New and Future Treatments for Diabetes

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BARS Oct 2014

Conflicts of interest

- Investigator “Carmelina” study of Linagliptin (Boehringer Ingelheim)
- Speaking fees Novo Nordisk
- Cure for diabetes would bring early retirement!

What's wrong with what we've got?

Type 1

- Hypoglycaemia
- Painful and inconvenient

Type 2

- Hypoglycaemia
- Drug-induced weight gain
- Don't address cardiovascular risk

Type 1 Diabetes

New Insulin Analogues

- Insulin Degludec “Tresiba”
- Basal Insulin PEG (polyethylene glycol) moiety Lispro “BIL”
- Insulin Glargine U300

Biosimilars

- “generic” – same amino acids, different manufacture

http://www.diabetes.org.uk/Upload/How%20we%20help/Magazines/Update/FactFile.pdf
http://www.nice.org.uk/Advice/esnm24

Pumps – closing the loop?

Open loop

- Pump users need “to think like a pancreas”
- Continuous Glucose Monitors

Closed loop

- Artificial pancreas
- Low glucose cut-off
- Algorithm to determine insulin delivery
- Overnight progress
- Mealtimes/exercise more difficult
- ?glucagon too

Transplants

- Islet Cell
- Simultaneous kidney and pancreas
- Single organ pancreas
- Stem cells

http://www.bts.org.uk/Member/Clinical/Pancreas.aspx

Type 2 Diabetes

- New drugs
  - Incretin manipulation 2005/6
  - SGLT-2 inhibitors 2013/14
- Drugs in Development
- Weight management surgery

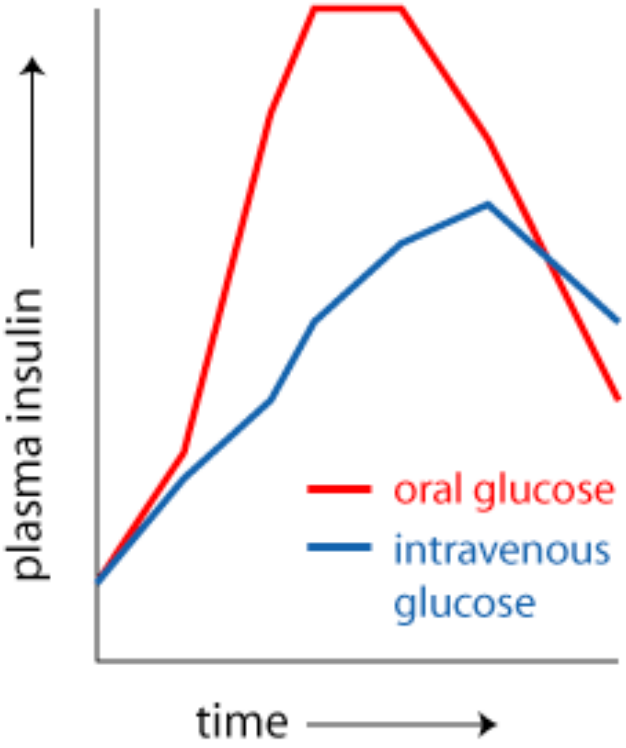
Why so many?

- Progressive disease: decline in beta cell function
- Side effects
- Add in new drugs rather than substitute

Incretin manipulation

Incretin effect

- Insulin response to oral glucose greater than to iv glucose
- Effect due to secretion of gut (incretin) hormones
  - GLP-1 (GlucagonLikePeptide-1)
  - GIP (Gastric inhibitory polypeptide, also known as glucose-dependent insulinotropic peptide)



Incretin effect

- **GLP-1**
  - Enhances postprandial insulin secretion
  - Inhibits glucagon secretion
  - Slows gastric emptying
  - Diminishes appetite
  - Stimulates insulin synthesis
  - Increases beta cell mass (animals)
- **Effects are glucose-dependent**

