


Diabetes Research and Novel Therapeutics Update

OC Collaborative Diabetes Conference
 April 26, 2014
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Disclaimer/Disclosure

- I do not have any personal financial relationships with ANY of the companies or products presented today
- I do not have any family member's with financial relationships with the companies or products presented today
- CHOC Children's Hospital receives funding from the NIH for work on TrialNet

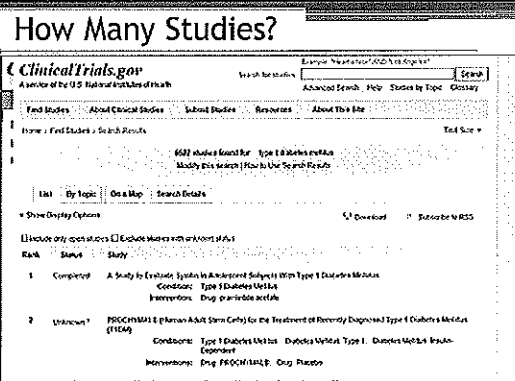
Diabetes 1921



Overview

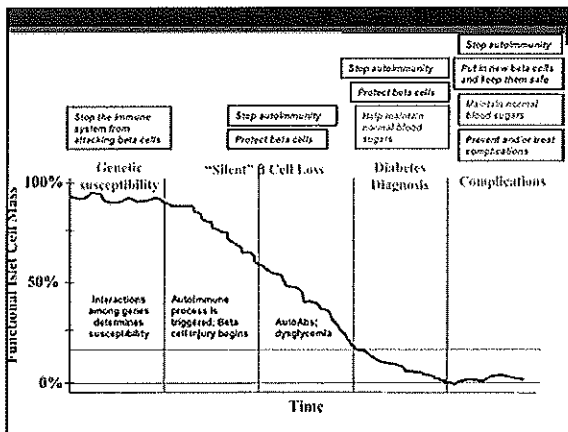
- Type 1 Diabetes Research
 - Natural History
 - Genetic and Environmental Determinants
 - The Problem of Autoimmunity
 - Transplants
- Type 2 Novel Therapeutics
 - Insulin advances
 - Non – insulin medications
- Apps

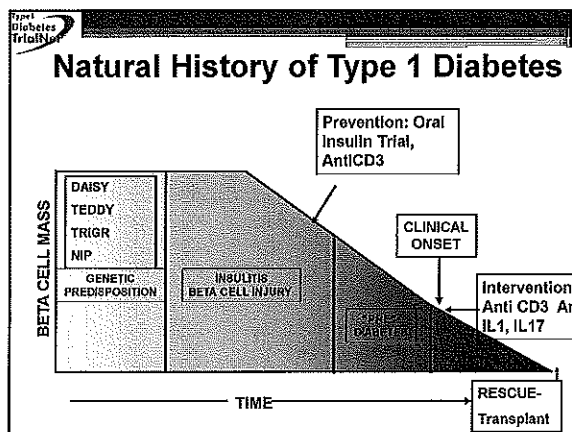
How Many Studies?



692 studies found for Type 1 Diabetes Mellitus

Rank	Status	Study
1	Completed	A Study to Evaluate Efficacy in Adolescent Subjects With Type 1 Diabetes Mellitus Conditions: Type 1 Diabetes Mellitus Interventions: Drug pramlintide acetate
2	Unknown	PROCHM118 (Phasor ADAM Data Core) for the Treatment of Recently Diagnosed Type 1 Diabetes Mellitus (T1DM) Conditions: Type 1 Diabetes Mellitus, Diabetes Mellitus Type 1, Diabetes Mellitus Insulin-Dependent Interventions: Drug PROCHM118, Drug Placebo
3	Completed	Effect of Fingertone on the Course of New Onset Type 1 Diabetes Mellitus

