Pharmacological Intervention for Diabetes

Dr Jason Ng

Associate Consultant

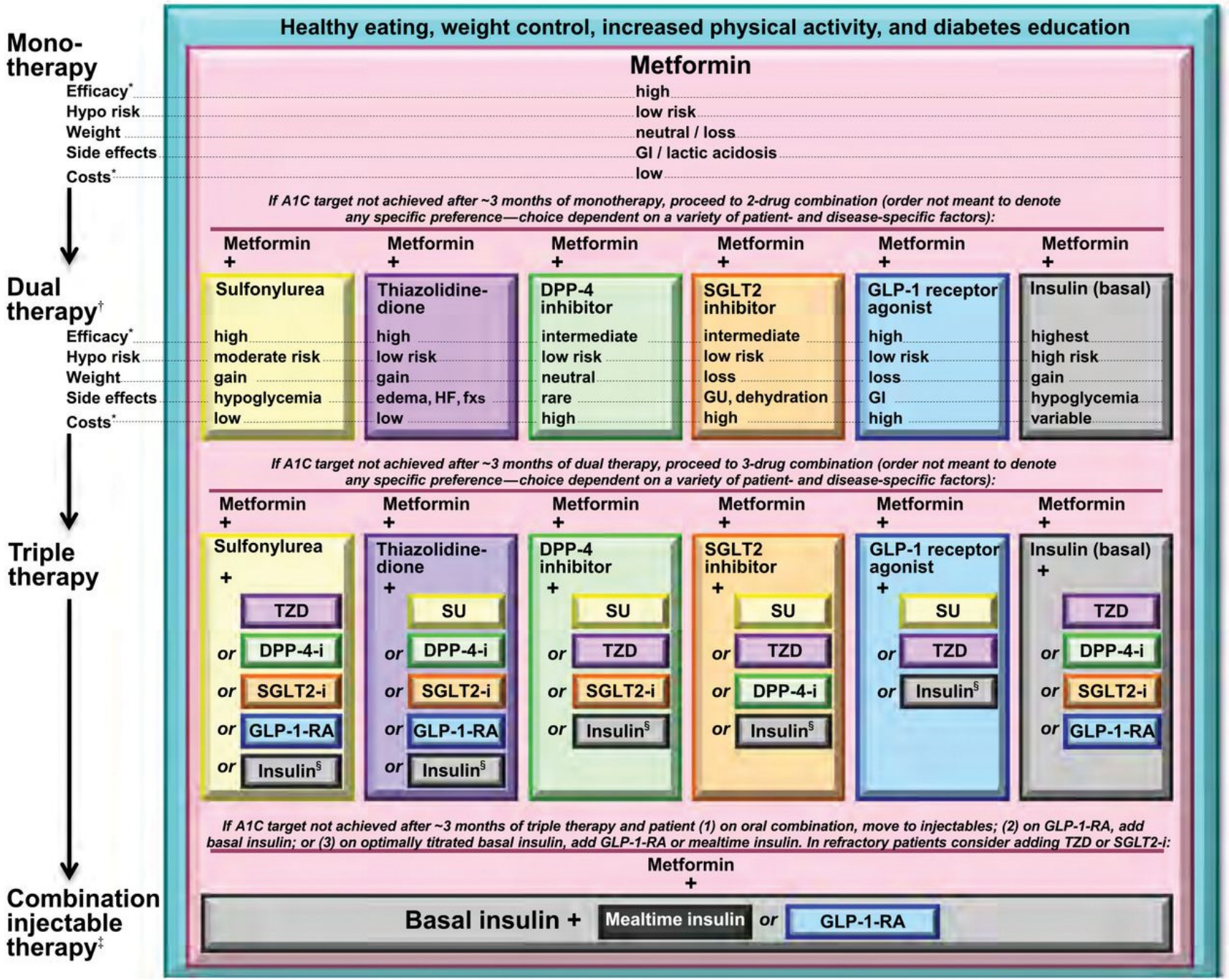
Endocrine Team, Queen Elizabeth Hospital

15th Nov 2018

DM medications

(a) Reduce insulin resistance (insulin sensitizers), including metformin and the thiazolidinediones (TZD);
(b) Stimulate endogenous insulin secretion (insulin secretagogues, including sulfonylureas and meglitinides) or supply exogenous insulin to the body (different insulin formulations);
(c) Target at the incretin pathway including glucagon-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP_4) inhibitors;
(d) Those that modulate food absorption such as α-glucosidase Inhibitors.
(e) Promote renal glucose excretion such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

HAHO Clinical Practice Guideline for Management of Type 2 Diabetes 2016


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral / loss
Side effects GI / lactic acidosis
Costs* low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~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- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

PROFILES OF ANTIDIABETIC MEDICATIONS

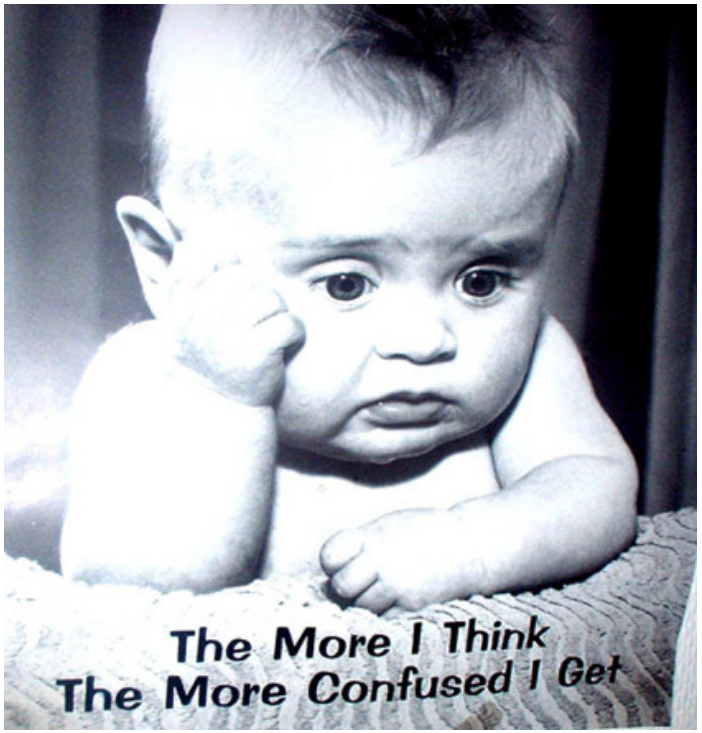
	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contraindicated if eGFR < 30 mL/min/1.73 m²	Exenatide Not Indicated CrCl < 30 / Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/min/1.73 m² / Genital Mycotic Infections / Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF / CARDIAC* / ASCVD	Neutral	Possible Benefit of Liraglutide / Possible CV Benefit	Possible Benefit of Empagliflozin / Possible CV Benefit	Possible Risk for Saxagliptin and Alogliptin / Neutral	Neutral	Moderate / May Reduce Stroke Risk	More CHF Risk / ?	Neutral / Benefit	Neutral / Safe	More CHF Risk / Neutral	Neutral
BONE	Neutral	Neutral	Canagliflozin Warning	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Occurring in T2D in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect | * FDA indication to prevent CVD death in diabetes plus prior CVD events

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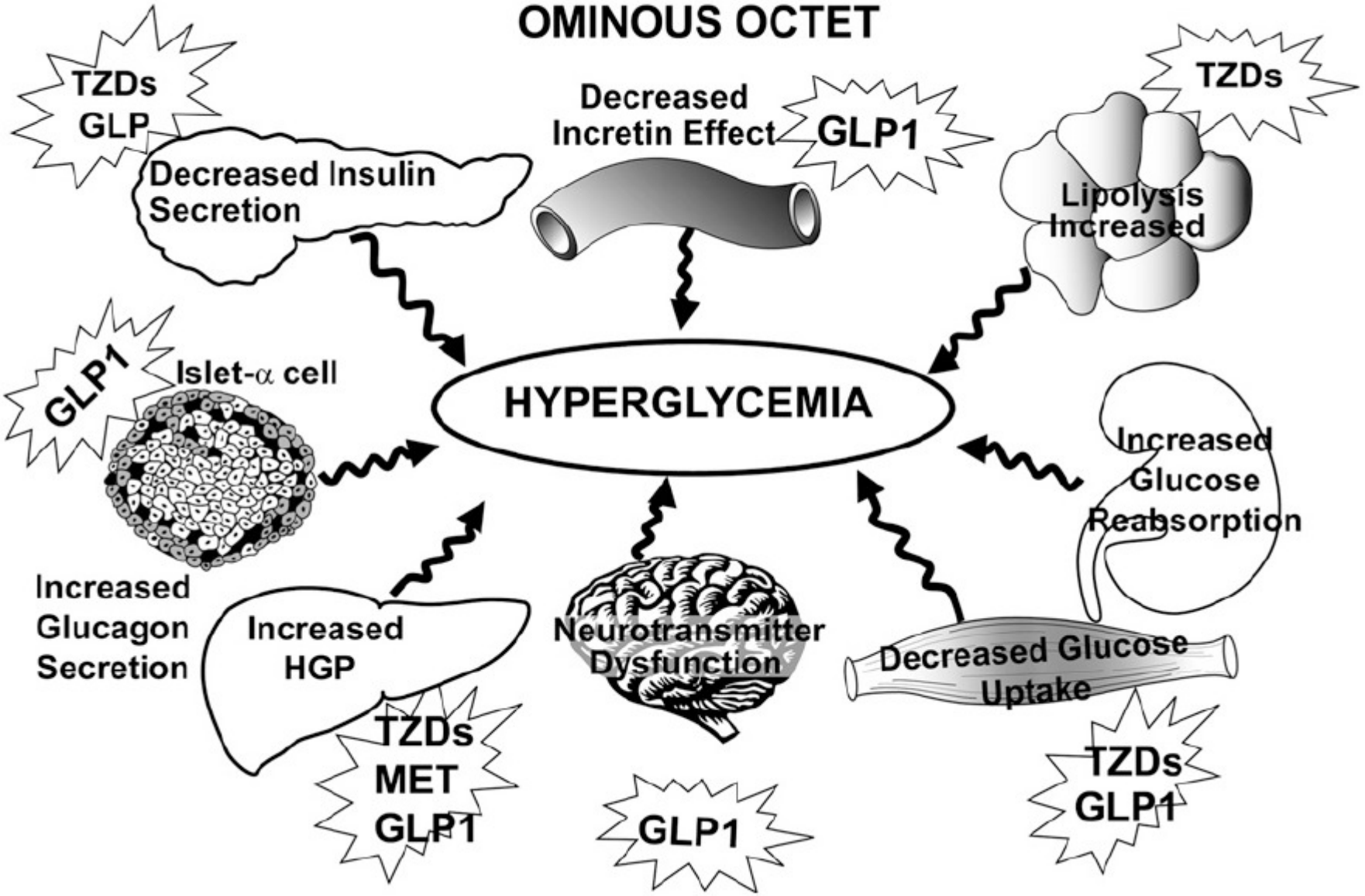

BOOOORING !!!


The More I Think
The More Confused I Get

PPP

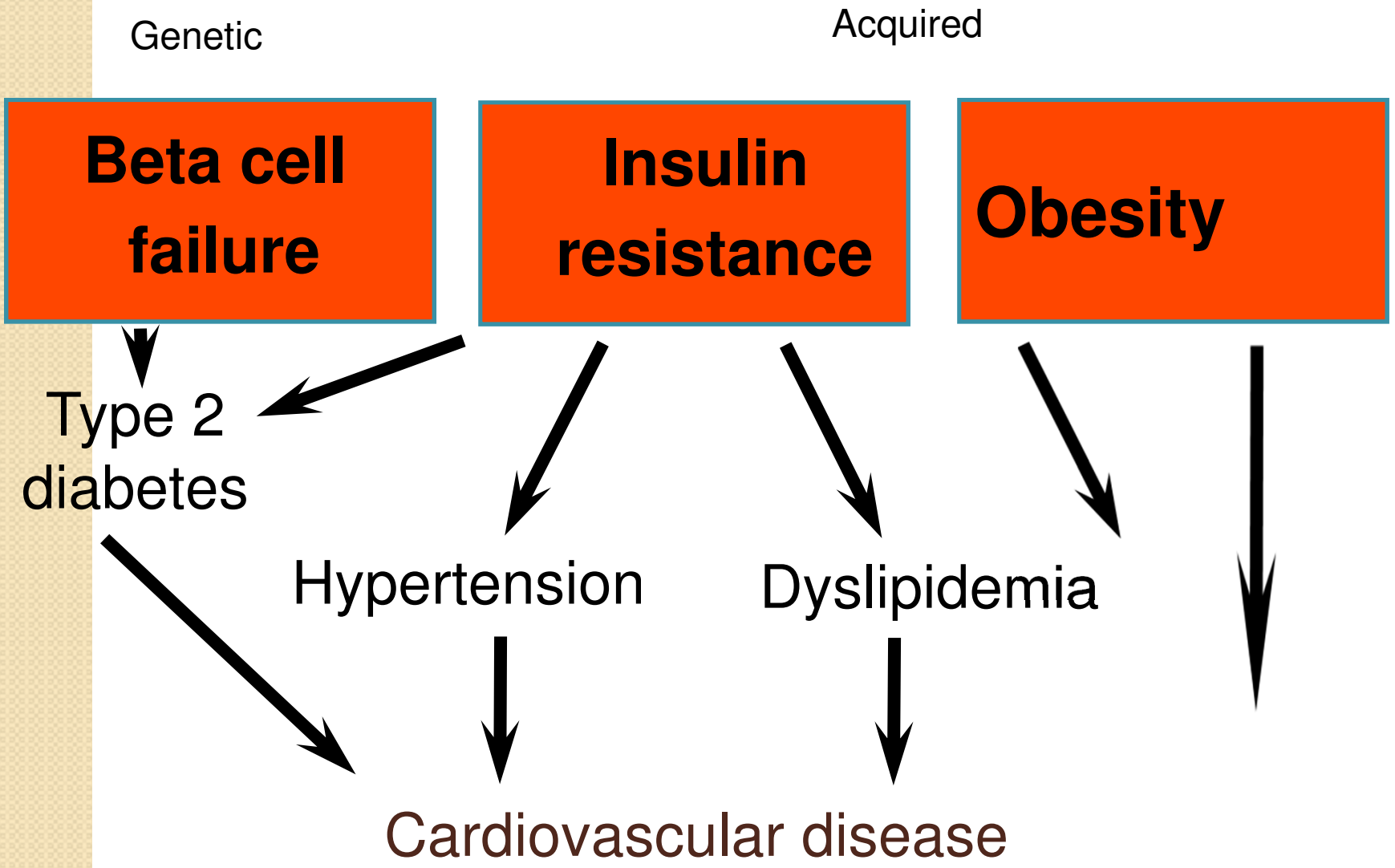
- Pharmacological properties
- Practical tips
- Pitfall

Pathophysiologic approach to therapy in T2DM



DIABETES CARE, VOLUME 36, SUPPLEMENT 2, AUGUST 2013

Pathogenesis of type 2 DM



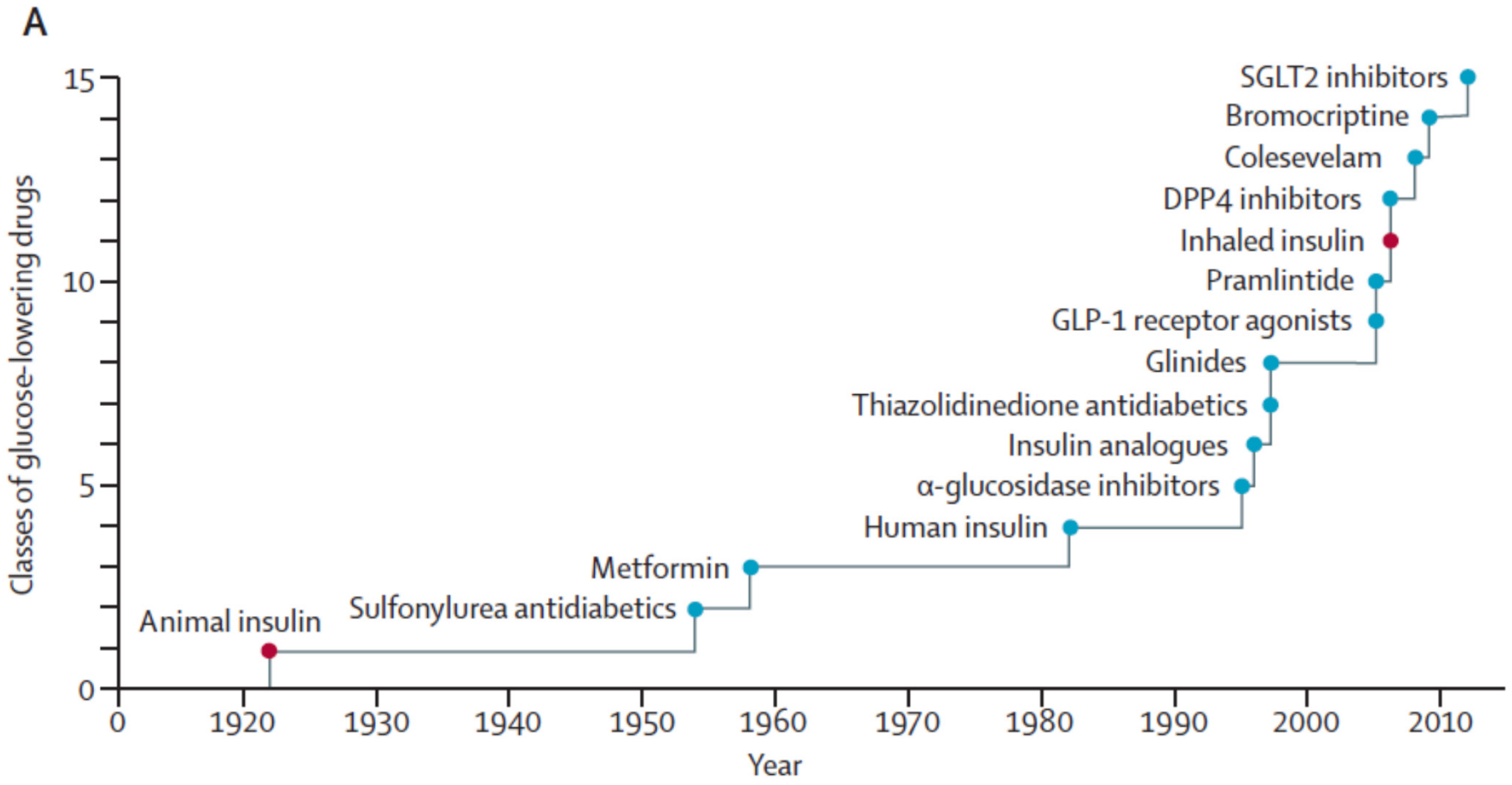
Classification of OHA

- Insulin secretalogues
- Insulin sensitizers
- Others

Classification of OHA

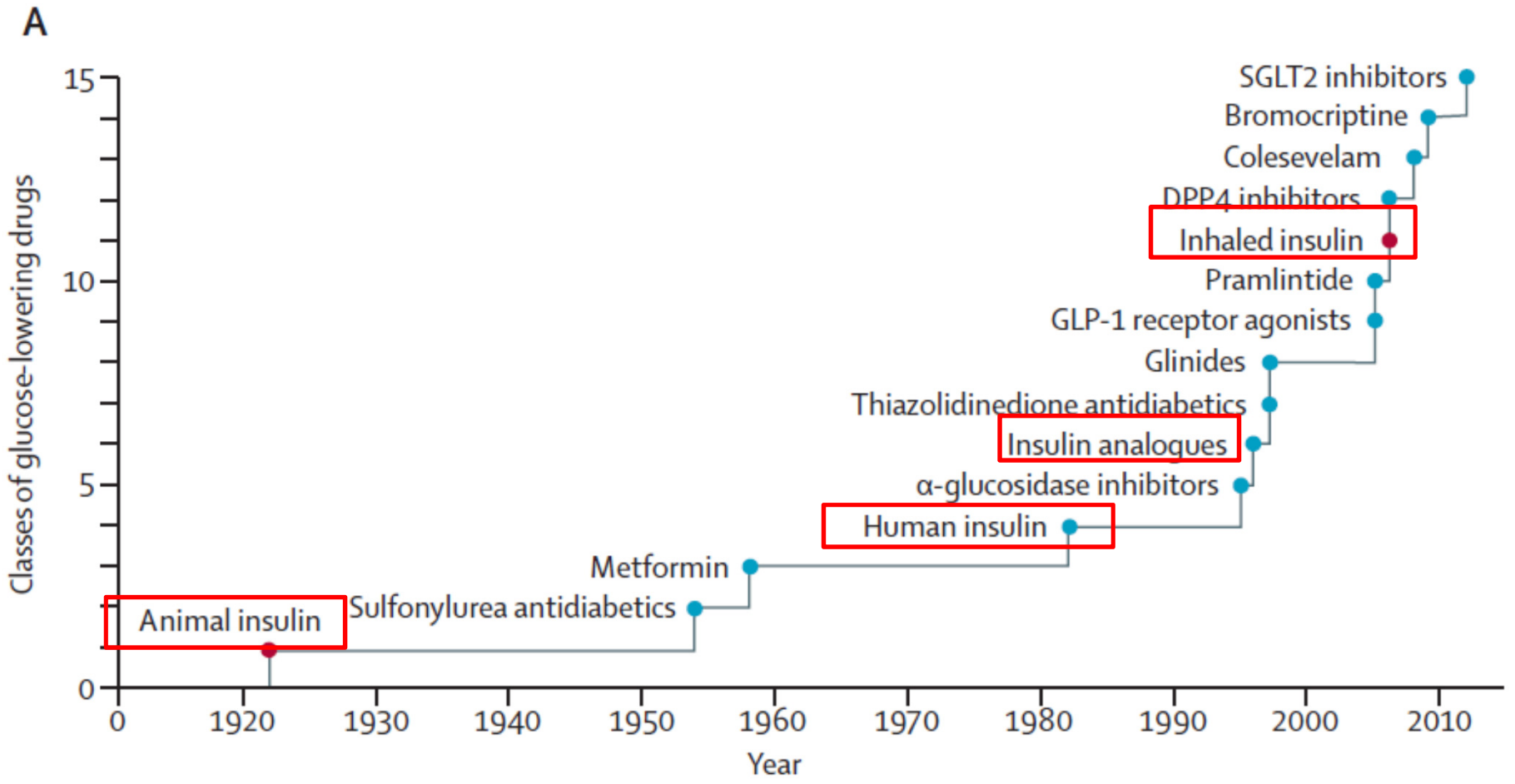
- Insulin secretalogues e.g. Diamicron
- Insulin sensitizers e.g. Metformin
- Others e.g. Acarbose

