Pro et contra of incretin therapy in type 2 diabetes

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14th EFLM Continuing Postgraduate Course in Clinical Chemistry and Laboratory Medicine, Dubrovnik, Croatia, October 26h 2014

382 000 000

590 000 000

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United Nations Resolution 61/225: World Diabetes Day

On 20 December 2006, the United Nations General Assembly passed Resolution 61/225. This landmark Resolution recognizes diabetes as a chronic, debilitating and costly disease associated with major complications that pose severe risks for families, countries and the entire world. It designates 14 November, the current World Diabetes Day, as a United Nations Day to be observed every year beginning in 2007.

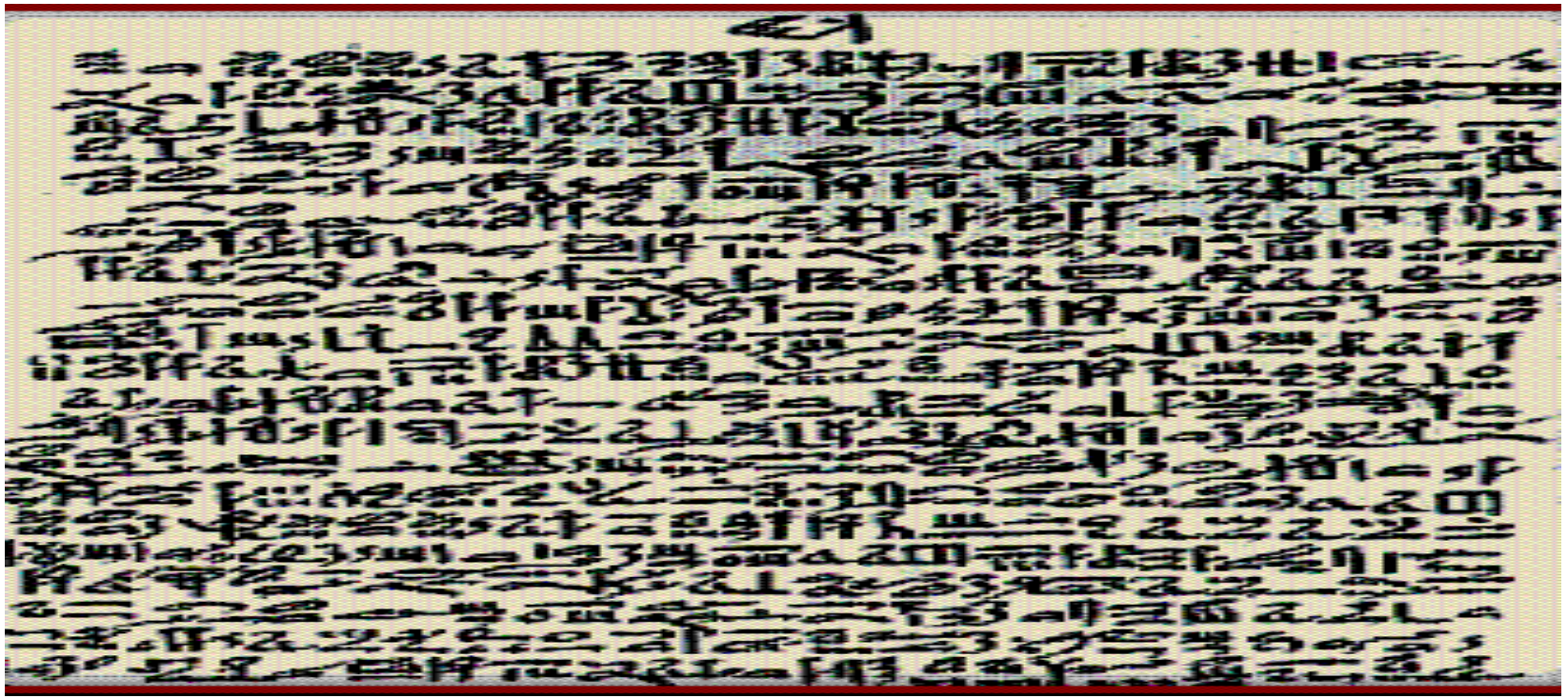
December 20, 2006
This United Nations resolution recognized that tackling diabetes is likely to be one of the most important challenges for the global public health community in the 21st century

President Obama proclaims November 2010 as National Diabetes Month to support diabetics

November 3, 2010 — President Barack Obama recently proclaimed November 2010 to be National Diabetes Month, during which he urged Americans to learn the risk factors and warning signs that are associated with type 1 and type 2 diabetes.

Approximately 24 million diabetics live with this diagnosis in the U.S. today. Type 1 diabetes - commonly known as juvenile onset diabetes - is most often diagnosed in young people, while the risk of type 2 diabetes is highest among individuals who are older, overweight, inactive or have a family history of diabetes.

1552 BC- an Egyptian healer Hesy-Ra wrote about a disease with frequent urination as one symptom

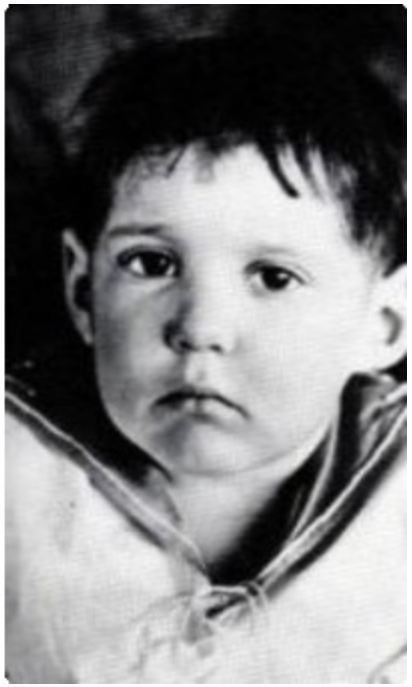


250 BC first time word *Diabetes* was mentioned

1921-Insulin discovery

First patient who received insulin: Leonard Thompson (1908 – 1935)

December 15th 1922



February 15th 1923

How First looks in pictures.....

Early advertisements informed the public of the availability of the first commercial insulin in 1923. It was manufactured and marketed by Eli Lilly and Company.

The first insulin vials and first U-20 and U-40 formulations were packaged in wooden containers. (1923)

First News paper publication – Toronto Daily Star

An insulin filling line (up) and finishing line 8down), at Eli Lilly and Company, the first company to mass produce insulin, beginning in 1923.

DIET ADJUSTMENT AND INSULIN THERAPY IN DIABETES MELLITUS*

By ERNEST S. du BRAY, M. D., San Francisco
(From the Department of Medicine in the University of California Medical School.)

I. *Introduction*—In a sub

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Notes, Comments, and Abstracts.

THE PRESENT POSITION OF INSULIN THERAPY.*

BY GEORGE GRAHAM, M.D., F.R.C.P.LOND.,
ASSISTANT PHYSICIAN, ST. BARTHOLOMEW'S HOSPITAL;
PHYSICIAN, ROYAL NORTHERN HOSPITAL.

IN opening a discussion on the present position of the treatment of diabetes with insulin it is unnecessary to speak about some aspects which had to be considered a rather discuss the principles which will agree that while it cannot

of the 15 to 20 per cent. which was common before. Further, the weight curve should be the guide to the total caloric value of the diet and should determine whether it should be increased or decreased. In children there should be a slow increase. This is necessary as the children have to grow, but they should never be allowed to become fat, and should always be underweight.

Indications for Insulin Therapy.

When insulin was first introduced it was said that if patients could take a reasonable amount of food, say 50 g. of carbohydrate and an adequate caloric value, without passing sugar, it was unnecessary to give them insulin. This view is still held by some, but I have never accepted it. The improvement which occurs in the clinical condition after a small dose of insulin, 5, 10, or 15 units, is very striking. The patient gains weight and feels capable of doing work, even if no change is made in the diet. This Joslin's view, and it would seem as if insulin other process besides the sugar other proof of this at

British Medical Journal

SATURDAY, FEBRUARY 15th, 1936

ADVANCES IN INSULIN THERAPY

acids containing one or more of the basic constituents lysine, arginine, and histidine. The raw material from which the protamines are obtained is the ripe sperm of fish. Investigating the solubility in serum of various protamines Hagedorn and his colleagues finally hit upon a protamine (not hitherto described) from the sperm of *Salmo irideus*, which formed a compound with insulin having a lower solubility than any they had so far used: the minimum solubility is reached at a *p*H of 7.3—that is, near the reaction of serum. For a period of more than two years they treated about eighty-five

Notes, Comments, and Abstracts.

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IN opening a discussion on the present position of the treatment of diabetes with insulin it is unnecessary to speak in detail about some aspects which had to be considered a year ago, and I would rather discuss the principles which are controlling its use. Everyone will agree that while insulin is invaluable in the treatment of diabetes it cannot be called a cure. The points which I would like to consider are these:—(1) The aims of treatment with insulin. (2) The type of case which should be treated with insulin. (3) The best type of diet. (4) The value of insulin in the treatment of coma. (5) The value of insulin in the treatment of other infections and minor complications.

The Aims of Treatment.

One of the chief difficulties in deciding these points is the improvement which takes place in the clinical condition of the patients on all varieties of treatment with insulin. The patients nearly always feel so much better that it is difficult to say which is the correct line of treatment, and another five years may have to pass before some of these questions can be answered with certainty. Before the introduction of insulin it was accepted that the patient's diet should be so adjusted that the urine did not contain any sugar, and that the fasting value of the blood-sugar was within the normal limits of 0·08 to 0·12 or 0·13 per cent. In order to achieve this it was necessary in severe cases to give a diet of very low caloric value, and the patients were all much under the normal weight. When insulin was available the natural thought of most workers was that the patient need no longer be undernourished. The carbohydrate was increased so that at some time of the day the blood-sugar was raised above the normal level and sugar was excreted in the urine. Of the eight groups of workers in Canada and the United States who took part in the early study of insulin only two, the Toronto school (Banting, Campbell, and Fletcher) and Allen's school, aimed at keeping the fasting value of the blood-sugar within normal limits; one, Joslin, tried to keep the urine sugar-free; but the other five all thought that it was unnecessary to keep of the 15 to 20 per cent. which was common before. Further, the weight curve should be the guide to the total caloric value of the diet and should determine whether it should be increased or decreased. In children there should be a slow increase. This is necessary as the children have to grow, but they should never be allowed to become fat, and should always be underweight.

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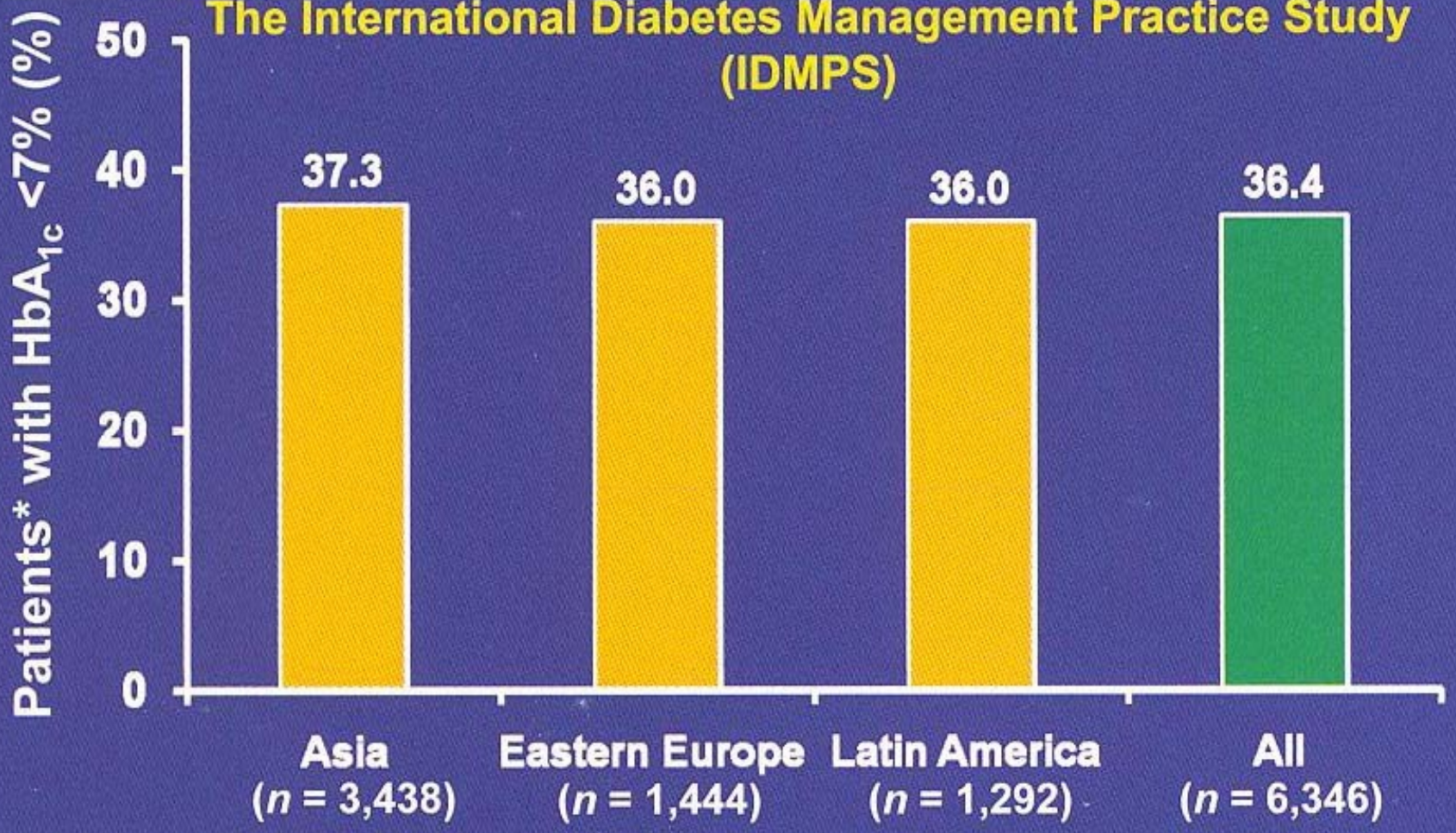
Insulin has been used in the treatment of the young adult who has had an acute attack of the disease and has come under observation a short while after the onset of symptoms. The sad experience of these cases before the introduction of insulin was that this type of patient responded well to dietetic treatment, but after one to two years began to lose tolerance in spite of all restrictions. The average duration of life of this type of patient for the age-period 20 to 40 was only 5·3 years (Joslin). It therefore seemed justifiable to treat these patients with insulin early in the disease in order to try to prevent the fall in sugar tolerance and perhaps cause a definite rise in sugar tolerance. If small amounts of carbohydrate are given together with sufficient insulin to deal with this sugar the work of the beta cells will be reduced to a minimum. I have been watching six patients and testing the sugar tolerance at intervals by means of a dose of sugar. The actual amount of carbohydrate varies, as four patients are taking 16 to 20 g., one 30 g., and one 60 g. The dose of insulin also varies from 8 to 15 units. It is usually given in one dose, but two patients take it in two doses.

