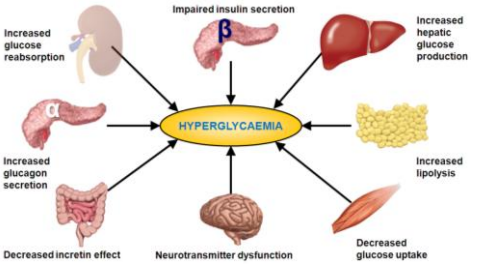


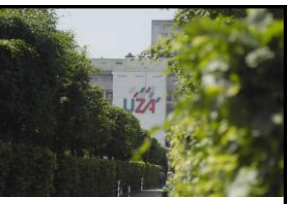
Piloot en diabetes?
Een veilige combinatie?

Universiteit Antwerpen

Christophe De Block, MD PhD
Diabetologie-Endocrinologie,
Vrijdag 21 september 2012

UZA
kennis / ervaring / zorg

Inhoud



- **Introductie:**
  - **luchtvaart-wetgeving**
  - **uitdagingen in de behandeling van DM: hypo**
  - **treatment guidelines**
- **DPP-4 inhibitoren & GLP-1 receptor agonisten:**
  - **fysiologie**
  - **effecten op HbA1c, hypoglycaemie, weight**
  - **Veiligheid**
- **Blik op de toekomst: SGLT-2 inhibitoren**

Luchtvaart - Wetgeving

Afdeling 4. - Metabolische, nutritionele en endocriene ziekten (JAR-FCL 3.175)

Art. 11. 1° De aanvrager of houder van een medisch attest van klasse 1 mag geen functionele of organische, metabolische, nutritionele of endocriene ziekte vertonen die een weerslag zou kunnen hebben op het volledig veilig uitoefenen van de voorrechten van de aangevraagde vergunning.
2° De aanvrager die een metabolische, nutritionele of endocriene dysfunctie vertoont, kan geschikt verklaard worden indien voldaan wordt aan de voorwaarden van hoofdstuk V, artikelen 79 en 82.
3° De aanvrager die lijdt aan diabetes mellitus kan slechts geschikt verklaard worden indien voldaan wordt aan de voorwaarden van hoofdstuk V, artikelen 80 en 81.
4° Insulinodependente diabetes heeft ongeschiktheid tot gevolg.
5° De aanvrager met een Body Mass Index (BMI) van 35 of meer kan geschikt verklaard worden op voorwaarde dat het overgewicht geen weerslag dreigt te hebben op het volledig veilig uitoefenen van de voorrechten van de aangevraagde vergunning. Bijkomend onderzoek mag geen verhoogd cardiovasculair risico aantonen. (Zie hoofdstuk V, artikel 103).

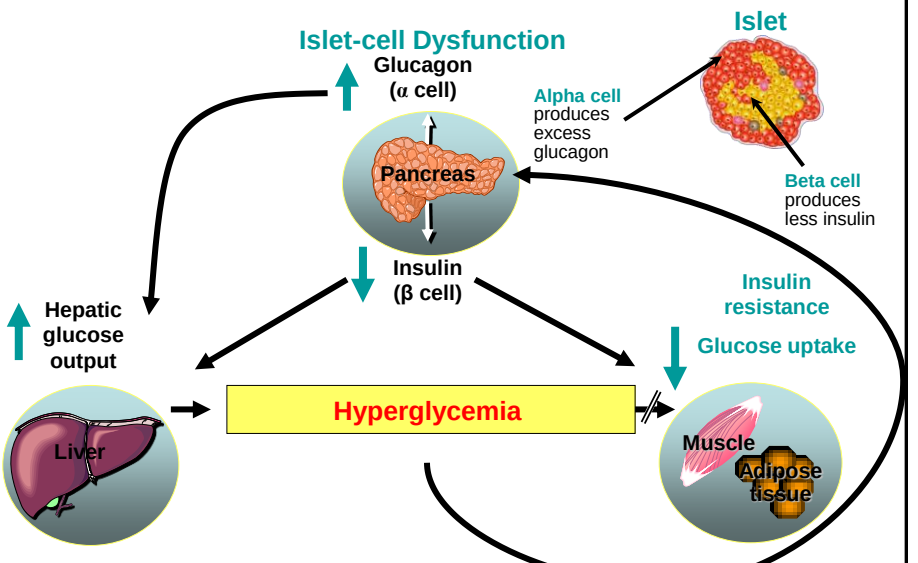
Afdeling 4. - Metabolische, nutritionele en endocriene stoornissen (JAR-FCL - Appendix 4)

Art. 79. Een metabolische, nutritionele of endocriene dysfunctie heeft ongeschiktheid tot gevolg. De geschiktheid kan overwogen worden door de SLG indien de aandoening asymptomatisch verloopt, klinisch gecompenseerd en stabiel is, met of zonder substitutietherapie, en indien zij regelmatig gecontroleerd wordt door een bevoegd specialist.

Art. 80. Het vaststellen van een glycosurie en een abnormale glycemie vereist bijkomend onderzoek. De geschiktheid kan door de SLG overwogen worden indien aangetoond wordt dat de glucosetolerantie normaal is (verlaagde nierdrempel) of bij gestoorde glucosetolerantie zonder diabetische pathologie de toestand van de kandidaat volledig onder controle is door dieet en regelmatige follow-up.

Art. 81. Een behandeling met antidiabetische geneesmiddelen heeft ongeschiktheid tot gevolg. In bepaalde gevallen evenwel, kan het gebruik van biguaniden of alfa-glucosidase inhibitoren toegestaan worden, mits een OML-beperking voor klasse 1 of zonder enige beperking voor klasse 2. Een behandeling met sulfonylurea kan aanvaard worden bij een wedergeldigmaking of hernieuwing van het medisch attest van klasse 2 met OSL-beperking.

Type 2 diabetes: pathogenese

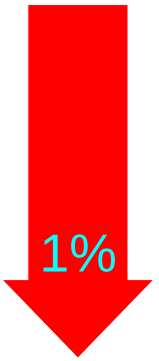


Adapted with permission from Kahn CR, Saltiel AR. *Joslin's Diabetes Mellitus*. 14th ed. Lippincott Williams & Wilkins; 2005:145–168; Del Prato S, Marchetti P. *Horm Metab Res*. 2004;36:775–781; Porte D Jr, Kahn SE. *Clin Invest Med*. 1995;18:247–254.

Belang van goede glycemiecontrole

betere metabole controle = minder complicaties

Bij t2DM: Elke 1% reductie in HBA_{1C}



	Risicoreductie
Sterfte tgv diabetes	-21%
hartinfarct	-14%
Microvasculaire complicaties	-37%
Perifeer vaatlijden	-43%

*p<0.0001

UKPDS 35. BMJ 2000; 321: 405-12.

Therapeutic goal: To achieve normoglycaemia without inducing hypoglycaemia

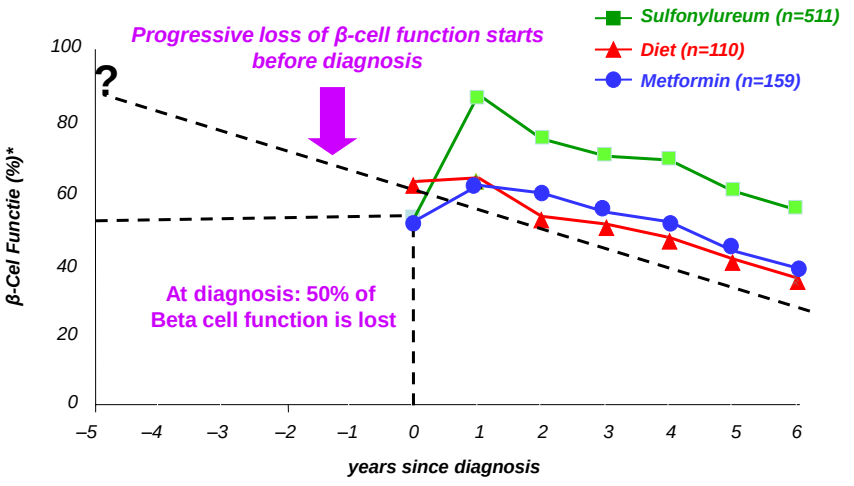
- **Glycaemic targets set by international guidelines**

