INTENDED AND UNINTENDED COMPLICATIONS OF DRUG THERAPY OF DM

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DRUGS FOR THE TREATMENT OF T2DM

DECREASE INTAKE

Incretin based tx

Metformin

Carbohydrate Load

Decrease absorption

INCREASE INSULIN SENSITIVITY

INSULIN RESISTANCE

Digestion of Polysaccharides

α-Glucosidase Inhibitors

Liver

Hyperglycemia

Adipose

Increased FFA

Thiazolidinediones

Increased Glucose Production

Metformin

Thiazolidinediones

Incretin based tx

Skeletal Muscle

Decreased Glucose Uptake and Utilization

Metformin

Thiazolidinediones

Pancreas

Impaired Insulin Secretion

INSULIN DEFICIENCY

Sulfonylureas

Meglitinides

Incretin based tx

INCREASE SECRETION

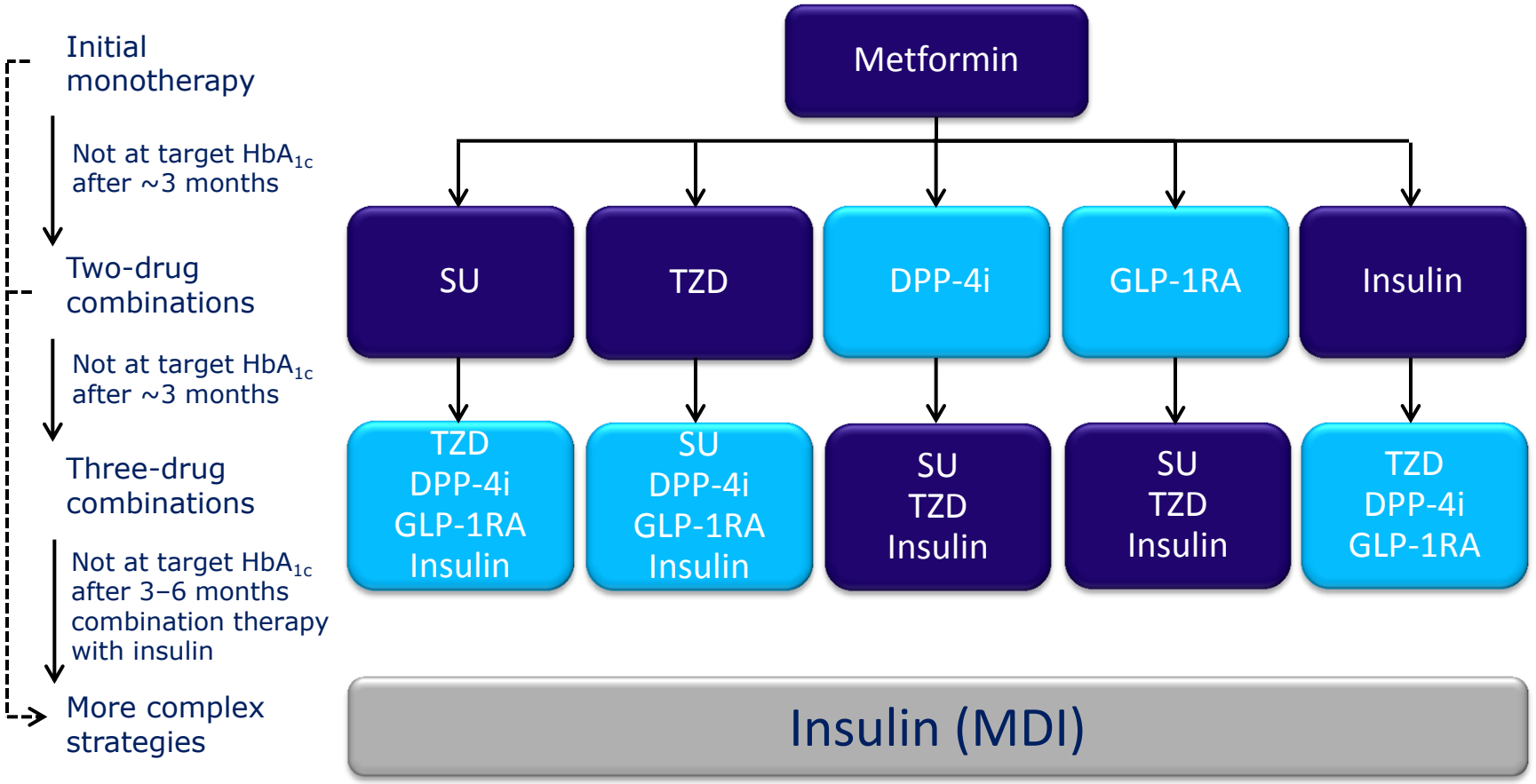
INSULIN

PROVIDE WHAT IS LACKING

Antidiabetics drugs

- Insulin secretagogues
  - Sulfonylureas
  - Meglitinides
- Biguanides: Metformin
- Thiazolidinediones
- Alpha-glucosidase inhibitors
- Insulin
- Incretin-based treatment
  - GLP-1 mimetics
  - DPP-IV inhibitors
- Amylin analog: Pramlintenide

ADA/EASD position statement 2012



ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; GLP-1RA, glucagon-like peptide-1 receptor agonists; MDI, multiple daily injections; SU, sulphonylurea; TZD, thiazolidinedione.

Inzucchi *et al. Diabetologia* 2012;55:1577–96.

Metformin(1957)reduces HbA1C 1-1.5%

- GASTROINTESTINAL:30%
  - Nausea & Vomitting, anorexia, abd discomfort, diarrhea
- Decreased absorption of Vit B12
- Hepatotoxicity

