



For more information on research at the
Population Health Research Institute, contact:

Population Health Research Institute
237 Barton Street East
Hamilton, ON L8L 2X2
CANADA
(905) 527-7327 ext. 40334
www.phri.ca

The Population Health Research Institute is affiliated with the academic teaching hospital of Hamilton Health Sciences
and McMaster University's Faculty of Health Sciences. For more information on these institutions, contact:



Research Administration
Hamilton Health Sciences
120 - 293 Wellington Street North
Hamilton, ON L8L 8E7
CANADA
(905) 521-2100 ext. 74595
www.hamiltonhealthsciences.ca



McMaster University
Faculty of Health Sciences
1280 Main Street West
Hamilton, ON L8S 4K1
CANADA
(905) 525-9140 ext. 22100
www.fhs.mcmaster.ca

GLOBAL HEALTH | GLOBAL PARTNERSHIPS | GLOBAL IMPACT



POPULATION HEALTH RESEARCH INSTITUTE



[RESEARCH REPORT | 2012]



OUR PEOPLE.
OUR TEAM.



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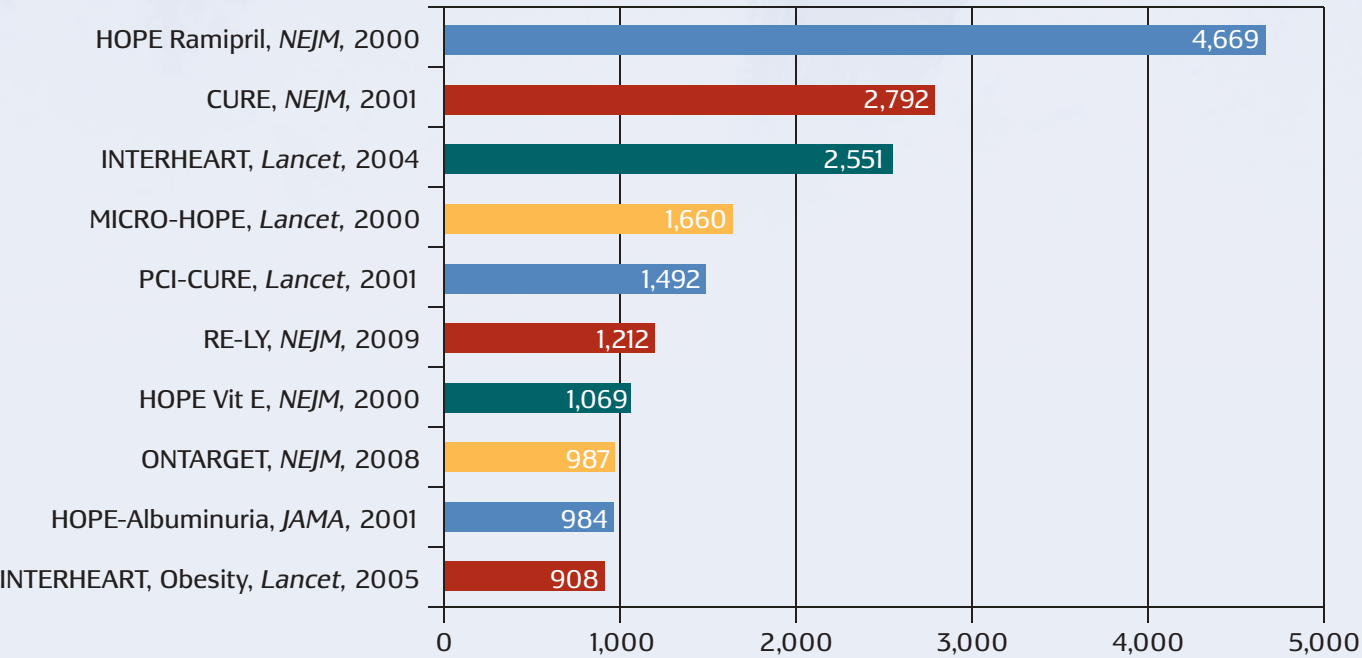
20 Years of Publications

1993	1994	1995	1996	1997	1998	1999	2000	2001	2002		2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
26	29	19	36	34	33	45	54	75	78		106	115	134	121	149	146	161	204	225	267

Highlights of PHRI studies supporting regulatory approvals around the world

STUDY NAME	DRUG	INDICATION
HOPE	Ramipril	Secondary Prevention
RESOLVD	Candesartan	Heart Failure
	Metoprolol CR	Heart Failure
OASIS-4	Clopidogrel	Unstable Angina/Non-ST Elevation MI
OASIS-5	Fondaparinux	Unstable Angina/Non-ST Elevation MI
OASIS-6	Fondaparinux	ST Elevation MI
ONTARGET/TRANSCEND	Telmisartan	Prevention of Cardiovascular Disease
RE-LY	Dabigatran	Prevention of Stroke in Atrial Fibrillation
AVERROES	Apixaban	Prevention of Stroke in Atrial Fibrillation

Top 10 Citations



6 Continents
86 Countries

Africa (15)

Benin Republic, Botswana, Cameroon, Egypt, Ghana, Kenya, Mozambique, Nigeria, Seychelles, Sierra Leone, South Africa, Sudan, Tanzania, Uganda, Zimbabwe

Asia (25)

Bahrain, Bangladesh, China, Hong Kong, India, Indonesia, Iran, Israel, Japan, Kuwait, Malaysia, Nepal, Oman, Pakistan, Philippines, Qatar, Russia, Saudi Arabia, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, Turkey, United Arab Emirates

Europe (29)

Austria, Belarus, Bulgaria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom

Oceania (2)

Australia, New Zealand

N. America (7)

Bermuda, Canada, Cuba, El Salvador, Guatemala, Mexico, United States

S. America (8)

Argentina, Brazil, Chile, Colombia, Ecuador, Peru, Uruguay, Venezuela

35
Researchers

250
Research Team

200,000 sq. ft.
Research Space

34
Research Fellows

1,250
Published Papers

80
Global Trials

1,500
Centres

1,000,000
Enrolled Participants

FAST FACTS



“
I am committed to assisting medical research and development in Hamilton which advances healthcare globally. That is why I supported the consolidation of our various locations into one state-of-the-art facility in the development of the David Braley Cardiac, Vascular and Stroke Research Institute, which houses the Population Health Research Institute.
”

David Braley

Atrium of the David Braley Cardiac, Vascular and Stroke Research Institute



“Our team has helped improve the prevention and the treatment of cardiovascular diseases and diabetes worldwide.”

Dr. Salim Yusuf
Executive Director, Population Health Research Institute



“The PHRI is renowned for excellence. Its international-level scientists have a passion for making an outstanding impact with far-reaching, evidence-based research that develops new knowledge and improves the management of cardiovascular diseases and diabetes for millions around the world. The last five years have been no exception and we anticipate continued success in the future.”

Dr. John Kelton
*Dean and Vice-President,
Faculty of Health Sciences, McMaster University*



“The work of the scientists at the PHRI has impacted care in Hamilton, Canada, and the world.”

Murray T. Martin
President and CEO, Hamilton Health Sciences



To conduct trans-disciplinary research to improve major health outcomes in common and neglected conditions affecting Canadians and populations across the world. – PHRI Mission Statement

These words succinctly summarize the goals of a global innovator. Canada's premiere global health research facility and a world leader in large clinical trials and population studies, the Population Health Research Institute (PHRI) marks an illustrious twenty-year history with an impressive list of accomplishments.

Originally formed with a focus on cardiovascular disease (CVD) and diabetes, PHRI's research areas have broadened to include population genomics, perioperative medicine, stroke, thrombosis, CV surgery, renal, obesity, childhood obesity, bone and trauma and implementation science. Over the years, the PHRI has developed unparalleled expertise in epidemiology, population health and clinical trials. Examining biological and genetic determinants of health, as well as social, environmental and policy factors, the research focuses on the prevention of cardiovascular disease, diabetes and other common conditions. PHRI's capacity to conduct several international studies concurrently, with tens of thousands of participants in each, is a capability very few organizations in the world can match. To date, PHRI studies have enrolled almost 1,000,000 participants worldwide.

A core strength of the PHRI is the multidisciplinary team of world-class scientists and research support teams. The environment promotes collaboration, resulting in a multifaceted approach which allows researchers to capitalize on the wealth of collective knowledge as they each bring an area of expertise to a single study.

PHRI research has led to more than 1,250 published papers in renowned medical journals. In 2012 PHRI scientists published close to 300 papers, with many in high impact journals—a number that has consistently been on the rise since the beginning. Several of these papers are "citation classics," with more than 1,000 citations, with the HOPE main report surpassing 4,500 citations in 2012.

The PHRI evolved from the highly successful Preventive Cardiology and Therapeutics Program established by Salim Yusuf in 1992. In 1999, with the expanding breadth and scope of its research program, it was renamed the Population Health Research Institute and established as a joint research institute of Hamilton Health Sciences and McMaster University. The PHRI has grown from three individuals in 1992, to its present strength of 250 scientists and research staff. In 2009, the PHRI moved to its current location, the David Braley Cardiac, Vascular and Stroke Research Institute (DBCVSI). The move was made possible through two large Canada Foundation for Innovation (CFI) grants, a Clinical Research Initiative Award, a generous gift from Senator David Braley and contributions from members of the PHRI and Hamilton Health Sciences. PHRI's new home includes over 200,000 square feet of state-of-the-art research space, which welcomes more than 2,500 guests annually through seminars, lectureships and symposia.