	American Diabetes Association[1]	American Association of Clinical Endocrinologists[2]	International Diabetes Federation[3]
HbA_{1c} (%)	<7	≤6.5	<6.5
Mean FBG, mmol/L (mg/dL)	5–7.2 (90–130)	≤6 (≤110)	<6 (<110)
Mean PPBG, mmol/L (mg/dL)	<10* (<180)	≤7.8** (≤140)	<8* (<145)

***1–2 hours postprandial; **2 hours postprandial**

1. ADA. Diabetes Care 2006;29(suppl 1):S4–42
2. AACE. Endocr Pract 2002;8(suppl 1):40–82
3. IDF Clinical Guidelines Task Force. Global guideline for Type 2 diabetes. Brussels: IDF, 2005 http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf (last accessed: 17-Aug-2006)

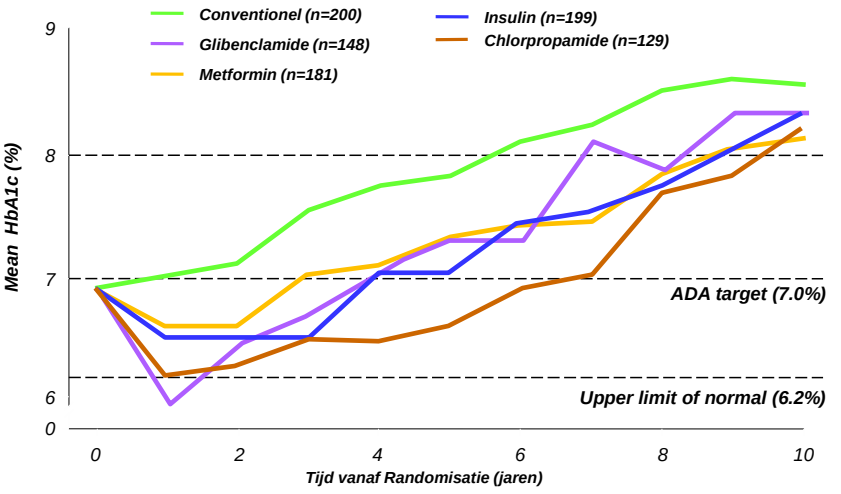
Decline of β-Cell function despite any form of treatment illustrates progressive nature of DM



*β-cell function : homeostasis model assessment (HOMA)
UKPDS Group. UKPDS 16. Diabetes. 1995; 44: 1249–1258.

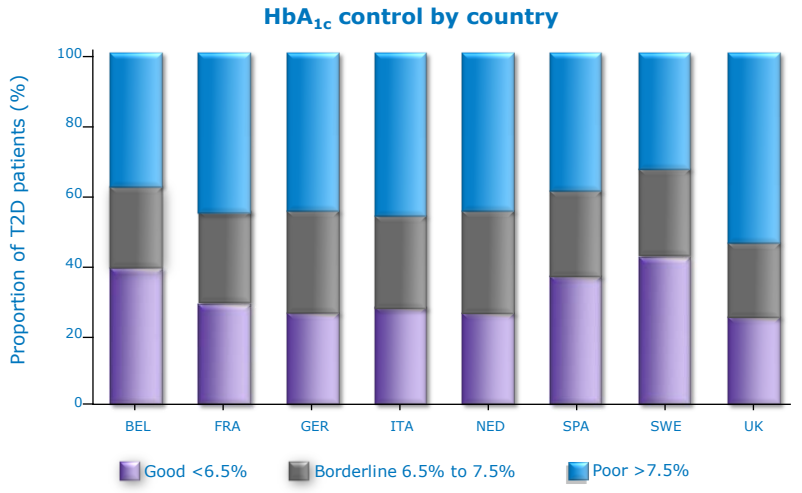
Challenges in type 2 diabetes

Glycemic control deteriorates with time / duration of DM



ADA=American Diabetes Association; HbA1c=hemoglobin A1c
Aangepast van UKPDS Group. Lancet. 1998; 352: 854–865.

Glycaemic control often not achieved in adults with type 2 diabetes

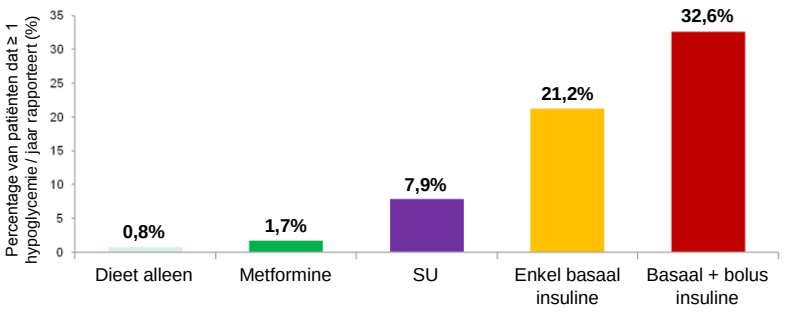


Liebl A, et al. Diabetologia. 2002;45:S23-S28.

Barrières voor een goede controle

Hypoglycemie geassocieerd aan de behandeling

- % patiënten met jaarlijks minstens 1 hypoglycemie in relatie tot de therapie.
- Type 2 diabetespatiënten uit UKPDS-studie.



Wright AD et al (2006) J Diabetes Complicat 20; 395-401.

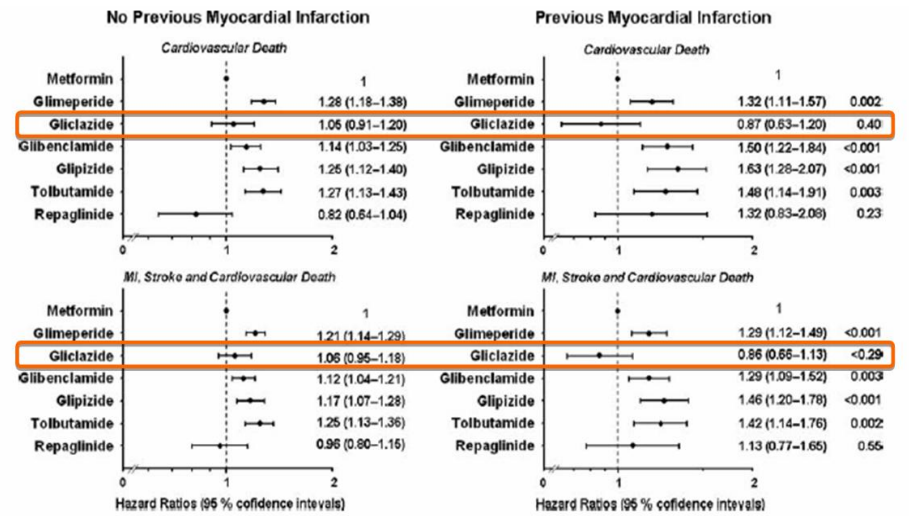
Challenges in type 2 diabetes

Hypoglycemia is a frequent acute complication of treatment

High risk[1]	Low risk[1,2]
Insulin	Metformin
Sulphonylureas	α-glucosidase inhibitors
Meglitinides	Thiazolidinediones
	GLP-1 receptor agonists
	DPP-4 inhibitors

1. Nathan DM, et al. Diabetologia. 2009;52:17-306. 2. Cefalu WT. Nature. 2007;81:636-49.

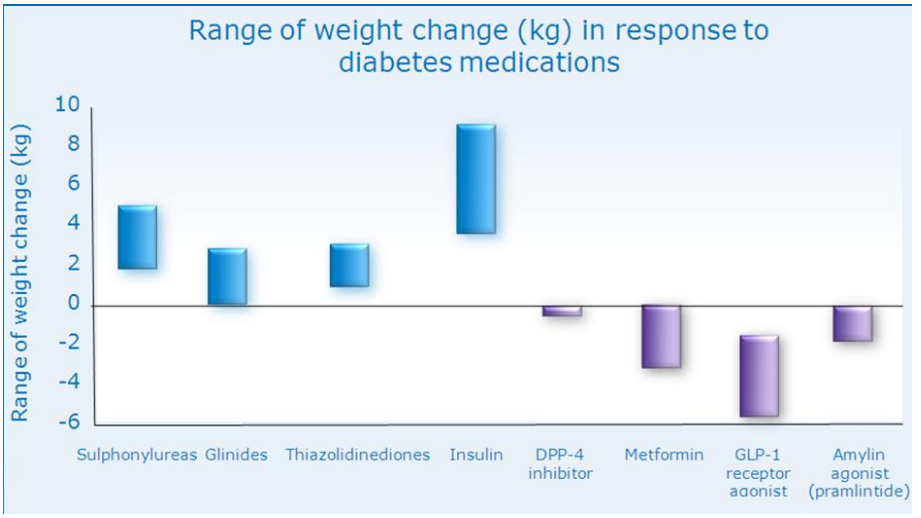
Mortality and CV risk: insulin secretagogues vs metformin



