George RESEARCH

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Landmark study shows intensive treatment for diabetes is safe and prevents kidney complications

New results from the world's largest ever study of diabetes treatments has shown intensive control of blood glucose (blood sugar) reduces the risk of kidney complications by one-fifth. In addition, researchers reported no evidence of an increased risk of death among patients receiving intensive treatment. Full results have been published by *The New England Journal of Medicine*.

According to Chief Investigator of the study, Professor Stephen MacMahon, Principal Director of The George Institute, "Diabetes is a major cause of kidney failure worldwide and up to 20% of people with diabetes will die from this cause. The ADVANCE study shows that intensive blood glucose control protects against kidney disease, one of the most common complications suffered by the 250 million of people living with diabetes today."

"Importantly, we also showed no evidence whatsoever of any increased risk of death among those receiving intensive therapy. This appears to contrast with initial results reported from the NIH sponsored ACCORD study, which suggested an increased risk of death among those receiving intensive glucose control," said Professor MacMahon.

The ADVANCE (Action in Diabetes and Vascular Disease) study is an investigator-initiated study conducted independently by a group of medical researchers from 20 countries worldwide. The study involved 11,140 patients with type 2 diabetes who were treated and followed up for five years. The study aimed to reduce levels of haemoglobin A1c (a marker of blood glucose control) to below 6.5%. This treatment included a sulfonylurea drug (modified release gliclazide) for all patients and other drugs as required to achieve the haemoglobin A1c target.

The ADVANCE study shows blood glucose control is important to reduce the risk of kidney complications among patients with diabetes

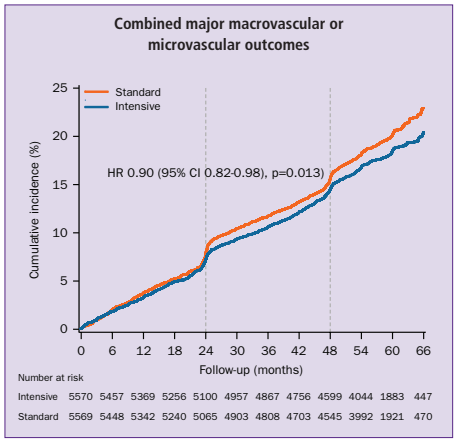
Announcing the results at the American Diabetes Association 68th Scientific Sessions in San Fransicso, Study Director, Associate Professor Anushka Patel from The George Institute, said, "The results clearly demonstrate that intensive control of blood glucose, as recommended by most current clinical guidelines, has an important role in the prevention of renal complications of type 2 diabetes. However, the results did not provide any benefit of intensive treatment for heart attack or stroke, which are also common complications of diabetes."

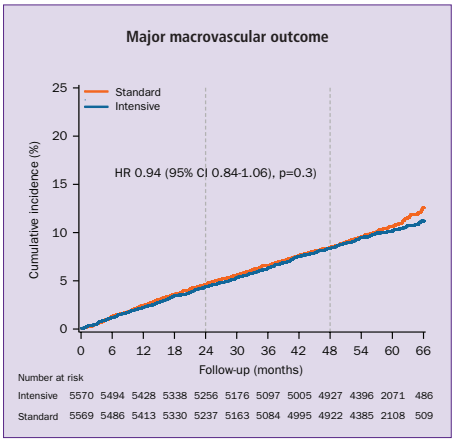
Overall, there was a very low incidence of hypoglycemia (low blood sugar) during the study. "Major hypoglycemic events were uncommon in both the intensive and standard treatment groups, although as expected they were somewhat more frequent among those receiving intensive treatment," added Associate Professor Patel.

