The Canadian VIGOUR Centre | 2013 Annual Report

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2013 Annual Report

CANADIAN VIGOUR CENTRE
Bridging Hearts and Minds to Enhance Cardiovascular Care

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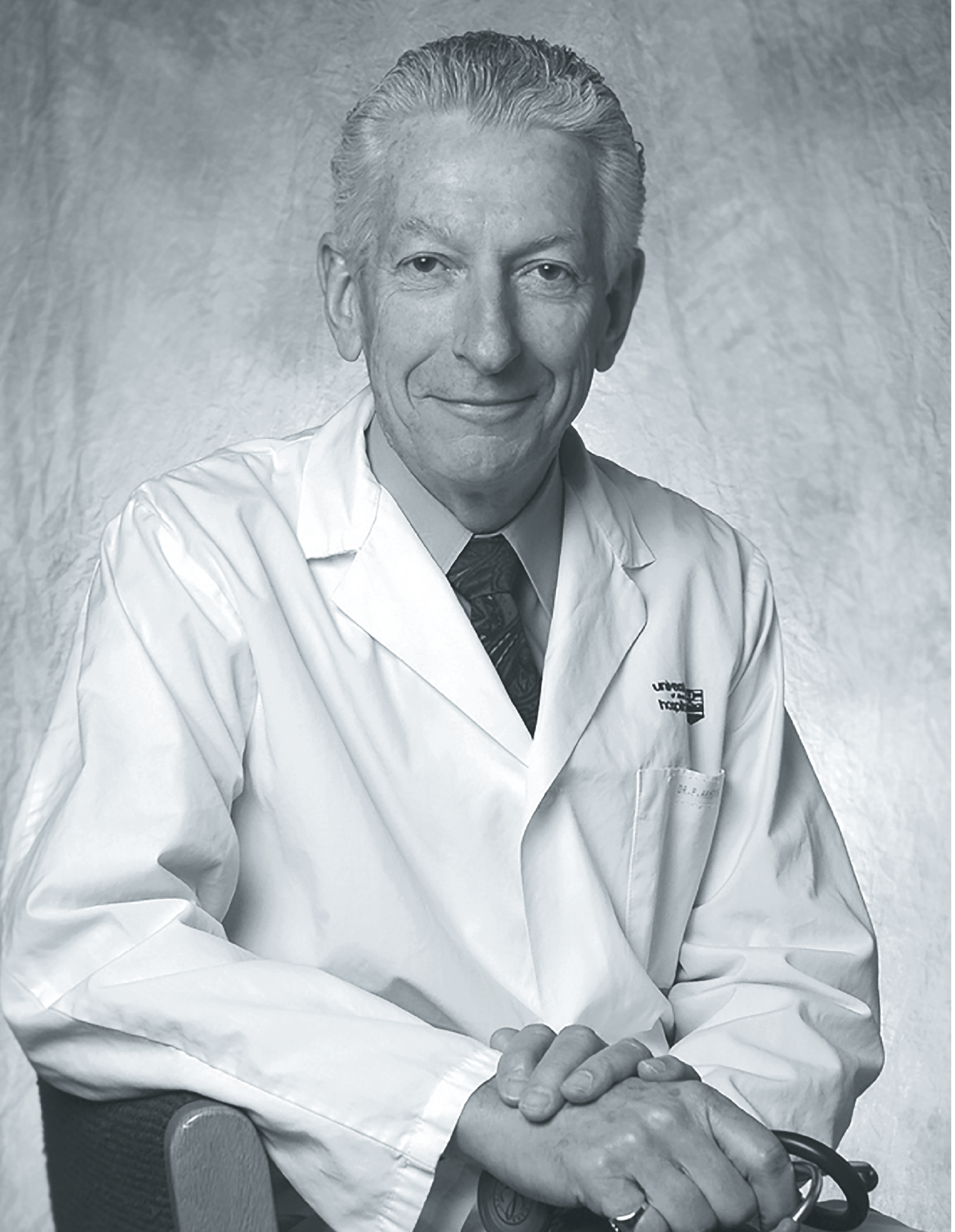
For further information about the Canadian VIGOUR Centre,
or to view this report or our brochure digitally, please see our website at www.vigour.ualberta.ca.

Our vision is to 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.



Message from the Director

As the cover of this year's annual report suggests, we at the Canadian VIGOUR Centre are a learning organization, engaged in the business of knowledge. As an academic research organization (ARO), we are uniquely positioned to work with a variety of key partners within the university, health care system, industry and granting agencies. This year's annual report articulates our distinct value proposition as an ARO and reflects our deep commitment to improving patient care and outcomes. We are forging new relationships with national and international collaborators in the pursuit of novel research directions, as well as translating and disseminating the resulting knowledge.

Our culture embraces the cycle of quality, described in the next few pages. This cycle begins with health science discovery, followed by its application to human disease using careful quantitative and qualitative measures. For any discovery to have impact, its efficacy must first be examined in controlled populations, i.e. the randomized clinical trial. Yet that is not enough since the effectiveness of any new therapy should be evaluated through performance measures in carefully crafted patient registries acquired in selected disease states. Still further along the cyclical process- if we are to achieve meaningful differences in health outcomes at the population level- there must be successful dissemination of new knowledge into clinical practice. Inevitably, a new appreciation for the unmet needs of the population at risk emerges from this phase galvanizing re-entry into the cycle, as the unending quest for improvement in clinical or health system outcomes continues.

With this context, I am pleased to share that 2013 has been a most eventful year for our organization and within the pages of this report we have selected a few highlights of how new knowledge can impact directly and meaningfully on the care of patients. Up close and personal in our own backyard (i.e. some of the smaller and more rural communities in Alberta), we have seen genuine improvements in the outcomes of patients with heart failure after exporting the lessons of a multidisciplinary clinic. As one explores heart failure care across the globe from a large clinical trial, we find large disparities in the quality of care, with high variability between geographic regions, reminding us that we can and should do better in managing this life-threatening disease. Recognizing we must find innovative and more cost effective ways to do clinical trials, we are committed to finding better mouse traps to harness risk assessment in a more dynamic context. It is also clear that we should be taking into consideration the variation and clinical relevance and importance of individual end points and the composite outcomes of our clinical trials since a new appreciation of these can add value and meaningful interpretation to the results.

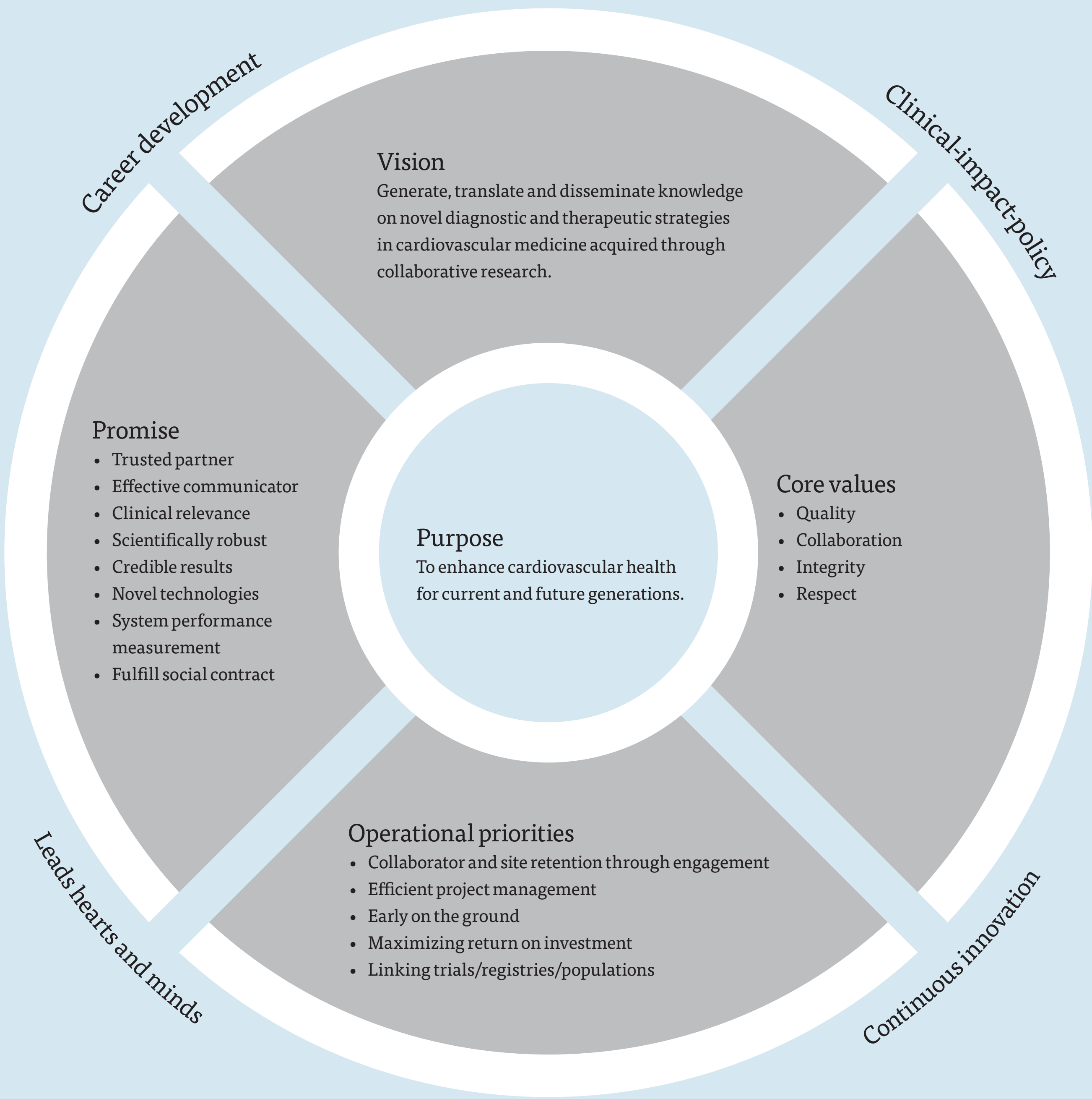
Knowledge is most worthwhile when it is used. Hence some of the outstanding academic visitors to our institution are chronicled in this year's report, and so too are some selected travels of our faculty to participate in national and international forums. We are also excited and enthusiastic about the prospects of a re-invigorated partnering with our friends and colleagues at the Duke Clinical Research Institute and extending that collaboration to Robert Harrington and Ken Mahaffey at Stanford University.

