



Medicine, Nursing and Health Sciences

Centre of Cardiovascular Research and Education in Therapeutics

Annual Report 2010



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Director's Report



2010 was again a year of consolidation and expansion of CCRE Therapeutics activities. Specifically, the Centre has expanded its focus even more widely with a record number of publications, presentations and teaching activities. In order to undertake these activities the Centre has expanded further its list of personnel, all with specific clinical research expertise.

In addition, CCRET continues to attract high quality post-doctoral Fellows internationally. Dr Masataka Watanabe has joined CCRE Therapeutics from Tokyo, Japan for a two year post-doctoral research fellowship.

Highlights of 2010 include:

- **SCREEN-HF:** The collection of data for the longitudinal SCREEN-HF study continues. SCREEN-HF is a project to collect a cohort of subjects at high risk for but without overt heart failure and then observe which patients go on to develop left ventricular dysfunction and/or symptomatic heart failure. This project is of great importance with regard to mechanisms of disease and potential use of biomarkers as early detection tools.
- **ASPREE:** This large-scale USD\$50+ million study has commenced full recruitment and is on its way to achieving its target of 19,500 randomised patients. CCRE Therapeutics is closely involved in the conduct of the study as well as its ongoing data collection and subsequent analysis.
- **ATMOSPHERE:** This global study of the effects of aliskiren in patients with systolic chronic heart failure aims to recruit >7000 participants. I have been appointed Chairman of the Steering Committee of the study, which is also being conducted locally at the Alfred Hospital.
- **Renal Denervation:** CCRE Therapeutics contributed to the randomised controlled trial published in the Lancet demonstrating the safety of the procedure versus a control group as well as its blood-pressure-lowering efficacy.
- **STABILITY:** This international trial of an investigational drug, darapladip, in patients with chronic coronary heart disease receiving standard practice care is being undertaken at our Clinical Trial Centre at Caulfield. CCRET achieved second highest recruitment Australia-wide. Patients will be followed every six months for approximately three and a half years.
- **Medical Education, eg CSANZ symposia:** CCRE Therapeutics continues its commitment to medical education programs and once again held two highly successful symposia at this year's CSANZ meeting, with further events scheduled for 2011.
- **Australian Cardiac Procedure Registry:** CCRE Therapeutics conducted a pilot project with funding from the Australian Commission of Safety and Quality in Health Care to test and validate the operating principles and standards for a national cardiac registry.

To summarise 2010 was again an exciting year for CCRE Therapeutics with further international recognition of the Centre.

Henry Krum, MBBS, PhD, FRACP, FCSANZ
Professor of Medicine

Mission Statement

To improve clinical outcomes at the individual and community level through the use of evidence, based on high quality clinical research.

Scientific Advisory Board



Director

**Professor Henry Krum,
MBBS, PhD, FRACP, FCSANZ, FESC**

Henry Krum completed his MBBS at the University of Melbourne in 1981, became a Fellow of the Royal Australasian College of Physicians in 1989 and completed a PhD at the University of Melbourne in 1991.

Professor Krum is a Consultant Physician based at the Heart Centre, Alfred Hospital and a specialist in heart failure management. Professor Krum's grant achievements include awarding of a five year NHMRC Program Grant for 2005–2009 in heart failure research which has recently been renewed for 2010–2014. He is the author of over 280 peer-reviewed manuscripts, 16 book chapters and is co-author of a text book of heart failure therapeutics. He has been Principal Investigator, Executive Committee member and Data Safety Monitoring Board Chairman for numerous international trials in cardiovascular therapeutics.



Associate Director

**Professor Christopher Reid,
BA, DipEd, MSc, CertHealthEcon, PhD**

Christopher Reid is a cardiovascular epidemiologist and Head of the Clinical Informatics and Data Management Unit in the School of Public Health and Preventive Medicine. He graduated from the University of Queensland in 1980 before undertaking graduate studies in the USA and a PhD in Preventive Medicine at Monash University. He holds a National Health and Medical Research Council Senior Research Fellowship in addition to being a Chief Investigator on both NHMRC Project (2008–2012) and Program Grants (2010–2014) focusing on cardiovascular disease prevention. His major research interests include randomised trials, clinical outcome registries, and epidemiological studies. He is a Principal Investigator of the 2nd Australian National Blood Pressure (ANBP2) Study, the Aspirin in Reducing Events in the Elderly (ASPREE) Study and the Australian arms of the HOPE-3 Study and the REACH and CLARIFY Registries. He is a Steering Committee Member of the Australian Cardiac Procedures Registry Project and the Melbourne Interventional Group (MIG) registries. He has over 160 publications, many of which are in leading journals including the New England Journal of Medicine, the Lancet and the BMJ. He has participated as a WHO consultant for prevention of cardiovascular disease in Mongolia, Vietnam and the West Pacific region.



**Professor Jamie Cooper,
MBBS, FRACP, MD, JFICM**

Professor Cooper has been Head of Trauma Intensive Care and a senior Intensivist at the Alfred Hospital since 1991. For most of this time he has been Associate Director, or more recently Deputy Director of ICU, and has acted as the Director of this large Department on many occasions. Through published research and involvement with Department of Human Service (DHS) committees concerning trauma and intensive care, he supported and highlighted the need for and the introduction of the current Victorian Trauma System. He chairs the DHS Trauma Quality Committee which monitors and provides expert interpretation for the impact of the Trauma System on trauma outcomes in Victoria. In 2004 he was appointed Associate Director (Clinical Research) of the National Trauma Research Institute, having responsibility for coordinating all clinical research relating to Trauma at the Alfred (all specialties including Intensive Care).



**Professor John McNeil,
MBBS, MSc, PhD, FRACP, FAFPHM**

Professor John McNeil has been Chair, Monash University Department of Epidemiology and Preventive Medicine at the Alfred Hospital, Melbourne since 1986.

He graduated in medicine from the University of Adelaide, subsequently completing a PhD in Clinical Pharmacology at the University of Melbourne and a Master of Science degree in epidemiology at the University of London. He completed specialty training as a physician and subsequently held senior medical staff positions at the Austin, Repatriation, Alfred and Monash Medical Centres in Victoria. His research interests focus on drug safety.

He is Scientific Secretary of the International Society of Cardiovascular Pharmacotherapy and a member of the Editorial Board of 'Cardiovascular Drugs and Therapeutics'. He is a Fellow of Food Standards Australia and New Zealand and chairs the Ethics Committee at the Alfred Hospital. He is also currently a member of the Colonial Foundation Board.

During his career he has been a member of a wide range of national scientific advisory committees established by the National Health and Medical Research Council, the Commonwealth Departments of Health, Aging and Veteran's Affairs, the Royal Australasian College of Physicians, the National Heart Foundation, the National Stroke Foundation and Food Standards Australia.

He has published over 300 scientific papers and in 2008 was made a member of the order of Australia in recognition of his contribution to Public Health.



**Professor Andrew Tonkin,
MBBS, FRACP**

Professor Andrew Tonkin is Head of the Cardiovascular Research Unit in the Department of Epidemiology and Preventive Medicine, Monash University.

He is also a Consultant Cardiologist at Austin Health. He has also been Chief Medical Officer with the National Heart Foundation of Australia.

Professor Tonkin is past Chairman of the Australian Expert Advisory Group on Heart, Stroke and Vascular Diseases, which advised Government and is a member of the Executive Board of the Council on Clinical Cardiology of the World Heart Federation.



**Professor Paul Myles,
MBBS, DipRACOG, MD, FRCA**

Professor Paul Myles is the Director of Anaesthesia and Perioperative Medicine at the Alfred Hospital, and Professor of Anaesthesia at Monash University. Professor Myles is involved in a number of large multi-centre trials aiming to improve outcomes after surgery and anaesthesia. These include an investigation of nitrous oxide in anaesthesia (the ENIGMA Trial), and aspirin with or without tranexamic acid in coronary artery surgery (the ATACAS Trial).



**Professor Andrew Forbes,
BSc(Hons), MSc, PhD**

Professor Forbes provides biostatistical expertise and professional leadership to CCRE Therapeutics. He worked in the pharmaceutical industry in the US, before joining Monash University to head one of the largest biostatistical units in Victoria, in the Department of Epidemiology and Preventive Medicine.

Director

Professor Henry Krum

Associate Director

Professor Christopher Reid

Research Fellows

Dr Nick Adrianopolous
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International Collaborating Academics

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Operational Review

CCRE Therapeutics can divide its core strengths into three main areas; Clinical Trials, Clinical Informatics and Pharmacoepidemiology/Translational Research.

Clinical Trials

Our clinical trials activities are conducted at the Clinical Pharmacology department and the ASPREE Clinical Trial Centre at the Alfred Hospital and also at the Clinical Trial Centre at Caulfield Hospital. Our clinical trials focus on mechanistic and hospital-based studies as well as community-based clinical outcome trials, a number of which are outlined in the next section.

ASPIrin in Reducing Events in the Elderly (ASPREE)

ASPREE is a large-scale, double-blind randomised, placebo-controlled trial of low dose aspirin for primary prevention of disease in healthy older people. The major research question is: 'Does low-dose aspirin prolong healthy, disability-free life in those aged 70 years and over?' The trial will recruit 19,000 participants (12,500 in Australia and 6,500 in the USA) who will be randomised to daily 100 mg of enteric-coated aspirin or placebo. Follow-up is planned for an average of five years.

Low-dose aspirin may be one of the most chemo-effective agents to prevent or delay the onset of cardiovascular disease, stroke, dementia and certain cancers, particularly bowel cancer in older people. Countering the potential beneficial effects of aspirin therapy are the risks associated with bleeding which are likely to increase as people age. ASPREE will use a composite endpoint – an extension of disability free years – to determine the balance of benefit versus risk of aspirin. In Australia, the trial is largely conducted through general practices and community awareness campaigns.

ASPREE Funding: National Institute on Aging (USA) (2009–2016).

