Victoria Heart Institute FOUNDATION

CV Research Victoria

September 2006

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- The ACCLAIM Trial (completed)
- BEAUTIFUL
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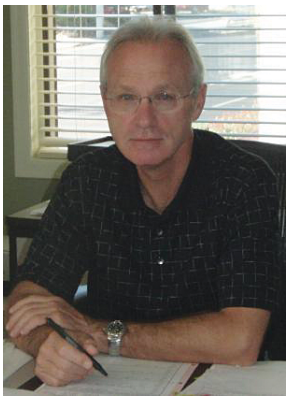


Dr. W. Peter Klinke
Research Director VHIF

Welcome to this second edition of ***CV Research Victoria,*** the Victoria Heart Institute Foundation (VHIF) newsletter.

We hope this format will provide useful information to our stakeholders, the physicians, and others who willingly encourage their patients to participate in clinical research.

Our goals are to provide you with brief descriptions of current trials and report on the results of these trials and how they might impact in your practice.

In addition, the newsletter will provide an educational component with either a brief clinical vignette and/or a longer and more comprehensive editorial review of a specific topic.

We hope that you will give us feedback on which items are useful for you and any suggestions you might have.

Featured Trials

The ACCLAIM Trial
(completed)

The ACCLAIM Trial was reported at the recent European Society of Cardiology Meeting. This was a double-blind, placebo controlled trial involving 2400 patients in 176 cardiac centres, with VHIF being one of them. Patients had NYHA Class II to IV chronic heart failure with a mean LVEF of less than 30% and were receiving current standard of care treatments. The therapy studied was Immune Modulation therapy, which was developed to exploit the principle that inflammation plays a key role in heart failure and other diseases. It involves removing a small amount of blood from the patient, subjecting it to oxidated stress in a special unit that is believed to trigger an immune response and then re-injecting the blood intramuscularly back into the same patient. The entire process requires about 30-minutes and is intended as a monthly therapy. A preliminary clinical trial in heart failure showed promising results, leading to the initiation of the larger ACCLAIM trial.

The primary endpoint, a composite all cause mortality or cardiovascular hospitalization, was not statistically different between Immune Modulation therapy and Placebo. Patients were well treated in this trial with greater than 90% being treated with an ace-inhibitor and beta blocker and greater than 70% on statin drugs. This may, in part, have contributed to only a 9% relative risk reduction, which was not statistically significant between the Immune Modulation group and the Placebo group.

When pre-specified subgroup analyses were conducted, two particular groups stood out in which there were benefits from the Immune Modulation therapy. These were patients with class 2 heart failure and those with no prior myocardial infarction (MI) showing a significant 31% reduction in the primary endpoint. Immune Modulation therapy was well tolerated, with no

Featured Trials (continued)

differences in blood pressure, heart rate, infection, or other health problems between the active and placebo groups. The ACCLAIM Steering Committee is now planning another trial in the patient population in which the benefit was suggested in the current study.

Study Snapshot	BEAUTIFUL
Patient Condition:	Coronary Disease, Left Ventricular Dysfunction
Official Title:	Effects of Ivabradine on Cardiovascular Events in Patients With Stable Coronary Artery Disease and Left Ventricular Systolic Dysfunction.
Intervention:	Drug: Ivabradine
Study Phase:	Phase III
Study Design:	Randomized, Double-Blind, Placebo Control, Parallel Assignment
Expected Enrollment:	10,000 patients
Victoria Enrollment:	32 patients
Principal Investigator:	W. Peter Klinke, M.D.
Co-Investigator:	Anthony Della Siega, M.D.
Co-Investigator:	J. David Hilton, M.D.
Co-Investigator:	Manjeet Mann, M.D.
VHIF Coordinator	Lynn Mitchell, RN
Sponsor:	Servier Canada Inc.
Study Progress:	Start 2004 — End 2008

The BEAUTIFUL Study

Purpose

The purpose of the BEAUTIFUL study is to evaluate whether the experimental drug ivabradine is effective at reducing cardiovascular events for those patients with coronary artery disease (CAD) and left ventricular systolic dysfunction.