It is gratifying to recognize the outstanding contributions of Drs. Justin Ezekowitz and Shaun Goodman and the assumption of their roles as Co-Directors of the Canada VIGOUR Centre. Dr. Ezekowitz's expertise in the full spectrum of heart failure and his investigation from bench to bedside to population health provides a deep and widely recognized level of expertise in this growing area that so often serves as the final common denominator of successful therapy of other forms of heart disease. Dr. Goodman's expertise in acute coronary syndromes and clinical registries is internationally recognized and his positioning at St. Michael's Hospital and University of Toronto provides a dynamic east/west axis. His leadership in a number of our clinical studies that are noted within the report and his appointment last year as an Adjunct Professor of Medicine at the University of Alberta signals the redeeming value of creative partnerships and collaboration. They are most welcome additions to our leadership team.

For an organization like ours to be successful, it must produce a dynamic synergy that is greater than the sum of its parts. I am proud of our multidisciplinary team who populate the pages herein and the key role they play in advancing the cause of cardiovascular medicine and research.

Research Priorities

Compass



Vision, Mission and Core Values

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

Mission
Aligned with the University of Alberta and the Mazankowski Alberta Heart Institute (MAHI), our mission is to:

- Design, conduct, analyze and disseminate findings arising from novel clinical research
- Interrogate clinical trial, registry and population health data to evaluate outcomes, identify unmet needs and inform future basic and clinical research directions
- Identify, inspire and nurture the next generation of health researchers and professionals.

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

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

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

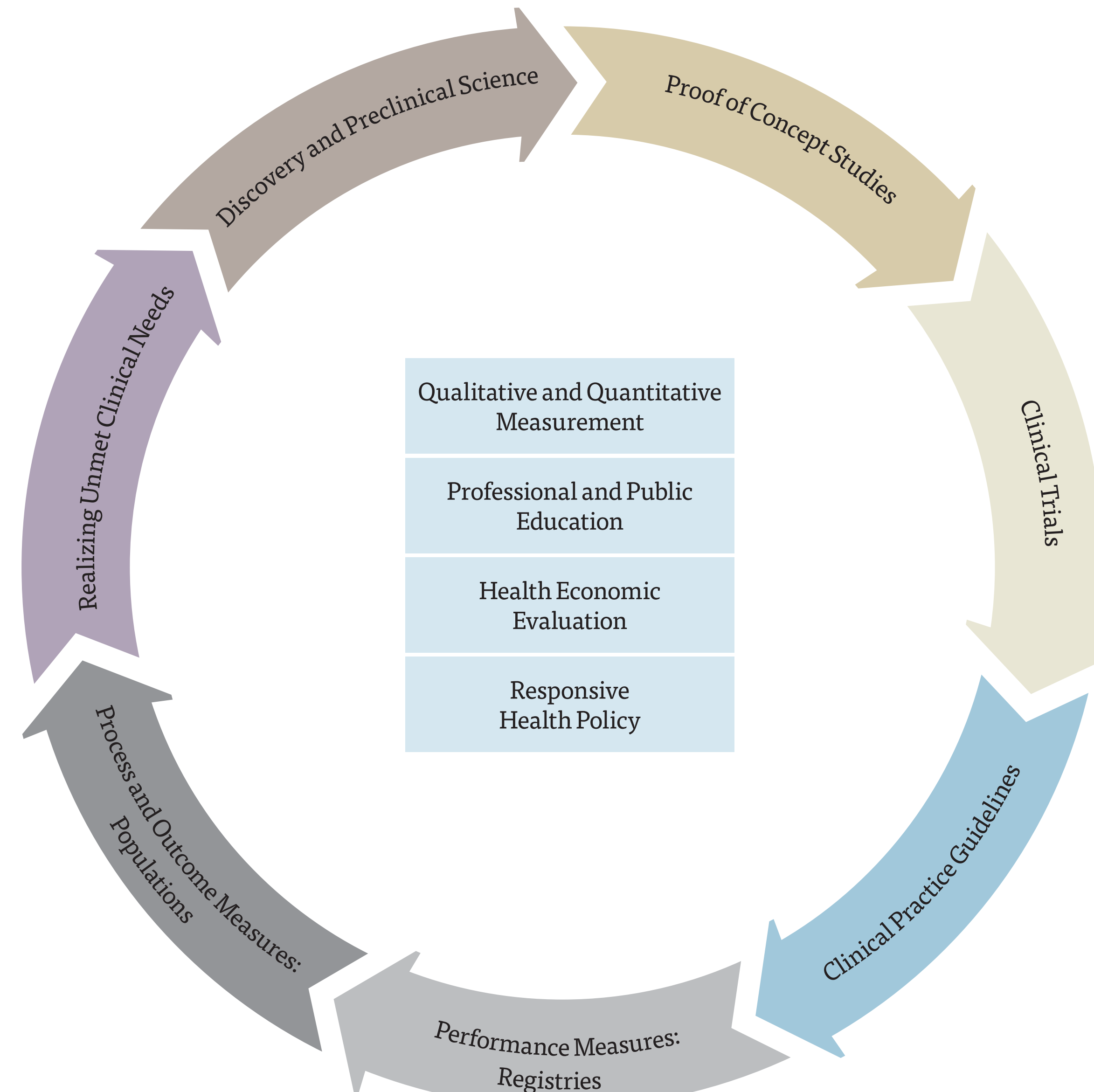
Respect
Create an innovative, engaging and inclusive work environment, appreciative of individual differences and contributions. Our workplace will be conductive to personal growth and development that is aligned with our overall mission.

The 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.



2013 Highlights

Metrics

54

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

146

Number of Principal Investigators participating in CVC managed trials.

223

Number of on-site monitoring visits that occured in Canada.

139

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

9

Number of industry and grant funded projects currently underway.

5,770

Number of ECGs analyzed by CVC.

500,000+

Size of data repository reflecting health of Albertans with cardiovascular disease.

Financial Summary

Grants

Project	Sponsor(s)	Grant Holders	Term	Total Granted (CAD)
Providing Rapid Out of Hospital Acute Cardiovascular Treatment (PROACT)	Mazankowski Alberta Heart Institute and University Hospital Foundation	Paul Armstrong (PI) Justin Ezekowitz Padma Kaul Finlay McAlister Robert Welsh	2010-2013	$325,000
SODIUM HF	Alberta Health Innovation Solutions University Hospital Foundation	Justin Ezekowitz	2012-2015	$50,000 $30,000
Team Grant: Diastolic Heart Failure	Alberta Innovates-Health Solutions	Jason Dyck (PI) Todd Anderson Justin Ezekowitz	2009-2014	$5,000,000
Evaluating the impact of a Province Wide Disease Management Program on Heart Failure Outcomes in Alberta	Canadian Institutes of Health Research	Finlay A. McAlister (PI) Padma Kaul Justin A Ezekowitz H Quan	2010-2013	$116,765
Long-term health outcomes of mothers with gestational diabetes mellitus and their children in Alberta	Canadian Institutes of Health Research	Padma Kaul (PI)	2009-2013	$100,000
Canadian health outcomes, performance and efficiency (CanHOPE) - project for analysis of AMI and stroke care data for policy making	Heart and Stroke Foundation	A. Ohinmaa (PI) S. Klarenbach P. Kaul P. Jacobs	2013-2014	$109,450
Gestational Diabetes Mellitus (GDM) in Alberta	Canadian Institutes of Health Research	Padma Kaul (PI)	2013 (announced) 2014-2017	$278,139
The VO2 Increase with Testosterone Addition - Heart Failure (VITA-HF)	University of Alberta Bridge Funding	Justin Ezekowitz (PI)	2012-2013	$40,000.00

Introducing CVC Co-Director Shaun Goodman

- 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; and,
  - Primary and secondary prevention of cardiovascular disease.

Shaun Goodman
MD, MSc

Introducing CVC Co-Director Justin Ezekowitz

Justin Ezekowitz
MBBCh, MSc

- 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 acute heart failure patients;
- Novel interventions for patients with chronic systolic and diastolic heart failure;
- The impact of comorbidities such as atrial fibrillation, anemia and hip fractures;
- Knowledge gaps for drugs and devices in heart failure.

Introducing New Faculty

“As a new faculty member with CVC, I now have the support to pursue meaningful projects in an academic peer-reviewed environment which will enhance the quality of my research.”

Kevin Bainey, MD

The Canadian VIGOUR Centre is proud to introduce to its faculty Kevin Bainey, MD. Currently an Assistant Professor and Academic Interventional Cardiologist at the Mazankowski Alberta Heart Institute, University of Alberta, he is completing his Masters in Health Research Methodology from McMaster University. Dr. Bainey's research interests align well with CVC's extensive research in reperfusion in STEMI. His work on spontaneous reperfusion has led to a definitive understanding of enhanced clinical outcomes seen in these patients.
As well, Dr. Bainey is a key faculty member involved in our COAPT study (Alberta Contemporary Acute Coronary Syndrome Patients Invasive Treatment Strategies: Impact on Clinical Outcomes and Health Care Resources). The CVC is pleased to mentor and collaborate with Dr. Bainey at this early stage in his career on several clinical trials and research projects and to foster his special interest in ethnic-based clinical research focusing primarily on South Asians with established coronary artery disease.