The blood-sugar curves after a dose of 50 g. show that the change in tolerance which has taken place has been very slight, but what change there is, is in favour of an improvement. It is too early to say much about these patients as it will be another four years before they reach the average of their class. Still it may prove a hopeful line of research.

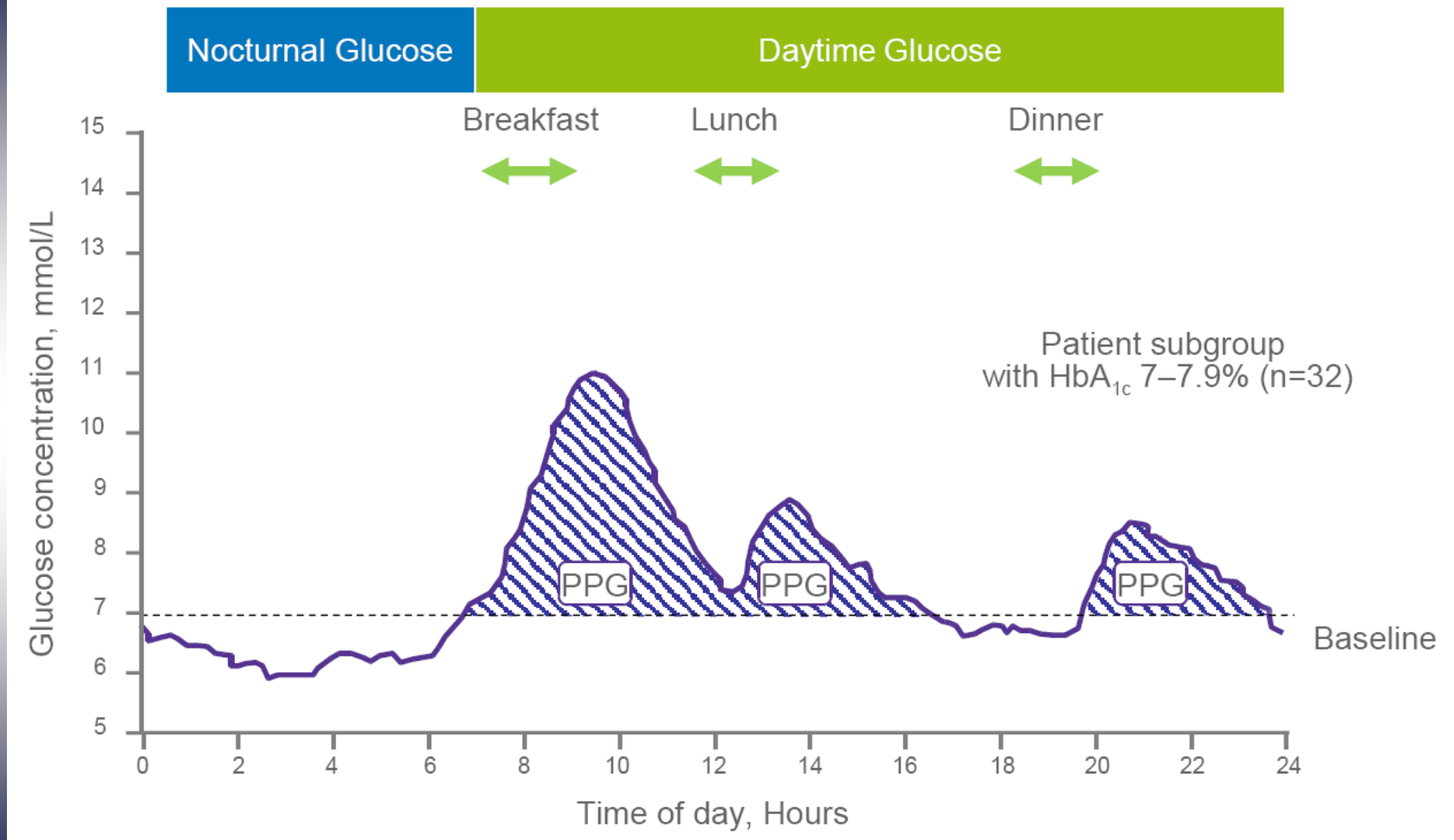
Only around one-third of patients* in developing countries achieve HbA_{1c} <7%:



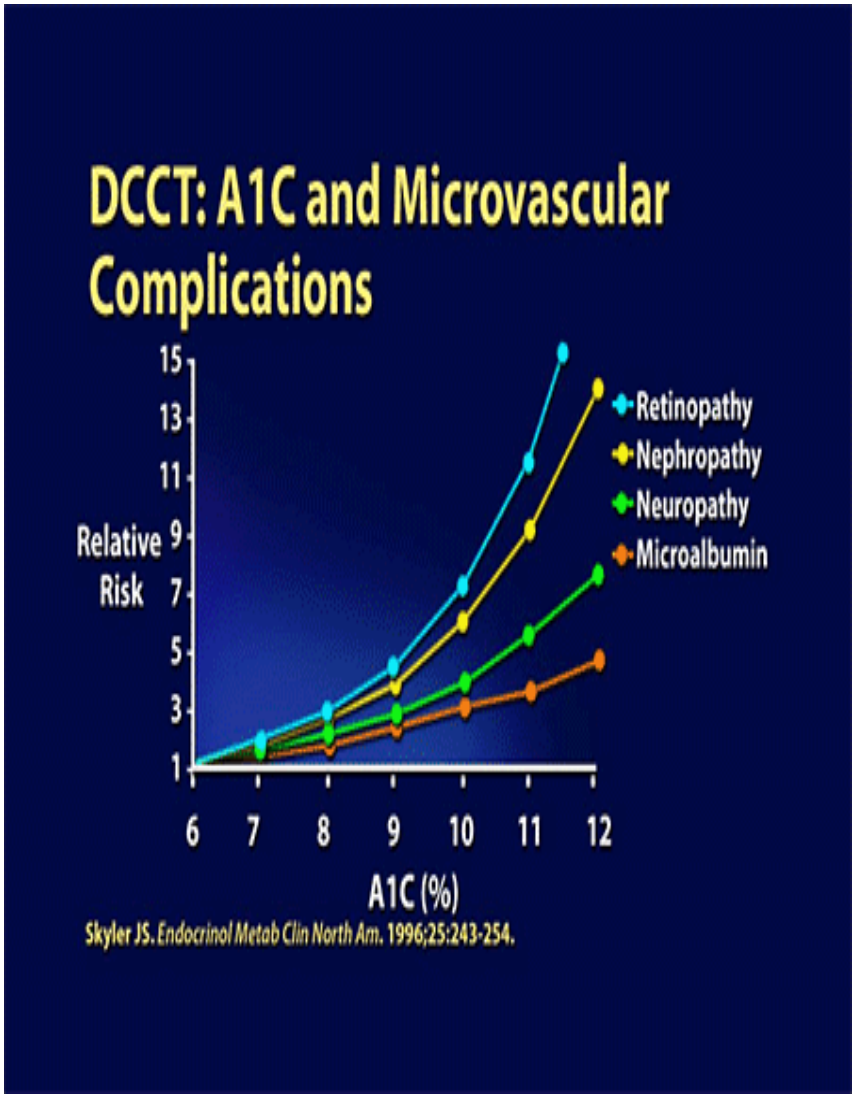
*Patients with HbA_{1c} test (36% of overall population)

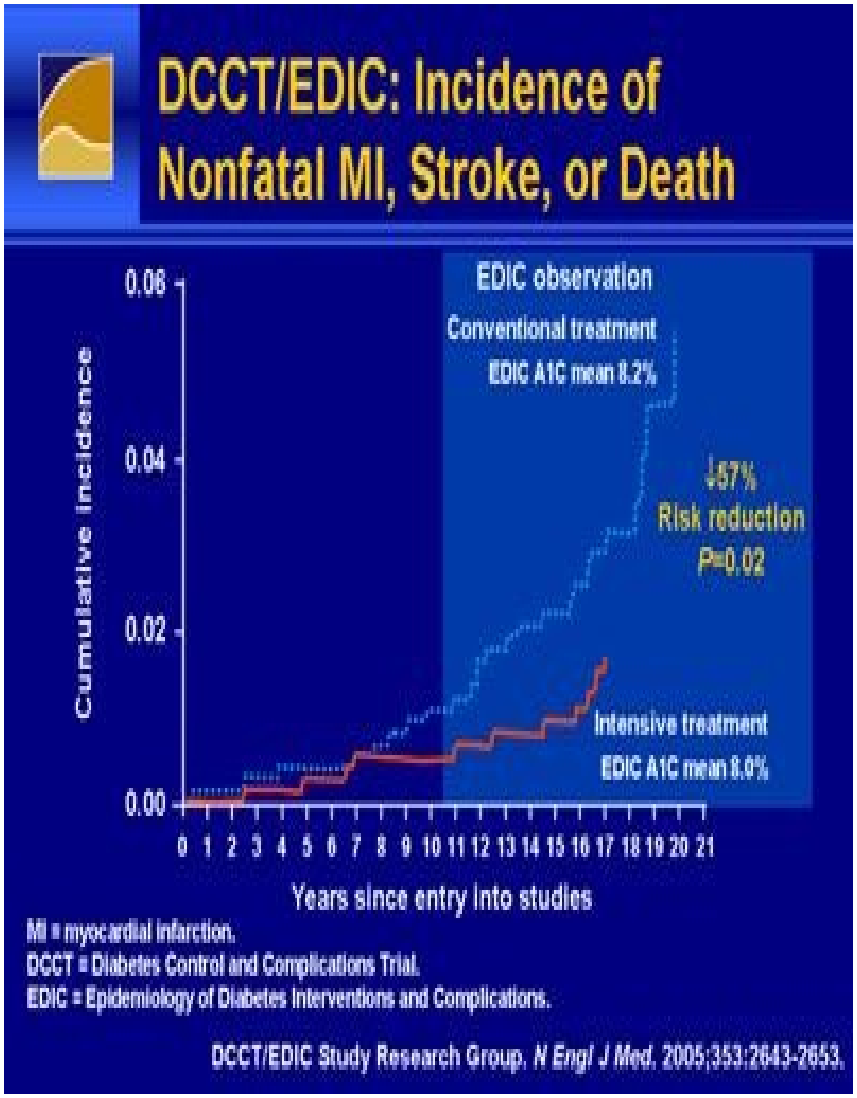
Chan JC, *et al. Diabetes Care* 2009;32:227–33.

PPG has a major impact on the 24-hour glucose profile in patients with type 2 diabetes



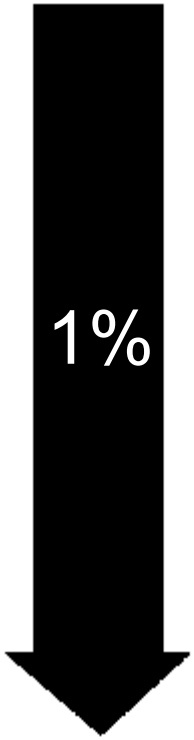
Landmark trials in type 1 diabetes





Lessons from UKPDS: better glucose control means fewer complications

EVERY 1% reduction in HbA_{1c}



REDUCED RISK*

Deaths from diabetes	–21%
Heart attacks	–14%
Microvascular complications	–37%
Peripheral vascular disorders	–43%

*p<0.0001

Stratton et al. UKPDS 35. BMJ. 2000;321:405–12

Landmark trials in type 2 diabetes

Lesson	Trial	Outcome	Detail	Therapy	Intervention group
1 Hyperglycemia is a treatable and reducible risk	UKPDS[7]	Better glycemic control improves outcome (microvascular- and diabetes-related end points)	HbA_{1c} 7.0% (6.2%-8.2%) in the intensive group compared with 7.9% (6.9%-8.8%) Clear microvascular effects and diabetes-related end points. MI borderline at P=0.052	Sulfonylurea	From diagnosis or insulin
2 Metformin is an effective first-line treatment	UKPDS[17]	Better glycemic control improves outcome (microvascular and macrovascular)	7.4% in the metformin group compared with 8.0% in the conventional group. Effects shown in diabetes-related end points, all-cause mortality, and MI	Metformin	In the overweight (>120% ideal body weight)
3 Treatment needs to focus on early glycemic control	UKPDS-PTM[16]	Early glycemic control has a legacy effect	Effects in the first ten years persist despite no later difference in control	Sulfonylurea, insulin, and metformin	In newly diagnosed patients studied for a median of 20 years
4 Aggressive treatment in those with established pathology is counterproductive	ACCORD[13]	Trial closed after 3.5 years because of a 25% increase in all-cause mortality in the intensive-control group	HbA_{1c} 6.4% and 7.5% in intensive and control groups, respectively	In the intensive group: insulin, 77% rosiglitazone, ≈92% sulfonylurea*, 78% metformin, 95%	Median duration of type 2 diabetes 10 years, and who had either established cardiovascular disease or additional cardiovascular risk factors
5 Progressive incremental therapy towards target late in diabetes reduces complications	ADVANCE[18]	Relative risk reduction, 14%; 95% CI, 3% to 23%; P=0.015	HbA_{1c} 7.3% and 6.5% at the end of the trial	Mainly gliclazide modified release (91%) and metformin (74%)	Median duration of diabetes 8 years

* Excluding gliclazide

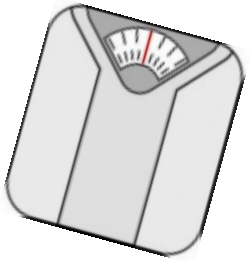
Table II. *Lessons learnt from trials of glycemia in diabetes.*

Abbreviations: ACCORD, Action to Control CardiOvascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study; UKPDS-PTM, United Kingdom Prospective Diabetes Study Post-Trial Monitoring.

