

The Cardiac and Renal Division researches and implements new strategies for the prevention and treatment of major vascular diseases such as stroke and heart attack, as well as kidney disease.

Worldwide, stroke and heart attack represent the two leading causes of death. With the incidence of ill health attributable to vascular diseases predicted to rise sharply in the next few decades, new treatments and prevention strategies are global health priorities.

Established risk factors for stroke and heart attack include blood pressure, tobacco, cholesterol, diabetes and obesity, with each being a major contributor to the total global burden of vascular disease.

Increasingly known to be another key cause of vascular disease, and growing rapidly as a health issue in its own right, is chronic kidney disease. The Cardiac and Renal Division works to improve equity in both health outcomes and access to health care for patients with kidney disease.

In recognition of this expanding focus, two separate programs were formed within the Division in 2005, the Cardiac Program and the Renal Program, with the appointment of experienced senior staff to head each. Throughout 2005, the Division completed several projects, commenced a number of new initiatives and was successful in attracting substantial new funding. Once again, developing countries featured highly in the research achievements, although the start of a major new collaborative project in renal research with the Australian and New Zealand Intensive Care Society Clinical Trials Group was a significant local success.

Research achievements for 2005 included two China-based dietary trials and a major survey of acute coronary syndromes in China. Work in India highlighted the extensive problem of cardiovascular disease in the country's rural areas (see page 14).

The outlook over the next few years remains extremely positive. Utilising funding provided by the NHMRC Program Grant it has been possible to establish a series of new academic and industry collaborations. Excellent progress has been made towards a series of large-scale research initiatives in the cardiovascular field.



## Associate Professor Bruce Neal Director, Cardiac and Renal Division

Bruce Neal is Director of the Cardiac and Renal Division at The George Institute. He is an Associate Professor in the Faculty of Medicine at The University of Sydney and an Honorary Consultant Epidemiologist at the Royal Prince Alfred Hospital. He holds a five-year career development award from the National Heart Foundation of Australia.

Bruce completed his medical training at Bristol University in the UK in 1990 and spent four years in clinical posts during which he gained membership of the UK Royal College of Physicians. Prior to taking up his current post in 1999, he worked as an epidemiologist at the Clinical Trials Research Unit in Auckland, New Zealand, where he completed a PhD in Medicine.

## Highlights

- The scope of the Division was expanded and renamed Cardiac and Renal.
- A major new renal research initiative was commenced with the Australian and New Zealand Intensive Care Society Clinical Trials Group.
- Funding was secured from the Wellcome Trust for the expansion of the surveillance system developed for the Andhra Pradesh Rural Health Initiative (APRHI).
- A large survey of management practices for acute coronary syndromes in hospitals in China was completed.
- Funding from the NHMRC Program Grant was utilised to establish a series of new academic and industry relationships.
- New approaches to addressing the enormous impact of vascular disease and diabetes in poor rural areas of India were investigated.



**Dr Anushka Patel**  
Head, Cardiac Program

Anushka Patel is Head of the Cardiac Program at The George Institute, and a Staff Specialist in the Department of Cardiology at Royal Prince Alfred Hospital. Anushka completed her undergraduate medical training at The University of Queensland in December 1989, and her training in cardiology (leading to Fellowship of the Royal Australian College of Physicians) in 1998. She has a Master of Science degree in Epidemiology from Harvard University, and completed her PhD in Medicine at The University of Sydney. Prior to joining The George Institute in 2001, Anushka was a Research Fellow at the NHMRC Clinical Trials Centre in Sydney.

## Studies in the Division

- Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation – ADVANCE
- Andhra Pradesh Rural Health Initiative - APRHI
- Blood Pressure Lowering Treatment Trialists' Collaboration - BPLTTC
- China Plant Sterol Trial - CPST
- China Salt Substitute Study - CSSS
- Clinical Pathways for Acute Coronary Syndromes in China - CPACS
- Dietary Intervention in e-shopping Trial - DIeT
- Heart Disease in Indians Study - HINDI
- Improving Indigenous Patient Access to Kidney Transplantation - IMPAKT
- Internet-based Cholesterol Assessment Trial - I-CAT
- Perindopril Protection against Recurrent Stroke Study - PROGRESS
- RCT of Normal vs. Augmented Level of Renal Replacement Therapy in ICU - RENAL
- Study of Heart and Renal Protection - SHARP
- Study of the Economic Impact of the Burden of Chronic Kidney Disease in Australia - CKD Burden



**Dr Alan Cass**  
Head, Renal Program

Alan Cass is Head of the Renal Program at The George Institute for International Health. He has trained and worked as a kidney diseases specialist physician, epidemiologist, and health services researcher. From 1998 to 2002, he undertook research into Aboriginal health and worked as a clinician in the Northern Territory. In 2003, he was awarded an Australian Harkness Fellowship in Health Policy at Harvard University where he examined access to, and quality of, renal care in Australia, New Zealand, Canada, and the United States. Alan has broad-based research skills and particular interest and expertise in translational research issues.

## Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation – ADVANCE

The aim of ADVANCE is to determine the effects of routine blood pressure lowering and intensive glucose control on the risks of major cardiovascular events in high-risk patients with type 2 diabetes. The study is a factorial, multi-centre, randomised controlled trial involving 11,140 participants. The primary outcomes will be major macrovascular complications (stroke and heart attack) and major microvascular complications (eye and renal disease). The trial completed recruitment on schedule and finalised the follow-up phase in late 2005. This project is well underway and is expected to be completed in 2009.

The George Institute works on this study in collaboration with the University of Melbourne; The University of Auckland; the Chinese Academy of Medical Sciences; Imperial College; the University of Montreal; Utrecht University and 215 clinical centres in 20 countries worldwide. The Institute acknowledges both Servier Laboratories and NHMRC, which are the key funding agencies for this study.

### Institute Investigators:

Anushka Patel, Stephen MacMahon, John Chalmers, Bruce Neal, Mark Woodward.

### Project Managers:

Helen Monaghan, Samantha Flynn.

## Andhra Pradesh Rural Health Initiative - APRHI

This study aims to formulate, implement and evaluate simple low-cost programs for the treatment and prevention of cardiovascular disease and injury, and is part of a broader rural development initiative in India. The project consists of a mortality surveillance system, a disease and risk factor survey, and trialling of primary health care interventions.

The mortality surveillance system has been incorporated into the existing primary health system, while a large-scale disease and risk factor survey has been completed. APRHI highlights the importance of chronic conditions in the villages and reports are now being prepared. The first intervention project addressing the treatment and prevention of cardiovascular disease is in early stages with evaluation ongoing over the next few years.

Under the initiative, the Institute works in collaboration with the Byrraju Foundation; CARE Hospital, Hyderabad; the Centre for Chronic Disease Control; and the School of Population Health, The University of Queensland.

The Institute would like to acknowledge the following organisations for their funding contributions for APRHI: The George Foundation; Byrraju Foundation; Australian Government Department of Education, Science and Technology; The University of Sydney; the National Heart Foundation of Australia; NHMRC; Initiative for Cardiovascular Health Research in Developing Countries (IC Health); The Wellcome Trust; The Future Forum.

### Institute Investigators:

Bruce Neal, Stephen MacMahon, Rohina Joshi, Magnolia Cardona, Clara Chow, Rebecca Ivers, Mark Stevenson.

## Blood Pressure Lowering Treatment Trialists' Collaboration - BPLTTC

The purpose of this study is to provide reliable evidence regarding the effects of different classes of blood pressure-lowering drugs on cardiovascular mortality and morbidity. Methods include prospectively-designed overviews (meta-analyses) of major trials addressing blood pressure lowering.

Reported results showed that the short-to-medium term effects of the major classes of blood pressure lowering drugs on major cardiovascular events were broadly comparable for patients with and without diabetes. The Collaboration is working on analyses to quantify the effects of blood pressure lowering regimens beyond their blood pressure lowering effects. A Renal Working Group has also been established to guide new analyses examining the effects of different drug types in patients with kidney disease. The Collaboration has grown from 29 trials in 2003 to 48 trials in 2005. A third cycle of overviews is planned for 2006.

The Institute works in collaboration with principal investigators from large-scale trials worldwide, including studies conducted in Australasia, Asia, North America and Europe.

The George Institute would like to acknowledge the following funding bodies of this trial: Analyses funding: NHMRC; National Heart Foundation of Australia. Sponsors of collaborator meetings: AstraZeneca; Bayer; Boehringer-Ingelheim; Merck; Pfizer; Servier; Solvay.

### Institute Investigators:

Fiona Turnbull, Bruce Neal, Charles Algert, Stephen MacMahon, Mark Woodward, John Chalmers, Hisatomi Arima, Vlado Perkovic, Nicole Li.

### APRHI



### China Plant Sterol Trial – CPST

This trial, involving 300 participants from urban Beijing, aims to evaluate the effectiveness of plant sterols in lowering adult serum cholesterol levels. The project commenced in March 2005, with 300 volunteers from three institutions participating in the trial. The effects of plant sterol on blood cholesterol levels were investigated in a double-blind randomised trial of six weeks duration. Study follow-up was finalised in July 2005, with reporting of results expected in 2006.