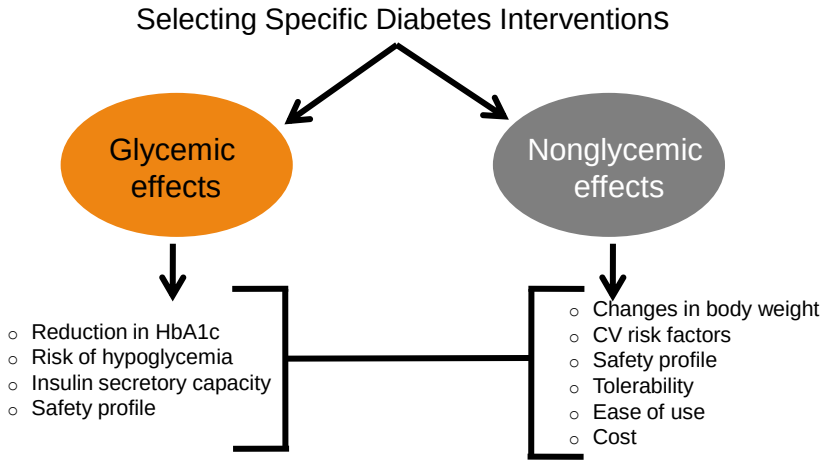
Schramm TK et al. *Eur Heart J* 2011; 32 (15): 1900-8

Challenges in type 2 diabetes

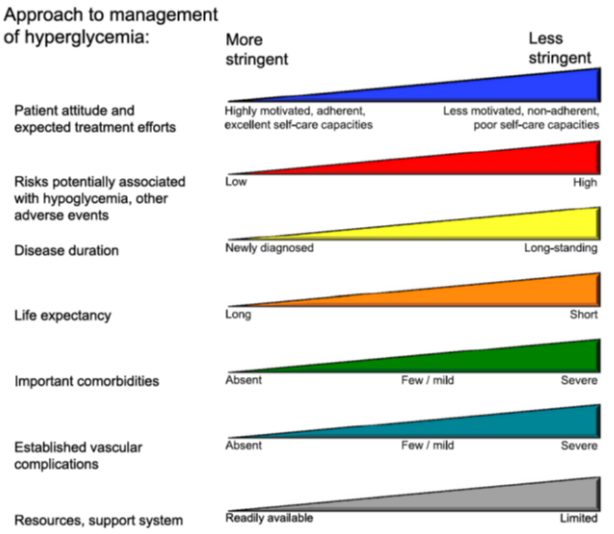
Weight increases with time



Selecting the Appropriate Therapeutic Agent for Individual Patients

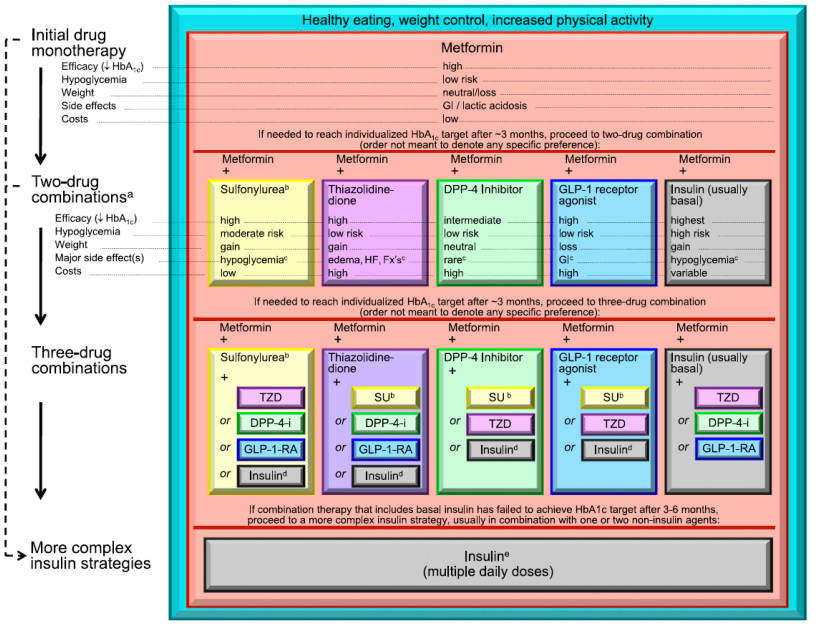


Elements of decision making used to determine appropriate efforts to achieve glycemic targets.



Inzucchi et al. Diabetes Care 2012

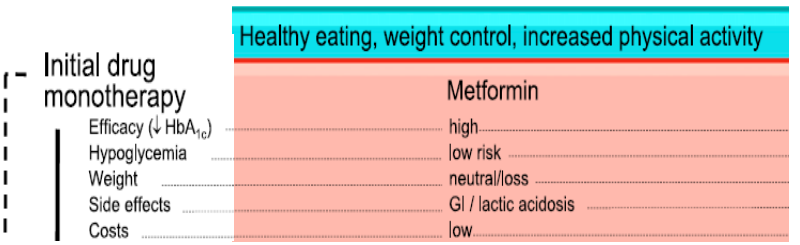
ADA/EASD 2012: Antihyperglycemic therapy in T2DM: recommendations.



Inzucchi et al. Diabetes Care 2012

ADA/EASD 2012: Antihyperglycemic therapy in T2DM

STAP 1



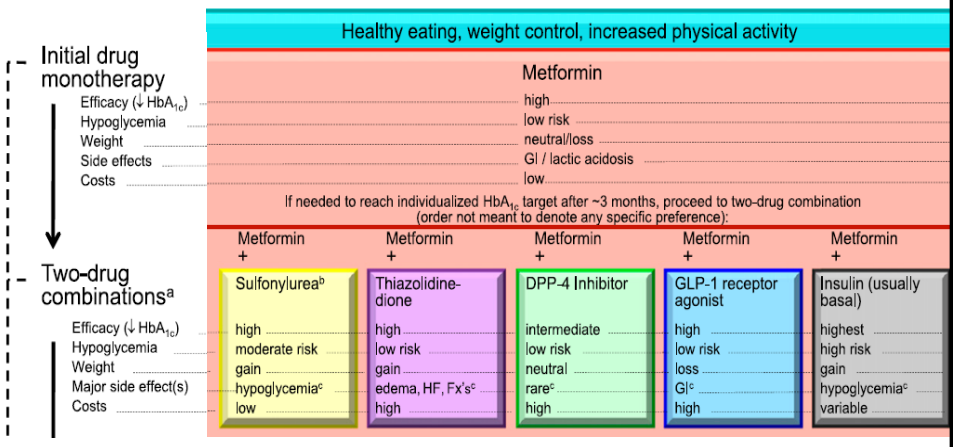
Effect

- **fasting plasma glucose ↓ 60-70 mg/dL**
- **↓ HbA1c 1.0-2.0%**

Inzucchi et al. Diabetes Care 2012

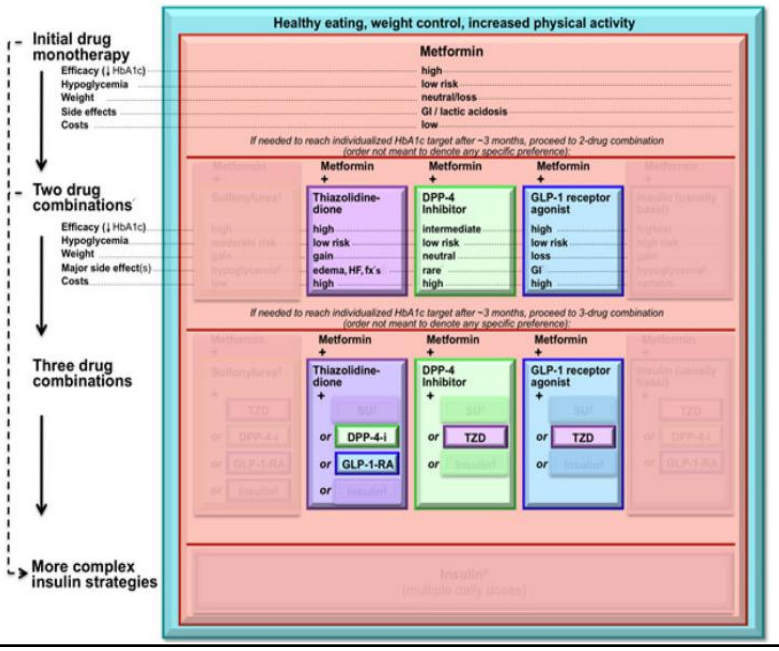
ADA/EASD 2012: Antihyperglycemic therapy in T2DM