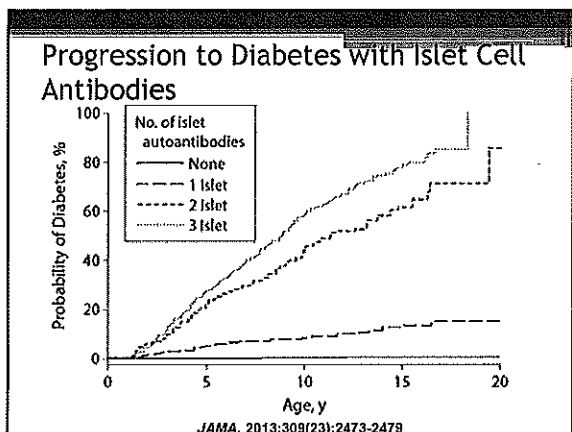




Type 1 Diabetes TrialNet

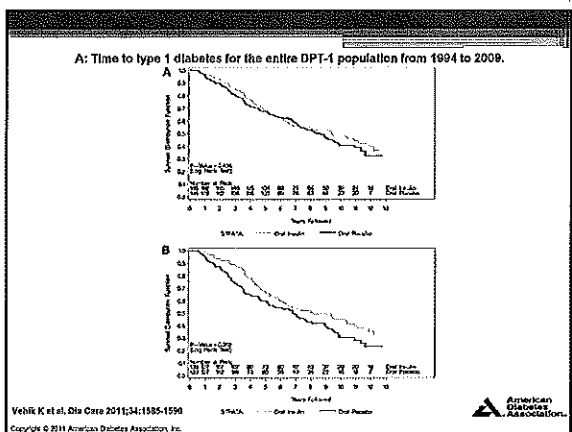
TrialNet is a network of 18 Clinical Centers and 150 affiliates in the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia, and New Zealand.

TrialNet is dedicated to the study, prevention, and early treatment of type 1 diabetes.



Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children

- Progression to type 1 diabetes at 10-year follow-up after islet autoantibody seroconversion in 585 children with multiple islet autoantibodies was 69.7%
- in 474 children with a single islet autoantibody was 14.5%
- Risk of diabetes in children who had no islet autoantibodies was 0.4%
- JAMA. 2013;309(23):2473-2479



Oral Insulin in TrialNet

- Relatives of patients with type 1 Diabetes are screened for presence of antibodies.
- If + micronized Insulin Autoantibody (mIAA), and one other antibody, then randomized to receive oral insulin or placebo.
- Endpoint is development of diabetes
- Started 2007 – Still ongoing!!!

Effectiveness of Early Intensive Therapy on β -Cell Preservation in Type 1 Diabetes

Click on image to view larger version.

	Intensive	Standard
n	47	20
C-peptide AUC (pmol/mL), geometric mean (95% CI) ^a	0.43 (0.34–0.52)	0.52 (0.32–0.75)
HbA _{1c} (%) ^b , mean \pm SD	7.4 \pm 1.2	7.3 \pm 1.1
HbA _{1c} (mmol/mol), mean \pm SD	57 \pm 13	57 \pm 12
CGM data median	N = 31	N = 15
Mean glucose (mg/dL)	150	152
71–180	69%	70%
<70	2.5%	0.7%
>180	27%	22%
CV (%)	33	33
	N = 48	N = 20
TDI (units/kg/day)	0.6 \pm 0.2	0.6 \pm 0.3
	N = 46	N = 19
BMI percentile ^c	58	62

Buckingham et al. Diabetes Care December 2013 Vol 36 No 12 4030–4035

Genetics and Environmental Determinants

- The first questions I am ALWAYS asked after giving the news to a family is:
- WHY DID THIS HAPPEN? WHAT CAUSES DIABETES?**

TEDDY

The Environmental Determinants of Diabetes in the Young

Finding diabetes early can prevent serious illness and complications.

Are you pregnant? Do you have no obvious symptoms?

Most of the new cases of type 1 diabetes occur in children who have no obvious history of the disease. Learn more about how TEDDY helps us understand what you can do to help prevent it.

Every child in the TEDDY study helps us come closer to preventing this disease. Would it be possible to prevent it before it starts?

<http://teddy.epi.usf.edu/>

- "The long-term goal of the TEDDY study is the identification of infectious agents, dietary factors, or other environmental agents, including psychosocial factors, which trigger type 1 diabetes in genetically susceptible individuals or which protect against the disease"
- Data Collection Complete in 2025!!!

