VICTORIA HEART INSTITUTE FOUNDATION

Victoria Heart Institute Foundation Cardiovascular Research

Volume 1, Issue 1 December 2012

Protect Arms Study (VHIF)

Dr. Imad Nadra, Principal Investigator

Gaining access to the heart through the radial artery in the arm has been the vascular access route of choice for almost 15 years in Victoria. This technique requires more skill, expertise and training than the conventional method of gaining access through the femoral artery at the top of the leg. However, because of recognized advantages of immediate patient ambulation and fewer vascular bleeding and ischaemic complications, it is now becoming the default access route by cardiologists around the world.

One limitation of this procedure however, is the potential occlusion (blockage) of the radial artery as a result of the procedure. Radial occlusion is rarely associated with any clinical problems, but does limit the choice and improved safety outcomes of future transradial access for the patient. At the end of the procedure when all the equipment is removed from the radial artery, applying an external pressure band to compress the artery stops the bleeding. The question of why patients lose the radial artery as a result of the procedure has recently been raised but remains poorly understood and under investigated.

"The question of why patients lose the radial artery as a result of the procedure has recently been raised but remains poorly understood and under investigated."

One hypothesis is that over compression of the radial artery following the procedure, which is intended to stop the bleeding, may lead to blood stagnating in the artery and subsequently clotting and blocking the vessel. Early data has shown that newer haemostasis methods such as 'patent haemostasis' i.e. applying just

Continued on page 2

Inside this issue:

enough pressure to stop bleeding but still maintaining the flow i.e. patency, of blood flow in the radial artery may significantly reduce the risk of radial occlusion, which may be as high as 12% in some patients. It is not known however if the type of device used or if early removal of the device can improve radial artery patency long term, out to 30 days. For this reason, we aimed to compare the effectiveness of one of the market leader bands known as the TR-band versus a newer extrinsic compression band known as the Bengal band.

This study known as the Preventing Radial Occlusion Through Effective Closure Therapy and Advanced Radial Management Study (PROTECT ARMS) is a large single centre randomized controlled clinical trial, comparing the 2 bands plus the use of the TR band using either standard compression of the artery either with a defined amount of air inflation or matching the pressure of the cuff to the patients own blood pressure. This study has been set up through the Victoria Heart Institute Foundation and has now been running since December 2010 and is near the end of completion. The study is unique in many ways but mostly in view of it needing a multidisciplinary team involving the investigators, doctors, research nurses, clinical cardiology nurses and most importantly the patient!

"We envisage that this study will not only give us more insight as to how we can better protect our patients but also help to set a standard of care across the world for patients undergoing a trans-radial vascular procedure."

Thus far, we have enrolled nearly 730 patients from across Vancouver Island and it is hoped that once the results are established, the outcome will be published in a major scientific/medical journal. We envisage that this study will not only give us more insight as to how we can better protect our patients but also help to set a standard of care across the world for patients undergoing a trans-radial vascular procedure. So stay tuned!

Aim Radial Conference

Debbie Richdale, Clinical Nurse Leader, Cardiac Short Stay, VIHA South Island

I had the pleasure of attending the Aim Radial Conference in Quebec City Sept 13-15th which was attended by international physicians with the focus of radial access for diagnostic and interventional procedures. The conference consisted of a variety of live interventional cases: carotid stenting, rotoblator, chronic total occlusions and bifurcation stenting done via radial access. Physicians spoke of their experiences with the evolution of radial site access for procedures and patients' recovery post.

Physicians discussed how their colleagues and centres have embraced the radial concept development. On average radial access rates in Canada, Europe and Japan are 75-90%. USA radial access rate is still only 40-50%.

Techniques to prevent radial artery occlusion, radial thrombus extraction, ulnar access, same day discharge and chair recovery were also discussed.

Many thanks to the Victoria Heart Institute for the opportunity for me to attend this conference. I am truly thankful.

Dr. W. Peter Klinke

Over the last 35 years, I have had the privilege to be involved in most of the major advancements in the diagnosis and treatment of adult heart diseases. My career started just as the use of coronary angiography and echocardiography became commonly available to augment the ECG, CXR and cardiac physical exam, as a means to identify and elaborate the anatomy and function of the heart. At the same time, our knowledge of physiology and biochemical processes involved in heart failure and coronary disease was rapidly expanding.

My first exposure to the use of a randomized trial to answer a clinical question was the NIH trial of medical vs surgery treatment for unstable angina. This was in the last year of my fellowship at the University of Florida, under Drs. Dick Conti and Carl Pepine—the 2 most influential mentors in my career.

My first job was CCU director at the Royal Alexandra Hospital in Edmonton in 1977, having only diuretics, morphine, digoxin and nitro as available drugs.