GLOBAL HEALTH

GLOBAL PARTNERSHIPS

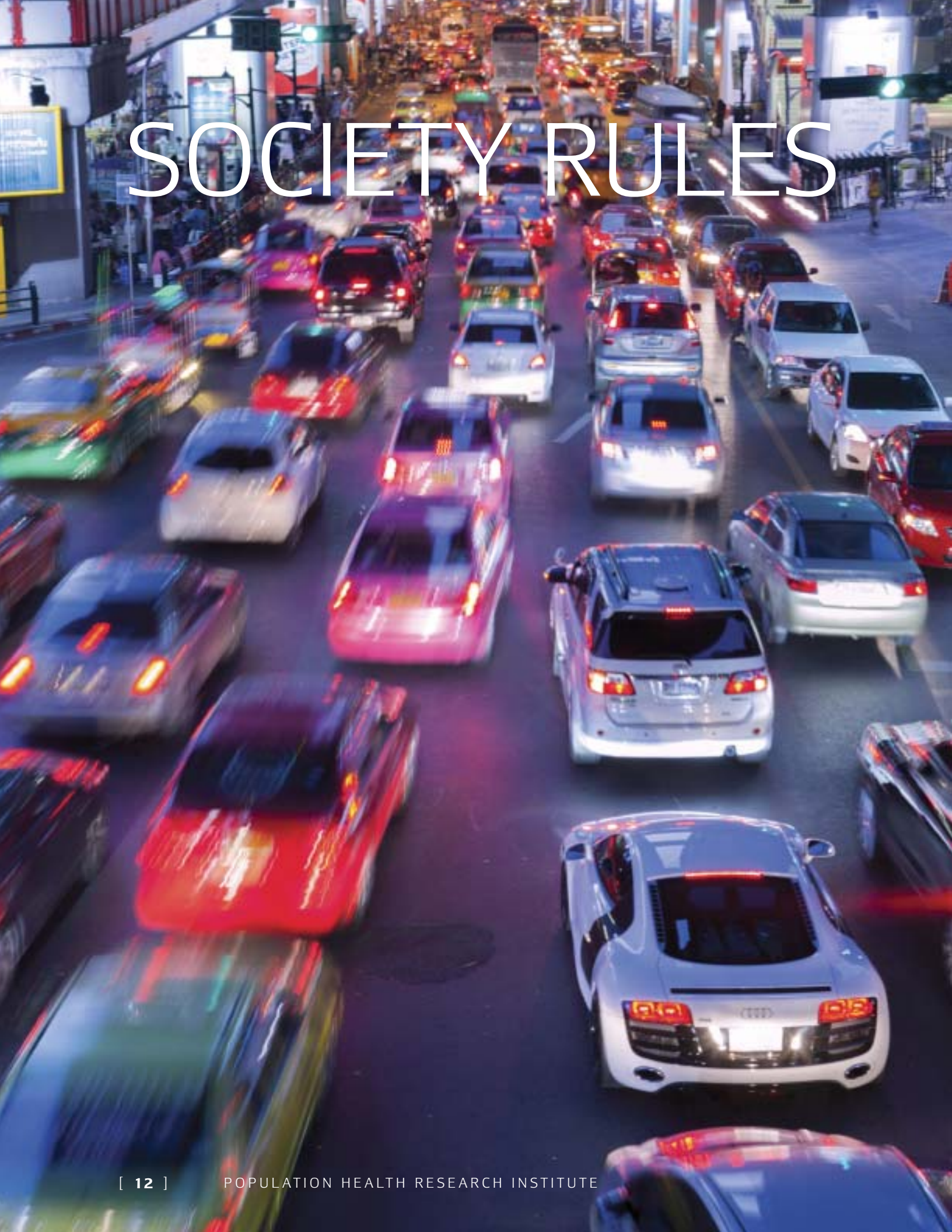
GLOBAL IMPACT



Of the 55 million deaths that occur every year in the world, approximately 80% occur in low- and middle-income countries.

Developing countries face a double burden as they struggle with the unfinished challenges of infectious diseases and undernutrition, while tackling the epidemics of diseases arising from globalization of unhealthy lifestyles: obesity, diabetes, cardiovascular disease and cancer. They also must deal with a third threat related to their underdeveloped health systems.

PHRI has built a global network involving over 1,500 centres in 86 countries in every inhabited continent, to work with scientists who share the same vision of improving global health. PHRI's work primarily investigates how societal changes influence health behaviours and how to better treat people with existing cardiovascular disease. Researchers are examining health systems to assess how to best meet the challenges of the burden of diseases described above. PHRI's researchers are also studying several neglected cardiovascular diseases such as tuberculous pericarditis, Chagas disease (a parasitic disease affecting the heart) and rheumatic heart disease that disproportionately affect the poor.



SOCIETY RULES

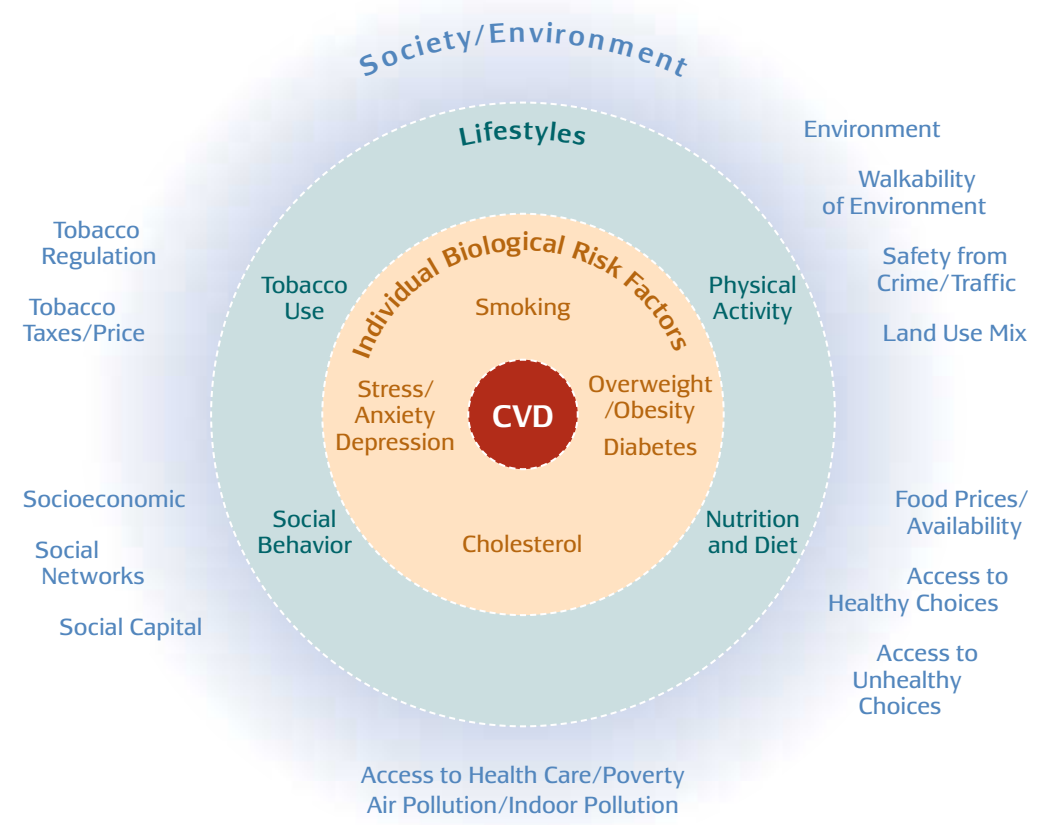


What are the Causes of the Causes?

Social changes have a large impact on how we live, eat and interact with each other. Urbanization and inequalities in social and economic development influence health to a greater extent than any other risk factor. The PURE study investigates the effects of societal influences on health behaviours, risk factors and ultimately on various diseases.

PURE (Prospective Urban Rural Epidemiologic Study)

17 countries → Urban and Rural = 600 communities → 154,000 adults + families = 400,000 participants



MODERNIZATION URBANIZATION —AND THE WAISTLINE

“The PURE study will help provide information that we can use to **create communities that support healthy living** by promoting activity and healthy nutrition.”

”
Dr. Scott Lear

What do countries as diverse as Brazil, China, India and South Africa have in common? They are all experiencing a trend toward increased obesity which has become a global epidemic.

The World Health Organization (WHO) estimates 2.3 billion adults will be overweight or obese by 2015. Once considered solely a problem of “rich nations,” obesity is increasing at an alarming rate in the world’s poorest countries. For the first time in history, obesity and undernutrition co-exist in several countries—often within the same city. Considering that cardiovascular disease (CVD) and diabetes are both common health consequences of obesity, it is, therefore, no surprise that diabetes rates are rapidly rising around the world and that by 2020 more than 85% of the CVD in the world is expected to occur in developing countries.

Any good news? Yes, obesity can be prevented.

PHRI’s PURE (Prospective Urban and Rural Epidemiological study), investigates the impact of urbanization and economic status on obesity in low- and middle-income countries. Covering an exhaustive assessment of societal, nutritional and lifestyle changes which accompany urbanization and economic development, the PURE study is helping to understand how modernization, urbanization and globalization increase obesity and other risk factors for CVD and diabetes. Utilizing standardized

data collection in both rural and urban communities from countries representing low-, middle- and high-income regions of the world, and involving 400,000 combined participants worldwide, PURE is the largest study of its kind.

PURE’s lifestyle and environment data facilitate analyses of the link between body size/fat and household devices which promote a sedentary lifestyle (TVs, computers and cars). These data also provide insight into the relationship between body size and the design of the community within which people reside. Add to the equation rural vs. urban, rich and poor, and diverse countries like Canada, China, India, Brazil and Zimbabwe, and the big picture starts to form. What emerges is a link between community profiles and health behaviours, as well as insights into how these relate to obesity, diabetes, hypertension, CVD, cancer and lung disease. The end-result is an extensive compilation of information regarding the link between social factors and health.

EATING RIGHT

“Promoting the importance of healthy eating by health professionals would **substantially reduce cardiovascular disease and save lives globally.**”

Dr. Mahshid Dehghan

PHRI's research on obesity and lifestyle risk factors involves in-depth studies examining the complex relationship between diet and increased risk of several diseases.

Dietary patterns of people in low- and middle-income countries—rich and poor; rural and urban—are changing. Increased consumption of unhealthy foods such as refined grains, trans-fat and processed foods is due to the shift from traditional home-prepared meals to convenient packaged foods.

The Nutrition Transition study of PURE investigates the extent and impact of dietary pattern change in developing and developed countries, and aims to identify why this occurs and how it relates to CVD and other diseases. By characterizing food and nutrition patterns in countries at different economic levels, and investigating the influence of processed foods on obesity, hypertension and cardiovascular

risk factors, the Nutrition Transition study aims to identify the association between dietary intake and cardiovascular disease in developing countries.

