WHERE TO START:
Oral Medical Treatment
-Vision 2016

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DISCLOSURE STATEMENT

Speaker:

M. Hamed Farooqi, MD

- Has disclosed that he serves on the Speaker's bureau and receives consulting fees and honoraria from Lilly, Novo Nordisk, MSD, AstraZeneca, J&J and Servier

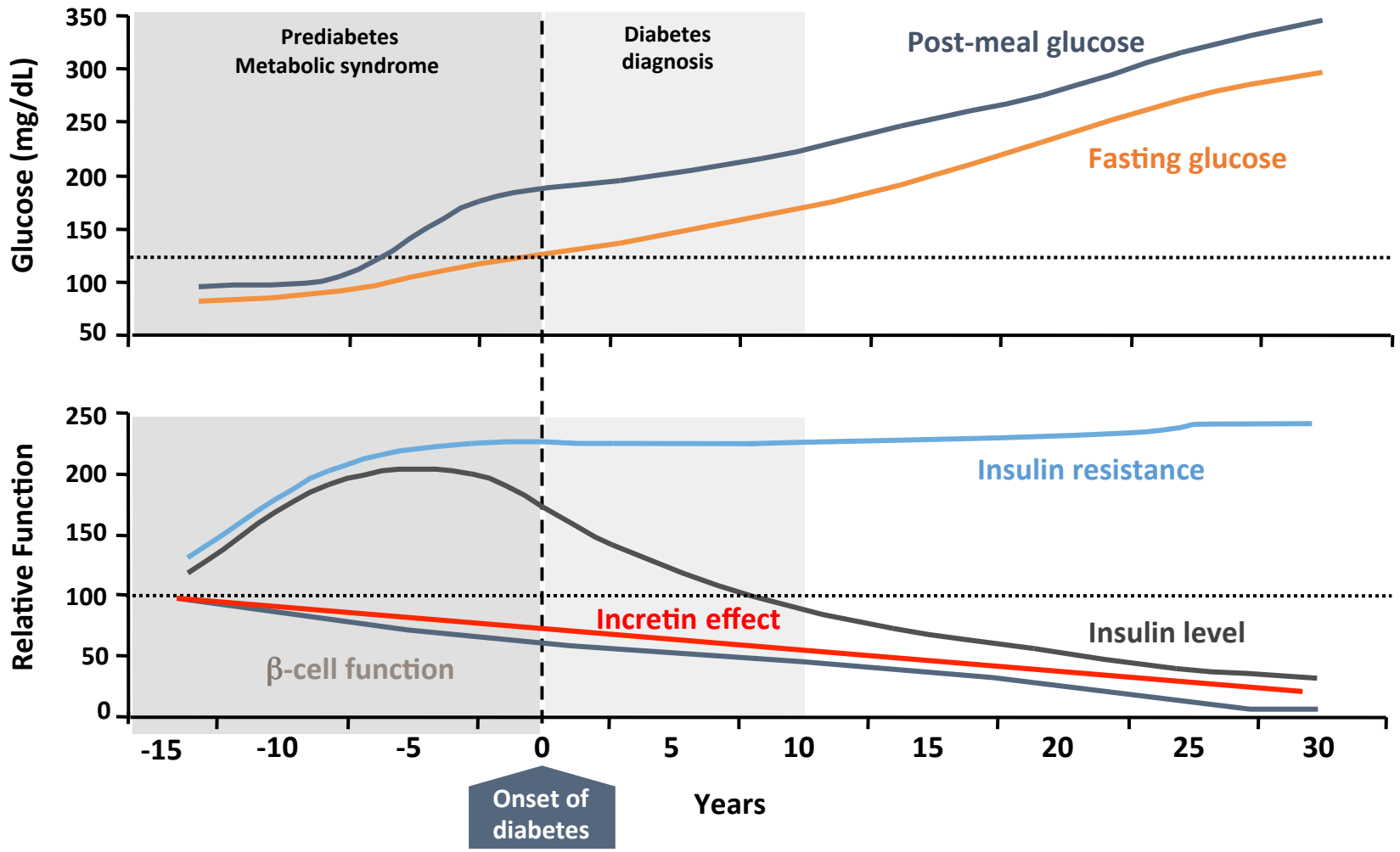
- Will not be discussing the off-label or investigational use of products

Weill Cornell Medicine-Qatar

Objectives

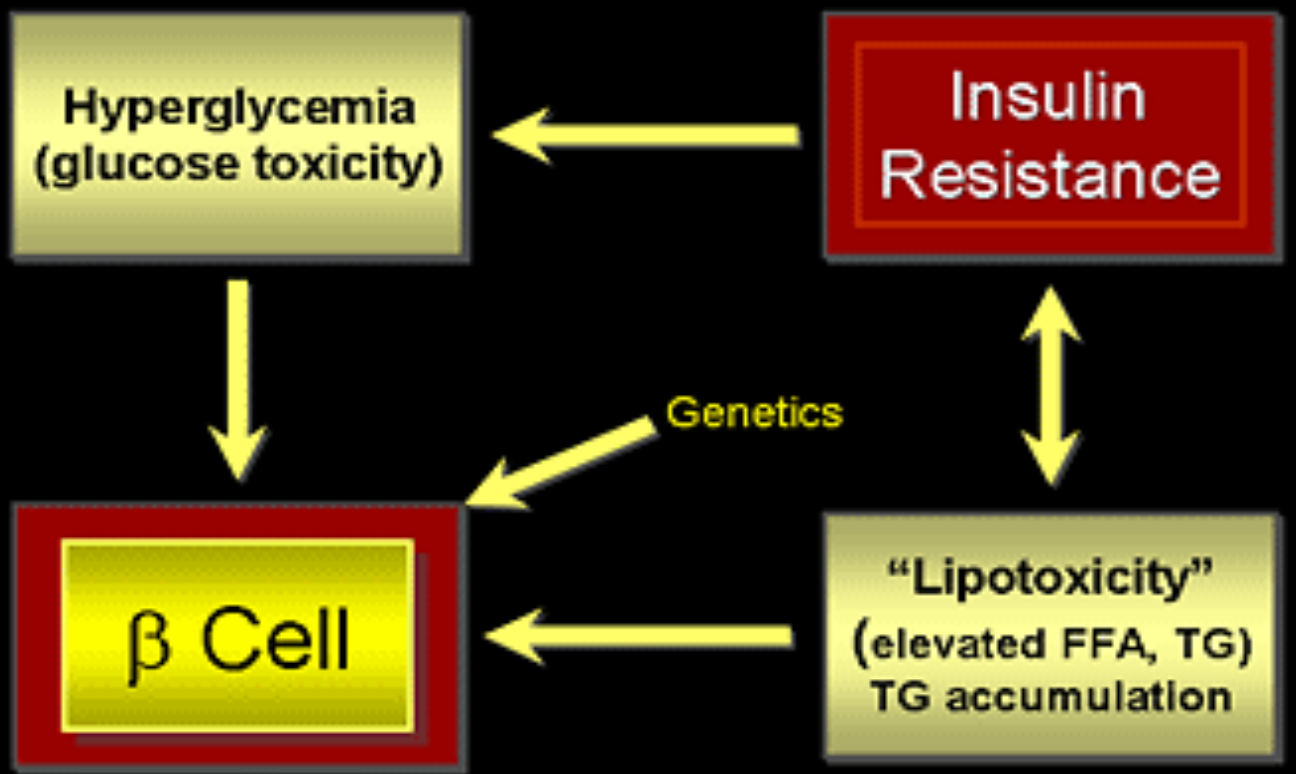
- When Metformin fails
- Dual therapy from the beginning
- Beta cell preservation: Reality or myth?