About the Researcher

- Undergraduate degree in Microbiology at the University of Alberta
- Doctor of Medicine from University of Alberta
- Internal Medicine and Cardiology training at the University of Alberta and Fellowship of the Royal College of Physicians and Surgeons of Canada
- Interventional Cardiology Fellowship at Harvard University's Brigham and Women's Hospital
- Clinical Scholar in Interventional Cardiology at McMaster University

Current Research Projects

- A Multi-center Randomized Trial of Remote Ischemic Conditioning in Patients with an ST-elevation Myocardial Infarction (RemCon-STEMI)
- A Multi-center Randomized Trial of Remote Ischemic Conditioning in Patients with an ST-elevation Myocardial Infarction: Cardiac Magnetic Resonance Imaging Sub-study (RemCon-CMR)
- Alberta Contemporary Acute Coronary Syndrome Patients Invasive Treatment Strategies: impact on Clinical Outcomes and Health Care Resources: Alberta COAPT study
- Cardiac Magnetic Resonance Imaging as a Surrogate Endpoint in Clinical Trials of ST-elevation Myocardial Infarction
- Use of Renin-Angiotensin System Blockers in Acute Coronary Syndromes: Findings from Get With The Guidelines-Coronary Artery Disease Program
- Clinical Perspectives on Reperfusion Injury in Acute Myocardial Infarction
- Infarct Location in ST-elevation Myocardial Infarction: Implications When Selecting a Reperfusion Strategy

Introducing New Faculty

“The valuable insight my colleagues have provided have undoubtedly improved the quality of my research projects and my success in garnering grants.”

Sean van Diepen, MD

The Canadian VIGOUR Centre is proud to introduce to its faculty Sean van Diepen, MD. Dr. van Diepen is an academic cardiologist-intensivist. He is currently an Assistant Professor of Critical Care Medicine in the Divisions of Critical Care and Cardiology at the University of Alberta.

Dr. van Diepen completed medical school at the University of Toronto. After moving west, he undertook his Internal Medicine, Cardiology, and Critical Care Training at the University of Alberta. He completed a clinical research fellowship at the Duke Clinical Research Institute in Durham, North Carolina and received his Masters of Science in Experimental Medicine from the University of Alberta.

His clinical interests lie in the care of critically ill cardiac patients. Dr. van Diepen attends in both the cardiovascular surgical intensive care unit and the coronary care unit at the Mazankowski Heart Institute at the University of Alberta. His research interests include critical care cardiology, cardiovascular surgical care, cardiovascular risks of cardiac and non-cardiac surgery and heart failure.

He has published multiple manuscripts in leading peer reviewed journals and has received multiple research awards including the Canadian Institute for Health Research Resident Research Prize. He is currently on the editorial board of the American Heart Journal.

About the Researcher

- Medical school at the University of Toronto
- Internal Medicine, Cardiology and Critical Care Training at the University of Alberta
- Clinical Research Fellowship at Duke Clinical Research Institute
- Masters of Science, Experimental Medicine at the University of Alberta

Current Projects

- COMParison of Angiotensin Converting enzyme inhibitor managemenT strategies prior to coronary artery bypass surgery (the COMPACT trial): a pilot randomized controlled registry study
- NT-proBNP, hsCRP, and Inflammatory Markers of Reperfusion in Patients with ST-segment Elevation Myocardial InfarctionGlobal Differences in Heart Failure Therapy and Resource Utilization among Patients Admitted to Intensive and Coronary Care Units: Insights from Ascend-HF
- Risk prediction of atrial fibrillation patients undergoing non-cardiac surgery
- Variation in critical care unit admissions for patients with acute coronary syndromes and heart failure among high and low volume cardiac hospitals
- Peri-operative Cardiac Outcomes and Bleeding Risk in Patients with Acute Coronary Syndromes and Ischemic Cardiomyopathy: TRACER Insights

Featured Publications

This high profile randomized trial was featured in last year's report. Since then it has been the subject of numerous national and international presentations and symposia, some of which are noted elsewhere in the annual report. Importantly, its impact on the care of patients has been practice changing both in our local community and internationally and the publication was even translated into Russian! We are continuing to learn from the rich data set STREAM provides and applying it to contemporary care of patients, as well as reflecting on the inevitable new questions arising from its lessons.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 11, 2013 VOL. 368 NO. 15

Fibrinolysis or Primary PCI in ST-Segment Elevation Myocardial Infarction

Paul W. Armstrong, M.D., Anthony H. Gershlick, M.D., Patrick Goldstein, M.D., Robert Wilcox, M.D., Thierry Danays, M.D., Yves Lambert, M.D., Vitaly Sulimov, M.D., Ph.D., Fernando Rosell Ortiz, M.D., Ph.D., Miodrag Ostojic, M.D., Ph.D., Robert C. Welsh, M.D., Antonio C. Carvalho, M.D., Ph.D., John Nanas, M.D., Ph.D., Hans-Richard Arntz, M.D., Ph.D., Sigrun Halvorsen, M.D., Ph.D., Kurt Huber, M.D., Stefan Grajek, M.D., Ph.D., Claudio Fresco, M.D., Erich Bluhmki, M.D., Ph.D., Anne Regelin, Ph.D., Katleen Vandenberghe, Ph.D., Kris Bogaerts, Ph.D., and Frans Van de Werf, M.D., Ph.D., for the STREAM Investigative Team*

ABSTRACT

BACKGROUND

It is not known whether prehospital fibrinolysis, coupled with timely coronary angiography, provides a clinical outcome similar to that with primary percutaneous coronary intervention (PCI) early after acute ST-segment elevation myocardial infarction (STEMI).

METHODS

Among 1892 patients with STEMI who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour, patients were randomly assigned to undergo either primary PCI or fibrinolytic therapy with bolus tenecteplase (amended to half dose in patients ≥75 years of age), clopidogrel, and enoxaparin before transport to a PCI-capable hospital. Emergency coronary angiography was performed if fibrinolysis failed; otherwise, angiography was performed 6 to 24 hours after randomization. The primary end point was a composite of death, shock, congestive heart failure, or reinfarction up to 30 days.

RESULTS

The primary end point occurred in 116 of 939 patients (12.4%) in the fibrinolysis group and in 135 of 943 patients (14.3%) in the primary PCI group (relative risk in the fibrinolysis group, 0.86; 95% confidence interval, 0.68 to 1.09; P=0.21). Emergency angiography was required in 36.3% of patients in the fibrinolysis group, whereas the remainder of patients underwent angiography at a median of 17 hours after randomization. More intracranial hemorrhages occurred in the fibrinolysis group than in the primary PCI group (1.0% vs. 0.2%, P=0.04; after protocol amendment, 0.5% vs. 0.3%, P=0.45). The rates of nonintracranial bleeding were similar in the two groups.

CONCLUSIONS

Prehospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early STEMI who could not undergo primary PCI within 1 hour after the first medical contact. However, fibrinolysis was associated with a slightly increased risk of intracranial bleeding. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT00623623.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Van de Werf at the Department of Cardiovascular Sciences, University Hospitals Leuven, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium, or at frans.vandewerf@med.kuleuven.be.

*Committees and investigators for the Strategic Reperfusion Early after Myocardial Infarction (STREAM) study are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on March 10, 2013, at NEJM.org.

N Engl J Med 2013;368:1379-87.
DOI: 10.1056/NEJMoa1301092

N ENGL J MED 368;15 NEJM.ORG APRIL 11, 2013 1379

Featured Publications

There are many satisfactions associated with participating in a leadership role within a large international clinical trial. In this publication, we teamed up with our friend and colleague at the University of Calgary, Jonathan Howlett. He and Justin Ezekowitz collaborated in exploring how the quality of acute heart failure care impacts on outcomes across five regions in the world. Because of our access to the largest ever acute heart failure study of over 7000 patients from 5 continents and 398 centres, they were able to examine how well individual centres and regions conformed to the best established medical therapy for this serious and life-threatening disorder. These measures included what drugs were used and whether or not electrical devices, such as implantable defibrillators and resynchronization with specialized pacemakers, were applied.

The analysis unmasks large gaps in quality of care with high variability between geographic regions. Despite participating in a clinical trial where more careful monitoring of treatment and outcomes is generally applied, there was only modest improvement in quality of care over time. This study then serves as a wake-up call that we can and should do better in managing this life-threatening disease.

Circulation
Cardiovascular Quality and Outcomes
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Original Article

Global Variation in Quality of Care Among Patients Hospitalized With Acute Heart Failure in an International Trial

Findings From the Acute Study Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF)

Jonathan G. Howlett, MD; Justin A. Ezekowitz, MB, BCh, MSc; Mohua Podder, PhD; Adrian F. Hernandez, MD, MPH; Rafael Diaz, MD; Kenneth Dickstein, MD; Mark E. Dunlap, MD; Ramón Corbalán, MD; Paul W. Armstrong, MD; Randall C. Starling, MD, MPH; Christopher M. O'Connor, MD; Robert M. Califf, MD; Gregg C. Fonarow, MD; on behalf of the ASCEND-HF Investigators

Background—Translation of evidence-based heart failure (HF) therapies to clinical practice is incomplete and may vary internationally. We examined common measures of quality of care in patients enrolled in the international Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial.

Methods and Results—Patients were admitted to 398 hospitals for acute HF in 5 regions (North America, n=3149; Latin America, n=658; Asia Pacific, n=1744; Central Europe, n=966; and Western Europe, n=490). Predefined quality indicators assessed at hospital discharge included the following: medications (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, aldosterone antagonists, hydralazine/nitrates, statin therapy, and warfarin), use (or planned use) of implantable intracardiac devices, and blood pressure control (<140/90 mm Hg). We determined regional variations in quality indicators as well as the temporal variation of these indicators during the course of the trial. There was significant variation in conformity among different quality indicators, ranging from 0% to 89%. Of all potential performance opportunities, 19 076 of 32 268 (59%) were met, with Central Europe highest at 64%, followed by North America (63%), Western Europe (61%), Latin America (56%), and Asia Pacific (51%; $P<0.0001$). North America, Central Europe, and Asia Pacific regions demonstrated a modest increase in quality indicator conformity over time, although there was no significant change in other regions.