STAP 2



Inzucchi et al. Diabetes Care 2012

Adapted recommendations: when goal is to avoid hypoglycemia

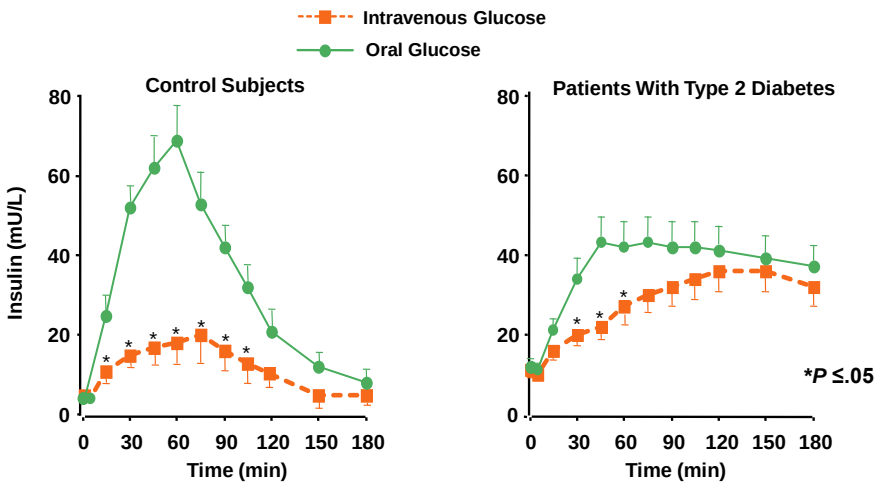


DPP-IV inhibitors

- mode of action
- efficacy
- safety

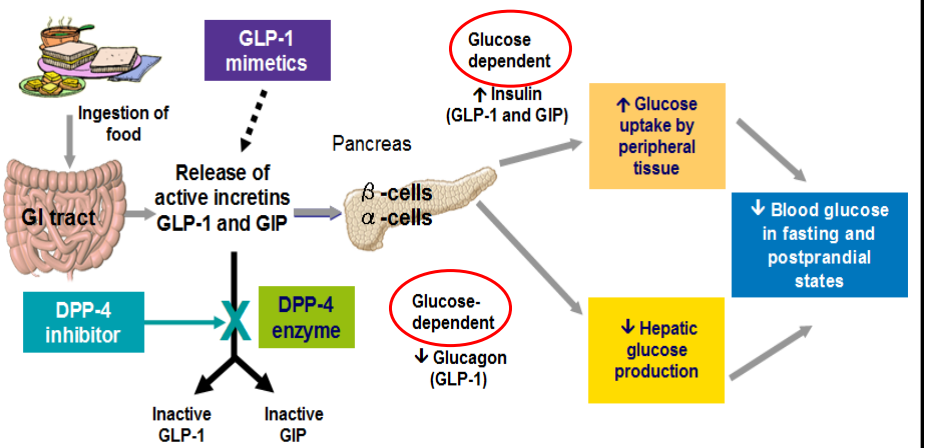
incretins

The incretin effect is reduced in patients with type 2 diabetes



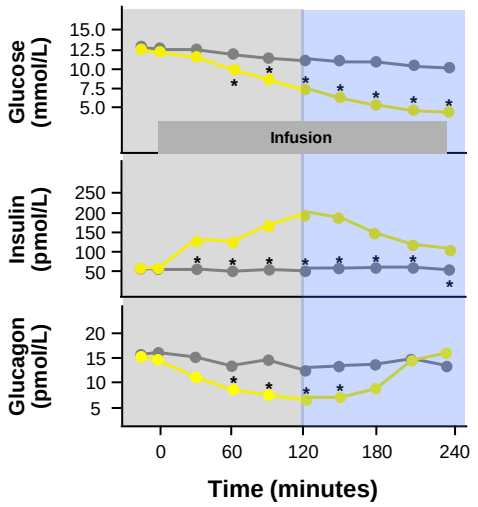
Nauck MA, et al, Diabetologia. 1986;29:46-52

Incretins Regulate Glucose Homeostasis Through Effects on Islet Cell Function



Adapted from Brubaker PL, Drucker DJ *Endocrinology* 2004;145:2653–2659; Zander M et al *Lancet* 2002;359:824–830; Ahrén B *Curr Diab Rep* 2003;3:365–372; Buse JB et al. In *Williams Textbook of Endocrinology*. 10th ed. Philadelphia, Saunders, 2003:1427–1483.

Effects of GLP-1 on Insulin and Glucagon are Glucose Dependent in Type 2 Diabetes



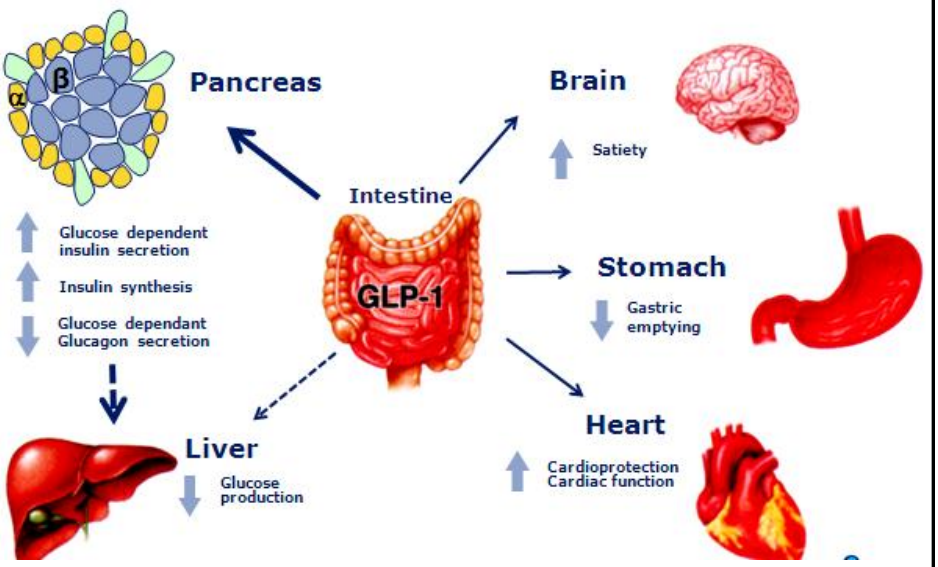
With hyperglycemia GLP-1 stimulated insulin and suppressed glucagon.

When glucose levels approached normal, insulin levels declined and glucagon was no longer suppressed.