My first large multinational trial in MI was the MIAMI trial , investigating the benefit of I.V. followed by oral metoprolol. My research nurse, Linda Kvill, and I randomized the most patients in Canada. 106 patients in one year, all STEMI patients and we were the only Canadian site to do the hemodynamic sub study with Swan-Ganz catheterization in a select number of patients.This was rapidly followed by the Metoprolol in dilated cardiomyopathy trial, of which we were the only Canadian site. This was the first study to show the benefit of beta blockade in heart failure.

The pace of new drug development based on pharmacology and physiology was fantastic in those early days. The in hospital mortality for MI was so high that any benefits of intervention were easy to find—no soft endpoints or combined outcomes were needed. With the invaluable help of Linda, we completed over 60 clinical trials before I moved to Victoria in 1993 and joined up with VHIF to continue clinical research.

At that time, VHIF consisted of one employee and had only participated in a handful of trials . As they say—the rest is history.

VHIF has become a major clinical trial center noted for its excellence in phase 2 and 3 trials. To date, we have participated in over 120 trials and employ 6 full time nurses, 2 part time nurses, 3 office/regulatory staff and Noreen as our office manager.

We have enrolled over 6000 patients into clinical trials. VHIF is often a top enroller in trials and has received a number of achievement awards and recognition for the quality of our work. Additionally Vic Heart has supported 37 cardiology fellows to train in the radial procedure and 18 summer students.

We are an independent self-supporting non profit organization and would not have achieved our current success, let alone exist without the support of many individuals.

Firstly we have to thank all the cardiologists and cardiac surgeons in the Department of Cardiac Services for their continuing support and participation in clinical research. We are also dependent on

Continued on page 4

the cooperation and hard work (often underappreciated) of the hospital staff nurses and technicians and the hospital ethics board.

Next, the staff at VHIF, both nurses and office staff, deserves special recognition for their very professional and personal management of study patients. In fact, many patients have such a good experience, that they volunteer to be considered for any and all trials.

Our staff have great luck to have one of the most accomplished office managers in the country. Noreen's invaluable guidance, persistence, and encouragement to out perform on every trial has allowed us to thrive and prosper. We have truly become a family. This will be the part I will truly miss.

Our Board of Directors have all volunteered to stay on as we enter a new phase. Most of the directors were elected way back in 1988, when Dr. John Morch, and Dr. Dick Brownlee, took the first steps to establish VHIF as a non profit organization.

Finally, I would like to introduce Dr. Anthony Della Siega, our new Director of Research and Drs. Simon Robinson and Imad Nadra, our new Co Directors. They will take over the day to day medical management at Vic Heart. Dr. Robinson and Dr. Nadra are former Vic Heart fellows and have the enthusiastic support of all staff.

I will certainly miss participating in trials. However, I realize that VHIF can thrive and grow, only if we give our younger colleagues the chance, and the responsibility to have the excitement and satisfaction of being at the leading edge of new science and discoveries in cardiovascular diseases.

Meet the Staff of VHIF:

Our New Director

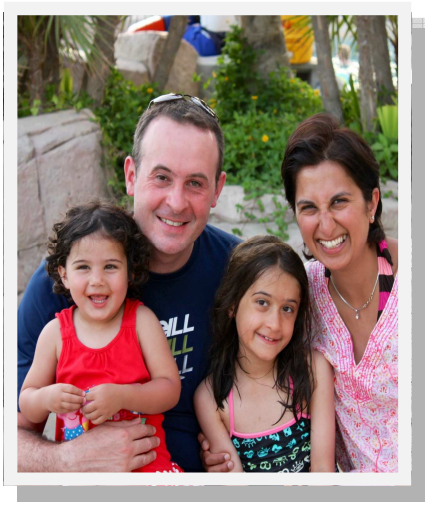
Dr. Anthony J. Della Siega received his MD from the University of British Columbia in 1994. Following completion of Internal Medicine and Cardiology residencies at U.B.C., he received certification by the Royal College of Physicians and Surgeons of Canada. He went on to complete an Interventional Cardiology Fellowship through the University of Toronto at Sunnybrook Hospital.

Dr. Della Siega is a staff Interventional Cardiologist and Director of the Cardiac Catheterization Laboratory and of the Interventional Fellowship program at the Royal Jubilee Hospital in Victoria, B.C. He is a board member and active participant in clinical research with the Victoria Heart Institute Foundation in both primary and co-investigator capacities. The group is extremely active with large-scale clinical trials as well as locally generated national and international trials. He currently serves as a Co-Director for the CAIC-CCS Interventional Cardiology Fellows Symposium and is an Executive Committee member of the Canadian Association of Interventional Cardiology.

Dr. Anthony Della Siega

He is otherwise dedicated to family. He is an active hockey player and coach and serves as a board member of the Victoria Racquet Club Minor Hockey Association.