Study Status

The BEAUTIFUL study is a very large trial involving over 750 sites world wide including thirty-five active sites within Canada.

Planned enrollment into this study is 10,000 study patients. The 9,000th study patient was enrolled on August 8, 2006. Patient enrollment is scheduled to be completed by October 2006. There are thirty two study patients enrolled in the BEAUTIFUL study in Victoria.

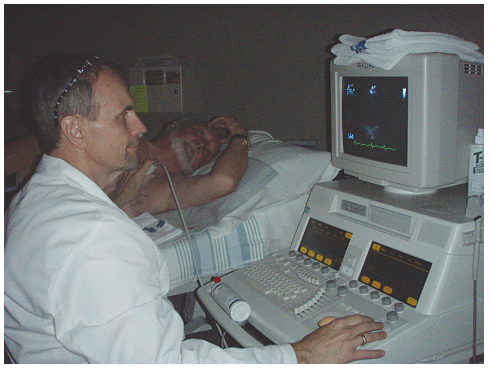
How It Happens In Victoria

- Potential study patients for BEAUTIFUL have left ventricular dilation (enlargement) with an ejection fraction (the % of blood ejected from the left ventricle with each heart beat) of less than 40% as detected by a diagnostic echocardiogram (ultrasound study of the heart).

- Following patient consultation and consent, study patients undergo screening procedures that include a protocol-specific echocardiogram performed by Vern Parkinson, Echo Sonographer, Royal Jubilee Hospital.

- Eligible study patients are randomized (assigned by chance) to groups who receive study medication of either ivabradine or placebo. Patients progress through the study medication titration period (dose fine tuning), and then will receive the study medication for between eighteen months and three years.

- Study patients visit the VHIF clinic every three to six months at which time they are seen by a Cardiologist, blood samples are drawn, and an ECG is done.



***Bob Grice** (patient) and **Vern Parkinson** during echocardiogram*

Knowledge Gained

This study is designed to evaluate the effectiveness of the study drug, ivabradine, in the reduction of cardiovascular events including hospital admissions for acute myocardial infarction (AMI), hospital admissions for new onset or worsening heart failure, and cardiovascular mortality.

A slower heart rate in persons with coronary artery disease and damaged/depressed heart function has been observed to prevent further damage to the heart and to preserve heart function. Ivabradine is a novel selective heart rate lowering agent without negative inotropic properties and has no effect on atrio-ventricular conduction nor ventricular repolarisation. Ivabradine decreases heart rate at rest and with exercise by inhibition of the sinoatrial pacemaker *If* current.

BEAUTIFUL
Worldwide Enrollment - August 2006

Country	Sites	Patients
Russia	53	1148
Poland	48	887
Ukraine	47	871
Netherlands	49	642
Czech Republic	27	560
Romania	36	550
Germany	67	494
Argentina	27	481
Bulgaria	16	441
Hungary	35	362
Denmark	28	339
Canada	**35**	**309**
France	64	296
Other sites		1621
Total		**9001**

The ASTRONOMER Trial

Purpose

The purpose of the ASTRONOMER trial is to determine whether lowering cholesterol levels through the use of a blood cholesterol lowering drug called rosuvastatin in patients with mild to moderate aortic valve stenosis (a narrowing of the aortic valve) can prevent or slow the progression of this disease.

Study Status

Patient enrollment into this all-Canadian trial was completed in January 2006. Twenty three sites across Canada are currently following 272 study patients. This study is scheduled to complete in December 2008.

How It Happens in Victoria

- Potential study patients were first identified following a diagnostic echocardiogram. After consultation and consent, study patients underwent a second protocol-specific echocardiogram, performed by John He, in the Echo Lab at the Royal Jubilee Hospital.

