New research in diabetes – what can we use in our patient interactions?

A/Prof Shane Hamblin
Head of Endocrinology & Diabetes, Western Health
Consultant endocrinologist, Alfred Health
Areas to be discussed

1. New diabetes technology
2. Possible prevention of Type 1 diabetes
3. Cardiovascular safety trials of diabetes medications
4. New drugs in the pipeline for treating Type 2 diabetes
New trials underway, planned or recently completed

ClinicalTrials.gov
New diabetes technology
Artificial pancreas for diabetes patients could be available within a year

July 2, 2018 - 4:34PM

Bridie Smith
Science Editor, The Age
View more articles from Bridie Smith

An artificial pancreas could replace insulin injections for type 1 diabetes patients. Photo: Matthew Bouwmeester

People living with type 1 diabetes could soon be free of regular insulin injections, after researchers said an artificial pancreas could become available within a year.
Artificial Pancreas Aliases

Bionic pancreas
Closed loop insulin delivery system
Artificial beta cell
The I don’t ever have to think about my diabetes again system
AUSTRALIAN ARTIFICIAL PANCREAS PROGRAM

Engineering a brighter future for people with type 1 diabetes

The Australian Artificial Pancreas incorporates closed loop technology to autonomously adjust insulin delivery as blood glucose levels rise and fall. Using an intelligent control algorithm, the device calculates a patient's insulin requirements in real time and initiates appropriate delivery. The goal is a fully autonomous system which will no longer require the patient to perform fingerprick BGL tests, calculate the carbohydrate content in each meal or adjust for exercise. It's exciting stuff and it can't arrive soon enough for people living with type 1 diabetes around the world.

The AP is being developed for type 1 diabetes and could be adapted for type 2 and other types of diabetes. The AAPP model has already achieved outstanding results in FDA approved pre-clinical trials and stage 1 clinical trials are currently underway.
Research, development and trials are being conducted at Centres of Research Excellence across Australia.

Engineers from the University of Newcastle School of Electrical Engineering and Computer Science are taking a fresh look at blood glucose regulation from a control engineering point of view.

The team of AAPP investigators at John Hunter Children's Hospital in Newcastle NSW are world leaders in paediatric endocrine diagnosis, treatment and research. For over a decade now studies at the centre have been gathering data that contributes to the Artificial Pancreas project.

Princess Margaret Hospital in Perth is an internationally recognised paediatric facility that treats children and adolescents from Western Australia. Its team of investigators is committed to research that will improve outcomes for people living with type 1 diabetes.

St Vincent's Hospital Melbourne is a major teaching, research and tertiary referral centre providing acute or chronic medical and surgical services, as well as clinical training. Its AAPP research team is dedicated to transforming health care.
Are you interested in being a trial participant?

Thank you for your interest in being involved in trials to develop the closed loop insulin pump. We are planning a number of new development studies this year. The **development studies** will be testing specific aspects of the closed loop insulin pump such as controlling overnight BGLs, hypo prevention and meals. These studies will involve the participant wearing a pump that is controlled by the AP system for up to 10 hours a day while they are being closely watched and monitored by our research team. People involved in these development studies will need to be motivated, have reasonable diabetes control, no diabetes related complications and be in good health (no other health issues). The reason for these requirements is that we need to know the effects we see are due to the changes in insulin and not due to some other issue. It is essential we complete these types of studies before we can consider trials for longer time periods, and larger scale trials. Once the development studies are complete we will undertake studies that look at the systems function in people with diabetes complications and other medical conditions.

If you would like to be involved in the development trials, please complete and submit the form below. When we are ready to start a study we will contact you.

If the development studies will not suit you then we hope you will still be interested in the larger **clinical trials**. Again, please complete the form below if you are interested in participating when we reach that stage.

Thank you for your interest in participating! It is people like you who make these studies possible.
The Artificial Pancreas System (An Autonomous System for Glycemic Control)

The illustration below describes the parts of a type of artificial pancreas device system and depicts how they work together.

