Review a Decade:
Injectable Anti-Diabetic Medications in Diabetes Care



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Specialist in Endocrinology, Diabetes & Metabolism
Visiting Scientist, Obesity, Metabolism and Nutrition Institute, MGH
Honorary Clinical Assistant Professor, the University of Hong Kong
Director, Weight Management Centre, Gleneagles Hospital, Hong Kong
Founding President, Hong Kong Obesity Society (Medical Chapter)

Outline

1. Why do we need injectable medications
2. Insulins over the year
3. Other non-insulin injectable medications
4. Over the horizon: New combination injectables
5. Advances in injection device

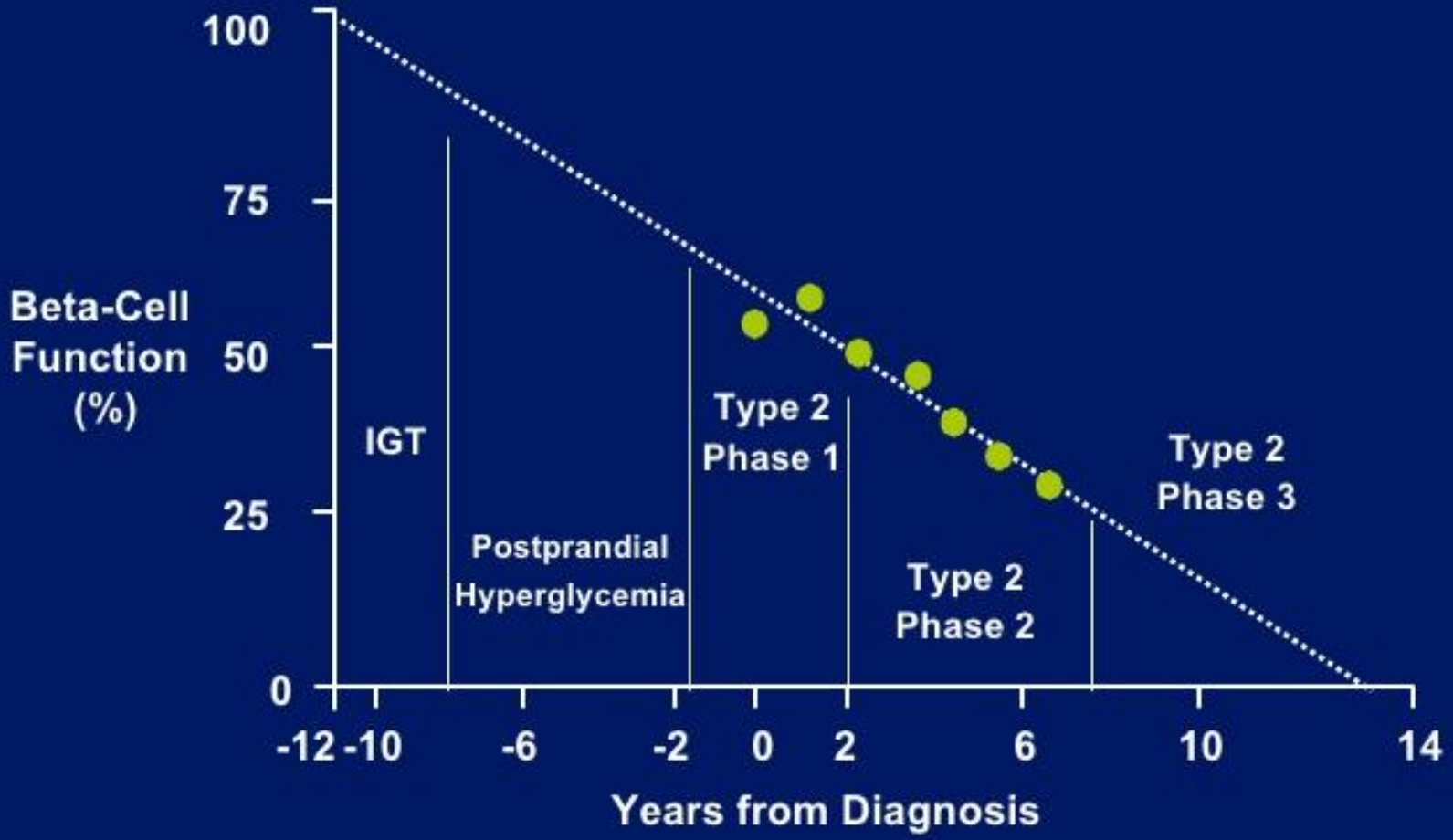
Outline

1. Why do we need injectable medications
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Injectable medications in diabetes

1. Insulins
2. GLP1 agonists

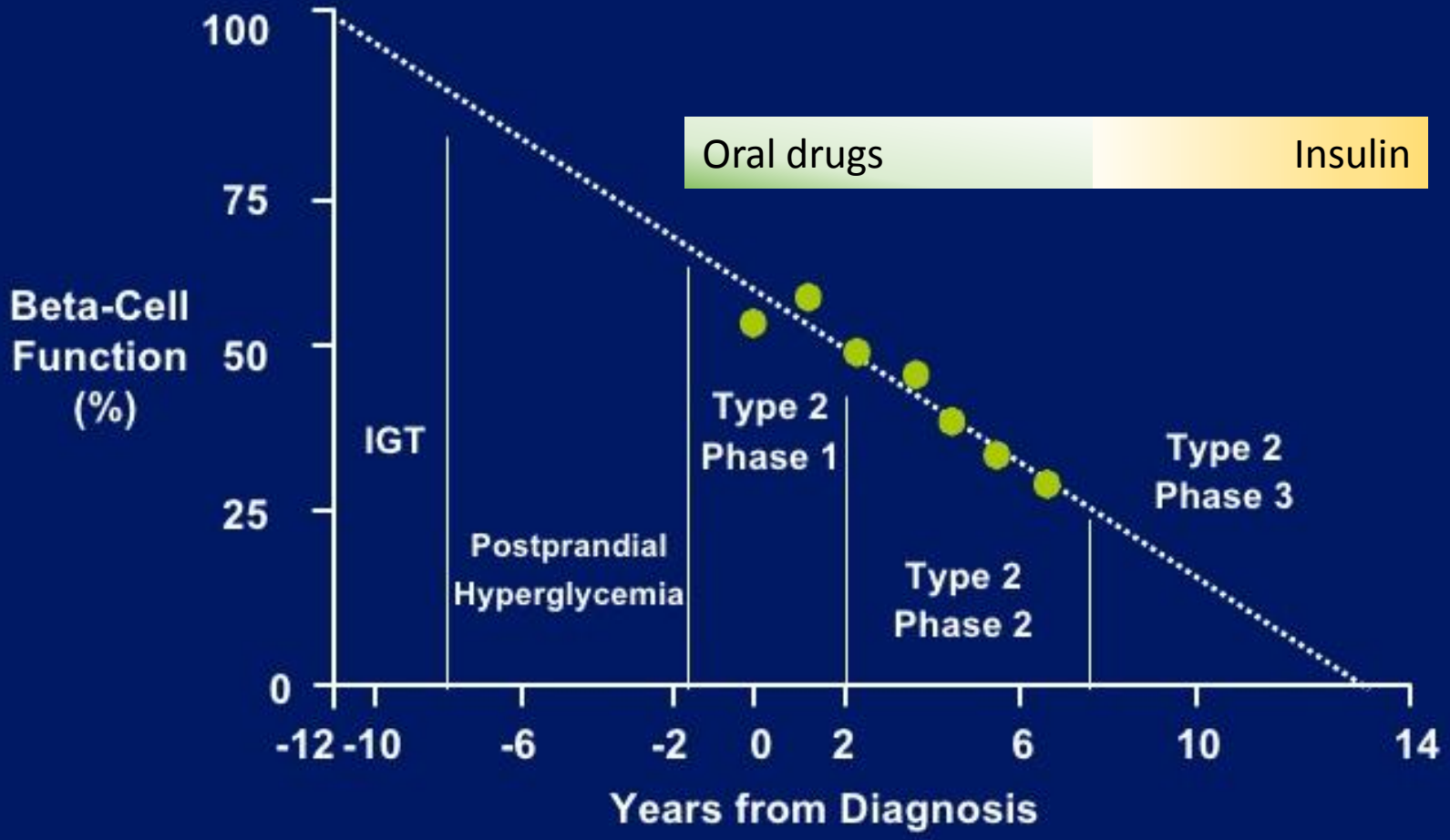
Stages of Type 2 Diabetes Related to Beta-Cell Function



Adapted from Lebovitz HE. *Diabetes Reviews*. 1999;7(3).

https://image.slidesharecdn.com/diabetes-slideshow4113/95/diabetes-slideshow-11-728.jpg?cb=1287655571

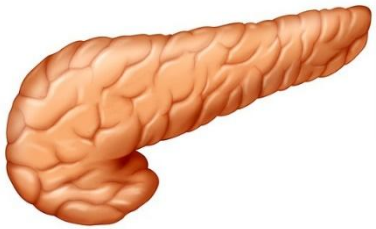
Stages of Type 2 Diabetes Related to Beta-Cell Function



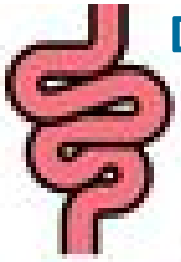
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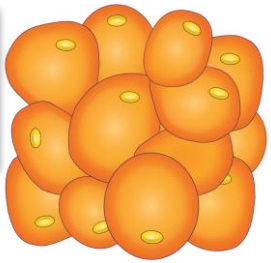
Ominous Octet in T2DM



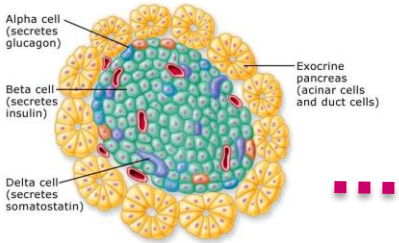
Decreased Insulin Secretion



Decreased Incretin Effect

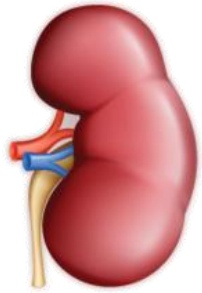


Increased lipolysis

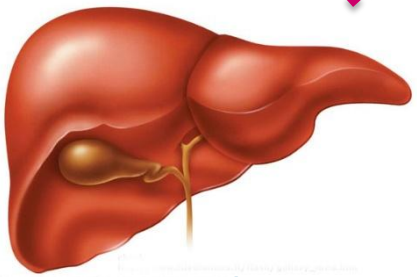


Increased Glucagon Secretion

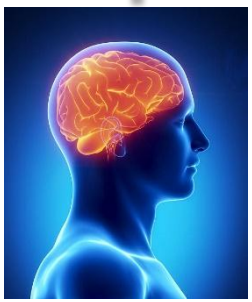
Hyperglycemia



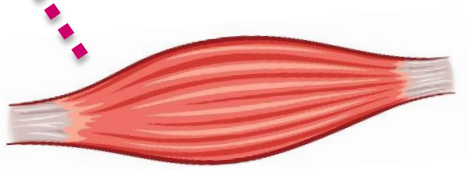
Increased Glucose Reabsorption



Increased HGP



Neurotransmitter Dysfunction



Decreased Glucose Uptake

Adapted from: DeFronzo RA. *Diabetes.* 2009;58:773–795; Tahrani AA, et al. *Lancet*. 2011;378:182–197.

Insulin
- Rapid-acting (Lispro, Apidra, NovoRapid)
- Short-acting (Actrapid, Humulin R)
- Intermediate-acting (Protaphane, Humulin N)
- Long-acting (Lantus, Levemir)
- Ultra-long acting (Toujeo)

Meglitinides
- Repaglinide (NovoNorm)

Sulfonylurea
- Glimepiride (Amaryl)
- Glibenclamide (Daonil)
- Gliclazide (Diamicron)
- Gliclazide MR (Diamicron MR)
- Glipizide (Minidiab)

GLP1
(腸泌素模仿物 (針劑))

DPP4-i
- Sitagliptin (Januvia)
- Vildagliptin (Galvus)
- Saxagliptin (Onglyza)
- Linagliptin (Trajenta)
- Alogliptin (Nesina)

Incretin Effect

Thiazolidindione
- Pioglitazone (Actos)

Increased lipolysis

Alpha-glucosidase inhibitors
- Acarbose (Glucobay)

Hyperglycemia

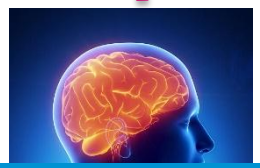
SGLT2-i
- Dapagliflozin (Forxiga)
- Empagliflozin (Jardiance)
- Canagliflozin (Invokana)

Increased Glucose Reabsorption

Glucagon Secretion

Metformin
- Metformin (generic / Glucophage)
- Metformin XR (Glucophage XR)

Increased HGP



GLP1a
- Exenatide (Byetta, Bydureon)
- Liraglutide (Victoza, Saxenda)
- Lixisenatide (Lyxumia)
- Dulaglutide (Trulicity)

Thiazolidindione
- Pioglitazone (Actos)

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Increased Glucose Reabsorption



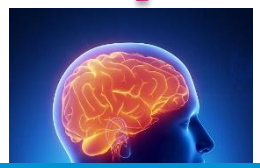
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Increased HGP



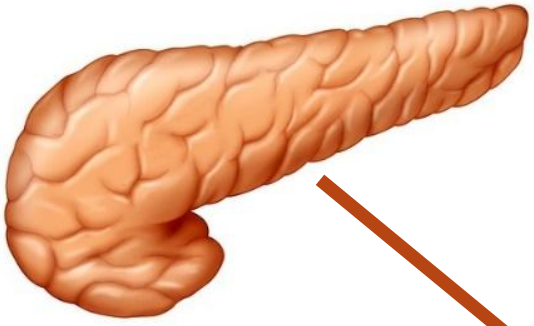
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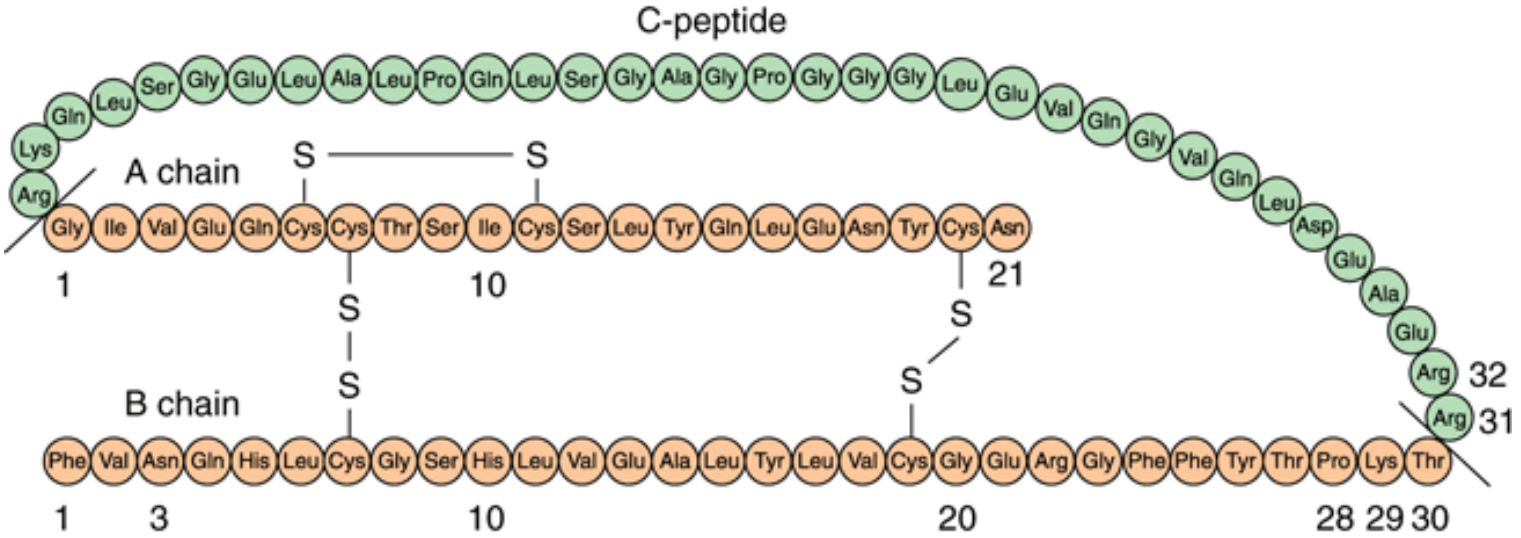
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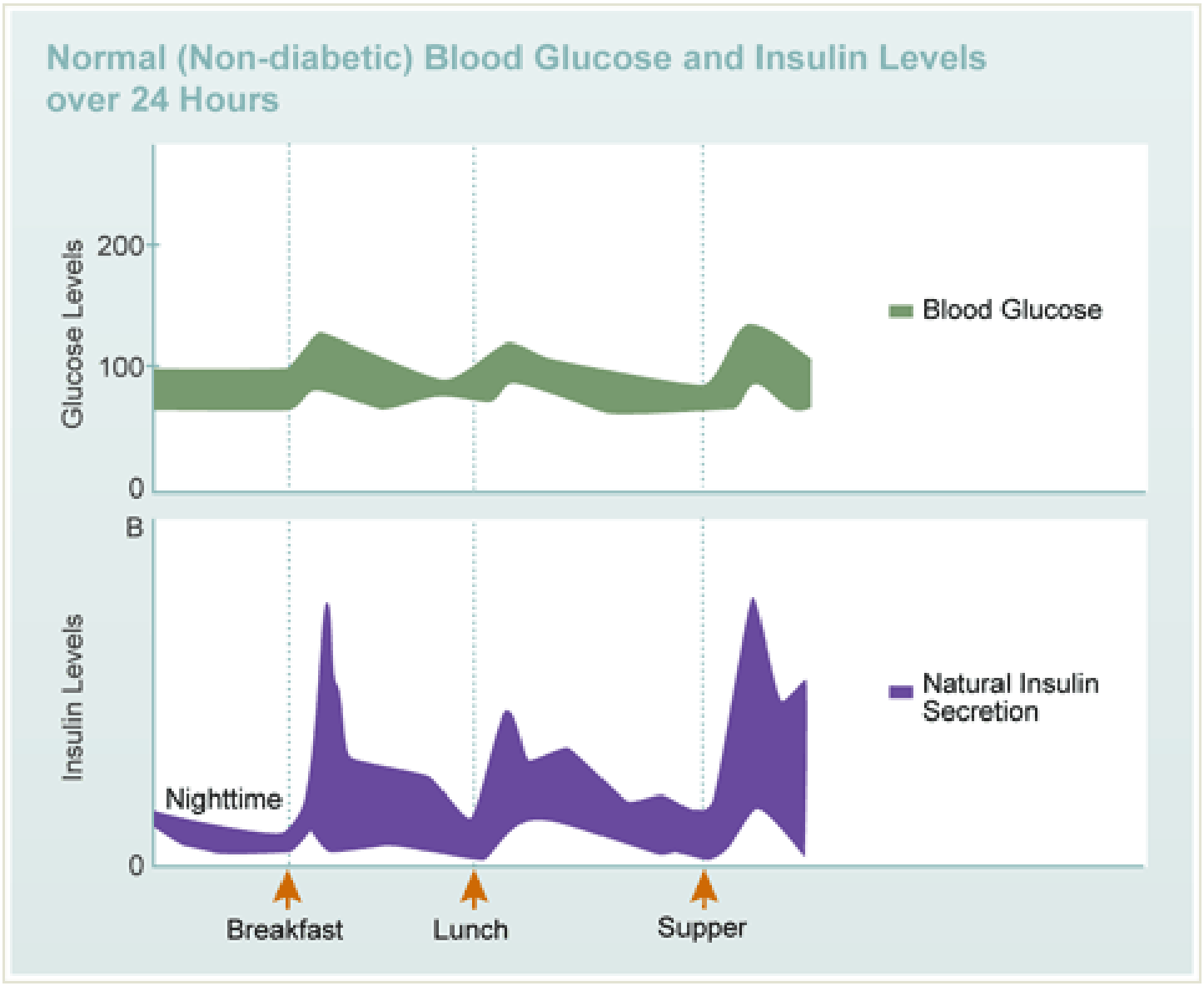
Insulin