PURE researchers are also conducting the largest study ever of sodium intake. PURE-Sodium aims to create a simple, practical and accurate system to measure sodium and potassium intake, utilize this system globally, and assess the relationship between sodium and potassium intake and blood pressure. PURE-Sodium results will clarify the optimal ranges of sodium consumption by relating it not only to blood pressure, but also to CVD and other diseases.

HEALTH STARTS EARLY

“Understanding the origins of risk factors in early life is essential in how we **avoid cardiovascular disease later in life.**”

Dr. Koon Teo

Believed to be the root cause of several ‘adult’ diseases, including cardiovascular disease (CVD) and type 2 diabetes, childhood obesity is quickly becoming a major health concern worldwide.

Whereas nutrition and activity influence childhood obesity, the reasons behind healthy or unhealthy behaviours are poorly understood. Similarly, very little is known about the factors that might matter during intrauterine life and early development. Just how early in life do CVD risk factors develop? What are the genetic and environmental determinants? What roles do a child’s ethnic origin and environment play in the development of CVD? Of the childhood obesity intervention programs currently in place, which approaches work and why?

Through an integrated, multidisciplinary approach, PHRI researchers are tackling the tough questions surrounding childhood obesity and its influence on CVD.

Setting the ground work

One of the most detailed studies of its kind, PHRI’s precedent-setting FAMILY (Family Atherosclerosis Monitoring In earLY life) prospective cohort study sets out to examine the fetal and early childhood genetic and family-based determinants for the development of obesity, CVD risk factors and atherosclerosis in childhood. The study observes babies at birth, followed by yearly or bi-yearly observations; mothers during pregnancy, then again at two, five and ten years; and fathers and older siblings at five and ten years.

By identifying early determinants for childhood obesity and CVD risk factors, the FAMILY study results will lead to prevention before obesity and diabetes set in.

HEALTH STARTS EARLY



“ I think **the key bit that needs to be understood is the cycle**—for example, a mom who has diabetes is at higher risk of having a child who has diabetes. So in the next generation, you’re going to have even greater increased risk. Our intent is to understand what the key places are where **we could potentially intervene to break that cycle.** ”

Dr. Katherine Morrison



The FAMILY study (conducted largely in white Canadians) has inspired the START and ABC studies which focus on the South Asian and Canadian Aboriginal populations respectively.

START (SouTh Asian biRth cohOrT) investigates why South Asians (who are known to have more diabetes) have greater body fat compared to white Caucasians, although the former appear to be lean—the “thin fat phenotype” as it has been dubbed. Why are South Asian babies lighter weight at birth than white Caucasian babies, yet possess more body fat? START examines South Asian mothers and babies from Ontario and urban and rural Karnataka in India.

The ABC study (Aboriginal Birth Cohort) addresses the same questions of intrauterine effects of genetic and environmental determinants on risk factors among aboriginal population of Six Nations (Ontario). Six Nations people exhibit traits opposite to those seen in South Asians and have a high risk for chronic disease. Both South Asians and Aboriginal people have high rates of gestational diabetes, yet aboriginal babies are born larger and South Asian babies are smaller. By contrasting these very different populations, START and ABC results will provide a better understanding of the determinants affecting each.

The RICH LEGACY study (Research in International Cardiovascular Health—Lifestyles, Environments and Genetic Attributes in Children and Youth) evaluates differences in body fat and its metabolic consequences among school-age Canadian children of European origin, Canadian children of South Asian origin and children in Bangalore, India. The study will simultaneously investigate the genetic, behavioural, attitudinal and environmental reasons of ‘why people do what they do’ while answering the underlying question of how individual, familial, school and community characteristics associated with urbanization and Westernization relate to childhood obesity and its metabolic consequences.

By targeting children at key developmental stages (ages 7–8, 14–15), the study will identify factors related to risk prior to manifestation of disease.

Covering a large expanse of the Canadian landscape is a multi-site registry called CANPWR (CANadian Pediatric Weight management Registry) which monitors overweight and obese children. CANPWR will document approaches to weight reduction in children and compare those that work with those that are less successful.

“
**Genetics is in the midst
of a revolution not unlike
electronics in the '70s.**

Technological advances and rapid
progress in our understanding of the
genetic code are leading the way
toward personalized health care.

”

Dr. Guillaume Pare

IS IT ALL YOUR PARENTS' FAULT?



Genetics of cardiovascular disease

Who has not noticed family traits while browsing the family photo album? Much like physical characteristics, diseases and response to treatments may also run in families. While the genetic basis for these observations remained a mystery for centuries, recent advances have allowed geneticists to identify thousands of genes responsible for specific human traits such as height, blood cholesterol or risk of heart attack.

Over the last five years, PHRI has developed a global program investigating genetic causes of cardiovascular diseases. Analysis of DNA samples from the large, international INTERHEART study led to novel insights into genetic determinants of myocardial infarction. Genetic data from the Arrhythmia team's ACTIVE and Acute Coronary Syndrome's CURE studies indicated that

pharmacogenetic testing had limited utility in identifying who would not benefit from clopidogrel therapy, one of the most widely prescribed anti-platelet drugs—a discovery that offers reassurance to the hundreds of thousands of patients taking this medication that they are likely to benefit irrespective of their genes. The RE-LY trial showed that 30% of Europeans carry a genetic variant protecting them from bleeding when taking the novel anticoagulant dabigatran. Such findings raise the possibility that genetic information may assist in how we treat patients with specific drugs.

The Genetic and Molecular Epidemiology Program of PHRI, conducts the most cutting-edge genetic techniques and will assess whether the promise of personalized medicine can be realized. The team explores the genetic risk of stroke, diabetes, obesity and the response to some of the most widely prescribed drugs for these diseases.

Smoking

Diabetes

Hypertension

Abdominal Obesity

Psychosocial Index

Fruits/Vegetables

Exercise

Alcohol

ApoB/ApoA1 Ratio

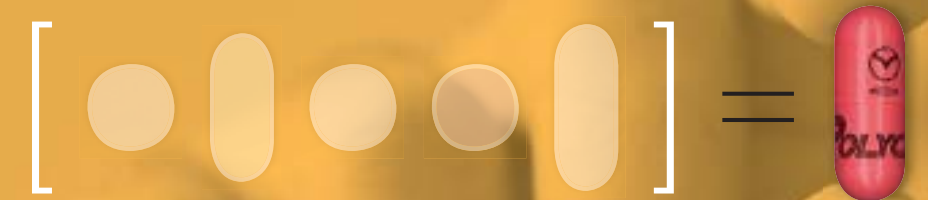
Atrial Fibrillation

THE 10 THAT MATTER

As recently as ten years ago, most researchers believed that we knew less than half of the causes of heart disease and strokes. The INTERHEART and INTERSTROKE studies demonstrated that nine or ten simple risk factors account for over 90% of the risk of heart attacks and strokes globally. In addition, the impact of these risk factors is approximately the same throughout the world. This means that we can change the course of cardiovascular diseases globally through similar approaches. The focus should now be directed to developing healthcare systems that are conducive to the implementation of effective preventative strategies.

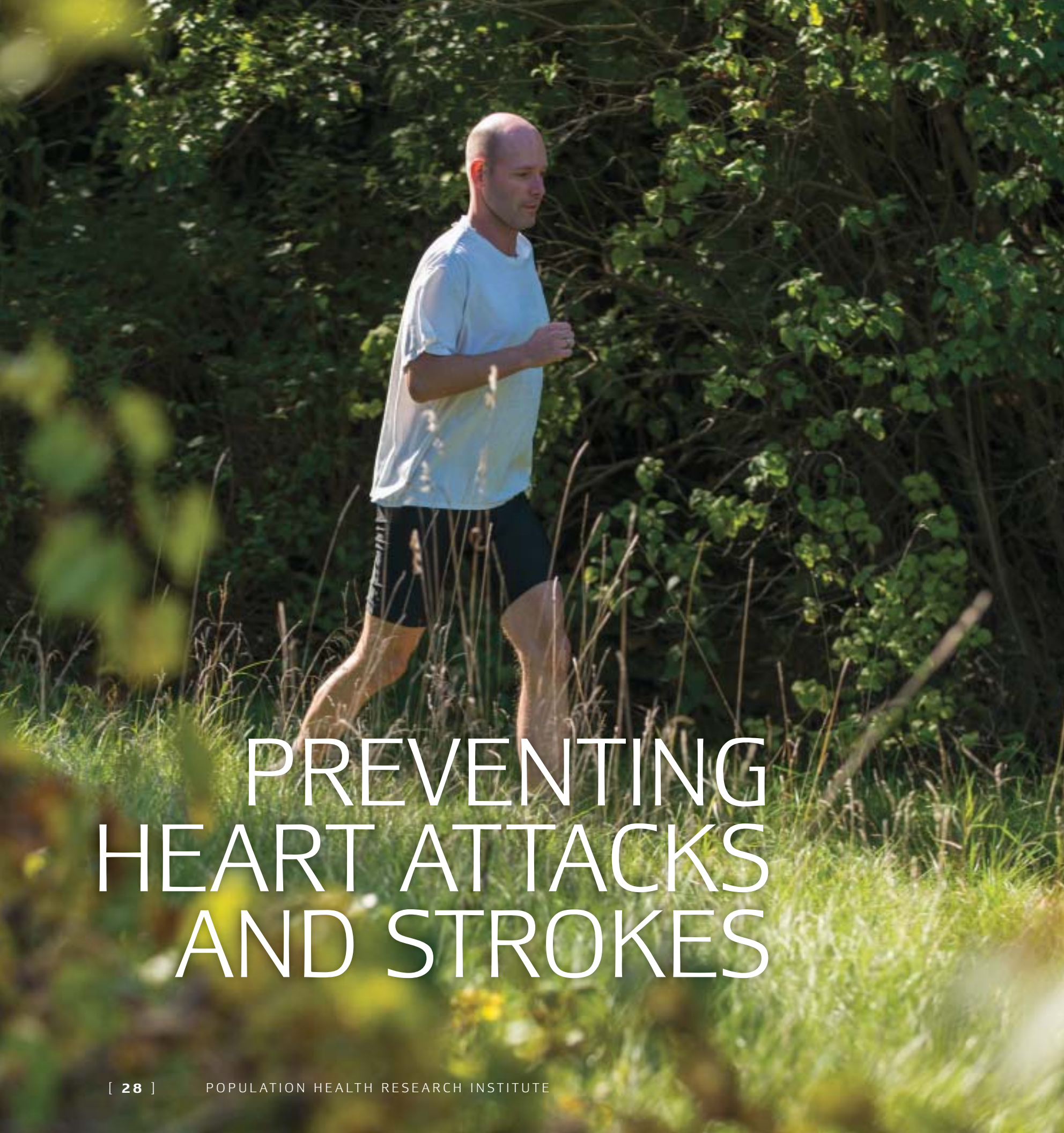


THE 5-IN-1 PILL



Can a single inexpensive pill reduce the risk of heart attacks and strokes by two-thirds?