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

3. ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options: Lifestyle**

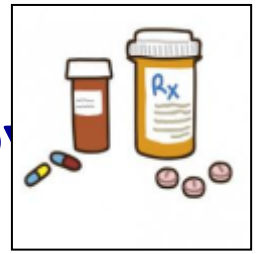


- Weight optimization

- Healthy diet

- Increased activity level

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]



3. ANTI-HYPERGLYCEMIC THERAP

- **Therapeutic options:**

Oral agents & non-insulin injectables

- Meglitinides
- α-glucosidase inhibitors
- Bile acid sequestrants
- Dopamine-2 agonists
- Amylin mimetics
- Metformin
- Sulfonylureas
- Thiazolidinediones
- DPP-4 inhibitors
- GLP-1 receptor agonists

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]

Major target organs and actions of non-insulin

GLP-1 analogs
Improve pancreatic islet glucose sensing, slow gastric emptying, improve satiety

DPP-4 inhibitors
Prolong GLP-1 action leading to improved pancreatic islet glucose sensing, increase glucose uptake

Biguanides
Increase glucose uptake and decreases hepatic glucose production

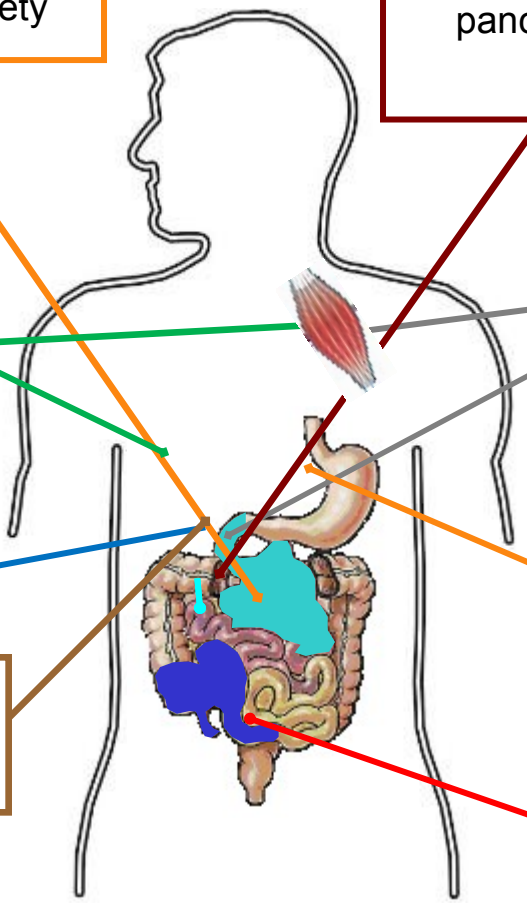
Thiazolidinediones
Decrease lipolysis in adipose tissue, increase glucose uptake in skeletal muscle and decrease glucose production in liver

Sulfonylureas
Increase insulin secretion from pancreatic β-cells

SGLT-2 inhibitors
Inhibit glucose reabsorption from renal tubules, thereby promoting urinary glucose excretion

Glinides
Increase insulin secretion from pancreatic β-cells

α-glucosidase inhibitors
Delay intestinal carbohydrate absorption

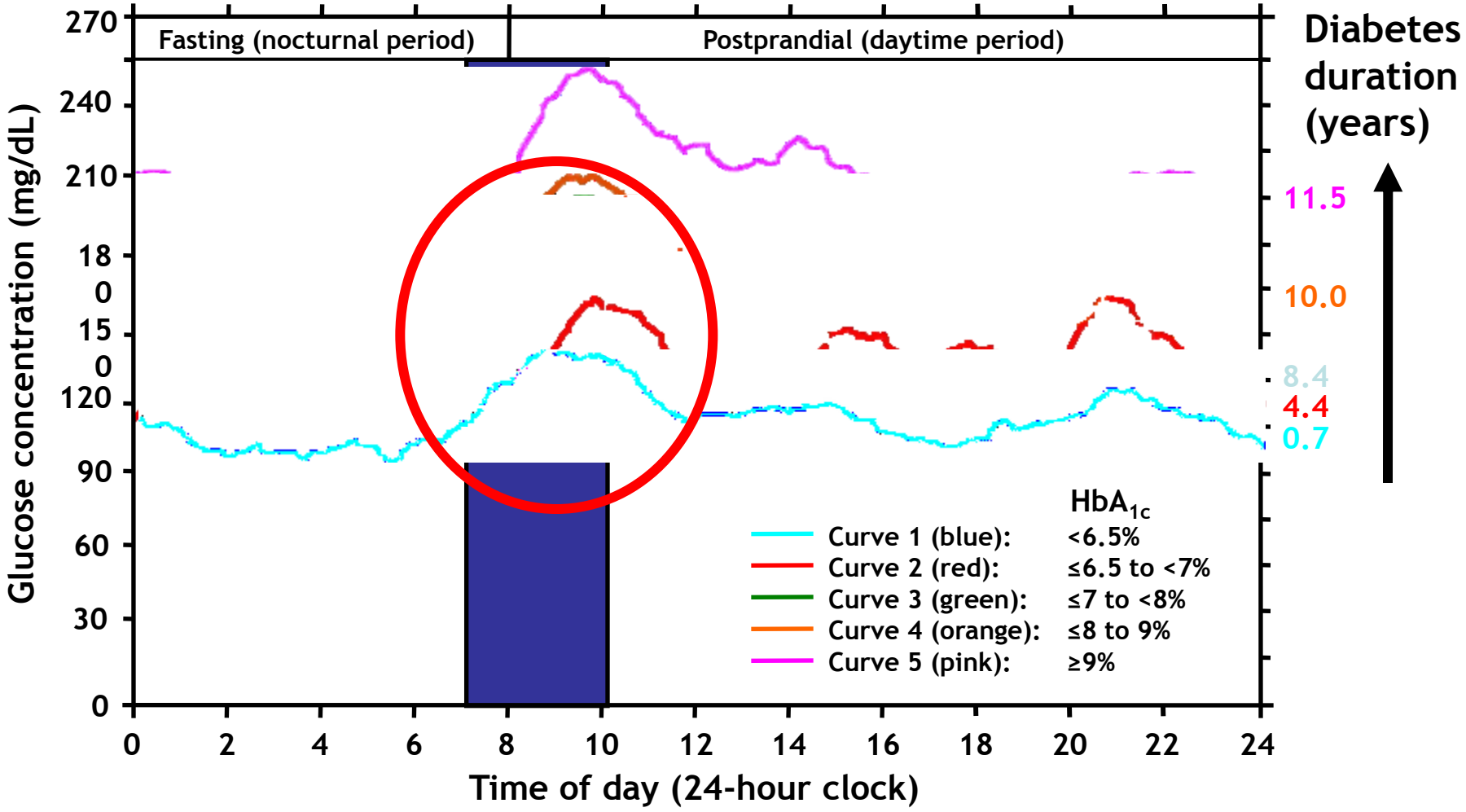


DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1; SGLT-2, sodium-glucose co-transporter
Cheng AY et al. *CMAJ*. 2005;172:213-26

Metformin

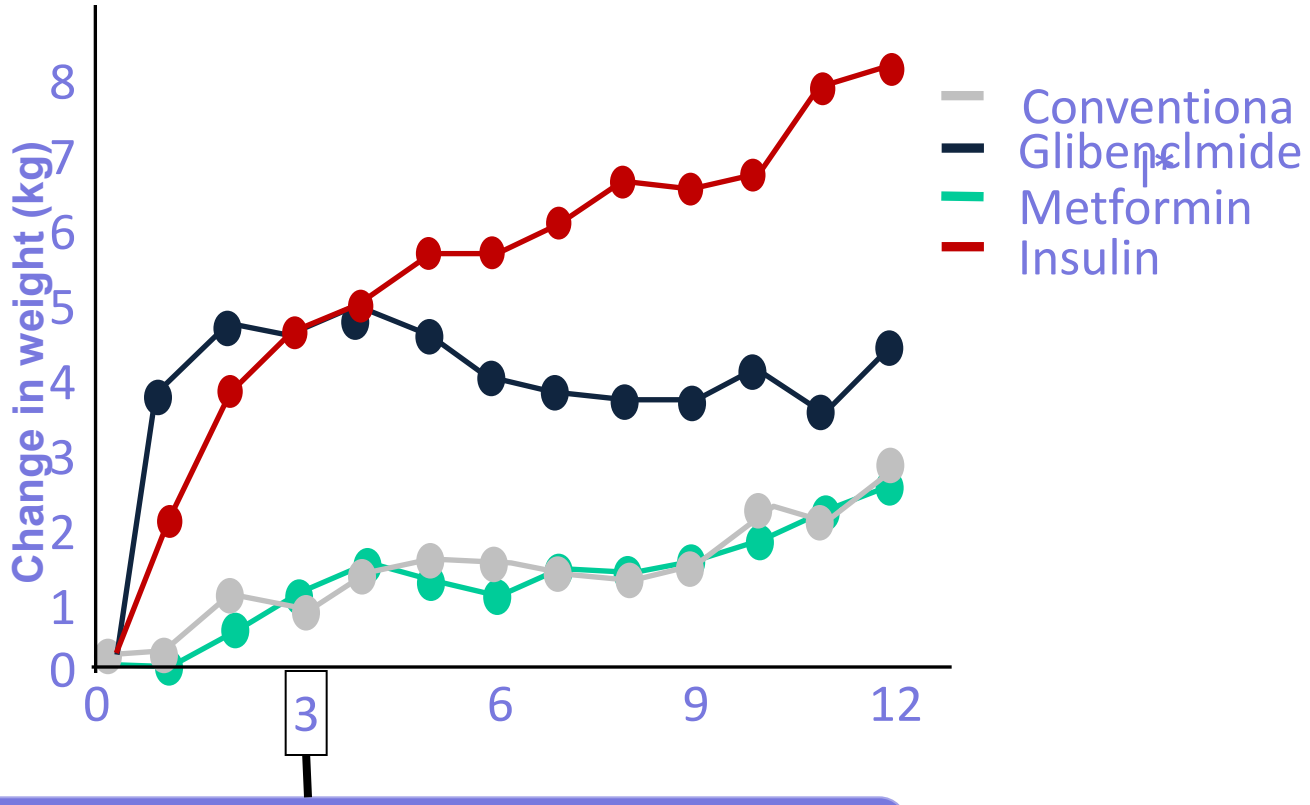

Stepwise approach?
INSULIN
OH
OH
OH
OH
OH
diet

PPG is the first recognized alteration in people with type 2 diabetes on the 24-hour glucose profile



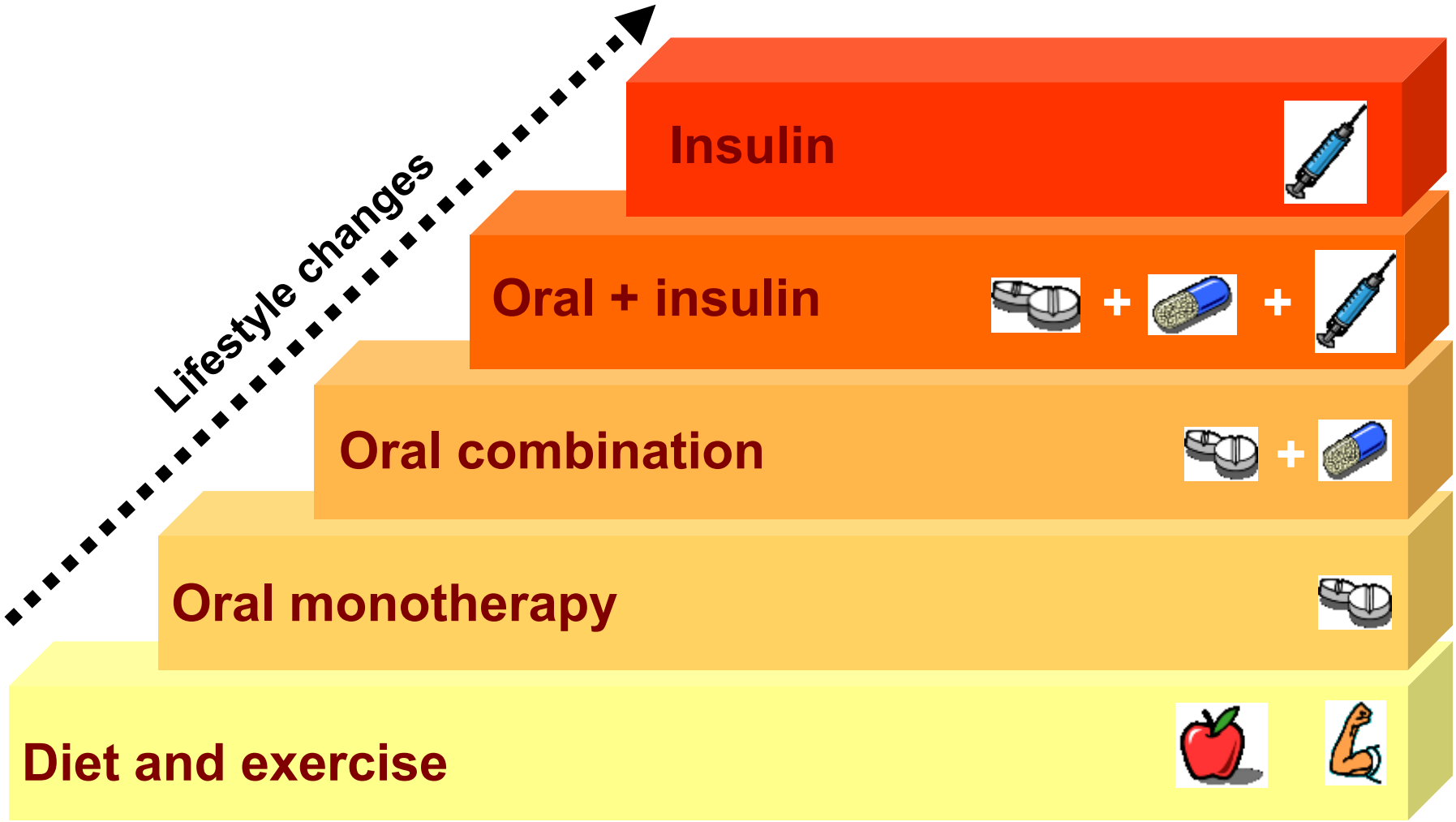
Monnier L, et al. Diabetes Care. 2007;30:263-9