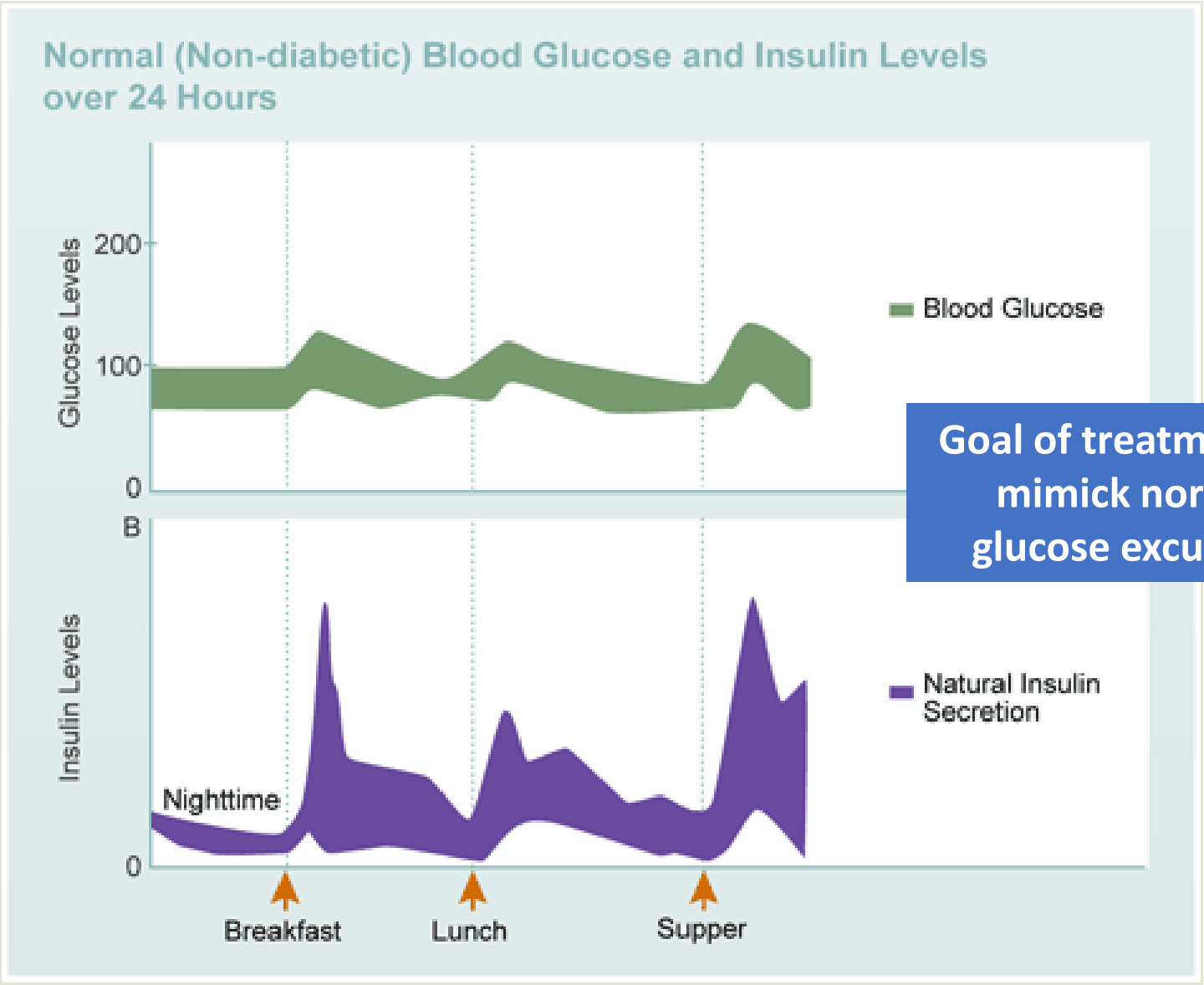
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

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To keep the blood glucose in a narrow range throughout the day, there is a low steady secretion of insulin overnight, fasting and between meals with spikes of insulin at mealtimes. Adapted: Jacobs DM Care 20:1279, 1997

https://dtc.ucsf.edu/types-of-diabetes/type2/understanding-type-2-diabetes/how-the-body-processes-sugar/controlling-blood-sugar/



Goal of treatment: to mimick normal glucose excursion

To keep the blood glucose in a narrow range throughout the day, there is a low steady secretion of insulin overnight, fasting and between meals with spikes of insulin at mealtimes. Adapted: Jacobs DM Care 20:1279, 1997

https://dtc.ucsf.edu/types-of-diabetes/type2/understanding-type-2-diabetes/how-the-body-processes-sugar/controlling-blood-sugar/

Trip down memory lane

A Brief History of Insulin





Apr-Nov 1921

Insulin discovered by Dr. Frederick Banting and Mr. Charles Best



Apr-Nov 1921

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Jan 1922

1st human (14 year old boy) to receive insulin by injection (Toronto Hospital)





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Mass production of bovine insulin by Eli Lilly





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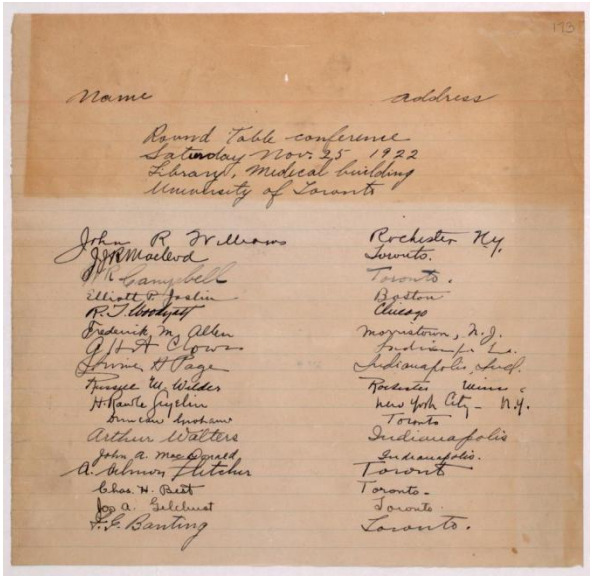
First roundtable on insulin


LEONARD THOMPSON
First patient to receive insulin in Toronto.

Jan 1922

1st human (14 year old boy) to receive insulin by injection (Toronto Hospital)


Patient JL, 15 pounds December 15, 1922 Patient JL, 29 pounds February 15, 1923


Name address

Round Table conference
Saturday Nov. 25 1922
Library, Medical building
University of Toronto

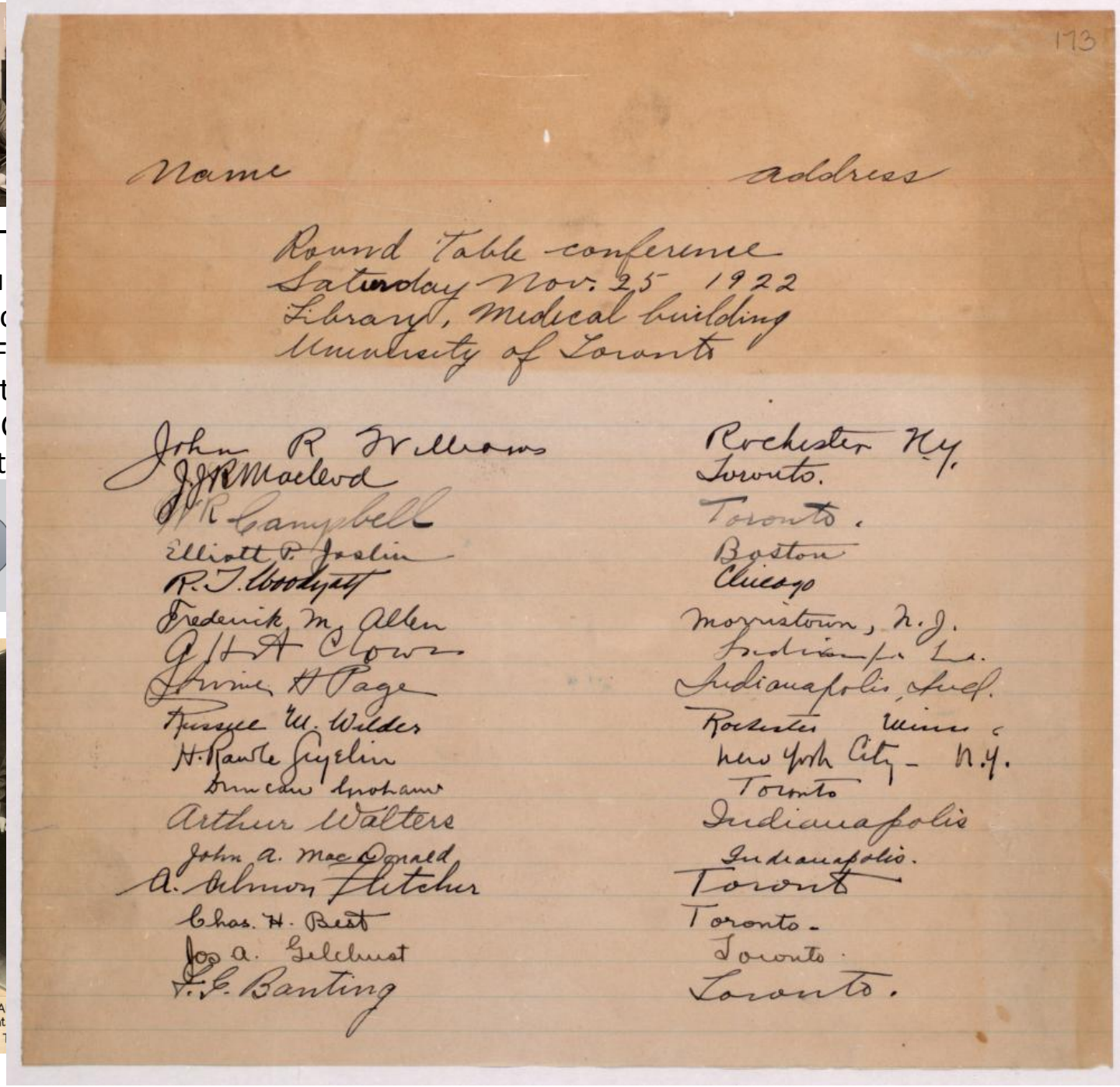
John R. Williams Rochester Ky.
J.J.R. Macleod Toronto.
J.G. Campbell Toronto.
Elliott P. Joslin Boston
R.T. Woodyatt Chicago
Frederick M. Allen Morristown, N.J.
Geo. A. Clowes Indianapolis, Ind.
Lewis A. Page Indianapolis, Ind.
Russell M. Wilder Rochester Minn.
H. Rantle Sayler New York City - N.Y.
Duncan Graham Toronto
Arthur Walters Indianapolis
John A. MacDonald Indianapolis.
A. Aylmer Fletcher Toronto
Chas. H. Best Toronto.
Jos. A. Gilchrist Toronto.
F.G. Banting Toronto.



Apr-

Insu
disc
Dr. F
Bant
Mr. C
Best





173

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Round Table conference
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John R. Williams	Rochester N.Y.
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Frederick M. Allen	Morristown, N.J.
G.H.A. Clowes	Indianapolis Ind.
Irving S. Page	Indianapolis, Ind.
Russell M. Wilder	Rochester Minn.
H. Rawle Geyelin	New York City - N.Y.
Duncan Graham	Toronto
Arthur Walters	Indianapolis
John A. MacDonald	Indianapolis.
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Oct 1923

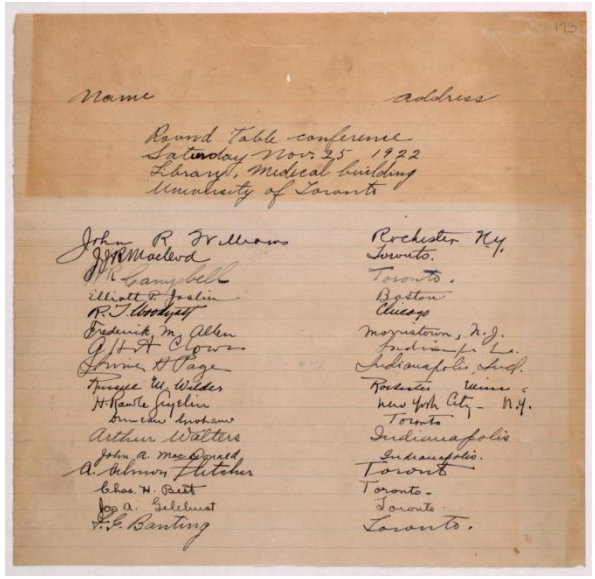
Banting & MacLeod won a Nobel Prize



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1923

- Farbwerke Hoechst, one of the forerunner's of Sanofi Aventis, produces commercial quantities of bovine insulin in Germany
- Hagedorn found the Nordisk Insulinlaboratorium in Denmark – forerunner of today's Novo Nordisk

Era of Stabilization and Standardization of Bovine / Porcine Insulin





1936

Hagedorn discovers that adding **protamine** to insulin prolongs the duration of action of insulin



1936

Hagedorn discovers that adding **protamine** to insulin prolongs the duration of action of insulin

1950



Nordisk markets NPH insulin

1953

Novo formulates **Lente** porcine and bovine insulins by adding **zinc** for longer lasting insulin



1936

Hagedorn discovers that adding **protamine** to insulin prolongs the duration of action of insulin

1953

Novo formulates **Lente** porcine and bovine insulins by adding **zinc** for longer lasting insulin

1973

The U.S. officially **"standardized"** insulin sold for human use in the U.S. to U-100 (100 units per milliliter). Prior to that, insulin was sold in different strengths, including U-80 (80 units per milliliter) and U-40 formulations (40 units per milliliter)



1950

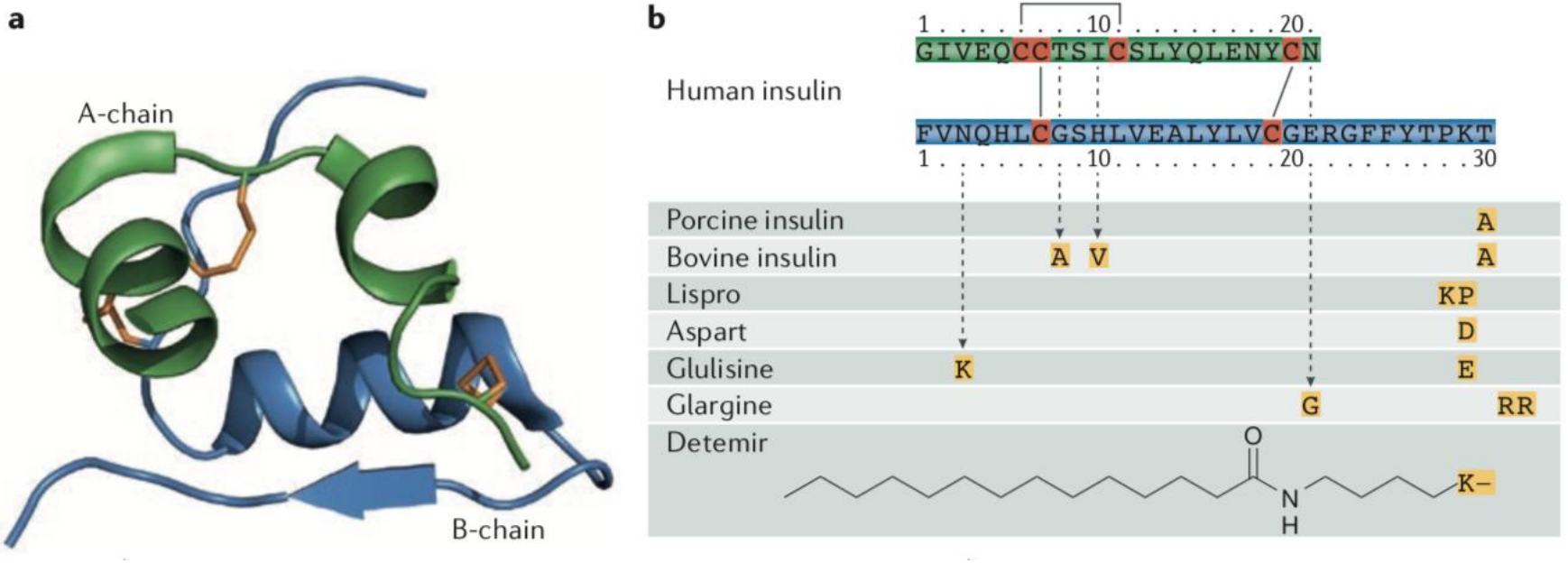
Nordisk markets NPH insulin

1973

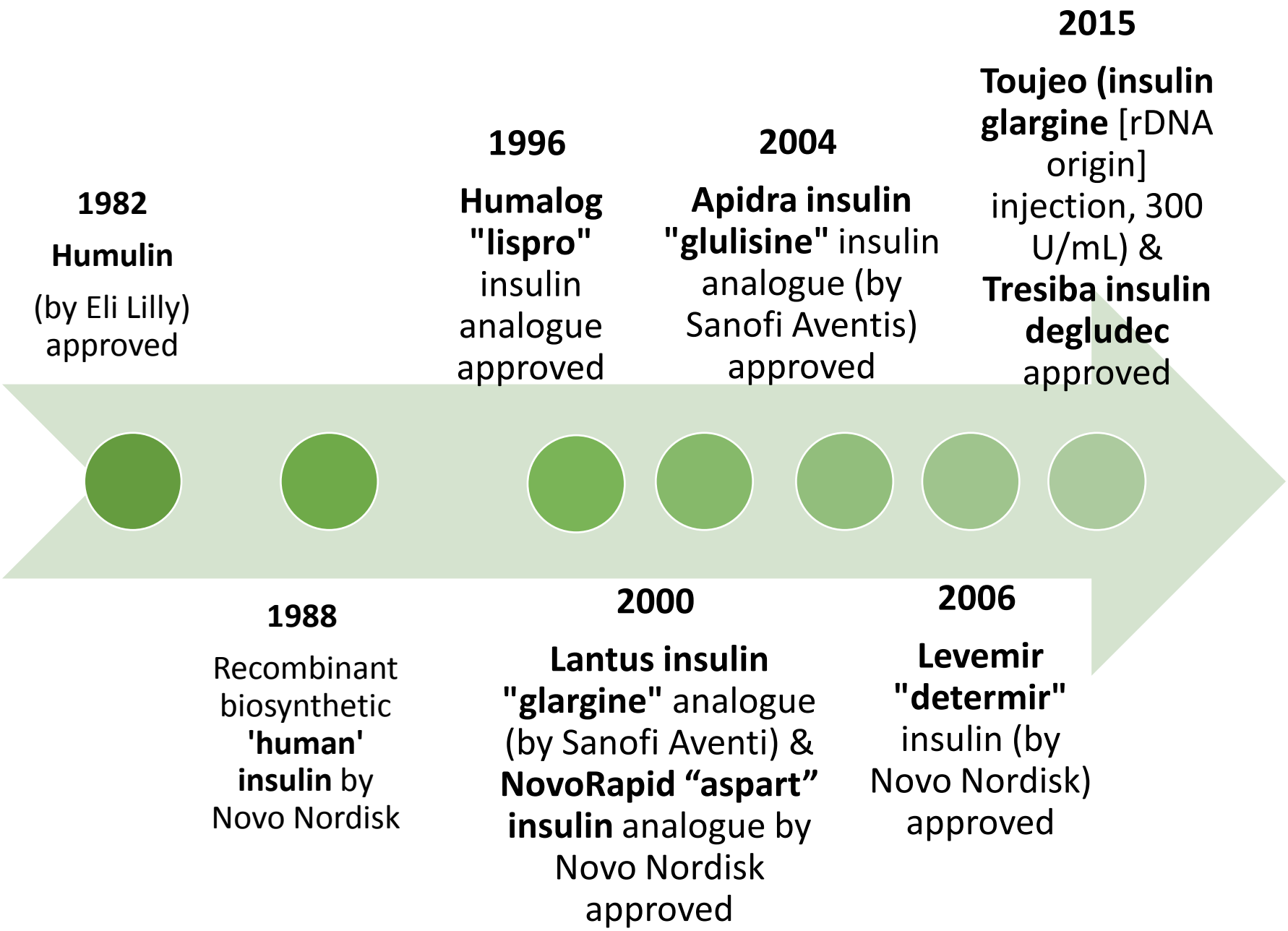
Purified **monocomponent (MC)** insulin is introduced