The Institute works on this study in collaboration with the School of Public Health, Peking University Health Science Center and would like to acknowledge Unilever Foods (China) for the funding of this project.

#### Institute Investigators:

Nicole Li, Bruce Neal.



### China Salt Substitute Study – CSSS

The CSSS evaluates the effects of a salt substitute on blood pressure in individuals living in northern China that are at high risk of cardiovascular disease. The study is a double-blind, randomised controlled trial. Over 600 high-risk individuals were recruited from northern China and assigned to use either salt substitute or normal salt for cooking. Blood pressure levels, electrolytes and preferred level of 'saltiness' were collected from participants during the follow up period. On completion of the follow-up, in August 2005, preliminary study results were made available.

The Institute works in collaboration with Fu Wai Hospital, China and the Clinical Trials Research Unit (CTRU), New Zealand. It acknowledges the following funding agencies: National Heart Foundation of Australia; The University of Sydney; Foundation for High Blood Pressure Research and China Capital Medical Science Development Fund.

#### Institute Investigators:

Nicole Li, Bruce Neal, Rachel Huxley.

### Study of the Economic Impact of the Burden of Chronic Kidney Disease in Australia - CKD Burden

This study is evaluating the impact of improved treatment of chronic kidney disease, the costs and benefits of screening for chronic kidney disease, the costs of provision of renal replacement therapy and the costs and benefits of increasing kidney transplant rates. Information on treatment characteristics and outcomes for patients treated with dialysis or kidney transplant was obtained from the Royal Prince Alfred Hospital and Australia and New Zealand Dialysis and the Transplant Registry (ANZDATA). Future healthcare costs and benefits of treatment for kidney disease were estimated. Ongoing modelling is underway to project the costs and benefits of earlier detection and treatment.

An initial report entitled *The Economic Impact of End-Stage Kidney Disease in Australia: Part I of the Study of the Economic Impact of the Burden of Kidney and Urinary Tract Disease in Australia* was submitted to Kidney Health Australia in September 2005. The second phase of the project includes a cost-benefit analysis of early detection and intervention during early stages of chronic kidney disease.

The Institute works on this research in collaboration with the School of Public Health, The University of Sydney; ANZDATA, Queen Elizabeth Hospital. The Institute gratefully acknowledges the funding of the study by Kidney Health Australia.

#### Institute Investigators:

Alan Cass, Vlado Perkovic, Sarah White.

#### Project Manager:

Alan Cass.

### Clinical Pathways for Acute Coronary Syndromes in China - CPACS

CPACS aims to develop, implement and evaluate clinical pathways for the management of acute coronary syndromes (ACS) in China. Recruitment for phase one included a total of 51 hospitals, 31 tertiary level centres, and 2975 ACS patients. A survey of the management of patients was completed in June 2005. Phase two will consist of development, implementation and evaluation of clinical pathways for ACS management. The pathways will be developed on the basis of data collected in phase one. Data was analysed late 2005, and the results are to be used to help design the second phase of this study.

For this project, the Institute works in collaboration with the Chinese Cardiology Society; Peking University Health Science Center and it would like to acknowledge Sanofi-Aventis, Guidant Corporation, and the Royal Australasian College of Physicians for the funding of this work.

#### Institute Investigators:

Anushka Patel, Fiona Turnbull, Charles Algert, LU Xin, Lucy Chen.

#### Project Managers:

HAN Dorothy, ZHANG Jean, XIOMAN Zou.

## Dietary Intervention in e-shopping Trial - DIeT

DIeT is determining the effects of tailored dietary advice on the amount of saturated fat purchased by consumers using a commercial internet-based shopping service. DIeT is a randomised, double-blind, controlled trial in which 500 participants were enrolled and followed over a three-month period. The intervention was successful in reducing the amount of saturated fat purchased by consumers. Further investigations of the data are ongoing, with publication of the main results anticipated shortly.

The Institute works in collaboration with the Department of Human Nutrition, The University of Sydney; Shopfast, Australia; the British Heart Foundation. It would like to thank Future Forum and the National Heart Foundation of Australia for the funding of this project.

### Institute Investigators:

HUANG Ling-Ya, Bruce Neal, Federica Barzi, Rachel Huxley.