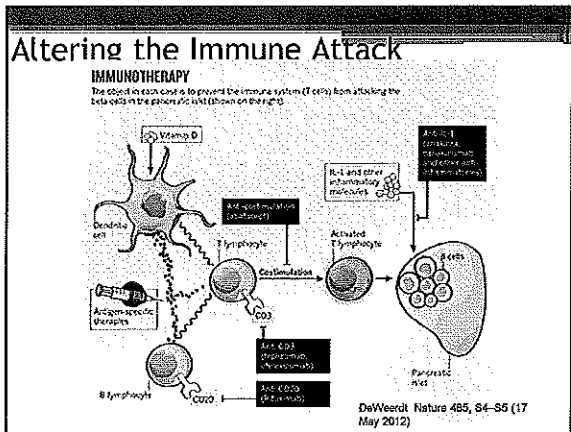
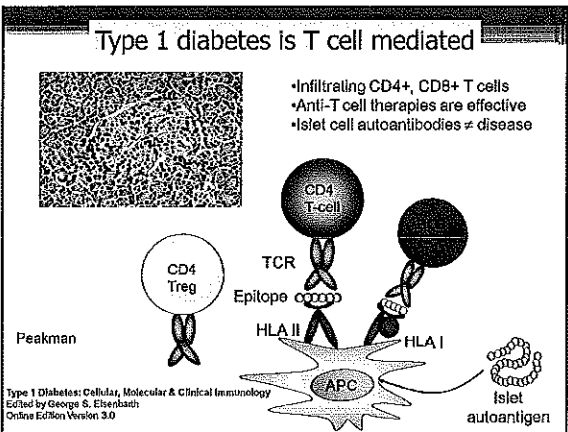
TRIGR

Trial to Reduce IDDM in the Genetically at Risk

TRIGR is an international, randomized, double-blind trial. The purpose is to see if a certain drug called Rituximab can help prevent type 1 diabetes in children who are genetically at risk of developing it. Learn more about the TRIGR trial.

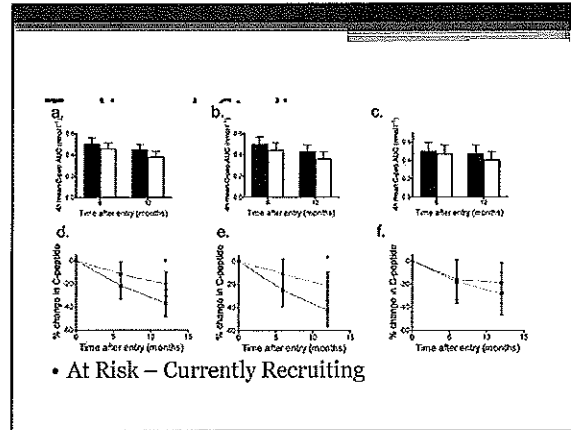
type 1 diabetes
DON'T WE PROTECT OUR CHILDREN?

Results Expected 2017



Immune Targeted Therapies

- Teplizumab – Anti CD3 Ab
 - Daily Infusions for 14 days.
 - “At Risk” vs Recent Onset vs Post recent Onset
- Secukinumab Anti IL17
- Canakinumab Anti IL1 Beta
 - Monthly Subcutaneous Injections
- Imatinib – GLEEVEC ???



Islet Transplants

- 1893: Minkowski transplants fragments of a sheep's pancreas into a diabetic 15-year-old boy. The boy dies three days after the operation.
- 1924: Pybus tries to transplant human cadaveric pancreas tissue in an attempt to cure diabetes, grafts rejected due to lack of immunosuppression.
- 1963: The immunosuppressant Azathioprine is discovered, starting an organ transplant revolution.
- 1966: The first whole pancreas transplant is performed.
- 1974: Researchers begin the first clinical trial of islet transplantation, using steroids and azathioprine as immunosuppressants. None of these patients achieve insulin independence.
- 1990: A few islet transplant recipients achieve prolonged and consistent insulin independence using steroid-free, tacrolimus based immunosuppression.
- 1999: The Edmonton group uses a new procedure to achieve an initial 100% success rate by using tacrolimus and sirolimus rather than cyclosporine and steroids,

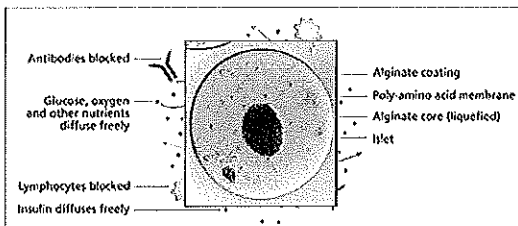
http://biomed.brown.edu/Courses/BI108/BI108_2004_Groups/Group09/history.htm

The Problem of Autoimmunity!