Conclusions—Quality of care for patients hospitalized with acute HF varies and remains suboptimal even within a randomized clinical trial, which included quality improvement interventions. Specific measures designed to improve performance measures should be implemented even within multicenter clinical trials.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00475852.
(*Circ Cardiovasc Qual Outcomes*. 2013;6:534-542.)

Key Words: acute decompensated heart failure ■ heart failure ■ performance measures ■ quality of health care ■ randomized controlled trial

Acute heart failure (AHF) is responsible for many millions of hospitalizations globally each year. Late mortality has been reported at 30% to 50%, and early rehospitalization is common at nearly 25% at 30 days and 50% at 180 days.[1,2] For 2010, costs associated with HF hospitalizations in the United States alone are estimated at $20.9 billion.[1] In addition to the high rate of healthcare use, significant discrepancies in care and outcomes between local regions occur, as well as between

Received January 18, 2013; accepted June 25, 2013.
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This article was handled independently by Peter Groeneveld, MD, as Guest Editor. The Editors had no role in the evaluation of the manuscript or in the decision about its acceptance.
The online-only Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.113.000119/-/DC1.
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***Circ Cardiovasc Qual Outcomes* is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/CIRCOUTCOMES.113.000119**

534

One of the most common critiques of contemporary clinical trials is the failure to enroll adequate numbers of elderly patients given the remarkable population demographic shift we are currently experiencing. Hence the TRILOGY trial, which represented a collaboration between DCRI and our CVC Co-Director Shaun Goodman, has finally lit a candle in the darkness by studying over 2000 patients 75 years or older who experienced an acute coronary event. The findings are remarkable and show a substantial increase in the rate of cardiovascular risk (i.e. death, heart attack and stroke) as well as the hazards of bleeding with new treatments. We can and should do better by this growing population and with the help of Padma Kaul are currently interrogating this data to understand how measures of frailty can further illuminate our path forward. Essentially the rings in the trunk of the tree can only provide some of the information we need and it is time to explore the bark and the branches.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Interventional Cardiology

Elderly Patients With Acute Coronary Syndromes Managed Without Revascularization

Insights Into the Safety of Long-Term Dual Antiplatelet Therapy With Reduced-Dose Prasugrel Versus Standard-Dose Clopidogrel

Matthew T. Roe, MD, MHS; Shaun G. Goodman, MD, MSc; E. Magnus Ohman, MB, ChB; Susanna R. Stevens, MS; Judith S. Hochman, MD; Shmuel Gottlieb, MD; Felipe Martinez, MD; Anthony J. Dalby, MD; William E. Boden, MD, PhD; Harvey D. White, MB, ChB, DSc; Dorairaj Prabhakaran, MD, MSc; Kenneth J. Winters, MD; Philip E. Aylward, MD; Jean-Pierre Bassand, MD; Darren K. McGuire, MD; Diego Ardissino, MD; Keith A. A. Fox, MB, ChB; Paul W. Armstrong, MD

Background—Dual antiplatelet therapy in older versus younger patients with acute coronary syndromes is understudied. Low-dose prasugrel (5 mg/d) is recommended for younger, lower-body-weight patients and elderly patients with acute coronary syndromes to mitigate the bleeding risk of standard-dose prasugrel (10 mg/d).

Methods and Results—A total of 9326 medically managed patients with acute coronary syndromes from the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial (<75 years of age, n=7243; ≥75 years of age, n=2083) were randomized to prasugrel (10 mg/d; 5 mg/d for those ≥75 or <75 years of age and <60 kg in weight) or clopidogrel (75 mg/d) plus aspirin for ≤30 months. A total of 515 participants ≥75 years of age (25% of total elderly population) had serial platelet reactivity unit measurements in a platelet-function substudy. Cumulative risks of the primary end point (cardiovascular death/myocardial infarction/stroke) and Thrombolysis in Myocardial Infarction (TIMI) major bleeding increased progressively with age and were ≥2-fold higher in older participants. Among those ≥75 years of age, TIMI major bleeding (4.1% versus 3.4%; hazard ratio, 1.09; 95% confidence interval, 0.57–2.08) and the primary end point rates were similar with reduced-dose prasugrel and clopidogrel. Despite a correlation between lower 30-day on-treatment platelet reactivity unit values and lower weight only in the prasugrel group, there was a nonsignificant treatment-by-weight interaction for platelet reactivity unit values among participants ≥75 years of age in the platelet-function substudy (*P*=0.06). No differences in weight were seen in all participants ≥75 years of age with versus without TIMI major/minor bleeding in both treatment groups.

Conclusions—Older age is associated with substantially increased long-term cardiovascular risk and bleeding among patients with medically managed acute coronary syndromes, with no differences in ischemic or bleeding outcomes with reduced-dose prasugrel compared with clopidogrel in elderly patients. No significant interactions among weight, pharmacodynamic response, and bleeding risk were observed between reduced-dose prasugrel and clopidogrel in elderly patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov/ct2/home. Unique identifier: NCT0069999.
(*Circulation*. 2013;128:823-833.)

Key Words: aging ■ drug therapy ■ fibrinolytic agents ■ myocardial infarction ■ receptors, purinergic P2Y12

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.
Received February 27, 2013; accepted June 28, 2013.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.002303/-/DC1.

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***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.002303**

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Featured Publications

Heart failure constitutes a huge social and economic burden both globally and in Alberta. In this insightful study that brings innovative patient care models and creative research approaches to patient outcome data in Alberta, McAlister and colleagues studied over 25,000 patients hospitalized with heart failure between 1999 and 2009. A key feature of this work was the evaluation of new heart function clinics (such as those that exist at the Mazankowski Heart Institute/University of Alberta) and recently established elsewhere in the province. The study found that access to heart failure management programs improves substantially with the implementation of these programs, and importantly, was associated with a significant improvement in mortality and heart failure re-admission thirty days after hospitalization. Whereas in years prior to the implementation of these programs, the outcomes of heart failure had deteriorated, they improved after the initiation of these programs without a negative impact on healthcare resources. This stands as an excellent example of research in action directly impacting outcomes in an important and common clinical problem.

Circulation
Heart Failure

Changes in Heart Failure Outcomes After a Province-Wide Change in Health Service Provision

A Natural Experiment in Alberta, Canada

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Background—The Alberta Cardiac Access (ACA) initiative was implemented in the spring of 2008 to increase access to specialized heart failure (HF) clinics after hospital discharge.

Methods and Results—We identified all adults hospitalized with a most responsible diagnosis of HF between April 1999 and December 2009. We randomly selected 1 episode of care per patient and evaluated outcomes using interrupted time series: the a priori specified primary outcome was all-cause readmission or death in the first 30 days postdischarge. Between 1999 and 2009, median length of stay increased from 8 days to 10 days (*P*<0.001), and 30-day mortality increased from 9.1% to 11.5% (*P*<0.001) in the 37 891 HF hospitalizations we examined. However, these temporal changes were attributable to the increasing comorbidity burden over time: the adjusted Risk Ratio for 30-day mortality in 2009 versus 1999 was 0.99, 95% confidence interval, 0.86 to 1.15. After adjusting for secular trends, the ACA initiative was associated with changes in 30-day postdischarge mortality or readmission rates (which were increasing 0.3% per month [0.2%–0.3%] pre-ACA and decreased 1.4% per month [0.3%–2.5%] in the 18 months post-ACA; *P*=0.008). After roll out of the ACA initiative, patients discharged from vanguard regions (those that had specialized HF clinics) exhibited lower 30-day postdischarge death/readmission rates than those discharged from other areas of the province (18.6% versus 22.2%, adjusted odds ratio 0.83, 95% confidence interval, 0.75–0.93).

Conclusions—An initiative which increased specialized HF clinic access was associated with a statistically significant improvement in 30-day postdischarge mortality/readmission rates. **(*Circ Heart Fail*. 2013;6:76-82.)**

Key Words: disease management epidemiology ■ heart failure ■ outcomes

Despite many advances in diagnosis and therapy during the past 2 decades, heart failure (HF) remains the most common cause of hospitalizations and readmissions in North America and Europe.[1–3] Although traditional strategies of knowledge dissemination have minimal effects on physician-prescribing habits in HF,[4] involvement of specially trained multidisciplinary teams or specialists in the care of patients with HF has been shown to improve the use of proven efficacious therapies and clinical outcomes.[5,6] However, there is still debate about whether wider implementation of specialized HF management programs will yield similar benefits as in randomized trials or whether there will be unanticipated consequences (such as increased hospitalizations or health resource use in other areas because of closer patient follow-up). Unfortunately, only a minority of patients, even in publicly funded health care systems with universal access like Canada, have access to these resources.

Clinical Perspective on p 82

Between April and May 2008, the Alberta provincial government initiated the Alberta Cardiac Access (ACA; see www.cardiacaccess.ab.ca for full details) initiative to improve access to cardiac care. One area of focus was to enhance access to specialized HF clinics for patients recently discharged after a HF hospitalization. The ACA initiative funded (1) training preceptorships for family physicians, pharmacists, and nurses in HF, (2) the expansion of capacity within the 6 specialized HF clinics, already existing pre-2008, and (3) the establishment of 5 new HF clinics in different regions of the province. Each of the specialized HF clinics implemented or expanded as a result of the ACA initiative were designed as high-intensity clinics that scored maximum points on the HF Disease Management Scoring Instrument[7] including: targeted both patients and caregivers, provision of education,

Received August 3, 2012; accepted November 29, 2012.

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The online-only Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.112.971119/-/DC1.