Natural History of Type 2 Diabetes



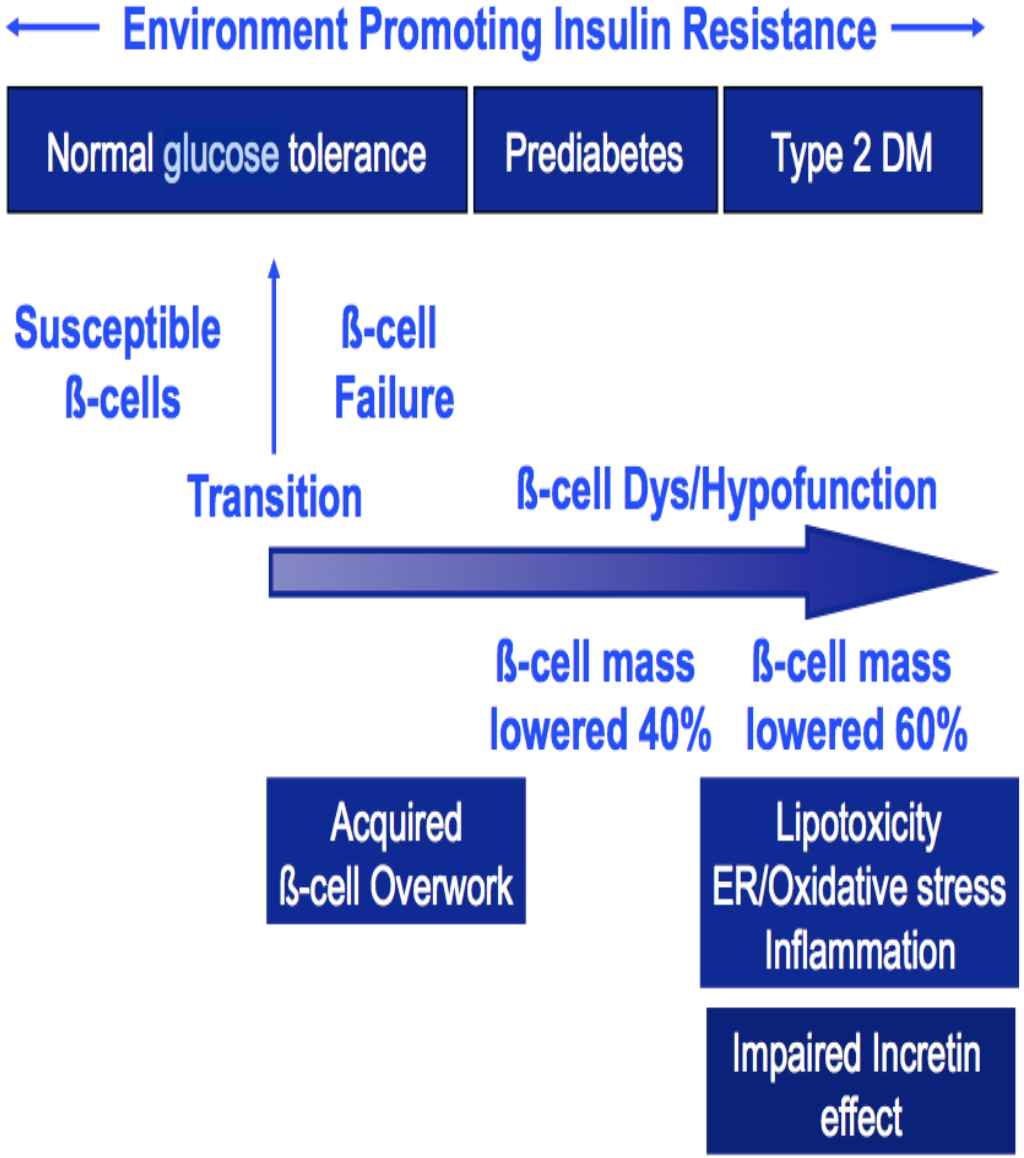
Kendall DM, et al. *Am J Med.* 2009;122(Suppl 6):S37-S50.

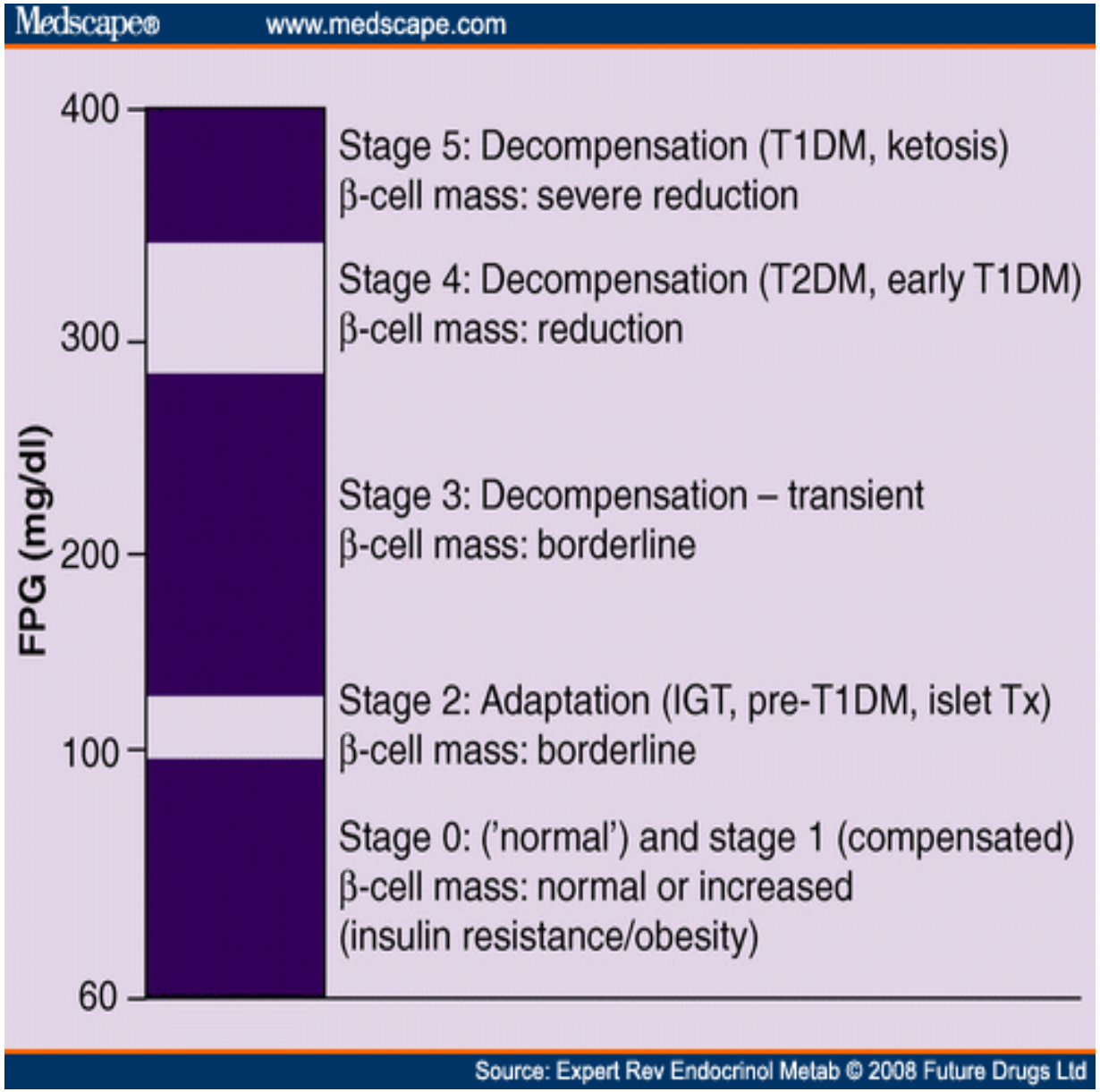
Factors That May Drive the Progressive Decline of β-cell Function



FFA=Free fatty acids; TG=Triglycerides.

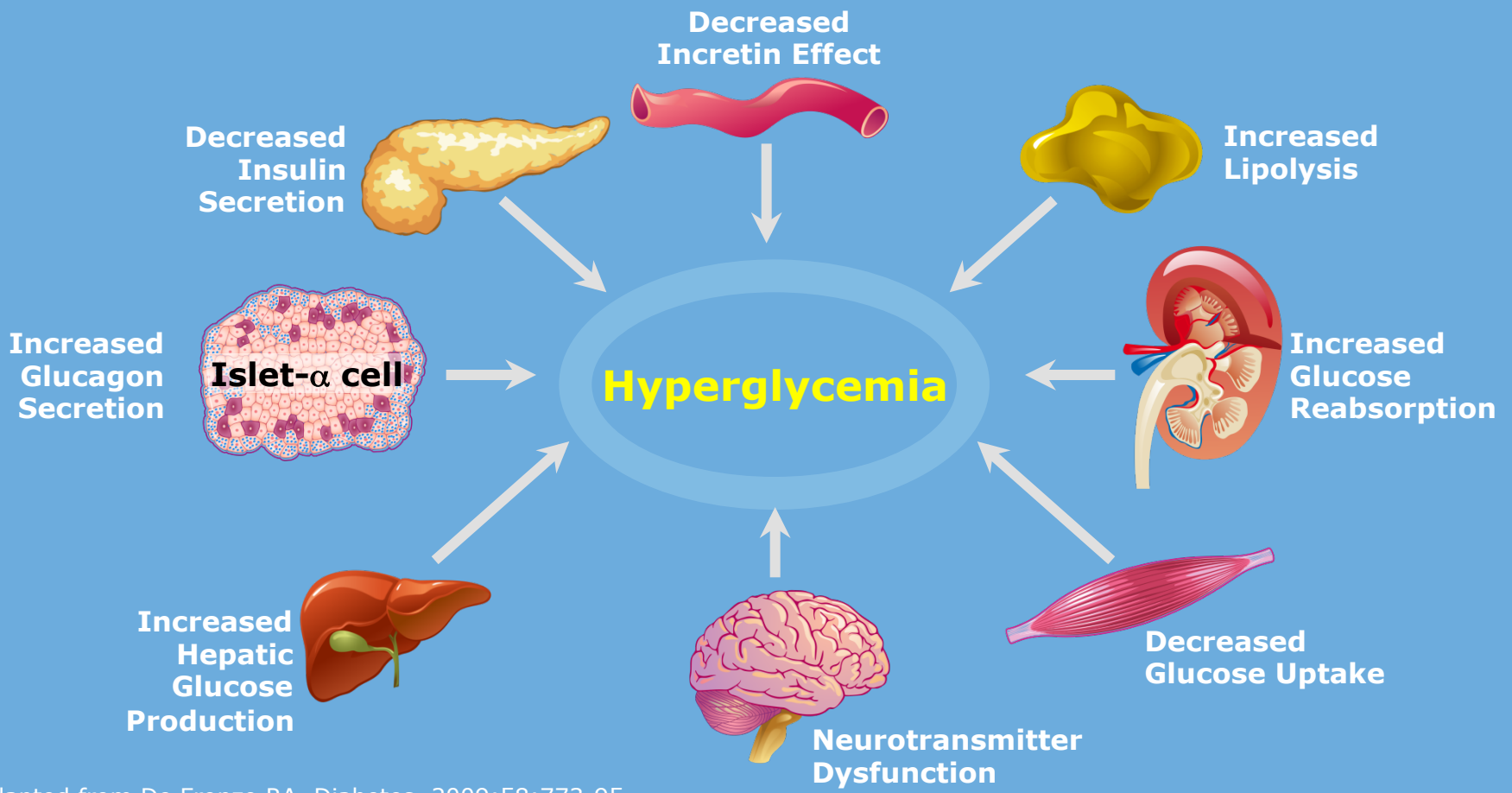
Adapted from: Kahn SE. *J Clin Endocrinol Metab.* 2001;86:4047-4058.
Adapted from: Ludwig DS. *JAMA.* 2002;287:2414-2423.