Era of the Recombinant Human Insulin

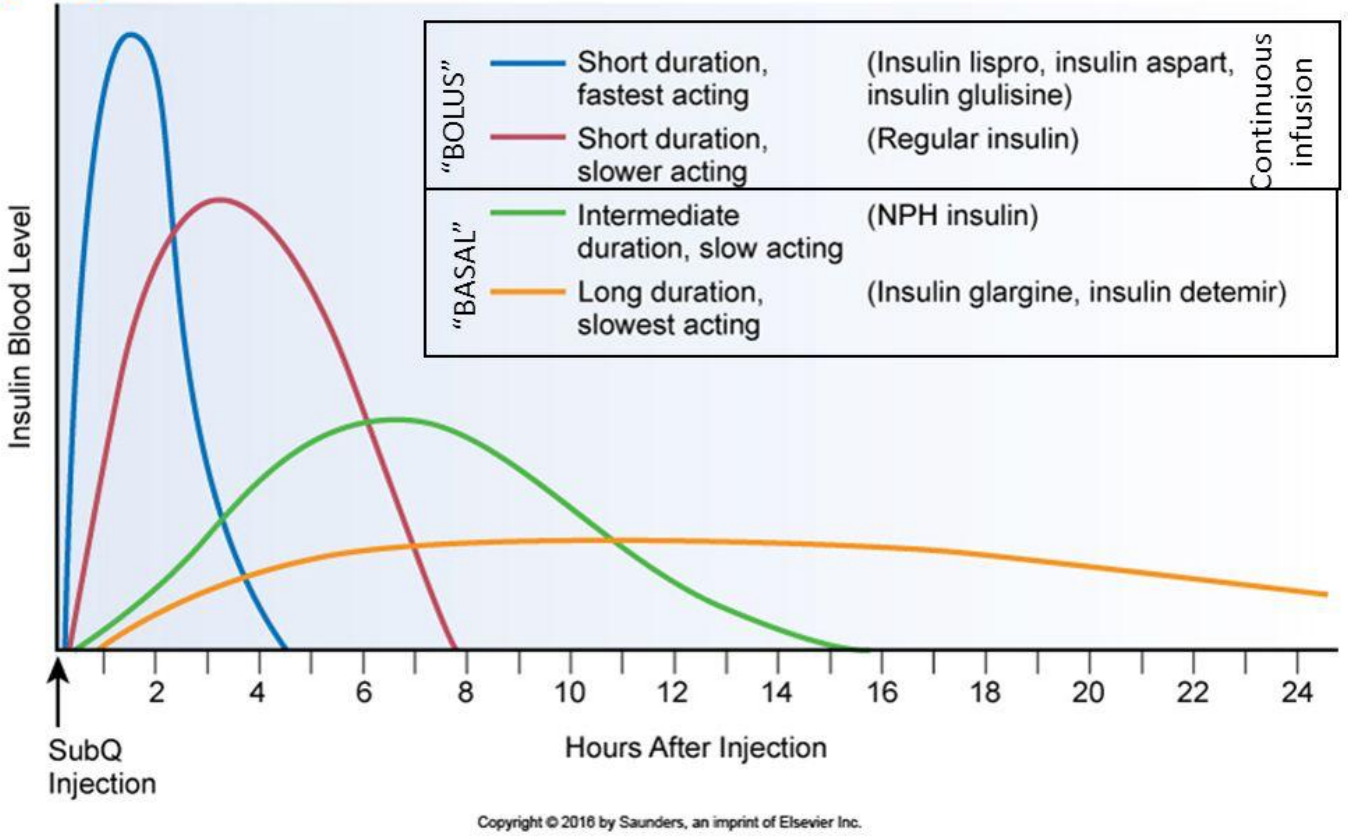


Zaykov et al. Nat Rev Drug Discov. 2016 Jun;15(6):425-39. doi: 10.1038/nrd.2015.36


1982
Humulin
(by Eli Lilly)
approved
1988
Recombinant biosynthetic 'human' insulin by Novo Nordisk
1996
Humalog "lispro" insulin analogue approved
2000
Lantus insulin "glargine" analogue (by Sanofi Aventi) & NovoRapid “aspart” insulin analogue by Novo Nordisk approved
2004
Apidra insulin "glulisine" insulin analogue (by Sanofi Aventis) approved
2006
Levemir "determir" insulin (by Novo Nordisk) approved
2015
Toujeo (insulin glargine [rDNA origin] injection, 300 U/mL) & Tresiba insulin degludec approved

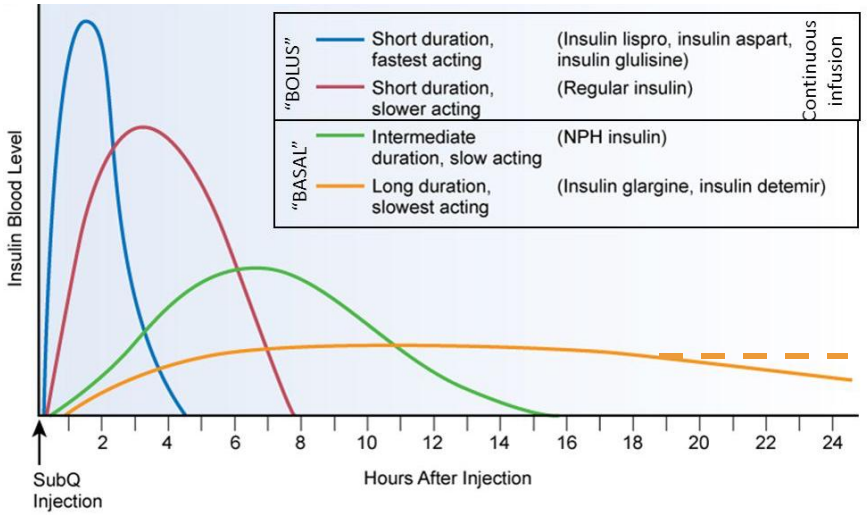
Types of Insulin: rate of onset, peak & duration

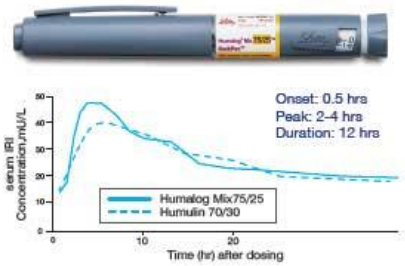
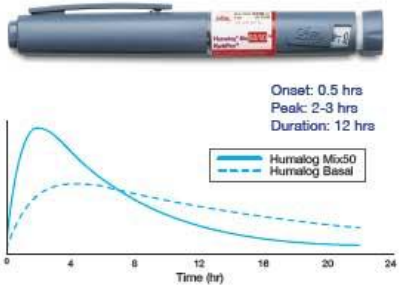
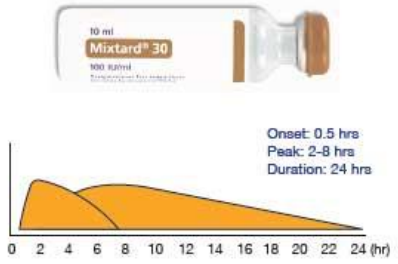
rapid acting (lispro); short-acting (regular); intermediate duration (NPH); long-duration glargine



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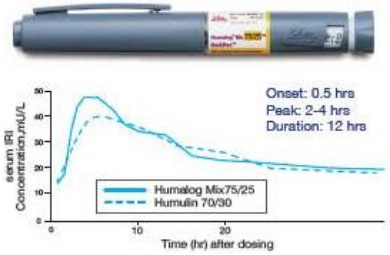
Drug Company	Usual dosage	Novo Nordisk	Eli Lilly	Sanofi
Rapid acting	tds	NovoRapid (insulin aspart)	Humalog (Insulin lispro)	Apidra (Insulin glulisine)
Short acting	tds	Actrapid	Humulin R	--
Intermediate acting	om / nocte / bd	Protaphane	Humulin N	--
Long acting	om / nocte / bd* (* for Levemir)	Levemir (Insulin detemir)	--	Lantus (Insulin glargine)
Ultra-long acting	daily	Tresiba (Insulin degludec)	--	Toujeo (Insulin glargine)

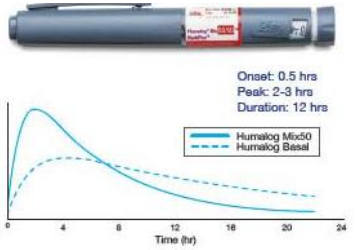
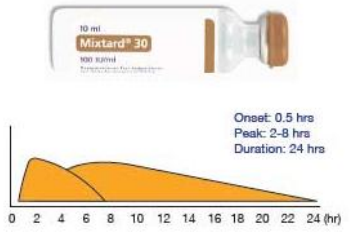


Onset of insulin action	Brand and type	Generic name	Type of insulin
15 min	NovoMix®30 FlexPen	Biphasic Insulin Aspart	
15 min	Humalog® Mix 75/25 KwikPen	Biphasic Insulin Lispro 25%/ Protamine 75%	
15 min	Humalog® Mix 50/50 Kwikpen	Biphasic Insulin Lispro 50%/ Protamine 50%	
15 min	Mixtard® 30	Biphasic 30% Soluble Human Insulin +70% NPH Insulin	

https://www.healthxchange.sg/diabetes/essential-guide-diabetes/diabetes-types-insulin-action-profiles

Drug Company	Usual dosage	Novo Nordisk	Eli Lilly
Rapid acting + Intermediate acting	bd / tds	**NovoMix 30** (30% Insulin aspart (rapid-acting) and 70% protamine-crystallised (intermediate-acting) insulin aspart)	**Humalog Mix 75/25** **Humalog Mix 50/50** (Lispro (rapid-acting) / Protamine (intermediate acting)
Short acting + Intermediate acting	bd / tds	**Mixtard 30** (soluble insulin 30% (short-acting) and isophane insulin 70% (intermediate-acting))	**Humulin 70/30** (insulin isophane (intermediate-acting) and insulin regular (short-acting))

NovoMix®30 FlexPen	Biphasic Insulin Aspart	
Humalog® Mix 75/25 KwikPen	Biphasic Insulin Lispro 25%/ Protamine 75%	

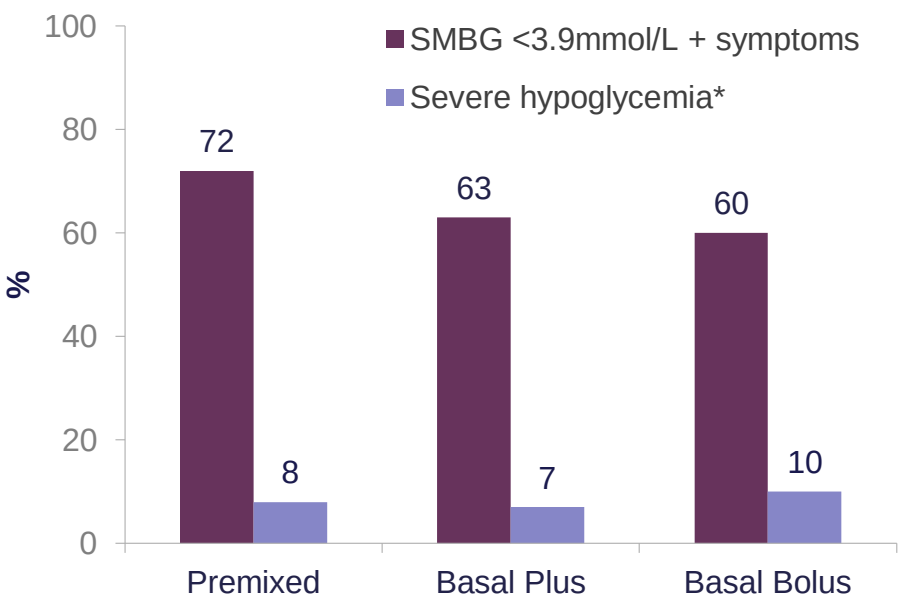
Humalog® Mix 50/50 Kwikpen	Biphasic Insulin Lispro 50%/ Protamine 50%	
Mixtard® 30	Biphasic 30% Soluble Human Insulin +70% NPH Insulin	

Side effects of insulin

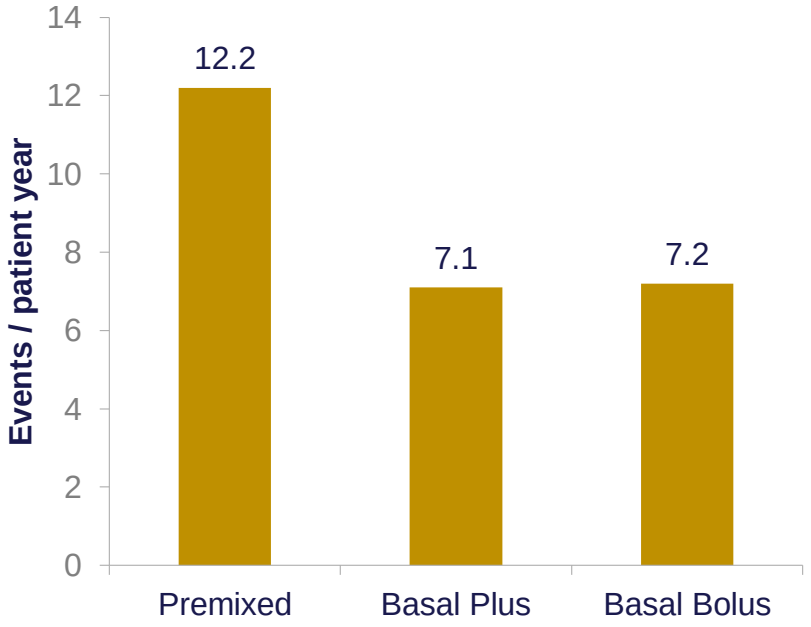
- Hypoglycemia
- Weight gain

High hypoglycemia rate associated with all 3 regimens

Adjusted incidence rate of hypoglycemia



Overall hypoglycemic event rates

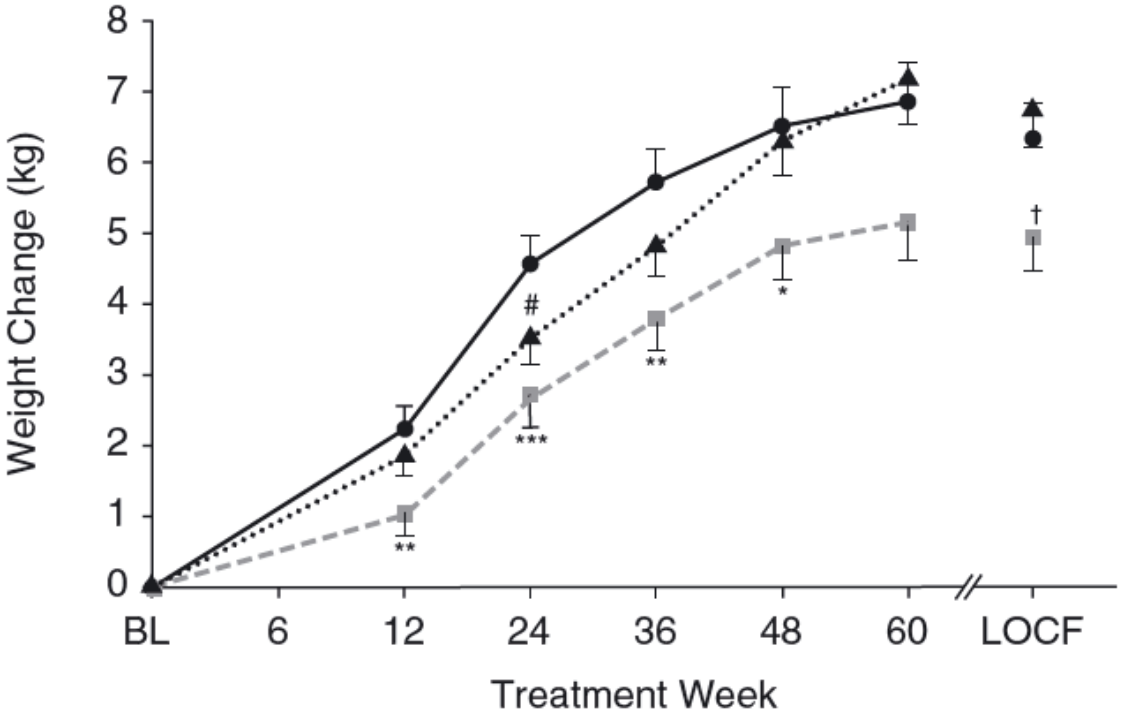


*Severe hypoglycemia requiring assistance and associated with either prompt recovery after oral carbohydrate or blood glucose <2.0 mmol/

Riddle MC et al. Diabetes, Obesity and Metabolism 2014; 16: 396–402,

Weight increased progressively with all 3 regimens

Mean Change in Weight over time



- Glargine + 3 insulin glulisine
- Premixed
- Glargine + 1 insulin glulisine

Mean weight increases at week 60

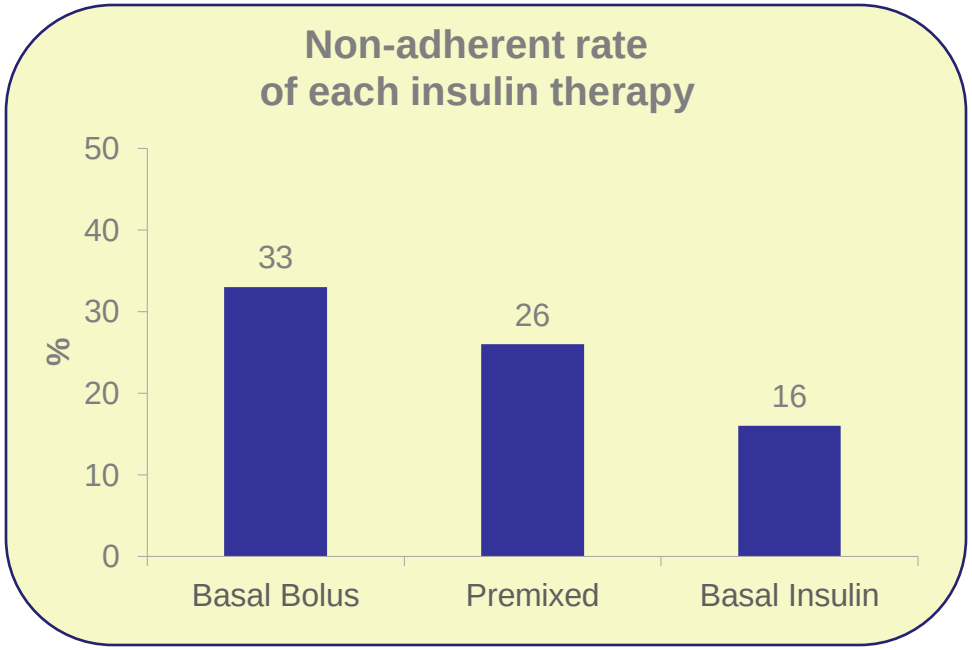
- **6.9**kg for Premixed
- **5.2**kg for Basal Plus
- **7.2**kg for Basal Bolus

Riddle MC et al. Diabetes, Obesity and Metabolism 2014; 16: 396–402,

Low Patient Compliance to multiple insulin injections, leading to Poor Glycemic Control

A questionnaire based phone interview survey of 433 insulin-naïve T2DM patients at the sixth month of insulin initiation in Turkey

The 2012 US National Health and Wellness Survey dataset was used, with N=1,198 using basal insulin. Nonadherence was assessed by Morisky Medication Adherence Scale (MMAS)

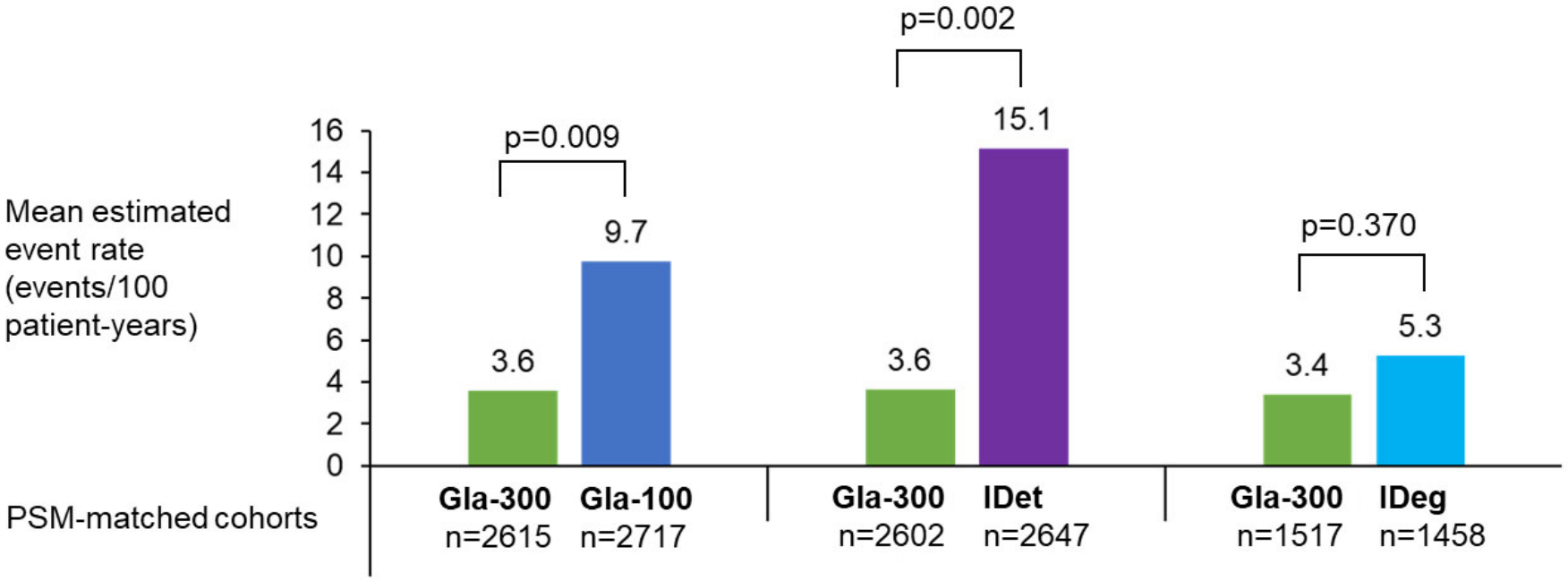


Each point increase in level of non-adherence was associated with

- **0.21** increase in **HbA1c**
- **4.6%** in no. of physician visits
- **20.4%** in emergency room visits
- **20.9%** in hospitalizations

Yavuz DG et al. Patient preference and adherence. 2015; 9: 1225-1231.
DiBonaventura M et al. Patient Preference and Adherence 2014:8 873–882.