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***Circ Heart Fail* is available at http://circheartfailure.ahajournals.org** **DOI: 10.1161/CIRCHEARTFAILURE.112.971119**

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Featured Publications

In this insightful analysis of bleeding occurring as a complication of treatment for patients with acute coronary syndromes, Padma Kaul explores whether men and women differ in their propensity for bleeding and how that bleeding ultimately affects their long term outcome. Taking data from nearly 3000 women and over 6000 men, she confirms that bleeding occurs more frequently in women than in men, but then surprisingly shows that it was the men versus the women that did worse when thirty day mortality was examined. Although the reasons for this are not entirely clear, Kaul and colleagues speculate that there may have been greater surveillance and sensitivity to bleeding in women versus men given their higher incidence of this problem. They also noted that the site of cardiac catheterization was more likely the source of bleeding in women and hence, potentially more readily recognizable and treatable.

Association between bleeding and mortality among women and men with high-risk acute coronary syndromes: Insights from the Early versus Delayed, Provisional Eptifibatide in Acute Coronary Syndromes (EARLY ACS) trial

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Background Female sex is an established risk factor for bleeding, which is an important safety end point in patients presenting with non–ST-segment elevation acute coronary syndromes (NSTE ACS). However, it is unknown whether the association between bleeding and mortality is modulated by sex in this patient population.

Methods We examined the interaction between sex and bleeding and 30-day mortality outcomes among 2,975 women and 6,431 men with high-risk NSTE ACS enrolled in the EARLY ACS trial. The Global Utilization of Strategies to Open Occluded Arteries (GUSTO) criteria were used to identify moderate or severe bleeds.

Results Women were older and had more comorbid disease compared with men. Bleeding rates were higher among women (8.2%) than among men (5.5%; $P < .01$). However, the association of bleeding and 30-day mortality was stronger among men (odds ratio 5.8, 95% CI 3.9-8.8) than among women (odds ratio 1.5, 95% CI 0.8-2.9; sex * bleeding interaction $P < .01$). Sex differences in the association of bleeding and mortality persisted in a landmark analysis of 120-hour survivors.

Conclusions In a contemporary high-risk NSTE ACS cohort, women had higher bleeding rates than did men. Paradoxically, the association between bleeding and mortality was worse among men than among women. (Am Heart J 2013;166:723-8.)

Evidence concerning the relationship between sex and outcomes in acute coronary syndromes (ACS) remains equivocal. Several studies including a pooled analysis of major ACS trials suggest that higher mortality rates among women with non–ST-segment elevation ACS (NSTE ACS) are explained primarily by women's older age at presentation, as well as the presence of comorbid disease.[1-7] However, female sex is an established risk factor for bleeding, an increasingly important safety end point that is independently associated with mortality in ACS.[8-13] What is not known is whether the association of bleeding and mortality is modulated by sex among patients with NSTE ACS.

The EARLY ACS trial was a multinational, randomized, double-blind study that examined the efficacy of a strategy of early, routine administration of eptifibatide compared with delayed, provisional administration during percutaneous coronary intervention (PCI) in reducing ischemic complications among high-risk patients with ACS treated with an invasive strategy.[14] This large contemporary cohort of patients with NSTE ACS offered a unique opportunity to examine whether the association between bleeding and mortality was similar among women and men.

Methods

The patient population comprised 2,975 women and 6,431 men enrolled in the EARLY ACS trial. The trial has been

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James A. de Lemos, MD, served as guest editor for this article.
Clinical trial registration information: clinicaltrials.gov; NCT00089895.
Submitted January 30, 2013; accepted July 11, 2013.
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http://dx.doi.org/10.1016/j.ahj.2013.07.014

Peer Reviewed Publications

Peer Reviewed Publications

Title	Authors	Journal
Age, treatment, and outcomes in high-risk non-ST-segment elevation acute coronary syndrome patients: Insights from the EARLY ACS trial.	Lopes RD, White JA, Tricoci P, White HD, Armstrong PW, Braunwald E, Giugliano RP, Harrington RA, Lewis BS, Brogan GX Jr, Gibson CM, Califf RM, Newby LK.	Int J of Cardiol. 2013;167(6):2580-2587.
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Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial.	Lopes RD, Al-Khatib SM, Wallentin L, Yang H, Ansell J, Bahit MC, De Caterina R, Dorian P, Easton JD, Erol C, Ezekowitz JA, Gersh BJ, Granger CB, Hohnloser SH, Horowitz J, Hylek EM, McMurray JJ, Mohan P, Vinereanu D, Alexander JH.	Lancet. 2012 Nov 17;380(9855):1749-1758. Erratum in: Lancet. 2013 Jan 19; 381(9862):204.

Mentoring

Mentoring

The CVC continues its enthusiastic commitment to foster 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. Below are testimonials from several of our young researchers, describing their experiences in collaborating with our faculty, and our biostatistical and research assistants. CVC has provided research opportunities for undergraduates, postdoctoral fellows and medical students, 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.

Reflections from our Trainees

"Undoubtedly, CVC is a place to learn from internationally recognized leaders in clinical research. My postdoctoral training has been strongly influenced by this academic experience with Drs. Ezekowitz, McAlister and Armstrong, and the CVC. The faculty's ability to share their knowledge and provide significant and positive feedback encourages 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 a part of this team."

— Eloisa Colin Ramirez,
Postdoctoral Fellow

"Dr. Paul W. Armstrong has moulded me and changed the way I look at things. The experience I gained at CVC is only the start of a longer learning process for me."

— Jay Shavadia, Co-Chief Resident
in Cardiology

"The CVC helped develop the way I think, look and perceive research. Through this experience, I have felt more mature in my thinking and developed a greater appreciation for clinical trials. Looking beyond the original objectives of a manuscript and gaining insights from the paper itself is a skill I learned here at VIGOUR. I am very thankful for all the great help and support I continue to receive."

— Naji Kholaif , Second Year
Cardiology Resident

Senior Mentors

- Dr. Paul W. Armstrong
- Dr. Justin Ezekowitz
- Dr. Shaun Goodman
- Dr. Finlay McAlister
- Dr. Robert Welsh

Making connections

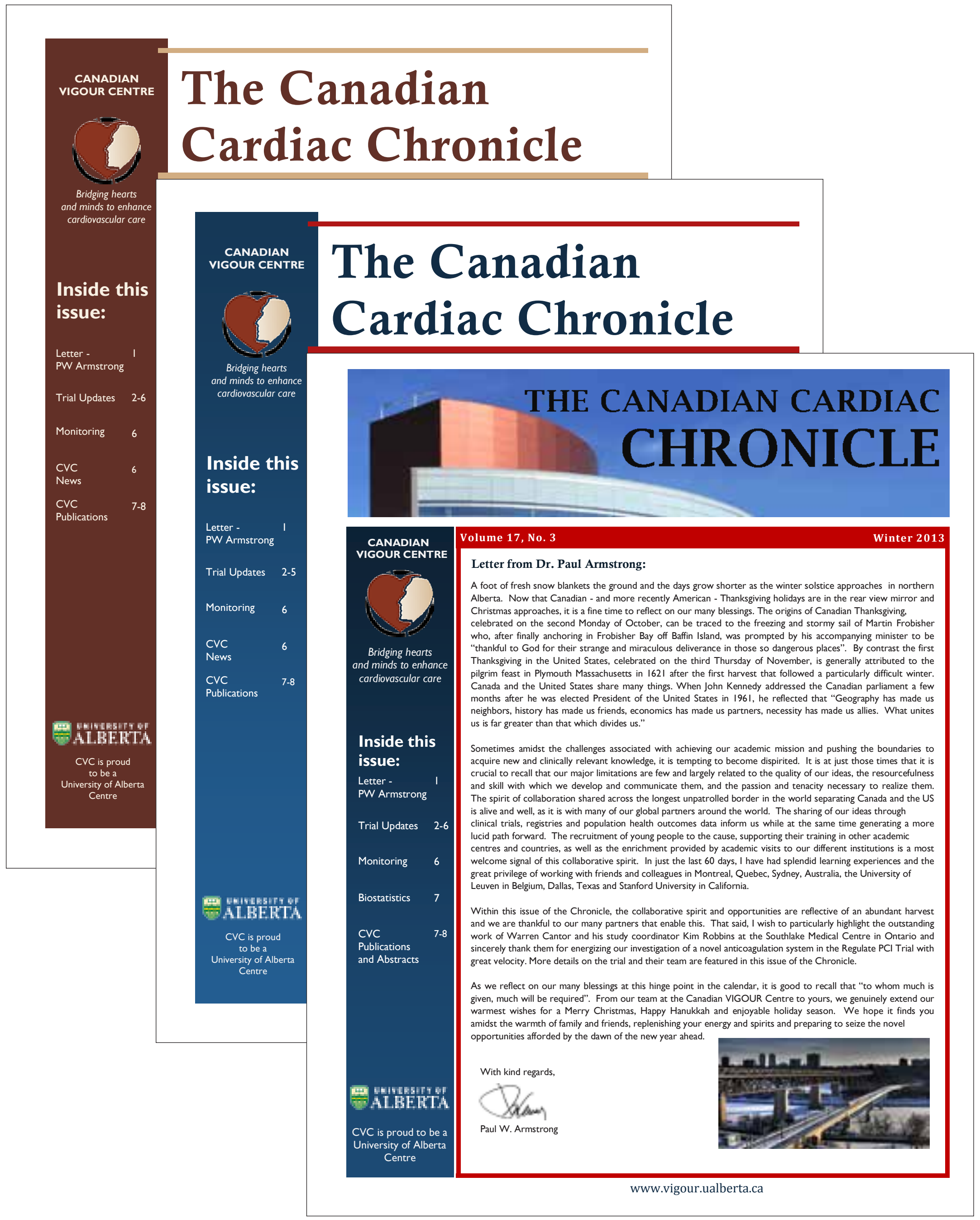
Beyond 2000

In October 2013, CVC hosted our 19th annual ground breaking symposium *New Concepts in Acute Coronary Syndromes: Beyond 2000*, held in Montreal in conjunction with the Canadian Cardiovascular Society and Congress and supported by an unrestricted educational grant 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 the exciting evolution of STEMI care, how to navigate our way through the antithrombotic sea amidst a stunning array of choices and how best to incorporate the emerging associated challenges of heart failure and diabetes. Because the future of clinical trials is now positioned at a critical juncture, a look up the ACS pipeline coupled with an examination of new approaches to our unanswered questions was undertaken. This year, topics and interactive case presentations probed new avenues we all travel within acute coronary syndromes, and better positioned us to care for this large and evolving population.