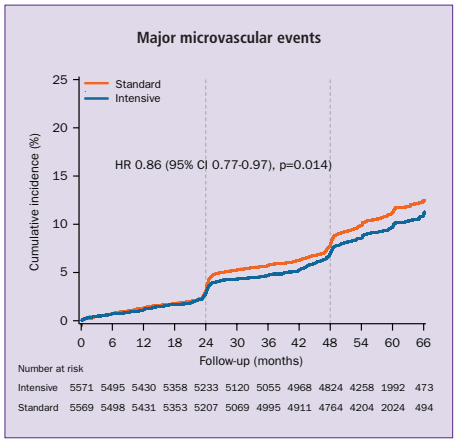
IN THIS ISSUE

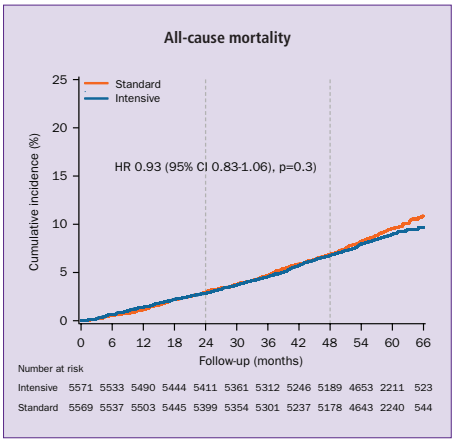
ADVANCE: Results of the world's largest study of diabetes treatments

New results from the world's largest ever study of diabetes treatments show that intensive blood glucose (sugar) control using modified release gliclazide and other drugs as required, protects patients against serious complications of the disease. In particular, intensive treatment reduces the risk of kidney disease by one-fifth. These graphs show the cumulative incidence of: A) combined major macrovascular or microvascular outcomes; B) major macrovascular outcomes; C) major microvascular events; D) all-cause mortality, among patients assigned intensive glucose control or standard glucose control.







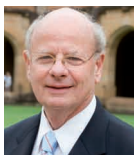


For more information regarding the ADVANCE study results visit www.thegeorgeinstitute.org

Messages from the experts

PROF STEPHEN MACMAHON
Principal Director,
The George Institute
ADVANCE Co-principal Investigator

"We are facing a global epidemic of diabetes. The ADVANCE results go beyond existing evidence as we have now shown that reducing the haemogloboin A1c level (a marker of blood glucose control) to 6.5% is a safe and effective way to reduce serious complications, particularly the risk of kidney disease, one of the most serious and disabling consequences of diabetes, leading to death in one in five people with diabetes."



PROF JOHN CHALMERS
Senior Director
The George Institute
ADVANCE Co-principal Investigator

"It is clear that the prevention of heart attack and stroke among people with diabetes requires a multi-factorial approach addressing all major risk factors including blood pressure and blood lipids."

ASSOC PROF ANUSHKA PATEL
Director, Cardiovascular Division
The George Institute
ADVANCE Study Director

"These findings reinforce that blood glucose lowering in diabetes is safe and has an important role to play in the prevention of serious complications."

PROF BRUCE NEAL
Senior Director
The George Institute
ADVANCE Management Committee

"The ADVANCE study provides important new information for millions of diabetic patients worldwide."

What GPs know about cardiovascular risk – and what they need to know

In older patients, a 'normal' blood pressure reading may still confer a substantial risk of heart attack or stroke. It is now well accepted that a patient's risk of cardiovascular disease is most accurately assessed by taking an absolute risk approach, rather than examining the individual risk factors such as blood pressure, diabetes, cholesterol and smoking independently. Although most GPs are aware of the need to use absolute risk-based methods, it is likely that this approach is not being fully implemented and treatment decisions are still based on the traditional management of single risk factors in isolation.

A new Australian study, AusHEART (Australian Hypertension and Absolute Risk Study) is currently recruiting patients from 534 randomly selected GPs who expressed an interest in participating in the study. It aims to examine what GPs, and their patients, understand of the risk factors for cardiovascular disease. Participating GPs will be eligible for 40 Category 1 RACGP QA&CPD and 30 ACRRM PDP extended skills points. When the study is finished, GPs will receive an individual report on each of their patients, as well as the findings for their state and the nation.

How AusHEART works

There are two parts to this observational study. The first part is the initial study visit – a snapshot of a patient's cardiovascular health on a routine visit to their GP, including a look at what both patient and GP think of the patient's chance of having a cardiovascular event in the next five years. Patients aged 55 years or over who go to their GP for any reason are eligible to participate. The aim is to recruit 4,000 patients from across Australia in this way.