ASPREE Regional Outreach Funding: Victorian Cancer Agency (2010–2012).

Support: Bayer HealthCare provides the enteric-coated low dose aspirin and matched placebo.

Collaborators: Monash University, the Menzies Research Institute in Tasmania, the Australian National University, the University of Melbourne and the University of Minnesota (USA).

Healthy Ageing Biobank

The Healthy Ageing Biobank is an important sub-study of ASPREE which aims to collect, process and store blood and urine specimens from 10,000 ASPREE volunteers. This Biobank will enable future analyses of biomarkers that may be predictors or diagnostics of diseases in the elderly, as well as factors linked to healthy ageing.

Funding: CSIRO (Preventative Health Flagship) plus in-kind support from each of the Collaborators.

Collaborators: CSIRO, Monash University, the Menzies Research Institute in Tasmania, the Australian National University and the University of Melbourne.

ENVIS-ion

Aspirin for the Prevention of Cognitive Decline in the Elderly: a Neuro-Vascular Imaging Study

ENVIS-ion is an ancillary study of ASPREE which will determine if aspirin slows down vascular changes in the brain that are linked to ageing and cognitive decline.

Brain MRI (Magnetic Resonance Imaging) changes correlate with white matter ischaemia, and may provide an efficient surrogate for cognitive decline. However, MRI is relatively costly and is not universally accessible, making it impractical for population screening. The retinal vasculature shares many features with blood vessels of the brain. If changes in the two were found to be highly correlated, retinal digital photography would provide a relatively inexpensive, widely available tool with automated



analysis to select those people likely to benefit most from a preventative intervention (eg regular low-dose aspirin treatment). The sub-study will also examine whether structural changes in brain and/or retinal vasculature correlate with a decline in cognitive function.

ENVIS-ion is being conducted in 600 people enrolled in the ASPREE trial (300 participants in Canberra and 300 in Melbourne).

Funding: NHMRC Project Grant (2008–2012).

Collaborators: Monash University, the Australian National University, the Canberra Hospital and Alfred Health.

2010 Progress

The year 2010 saw a great deal of growth and change for the ASPREE trial. The National Co-ordinating Centre and ASPREE Healthy Ageing Biobank moved from the Clinical Trials Centre (CTC) in Caulfield, to the Burnet Building at the Alfred Hospital campus in Prahran.

During 2010 ASPREE recruited GPs and participants across Melbourne, regional Victoria, Tasmania and the ACT. As a result of funding from the Victorian Cancer Agency, ASPREE established four new key clinical trial centres in regional Victoria based in Bendigo, Ballarat, Geelong and Traralgon. The trial engaged local health service providers, developed new relationships within regional groups and brought international medical research to these communities.

The first Healthy Ageing Biobank 'Biobus', a mobile laboratory, was deployed around Victoria in 2010.

Research staff used the specially equipped bus to collect specimens for the Biobank and for clinical assessments of potential trial participants in rural and metropolitan regions.

By December more than 430 GPs were engaged as co-investigators to the trial and nearly 1000 ASPREE participants across three states were randomised.

Renal Denervation

Renal denervation involves a catheter-based approach via femoral access to knock out the sympathetic nerves that run adjacent to the renal arteries. Percutaneous approach is minimally invasive and the procedure takes about 40 minutes.

CCRE Therapeutics was involved in the randomised controlled trial published in the Lancet in 2010. This study confirmed the initial proof-of-concept findings published in the Lancet the year previously but this time showing a significant blood pressure reduction against placebo with further evidence of the safety of this approach.

Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE)

Henry Krum has been appointed as Study Chair of the ATMOSPHERE study which is being conducted at the Alfred Hospital and approximately 800 other sites throughout the world. The aim is to recruit >7000 patients with systolic chronic heart failure to test the question of whether direct renin inhibition with the agent, aliskiren, is useful as add-on therapy to the gold standard agent (ACE-inhibitors) or may even be used as an alternative to these agents.

ATACAS Trial

Cardiac surgery activates platelets and coagulation factors, and the fibrinolytic pathway. Excessive bleeding is common. This may require surgical re-exploration and increases morbidity and mortality. Recent aspirin exposure increases surgical bleeding, and so it is routine practice in most cardiac surgical centres for aspirin to be ceased one week before elective cardiac surgery. But a recent study found that aspirin had a lower mortality, as well as less stroke, renal failure and bowel infarction (all $P < 0.01$). Another drug, tranexamic acid (TxA), is sometimes used to reduce bleeding after cardiac surgery. It works by blocking fibrinolysis ('clot breakdown') during and after surgery. It can block the bleeding risk associated with aspirin, and does not increase thrombotic risk. Meta-analyses of trials have shown that antifibrinolytic therapy reduces blood loss, need for blood transfusion and re-operation for bleeding in cardiac surgery.

This large, multi-centre, randomised, double-blind, factorial trial in 4,600 cardiac surgical patients is looking for a reduction in major complications or death with aspirin and/or TxA. We have established a trial network of at least 15 hospitals, with support from cardiac surgeons and anaesthetists from Australia, Canada and UK. Patient enrolment currently stands at 1,157 patients to date (www.atacas.org.au).

This study has received a second NHMRC Project Grant with \$3.3 million funding for four years.

ENIGMA-II Trial

More than 2.5 million anaesthetics are given each year in Australia (1:10 Australians), with the majority receiving nitrous oxide. Approximately 25 per cent of patients undergoing major surgery have known coronary artery disease (CAD) or risk factors for CAD. In 1990, approximately one million of the 25 million Americans who underwent non-cardiac surgery suffered a perioperative cardiac event, resulting in \$20 billion in costs.

Nitrous oxide interferes with vitamin B12 and folate metabolism. This impairs production of methionine (from homocysteine), used to form tetrahydrofolate and thymidine during DNA synthesis. It has been repeatedly demonstrated that nitrous oxide anaesthesia increases postoperative homocysteine levels. Chronic hyperhomocysteinaemia is associated with cardiovascular disease, and acute hyperhomocysteinaemia is known to cause endothelial dysfunction. One small trial has demonstrated an increased incidence of postoperative myocardial ischaemia in patients receiving nitrous oxide anaesthesia. Reducing postoperative myocardial infarction and death are important aims for those with CAD undergoing major surgery.

The study design and rationale underwent peer review and was published in the *American Heart Journal* (March 2009). This NHMRC-funded clinical trial involves 7,000 patients to provide a definitive evaluation of the safety of nitrous oxide anaesthesia. The primary endpoint is a composite of death and serious cardiovascular events within 30 days of surgery. To date we have enrolled over 3,808 patients in 30 centres throughout the world (www.enigma2.org.au).

INTERSTROKE

Stroke is a major global health problem, yet few studies have examined the risk factors for stroke and its subtypes in different ethnic populations representing different regions of the world. Compared to coronary heart disease, traditional risk factors (eg hypertension, hypercholesterolemia) appear to exert different magnitudes of risk for stroke and within stroke subtypes. Any effective global strategy to reduce the risk of stroke mandates a systematic and standardised study of the contribution of traditional and emerging risk factors within defined ethnic groups and geographical locations for each of the stroke subtypes. In order to provide reliable answers, these studies need to be very large, so as to include large numbers of cases of strokes of each subtype.

INTERSTROKE has been designed to achieve this by utilising a global research network of investigators centrally coordinated through the Public Health Research Institute in Hamilton, Ontario, Canada. Many members of this research network completed a similar study in 2005 for myocardial infarction (MI) called INTERHEART. INTERHEART included 30,000 participants from 52 countries and showed that nine modifiable risk factors accounted for over 90 per cent of the risk.

A similar study is necessary in stroke because:

1. the causes of stroke are far more diverse than MI;
2. many of the common risk factors for stroke and MI (eg lipids) appear to exert very different magnitudes of risk for stroke compared with MI; and
3. there are limited epidemiological studies in stroke.

This study compares risk factors in people with stroke (cases) to people without stroke (controls) in a large, international case control study that includes research centres from about 40 countries.

The results of the pilot phase of INTERSTROKE were presented at the World Congress of Cardiology in Beijing China in July 2010. Overall, self-reported hypertension was the strongest risk factor for stroke and was stronger for intracerebral haemorrhage than for ischemic stroke. A history of hypertension was associated with a more than 2.5-fold increased risk of stroke. Along with hypertension, current smoking, abdominal obesity, diet, and physical activity accounted for 80 per cent of the global risk of stroke, explaining 80 per cent of the risk of ischemic stroke and 90 per cent of the risk of haemorrhagic strokes. When additional risk factors were included in the model, including diabetes mellitus, alcohol intake, psychosocial factors, the ratio of apolipoprotein B to A1, and cardiac causes (atrial fibrillation or flutter, previous MI, and valve disease), these ten risk factors accounted for 90 per cent of the risk of stroke. Hypertension, smoking, abdominal obesity, diet, and alcohol intake were the most important risk factors for intracerebral haemorrhagic stroke.

Now that the Pilot Phase has been completed, the study has moved into the main study phase with an estimated 20,000 cases and matching controls expected to be recruited over the next two years. This phase will look at inter country and subgroup variability with the aim of developing public health strategies to reduce the incidence and severity of stroke in low and high income countries.

It is planned that up to ten centres in Australia will participate. To be successful, INTERSTROKE will involve national and international collaboration. John Varigos, from CCRE Therapeutics, is the national coordinator and, together with Graeme Hankey from the Royal Perth Hospital, will coordinate the Australian arm of the study. INTERSTROKE will have enormous implications for our understanding of the causes of stroke within Australia and around the world.



Clinical Informatics and Data Management

The Clinical Informatics and Data Management Unit (CIDMU) provides key platform technologies for the conduct of epidemiological, clinical trial and health services research. The platform technologies include;

- multi-centre clinical trials and registry data management;
- web-based, e-CRF, fax- and paper-based data capture facilities;
- web-based or telephone-based randomisation services;
- trial and site management capabilities;
- trial and site monitoring capabilities; and
- statistical data analysis and study design capabilities.