INSULIN AND SULPHONYLUREA PROMOTE WEIGHT GAIN



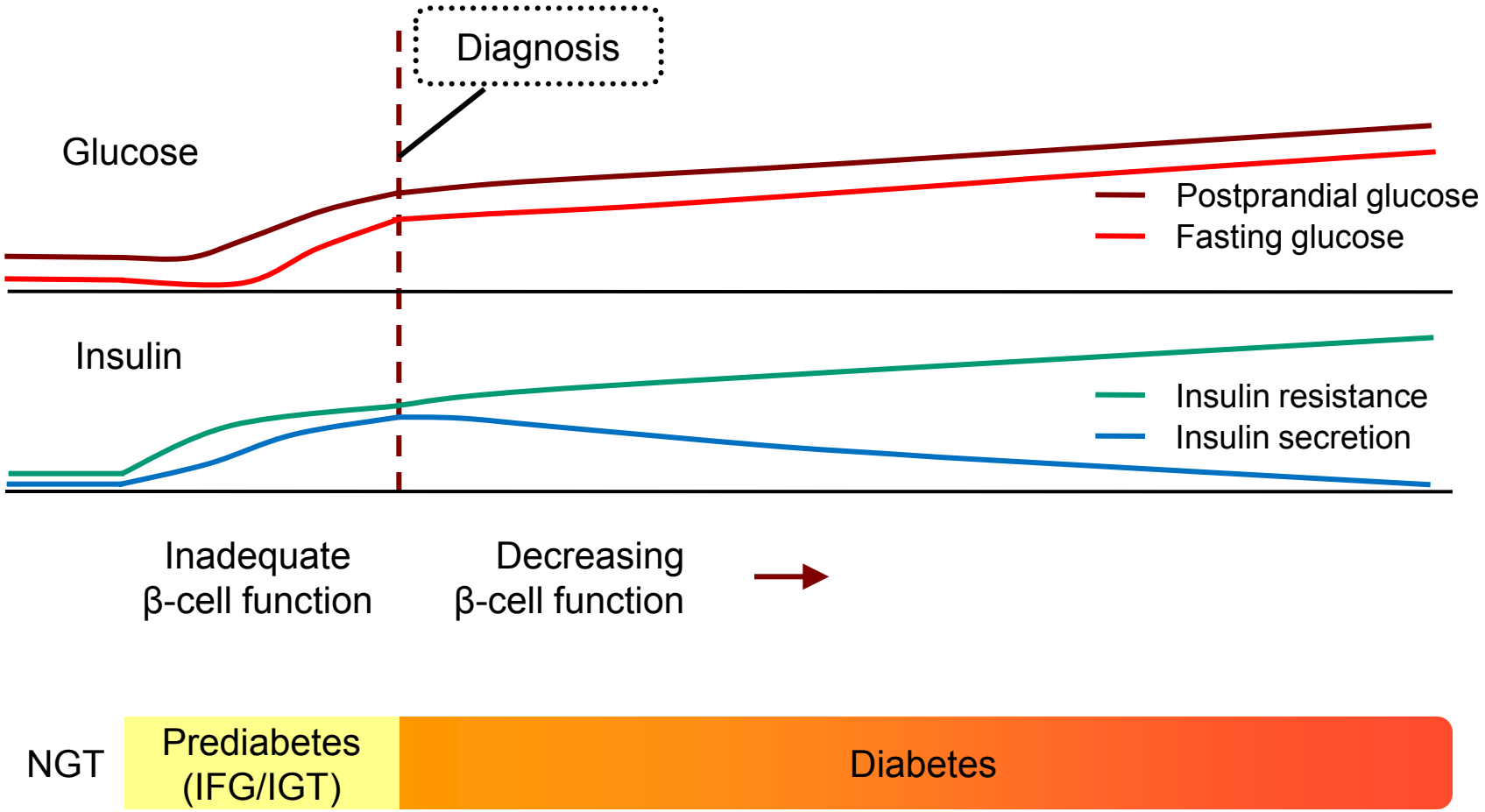
Up to 5 kg is already gained within just 3 years with a sulphonylurea or insulin

General approach to the management of T2DM



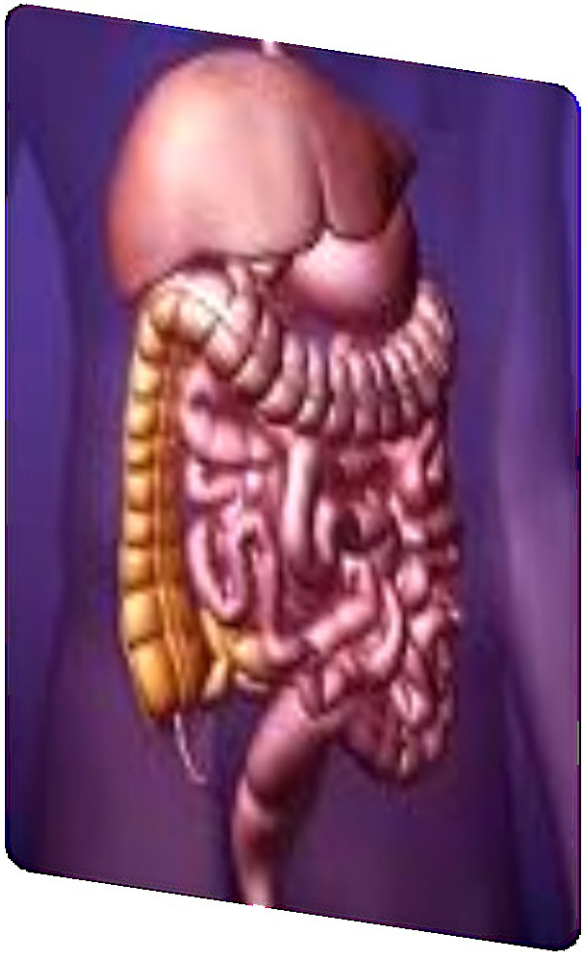
Adapted from Riddle MC. Endocrinol Metab Clin North Am. 2005;34:77–98

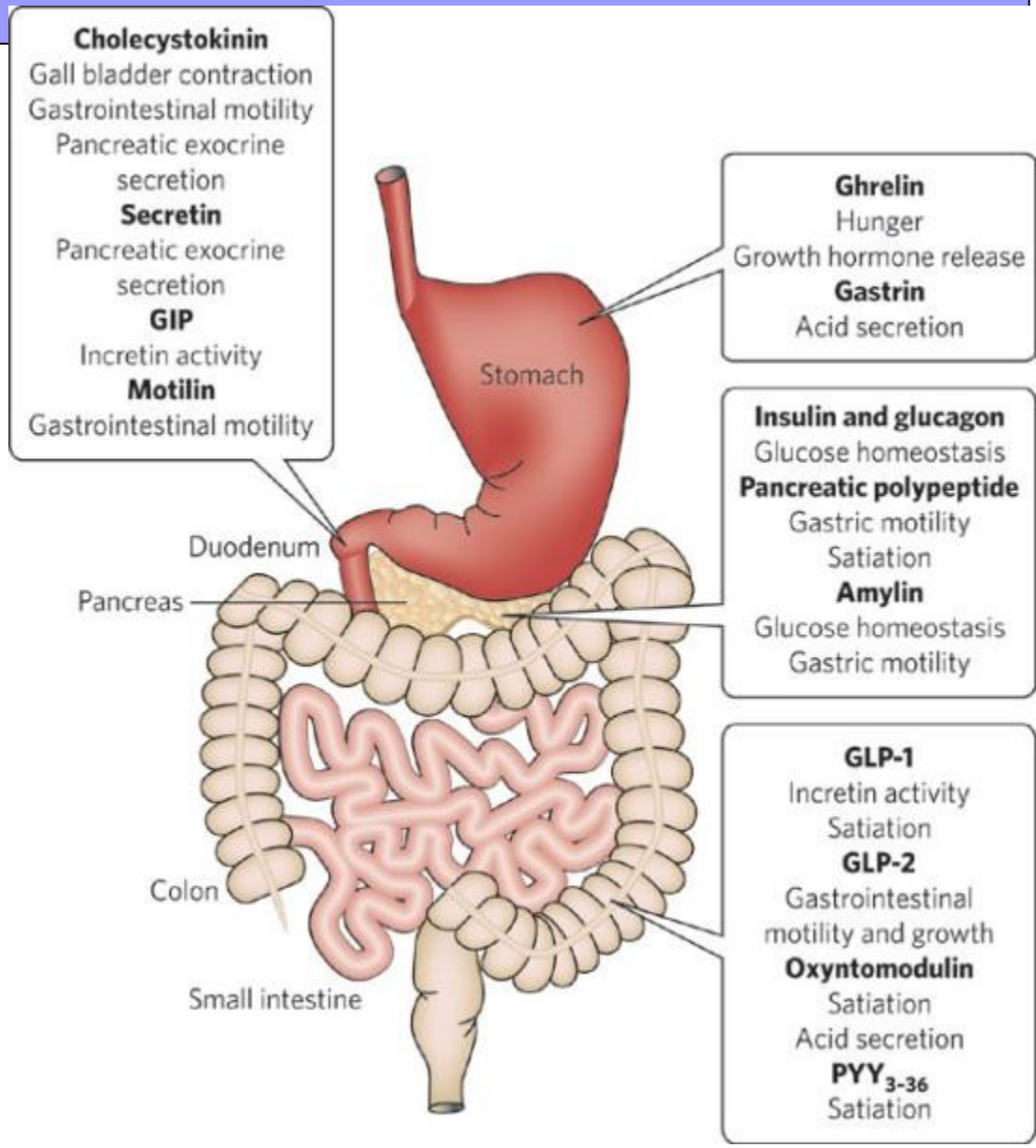
Pancreatic islet function deteriorates over time, causing disease progression



IFG=impaired fasting glucose ; NGT = normal glucose tolerance ; IGT = impaired glucose tolerance
Adapted from Rickheim P, Flader J, Carstensen AK. Type 2 Diabetes BASICS. International Diabetes Center; 2000

GUT AS ENDOCRINE ORGAN





INCRETINS

- gut hormones that are secreted from enteroendocrine cells into the blood within minutes after eating

- stimulate a decrease in blood glucose levels

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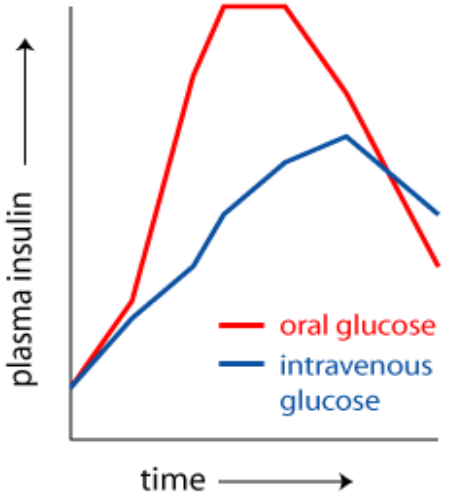
Intestine Secretion
Insulin



Creutzfeldt; 1985

GLP-1 Glucagon-like peptide-1	GIP Glucose-dependent insulinotropic polypeptide
• 30-amino acid peptide secreted in response to the oral ingestion of nutrients by L cells, primarily in the ileum and colon	• 42- amino acid peptide secreted by the K cells of the proximal duodenum and proximal jejunum
• Receptors present in islet α- and β-cells and in peripheral tissues including the central and peripheral nervous systems, heart, kidneys, lungs and GI tract	• Receptors present predominantly in islet β-cells, and in adipose tissue and the central nervous system

Healthy

Physiological levels

- Enhancement of glucose-dependent pancreatic insulin secretion
- Inhibition of glucose-dependent pancreatic glucagon secretion

Pharmacological levels

- Slowing of gastric emptying
- Appetite

Healthy

- Augments glucose-dependent insulin secretion

DM type 2

- GIP levels are normal or modestly elevated
- Insulinotropic actions of the peptide are diminished

DM type 2

- Incretin effect may be reduced due to defective secretory response of incretin hormones at mealtimes or diminished hormonal effect despite near-normal secretion
- Insulinotropic actions are diminished in association with loss of first phase of insulin secretion

Efendic S et al. Horm Metab Res. 2004;36(11-12):742-746;
Drucker DJ. J Clin Invest. 2007;117(1):24-32