1. Continuous Glucose Monitor
2. Computer-Controlled Algorithm
3. Insulin Pump
4. Patient Effect

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/
Figure 1.1: An illustration of the concept behind an artificial pancreas. The control algorithm could potentially be implemented on a smartphone as illustrated here. Modified from [75, 68]
Simply it’s in the maths

\[ dx_t = f(x_t, u_t, t, \theta)dt + \sigma(u_t, t, \theta)d\omega \]  \hspace{1cm} (1)

\[ y_k = h(x_{k-1}, u_{k-1}, t_{k-1}, \theta) + e_k \]  \hspace{1cm} (2)
...and a little more maths

\[ dx_t = f(x_t, u_t, t, \theta)dt + \sigma(u_t, t, \theta)d\omega \]  \hspace{1cm} (1)

\[ y_k = h(x_k, u_k, t_k, \theta) + e_k \]  \hspace{1cm} (2)

\[ dI_{subc} = \frac{1}{\tau_1} \left( \frac{ID}{C_I} - I_{subc} \right) dt + \sigma_{I_{subc}} d\omega_1 \]  \hspace{1cm} (3)

\[ dI_p = \frac{1}{\tau_2} (I_{subc} - I_p) dt + \sigma_{I_p} d\omega_2 \]  \hspace{1cm} (4)
\[ dI_{\text{eff}} = p_2(S_1 I_p - I_{\text{eff}})dt + \sigma_{I_{\text{eff}}} d\omega_3 \]

\[ dG_p = \left( - (GEZI + I_{\text{eff}})G_p + EGP + \frac{D_2}{\tau_m} + \frac{G_{IV}}{\tau_g V_g} \right) dt + \sigma_{G_p} d\omega_4 \]

\[ dD_1 = \left( \frac{AgCHO}{V_g} + \frac{D_1}{\tau_m} \right) dt + \sigma_{D_1} d\omega_5 \]

\[ dD_2 = \frac{1}{\tau_m} (D_1 - D_2) dt + \sigma_{D_2} d\omega_6 \]
Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes


Uses a bi-hormonal pump: Insulin & Glucagon
Figure 1. Variation in the Mean Glucose Level among Adults and Adolescents.
Figure 3. Distributions of Mean Glucose Levels and Hypoglycemia among Adults and Adolescents.

Panel A shows the mean glucose level in each adult on days 2 through 5 of the control period (red circles), which is connected to the corresponding mean glucose level during the bionic-pancreas period (black circles). The diameter of each circle is proportional to the percentage of time that the patient spent with a low glucose value (<70 mg per deciliter) on days 2 through 5. The dashed red line indicates a mean glucose threshold of 154 mg per deciliter, which corresponds to a glycated hemoglobin level of 7%, the upper limit of the therapeutic goal for adults as outlined by the American Diabetes Association. This goal was met in all patients during the bionic-pancreas period. Panel B shows a similar distribution for each of the adolescents, with a cutoff point for the mean glucose level of 168 mg per deciliter, which corresponds to a glycated hemoglobin level of 7.5%, as recommended for adolescents. The one patient in whom this level was not reached on days 2 through 5 had a mean glucose level of 148 mg per deciliter on days 3 through 5. In the two panels, the solid red line indicates the mean for all the patients in the study group. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
Home Use of an Artificial Beta Cell in Type 1 Diabetes


Using a pump with Insulin only (no glucagon)
THREE MONTH TRIAL
Figure 1. Sensor Glucose Levels and Insulin Delivery.
Shown are the median sensor glucose levels and the median values for insulin delivery during the day-and-night closed-loop study involving adults (Panel A) and the overnight closed-loop study involving children and adolescents (Panel B). The bands indicate interquartile ranges. To convert the values for glucose to millimoles per liter, multiply by 0.05551.
Figure 2. Overnight Glucose Levels.