Our Co-Directors



Dr. Imad Nadra

Dr. Nadra was brought up in North Wales in the United Kingdom where he did most of his schooling before attending medical school. It was at an early age of about 13 when he remembered that he wanted to become a doctor mostly inspired but his father who was an old style family physician that was utterly dedicated to look after the health needs of the local people irrespective of the time of day and whether he was on duty or not. Imad attended Medical school at Edinburgh University in Scotland where for 6 years he read medicine and surgery along with all it's related disciplines but also took a year out to study for a bachelors of science in Immunology. Post graduation he studied and practiced internal medicine for 3 years and then cardiology for 11 years in several of the most prestigious institutions the UK. These included Edinburgh Royal Infirmary, Queens Medical Centre University Hospital Nottingham and then within London at the Royal Brompton National Heart and Lung Hospital, Hammersmith Hospital, and finally Guys and St.Thomas' Hospital.

During his time in London he was fortunate enough to have been awarded a British Heart Foundation Clinical Research Fellowship which allowed him to focus more closely on his own research interests in vascular immunology by looking at the role of inflammation in the development in atherosclerosis. From his time in research Imad was not only awarded a Doctor of Philosophy (PhD) by Imperial College School of Medicine, Science and Technology but also it consolidated his research skills before sub specializing in percutaneous coronary intervention.

Over his last 4 years of training in London he sub specialized in percutaneous coronary and structural intervention having been trained to a high level but during which he was also given the opportunity to come to Victoria for a year on an international fellowship.

During this time Imad became a high volume operator carrying out his interventions almost exclusively via the radial artery access route. On completion of his training and on obtaining his certificate for completion of higher speciality training Imad had taken a consultant position at the Trent Cardiac Centre, Nottingham University Hospitals where he had been practicing interventional and general cardiology for the last year and a half. However, having been given the opportunity to return to Victoria with his family he took it with glee and is looking forward to the challenges of setting up practice and promoting and further developing clinical research.

Through all his time training and working it has become increasingly difficult to sustain interests outside of medicine, but if not spending time with his wife and 2 young daughters and given half the chance you would find him out on the golf course, cycling or sailing.

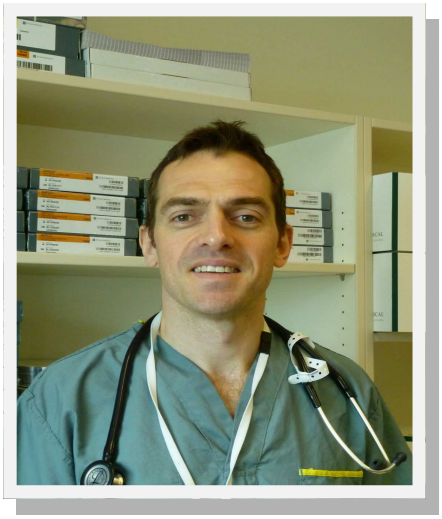
Dr. Simon Robinson took up his post as interventional cardiologist in May 2010 . He completed his medical school and residency training in Edinburgh, Scotland. After this he spent 2½ years as a British Heart Foundation research fellow studying the effects of inflammation, cigarette smoking and air pollution on vascular function and coagulation systems in patients with coronary heart disease. He was awarded a research doctorate in 2007 by Edinburgh University and he has co-authored more than 20 original scientific papers to date.

He moved to the North East of England in 2004 for advanced training in internal medicine and cardiology before sub-specializing in interventional cardiology. This training period included one year as a fellow at the Royal Jubilee Hospital Victoria from 2007-08 following which he returned to the UK to work in one of the UK's largest cardiology hospital centers.

His fellowship time spent in Victoria made a great impression on him and his wife prompting him to proudly accept a job offer to return as one of the staff cardiologists in 2010.

His clinical specialty is in percutaneous coronary intervention (PCI) and as part of the Vancouver Island Transcatheter Valve program he hopes to help bring new treatment options for patients with severe valve disease who might not be suitable for open heart surgery. His research experience highlights his desire to help support the work of the Victoria Heart Institute Foundation. He believes that participation in clinical research is essential to the development of new therapies which will benefit the residents of Vancouver Island and beyond.

When not working as a cardiologist Dr. Robinson will often be found running or cycling around Victoria, hurtling down a snow slope or spending time with his wife and young daughter.



Dr. Simon Robinson

Vic Heart's Tour de France!

Our Nurses and Administrative Staff (left to right)

Barbara Conti, RN, Research Coordinator
Sheryll Sorensen, RN, Research Coordinator
Kim Allen, Regulatory Coordinator
Sarah Nelson, BN, Research Coordinator
Liz Martin, RN, Research Coordinator
Lynn Mitchell, RN, Research Coordinator
Noreen Lounsbury, BN, Manager
Celeste Asselbora, Regulatory/Fellowship Coordinator
John Cantelon, Financial Officer
Liza Pelzer, BN, Research Coordinator

Missing from photo:
Peta Tibbetts, BN, Research Coordinator
Catherine Graves, Research Assistant
Alix Wong, Student
Kate Smith, Administrative Assistant

Dr. Reginald Smith

Investigator

Reginald ("Reg") Smith obtained his pharmacy degree from UBC in 1988 and completed a hospital residency at Burnaby Hospital in Vancouver. He then completed a Doctor of Pharmacy degree from the University of Kentucky in Lexington. Reg is originally from Victoria, graduating from Spectrum Community School in 1982 and was actually born in the hospital in which he now works! In the early 1990s he and his wife spent two years working at the King Fahd National Guard Hospital in Riyadh, Saudi Arabia, close to the end of the First Gulf War.

