Novel Treatments in Diabetes

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Conflict of interest

No apparent or real conflict of interest for this presentation

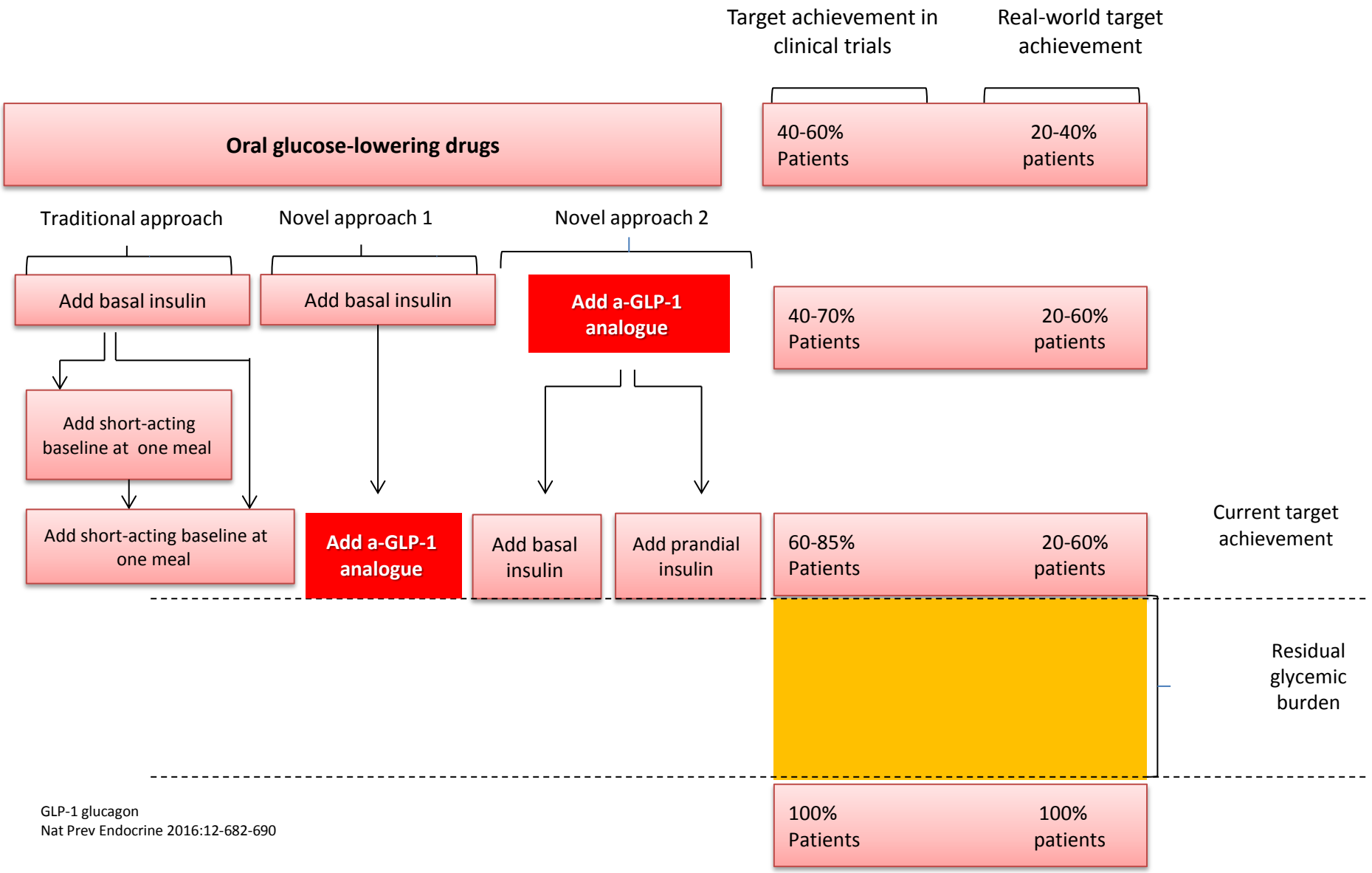
Agenda

- Delivery systems
- Combination partners
- Smart insulin
- Investigational insulin secreatagous
- Gut microbioms

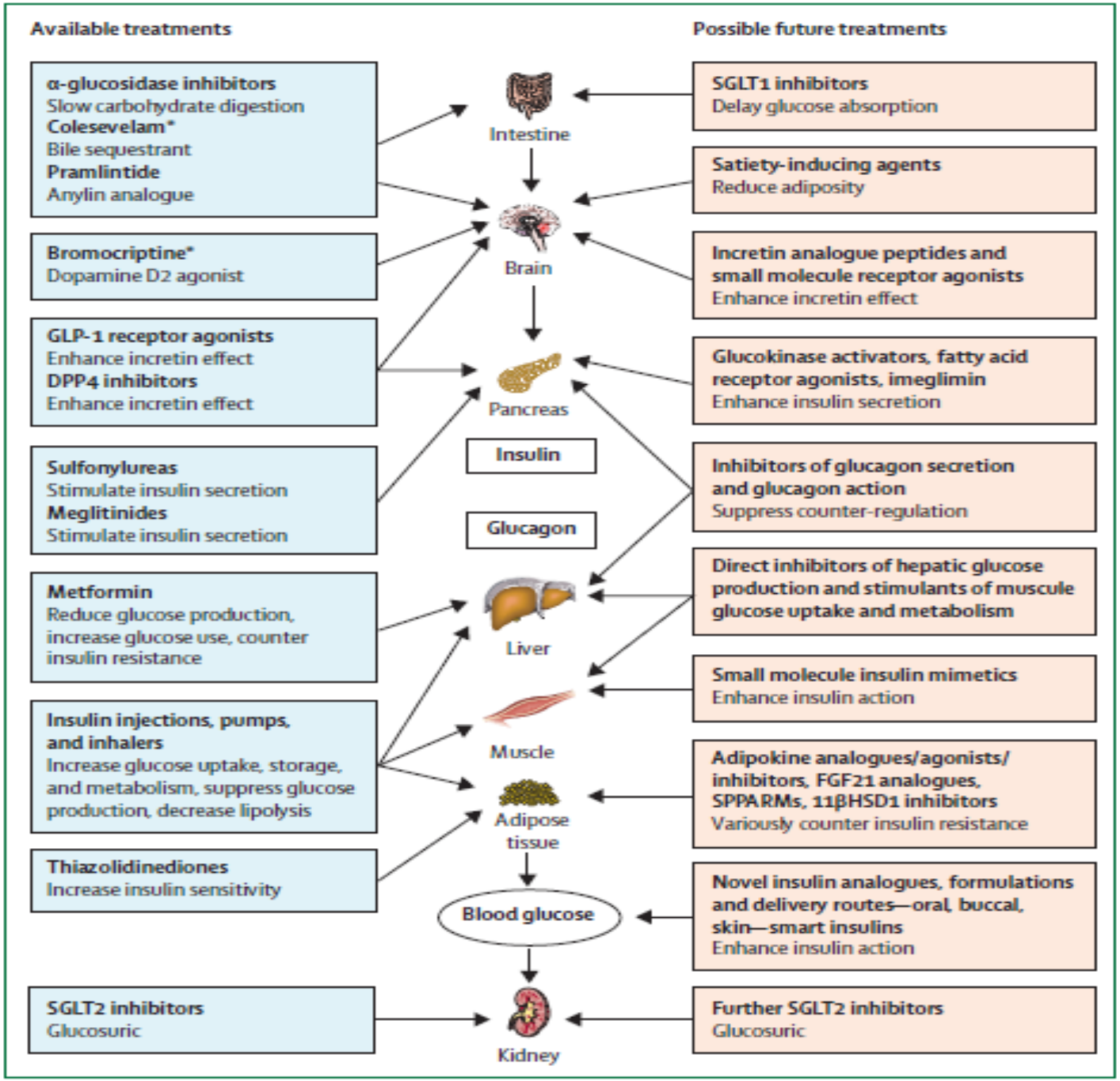
- Early, effective, and sustained glycaemic control reduces the severity of associated complications.
- More than a third of all patients with diabetes do not achieve or maintain an appropriate glycaemic target.

Clin Endocrinol (Oxf) 2014; 80: 47–56

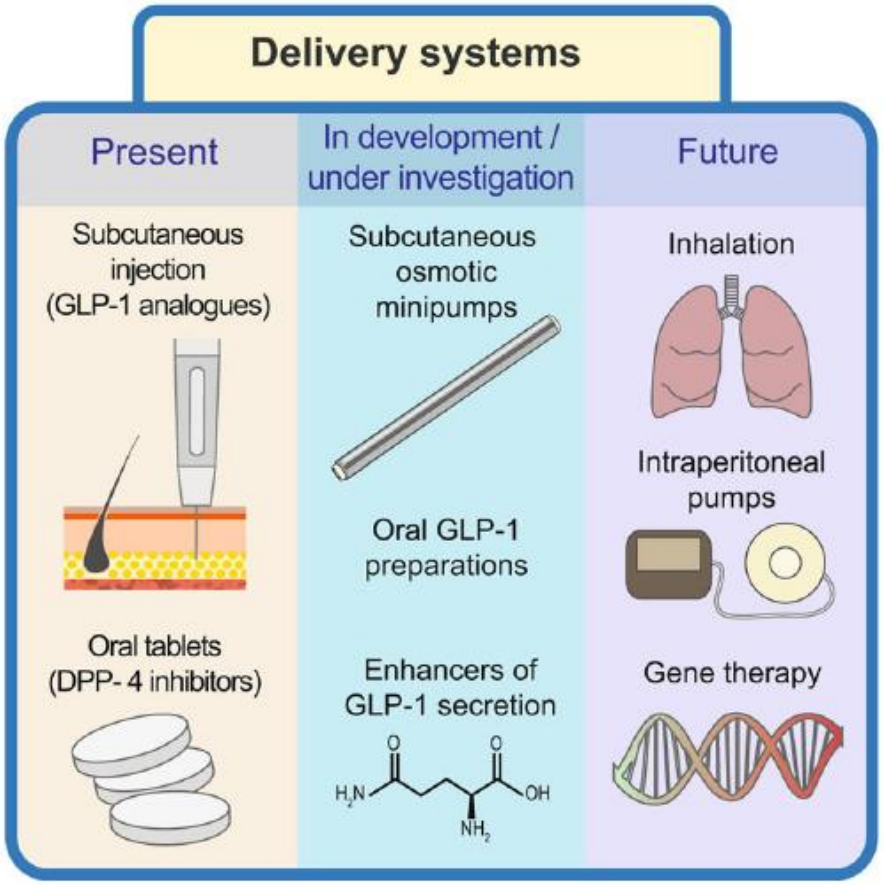
Current treatment approaches: Glycemic target achievement