Breakthrough in DM Drug Development



Insulin

Breakthrough in DM Drug Development



Discovery of insulin

- DM
  - lethal disease before discovery of insulin 19th century
  - Strict diet
  - Eventually died few years later with starvation
- Deceased DM patient have damaged pancreas



- 1869 German student
  - Paul Langerhans
  - pancreas secrete digestive juices
    - clusters of cells of unknown function
    - later shown insulin-producing beta cells
    - named ‘islet cells of Langerhans’



- In 1889 Germany
- Physiologists
  - Oskar Minkowski
- Physician
  - Joseph von Mering

- 1) Removal of pancreas from a dog
  - diabetes
- 2) Ligation of the duct
  - pancreatic juices couldn't reach the intestine
  - developed minor digestive problems
  - but no diabetes

Pancreas

- 1890
- At least two functions
  - To produce:
    - digestive juices
    - a substance that regulates the sugar glucose

Development was slow until 1921…

- Toronto, Canada
- Dr Frederick Banting, surgeon
  - Ligate the pancreatic duct to shrink the cells that produce digestive juices
  - then can extract those cells with anti-diabetic function without harming the pancreas
- Professor John Macleod at the University of Toronto
  - a leading figure in the study of diabetes in Canada

Experiments on 10 dogs

- Lab with basic equipment
- 10 dogs
- 1 Medical student, Charles Best



Banting, right, and Best, left, with one of the diabetic dogs used in experiments with insulin.
Credits: University of Toronto Archives

Charles & Best

- Remove the pancreas from a dog
  - blood sugar rose
  - became thirsty, drank lots of water, and urinated more often (polyuria, polydipsia)
  - became weaker and weaker

Charles & Best



- another dog
  - Surgically ligated the pancreas
  - stopping the flow of nourishment, so that the pancreas degenerated
  - removed the pancreas, sliced it up, and froze the pieces in a mixture of water and salts
  - half frozen, ground up and filtered
  - = isolated substance was named "isletin."

Who was the first patient receiving insulin?

The first patient treated with insulin

- **The Banting & Best experiment, 1921**
  - Ligated the pancreatic duct inducing digestive cell necrosis
  - Homogenized and filtered the remaining parts of pancreas
  - Kept the pancreatectomized dog, Marjorie, alive several months by injections of the isolated substance "isletin"

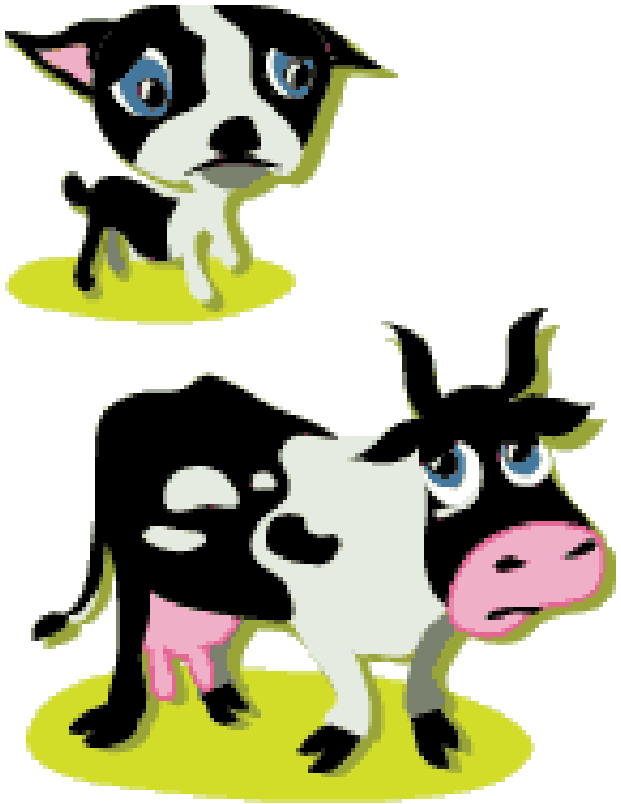


Best, Banting, and one of the dogs

Banting FG, Best CH, Macleod JJR. *Am J Physiol*. 1922;59:479.

Extension of tests

- ox



Biochemist Bertram Collip

- purify the insulin
- clean enough for testing on humans

Testing on humans?

- Banting and Best inject extract to themselves
  - Weak
  - Still okay
- Titrate dosage of isletin and glucose
- Treated with glucose -orange juice and honey



volunteer

- January 1922 in Toronto, Canada
- 14-year-old boy, Leonard Thompson
  - first person with diabetes to receive insulin
  - near death
  - rapidly regained his strength and appetite after injection
  - more and more volunteers
  - Dying DKA children, comatose patients
    - Awaken!

The first (human) patient treated with insulin

Leonard Thompson
(1908 – 1935)

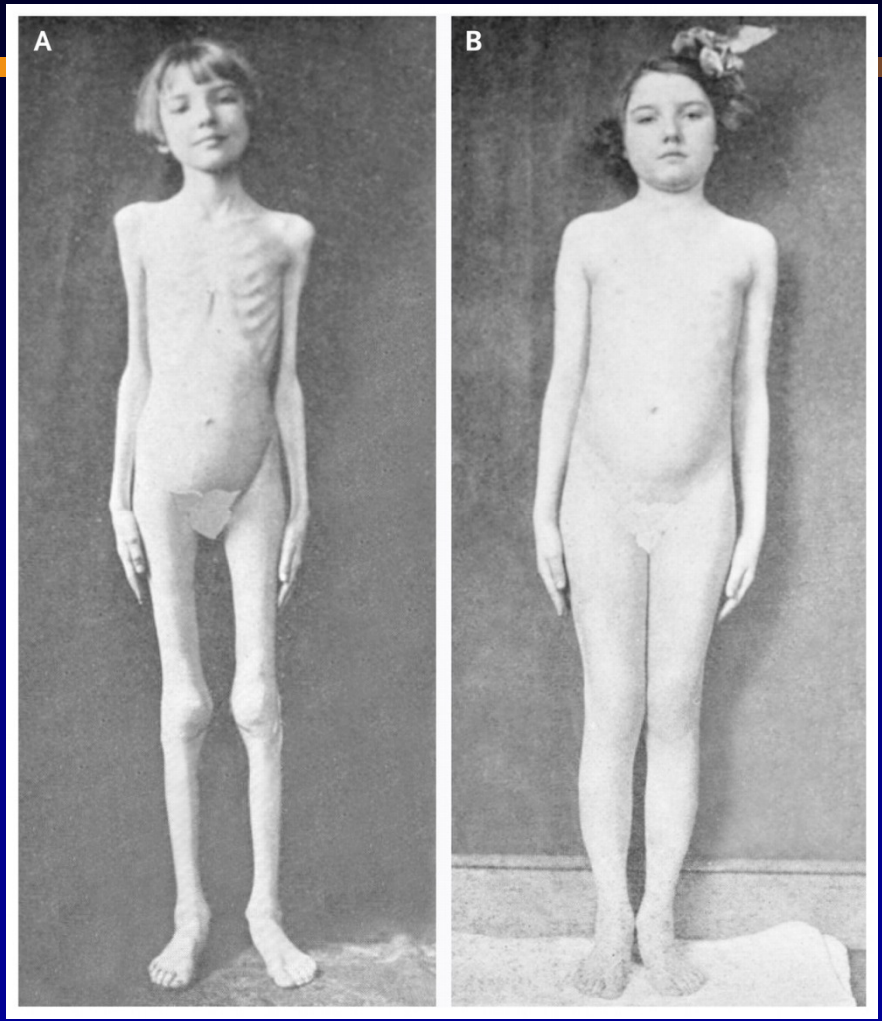
Dying from diabetes, he was the first human to get the extract in January 1922

Survived until the age of 27.



Banting FG, Best CH, Macleod JJR. *Am J Physiol*. 1922:59:479.

Effects of Insulin Therapy.



Polonsky KS. N Engl J Med 2012;367:1332-1340.

The NEW ENGLAND JOURNAL of MEDICINE



Nobel prize 1923

- Banting & Macleod



Insulin therapy – key developments

1920s
Discovery of insulin and insulin replacement therapy

1923
Lilly marketed insulin derived from crude extracts of the pancreas gland of pigs and cows

1982
Genetically engineered human insulin developed

1995
First rapid-acting insulin analogue (lispro) developed

Today
There are many different insulins available, with a range of time-action profiles

http://www.trumanlibrary.org/histday/insulin/eli-lilly-and-company.html. Accessed Nov 7 2011.
http://www.nobelprize.org/educational/medicine/insulin/discovery-insulin.html. Accessed Nov 7 2011.

B

Terms

- HM = produced through biotech
  - Actrapid HM – human insulin
- MC = insulin is of animal origin

- ACTRAPID
- ACT RAPID
- NOT RAPID ENOUGH
- NOT SLOW ENOUGH

Intermediate acting insulin



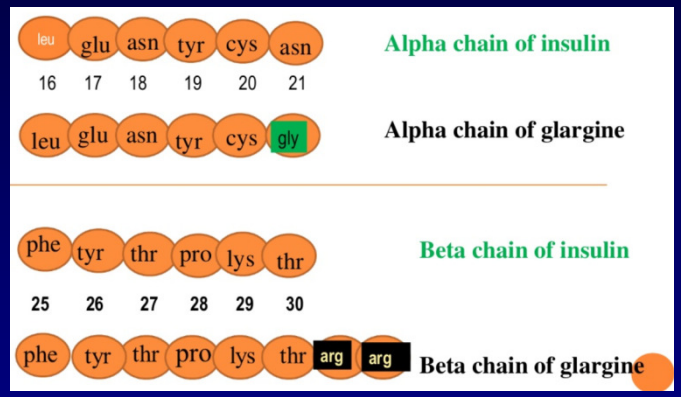
- **NPH** (neutral protamine Hagedorn) **insulin**, also known as **isophane insulin**
- Hans Christian Hagedorn mixed insulin with a basic protein
  - iso-electric point closer to the neutral pH and prolong its action
- **Protamine**
  - derived from semen of rainbow trout



- Later on, addition of zinc led to a stable compound with a prolonged duration of action

Glargine

Chemistry



Modifies the isoelectric point of the protein

→ decreases solubility at physiologic pH

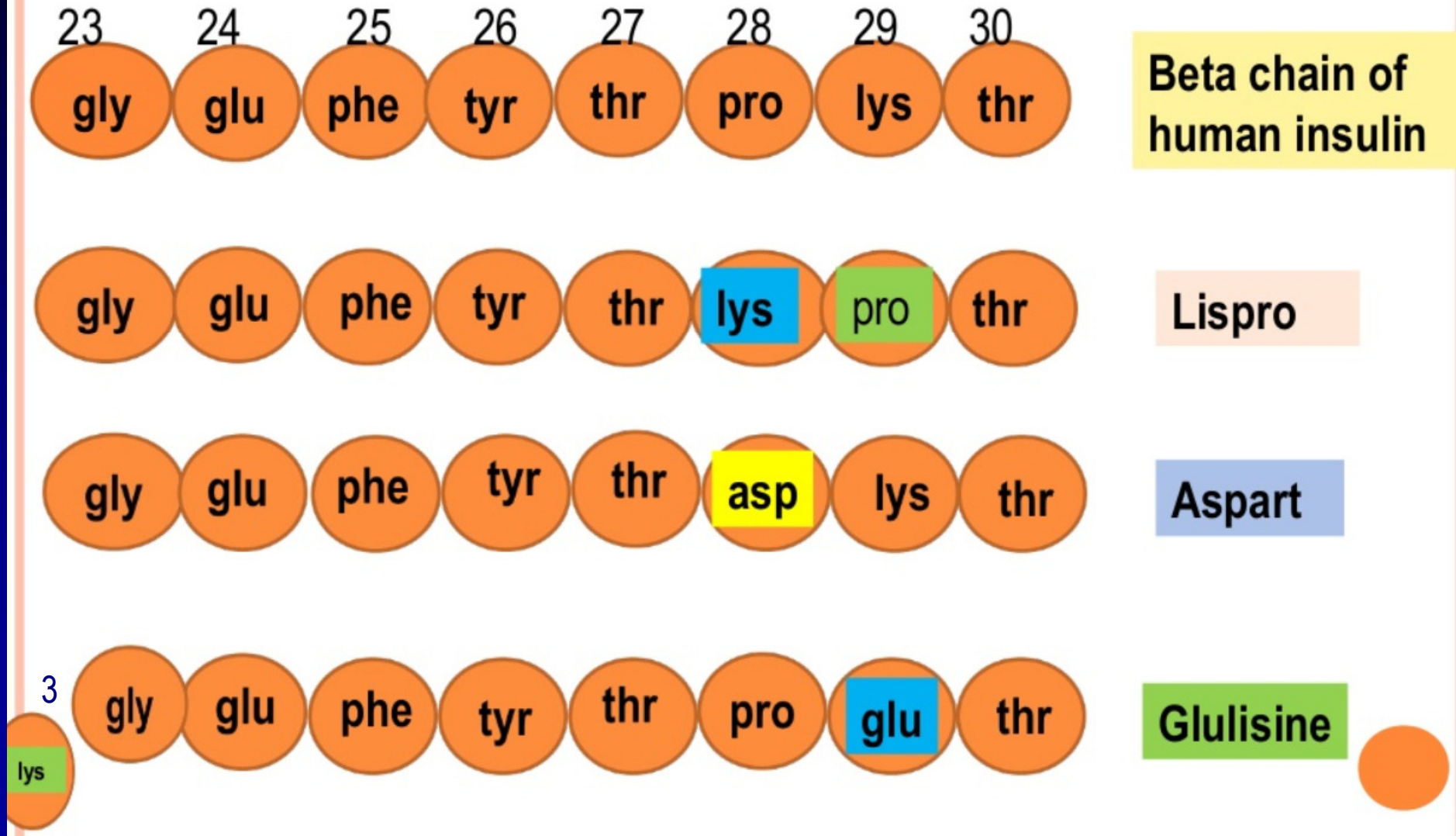
→ precipitates in the subcutaneous tissue

→ delays the absorption

Profile

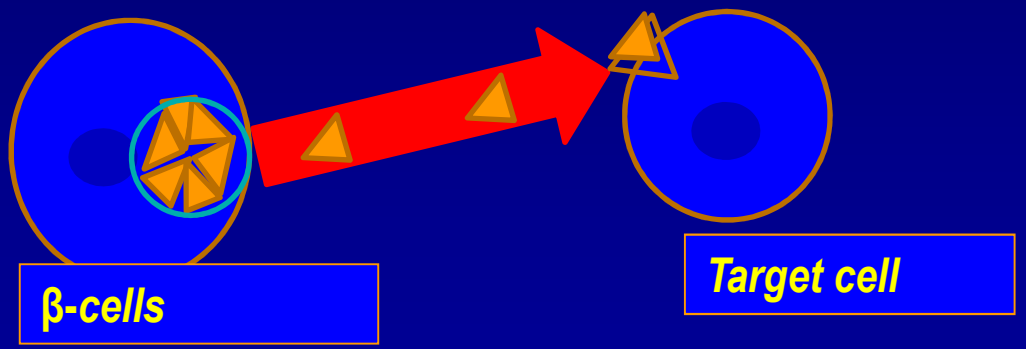
- Flatter PK/PD profile
- Longer duration
- Less variability

LISPRO , ASPART & GLULISINE



Insulin forms

- **Hexamers** are composed of 6 monomers
  - storage form in the β-cell (high concentration)
- **Monomers**
  - Insulin active form, circulates in the blood and binds to the target cell receptor



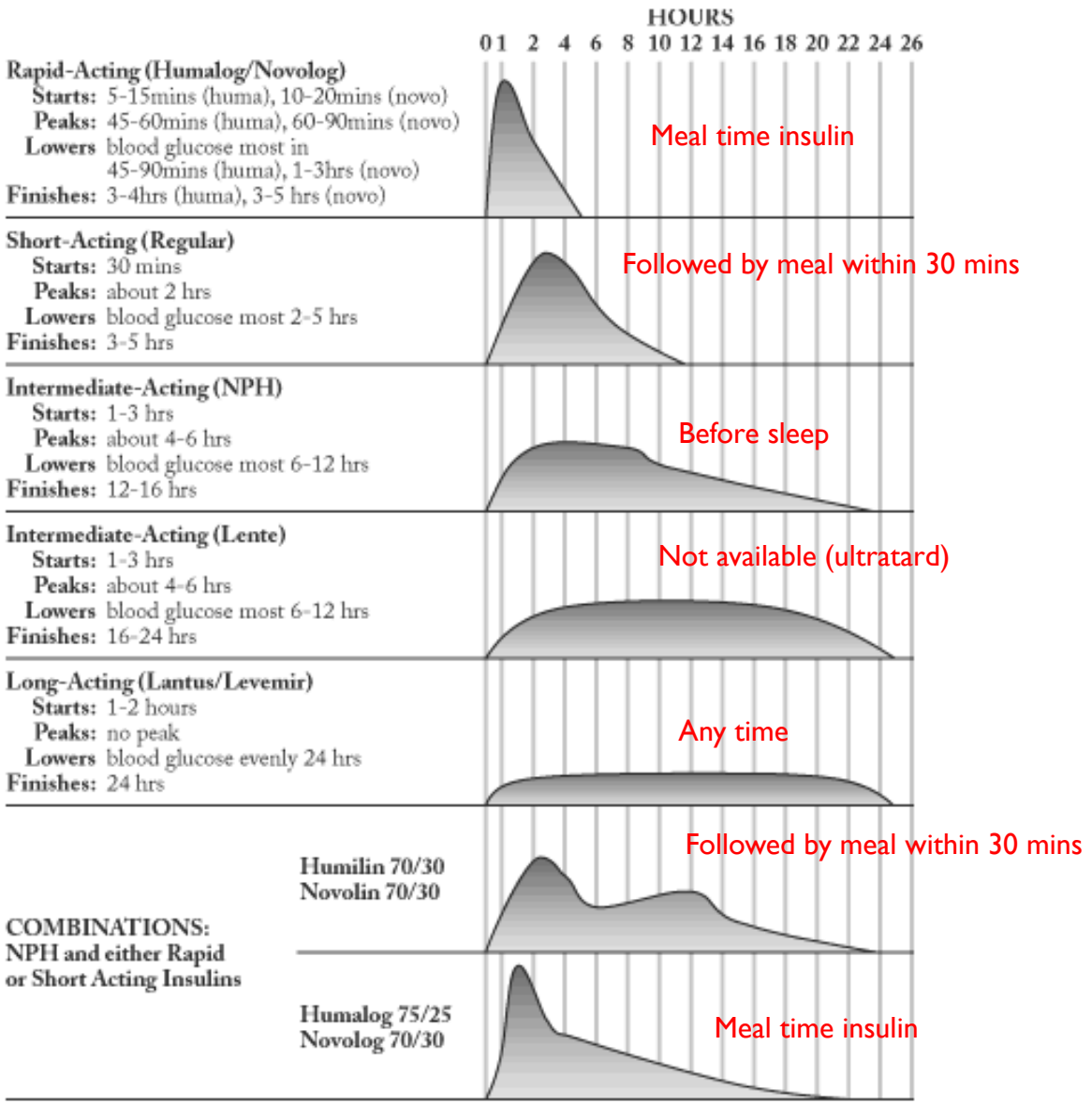
Bilous R & Donnelly R.
Handbook of Diabetes.
Wiley-Blackwell 4th ed.