The initial study visit will take approximately 10 minutes with the doctor and then the patient will have a simple, five minute questionnaire to fill in. All information collected by the doctor will be identified with a code number and no patient-identifying information will be published.

The second part is a follow-up study of the patients over five years. Those who give their Medicare number to the study will have their healthcare costs and major cardiovascular events tracked for up to five years from the initial visit. Patients have the opportunity to consent to both parts of the study, or the first part alone, and to withdraw their consent at any point.

First study of its kind

AusHEART is the first study of its kind to take such a comprehensive and long-term approach to examining the absolute risk profile of cardiovascular risk in Australian patients aged 55 and over. Many studies have concentrated on the effects of blood pressure or other single factors, but in reality many factors contribute to a patient's overall cardiovascular risk.

The key findings of the study will be published and presented at medical meetings around the country. This important study will raise awareness of unmet needs in the assessment and management of cardiovascular risk, and thus help to improve future patient care.

For further information please contact The George Institute on +61 2 9993 4516.

Glucosamine – an osteoarthritis patient's only friend or just a waste of money?

Osteoarthritis (OA) is the leading health problem among older Australians; it is a painful condition for which there is no known cure. Many people turn to the dietary supplements glucosamine and chondroitin, motivated in part by marketing that these products are able to slow the rate of joint destruction and help ease joint pain – all with little risk of side effects.

Yet the few clinical trials conducted to date on these products have provided contradictory results. The LEGS (Long-term Evaluation of Glucosamine Sulphate) study aims to address this uncertainty. Funded by the National Health and Medical Research Council (NHMRC), this major three-year study is likely to influence the management of OA in general practices worldwide.

LEGS is a double-blind, placebo-controlled, randomised clinical trial that will evaluate the effectiveness of glucosamine, with or without chondroitin, in a group of 940 patients with OA of the knee. Designed and led by The George Institute, it is a collaborative effort of the Royal Australian College of General Practitioners and the University of Sydney.

A chance for GPs to become involved in this landmark study

LEGS is currently seeking GPs to help recruit patients for the study. GPs will be remunerated for each patient randomised. Those interested in participating should email LEGS@george.org.au.

Staff Profile

Dr Milana Votrubec
MB BS MA MM Grad Dip (Higher) Ed USyd
Project Manager: LEGS Study

Just a few years ago, after working as a 'solo 24/7 suburban GP' for many years, Dr Milana Votrubec finally made the decision to concentrate on an area of concern to her and of great need in the community – the management of pain.

"As a GP," she says, "Pain is something you see every day, in many forms. Yet often we don't have enough solid evidence on which to base the treatment of pain. Patients and doctors alike are subjected daily to marketing campaigns supporting one remedy or another."

With this in mind, Milana has become involved in a study designed to make sense of the debate over treatment of a very common cause of pain, osteoarthritis (OA). She is now the Project Manager for the LEGS (Long-term Evaluation of Glucosamine Sulphate) study, run by the Musculoskeletal Division at The George Institute.

LEGS is a randomised controlled trial examining the effectiveness of the popular dietary supplements glucosamine and chondroitin in reducing the pain of OA. Studies on these products have so far yielded inconclusive results, so LEGS aims to clear the air by providing reliable results through a long-term study of a group of 940 OA patients in Sydney.

While focusing on LEGS, Milana continues to have her finger in many pies. She contributes to community-based projects through the Manly Warringah Division of GPs, is a Clinical Lecturer for the Graduate Program at the University of Sydney, and was Chair of the Royal Australian College of General Practitioners' Curriculum Review on Pain Management.

There is no likelihood that pain is ever going to disappear in this world, yet Milana is working on many fronts to reduce its burden and to bring common sense and reliable results to the ongoing discussion on how it can best be treated.

Vaccine for type 1 diabetes may spell an end to daily injections

Type 1 diabetes (T1D) is a disease in which the body's immune system reacts against and destroys insulin-producing beta cells in the pancreas, essentially stopping the production of insulin. For those with T1D, typically children and young adults (the median age for contracting the disease is 11), it can require up to 12 finger pricks a day to monitor blood sugar levels and up to five daily injections of insulin.