- One Solution:



Islet Cell Encapsulation



From MicroIslet Webpage

In An Open Label, Pilot Investigation, to Assess the Safety and Efficacy of Transplantation of Micro-encapsulated Human Islets Within the Biotransfused Pancreas Beta-O2 in Patients With Type 1 Diabetes Mellitus

This study is currently recruiting participants. **CONTACT: 617-355-2274**
 01-27-2014
 Sponsor: **Uppsala University Hospital**
 Collaborator: **Beta O2 Technologies LLC**

No More Frequent Glucose Monitoring & Insulin Injections

The BETA-O2 system is a bioartificial pancreas that can be implanted subcutaneously. The BETA-O2 system which biologically regulates glucose levels in Type 1 diabetes patients has two major components:

- **Open generator**
- **Islet generator** - contains islets of Langerhans, bioactive protection material and bio-sensors.

The islet generator is a ball of cells, where the outer surface is an impermeable surface and the inner membrane is made of a permeable material. The outer membrane allows for glucose entry and insulin output. The inner membrane contains the islets of Langerhans embedded within a special biopolymer. The BETA-O2 senses the glucose and secretes only the appropriate amount of insulin required to returning the glucose level to normal.

The device is implanted subcutaneously in a minor trans procedure.

ViaCyte - Cross Section of Encaptra® Drug Delivery System

HOW TO MAKE
Microcapsules

Technology

- Pumps
- Sensors
- Sensor Augmented Pumps
- Threshold Suspend Pump
- Hybrid Closed Loop Pumps

Diabetes Technol Ther. 2014 Jun 17; 16(6):e143-52.

The Effects of Lowering Nighttime and Breakfast Glucose Levels with Sensor-Augmented Pump Therapy on Hemoglobin A1c Levels in Type 1 Diabetes.

Starling M, Cobelli B, Sparrow D, et al. *Diabetes Technol Ther*. 2014 Jun 17; 16(6):e143-52.

- Star 3 trial
- 196 patients analyzed
- After multivariate analysis
 - Improving Breakfast Period Glucose CGM had the largest effect on improving A1C
 - Other periods did NOT seem to affect A1C
 - Lending new credence to “Breakfast is the...”

But Is Someone Trying To “Close the Loop?” circa 2011

Imported Evaluation of an Automated Closed-Loop Control of Insulin System (CL2)

This study is currently recruiting participants. Visit at April 2013 on ClinicalTrials.gov. Identifier: NCT01783419. Last updated: July 4, 2013. Archived April 2011. Medical Center.

Feasibility Study Assessing The Ability Of An Insulin Pump-Controlling Algorithm To Minimize Hypoglycemia And Hyperglycemia In Patients With Type 1 Diabetes In A Clinical Research Setting

This study is currently recruiting participants. Visit at July 2013 on ClinicalTrials.gov.

Getting Closer to Real World!

Closing the Loop in Children and Adolescents With Type 1 Diabetes In the Home Setting (APCarr08)

This study is currently recruiting participants. Visit at December 2013 on ClinicalTrials.gov. Identifier: NCT01783419. First received: January 25, 2013. Last updated: December 19, 2013. Last verified: December 2013. History of Changes.

Sponsor: University of Cambridge

Collaborators: Cambridge University Hospitals NHS Foundation Trust, University College London Hospitals, The Leeds Teaching Hospitals NHS Trust

Information provided by (Responsible Party): Dr Robert Hovorka, University of Cambridge

Integration of Continuous Glucose Monitoring Into a BI-Hormonal Closed-Loop Artificial Pancreas for Automated Management Of Type 1 Diabetes (CL2)

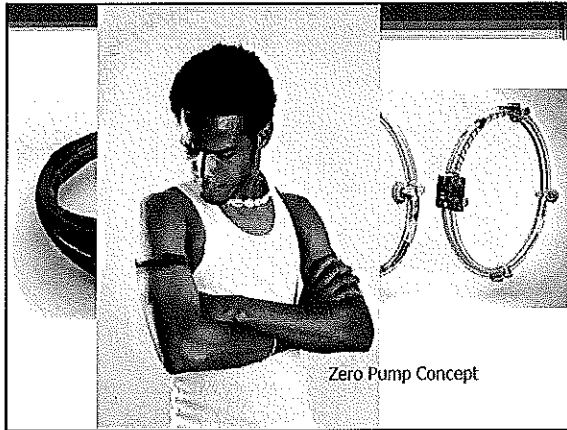
This study has been completed.