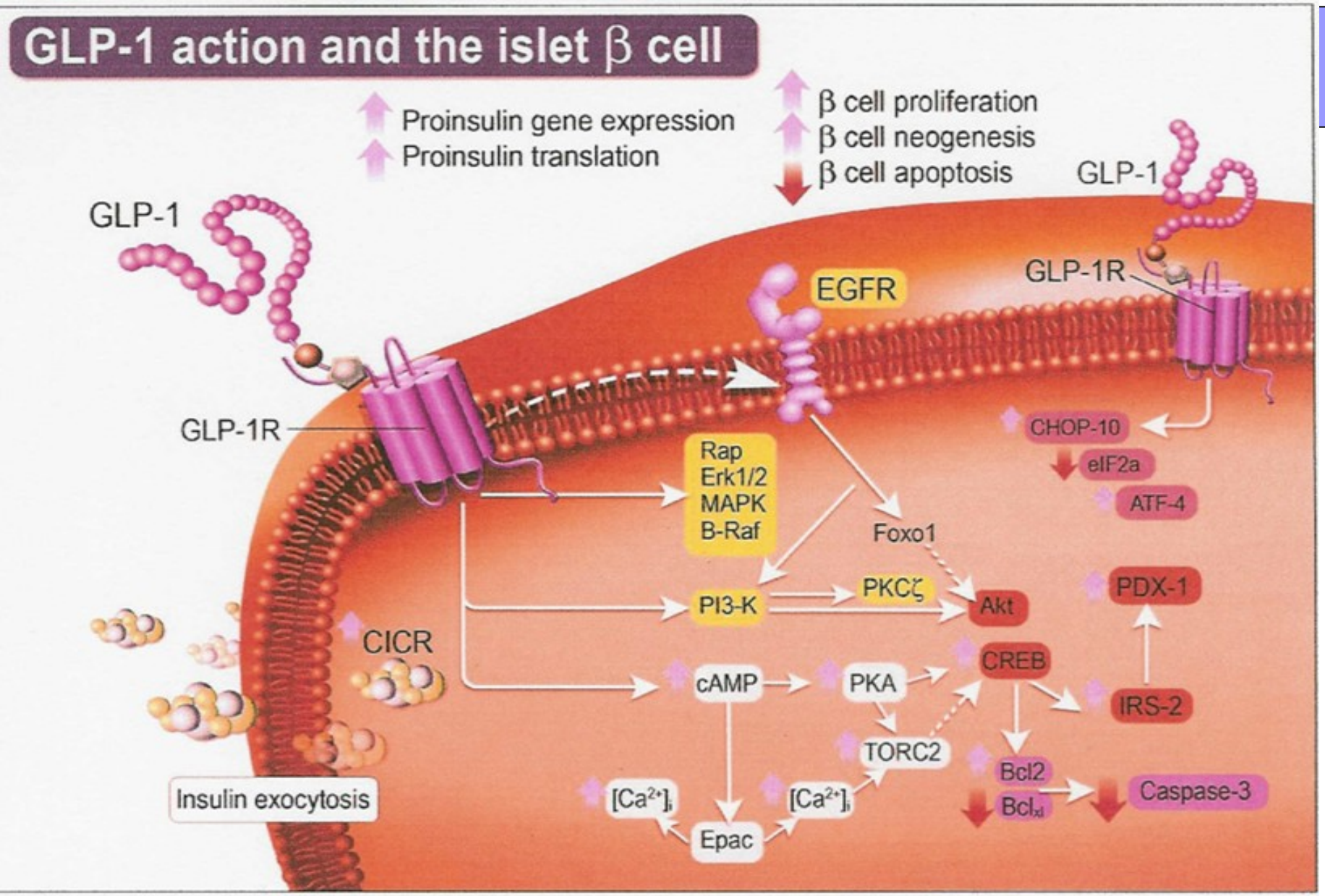
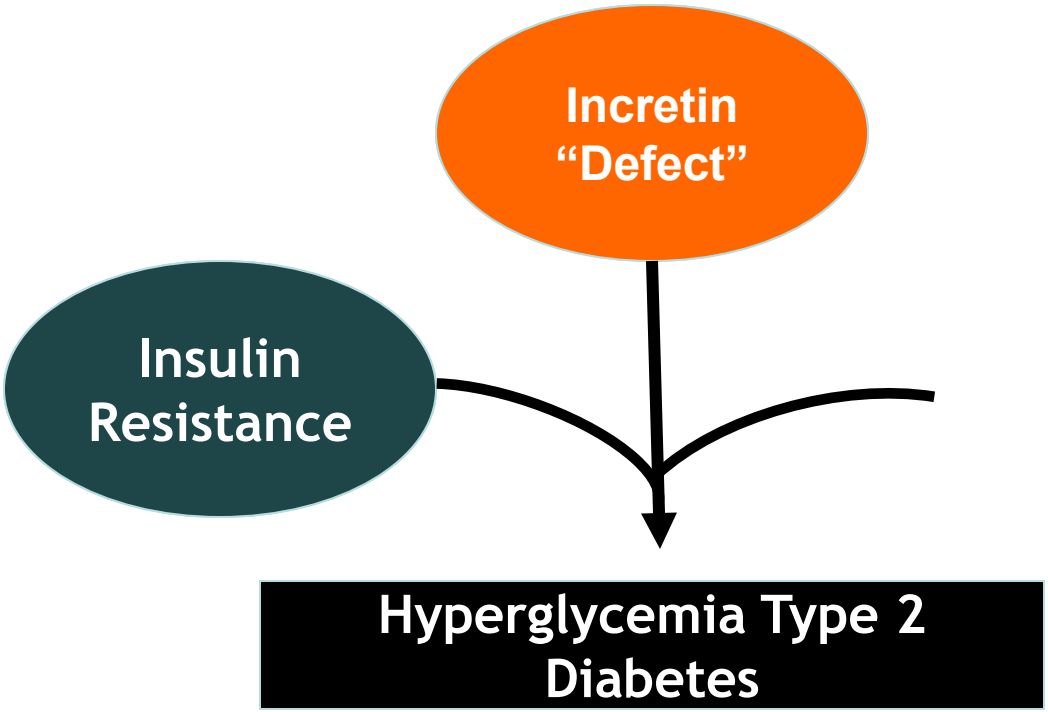


Figure 3. GLP-1 receptor signal transduction pathways in the pancreatic β cell

GLP-1 receptor activation leads to insulin release via stimulation of exocytotic pathways and recruits signaling mechanisms leading to promotion of cell proliferation and survival.

The Incretin Defect in Type 2 Diabetes



Incretin effect accounts for up to 70% of the insulin response to oral glucose intake[1]

1. Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. Am J Physiol Endocrinol Metab. 2004;287(2):E199-E206.

1996 San Francisco:
ADA meeting

1992 Bronx:
discovery of
exenatide

INCRETIN

1921 Toronto:
insulin discovery

METFORMIN

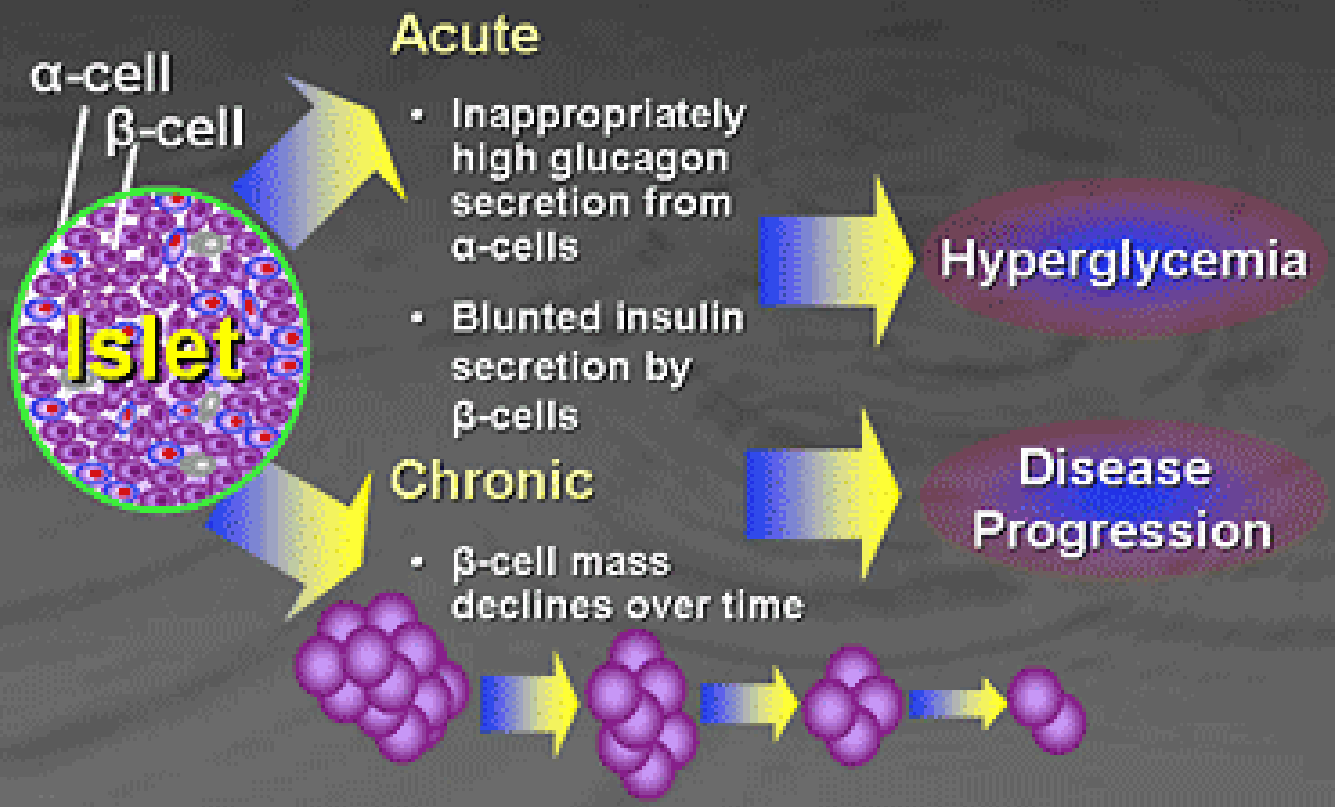
SULPHONYLUREA

INSULIN

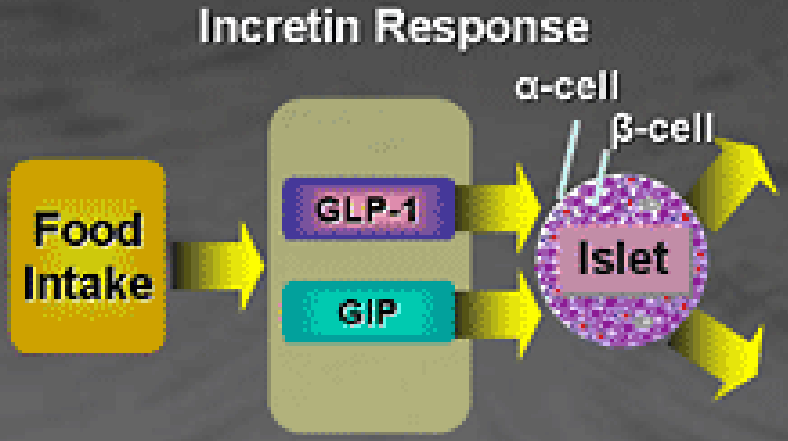
1900 1910 1920 1930 1940 1950 1960 1970 1980 1990 2000

Galvus vildagliptin Eucreas vildagliptin/metformin

Islet Dysfunction Contributes to Both Acute and Chronic Aspects of Type 2 Diabetes



Incretin Hormones Improve Acute and Chronic Aspects of Pancreatic Islet Function



Islet Function

Acute Effects

- Suppression of glucagon secretion (α-cell)
- Improved insulin secretion (β-cell)

Chronic Effects

- Rejuvenation of pancreas
  - ↑ β-cell proliferation
  - ↓ β-cell death

Incretin based therapeutic options

DPP-4 inhibitors
Prevent the degradation of the natural GLP-1 by DPP-4 enzyme

GLP-1 RA
Incretin mimetic
(imitating the effect of natural GLP-1)

DPP-4=dipeptidyl peptidase-4, GLP-1=glucagon-like peptide-1, RA=receptor agonists

DPP-4 inhibitors

SITAGLIPTIN (Januvia)
VILDAGLIPTIN (Galvus)
SAXAGLIPTIN (Onglyza)
LINAGLIPTIN (Trajenta)
ALOGLIPTIN (Vipidia)

Anagliptin approved 2012 in Japan
Teneligliptin approved 2012 in Japan

Gemigliptin (Zemiglo, LG Life sci; phase III)

GLP-1 agonists

Exenatide - byetta

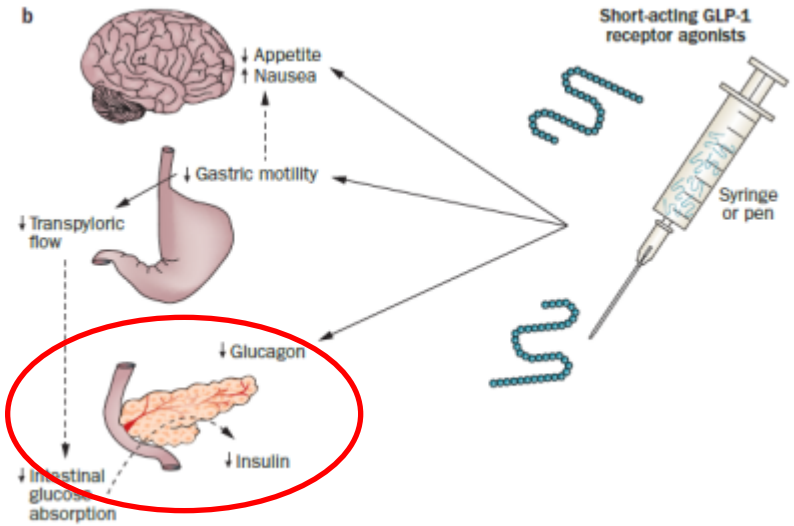
Exenatide LAT - Bydureon

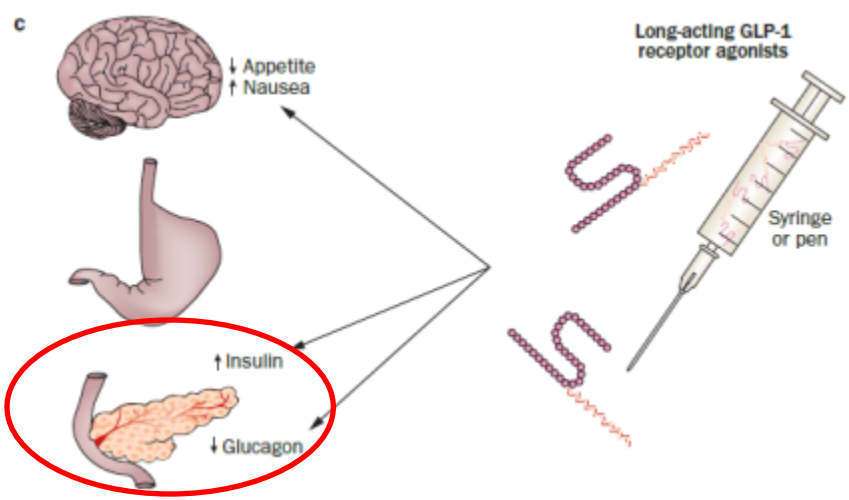
Liraglutide - Victoza

Lixisenatide - Lyxsumia

Albiglutide

Dulaglutide





PRANDIAL
GLP-1 Receptor Agonists

Effect on **FPG**

Effect on **PPG**

NONPRANDIAL
GLP-1 Receptor Agonists

Effect on **FPG**

Effect on **PPG**

GUP-NT = Glikemija u plazmi na tašte GUP-PP= glikemija u plazmi postprandijalno

Meier JJ. Nat Rev Endocrinol 2012; 8: 728–42.

