outcomes and their implications for quality of life and health care costs. Finally we are well positioned to study health care outcomes at a population level for all Albertans to assess how well new advances are being applied and whether they are making a meaningful difference.

PAUL W. ARMSTRONG

MD

- Distinguished University Professor, Division of Cardiology, University of Alberta
- Formerly Chair of the Department of Medicine, University of Alberta
- Founding Director, Canadian VIGOUR Centre
- 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

Dr. Armstrong's research interests include:

- Development of novel methods to enhance clinical trial methodology
- Cardiovascular disease and its implications in the elderly
- Pathophysiology and novel therapeutic approaches of congestive heart failure
- Diagnosis and management of acute coronary syndromes. with emphasis on timely interventions

JUSTIN EZEKOWITZ

MBBCh, MSc

- Co-Director, Canadian VIGOUR Centre
- Associate Professor, Division of Cardiology, University of Alberta
- Director, Heart Function Clinic, Mazankowski Alberta Heart Institute
- Alberta Innovates - Health Solutions Population Health Investigator

Dr. Ezekowitz' research interests include:

- Testing the impact of drugs and processes of care for patients with acute heart failure
- Novel interventions for patients with chronic systolic and diastolic heart failure
- The impact of comorbidities such as atrial fibrillation, anemia and hip fractures in patients with heart failure
- Knowledge gaps for drugs and process of care in heart failure

SHAUN GOODMAN

MD, MSc

- Co-Director, Canadian VIGOUR Centre
- 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
- Adjunct Professor, Department of Medicine, University of Alberta

Dr. Goodman's research interests include:

Facilitating clinical trial, observational, and knowledge translation research in cardiovascular disease in Canada with a focus on:

- Diagnosis, management, and prognosis of acute coronary syndromes
- Optimal stroke prevention risk stratification and management in atrial fibrillation
- Primary and secondary prevention of cardiovascular disease

ROBERT WELSH
MD

- Professor, Division of Cardiology, University of Alberta
- Interventional Cardiologist, Mazankowski Alberta Heart Institute
- Director, Adult Cardiac Catheterization and Interventional Cardiology program
- Vice-President, Canadian Association of Interventionla Cardiologists
- Co-chair of Vital Heart Response
- Co-chair of the Mazankowski TAVI Program

Dr. Welsh's research interests include:

- Acute Coronary Syndromes and Interventional Cardiology
- Cardiovascular disease and diabetes
- Exercise physiology and cardiac physiology
- Pre-hospital management of STEMI and the interaction of pharmacological (antithrombotic and fibrinolytic) and mechanical interventions (primary and rescue angioplasty)

FINLAY A. MCALISTER
MD, MSc

- Professor of Medicine, University of Alberta
- Director, Patient Health Outcomes Research and Clinical Effectiveness Institute, University of Alberta
- Senior Health Scholar, Alberta Innovates -Health Solutions (2010 - 2017)
- Capital Health Chair in Cardiovascular Health Outcomes
- 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

PADMA KAUL
PhD

- Director, Outcomes Research, Canadian VIGOUR Centre
- Associate Professor, Department of Medicine, University of Alberta
- Adjunct Assistant Research Professor, Duke University Medical Center
- 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 and delivery of care at a population level
- Health economics

KEVIN BAINEY
MD

- Assistant Professor and Academic Interventional Cardiologist, Mazankowski Alberta Heart Institute, University of Alberta
- Director, Interventional Cardiology Fellowship Program, Mazankowski Alberta Heart Institute, University of Alberta

Dr. Bainey's research interests include:

- Reperfusion strategies in ST-elevation myocardial infarction
- Ethnic-based clinical outcomes focusing primarily on South Asians with coronary artery disease

SEAN VAN DIEPEN
MD

- Assistant Professor of Critical Care Medicine, Division of Critical Care and Cardiology, University of Alberta
- Academic Cardiologist-Intensivist

Dr. Van Diepen's research interests include:

- Critical care cardiology
- Cardiovascular surgical care
- Cardiovascular risks of cardiac and non-cardiac surgery and heart failure

Worldwide Collaborators

PROFESSEUR PHILIPPE GABRIEL STEG,
Departement de Cardiologie
Hopital Bichat, Assistance Publique-
Hopitaux de Paris

BRAZILIAN CLINICAL RESEARCH INSTITUTE
Sao Paulo, Brazil

DUKE CLINICAL RESEARCH INSTITUTE
Durham, USA

ESTUDIOS CLINICOS LATINOMERICA
Rosario, Argentina

GREEN LAKE COORDINATING CENTER
Auckland, New Zealand

FLINDERS MEDICAL CENTRE
Adelaide, Australia

LEUVEN COORDINATING CENTRE
Leuven, Belgium

NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL – CLINICAL TRIALS CENTRE
Sydney, Australia

TRIALS ARGENTINE GROUP ORGANIZATION
Buenos Aires, Argentina

UPPSALA CLINICAL RESEARCH CENTRE
Uppsala, Sweden

Acknowledgments

CVC gratefully acknowledges and thanks:

- The patients, for their willing participation in trials, they are the heroes of clinical research.
- the CVC faculty, external advisors and collaborators for their contributions and for providing ongoing research opportunities, we look forward to providing continued services and to future collaborations;
- the CVC staff and management for their dedication, professionalism, excellent contributions and ingenuity that enhances the quality of our research work;
- our mentees for their commitment and enthusiasm as the next generation of researchers;
- the sponsors and granting agencies, without their financial support these trials and educational activities would not be possible;
- Shaffin Kherani, Ellen Pyear, and Oksana Grant for their time and the dedication required to produce this report;
- AM/FM for the concept and design;
- Photographer Stephen Wreakes for many of the images enclosed in this report;
- McCallum Printing Group Inc. for their service in printing this report and our Chronicle.

THE CANADIAN VIGOUR CENTRE
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