Less convenient dosing

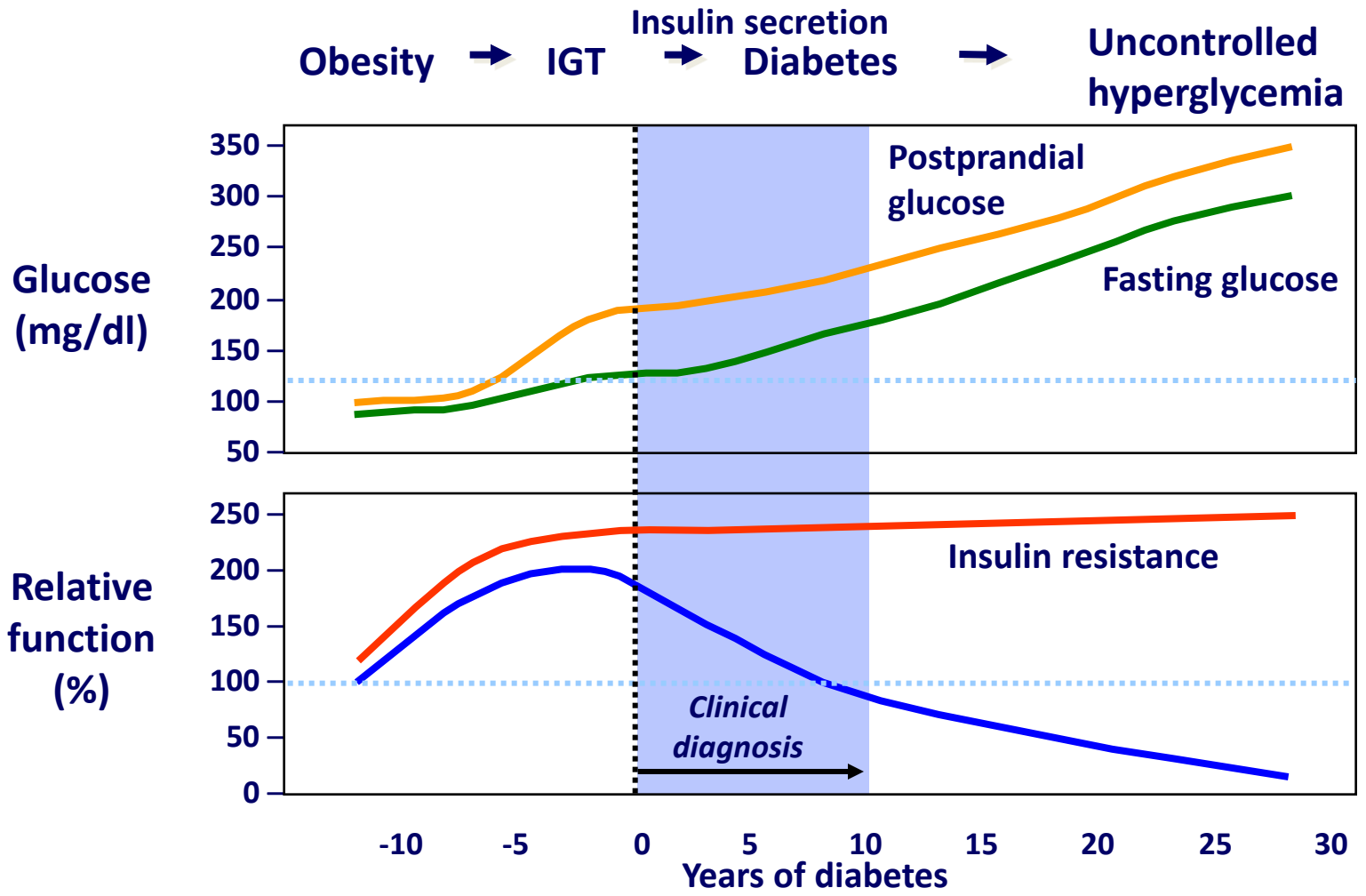
Metallic taste

Weight neutral/loss ~2.4 kg

- Cyclic AMP ~ hepatic gluconeogenesis
- Increase peripheral uptake of glucose

- Anorectic PYY secretion

Insulin resistance and β-cell dysfunction are fundamental to type 2 diabetes



Adapted from Bergenstal RM, et al. Diabetes mellitus, carbohydrate metabolism and lipid disorders. In Endocrinology. 4th ed. 2001.

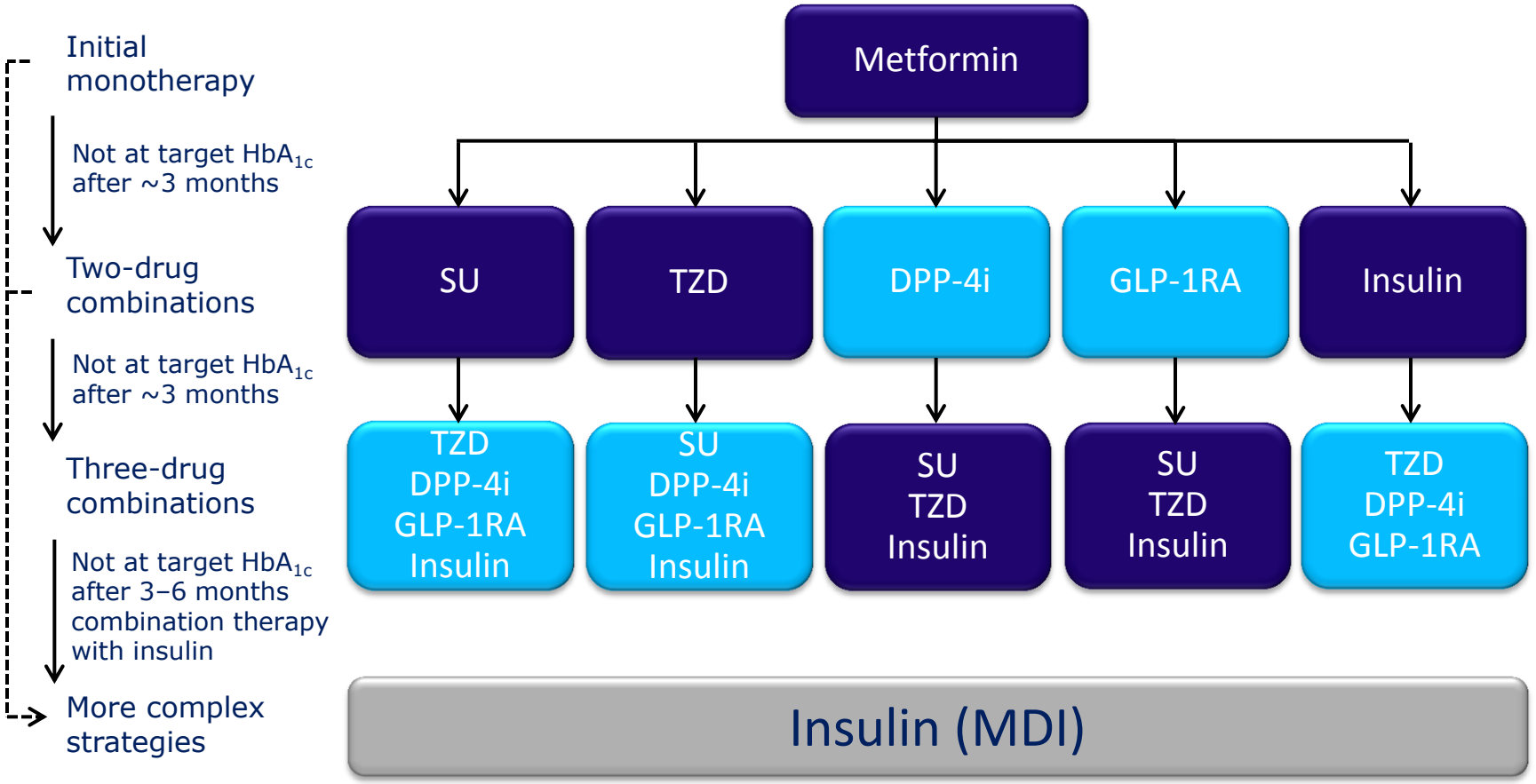
Metformin

- Lactic acidosis 1.5/100000 patient yr

1. Caution advised in
   - Renal disease
   - Hepatic disease
   - Cardiovascular compromise
   - With intravenous contrast media