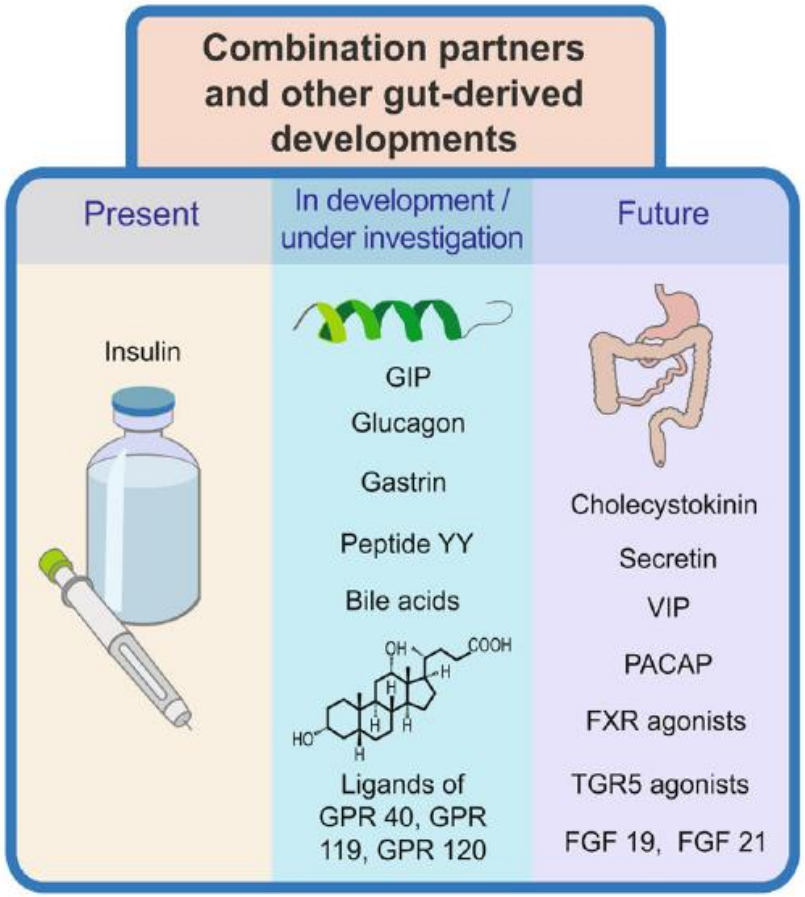


GLP-1 glucagon
Nat Prev Endocrine 2016:12-682-690


Available treatments
Possible future treatments
α-glucosidase inhibitors
Slow carbohydrate digestion
Colesevelam*
Bile sequestrant
Pramlintide
Anylin analogue
Bromocriptine*
Dopamine D2 agonist
GLP-1 receptor agonists
Enhance incretin effect
DPP4 inhibitors
Enhance incretin effect
Sulfonylureas
Stimulate insulin secretion
Meglitinides
Stimulate insulin secretion
Metformin
Reduce glucose production, increase glucose use, counter insulin resistance
Insulin injections, pumps, and inhalers
Increase glucose uptake, storage, and metabolism, suppress glucose production, decrease lipolysis
Thiazolidinediones
Increase insulin sensitivity
SGLT2 inhibitors
Glucosuric
Intestine
Brain
Pancreas
Insulin
Glucagon
Liver
Muscle
Adipose tissue
Blood glucose
Kidney
SGLT1 inhibitors
Delay glucose absorption
Satiety-inducing agents
Reduce adiposity
Incretin analogue peptides and small molecule receptor agonists
Enhance incretin effect
Glucokinase activators, fatty acid receptor agonists, imeglimin
Enhance insulin secretion
Inhibitors of glucagon secretion and glucagon action
Suppress counter-regulation
Direct inhibitors of hepatic glucose production and stimulants of muscule glucose uptake and metabolism
Small molecule insulin mimetics
Enhance insulin action
Adipokine analogues/agonists/ inhibitors, FGF21 analogues, SPPARMs, 11βHSD1 inhibitors
Variously counter insulin resistance
Novel insulin analogues, formulations and delivery routes—oral, buccal, skin—smart insulins
Enhance insulin action
Further SGLT2 inhibitors
Glucosuric

What does the future hold for incretin-based therapies?





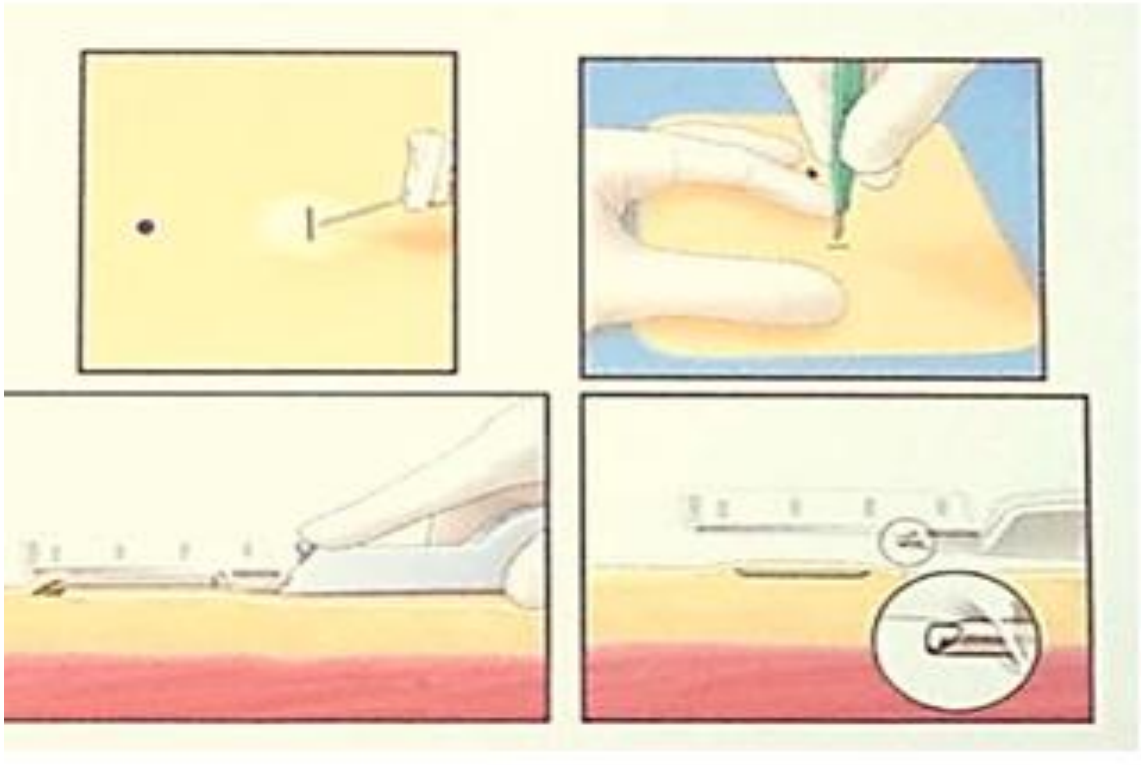
Diabetologia (2015) 58:1745–1750

Efficacy and Safety of ITCA 650, a Novel Drug-Device GLP-1 Receptor Agonist, in Type 2 Diabetes Uncontrolled with Oral Anti diabetes Drugs: The FREEDOM-1 Trial

Julio Rosenstock,[1] John B. Buse,[2] Rehan Azeem,[3] Prakash Prabhakar,[3] Lise Kjems,[3] Holly Huang,[3] and Michelle A. Baron[3]

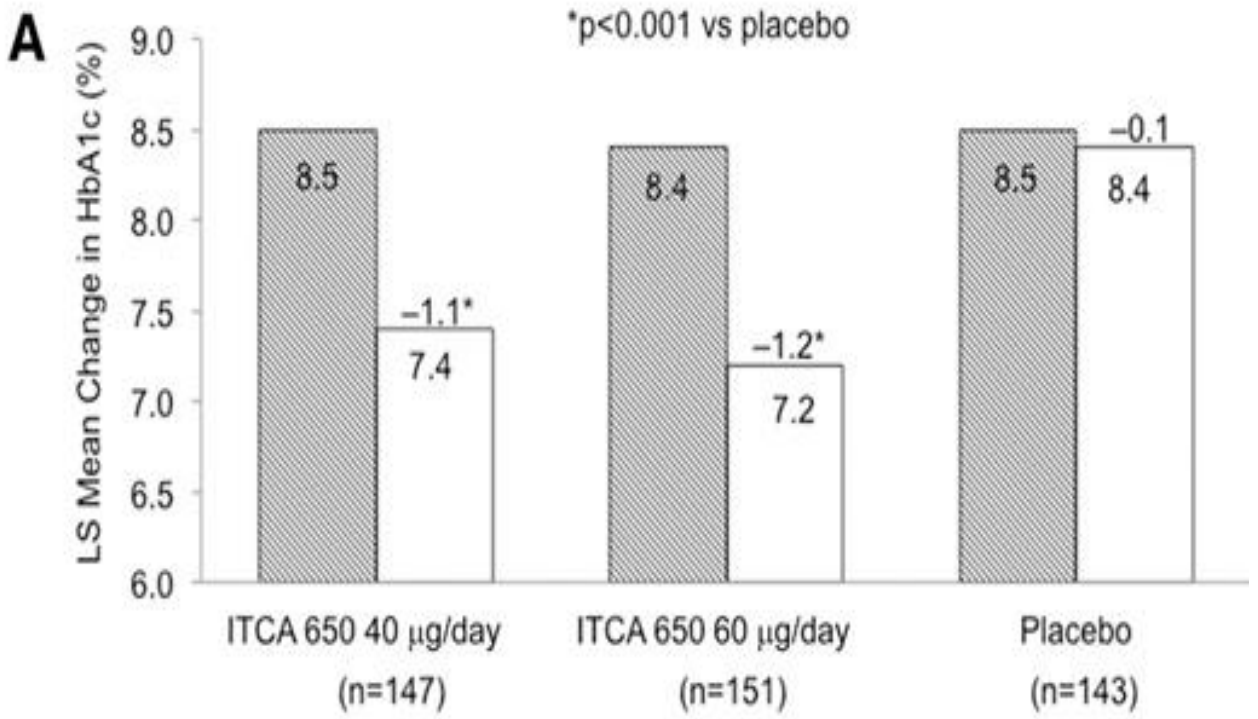
Diabetes Care 2018; 41:333–340 | https://doi.org/10.2337/dc17-1306

Subcutaneous delivery of exenatide by *ITCA 650*: Optimizing patient adherence to GLP-1 analogues