Insulin Effectiveness by Type

Type	Onset	Peaks	Duration
Rapid Acting			
Humalog (Lispro)	<15 min.	30-90 min.	<5 hrs.
Novolog (Aspart)	10-20 min.	1-3 hrs.	3-5 hrs.
Apidra (Glulisine)	10-15 min.	.5-1.5 hrs.	<3 hrs.
Regular (R)			
Humulin R	30-60 min.	2-3 hrs.	4-6 hrs.
Novolin R	30 min.	2.5-5 hrs.	8 hrs.
actrapid			
NPH			
Humulin N	2-4 hrs.	4-10 hrs.	14-18 hrs.
Novolin N*	90 min.	4-12 hrs.	up to 24 hrs.
protaphane			
Pre-Mixed			
Humalog 75/25	15 min.	1-6.5 hrs.	18-26 hrs.
Humulin 70/30	15-30 min.	2-12 hrs.	18-24 hrs.
Novolin 70/30	30 min.	2-12 hrs.	up to 24 hrs.
Humulin 50/50	15-30 min.	2-12 hrs.	18-24 hrs.
NovoLogMix 70/30	10-20 min.	1-4 hrs.	up to 24 hrs.
Mixtard 70/30			
Peakless Basal			
Lantus (Glargine)	1-4 hrs.	minimal	24 hrs.
Levemir (Detemir)	1-4 hrs.	minimal	up to 24 hrs.

Toujeo (lantus 300u/ml)

Degludec (long levemir) 30-90mins minimal 42hours


HOURS
0 1 2 4 6 8 10 12 14 16 18 20 22 24 26
Rapid-Acting (Humalog/Novolog)
Starts: 5-15mins (huma), 10-20mins (novo)
Peaks: 45-60mins (huma), 60-90mins (novo)
Lowers blood glucose most in 45-90mins (huma), 1-3hrs (novo)
Finishes: 3-4hrs (huma), 3-5 hrs (novo)
Meal time insulin
Short-Acting (Regular)
Starts: 30 mins
Peaks: about 2 hrs
Lowers blood glucose most 2-5 hrs
Finishes: 3-5 hrs
Followed by meal within 30 mins
Intermediate-Acting (NPH)
Starts: 1-3 hrs
Peaks: about 4-6 hrs
Lowers blood glucose most 6-12 hrs
Finishes: 12-16 hrs
Before sleep
Intermediate-Acting (Lente)
Starts: 1-3 hrs
Peaks: about 4-6 hrs
Lowers blood glucose most 6-12 hrs
Finishes: 16-24 hrs
Not available (ultratard)
Long-Acting (Lantus/Levemir)
Starts: 1-2 hours
Peaks: no peak
Lowers blood glucose evenly 24 hrs
Finishes: 24 hrs
Any time
COMBINATIONS:
NPH and either Rapid or Short Acting Insulins
Humilin 70/30
Novolin 70/30
Followed by meal within 30 mins
Humalog 75/25
Novolog 70/30
Meal time insulin

Side effect of Insulin

- Endocrine
  - Hypoglycemia , weight gain
- Ocular
  - bilateral presyopia
  - due to changes in the osmotic equilibrium between the lens and the ocular fluids, and is usually self-limited
- Dermatology
  - lipohypertrophy
- Immulogic
  - Antibodies
- Cardivascular
  - Atherogenic
  - HT
  - increase HR due to hypoglycemia





Inhaled Insulin



- A rapid-acting insulin
  - administered prior to meals or within 20 minutes of starting a meal
- Not a substitute for long-acting insulin
- Must be used in combination with long-acting insulin in type 1 DM

Inhaled insulin

- Not recommended for
  - tx of DKA or in smokers or who have chronic lung disease
- ? Risk of lung cancer
  - Greater lung exposure to inhaled insulin than injection
  - Increased insulin receptor expression and sensitivity to insulin's mitogenic effect over that of normal bronchial epithelium

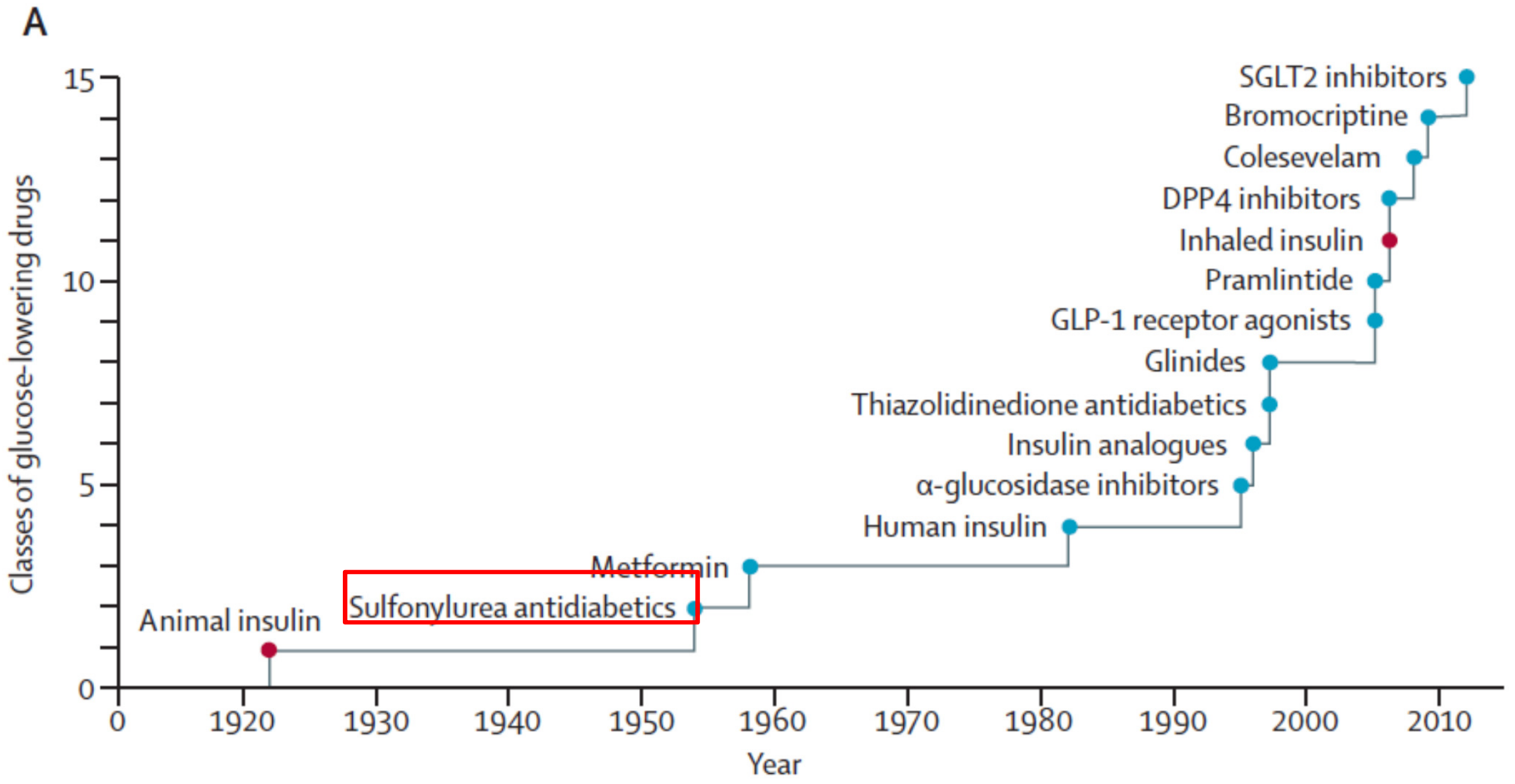
Practical tips

- Insulin
  - Type 1, GDM
  - Type 2, Failed OHA
    - Combination therapy
      - Stop SU if total daily dose >30units
      - Continue insulin sensitizer
      - Stop TZD/ DDPIV-I if A1c not able to improve to <8% in 6-8 months

Practical tips

- Adjust long acting insulin
  - Fasting h'stix
- Adjust short acting insulin
  - Post prandial insulin

Breakthrough in DM Drug Development



Insulin secretalogues

Sulphonylurea

Non-sulphonylurea- metiglinide

- Sulphonylurea
  - Tolbutamide
  - Minidiab – glipizide
  - Diamicron - gliclazide
  - Diamicron MR
  - Daonil - glibenclamide
  - Amaryl – glimepiride

Sulphonylurea discovery



- Accidental
- 1942, WWII
- Food shortage
- eat raw food or contaminated food
- Infectious disease clinic of Medical School in Montpellier, France
- French physician, Janbon
  - Sulphonamide – to treat typhoid fever
  - Hypoglycemia with seizure, even coma
    - Especially in undernourished patient

Janbon

- Give Sulphonamide to
  - Normal dog
    - Hypoglycemia
  - Dog with pancreatectomy
    - No hypoglycemia
- Perfuse Sulphonamide to the pancreas of normal dog
  - Hypoglycemia

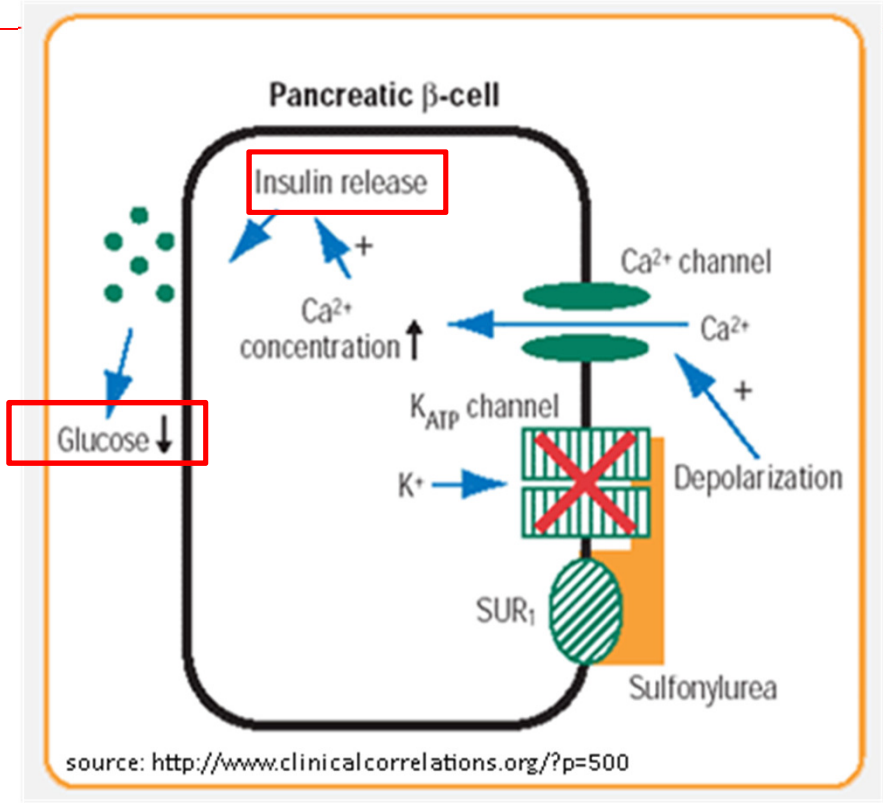
Sulphonylurea

- Major target of the sulphonamide
- Causing release of insulin

- Sulphonylurea was developed based on this finding

- In 1956, the first sulfonylurea, tolbutamide, was introduced commercially in Germany

increase insulin release to lower glucose - HYPOGLYCEMIA



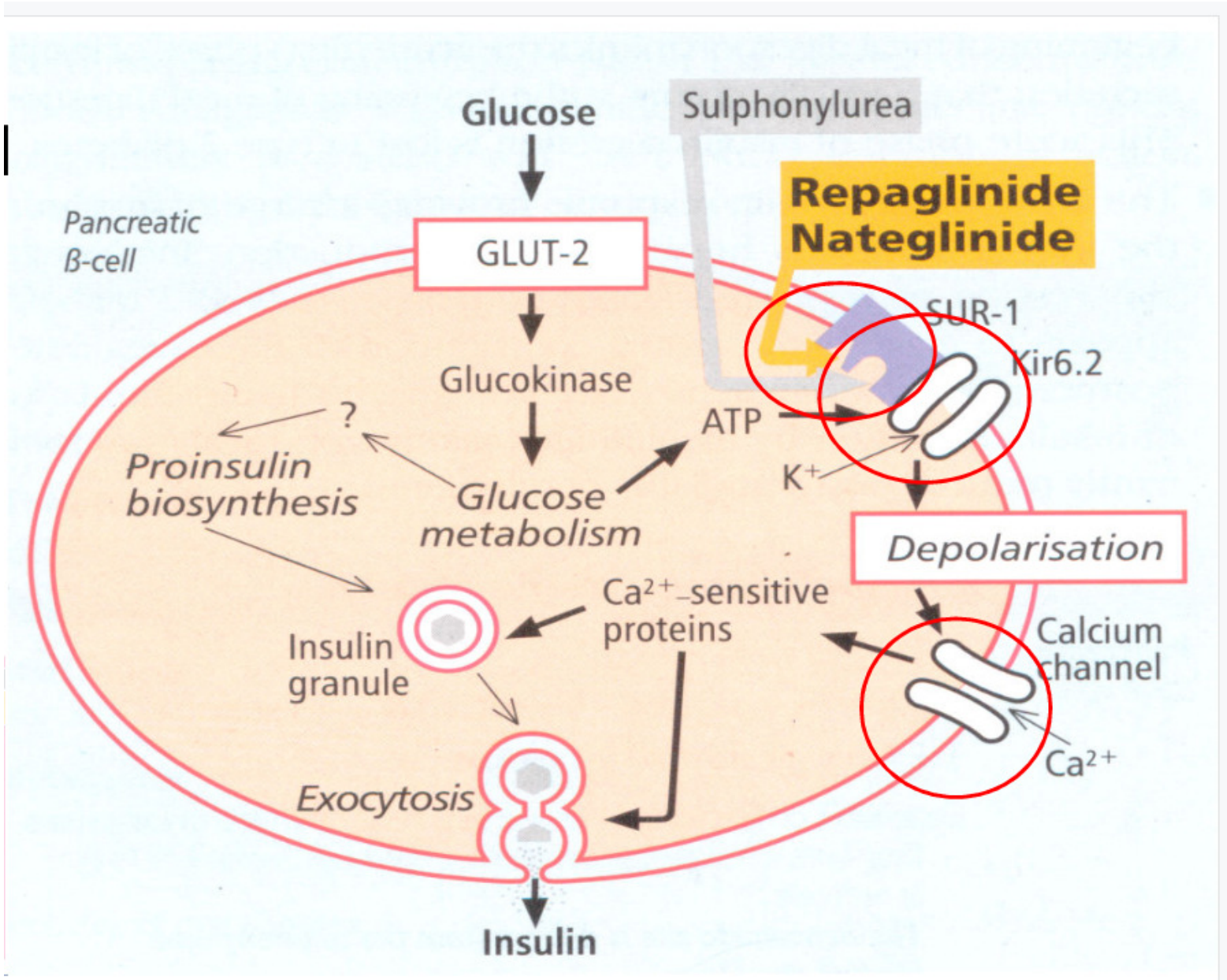
Sulphonylureas

- Expected GLYCEMIC effects
  - HbA1c → ↓ 1 – 2 %
  - Fasting plasma glucose → ↓ 2 – 4 mmol/l
  - Onset of effect → *Rapid*, usually evident on first day of treatment
  - Near-maximal effect of single dose → usually 2 weeks

Non-sulphonylurea - metiglinide

- Novonorm – repaglinide
- Glufast – mitiglinide
- Netiglinide - starlix

  - Non sulphnylurea D-phenylanine derivatives
  - Short acting agent that stimulates pancreatic insulin release
  - Take with each meal "one meal one dose, no meal no dose", lower postprandial glucose

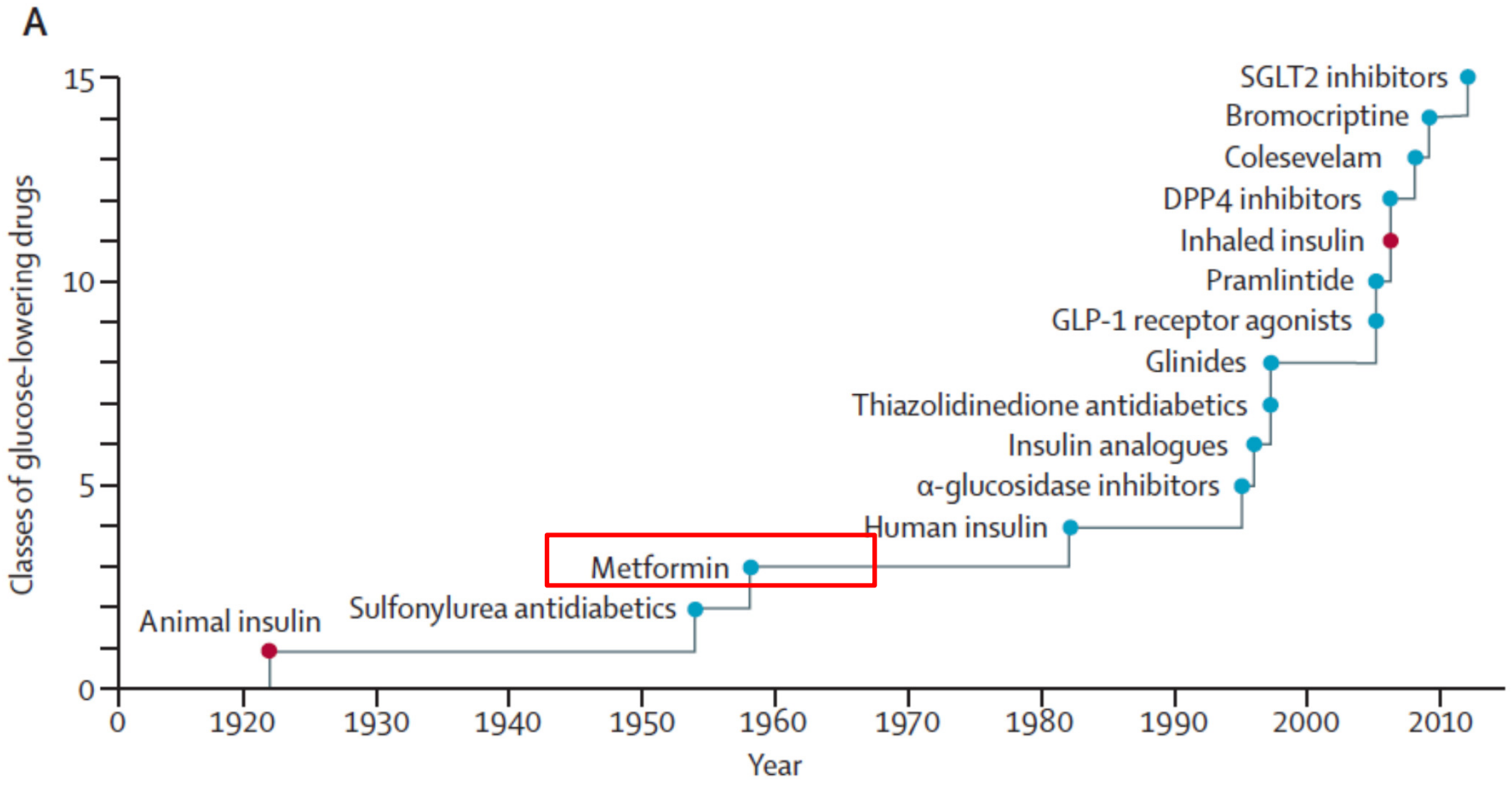

Glucose
Sulphonylurea
Repaglinide
Nateglinide
Pancreatic
ß-cell
GLUT-2
SUR-1
Kir6.2
Glucokinase
?
ATP
K+
Proinsulin
biosynthesis
Glucose
metabolism
Depolarisation
Ca2+-sensitive
proteins
Insulin
granule
Calcium
channel
Ca2+
Exocytosis
Insulin