Shown are the individual overnight mean sensor glucose levels in adults (Panel A) and in children and adolescents (Panel B). Adults used the closed-loop systems day and night and children and adolescents used the closed-loop systems overnight. The size of the bubble indicates the proportion of time overnight during which the glucose level was below 50 mg per deciliter (2.8 mmol per liter).
Other technology

Micro-needle array patch containing insulin held within hyaluronic vesicles.
The hyaluronic acid vesicles are sensitive to hypoxia.
When blood glucose is high, it is oxidised by glucose oxidase.
This causes local hypoxia triggering release of insulin from vesicles.

\[
\text{Glucose} + \text{O}_2 + \text{H}_2\text{O} \xrightarrow{\text{GOx}} \text{Gluconic Acid} + \text{H}_2\text{O}_2
\]
Smart insulin patches

Fig. 1. Schematic of the glucose-responsive insulin delivery system using hypoxia-sensitive vesicle-loading MN-array patches. (A) Formation and mechanism of GRVs composed of HS-HA. (B) Schematic of the GRV-containing MN-array patch (smart insulin patch) for in vivo insulin delivery triggered by a hyperglycemic state to release more insulin.
Smart contact lens

- Google (tech giant) & Alocon (contact lens manufacturer, a division of Novartis)
- Super-small sensor and thinner-than-hair antenna will be embedded between two soft contacts lenses
- A small hole in the lens will let tears reach the sensor, which will determine a glucose value—once per second if the researchers get their way.
- That data will wirelessly transfer to a mobile device for monitoring.
Afrezza® is an inhaled human insulin indicated to help improve glycemic control in adults with diabetes mellitus.
Oral Insulin

Figure 1

Different types of insulin forms, functional excipients, and delivery systems used in oral insulin dosage forms. Reproduced with permission from Journal of Drug Targeting.
Pathways for insulin nanoparticle translocation through the intestinal epithelium. Schematic focus on phagocytosis, macro-pinocytosis, and caveolin-mediated endocytosis. Reproduced with permission from *Biomaterials*.14
What about stem cells?
**ClinicalTrials.gov**
A service of the U.S. National Institutes of Health

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**Home > Find Studies > Search Results**

**189 studies found for:** stem cells and diabetes

**Modify this search** | **How to Use Search Results**

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### Rank Status Study

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<td>Reversal of Type 1 Diabetes in Children by Stem Cell Educator Therapy</td>
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<td>Treatment of Patients With Newly Onset of Type 1 Diabetes With Mesenchymal Stem Cells</td>
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<td><strong>Intervention:</strong> Biological: Mesenchymal stem cells</td>
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<td>Autologous Adult Stem Cells to Patients With Type 1 Diabetes and a Successful Renal Transplant</td>
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<td><strong>Conditions:</strong> Type 1 Diabetes; Type 2 Diabetes</td>
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<td><strong>Intervention:</strong> Biological: Autologous CD34+ stem cells</td>
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<td>6</td>
<td>Unknown†</td>
<td>Efficacy and Safety Study of Autologous Hematopoietic Stem Cell Transplantification to Treat New Onset Type 1 Diabetes</td>
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**Show Display Options**

- Include only open studies
- Exclude studies with Unknown status

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Capsule functions as a medical drug delivery system

Selectively porous cell membrane that encapsulates pancreatic islet stem cells (or mature islet cells) collected from human embryonic stem cells

Device protects implanted cells from immune rejection

Provides a platform for vascularisation

Prevents transplanted islet cells from leaving the implantation site

Allows nutrients, oxygen and insulin to diffuse freely through the membrane

Pancreatic progenitor cells have capacity to regenerate, differentiate and evolve to function in a hypoxic environment until vascularisation has been completed

Insulin stem cells, glucagon stem cells and somatostatin stem cells
Encapsulated islet cell transplant
A Safety, Tolerability, and Efficacy Study of VC-01™ Combination Product in Subjects With Type I Diabetes Mellitus

Sanford Stem Cell Clinical Center at the University of California, San Diego, California, USA

Test if VC-01™ combination product can be implanted subcutaneously in subjects with Type 1 Diabetes and is an effective treatment for subjects with Type 1 Diabetes

40 subjects to be recruited for 2 year trial of implanted encapsulated islet cells

Phase 1 and Phase 2 trial

Recruitment started September 2014

Completion date expected August 2017

https://clinicaltrials.gov/ct2/show/NCT02239354
Diabetes prevention after pancreatectomy for chronic pancreatitis

Safety and tolerability to mesenchymal stromal cells (MSCs) product

Autologous in nature, expanded using a non-xenogeneic, human component expansion media (pooled human platelet lysate) and delivered fresh.