Risk of Hypoglycemia Reduced with New Generation Ultra-long acting insulin analogues

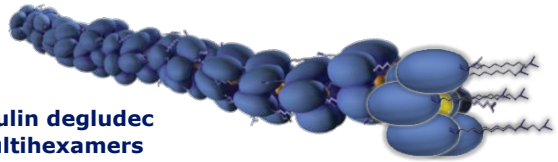


Severe hypoglycemia was defined as any hypoglycemic event (identified by ICD 9/10 codes or plasma glucose levels) related to an inpatient or emergency department encounter. HbA_{1c} reduction for each comparison was: Gla-300 vs Gla-100, 0.59 % vs 0.56 %; Gla-300 vs IDet, 0.59 % vs 0.50 %; Gla-300 vs IDeg, 0.80 % vs 0.89 %.
ICD, International Classification of Diseases; PSM, propensity score matching

The LIGHTNING Study. Presented at at the 11th Annual Conference on Advanced Technologies and Treatments for Diabetes (ATTD) in Vienna, Austria

Insulin degludec: slow release following injection

Subcutaneous depot [Zn^{2+}]

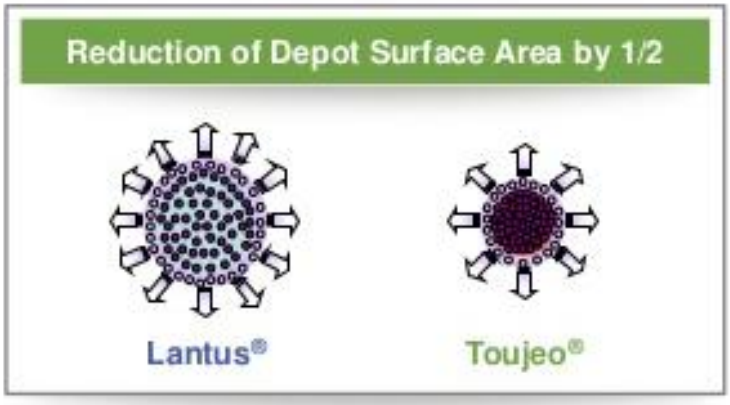


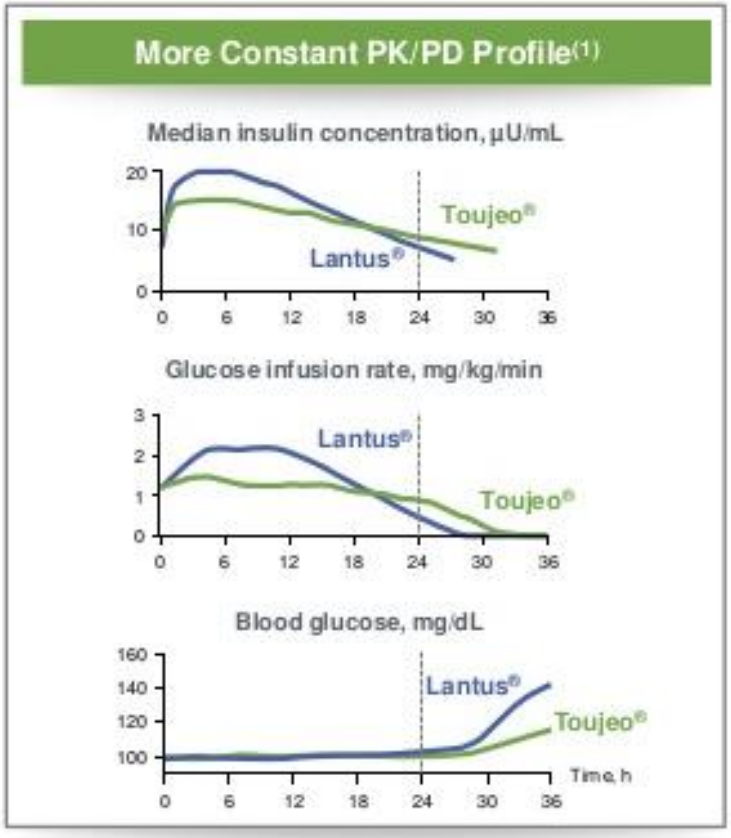
Insulin degludec multihexamers

Zinc diffuses slowly causing individual hexamers to disassemble, releasing monomers

Monomers are absorbed from the depot into the circulation

Jonassen *et al. Pharm Res* 2012;29:2104–14





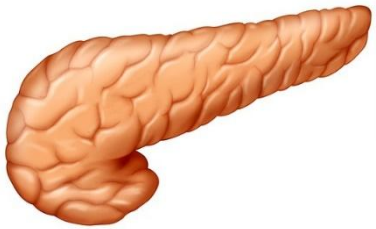
PK/PD Profile: Pharmacokinetic/Pharmacodynamic Profile

(1) Steinstraesser A et al. Diabetes Obes Metab. 2014;16:873-6. Becker RHA et al. Diabetes Care. 2014 Aug 22 pii:DC_140006

Outline

1. Why do we need injectable medications
2. Insulins over the year
3. Other non-insulin injectable medications
4. Over the horizon: New combination injectables
5. Advances in injection device

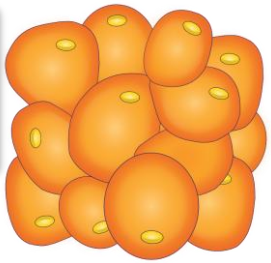
Ominous Octet in T2DM



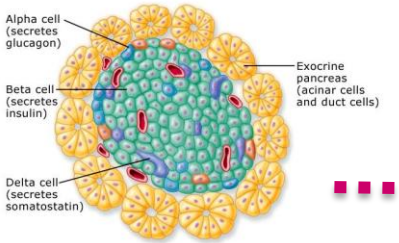
Decreased Insulin Secretion



Decreased Incretin Effect

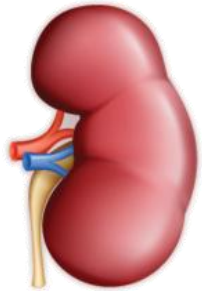


Increased lipolysis

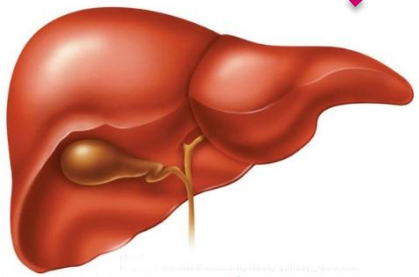


Increased Glucagon Secretion

Hyperglycemia



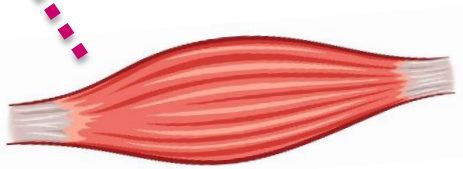
Increased Glucose Reabsorption



Increased HGP



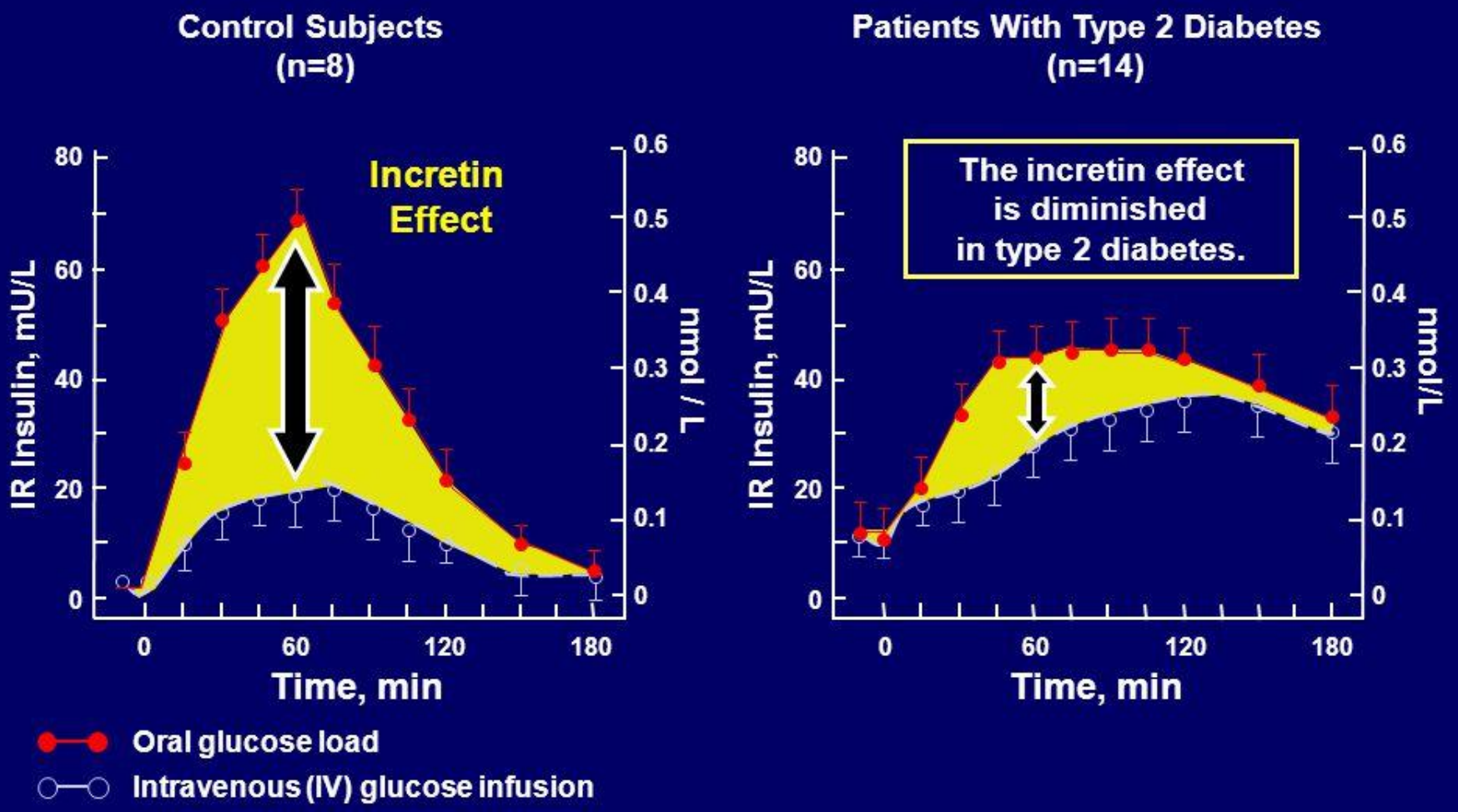
Neurotransmitter Dysfunction



Decreased Glucose Uptake

Adapted from: DeFronzo RA. *Diabetes.* 2009;58:773–795; Tahrani AA, et al. *Lancet*. 2011;378:182–197.

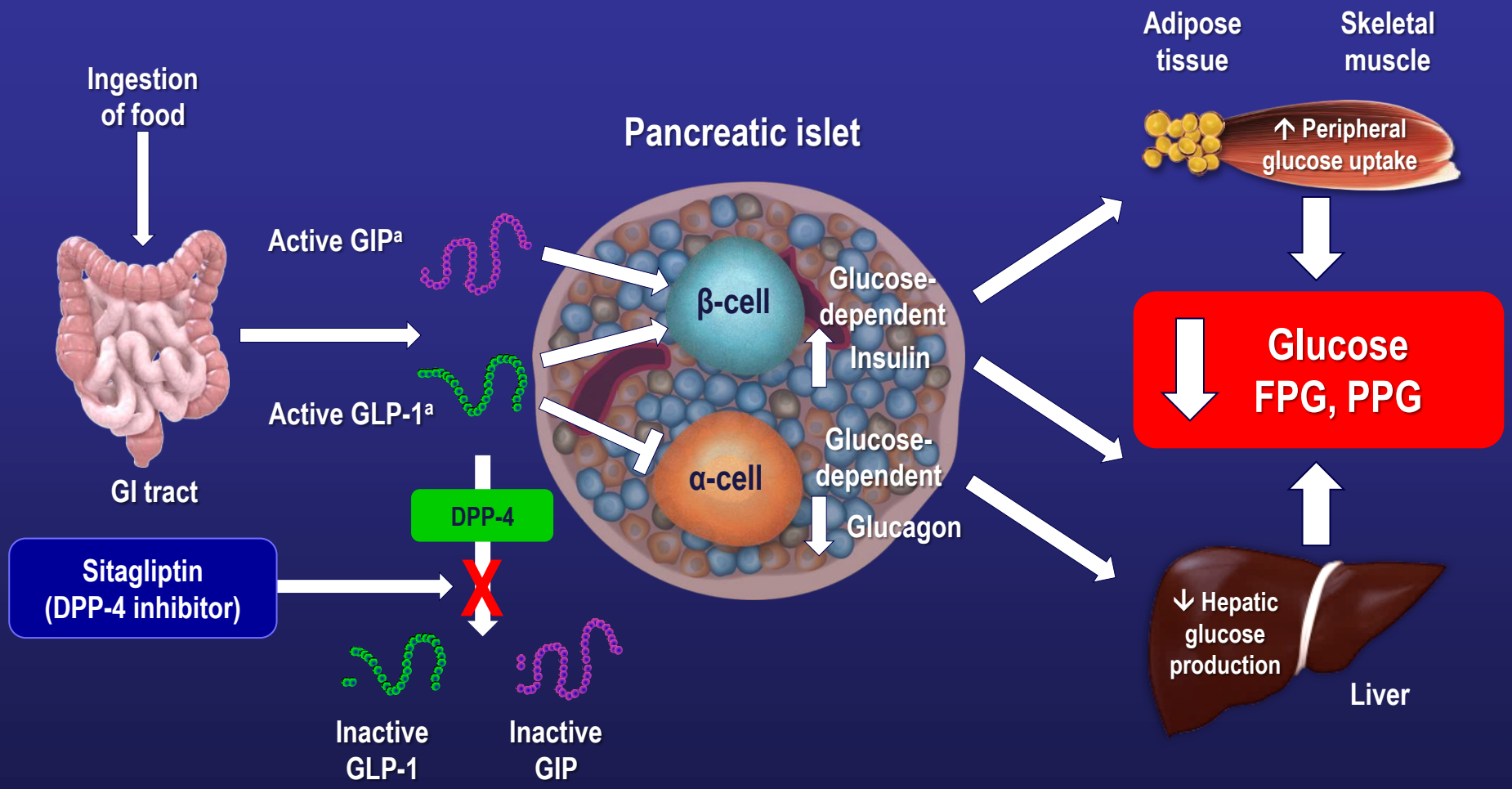
The Incretin Effect in Subjects With & W/O DM2



Adapted with permission from Nauck M et al. *Diabetologia*. 1986;29:46–52. Copyright © 1986 Springer-Verlag.

http://slideplayer.com/slide/4129941/13/images/37/The+Incretin+Effect+in+Subjects+With+&+W/O+DM2.jpg

DPP-4 Inhibition Increases Concentrations of Active Incretins[1–4]

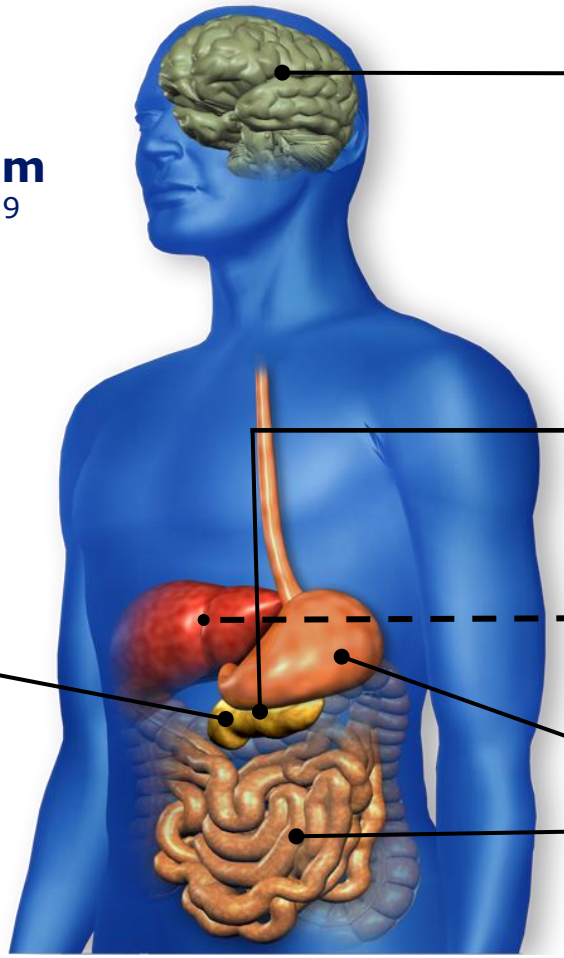


[a]Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels increase in response to a meal.

GI = gastrointestinal; GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; PPG = postprandial plasma glucose.

1. Ahrén B. *Curr Diabetes Rep*. 2003;3:365–372. **2.** Drucker DJ. *Diabetes Care*. 2003;26:2929–2940. **3.** Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430–441.
4. Adapted with permission from Drucker D. *J Clin Invest*. 2007;117:24–32.