A proposed vaccine for T1D has shown very promising results in laboratory experiments with mice, and it is now being tested on humans in a pioneering new trial, INIT II (Intranasal Insulin Trial). This randomised, double-blind, placebo-controlled trial aims to test the effectiveness of the vaccine in a group of 264 children and young adults.

The simple 'trick' of the vaccine is that it is administered nasally. Ingesting an insulin spray through the nose presents the insulin not to the bloodstream but to the mucosal immune system. Within the mucosal immune system there can be a 'seesaw' battle between inflammatory T-cells (which kill the insulin-producing beta cells) and regulatory T-cells (which control the inflammatory T-cells). The nasal spray aims to tip the seesaw strongly in favour of the regulatory T-cells.

init II
intranasal insulin trial

As already noted, preliminary testing with mice has shown excellent results, with consistent success in preventing T1D among mice that are genetically likely to contract the disease.

How INIT II works

Participants in the trial will self-administer the insulin solution or placebo using a nasal spray every morning for seven consecutive days and then once a week for 12 months. They will be monitored for a further four years after completing the trial.

The trial is currently at the proof of concept stage. The sample will be small yet highly reliable, due to the rigorous input of experts in statistical analysis and design from The George Institute. If all goes well, it will progress to the next stage, involving thousands of participants worldwide.

The trial is being run by the Sydney-based Diabetes Vaccine Development Centre with support from the National Health and Medical Research Council (NHMRC) and the US philanthropic organisation Juvenile Diabetes Research Foundation. The George Institute is providing statistical and database management.

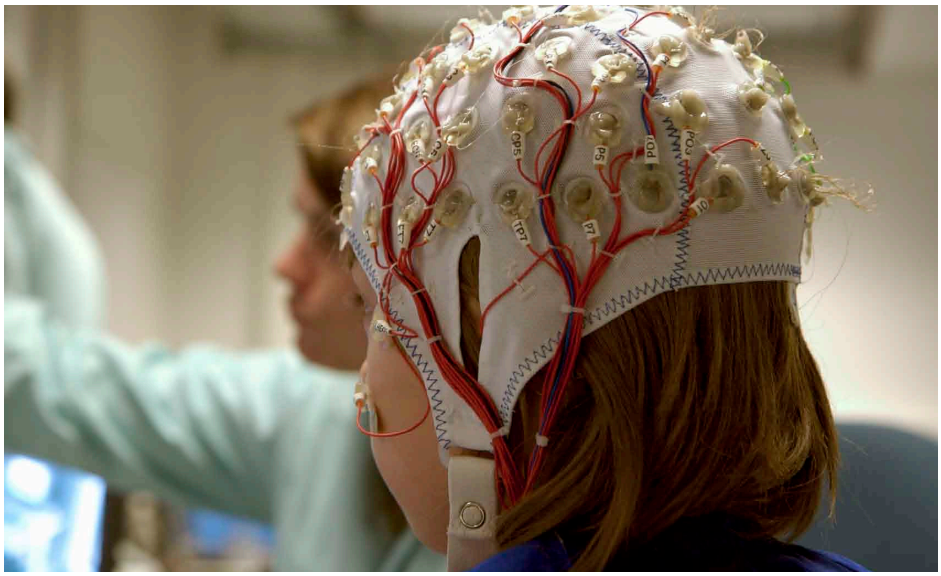
How GPs can contribute

The trial will be targeting children and young adults (age range 4 to 30) identified as at risk of contracting T1D, usually siblings of those who have already developed the disease. There is a very small window of opportunity to find the right recruits: they must be exhibiting the early signs of the disease yet still be basically healthy.

To find such a group requires wide screening. In fact, while this study will involve only 264 patients, the researchers must screen a massive 20,000+ children and young adults to find the 2% of patients who exactly fit the profile.

The researchers are therefore keen to hear from any GPs who would like to contribute by talking to their patients about becoming involved in the trial. GPs interested in being involved should call 1300 138 712. More information is available at www.stopdiabetes.com.au.