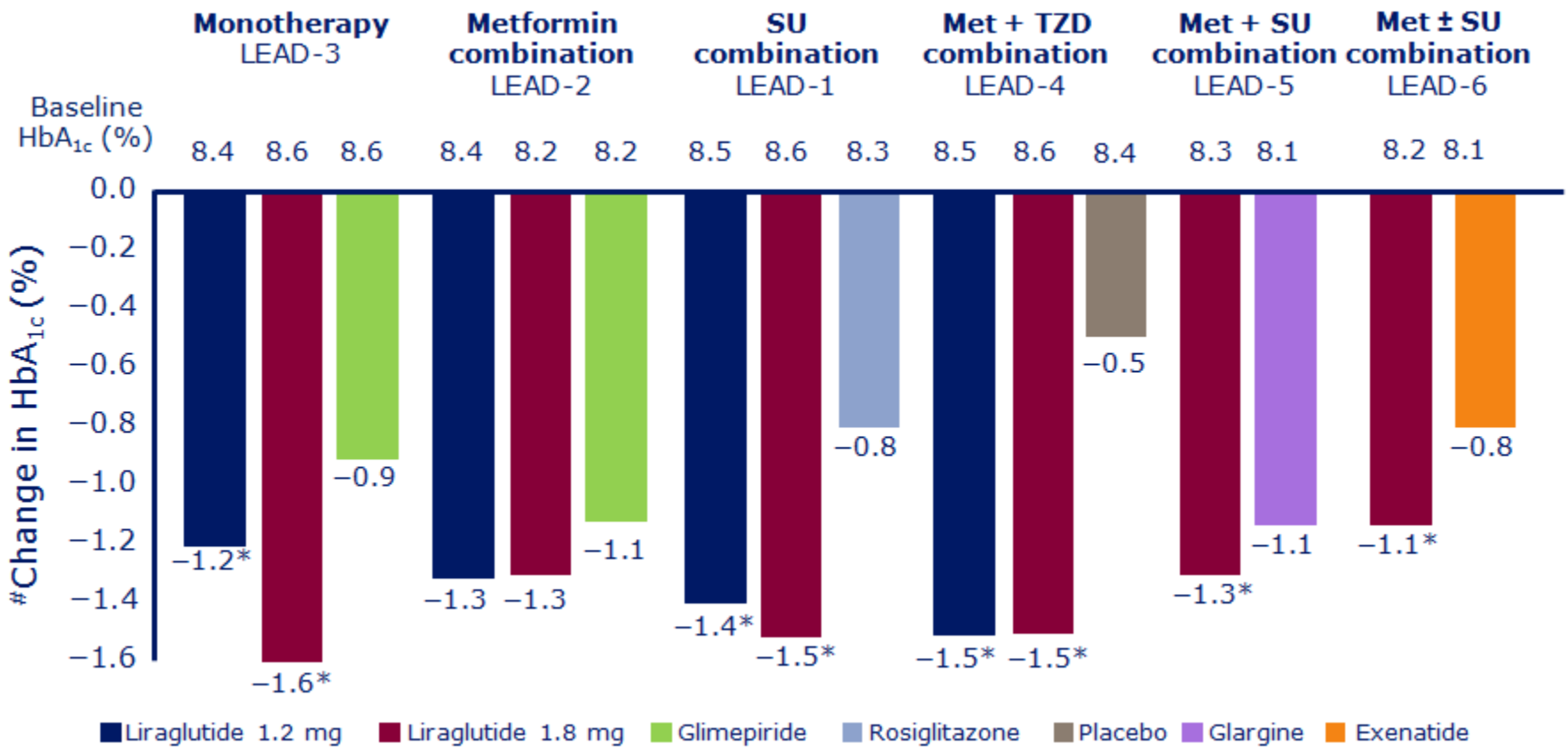
Table 1 | Comparison of short-acting versus long-acting GLP-1 receptor agonists

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)

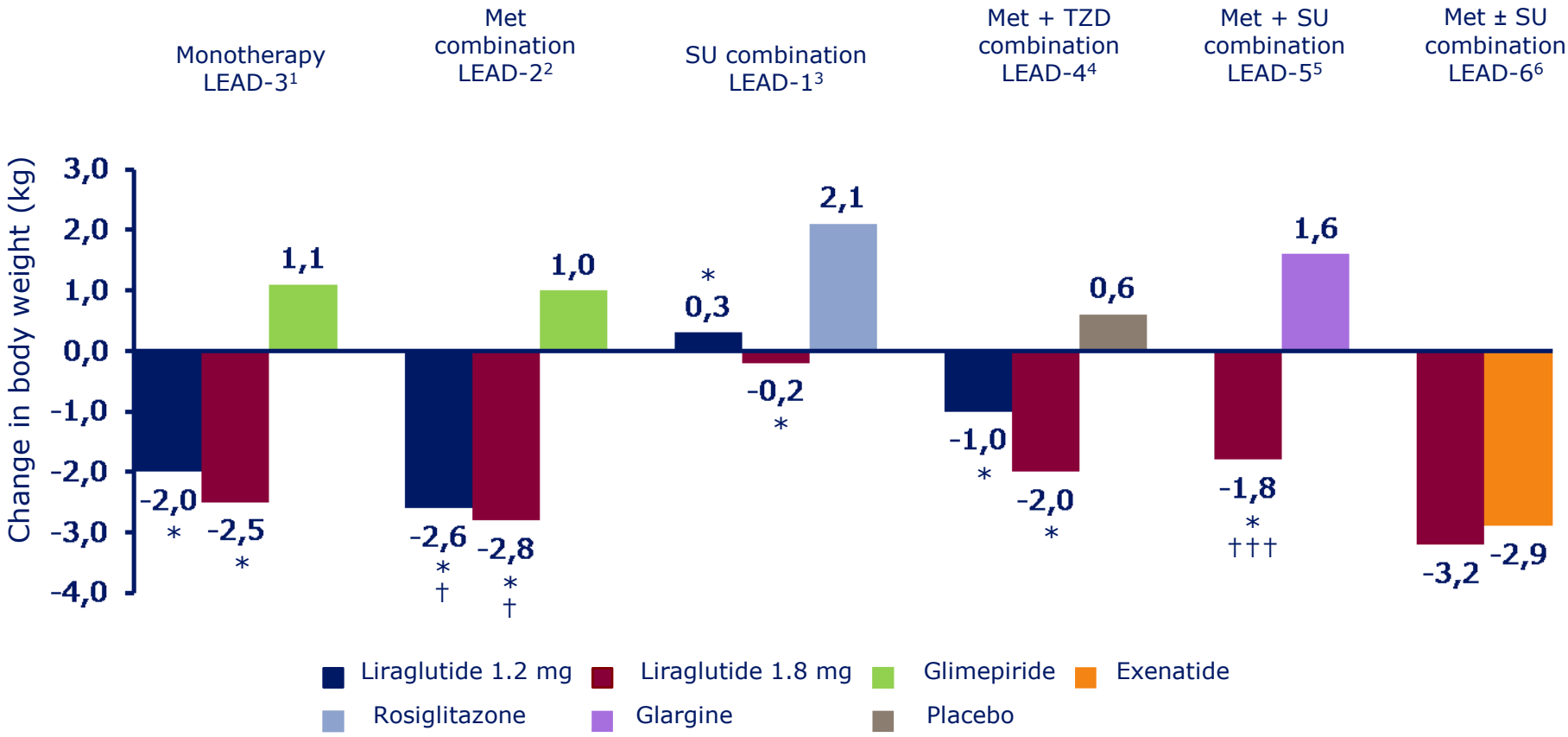
Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.

Meier JJ. Nat Rev Endocrinol 2012; 8: 728–42.

Effect on HbA_{1c} across the LEAD trials



Weight effects across LEAD trials



*$p \leq 0.0001$ vs active comparator; †$p \leq 0.01$, †††$p \leq 0.0001$ vs placebo (active comparators vs placebo not shown)
Data from core trials
MET, metformin; SU, sulphonylurea; TZD, thiazoladinedione.

1. Garber A et al. *Lancet* 2009;373:473–481; 2. Nauck M et al. *Diabetes Care* 2009;32;84–90; 3. Marre M et al. *Diabet Med* 2009;26;268–278; 4. Zinman B et al. *Diabetes Care* 2009;32:1224–1230; 5. Russell-Jones D et al. *Diabetologia* 2009;52:2046–2055; 6. Buse JB et al. *Lancet* 2009;374:39–47.

GLP-1RA comparative studies: Hypoglycaemia

Hypoglycaemia	LEAD-6[1]		DURATION-6[2]		HARMONY-7[3]		Kapitza et al.[4§]	
	Lira 1.8 mg OD n=233	Exe 10 µg BID n=231	Lira 1.8 mg OD n=450	Exe 2 mg OW n=461	Lira 1.8 mg OD n=408	Albi 50 mg OW n=404	Lira 1.8 mg OD n=71	Lixi 20 µg OD n=77
Proportion of subjects experiencing hypoglycaemia* (%)	NR	NR	4.0	3.0	20.8	16.3	0‡	0‡
Hypoglycaemia* rate/patient year	1.9	2.6	NR	NR	NR	NR	NR	NR
Major hypoglycaemia† (%)	0	0.2	0	0	NR	NR	NR	NR

*Minor hypoglycaemia (signs or symptoms associated with hypoglycaemia and fingerstick blood glucose level 3 mmol/L that were either self-treated or resolved on their own)
†Requiring medical assistance
§4-week study
‡Event with clinical symptoms with either plasma glucose <3.3 mmol/L or prompt recovery after oral carbohydrate administration if no plasma glucose measurement available
Albi, albiglutide; BID, twice daily; Exe, exenatide; GLP-1RAs, glucagon-like peptide-1 receptor agonists; Lira, liraglutide; NR, not reported; OW, once weekly

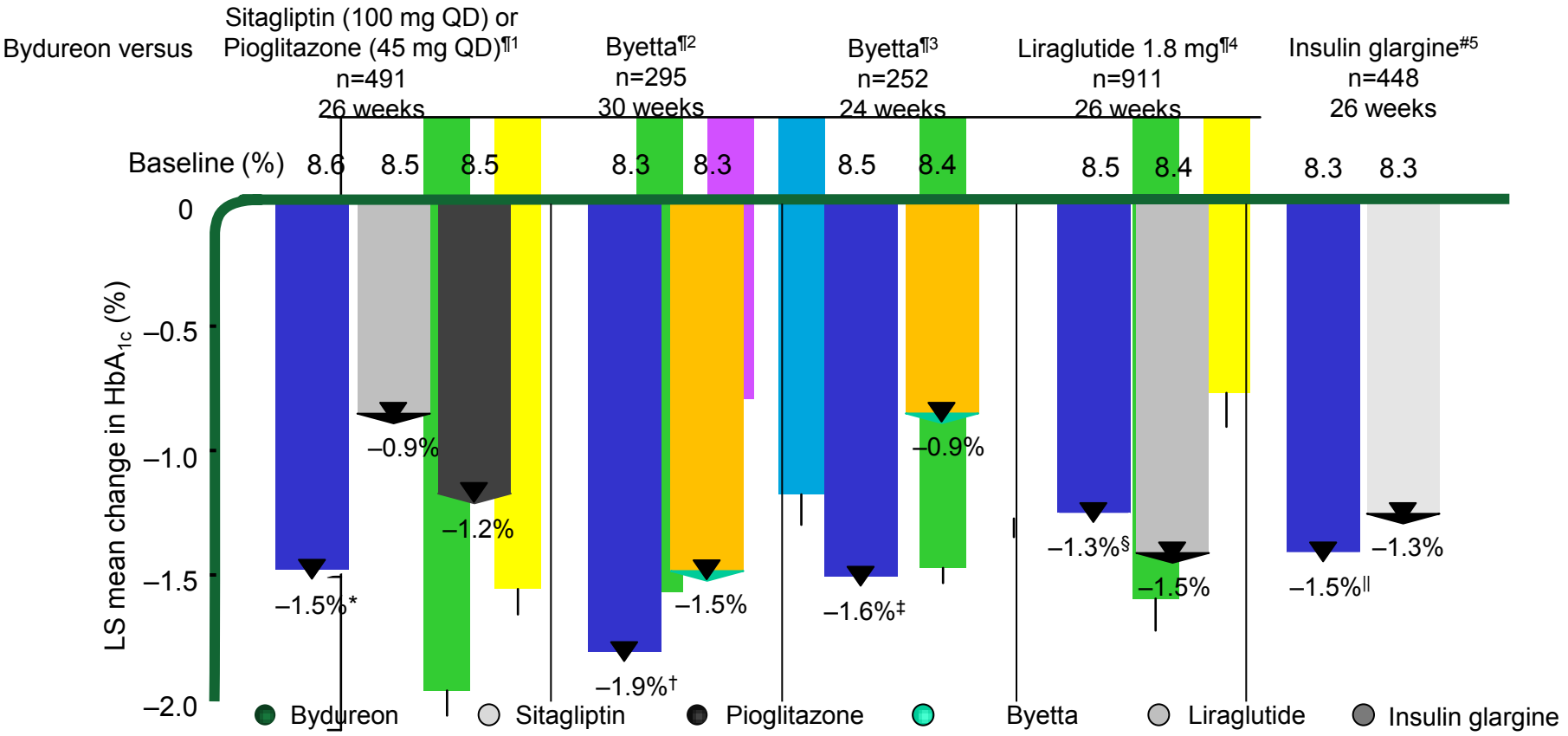
1. Buse JB et al. *Lancet* 2009;374:39-47; 2. Buse JB et al. *Lancet* 2013;381:117-124; 3. Pratley R et al. ADA 2012 poster presentation 945-P;
4. Kapitza C et al. *Diabetes Obes Metab* 2013;15:642-649

Bydureon clinical trials

Trial	Comparator	Background	Subjects	Publication
DURATION-1	Byetta Open label	Drug naïve, mono and combo failures	295	Drucker, *et al.* *Lancet* 2008
DURATION-2	Sitagliptin (100 mg QD) or pioglitazone (45 mg QD) Double blind	Metformin	491	Bergenstal, *et al. Lancet* 2010
DURATION-3	Insulin glargine Open label	Metformin ± SU	456	Diamant, *et al.* *Lancet* 2010
DURATION-5	Byetta Open label	Drug naïve, mono and combo failures	252	Blevins, *et al.* *J Clin Endocrin Metab* 2011
DURATION-6	1.8 mg liraglutide Open label	Mono and combo failures	911	Buse, *et al.* *Lancet* 2012

The DURATION-4 clinical trial of Bydureon monotherapy versus metformin, sitagliptin, or pioglitazone monotherapy was conducted in adult patients uncontrolled on diet and exercise alone. Bydureon is not indicated as first-line monotherapy in patients uncontrolled on diet and exercise alone.
QD, daily.