- Acute medical condition
- Creatinin>1.5

ADA/EASD position statement 2012



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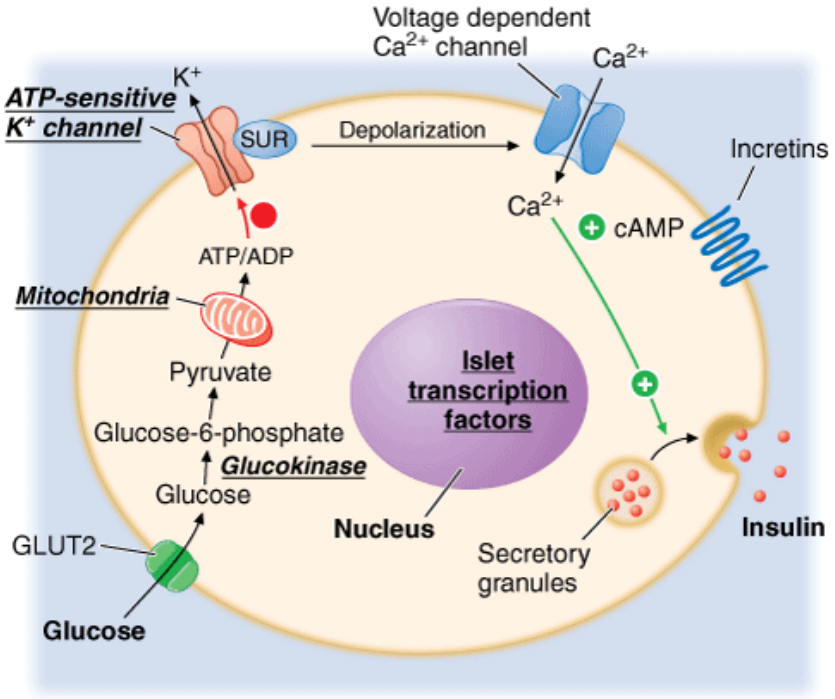
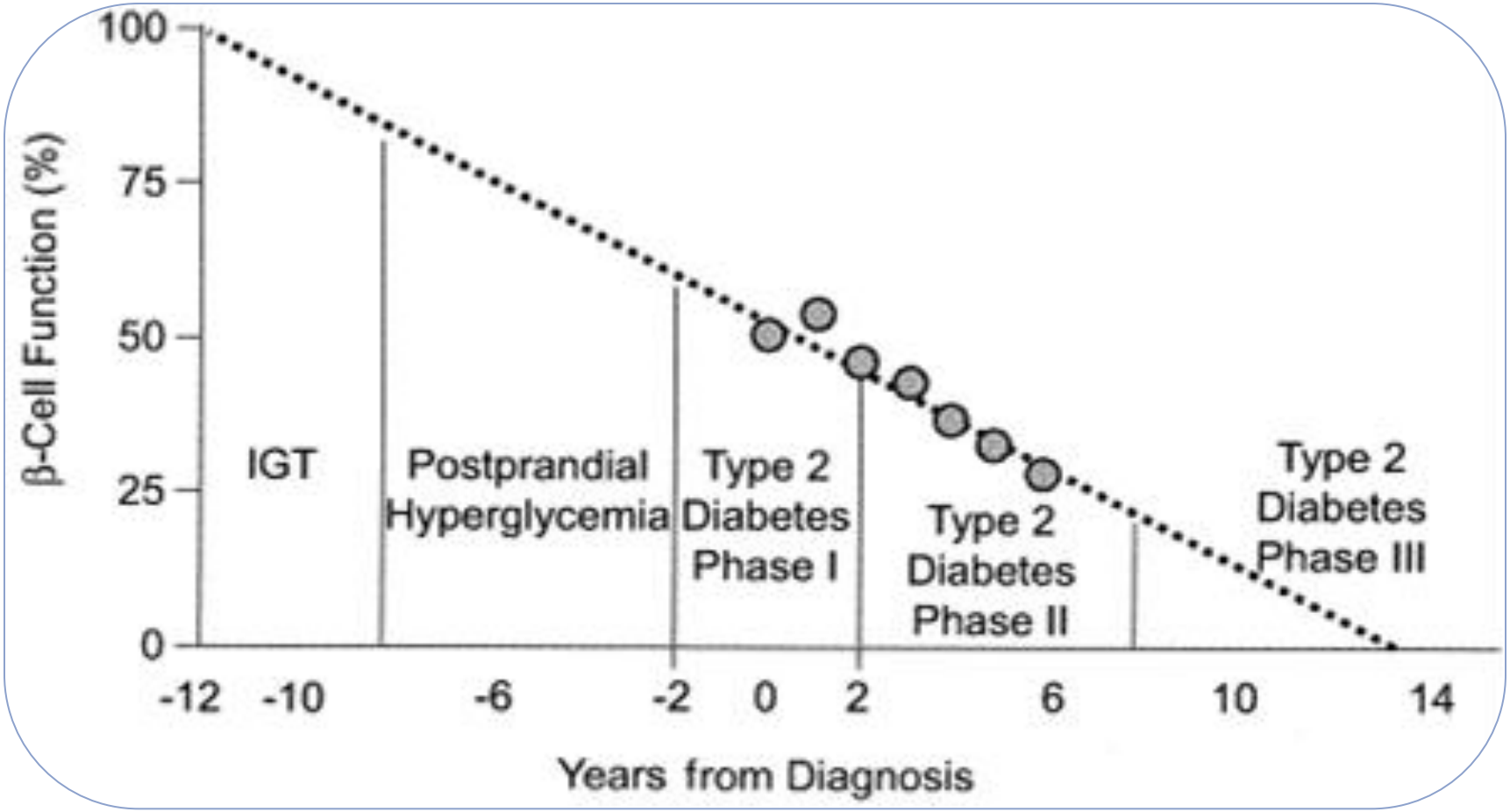
Sulfonylureas (1946)reduces HbA1C 0.8-2%

- Relatively glucose-independent stimulation of insulin secretion: ***Hypoglycemia***, including episodes necessitating hospital admission and causing death
- 2nd gen: Glubenclamide > Glipizide > Glimepiride
- Weight gaingain;5-10lbs



Progressive β-cell dysfunction in type 2 diabetes



SUs

- Not <40yr ;>10 yr duration
- Drug interactions, Allergy
- Pronounced hyperglycemia reduces absorption
- Prolonged stimulation of beta cells may lead to loss -of beta cell function-Exhaustion & SU failures - 5-10% per year>Low “durability

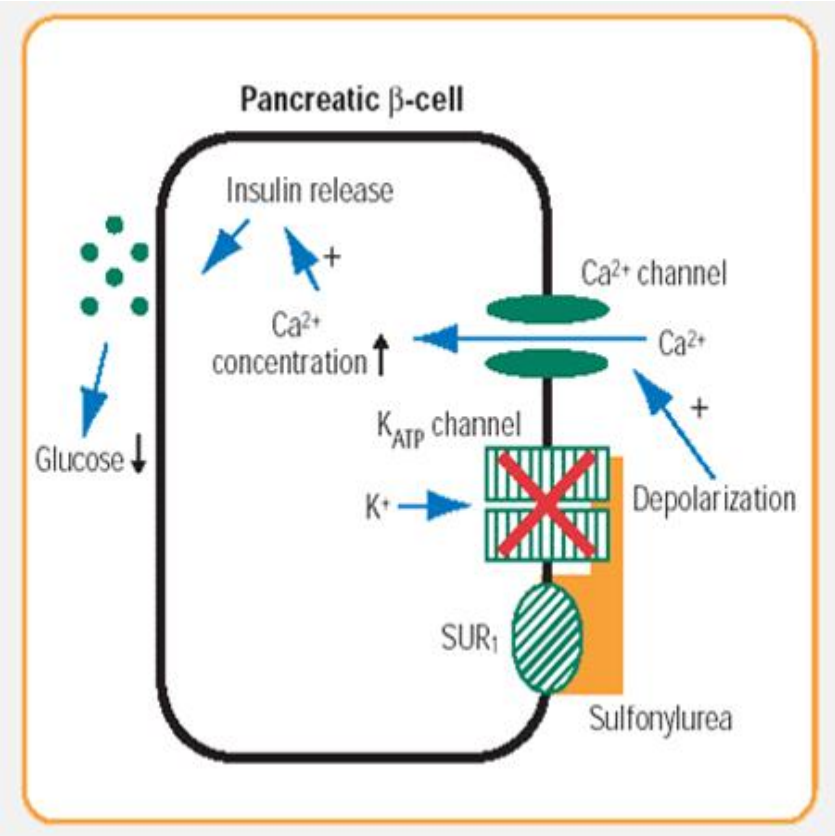
- May blunt myocardial ischemic preconditioning
- Drug interactions

- Glibenclamide/Glyburide
- Glipizide
- Gliclazide
- Glimepiride
- *Closes K_{ATP} channels on β-cell plasma membranes*

SU'S: ADVERSE EFFECTS
(MORE COMMON FOR 1ST GEN)

- Nausea, vomiting
- Cholestatic jaundice
- Dilutional hyponatremia
- Hematologic: agranulocytosis, thrombocytopenia, transient leukopenia, anemia (aplastic / hemolytic)
- Disulfiram-like effect with ROH
- Allergic and dermatologic reactions