N=10 patients with type 2 diabetes. Patients were studied on two occasions. A regular meal and drug schedule was allowed for one day between the experiments with GLP-1 and placebo. *p<0.05 GLP-1 vs. placebo

Nauck MA et al *Diabetologia* 1993;36:741–744.

physiological actions of GLP-1

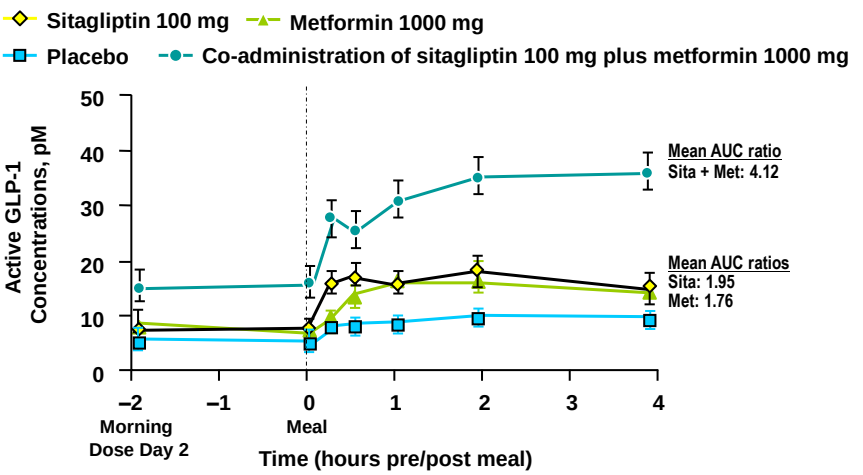


Baggio & Drucker. Gastroenterology 2007; 132: 2131-2157

DPP-IV inhibitors

- mode of action
- efficacy
- safety

Co-administration of Sitagliptin and Metformin in Healthy Adults Increased Active GLP-1 Greater Than Either Agent Alone

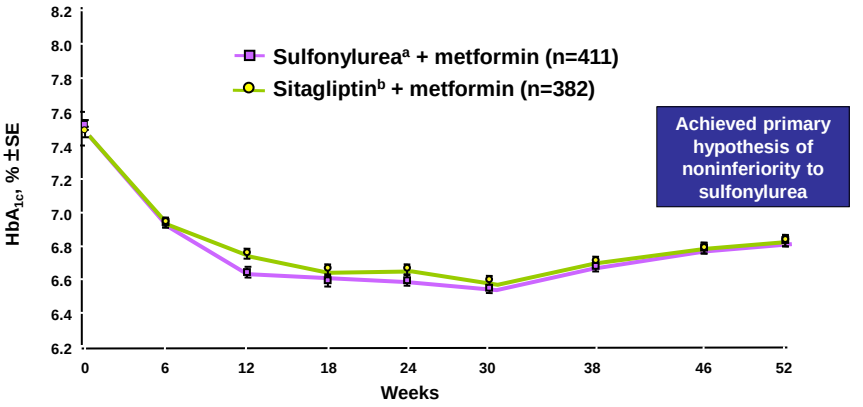


N=16 healthy subjects.
AUC=area under the curve

Values represent geometric mean±SE.

HbA_{1c} With Sitagliptin or Glipizide as Add-on Combination With Metformin: Comparable Efficacy

Per-protocol Population
LSM change from baseline at 52 weeks (for both groups): –0.7%

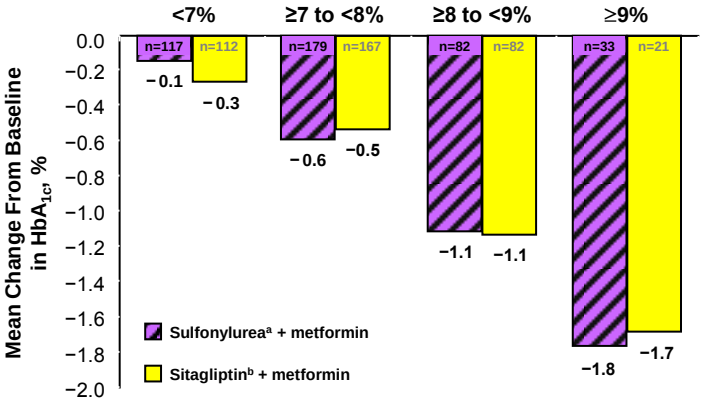


[a]Specifically glipizide ≤20 mg/day;
[b]Sitagliptin 100 mg/day with metformin (≥1500 mg/day).
LSM=least squares mean.
SE=standard error.

Adapted from Nauck MA, et al, *Diabetes Obes Metab.* 2007;9:194–205

Greater Reductions in HbA_{1c} Associated With Higher Baseline HbA_{1c}– 52-Week Post Hoc Analysis

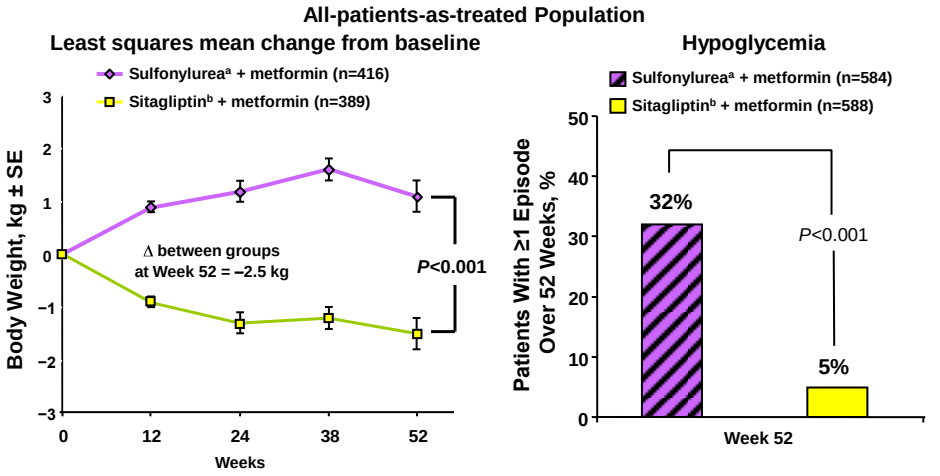
Per-protocol Population
Baseline HbA_{1c} Category



[a]Specifically glipizide ≤20 mg/day.
[b]Sitagliptin 100 mg/day with metformin (≥1500 mg/day);
Add-on sitagliptin with metformin vs sulfonylurea with metformin study.

Adapted from Nauck MA, et al, *Diabetes Obes Metab.* 2007;9:194–205

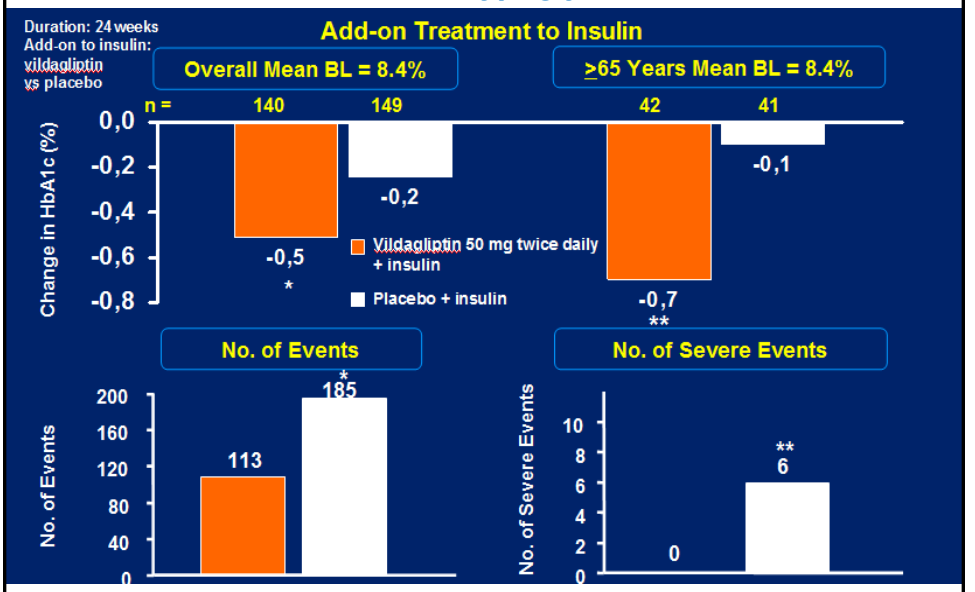
Sitagliptin with metformin provided weight reduction (vs weight gain) and a much lower incidence of hypoglycemia



Least squares mean between-group difference at week 52 (95% CI): change in body weight at Week 52 = –2.5 kg [–3.1, –2.0] (*P*<.001); Least squares mean change from baseline at week 52: glipizide: +1.1 kg; sitagliptin: –1.5 kg (*P*<.001).