## HINDI



## Heart Disease in Indians Study - HINDI Study

The HINDI study seeks to ascertain why South Asian Indians living in Australia have such disproportionately high levels of cardiovascular disease. It includes surveys of two South Asian Indian populations and a comparator Australian population (South Asian populations are a non-migrant population living in Andhra Pradesh, India, and a migrant population of South Indians living in Sydney, Australia). The whole study will involve a total of approximately 2,000 people. Cardiovascular risk factors and measures of atherosclerosis will be recorded in each and comparisons will be made between them.

The Andhra Pradesh component of the study is now completed. The Australian component of the study began recruiting in late 2005, with the first results anticipated in 2006.

The Institute works in collaboration with the Department of Cardiology, Royal Prince Alfred Hospital, Sydney; the Byrraju Foundation; CARE Hospital, Hyderabad.

Acknowledgment is made of the Byrraju Foundation; NHMRC; the Initiative for Cardiovascular Health Research in Developing Countries (IC Health) and The George Foundation for supporting this project.

### Institute Investigators:

Clara Chow, Bruce Neal.

## Improving Access to Kidney Transplants - IMPAKT

IMPAKT identifies the barriers to Indigenous Australians accessing renal transplantation and proposes strategies that will reduce disparities. The project involves a survey of Australian nephrologists' attitudes and practices. It also includes a study of the knowledge, attitudes, education and decision-making processes of Indigenous and non-Indigenous Australians in relation to transplantation, follow-up of patients commencing dialysis at renal units in urban, rural and remote areas and modelling of the impact of alternative strategies for kidney transplant allocation. The survey of nephrologists has finished, while the study of patients is scheduled for completion in 2006. Data analysis of these first components will commence in February 2006 and the full study results will be available in 2007.

IMPAKT is undertaken in collaboration with the Menzies School of Health Research, Darwin; the Cooperative Research Centre for Aboriginal Health; specialist renal units in Sydney, Dubbo, Brewarrina, Darwin, Alice Springs, Brisbane, Cairns, Townsville, Adelaide, Port Augusta, Perth, Kalgoorlie, Broome. The IMPAKT study is funded by a three-year project grant from the NHMRC.

### Institute Investigators:

Kate Anderson, Alan Cass, Cilla Preece.

## IMPAKT



## Internet-based Cholesterol Assessment Trial - I-CAT

The aim of the I-CAT is to discover whether advice about cholesterol provided via the internet can improve an individual's management of their cholesterol levels. I-CAT is a large-scale randomised controlled trial that is planned to include 3,500 participants. The principal determinant of success will be the number of participants that commence or increase their use of cholesterol-lowering medication following use of the study website. Participants will be recruited via the general media, advertising, healthcare facilities and through email networks. Recruitment took place in 2005, and final results are anticipated in 2006.

I-CAT is a collaborative study with the School of Public Health, The University of Sydney; the Lipid and Cardiovascular Risk Assessment Clinic, Westmead Hospital; and the Lipid Clinic, Royal Prince Alfred Hospital. The Institute would like to thank the following funding agencies: Medical Benefits Fund (MBF); National Heart Foundation of Australia; Pfizer.

### Institute Investigators:

Stephen Li, Bruce Neal, Nicola Lewis, Kathy Jayne.

## Studies

### Perindopril Protection against Recurrent Stroke Study - PROGRESS

PROGRESS was a large-scale trial that achieved its primary goal of demonstrating the huge benefits to be gained from the use of routine blood pressure lowering amongst patients with a history of cerebrovascular disease. Since reporting of the main results, a series of subsidiary analyses have been commenced utilising the data collected and new funding has been awarded. To date, several papers have been completed reporting important findings additional to those documented in the initial report.

PROGRESS is a collaboration with The University of Auckland; the University of Melbourne; the Chinese Academy of Medical Sciences; the National Cardiovascular Centre, Japan; the University of Glasgow; the Lariboisiere Hospital; Universita degli Studi di Milano; Uppsala University; and 172 other hospital and university centres worldwide.

The Institute would like to thank the following funding agencies: the Health Research Council of New Zealand (HRC); NHMRC; the US National Institutes of Health; the Australian Health Management Group; Pfizer Cardiovascular Lipid Grants and Servier.

#### Institute Investigators:

John Chalmers, Stephen MacMahon, Bruce Neal, Mark Woodward, Anushka Patel, Hisatomi Arima, Craig Anderson.

#### Project Manager:

Rochelle Currie.