The platform technologies have been developed in accordance with international regulatory and national privacy and ethical guidelines. The following projects are being managed and conducted by CIDMU.

Melbourne Interventional Group (MIG)

The Melbourne Interventional Group (MIG) remains the only Percutaneous Coronary Intervention (PCI) Registry collecting standardised procedural and follow up data on consecutive patients across multiple sites in Victoria since June 2004.

Enrolment currently sits at over 14,500 PCI procedures. Thirty day and twelve month follow up are undertaken routinely on all participants.

Longer term outcome data is now available as linkage with the National Death Index has been undertaken in 2009. This will continue to be undertaken on a regular basis.

Since inception, MIG has continued to present widely at national and international cardiology meetings. In addition to the 17 manuscripts already published, several more are either in review or well underway.

MIG continues to collaborate widely, especially with the cardiac surgeons and the ASCTS registry.

Funding: *Industry Consortium*: Abbott, Astra-Zeneca, Biotronik, Boston-Scientific, Bristol-Myers Squibb, CSL, Johnson & Johnson, Medtronic, Pfizer, Schering-Plough, Sanofi-Aventis, Servier, St Jude, Terumo.

Publications

Lancefield T, Clark DJ, **Andrianopoulos N**, Brennan AL, Reid CM, Johns J, Freeman M, Charter K, Duffy SJ, Ajani AE, Proietto J, Farouque O; MIG (Melbourne Interventional Group) Registry. Is there an obesity paradox after percutaneous coronary intervention in the contemporary era? An analysis from a multicenter Australian registry. *JACC Cardiovasc Interv.* 2010 Jun;3(6):660-8.

Al-Fiadh AH, **Andrianopoulos N**, Farouque O, Yan BP, Duffy SJ, Charter K, Tongyoo S, New G, Yip T, **Brennan A**, Proimos G, **Reid CM**, Ajani AE, Clark DJ; on behalf of the Melbourne Interventional Group. Contemporary outcomes in women undergoing percutaneous coronary intervention for acute coronary syndromes. *Int J Cardiol.* Epub 2010 Jun 8.

Gurvitch R, Lefkovits J, Warren RJ, Duffy SJ, Clark DJ, Eccleston D, Yan BP, **Reid CM**, Brennan A, **Andrianopolous N**, Ajani AE. Clinical outcomes of drug eluting stent use in patients with ST elevation myocardial infarction. *Inter J Cardiol* 2010;143(3):283-288.

Chan W, Clark DJ, Ajani AE, Yap CH, **Andrianopoulos N**, Brennan AL, Dinh DT, Shardey GC, Smith JA, **Reid CM**, Duffy SJ. Progress towards a National Cardiac Procedure Database--development of the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) and Melbourne Interventional Group (MIG) registries. *Heart Lung Circ.* Epub 2010 Nov 3.

ASCTS

The Australian Society of Cardiothoracic Surgeons (ASCTS) National Cardiac Database Program records details of all adult cardiac surgical procedures performed in participating units across Australia. The Program publishes annual reports describing the activities and outcomes of participating units in a comparative, de-identified format.

Currently, 19 of 25 Public Hospital Units are members of the Program and six private hospitals are also participating in the registry. Since the instigation of the project in 2001, the ASCTS web database portal contains over 45,000 records. To date, 13 manuscripts arising from the project have been published include papers on an Australian Risk Prediction Model for Coronary Surgery (AusSCORE), on the short and longer term outcomes and in collaboration with other interventions.

Funding: *Industry/Government Consortium*: DHS Victoria, NSW Area Health Services, Private Hospitals (Canberra, Cabrini, Epworth, Jessie MacPherson, Lake Macquarie, Mater Health Services – Nth QLD, Flinders Medical Centre, Royal Perth Hospital, Sir Charles Gairdner, Townsville, Holy Spirit Northside – QLD).

Publications

Billah B, Reid CM, Shardey GC, Smith JA. A preoperative risk prediction model for 30-day mortality following cardiac surgery in an Australian cohort. *European Journal of Cardio-thoracic Surgery* 2010;37:1086-1092.

Chan W, Clark DJ, Ajani AE, Yap CH, Andrianopoulos N, Brennan AL, Dinh DT, Shardey GC, Smith JA, Reid CM, Duffy SJ. Progress towards a National Cardiac Procedure Database--development of the Australasian Society of Cardiac and Thoracic Surgeons (ASCTS) and Melbourne Interventional Group (MIG) registries. *Heart Lung Circ*. Epub 2010 Nov 3.

Reid CM, Brennan AL, Dinh DT, Billah B, Costoloe C, Shardey GC, Ajani AE. Measuring safety and quality to improve clinical outcomes - current activities and future directions for the Australian Cardiac Procedures Registry. *MJA Supplement*, 18 October 2010.

Dinh DT, Vijayasingham L, Ariyaratne TV, Billah B, Shardey G, Reid CM on behalf of the Australian Society of Cardiac and Thoracic Surgeons Database Project Steering Committee. ASCTS National Cardiac Surgery Database Project Annual Report 2008-2009. Melbourne VIC 2010.

Dinh DT, Vijayasingham L, Ariyaratne TV, Billah B, Shardey G, Reid CM on behalf of the Australian Society of Cardiac and Thoracic Surgeons Database Project Steering Committee. ASCTS NSW Health Services Report 2008-2009. Melbourne VIC 2010.

Australian Rheumatology Association Database (ARAD)

Collaborations between the Australian Rheumatology Association and CCRE have resulted in the establishment of the Australian Rheumatology Association Database (ARAD) – a voluntary national registry which collects important health information from Australian patients with inflammatory arthritis. The aim of the registry is to monitor the short and long term benefits and safety of new biological disease-modifying anti-rheumatic drugs.

Information is collected from patients via questionnaires every six months, which include questions about medical history, medication history, responses to medications, physical functioning and quality of life. Rheumatologists are provided bi-annual reports. CCRE Therapeutics has recently developed a web-based system which allows individuals to complete their questionnaire on-line, which has been very well received by participants.

Patients and rheumatologists across Australia contribute to ARAD, with over 4,000 participants enrolled in the registry and over 200 rheumatologists referring patients to ARAD.

Funding: NHMRC Enabling Grant, Australian Rheumatology Association.

Publications

Staples MP, March L, Lassere M, Reid C, Buchbinder R. Health-related quality of life and continuation rate on first-line anti-tumour necrosis factor therapy among rheumatoid arthritis patients from the Australian Rheumatology Association Database. *Rheumatology* Epub 2010 Oct 7.

ANZIC-RC Collaborations

The Clinical Informatics and Data Management Unit (CIDMU) provides data management services for a number of investigator-initiated clinical studies being undertaken by the Australia and New Zealand Intensive Care Research Centre (ANZIC-RC). Actively recruiting studies during 2010 included the STATInS study; a phase II randomised controlled trial of atorvastatin therapy in intensive care patients with severe sepsis, SPICE study; a prospective, observational inception cohort study of Sedation Practices in Intensive Care, the Blood Observational Study; a study to benchmark current blood transfusion practices in intensive care units across Australia and New Zealand, INFINITE study; a 'real time' registry of all patients admitted with Influenza A to Australian and New Zealand ICUs between 1 June 2009 to the end of winter 2010 and EPO-TBI study; determining the efficacy of erythropoietin in improving neurological function after traumatic brain injury. A web data management system has recently been developed for EPO-TBI study. This web-based system has paved the way for faster and more efficient data capture for clinical studies.

Funding: NHMRC Project Grants

Sentinel Surveillance Study

The Sentinel Study is a linked sentinel survey of chlamydia, HIV, syphilis and hepatitis C in Victoria developed by the Burnet Institute and undertaken in collaboration with the Department of Human Services Victoria, the Victorian Infectious Disease Reference Laboratory and the Melbourne Sexual Health Centre. The Clinical Informatics and Data Management Unit (CIDMU) is undertaking data management for this study that will be used to monitor HIV, hepatitis C and sexually transmitted infections incidence, prevalence, risk behaviour and testing patterns in order to inform and evaluate relevant public health strategies. There are sixteen sites across Victoria actively involved in recruiting participants to the study, with over 35,000 participants having completed sentinel surveys to date. Department of Health has extended its funding until 2012.

Funding: Industry

TRIAGE

TRIAGE is a prospective study conducted in eight metropolitan and regional hospitals nation-wide. The primary aim is to improve the accuracy and speed of diagnosis of congestive heart failure (CHF) and acute coronary syndromes (ACS) in the Emergency Department. This was done by comparing the Biosite Triage SOB panel (using Troponin I, Myoglobin, CKMB, D-dimer, BNP) with clinical assessment (history and physical examination) for the presence or absence of CHF, ACS and pulmonary emboli in patients presenting with breathlessness with or without chest pain.

A total of 703 patients were enrolled nation-wide. Participant follow-ups were conducted at 24 hour, 30 day and 6–12 month time periods.

Abstracts based on 30 day outcome data have been presented nationally and internationally. Longer-term outcome analysis has been undertaken on 687 eligible patients. Works are being undertaken towards multiple papers utilising longer-term outcome data, with the view to publication and presentation of results in the near future.

Funding: Industry





ASia Pacific Evaluation of Chest pain Trial (ASPECT)

The purpose of this study was to validate a clinical pathway ('accelerated chest pain algorithm') of using ECG and/or Risk Stratification Tools in conjunction with serial biomarkers (with blood levels of Troponin I, CKMB 'Delta', and Myoglobin 'Delta' measurements) in patients presenting with ACS.

Recruitment occurred at 14 urban emergency departments in nine countries in the Asia-Pacific region between November 2007 and July 2010. A total of 3651 patients were recruited. Site auditing was completed in 2010 with all sites being visited by CCRE staff who were trained to undertake the audit activity.

Final results are awaiting publication in a leading medical journal.