Subsequently, the investigators intend to test whether infusion of MSCs immediately after islet autograft can reduce onset of diabetes and improve glycemic control after total pancreatectomy and islet autotransplantation.

https://clinicaltrials.gov/ct2/show/NCT02384018
Possible prevention of Type 1 diabetes
Possible prevention of Type 1 diabetes
### ClinicalTrials.gov

A service of the U.S. National Institutes of Health

#### Find Studies > Search Results

**Search for studies:**

- Example: “Heart attack” AND “Los Angeles”

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**700 studies found for:** type 1 diabetes prevention

**Modify this search** | **How to Use Search Results**

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**Show Display Options**

- Include only open studies
- Exclude studies with Unknown status

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**List** | **By Topic** | **On Map** | **Search Details**

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**Rank** | **Status** | **Study**

1 | Completed | The Diabetes Prevention Trial of Type 1 Diabetes (DPT-1)
   - **Condition:** Diabetes Mellitus, Type 1
   - **Intervention:** Drug: Crystallized human recombinant insulin

2 | Active, not recruiting | Diabetes Prevention - Immune Tolerance
   - **Conditions:** Prediabetes; Type 1 Diabetes
   - **Interventions:** Other: Placebo comparator, Drug: Diamyd

3 | Active, not recruiting | Oral Insulin for Prevention of Diabetes in Relatives at Risk for Type 1 Diabetes Mellitus
   - **Condition:** Diabetes Mellitus, Type 1
   - **Intervention:** Drug: Oral Insulin

4 | Completed | Feasibility Study of 2000 IU Per Day of Vitamin D for the Primary Prevention of Type 1 Diabetes
   - **Condition:** Type 1 Diabetes
   - **Intervention:** Dietary Supplement: vitamin D3

5 | Recruiting | CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At Risk for Type 1
   - **Conditions:** Abnormal Glucose Tolerance, Type 1 Diabetes
   - **Interventions:** Drug: CTLA4-Ig (Abatacept); Drug: Placebo
Some interesting Type 1 diabetes prevention trials actively recruiting

CTLA4-Ig (Abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1 diabetes

Teplizumab for Prevention of Type 1 Diabetes In Relatives "At-Risk"

Fr1da Insulin Intervention (oral insulin as an immune modulator)

Pre-POINT-Early Study (oral insulin as an immune modulator)

Immune Effects of Oral Insulin in Relatives at Risk for Type 1 Diabetes Mellitus (TN20) (oral insulin)

Imatinib Treatment in Recent Onset Type 1 Diabetes Mellitus (Glivec)
45 studies found for environmental determinants type 1 diabetes

Modify this search | How to Use Search Results

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<thead>
<tr>
<th>Rank</th>
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<td>TEDDY - The Environmental Determinants of Diabetes in the Young</td>
<td>Type 1 Diabetes Mellitus</td>
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<td>2</td>
<td>Recruiting</td>
<td>Genetic and Environmental Risk Factors of Type 1 Autoimmune Diabetes and Its Early Complications</td>
<td>Diabetes Mellitus; Insulin-Dependent</td>
<td>Other: Collect of environmental data on T1D patients before diagnosis; Genetic: Collect of blood samples for DNA extraction and genetic characterization (GWAS); Other: Collect of clinical data on the disease and its evolution; Other: Collect of environmental data on French controls (age-matched for T1D patients)</td>
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<tr>
<td>3</td>
<td>Recruiting</td>
<td>T1D Risk Assessment In Kids With Relatives</td>
<td>Type 1 Diabetes</td>
<td>Biological: Analysis of early immune modifications; Other: Collection of clinical and socio-demographic data</td>
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<td>Unknown</td>
<td>Prospective Assessment in Newborns for Diabetes Autoimmunity</td>
<td>Type 1 Diabetes; Autoimmunity</td>
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<tr>
<td>5</td>
<td>Completed</td>
<td>Predictive and Protective Factors In The Cause of Diabetes - A Study In Twins</td>
<td>Diabetes; Type 1 Diabetes</td>
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</tbody>
</table>
Why are more children getting Type 1 Diabetes?