Sponsor: Boston University

Collaborators: Massachusetts General Hospital, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Juvenile Diabetes Research Foundation, Leonard and Mary B. Healey Charitable Trust

Information provided by (Responsible Party): Edward R. Damiano, Boston University

ClinicalTrials.gov Identifier: NCT01101662. First received: July 12, 2010. Last updated: October 21, 2013. Last verified: October 2013. History of Changes.



And Now for Something Completely Different

Effects of Metreleptin in Type 1 Diabetes Mellitus

This study is currently recruiting participants.
 Started June 2013 by University of Texas Southwestern Medical Center
 Sponsor: University of Texas Southwestern Medical Center
 Collaborators: Juvenile Diabetes Research Foundation, Amylin Pharmaceuticals, LLC
 Information provided by the responsible party: Adhansorg Corp., University of Texas Southwestern Medical Center

ClinicalTrials.gov Identifier: NCT01265814
 First posted: December 22, 2010
 Last updated: June 12, 2013
 Last verified: June 2013
 History of Changes

- Leptin – Hormone Secreted from the Fat Cell
 - Blocks Lipogenesis (fat breakdown) and excess glucagon secretion
 - Thus, can help smooth out the variability/hyperglycemia seen in insulin treated patients

BIOLOGICAL SOLUTIONS And NOVEL INSULIN DELIVERY

MannKind And Afrezza®

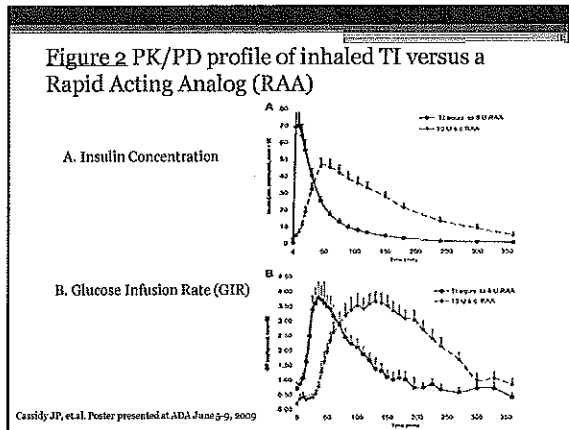
Delivery Systems

Dreamboat

AFREZZA or Technosphere Insulin (TI)

Figure 1 Technosphere inhalation insulin device.

2.5 µm
 Microparticle
 Pimarlyl Diketopiperazine



Results for Change in A1c level with Technosphere Insulin (TI) vs. Aspart with Glargine.

- The initial A1C was between >7.0% and ≤11.0%
- The change in A1C was
 - -0.11% for TI and
 - -0.36% for Aspart, making TI non-inferior to Aspart.

J Diabetes Sci Technol Vol 6, Issue 4, July 2012

Results for Hypoglycemia in Technosphere Insulin (TI) vs. Aspart with Glargine in Type 1 diabetes.

- TI group showed reduced incidence of mild/moderate hypoglycemia.
 - [odds ratio (OR), 0.474; 95% CI, 0.0271 to 0.831; $p = .0091$]
- TI group showed less overall hypoglycemia
 - (OR, 0.488; 95% CI, 0.278 to 0.856; $p = .0124$) compared with the Aspart group.

J Diabetes Sci Technol Vol 6, Issue 4, July 2012

SmartInsulin™

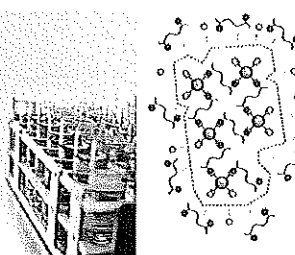
Welcome

SmartInsulin, Inc. is developing "smart insulin," a new insulin, with signaling, adjustable formulation for people with diabetes. It is designed to provide several important advantages for diabetes patients:

- Reduce the incidence of hypoglycemia
- Provide lower glycemic and less glucose variability
- Reduce both fasting and nocturnal glucose levels with a single dose

SmartInsulin is currently in pre-clinical (pre-human) testing. Based on concept studies, both in vitro and in vivo, we anticipate early control of blood glucose levels and rapid, reversible response to glucose fluctuations.