Funding: Alere Pty Ltd

Australian Cardiac Procedures Registry (ACPR)

The ACPR began in 2008 as a pilot project with funding provided by the Australian Commission on Safety and Quality in Healthcare. The aim of the pilot was to test and validate the draft 'Operating Principles and Technical Standards' for Australian Clinical Quality Registries' whilst monitoring the safety and quality of cardiac procedures.

Minimum core datasets were developed across three areas – Percutaneous Coronary Interventions (PCI), Cardiac Surgery and Implantable Cardioverter Defibrillator (ICD) devices and Cardiac Resynchronisation Therapy (CRT) devices. The surgery and PCI datasets were modelled on the Australian Society of Cardiothoracic Surgeons Victorian database project and the Melbourne Interventional Group PCI registry, with the device dataset a new development. Work commenced in 2010 to expand the device dataset to include pacemakers.

Eleven sites across four states participated in the ACPR pilot with data collection ceasing in August 2010.

Significant work has been undertaken during 2010 towards developing a sustainable funding model for both the ACPR and clinical quality registries. Once sustainable funding has been secured ACPR will be rolled out to private and public hospital across Australia utilising the framework and governance developed over the past two years.

Funding: Australian Commission of Safety and Quality.

Publications

Reid CM, Brennan AL, Dinh DT, Billah B, Costolloe CB, Shardey GC, Ajani AE. Measuring safety and quality to improve clinical outcomes – current activities and future directions for the Australian Cardiac Procedures Registry. *MJA* 2010;193(8):S107-S110.

Pharmacoepidemiology/ Translational Research

Clozapine and Myocarditis Study

Clozapine is an exceptionally effective drug for the treatment of schizophrenia, and one measure of its effectiveness is the very low rate of suicide while patients are taking it. However, it has two serious side effects, one of which is agranulocytosis, which is prevented by a mandatory blood monitoring scheme. The other adverse effect is myocarditis, or inflammation of the heart muscle, which occurs in about two per cent of people starting clozapine and is fatal in about ten per cent of these.

The clozapine and myocarditis study is a case control study designed to identify risk factors for myocarditis, including a genetic mutation which may predispose the individual to developing this adverse effect. If such a mutation is identified, genetic screening preceding clozapine prescribing will permit clozapine to be used both more widely and more safely.

Because most patients start clozapine as inpatients, we have been able to document daily clozapine doses, concomitant medication, vital signs, pathology results, smoking status and concurrent disease. This will enable us to determine whether any of these factors may modify the genetic predisposition. A possible outcome, which will need further investigation, is that those with the genetic predisposition will be able to take clozapine safely with modification of factors like clozapine dose and other medication.

At the end of 2010, we had documented 106 cases and 296 controls, and had samples for genetic analysis from 61 individuals (24 cases). Our aim is to conduct the DNA analysis on 50 cases and 100 controls. This will give us similar numbers to those used for the successful genetic analysis of other drug hypersensitivity reactions.

Publications

Ronaldson KJ, Taylor AJ, Fitzgerald PB, Topliss DJ, Elsik M, McNeil JJ. Diagnostic characteristics of clozapine-induced myocarditis identified by an analysis of 38 cases and 47 controls. *J Clin Psychiatry*. 2010 Aug;71(8):976-81.

The Cardiovascular Disease Epidemiological Modelling Project

This research collaboration with Sanofi-Aventis, and colleagues from the Baker IDI Heart & Diabetes Institute and the Royal Melbourne Hospital aims to use innovative statistical modelling techniques to model the burden of cardio-metabolic diseases in the Australian population. It also aims to look at the effectiveness and cost-effectiveness of preventive interventions to address these chronic diseases and their sequelae. Supported by an ARC Linkage grant, this program of research includes scholarship support for PhD candidate Ella Zomer. Ella's research focuses upon modelling the effectiveness of potential strategies for reducing cardiovascular disease risk in Australians with metabolic syndrome or 'pre-diabetes'.

Major activities of this project during 2010 included economic implications of atherothrombotic disease, using modelling to prioritise CVD risk factor targeting in metabolic syndrome and modelling of non-pharmacological CVD risk reduction strategies.

Funding: ARC Linkage Grant

Publications

Zomer E, Owen A, Magliano DJ, Liew D, Reid C. Validation of two Framingham cardiovascular risk prediction algorithms in an Australian population: the 'old' versus the 'new' Framingham equation. *Eur J Cardiovasc Prev Rehabil*. Epub 2010 May 13.

INTEGRATE

Conducted by CCRE in collaboration with Bristol-Myers Squibb, the INTEGRATE study focussed upon evidence-based management of hypertension in general practice in Australia. More than 350 General Practitioners participated in the initial clinical audit of hypertension management, which examined the factors contributing to achievement of blood pressure targets in Australian patients. This was followed by a trial of an education program designed to assist GPs to utilise clinical guidelines to optimise blood pressure control in their patients. With data collection completed in late 2009, in 2010 findings from the INTEGRATE study were presented at the High Blood Pressure Research Council of Australia Annual Scientific Meeting. INTEGRATE has informed the development of an expanded program of research by CCRE focussing upon evidence-based management of cardiovascular disease.

Funding: Bristol-Myers Squibb

Caulfield Clinical Trial Centre

The Caulfield Clinical Trial Centre acts as our community-based research clinic. Most of the studies involve working with general practitioners across Melbourne and Australia as well as with healthy volunteer subjects who donate their valuable time to assisting with our research.

SCREEN-HFL (SCReening Evaluation of the Evolution of New Heart Failure) – a longitudinal study

Chronic heart failure (CHF) is a major burden on the community due to the poor quality of life and premature death of affected individuals, as well as the costs of care. Effective therapies for the treatment and prevention of CHF are readily available, and there is great potential to cost-effectively improve the application of these therapies through improved identification of two key patient groups: those with unrecognised CHF, and those at greatly increased risk of CHF due to left ventricular dysfunction (LVD).

Studies have demonstrated the utility of both BNP and NT-proBNP as screening tools for heart failure during acute presentations of shortness of breath to the Emergency Room. However, despite a large and rapidly expanding database regarding the utility of BNP and NT-proBNP in clinical practice, little is known about the peptide as a screening test for LV dysfunction in patients at high-risk for subsequent development of this condition and/or overt heart failure.

The objective of the SCREEN-HFL, a longitudinal study, is to establish the utility of plasma NT-proBNP level, and change in NT-proBNP level, in the identification of individuals with cardiovascular risk factors destined to develop CHF and/or echocardiographic evidence of LVD during five years of observation.

The study investigators, in collaboration with St Vincent's Research Institute and St Vincent's Health, began a joint undertaking in 2009 for a follow-up of the entire SCREEN-HF study cohort – a total of 3997 study participants. The inclusion criteria for the SCREEN-HF cross-sectional study were age 60 and over, not previously diagnosed with heart failure but having one or more risk factors for heart failure (such as a heart attack, stroke, diagnosed hypertension or diabetes).

By the end of 2010, a total of 2801 study participants have attended a study visit at either Caulfield CCRC Clinical Trial Centre or St Vincent's Hospital Cardiology unit to undergo an echocardiography, ECG, clinical examination and quality of life assessments and have been reviewed in regards to cardiovascular events, symptoms of heart failure and current medications. Blood samples are also collected and stored for later measurement of novel cardiovascular biomarkers. It is anticipated that the remainder of echocardiography examinations will be completed by mid-2011. The study participants will be followed up on an annual basis via phone in regards to cardiovascular events, symptoms of heart failure and current medications.



The study endpoints are:

- Combined **prevalence** of previously undiagnosed CHF and/or LVD.
- Combined **incidence** of cumulative new CHF at five years and new LVD at three years, in those who were free of CHF and LVD at baseline.
- **Cost-effectiveness analysis** of the use of a threshold plasma NT-proBNP level to determine whether echocardiography should be performed to detect LVD.

This study will address one of the key issues in the utility of screening of high-risk patients for subsequent heart failure using a simple blood-based screening test.

Funding: NHMRC Project Grant, MBF.

The Second Australian National Blood Pressure (ANBP2) Follow-up Study

The Second Australian National Blood Pressure Study (ANBP2) was a randomised controlled trial designed and conducted by the High Blood Pressure Research Council of Australia. It was designed to determine if there was any difference in outcome (defined by total cardiovascular events and mortality) between elderly hypertensive patients, aged 65 to 84 years, who were randomised to active treatment with an angiotensin-converting enzyme (ACE)-inhibitor based-regimen or treatment with a diuretic-based anti-hypertensive regimen.

ANBP2 was conducted in general practices throughout Australia, with recruitment taking place between April 1995 and June 1998. In total, 6083 subjects (mean age of 71.9 years at baseline) were enrolled in the study from 1594 general practices and followed for a median of 4.1 years. The results of ANBP2 showed that initial treatment based on ACE inhibitor therapy provided an 11 per cent reduction on all cardiovascular events or death from any cause in comparison to basing treatment on a diuretic.

The ANBP2 Follow-up Study is examining the risk of heart failure in older Australians with hypertension (high blood pressure). This study is designed to undertake a prospective cohort follow up study of all subjects in ANBP2 (who had consented to follow up) with the primary aim being to determine the rate of all-cause and cardiovascular mortality and morbidity in this elderly hypertensive population. In addition, the study will determine the progression from hypertension to CHF of the population and the effect of initiating treatment based on ACE inhibitor versus that based on diuretic on subsequent CHF, together with healthcare utilisation and costs associated with this management of these elderly Australian hypertensives. This will permit modelling of healthcare resource requirements in an ageing cohort and quantification of disease burden in an elderly Australian cohort.

The ANBP2 participants, who gave consent at the end of the ANBP2 study for further contact, were sent questionnaires in the mail to complete and were also asked to give a questionnaire to their general practitioner to complete and return. Participants (1726) and GPs (1222) returned questionnaires which will allow determination of the long-term cardiovascular consequences of antihypertensive treatment, comparing outcomes in those randomised to treatment with ACE-inhibitors with those treated with diuretic agents. Through data linkage with the National Death Index and re-contacting of participants ten years after completion of the original study, it was ascertained that approximately 32 per cent of the original study participant cohort have died.