Practical tips

- SU + meglitinide same downstream mechanism
  - Theoretically no beneficial effect of combination

- Cause of hypoglycemia
- Combination with insulin / insulin sensitizers
- Stop if TTD of insulin >30 units

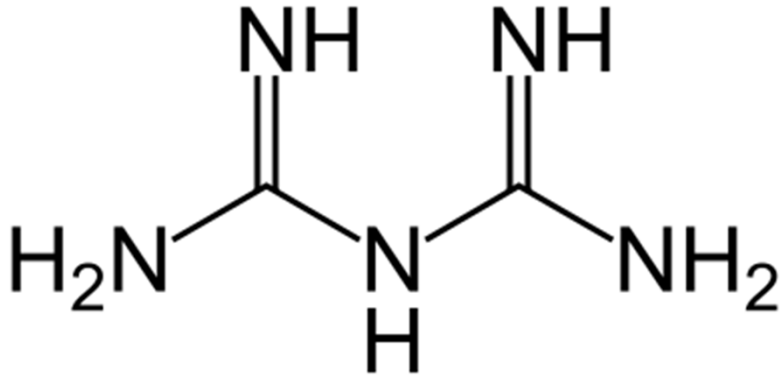
Breakthrough in DM Drug Development



Insulin sensitizer
Biguanides

Metformin

Biguanides



- Marketed since 1979 in France
- Metformin
- Phenformin – banned

- 17th century
- Herbal medicine
- Extract from leaves of
  - Goat's rue 山羊豆,美洲灰葉



- Treat fever, plague and diabetes

STUDIES IN THE METABOLIC CHANGES INDUCED BY ADMINISTRATION OF GUANIDINE BASES.

I. INFLUENCE OF INJECTED GUANIDINE HYDROCHLORIDE UPON BLOOD SUGAR CONTENT.

By C. K. WATANABE.

(*From the Laboratory of Pathological Chemistry, School of Medicine, and the Sheffield Laboratory of Physiological Chemistry, Yale University, New Haven.*)

(Received for publication, December 13, 1917.)

It is indicated in the work of many former investigators that there exists an intimate relation between idiopathic tetany and disturbed parathyroid function. The fact that the symptoms of tetany and tetania parathyreopriva are almost identical has had experimental confirmation.

Paton and Findlay (1) confirmed the results of former workers in a series of critical investigations, in which they found that true tetany developed only after complete parathyroidectomy and that when one external parathyroid was left with its blood supply intact, no symptoms, or at most transient tremors, appear.

Many hypotheses concerning the cause of tetany have been proposed, especially from the standpoint of parathyreopriva. One states that the lack of the parathyroid produces a toxic substance in the body, or the normal function of this gland is to neutralize the toxins formed during normal metabolism. The other concerns the deficiency of some essential substance in the blood and tissues, especially calcium, which exerts an inhibition on the hyperexcitability of the nerves. It is well known that injection of calcium salts removes the symptoms for a time, but that bleeding and transfusion of saline solution (2, 3) and that bleeding followed by injection of an indifferent solution free from calcium (Ringer's solu-

Downloaded from http://www.jbc.org/ by guest on August 26, 2015

In 1920, Slotta and Tschesche discovered its sugar-lowering action in rabbits

6. 1.4-*endo*-Methylen-2-[dimethyl-amino]-6-imino-1.3.5-triazin-Hydrochlorid.

Der bei der Umsetzung zwischen 1.1-Dimethyl-biguanid und Chloressigester erhaltene, in Wasser unlösliche Anteil (E 5) wurde aus Äthanol umgelöst. Sargdeckel-artige Krystalle mit schief zueinander stehenden Kanten und häufiger Zwillingsbildung. Ausbeute 14.5 g. Sehr schwer löslich in Wasser, mäßig in Alkohol, schlecht in Aceton. Schmp. 176° (unter Dunkelfärbung). Gibt keine rote Kupferverbindung. Durch Kochen mit 2-*n*. Natronlauge erhält man die freie Base, die in Alkohol und Wasser völlig unlöslich ist und beim Kochen mit 2-*n*. Natronlauge kein Ammoniak abspaltet.

0.1012 g Sbst.: 0.1440 g CO_2, 0.0508 g H_2O, 0.0193 g Cl. — 0.0637 g Sbst.: 20.9 ccm N (19°, 758 mm, 23-proz. Lauge).

$C_6H_{10}N_5Cl$. Ber. C 38.5, H 5.3, Cl 18.7, N 37.4. Gef. C 38.8, H 5.6, Cl 19.1, N 37.5.

---

216. K. H. Slotta und R. Tschesche: Über Biguanide, II.: Die blutzucker-senkende Wirkung der Biguanide.

[Aus d. Chem. Institut d. Universität Breslau.]

(Eingegangen am 3. April 1929.)

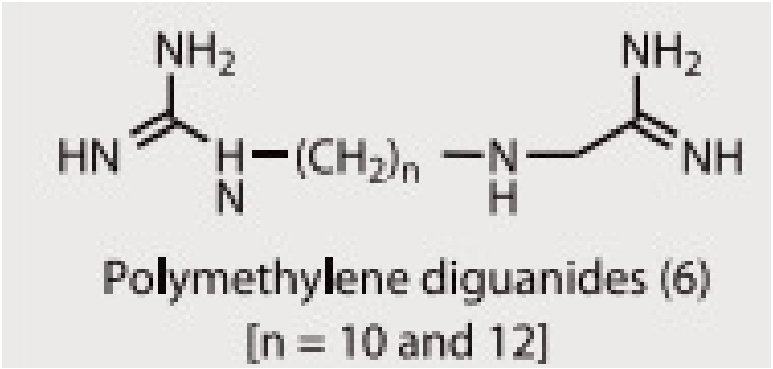
Die pharmakologische Untersuchung der in der voranstehenden Arbeit beschriebenen Biguanide[1]) ergab eine starke blutzucker-senkende Wirkung dieser Stoffklasse. Wir stellten daraufhin eine noch größere Anzahl substituierter Biguanide dar, um über die Beziehung zwischen chemischer Konstitution und hypoglykämischer Wirkung Klarheit zu gewinnen.

Es zeigte sich bald, daß überhaupt nur eine Aminogruppe im Molekül substituiert werden darf, wenn die blutzucker-senkenden Eigenschaften erhalten bleiben sollen. In der Reihe Methyl-[2]), Äthyl-[3]), Propyl-, Isobutyl-[4]), Isoamyl-biguanid liegt das Maximum der Wirksamkeit beim Methylkörper, und durch Vergrößerung des Alkyls wird sie in keiner Weise gesteigert. In der Reihe der durch ungesättigte Alkyle, wie Allyl[5]),

the forgotten

In 1950…

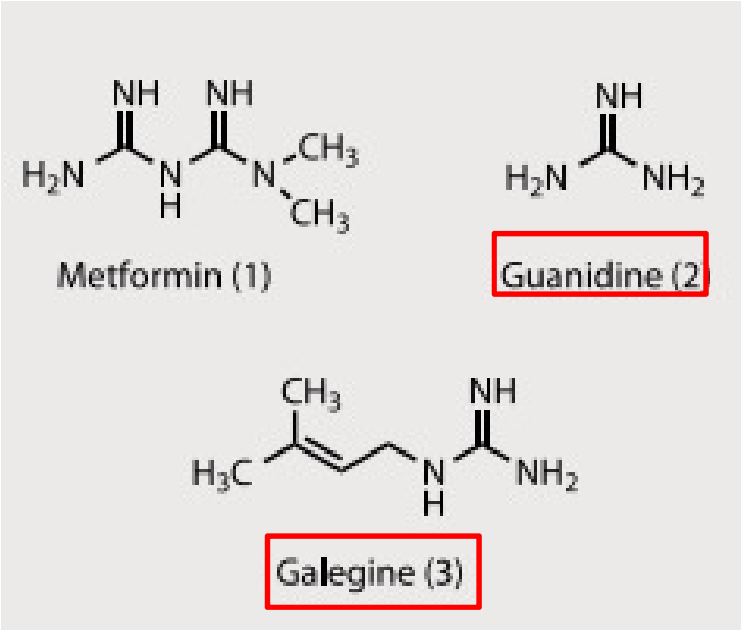
- Garcia, ID specialist in Philippines
- Use Flumamine to treat influenza
  - Fever and headache subsided after single dose
  - Similar structure as polymethylene diguanides
  - May be used to treat malaria as glucose lowering properties



Polymethylene diguanides (6)
[n = 10 and 12]

bacteriostatic, antiviral, antimalarial, antipyretic and analgesic action

extract from goat's rue
山羊豆,美洲灰葉





- Jean Sterne, specialist in diabetes
- antihyperglycemic properties of galegine, an alkaloid isolated from Goat's Rue

France



- Spotting Garcia's comment
  - flumamine reduced blood sugar concentration

- 1957
  - Sterne selected dimethyl-biguanide (metformin) for clinical development
  - name 'Glucophage' (glucose eater)

Phenformin

- 1977 banned by FDA
  - Severe lactic acidosis
- 2008 still legally available in Italy, Brazil, Uruguay, China, Poland, Greece and Portugal
- Now, herbal medicine/ OTC containing phenformin
- 2000, FDA recalled 5 Chinese herbal products
  - glyburide and phenformin

ephine Bust & Slimming

要聞港聞 2014年01月04日 中醫涉開違禁西藥攞命　糖尿婦服後亡　重案組拉人

中醫涉開違禁西藥攞命 糖尿婦服後亡　重案組拉人

213,251



讚 50 分享 0 Tweet 0 50

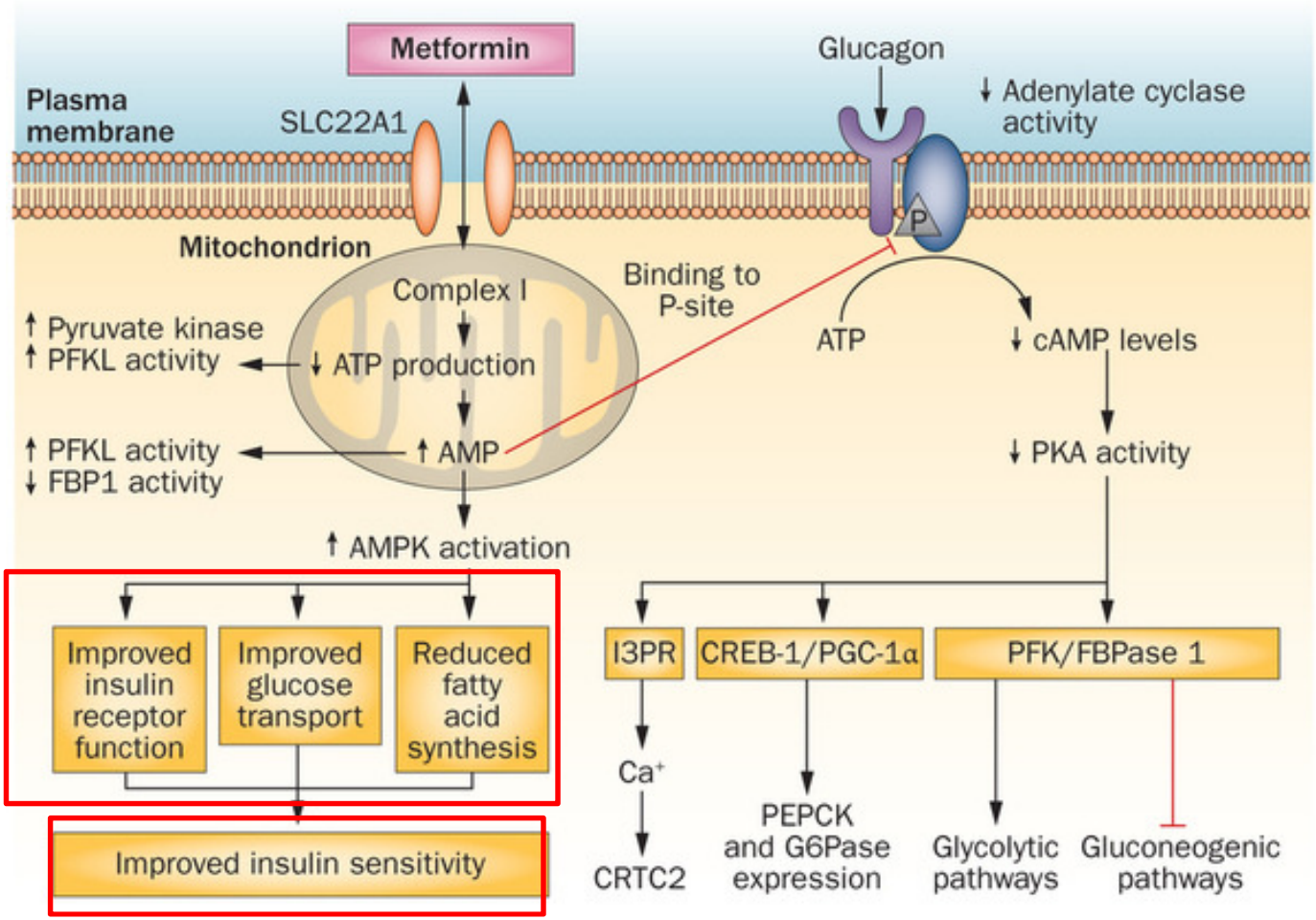
A A

【本報訊】八旬老婦早前肺炎急症入院，兩日後病情突然惡化死亡，法醫在她體內發現一種含有「苯乙雙胍」（Phenformin）禁藥成份的殘餘藥物，疑老婦因服用違禁藥導致死亡，深水埗警區重案組接手偵查，懷疑違禁藥來自油麻地一間中醫診所，昨午到診所帶走一名中醫師調查，同時撿走大袋中成藥化驗，正調查是否有人在



Antihyperglycemic – improve insulin sensitivity

X hypoglycemia



IDF global guideline for T2DM 2005

- Glucose control: Oral therapy
- Begins with Metformin
- Unless evidence or risk of renal impairment
- isolated case of lactic acidosis

3. Update on the Use of Metformin at the Time of or Before an Iodinated Contrast Imaging Procedure

- New recommendation is made on the use of metformin at the time of or before an iodinated contrast imaging procedure:

2016 FDA warnings (DH issued letter in regard to this warning)	2018 American College of Radiology Manual on Contrast Media
Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with **1. eGFR 30-60** 2. History of liver diseases, alcoholism, or heart failure 3. Intra-arterial contrast	In patients with no evidence of AKI and with **eGFR ≥30 mL/min/1.73m^2**, there is no need to discontinue metformin

- CRC was consulted and responded positively to 2018 recommendation, views would also be sought from COC(Rad) & COC(Med)
- Members are invited to advise in accordance with the change



Metformin

Metformin

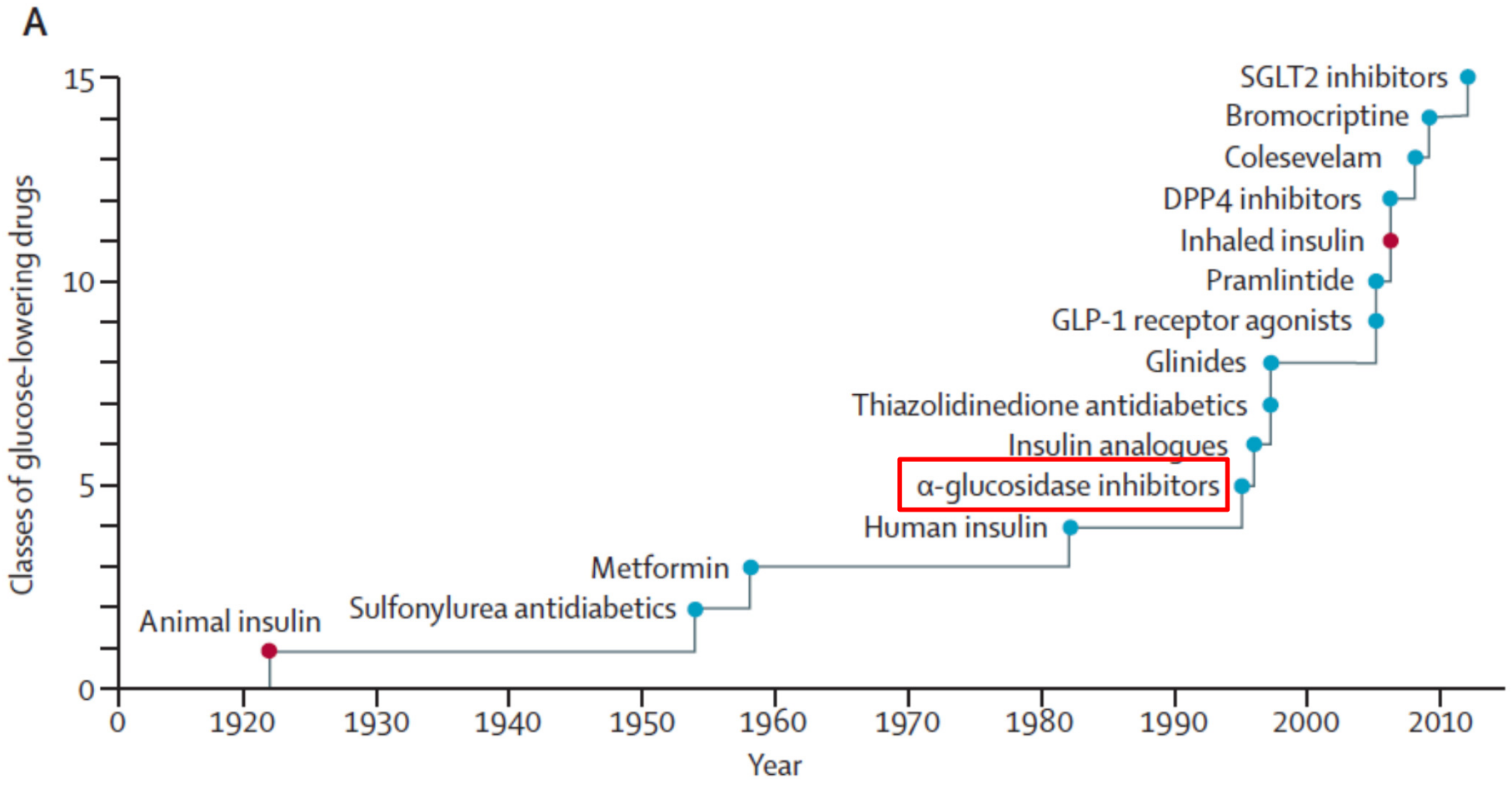
- Metformin ↔ lactic acidosis
  - Estimated risk: 1 in 30,000 patient-years