SmartInsulin makes use of a polymer-based dosing technology developed at MIT, by SmartInsulin's founder, Dr. Todd H. Jones. This breakthrough makes possible a new regulator of the release of a therapeutic based on the physical concentration of a molecular inhibitor.



From <http://www.toddj.org/journal.com/biomedicine/216131/>

Degludec


- Insulin Degludec (Danne et. al.)
 - Ultra Long Lasting Insulin
 - Maximal concentration by 10-11 hours
 - Lasts up to 72 hours in children

FDA Rejects Novo Nordisk's Insulin Degludec
From E. Taylor | Diabetes
 February 11, 2012

The US Food and Drug Administration (FDA) has declined to approve Novo Nordisk's insulin degludec, listing it as a "complete response letter" in which it requests additional cardiovascular outcomes data from a dedicated trial.

DRUG & REFERENCE INFORMATION
 Hypersomolar Hyperglycemic State

Genetic mutation may protect against Type 2 diabetes



People with a specific genetic mutation may have some protective immunity against Type 2 diabetes, even if they have other risk factors for the disease such as obesity and old age.

A study that analyzed the genomes of 150,000 people found that people who had a rare mutation in the *TCF7L2* gene had a 6% percent lower chance of developing Type 2 diabetes compared to those with perfect copies.

Incretins

- GLP-1 Agonists
- DPP-4 Inhibitors

- Recent safety concerns for pancreatitis

GLP-1 Agonists

- Exenatide
- Liraglutide
- Albiglutide – Once Weekly!!!

DPP-4

- Dipeptidyl Peptidase 4 Inhibitors
 - sitagliptin (Januvia), saxagliptin (Onglyza) alogliptin (Nesina), linagliptin (Tradjenta)
 - Prevents breakdown of endogenous GLP1

Saxagliptin vs. Placebo

- Scirica et al NEJM 2013. A randomized placebo control study of 16,492 patients showed that although the A1C was significantly improved in those using Saxagliptin (7.5% vs 7.8% at 2 years), there was NO improvement in total cardiovascular events (MI, Stroke, Cardiovascular death, etc)

Scirica B et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *New Engl J Med* 2013 Oct 3; 369(14):6-16: 1317-26.

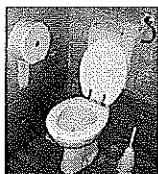
Table 2. Prespecified Clinical End Points.*

End Point	Saxagliptin (N = 8249) no. (%)	Placebo (N = 8243) no. (%)	Hazard Ratio (95% CI)	P Value
Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point	613 (7.3)	609 (7.2)	1.00 (0.83-1.12)	0.99
Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point	1059 (12.8)	1034 (12.4)	1.02 (0.94-1.11)	0.66
Death from any cause	420 (4.9)	378 (4.2)	1.11 (0.96-1.27)	0.15
Death from cardiovascular causes	269 (3.2)	260 (2.9)	1.03 (0.87-1.22)	0.72
Myocardial infarction	265 (3.2)	278 (3.4)	0.95 (0.80-1.12)	0.52
Ischemic stroke	157 (1.9)	143 (1.7)	1.11 (0.83-1.49)	0.38
Hospitalization for unstable angina	97 (1.2)	81 (1.0)	1.19 (0.89-1.60)	0.24
Hospitalization for heart failure	259 (3.1)	225 (2.8)	1.27 (1.07-1.51)	0.007
Hospitalization for coronary revascularization	421 (5.1)	459 (5.6)	0.91 (0.80-1.04)	0.18
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dl (530 µmol/liter)	194 (2.3)	176 (2.0)	1.06 (0.83-1.32)	0.46
Hospitalization for hypoglycemia	53 (0.6)	41 (0.5)	1.22 (0.81-1.83)	0.33

* Event rates and percentages are 2-year Kaplan-Meier estimates.

SGLT2 Inhibitors

- Canagliflozin -- Invokana
- Dapagliflozin -- Farxiga
 - Initial study showed increased occurrence of bladder cancer



A Big "APP"etite for Diabetes