In 2010, Melbourne metropolitan participants were invited to attend for further follow-up and 150 participants consented and attended the CCRE Clinical Trial Centre. The study visit included an ECG and echocardiographic and clinical examination (including blood pressure, ankle brachial index, pulse wave analysis, body composition) and also included data collection relating to current medications, updating medical history, heart failure symptoms, administration of a standardised validated depression questionnaire.

Blood samples were also collected with haemoglobin, FBE, urea and electrolytes and NT-proBNP being measured. Additional aliquots collected from each participant have been stored in a -80° freezer for later measurement of cardiac biomarkers. The mean age of this cohort was 83.6 years, with eight per cent being over the age of 90 years. The data for this study will be fully analysed and presented in 2011.

Publications

Nelson MR, Ryan P, Tonkin AM, Ramsay E, Willson K, Wing L, Reid CM on behalf of the Second Australian National Blood Pressure Study Management Committee. Prediction of cardiovascular events in subjects in the Second Australian National Blood Pressure Study. *Hypertension* 2010;56:44-48.

Nelson MR, Alkhateeb AN, Ryan P, Willson K, Gartlan J, Reid CM on behalf of the Second ANBP2 Management Committee. Physical activity, alcohol and tobacco use and associated cardiovascular morbidity and mortality in the Second Australian National Blood Pressure study cohort. *Age and Ageing* 2010;39:112-116.

CLEAR (Cardiovascular Longitudinal Evaluation and Assessment of Risk)

This study is a cross-research database to incorporate current and future investigator-driven studies at CCRE. The aims are to improve data collection, standardise cardiovascular risk information and enhance recruitment into research projects.

Future CCRE studies will incorporate the use of standardised case report forms. Participants, at the time of recruitment, will be consented to include their study data in the CLEAR database, allowing long-term follow up of cardiovascular morbidity and mortality. Currently, clinical trials have a finite follow up period; the CLEAR study involves lifetime follow up and will establish a cohort of volunteers suitable for recruitment into future studies. Of the SCREEN-HF study participants 2617 have additionally consented to the CLEAR follow-up.

HOPE-3 (Heart Outcomes Prevention Evaluation)

HOPE-3 is a five-year multinational double blind longitudinal study to evaluate the effects of the 'polypill', namely combined cholesterol and blood pressure lowering, in 12,500 study participants who are without vascular disease at baseline. The study is expected to identify safe and effective CV prevention strategies which could substantially reduce the risk of CVD in large proportions of the adult population worldwide.

The trial participants are those who do not have a clear indication or contraindication to lipid lowering or blood pressure lowering with any of the study drugs. In order to exclude very low risk people, in addition to age, one additional CV risk factor is required for eligibility in the trial.

The inclusion criteria for the study are women aged over 60 years and men aged over 55 years, with one additional CV risk factor such as current or recent smoker, waist/hip ratio over 0.90 in men and over 0.85 in women, family history of premature CHD in first degree relatives (age under 55 years in men or under 65 years in women).

The primary outcome is the composite of CV death, nonfatal myocardial infarction (MI), nonfatal ischemic stroke, resuscitated cardiac arrest and arterial revascularisations. Follow-up study visits occur every six months for an average of at least five years.

The study, being conducted in over 20 countries, first began recruitment in May 2007 and after much slower than expected recruitment worldwide, study recruitment was officially closed on November 9, 2010 as the last participant was finally randomised. Australia ended recruitment with 45 randomised study participants. The key part of the study is to ensure full follow-up of all study participants and to try and maintain study medication adherence. Two year annual visits have commenced. Australian study participants have a rate of 2.2 per cent of study participants 'off study medication', a much lower rate than most other countries, with Canada – 8.1 per cent, South Africa – 14.2 per cent and Slovakia – 20 per cent. Australian sites also maintain excellent data quality standards with few unresolved data queries.

CCRE CTC recruited study participants as well as coordinating and monitoring the other sites in Australia: The George Institute for International Health, Sydney; The George Institute for International Health, School of Rural Health Research Centre, Dubbo; and Canberra Hospital.

Funding: This investigator-initiated study is sponsored by the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Canada.

HOPE-3 arterial compliance sub-study

Funding was obtained from the National Heart Foundation (NHF) to conduct a sub-study to assess the independent and the combined effects of blood pressure lowering and lipid lowering on arterial stiffness in the HOPE-3 study participants who attend CTC.

Prior to receipt of study medication, those subjects willing to participate in the sub-study had an arterial stiffness assessment conducted at the Clinical Trial Centre. Pulse wave velocity (PWV) is measured between the carotid artery and the femoral artery using non-invasive applanation tonometry. Systemic arterial compliance is a non-invasive test of the elasticity of the arteries and involves measurements of blood pressure and blood flow using ultrasound transducers positioned above the sternum to image the ascending aorta. Unfortunately only three study participants were recruited to this sub-study.

SAVE (Sleep Apnea cardioVascular Endpoints)

The SAVE study is a collaborative, Phase III, multi-centre, open-label randomised controlled trial of continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnoea (OSA) to prevent cardiovascular disease. The primary objective of the study is to evaluate the hypothesis that in patients with moderate to severe OSA, CPAP added to standard care will reduce the incidence of major and minor CV events relative to standard care alone, as measured by the composite endpoint cluster of CV death, myocardial infarction, stroke, hospitalisation for heart failure and hospitalisation for an acute ischaemic cardiac event or cerebral event.

OSA is a condition in which a person, because of relaxation of throat muscles, stops breathing for several seconds at a time, many times over, during sleep. Research indicates that it may lead to high blood pressure and increase the risk of heart attacks and strokes. One of the current treatments available for severe OSA is the use of CPAP. CPAP involves the use of a small mask placed over the nose or nose and mouth, during sleep where air is gently pushed into the lungs and allows people to continue breathing normally. CPAP has been shown to effectively reduce snoring, obstructive episodes and daytime sleepiness. Some short-term research studies have shown that CPAP may help to reduce blood pressure.

This CPAP device is approved in Australia and internationally for use in the treatment of sleep apnoea. Participants are eligible for the study if they have at least one of the following risk factors for OSA: a previous heart attack; heart disease requiring bypass graft surgery, angioplasty or stenting; stroke, or a transient ischaemic attack (TIA); or angina.



It is anticipated that about 5000 patients world-wide will be recruited and that the study will last up to five years. Recruitment is continuing and the global total of 829 patients is inclusive of Australia randomising 124 patients, New Zealand randomising 25 patients, and China randomising 680 patients. Due to the difficulty of finding suitable study participants and staffing constraints, CTC is no longer actively recruiting for SAVE but is continuing with study follow-up for all those randomised to date.

This investigator initiated study is being conducted by an international group of researchers based in China, Europe, USA and Australia. The SAVE International coordinating centre is based at the Adelaide Institute for Sleep Health, Adelaide, South Australia. In the NHMRC grants announced at the end of 2010, the SAVE study received \$2.9 million over five years, which will see the study into 2014.

STABILITY (The STabilisation of Atherosclerotic plaque By Initiation of darapLadIb TherapY

This is a randomised, placebo-controlled, double-blind, parallel-group, multi-centre, event-driven trial of an investigational product called darapladip, in people with chronic coronary heart disease receiving standard practice care at the time of entry into the study. Coronary Heart Disease (CHD) is a condition in which deposits of fat and cholesterol, called plaque, build up over time in the heart or the blood vessels that supply blood to the heart muscle. This build up of plaque is part of a process called 'atherosclerosis', or hardening of the arteries. People with CHD are at risk of having a heart attack or stroke.

Darapladip reduces the activity of a naturally occurring chemical in the body, an enzyme known as Lp-PLA2. Increased plasma levels of this enzyme are associated with an increased risk of cardiovascular events. Clinical studies of darapladip have shown dose-dependent inhibition (the higher the dose the greater the inhibition) of both plasma and intra-plaque Lp-PLA2 activity. Stopping the production of this enzyme may be beneficial to cardiovascular patients who are also taking standard therapies such as lipid lowering medication called statins. This international study recruited 15,828 participants who were randomised to study medication with 50 per cent allocated to the darapladip group (receiving 160mg of enteric coated darapladip daily) and 50 per cent to the placebo group. The study participants will be followed for up to three years.

The study recruitment closed in 2009, with 306 participants at 16 sites in Australia. Twenty-three participants were recruited by the Clinical Trial Centre with twenty-one of the study participants being followed every six months (one study participant has moved to Queensland and is attending study visits at one of the study sites in Brisbane). The eighteen month follow-up visits were conducted in 2010. This study is funded by the pharmaceutical company, GlaxoSmithKline.

Funding: GlaxoSmithKline Australia Pty Ltd.

KANYINI-GAP (Kanyini Guidelines Adherence with the Polypill Study)

The Guidelines Adherence with the Polypill collaboration has been formed between the George Institute for International Health, the Department of General Practice, Western Clinical School, University of Sydney, CTC, Monash University and the Baker IDI.

The Kanyini-GAP study is a prospective, open, randomised controlled clinical trial (n=1000 non-Indigenous and Indigenous individuals) of a polypill-based strategy compared to usual care among individuals at high risk of cardiovascular events based in general practices and Indigenous specific health services, augmented by a cost-effectiveness analysis and a formal process evaluation.

Current Australian therapeutic guidelines recommend, on well-established evidence, long-term treatment of individuals at high cardiovascular risk with antiplatelet, blood pressure-lowering and cholesterol-lowering drugs. However, there is a large gap between recommendations and actual practice, and innovation is required to realise the full potential of these preventive treatments. Fixed-dose combination therapy with a 'polypill' is possibly a more simple way of providing these guideline-indicated medications and represents a major new opportunity to address this gap. It has been proposed that a polypill could improve adherence to recommended treatment by reducing the overall complexity of dosing regimens for doctors and patients, and improve access to treatment by reducing costs.