Environment Promoting Insulin Resistance
Normal glucose tolerance
Prediabetes
Type 2 DM
Susceptible ß-cells
ß-cell Failure
Transition
ß-cell Dys/Hypofunction
ß-cell mass lowered 40%
ß-cell mass lowered 60%
Acquired ß-cell Overwork
Lipotoxicity ER/Oxidative stress Inflammation
Impaired Incretin effect


Medscape®
www.medscape.com
FPG (mg/dl)
400
300
200
100
60
Stage 5: Decompensation (T1DM, ketosis)
β-cell mass: severe reduction
Stage 4: Decompensation (T2DM, early T1DM)
β-cell mass: reduction
Stage 3: Decompensation – transient
β-cell mass: borderline
Stage 2: Adaptation (IGT, pre-T1DM, islet Tx)
β-cell mass: borderline
Stage 0: ('normal') and stage 1 (compensated)
β-cell mass: normal or increased
(insulin resistance/obesity)
Source: Expert Rev Endocrinol Metab © 2008 Future Drugs Ltd

Pathogenesis of type 2 diabetes - the ominous octet

Multiple defects contribute to the progression of type 2 diabetes mellitus



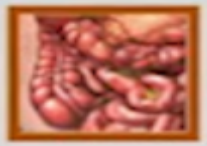
Adapted from De Fronzo RA. Diabetes. 2009;58:773-95.

3A. β-Cell-Centric Construct: Egregious Eleven

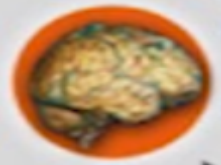
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage

1. *Pancreatic β-cells*
↓ β-Cell function
↓ β-Cell mass
⬇ Insulin
FINAL COMMON DENOMINATOR

8. Colon/Biome
Abnormal-microbiota; possible decreased GLP-1 secretion



7. Brain
Increased appetite
Decreased morning dopamine surge
Increased sympathetic tone



9. Immune Dysregulation/ Inflammation

2. ↓Incretin effect

3. α-cell defect
↓
↑ Glucagon

↓Amylin

10. Stomach/ Small intestine

Increased rate of glucose absorption

HYPERGLYCEMIA

Upregulation of SGLT-2

11. Kidney
Increased glucose re-absorption

INSULIN RESISTANCE

6. Liver

Increased glucose production

5. Muscle

Decreased peripheral muscle uptake

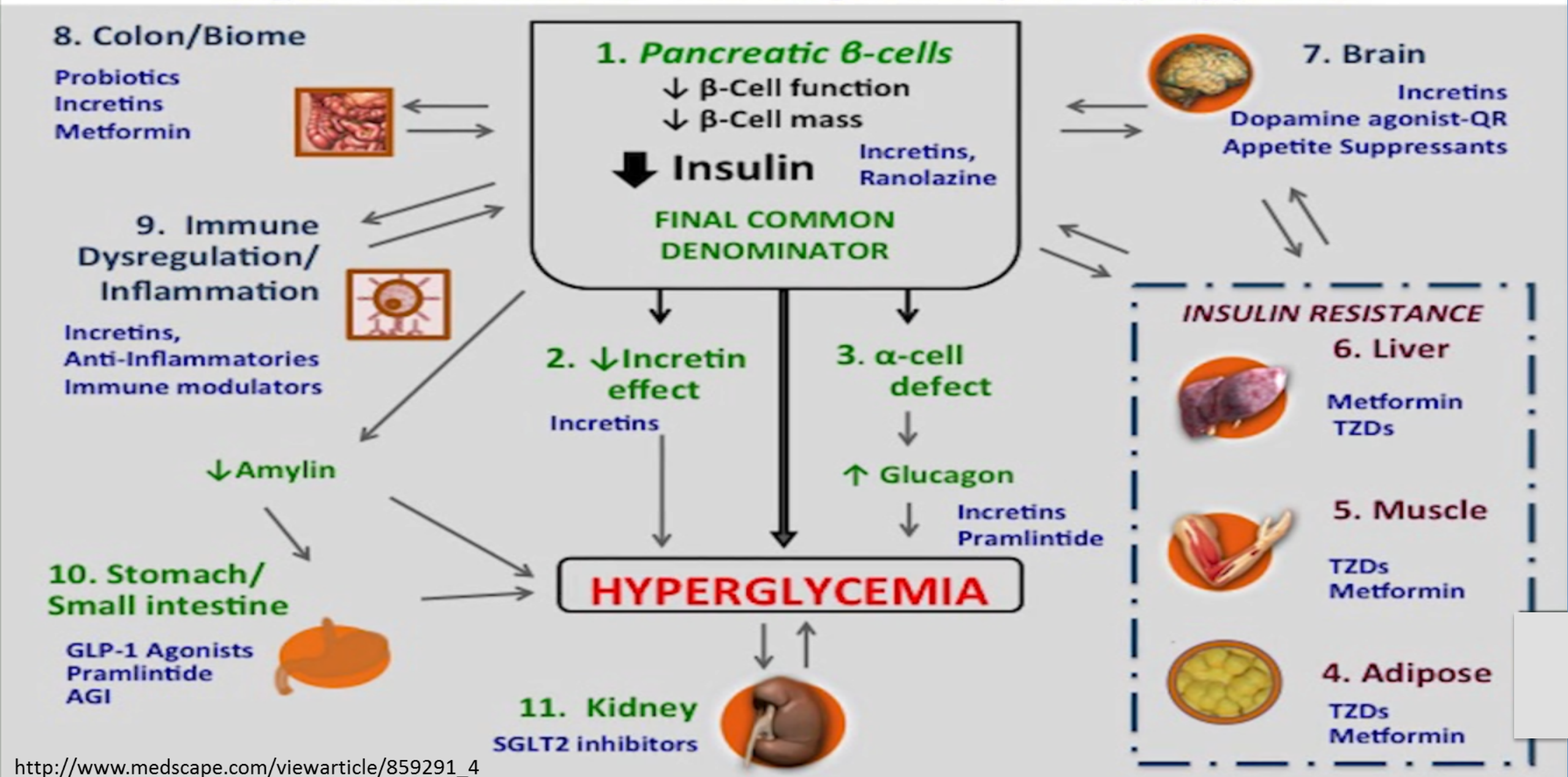
4. Adipose

Increased lipolysis

http://www.medscape.com/viewarticle/859291_4

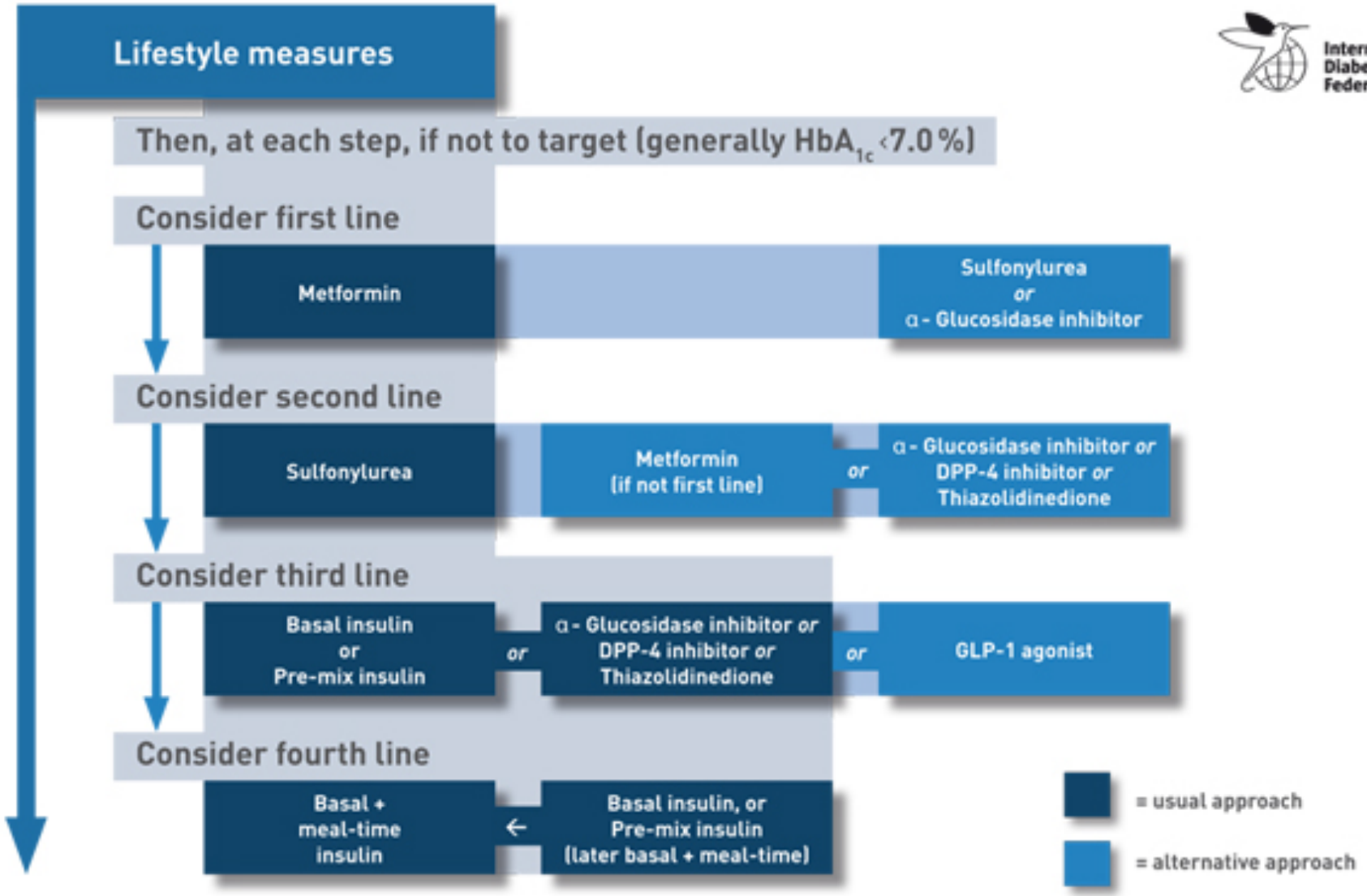
3B. β-Cell-Centric Construct: Egregious Eleven