Ripaglinides(1997)reuces Hba1c 0.8-1.5%

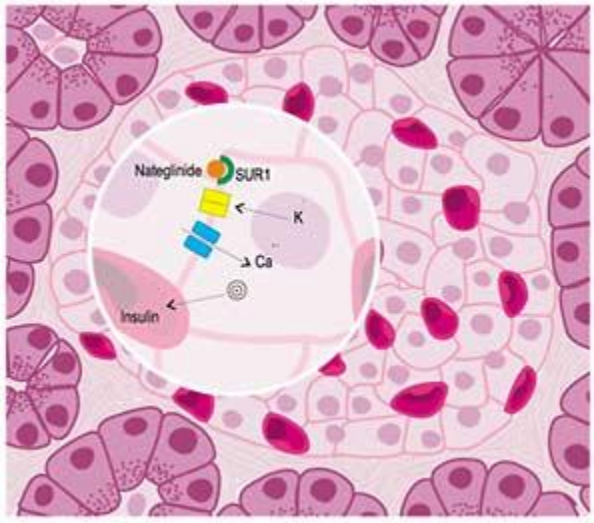


Meglitinides: have 2 common binding sites w/ SU and 1 unique binding site

- Hypoglycemia, weight gain
- May blunt myocardial ischemic preconditioning
- Dosing frequency
- Cost Medium

- No meal no pill

NATEGLINIDE



- Hypoglycemia, weight gain
- May blunt myocardial ischemic preconditioning
- Dosing frequency
- Cost high

- No meal no pill

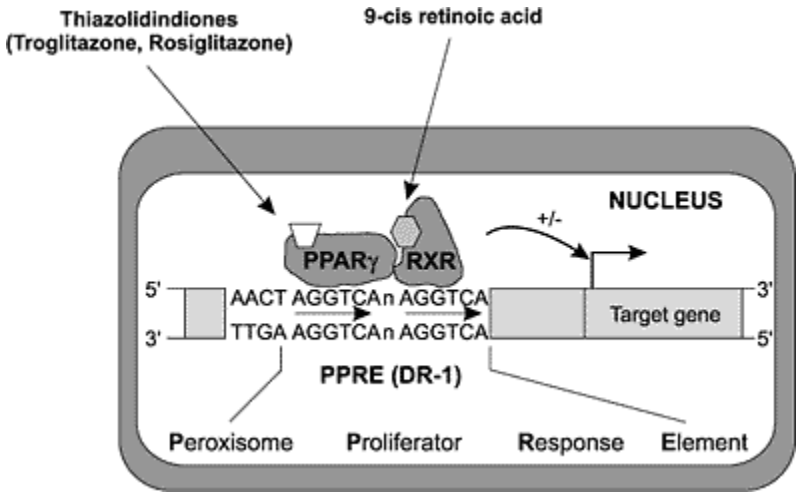
Thiazolidinediones (Glitazones)(1997);reduces HbA1C 0.8-1%

- Troglitazone– Abandoned in 90s fro hepatotxicity from market
- Rosiglitazone-Abandoned from EU market 2010;black box warning FDA
- Pioglitazone-warning in use in heart failure

- Activates the nuclear transcription factor PPAR-γ
- Peripheral insulin sensitivity $\uparrow$

Pioglitazone

LIVER, MUSCLE, FAT
Activate insulin-responsive genes
regulating
- Glc and lipid metab



- Edema,anemia
- Bone fractures
- Increased risk of bladder cancer
- URI, sinusitis, pharyngitis,Myalgia ,Headache
- Increase LDL
- May cause or exacerbate heart failure with risk of fluid retention
- Weight gain ~ 5 kg

PPAR-γ activators
Insulin sensitizers
delay from 4-12 weeks in the onset of their therapeutic benefits

Rosiglitazone

- Anemia –dilutional
- Edema-Heart failure
- Bone fractures
- Increased risk of bladder cancer
- URI, sinusitis, pharyngitis,Myalgia ,Headache

- ****still many things to be explored***

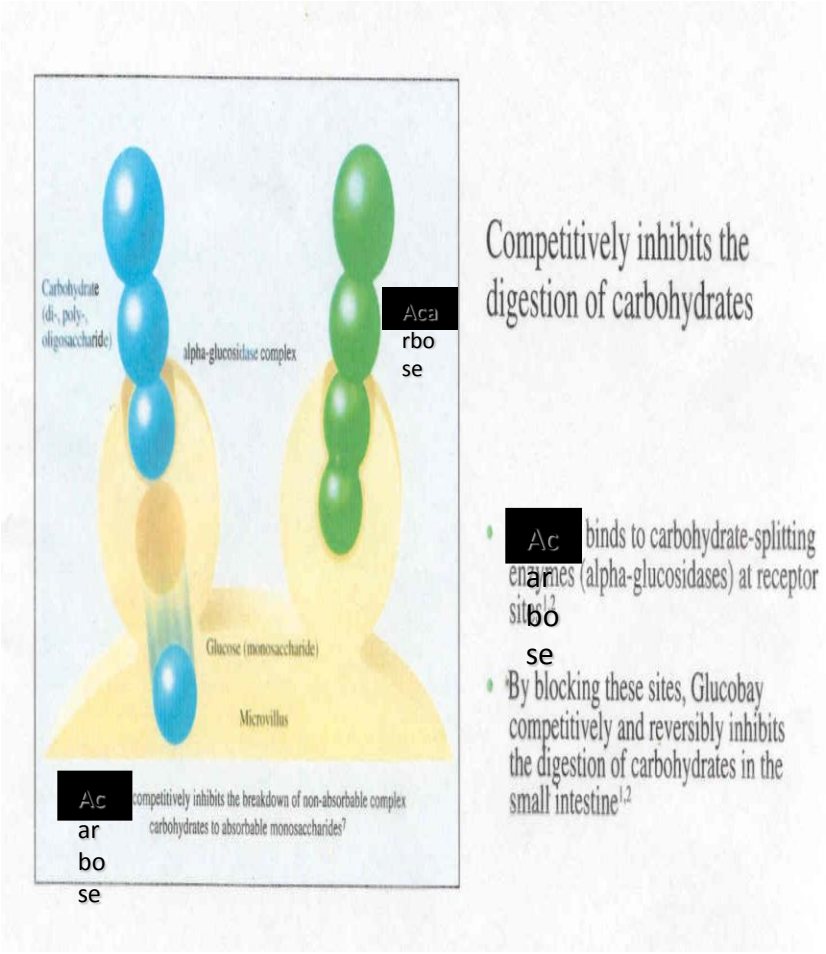
- Genome effect-PPRA
- VEGF
- Lipid profile(raised LDL,TG)

α-GLUCOSIDASE INHIBITORS (1995)reduces HbA1c 0.5-0.8%

- Gastrointestinal side effects (gas, flatulence, diarrhea)
- Dosing frequency
- <u>Expensive effect on HbA1c minimal compared to OHAs</u>

High carbohydrate diet required for efficacy

Cannot treat hypoglycemia with sucrose, maltose or starch



α-GLUCOSIDASE INHIBITORS (1995)reduces HbA1c 0.5-0.8%

- Acarbose
- Miglitol

- USA not used due to GI effects

New drugs

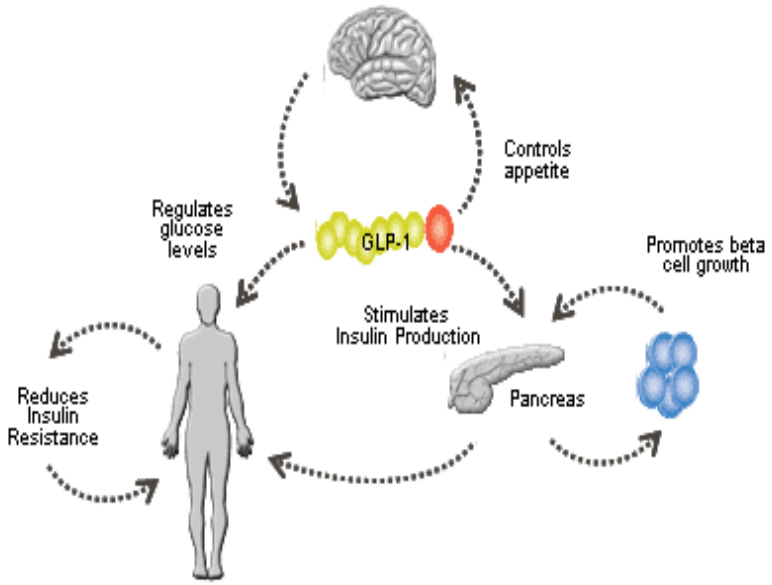
- Incretin-based treatment
  - GLP-1 mimetics
  - DPP-IV inhibitors
- Amylin analog: Pramlintenide