- *Beware of impaired renal function (British recommendation → stop if ***serum Cr > 150 μmol/L***)

Practical tips

- Metformin
  - For all T2DM patients
  - Won't cause hypoglycemia
  - Cautious in renal impairment and liver impairment
  - GI upset
    - Step up approach

Breakthrough in DM Drug Development

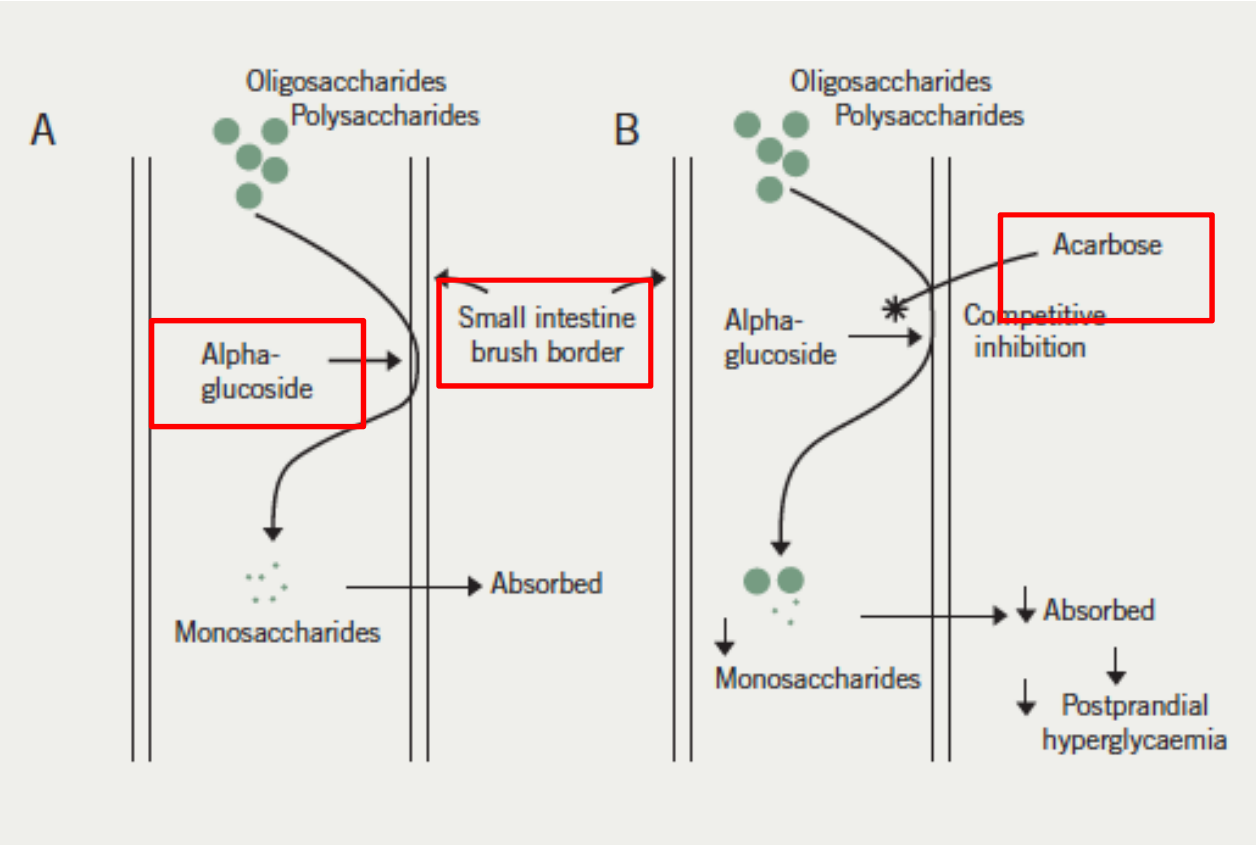


Alpha-glucosidase inhibitor

Acarbose (Glucobay拜糖平)

Alpha-glucosidase inhibitor

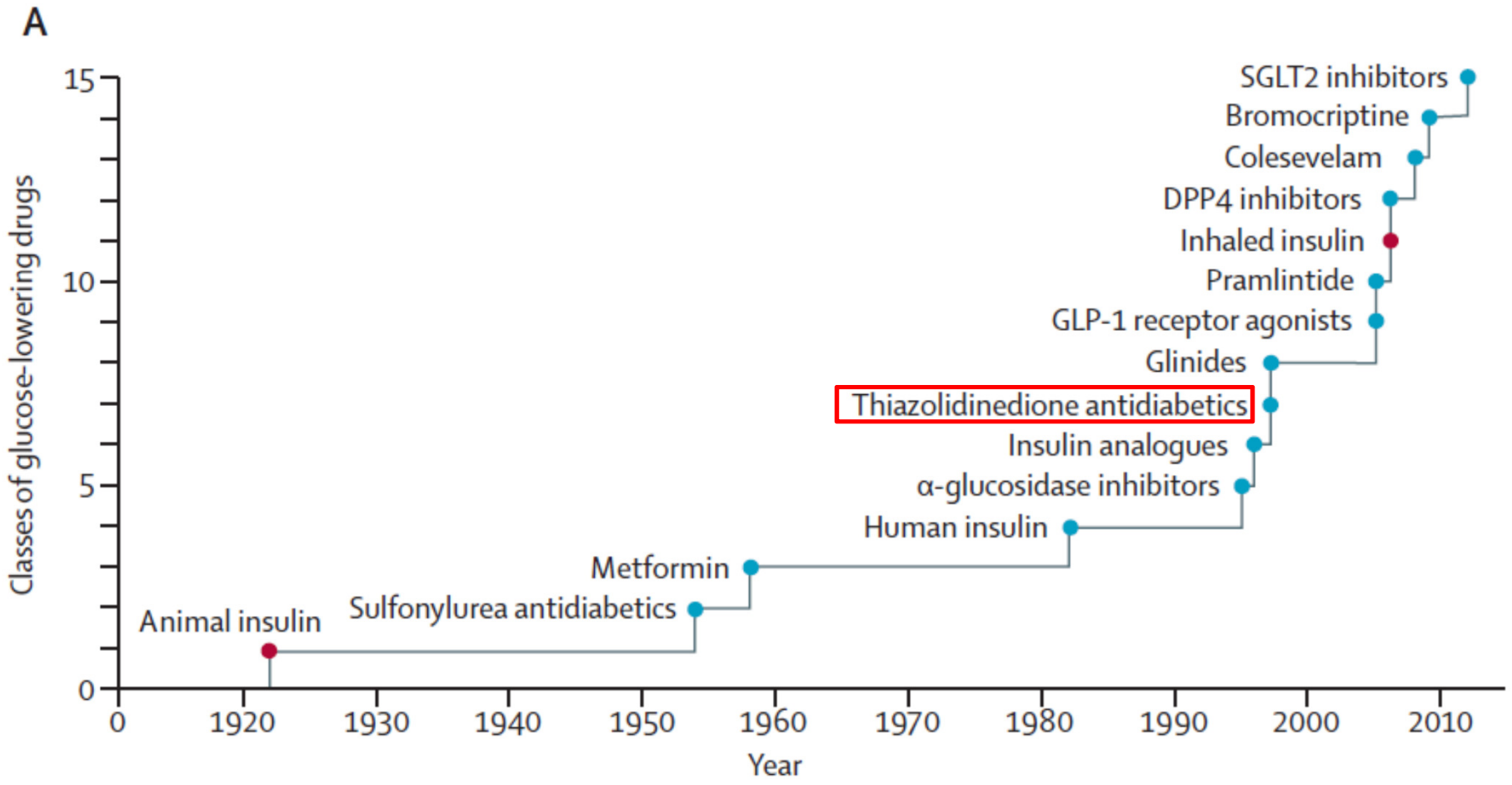
- Acarbose (Glucobay拜糖平)
- weak



Practical tips

- Take with meal
- GI side effect
  - GI upset, flatulence
- Hypoglycemia
  - Relieved with food containing monosaccharides
  - Glucose tablet, candy
- Not suitable in inflammatory bowel disease , chronic renal failure, history of intestinal obstruction

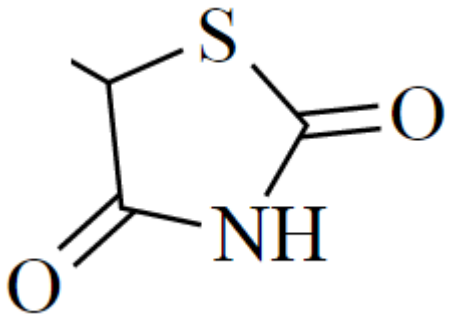
Breakthrough in DM Drug Development



Insulin sensitizers

Thiazolidinedione

Thiazolidinedione



- Glitazones
  - Dione

- Rosiglitazone (Avandia) 安糖健
- Pioglitazone (Actos)愛妥糖

- Reduce insulin resistance
- Reduce FFA

Discovery

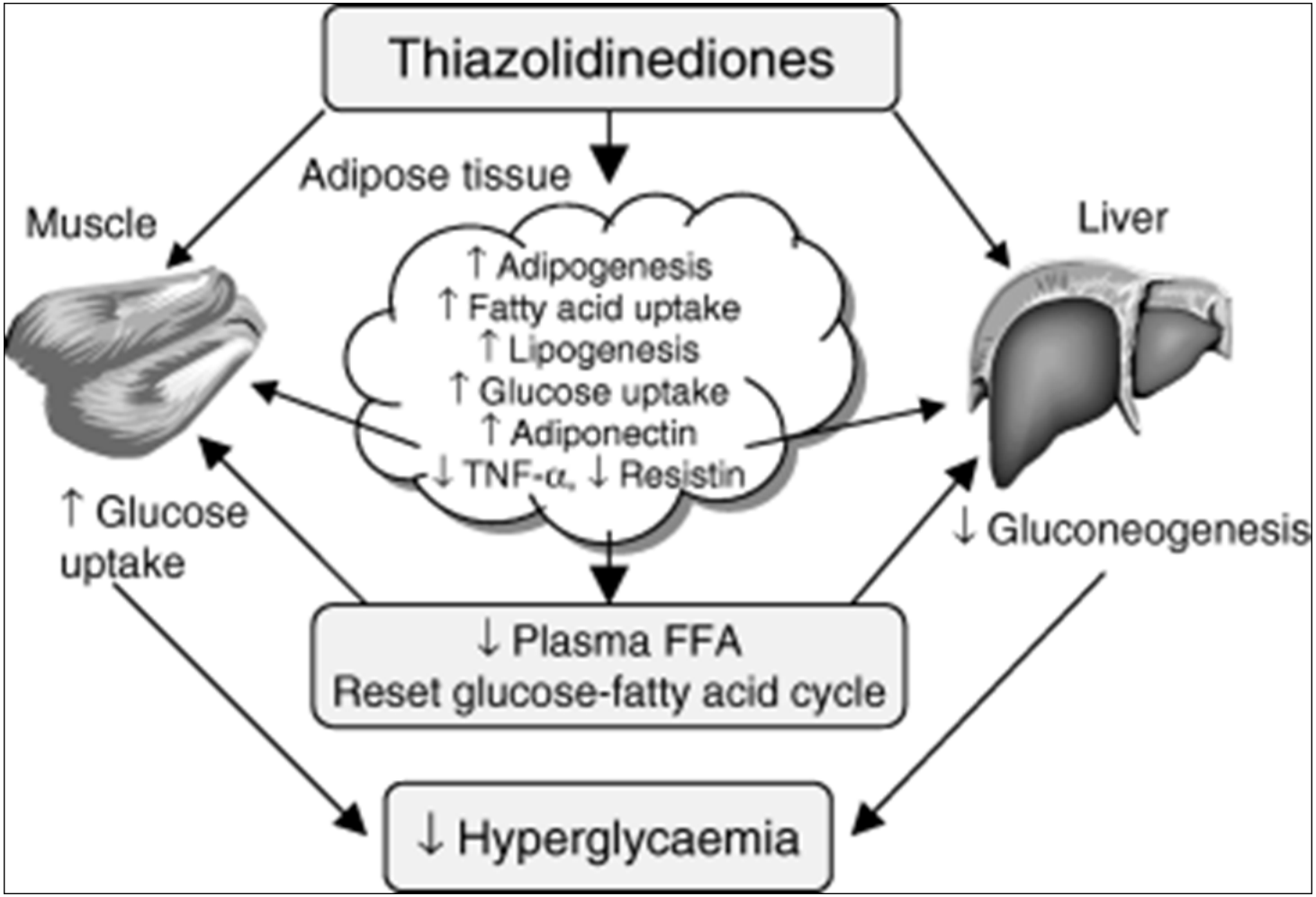
- Japanese
- 1980s
- Takeda
- Fibrate, lipid lowering drug
- Hypolipidemic and hypoglycemic in mice
- Incidental finding of activating PPAR-γ to lower glucose level

- Japan Takeda: Ciglitazone - animal studies, weak, never market
- USA 1997: Troglitazone first marketed
  - withdrawn in 2000 due to liver injury
- UK 1983, (1997 FDA): rosiglitazone
  - AMI & cardiovascular death
- Japan Takeda (1997 FDA): pioglitazone Actos

Peroxisome Proliferation-Activated Receptors (PPARs)

	PPARα	PPARδ	PPARγ
Tissue expression profile	Liver, kidney, skeletal, muscle, brown adipose tissue	Ubiquitous	Adipose tissues, skeletal muscle, heart, liver, kidney, gut, macrophages, vascular smooth muscle cells (VSMCs)
Isoforms	α	δ	γ_1, γ_2
Pharmacological activators	Fibrates, hypolipidemics		Thiazolidinediones

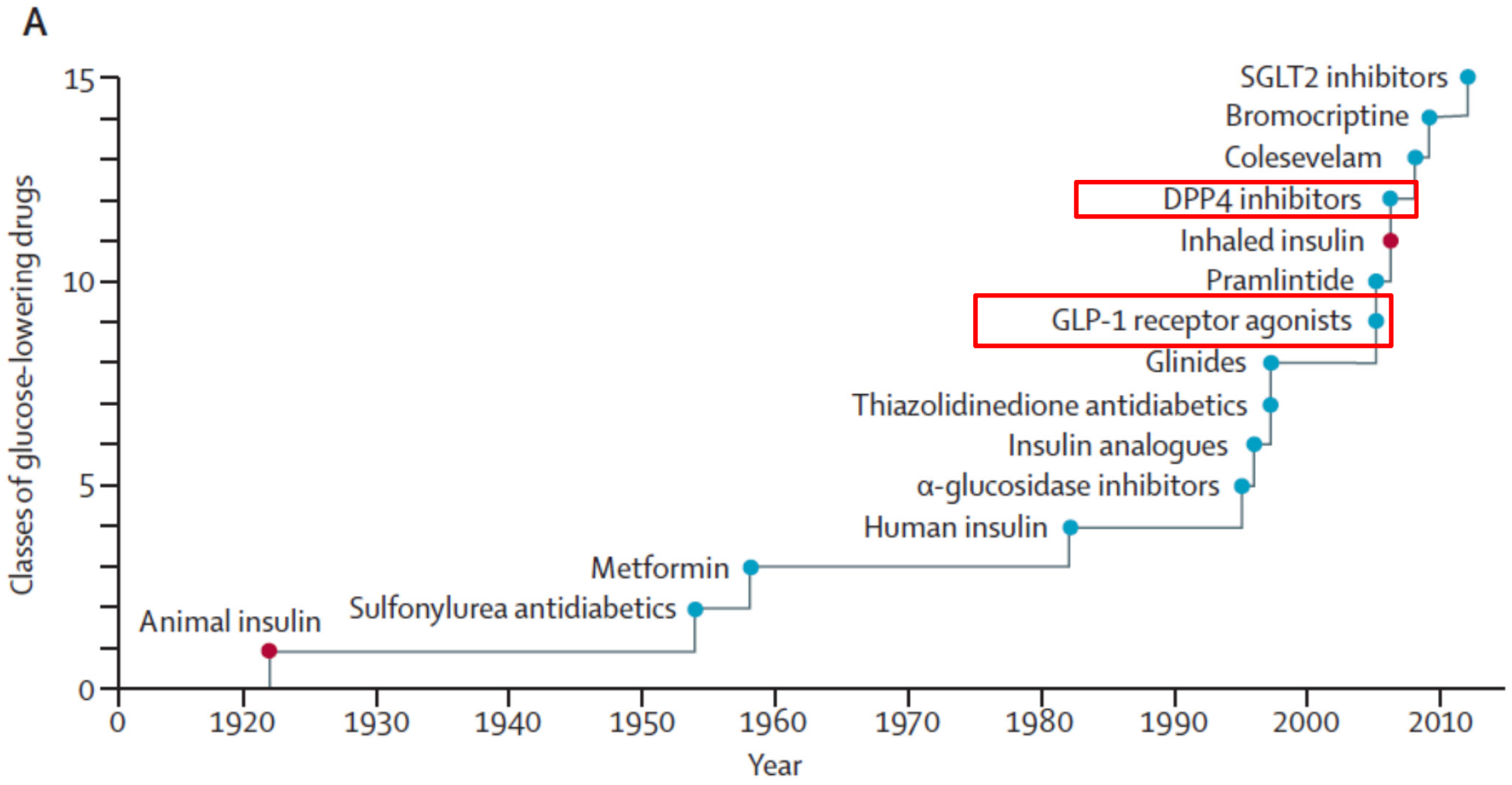
Saltiel AR et al, *Diabetes* 1996.