Utilizing a combination of three different BP-lowering drugs, a statin to lower LDL cholesterol, and aspirin, may reduce the risk of future heart attacks and strokes by 65% to 70%. Combining all five active drugs into a single, low-cost pill could prevent most heart attacks and strokes in high-risk individuals. PHRI researchers have worked with the Indian company Cadila to develop such a 5-in-1 pill, called the Polycap. They are testing its impact on reducing risk factors and its tolerability in three successive studies involving more than 8,000 individuals. With support from the Wellcome Trust, Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, and Cadila, PHRI in collaboration with St. John's National Academy of Health Sciences in Bangalore, India, has embarked on a global trial of more than 5,000 individuals to assess whether the Polycap can reduce cardiovascular disease by at least 50% to 60%. If this benefit is confirmed, the Polycap could revolutionize global approaches to cardiovascular disease prevention, and ultimately benefit millions of individuals.



PREVENTING HEART ATTACKS AND STROKES



"The vascular imaging laboratory identifies high-risk individuals and tracks artery changes during treatment. High resolution ultrasound provides direct confirmation of artery improvement."

Dr. Eva Lonn

With the right health behaviour and drug treatments, premature heart disease and stroke may become a thing of the past. – Dr. Salim Yusuf

PHRI's landmark epidemiological studies INTERHEART and INTERSTROKE showed that nine or ten common, easily measurable and easily modifiable risk factors are associated with 90% of heart attacks and strokes globally and in all regions and ethnic groups of the world. These studies demonstrated that changes to lifestyle (promoting smoking cessation, physical activity and a healthy diet) and adding effective BP and cholesterol drugs could substantially lower the risk of CVD. The ongoing PURE and HOPE-3 studies examine the reasons for failing to optimize lifestyle and pharmacological approaches to cardiovascular prevention. By identifying barriers such as insufficient knowledge, access to resources and facilities and lagging healthcare policies, tailored strategies can be implemented to help millions of people worldwide.

PREVENTING HEART ATTACKS AND STROKES



“
The development
of rivaroxaban as
a safe and more
effective treatment
than aspirin
**could help to
prevent major
cardiovascular
events in millions
of individuals
globally.**

”

Dr. John Eikelboom



Clinical Trials in Cardiovascular Prevention

The trials HOPE, HOPE-TOO and ONTARGET/TRANSCEND demonstrated that drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are effective in the secondary prevention of cardiovascular diseases. Equally important, these trials also showed that the widely used supplements vitamin E, fish oils, folic acid and other B vitamins are ineffective. Findings have been adopted as practice guidelines.

The ongoing HOPE-3 and TIPS-3 trials are testing novel approaches to primary prevention by evaluating the lowering of cholesterol and blood pressure in people at moderate risk but without known cardiovascular disease and with average cholesterol and blood pressure levels. TIPS-3 is evaluating the use of the Polycap, which combines five pills proven to reduce the risk of heart attacks and strokes into one single pill. This simplified treatment is expected to result in higher compliance rates and improved outcomes. If proven to be true, the results will change global approaches to primary prevention.

PHRI's latest trial, COMPASS (Cardiovascular Outcomes for People using Anticoagulation StrategieS) is testing whether the oral anticoagulant, rivaroxaban, is effective in the prevention of atherothrombotic events in patients with coronary artery disease (CAD) or peripheral artery disease (PAD). Over 20,000 patients from more than 450 sites in 29 countries are participating in the study.

The potential impact of COMPASS is enormous. The development of rivaroxaban as a safe and more effective treatment than aspirin will help to prevent major cardiovascular events in millions of individuals globally. In addition, COMPASS MIND (MRI), a substudy of brain structure and function, will provide greater insights into silent brain lesions (micro-infarcts, micro-bleeds, white matter disease), while a sub-group of post-coronary artery bypass surgery (CABG) patients will be examined to determine if rivaroxaban enhances the benefits of CABG surgery by improving graft patency.

The Prevention Group's many successes are due to its multidisciplinary approach which includes local and global collaborations with epidemiologists, clinical trialists, physicians (with expertise in heart disease, stroke, diabetes, hypertension, dyslipidemias and thrombosis), geneticists, sonographers, nutritionists, study nurses and other healthcare professionals.

SHOCKING & STIMULATING FACTS

“ Both Dabigatran and Apixaban are better than existing therapies... **We now have better treatments to safely prevent stroke** and this is going to lead to an important benefit in stroke reduction worldwide—there is no doubt about it.

”
Dr. Stuart Connolly

Atrial fibrillation is the most common serious rhythm disorder which affects 1% of the population and also increases the risk of stroke five-fold.

Atrial fibrillation (AF) is a heart rhythm disorder where the atria (upper chambers) beat too quickly and irregularly. The resulting irregular rhythm pumps blood unevenly, allowing it to stagnate and form blood clots in the atria. Once dislodged, these blood clots are transported to the brain where they cause a stroke. It is estimated that about 20% of all strokes are caused by AF.

Over the last decade, PHRI's Arrhythmia Research Program has made significant headway in preventing strokes in AF. The team's focus on the development and testing of better treatments for the prevention of stroke in atrial fibrillation has culminated in the considerable success of the international clinical trial, RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) which tested a new drug called dabigatran. Showing significant improvement over previous therapies such as warfarin, dabigatran

lowers the risk of stroke, has less bleeding and is easier to use. RE-LY study results have led to worldwide approval of dabigatran for the prevention of stroke in atrial fibrillation. The RELY-AF Registry, a global registry, looks at stroke and other outcomes in atrial fibrillation patients in 40 countries.

Equally important is the AVERROES (Apixaban VERsus Acetylsalicylic Acid (ASA) to PRevent StrOkES) trial which focuses on a unique segment of atrial fibrillation patients for whom aspirin is the only available intervention. Involving 5,600 patients in 36 countries, AVERROES demonstrated that apixaban is an extremely effective therapy and a viable alternative to aspirin. The research at PHRI has transformed the way we treat patients with AF.

“Clinical trials of the past 20 years have taught us which patients benefit from pacemakers and implantable defibrillators. **Today’s trials are now teaching us how to minimize the potential complications** of these devices and how to make appropriate use of the technology that modern devices contain.”

Dr. Jeff Healey

SHOCKING & STIMULATING FACTS

Device Therapies

Building on a long history of major global device trials such as the Canadian Implantable Defibrillator Study, the Defibrillators and Myocardial Infarction Study, and the Canadian Trial of Physiologic Pacing, the Arrhythmia Research team is moving forward with several groundbreaking device trials. The SIMPLE (Shockless IMPLant Evaluation) trial investigates whether the common procedure of assessing defibrillation thresholds by inducing cardiac arrest during implant surgery is safe.

About 2% of patients who have a device implanted experience a serious infection around the device, increasing their risk of death three-fold. Although the standard approach in some centres is to use antibiotics at the time of the implant, there is great variability. In order to identify the most effective approach, PHRI investigators are collaborating with 40 centres in an innovative 11,000-patient cluster crossover trial, PADIT III (Prevention of Arrhythmia Device Infection Trial) using a new methodology for testing clinical effectiveness of treatments.

Subclinical Atrial Fibrillation

Using newly implanted pacemakers to track the heartbeat of 2,400 elderly patients who were known not to have AF, the ASSERT study discovered that subclinical AF was very common and present in one third of the people, and that it increased the risk of stroke by 2.5-fold.

Whether older patients without pacemakers have silent AF is being addressed by the second ASSERT study. The goal of ASSERT and its subsequent studies is stroke prevention. By identifying AF in a high-risk population which would otherwise not be diagnosed, effective preventative therapies can be introduced thereby decreasing the likelihood of stroke.



EARLY HOURS OF A HEART ATTACK



"It is an honour and pleasure to work in a place that is constantly creating new knowledge to improve patient care in cardiovascular medicine."

Dr. Sanjit Jolly



70,000 Canadians suffer a heart attack each year—of whom 16,000 die

The longer an artery remains blocked after a heart attack, the more heart muscle damage will occur. In patients with unstable angina ("pre-heart attack") or minor heart attacks, if the narrowed artery is opened rapidly, heart muscle damage can be prevented or limited. The optimal timing of intervention has never been determined. PHRI's TIMACS trial (TIMing of intervention in Acute Coronary Syndromes) investigated early (24-hours or less) versus delayed coronary angiography intervention. Results from the 3,000-patient study revealed that early intervention was more beneficial than delayed intervention only in high-risk patients. By comparison, in the average patient both early and delayed intervention were equally effective. TIMACS results have influenced guideline recommendations globally.

Currently the routine treatment for patients with severe heart attacks or STEMIs is percutaneous coronary intervention (PCI), a procedure in which the cardiologist opens the blocked coronary artery with a balloon and stent. The TOTAL trial (ThrOmbectomy vs. PCI ALone for STEMI), which will include 4,000 patients in 60 centres across 12 countries, is testing whether aspirating the blood clot using a specialized tube through the coronary artery prior to the deployment of a stent improves outcome when compared to PCI alone.

Also focusing on PCI is the new trial COMPLETE, which aims to determine if incidentally discovered "non-culprit" lesions should be treated along with the "culprit" lesion during the intervention. A CANNeCTIN initiative with industry support, the trial will include 4,000 patients from 15 countries.