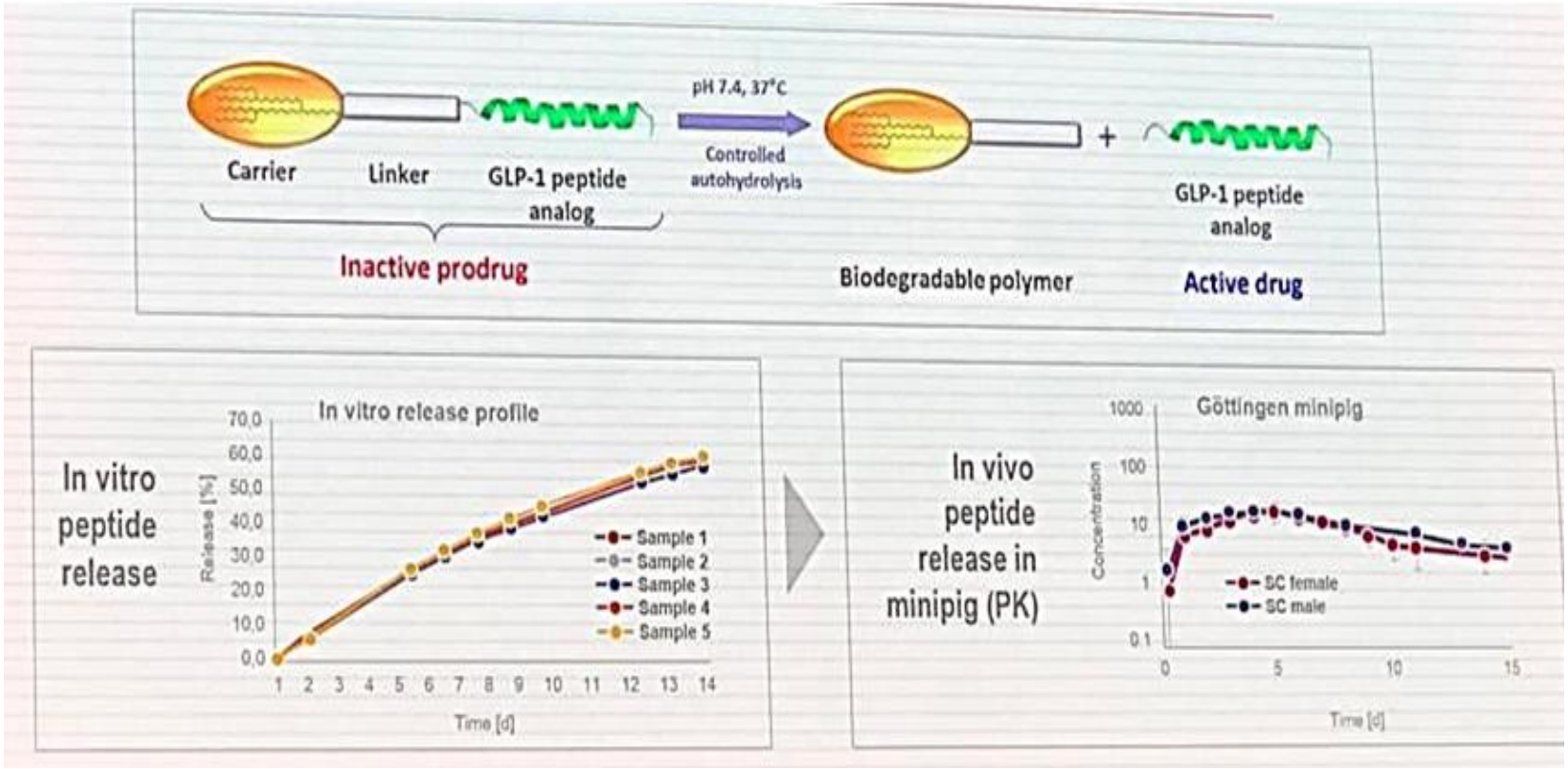


- ITCA 650 (Exenatide in osmotic mini-pump) continuously delivers exenatide Subq. for 3–6 months
- 39-week, phase 3, double-blind, placebo-controlled trial
- HbA1c: 7.5–10%
- ITCA 650: 40 mg/day, or ITCA 650: 60 mg/day

FREEDOM-1: Reduction in HbA1c from baseline after 39 weeks of treatment with ITCA 650



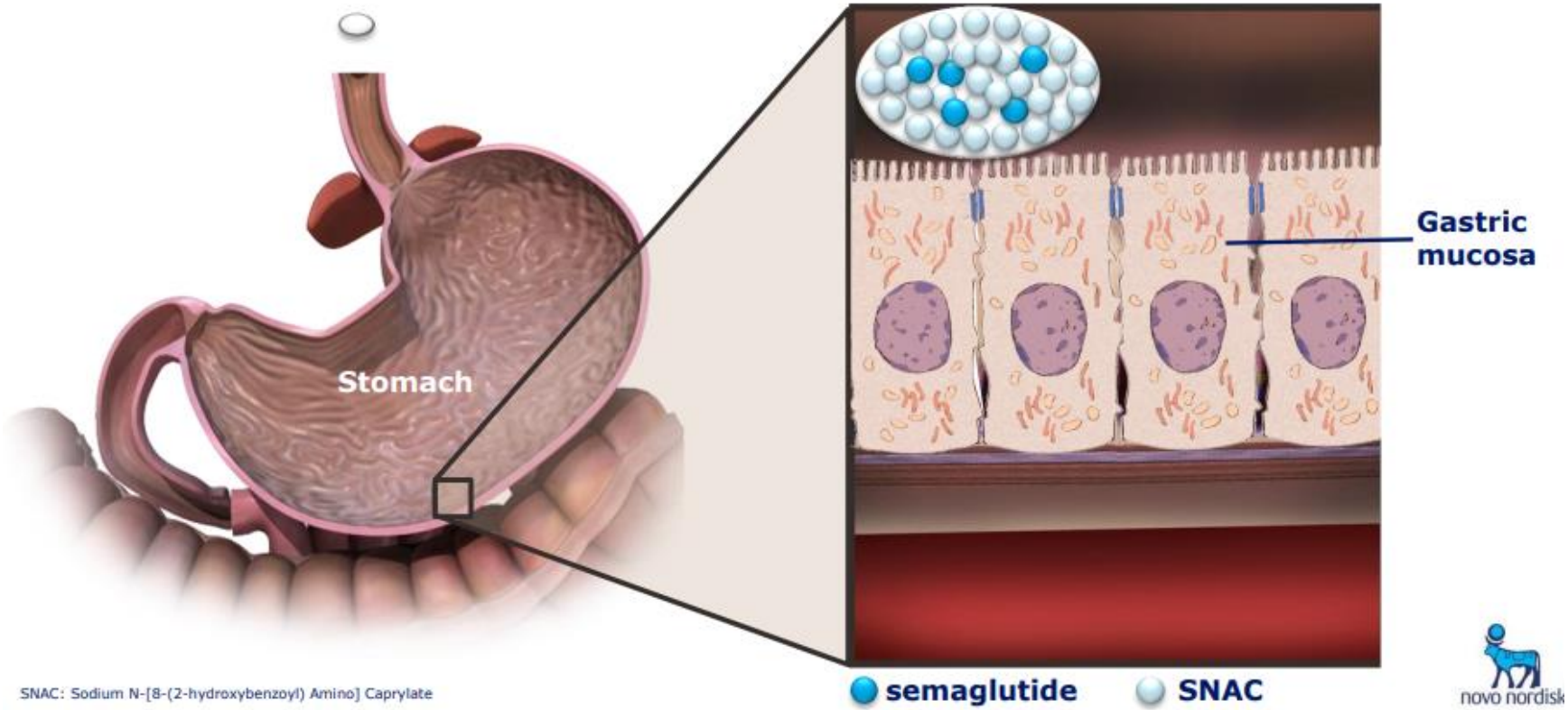
Sustained Delivery of peptides following SC Administration



Absorption of oral semaglutide via the stomach

- Semaglutide co-formulated with SNAC
- SNAC: an absorption enhancer
- SNAC and Semaglutide undergo transcellular absorption

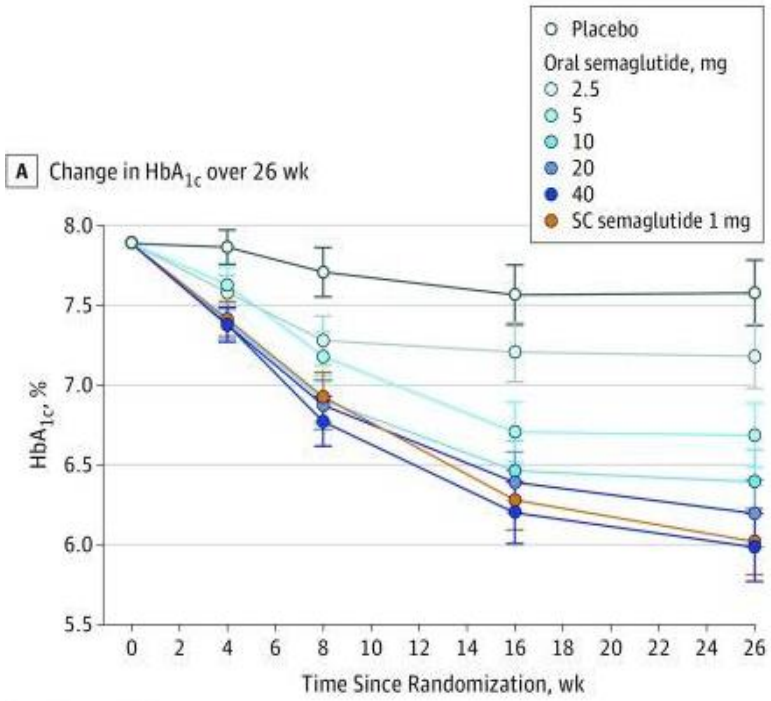
1 SNAC carrier facilitates semaglutide absorption



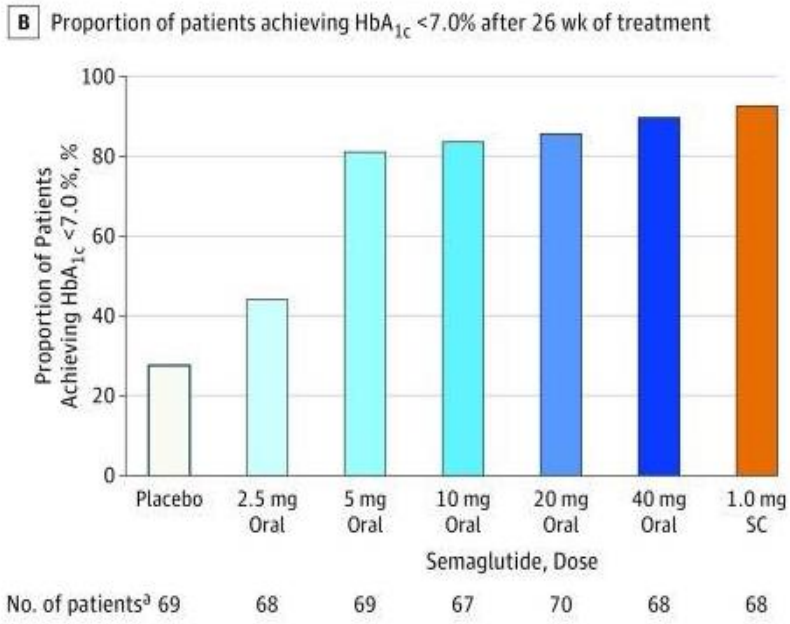
SNAC: Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate

novo nordisk

Oral versus SC semaglutide: Phase 2
HbA1c over time and change at week 26



No. of patients[a]					
Placebo	69	69	64	57	51
Oral semaglutide, mg					
2.5	68	68	64	61	56
5	69	69	63	61	58
10	66	66	61	61	57
20	70	70	60	53	48
40	68	68	63	55	46
SC semaglutide 1 mg	67	67	66	61	48

