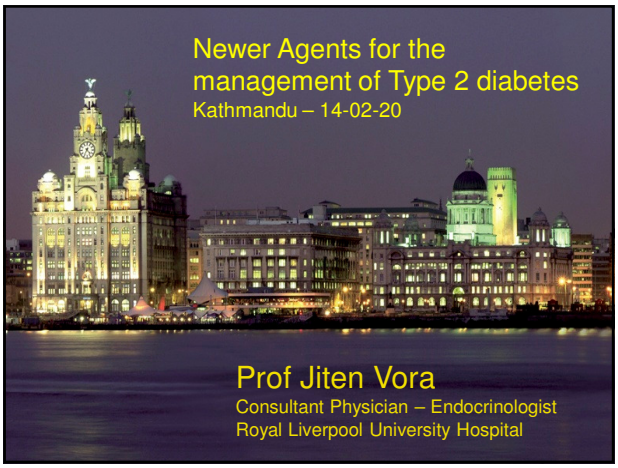
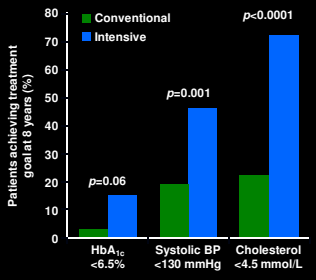



## STENO-2: unmet glycaemic targets with current treatments

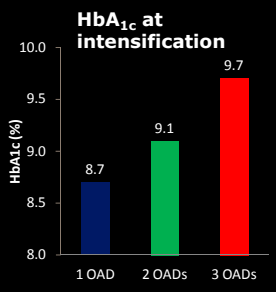
Shortcomings of current treatments:

- Progressive beta-cell decline not counteracted
  - Efficacy of some currently available drugs is not sustained
- Treatment-related trade-offs
  - Weight gain
  - Hypoglycaemia
  - Complex regimens
  - Tolerability issues




Gaede *et al. NEJM* 2003

## Intensification of glucose-lowering treatment delayed despite OAD failure

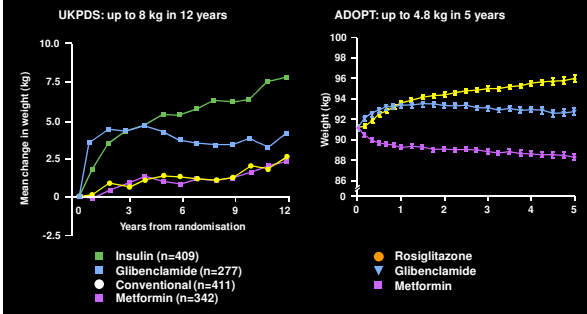



**Years (median) to intensification or control if $HbA_{1c}$ >7%**

- **1 OAD: 2.2 years**
- **2 OADs: >7.2 years**
- **3 OADs: >7.1 years**

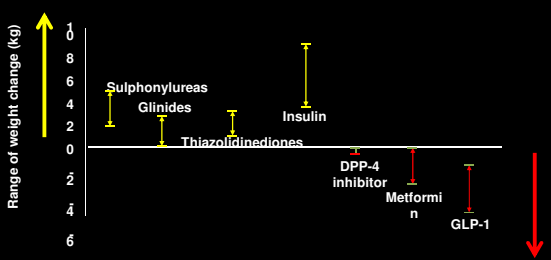
OAD, oral antidiabetic drug
Khunti *et al. Diabetes Care* 2013;36:3411–7

## Most current therapies result in weight gain over time




UKPDS Group. *Lancet* 1998;352:854–865.
Kahn SE *et al. NEJM* 2006;355:2427–2443.

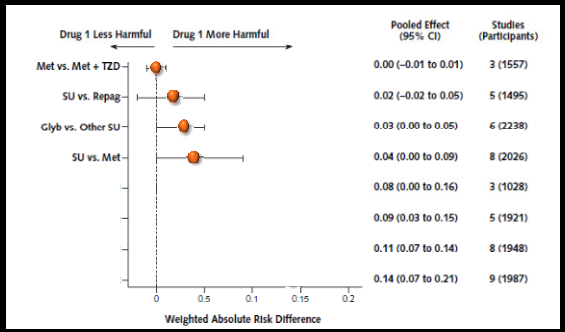
## Glucose-lowering medications and weight profile



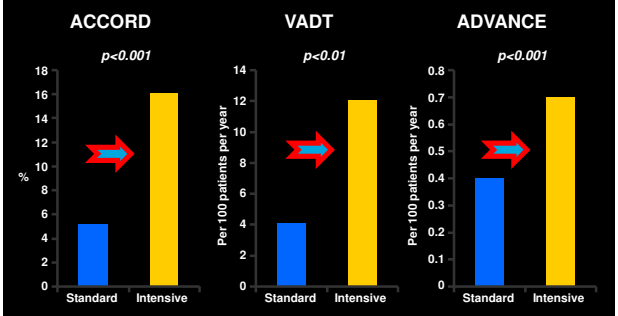

Adapted from: Mitri J, Hamdy O. *Expert Opin. Drug Saf.* 2009;8:573–84.