The objective of the study is to assess whether provision of a polypill (containing low dose aspirin, a statin and two blood pressure lowering medicines) compared to usual cardiovascular medications improves adherence and clinical outcomes in high-risk patients at two years. The secondary aims are to measure prescription of combination therapy, barriers to adherence, quality of life, safety, cardiovascular events, renal events, prescriber acceptability, and healthcare resource consumption. The study is being conducted in mainstream general practice in both NSW and Victoria as well as in several Aboriginal Community Controlled Health Services (ACCHS) in metropolitan, rural and remote communities in NSW, NT, and QLD and one government funded Indigenous health service in QLD.

Originally Monash University was to be responsible for recruiting approximately 100 non-Indigenous study participants in the Melbourne area in association with local general practices. However due to the fact that Monash has recruited well to date, The George Institute have now extended recruitment to 200 study participants in Victoria. To date, 94 study participants have been enrolled and 83 had been randomised at six general practices in the Dandenong /Mornington Peninsula area.



The general practices collaborating with CCRE CTC are: Select Medical Centre, Bangholme; Beach St Medical Centre, Frankston; Langton Medical Centre, Dandenong, Dandenong Medical Centre, Dandenong; Lesdon Avenue Medical Centre, Cranbourne; and Mount Martha Village Clinic, Mount Martha. A number of other GPs have agreed to take part in the study and these GP practices will be initiated in 2011.

Funding: This is an investigator-initiated study sponsored by The George Institute for International Health and is funded by an NHMRC grant.

Publications

Liu H, Patel A, Brown A, Eades S, Hayman N, Jan S, Ring I, Stewart G, **Tonkin A**, Weeramanthri T, Wade V, Rodgers A, Usherwood T, Neal B, Peiris D, Burke H, **Reid CM**, Cass A. Rationale and design of the Kanyini guidelines adherence with the polypill (Kanyini-GAP) study: a randomised controlled trial of a polypill-based strategy amongst Indigenous and non Indigenous people at high cardiovascular risk. *BMC Public Health* 2010;10:458.

ABIDING (Ankle Brachial Index Determination by oscillometric method IN General practice)

The ABIDING Study aimed to determine if the oscillometric determination of ankle brachial index (ABI) by general practice nurses is a valid and reliable method. Practice nurses were chosen rather than GPs as, with the current GP workforce shortage and the promotion of the concept of a 'primary care team' supported by MBS item numbers for nurses, it was thought to be more likely to be implementable. GPs have ready access to oscillometric sphygmomanometers as recently they were distributed to GPs through the High Blood Pressure Research Council of Australia.

The REACH Registry Australian DMC, located at the Department of Epidemiology and Preventive Medicine, Monash University, was used to recruit GP practices to participate in the study. The REACH Registry was an international register of those with established cardiovascular disease or at high risk of it. It was demonstrated in the REACH Registry that peripheral arterial disease (PAD) is prevalent in high risk individuals in the Australian primary care environment. In addition, it was shown that those with the condition had the highest level of cardiovascular disease (CVD) morbidity and mortality over the subsequent year.

Oscillometric devices allow Ankle-Brachial Index (ABI) measurement without a Doppler device and the study aimed to validate these devices in an Australian general practice setting. Secondary aims of the study are to establish the change in prevalence over time of PAD in a defined high risk general practice population, to ascertain the utility of oscillometric devices for the diagnosis of PAD and to monitor the change since baseline of the ABI using the standard technique, BMI, waist circumference measure and Edinburgh Claudication score.

Study participants (250) at 45 general practices in the Melbourne metropolitan area, Kyneton, Kilmore, Sunbury, Woodend, Warrnambool and Port Fairy were consented and took part in the study. One of the limiting factors in the study was the availability of the practice nurses. Some of the REACH practices did not have practice nurses and so were unable to take part in the ABIDING study. Data will be analysed and presented in 2011.

Funding: This study was funded by an NHMRC grant and was led by Professor Mark Nelson, University of Tasmania.

CLARIFY (prospective observational Longitudinal Registry of patients with stable coronary artery disease)

CLARIFY is an international, prospective, observational, longitudinal registry in stable coronary artery disease (CAD) outpatients with five-year follow-up. The CLARIFY registry is being undertaken to improve knowledge about the care of outpatients with CAD and 73 cardiologists around Australia were recruited and provided baseline patient data for the registry. Each cardiologist invited to participate to take part in this registry in Australia was asked to recruit approximately 15 consecutive participants who satisfied the inclusion/exclusion criteria and to follow these participants for up to five years. The patient population of the CLARIFY registry is intended to reflect the entire international spectrum of outpatients with CAD.

CAD is the major cause of mortality worldwide today and continues to be a major burden on public health. The ageing population and the ever improving prognosis of coronary patients due to more effective treatments for acute coronary syndrome, revascularisation, and improved prevention, means that an increasing number of patients now live as outpatients, with or without angina symptoms.

To better characterise these patients, this large international observational, longitudinal registry has been designed to collect data on the current status of outpatients with stable CAD including their demographic characteristics, clinical profiles, therapeutic strategies, and outcomes. For the CLARIFY registry, stable CAD is defined as a history of documented myocardial infarction of more than three months, prior coronary revascularisation, chest pain with documented myocardial ischaemia or coronary stenosis of >50 per cent proven by angiography. Patients were excluded from taking part in the registry if, at baseline, they had been hospitalised for cardiovascular disease within the previous three months, had a planned revascularisation, severe cardiovascular disease such as advanced heart failure, severe valve disease, history of valve repair/replacement, or had any conditions that could impede participation for the five-year follow-up.

The registry enrolled participants in more than 30 countries over four continents, 30,000 outpatients and will follow them up annually for approximately five years. The information collected includes information regarding risk factors, medical history, anthropometric indices, blood pressure, and heart rate, laboratory measurements, treatments and cardiovascular events and procedures. In Australia, 73 physician investigators enrolled 846 participants in the registry. CCRE CTC is working with Servier Aust Pty Ltd and together were responsible for the supervision of all site initiations and for the on-going motivation of physician investigators.

Funding: Servier Australia Pty Ltd.

Research Training and Education

Research Student Reports

Fourth Year

Dr Michele McGrady, MBBS, FRACP

Thesis title: Epidemiology of Left Ventricular Dysfunction and Heart Failure in High Risk Populations

Concerns over the rising prevalence of heart failure, with its attendant high morbidity, mortality and cost of care, are leading to an increased focus on earlier diagnosis and prevention when treatments are likely more effective and cost effective. The prognosis once a heart failure hospital admission has occurred remains grim.

Prior to the development of symptoms of heart failure there are structural and functional changes in the heart that can be detected on echo and proven treatment that improves quality of life and survival. Drivers of increasing heart failure prevalence include not only increasing longevity and improved survival with heart failure but also increasing heart failure risk factors, such as diabetes, obesity and hypertension. Australia has limited data on the prevalence of heart failure, asymptomatic left ventricular dysfunction and the underlying causes.

Our work involves two high risk populations looking at epidemiology of heart failure and asymptomatic LV dysfunction and the underlying predictors of these changes. The two populations are:

SCReening Evaluation of the Evolution of New Heart Failure (SCREEN HF).

An elderly high risk population (>60 years plus >1 heart failure risk factor) without a previous diagnosis of known HF or left ventricular dysfunction. Following initial screening (n=3500), the 665 participants with NT-proB natriuretic peptide (NT-proBNP) in the highest quintile, and 50 from the lowest quintile, have completed cardiac assessment including echocardiogram to assess cardiac structure and function. A significant burden of LV dysfunction has been observed in this high risk population.

The Heart of the Heart study. A population of Aboriginal adults living in Central Australia. This very young population, with median age 20 years has twice the mortality from heart failure as the non-Indigenous Australian general population. High prevalent heart failure risk factors have been previously documented including coronary disease, hypertension, and diabetes; however, there is also a high prevalence of rheumatic heart disease. The cause of heart failure in these people has not been previously documented. Four hundred and thirty-six adults, in diverse geographical settings from Alice Springs Town to remote communities and town camps, had full cardiovascular assessment including echocardiograph. Preliminary findings are of a high burden of structural cardiac changes and heart failure.



Ms Zanfeni Ademi, MPharm, MPH

Thesis title: Quantifying the value of therapeutic approaches to disease management using registries to undertake cost of illness and cost-effectiveness analysis

Chronic diseases such as cardiovascular disease impose a major burden on health and on the economy of a country, impacting directly through higher health care expenditure and indirectly through productivity losses. A number of cardiovascular registries focussing on primary and secondary prevention have been running for a number of years. They have contributed significantly to knowledge about the natural history and treatments of cardiovascular disease. However, not many cardiovascular patient registries report the cost of illness and cost-effectiveness data. We recommend that to expand their spectrum of importance, relevance and to fill evidence gaps, cardiovascular registries should endeavour to report cost data alongside other epidemiological outcomes.

In general, the aim of the study is to provide the best available data to health practice from a variety of sources, in order to better understand the burden of atherosclerosis. There is currently limited information about the economic burden of atherosclerosis in Australia, and its determinants. Without such information, decision-makers are unable to address prevention strategies and advise on future resource allocations. Specifically, the objectives are to estimate the costs of managing cardiovascular disease in the contemporary, Australian setting, and to examine the cost-effectiveness of improving treatment coverage among people with, or at high risk, of cardiovascular disease.

The analyses are based on Australian data drawn from a large, prospective cardiovascular registry: the REACH registry. The study applied the bottom up costing approach to health expenditures using one year and two year follow up data from Australian subjects recruited into the international REACH Registry. It applied regression and count models to ascertain the impact of cardiovascular risk factors and outcomes in healthcare costs, and have explored the causes of any difference found. In addition, it used decision analysis tree model to show the cost-effectiveness and treatment gap between clinical practice and recommendations with regard to cardiovascular disease.