Adapted from Nauck MA, et al, *Diabetes Obes Metab.* 2007;9:194–205

Vildagliptin Add-on to Insulin: Significant Reduction in HbA1c and Fewer Hypoglycemic Events

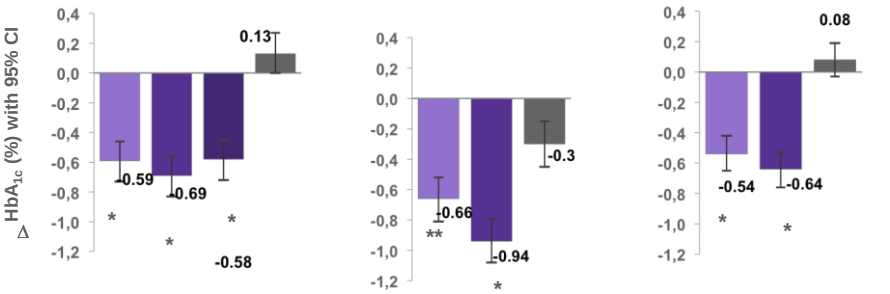


*BL=baseline; HbA1c=hemoglobin A1c. *P <0.001; **P <0.05 between groups.*
Fonseca V, et al. Diabetologia. 2007; 50: 1148–1155.

Saxagliptin add-on to metformin, TZD and SU[1]

Change from baseline HbA_{1c} at Week 24

	SAXA + MET [2]			PBO + MET [2]	SAXA + TZD		PBO + TZD	SAXA + GLY		PBO + GLY
Dose	2.5	5	10		2.5	5		2.5	5	
n =	186	186	180	175	192	183	180	246	250	264
Bsl Mean (%)	8.08	8.07	7.98	8.06	8.25	8.35	8.19	8.36	8.48	8.44



* *P*<0.0001 vs PBO + MET

**P*<0.0001 vs PBO + TZD
***P*=0.0007 vs PBO + TZD

* *P*<0.0001 vs PBO + GLY

SAXA: Saxagliptin; MET: Metformin, TZD: Thiazolidinediones; SU: Sulphonylureas; PBO: Placebo.

1. http://www.fda.gov/ohrms/dockets/ac/cder09. Accessed on 7th July 09. 2. Defronzo RA, et al. Diabetes Care. 2009 Jun 23

DPP-4 inhibitors lower HbA1c at all stages in T2DM

Broadly similar efficacy to existing OADs

Lower HbA1c by 0.6% to up to ~2%, depending on initial HbA1c level

Data showing efficacy as

- Monotherapy (when metformin not indicated or tolerated)
- Initial combination therapy
  - with metformin or glitazones
- Add-on to insulin

DPP-IV inhibitors

- mode of action
- efficacy
- safety

DPP-4 Inhibition Appears Safe and Well-Tolerated

12 large Phase II / III studies up to 2 years in duration

Sitagliptin 100 mg/day (3415 patients)
1343 patients treated for at least 1 year; 356 of these patients treated for 2 years

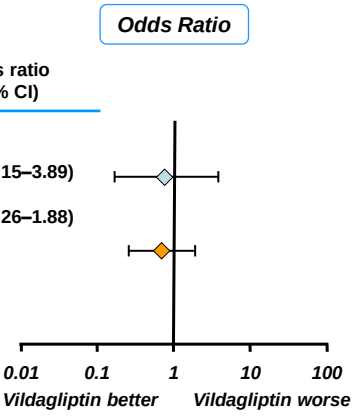
Non-exposed (2724 patients)
981 patients treated for at least 1 year; 290 of these patients treated for 2 years

No difference from non-exposed group for side effects or adverse events including:

- **Hypoglycaemia (except when compared to SU, when sitagliptin is lower)**
- **Nausea or gastrointestinal side effects**
- **Nasopharyngitis**
- **Upper respiratory tract infections**
- **Urinary tract infections**
- **Myocardial infarction**
- **Coronary artery disease**

Vildagliptine: no increased risk for pancreatitis-related side effects

	Vildagliptin n / N (%)	All comparators n / N (%)	odds ratio (95% CI)
Pancreatitis events			
Vilda 50 mg qd*	2 / 1502 (0.13)	4 / 1662 (0.24)	0.76 (0.15–3.89)
Vilda 50 mg bid*	7 / 6116 (0.11)	9 / 4872 (0.18)	0.70 (0.26–1.88)

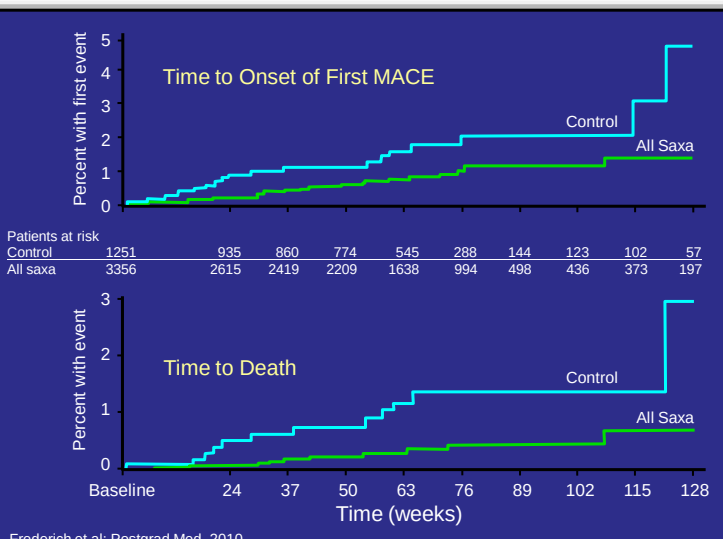


AEs=adverse events; bid=twice daily; CI=confidence interval; qd=once daily; vilda=vildagliptin.
**Vs comparators (all non-vildagliptin treatment groups). All-study safety (excluding open-label) population.*

Ligueros-Saylan M, et al. DOM 12: 495-509, 2010

Saxagliptin may reduce risk of CV death, MI and/or stroke (Meta-analysis of 8 phase IIb/III studies)

Patients previously drug-naïve or on monotherapy; duration of diabetes ~4 yr)



Cox hazard ratio
0.44 (0.24, 0.82)
Saxagliptin vs comparators;
(composite of CV death/MI/stroke)

Frederich et al; Postgrad Med, 2010

incretines

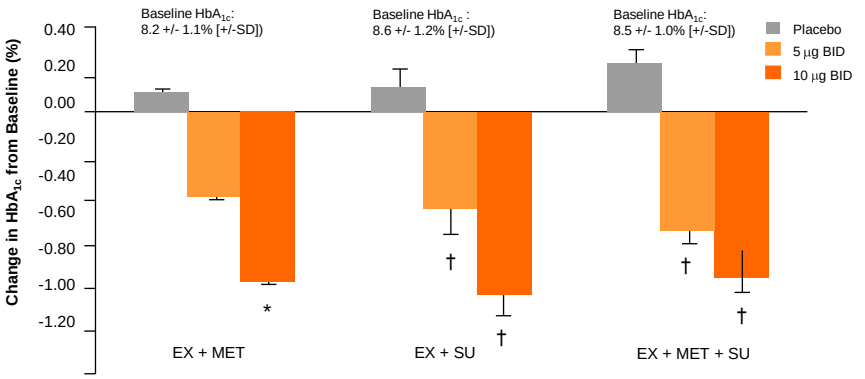
Current GLP-1–based approaches for improving glycaemic control

- **Agents that mimic the actions of GLP-1 (incretin mimetics)**
  - **–DPP-IV–resistant GLP-1 derivatives**
    - **GLP-1 analogues, albumin-bound GLP-1 (liraglutide= Victoza)**
  - **–Novel peptides that mimic the glucoregulatory actions of GLP-1**
    - **Exenatide (Byetta)**

- **Agents that prolong the activity of endogenous GLP-1**
  - **–DPP-IV inhibitors: sitagliptine (Januvia), vildagliptine (Galvus), saxagliptin (Onglyza)**