Thiazolidinediones
Adipose tissue
Muscle
Liver
↑ Adipogenesis
↑ Fatty acid uptake
↑ Lipogenesis
↑ Glucose uptake
↑ Adiponectin
↓ TNF-α, ↓ Resistin
↑ Glucose uptake
↓ Gluconeogenesis
↓ Plasma FFA
Reset glucose-fatty acid cycle
↓ Hyperglycaemia

Practical tips

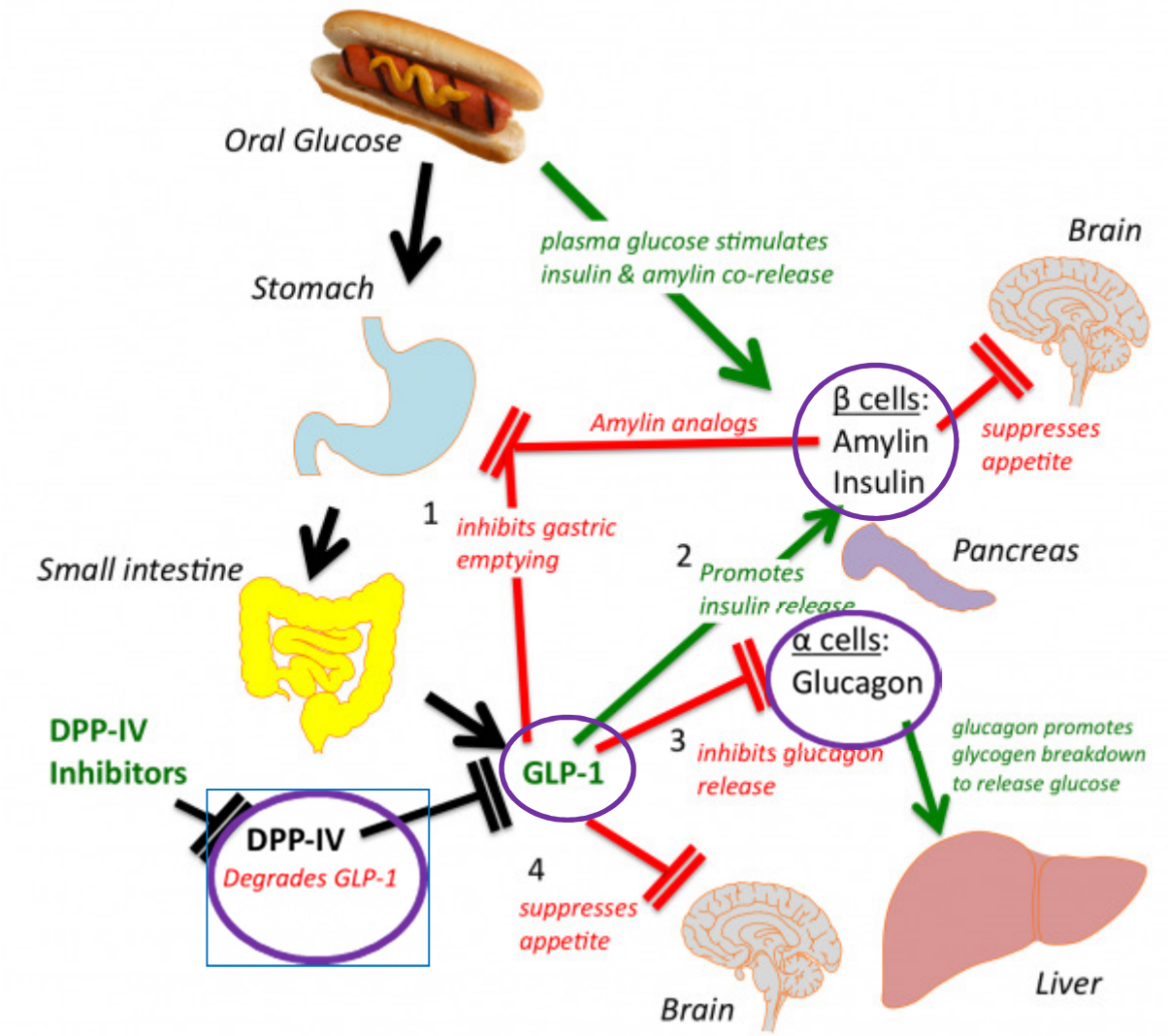
- No hypoglycemia
- Pioglitazone
  - ? CA bladder
  - Osteoporosis

Breakthrough in DM Drug Development



GLP-1 and DPP4I

- GLP-1
  - Glucagon-like-peptide-1-agonist
- DPP4 Inhibitors
  - Dipeptidyl peptidase-4 inhibitors


Oral Glucose
Stomach
plasma glucose stimulates
insulin & amylin co-release
Brain
β cells:
Amylin
Insulin
Amylin analogs
suppresses
appetite
1
inhibits gastric
emptying
Small intestine
2
Promotes
insulin release
Pancreas
α cells:
Glucagon
DPP-IV
Inhibitors
GLP-1
3
inhibits glucagon
release
glucagon promotes
glycogen breakdown
to release glucose
DPP-IV
Degrades GLP-1
4
suppresses
appetite
Brain
Liver


53

Eating Slowly Increases the Postprandial Response of the Anorexigenic Gut Hormones, Peptide YY and Glucagon-Like Peptide-1

Alexander Kokkinos,* Carel W. le Roux,* Kleopatra Alexiadou, Nicholas Tentolouris, Royce P. Vincent, Despoina Kyriaki, Despoina Perrea, Mohammad A. Ghatei, Stephen R. Bloom, and Nicholas Katsilambros

First Department of Propaedeutic Medicine (A.K., K.A., N.T., D.K., D.P., N.K.), Athens University Medical School, Laiko General Hospital, 11527 Athens, Greece; and Department of Metabolic Medicine (C.W.I.R., R.P.V., M.A.G., S.R.B.), Hammersmith Hospital, Imperial College, London W12 ONN, United Kingdom

Context: The rate at which people eat has been suggested to be positively associated with obesity, although appetite and related gut hormones have not been measured.

Objective: The objective of the study was to determine whether eating the same meal at varying speeds elicits different postprandial gut peptide responses.

Design and Setting: This was a crossover study at a clinical research facility.

Study Participants: Seventeen healthy adult male volunteers participated in the study.

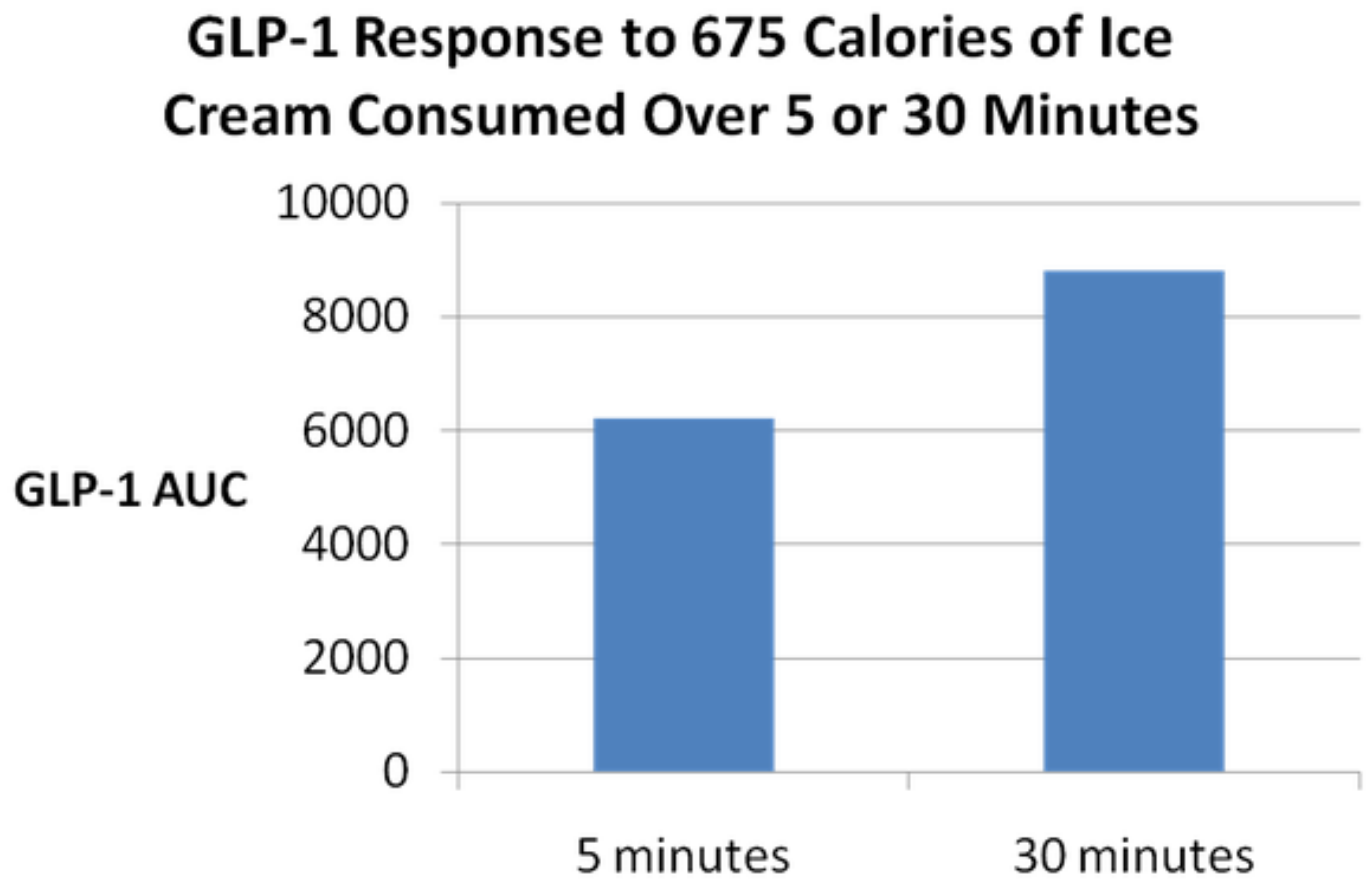
Intervention: A test meal consisting of 300 ml ice cream (675 kcal) was consumed in random order on two different sessions by each subject: meal duration took either 5 or 30 min.

Main Outcome Measures: The postprandial response of the orexigenic hormone ghrelin and the anorexigenic peptides peptide YY and glucagon-like peptide-1 over 210 min was assessed. Visual analog scales for the subjective feelings of hunger and fullness were completed throughout each session.

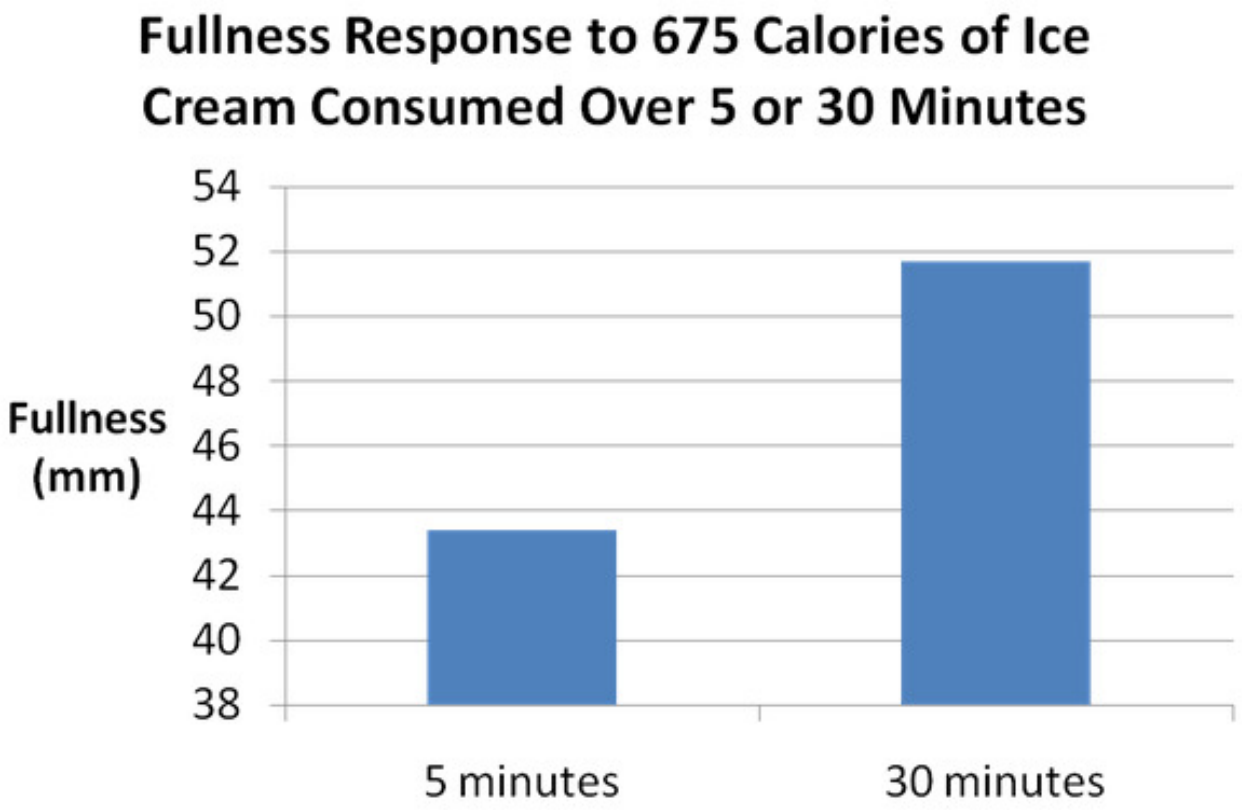
Results: Peptide YY area under the curve (AUC) was higher after the 30-min meal than after the 5-min meal (mean ± SEM AUC 5 min meal: 4133 ± 324, AUC 30 min meal: 5250 ± 330 pmol/liter · min, $P = 0.004$), as was glucagon-like peptide-1 AUC (mean ± SEM AUC 5 min meal: 6219 ± 256, AUC 30 min meal: 8794 ± 656 pmol/liter · min, $P = 0.001$). There was a trend for higher visual analog scale fullness ratings immediately after the end of the 30-min meal compared with immediately after the 5-min meal. There were no differences in ghrelin response.

Conclusions: Eating at a physiologically moderate pace leads to a more pronounced anorexigenic gut peptide response than eating very fast. (***J Clin Endocrinol Metab*** **95: 333–337, 2010)**

GLP-1 was also significantly higher when the ice cream was consumed more slowly:



While there were no significant differences in hunger ratings, there was a trend for feelings of fullness to be higher when the ice cream was consumed more slowly:



Slow Down...You Eat Too Fast...You Got to Make Your Meal Last...

GLP1

- Circulating level of intact of GLP1 decreases rapidly because of enzymatic inactivation (mainly DPP 1V) and renal clearance
- Short half-life of ~2 minutes only



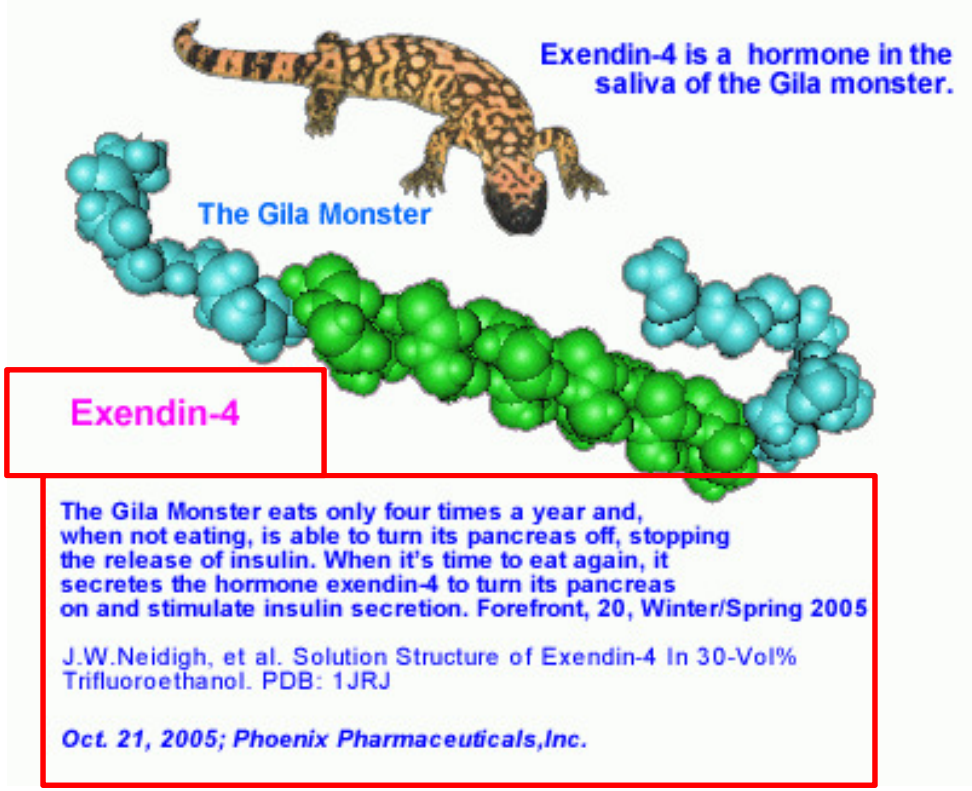
GLP-1

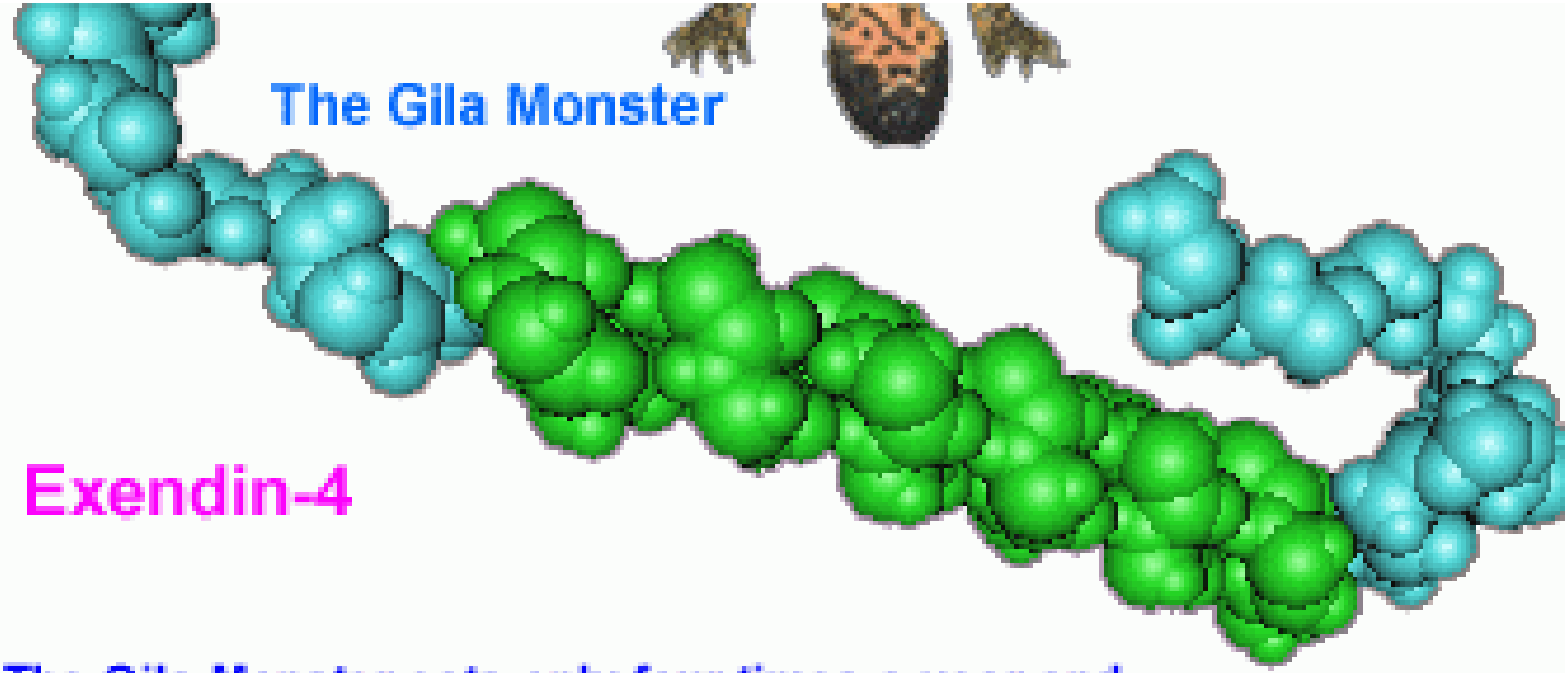


- Gila Monster美國毒蜥
- Venomous lizard
- Feed 4 times / year



- Four potentially lethal toxins and many bioactive peptides in saliva





The Gila Monster eats only four times a year and, when not eating, is able to turn its pancreas off, stopping the release of insulin. When it's time to eat again, it secretes the hormone exendin-4 to turn its pancreas on and stimulate insulin secretion. Forefront, 20, Winter/Spring 2005

J.W.Neidigh, et al. Solution Structure of Exendin-4 In 30-Vol% Trifluoroethanol. PDB: 1JRJ

Oct. 21, 2005; Phoenix Pharmaceuticals,Inc.