## Incidence of hypoglycaemia with different glucose-lowering agents for type 2 diabetes

Bolen S, et al. *Ann Intern Med.* 2007;147:386-399.



## Severe hypoglycaemia events in ACCORD, ADVANCE and VADT



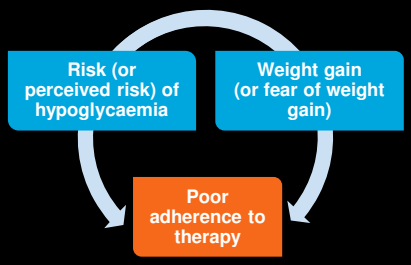

## ACCORD: What predicted death?

| Parameter | Hazard ratio |
|---|---|
| Prior CV event | 3.068 |
| Age | 2.112 |
| $HbA_{1c}$ at baseline | 1.182 |
| HDL on study | 0.193 |
| Creatinine on study | 1.788 |
| Recent severe hypoglycaemia | 3.726 |

ADA sessions 2009.

8

## Weight gain and hypoglycaemia influence patient adherence

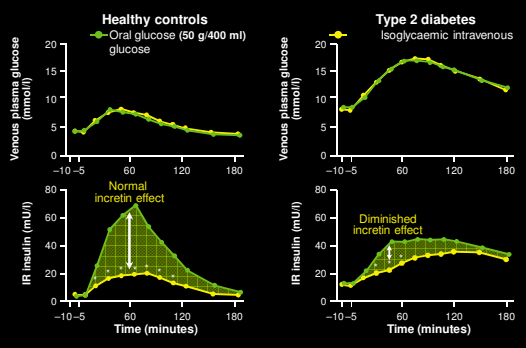



Khunti K et al (2010) *Diabetes Obes Metab* **12**: 474–84

## The "ideal" drug for type 2 diabetes

- Safe
- Efficacious
- Durable control
- Well tolerated
- Low risk of hypoglycaemia
- Weight neutral or weight loss
- Can be used in declining renal function and hepatic impairment
- Can be used in elderly patients (>75 years of age)
- Effective and tolerated when used in combination with other medications

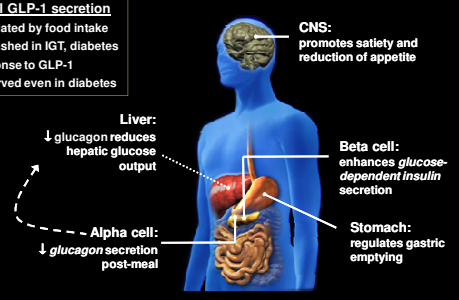
## Incretin effect – normals and type 2 diabetes




. Adapted from Nauck M et al *Diabetologia* 1986;29:46–52.

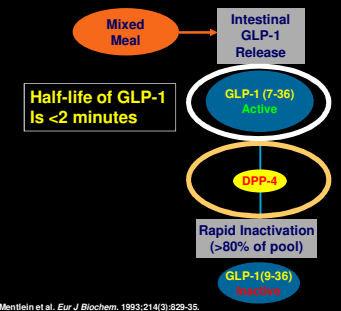
## Glucagon Like Polypeptide -1 : Effects in Humans Understanding the Potential of Incretins

**Normal GLP-1 secretion**
- Stimulated by food intake
- Diminished in IGT, diabetes
- Response to GLP-1 preserved even in diabetes




Flint A et al. *J Clin Invest.* 1998;101:515-520. Larsson H et al. *Acta Physiol Scand.* 1997;160:413-422
Nauck MA et al., *Diabetologia.* 1996;39:1546-1553. Drucker DJ. *Diabetes.* 1998;47:159–169.