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.

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 300 recipients, including our investigative sites, sponsors and international collaborators.

Distinguished Visitors


Professor Hans Boetker


Professor John McMurray


Professor William Boden


Professor John Spertus

In 2013, the faculty of CVC were privileged to host a quartet of outstanding, internationally renowned academics through the continuation of 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.

In March, 2013, Professor Hans Boetker from the Department of Cardiology, Aarhus University Hospital in Denmark, addressed the subject of Remote Conditioning and its impact on myocardial infarction and stroke. This subject is dear to the hearts of Drs. Robert Welsh and Kevin Bainey who are currently conducting a pre-hospital trial addressing this potential opportunity to help patients with myocardial infarction. Professor Boetker then went on to provide a keynote address at the ACC Rockies meeting chaired by Dr. Welsh.

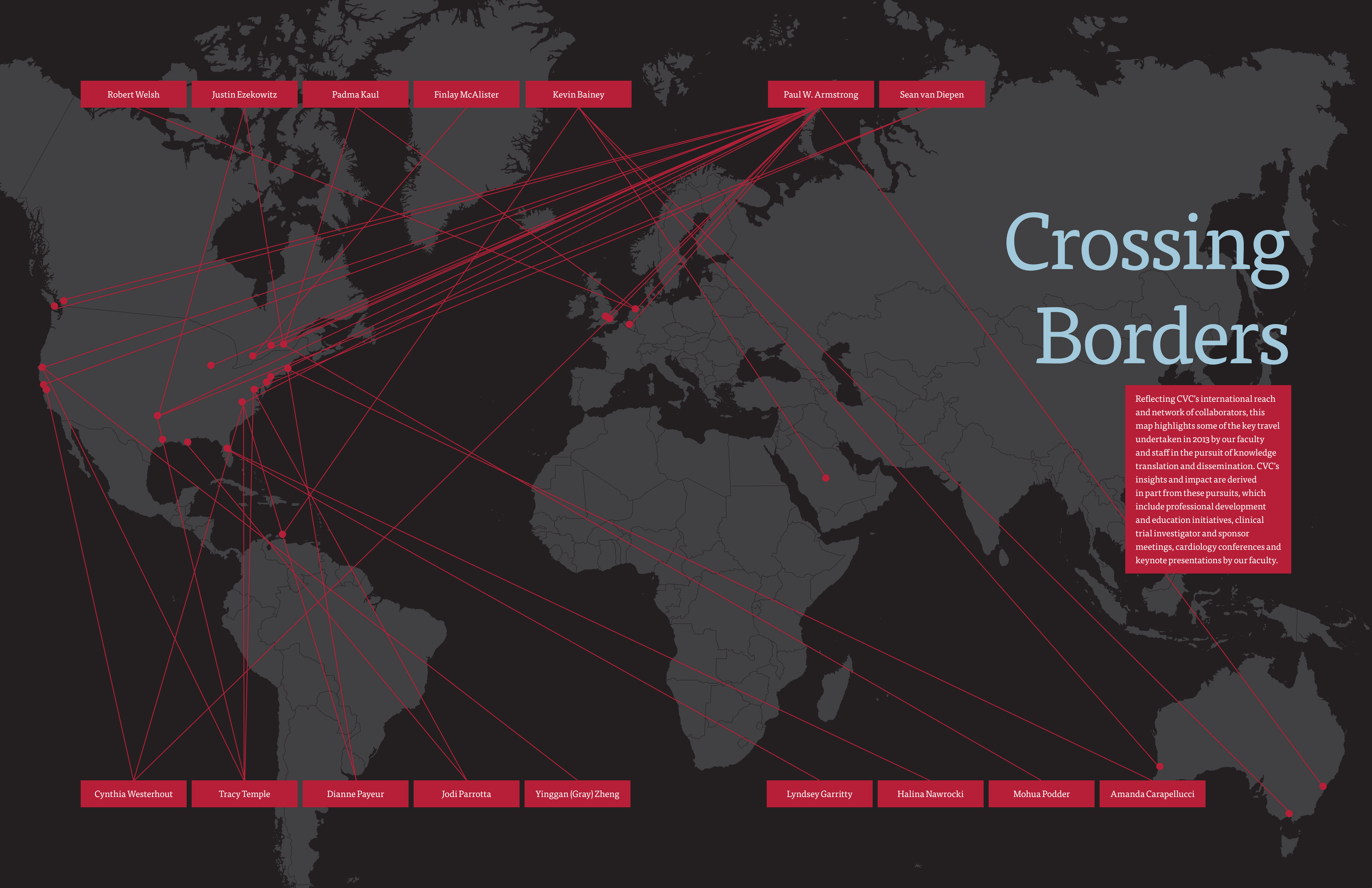
Our next visitor in April of 2013 was from Professor John McMurray from the Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre. Professor McMurray collaborated with Drs. Ezekowitz and McAlister and provided new insights into the challenges associated with heart failure research and how best to conduct and analyze it. As the Chair of the recently published European Society of Cardiology and Heart Failure Guidelines, he was well positioned to provide august advice about our own research in this area and extend the possibility of future collaboration.

In October, Professor William Boden, Chief of Medicine at the Albany Stratton VA Medical Center and head of the COURAGE trial, addressed the subject of how clinical trials create scientific evidence which goes on to shape local clinical practice. He also provided new insight into the AIM-HIGH trial on HDL-raising therapy and reasons for the complexity of that result.

Our quartet of visitors was rounded out in December by Professor John Spertus, Clinical Director of Cardiovascular Education and Outcomes Research at the Mid America Heart Institute in Kansas City. We learned about the opportunities and challenges of implementing personalized medicine, how to create a risk prediction model for clinical use and emerging from that will be new insights for collaborative opportunities.

Crossing Borders

Reflecting CVC's international reach and network of collaborators, this map highlights some of the key travel undertaken in 2013 by our faculty and staff in the pursuit of knowledge translation and dissemination. CVC's insights and impact are derived in part from these pursuits, which include professional development and education initiatives, clinical trial investigator and sponsor meetings, cardiology conferences and keynote presentations by our faculty.



Featured Presentations

Palo Alto

Paul Armstrong
39th Louise and Dorothy Kovitz Visiting Professor at Stanford University December 2013:

- Acute Myocardial Infarction 2014: Reflections of a Clinical Investigator"
- Cardiovascular Clinical Trials at the Cross Roads: A Potential Way Forward

Dallas

Justin Ezekowitz
November 2013 Invited speaker at the American Heart Association meeting in Dallas Texas: Heart rate as a Risk Factor

Paul Armstrong
Invited Speaker American Heart Association Annual Meeting, Dallas, Texas

- Joint AHA/Oman Heart Association Session: Reperfusion in STEMI - Achievements and Challenges Combined Reperfusion Strategy: Is It One Size Fits All?"
- Plenary session: Novel Oral Anticoagulants: Clinical Conundra : New Anticoagulants in Patients Receiving Dual Antiplatelet Therapy

Toronto

Finlay McAlister
Canadian Society of Internal Medicine Annual October 2013 Scientific Meeting, Toronto, Canada: The PREVENTION Trial primary results.
Canadian Society of Internal Medicine Annual October 2013 Scientific Meeting, Toronto, Canada: Presentation as Recipient of Sackett Senior Investigator Award: General Medicine in Canada

Montreal

Justin Ezekowitz
October 2103 Invited Late Breaking Trial presentation: Canadian Cardiovascular Meeting : Montreal PQ: Providing Rapid Out of Hospital Acute Cardiovascular Treatment: PROACT-3

Amsterdam

Robert Welsh
Invited Speaker European Society Cardiology Amsterdam September 2013: Meet the Expert Session: Acute Coronary Syndrome

Leuven

Paul Armstrong
Invited Speaker University of Leuven, Belgium Symposium honoring Professor Frans Van de Werf: Major lessons from randomized controlled trials: challenges for the next decade

Duke University / Duke Clinical Research Institute Visit

In August, members of the CVC leadership team (Paul Armstrong, Dianne Payeur, Cindy Westerhout and Tracy Temple) travelled to the Duke Clinical Research Institute for an in-person collaboration session hosted by its Director Dr. Eric Peterson. This key meeting of the minds was held to reinvigorate and renew our mutual objectives and long standing relationship. Agenda items included an environmental scan of innovations and key players in the international clinical trial arena, opportunities for increased efficiencies in our approach to clinical trials, and a recommitment to our Canadian and U.S investigative sites to offer more value in their collaborations on jointly managed CVC and DCRI clinical trials. Break out discussions across thought leadership, clinical operations and finance/contracts enriched a final plenary planning session.

Stanford University Visit

In conjunction with this academic visit Dr. Armstrong met with key faculty members, including Dr. Ken Mahaffey (Vice Chair of Clinical Research) who was recently recruited by Dr. Robert Harrington (Chair of the Department of Medicine) to plan future collaborative ARO opportunities.

Worldwide Collaborators

Professeur Philippe Gabriel Steg,
Département de Cardiologie
Hôpital Bichat, Assistance Publique - Hôpitaux de Paris

Brazilian Clinical Research Institute
São Paulo, Brazil

Duke Clinical Research Institute
Durham, USA

Estudios Clinicos Latinoamérica
Rosario, Argentina

Green Lane Coordinating Centre
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

ARO Services

Population and Economic Health Outcomes Research

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

Clinical Trials

- Investigator selection, qualification and recruitment
- Investigative site start-up and training
- Ensuring site regulatory compliance
- Project, Site and 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
- Define 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 substudies aimed at mechanistically informing primary clinical trial results
- Mentoring junior faculty, medical trainees, students and allied health professionals

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 publishing insightful and unbiased research and health outcomes is strongly influenced by clinical practice and health care.