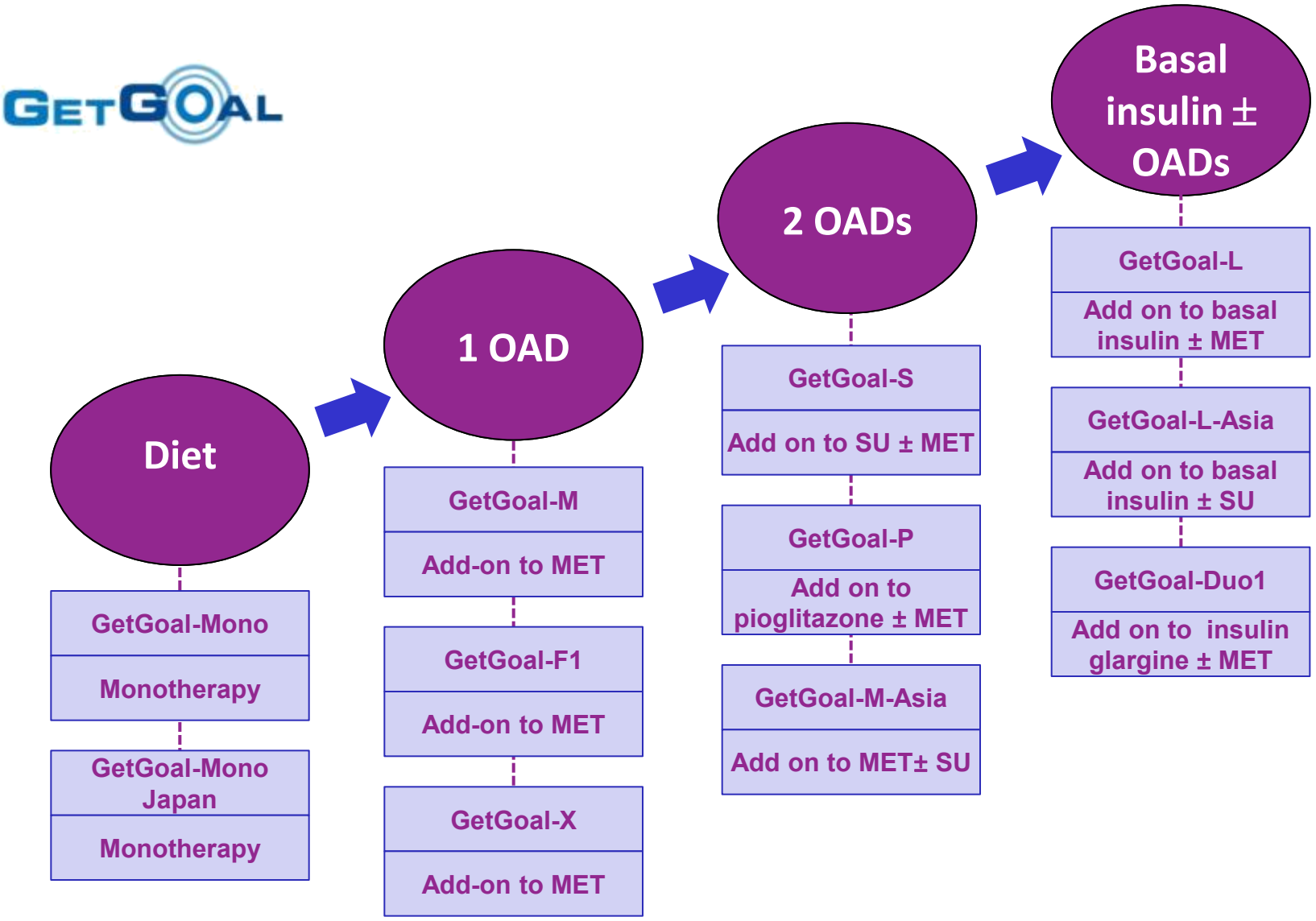
In the DURATION clinical trials, Bydureon demonstrated HbA_{1c} reductions of –1.3% to –1.9%



Data from 24–30 Weeks; *p<0.05 versus both; †p<0.01; ‡p<0.0001; §p=0.02; ||p=0.017; ¶ITT populatio
#Modified ITT population.

1. Bergenstal RM, *et al*. *Lancet* 2010;376:431-9; 2. Drucker DJ, *et al*. *Lancet* 2008;372:1240-50;
3. Blevins T, *et al*. *J Clin Endocrin Metab* 2011;96:1301-10; 4. Buse JB, *et al*. *Lancet* 2013;381:117-2
5. Diamant M, *et al*. *Lancet* 2010;375:2234-43.

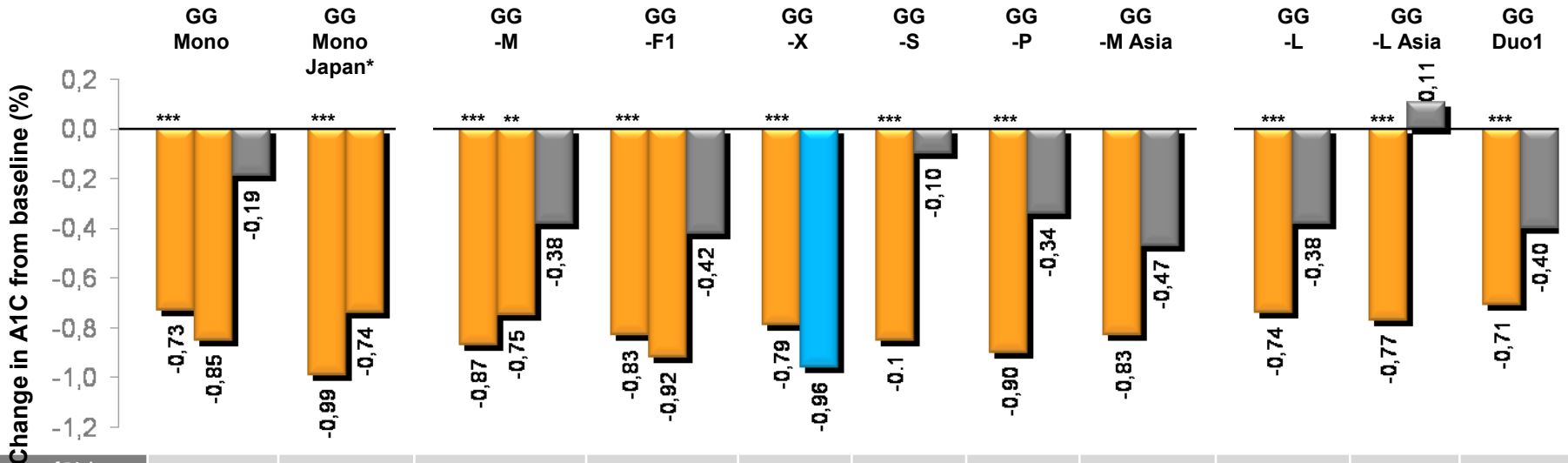
Lixisenatid GetGoal Program



GetGoal : change in HbA1C

BI = Basal Insulin
IG = Insulin Glargine
M = Metformin
P = Pioglitazone
SU = Sulfonylurea

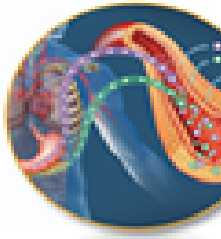
Lixisenatide
Exenatide
Placebo

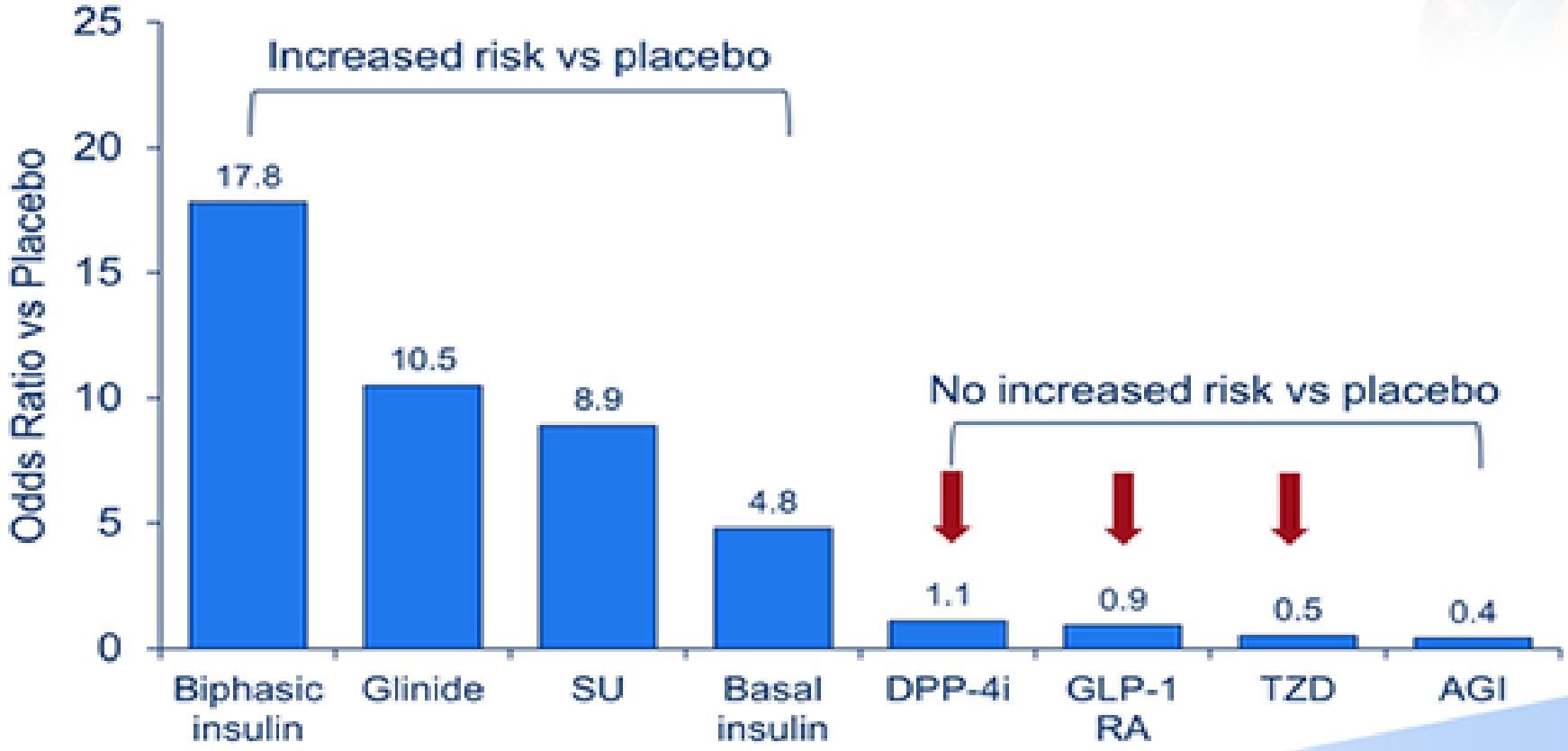


Duration of Diabetes (years)	1.4/1.1/1.4	8.0/9.0	6.2/6.2/5.9	6.0/5.8/6.2	6.8/6.8	9.1/9.8	8.1/8.1	6.5/6.8	11/11	13.7/14.1	9.6/8.7
Baseline A1C (%)	8/8.1/8.1	8.4/8.1	8.0/8.1/8.1	8.1/8.0/8.0	8.0/8.0	8.3/8.2	8.1/8.1	8.1/8	8.4/8.4	8.5/8.5	7.7/7.7
Baseline mean body weight (kg)	89.0/86.5/86.1	70.8/66.7	90.1/89/90.4	88.1/90.3/87.9	94.5/96.7	82.6/84.5	92.8/97.0	73.6/72.9	87.4/89.1	65.9/65.6	87.3/86.8
Baseline mean BMI (kg/m^2)	32.3/31.6/31.8	25.2/24.8	33.3/32.6/33.3	32.1/33.1/32.5	33.7/33.5	30.1/30.4	33.7/34.4	26.8/27.1	31.9/32.6	25.4/25.2	32/31.7
Background therapy	None	None	M	M	M	SU ± M	P ± M	M ± SU	BI ± M	BI ± SU	IG + M
Study duration (wks)	12	52 + ext	24 + ext	24 + ext	24 + ext	24 + ext	24 + ext	24	24 + ext	24	24