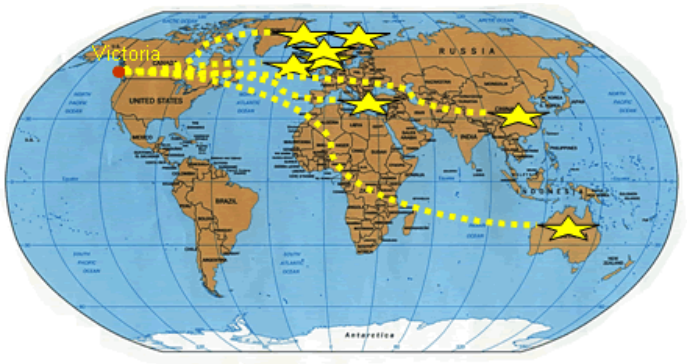
Reg is a Clinical Pharmacy Specialist in Cardiology and Thrombosis at the Royal Jubilee Hospital. He began working with the Victoria Heart Institute as a co-investigator in 1995 and joined the Board of Directors in 1996. He divides his time between acute care cardiology and an anticoagulation practice in the Deep Vein Thrombosis Clinic. With the help of VHIF staff, Reg has been participating in clinical trials seeking out safer and easier to use alternatives to warfarin (COUMADIN®) in the treatment and prevention of thromboembolism.

Reg is a member of the Canadian Cardiovascular Society and serves on the Executive Board of the Canadian Cardiovascular Pharmacists Network (CCPN). He is also a member of the Thrombosis Interest Group of Canada and an Adjunct Associate Professor of Medicine at UBC. Reg enjoys teaching and can frequently be seen around the Royal Jubilee Hospital with a cluster of pharmacy, nursing or medical students and residents.

Vancouver Island Interventional Cardiology Fellowship

Our interventional fellowship program has been established for over 10 years, with fellows from Canada, the United Kingdom, Europe, and Asia.

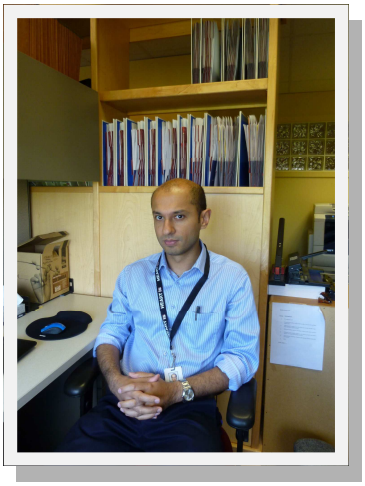
The program typically consists of four full lab days and one research day each week. The fellow can expect to complete at least 500 procedures, with a large proportion being performed as solo operator (depending on individual experience and progress).



Program Director: Dr. Anthony Della Siega
Program Coordinator: Celeste Asselbora

Please visit our website (www.vhif.org) for program information or contact the Coordinator at casselbora@vhif.org

Our Interventional Cardiology Fellows



Dr. Jehangir Din
February 2011-June 2012

Jehangir was a visiting interventional cardiologist fellow from Edinburgh, Scotland. He completed his medical degree at Edinburgh University with BSc Honours in immunology. He undertook his cardiology training at Edinburgh Royal Infirmary. He has a research interest in the cardiovascular effects of omega 3 fatty acids and fish oils, in particular looking at their mechanism of action and effects on vascular function and thrombosis. Despite spending 3 years studying the effects of fish oils in Edinburgh, he didn't catch his first fish until he went fishing up in Campbell River last summer! Jehangir has recently accepted a consulting job in Bournemouth, England. The staff at VHIF wish him all the best with his new position.

Dr. Aengus Murphy
March 2012 –November 2012

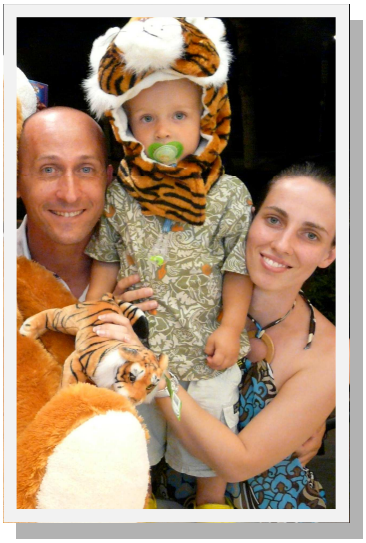
Aengus grew up in Maghera, a small town in the centre of Northern Ireland, approximately 40 miles from Belfast. He studied Medicine in Trinity College, Dublin and after graduating with Honours in 2001, moved to Glasgow, Scotland to begin his post-graduate career.