Biostatistical Analysis

- 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 and 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 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

Clinical Trials

The clinical trials services of CVC generate valuable data to help support and influence change within clinical practice and the care of patients. In 2013 the CVC was involved in eight Phase III studies, two grant funded studies, and in the initial planning and negotiations for one Phase II study. With a network of over 230 sites across Canada, we had more than two thirds of those sites involved in at least one of our clinical trials enrolling a total of 569 patients in Canada from four recruiting trials in calendar 2013. Since CVC's inception, the sites collaborating with CVC across Canada have enrolled a total of 19, 587 Canadian patients, contributing to the 290, 535 patients recruited globally from the 51 Phase II and III trials we have been involved in.

The clinical trials team led by Assistant Director of Clinical Trials, Tracy Temple, is comprised of five Clinical Trial Project Leads and four regulatory and site coordination support staff. Based regionally across the country, the monitoring team, led by Halina Nawrocki, includes a team of six monitors and one report reviewer. In addition to all of our monitors 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 clinical trials run smoothly, our Clinical Trial team works closely with our sites to strive for efficient start up, for meeting recruitment and retention targets, for data entry that is accurate, and for meeting trial milestones and timelines from study start-up to study completion. As the primary contact for the Canadian sites, the Clinical Trial Project Leads have a good understanding of all aspects of the study, enabling them to closely monitor trends and issues across Canada. Our Clinical Trial Project Leads 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 as well as ensuring they are audit and inspection ready. With the ongoing support and expertise of our project and monitoring team and well prepared sites, all CVC monitored sites who underwent inspections in 2013 received compliant ratings.

Seeking out more efficient ways to run clinical trials in Canada, in late 2013 we commenced planning for a CVC Clinical Trials Research Colloquium to be held in Banff, AB in March 2014 in conjunction with the ACC Rockies Meeting. The intent of this meeting will be 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 meet in person to discuss the survey findings, in an effort to enhance start up and overall efficiencies of clinical trials in Canada. 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.

Tracy Temple, RN, BSc
Assistant Director, Clinical Trials

Halina Nawrocki, RN
Lead Clinical Research Associate

Paula Priest
Project Coordinator

Jodi Parrotta, MA
Clinical Trials Project Lead

Amanda Carapellucci, BSc
Clinical Trials Project Lead

Lyndsey Garritty, BA
Clinical Trials Project Lead

Kalli Belseck, BA
Clinical Trial Research Coordinator

Melisa Spaling, M Ed.
Clinical Trials Project Lead

Courtney Gubbels, BA
Clinical Trials Project Lead

Clinical Trials

TECOS

Trial Evaluating Cardiovascular Outcomes with Sitagliptin

Protocol #:	082-04
Sponsor:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Drug:	Sitagliptin
Anticipated timeline:	August 2008 - March 2015
Study definition:	Randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with sitagliptin in patients with Type 2 diabetes mellitus and inadequate glycemic control
Trial status:	Target enrollment reached; now in patient retention and event accrual stage

481 / 14,000

Patient Enrollment Target (Canada / Global)

549 / 14,745 COMPLETED

Patient Enrollment Achieved to date (Canada / Global)

26 / 681

Number of Sites participating (Canada / Global)

Clinical Trials

EXSCEL

Exenatide Study of Cardiovascular Event Lowering

Protocol #:	BCB109
Sponsor:	Amylin Pharmaceuticals, LLC a subsidiary of Bristol-Myers Squibb
Drug:	Exenatide
Anticipated timeline:	May 2009 - December 2017
Study definition:	A randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus
Trial status:	Actively enrolling

425 / 9,500

Patient Enrollment Target (Canada / Global)

363 / 8,558

Patient Enrollment Achieved to date (Canada / Global)

24 / 461

Number of Sites participating (Canada / Global)

Clinical Trials

ODYSSEY Outcomes

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

357 / 18,000

Patient Enrollment Target (Canada / Global)

29 / 2,124

Patient Enrollment Achieved to date (Canada / Global)

29 / 960

Number of Sites participating (Canada / Global)

Clinical Trials

IMPROVE IT

IMProved Reduction of Outcomes:Vytorin Efficacy International Trial

Protocol #:	P04103
Sponsor:	Merck & Co. Inc.
Drug:	Vytorin
Anticipated timeline:	March 2005 - December 2014
Study definition:	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
Trial status:	Target enrollment reached; now in patient retention and event accrual stage

500* / 18,000

Patient Enrollment Target (Canada / Global)

682 / 18,142 COMPLETED

Patient Enrollment Achieved to date (Canada / Global)

36 / 1,159

Number of Sites participating (Canada / Global)

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

Clinical Trials

STREAM

STrategic Reperfusion Early After Myocardial Infarction

Protocol #:	1123.28
Sponsor:	Boehringer Ingelheim
Drug:	Tenecteplase
Anticipated timeline:	August 2007 - September 2013
Study definition:	Open label, prospective, randomized, parallel and comparative international multi-centre trial comparing the efficacy and safety of a strategy of early fibrinolytic treatment with tenecteplase and additional antiplatelet and antithrombin therapy followed by catherisation within 6-24 hours or rescue coronary intervention versus a strategy of standard primary PCI in patients with acute myocardial infarction within 3 hours of onset of symptoms
Trial status:	Database Locked, 1 year follow up and closing out sites

UP TO 300 / 2,000

Patient Enrollment Target (Canada / Global)

92 / 1,915 COMPLETED

Patient Enrollment Achieved to date (Canada / Global)

4 / 134

Number of Sites participating (Canada / Global)

Clinical Trials

STABILLTY

The STabilisation of Atherosclerotic plaque By Initiaion of darapLadIb TherapY

Protocol #:	LPL100601
Sponsor:	GlaxoSmithKline Pharmaceuticals
Drug:	Darapladib
Anticipated timeline:	September 2008 - December 2013
Study definition:	Randomized, placebo-controlled, doubleblind, parallel group, multicenter, event driven trial. A Clinical outcomes study of darapladib vs placebo in subjects with chronic coronary heart disease to compare the incidence of major adverse cardiovascular events
Trial status:	Database locked and closing out sites

775 / 15,500 CAPPED FOR EACH COUNTRY

Patient Enrollment Target (Canada / Global)

779 / 15,839 COMPLETED

Patient Enrollment Achieved to date (Canada / Global)

36 / 1,159

Number of Sites participating (Canada / Global)

Clinical Trials

REGULATE PCI

Protocol #:	REG1-CLIN310
Sponsor:	Regado Biosciences Inc.
Drug:	REG1 Anticoagulation System (pegnivacogin & anivamersen)
Anticipated timeline:	July 2013 - September 2016
Study definition:	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
Trial status:	Actively Enrolling

405 / 13,200

Patient Enrollment Target (Canada / Global)

47 / 196

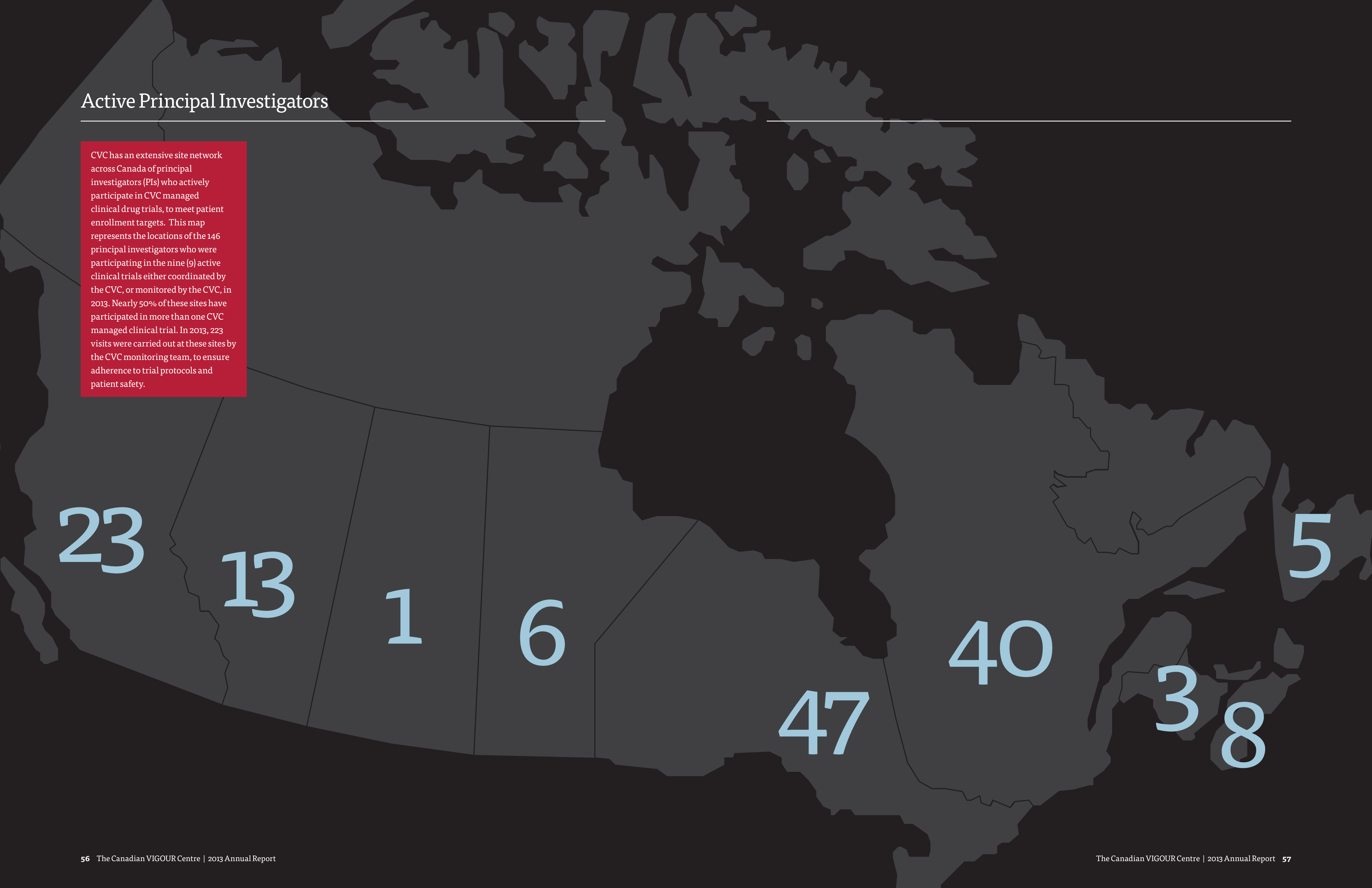
Patient Enrollment Achieved to date (Canada / Global)

3 / 58

Number of Sites participating (Canada / Global)

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 the 146 principal investigators who were participating in the nine (9) active clinical trials either coordinated by the CVC, or monitored by the CVC, in 2013. Nearly 50% of these sites have participated in more than one CVC managed clinical trial. In 2013, 223 visits were carried out at these sites by the CVC monitoring team, to ensure adherence to trial protocols and patient safety.