Targeted Treatments for Mediating Pathways of Hyperglycemia



http://www.medscape.com/viewarticle/859291_4

IDF Treatment Algorithm for People with Type 2 Diabetes



International Diabetes Federation

NICE National Institute for Health and Care Excellence

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

- Reinforce advice on diet, lifestyle and adherence to drug treatment.
- Agree an individualised HbA1c target based on: the person's needs and circumstances including preferences, comorbidities, risks from polypharmacy and tight blood glucose control and ability to achieve longer-term risk-reduction benefits. Where appropriate, support the person to aim for the HbA1c levels in the algorithm. Measure HbA1c levels at 3/6 monthly intervals, as appropriate. If the person achieves an HbA1c target lower than target with no hypoglycaemia, encourage them to maintain it. Be aware that there are other possible reasons for a low HbA1c level.
- Base choice of drug treatment on: effectiveness, safety (see MHRA guidance), tolerability, the person's individual clinical circumstances, preferences and needs, available licensed indications or combinations, and cost (if 2 drugs in the same class are appropriate, choose the option with the lowest acquisition cost).
- Do not routinely offer self-monitoring of blood glucose levels unless the person is on insulin, on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery, is pregnant or planning to become pregnant or if there is evidence of hypoglycaemic episodes.

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (8.6%) on lifestyle interventions:
- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified-release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.6%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - *metformin and an SGLT-2i*[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.6%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - *metformin, pioglitazone[a] or an SU, and an SGLT-2i*[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:
- have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- have a BMI lower than 35 kg/m², and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (8.6%) on lifestyle interventions:
- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i or pioglitazone or 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.6%):
- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 68 mmol/mol (7.6%):
- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

Insulin-based treatment

- When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies[f].
- Offer NPH insulin once or twice daily according to need.
- Consider starting both NPH and short-acting insulin either separately or as pre-mixed (biphasic) human insulin (particularly if HbA1c is 75 mmol/mol (9.0%) or higher).
- Consider, as an alternative to NPH insulin, using insulin detemir or glargine[g] if the person: needs assistance to inject insulin, lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or would otherwise need twice-daily NPH insulin in combination with oral blood glucose lowering drugs.
- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if: the person prefers injecting insulin immediately before a meal, hypoglycaemia is a problem or blood glucose levels rise markedly after meals.
- Only offer a GLP-1 mimetic[c] in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[h].
- Monitor people on insulin for the need to change the regimen.
- *An SGLT-2i in combination with insulin with or without other antidiabetic drugs is an option*[b].

t cover DPP-4 inhibitors. GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

a. When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

b. Treatment with combinations of drugs including sodium–glucose cotransporter 2 inhibitors may be appropriate for some people at first and second intensification: see NICE technology appraisal guidance 288, 315 and 336 on dapagliflozin, canagliflozin and empagliflozin respectively. All three SGLT-2 inhibitors are recommended as options in dual therapy regimens with metformin under certain conditions. All three are also recommended as options in combination with insulin. At the time of publication, only canagliflozin and empagliflozin are recommended as options in triple therapy regimens. The role of dapagliflozin in triple therapy will be reassessed by NICE in a partial update of TA288. Serious and life-threatening cases of diabetic ketoacidosis have been reported in people taking SGLT-2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) or shortly after stopping the SGLT-2 inhibitor. MHRA guidance (2015) advises testing for raised ketones in people with symptoms of diabetic ketoacidosis, even if plasma glucose levels are near normal.

c. Only continue GLP-1 mimetic therapy if the person has a beneficial metabolic response (a reduction of HbA1c by at least 11 mmol/mol [1.0%] and a weight loss of at least 3% of initial body weight in 6 months).

d. Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

e. Be aware that the drugs in dual therapy should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug.

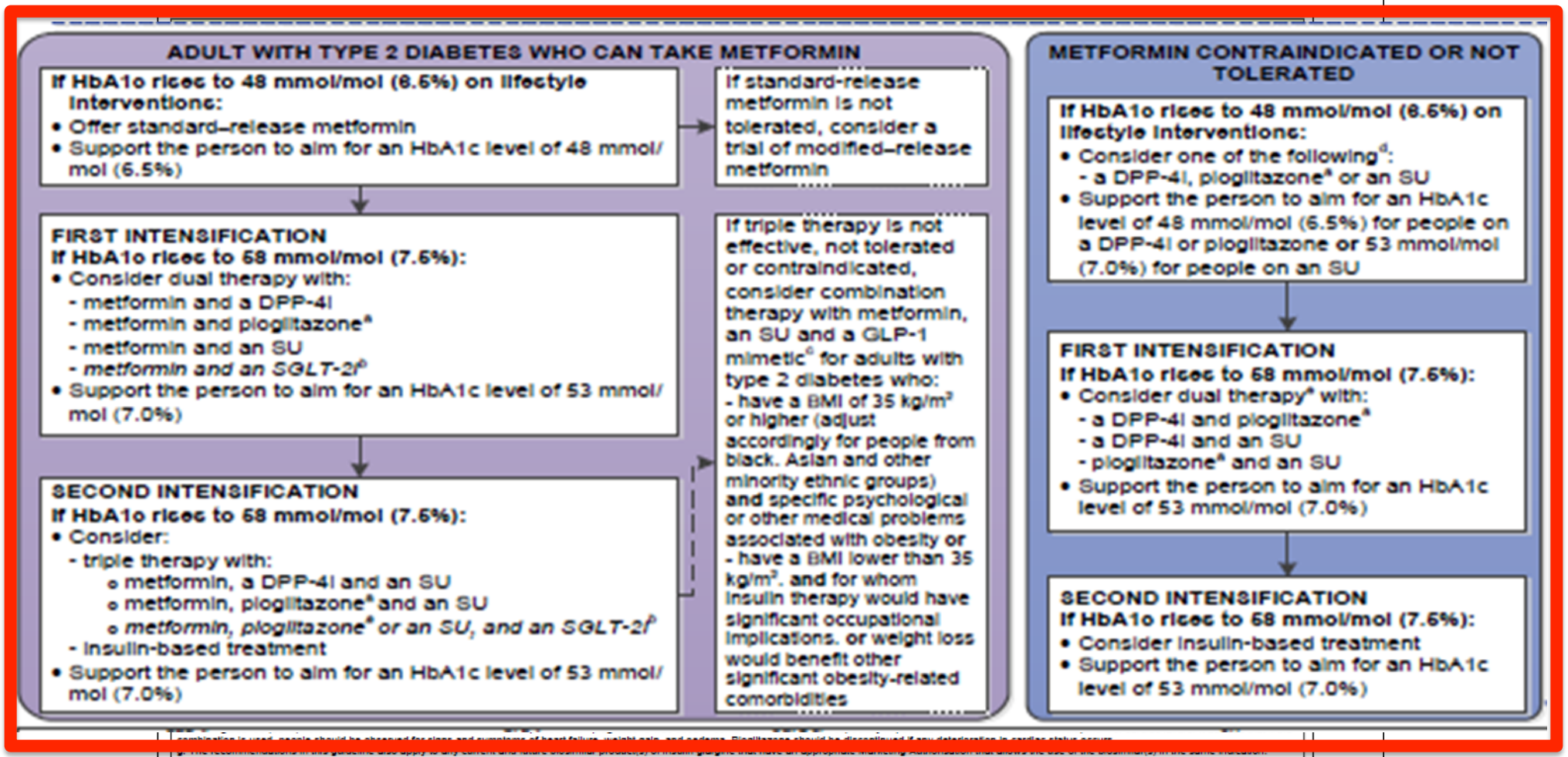
f. MHRA guidance (2011) notes that cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. It advises that if the combination is used, people should be observed for signs and symptoms of heart failure, weight gain, and oedema. Pioglitazone should be discontinued if any deterioration in cardiac status occurs.

g. The recommendations in this guideline also apply to any current and future biosimilar product(s) of insulin glargine that have an appropriate Marketing Authorisation that allows the use of the biosimilar(s) in the same indication.