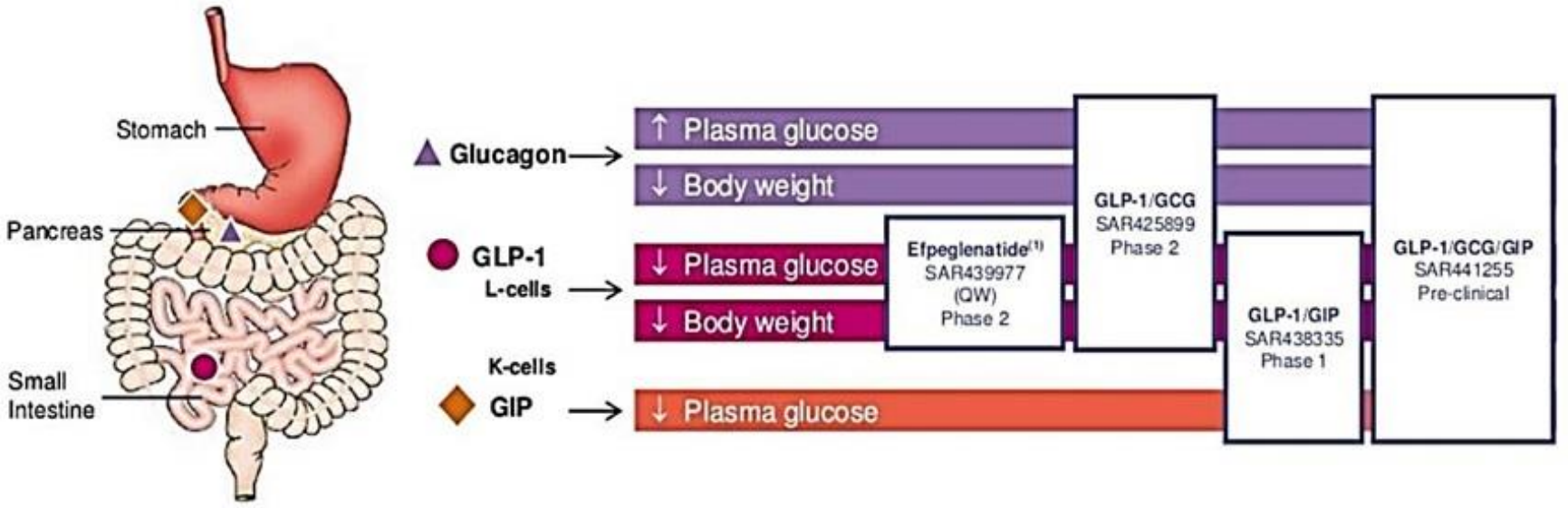


No. of patients[a]	69	68	69	67	70	68	68

JAMA, 2017 Oct 17; 318(15): 1460–1470

Novel peptide platform for diabetes

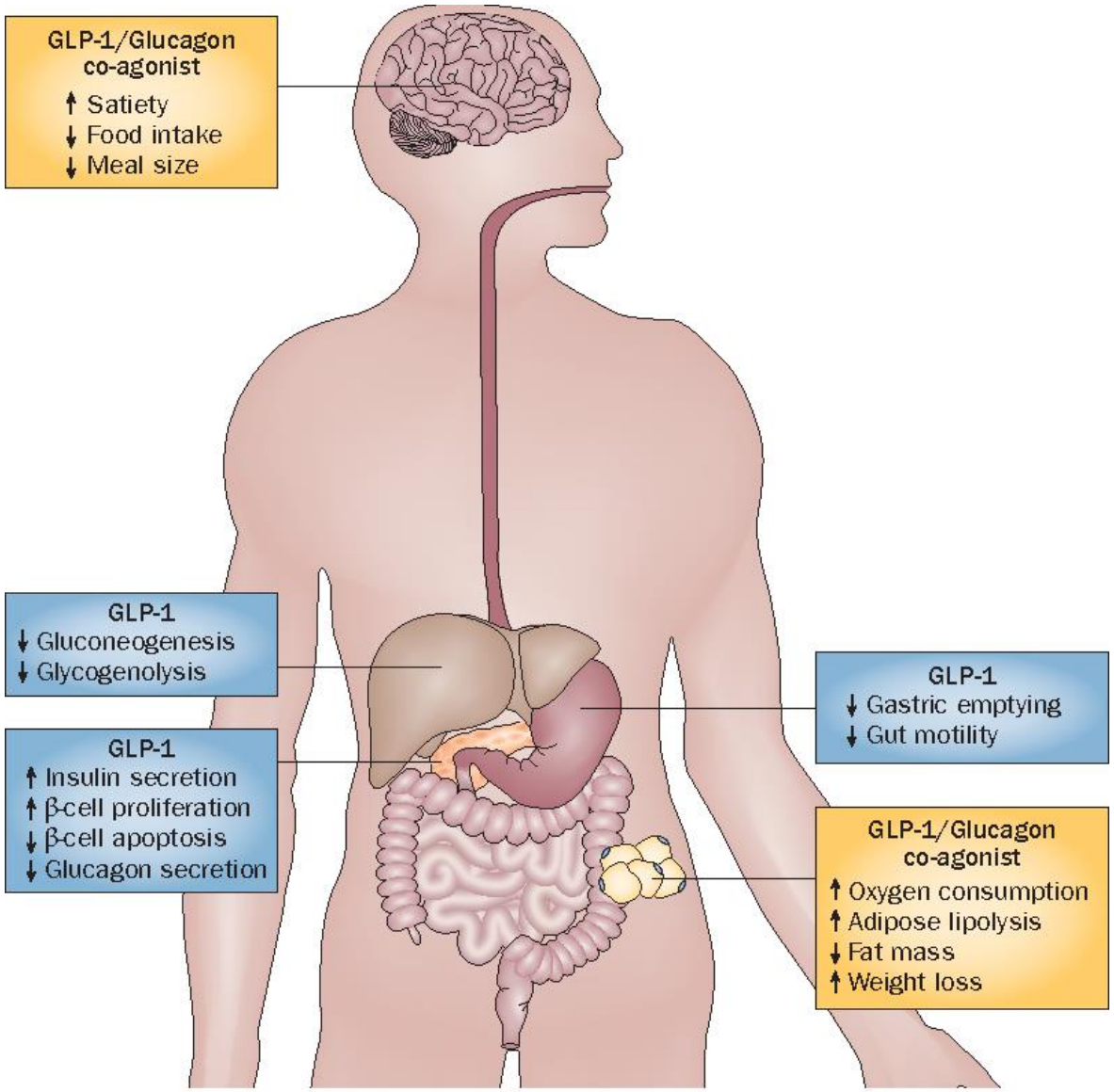
Dual- and triple agonist adding pharmacology or GIP and/or Glucagon



Dual and Triple Agonist adding Pharmacology of GIP and/or Glucagon

Holst J.J. et al., Trends Mol Med, 2008; Murphy K.G. & Bloom S.R., Nature, 2006; Sadry S.A. & Drucker D., Nat. Rev. Endocrinol, 2013
GLP-1= Glucagon-Like Peptide-1; GIP= Gastric inhibitory polypeptide; GCG= Glucagon
(1) Collaboration with Hanmi

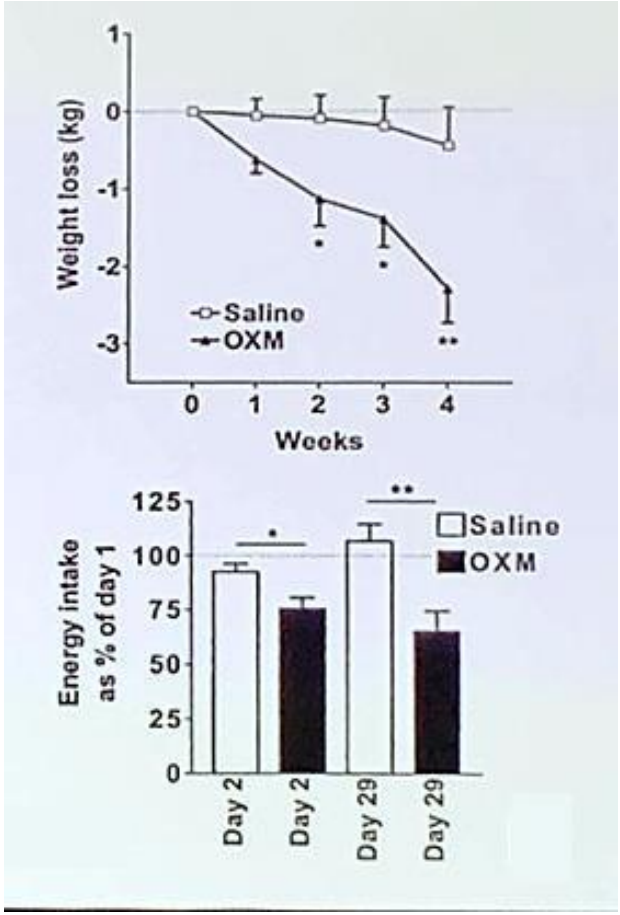
GLP-1/glucagon co-agonists



Nat Rev Endocrinol. 2013 Jul;9(7):425-33.

