

New Treatments for Type 2 Diabetes

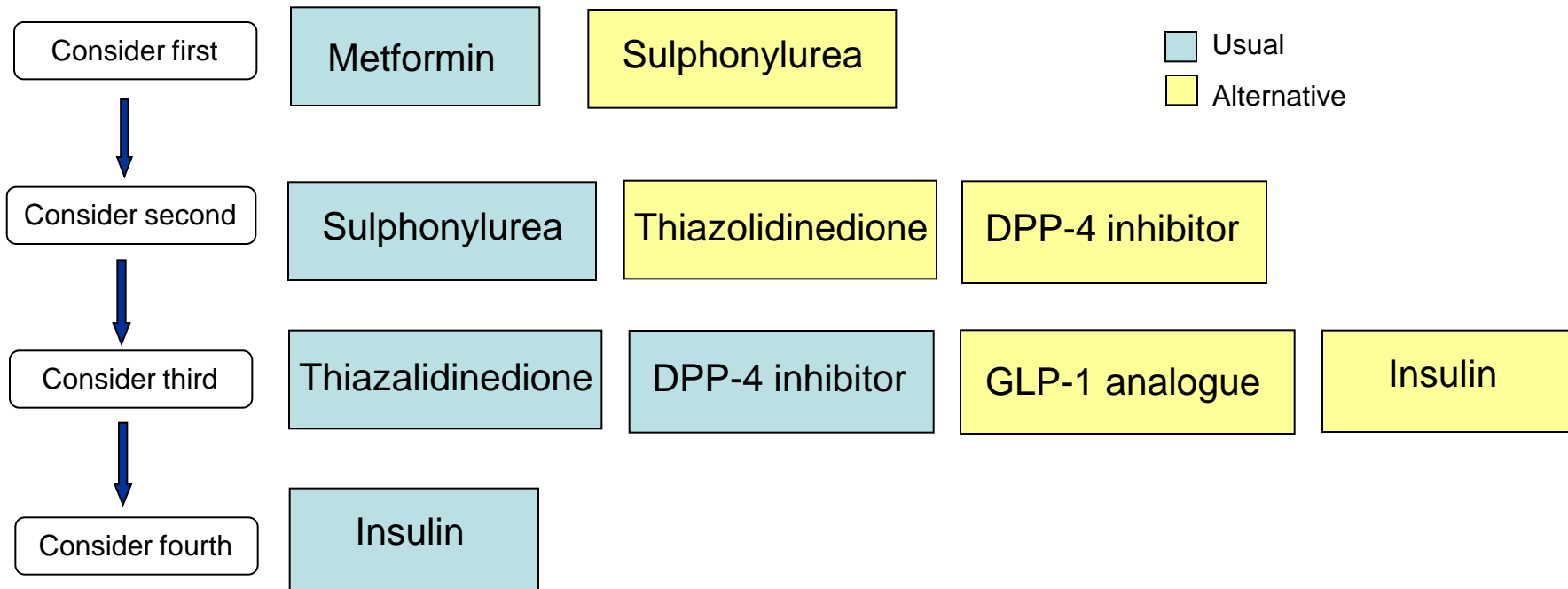
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Recent Guideline Updates

- NICE:
 - CG87: Type 2 diabetes – newer agents
- This guidance partially updates NICE clinical guideline 66 and replaces it, in particular with recommendations regarding the place in therapy of DPP-4 inhibitors and GLP-1 analogues.