Glucagon-Like Peptide-1 agonists (GLP1 agonists)



Brain
- ↓ Body weight:[6–8]
- ↑ Satiety
- ↓ Energy intake

Cardiovascular system
- ↓ Systolic blood pressure[9]

Pancreas α cell
- ↓ Glucagon secretion[4] (glucose-dependent)

Pancreas β cell
- ↑ Insulin secretion[2,3] (glucose-dependent) and beta-cell sensitivity
- ↑ Insulin synthesis[4]

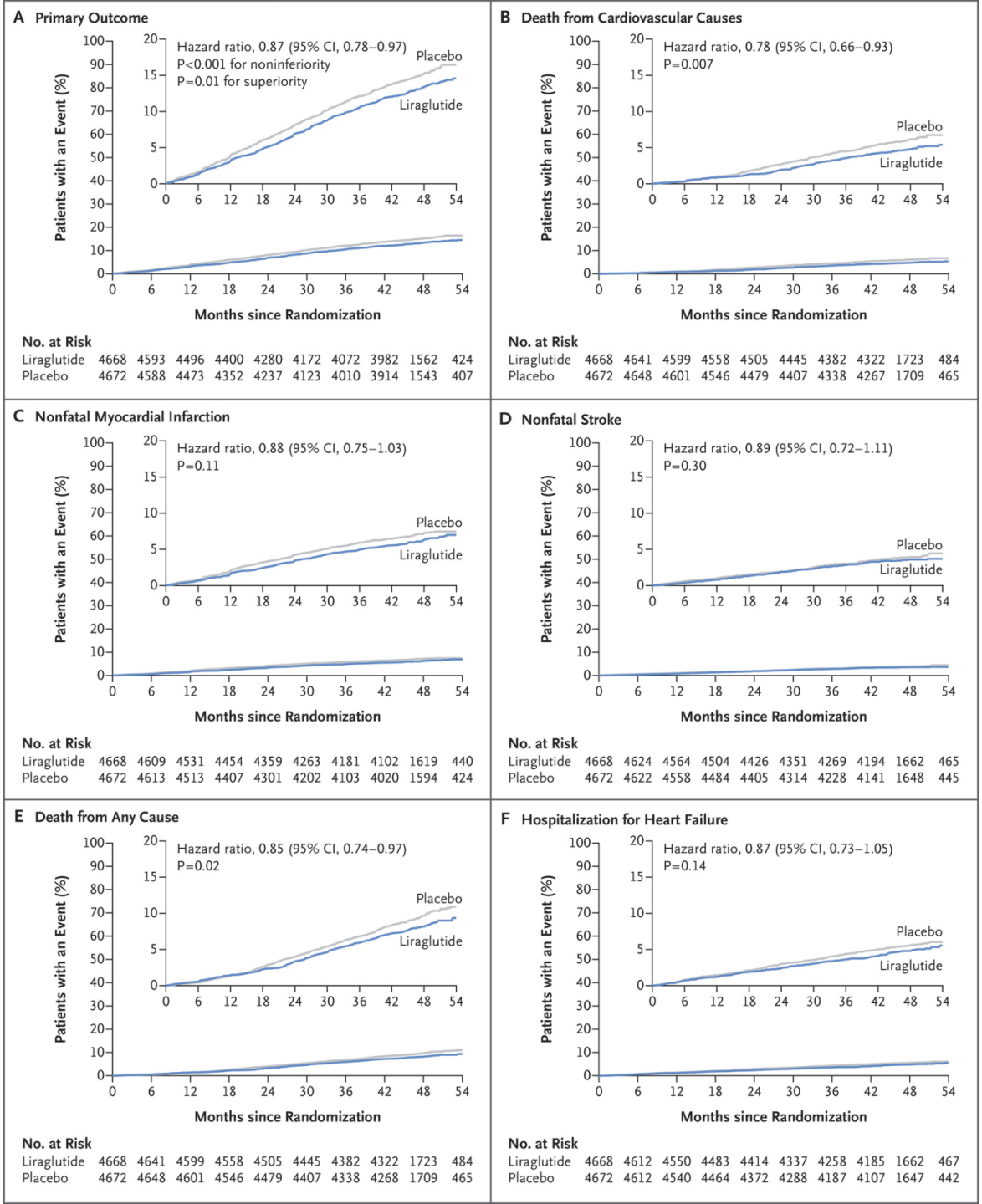
Liver
- ↓ Hepatic glucose output[5]

Stomach
- ↓ Delay gastric emptying

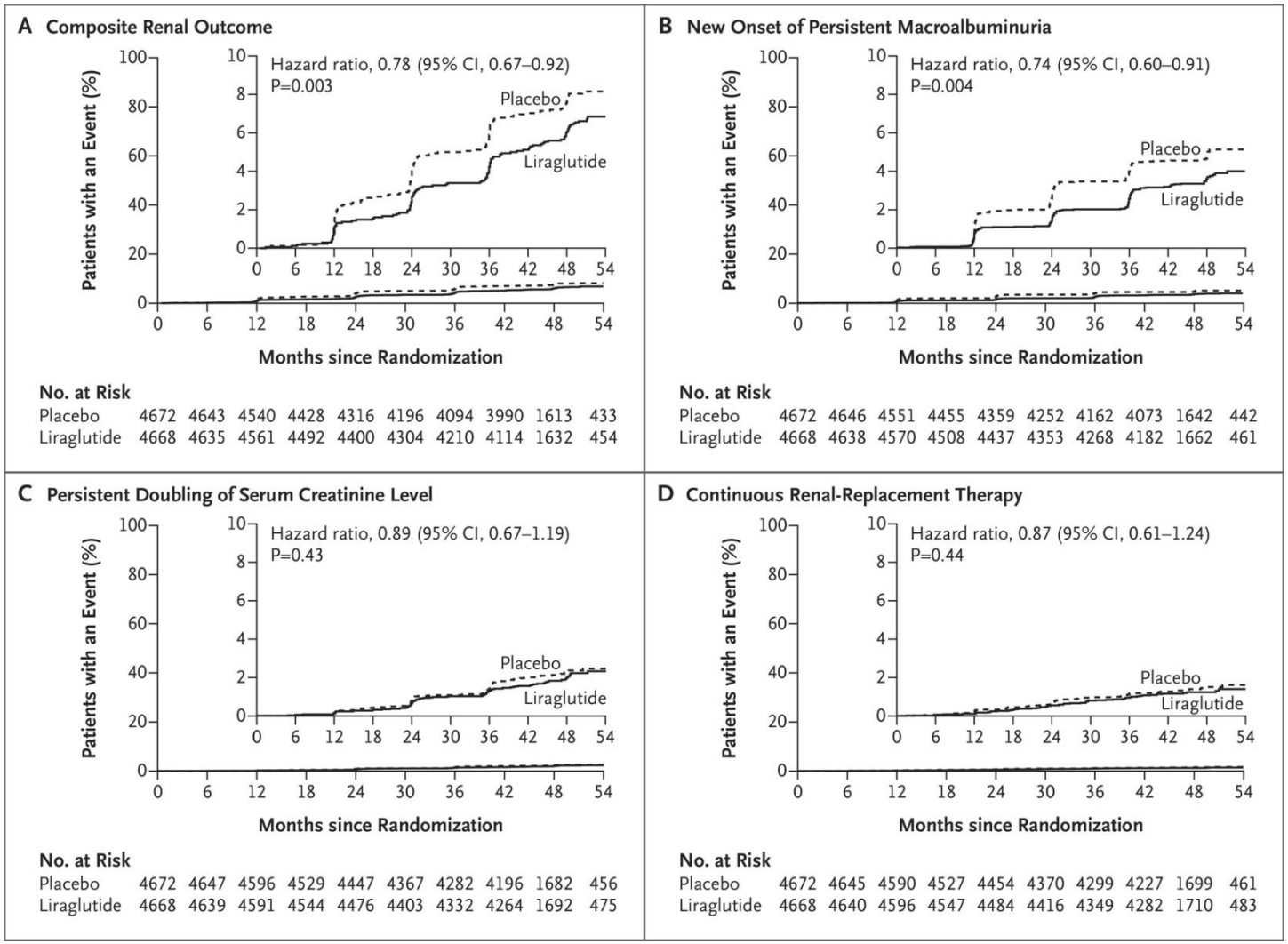
GLP-1 accounts for ~60% of total insulin release after a meal

GLP1 agonists

Drug Company	**AstraZeneca**	**Novo Nordisk**	**Eli Lilly**	**Sanofi**
bd	**Byetta** (exenatide)	--	--	--
Daily	--	**Victoza** (liraglutide) ****Saxenda** (for weight reduction)	--	**Lyxumia** (lixisenatide)
Weekly	**Bydureon** (exenatide)	--	**Trulicity** (dulaglutide)	--



Marso et al. for the LEADER Steering Committee on behalf of the LEADER Trial Investigator. N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827

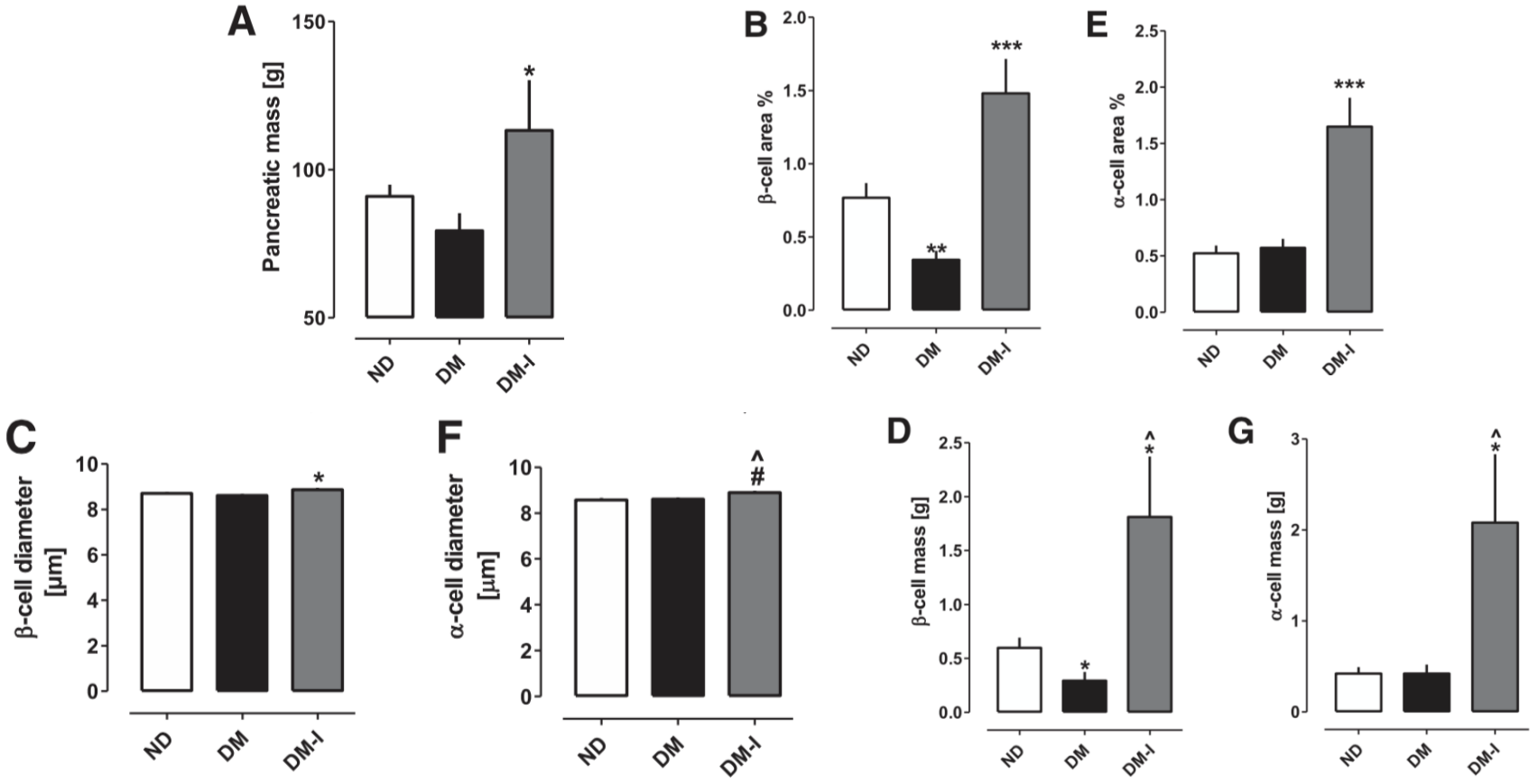


Mann et al. for the LEADER Steering Committee on behalf of the LEADER Trial Investigator. N Engl J Med 2017; 377:839-848
DOI: 10.1056/NEJMoa1616011

Side effects of GLP1a

- Pancreatitis
- Pancreatic cancer
- Medullary thyroid cancer

Marked Expansion of Exocrine and Endocrine Pancreas With Incretin Therapy in Humans With Increased Exocrine Pancreas Dysplasia

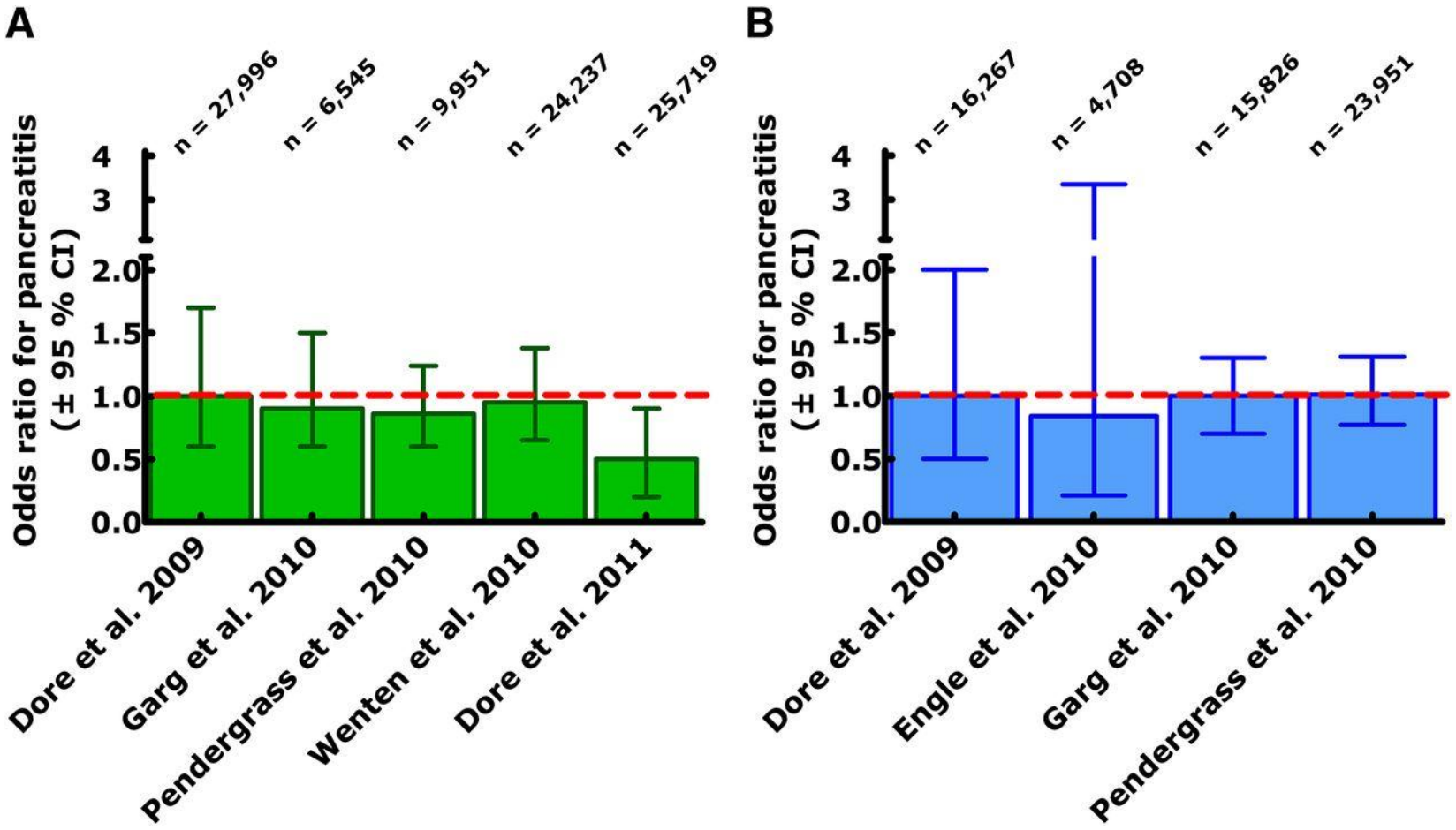


The increase in beta-cell and alpha-cell mass with incretin treatment was predominantly due to endocrine hyperplasia rather than hypertrophy.

All pancreata were procured from brain-dead organ donors by the JDRF Network for Pancreatic Organ Donors with Diabetes (nPOD) coordinated through the University of Florida in Gainesville, Florida. ND n=14, DM n=12, DM-I n=8

Butler AE et al. Diabetes. 2013 Jul; 62(7): 2595–2604

Odds ratio and 95% CIs for chronic pancreatitis in studies examining the risk of pancreatitis in patients with type 2 diabetes receiving treatment with the GLP-1 receptor agonist exenatide (A) or the DPP-4 inhibitor sitagliptin (B) relative to other glucose-lowering medications.



Michael A. Nauck, and Nele Friedrich Dia Care 2013;36:S245-S252

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American Diabetes Association.

Diabetes, Obesity and Metabolism 13: 559–566, 2011.
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A cohort study of acute pancreatitis in relation to exenatide use

D. D. Dore[1,2], G. L. Bloomgren[3], M. Wenten[3], C. Hoffman[1], C. R. Clifford[1], S. G. Quinn[1], D. K. Braun[4], R. A. Noel[4] & J. D. Seeger[1,5,6]

[1] *i3 Drug Safety, Waltham, MA, USA*
[2] *Department of Community Health, The Warren Alpert Medical School of Brown University, Providence, RI, USA*
[3] *Biogen Idec, Cambridge, MA, USA*
[4] *Eli Lilly and Company, Indianapolis, IN, USA*
[5] *Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical School/Brigham and Women's Hospital, Boston, MA, USA*
[6] *Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA*

Table 2. Propensity score adjusted association between exenatide and acute pancreatitis relative to other antihyperglycaemic medications.

	Exenatide			Other antihyperglycaemic drugs*				
	Number of cases	Person–years	IR/1 00 000 person–years	Number of cases	Person–years	IR/1 00 000 person–years	Adjusted RR†	95% CI
Cohort, time-on-drug analysis†								
Current use‡	11	17 629	62.4	223	2 15 643	103.4	0.5	0.2–0.9
Recent use§	4	1927	207.6	22	14 120	155.8	1.1	0.4–3.2
Past use||	26	10 165	255.8	47	50 816	92.5	2.8	1.6–4.7

CI, confidence interval; IR, incidence rate; RR, rate ratio.
*Includes initiators of metformin, thiazolidinediones, insulin, sulphonylureas, non-sulphonylurea secretagogues, sitagliptin, pramlintide and α-glucosidase inhibitors.
†Adjusted for propensity score. Rate ratios in the time-on-drug analysis compare periods of current, recent and past exposure to exenatide to corresponding periods of use of comparison medications.
‡Time during current days supply + 31 days.
§Time following current use + an additional 31 days excluding subsequent current use.
||Time following recent use excluding subsequent current or recent use.

original article

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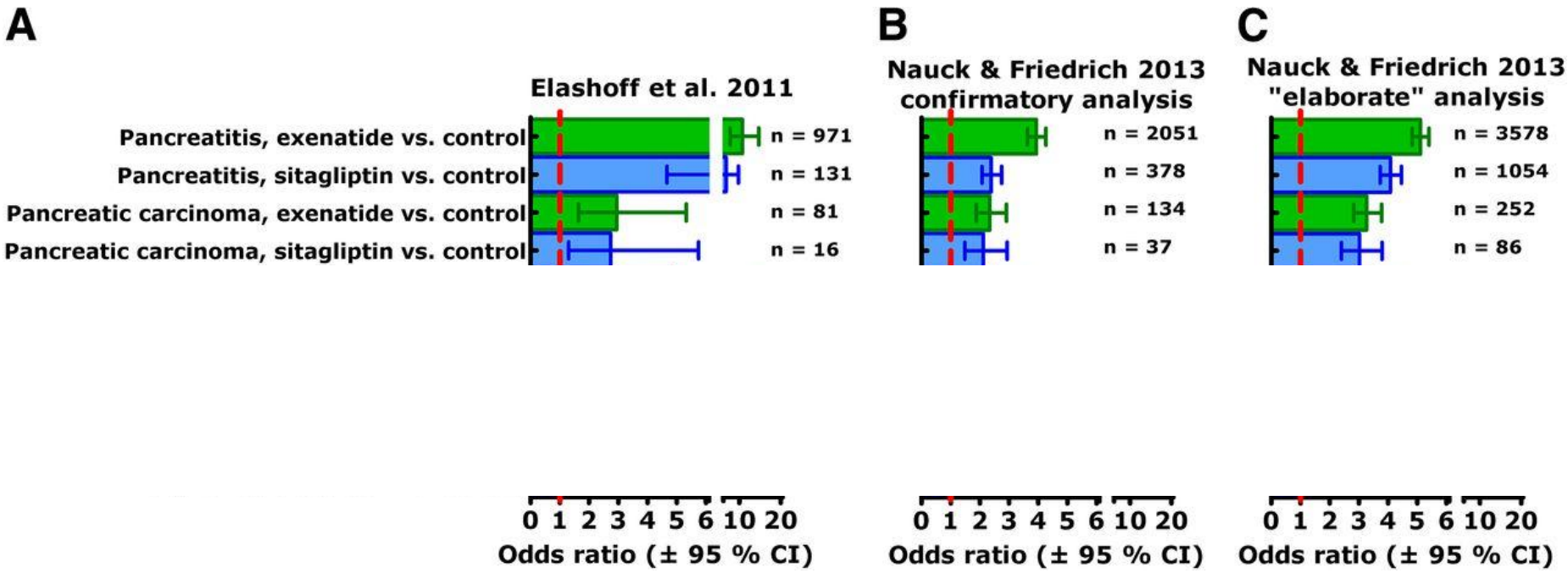
- The study population came commercial health insurance claims data environment.
- No alcohol drinking records or triglyceride level documentation

Table 2. Propensity score adjusted association between exenatide ar

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Odds ratios (95% CI) for reporting pancreatitis, pancreatic carcinoma, thyroid carcinoma, and other/all malignancies in patients with type 2 diabetes prescribed exenatide (green bars) or sitagliptin (blue bars) relative to those taking control diabetes medications, taking into account the frequency of reporting control events (back pain, chest pain, cough, syncope, and urinary tract infection) based on data retrieved from the FDA Adverse Event Reporting System (A), as described by Elashoff et al.