At the core of PHRI's Acute Coronary Syndromes Program is the highly successful series of eight OASIS trials conducted over 20 years. Results of these trials have led to the acceptance of new, more effective and safer therapies such as clopidogrel and fondaparinux. CURRENT (OASIS-7), the largest trial of anti-platelet therapy in patients with ACS (25,000 patients, 597 centres, 39 countries), examined double-dose versus standard-dose clopidogrel, and high-dose versus low-dose aspirin. Trial results showed that a seven-day double-dose clopidogrel regimen was associated with a reduction in cardiovascular events and stent thrombosis compared with the standard dose. The subsequent trial, FUTURA (OASIS-8), showed that adding standard heparin for ACS patients pre-treated with fondaparinux undergoing PCI is safe and effective.

Shifting the focus to invasive treatments is RIVAL (The Radial Vs femoral access for coronary intervention), a trial which compared using the radial artery in the wrist versus the femoral artery in the groin for coronary angiography and intervention. With 7,000 patients from 32 countries, RIVAL showed that access for angiography through the wrist is safer than through the groin by reducing bleeding.



FIXING HEARTS

“
PHRI has the capacity to do large and rigorous studies
in cardiac surgery that have never been done before.
”

Dr. Andre Lamy



“Steroids are cheap and widely available, so if we demonstrate that the suppression of this inflammatory reaction to the heart-lung machine results in better clinical outcome for the patient ... [SIRS] could impact and improve the care of millions of people undergoing heart surgery globally.”

Dr. Richard Whitlock



Investigating the effectiveness of new drugs and techniques in cardiac surgery

The standard coronary artery bypass surgery (CABG) technique developed 40 years ago is cardiopulmonary by-pass, the ‘on-pump’ procedure, in which the patient’s heart is stopped and a heart-lung machine is used to pump blood while the surgeon bypasses blocked arteries. The more-recently developed off-pump technique allows the heart to beat during the entire procedure. The team recently completed the groundbreaking seven-year, Canadian Institutes of Health Research (CIHR)-funded study, CORONARY (CABG Off- or ON-pump Revascularization Study), which examined the benefits and risks of off- and on-pump bypass surgery techniques. CORONARY assessed 4,752 patients in 19 countries and demonstrated that both techniques were equally effective, with the off-pump patients experiencing less bleeding, fewer blood transfusions and lung infections, which resulted in shorter stays in intensive care. The next stage includes assessment of total costs and neurocognitive results at 30 days, as well as safety and efficacy at five years.

A patient on a heart-lung machine may experience a severe systematic response that provokes an acute inflammatory reaction, which can lead to organ damage. SIRS (Systemic Inflammatory Response Syndrome) is investigating whether steroids suppress the inflammatory response and decreases death, heart injury and organ injury.

About 10% of patients who undergo coronary artery bypass surgery have atrial fibrillation which increases the risk of stroke five-fold. LAAOS (Left Atrial Appendage Occlusion Study) evaluates the benefits of removing the left atrial appendage, which is thought to be the source of strokes in people with atrial fibrillation.

A large registry of 5,000 people undergoing cardiac surgery, the Cardiac-VISION study will assess the rates and causes of major vascular events in cardiac surgery. This can lead to better results during cardiac surgery.

BRAIN MATTERS

By the time you finish reading this page, 86 people will have suffered a stroke worldwide.

Second only to ischemic heart disease, stroke is responsible for 4.9 million (9%) of the total 55 million global deaths each year. Low- and middle-income countries have the largest burden of stroke, and account for 85% of stroke-related deaths worldwide. Of those who survive, 25% will suffer another stroke within five years. Whereas Canada and other developed countries are experiencing a steady decline, stroke is an increasing problem in the developing world as their population ages.

The overriding theme of PHRI's stroke research is prevention. Through a series of interdisciplinary programs, investigators are focusing on the prevention of covert strokes, vascular cognitive decline, lacunar stroke, cryptogenic stroke and preventative treatment of atrial fibrillation. Augmenting the central focus of prevention is an intense interest in the epidemiology of risk factors in low- and middle-income countries.

What causes strokes globally?

INTERSTROKE, a study of 24,000 stroke cases in 30 countries, set out to determine the role of known and emerging risk factors in different regions of the world and different ethnic groups. INTERSTROKE found that ten risk factors account for 90% of the risk of stroke, and targeted interventions that reduce blood pressure and smoking, promote physical activity and encourage a healthy diet could substantially reduce the burden of stroke. INTERSTROKE Phase 2 seeks to further explore the importance of risk factors in different regions and ethnic groups worldwide, as well as to determine whether these risk factors vary for the different types of stroke.

MRI Head Scan
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BRAIN MATTERS

“ Clinical trials of blood pressure control and antithrombotic agents led by PHRI have resulted in **prevention of scores of thousands of strokes yearly**, and we will keep going to explore new opportunities for stroke prevention. ”

Dr. Robert Hart



Novel oral anticoagulants, atrial fibrillation and brain ischemia

About one stroke in five occurs due to the heart rhythm disturbance, atrial fibrillation. These unduly large strokes are preventable by use of anti-clotting drugs. Through studies like RE-LY and AVERROES, PHRI researchers discovered new convenient and safer atrial fibrillation oral anticoagulant treatments which will significantly reduce strokes worldwide. The next stage of study, AVERROES MRI, aims to determine the optimal use of novel oral anticoagulants by investigating their effects on the complication of brain haemorrhage and subclinical brain ischemia, and their use in patients with prior stroke.

Silent brain ischemia

Clinical strokes are only the tip of the iceberg. Brain damage from blood vessel disorders is common among the elderly, accounting for an estimated 30% of cognitive problems in the general population. Subclinical “covert” strokes are thought to be even more frequent than clinical strokes and are not benign. Recognizing the enormous potential of this area of study, PHRI is committed to further advance subclinical brain ischemia research through a series of studies and plans to integrate leading-edge MRI technology into its state-of-the-art complex at the David Braley Cardiac, Vascular and Stroke Research Institute, Hamilton, Canada. Complementing this area of research is a series of studies assessing the effects of interventions to improve intellectual capabilities from blood vessel diseases.

Secondary prevention of lacunar stroke

Small strokes located in the central areas of the brain are called lacunar strokes and comprise about 25% of all strokes. They are most commonly caused by high blood pressure and diabetes, and they are particularly prevalent among Blacks and Hispanics. Sponsored by the National Institutes of Health (NIH), an agency of the US Department of Health, the international randomized trial SPS3 (Secondary Prevention of Small Subcortical Strokes) is testing aggressive vs. usual targets for blood pressure control and the combination of clopidogrel and aspirin in patients with a recent lacunar stroke. Co-principal investigator, Dr. Robert Hart, and PHRI colleagues are involved with the conduct and analysis of SPS3, the first large randomized trial focusing on well-defined patients with this common stroke type, which will importantly influence the treatment for prevention of subsequent stroke and cognitive decline.

Secondary prevention of cryptogenic stroke

Cryptogenic means “hidden cause.” Even with today’s modern diagnostic tests, in about 25% of strokes, no clear cause is identified. There is some evidence that many strokes, perhaps most, could be due to clots from the heart or aorta, which are preventable with anticoagulant drugs. However, clinical trials are necessary to test this concept. PHRI investigators are leading an international consensus committee that will establish diagnostic standards and criteria in preparation for launching clinical trials to define better treatments to optimally reduce recurrent stroke for millions of people with cryptogenic strokes.

“
Patients undergoing surgery today are older and have other comorbidities which increase their risk of complications. We intend to avoid complications by identifying those at high risk and better managing them.
”

Dr. P.J. Devereaux

MAKING SURGERIES SAFER

Over 200 million adults worldwide undergo major surgery every year. Within one month of surgery five million of these patients will experience a complication which, if undetected, can be fatal.

Understanding the rates and causes of complications after surgery is the focus of several international studies led by the Perioperative Medicine and Surgical Research Unit. Using representative samples of people undergoing various types of surgeries, PHRI studies track rates of complications and impact on short- and intermediate-term health and costs—to both the individual patient and to society. The three fundamental themes of research are: identification of causes, prevention, and management.

Identifying the Causes

The POISE trial (PeriOperative Ischemic Evaluation) demonstrated that many post-surgery complications will be missed if one does not actively look for them. This important discovery formed the basis for VISION (Vascular events In noncardiac surgery patients cohort EvaluatiON) which is the largest international prospective cohort study evaluating complications after surgery. VISION and its 20 substudies monitor a broad spectrum of post-surgery markers in the blood, utilizing a large number of samples stored

in a biobank and linking these to changes with the heart and brain using imaging studies (cardiac MRIs, cardiac CT angiographies and brain MRIs). VISION has demonstrated that a simple blood test called Troponin T can identify those who are at high risk of dying within 30 days after surgery. Once elevated Troponin levels are identified, physicians have the opportunity to provide enhanced monitoring and appropriate interventions to improve the outcome.

Strokes after surgery can be fatal or disabling. Through the Neuro-VISION substudy, researchers are studying whether strokes identified on brain MRIs are significant. By investigating these covert strokes, researchers will better understand the rate of occurrence, impact on cognitive decline and the risk of clinically overt stroke in the coming year. Additional substudy investigations include post-surgery bleeding, acute kidney injury, pneumonia/sepsis and chronic pain.



MAKING SURGERIES SAFER



Prevention

POISE, the world's largest trial on the prevention of cardiovascular complications around surgery, examined the standardized practice of using beta-blocker drugs at the time of surgery. Beta-blockers were thought to be beneficial in preventing heart attacks, *and* with no risk. Although POISE confirmed the benefits of heart attack prevention, it also demonstrated that beta-blockers double the risk of serious strokes and significantly increase the risk of death. POISE results have changed guidelines and practice worldwide.

Expanding on the results of POISE, an international group of investigators are moving forward with POISE II. Through a 10,000-patient, randomized controlled factorial trial involving 25 countries, POISE II seeks to assess the value and safety of low-dose clonidine versus placebo and low-dose acetyl-salicylic acid (ASA) versus placebo in high-risk individuals undergoing non-cardiac surgery.