After working in various locations around the west of Scotland, he began a 2 year Cardiology Research Fellow post in 2005 in the Western Infirmary, Glasgow. He studied the impact of renal impairment on cardiovascular outcomes in the Glaswegian population and this led to the award of an MD. Since 2007 he has been part of a cardiology training program in the West of Scotland, latterly sub-specializing in PCI.

He was awarded the Boston Scientific Travelling Fellowship in 2011 and arrived in Victoria in February 2012. He is delighted at the variety and volume of PCI experience he is receiving in the Royal Jubilee Hospital. Through the VHIF, he intends to study the long term outcome of patients who have undergone coronary artery bypass grafting in British Columbia within the past 10 years.

His wife Grace and two year-old son Lucan accompanied him to Victoria; they were joined by their brand new daughter Ivy Jane Victoria who arrived a little earlier than expected on May 15th! Aengus has now completed his fellowship and has gone back to Lanarkshire to start a new position.

Marco Moccetti was born 40 years ago in Lugano, a small Swiss city surrounded by mountains, with a beautiful lake in the southern part of Switzerland. Before moving to Canada, he and his partner Laura, and their 5 year old son , Romeo had the opportunity to experience many different cultures while practicing medicine in Italy (University Hospital of Insubria, Varese), in the Italian (University Hospital Cardiocentro Ticino, Lugano) and German part of Switzerland (University Hospital of Zurich), as well as in Hungary (Semmelweis University, Budapest). His field of interest is interventional cardiology, which is why he applied for a fellowship at the Victoria Heart Institute Foundation and at the Royal Jubilee Hospital, in consideration of its renowned educational program and high reputation worldwide. After having been here only a few months, the friendliness of the people in and out of the hospital convinced him and his family that the move to Victoria was the best choice they could ever make. He feels that it has given them the opportunity to enrich their lives in a new and friendly environment . For that reason, he would like to particularly thank Dr. Della Siega, Dr. Klinke and Ms. Asselbora, who made his professional stay at RJH possible. Grazie.

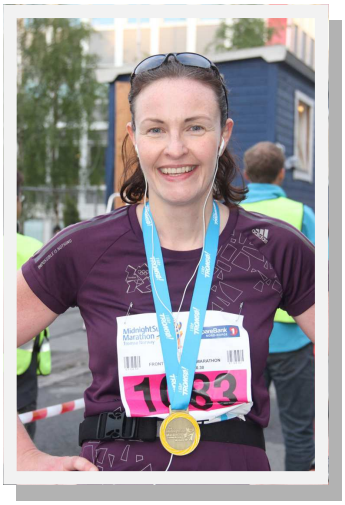


Dr. Marco Moccetti
May 2012

Cara Hendry is an Interventional Fellow from the UK. She hails from Scotland and obtained her primary medical qualification (MBChB), from the University of Glasgow in 1997. Whilst working as a fellow in Glasgow, in 2000, she obtained the MRCP. Since then, she has spent a number of years working in North West England as a Specialist Registrar in Cardiology, and was entered onto the Specialist Register as a Consultant in March 2012. She also spent two years in London, England, (2008-2010) undertaking a period of postgraduate research in the field of cardioprotection under the supervision of Professor Derek Yellon.

She has recently submitted her thesis for the Higher Degree of MD (Research) from University College London.

When she is not working, she manages to find the time to enjoy her favourite sports of long-distance running and cycling. Since her arrival in Victoria, she has a new found love of camping. Just don't ask her to chop the firewood!



Dr. Cara Hendry
August 2012

Omega-3 Fatty Acids and Cardiovascular Disease: Fishing for a Natural Therapy

(Presented at Heart Day 2012)

Dr. Jehangir Din

Fish and fish oils contain omega-3 fatty acids which may protect against coronary heart disease (CHD). Both health professionals and the public are increasingly interested in their role in the prevention and management of CHD. In this era of multiple pharmacological treatments for CHD many feel that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits.

Omega-3 fatty acids, along with omega-6 fatty acids, are essential polyunsaturated fatty acids. There is an abundance of omega-6 fatty acids in the Western diet mainly from vegetable oils rich in linoleic acid. However, humans lack the necessary enzymes to convert omega-6 to omega-3 fatty acids, and the latter must be obtained from separate dietary sources. While α-linolenic acid (ALA) is available from certain plants, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are derived from fish and fish oils (Figure).