Exenatide reduces 0.5-1.0%

Though enough data are not available, but we have to be careful for

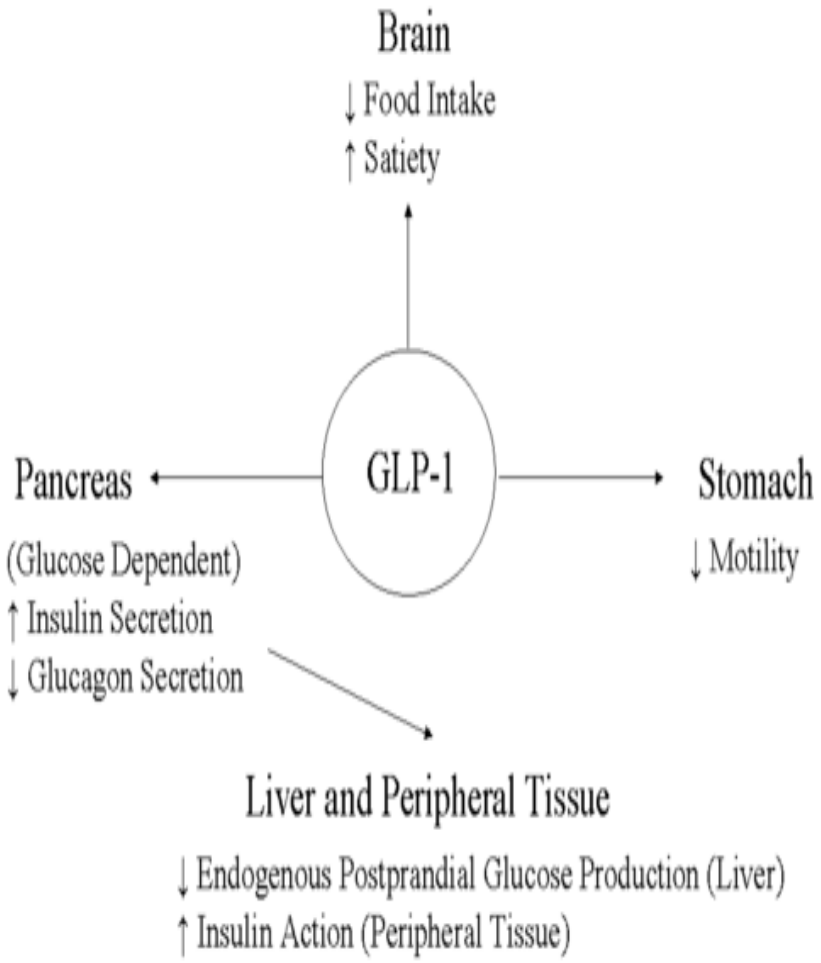
1. Pancreatitis (both acute and chronic)
2. Pancreatic cancer
3. Thyroid C cell tumor
4. Renal failure

- SC injections: absorbed equally from arm, abdomen, thigh
- Peak: 2 hrs
- Duration: up to 10 hrs

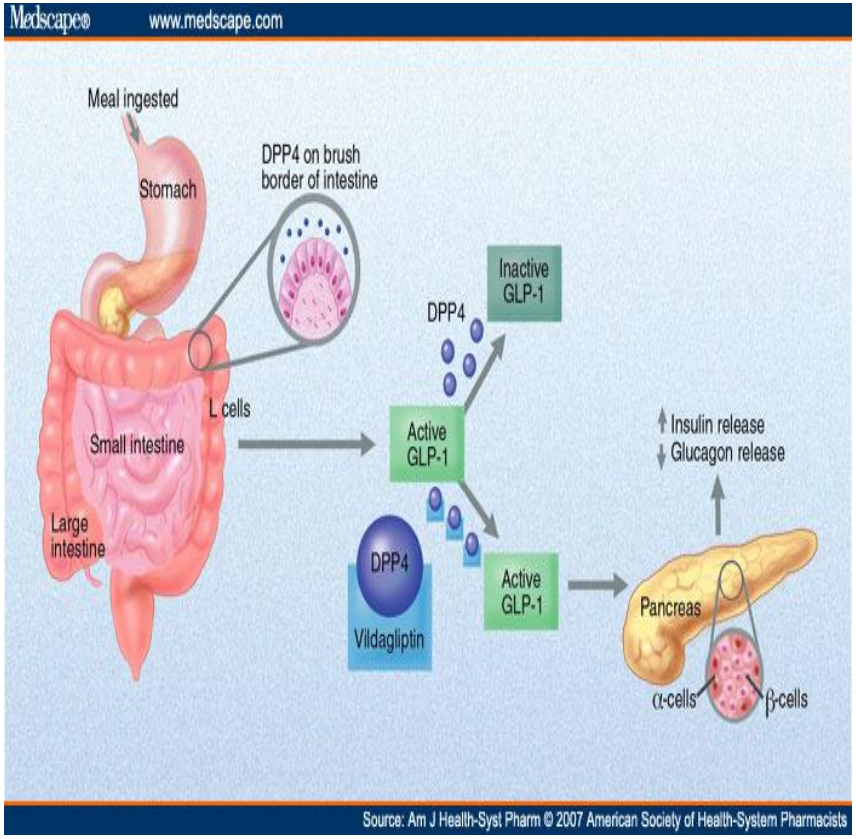


Liraglutide reduces HbA1c 0.5-1.0

- Gastrointestinal side effects (nausea, vomiting, diarrhea)
- Cases of acute pancreatitis observed
- Pancreatic cancer
- C-cell hyperplasia/medullary thyroid tumors in animals (liraglutide)
- Injectable
- Long-term safety unknown
- High cost



Vildagliptine-reduces HbA1c 0.5-0.9%



- Liver enzyme elevation
- Occasional reports of urticaria/angioedema
- Cases of pancreatitis observed
- Long-term safety unknown
- Nasopharyngitis/URI
- Headache
- High cost

DPP1V inhibitors

- DPP1V inhbits substrates in varied organs
- Sitagliptin
- Vildagliptin
- Saxagliptin
- Linagliptin

- Allergy:Occasional reports of urticaria/angioedema
- Nasopharyngitis/URI
- Headache

Noninsulin Therapies for Type 2 Diabetes

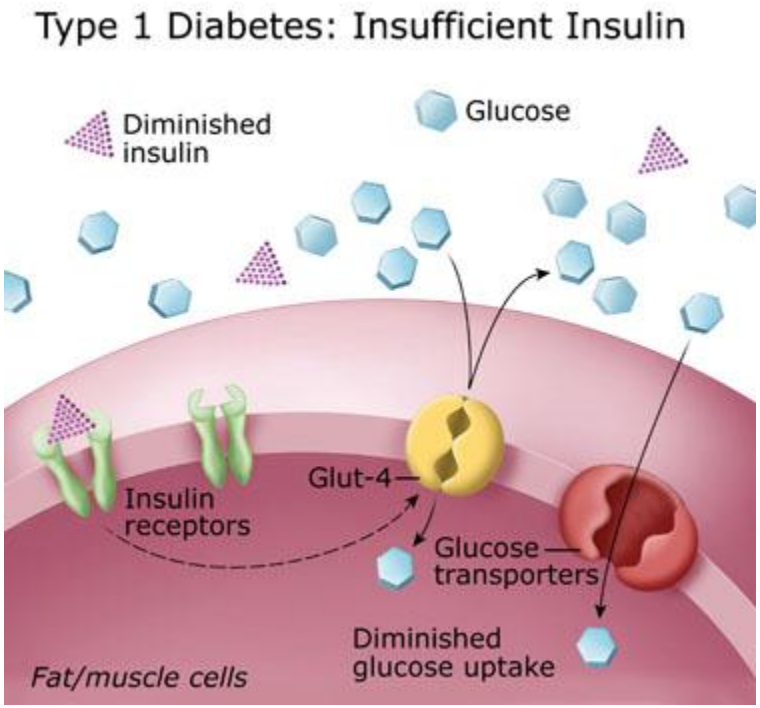
Class	Dopamine-2 agonists
Compound	Bromocriptine
Mechanism	Activates dopaminergic receptors
Action(s)	• Alters hypothalamic regulation of metabolism • Insulin sensitivity ↑
Disadvantages	• Dizziness/syncope • Nausea • Fatigue • Rhinitis • Long-term safety unknown
Cost	Medium