Dr Suree Lekawanvijit, MD (Hons 1), FRCPATH

Thesis title: Cardiorenal Syndrome: Pathophysiology and Role of Protein-Bound Uremic Toxins & Biomarkers

Heart failure (HF) and chronic kidney disease (CKD) are closely interrelated. Failure of one organ can cause dysfunction of the other which in turn accelerates failure of both, leading to the term 'cardiorenal syndrome'. However, the pathophysiology is still unclear especially when the first damaged organ is the heart. The first in vivo study using chronic heart failure model induced by coronary arterial ligation (myocardial infarction (MI) model) shows that MI animals develop renal dysfunction. Post-MI renal dysfunction is reversible at early stages but seems to be progressive and permanent over time in association with progressive renal fibrosis mediated by the Smad-dependent TGF- β signalling pathway. This study also identifies kidney injury molecule-1 (KIM-1) as a potential biomarker for kidney injury in post-MI setting. This work was presented at AHA Scientific Sessions 2009. The manuscript is under review for publication.

In the setting of CKD, traditional cardiovascular risk factors such as hypertension, diabetes and hyperlipidemia alone are not enough to explain the unacceptably high cardiovascular (CV) death observed. Indoxyl sulfate (IS), a protein-bound uraemic toxin accumulated in CKD patients, is ineffectively removed by current conventional hemodialysis and is associated with renal fibrosis and CKD progression. We therefore hypothesize that IS has adverse cardiac effects (which may contribute to CV mortality in CKD). In this in vitro study, IS has been demonstrated pro-fibrotic and pro-hypertrophic effects on cultured cardiac cells, for the first time, as well as a pro-inflammatory effect on monocytic cells. This work was presented at AHA Scientific Sessions 2008 and won the AHA Best Scientific Poster Award (Basic Science). The paper has been published in the European Heart Journal (2010).

Further to the IS project, we conducted another in vivo study in a renal failure (five out of six of kidney tissue removed) model using AST-120 treatment (an IS lowering agent, blocking absorption of IS precursors through the gut). This study determined if AST-120 prevent cardiac fibrosis, hypertrophy and inflammation; and also to confirm such findings previous found in the IS in vitro study. AST-120 improved cardiac fibrosis (in a blood pressure-independent manner) in association (and correlated) with reduction in serum IS levels. This work has been accepted to be presented at ACC 2011.



This project aims to use epidemiological modelling to explore different intervention strategies and identify the most effective and cost-effective means of cardiovascular disease prevention in patients with metabolic syndrome.

Findings from this study have been presented both nationally at the High Blood Pressure Research Council 2008 and Cardiac Society of Australia and New Zealand 2010, and internationally at the European Society of Cardiology 2009.

Ella plans to submit her thesis by publication in late 2011.

Publications

Zomer E, Owen A, Magliano DJ, Liew D, Reid C. Validation of two Framingham cardiovascular risk prediction algorithms in an Australian population: the 'old' versus the 'new' Framingham equation. *Eur J Cardiovasc Prev Rehabil*. Epub 2010 May 13.

Second Year

Ms Thathya Venu Ariyaratne, BBiomedSci (Hons)/BEconSc

Thesis title: Long-term outcomes and cost effectiveness of coronary artery bypass graft surgery (CABG) and percutaneous coronary interventions (PCI)

Coronary heart disease (CHD) is the most common cause of death in Australia and a major cause of disability. Two common procedures used to treat patients with CHD are coronary artery bypass graft (CABG) surgery and percutaneous coronary intervention (PCI). Sometimes the best choice of treatment for a particular patient is not clear, and to date there has not been a large population study on the long term outcomes for patients and health system costs associated with each of these procedures in an Australian context.

The project would involve record linkage of several separate data sources (ASCTS, MIG and the Victorian Admissions Episode Dataset (VAED) to determine the costs and long term outcomes for CABG and PCI patients. The results of this study will help policy makers and clinicians to make informed decisions about the best care for patients with CHD.

Progress to date

The record linkage to VAED has been ethically approved by the majority of Victorian hospitals participating in the ASCTS and MIG registries, Monash University and the Department of Health.

Scholarship: National Heart Foundation Postgraduate Research Scholarship.

Circulating IS was also found to be increased in MI animals (in which progressive renal fibrosis has been demonstrated) compared to sham animals. We have conducted a further intervention study of 16-week MI model with AST-120 treatment. The preliminary analysis shows a reduction in renal fibrosis in AST-120 treatment groups. Further investigation is under way.

Publications

Lekawanvijit S, Adrahtas A, Kelly DJ, Kompa AR, Wang BH, Krum H. Does indoxyl sulfate, a uraemic toxin, have direct effects on cardiac fibroblasts and myocytes? *Eur Heart J* 2010;31:1771-79.

Third Year

Ms Ella Zomer, BBiomedSci(Hons)

Thesis title: Epidemiological modelling of metabolic syndrome and cardiovascular disease in Australia

Metabolic syndrome (MetS) is a clustering of risk factors that increase the risk of developing cardiovascular disease and type 2 diabetes; two–three fold and five-fold respectively. It is highly prevalent, with rates continuing to rise as a result of increasing obesity and sedentary lifestyles.

First Year

Enayet Karim Chowdhury, MBBS, MPH

Thesis title: Epidemiological modelling of chronic disease – particularly cardiovascular disease and its economic implications

Chronic diseases, particularly cardiovascular diseases, are currently the second leading cause of disease burden after cancer in Australia. High blood pressure (BP) is one of the well established independent risk factors that contribute to morbidity and mortality related to cardiovascular disease such as coronary heart disease, stroke, heart failure and peripheral vascular diseases. About 25–30 per cent of the adult population in Australia have high blood pressure. A number of anti-hypertensive drugs are available and research findings suggests that treatment with any of the antihypertensive medicine in lowering BP levels is beneficial and reduce the risk of cardiovascular events. However, despite this nearly half of the treated hypertensive patients in Australia fail to achieve target blood pressure levels of <140 and <90 mmHg for systolic and diastolic BP respectively. Therefore, uncontrolled BP is still an unresolved public health concern.

In addition, with the increasing prevalence of obesity, hyperlipidemia and diabetes, the incidence of heart failure is also accelerating in elderly hypertensive patients. Heart failure is one of the major contributors to cardiovascular disease events. There is no major Australian heart failure register, therefore precise information relating to economic burden is lacking. The information on the long term effect of the newer antihypertensive drug on prevention of cardiovascular events such as heart failure is also limited.

The aim of the PhD work is to focus on the epidemiology of blood pressure control on clinical outcomes including the development of heart failure and renal disease. The PhD work will also undertake epidemiological modelling to explore the potential benefits of interventions at the population level, and to help in planning current and future health services for hypertensive patients. Much of this work will be conducted utilising data collected for the Second Australian National Blood Pressure Study including its follow-up study.

Findings from the work have been presented at the High Blood Pressure Research Council 2010 annual meeting.

Dr Alexander Hodge, MBBS (Hons), BSC, FRACP

Thesis title: Efficacy and mechanism of action of a novel antifibrotic agent in rodent models of liver disease

Background

There are many causes of liver disease but over time most result in liver cirrhosis with life threatening complications. Treatment of the underlying cause of disease is often either unsuccessful or not possible with the only effective treatment for liver cirrhosis being transplantation. There is a great need of therapies to reverse or prevent the development of advanced fibrosis and cirrhosis.

Study

Fibrosis is not a process unique to the liver and is a consequence of many diseases that affect the lungs, kidney and heart. In the latter two a specific antifibrotic agent, tranilast, has been developed which was found to be of benefit in kidney disease but with considerable side effects. A Melbourne based company, Fibrotech Therapeutics, has developed a number of tranilast derivatives in an attempt to increase antifibrotic efficacy with a reduced side effect profile. Alex's PhD project focuses on studying one or two of these compounds ability to treat fibrotic/cirrhotic liver disease. The compounds efficacy will be evaluated in primary liver cell cultures and rodent models of liver disease. Attention will be paid to mechanisms through which these may work and comparisons made to the parent compound tranilast in relation to efficacy and side effect profile.

Significance

The prevalence of liver fibrosis/cirrhosis only looks to increase in light of the impending non-alcoholic fatty liver disease epidemic and current disease burden of chronic viral hepatitis. There is sense of urgency to develop agents targeting and ameliorating liver fibrosis and cirrhosis.

Scholarship: National Health and Medical Research Council postgraduate research scholarship.

Ms Shan Liu, MEngSci

Thesis title: Cardiorenal syndrome: pathophysiology and role of uremic toxin

Background

A close relationship between renal dysfunction and heart failure has been demonstrated. Failure of one organ can worsen the function of the other which in turn further accelerates the progression of failure of both cardiorenal syndrome (CRS). This study aims to determine the pathophysiological mechanisms involved in CRS and to investigate the molecular mechanisms involved in the uremic toxin-induced cardiac effects.

Specifically, two pre-clinical models are utilised to clarify that whether the combined chronic heart failure and chronic kidney disease cause more severe functional, biochemical and molecular impairment compared with chronic heart failure or chronic kidney disease alone. Two in vitro projects are applied to determine whether the pathways of organic anion transporters one and three (OAT1/3) and apoptosis signal-regulating kinase-1 (ASK-1) are involved in the detrimental effects of indoxyl sulfate (IS) on cardiac cells.

Scholarship: International Postgraduate Research Scholarship and Monash Graduate Scholarship.

Meetings and Symposia

Cardiac Society of Australia and New Zealand Adelaide, 5 to 8 August 2010

The Cardiac Society of Australia and New Zealand Annual Scientific Meeting is the major event on the Australian Cardiology calendar.

In line with its commitment to education in therapeutics, CCRE Therapeutics organised the scientific content of satellite symposia at this event and, in conjunction with CSL Biotherapies and Abbott Australasia, put together an expert team of local and international speakers for two very interesting sessions.