ECG Core Lab

The aim of our ECG Core Laboratory is to translate research results into information useful for clinical applications. Using the ECG parameters to generate an improved understanding of the pathophysiologic processes involved in acute coronary syndromes (ACS) enables improvements in managing cardiac patients, prediction of outcomes, and further stimulates cardiovascular scientific research.

The main projects for the ECG Core Lab in 2013 were PROACT, the J-Point project, and the Vital Heart Response project. In addition, the STREAM study came to its conclusion with the presentation of the primary study results and publication in the New England Journal of Medicine in April 2013. The examination of the STREAM ECGs included the determination of ST deviation (area at risk), ST resolution (as marker of myocardial reperfusion) and QRS Scoring (for infarct size) in patients experiencing Acute Myocardial Infarction (AMI). These data are now being incorporated into novel presentations and publications to enhance our understanding of the STREAM results.

The Core Lab also provided central adjudication for patients with rescue percutaneous coronary intervention (PCI) to determine whether they met the clinical indication for this procedure.

In 2013, the ECG Core Lab was involved in PROACT-3, the third stage of the PROACT project. A key component of this project is the timely recognition of patients' needs, and how best to direct health resources for better and more efficient patient care. Our ECG Core Lab has continued their important role in analyzing the ECGs derived from this project, which will contribute to a database rich in information about outcomes of local Edmonton patients under current practices, and how we can change practice and redirect health care resources to improve patient outcomes for those suffering from acute coronary syndromes and heart failure.

The J-Point Project, begun in 2011, was designed by the CVC ECG Core Lab to establish optimal measurement points on ECGs with respect to feasibility, applicability and interobserver agreement. This project involved the collaboration with two other experienced, well-respected ECG Core Labs at the Duke Clinical Research Institute and the St. Louis University. The results of the first phase of the J-Point Project seeded the second phase, completed in 2013, which tested the inter-reader reliability on the application of the universal definition of myocardial infarction in a broad spectrum of ACS patients. The publication of this project was accepted by the Journal of Electrocardiography and was published online in October 2013. The study demonstrated excellent agreement on ST-segment measurements between the two core labs' experienced readers and will be a real asset and confidence builder for future investigators.

Begun in 2005, the Vital Heart Response (VHR) project is a regional initiative that aims to implement timely, evidence-based reperfusion strategies to maximize the outcomes of patients with ST-segment myocardial infarction (STEMI). In 2013, the ECG Core Lab become involved in analyzing the ECGs collected from VHR patients in order to compare primary PCI to pharmacoinvasive strategies. Numerous ECG measurements are collected in order to assess outcomes of patients with STEMI.

In 2013, the ECG Core Lab at the CVC continued its mandate of conducting quality analyses using clinical research data. The Core Lab has accumulated a wealth of experience in its readers and continues to mentor and serve as a valuable training ground for the next generation of talented researchers. To date, ECGs from over 70,928 patients, enrolled in studies around the world, have been analyzed. This provides an excellent database for additional sub-studies, analyses and research.

Pushpa Jagasia, MD
Senior ECG Reader

Neda Dianati Maleki, MD
Research Assistant

Biostatistical Analysis

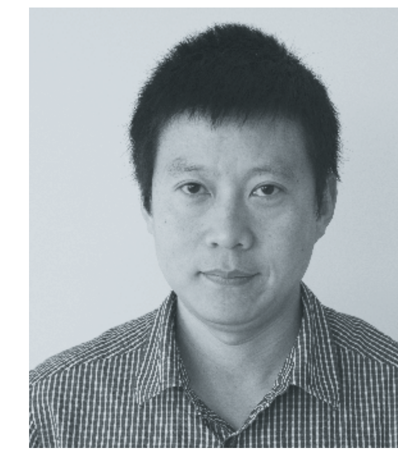
The CVC houses databases from over 25 clinical trials, which provide a rich cache of patient characteristics, ECGs, treatment and outcomes. The CVC also has access to population based data for over 500,000 Albertan patients seeking cardiovascular medical care between the fiscal years 1999/2000 and 2009/2010, as well as those participating in the following registries or studies:

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

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, acute and chronic heart failure, cardiac arrest, arrhythmias, and diabetes. Areas of interest include: international and regional differences, 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 biostatistical 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. There are two main data sources on which academic research projects are based: (i) clinical trials and (ii) population-based databases and registries.

In 2013, 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 and meta-analysis to a novel analysis of composite endpoints in STEMI trials (i.e., weighted composite endpoint). The latter has garnered increased interest from various stakeholders and remains a key area of research. In keeping with a key component of 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.

Cynthia Westerhout, PhD
Assistant Director, Biostatistics and, Senior Research Associate



Yinggan (Gray) Zheng, MA, M Ed
Senior Biostatistician

Mohua Podder, PhD
Biostatistician

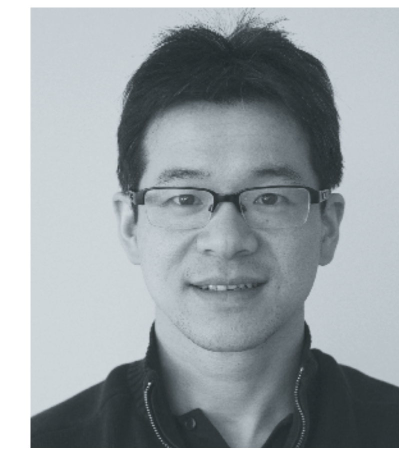
Population and Economic Health Outcomes Research / Clinical Registries

The CVC Outcomes Group (led by Drs. Kaul, Ezekowitz and McAlister) has been actively involved in building the crosswalk between trials, registries, and populations. A prime example of this is our work on the Acute Study of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial. The trial enrolled 7141 patients internationally, including 465 Canadians at 31 sites in six Canadian provinces. However, randomized controlled trials (RCT) are often limited by their generalizability to the broader non-trial population. To provide a context for the trial, Dr. Ezekowitz and colleagues designed a complementary Canadian registry of 697 patients from a subset of eight sites (three community hospitals and five tertiary care hospitals). Dr. Kaul and colleagues in turn extended the comparison to heart failure hospitalizations at all acute care hospitals in all Canadian provinces (except Quebec) using data from the Canadian Institutes of Health Information (CIHI). The result was, for the first time, we were able to describe the difference in the characteristics of clinical trial patients and the population at large living with acute heart failure in Canada. The dichotomy of observed outcomes in the trial and population- level data highlighted the important role that each plays in observational studies and informing clinical practice.

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. This is exemplified by the work by Dr. McAlister and colleagues examining the changes in heart failure outcomes after the implementation of the Alberta Cardiac Access Collaborative (ACAC), a province-wide initiative to increase access to specialized heart failure clinics after hospital discharge. Based on administrative data received from Alberta Health, the CVC Outcomes group has developed an integrated longitudinal database 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, non-acute ischemic heart disease, cardiac arrhythmias and congenital heart disease between 1999 and 2009 in Alberta. Using these data, Dr. McAlister was able to demonstrate that the ACAC increased specialized heart failure clinic access and was associated with a statistically significant improvement in 30-day post-discharge mortality/readmission rates.

The CVC continues to expand our data repository of clinical registries and provincial and national healthcare administrative databases. 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. These research objectives are completely aligned with the Canadian Institutes of Health Research funded Alberta SPOR Support Unit.

Padma Kaul, PhD
Director, Outcomes Research



Wei Lui, MSc
Data Analyst

Anamaria Savu, PhD
Biostatistician

Business Office and Administration

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.

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Assistant Director, Operations

Carla Price, BSc
Business and Research Administrator

Ellen Pyear, MA
Assistant to AD, Operations

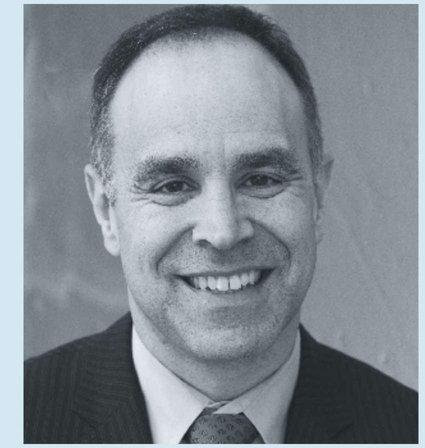
Yvonne Regnier
Executive Assistant to Dr. Armstrong

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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Acknowledgements

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;
- Dianne Payeur, Carla Price, and Ellen Pyear for their time and the dedication required to produce this report;
- Kathy Watts and Bryan MacNeill from Watts Communications 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.