Incretin manipulation

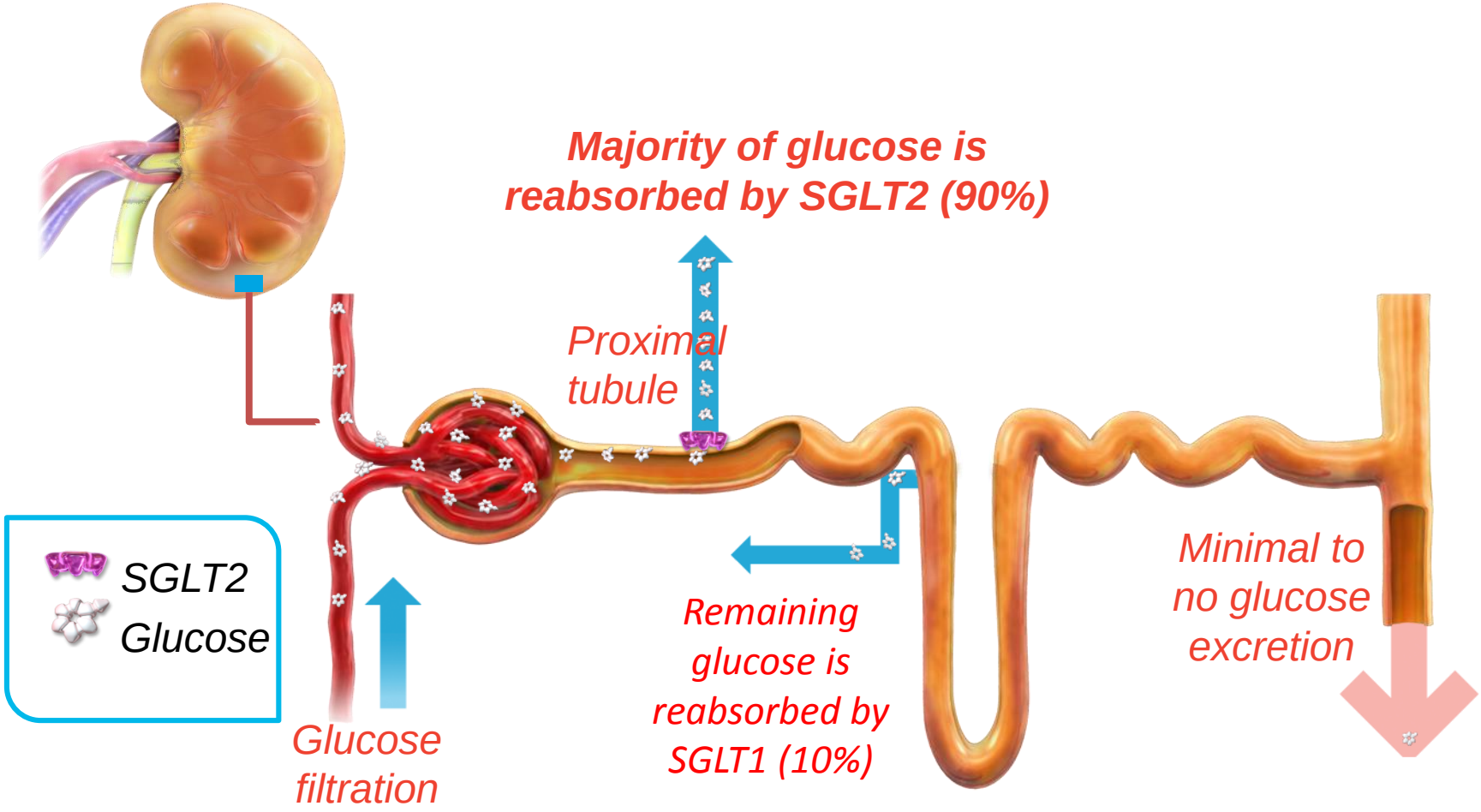
- **Incretin mimetics**
  - **Exenatide, Liraglutide , Lixisenatide**
  - GLP-1 receptor agonists
  - injection
  - Nausea ++, weight loss
- **Gliptins –Sitagliptin, Vildagliptin, Alogliptin, Saxagliptin, Linagliptin**
  - specific inhibitors of DPP-4
    - raise incretin levels
  - Tablets
  - Cardiovascular safety
    - Increased hospital admissions for heart failure with Saxagliptin

Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-1326

Sodium GLucose coTransporter 2 inhibitors

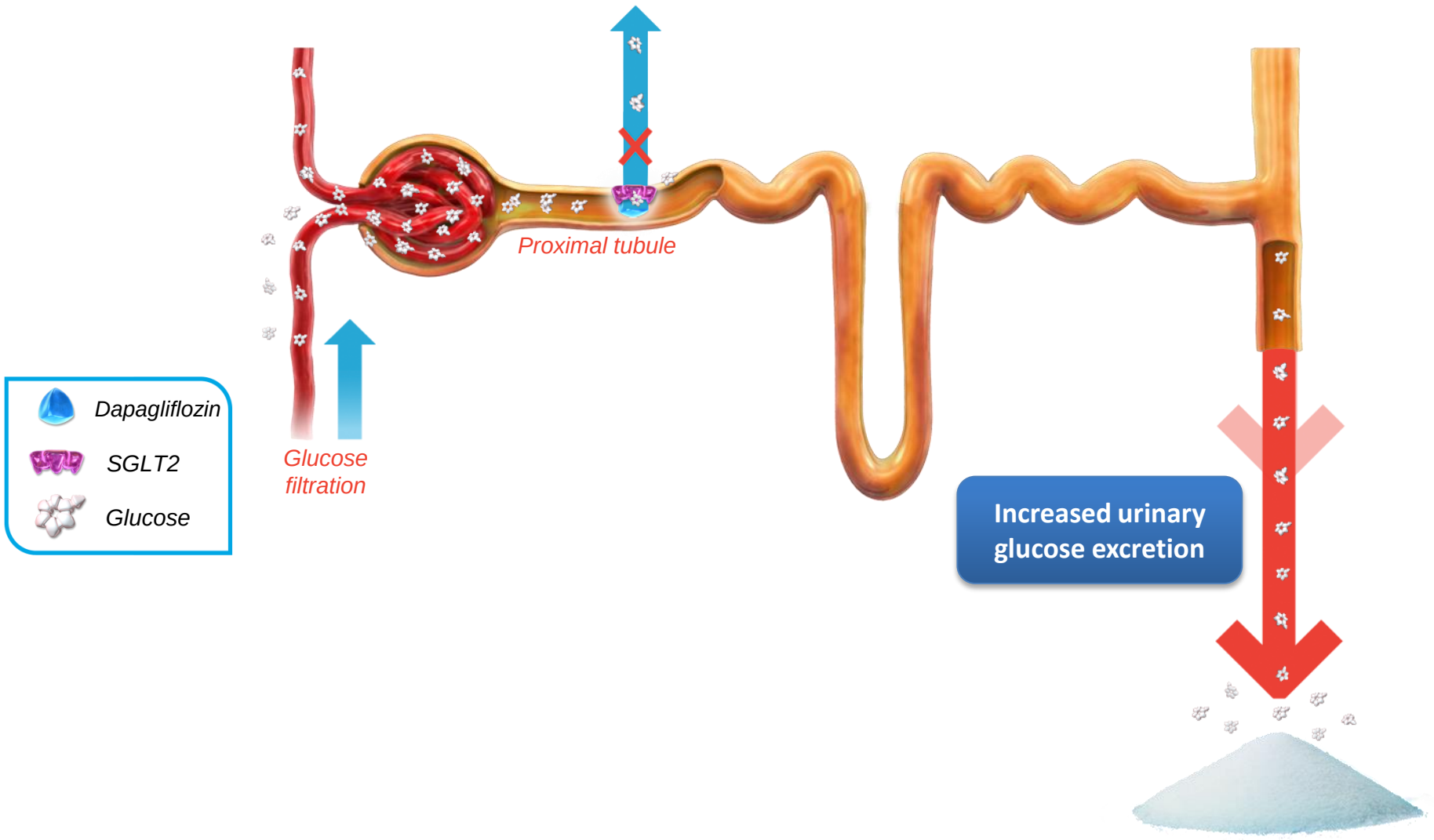
SGLT-2 INHIBITORS

Normal renal glucose handling



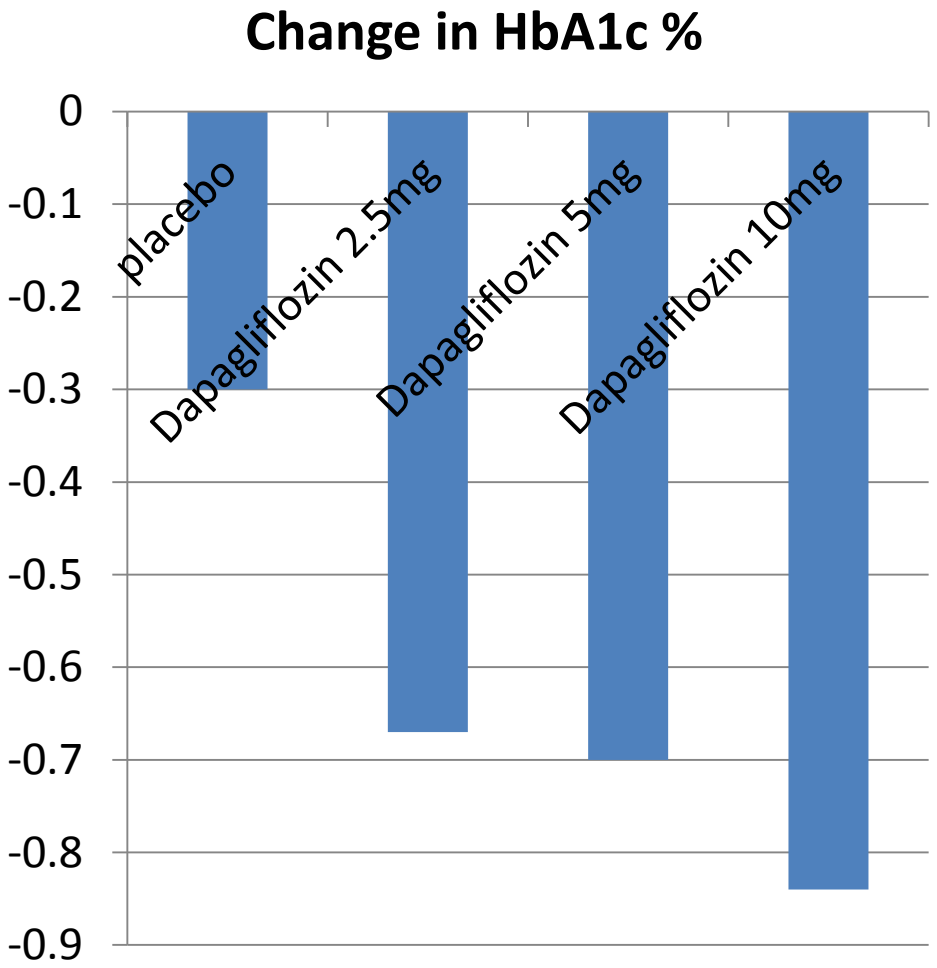
Sodium GLucose coTransporter 2 inhibitors

eg Dapagliflozin, canagliflozin



SGLT2 inhibitors

- Result in daily urinary glucose excretion of approximately 70g
- Significant and sustained HbA_{1c} reductions versus placebo
- Eg after 6 months:



Other aspects of SGLT-2 inhibitors

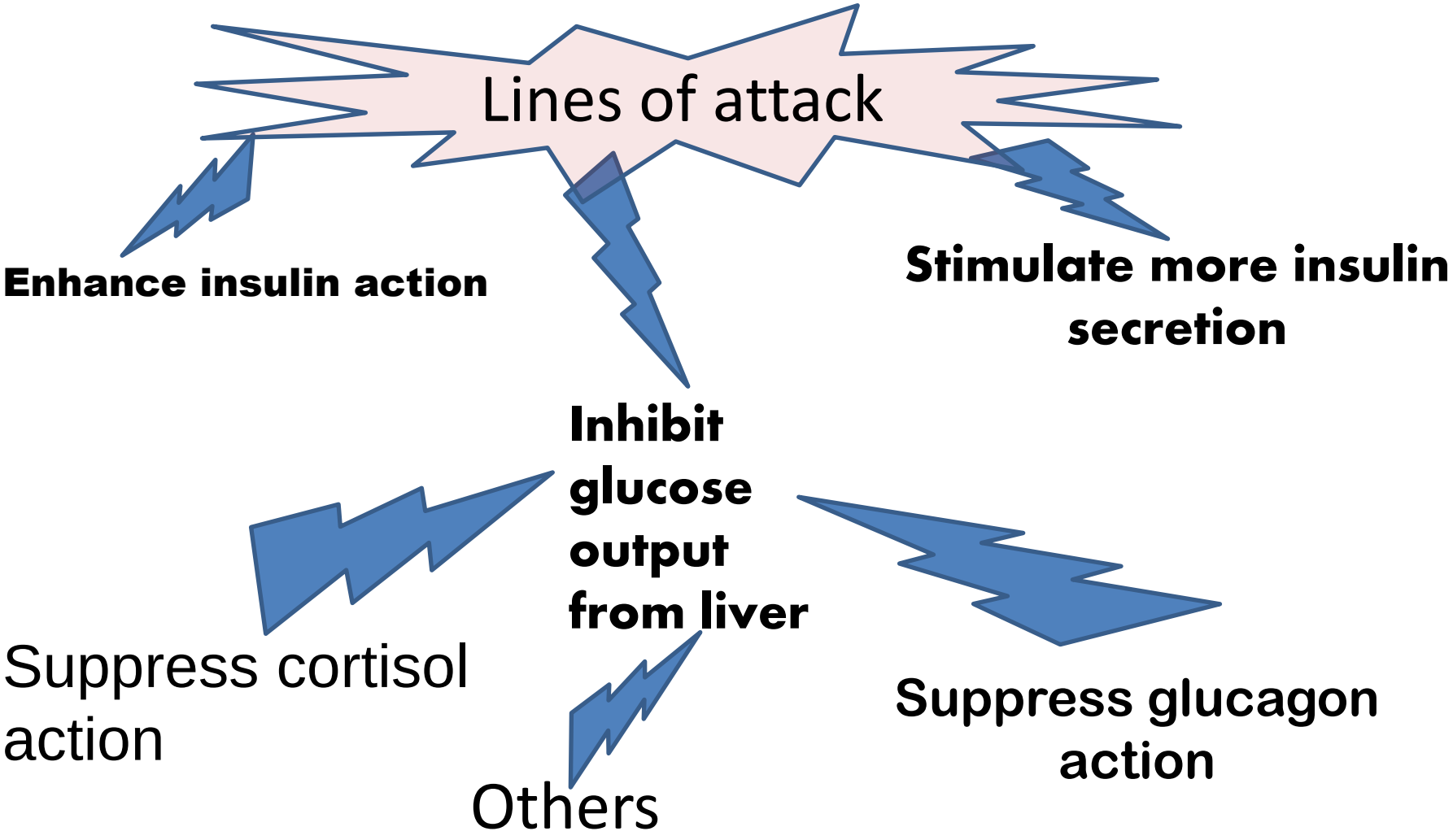
Secondary benefits

- weight loss
- lower Blood Pressure

Drawbacks

- Urinary infections
- Genital thrush
- Volume depletion
- Ineffective in poor renal function