- Exendin-4
  - = action with GLP-1

- 2005
  - Exenatide

GLP-1 RAs: Dosing

Drug	Initial	Titrate	Max	Dose Adjustments
Exenatide IR (Byetta®)	5 mcg BD within 60 mins of a meal (≥ 6H between doses)	↑ to 10 mcg bd after 1 month	10 mcg bd	Renal impairment: CrCl 30-50 mL/min: use caution; CrCl < 30 mL/min not recommended Hepatic impairment: not studied
Exenatide ER (Bydureon®)	2 mg once weekly	N/A	2 mg once weekly	
Liraglutide (Victoza®)	0.6 mg qd x 1/52	1.2 mg qd	1.8 mg qd	Renal & hepatic impairment: use caution – limited experience
Lixisenatide (Lyxumia®)	10 mcg qd x 2/52	20 mcg qd	20 mcg qd	Renal impairment: use caution
Albiglutide (Tanzeum®)	30 mg once weekly	50 mg once weekly	50 mg once weekly	Renal impairment: use caution when initiating or escalating doses Hepatic impairment: not studied, unlikely required
Dulaglutide (Trulicity®)	0.75 mg once weekly	1.5 mg once weekly	1.5 mg once weekly	Renal impairment: use caution when initiating or escalating doses Hepatic impairment: use with caution

DPP IV- I

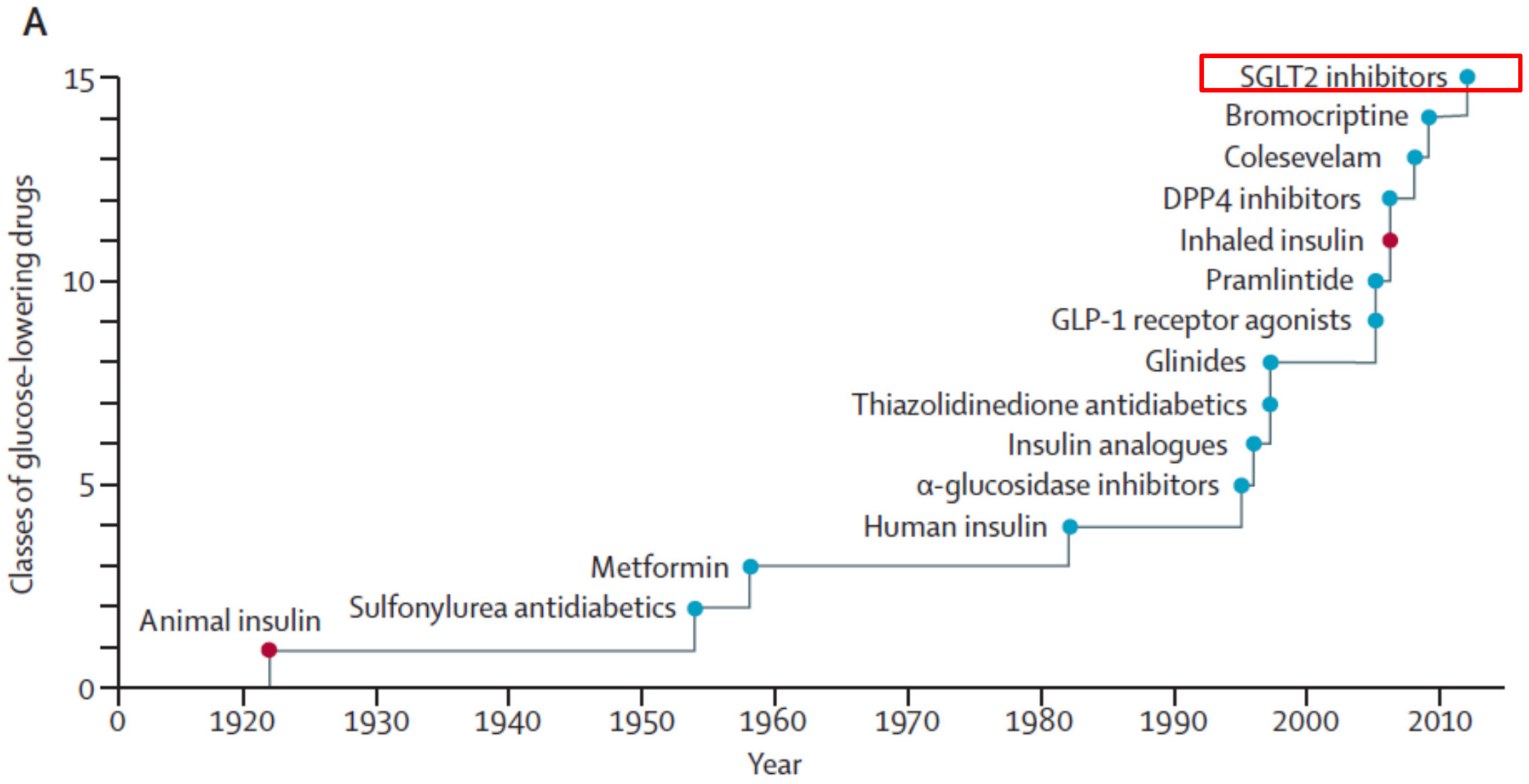
- Sitagliptin (Januvia健諾胰) – daily
- Alogliptin - daily
- Vildagliptin (Galvus佳維樂) - bd
- Saxagliptin (Onglyza) - daily
- Linagliptin (Tradjenta) – daily
  - not renal excreted, safe in renal failure patient

- Incretin mimetic (exenatide / liraglutide)
  - Reduces HbA1c: 1-2%
- Incretin enhancers (sitagliptin/ vildagliptin)
  - Reduces HbA1c: 0.5-1% (mono-or combination therapy)



- Price

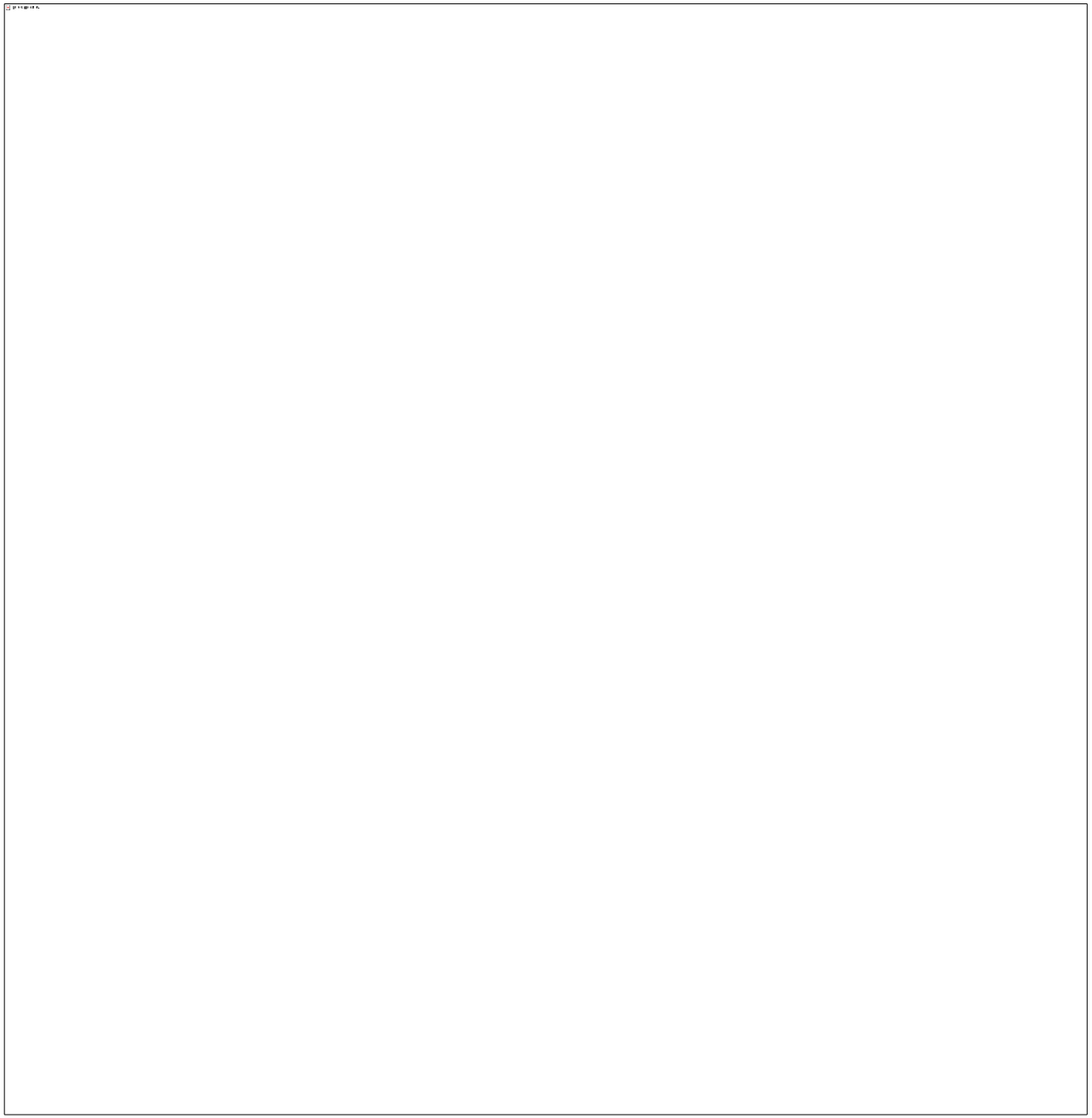
Breakthrough in DM Drug Development



SGLT2

- sodium/glucose cotransporter 2
  - Reduce glucose reabsorption
  - Increase glucose excretion

- 糖尿



SGLT2

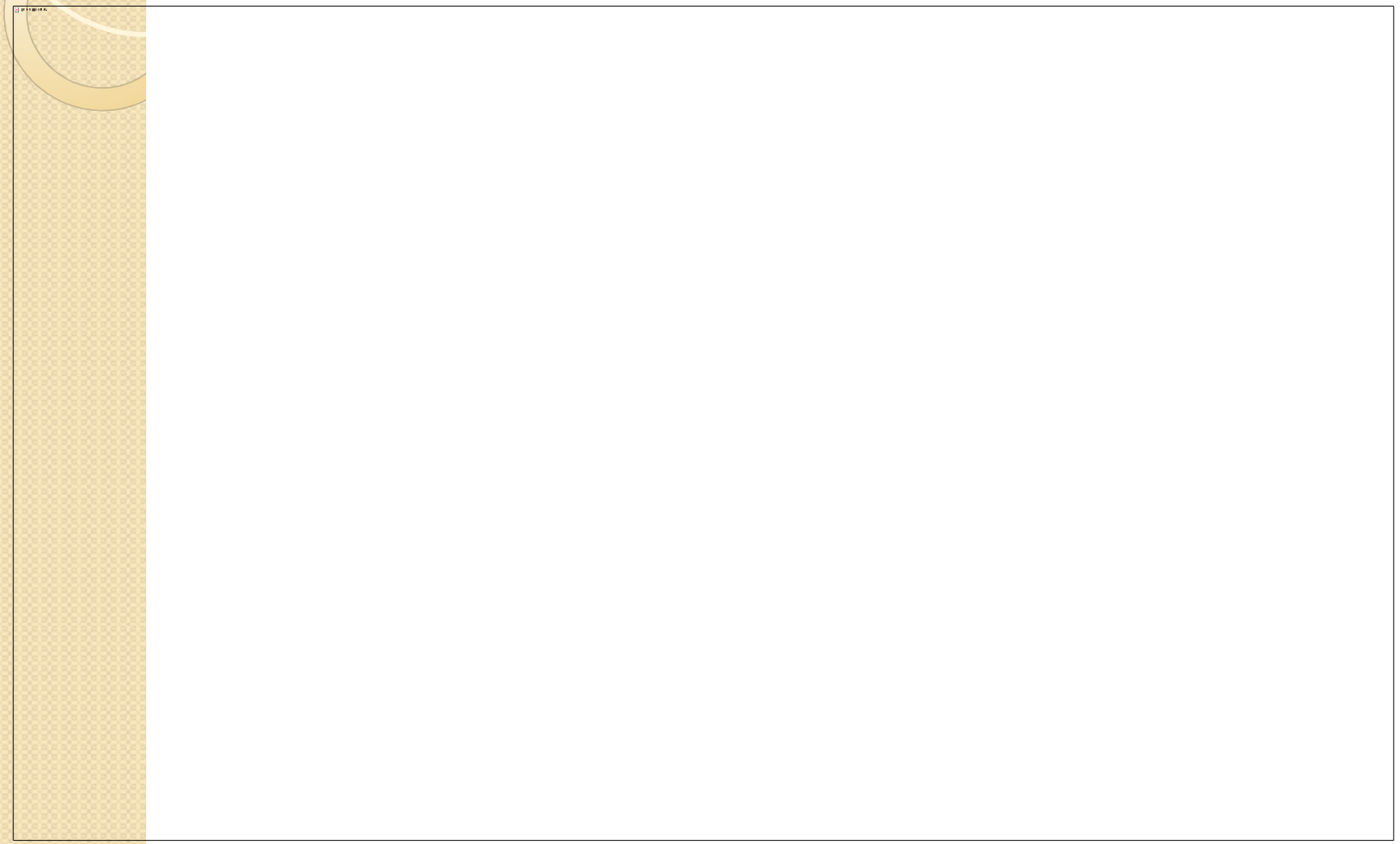
- Dapagliflozin (Forxiga)
- Canagliflozin
- Ipragliflozin
- Tofogliflozin - japan
- Empagliflozin (Jardiance)

Side effect

- UTI
- Candida vulvovaginitis
- Hypoglycemia
- Euglycemic DKA
- Fournier gangrene
- Lower limb amputation

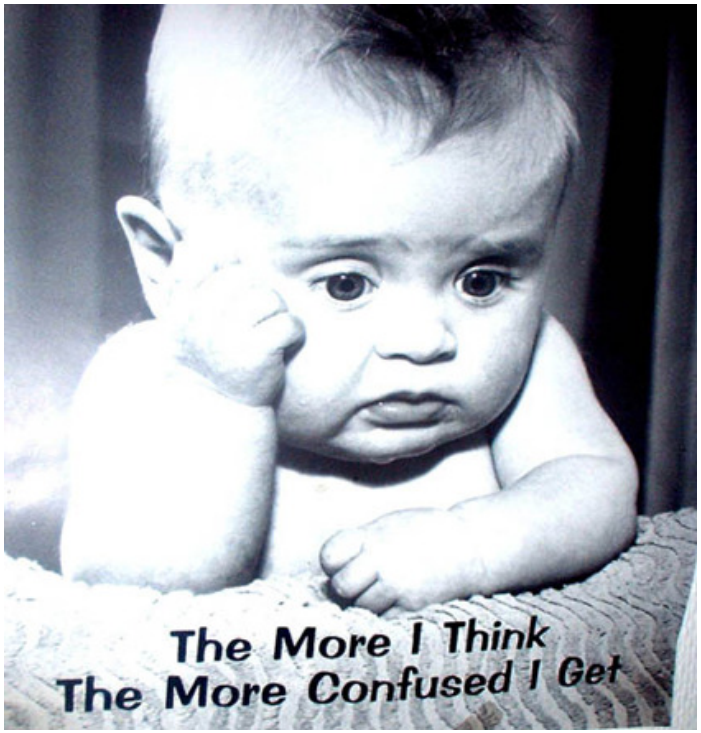


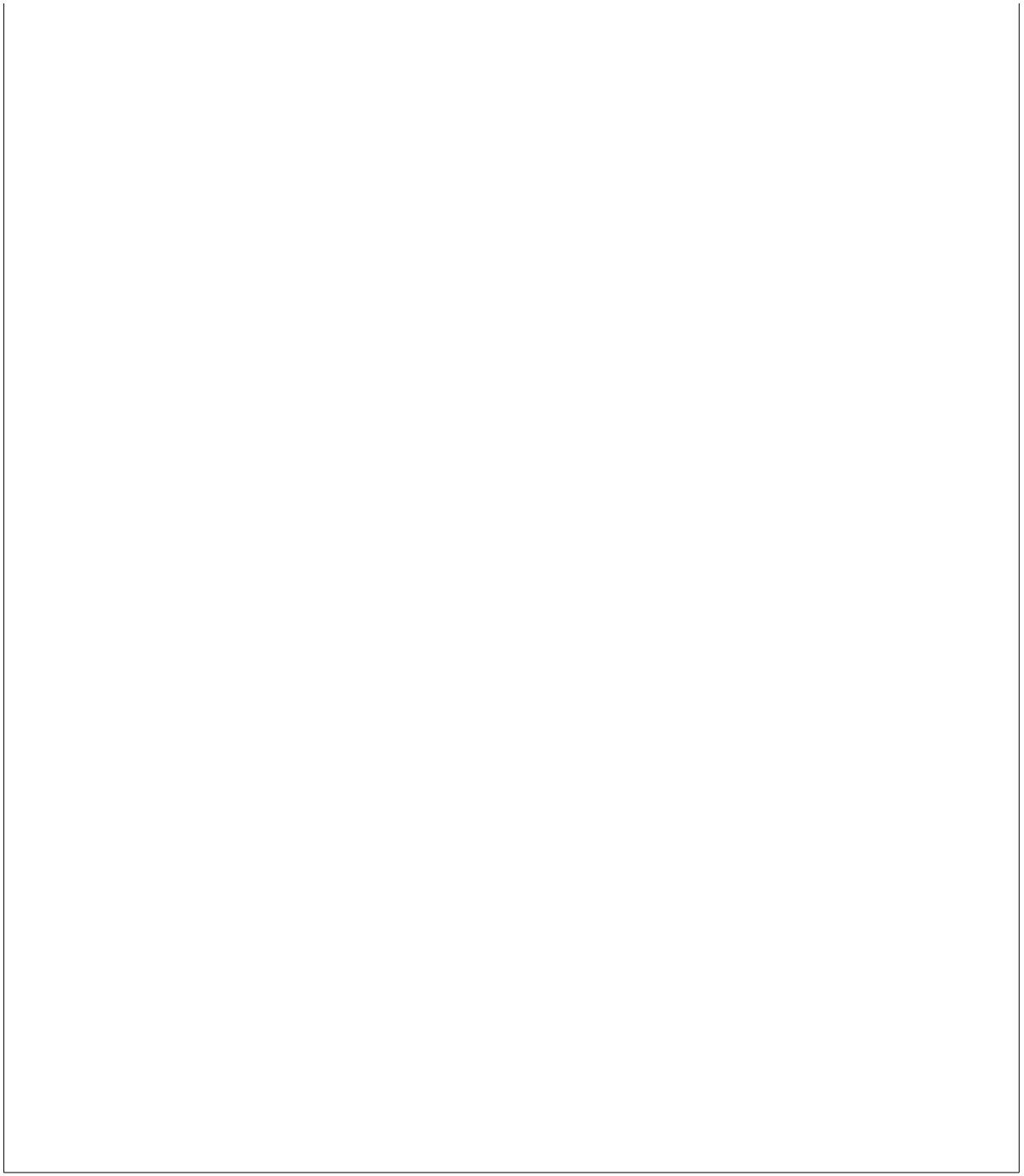
Why DKA?