Drugs not used

- Bromocriptine
- Bile acid sequestrants
- Alternate medicines

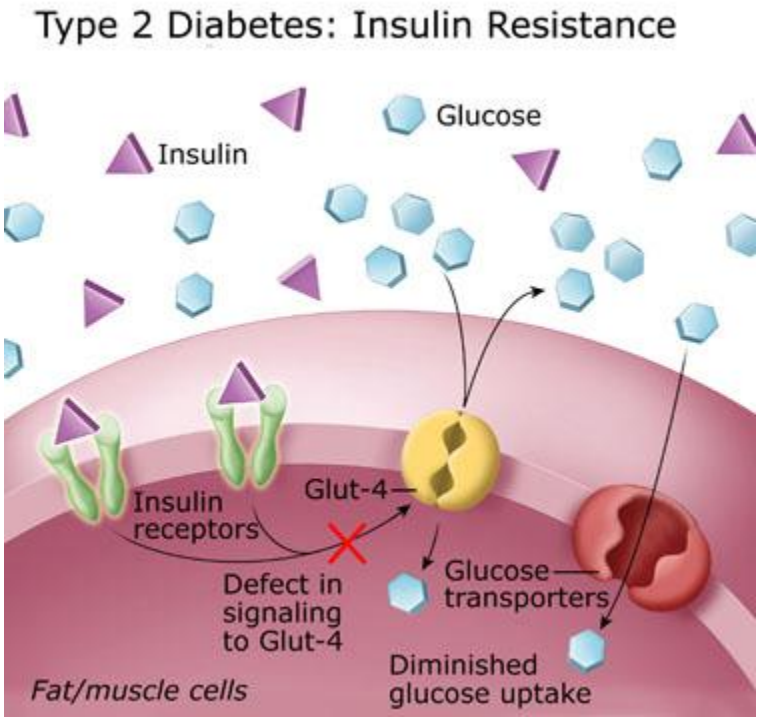
- Alters hypothalamic regulation of metabolism
- Insulin sensitivity ↑
- Unknown mechanism
- No validated studies

Insulin



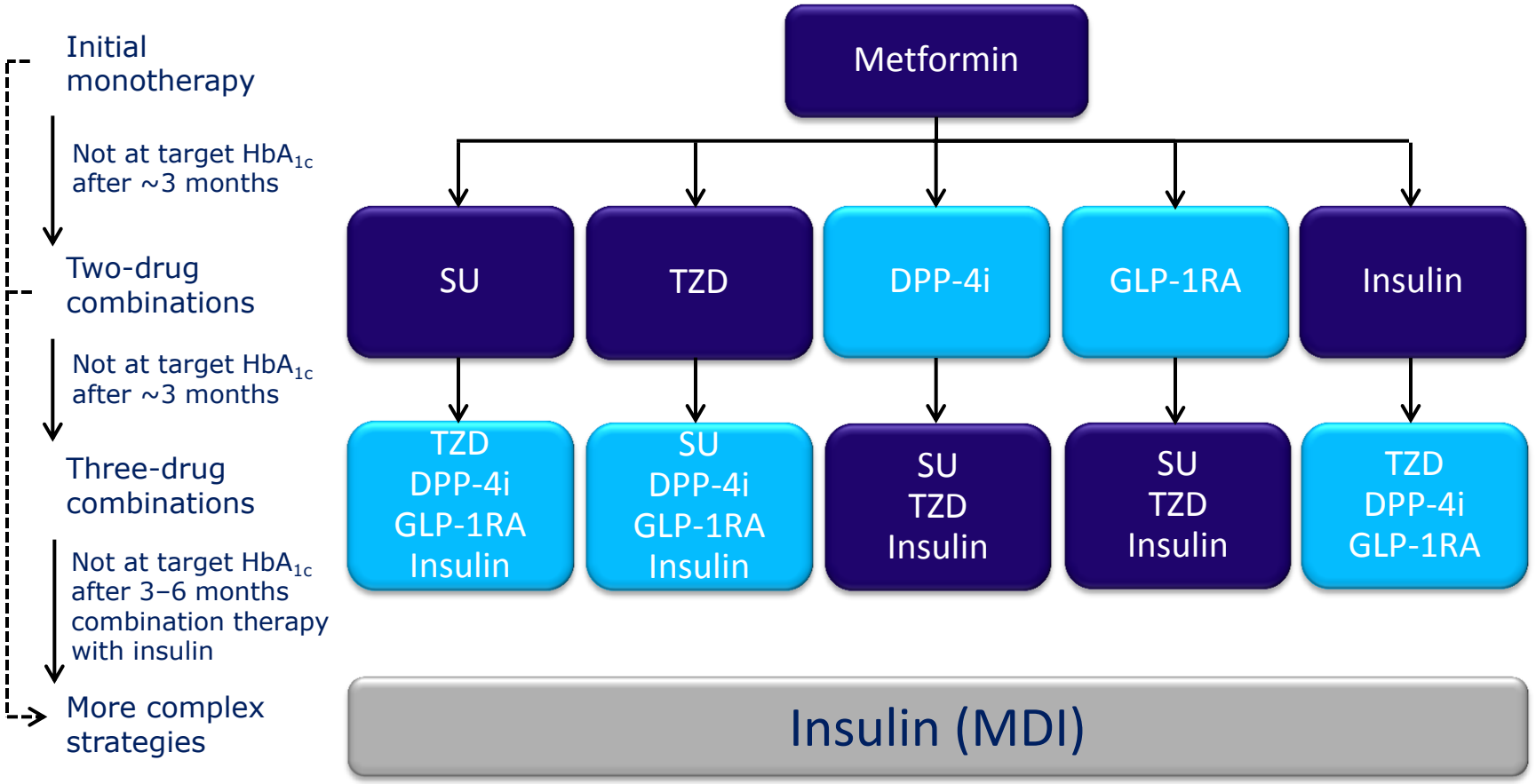
- Hypoglycemia
- Weight gain
- No maximum dose

Insulin



- Lipodystrophy at injection sites (hypertrophy)
  - Avoid by site rotation
- Immunogenicity - rare
  - Insulin allergy (IgE-mediated) – local reactions, anaphylaxis
    - Often due to non-insulin protein contaminants
    - Less frequent with insulin analogs
  - Immune insulin resistance (IgG mediated)
    - Neutralize insulin action

ADA/EASD position statement 2012



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Inzucchi *et al. Diabetologia* 2012;55:1577–96.