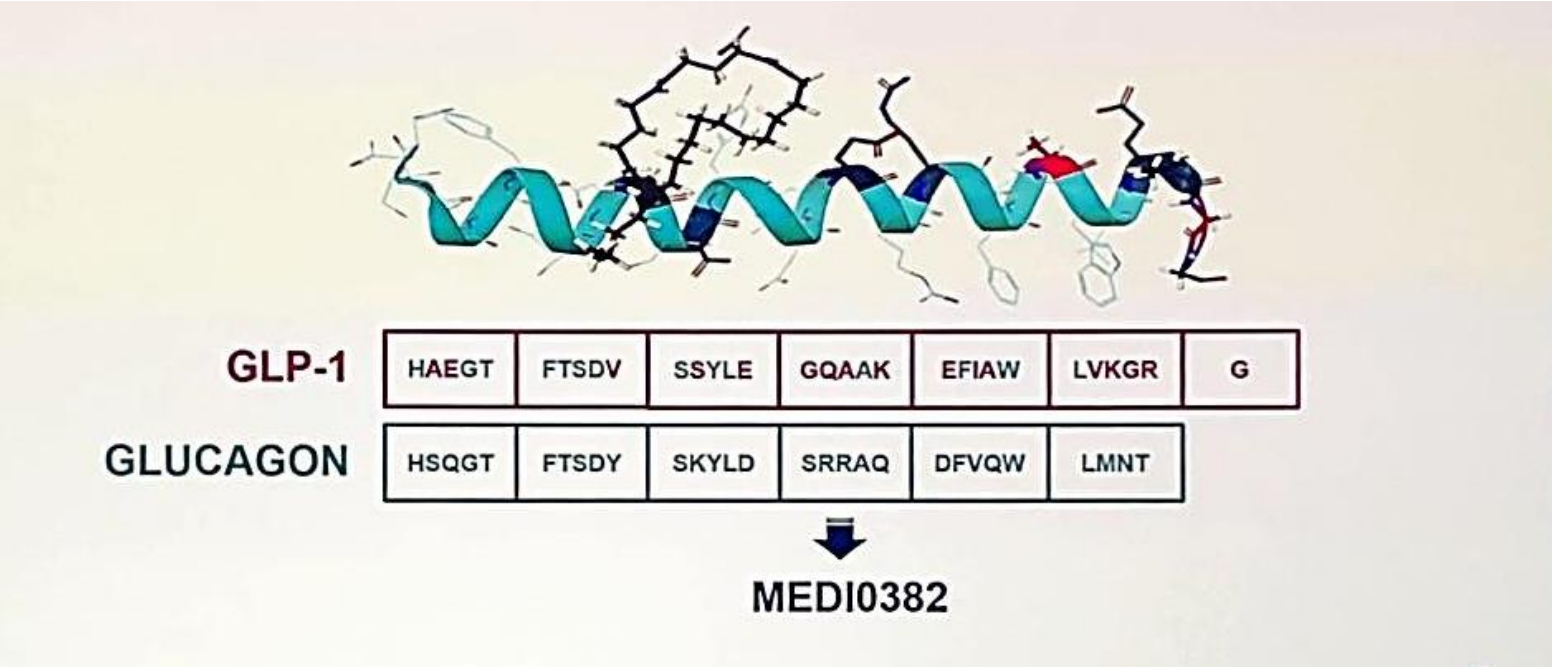
Oxyntomodulin:
An Endogenous GLP-1 and Glucagon Receptor Dual Agonist

- **In response to meals, oxyntomodulin:**
  - Is secreted by enteronedocrine L-cells along with GLP-1
  - Activates both **GLP-1** and **glucagon receptors**
  - Is significantly upregulated after bariatric surgery (along with GLP-1)
  - **Reduces appetite** and **increases energy expenditure**, leading to substantial weight loss in overweight loss in overweight and obese individuals



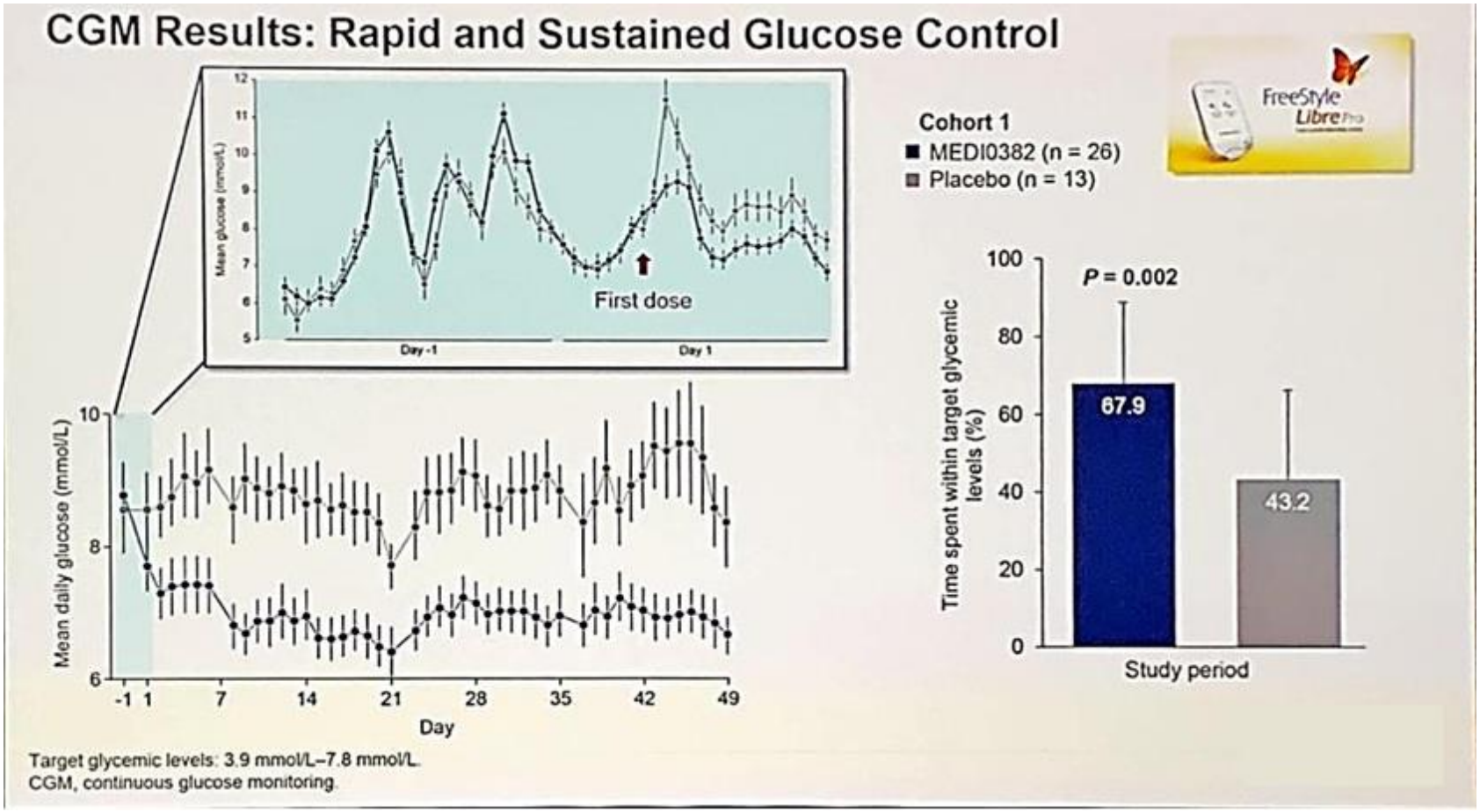
Lount et al. Obesity (Silver Spring). 2013;21:1093-1103
Laferrere et al. J clin Endocrinol Metab 2010;95:4072-4076
Wynne et al. Int J Obesity 20069;30:1729-1736

MEDI0382: An Oxyntomodulin-like Peptide with Targeted GLP-1 and Glucagon Receptor Activity



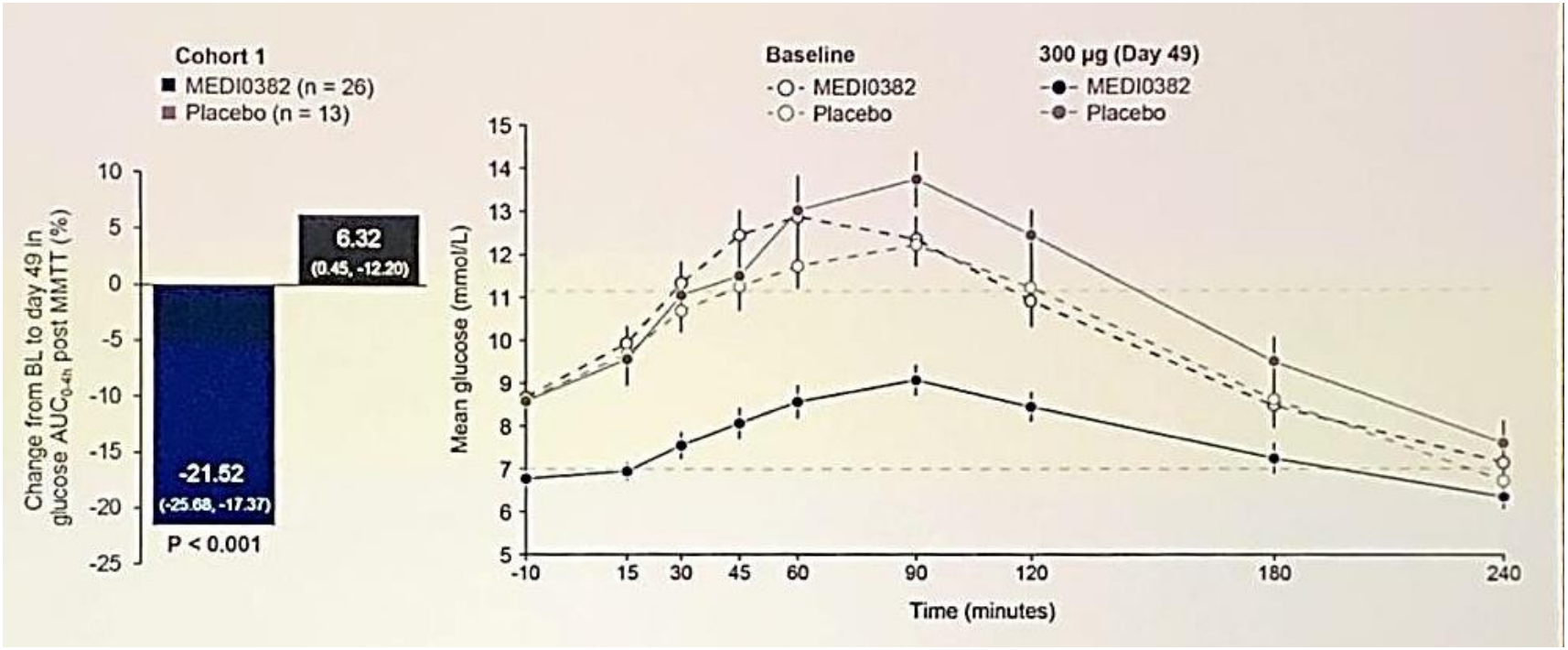
Ambery et al. Lancet 2018;391:2607-2618

CGM Results: Rapid and Sustained Glucose control



Target glycemic levels:3.9 mmol/L-7.8 mmol/L
CGM, continuous glucose monitoring

Coprimary Endpoint: Glucose Control



Upper dashed line is in reference to the definition of the definition of postprandial glucose levels (11.1 mmol/l in diabetes.
Lower dashed line in reference to the definition of fasting glucose levels (7.0 mmol/l) in diabetes
Aus area under the curve from 0 to 4 hours; BL, baseline; MMTT, mixed-meal tolerance test.