The ENDIA study

Australia's largest study into the causes of Type 1 Diabetes
Type 2 diabetes

Notes: Age-standardised to the 2001 Australian population. All ages. Based on self-reported data.
Cardiovascular safety trials in Type 2 diabetes

EMPAGLIFLOZIN (Jardiance)
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Matheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Figure 1. Cardiovascular Outcomes and Death from Any Cause.
Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*
Figure 1. Kaplan–Meier Analysis of Two Key Renal Outcomes.
Shown are estimates of the probability of a first occurrence of a prespecified renal composite outcome of incident or worsening nephropathy (Panel A) and of a post hoc renal composite outcome (a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease) (Panel B) among patients who received at least one dose of either empagliflozin or placebo. The inset in Panel B shows the data on an expanded y axis. Hazard ratios are based on Cox regression analyses. Because of the declining numbers of patients at risk, Kaplan–Meier curves have been truncated at 48 months.
<table>
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<tr>
<th>Renal Outcome Measure</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tr>
<td></td>
<td>no. with event/</td>
<td>no. with event/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rate/1000</td>
<td>rate/1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>patient-yr</td>
<td>patient-yr</td>
<td></td>
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<tr>
<td>Incident or worsening nephropathy or cardiovascular death</td>
<td>675/4170 (16.2)</td>
<td>497/2102 (23.6)</td>
<td>0.61 (0.55–0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>525/4124 (12.7)</td>
<td>388/2061 (18.8)</td>
<td>0.61 (0.53–0.70)</td>
<td>&lt;0.001</td>
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<tr>
<td>Progression to macroalbuminuria</td>
<td>459/4091 (11.2)</td>
<td>330/2033 (16.2)</td>
<td>0.62 (0.54–0.72)</td>
<td>&lt;0.001</td>
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<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²</td>
<td>70/4645 (1.5)</td>
<td>60/2323 (2.6)</td>
<td>0.56 (0.39–0.79)</td>
<td>&lt;0.001</td>
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<tr>
<td>Initiation of renal-replacement therapy</td>
<td>13/4687 (0.3)</td>
<td>14/2333 (0.6)</td>
<td>0.45 (0.21–0.97)</td>
<td>0.04</td>
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<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease</td>
<td>81/4645 (1.7)</td>
<td>71/2323 (3.1)</td>
<td>0.54 (0.40–0.75)</td>
<td>&lt;0.001</td>
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<tr>
<td>Incident albuminuria in patients with a normal albumin level at baseline</td>
<td>1430/2779 (51.5)</td>
<td>703/1374 (51.2)</td>
<td>0.95 (0.87–1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Figure 2. Risk Comparison for Seven Renal Outcomes.**

All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All the analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease. The abbreviation eGFR denotes estimated glomerular filtration rate.
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*
**Primary Outcome**

Hazard ratio, 0.17 (95% CI, 0.78–0.87) for noninferiority

P<0.001 for noninferiority

P=0.01 for superiority

**Death from Cardiovascular Causes**

Hazard ratio, 0.78 (95% CI, 0.66–0.93)

P=0.007

**Nonfatal Myocardial Infarction**

Hazard ratio, 0.38 (95% CI, 0.75–1.03)

P=0.11

**Nonfatal Stroke**

Hazard ratio, 0.89 (95% CI, 0.72–1.11)

P=0.30

**Death from Any Cause**

Hazard ratio, 0.15 (95% CI, 0.74–0.97)

P=0.02

**Hospitalization for Heart Failure**

Hazard ratio, 0.87 (95% CI, 0.73–1.05)

P=0.14
‘The ominous octet’ in T2 diabetes

Figure 1. The ominous octet. Multiple defects contribute to the development of glucose intolerance in type 2 diabetes. HGP, hepatic glucose production.
Currently available drugs for diabetes - what works where?