Combination Therapy

Hypoglycemia

Difficult to treat

Poly Pharmacy

Drug Interaction

Hypoglycaemia is the principal limiting factor in glycaemic management

Non-severe events

- Self-treated[1]
- Typically followed by increased blood glucose monitoring[2]

Severe events

- Require third-party assistance
- May require hospitalisation and inpatient care[3]

Nocturnal hypoglycaemia

- Poor sleep quality
- Often associated with reduced productivity the next day[2]

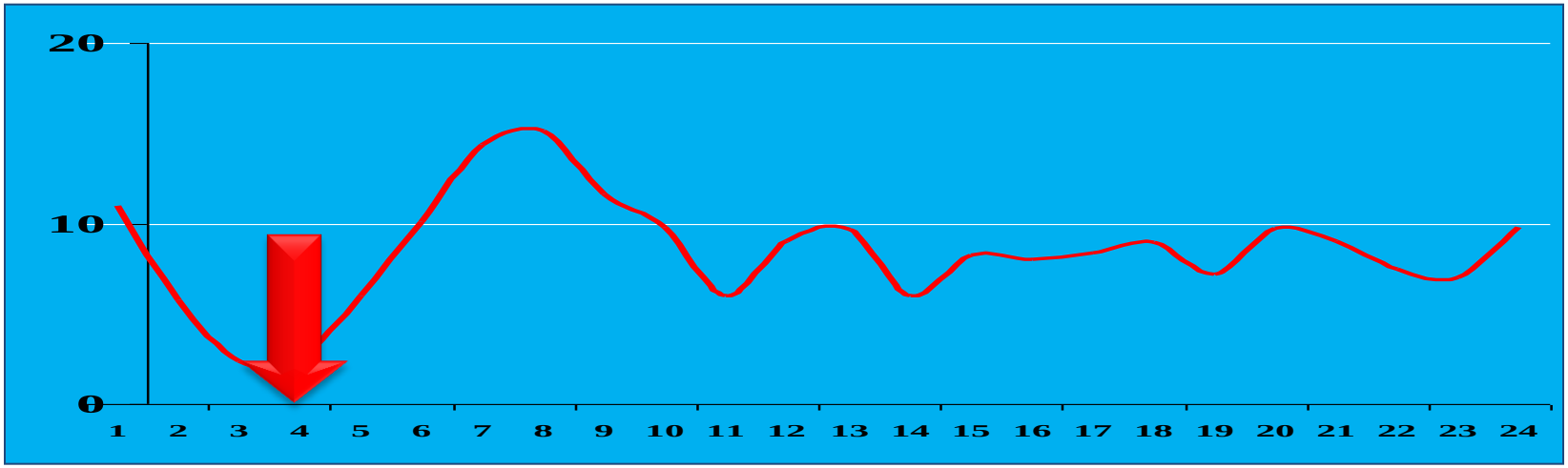
1. Cryer *et al. Diabetes Care* 2003;26:1902–12; 2. Brod *et al. Value Health* 2011;14:665–71; 3. Leese *et al*. *Diabetes Care* 2003;26:1176–80

The clinical consequences of hypoglycaemia are not trivial

Morbidity associated with hypoglycaemic episodes[1]	
Accidents	• Fractures, joint dislocations, head injuries • Soft-tissue injuries
Neurological	• Convulsions, coma • Paralysis, transient ischaemic events, focal lesions
Cardiac	• Arrhythmias • Myocardial ischaemia/infarction • Cardiac failure

1. Frier. *Br J Diabetes Vasc Dis* 2011;11:(Suppl 1)S10–2

Somogyi Phenomenon



Cause:

Counter regulatory hormones response to hypoglycemia at med-night.

Increase in hepatic glucose production.

Insulin resistance because of the Counter regulatory hormones.

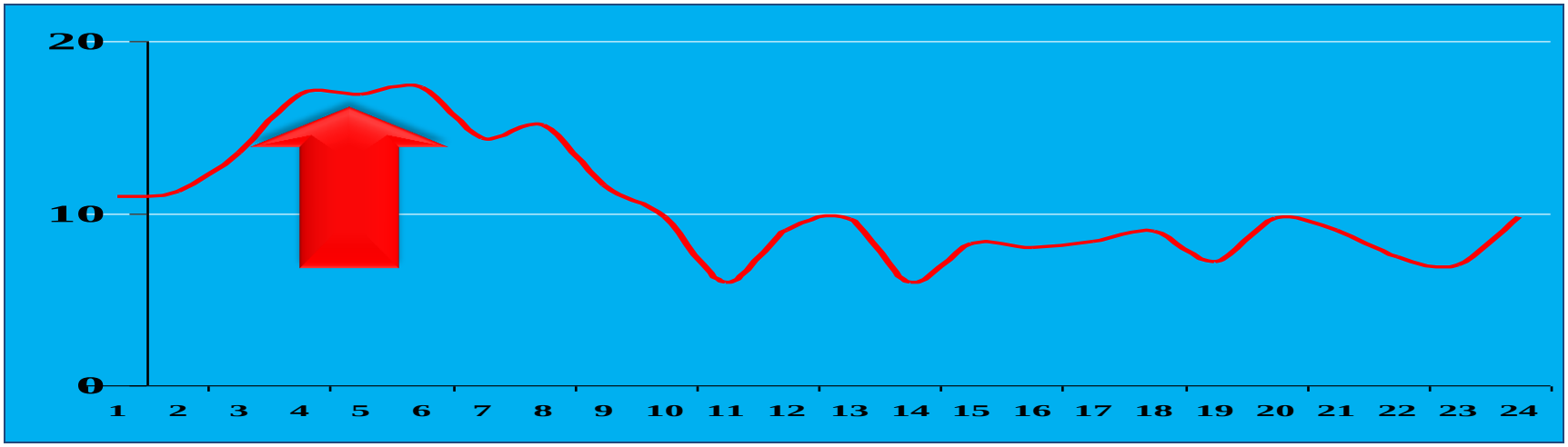
Treatment:

Decrease pre-supper intermediate insulin.

Defer the dose to 9 PM.

Change or start pre-bed snack.

Dawn Phenomenon



Cause:

Less insulin at bed time.

More food at bed time.

Not using NPH at night.

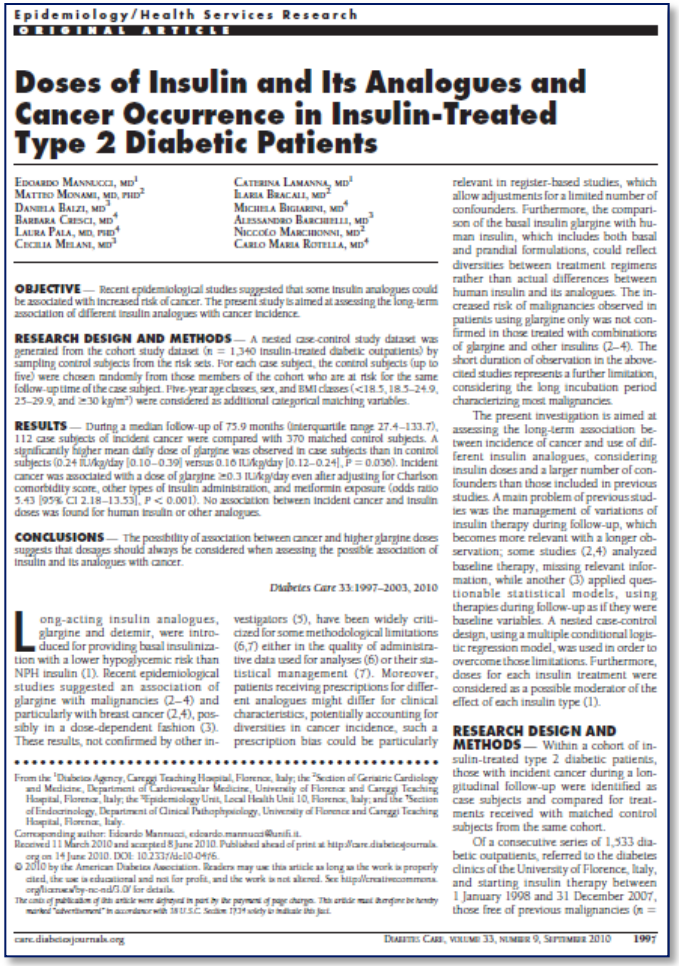
Treatment:

Use enough dose.