***John He,** Echo Sonographer, Royal Jubilee Hospital*

- Cardiologist Dr. Randall Sochowski reviewed the results of the echocardiogram against the inclusion and exclusion criteria of the ASTRONOMER trial protocol.
- Study patients were then assigned (randomized) to study medication (rosuvastatin or placebo).
- Study patients continue to be seen at the VHIF clinic every three months over the five year duration of the trial. During their clinic visits, study patients undergo physical exams and have blood samples drawn. An annual echocardiogram is completed to access the progression of aortic stenosis (AS).

Study Snapshot	ASTRONOMER
Patient Condition:	**Mild to moderate aortic stenosis**
Official Title:	A randomized, controlled trial of the effect of cholesterol lowering with Rosuvastatin on the progression of aortic stenosis in patients with mild to moderate aortic stenosis.
Intervention:	Drug: Rosuvastatin
Study Phase:	Phase III
Study Design:	Double-blind, placebo controlled, randomized, multi-centre
Expected Enrollment:	300 patients
Victoria Enrollment:	25 patients
Principal Investigator:	Randall Sochowski, M.D.
Co-Investigator:	Ken Yvorchuk, M.D.
Co-Investigator:	Manjeet Mann, M.D.
Co-Investigator:	W. Peter Klinke, M.D.
Co-Investigator:	Dennis Morgan, M.D.
VHIF Coordinator	Noreen Lounsbury, BN, CCRN
Sponsor:	Canadian Institutes of Health Research and AstraZeneca
Study Progress:	Start: Nov 2002 — End: Dec 2008

Knowledge Gained

AS is the most common valvular disease affecting about three percent of the elderly population in the western world and AS is the most common reason for heart valve replacement.

An effective strategy that prevents or impedes the progression from mild or moderate to severe aortic valve stenosis should yield major health benefits.

The FREEDOM Trial

Purpose

The purpose of the FREEDOM trial is to compare the effectiveness of two treatments for diabetic individuals with multi-vessel coronary artery disease (CAD). This study is designed to evaluate whether percutaneous coronary drug-eluting stenting (DES) is more or less effective than coronary artery bypass grafting (CABG).

Study Status

This is a large, multi-national study involving close to 2400 study patients in the United States, Europe, South America, and Canada. There are six study patients presently enrolled in the FREEDOM trial in Victoria.

How it Happens in Victoria

- Potential study patients are first identified based on the results following a diagnostic coronary angiogram procedure.
- The coronary angiogram images (films) are presented

Study Snapshot	FREEDOM
Patient Condition:	**Diabetes mellitus and coronary artery disease**
Official Title:	Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease
Intervention:	Procedure: Coronary Artery Bypass or Percutaneous Coronary Intervention with DES
Study Phase:	Phase III
Study Design:	Treatment, Randomized, Open Label, Parallel Assignment, Efficacy Study
Expected Enrollment:	2400 patients
Victoria Enrollment:	6 patients
Principal Investigator:	J. David Hilton, M.D.
Co-Investigator:	W. Peter Klinke, M.D.
Co-Investigator:	Richard R. Mildenberger, M.D.
Co-Investigator:	R. David Kinloch, M.D.
Co-Investigator:	Eric Fretz, M.D.
Co-Investigator:	J. W. Dutton, M.D.
Co-Investigator:	Anthony Della Siega, M.D.
Co-Investigator:	Malcolm Williams, M.D.
Co-Investigator:	David Miller, M.D.
VHIF Coordinators	Liz Reimer, RN
Sponsor:	National Heart, Lung, and Blood Institute (NHLBI)
Study Progress:	Start: 2004 — End: 2010

Featured Trials (continued)

at Cardiac Services rounds where the opinion is reached for treatment of either CABG or DES.

- Patients are consulted, and should they consent to participate in the FREEDOIM trial, they will be randomized (assigned by chance) and treated with either DES or CABG.
- Following treatment, study patients will be seen by Research Nursing staff in follow-up at the VHIF clinic every six months for five years. Telephone follow-ups are conducted every two to four months over this same period. Study patients are also asked to complete quality-of-life questionnaires.

Knowledge Gained
This study addresses the critically important problem of how to best revascularize diabetic individuals with multi-vessel CAD.

The FREEDOM trial is an opportunity to gather the evidence necessary to support the strategy that provides optimal revascularization in diabetic individuals.