Inhaled Insulin

Exubera

- ✓ Inhaled form of rapid acting insulin developed by Pfizer
- ✓ The first inhaled insulin product to be marketed in 2006
- ✓ Higher dose of insulin is required due to inefficient absorption
- ✓ The use of a bulky device to dispense powdered insulin
- ✓ Little dosing flexibility

Afrezza

Pros:

- ✓ Rapid acting inhaled insulin
- ✓ Safe and effective
- ✓ Technosphere technology:
  more convenient , greater dosing flexibility

Cons:

- ✓ Increase in serum antibody levels
- ✓ Acute bronchospasm in patients with asthma and COPD
- ✓ Significant decrease in Diffusing Capacity of Lungs (DLCO)
- ✓ Smoking enhances insulin absorption

Journal of Clinical and Diagnostic Research 2017 Apr, Vol-11(4)

Smart insulin
Glucose-responsive insulin

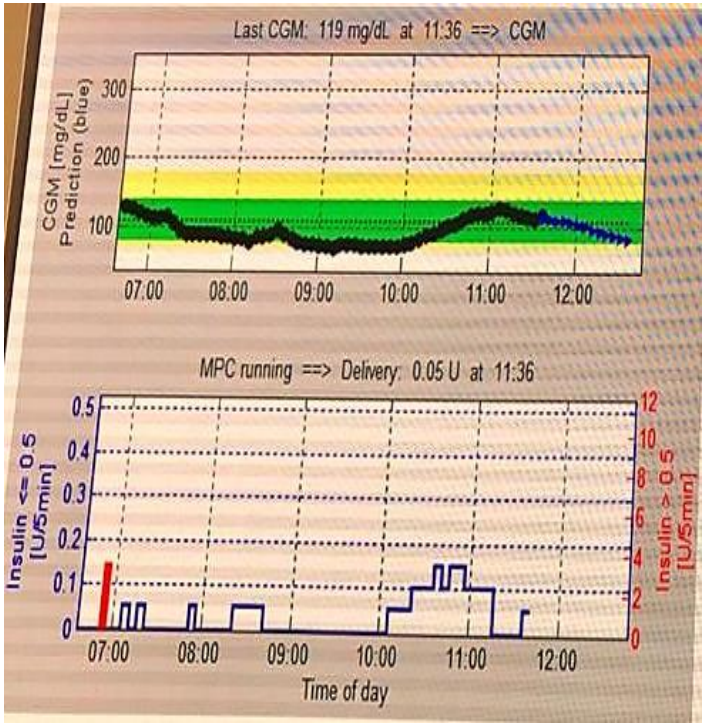
- ✓ Mechanical GRIs:
  Insulin pump, real time CGM, predictive algorithms

- ✓ Polymer and Matrix-Based GRIs:
  The matrix sense ambient glucose concentrations and release a proportional amount of insulin

- ✓ Molecular GRIs:
  The insulin molecule or its formulation have intrinsic glucose-responsive activity

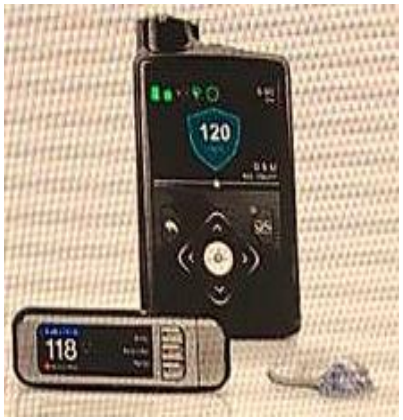
Curr Opin Endocrinol Diabetes Obes. 2017 .24(4): 267–278

Artificial Pancreas- closing the loop



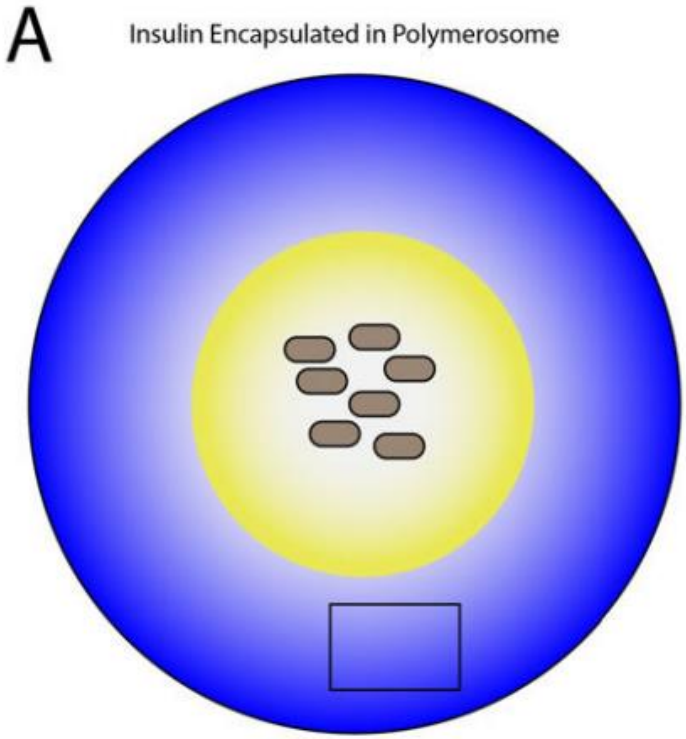
- Time in target **12.6%** higher with AP
- Dual-hormone AP – greater improvement in time in target range (**19.5%**)

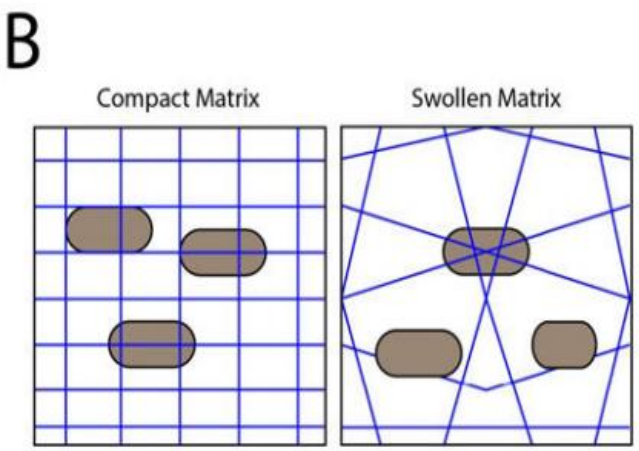
" AP systems uniformly improved glucose control in outpatient settings, despite heterogeneous clinical and technical factors"



BMJ 2018, 361:k1310

Lancet Diabetes Endocrinol, 2017 Jul; 5(7): 501-512



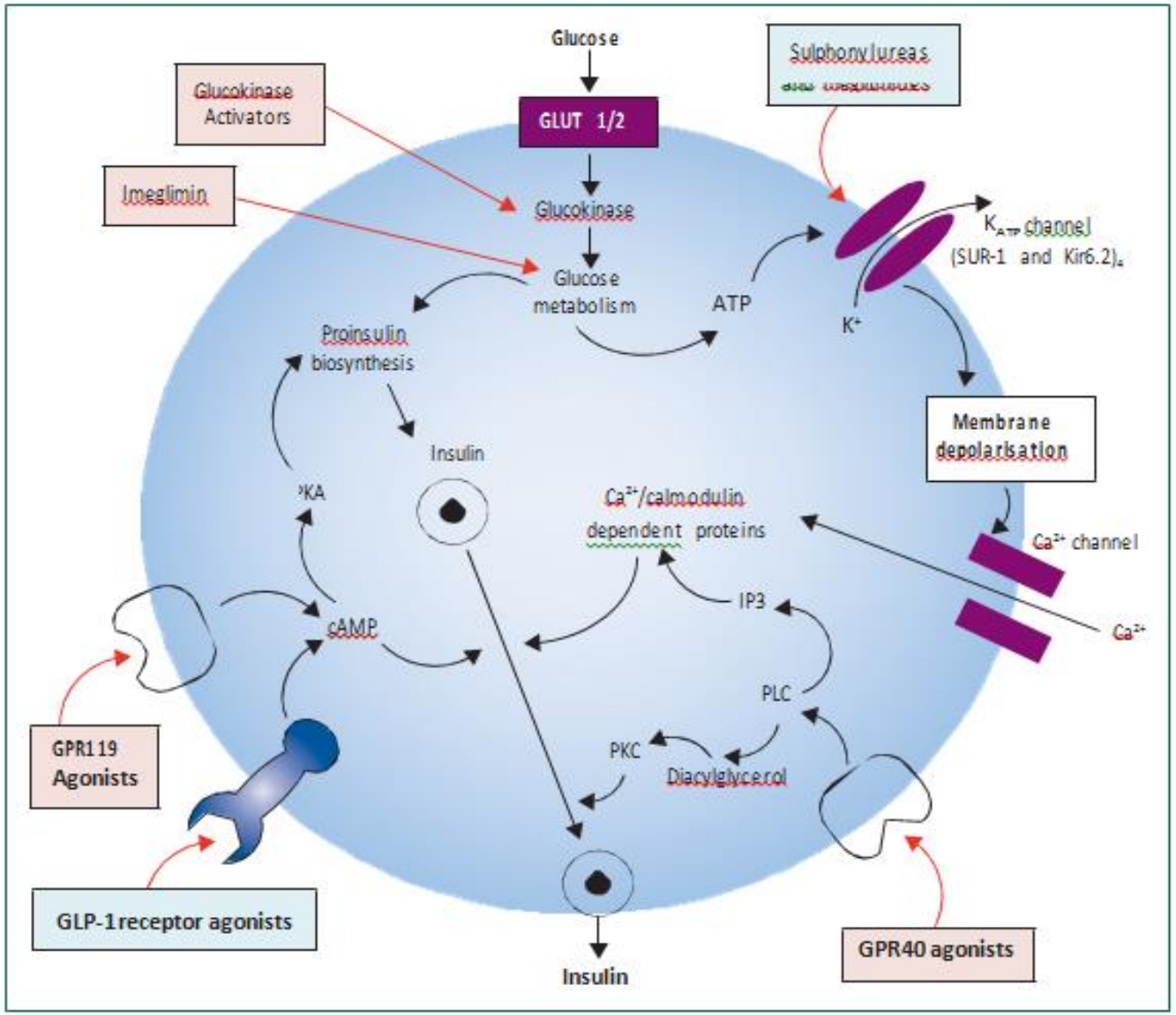


Matrices are compact during hypo- or euglycemia, but swell during hyperglycemia to release sequestered insulin

Insulin-degrading enzyme

- IDE represents a pathophysiological link between late onset Alzheimer's disease (AD) and type 2 diabetes (T2DM)
- Selective IDE inhibitors: positively affect (AD)
- Degrades many other targets including atrial natriuretic peptide, glucagon, and beta- amyloid peptide
- Sustained treatment with systemic IDE modulators should be tested carefully in animal studies
- Development of substrate-selective IDE modulators could overcome possible adverse effects of IDE modulators

Ann Med 2016; 48: 614–624.