Reduce bed time snack.

Add NPH pre-supper.

Recent Database Study on Insulin Analogues and Cancer in Type 2 Diabetes



Epidemiology/Health Services Research

ORIGINAL ARTICLE

Doses of Insulin and Its Analogues and Cancer Occurrence in Insulin-Treated Type 2 Diabetic Patients

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OBJECTIVE — Recent epidemiological studies suggested that some insulin analogues could be associated with increased risk of cancer. The present study is aimed at assessing the long-term association of different insulin analogues with cancer incidence.

RESEARCH DESIGN AND METHODS — A nested case-control study dataset was generated from the cohort study dataset (n = 1,340 insulin-treated diabetic outpatients) by sampling control subjects from the risk sets. For each case subject, the control subjects (up to five) were chosen randomly from those members of the cohort who are at risk for the same follow-up time of the case subject. Five-year age classes, sex, and BMI classes (<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m²) were considered as additional categorical matching variables.

RESULTS — During a median follow-up of 75.9 months (interquartile range 27.4–133.7), 112 case subjects of incident cancer were compared with 370 matched control subjects. A significantly higher mean daily dose of glargine was observed in case subjects than in control subjects (0.24 IU/kg/day [0.10–0.39] versus 0.16 IU/kg/day [0.12–0.24], P = 0.036). Incident cancer was associated with a dose of glargine ≥0.3 IU/kg/day even after adjusting for Charlson comorbidity score, other types of insulin administration, and metformin exposure (odds ratio 5.43 [95% CI 2.18–13.53], P < 0.001). No association between incident cancer and insulin doses was found for human insulin or other analogues.

CONCLUSIONS — The possibility of association between cancer and higher glargine doses suggests that dosages should always be considered when assessing the possible association of insulin and its analogues with cancer.

Diabetes Care 33:1997–2003, 2010

Long-acting insulin analogues, glargine and detemir, were introduced for providing basal insulinization with a lower hypoglycemic risk than NPH insulin (1). Recent epidemiological studies suggested an association of glargine with malignancies (2–4) and particularly with breast cancer (2,4), possibly in a dose-dependent fashion (3). These results, not confirmed by other investigators (5), have been widely criticized for some methodological limitations (6,7) either in the quality of administrative data used for analyses (6) or their statistical management (7). Moreover, patients receiving prescriptions for different analogues might differ for clinical characteristics, potentially accounting for diversities in cancer incidence, such a prescription bias could be particularly relevant in register-based studies, which allow adjustments for a limited number of confounders. Furthermore, the comparison of the basal insulin glargine with human insulin, which includes both basal and prandial formulations, could reflect diversities between treatment regimens rather than actual differences between human insulin and its analogues. The increased risk of malignancies observed in patients using glargine only was not confirmed in those treated with combinations of glargine and other insulins (2–4). The short duration of observation in the above-cited studies represents a further limitation, considering the long incubation period characterizing most malignancies.

The present investigation is aimed at assessing the long-term association between incidence of cancer and use of different insulin analogues, considering insulin doses and a larger number of confounders than those included in previous studies. A main problem of previous studies was the management of variations of insulin therapy during follow-up, which becomes more relevant with a longer observation; some studies (2,4) analyzed baseline therapy, missing relevant information, while another (3) applied questionable statistical models, using therapies during follow-up as if they were baseline variables. A nested case-control design, using a multiple conditional logistic regression model, was used in order to overcome those limitations. Furthermore, doses for each insulin treatment were considered as a possible moderator of the effect of each insulin type (1).

RESEARCH DESIGN AND METHODS

— Within a cohort of insulin-treated type 2 diabetic patients, those with incident cancer during a longitudinal follow-up were identified as case subjects and compared for treatments received with matched control subjects from the same cohort.

Of a consecutive series of 1,533 diabetic outpatients, referred to the diabetes clinics of the University of Florence, Italy, and starting insulin therapy between 1 January 1998 and 31 December 2007, those free of previous malignancies (n =

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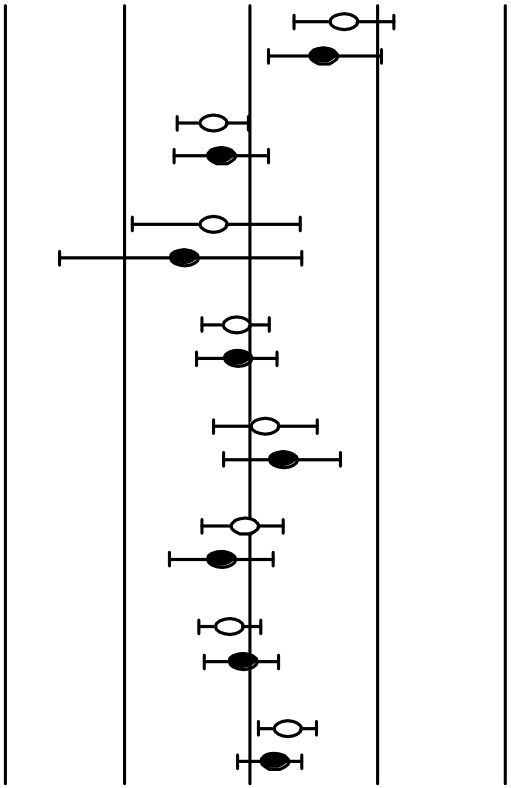
- There was a suspicion and warning by FDA but substantiated later

Increased Risk of Cancer Associated with Modern Insulin Analogues



	HR	95% CI		*p*
Glargine	5.43	2.18	13.53	<0.01
	3.71	1.32	10.36	0.013
Lispro	0.50	0.26	0.94	0.031
	0.57	0.24	1.34	0.20
Aspart	0.50	0.11	2.36	0.38
	0.29	0.03	2.52	0.26
Human	0.75	0.41	1.37	0.35
	0.76	0.37	1.57	0.46
Prandial	1.27	0.49	3.30	0.62
	1.76	0.60	5.16	0.30
Basal	0.85	0.41	1.77	0.66
	0.57	0.22	1.47	0.24
Prandial insulin	0.66	0.39	1.12	0.13
	0.83	0.42	1.64	0.59
Basal insulin	1.90	1.10	3.28	0.021
	1.50	0.76	2.43	0.24

HRs were calculated for the risk of cancer associated with doses of each insulin type ≥0.3 IU/kg, adjusted for comorbidity, exposure to metformin

Manucci *et al. Diabetes Care* 2010;33:1997–2003

PRAMLINTIDE

AMYLIN

1. Suppression of endogenous glucagon production (especially in the postprandial state)
2. Reduction in postprandial hepatic glucose production
3. Reduction in gastric emptying time
4. Centrally mediated induction of satiety
5. Reduction in postprandial glucose levels

AMYLIN

- Side effects:
  - Hypoglycemia
  - GI: N & V, anorexia
  - Only ised in USA
  - Sc inj with insulin

Non drug therapy

Diet

- Calorie as per actvities
- 20% breakfast,35% lunch,30% dinner
- Protein 1-1.5 gm/kg/day
- Fat <30%
- CHO –remaining ;minmize suger,maximize fibre
- Monotonous-exchange
- Difficult to adjust with desire

Non drug therapy

Exercise

- Minimumum 30 min a day
- Adequate:Heart rate =(220-age in yrs)*50-75%
- Reduce 20 % snacks to avoid Hypoglycemias
- Daily life never easy
- Need to be avoided
- In MSK,Heart disease,retinopathies

Conclusion

- Different pharmacological approaches are available

- Every pharmacological preparation has some desired and undesired complications of side effects
- Effects of Secretagauges wanes with time
- Sensitizers are emerging with side effects

- Appropriate clinical assessment is essential before suggesting a medication to the patient

Take home message

- **Therapy should be individualised**
- **With**
- **Active patient participation**

Thanks

unite for diabetes