Clinical Trials In-Process at VHIF

Cardiovascular clinical trials conducted through VHIF focus on treatments for cardiovascular patients. All clinical trials have been approved by the Research Review and Ethical Approval Committee (RREAC) of the Vancouver Island Health Authority (VIHA).

Twenty-three clinical trials are underway through VHIF as at September 2006.

	Enrolling Study	Patient Diagnosis
1	APPRAISE-1	Acute Cornoary Syndrome (ACS)
2	BEAUTIFUL & Echo Substudy	Coronary Artery Disease (CAD) and Congestive Heart Failure (CHF)
3	CENTAURUS	ACS
4	EarlyACS	ACS
5	ERASE	ACS
6	EVEREST-II	Valvular Heart Disease (VHD)
7	FREEDOM	Diabetes, CAD
8	FRONTIER-II	CAD
9	IMPROVE-IT	ACS
10	NORTHERN	Inoperable-CAD
11	SNAPIST-III	CAD
12	SOX	Peripheral Vascular Disease (PVD)
13	ZESCA	ACS
	No Longer Enrolling, Study Patients in Follow-Up:	
14	A5091005	CAD
15	AGENT4	Inoperable-CAD
16	ASSENT4	Acute Myocardial Infarction (AMI)
17	MerlinTIMI36	ACS
18	ASTRONOMER	VHD
19	C-CIRUS	CAD
20	IPRESERVE	CHF
21	OAT	CAD
22	PERISCOPE	Diabetes, CAD
23	STRADIVARIUS	CAD

Clinical Vignette:
Aspirin for the Primary Prevention of Cardiovascular Events in Women and Men

W. Peter Klinke, M.D.
Director of Research

A sex specific meta-analysis of six (6) trials of aspirin for the primary prevention of cardiovascular events has found that aspirin reduces the risk of stroke in women, but not in men. For men, it reduces the risk of MI (myocardial infarction), but this benefit is not extended to females. There is a price to pay for both sexes in the form of an increased risk of bleeding. The meta-analysis included three (3) trials of aspirin for primary prevention in men only, one (1) conducted only in women, and two (2) that were conducted in both sexes. In total, there were just over 50,000 women and 40,000 men in the meta-analysis.

Among the women, there was a 24% reduction in rate of ischemic stroke, but no significant effect on MI or cardiovascular death. Among the men, aspirin was associated with 32% reduction in MI, but no significant effect on stroke or cardiovascular death. Aspirin treatment resulted in approximately 70% increase in major bleeding, among both sexes.

Based on this meta-analysis, aspirin therapy for an average of 6.4 years resulted in an average absolute benefit of approximately three (3) cardiovascular events per 1000 women, and four (4) cardiovascular events per 1000 men. In terms of harm, aspirin treatment for 6.4 years caused an average absolute increase of approximately 2.5 major bleeding events per 1000 women, and 3 per 1000 men. Both the beneficial and harmful effects of aspirin should be considered before initiating aspirin for primary prevention of cardiovascular disease in both sexes. At present, there is no need to prescribe aspirin for primary prevention in women with no cardiovascular risk factors.

Reference:
Aspirin for Primary Prevention of Cardiovascular Events in Women and Men: A Sex-Specific Meta-Analysis of Randomized Controlled Trials, JAMA, Jan 18, 2006; 295:306-313

A Refresher – "Reading a Published Study"

Dr. Reginald Smith

In the June 2006 edition of CV Research Victoria, we summarized how clinical trials progressed, study phases and the ethics approval process in Victoria. Reading the results of a clinical trial when published in a journal can be a confusing and daunting task. In this edition we will discuss the three main types of studies then give a quick synopsis of statistical terms which will help guide you in reading and understanding a research article.