NICE Guideline CG87



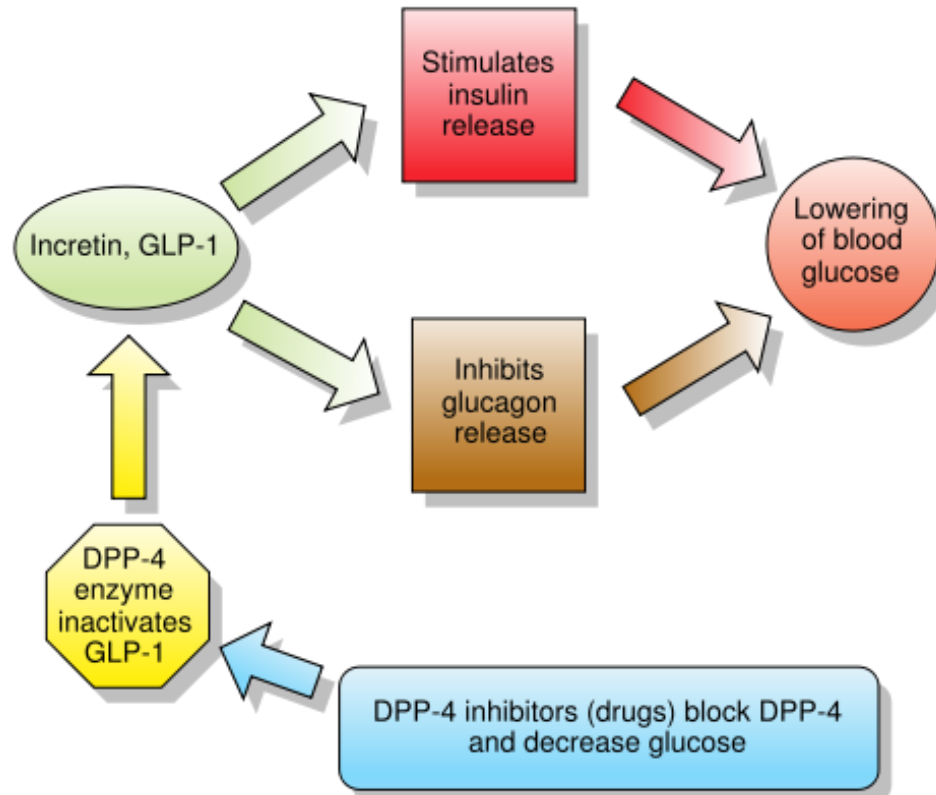
Caution – Is intensive treatment worth the effort?!

- **ACCORD:** Significantly higher all-cause mortality¹
- **ADVANCE:** No difference in all-cause mortality or macrovascular complications. Fewer major microvascular events²
- **VADT:** No difference in micro- or macrovascular complications³

Incretin and Glucose Control

- Incretins are naturally occurring hormones that the gut releases throughout the day - the level of active incretins increases significantly when food is ingested.
- Endogenous incretins GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic peptide) facilitate the response of the pancreas and liver to glucose fluctuations through their action on pancreatic β - and α -cells.
- The activity of incretins is limited by the enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades active incretins.

Incretin and Type 2 Diabetes



The incretin effect is diminished in type 2 diabetes:

- Levels of GLP-1 are decreased
- The insulinotropic response to
- GIP is diminished but not absent

Dipeptidyl peptidase 4 (DPP 4) inhibitors – Gliptins

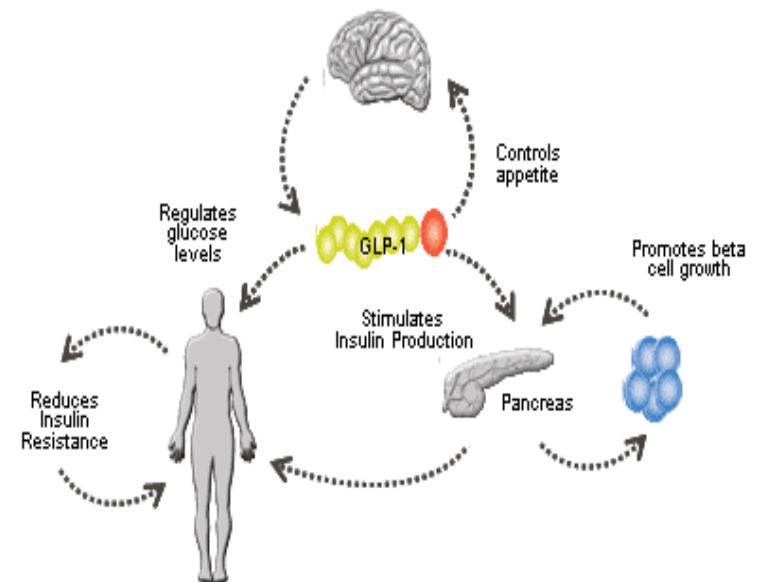
- “Incretin enhancers”
- Sitagliptin and Vildagliptin both licensed in the UK. Most recent addition is Saxagliptin^{4,5,6}
- Can be used as: monotherapy, dual therapy (with metformin, sulphonylureas or glitazones) and sitagliptin can be used in triple therapy (with metformin and sulphonylureas)

Gliptins

- Low incidence of hypoglycaemia in combination with metformin vs metformin + glipizide
- Weight neutral in combination with pioglitazone or metformin.
- Not for use in severe (NYHA III – IV) heart failure (vildagliptin).
- Not recommended in moderate to severe renal impairment.
- May be safe in hepatic impairment.
- Most common side effect – Nausea
- Rare reports of pancreatitis