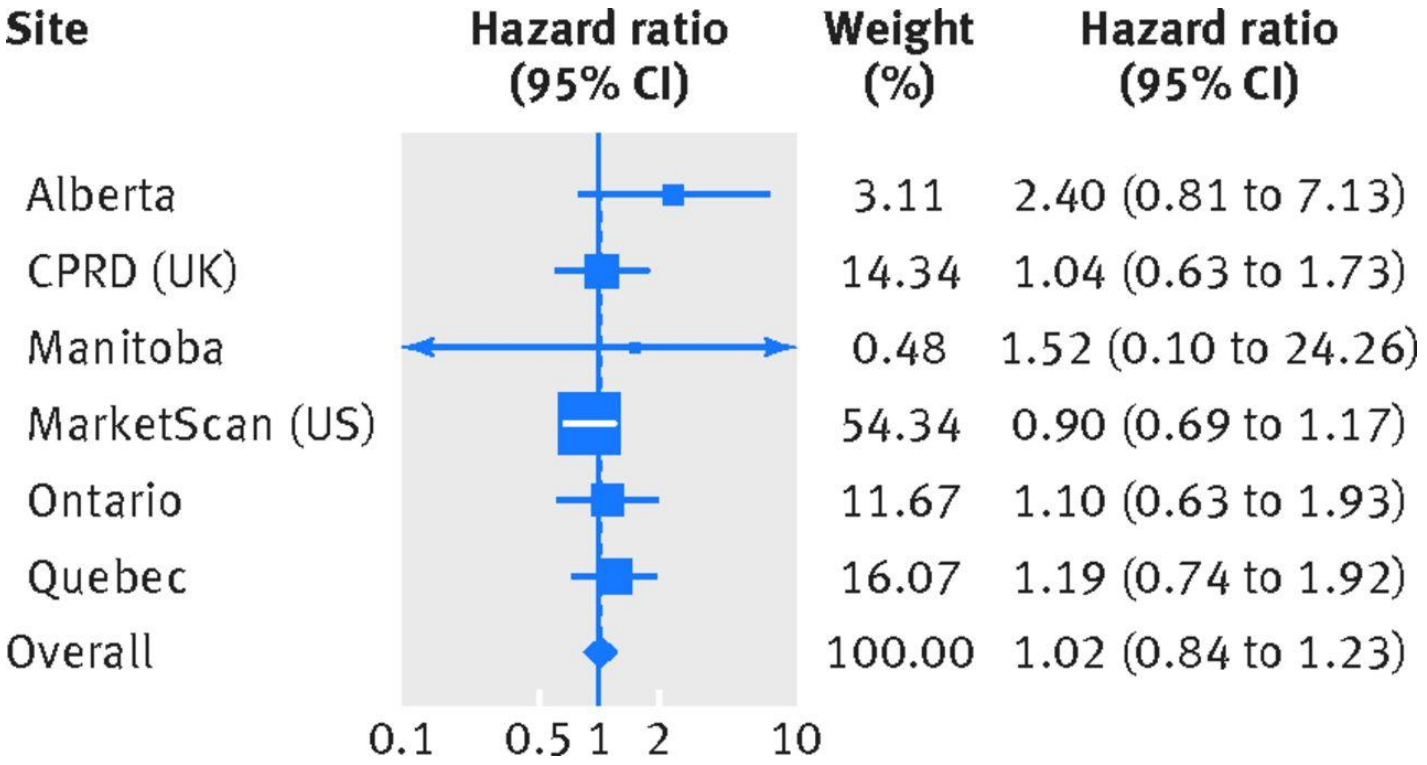


Michael A. Nauck, and Nele Friedrich Dia Care
2013;36:S245-S252

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American Diabetes Association.

Forest plot of association between use of incretin based drugs and risk of pancreatic cancer among patients with type 2 diabetes



*Reference category was use of sulfonylureas. box size is proportional to weight of participating site in random effects meta-analysis (i2=0%)

Laurent Azoulay et al. BMJ 2016;352:bmj.i581

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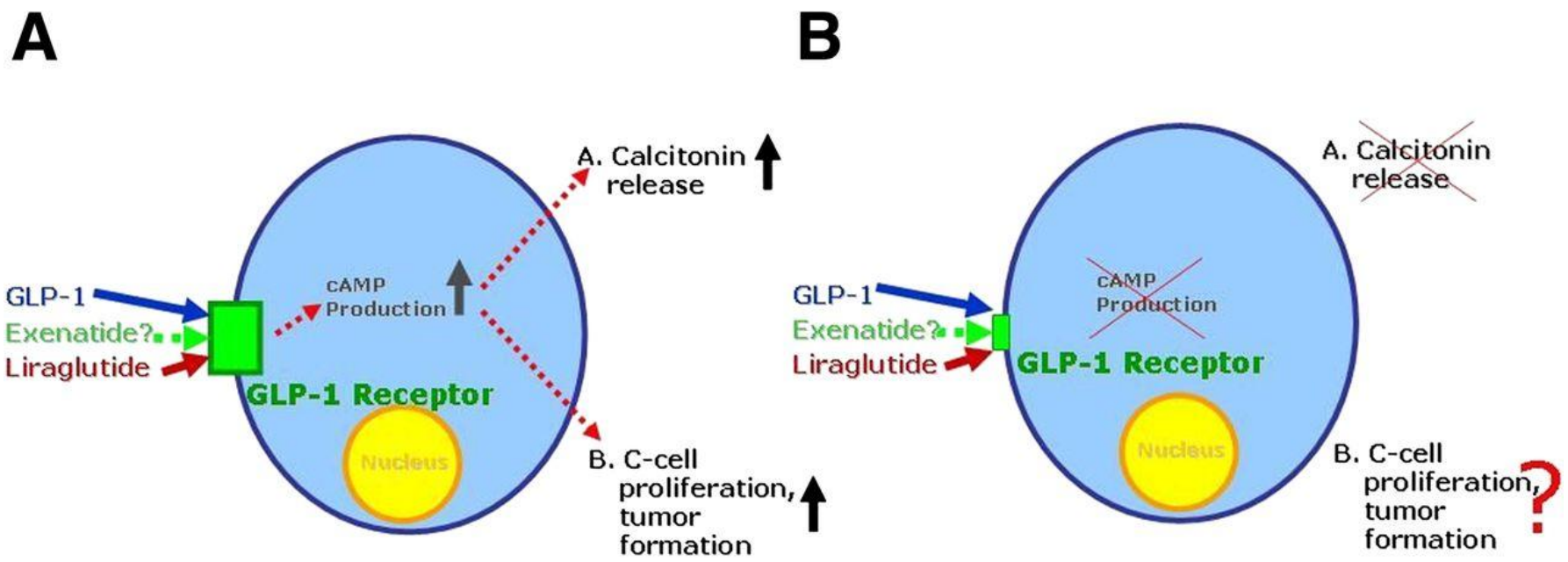
Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

Amy G. Egan, M.D., M.P.H., Eberhard Blind, M.D., Ph.D., Kristina Dunder, M.D., Pieter A. de Graeff, M.D., B. Timothy Hummer, Ph.D., Todd Bourcier, Ph.D., and Curtis Rosebraugh, M.D., M.P.H.

- The FDA and the EMA agree that assertions concerning a causal association be-tween incretin-based drugs and **pancreatitis** or **pancreatic cancer**, as expressed recently in the scientific literature and in the media, are **inconsistent with the current data**
- The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship.
- Although the totality of the data that have been reviewed provides reassurance, **pancreatitis will continue to be considered a risk** associated with these drugs **until more data are available**
- Both agencies continue to investigate this safety signal.

N Engl J Med 2014; 370:794-797. DOI: 10.1056/NEJMp1314078

Schematic representation of thyroid C cells, their equipment with GLP-1 receptors, and physiological responses to stimulation with GLP-1 or GLP-1 receptor agonists like exenatide and liraglutide comparing rodent (A) and human (B) C cells.

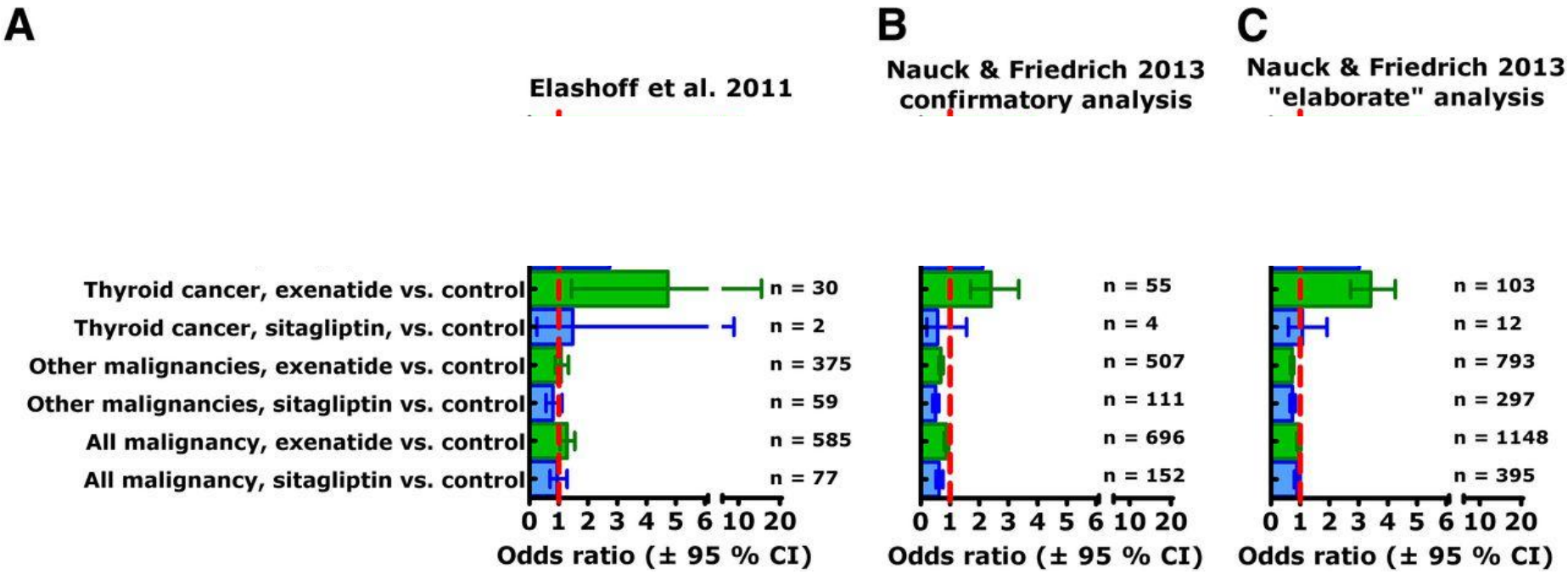


Michael A. Nauck, and Nele Friedrich Dia Care 2013;36:S245-S252

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Outline

1. Why do we need injectable medications
2. Insulins over the year
3. Other non-insulin injectable medications
4. Over the horizon: New combination injectables
5. Advances in injection device

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

Cefalu, WT *et al*. ADA Standards of Medical Care in Diabetes – 2017.

Glycemic Control Algorithm

INDIVIDUALIZE GOALS

- **A1C ≤ 6.5%** — For patients without concurrent serious illness and at low hypoglycemic risk
- **A1C > 6.5%** — For patients with concurrent serious illness and at risk for hypoglycemia

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

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Prandial GLP-1 RAs are more effective in lowering PPG, and delay gastric Emptying

Parameters	Short-acting GLP-1 receptor agonists	Long-acting GLP-1 receptor agonists
Compounds	Exenatide Lixisenatide	Albiglutide Dulaglutide Exenatide LAR Liraglutide
Half life	2–5 h	12 h–several days
Effects		
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial hyperglycaemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

GLP-1, glucagon-like peptide 1; LAR, long-acting release.

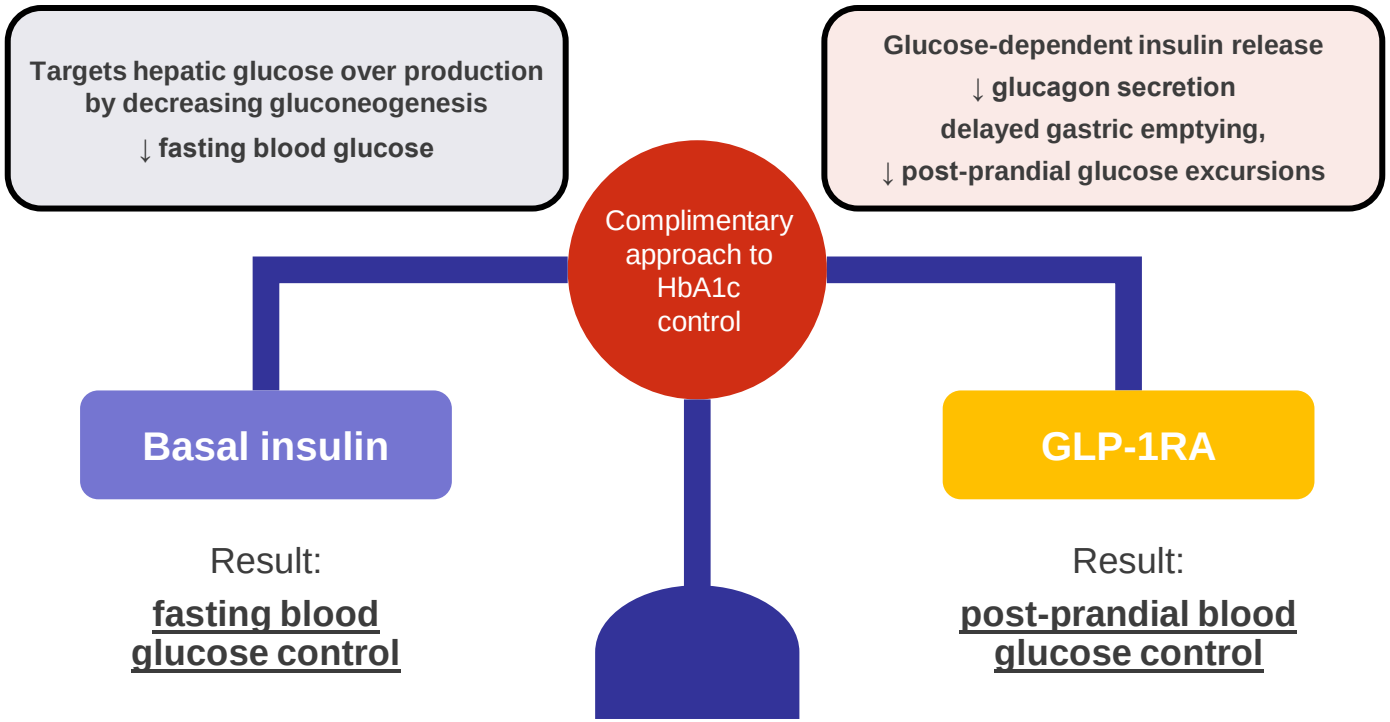
Ther Adv Endocrinol Meta 2014, Vol. 5(5) 95-123

What is iGlarLixi?

Novel fixed-ratio combination
of a basal insulin (Lantus®, glargine 100 U/mL [iGlar])
and a GLP-1RA (Lyxumia®; lixisenatide)
available as a once-daily injection for adult patients with T2DM



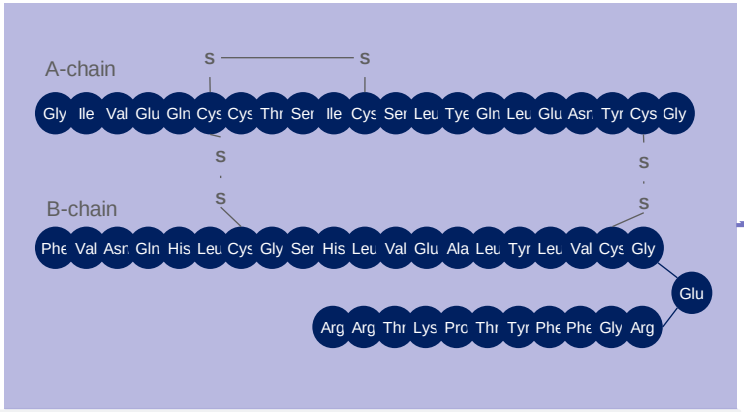
The complementary modes of action of basal insulins and GLP-1 RAs provide control of both FPG and PPG



1. Balena R, et al. Diab Obes Metab 2013;15:485–502; 2. Baggio LL and Drucker DJ. Gastroenterol 2007;132: 2131–57
3. Wang Z, et al. Diab Care 2010;33:1555–60; 4. Holst JJ, et al. Physiol Rev 2007;87:1409–39

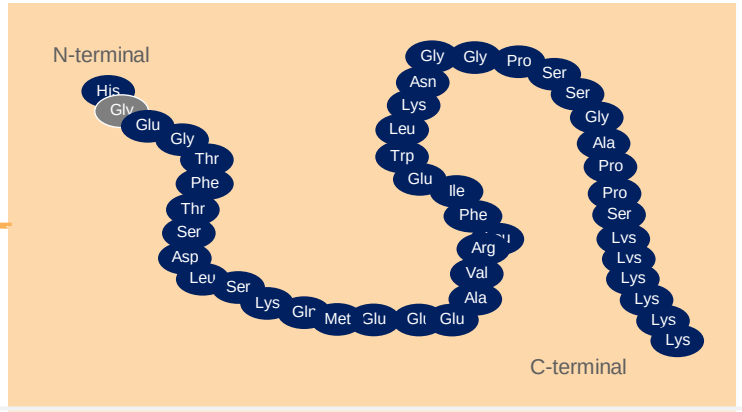
iGlarLixi: Complementary mechanisms of action of iGlar and lixisenatide in a single daily injection

Basal insulin (glargine 100 U/mL [iGlar])



Reduces fasting blood glucose

GLP-1RA (lixisenatide)



Reduces post-prandial blood glucose

Expected advantages of iGlarLixi

Fasting + post-prandial glucose control

Effective HbA1c reduction

More patients achieving glycemic targets

Mitigating weight increase of basal insulin

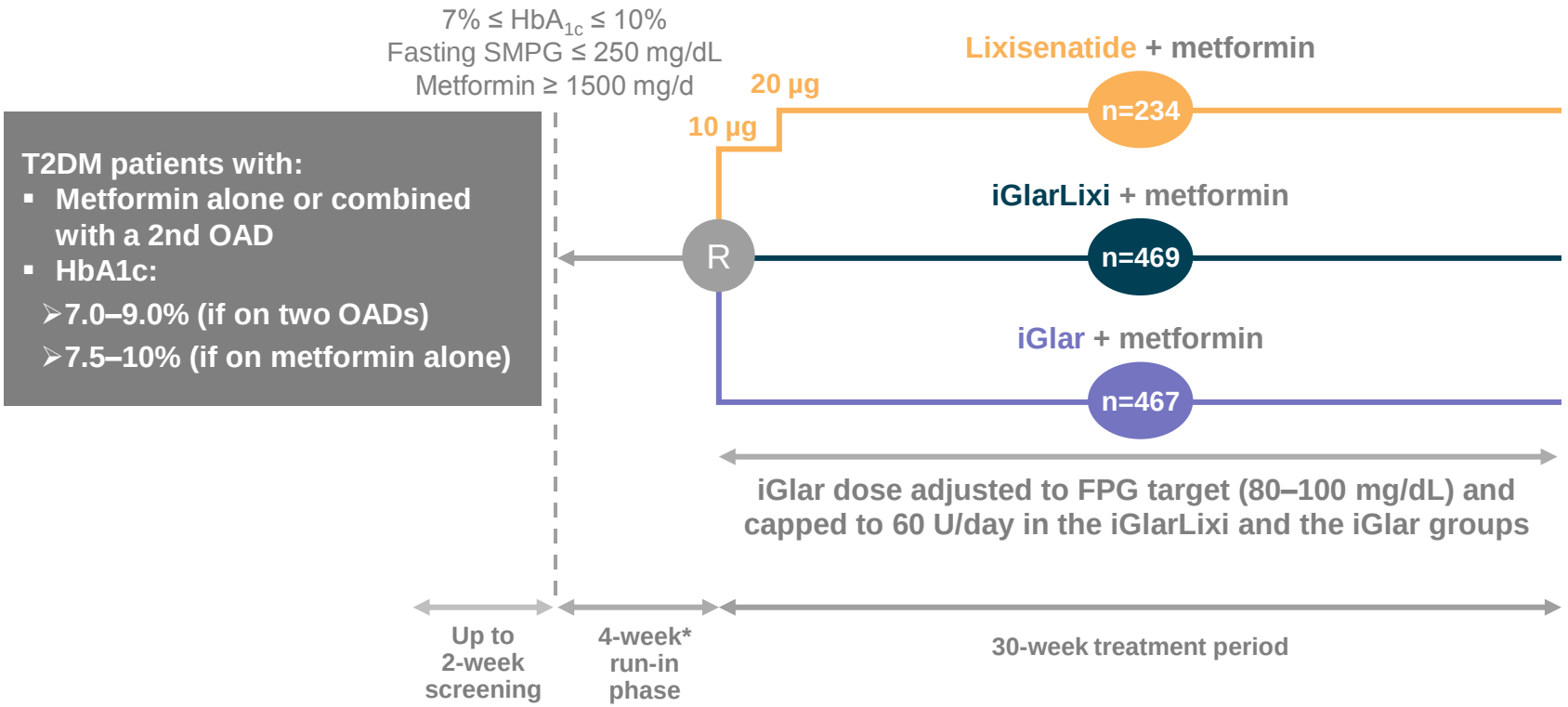
No additional risk of hypoglycemia vs. basal insulin