h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

NICE National Institute for Health and Care Excellence

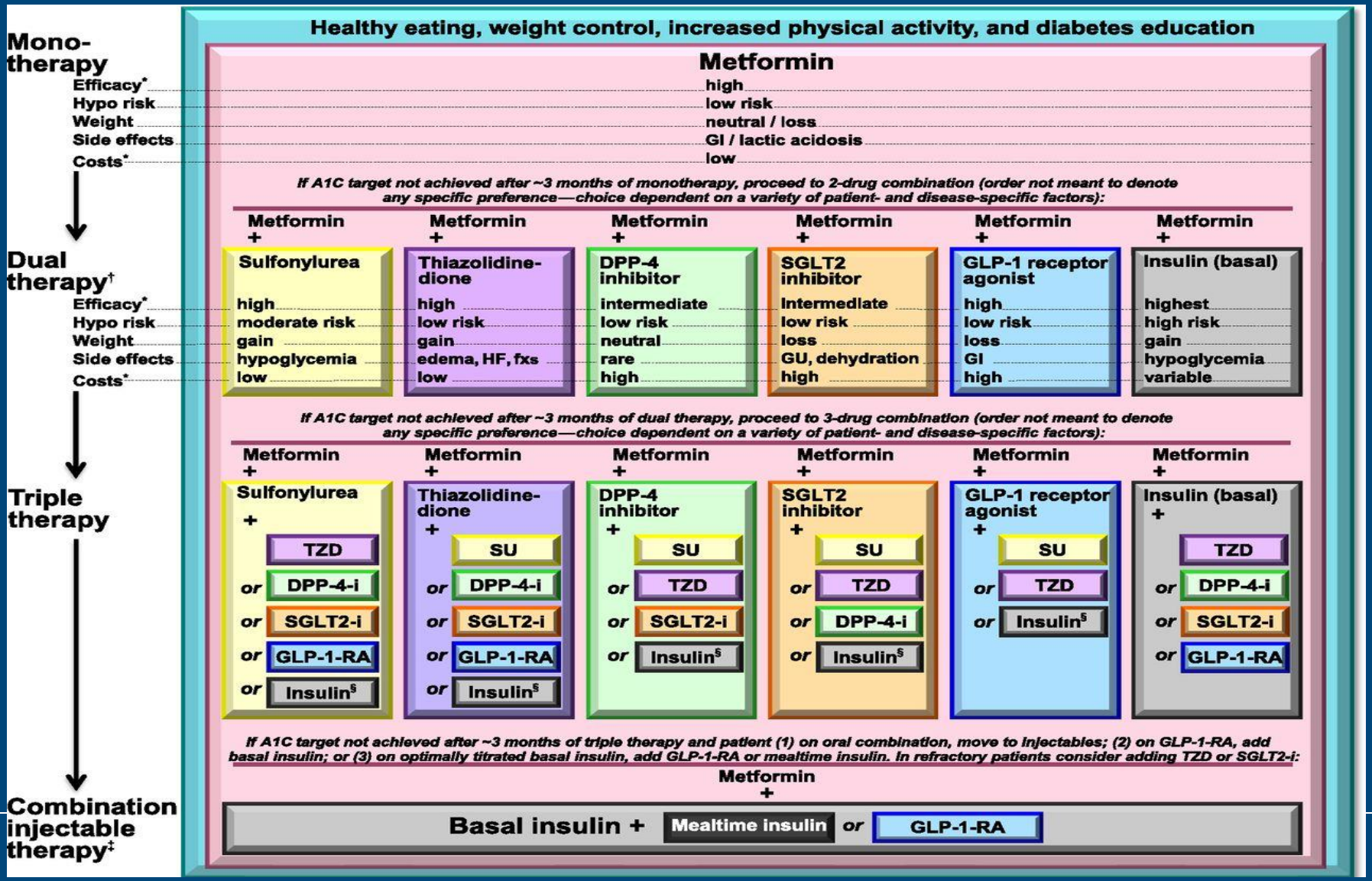
Algorithm for blood glucose lowering therapy in adults with type 2 diabetes



h. A consultant-led multidisciplinary team may include a wide range of staff based in primary, secondary and community care.

'Type 2 diabetes in adults: management', NICE guideline NG28 (December 2015)

Antihyperglycemic Therapy in Type 2 Diabetes



American Diabetes Association®

ADA Standards of Medical Care in Diabetes. Approaches to Glycemic Treatment. *Diabetes Care* 2016; 39 (Supl.1): SX

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

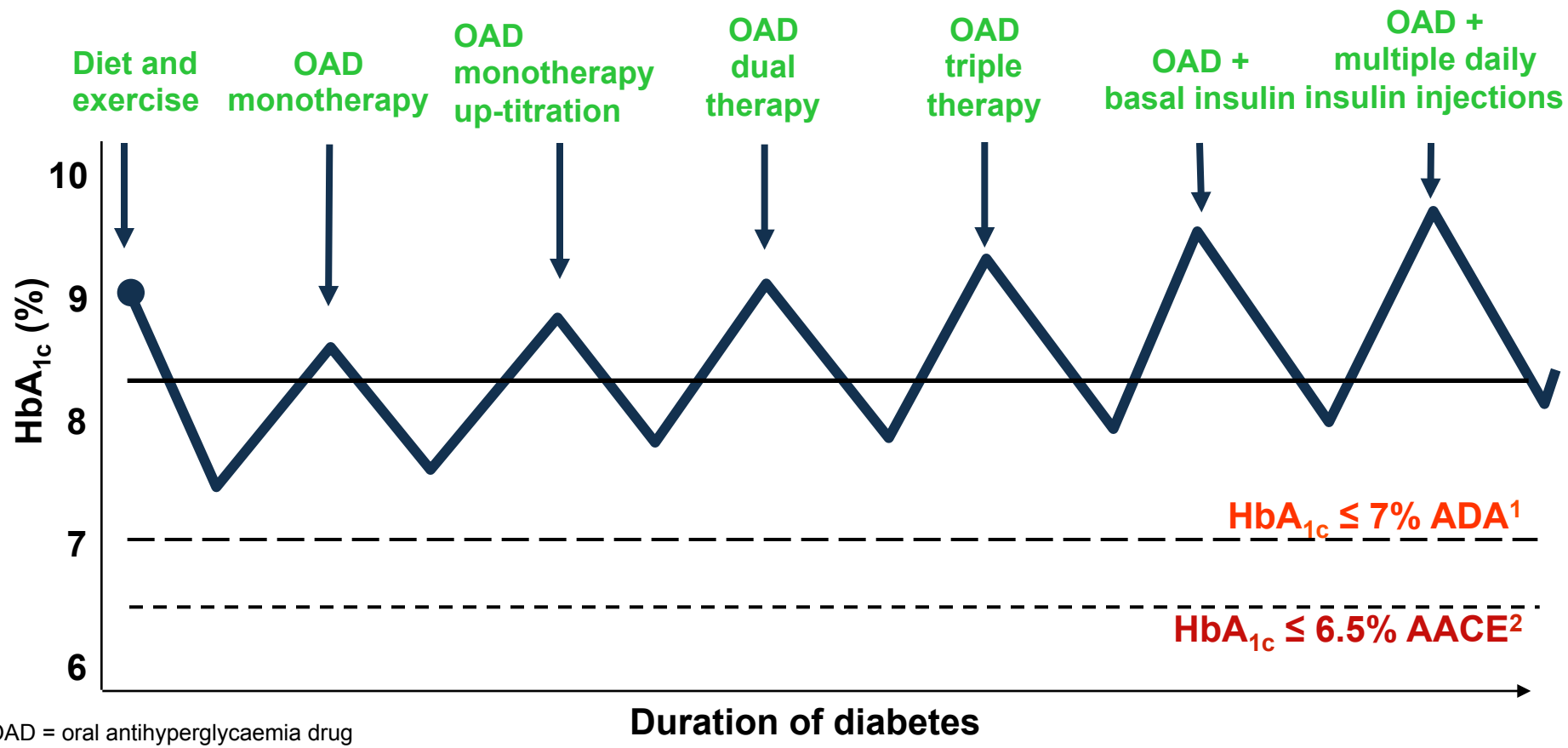
Before starting Metformin, obtain the patient's eGFR.
Obtain an eGFR at least annually in all patients taking Metformin.
High risk patients, such as the elderly, renal function should be assessed more frequently.
eGFR > 45mL/min/1.73m2: Metformin can be used
eGFR between 30–45mL/min/1.73m2: Starting Metformin is not recommended.
eGFR <30mL/min/1.73m2: Metformin is contraindicated.
If the eGFR later falls <45mL/min/1.73m2, assess the benefits and risks of continuing treatment
If eGFR further falls <30mL/min/1.73m2: Discontinue Metformin

If the eGFR is between 30–60mL/min/1.73m2, discontinue Metformin:

- In patients with a history of liver disease, alcoholism, or heart failure
- At the time of or before an iodinated contrast imaging procedure in patients as well as in normal patients, who will be administered intra-arterial iodinated contrast.

  Re-evaluate eGFR 48 hours after the imaging procedure; restart Metformin if renal function is stable.