Glucagon-like peptide (GLP-1) analogues

- GLP-1 contributes to the incretin effect, the augmentation of glucose-stimulated insulin secretion after ingestion of a meal.
- GLP-1 also inhibits gastric emptying and reduces appetite and food intake.
- Importantly, GLP-1 has been shown to stimulate the growth and differentiation of pancreatic β -cells in tissue culture and in animal models of diabetes.
- Some studies have also suggested that GLP-1 may improve insulin sensitivity or increase glucose effectiveness



Exenatide (Byetta) and Liraglutide (Victoza)

- THESE ARE NOT INSULINS!!!!
- Can be used with glitazones, metformin or sulphonylureas^{7,8,9,10,11}
- Most common side effect is nausea
- To improve GI tolerability, the starting doses are low and titrated
- Likely only to cause hypoglycaemia in combination with sulphonylureas
- Causes weight LOSS
- Exenatide: Twice daily injection 60-30 min before a meal – not after
Liraglutide: Once daily injection at same time each day, not in relation to meals



Exenatide (Byetta) and Liraglutide (Victoza)

- Dose as normal in mild renal impairment. Titrate with care to higher doses in moderate renal impairment. Not for use in severe or end-stage renal disease.
- No dose adjustment in hepatic impairment
- Should not be used in patients with inflammatory bowel disease or diabetic gastroparesis due to lack of data in these patients and known side effects
- There have been rare, reports of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain.
- Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotizing or haemorrhagic pancreatitis and/or death have been reported. Treatment with GLP-1's should not be resumed after pancreatitis has been diagnosed.

Cardiovascular Risk – The Glitazone Legacy

- Four out the five classical oral antidiabetic drug groups (biguanides, sulfonylureas, meglitinides, glitazones and alpha-glucosidase inhibitors) present proven or potential cardiac hazards
- These hazards are not mere 'side effects', but biochemical phenomena which are deeply rooted in the drugs' mechanism of action
- RECORD and PROactive trials – what to believe?
- The risk of heart failure is a class effect of the thiazolidinediones, whereas the ischemic cardiovascular risk appears confined to rosiglitazone but not to pioglitazone.

New Drugs and CV Risk

- In December 2008 the FDA produced recommendations that applies to all diabetes drugs currently under development.
- Manufacturers developing new drugs and biologics for type 2 diabetes must provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack.
- The FDA also recommends that manufacturers have any cardiovascular events in their clinical trials analysed by committees of outside cardiologists
- The novel incretin drugs (GLP-1 mimetics and DPP-4 inhibitors) appear to be satisfactory adjuvant drugs due to the lack of known undesirable cardiovascular effects
- Saxagliptin (licensed July 2009) is first new anti-diabetic medication to pass cardiovascular risk safety review.

Just as you're getting comfortable...!

- Pramlintide – amylin analogue
- Glitazars – PPAR α , γ (dual peroxisome proliferator activated receptor agonists)
- Generex Oral-lyn™ - buccal insulin
- Sodium Glucose Co-transporter (SGLT2) Inhibitors
- FBPase (fructose 1,6-bisphosphatase) Inhibitors

References

1. *The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59*
2. *The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72*
3. *Duckworth W, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360.*
4. *Herman GA, et al. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clinical pharmacology and therapeutics. 2005. 78(6):675-88.*
5. *Ahren B, et al. Improved Meal-Related β -Cell Function and Insulin Sensitivity by the Dipeptidyl Peptidase-IV Inhibitor Vildagliptin in Metformin-Treated Patients With Type 2 Diabetes Over 1 Year. Diabetes Care 2005. 28(8): 1936*
6. *Rosenstock J, et al. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. Current Medical Research and Opinion. 2009. 25: (10) 2401-2411*
7. *Kendall DM et al. Effects of exenatide on glycaemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulphonylurea. Diabetes care. 2005. 28:1083-1091*
8. *Blonde L et al. Interim analysis of the effects of exenatide treatment on HbA1c, weight, and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab. 2006. 8:436-447*
9. *Nauck et al. LEAD-2: Liraglutide added on to metformin versus glimepiride. Diabetes Care. 2009. 32:84-90*
10. *Garber et al. LEAD-3: Liraglutide as monotherapy versus glimepride. Lancet. 2009. 373:473-481*
11. *Buse et al. LEAD-6: Liraglutide added on to metformin and/or sulphonylurea versus exenatide. Lancet. 2009.*