## Release and Action of Glucagon-Like Peptide-1 (GLP-1)



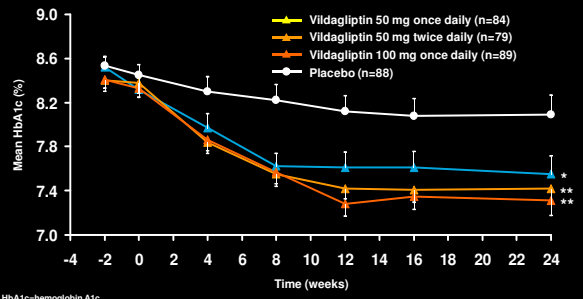

Resistant to DPP-4 Inactivation
- Exenatide
- Exenatide LAR*
- Liraglutide*

Block DPP-4 enzyme Activity -gliptins
- Sitagliptin
- Vildagliptin
- Alogliptin
- Saxagliptin
- Alogliptin

Mentlein et al. *Eur J Biochem.* 1993;214(3):829-35.
Eng J, et al. *J Biol Chem.* 1992;267:7402-7405

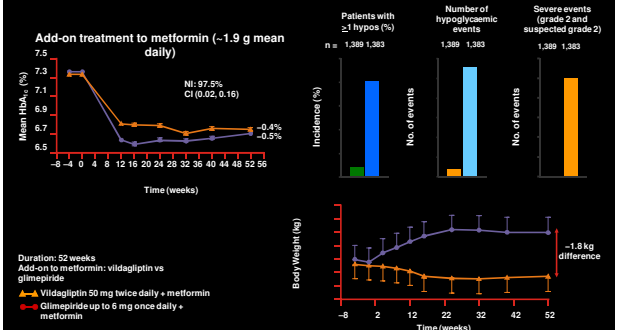
## Vildagliptin Monotherapy: Reductions in HbA1c over 24 Weeks

Duration: 24 weeks




HbA1c=hemoglobin A1c
Primary intention-to-treat population. *P≤0.01; **P<0.001 vs placebo.
Pi-Sunyer FX, et al. *Diabetes Res Clin Pract.* 2007; 76: 132–138.

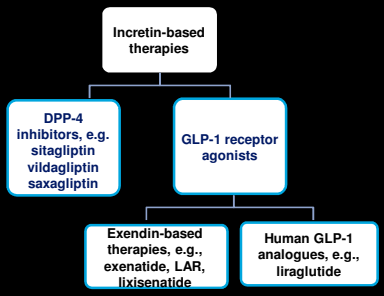
## Vildagliptin: as effective as glimepiride when added to metformin at 52 weeks no weight gain and low incidence of hypoglycaemia




Duration: 52 weeks
Add-on to metformin: vildagliptin vs glimepiride
Vildagliptin 50 mg twice daily + metformin
Glimepiride up to 6 mg once daily + metformin

Ferrannini et al. Diabetes Obes Metab 2009;11:157–66; Data on file, Novartis Pharmaceuticals, LAF237A2308

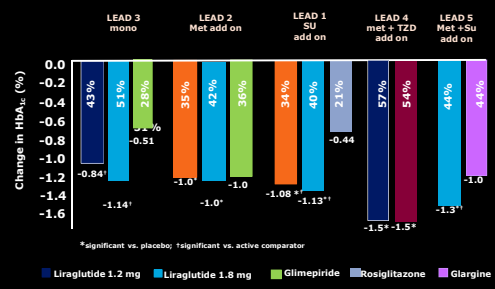
## The family of incretin-based therapies




Drucker and Nauck, Lancet 2006;368:1696-705

## Liraglutide: Change in $HbA_{1c}$

Change in $HbA_{1c}$ from baseline for overall population LEAD 1 2 3 4 & 5

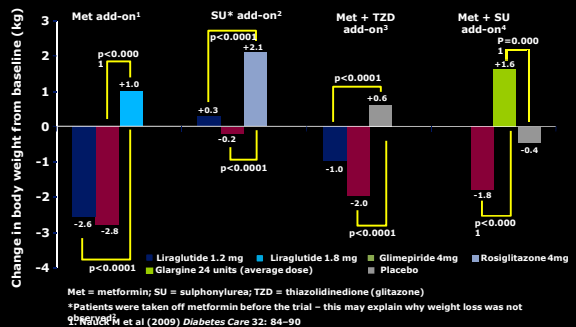



*significant vs. placebo; †significant vs. active comparator

Liraglutide 1.2 mg Liraglutide 1.8 mg Glimepiride Rosiglitazone Glargine

LEAD 1, Marre M et al, Diabetic Medicine 2009, Accepted Article; doi: 10.1111/j.1464-5491.2009.02666.x
LEAD 2, Nauck M et al, Diabetes Care 2008, Accepted Article; doi: 10.2337/dc08-1355
LEAD 3, Garber A et al, Lancet 2008. Published online September 25, 2008 doi:10.1016/S01041-6736(08)61246-5.
LEAD 4, Zinman et al Diabetologia 2008; 51 (Suppl. 1) Abstract 898-P