The pilot study HIP ATTACK (HIP fracture Accelerated surgical Treatment And Care track), investigates the prevention of complications after a hip fracture. Associated with old age, hip fracture incidents are expected to rise as Canada's aging population increases. Incredibly high mortality rates have remained unchanged for over a decade—9% of men and 6% of women die within 30 days of hip fracture surgery. HIP ATTACK is different from all previous hip fracture studies with the fundamentally novel approach of treating hip 'attacks' like acute heart

attacks or acute strokes. As such, a patient diagnosed with a hip fracture receives accelerated medical clearance and access to OR within six hours—versus the current average Canadian wait time of 42–44 hours. Urgent treatment of hip fractures may result in fewer complications, shorter recovery and rehab time, improved outcomes and less burden on the healthcare system. This paradigm shift in how to treat patients with hip fractures may radically change treatment and our understanding of complications around surgery.

Management

How to treat people who have heart attacks after surgery is a question that has never been investigated in a trial. About 10 million adults suffer a post-surgery heart attack each year. MANAGE (Management of myocardial injury After NonCardiac surGery), a 3,200-patient randomized control trial, will evaluate two interventions: the blood thinner dabigatran vs. placebo; and a proton-pump inhibitor omeprazole vs. placebo. Results could potentially identify treatments which could save countless lives.

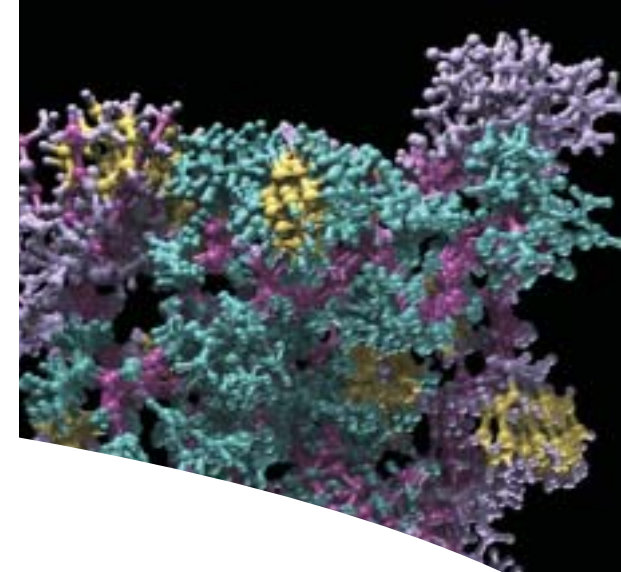
IMPROVING OUTCOMES IN DIABETES

We can reverse the diabetes epidemic and reduce its serious health consequences.

This is directly relevant to millions of affected people worldwide.

”

Dr. Hertzell Gerstein



About 350 million people worldwide have diabetes; of those more than 80% live in low- and middle-income countries.

According to the World Health Organization (WHO), these staggering numbers are only going to get worse, with diabetes deaths expected to double between 2005 and 2030. Low- and middle-income countries, with their double burden of increasing diabetes prevalence and limited resources for intervention, will be the hardest hit.

Diabetes has been a focus of research at PHRI for 20 years. The Diabetes/Dysglycemia Program's primary focus on the prevention of diabetes and its consequences are supported by several themes of study: identification and testing of novel pharmacologic approaches; exploring the effect of these interventions on the incidence of cardiovascular outcomes, renal disease, dementia, fractures, erectile dysfunction, cancers and other long-term complications; identifying novel risk factors for diabetes; and assessing strategies to promote diabetes remission.

The most recent example is the international clinical trial ORIGIN (Outcome Reduction with Initial Glargine Intervention), which demonstrated that the early introduction of long-acting basal insulin glargine maintained excellent glycemic control, slowed progression from prediabetes to diabetes and had a neutral effect on cardiovascular and other serious health outcomes. The trial also revealed that omega-3 fatty acid supplements had no effect on

cardiovascular or other serious health outcomes in people with prediabetes and early diabetes during the six-year observation. A prospective observational follow-up study, ORIGINALE (ORIGIN And Legacy Effects), will continue to collect data for two additional years to provide insight regarding longer-term effects of these therapies.

PHRI's large epidemiologic studies, such as FAMILY, PURE and VISION, continue to identify novel risk factors for incident diabetes and the consequences of dysglycemia. These factors include environmental, genetic and risk factors identified in the blood that may suggest promising new approaches. To date, obesity and specifically abdominal obesity, ectopic fat deposition, inactivity, dietary factors and non-European ethnicity have clearly been established as important risk factors for diabetes in PHRI studies in both rural and urban environments.

Existing evidence suggests that early diabetes can be “reversed” through metabolic interventions or surgery—a concept being explicitly tested in the REMIT (Remission Evaluation of Metabolic Interventions in Type 2 diabetes) pilot study using intensive lifestyle therapy and short-term combination drug therapy. Whether surgery can halt or reverse diabetes is also being studied in a large Bariatric Registry, which is established across Ontario.

SERVING THE NEGLECTED

“
Little research has been done into heart disease caused by infections — perhaps because they occur largely among the poor.

”
Dr. Salim Yusuf



PHRI is committing resources, researchers and expertise to tackle some of the world's most serious heart diseases of the poor through its broad global network.

Neglected diseases, common in low-income populations or those in developing countries, are often overlooked by Western nations. PHRI's commitment to heart diseases of the poor involves studying the causes of common diseases in low-income countries, assessing barriers to care in resource-poor settings, evaluating interventions that have the potential to help millions of individuals worldwide, as well as training individuals and assisting in developing capacity for clinical trials.

Chagas Disease

Once confined to Latin America, Chagas disease is now spreading to other parts of the world. A potentially life-threatening illness caused by the parasite *Trypanosoma cruzi* (*T. cruzi*) and transmitted via bite of an infected triatomine bug, Chagas disease thrives in the poor housing conditions of rural areas of Latin America, where 8 million people are estimated to be infected and an additional 25 million are thought to be at risk of contracting the infection. Through migration the disease is showing up on other continents—with an estimated 300,000 cases in the US and 90,000 in Spain. The heart is the most affected organ in individuals with chronic Chagas disease, where cardiomyopathy is progressive with high rates of mortality due to heart failure and sudden cardiac arrest.

Funded by the Canadian Institutes of Health Research and the World Health Organization, the landmark trial, BENEFIT (BENZnidazole Evaluation For Interrupting Trypanosomiasis) is the largest study of Chagas disease ever conducted. With 50 centres and nearly 3,000 individuals from six countries in South America, BENEFIT sets out to define the impact of treating the parasite with a drug (benznidazole) in the early stage of cardiomyopathy, which could arrest the progression of the disease by eliminating the parasite, thereby improving outcomes. One of BENEFIT's earliest contributions was the development of a PCR technique to better detect the parasite. Another significant discovery is the vast differences in parasite loads between countries. By taking into account the three known types of *T. cruzi* parasite, the study will now explore whether there is a relationship between parasite types, different levels of parasite loads (which vary across countries) and disease progression. BENEFIT's early successes have generated interest from the pharmaceutical industry, which has recently developed new drugs for this condition. Spin-off studies, such as Stop-Chagas, which tests new medications and combinations of medications, are shifting Chagas disease to a not-so-neglected disease.

SERVING THE NEGLECTED

“
PHRI is playing a crucial role in extending research to chronic diseases of the bottom billion —
the poorest billion who live on less than \$1 a day. They are neglected... It is a very important part of the work of PHRI which most institutions in rich countries do not do.”

Dr. Bongani Mayosi,
PHRI International Scholar,
University of Cape Town

Rheumatic Heart Disease

The second leading cause of heart disease in sub-Saharan Africa after hypertension is rheumatic heart disease. A condition which knows no age barriers, rheumatic heart disease affects those as young as five years of age and as old as 90; yet, it is entirely preventable. In some individuals, untreated and recurring episodes of streptococcus infection of the throat leads to rheumatic fever, which leads to heart valve damage (rheumatic heart disease). Treating strep throat with penicillin should easily prevent rheumatic heart disease. Although this seems simple, low-income countries face huge barriers in implementing even the most basic surveillance and intervention programs.

Enter the study called the Rheumatic Heart Disease Registry, or REMEDY, which sets out to monitor the burden of rheumatic heart disease and to assess why regular penicillin injections to prevent subsequent attacks of strep throat are not widely used. By systematically identifying and following patients, healthcare workers can monitor them to ensure penicillin intervention is adhered to. REMEDY has already made a significant impact on health policy in South Africa, where researchers have convinced the department of health to make rheumatic heart disease a reportable condition. It is hoped other countries will soon follow suit. With centres in India, Yemen and multiple centres in Africa, REMEDY is already the largest registry of rheumatic heart disease in the world. The aim is to increase REMEDY's reach from the current 3,000 people to more than 10,000 people.

Tuberculosis Pericarditis

In Zulu, the word *impi* means warriors. It is therefore no coincidence that an innovative study that goes places where no one has been in terms of conducting clinical trials is aptly named IMPI —Investigation of Management of Pericarditis. One out of ten patients with heart failure in Africa is diagnosed with tuberculosis of the heart. Despite the relatively young age of these individuals (average of 35 years), about 40% of individuals die within six months in spite of treatment with anti-TB drugs. Can we mitigate this risk? The IMPI study is testing two promising interventions: steroids and an immune-strengthening vaccine (Mw bacterium), if found to be effective, either or both can easily and affordably be incorporated into policy and practice. Participating countries include South Africa, Kenya, Mozambique, Nigeria, Sierra Leone, Uganda, Malawi and Zimbabwe.

BRINGING CANADA TOGETHER

“
If **Canadian researchers
work together**, they can make
enormous strides, well beyond
that of a single researcher.
”

Dr. John Cairns,
Co-Chair CANNeCTIN Steering Committee,
University of British Columbia



Putting Canadian researchers on the world map.

CANNeCTIN (CANadian NETwork and Centre for Trials INternationally) is a national network funded by the Canadian Institutes for Health Research (CIHR) and the Canada Foundation for Innovation (CFI) Clinical Research Initiative program to improve the prevention and treatment of cardiac and vascular diseases and diabetes. One of the main goals of the network is to promote Canadian investigators and institutions to work together to address major health challenges and translate discoveries into practice.