Daily burden of epilepsy can outweigh clinical symptoms



Many practitioners think of epilepsy as a clinical problem involving seizures and other major events, primarily requiring treatment using medication and monitoring. Yet the daily burden of living with epilepsy – the psychosocial, educational and economic pressures it can bring – are considerable, though little studied.

The George Institute's SEISMIC (Sydney Epilepsy Incidence Study to Measure Illness Consequences) study will for the first time take a comprehensive look at the lives of people newly diagnosed with epilepsy in Australia.

The study will take focus on the diverse population of the Sydney South West region. The aim is to recruit a group of up to 600 patients from various ethnic backgrounds and socioeconomic groups. These will include migrants and non-English-speaking residents. Extending the range even further, the study will be looking at all age groups, with a view to understanding how the consequences of epilepsy affect people and their families at different stages – educational opportunities for the young, economic opportunities for adults, and so on.

To achieve this diversity, the researchers are casting the net beyond the usual EEG units and epilepsy specialists to include aged care facilities, a range of specialists and – for the first time in such a study – general practitioners. As epilepsy is often managed by specialists and GPs collaboratively, it is hoped the study will benefit GPs by giving them a greater understanding of epileptic patients' lives and the effectiveness of non-medication interventions.

SEISMIC will begin in August 2008. Each patient recruited will be interviewed soon after diagnosis and then followed up for a year. With two years for recruitment, this means the study will last for three years overall. SEISMIC is a joint investigative effort between The George Institute, Epilepsy Action and key NSW neurologists.

GPs or others who are keen to become involved in SEISMIC should contact Dr Nick Glozier at The George Institute on +612 9993 4500.

Staff Profile

Dr Bassel Hassan
BSc(Med) MBBS(Hons)
Research Fellow

Some people know from a young age what they want to do in life. Not Bassel Hassan.

On finishing school and gaining the marks for medicine, he figured he may as well do it: "I stumbled in rather naively". Yet it immediately clicked. "I've been pursuing a medical career for 14 years now, and every year I enjoy it more and more".

Along the way he developed a particular interest in neurology, the study of nerves and the nervous system. "Neurology is exploding at the moment. Even when I was a student there were far fewer treatment options. With more research there are new ideas coming up every day."

Before starting at The George in January this year, Bassel was working at Nepean and Westmead hospitals in Sydney as a Neurologist. Armed with this expertise, Bassel is now doing a fellowship in neurology with The George Institute, working on the SEISMIC epilepsy project (see opposite). It aims to give, for the first time, reliable data on the impact of epilepsy in Australia.

"Currently I am involved in study design and implementation of SEISMIC. When the study is up and running, I will be a link between The George Institute researchers and the clinicians, getting them to sign on to the study and initially to ensure that potential patients are comprehensively screened. A major part of my role will also be to promote the study to the neurology and medical community as a whole to ensure maximal participation in this population based study."

And this is exactly where Bassel wants to be heading in his career. "I'm interested in the interface between clinical practice and research. I think the people at this interface have a unique opportunity to improve the quality of research. With their clinical insight, they tend to produce research that is relevant, practical and likely to be achieved."

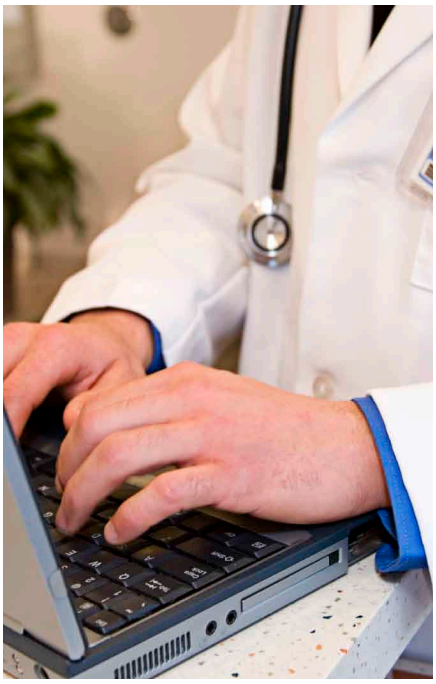
Outside of work Bassel's major interest is in international affairs and modern history. He is a keen chess and judo player, but says his main priority is his family.