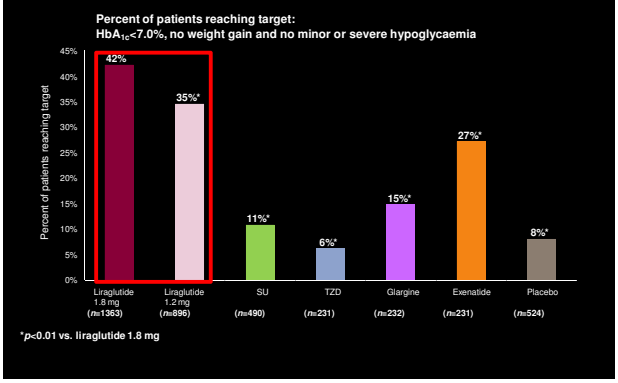
## Liraglutide reduces weight in most patients with T2DM



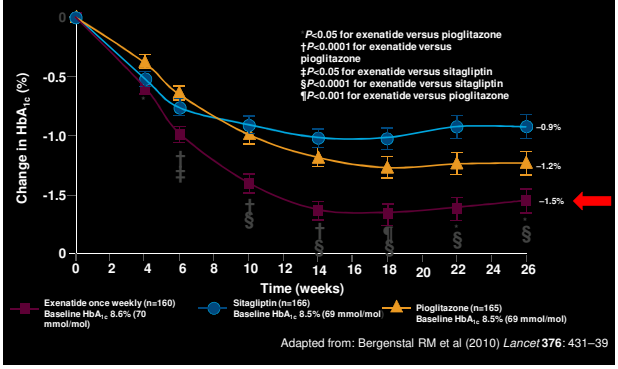

Met = metformin; SU = sulphonylurea; TZD = thiazolidinedione (glitazone)
*Patients were taken off metformin before the trial – this may explain why weight loss was not observed
1. Nauck M et al (2009) *Diabetes Care* 32: 84–90
2. Marre M et al (2009) *Diabetic Medicine* 26: 268–78
3. Zinman B et al (2009) *Diabetes Care* 32: 1224–30
4. Russell-Jones D et al (2009) *Diabetologia* 52: 2046–55

All trials 26 weeks duration

## Liraglutide - Composite endpoint: $HbA_{1c}$<7.0%, no weight gain and no hypos

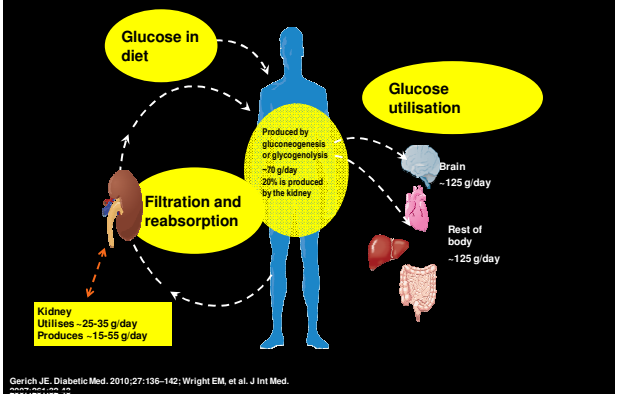



## DURATION-2: Change in $HbA_{1c}$ Exenatide once weekly vs. sitagliptin or pioglitazone in people uncontrolled on metformin



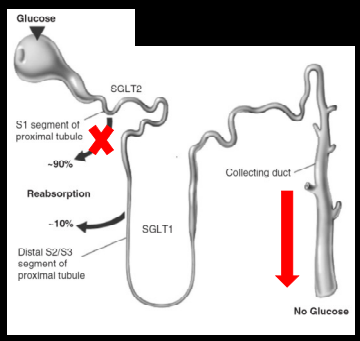

Adapted from: Bergenstal RM et al (2010) *Lancet* **376**: 431–39

## The kidney plays a significant role in glucose balance by reabsorbing ~180g of glucose per day




Gerich JE. Diabetic Med. 2010;27:136–142; Wright EM, et al. J Int Med.