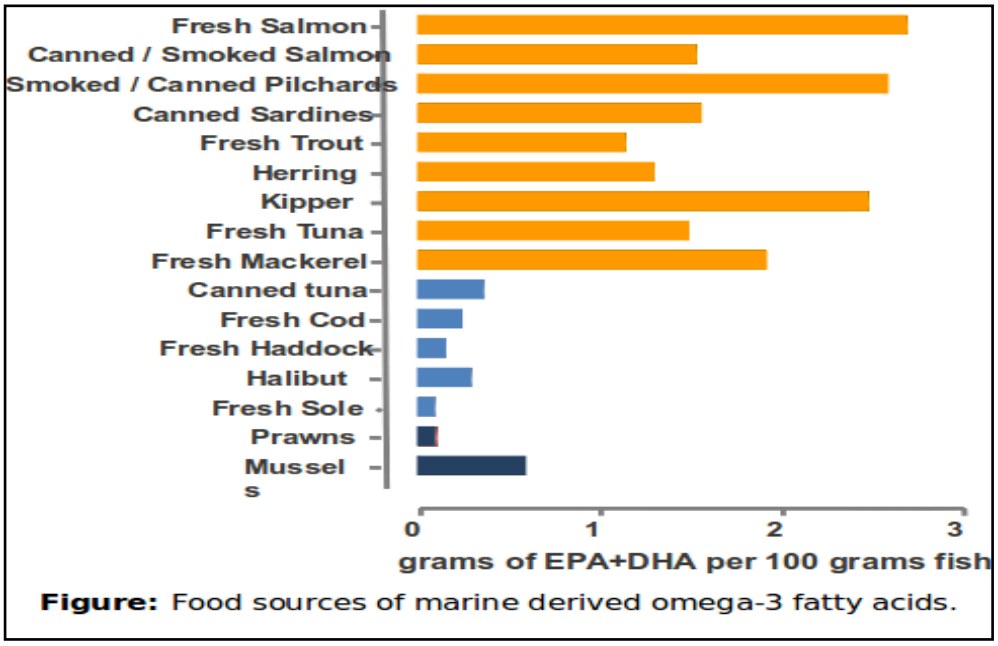


Figure: Food sources of marine derived omega-3 fatty acids.

More prospective observational studies and randomized controlled trial have investigated the effects of fish or omega-3 fatty acids on cardiovascular outcomes than any other food or nutrient. Overall, consumption of fish oil or omega-3 fatty acids appears to reduce CHD mortality. However, not all trials have shown a benefit and there is still some uncertainty as to the benefit of omega-3 fatty acids in CHD patients on modern optimal medical therapy (Table-page 11).

The mechanism through which omega-3 fatty acids may confer cardiovascular benefits remains unclear. Although omega-3 fatty acids have several potentially cardioprotective actions on heart rate, blood pressure, triglycer-

Continued on page 11

ides, arrhythmia, inflammation, vascular function and thrombosis, the relative contribution of these effects to clinical outcomes is not fully understood.

Overall, current data suggests that omega-3 fatty acids may reduce CHD mortality, and continuing research will help clarify the presence and magnitude of any clinical benefits and underlying mechanisms of action. Most guidelines recommend a daily intake of >250 mg EPA+DHA or at least 2 servings per week of oily fish for the general population.

Trial	Population	Intervention	Follow up	Events	RR (95% CI)
DART 1989	N=2033 Recent MI	Advice to eat fish 2xwk	2 years	CHD events 12.5% vs 14.6% CHD deaths 7.7% vs 11.4%	0.84 [0.66-1.07] 0.68 [0.49-0.94]
GISSI-P 1999	N=11324 Recent MI	882 mg omega 3 vs control	3.5 years	Cardiac death 4.0% vs 5.2% Sudden deaths 2.2% vs 2.9%	0.78 [0.65-0.92] 0.74 [0.58-0.93]
DART 2 2003	N=3114 Angina	Advice to eat fish 2xwk	3-9 years	Cardiac deaths 11.5% vs 9% Sudden deaths 4.6% vs 3%	1.26 [1.00-1.58] 1.54 [1.06-2.23]
JELIS 2007	N=18645 Chol>6.5	1.8g EPA vs usual care	5 years	MACE 2.8% vs 3.5% CHD deaths 0.3% vs 0.3%	0.81 [0.69-0.95] 0.94 [0.57-1.56]
ALPHA-OMEGA 2010	N=4837 Prior MI	376mg EPA+DHA vs placebo	3.3 years	MACE 14% vs 13.8% CVD deaths 3.3% vs 3.4%	1.01 [0.87-1.17] 0.98 [0.68-1.32]
OMEGA 2010	N=3851 Recent MI	840 mg/d EPA+DHA vs placebo	1 year	MACE 10.4% vs 8.8% Sudden deaths 1.5% vs 1.5%	1.21 [0.96-1.52] 0.95 [0.56-1.60]
SU.FOL.OM3 2010	N=2501 CHD/TIA/Stroke	600 mg/d EPA+DHA vs placebo	4.2 years	MACE 6.5% vs 6.1%	1.08 [0.79-1.47]

Table: RCTs of fish or omega-3 fatty acids and clinical cardiovascular outcomes.. Beneficial outcomes are highlighted in green.