Pancreatic β cell showing cellular mechanisms of insulin-releasing drugs

Investigational insulin secretagogues

- Insulin secretory defects: key features in the pathophysiology of type 2 diabetes
- New insulin secretagogues should be able to offer major advantages compared to sulfonylureas and gliptins
- Less hypoglycemia/ better durability of glucose control over time
- GK activators and FFAR (GPR) agonists
- Unfavorable benefit/risk balance
- More liver selective GK activators
- FFAR1 selective agonists are effective in promoting insulin secretion in a glucose concentration-dependent manner

Expert Opin Investig Drugs 2016; 25: 405–422

- *Glucokinase Activators:*

  Glucokinase: an important role on glucose metabolism in the liver by glycogen synthesis and glycolysis.

  It has been seen that mutations that increase the enzyme's affinity for glucose had a blood glucose lowering effect.

Imeglimin

- An oxidative phosphorylation blocker
- Targets mitochondria bioenergetics and improves mitochondrial function
- Improve not only insulin action but also glucose-dependent insulin secretion
- Increase glucose uptake by muscle tissue, decreased hepatic gluconeogenesis , and decreased beta-cell apoptosis
- superior to placebo and as effective as metformin
- good tolerance and safety profile in Phase II trials

Expert Opin Investig Drugs 2016; 25: 405–422

GUT MICROBIOMES

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

The association of type II diabetes with gut microbiota composition

Fatemeh Navab-Moghadam [a], Mansour Sedighi [a], Mohammad E. Khamseh [b], Fariba Alaei-Shahmiri [c], Malihe Talebi [a], Shabnam Razavi [a, d, **], Nour Amirmozafari [a, d, *]

[a] Department of Microbiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[b] Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[c] Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[d] Microbial Biotechnology Research Center, Iran University of Medical Sciences, Tehran, Iran

Microbial Pathogenesis 110 (2017) 630e636

- ✓ Faecalibacterium prausnitzii: significantly lower in patients with T2D
- ✓ Bacteroides fragilis was under-represented in people with diabetes
- ✓ No difference for Bifidobacterium longum

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

Comparison of gut microbiota in adult patients with type 2 diabetes and healthy individuals

Mansour Sedighi [a], Shabnam Razavi [a, b, *], Fatemeh Navab-Moghadam [a], Mohammad E. Khamseh [c], Fariba Alaei-Shahmiri [d], Amirhosein Mehrtash [e], Nour Amirmozafari [a, b, **]

[a] Department of Microbiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[b] Microbial Biotechnology Research Center, Iran University of Medical Sciences, Tehran, Iran
[c] Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[d] Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[e] Molecular Medicine Department, Biotechnology Research Center, Pasteur Institute of Iran, Tehran, Iran

Microbial Pathogenesis, 2017, 111, 362-369

- *Lactobacillus* group was significantly higher in the diabetics compared to the healthy individuals (P <0.001)

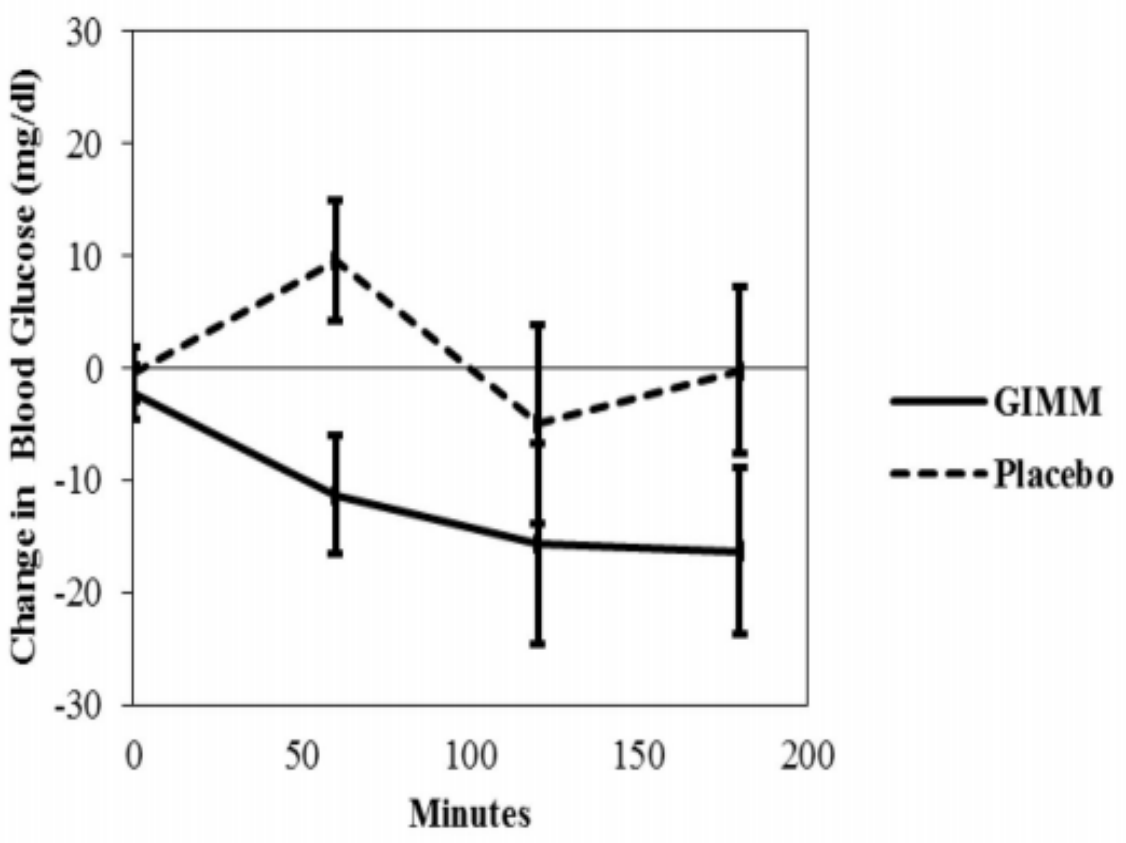
- *Bifidobacterium* group was significantly more frequent in the healthy subjects compared with the T2DM patients (P <0.001)

- Diabetes is associated with the shifts and fluctuations in the composition of gut microbiota

GUT MICROBIOMES: POTENTIAL THERAPUTIC TARGETS

- Randomized controlled trial
- Effects of a gastrointestinal microbiome modulator (GIMM) containing blueberry anthocyanins, inulin, b-glucan, and blueberry poly- phenols on satiety, metabolic parameters, and fecal markers of gut microbiota
- No statistically significant differences in plasma satiety hormones, insulin sensitivity, fecal markers of gut microbiota, or serum lipid concentrations between the two groups

J Diabetes Complications 2015; 29: 1272–1276


30
20
10
0
-10
-20
-30
Change in Blood Glucose (mg/dl)
0
50
100
150
200
Minutes
GIMM
Placebo

Probiotic approach

- Increase in Lactobacillus species in type 2 diabetes has never been demonstrated to have a direct impact on the disease
- Major probiotic strains shown beneficial effects on glucose metabolism in human: Lactobacillus genus, L. acidophilus and L. gasseri
- The effects obtained using probiotics are probably strain-specific
- A. muciniphila counteract fasting hyperglycaemia in diet-induced mouse model of type 2 diabetes
- F. prausnitzii, plays an important role in the maintenance of the gut barrier and in the control of inflammation

Diabetologia 2015; 58: 2206–2217.

Microbiota transfer

- Infusion of faecal microbiota from lean donors to recipients with the metabolic syndrome
- Increase the levels of butyrate-producing bacteria and insulin sensitivity in insulin-resistant recipients
- A proof-of-concept rather than a potential therapy

Diabetologia 2015; 58: 2206–2217.

Non-bacterial ‘colonisers’ of the gut

- The yeast Saccharomyces boulardii changed the gut microbiota and reduced certain features of the metabolic syndrome in genetically obese and diabetic mice

Diabetologia 2015; 58: 2206–2217.

PLOS ONE

RESEARCH ARTICLE

Effect of Probiotics on Glycemic Control: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials

Yuting Ruan[1☯], Jia Sun[1☯], Jie He[2], Fangyao Chen[3], Rongping Chen[1]*, Hong Chen[1]*

1 Department of Endocrinology, Zhujiang Hospital, Southern Medical University, Guangzhou, China, **2** The Second Clinical College of Southern Medical University, Guangzhou, China, **3** Department of Biostatistics, School of Public Health and Tropical Medicine, Southern Medical University, Guangzhou, China

☯ These authors contributed equally to this work.
* rubychq@163.com (HC); rpink_fimmu@qq.com (RC)