CSL Symposium: β -Blockers in Elderly Patients with HF – New Information

Chair: Professor Henry Krum

The meeting started with a presentation by Dr Marcus Flather, cardiologist and Director of the Clinical Trials and Evaluation Unit, Royal Brompton Hospital, London, who addressed the practical implications of β -blockers in heart failure. His address was followed by Dr Dirk van Veldhuisen from the University Medical Center Groningen, The Netherlands who presented data on the effect of β -blockers in elderly patients with impaired and preserved ejection fraction and the meeting finished with Professor Andrew Coats from the UK summarising the data on the effect of β -blockers in elderly patients with impaired renal function.

Following the presentations, Professor Krum led a lively Q&A and discussion session.

Abbott Symposium: Omega-3 Fatty Acids and Cardiovascular Disease: the Evidence Span from Bench to Bedside

The meeting started with Professor Peter McLennan, Research Director, Graduate School of Medicine, University of Wollongong, NSW, setting the scene with a summation of the evidence in identifying the role of omega-3 fatty acids from fish for preventing sudden heart-attack death by inhibiting fatal heart rhythm disturbances. This was followed by Prof Fabio Turazza of the Mario Negri Institute for Pharmacological Research in Milan, Italy presenting (via video link) the results of their recent ground-breaking GISSI Prevenzione trial that demonstrated that three-year treatment with low-dose n-3 PUFA (a derivative of fish oil) was associated with a significant total mortality reduction in patients who survived a recent heart attack.

The session was completed with a summation by Professor David Colquhoun, School of Medicine, University of Queensland, of the role of Omega-3 fatty acids in the treatment and prevention of cardiovascular disease and The National Heart Foundation Position Statement on Fish, Fish Oils, n-3 Polyunsaturated Fatty Acids and Cardiovascular Health. David led an interesting Q&A and discussion session.



Both symposia brought together local and international experts who presented valuable information from recent clinical and laboratory research and offered an opportunity for discussion in a more intimate environment.

Renin Academy

The renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure and water (fluid) balance. An overactive RAAS system can lead to high blood pressure with the resulting increase in the incidence of stroke, heart attacks and other major harmful effects. There has been a huge volume of work published on the development of interventions that interrupt different steps in this system to lower blood pressure since the identification of RAAS and its effect on blood pressure. While the RAAS is a common target for antihypertensives, many current treatments, though effective, can cause an increase in some of the system intermediates leading to side effects. With greater understanding, researchers hope to optimise suppression of the RAAS.

Following the success of the International and Japanese Renin Academies and with the support of an unrestricted Educational Grant from Novartis Pharmaceuticals, CCRET has established the Australasian Renin Academy.

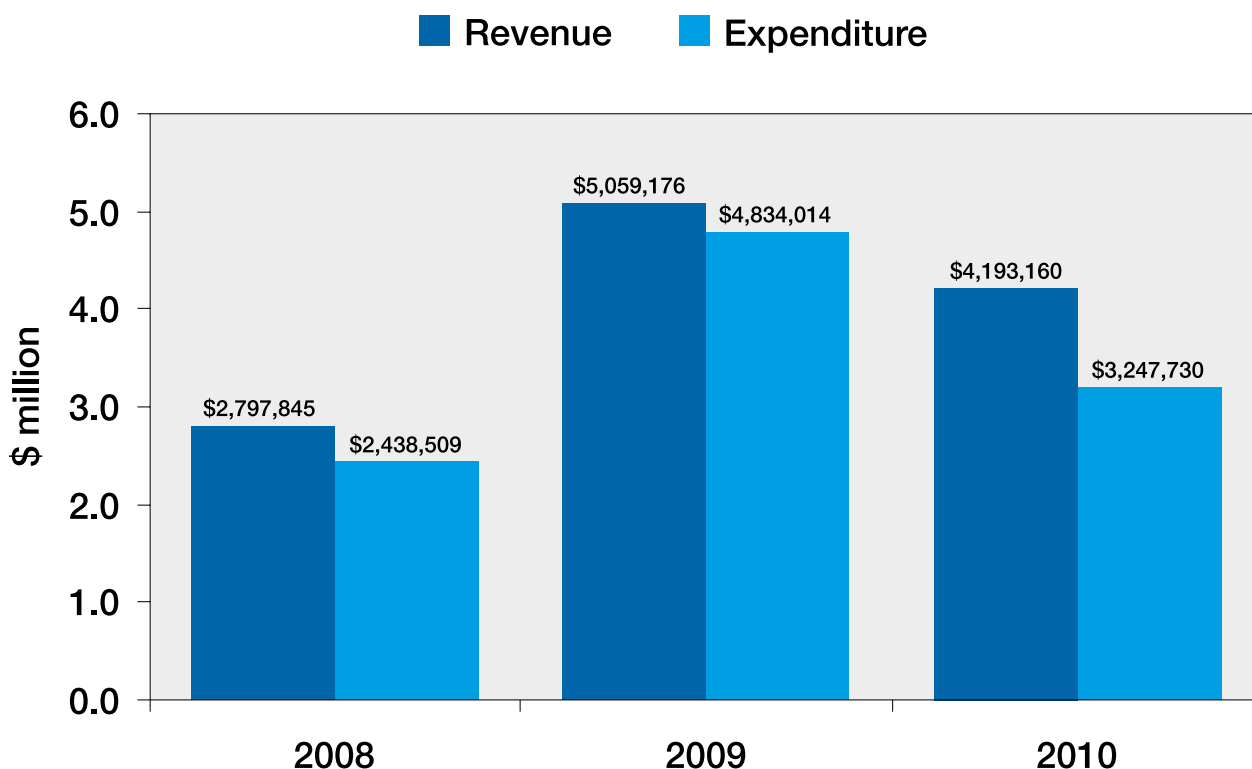
The Academy aims to act as a central resource in Australia for information relating to RAAS and its impact on hypertensive disease, collating existing data and acting as a vehicle for leading-edge research in this exciting field. Its three-fold mission will involve raising awareness, developing educational initiatives and strengthening scientific endeavour by optimising RAAS suppression.

The Academy brings together a panel of Australian experts on RAAS under the Chairmanship of Professor Henry Krum, Director of the CCRET.

Financial Report

CCRE Therapeutics was again successful in receiving an NHMRC Program Grant (2010–2014) with both Directors as Principal Investigators. This follows completion of the first Program Grant received by Professor Krum (2000–2009).

Not appearing on the graph below is National Institute of Health (NIH) support. A successful Rapid Access to Investigational Drugs (RAID) grant secured in-kind support of US\$2,900,000. The NIH also awarded CCRE Therapeutics US\$50,000,000 over seven years for the large-scale ASPREE study which began new recruitment this year.



Grants

NHMRC

H Krum, D Kelly, C Reid

'Prevention and treatment of chronic heart and kidney disease'
2010–2014 \$5,390,000 (Program).

S Stewart, P Scuffham, T Marwick, J Horowitz,

H Krum, P Davidson, P Macdonald, C Reid

'Which Heart failure Intervention is most Cost-effective and consumer friendly in reducing Hospital care: The WHICH study'
2007–2011 \$878,702 (Health Services).

J Simes, D Gherzi, M Stockler, T Keech, S Green,

D Henderson-Smart, **H Krum, G Jennings**

'A National Clinical Trials Register'

2005–2010 \$1,500,000 (Enabling).

R Buchbinder, L March, M Lassaie, **C Reid**

'The Australian Rheumatology Association Database (ARAD)'

2006–2010 \$1,250,000 (Enabling).

Reid CM

Senior Research Fellowship

2008–2012 \$537,500.

Budge M, Storey E, **Tonkin AM,**

Wong T, **Reid CM, Ames D**

'Aspirin for the prevention of cognitive

decline in the Elderly (EnVISION)'

2008–2012 \$1,271,102 (Project).

L Bach, J-P Liu, J Wilkinson-Berka, R Medcalf, **H Krum**

'MF-ChemiBis 3.2 Bioluminescence Imaging System'

2010 \$53,000 (Equipment).

NHF

DL Hare, D Clarke, **H Krum**

'The Melbourne Depression in Heart Failure Collaborative Medication trial'

2008–2012 \$893,581 (NHF & Beyond Blue).

A Owen, C Reid, P McLennan, H Krum

'Omega-3 fatty acid status and cardiovascular risk in older Australians'

2009–2010 \$130,800 (Grant-in-Aid).

Industry

GlaxoSmithKline Australia Pty Ltd

H Krum

'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) – STABILITY Trial'
2009–2010 \$219,600.

MBF Foundation

H Krum

'Utility of serial brain natriuretic peptide measurement in early detection of heart failure'

2010–2012 \$191,500.

CSIRO P-Health Flagship Grant

McNeil JJ, Woods RL, Reid CM, Gibbs P,

Ames D, Budge M, **Nelson M**

'ASPREE Healthy Ageing Bio-bank'

2009–2012 \$3,413,000.

National Institute of Health (USA)

Rapid Access to Investigational Drugs (RAID)

R Gilbert, D Kelly, **H Krum, S Williams**

'Treatment of Diabetic Nephropathy

Using a Purpose-Designed Anti-Fibrotic Drug'

2008–2010 US\$2,900,000 (in-kind support).

R Grimm, **J McNeil, A Tonkin, C Reid,**

M Nelson, R Woods

'ASpirin in Reducing Events in the Elderly (ASPREE)'

2009–2015 US\$50,445,006.

RACP

Collaborative Research Initiative Grant

F Ierino, N Isbel, **H Krum**

'A randomised controlled trial of the beta-blocker carvedilol versus placebo to reduce cardiovascular morbidity and

mortality in patients receiving dialysis'

2008–2010 \$704,400.

Other

Hong Kong Research Grant Committee (RGC),

General Research Fund

Yan Bj, **Reid CM, Yu CM, Lee V**

'Efficacy, Safety and Cost-effectiveness of Drug-eluting Stents in Real World Hong Kong Cardiology Practice'

2009–2011 \$1,123,286.

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