** 24 week data, longer term data was pooled** 2-step PM dosing) *** 2-step AM dosing*
Note: All lixisenatide dosing is 1-step AM regimen, unless otherwise noted
Source: Previous GetGoal sources

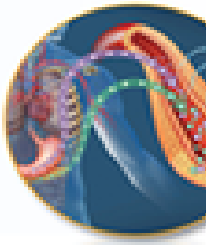
Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin

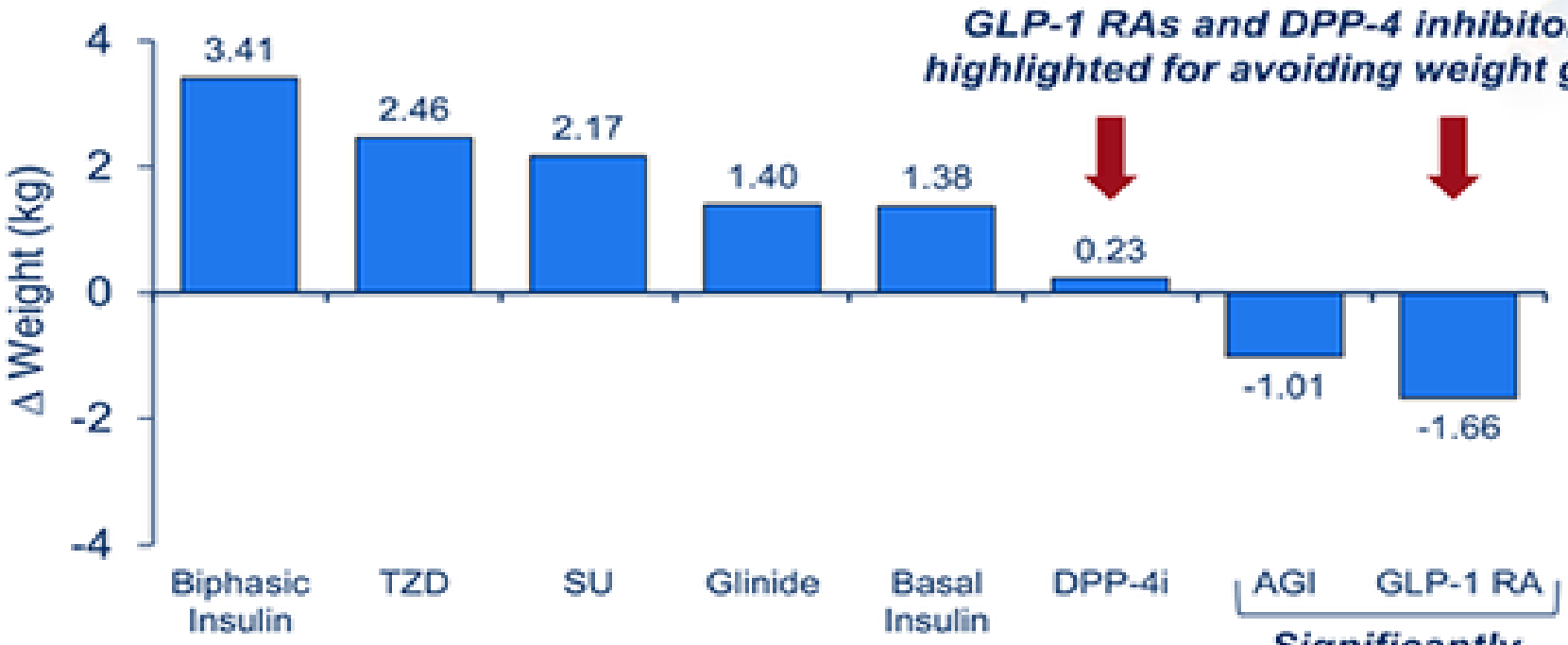




Liu S et al. *Diabetes Obes Metab*. 2012;14:810-820.

Meta-analysis: Weight Changes With Antihyperglycemic Agents Added to Metformin[1]





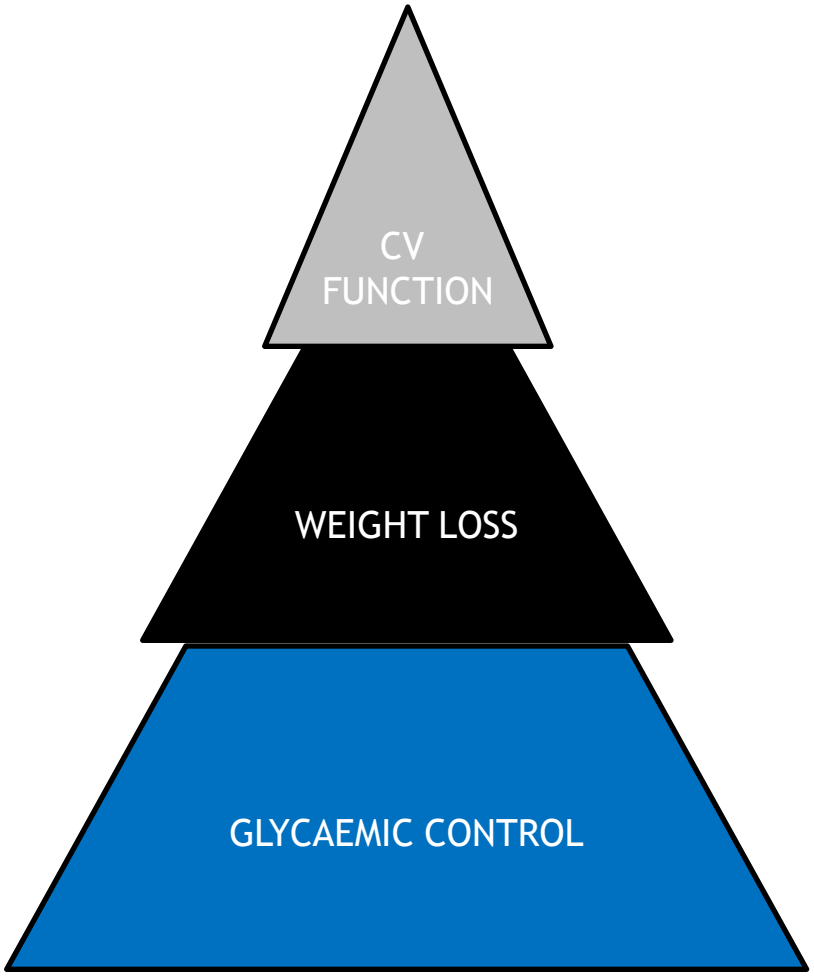
In a separate analysis, the SGLT-2 inhibitor canagliflozin was associated with significantly greater weight loss vs sitagliptin over 1 year (–2.3 vs 0.1 kg, respectively; *P* < .001).[2,a]

AGI, α-glucosidase inhibitor.

Added to MET + SU.

1. Liu SC et al. *Diabetes Obes Metab*. 2012;14:810-820.
2. Schernthaner G et al. *Diabetes Care*. 2013; Apr 5. [Epub ahead of print].

GLP-1RAs have desirable effects beyond glycaemic control



Myocardial function and survival in animal models[1,2]

Improved biomarkers of cardiovascular risk[1,2]

Systolic blood pressure[1]

Delayed gastric emptying[1,2]

Fullness and satiety[1,2]

Food intake[1,2]

Insulin secretion[1,2]

Insulin biosynthesis[1,2]

Beta-cell glucose sensitivity[2]

Glucagon secretion[2]

CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus

1. Vilsbøll T & Garber AJ. *Diabetes Obes Metab* 2012;14(suppl 2):41–49; 2. Baggio LL & Drucker DJ. *Gastroenterology* 2007;132:2131–2157

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DOI: 10.3748/wjg.v20.i23.7356

World J Gastroenterol 2014 June 21; 20(23): 7356-7365
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (12): Nonalcoholic fatty liver disease

Incretin based therapies: A novel treatment approach for non-alcoholic fatty liver disease

Kristina Blaslov, Tomislav Bulum, Karin Zibar, Lea Duvnjak

Incretin based therapy

CONTRA

Non responders

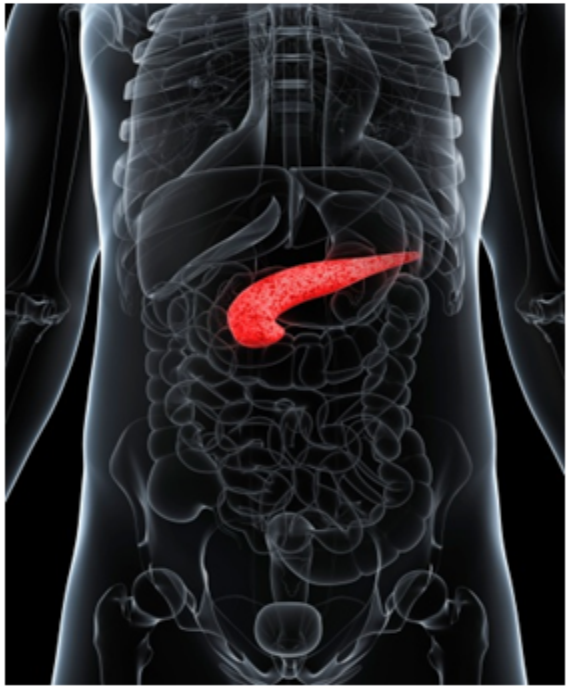
Thyroid C-cell cancer in animal models

Pancreatitis

Pancreatic neoplasm

Pancreatic Safety of Incretin-based Drugs

"Both [the FDA and EMA] agree that assertions concerning a causal association between 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."*

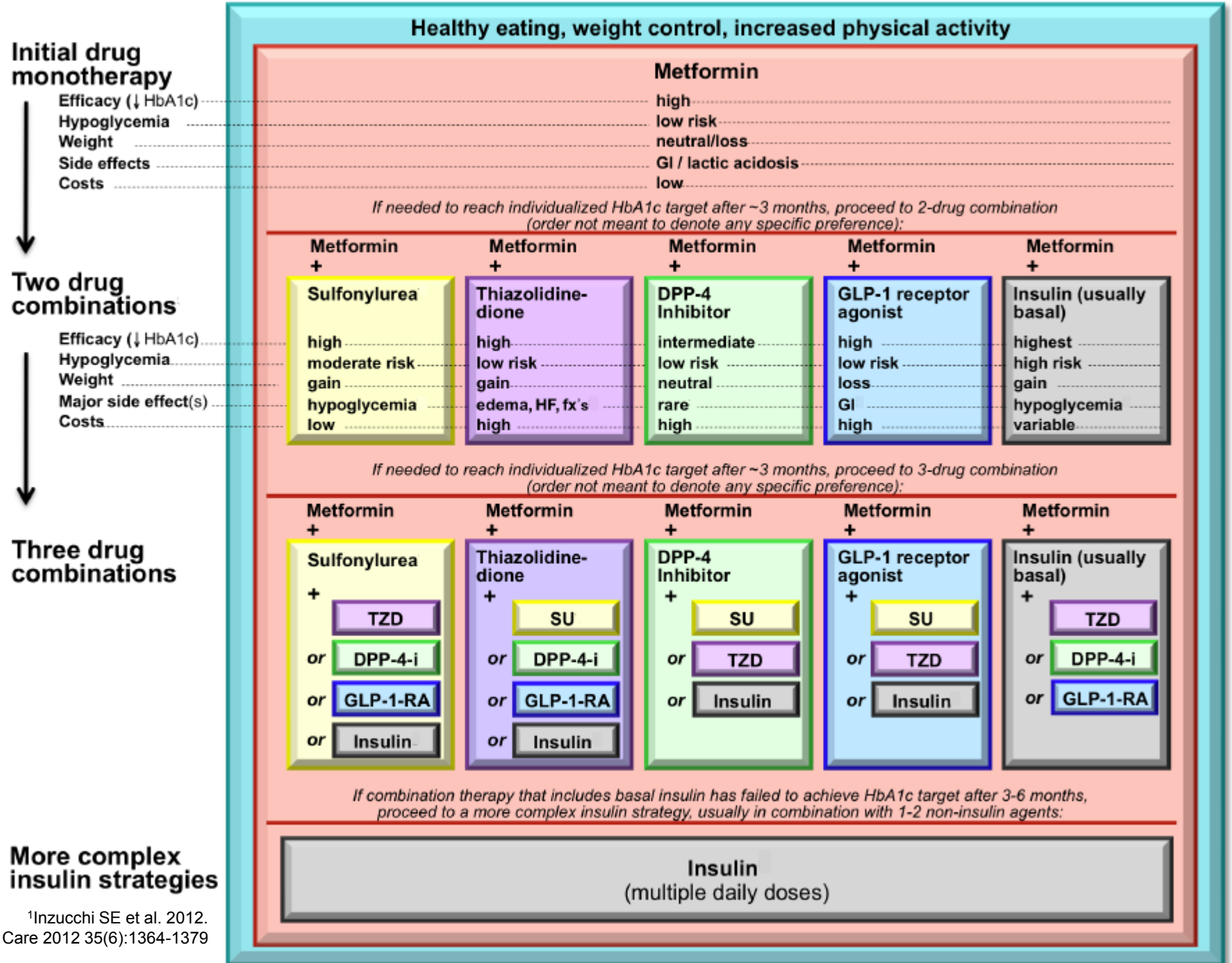


***Note that the FDA and EMA have not reached a final conclusion regarding a potential causal association.**

a. Egan AG, et al. *N Engl J Med*. 2014;370:794-797[11]; b. European Medicines Agency website.[12]

Incretin based therapeutic options

- Incretin effect is necessary for normal α- and β- cell function
- Incretin effect is reduced in people with type 2 diabetes
- Increasing the incretin effect should improve α- and β-cell function and glycemic control



[1]Inzucchi SE et al. 2012. Diabetes Care 2012 35(6):1364-1379