Types Of Studies

When reading a published study the first task at hand is identifying to which study type the paper belongs. There are three main types of studies: case-control, cohort, and randomized clinical trials. Case-control studies look at the relationship between people with a certain disease (case) and those without the disease (control). An example of this would be the discovery of the relationship between smoking and lung cancer. Cohort studies look at a group of individuals who share a common experience or characteristic within a specific time period. The Framingham Heart Study is an example of a cohort study that has been going on for more than 50 years, and is where many of the known risk factors for coronary disease were identified. Randomized clinical trials or controlled clinical trials are studies designed to assign people by chance to separate groups that compare different treatments. In a prospective randomized trial the investigator makes an intervention (i.e. starts an investigational drug or device) and the patients who are randomly assigned to the intervention group are compared to those randomly assigned to the control group. Often the new treatment is compared to the best current treatment. It is important to know the type of study, since it influences the kind of conclusions that can be drawn from the study. For example, the best kind of study for determining a cause and effect relationship is a randomized trial. Cohorts and case control studies may show associations between variables, but they are not well suited to showing cause and effect. Many of the studies conducted through VHIF are prospective randomized clinical trials.

Randomization

In part, randomization is why a cause and effect relationship can be drawn from a randomized clinical trial. If patients are randomly assigned to experimental therapy and control group, then both groups should be equally balanced in terms of age, sex, comorbid illnesses, medications, socioeconomic factors, and etcetera. Randomization will help ensure that the only significant difference between the two groups is the intervention, and if a difference is detected, it is most likely due to the intervention and not some other unforeseen difference between the groups. When reading a paper, scan the patient characteristics columns and see if the groups are balanced.

Power and Sample Size and Beta Error

Once the study hypothesis and population has been defined, the question you ask yourself next is, are there enough participants enrolled in the study to demonstrate a statistical significance between the study and control groups, if a difference exists. The smaller the difference that you are trying to detect, the larger the sample size needed to detect the difference. Beta error is the chance of doing a study and concluding there is no difference between the groups when in fact there is a difference. For example a study may state that it has an 80% power to detect a 15% difference. Power is 1-beta, so this study would have a 20% chance of saying there is no difference when there is a difference. Statisticians will utilize the beta error when calculating the number of subjects needed for the study.

Alpha Error and p Values

An alpha error (also called Type I, or false-positive) is the probability of stating that a difference between two groups exists, when in fact there is no difference. A commonly chosen acceptable risk of alpha error to determine statistical significance is 5%, which is reflected by a p value of < 0.05. If there is a difference between the two groups and the p value is 0.05, then there is a 5% possibility that the difference detected is due to chance, and not the intervention that was made. A common misconception is that the more zeros a p value has, the more significant the results. A lot of p values (i.e. p= 0.0000001) only means it is less likely the difference seen was due to chance.

Relative Risk Reduction (RR) and Number Needed to Treat (NNT)

When the therapy reduces risk compared to a control and the therapy reduces risk compare to the control, there is a relative risk reduction. A relative risk reduction is the proportion of risk that is removed by the treatment. Absolute risk is a number between zero and one. If the risk is 1 then the outcome is a certainty. Say for example, the risk of death within a year from some illness is one, and a new treatment reduced that risk from 1 to 0.5 (i.e. 50% of treatment subjects don't survive a

A Refresher (continued)

year compared to 100% of controls), then that is a 50% relative risk reduction, 50 % of the risk has been removed. Relative risk reduction is useful in clinical trials because it gives us "clinical" vs. "statistical" significance, in terms of the new treatment being better than the old. However, relative risk reduction can be misleading in terms of the "real world" value of the treatment. Reducing mortality from 2% to 1% is still a 50% relative reduction, but only a 1% absolute reduction (2%-1%=1%). This is where NNT is a particularly useful tool to use when reading the results of a study. The NNT will tell you how many patients need to receive the new treatment compared to the old treatment to avoid (or delay) the endpoint. The NNT is simple to calculate. Just find the absolute risk reduction and divide one by it (i.e. press the 1/x button on your calculator) and multiply it by 100. That will give you the NNT. So, going back to our two examples, reducing mortality at one year from 100% to 50% is both a relative risk reduction of 50% and an absolute reduction of 50% (100%-50% = 50%). This gives an NNT of two, so for every 2 patients treated one death is delayed or avoided. In the second example the treatment reduces mortality from 2% to 1%, which is a 50% relative reduction, but only 1% absolute reduction (2%-1%=1%). If we do our NNT calculation now, we get an NNT of 100, which is considerably higher than the NNT in the first example, so the intrinsic "real world" value of the first example is greater than the second example. Readers of clinical papers should do the NNT calculation when possible, if the calculation has not been done in the publication.