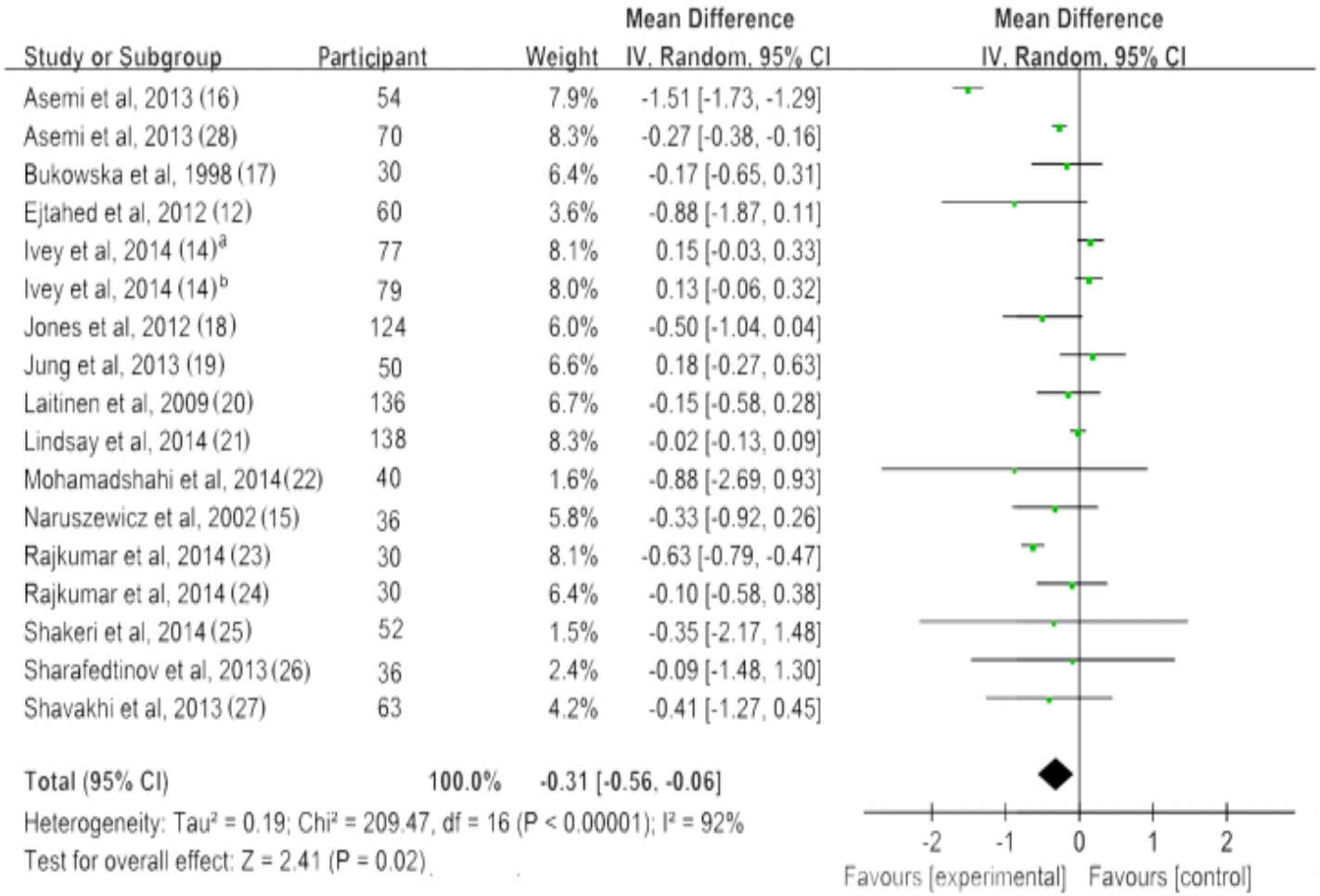


Fig 2. Forest plot of randomized controlled trials comparing the effect of probiotics on fasting blood glucose with placebo/comparator. Weighted mean differences (95% CIs) for fasting blood glucose are shown. Pooled estimates (*diamonds*) calculated by the random effects method. IV, inverse variance.

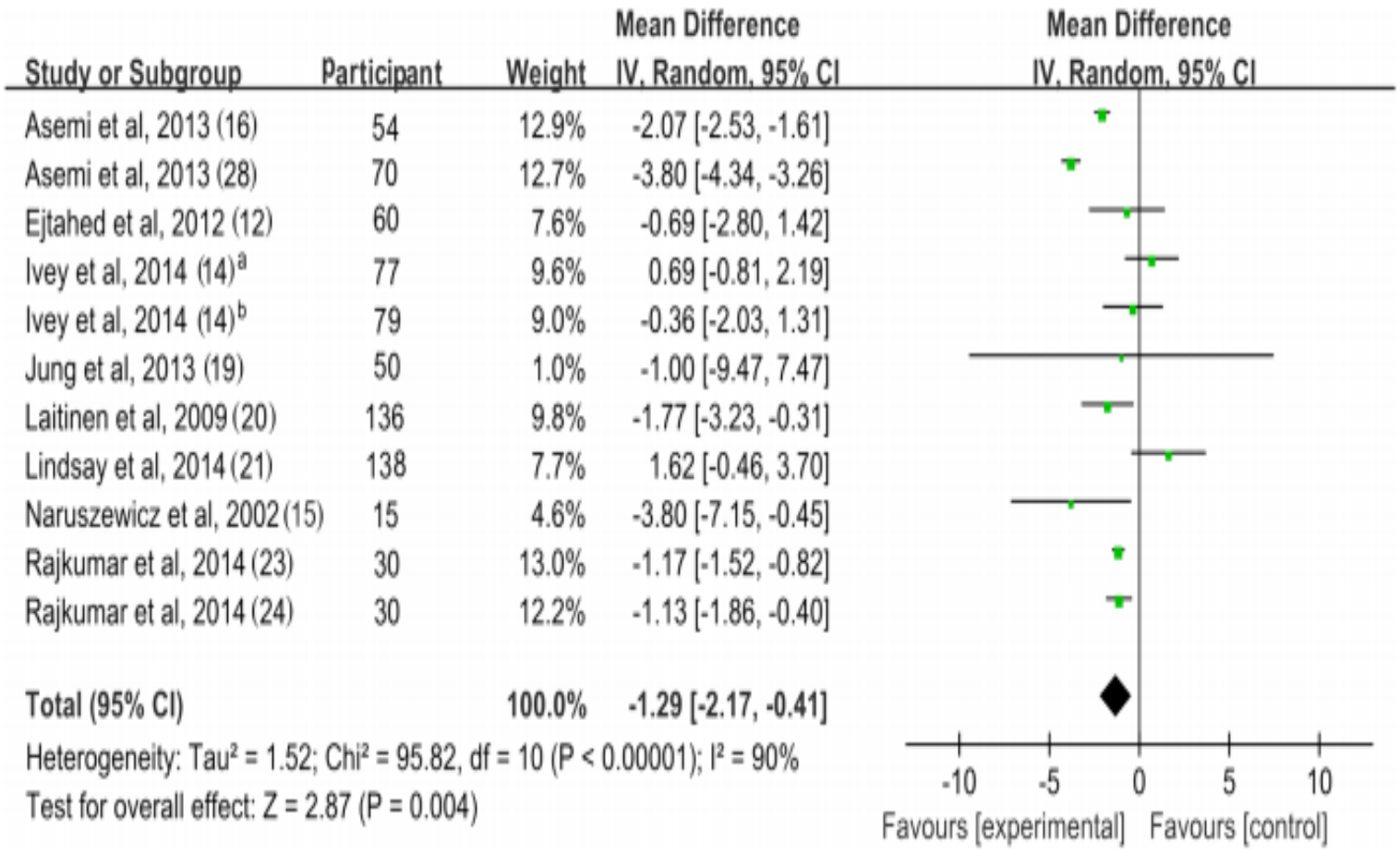


Fig 4. Forest plot of randomized controlled trials comparing the effect of probiotics on fasting plasma insulin with placebo/comparator. Weighted mean differences (95% CIs) for fasting plasma insulin are shown. Pooled estimates (*diamonds*) calculated by the random effects method. IV, inverse variance.

- ✓ Consumption of probiotics can modestly benefit glycemic control
- ✓ The specific strains need more study
- ✓ the evidence supports modification of gut microbiota through probiotic supplementation as a safe method to help to control blood glucose in clinical practice

New Hepatic Targets for Glycaemic Control

- *Glucose 6-phosphatase Inhibitors:*

✓ Peroxovanadium compounds

✓ Glucose 6-phosphatase catalyses the final reaction in hepatic glucose production from gluconeogenesis and glycogenolysis.

✓ Counteract the hyperglycaemic response to glucagon

- *Limitations:*

✓ Acute suppression of hyperglycaemia posing a risk for hypoglycaemia

✓ Enzyme inhibition leading to accumulation of glucose 6-phosphate and glucagon: inducing lipogenic enzymes resulting in hepatic steatosis

✓ *In Phase 1 and animal studies*

IMMUNOTHERAPY FOR TYPE 1 DIABETES

- Humanized anti-CD3 Monoclonal Antibodies
  Otelixizumab and *Teplizumab* bind to CD3/TCR complex and block full T cell activation, proliferation and cytokine release

- Down regulation of T-effector cells, may lead to a reduced autoimmune attack on the beta cells

- Otelixizumab: administered for 8 consecutive day- subjects have been followed up to observe remission of new onset Type 1 diabetes mellitus

- Teplizumab has been used in new onset Type 1 diabetes mellitus, with the administration of 14 consecutive day injections

Efficacy and safety of otelixizumab use in new-onset type 1 diabetes mellitus

- The results of the Phase I and II studies have been positive
- The results of the Phase III studies are contradictory
- High doses of otelixizumab: have beneficial effects on the beta cell function
- Lower doses(to avoid adverse effects) was not effective for beta cells preservation
- Otelixizumab is a drug of possible interest in the treatment of new onset T1DM patients
- It should be considered for use in combination with other immunomodulatory agents

Expert Opin Biol Ther 2016; 16: 841–846

Future glucose-lowering drugs for type 2 diabetes

- Adiponectin receptor agonists
- Selective PPAR modulators
- Cellular glucocorticoid inhibitors
- Analogues of FGF 21
- Oral insulin (ORMD-0801), 2019

Lancet Diabetes Endocrinol. 2016; 4: 3509

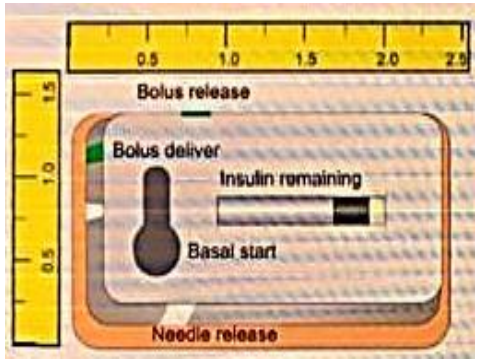
Take home messages

- Advancements in delivery systems is promising
- Novel peptide platform, dual & triple agonists
- Glucose responsive insulins
- Gut microbiota
- Immunotherapy for type one diabetes

Patch Insulin Pumps

Simplified Mechanical Patch Pumps

V-Go Valeritas (US and Europe)
PAQ by CeQur (Europe only)
One Touch Via by JNJ (not yet available)

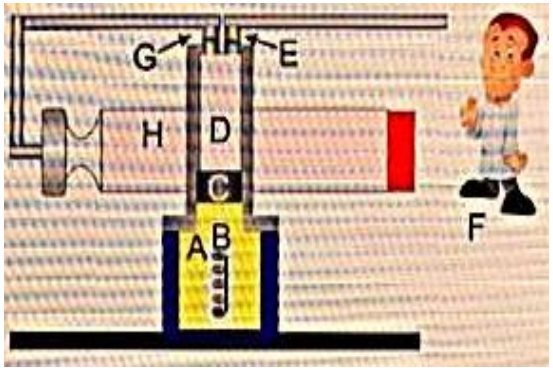


The V-Go by Valeritas

- Type 2 diabetes
- Small, light, connect directly without tubing
- Relatively inexpensive
- Limited number of fixed basal doses
- Don't keep track of how much insulin taken
- Devices cannot be taken off

Full-Featured Electromechanical Patch Pumps

Omnipod by Insulet
Cellnovo
JewelPump by Debiotech
Solo by Roche
SFC Fluidics Patchpump
Libertas by BD
Medtronic Patchpump
Eopatch by EOFlow



- All type 1 diabetes and some type 2 diabetes
- Flexibility in basal and bolus doses
- Some can be removed
- All track doses
- Most need controller
- More expensive