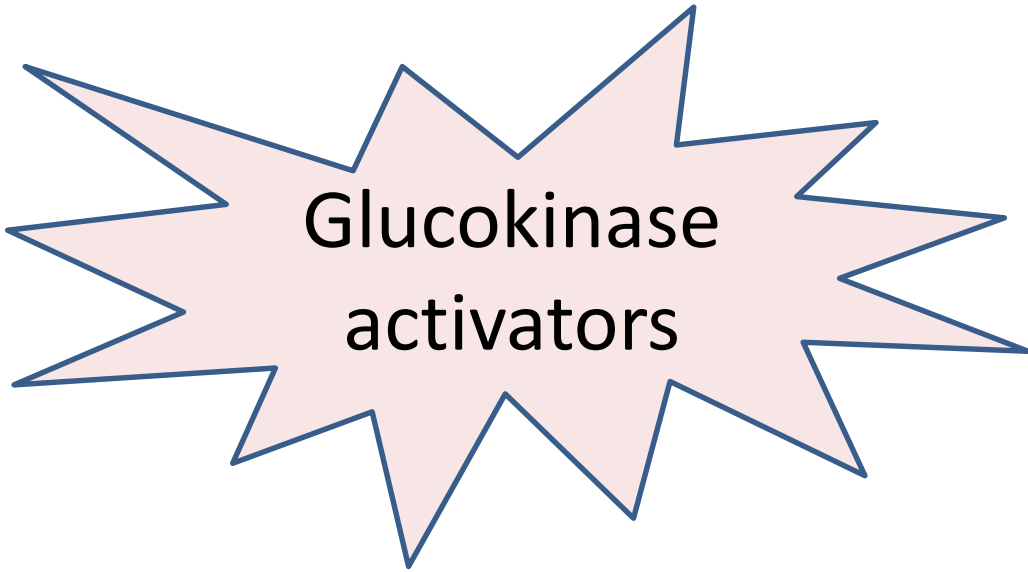
Drugs in development



A A Tahrani CJ Bailey S Del Prato AH Barnett . Management of type 2 diabetes: new and future developments in treatment. *Lancet* 2011;**378**: 182 – 197