CANNeCTIN brings together the best Canadian scientists and clinicians from 20 universities across Canada to work collaboratively on major studies that would be impossible for a single centre to conduct on its own. Investigators with expertise in cardiology, diabetes, obesity, cardiac surgery, anaesthesia, internal medicine, epidemiology, genetics and biostatistics are working together to address some of the most important health issues that occur in Canada and other countries.



CLOSING THE GAP

“
We need to understand barriers to optimal cardiovascular care at the level of the patient, provider and health system, and **find ways to overcome such barriers.**”

”
Dr. Robby Nieuwlaat

“
Each year billions of dollars are invested in developing new drugs and technologies; **yet surprisingly little is spent ensuring the adequate delivery of proven treatments** to patients.”

”
Dr. J-D Schwalm (right)

Future improvements in health care will depend more on incorporating current knowledge into efficient delivery systems for prevention and care, than on new scientific discoveries. – Dr. Salim Yusuf

Proving something works in a research study is not enough. We need to ensure that these interventions are used in practice. In fact, the majority of premature cardiovascular disease could be prevented if existing knowledge was applied and implemented more fully. Unfortunately, extensive gaps exist between knowledge gained in research and what is actually done in practice (knowledge-practice gaps). *Knowledge translation* (KT), also called Implementation Science, aims to close the knowledge-practice gaps and move knowledge into action.

Knowledge translation research forms the scientific basis for how to achieve this, by addressing the following questions: Which knowledge-practice gaps are most substantial? What are the main causes of these gaps, and are they modifiable? How can we close these gaps?

PHRI's Implementation Science team is dedicated to answering these questions internationally in collaboration with health-system experts, clinical specialists, community practitioners, behavioural psychologists, statisticians and IT specialists.

HOPE-4 study (Hypertension Outcomes Prevention and Evaluation) will develop, implement and evaluate an equity-focused, evidence-based, cost-effective and contextually appropriate program for cardiovascular disease risk assessment, treatment and control, with a focus on hypertension and secondary prevention. The ultimate aim of HOPE-4 is to integrate this program into many health systems, by tailoring it to the local context and by using available resources, health workers, and low-cost combination therapy.

PHRI is conducting multiple studies to test specific KT intervention strategies that provide clinical decision support to healthcare providers and engage patients with self-care. The RELY-ABLE study, with 6,000 atrial fibrillation patients from 550 clinical centres, is testing whether computer-automated feedback to patients and their physicians regarding the observed quality of comprehensive cardiovascular care can improve patient outcomes. The DERLA-STEMI study is assessing 800 patients who received medication prescriptions following a hospitalization for a myocardial infarction to determine if repeated educational messages and treatment reminders will improve long-term adherence to medications. PHRI-designed Patient Decision Aids educate patients on an important health decision to help them make the best possible choice. One PHRI study showed that the Patient Decision Aid improved patient knowledge of the differences in risks and benefits of two methods to undergo an invasive cardiac procedure, and improved patient satisfaction with the choice made. Further, the development of a simple and cost-effective clinical decision support tool to help physicians better manage the blood thinner warfarin has been shown safe and effective in several observational and experimental studies. PHRI is dedicated to make such a tool widely available to healthcare practitioners the world over.

NUMBERS TELL THE STORY



“Large gains in trial efficiencies can be made through the use of **innovative study designs and thoughtful statistical analysis.**”

Dr. Janice Pogue

Researchers ask questions. In a most general sense, it could be said that without statistics, there would be no answers.

Statistics transforms data into numbers, numbers into patterns and patterns tell a coherent story. Simply put, statistics finds meaning in data and brings the researcher one step closer to finding the answer. In fact, statistics often offers the researcher much more insight than originally anticipated.

Evidence with Confidence

PHRI's Statistics Program is an integral part of research initiatives, supporting researchers in their mission of building an evidence-based approach to medical practice. A team of dedicated, highly skilled statisticians and epidemiologists work alongside the principal investigator and the project management team from the earliest stages of an epidemiological or experimental study, until the final stage.

As experts in clinical trials methodology, meta-analysis, and multivariate methods, the Statistics team analyzes the compiled data to make their meaning clear, and conclusions are drawn to help better understand population health and enhance medical care.

In addition to working jointly with researchers on all studies, PHRI statisticians are involved in their own research initiatives. One such initiative is a series of studies investigating efficient trial methodology, or “to study the study methodology.” Examining the vast collection of data from past PHRI studies, these studies examine which areas of the scientific method can be enhanced by further research.

BIOBANKING FOR THE FUTURE

“ Many biomarkers for cardiovascular disease and for diabetes have been identified during the past decade. **Samples stored from well-designed and well-conducted studies are the most efficient and effective way to identify the real clinical value** of these biomarkers. ”

Dr. Matthew McQueen

Matthew J. McQueen, M.D.
Laboratory Medicine

2.5 million samples—and growing...

That PHRI's studies are unique in size and scope is undeniable. Very few organizations in the world can design and conduct an international study of 150,000 people. In addition to massive quantities of electronic data, these studies also collect large numbers of biological samples. The logistics of collecting, organizing, storing and transporting thousands of samples across international borders is an enormous undertaking. Once received, the samples must be catalogued and stored for future analyses.

One of PHRI's oldest core units and collaborators is the Clinical Research Clinical Trials Laboratory (CRCTL). Much like the PHRI, the CRCTL started at the Hamilton General Hospital some twenty years ago and grew to become a world-class facility.

A growing demand for lab support for PHRI's large multi-national studies, such as INTERHEART and HOPE, led to significant CRCTL expansions in the early 1990s. The Biobank was established to provide high-quality storage facilities for the many biological samples being collected. Presently there are more than 2.5 million samples stored in nitrogen vapour at -160 to -190°C. The Biobank has recently undergone further expansion and now has the capacity to accommodate 100 large storage tanks, each holding approximately 80,000 vials. PHRI-collected samples in the Biobank are linked to relevant clinical information and enable investigation of novel questions relating to diabetes, obesity, cardiovascular disease, hypertension, stroke, kidney disease, fractures and cancer.

Current collaborations include: a European Union funded consortium, SysKid, which examines the role of genetics in the development of chronic kidney disease in individuals with diabetes from the ONTARGET/TRANSCEND studies; the interaction of the environment and lipid levels in the PURE study; markers for acute myocardial infarction, stroke and kidney disease during surgery, bioVISION; and the clinical significance of Lp(a) in the INTERHEART study using insights provided through genetic and biochemical investigations.

The laboratory has extensive expertise in the shipping (utilizing unique vapour shippers), receiving, storage, and analysis of very large numbers of samples from more than 60 countries. Laboratory investigations have been funded by peer-reviewed grants from Canada, the US, the European Community, as well as pharmaceutical and diagnostics industries. Based on the experience from these large studies the laboratory was asked to provide biological sample storage and other support for the CHILD (Canadian Healthy Infant Longitudinal Development) study, which is a collaboration of pediatric hospitals across Canada.

GATHERING DATA ACROSS NEW FRONTIERS

“
A simple, stable and secure
environment—**delivering
innovative, effective and
efficient data solutions.**
”

Andrew Renner

Receive. Access. Share. Store. Retrieve.
Transmit. Repeat. Or, in the case of the PHRI,
repeat countless times, across international
borders and time zones.

On any given day, up to 14,000 users communicate and manage data relying on a seamlessly-integrated workflow system that is an essential part of all PHRI day-to-day research activity—24/7, 365 days a year.

PHRI's Information and Communication Technologies (ICT) department provides the infrastructure, operational support, business solutions and data management systems required for its rapidly evolving research and administrative activities. The research conducted at PHRI typically involves several hundred collaborating sites from over 80 countries around the world. While each country presents its own unique challenges, the ICT team is responsible for the development, deployment and ongoing maintenance of the systems that are at the heart of the clinical data and trial operations.

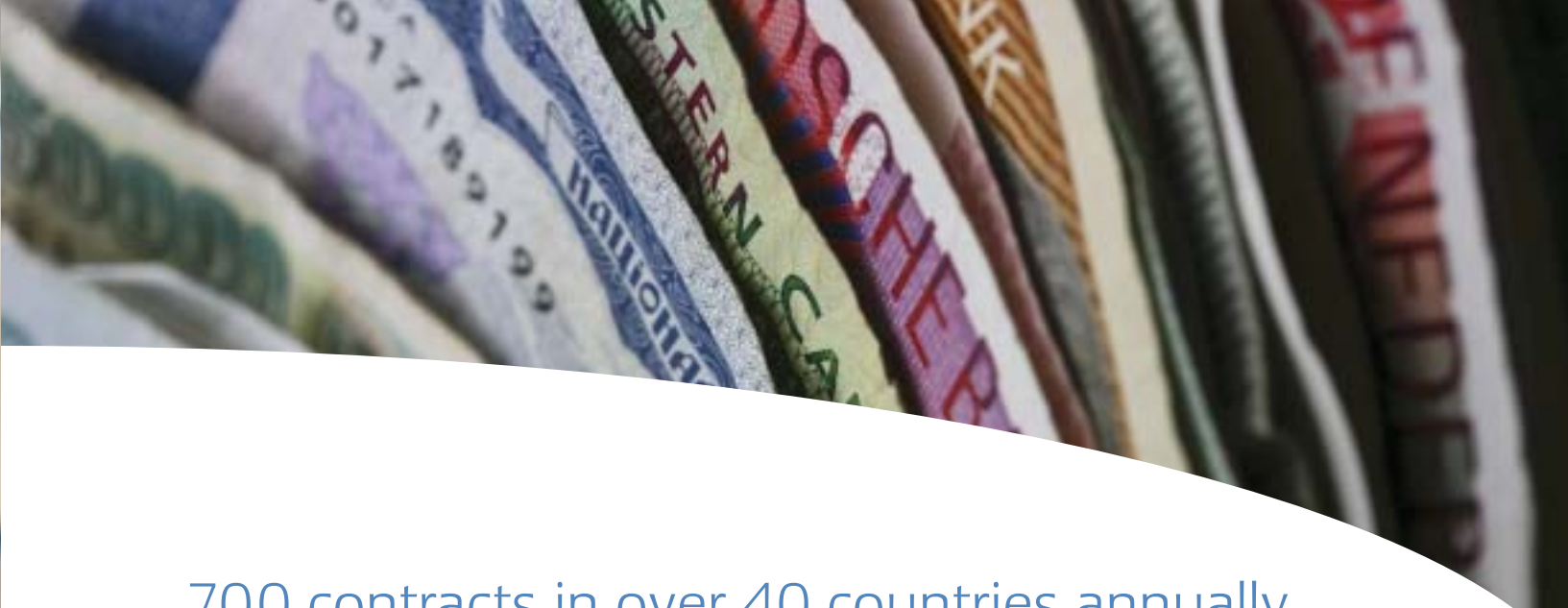
Whether in Seoul or São Paulo, Tokyo or Toronto, each site has the capacity to manage trial workflows (enrolment, randomization, resupply of drugs, trial supply logistics, etc.) through a variety of systems and solutions including IVR (Integrated Voice Response), IWR (Integrated Web Response), EDC (Electronic Data Capture), online\offline applications, mobile applications and traditional fax technology.