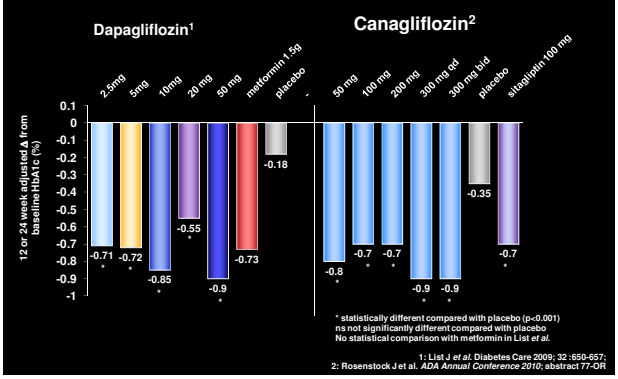
## Sodium - Glucose Transporters in the Renal Proximal Tubule




- Volume of plasma filtered daily = 180 L
- Normal glucose filtered daily =180 g
- Maximal reabsorptive capacity = 375 mg/min
- Normal subjects – no glycosuria
- Hyperglycaemia increases SGLT2 expression and absorption capacity

Bays H. CMRO. 2009;25:671-681.

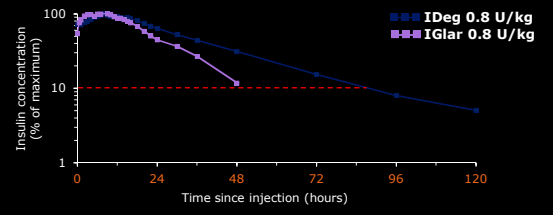
## Dapagliflozin and canagliflozin: HbA1c changes from baseline




## Requirements for a ideal basal insulin

- 24-hour duration of action to cover needs throughout the day with single injection
- A flat pharmacokinetic profile, without peaks
- A reproducible pharmacodynamic profile, providing a predictable glucose-lowering effect from day to day
- Flexibilty - ability to change administration time from day to day

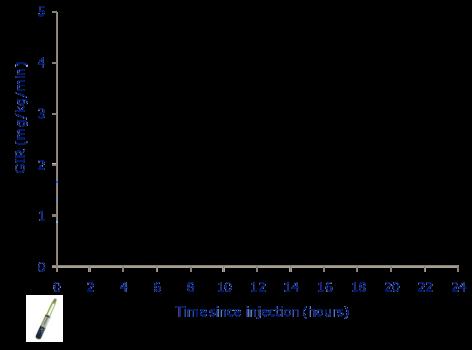
## Serum concentration and half-life of insulin degludec and insulin glargine




| | IDeg | | | IGlar | | |
|---|---|---|---|---|---|---|
| | 0.4 U/kg | 0.6 U/kg | 0.8 U/kg | 0.4 U/kg | 0.6 U/kg | 0.8 U/kg |
| Half-life (hours) | 25.9 | 27.0 | 23.9 | 11.8 | 14.0 | 11.9 |
| Mean half-life | 25.4 | | | 12.5 | | |

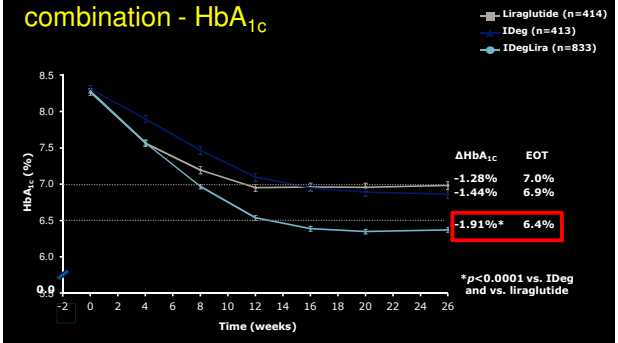
IDeg, insulin degludec; IGlar, insulin glargine
Heise *et al. Diabetes* 2011;60(Suppl. 1):LB11; Heise *et al. Diabetologia* 2011;54(Suppl. 1):S425

## Insulin degludec PD profiles in type 2 diabetes at steady state




PD, pharmacodynamic; GIR, glucose infusion rate; FAS; n=49
Heise *et al. Diabetes Obes Metab* 2012;14:944–50

## Insulin Degludec and Liraglutide combination - $HbA_{1c}$




EOT, end of trial
Buse et al. ADA 2013: 65-OR; Gough et al. EASD 2013: 219-OR

## CONCLUSIONS

- Type 2 diabetes is a very common condition
- Many patients do not achieve appropriate glucose control
- This maybe related to the inadequacies of current therapies and their side – effects
- Newer therapies offer the opportunity to improve glycaemic control with less adverse effects