Recommended reading to further your statistical knowledge; Studying a Study and Testing a Test 5th Edition, author Richard K. Riegelman, publisher Lippincott Williams & Wilkins.

Clinical Fellowships

Cardiovascular Clinical Fellowships

Dr. Andrew Small (Australia) continues in his Fellowship training since his arrival in Victoria in April, 2006.

Dr. Andrew Small

Dr. Alex Chase (England) has now completed his 12-month Fellowship training. We thank Dr. Chase for his contributions to cardiovascular patient care and clinical research during his stay in Victoria.

And, best wishes to Dr. Chase and his family as they depart on a cross-Canada RV trip prior to their return to England. Later this month we anticipate the arrival of Dr. Mark Spence (Australia), and Dr. Jon Byrne (England), who will begin training in advanced interventional cardiology techniques under Dr. J. David Hilton, FRCP(C), FACC, Director of Fellowship Training, in the Heart Cath Lab of the Royal Jubilee Hospital.

Dr. Alex Chase

Thrombosis Research Fellowship

VHIF has offered for the first time this year a Thrombosis Research Fellowship.

Amy Mailhot, B.S.N., RN, began as the first thrombosis fellow in June 2006. The focus of this one year fellowship is to provide the fellow with post graduate training in thromboembolism, and to complete an original clinical research project.

In recent years more patients are having more complex surgical

Amy Mailhot, B.S.N., RN

procedures in day care surgical settings. Because of the short nature of these surgeries, most of these patients do not receive prophylaxis when compared to in-house surgical patients who traditionally receive thrombosis prophylaxis. This year's research project will focus on comparing the thromboembolism risk of a cohort of patients having day surgeries with a cohort of patients having traditional inpatient surgeries.

Other thromboembolism clinical trials that Amy will be participating in include the SOX trial which evaluates if compression stockings decrease Post Thrombotic Syndrome in deep vein thrombosis patients, and the EQUINOX trial which evaluates the effectiveness of idraparinux injection in the treatment of deep vein thrombosis.

Recent Publications

1. Frans Van der Werf et al on behalf of the ASSENT-4 Investigators. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT 4-PCI) Investigators. Lancet published online February 14, 2006
   http://www.thelancet.com/journals/lancet/article/PIIS0140673606681476/fulltext

2. Peter Carson et al on behalf of the I-Preserve Investigators. The Irbesartan in Heart Failure with Preserved Systolic Function (I-Preserve) Trial: Rationale and Design. J Cardiac Fail; Vol. 11 No. 8 2005.

3. Deepak L. Bhatt et al on behalf of the CHARISMA Investigators. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. N Eng J Med; March 12, 2006.

(Contact vhif@vhif.org for reprints)

ACC Lake Louise 2007

VHIF will again be assisting Dr. Peter Klinke and Dr. Wayne Warnica (University of Calgary), with their preparations for the 23rd Annual Cardiovascular Conference at Lake Louise.
Conference details will be available on the website:
www.acclakelouise.com

Lake Louise
Annual Cardiovascular Conference

VHIF Personnel

Director of Research:	Dr. W. Peter Klinke, MD, FRCP(C), FACC, FACP
Director, Interventional Cardiology Fellowship Training Program:	Dr. J. David Hilton, M.D., FRCP(C), FACC
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	Dr. Andrew Small
	Dr. Mark Spence
Thrombosis/Anticoagulation Research Fellow:	Amy Mailhot, RN, BSc
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	Liza MacRae, RN
	Lynn Mitchell, RN
	Liz Reimer, RN
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Mission Statement

The Victoria Heart Institute Foundation 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.