A strong team of experienced and dedicated technology professionals uphold ICT's core goal: to provide a simple, stable and secure infrastructure. To this end, ICT has partnered with leading technical vendors to build an impressive host of services, including storage, servers, networking, communications and data centre facilities. This state-of-the-art data centre is a secure concrete-enclosed room designed with redundancy at all levels, and features two disparate power and internet feeds, steel fireproof doors, FM 200 fire suppression, 24/7 environmental monitoring and video surveillance.

Continually raising the bar with innovative, effective and efficient solutions to increasingly complex problems, the ICT team is an integral part of the success of PHRI trials.



ACCOUNTABILITY AND FISCAL RESPONSIBILITY



700 contracts in over 40 countries annually...

Clear agreements and careful financial management are key to ensuring that global studies involving hundreds of sites are kept on track, the Finance and Contracts team is responsible for all of these in PHRI studies. The intricate process of initiating a study, especially one with international sites across the globe, requires in-depth knowledge to navigate the complex maze of international policies, sensitivities and national regulations. The Contracts team is responsible for preparing and executing contracts with the funding sources, as well as with all study sites, national leader offices, study committee members and subcontractors. Considering the enormous responsibility undertaken in studies, some of which may involve tens of thousands of participants, it is no surprise that contracts are in place before key activities are initiated. Respecting the needs of all stakeholders, the team must skilfully and rapidly negotiate contracts to meet project requirements and secure PHRI's essential requisite to retain scientific independence.

On average, the team executes about 700 contracts annually, in over 40 countries in many different languages. Every quarter, the team issues over 2,500 payments to over 72 countries in multiple currencies. The Finance and Contracts team is also responsible for generating timely financial reports, internal management reports, as well as external reports to funders and auditors.

High levels of activity, diversified needs of projects, funders, collaborators and countries, and ongoing changes to regulations, combine to provide an ever-changing and challenging environment which PHRI's Finance and Contracts team embraces and meets with vigour.



Having superb research support allows scientists to focus on what they do best —science.

THE TEAM



Individual commitment + group effort = team achievement = scientific discoveries = improved health.

PHRI's many successes are the result of the combined efforts of its 250 dedicated and highly skilled experts. PHRI's team embraces the challenges and demands of large-scale international research. Whether involved directly in research, its administration or a related support function, everyone at PHRI contributes to the vision and achievement of the goals of the Institute.

Research Study Teams

Project managers, research coordinators and research assistants coordinate the operations related to PHRI studies by assisting in the protocol preparation, submission for funding, ethics and regulatory approval. In addition, study teams assist in the training of the participating investigative sites in relevant study-related tasks and ensure that all appropriate regulations are followed. The research teams are the hub for all support activities.

Diagnostic Specimen Unit

The primary responsibility of the Diagnostic Specimen Unit (DSU) is the management of specimens. This entails the assembly and shipping of up to 10,000 diagnostic specimen collection

kits every month; tracking and monitoring of specimen shipments from sites in 50 countries; and management of an international fleet of about 100 dry shippers—each of which is capable of transporting 600 vials of specimen in nitrogen vapour at -150°C or colder.

Quality Assurance

With the element of quality, comes the confidence in what we have. The Quality Assurance Department provides support to all studies to achieve quality research. The program is comprised of three main components: the development and management of Standard Operating Procedures, an Audit Program and Continuous Quality Improvement efforts.

Administration

PHRI's team of administrators support the daily operations keeping the entire organization on track and moving forward. This includes infrastructure for facilities, human resources, strategic planning, and reporting.



Collaborations and Partnerships

Over the past twenty years, PHRI has built solid relationships with many of the world's leading health organizations from the public, academic and private sectors. PHRI has the expertise and flexibility to collaborate on comprehensive research projects for the unique needs of each sector. This ability to adapt, while maintaining the utmost level of academic research integrity, has led to long-standing relationships with the organizations listed below.

Companies, Government and other Agencies who have funded PHRI in the last 5 years

- Abbott Laboratories
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Boston Scientific
- Bristol-Myers Squibb
- Cadila
- Canada Foundation for Innovation (CFI)
- Canadian Diabetes Association
- Canadian Institutes of Health Research
- Canadian Stroke Network
- Eli Lilly
- The European Commission
- GlaxoSmithKline
- Heart and Stroke Foundation of Canada
- Heart and Stroke Foundation of Ontario
- Johnson & Johnson
- Medtronic
- Merck
- Ministry of Economic Development and Innovation (Ontario)
- National Institutes of Health
- Novartis
- Novo Nordisk
- Octapharma Canada Inc.
- Ontario Ministry of Health and Long-Term Care
- Pacesetter Inc.
- Pfizer
- Portola
- Public Health Agency of Canada
- Roche
- Sanofi-Aventis
- Servier
- St. Jude Medical
- Toyota Tsusho America Inc.
- United Health Group
- Wellcome Trust

PHRI International Scholar and International Fellow Awards

PHRI International Fellows

Previously trained at PHRI, these are highly productive independent researchers who continue to do collaborative work with PHRI and hold a faculty position at an international institution.

- Alvaro Avezum - *Dante Pazzanese Institute of Cardiology, Brazil*
- Clara Chow - *George Institute, Australia*
- Abhi Goyal - *Vanderbilt University, USA*
- Ganesan Karthikeyan - *All India Institute of Medical Science, India*
- Martin O'Donnell - *NUI Galway, Ireland*
- Prem Pais - *St. John's Research Institute, India*
- Dorairaj Prabhakaran - *Public Health Foundation of India, India*
- Denis Xavier - *St. John's Research Institute, India*

PHRI International Scholars

These highly productive and successful researchers are of international renown and are longstanding collaborators of PHRI. They hold a faculty position at an international institution.

- Colin Baigent - *University of Oxford, United Kingdom*
- Rafael Diaz - *Instituto Cardiovascular Buenos Aires, Argentina*
- Maria Grazia Franzosi - *Mario Negri Institute, Italy*
- Bernard Keavney - *Newcastle University, United Kingdom*
- Scott Lear - *Simon Fraser University, Canada*
- Johannes Mann - *Ludwig Maximilians University of Munich, Germany*
- Bongani Mayosi - *University of Cape Town, South Africa*
- Martin McKee - *London School of Hygiene and Tropical Medicine, United Kingdom*
- Srinath Reddy - *Public Health Foundation of India, India*
- Dan Sessler - *Cleveland Clinic, USA*
- Karen Sliwa - *University of Cape Town, South Africa*

For a complete list of studies and published papers,
please visit www.phri.ca

Acute Coronary
Syndrome

- COMPLETE (CANNeCTIN)
- CREATE (OASIS-3)
- CURE (OASIS-4)
- CURRENT (OASIS-7)
- FUTURA (OASIS-8)
- MICHELANGELO (OASIS-5)
- MICHELANGELO (OASIS-6)
- RADIATION PROTECT
- RIVAL (CANNeCTIN)
- TIMACS
- TOTAL (CANNeCTIN)
- VELETI II (CANNeCTIN)

Arrhythmia

- ACTIVE A
- ACTIVE I
- ACTIVE W
- ASSERT (I, II and III)
- AVERROES
- CEASE-VT
- I-PACE
- PADIT (CANNeCTIN)
- PALLAS
- RAAFT
- RE-LY
- RELY-Able
- RELY-AF Registry
- SIMPLE

Diabetes

- DREAM
- ORIGIN
- ORIGINALE
- REWIND

Global Health

- DISCOVER
- FAMILY
- HOPE-4 (CANNeCTIN)
- INTER-CHF Registry
- INTERHEART
- INTERSTROKE
- PURE
- REMEDY
- RICH LEGACY (CANNeCTIN)
- SAHARA (CANNeCTIN)
- START

Knowledge
Translation

- DERLA STEMI
- HOPE-4, KT (CANNeCTIN)
- KT-INR (CANNeCTIN)
- PURE, KT
- RELY-ABLE, KT
- SMART AMI
- Vascular Access Decision Aid

Neglected Diseases

- BAV (CANNeCTIN)
- BENEFIT
- IMPI (CANNeCTIN)
- REMEDY (CANNeCTIN)
- STOP CHAGAS

Perioperative

- CORONARY (CANNeCTIN)
- HIP ATTACK
- LAAOS (I, II, III) (CANNeCTIN)
- MANAGE
- POISE I
- POISE II (CANNeCTIN)
- PRACTICE
- REMOTE IMPACT (CANNeCTIN)
- SIRS (CANNeCTIN)
- SUPERIOR (CANNeCTIN)
- VISION (CANNeCTIN)
- VISION Cardiac Surgery (CANNeCTIN)

Prevention

- APOLLO
- Bariatric Registry (CANNeCTIN)
- CANPWR (CANNeCTIN)
- COMPASS
- FLUID
- HOPE
- HOPE-3
- ONTARGET/TRANSCEND
- PHASE (CANNeCTIN)
- TIPS (1, 2, 3) (CANNeCTIN)



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