Conservative management of glycemia: Traditional Stepwise Approach

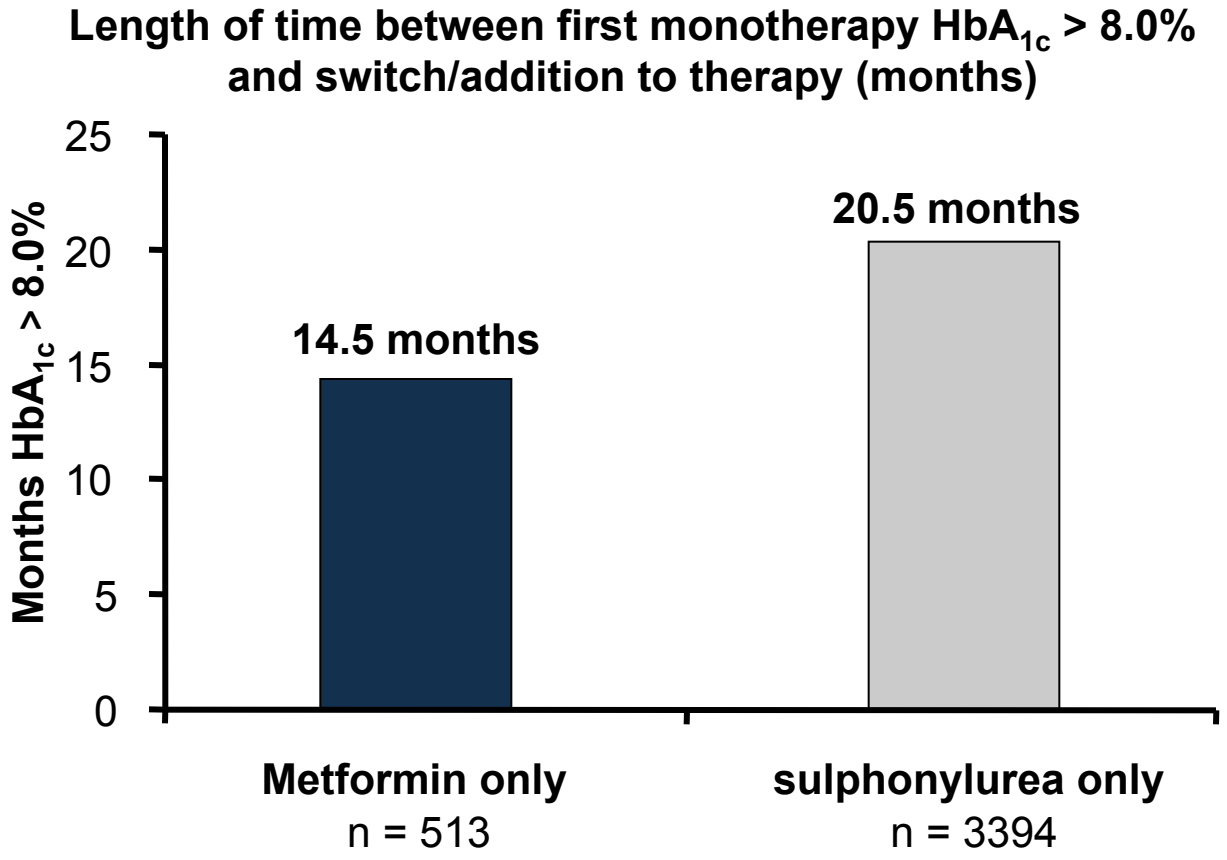


OAD = oral antihyperglycaemia drug

Adapted from Campbell IW. *Br J Cardiol*. 2000;7:625–631.

1. American Diabetes Association Clinical Practice Recommendations: *Diabetes Care.* 2010;33(suppl.1):S4–S10;
2. AACE/ACE. *Endocr Prac*. 2009;15:540–559.

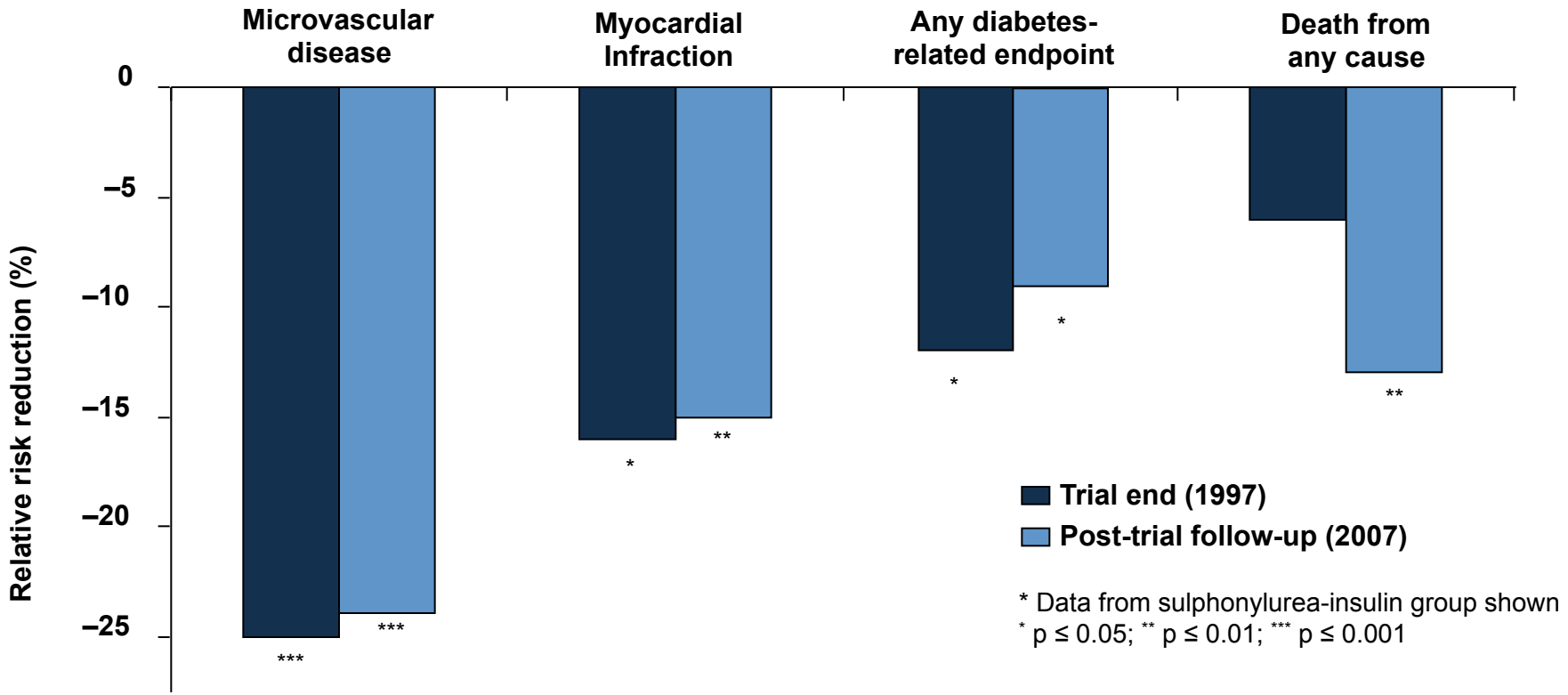
Delay between stepping up from monotherapy to combination therapy



Brown JB et al. *Diabetes Care*. 2004;27:1535–1540.

The Legacy Effect

10-year post-trial monitoring from 1997 to 2007 of UKPDS Study*

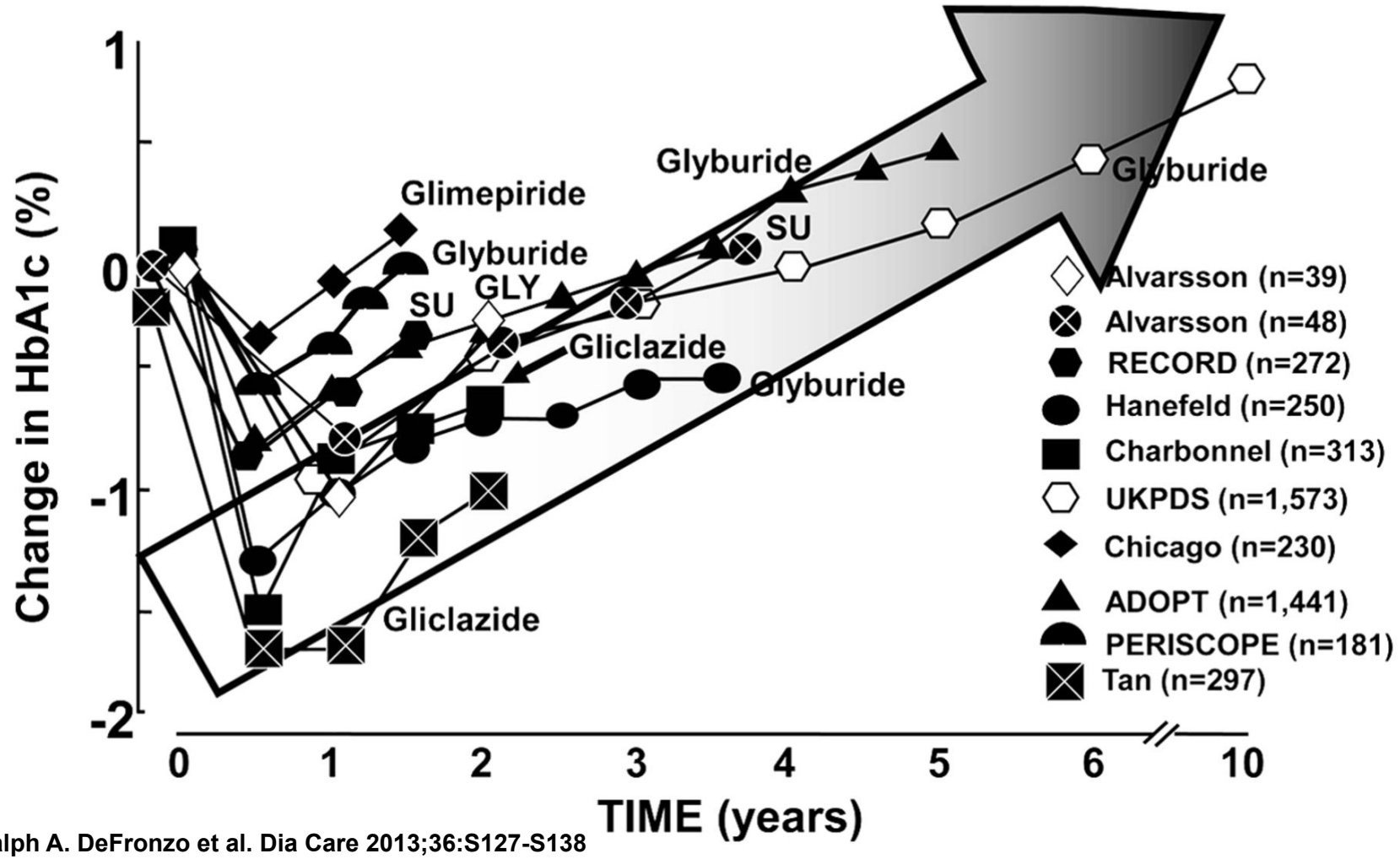


- Randomized intervention to achieve either intensive or conventional targets - stopped at the trial end (1997)
- Differences in mean HbA_{1c} between the 2 groups were lost by Year 1 of post-trial follow-up
- Relative reductions in risk in patients who had been treated to intensive goals, compared with conventional targets, persisted after 10 years

The legacy effect – a reduction in complications persists 10 years after intensive therapy

1. UKPDS 33 Study Group. *Lancet*. 1998;352:837–853; 2. Holman RR, et al. *N Engl J Med*. 2008;359:1577–1589; 3. Chalmers J and Cooper ME. *N Engl J Med*. 2008;359:1618–1620.