Heart Day Conference 2013

Wednesday, April 10th
12:00pm—5:00pm
Keynote speaker: Dr. David Lau
From the University of Calgary (Foothills Hospital)
on
Metabolic Syndrome

Current Studies Being Conducted at VHIF

Amplify	Apixaban vs. warfarin and Enoxaparin for acute DVT/PE.
Bridge	Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery.
Paradigm HF	A Multicenter, Randomized, Double-Blind, Parallel Group, Active-Controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients with Chronic Heart Failure and Reduced Ejection Fraction.
Pegasus TIMI 54	Randomized, double-blind trial to assess the prevention of thrombotic events with TIGAGRELOR compared to placebo on a background of ASA in patients with a history of MI (1-3yrs).
Prose	Thromboembolic Complications - Randomized Trial of Previous and Current Generation Mechanical Prostheses.
Protect Arms	Preventing radial occlusion through more effective closure therapy and advanced radial management study.
Signify	Effects of ivabradine in patients with stable CAD without clinical heart failure. A randomized double-blind placebo controlled study.
BP Select ACS	Multi-centre, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of 2 doses of R1512 administered to patients with non-STEMI undergoing PCI.
Cain 003	(Canadian Atherosclerosis Imaging Network) Correlation Between Coronary and Carotid Atherosclerotic Disease (CAD) and Links with Clinical Outcomes.
Chi Square	Can HDL infusions significantly quicken atherosclerosis regression? Infusions plus IVUS.
Improve It	A multicenter, double-blind, randomized study to establish the clinical benefit and safety of Vytorin (ezetimibe/simvastatin tablet) vs. simvastatin monotherapy in high-risk subjects presenting with acute coronary syndrome.
Savor TIMII 53	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus A Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Saxagliptin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischaemic Stroke in Patients with Type 2 Diabetes.
Stability	A Clinical Outcomes Study of Darapladib versus Placebo in Subjects with Chronic Coronary Heart Disease to Compare the Incidence of Major Adverse Cardiovascular Events (MACE).
Solid TIMI 52	Clinical outcomes study of darapladib vs placebo in patients following ACS < 30 days post ACS.

Paradigm Heart Failure Study

Paradigm is a multicentre, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fractions.

A number of compensatory neurohormonal mechanisms are in place with patients with heart failure. Increases in the renin-angiotensin-aldosterone system (RAAS) with increase in sympathetic activity are believed to be harmful long-term. The increase in natriuretic peptides (NPs) are thought to be beneficial leading to vasodilation with natriusesis. Increasing NPs by inhibiting neprilysin (NEP) represents a promising therapeutic approach.

LCZ696, a dual acting angiotensin receptor neprilysin inhibitor (ARNi), provides angiotensin receptor blockade via ARB moiety with NEP inhibition via a prodrug.

This trial, if positive, could represent a real PARADIGM SHIFT in how clinicians treat chronic congestive heart failure. Special thanks to Dr. Liz Swiggum and her heart failure clinicians for supporting VHIF in this exciting project.

Featured Upcoming Trials

Velocity Study

Current clinical applications for therapeutic hypothermia include traumatic brain injury, fever reduction in post-neurosurgical patients, cardiac arrest and prevention of reperfusion injury in acute MI and stroke.

The Royal Jubilee Hospital instituted a “cooling protocol” approximately 5 years ago for cardiac arrest patients. This protocol is often initiated in the ER with ice packs and eventually the ARtic Sun vest is applied and patients are gradually cooled. Dr. Fretz indicated that patients who survived their cardiac arrest and have the cooling protocol often awake mentally intact, “the results have been very encouraging". This pilot study will evaluate ultrafast hypothermia before reperfusion in patients with acute ST-elevation myocardial infarction. The primary objective is to assess the safety and feasibility of inducing mild hypothermia with the APLS (Automated Peritoneal Lavage System) prior to reperfusion as a means of reducing infarct size in patients with acute STEMI.

In Velocity, patients will be randomized to routine primary angioplasty or hypothermia prior to primary PCI.

Patients that are randomized to hypothermia will have a small peritoneal catheter inserted and the APLS will infuse patients with cool fluid to quickly lower core temperature. When patients reach a core temperature of $\leq$ 34.9c the PCI will be performed. Patients are cooled for 3 hours and them warmed for 3 hours. Fluid is removed from the peritoneal cavity and the catheter is removed.

Infarct size will be determined by cardiac MRI at 3-5 days post procedure and at 30 days.

Dr. Eric Fretz, Principal Investigator, and his study team, look forward to initiating this very exciting protocol in the Winter of 2013.

Cantos Study

A randomized, double-blind, placebo-controlled trial of quarterly subcutaneous canakinumab for stable post-myocardial infarction patients with elevated hs-CRP.