Helping GPs cover all bases – a new electronic decision support tool for managing vascular risk

For busy GPs wrestling with the competing demands of various guidelines, assessing multiple cardiovascular risk factors in patients can be a challenging task. The George Institute is currently piloting a new electronic decision support (EDS) tool to facilitate guidelines-based assessment and management by automatically integrating a number of assessment indicators.

The EDS tool will be pilot-tested among 100 patients attending 10 general practices in Western and South Western Sydney, 50 patients attending a multidisciplinary vascular clinic at Royal Prince Alfred Hospital, and 30 patients attending three Aboriginal Medical Services in Sydney.

For the pilot testing, a research assistant will access the relevant patient records and enter the risk factor data into the EDS software. The research assistant will then give the doctor an



individualised printed recommendation on risk management for the patient for consideration during the consultation.

At the end of each consultation, a questionnaire will capture whether the recommendations were implemented, and the specific reasons why this may have not occurred. In addition, an interview with each participating doctor will be conducted at the completion of all data collection to determine the strengths and weaknesses of the EDS tool and gather suggestions to improve it.

This pilot program aims to text the feasibility of the EDS tool by confirming its reliability and relevance, providing direction for further development of the tool, and determining whether the tool is acceptable to GPs. To become involved in this innovative trial, GPs should contact Dr Rohina Joshi on +612 9993 4572.

Adhering to guidelines with the polypill

People with previous heart attack, stroke or other vascular diseases are among those at highest risk of having a future cardiovascular event. Despite the availability of a number of simple, safe and effective drugs that reduce this risk, a substantial proportion of patients do not receive 'indicated' treatments, and particularly, appropriate combinations of these drugs that would maximize their beneficial effects.

The are many reasons for this 'evidence-practice gap', including the complexity, inconvenience and costs of prescribing (by doctors) and taking (by patients) of multiple drugs.

A potential innovative strategy to help this scenario is a 'polypill' – a single tablet containing fixed-dose combinations of treatments. This strategy holds considerable promise, but the effectiveness of the polypill in improving adherence to indicated drug treatments and, thus, patient outcomes, needs to be evaluated in clinical trials.

The Guidelines Adherence with the Polypill (GAP) study, funded by the National Health and Medical Research Council, is designed to do just that. The GAP study has been developed by researchers at The George Institute and will involve approximately 1000 patients in 60-100 general practices in NSW and Victoria. Patients at high risk of a cardiovascular event will be randomised to a polypill-based strategy or usual care. The polypill contains aspirin, two blood pressure lowering drugs and a cholesterol lowering drug. Participants will be evaluated at the end of two years to determine whether the polypill-based strategy has improved adherence to 'indicated' drugs, and as a consequence, results in improved blood pressure and cholesterol levels. The George Institute will commence recruitment towards the end of 2008 or early 2009.

New research into safety benefits of motorcycle clothing

Little is known about whether protective clothing can prevent or reduce injuries from motorcycle crashes. A new three-year research project will help the motorcycling and medical communities understand how effective motorcycle protective clothing is.

The study will look at the association between the use of protective clothing in motorcycle crashes and the severity and long-term consequences of any injuries sustained.

Its findings will be of great value to all bike riders. It is also expected that this research will help pave the way for refining and improving the effectiveness of protective clothing used by motorcyclists around the world.

According to researcher Liz de Rome from The George Institute, previous studies in this area have solely concentrated on hospitalised riders and have shown protective clothing can reduce the severity of injuries and time away from work. This study is unique in that it will include all riders involved in motorcycle crashes, those who escaped serious injury and those hospitalised.

"Standards have been developed for motorcycle protective clothing in Europe, but they are not enforceable in Australia," said Ms de Rome. "This research will provide Australian riders with better information about the protective clothing they wear."

The study will be conducted by The George Institute, sponsored by Australia's leading motorcycle insurer Swann Insurance. The full report is expected to be delivered around December 2009.

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