Drugs in development

Stimulate more insulin secretion



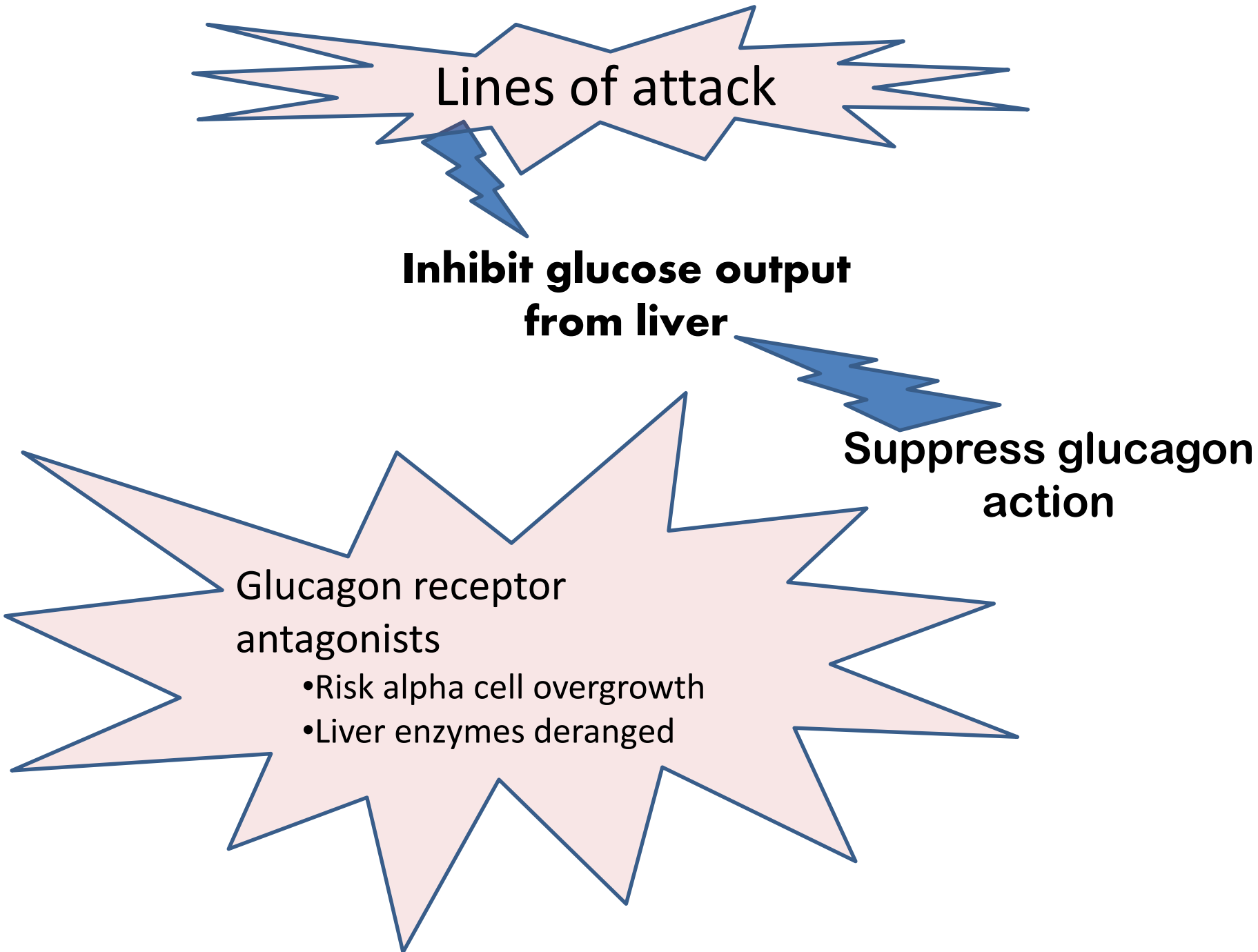
Glucokinase activators

- Stimulate:
  - Insulin secretion
  - Liver metabolism of glucose
- Beware:
  - Increase triglycerides
  - Liver fat / steatosis
  - Hypoglycaemia
- eg Piragliatin

Lines of attack

Enhance stimulation of insulin secretion

- Pancreatic-G-protein-coupled fatty-acid-receptor 40 (GPR40) = free fatty acid receptor
- Fatty acids enhance insulin secretion.
- Phase II clinical trials of GPR40 agonist TAK-875 reduced HbA_{1c} as effectively as glimepiride


Lines of attack
Inhibit glucose output from liver
Suppress glucagon action
Glucagon receptor antagonists
•Risk alpha cell overgrowth
•Liver enzymes deranged