The purpose of this trial is to test the hypothesis that treating patients who have had a recent MI and elevated hs-CRP, with canakinumab will reduce recurrent cardiovascular events. A secondary hypothesis is that patients with pre-diabetes will not develop diabetes when treated with canakinumab.

Atherosclerosis is characterized by a chronically high inflammatory state. Interleukins are key mediators in the chronic vascular inflammatory response. Canakinumab is being developed for the treatment of interleukin-1 beta (IL-1β) driven inflammatory diseases. It is designed to bind to human IL-1β, thus block the interaction of this cytokine with its receptors.

Type 2 diabetes is also a disease characterized by a high inflammatory state. It is thoughts that IL-1β could be of key importance in the progressive functional impairment and destruction of βcells in type 2 diabetes. IL-1β antagonism inhibits B cell death, promotes B cell proliferation, and improves insulin sensitivity. Therefore, canakinumab is expected to prevent new onset T2DM in patients with recent MI who are pre-diabetic.

Clinical trial data has demonstrated that persistent elevations of hs -CRP is an independent risk factor for future cardiovascular events. Dr. Simon Robinson, Principal Investigator, and his team will be initiating this protocol in Winter 2012/2013.

Results of Studies Conducted at VHIF

DAL-OUTCOMES Study

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

The dal-Outcomes Study enrolled 15, 871 patients who had a recent hospitalization for acute coronary syndrome (ACS). patients received either the CETP inhibitor dalcetrapib 600mg daily or placebo.

The primary efficacy end point was a composite of death from coronary heart disease, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation.

Over the course of the trial HDL cholesterol levels increases from baseline by 4 to 11 % in the placebo group and by 31 to 40 % in the dalcetrapib group. Dalcetrapib had a minimal effect on LDL cholesterol.

After a median of 31 months, end point events were analyzed and the independent safety monitoring board recommend the trial end due to futility. Dalcetrapib did not have a significant effect on any component of the primary end point or total mortality.

Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes (TRACER Study)

Vorapaxar is a new oral protease-activated-receptor 1 (PAR-1) antagonist that inhibits thrombin-induced activation. TRACER was a multinational, double-blind randomized trial, comparing vorapaxar with placebo in 12,944 patients who had acute coronary syndromes without ST-segment elevation. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalisation, or urgent coronary revascularization.

In patients with acute coronary syndromes, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite end point but significantly increased the risk of major bleeding, including intracranial hemorrhage.

AIM-HIGH Study

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes trial (AIM-HIGH) randomized 4,414 patients to simvastatin (Zocor, 40 to 80 mg) in combination with high-dose niacin (1,500 to 2,000mg) or a placebo spiked with 50 mg niacin per tablet to cause flushing to maintain blinding.

Extended-release niacin (Niaspan) was associated with a clinical event rate of 16.4 % compared with 16.2 % in the control group, for a slim 2 % relative risk reduction that was not significant at p=0.79 in the AIM-HIGH trial.
That primary trial endpoint encompassed coronary heart disease death, nonfatal myocardial infarction (MI), ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.
None of the individual outcomes differed significantly between groups either.

"Yesterday's research is today's best practice… Today's research leads to tomorrow's breakthroughs"

SATURN Study

Effects of two statin regimens on progression of coronary disease.

The trial involved 1039 patients with coronary artery disease who were treated with either Atorvastatin 80 mg or Rosuvastatin 40 mg daily. Serial intravascular ultrasonography was performed at baseline and after 104 weeks of statin therapy. IVUS was utilized to assess the progression of coronary atherosclerosis.

After 104 weeks of therapy the Rosuvastatin group had lower levels of LDL than the Atorvastatin group 1.62 vs 1.82 mmol/L and higher levels of HDL (1.30 vs 1.26 mmol/L), P=6.01. Both agents induced regression in the majority of patients: 63.2% with Atorvastatin and 68.5% with Rosuvastatin for percent atheroma volume and 64.7% and 71.3% respectively for total atheroma volume.

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VHIF Mission & Values

The Victoria Heart Institute Foundation (VHIF) is a non-profit, charitable organization dedicated to conducting and supporting cardiovascular research in Victoria.

With the knowledge we acquire in the etiology and management of cardiovascular disease from the results of clinical trials, we seek to improve the health status of cardiovascular patients in British Columbia.

⇒ We value contributing to the global body of cardiovascular clinical knowledge to improve patient care and health outcomes.

⇒ We value participation in ethical research.

⇒ We value our study patient volunteers.

⇒ We value our not-for-profit status as a preferred research environment.

⇒ We value our autonomy.

⇒ We value our principal investigators, staff, and research partners.

Would you like to donate to VHIF or create a legacy memorial?

Contact us about donor opportunities. Your contribution will directly support clinical education and research therapy for heart patients. VHIF does not sell, trade or rent its donor information, and each gift is gratefully acknowledged with a tax deduction receipt.

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