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Figure 2. Pathophysiological abnormalities targeted by currently available antidiabetic medications. DPP4i, dipeptidyl peptidase-4 inhibitor; GLP1 RA, glucagon-like peptide-1 receptor agonist; HGP, hepatic glucose production; MET, metformin; SGLT2i, sodium glucose co-transporter 2 inhibitor; TZD, thiazolidinedione.
Insulin sensitisers
Drugs in development that target mitochondria: insulin sensitisers

Mitochondria: powerhouses of the cell

Mitochondrial complex (mToT) contains two proteins Mpc1 & Mpc2 that modulate pyruvate entry into mitochondria and regulate pyruvate oxidation
Mitochondrial agents for diabetes (potentially)

MSCD-602: New agent targets these proteins to make the cell more sensitive to insulin

Short phase 2 trials to date: 2 different agents (‘new drugs” potentially)

Results as good as TZDs in making the cell more sensitive to insulin
Drugs targeting Muscle and/or Liver
Pyruvate dehydrogenase (PDH) complex

Key enzymes controlling energy production within cells
PDH converts pyruvate to acetyl CoA and CO$_2$
End result is lowered glucose production by the liver and more glucose burnt up in muscle
PDH is inactive when phosphate is attached (i.e. phosphorylated)
PDH is phosphorylated by enzymes protein KINASES
Drugs in development: Pyrophosphate dehydrogenase kinase inhibitors (PDHK inhibitors)

Agents which INHIBIT phosphorylation of PDH will cause greater activity of PDH

This will lead to

• Less release of glucose from the liver
• More muscle glucose metabolism
• END RESULT: LOWER BLOOD GLUCOSE
Pyruvate Dehydrogenase Kinase inhibitors have shown promise in pre-clinical studies

AZD2545 (Roche)
JTT-251 (Japan Tobacco & Akros Pharma)
Agents that work on insulin receptor phosphorylation

When the insulin receptor binds insulin, the activated receptor phosphorylates the IRS-1 protein. IRS-1 can lead to recruitment of GRB2, activating the Ras pathway.

IRS-1 activates PI 3-kinase, which catalyzes the addition of a phosphate group to the membrane lipid PIP₂, thereby converting it to PIP₃. PTEN can convert PIP₃ back to PIP₂.

PIP₂ binds a protein kinase called Akt, which is activated by other protein kinases.

Akt catalyzes phosphorylation of key proteins, leading to an increase in glycogen synthase activity and recruitment of the glucose transporter, GLUT4, to the membrane.
Protein tyrosine phosphatase 1B inhibitors

These agents inhibit enzymes which work to remove phosphate residues from tyrosine (which is part of insulin receptor) which is activated for longer.

End result is: more bang for your buck from the insulin receptor.
Other agents being studied

Fibroblast Growth Factor 21 (FGF21)
Produced by liver and adipose tissue
Enhances insulin sensitivity, lowers glucose and reduces lipids
Novel mechanism of action, not well understood
Lilly has an analogue product in development
Glucagon receptor antagonists

T2 diabetes is associated with higher than normal glucagon levels and the liver is more sensitive to glucagon.

Blocking glucagon receptor may lead to improved blood glucose levels.

Merck developed a product, but discontinued because of elevation of LDL.

Lilly has studied an agent in this class, but LFT rises seen.
11 B hydroxysteroid dehydrogenase inhibitors

These block conversion in the liver of cortisone (inactive) to cortisol (active) in the liver and thereby may improve insulin sensitivity and improve hyperglycaemia.

Modest effects at best
Diacylglycerolacyl Transferase-1 Inhibitors (DGAT) inhibitors

These agents reduce hypertriglyceridaemia after a meal

By doing this they act as insulin sensitisers

Roche is studying an agent of this type
Others

Glucose kinase activators
Fructose 1,6 biphosphatase inhibitors
Anti-inflammatories: mostly disappointing
Combined inhibition of IKKβ/NF-κB and MAP pathways may hold promise
Technology & diabetes: fruitful areas for progress

Innovative use of engineering, mathematics and computer science as important as biological science

Therapeutic possibilities:

- nanotechnology
- microneedle array patches
- inhaled insulin
- oral insulin

Better Type 2 diabetes drugs related to better understanding of basic science

Complications of diabetes reduced with Empagliflozin
Never been a more exciting time to be an Australian

Malcolm Turnbull
Never been a more exciting time to be an Australian a diabetes educator

Malcolm Turnbull Shane Hamblin