Lines of attack

Inhibit glucose output from liver

Suppress cortisol action

11β-hydroxysteroid dehydrogenase1 inhibitors

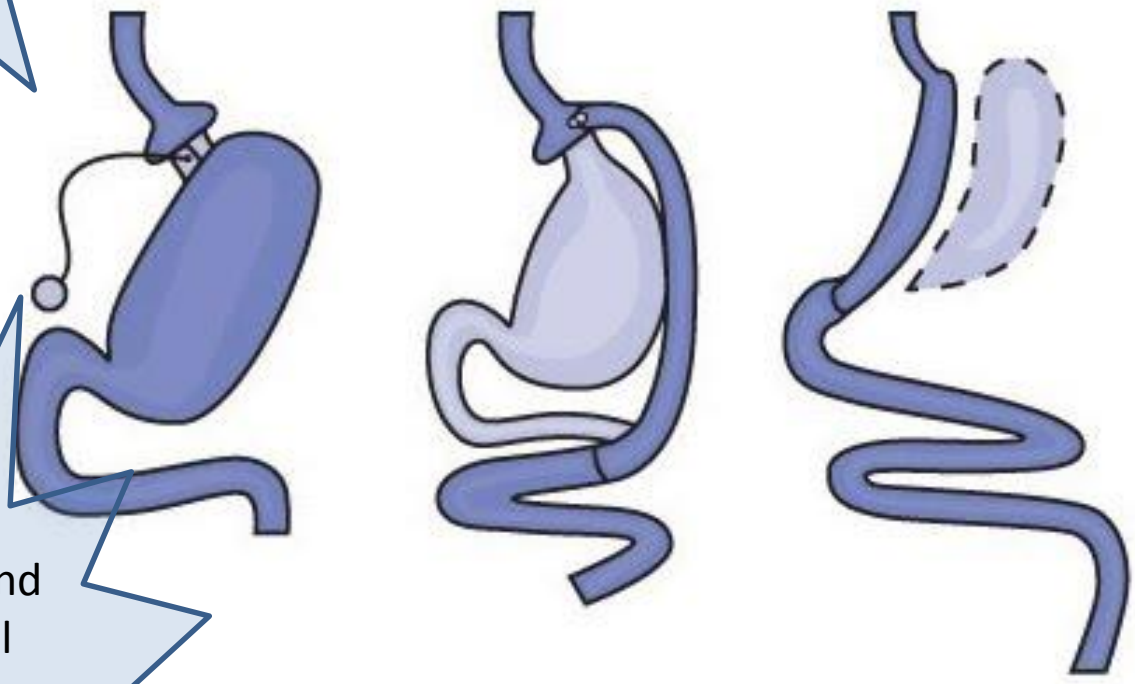
- *Small* improvements in glycaemic control, lipid profile and blood pressure

Anderson A1, Walker BR. 11β-HSD1 inhibitors for the treatment of type 2 diabetes and cardiovascular disease.Drugs. 2013(13):1385-93.

Bariatric Surgery

operative mortality 0.1 to 0.5%

Intestinal and nutritional complications vary by procedure.



Adjustable Gastric Band (AGB)

Roux-en-Y Gastric Bypass (RYGB)

Vertical Sleeve Gastrectomy (VSG)

Diabetes after bariatric surgery – cured, in remission or partially treated?

Puzziferri 2014

- **Long-term follow-up after bariatric surgery: a systematic review.**
- 7971 patients

Outcomes after 2+ years:

	Gastric Bypass	Gastric Band
% excess weight loss	66%	45%
Remission from T2 Diabetes	67%	29%
Remission from hyper-tension	38%	17%

Puzziferri N, Roshek TB, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. JAMA. 2014;312:934-42.

Diabetes after bariatric surgery – cured, in remission or partially treated?

Brethauer 2013

- **217 patients**
- **5+ year follow-up, mixture of surgical procedures**
- **Outcomes**
  - 24% Complete remission
  - 26% Partial remission
  - 34% improved
  - 16% unchanged
- **Recurrence**
  - 19%
- **Nephropathy** regressed (53%) or stabilized (47%).
- **No retinopathy data**

Remission more likely :

- Shorter duration of T2DM
- higher long-term weight loss

Recurrence more likely:

- longer duration of T2DM
- less weight loss
- weight regain

Brethauer SA, Aminian A, Romero-Talamás H, Batayyah E, Mackey J, Kennedy L, Kashyap SR, Kirwan JP, Rogula T, Kroh M, Chand B, Schauer PR. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg. 2013 Oct;258(4):628-36

Summary

- Type 1 diabetes
  - “New” insulins to lower risk hypos
  - Quest for artificial pancreas technology
  - Transplants
- Type 2 diabetes
  - Increase insulin secretion
  - Suppress glucose release from liver
  - Bariatric surgery

THANK YOU