Drucker DJ, et al Diabetes Care. 2003; Baggio LL, et al Diabetes. 2004

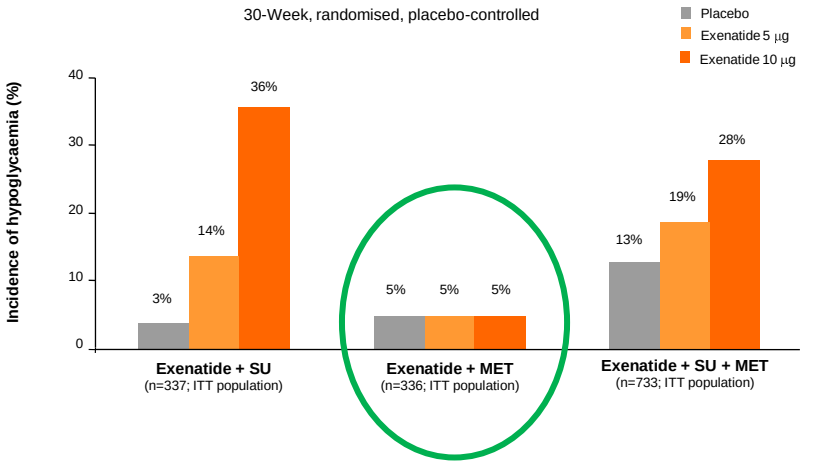
Exenatide: Effects on glycaemic control in combination with current oral therapies (AMIGO)



*P<0.001 vs placebo; †P<0.0001 vs placebo.
EX: Exenatide; MET: Metformin; SU: Sulphonylurea

1. Buse JB, et al. Diabetes Care. 2004;27:2628-35. 2. DeFronzo RA, et al. Diabetes Care. 2005;28:1092-100.
3. Kendall DM, et al. Diabetes Care. 2005;28:1083-91.

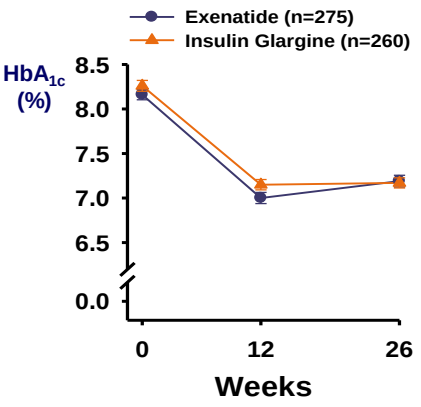
Exenatide + oral agents
Summary of hypoglycaemia data (AMIGO)

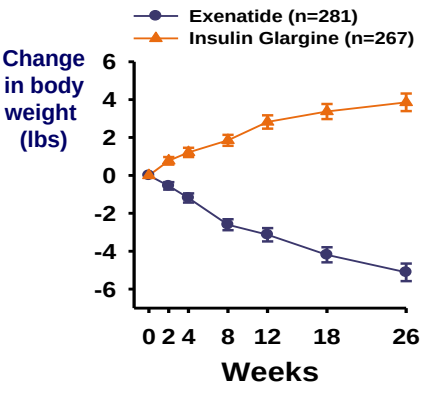


1. Buse JB, et al. Diabetes Care. 2004;27:2628-35. 2. DeFronzo RA, et al. Diabetes Care. 2005;28:1092-100. 3. Kendall DM, et al. Diabetes Care. 2005;28:1083-91.

Incretins: Exenatide (Byetta)

- **Exenatide: HbA1c & weight**



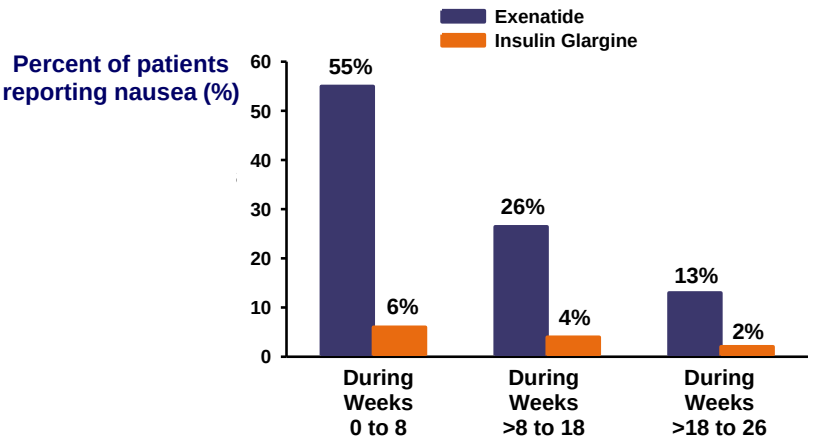


*** p<0.0001, exenatide vs insulin glargine at same time point**

Heine R, Van Gaal L et al. Ann Intern Med 2005

Incretins: Exenatide (Byetta)

Incidence of nausea by time

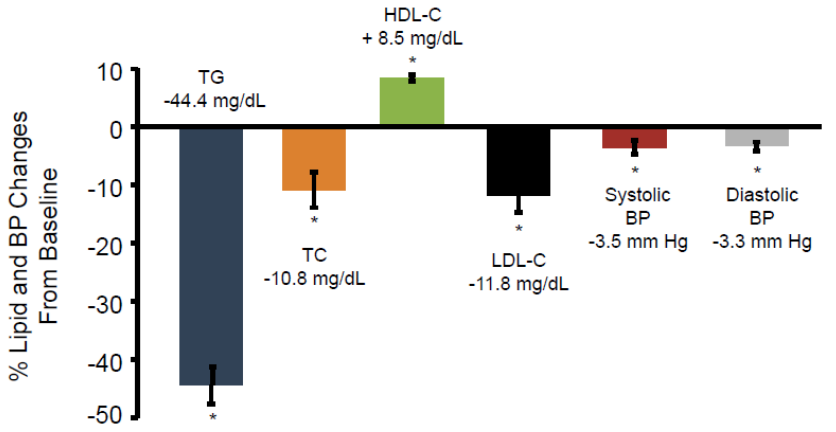


ITT patient sample shown

Heine R, Van Gaal L et al, Ann Intern Med, 2005

Improvement in Cardiovascular Risk Factors With 3.5 Years of Exenatide Treatment

Placebo-controlled/Open-label Extension (Combined)



N=151; *p<.05.
Klonoff DC, et al. Curr Med Res Opin 2008;24:275-286.

Improvement of glycemic control and loss of body weight with Exenatide in type 2 diabetic patients:

Results from an observational multicentric study in Belgium

C. De Block[1], N. Paquot[2], N. Daoudi[3], D. Ballaux[4], L.F. Van Gaal[1] and A.J. Scheen[2]

1) UA, Diabetologie-Endocrinologie en Metabole ziekten
2) CHU Liège, Service de Diabétologie, Nutrition et Maladies métaboliques
3) Hopital civil de Charleroi , Service de Diabétologie-Endocrinologie
4) AZ Nikolaas, Sint-Niklaas, afdeling Endocrinologie-Diabetologie

De Block et al. Rev Med Liège 2009; 64 : 10 : 488-495

Incretines: GLP-1 Rec agonisten

THE LANCET

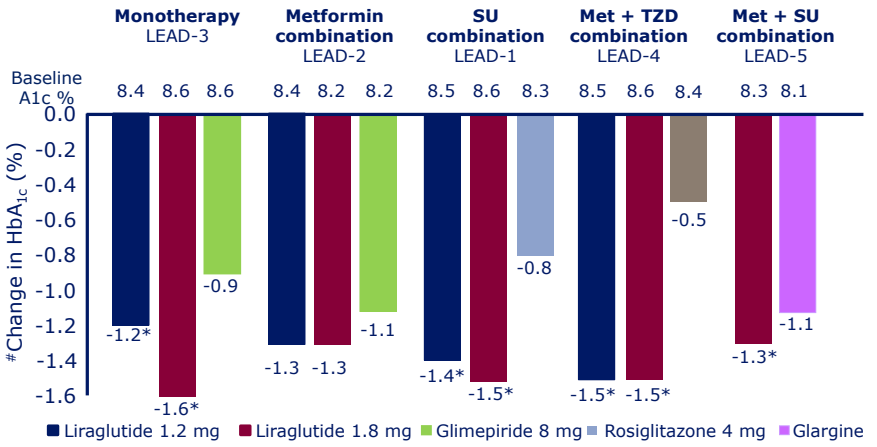
Comment Jun 08, 2009

GLP-1 receptor agonists for type 2 diabetes

Christophe EM De Block, Luc F Van Gaal

	Liraglutide	Exenatide
Aminoacid identity with GLP-1	97%	53%
Half life (h)	13	2
Frequency of injection	Once a day	Twice a day
Mode of administration	SC injection	SC injection
Antibody production	9–13%	40–45%
Insulin secretion	↑	↑
Glucagon suppression	↓	↓
Gastrointestinal motility	?	↓