Improved GI tolerability vs. GLP-1RAs

1. Kramer W. Exp Clin Endocrinol Diabetes 1999;107(suppl 2):S52–61
2. Werner U, et al. Regul Pept 2010;164:58–64; 3. Thorkildsen C, et al. J Pharmacol Exp Ther 2003;307:490–6

LixiLan-O: Patients with T2DM not controlled on OADs

DESIGN: Randomized, open label, active controlled, 3-arm parallel-group study



Primary objective: superiority of iGlarLixi over lixisenatide and non-inferiority of iGlarLixi over iGlar (pre-specified sequential non-inferiority then superiority tested) in HbA1c change at Week 30

Rosenstock J, et al. Diabetes Care 2016;epub ahead of print: dc160917

*Stop 2nd OAD, and titrate metformin up to ≥2,000 mg/day or maximal tolerated dose (≥1,500 mg/day to allow randomization)
Two fixed ratio pens (10–40 Pen and 30–60 Pen) allow titration of iGlar from 10–60 U/day, with lixisenatide daily dose capped at 20 µg once daily

LixiLan-O: Baseline characteristics

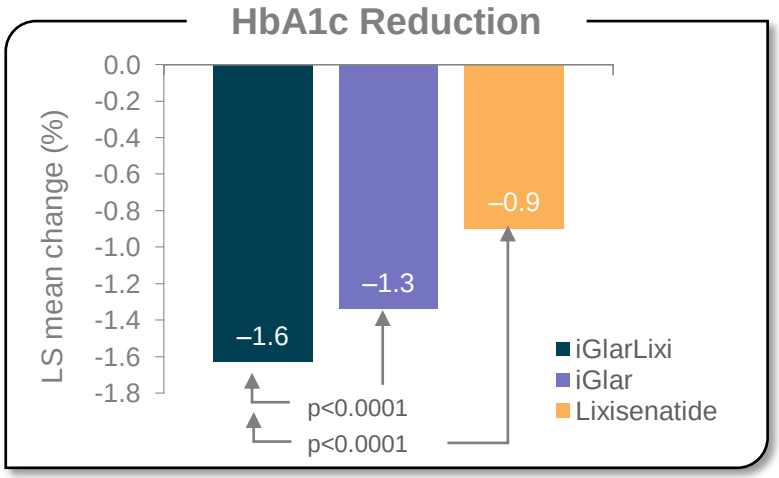
LixiLan-O

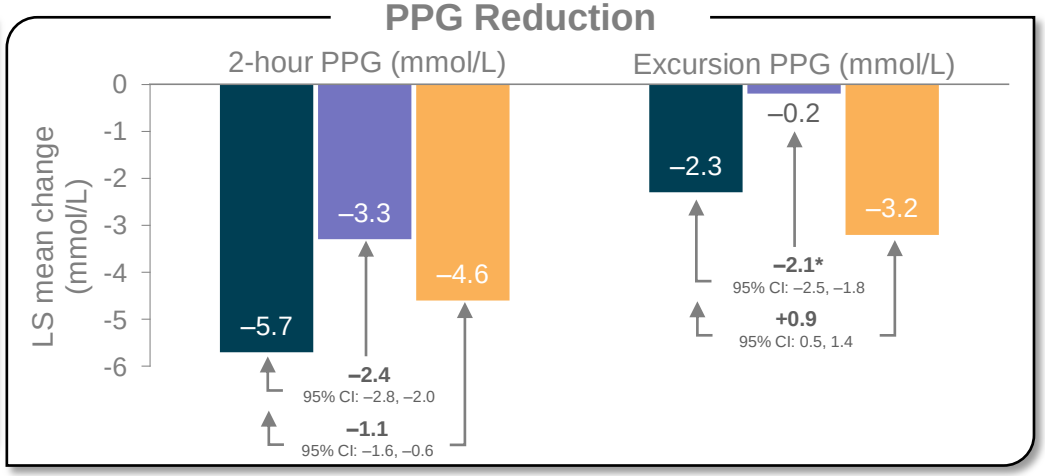
	OAD uncontrolled population		
	iGlarLixi (n=469)	iGlar (n=467)	Lixisenatide (n=234)
Mean (SD) age, years	58.2 (9.5)	58.3 (9.4)	58.7 (8.7)
Male, %	47.3	50.7	56.8
Race, % Caucasian Black	 88.9 7.0	 90.1 7.1	 92.3 5.1
BMI, kg/m^2	31.6 (4.4)	31.7 (4.5)	32.0 (4.4)
Mean (SD) HbA1c*, %	8.2 (0.7)	8.2 (0.7)	8.3 (0.7)
Mean (SD) T2DM duration, years	8.9 (5.5)	8.7 (5.6)	8.9 (6.3)

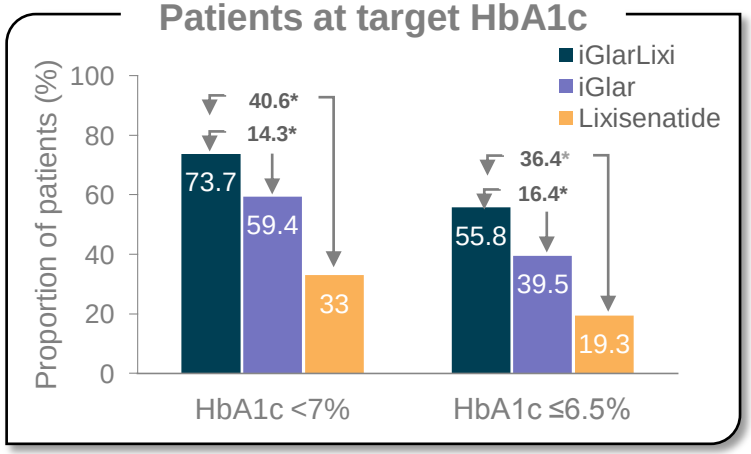
Rosenstock J, et al. Diabetes Care 2016;epub ahead of print: dc160917

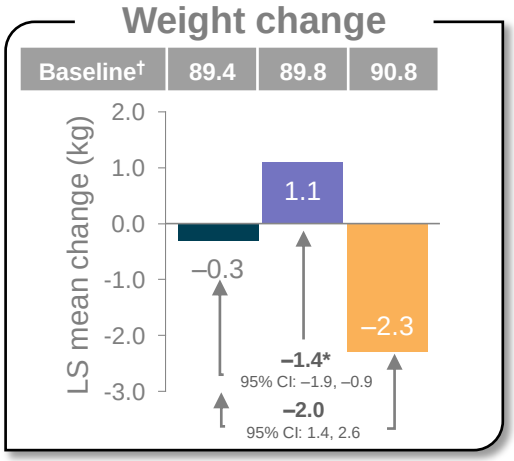
*HbA1c at screening

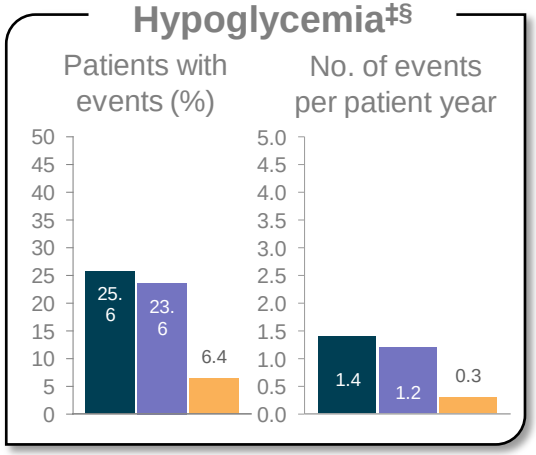
LixiLan-O: Key results







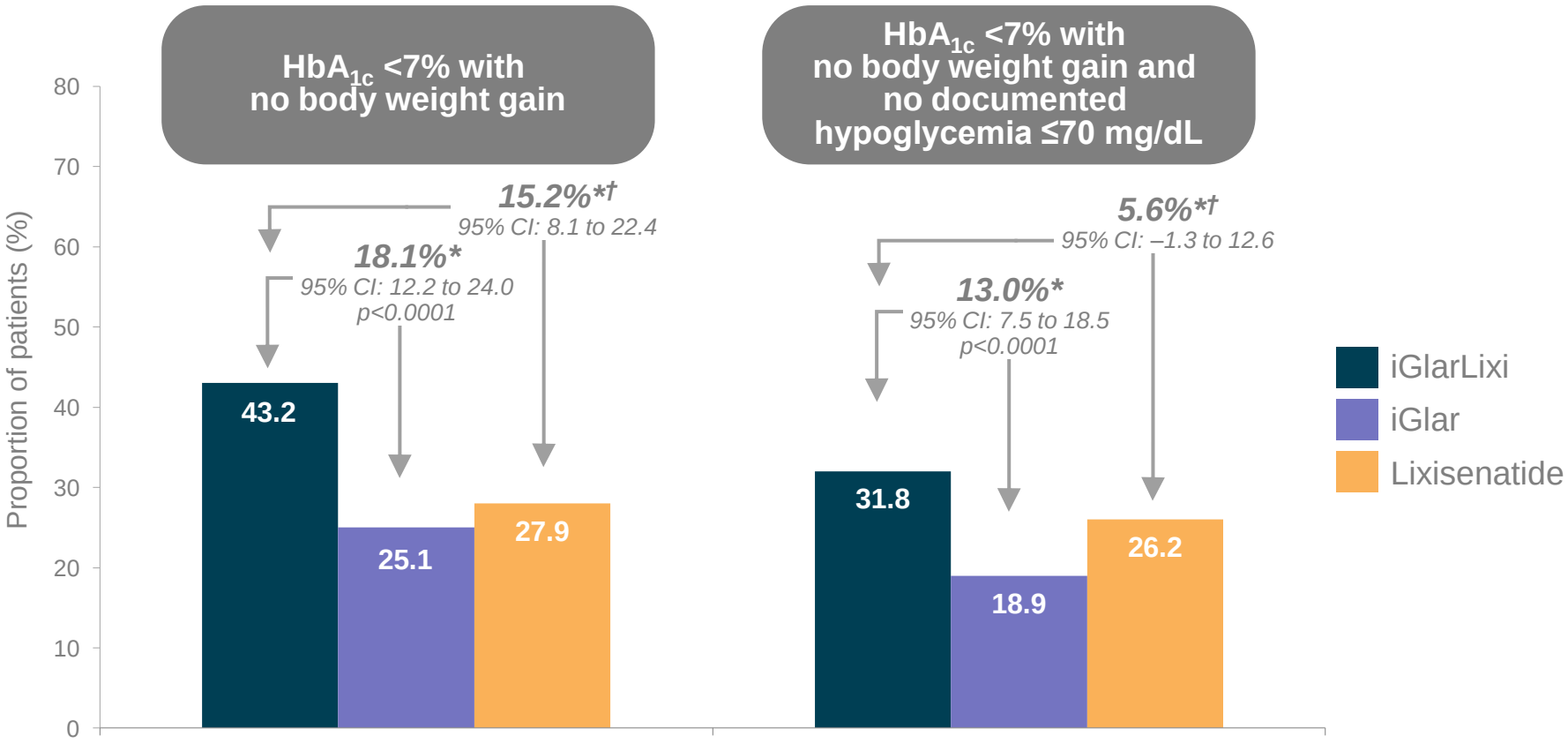




Rosenstock J, et al. Diabetes Care 2016;epub ahead of print: dc160917

*p<0.0001; †Mean body weight (kg) at baseline; ‡Documented symptomatic hypoglycemia, defined as plasma glucose ≤70 mg/dL
§One event of severe hypoglycemia was reported during the study and occurred in the iGlar group

Patients achieving composite endpoints



Rosenstock J, et al. Diabetes Care 2016; epub ahead of print: pii, dc160917

mITT population

*Weighted average of proportion difference between treatment groups

†No p-value available as comparison not specified in step-down testing procedure

Overview of adverse events profile

Patients, n (%), with at least one…	iGlarLixi (n=469)	iGlar (n=467)	Lixisenatide (n=233)
TEAE			
Any	267 (56.9%)	227 (48.6%)	157 (67.4%)
Serious	18 (3.8%)	19 (4.1%)	9 (3.9%)
Leading to Death	2 (0.4%)	3 (0.6%)	1 (0.4%)
Leading to Discontinuation	12 (2.6%)	9 (1.9%)	21 (9%)
GI TEAEs			
Nausea	45 (9.6%)	17 (3.6%)	56 (24.0%)
↳ *discontinuation*	*2 (0.4%)*	*0*	*6 (2.6%)*
Vomiting	15 (3.2%)	7 (1.5%)	15 (6.4%)
↳ *discontinuation*	*2 (0.4%)*	*0*	*4 (1.7%)*
Diarrhea	42 (9.0%)	20 (4.3%)	21 (9.0%)
↳ *discontinuation*	*1 (0.2%)*	*0*	*2 (0.9%)*

Rosenstock J, et al. Diabetes Care 2016; epub ahead of print: pii, dc160917

Safety population
Data analyses are descriptive
TEAE, treatment emergent adverse event

iGlarLixi: Simple therapeutic strategy

- iGlarLixi is administered via a once-daily injection
- iGlarLixi is administered using a redesigned SoloStar® pen
  - This prefilled pen is already widely used with Lantus (iGlar) and patients, PCPs and nurses are familiar with this device
- iGlarLixi is titrated like basal insulin
- iGlarLixi is available in two fixed-ratios for individual patient needs

Dose range: 10 to 40 U of iGlar
(2 U iGlar:1 µg lixisenatide ratio)



Dose range: 30 to 60 U of iGlar
(3 U iGlar:1 µg lixisenatide ratio)



iGlarLixi is not currently available for use in treatment in Hong Kong

Outline

1. Why do we need injectable medications
2. Insulins over the year
3. Other non-insulin injectable medications
4. Over the horizon: New combination injectables
5. Advances in injection device

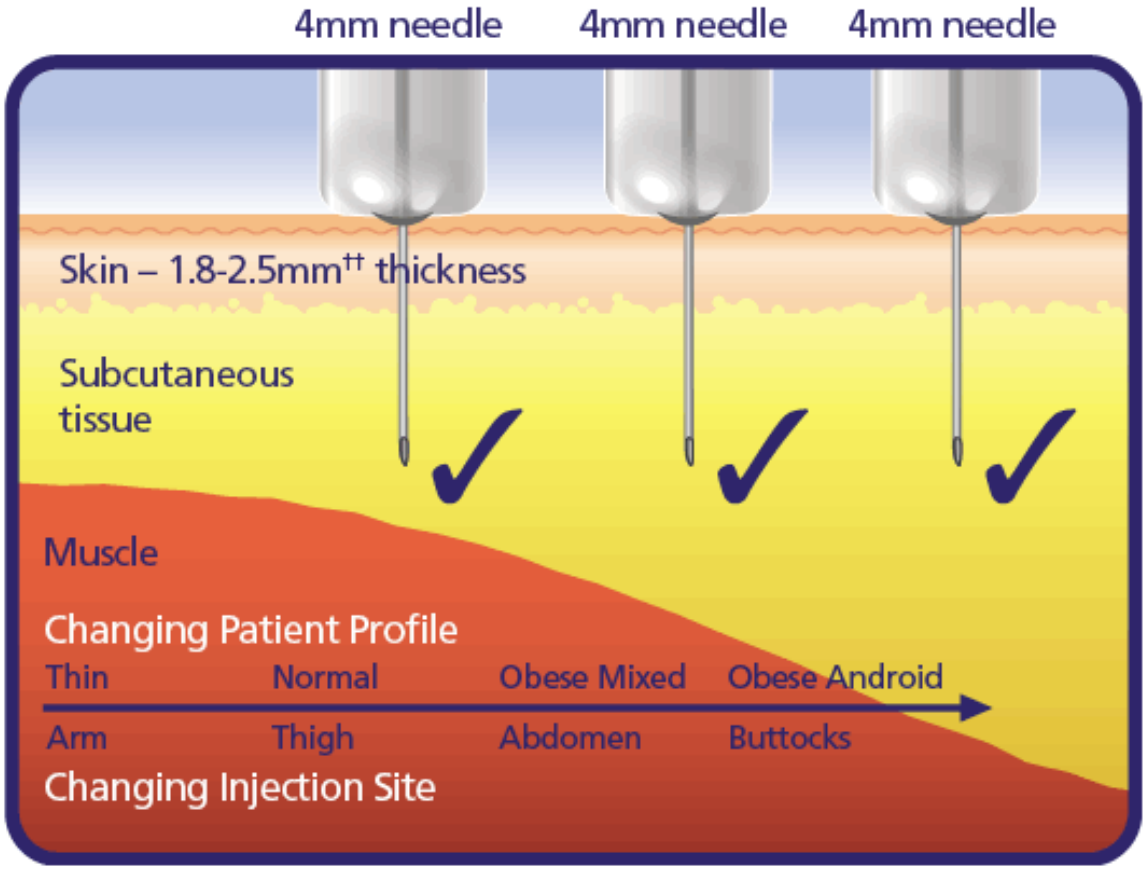
Needles

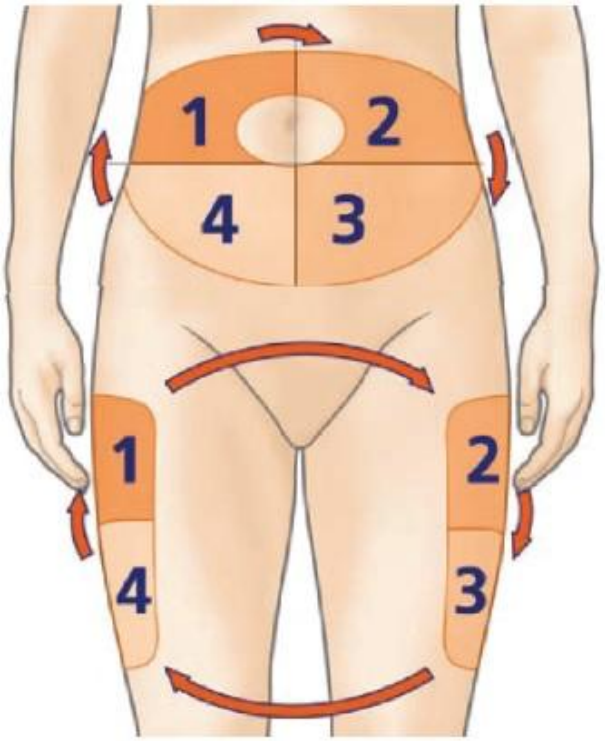
BD (Becton-Dickinson)