### Randomised Controlled Trial of Normal vs. Augmented Level of Renal Replacement Therapy in Intensive Care Units - RENAL

This study seeks to determine if increasing the dose of continuous renal replacement therapy (CRRT) reduces mortality in intensive care patients with acute renal failure. The study is a multi-centre, randomised, controlled trial of two different doses of continuous renal replacement therapy. Fifteen hundred patients will be recruited from 34 centres across Australia and New Zealand. Recruitment commenced in November 2005.

RENAL is a joint initiative of the Australia and New Zealand Intensive Care Society Clinical Trials Group and The George Institute. The Renal study is funded by a four-year Project Grant from NHMRC.

#### Institute Investigators:

Alan Cass, Martin Gallagher, Robyn Norton.

#### Project Manager:

David Ali.

### SHARP: The Role of Lipid-Lowering in Preventing Cardiovascular Disease in People with Chronic Kidney Disease

Individuals with kidney disease have much higher mortality compared to healthy people of the same age and sex. In people on dialysis, approximately one in six die each year and half of this mortality is due to heart disease. In the general population, lowering serum cholesterol using HMG CoA reductase inhibitors, or statins, has been proven to reduce mortality from heart disease.

What evidence is available to support the routine use of cholesterol-lowering treatments in people with kidney disease, who are at very high risk of premature heart attack and stroke?

Despite a markedly increased risk of death from heart disease in patients with kidney disease, almost all the studies examining the effects of lowering cholesterol upon mortality and heart disease have excluded such patients. With increasing rates of kidney disease in ageing populations, the effect of lowering cholesterol on heart disease and mortality in patients with kidney disease is an important, yet unanswered, research question with major implications for national and global health expenditure and population health.

By enrolling only people with significant kidney disease, the SHARP study is designed to provide a definitive answer to this question. With an enrollment of 9,000 people in almost 20 countries, it is the largest ever randomised controlled trial undertaken in chronic kidney disease. SHARP will contribute significantly to our knowledge of how best to manage people with kidney disease and how to prevent its progression.



## Study of Heart and Renal Protection - SHARP

SHARP aims to determine the effects of cholesterol lowering (using a combination of simvastatin and ezetimibe) on the risk of major vascular complications in patients with chronic kidney disease. The study is a randomised placebo-controlled trial that recruited 9,000 individuals from approximately 300 centres worldwide. The George Institute coordinates recruitment and follow-up of one-quarter of participants from centres in Australia, New Zealand, Malaysia and Thailand. The planned average follow-up for participants will be four and a half years.

Recruitment of patients commenced in Australia and Malaysia in October 2003, New Zealand in February 2004 and Thailand in August 2004. Recruitment should continue until mid-2006. To date, researchers have randomised over 70% of the target of 2,400 patients. Approximately 300 training and monitoring visits to the study sites have taken place. The results of SHARP are expected to be available in 2009.

SHARP is a collaboration with the University of Oxford; the Australia and New Zealand Society of Nephrology; the Clinical Research Centre, Kuala Lumpur Hospital and 64 specialist renal centres in Australia, New Zealand, Malaysia and Thailand. Grateful acknowledgement is made of both NHMRC and the University of Oxford for funding this research project.

### Institute Investigators:

Alan Cass, Martin Gallagher, Bruce Neal, Vlado Perkovic.

### Project Manager:

Rochelle Currie.

## A Low-Sodium, High-Potassium Salt Substitute – The Answer To Blood Pressure Control In China and Beyond

Salt (sodium chloride), the common seasoning added to food every day across the world, raises blood pressure levels, and is a leading cause of heart attacks and strokes. The problem is particularly marked in China, where salt consumption is very high, elevated blood pressure levels are extremely prevalent and the predominant vascular disease is stroke, which is most strongly blood pressure dependent.

Despite compelling evidence of the value of reducing sodium intake, long term restriction of salt consumption has proved difficult to achieve. The recently completed China Salt Substitute Study, a double-blind randomised controlled trial of 12 months duration, provides new hope in this area. The trial, which investigated the blood pressure lowering effects of a low-sodium high-potassium salt substitute among 600 high risk individuals in rural Northern China showed that replacing normal salt with salt substitute could reduce blood pressure to almost the same extent as drug therapy. Furthermore, these effects were not only achieved at low cost but increased over time as the salt substitute was incorporated into progressively more of the daily diet.

The evidence from this study will form the basis for new initiatives designed to persuade Chinese policy makers to increase the use of salt substitute. Either through immediate efforts to modify national salt supply through the state monopoly of salt manufacture and distribution, or through the commissioning of an even larger piece of research that will demonstrate the direct beneficial effects of the salt substitute on cardiovascular disease itself. In the latter case, the results would likely influence the use of salt substitutes in many other developed and developing countries worldwide.