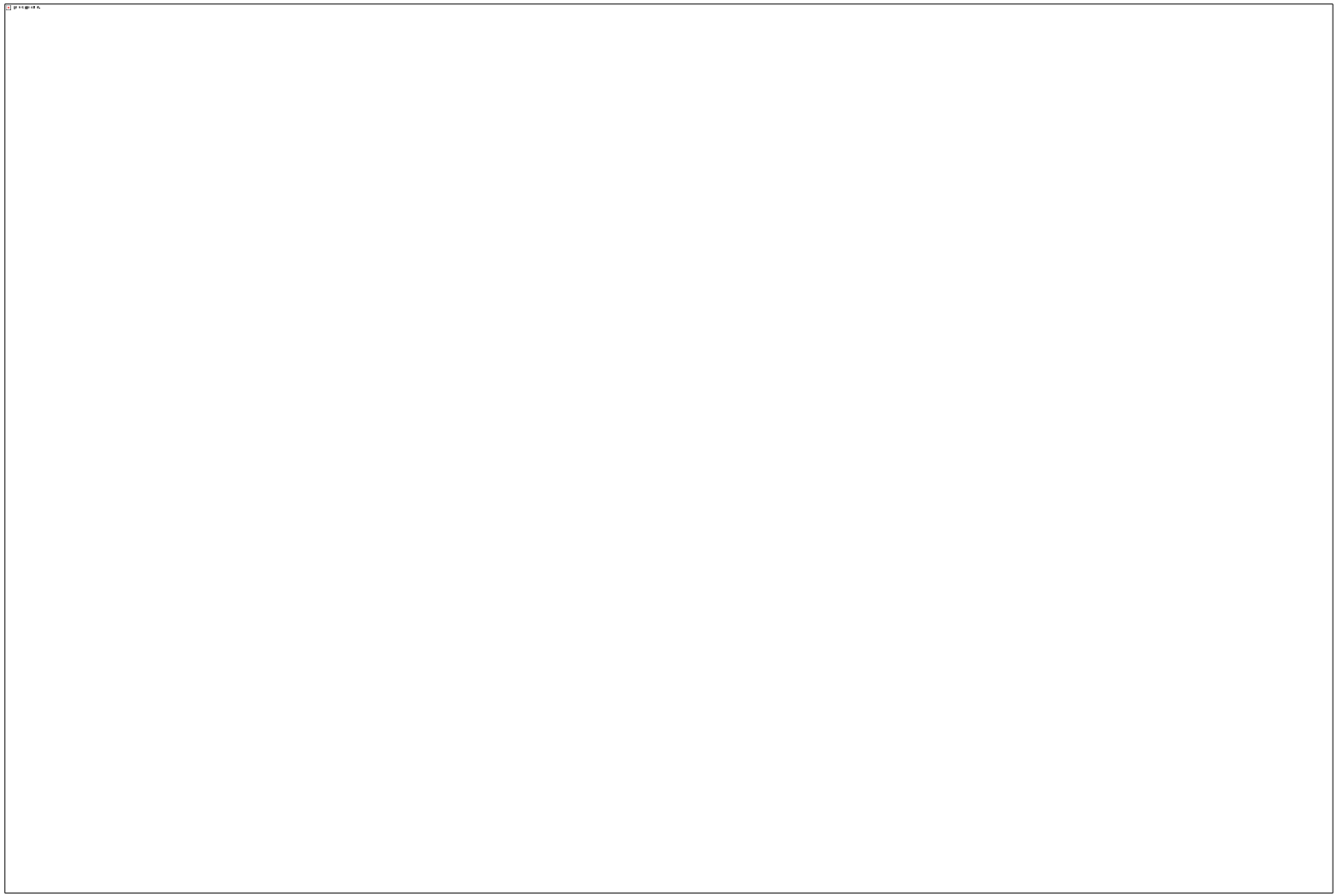


SGLT2 inhibitors

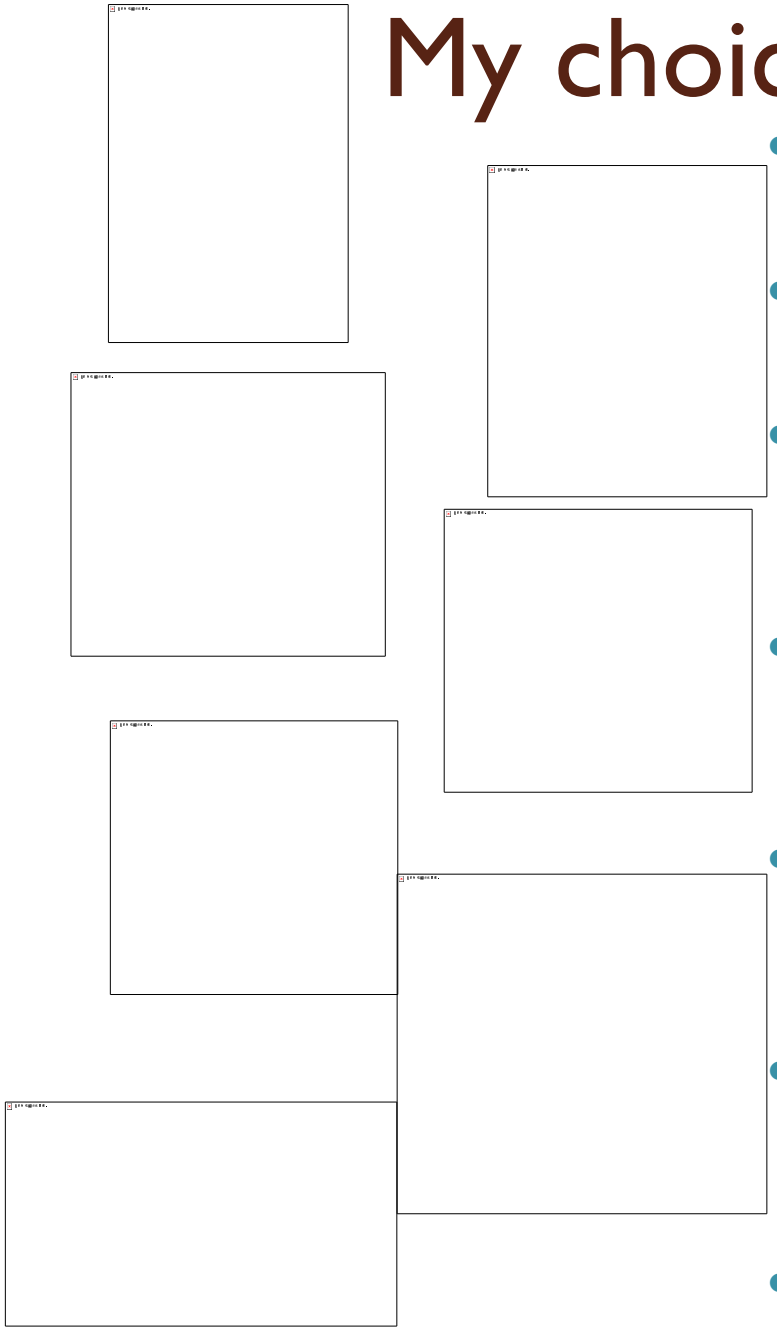

BOOOORING !!!


The More I Think
The More Confused I Get

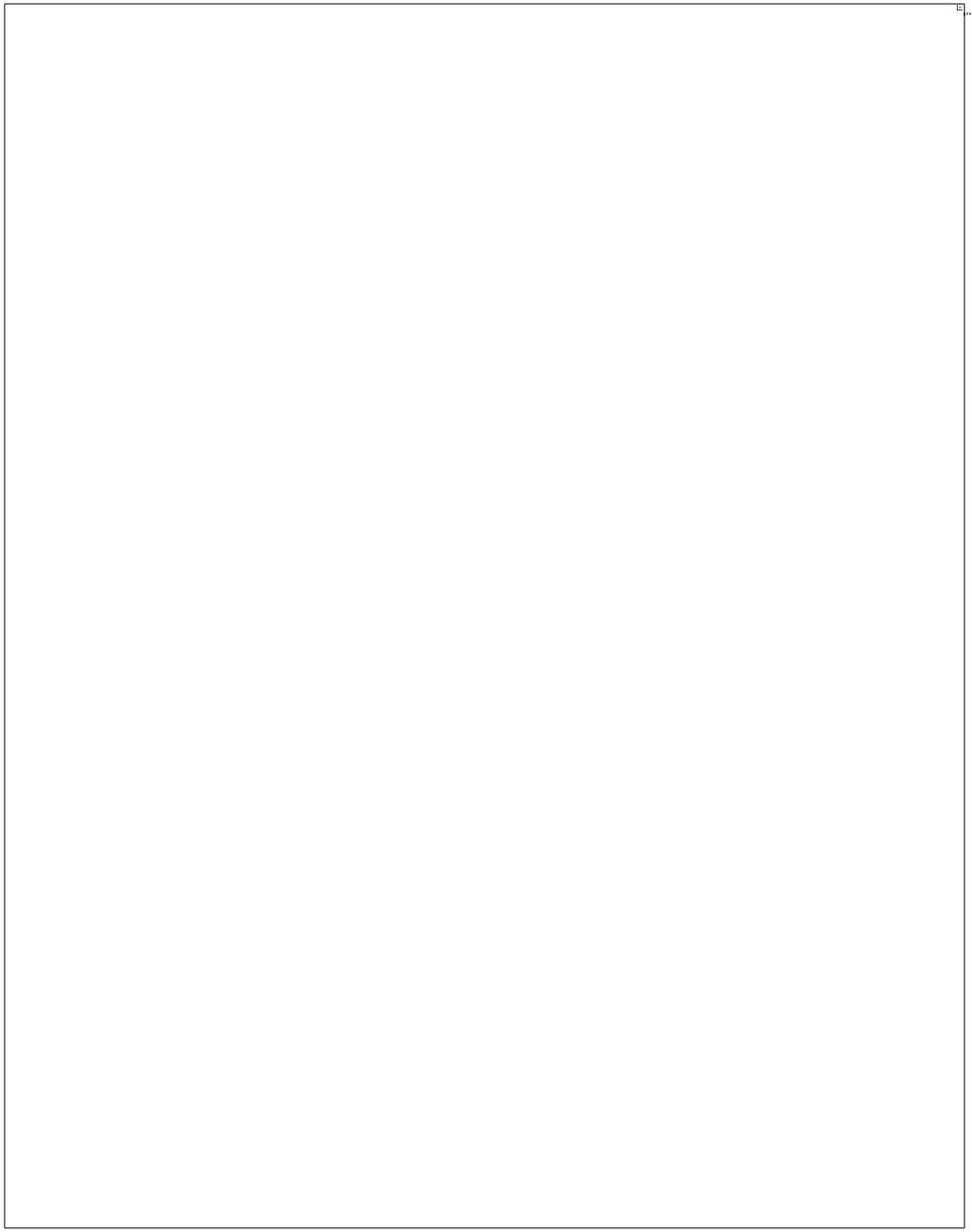


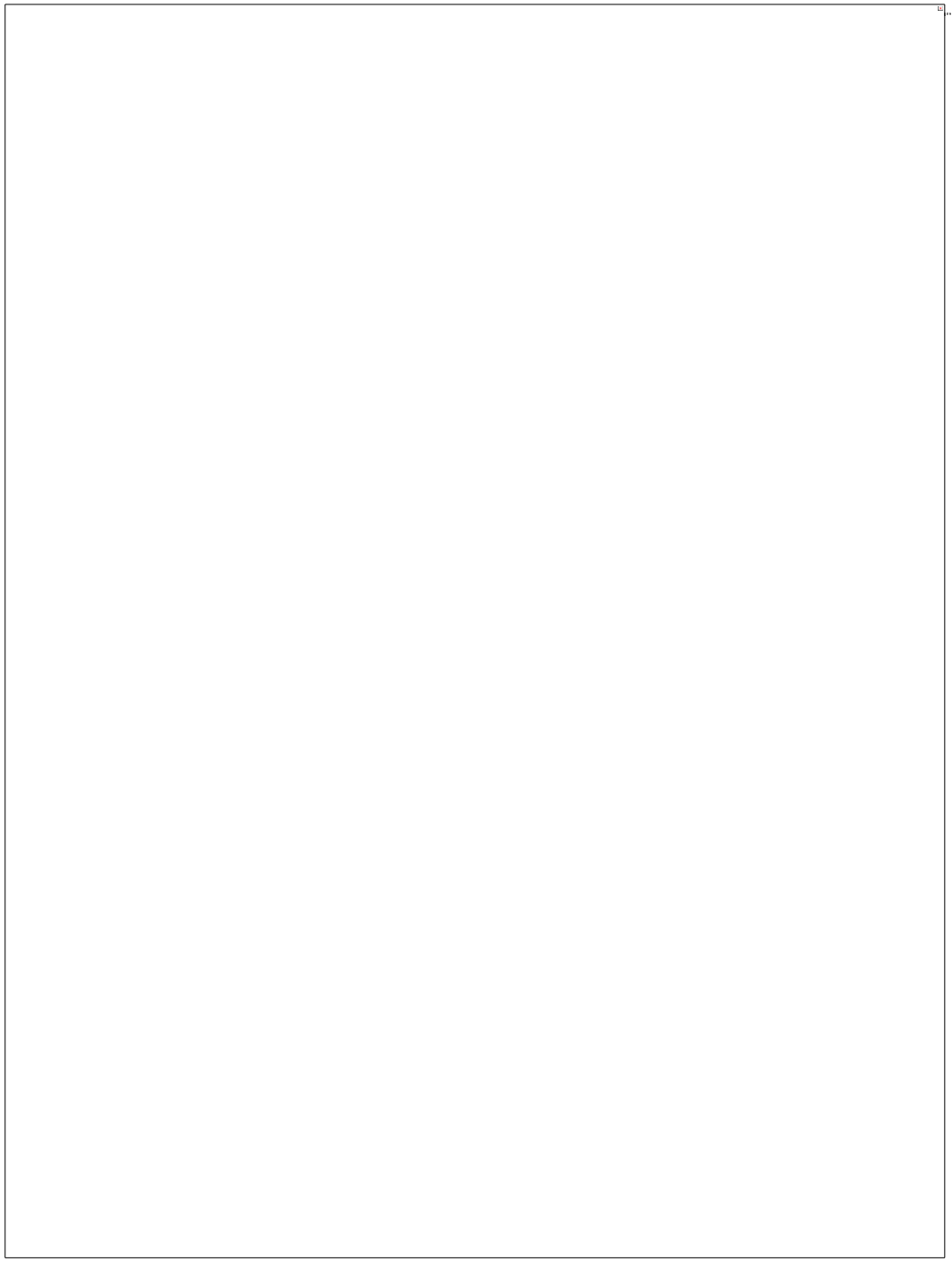


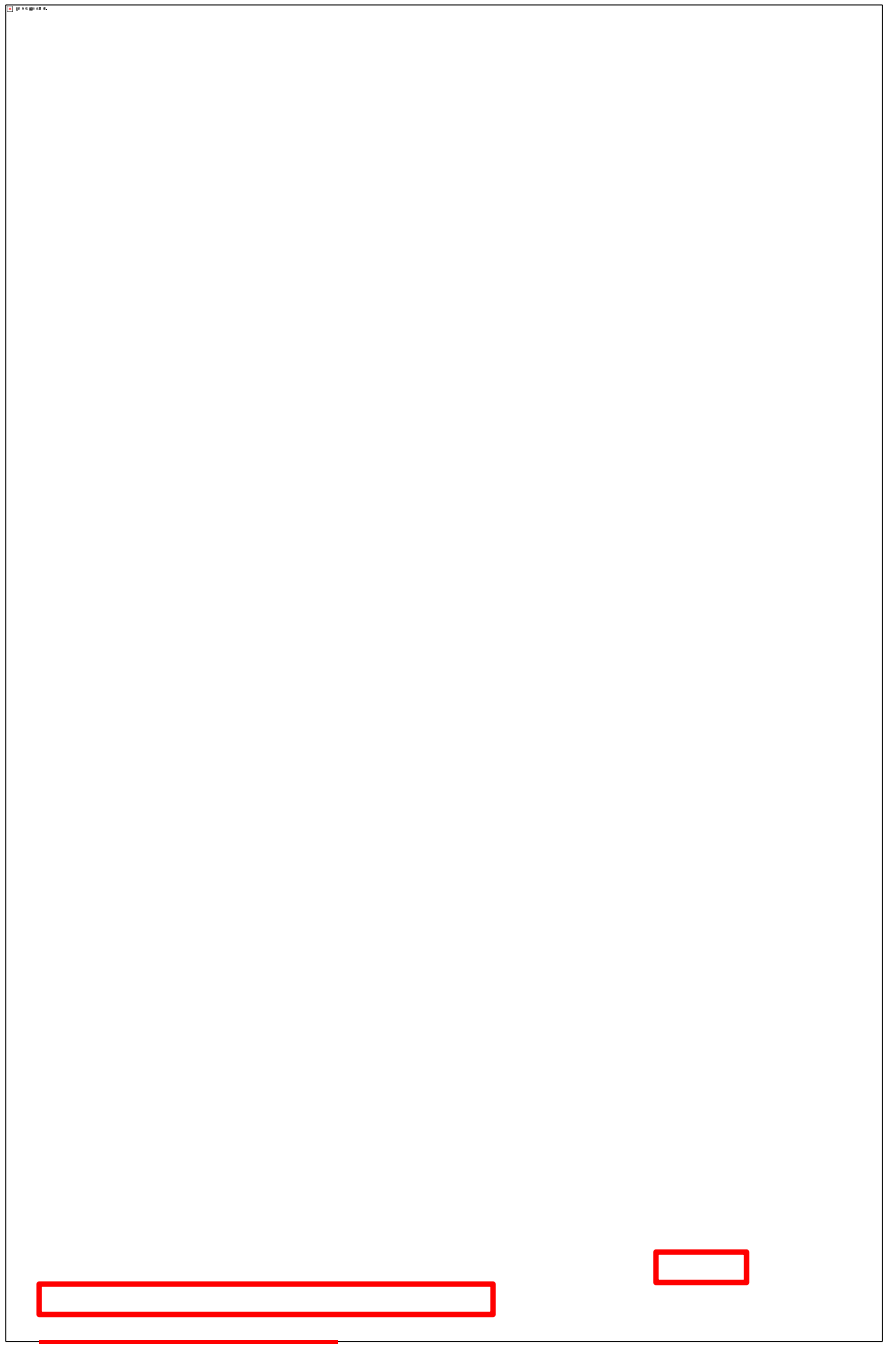
My choice

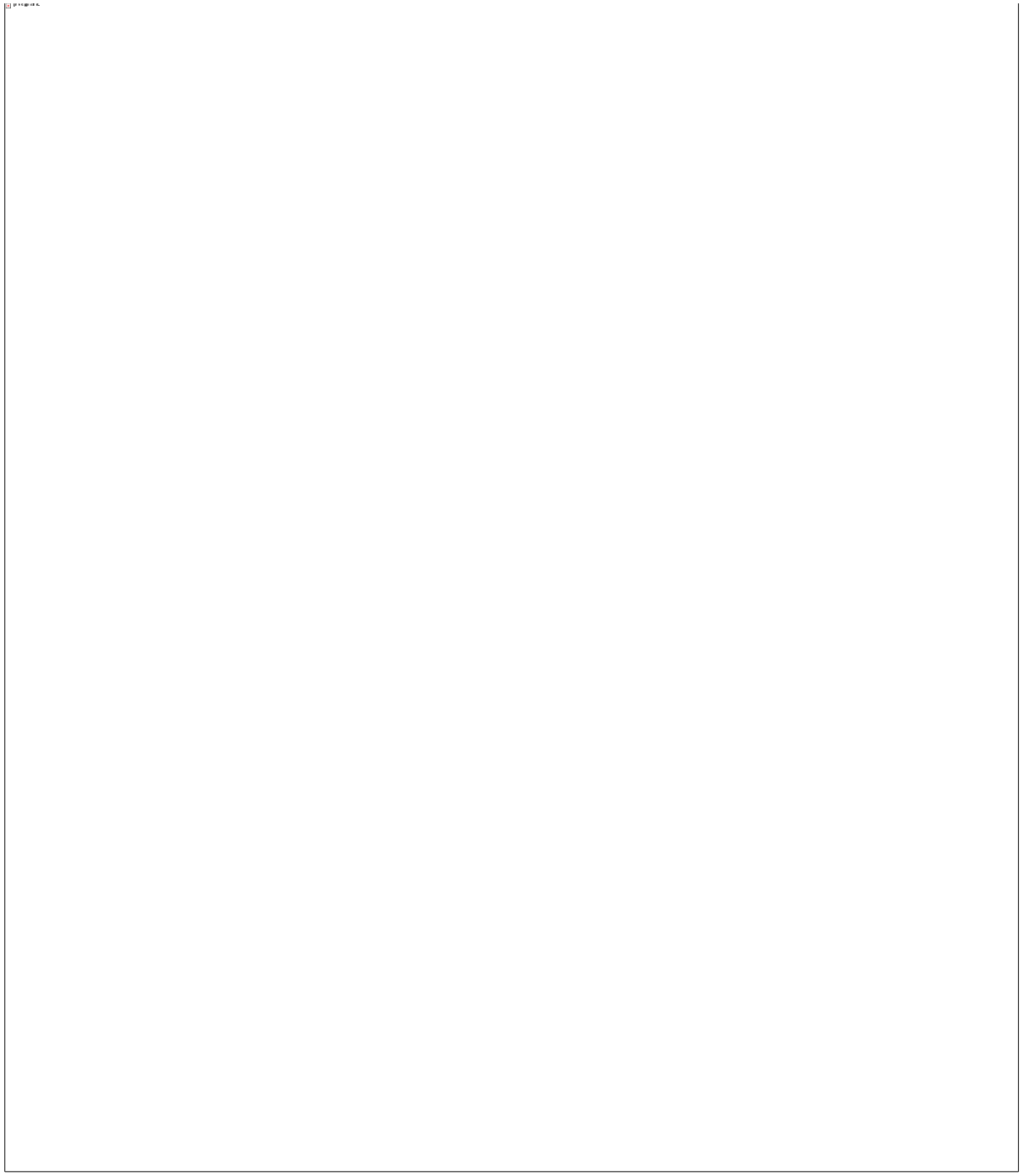


- Metformin
- Pioglitazone
- GLP1 receptor agonist
  - e.g. Victoza
- SGLT2 inhibitor
  - e.g. Empagliflozin
- DPPIVI
  - e.g. Sitagliptin
- SU
  - e.g. Diamicron
- Insulin









Conclusion

There is no such thing as ‘The BEST DRUG’, but only ‘The SUITABLE DRUG’