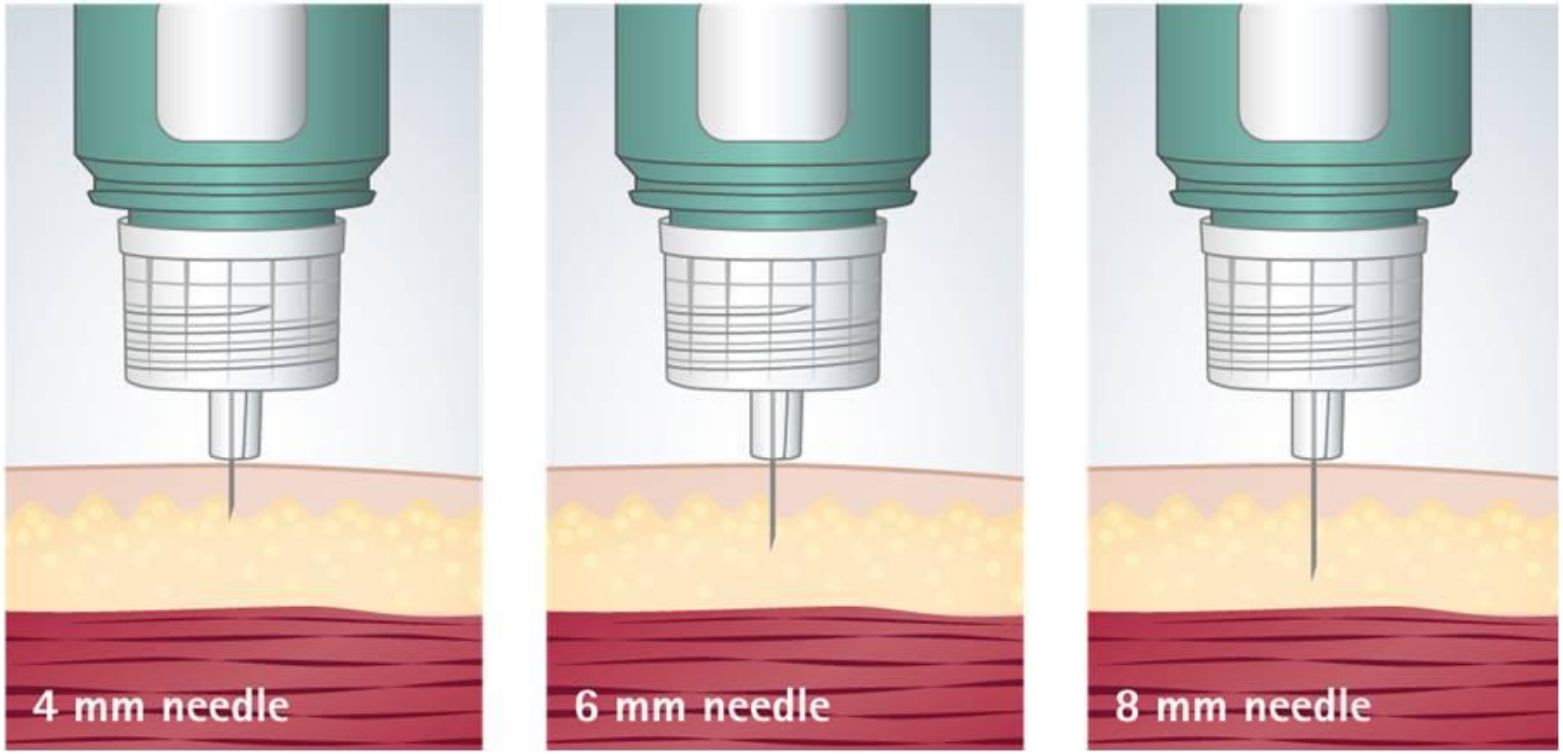




https://www.diabetes.co.uk/images/products/bd-microfine-needle-lengths.gif

The right needle, the perfect technique

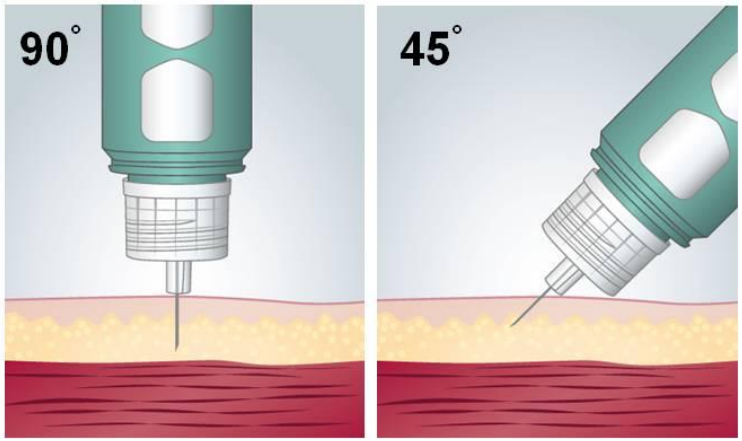
Shorter needles allow for lower pain on injection. [1] Regarding absorption of regular insulin, it is the same whether it is injected into subcutaneous fat deeply or superficially. [2,3] The reason is the fairly constant thickness of skin – regardless of site, age, ethnic background, gender or body mass index. There is no clinical reason for recommending needles longer than 6 mm.



https://www.bbraun.co.uk/en/products-and-therapies/diabetes-care/insulin-injection/needle-length-injection-technique.html

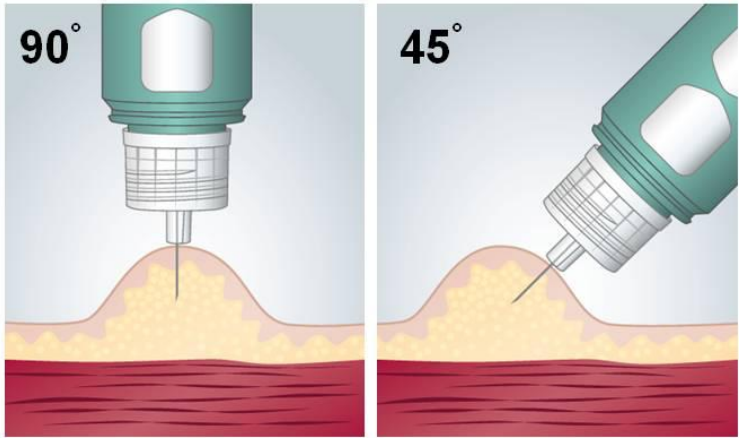
Injection technique

Every patient has to find the best injection technique for themselves. A few parameters, however, may be beneficial. The table below shows which technique is suitable for which individual. And the following tips may also help with the first steps.



Without skin fold

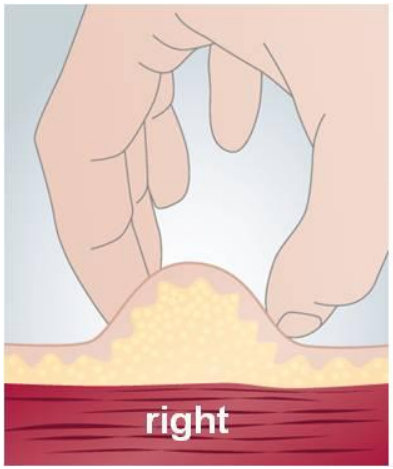
You inject without a skin fold if you use shorter needles between **4 and 6 mm**. For children, needles should never be longer than 4 mm. The insulin should be administered at a 90-degree to the skin surface.



With skin fold

Creating a skin fold is highly recommended for slim individuals and small children (up to six years). Alternatively, insertion at a 45-degree angle is sensible. Both techniques can be combined. The use of a lifted skin fold or injection at a 45-degree angle is suggested whenever a needle **longer than 6 mm** is used.

https://www.bbraun.co.uk/en/products-and-therapies/diabetes-care/insulin-injection/needle-length-injection-technique.html
https://www.bbraun.co.uk/en/products-and-therapies/diabetes-care/insulin-injection/needle-length-injection-technique.html





How to build a skin fold?

Raise a fold of skin between thumb and fingers. Try not to pinch the flesh too tightly. The area in which you inject should be soft and big enough to insert the needle. Do not grasp too much tissue to avoid raising the muscle. The shorter the needle is, the less important a skin fold becomes.

The right needle length and injection technique at a glance

Generally, needle lengths of 4, 5 and 6 mm are suitable for all adult patients. Even with a higher BMI, shorter needles have been shown to be equal in efficacy, safety, and tolerability.

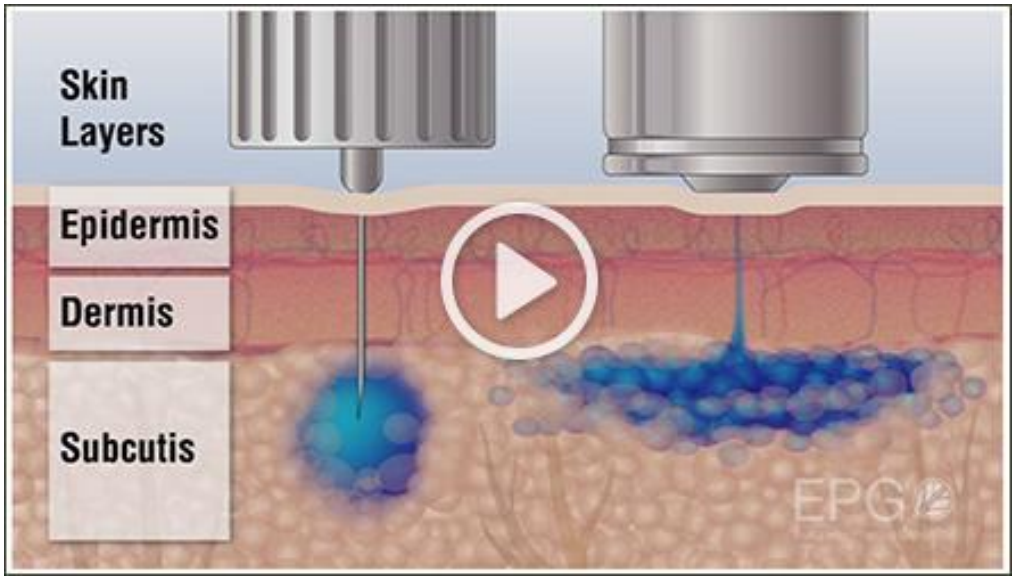
https://www.bbraun.co.uk/en/products-and-therapies/diabetes-care/insulin-injection/needle-length-injection-technique.html

Needle length	Children	Very slim adults	Adults of normal weight	Adults who are overweight or obese
4 mm	90° with or without skinfold	90° with or without skinfold	90° rarely with skinfold	90° without skinfold
5 mm	45° or 90° with skinfold	45° or 90° with skinfold	90° with skinfold	90° without skinfold
6 mm	45° or 90° with skinfold	45° without skinfold or 90° with skinfold	90° with skinfold	90° without skinfold
8 mm		45° with skinfold	45° with skinfold	45° or 90° without skinfold
> 12 mm*			45° with skinfold	45° without skinfold or 90° with or without skinfold

* not generally recommended

https://www.bbraun.co.uk/en/products-and-therapies/diabetes-care/insulin-injection/needle-length-injection-technique.html

InsuJet



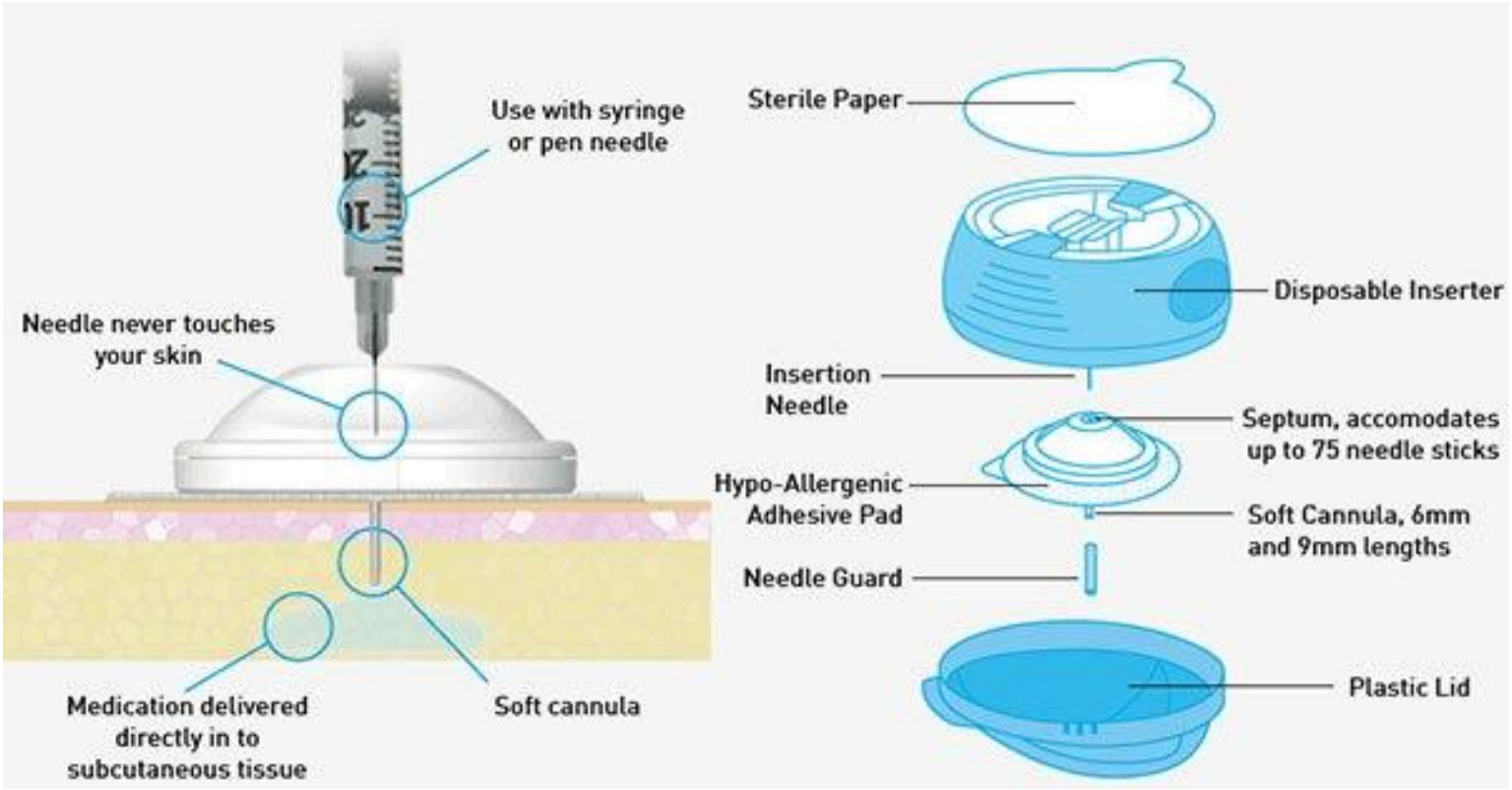
- Very limited evidence for administration of insulin aspart only in less than 20 subjects



i-Port



- Medtronic
- Cleared by the FDA
- Indicated for patients who administer multiple daily subcutaneous injections of physician prescribed medications, including insulin



Closed loop system

SmartGuard™ features:

AUTO MODE‡

- Automatically adjusts your basal (background) insulin every five minutes based on your CGM readings.*,#
- Helps keep your sugar levels in your target range for fewer lows and highs — day and night

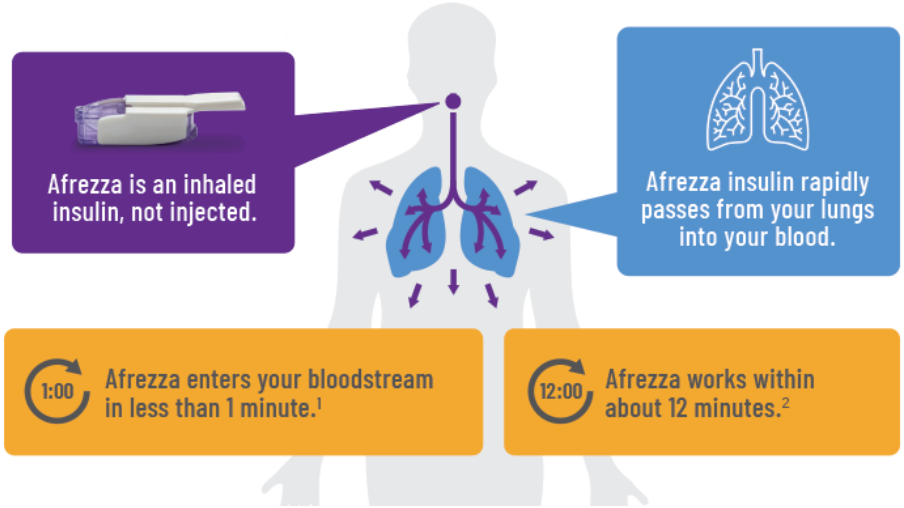
SUSPEND BEFORE LOW§

- Stops insulin up to 30 minutes before reaching your preset low limits.
- Automatically restarts insulin when your levels recover without bothersome alerts.#
- Helps you avoid lows and rebound highs.[1]



Medtronic MiniMed™ 670G hybrid closed loop system has been FDA approved for children with Type 1 diabetes aged 7-13 years (June 21, 2018)

- ultra-rapid-acting insulin peaking 12 to 15 minutes following inhalation and exits your body within 2-3 hrs
- FDA approved for both type 1 and 2 DM on Jun 27, 2014
- Contraindicated in COPD, asthma, active or immediate ex-smokers (quit < 6 months)
- Sales poor, stocks price down





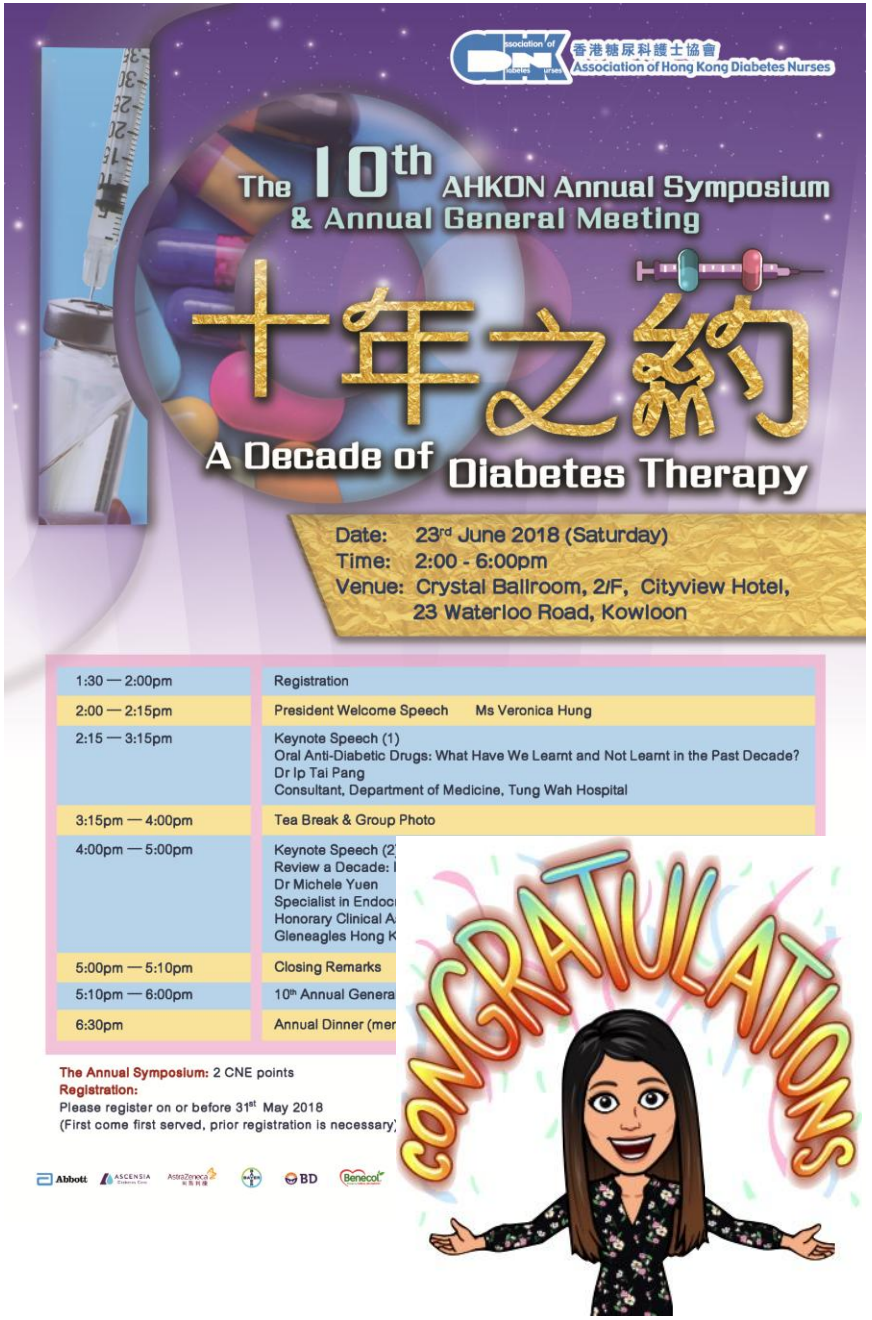
afrezza® (insulin human) Inhalation Powder

Injected Mealtime Insulin Dose	AFREZZA® Dose	# of **4 unit** (blue) cartridges needed	# of **8 unit** (green) cartridges needed
up to **4** units	**4** units		
5-8 units	**8** units		
9-12 units	**12** units	+	
13-16 units	**16** units		
17-20 units	**20** units	+	
21-24 units	**24** units		

Take home message

- Diabetes is still a dynamic field especially in the past decade.
- Many new technology emerging and will be guiding further development
- Main aim is to minimize treatment side effects, ensure stable drug delivery and improve patient comfort and compliance





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Honorary Clinical Assistant Professor, the University of Hong Kong
Director, Weight Management Centre, Gleneagles Hospital, Hong Kong
Founding President, Hong Kong Obesity Society (Medical Chapter)