Durability of glycemic control with sulfonylureas



Ralph A. DeFronzo et al. Dia Care 2013;36:S127-S138

American Diabetes Association.

Early Dual Therapy

After diet and lifestyle modification, monotherapy may assist patients in achieving a target of HbA1c less than 7%. However, with disease progression, usually the monotherapy loses efficacy over time as evidenced by a continued increase in A1c.
For example, in patients with high mean baseline A1c of 8.2–8.4%, glycemic control was reached by only 25% of patients with metformin monotherapy.

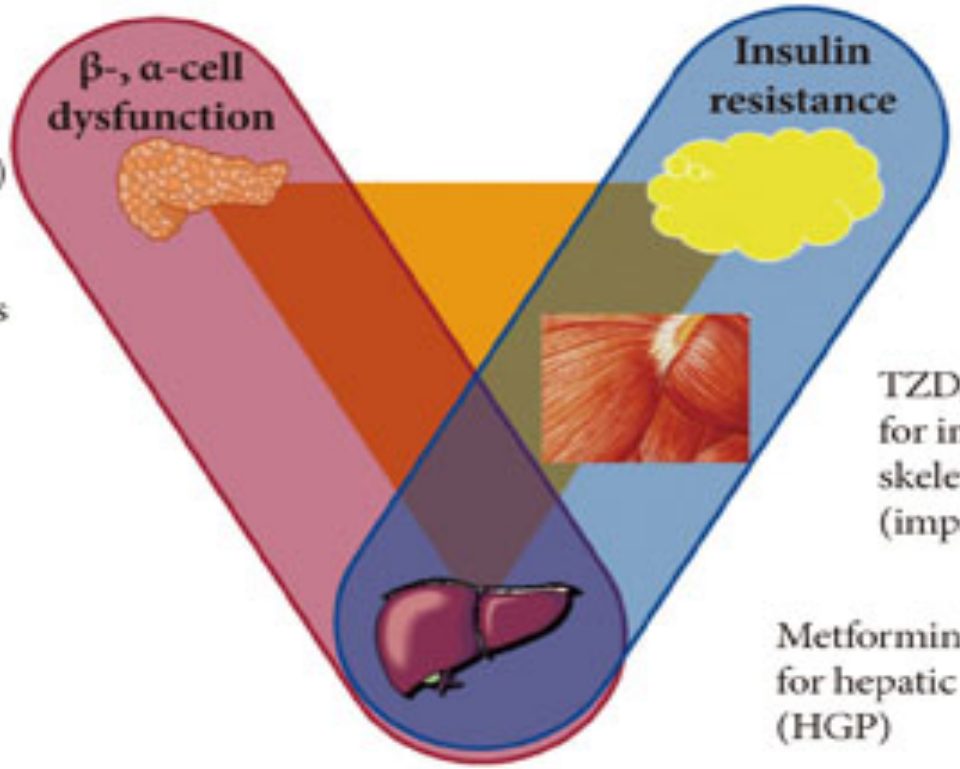
The primary objective of combining oral antidiabetic treatments is to address the dual problems of insulin deficiency and insulin resistance. This has been shown to be helpful in establishing glycemic control and lowering A1c levels by an additional 0.5–1.0%.

The chosen regimen, should ideally exert a physiologically rapid prandial insulin response to maintain tight glycemic control with minimal side effects such as hypoglycemia and weight gain. It is also important for the combination to be at least additive and possibly synergistic in their mechanisms of action.

http://www.medscape.com/viewarticle/722513_2

What about early Triple Therapy?

The combination of metformin, TZD and GLP-1 analog (or DPP-IV inhibitor) addresses the 3 core defects of type 2 diabetes in a complementary manner (up to HbA1c Δ -2%)



GLP-1 analog (or DPP-IV inhibitor) for islet β-, α-cell dysfunction and extra-islet actions

TZD for insulin resistance in adipose tissue (lipolysis)

TZD, metformin for insulin resistance in skeletal muscle (impaired glucose uptake)

Metformin, TZD for hepatic insulin resistance (HGP)

http://dx.doi.org/10.4093/kdj.2010.34.6.331

Beta cell Preservation

- Intensive Lifestyle Modification
- Sulfonylureas
- Metformin
- Acarbose
- Thiazolidinediones (TZDs)
- GLP-1 Receptor Agonists
- Bariatric Surgery

Intensive Lifestyle Modification

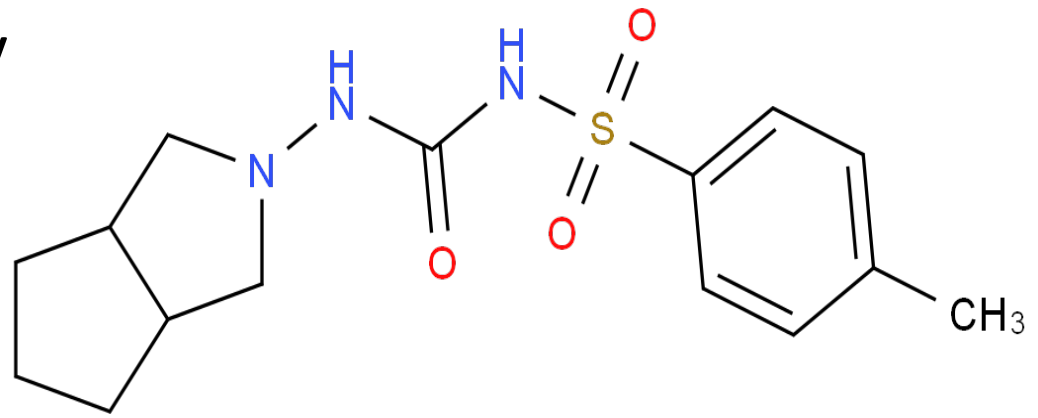
Study	Participants at high-risk for diabetes	Intervention	Relative reduction in risk of diabetes[a]
DPP	IGT	Lifestyle	58 %
Finnish DPS	IGT	Lifestyle	58 %
XENDOS	IGT	Orlistat + lifestyle	45%[b]
TRIPOD	Prior GDM	Troglitazone	55 %
DPP	IGT	Troglitazone	75 %
DREAM	IGT	Rosiglitazone	60 %
ACT NOW	IGT	Pioglitazone	72 %
DPP	IGT	Metformin	31 %
Stop-NIDDM	IGT	Acarbose	25 %

DPP Diabetes Prevention Program, DPS Diabetes Prevention Study, TRIPOD troglitazone in prevention of diabetes, DREAM diabetes reduction assessment with ramipril and rosiglitazone medication, ACT NOW Actos now, IGT impaired glucose tolerance, GDM gestational diabetes mellitus

avs placebo and/or usual care

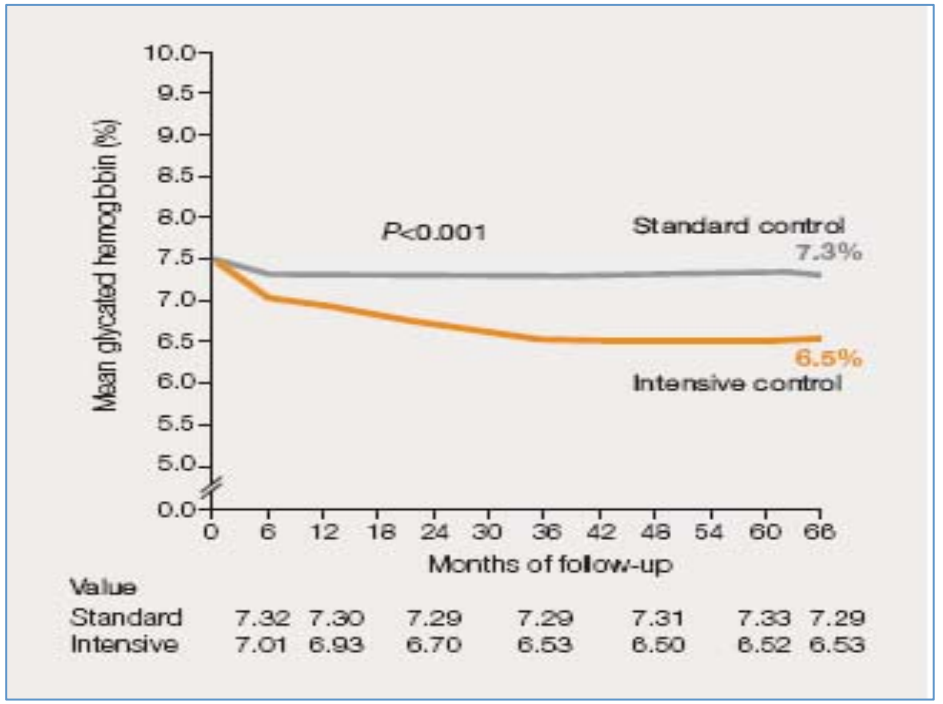
Sulfonylureas

ADVANCE trial indicates that Gliclazide, may protect β cells from apoptosis potentially through antioxidant effects of the aminoazabicyclo-octyl ring grafted onto the sulfonylurea group.