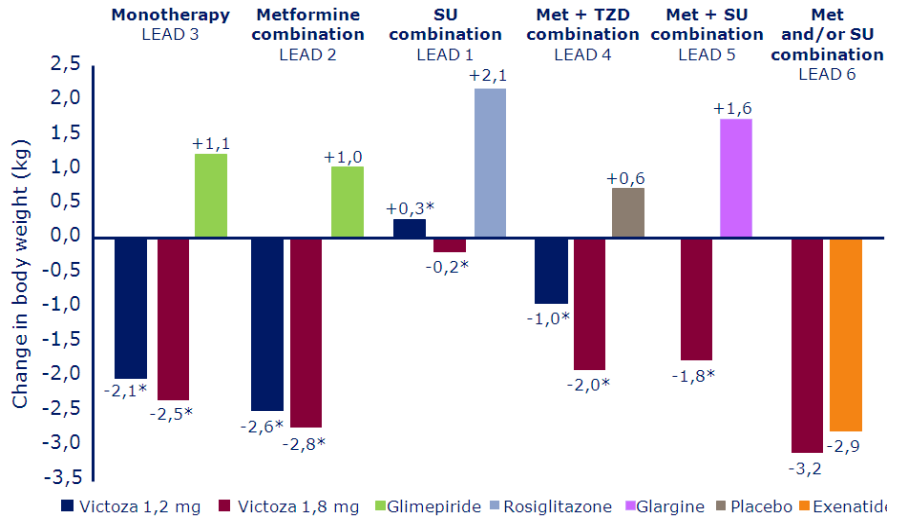
LEAD programme: reductions in HbA_{1c} with liraglutide



Significant *vs. comparator; #Change in HbA_{1c} from baseline for overall population (LEAD-4,-5) add-on to diet and exercise failure (LEAD-3); or add-on to previous OAD monotherapy (LEAD-2,-1).

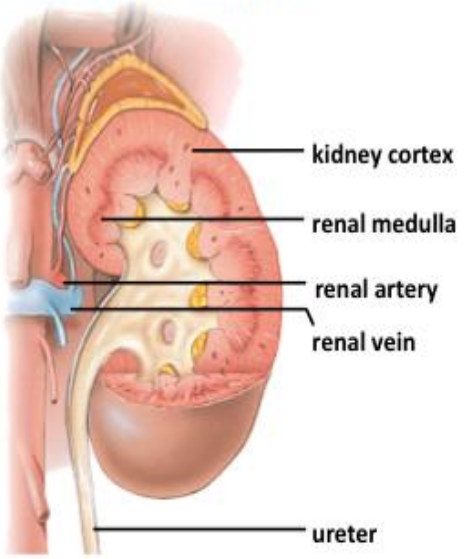
Marre et al. Diabetic Medicine 2009;26;268–78 (LEAD-1); Nauck et al. Diabetes Care 2009;32;84–90 (LEAD-2); Garber et al. Lancet 2009;373:473–81 (LEAD-3); Zinman et al. Diabetes Care 2009;32:1224–30 (LEAD-4); Russell-Jones et al. Diabetologia 2009;52:2046-2055 (LEAD-5);

Liraglutide: effect op gewicht



Marre et al. Diabetic Medicine 2009;26;268–78 (LEAD-1); Nauck et al. Diabetes Care 2009;32;84–90 (LEAD-2); Garber et al. Lancet 2009;373:473–81 (LEAD-3); Zinman et al. Diabetes Care 2009;32:1224–30 (LEAD-4); Russell-Jones et al. Diabetologia 2009;52:2046-2055 (LEAD-5); Buse et al. Lancet 2009;374 (9683):39–47 (LEAD-6)

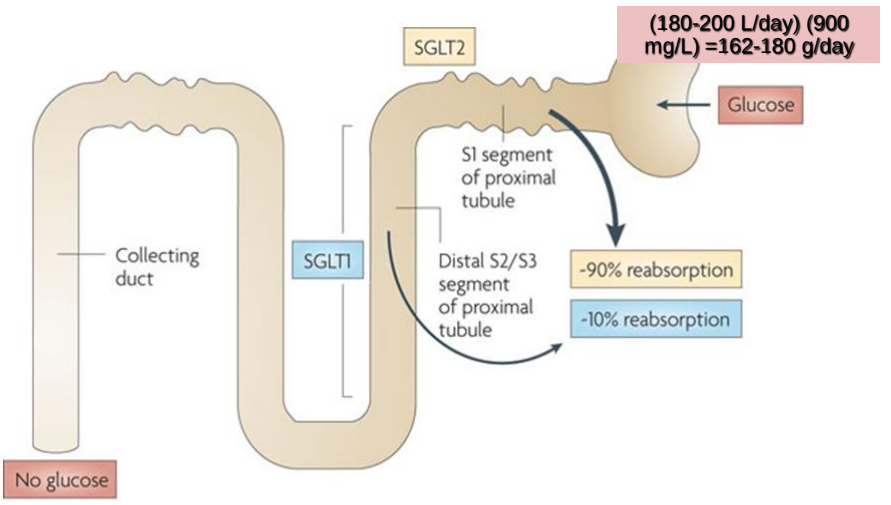
Renal Handling of Glucose: A Potential New Drug Target?



"Normal" individuals:

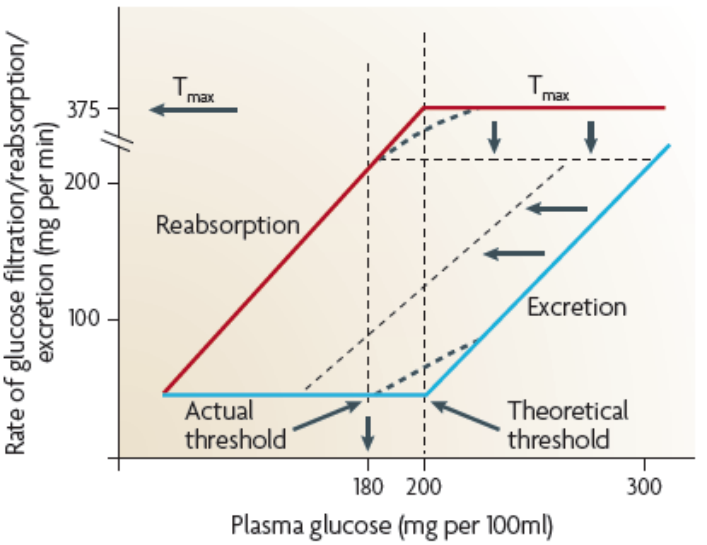
- Filtered glucose load: approximately 180 g/day
- Urinary glucose: less than 0.5 g/day
- Glucose reabsorption occurs in the proximal tubule through the action of SGLT1 and SGLT2

Sodium glucose co-transporter 2 (SGLT2):
crucial role for glucose reabsorption in the renal tubules



Chao & Henry. Nature Rev Drugs Discovery 2010

Renal glucose handling & effect of SGLT2 inhibition



Chao & Henry. Nature Rev Drugs Discovery 2010

Implications

- An adaptive response to conserve glucose (ie, for energy needs) becomes *maladaptive* in diabetes
- Moreover, the ability of the diabetic kidney to conserve glucose may be augmented in absolute terms by an increase in the renal reabsorption of glucose

Dapagliflozin: Glucosuric and Metabolic Effects

Glucosuria	↑ 52-85 g/day
FPG	↓ 16-30 mg/dL
PPG	↓ 23-29 mg/dL
Body weight	↓ 2.2-3.2 kg (↓ 2.5%-3.4%)
Urine volume	↑ 107-470 mL/day

SGLT2 Inhibition: Meeting Unmet Needs in Diabetes Care