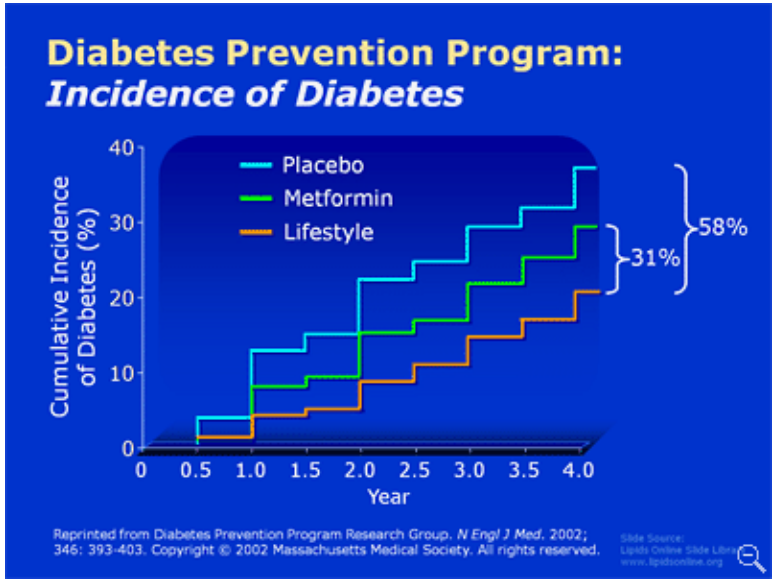
This causes inhibition of LDL oxidation. It has been shown to scavenge superoxide radicals, hydroxyl radicals, and NO in a dose-dependent manner.

No clinical studies have demonstrated a beneficial effect of sulfonylureas in the <u>prevention</u> of T2DM

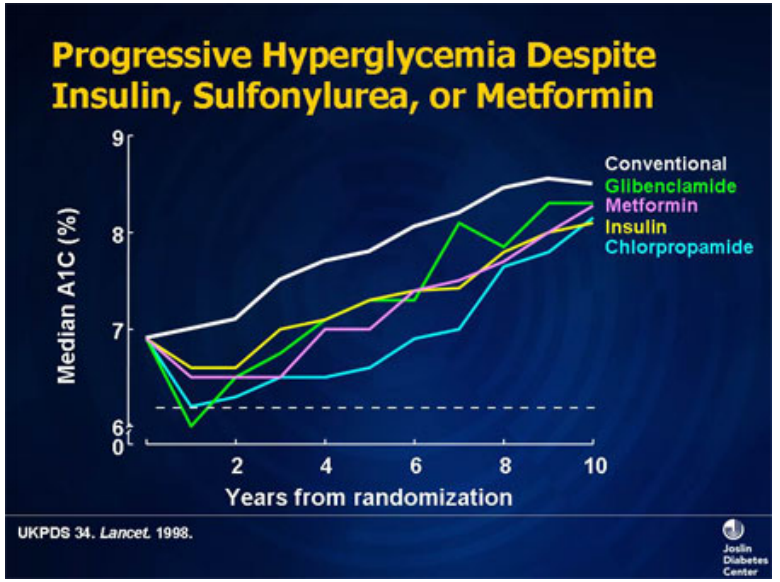


Metformin

Metformin is effective at reducing hyperglycemia primarily by inhibiting hepatic glucose production and by increasing insulin sensitivity DPP showed that metformin reduced the conversion from IGT to T2DM by 31 % suggesting that it has modest effects on slowing the progression of T2DM.

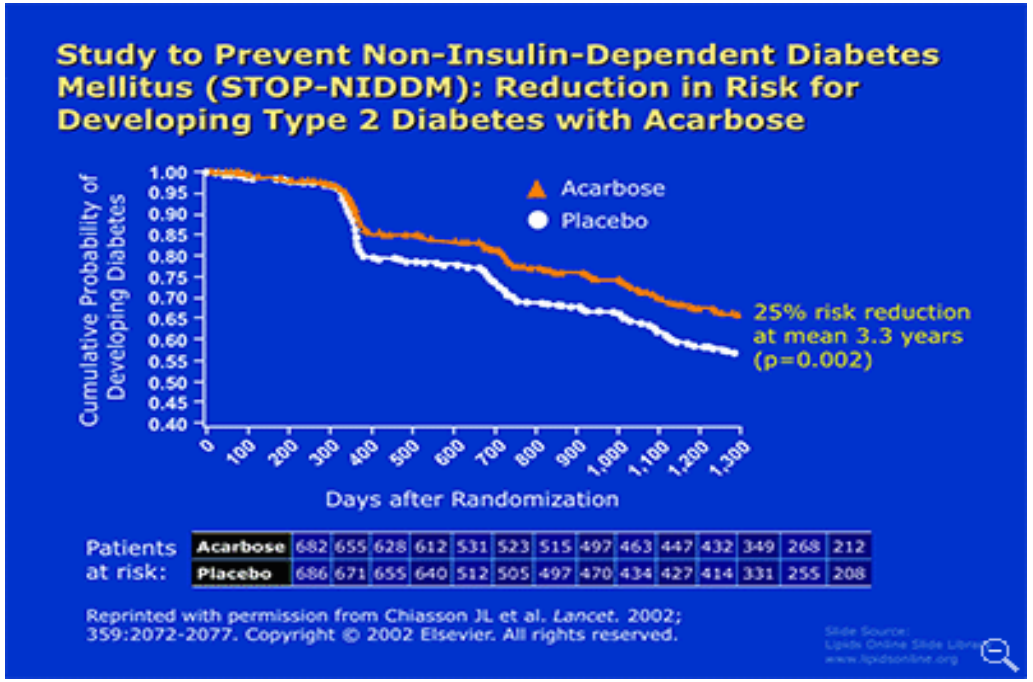


UKPDS showed similar rates of deterioration of β-cell function (assessed with HOMA-B index) and loss of glycemic control with metformin treatment compared with sulfonylureas or insulin treatment in patients with recently diagnosed T2DM.



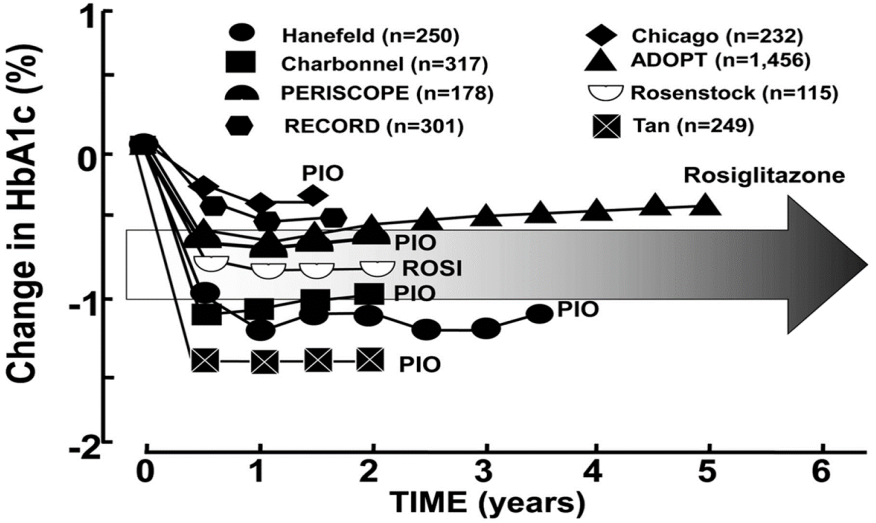
Acarbose

Acarbose is an α-glucosidase inhibitor that improves post-prandial hyperglycemia by inhibiting the activity of enzymes in the small intestine resulting in reduced glucose absorption. The Study to Prevent NIDDM (STOP-NIDDM) found a 25 % relative risk reduction in the development of T2DM over 3.3 years in patients with impaired glucose levels treated with acarbose compared with placebo. However, in the 3-month observation period after acarbose was discontinued, the incidence of diabetes in patients who had not converted was higher in the group initially assigned to acarbose (15 %) compared with group first randomized to placebo (10 %) suggesting that the benefit of acarbose is lost after discontinuation of active treatment



Thiazolidinediones (TZDs)

TZDs reduce lipotoxicity, prevent β-cell apoptosis, increase serum adiponectin levels and improve β-cell function.
Prevention trials show that TZDs prevent the onset of T2DM in high-risk patients by ~50 %–75 % including DPP, TRIPOD, PIPOD, DREAM, ACT-NOW.
TRIPOD showed that protection from diabetes in women with previous gestational diabetes persisted 8 months after T2DM treatment stopped, and patients who were protected from diabetes during TZD treatment had stable β-cell function and insulin resistance for almost 5 years. This was supported by DREAM and DPP, in which the protection from diabetes that was achieved during treatment persisted after treatment was stopped.
The clinical use of TZDs for the prevention of T2DM is limited due to adverse side effects, including fluid retention and weight gain, increased risk for bone fractures and bladder cancer.



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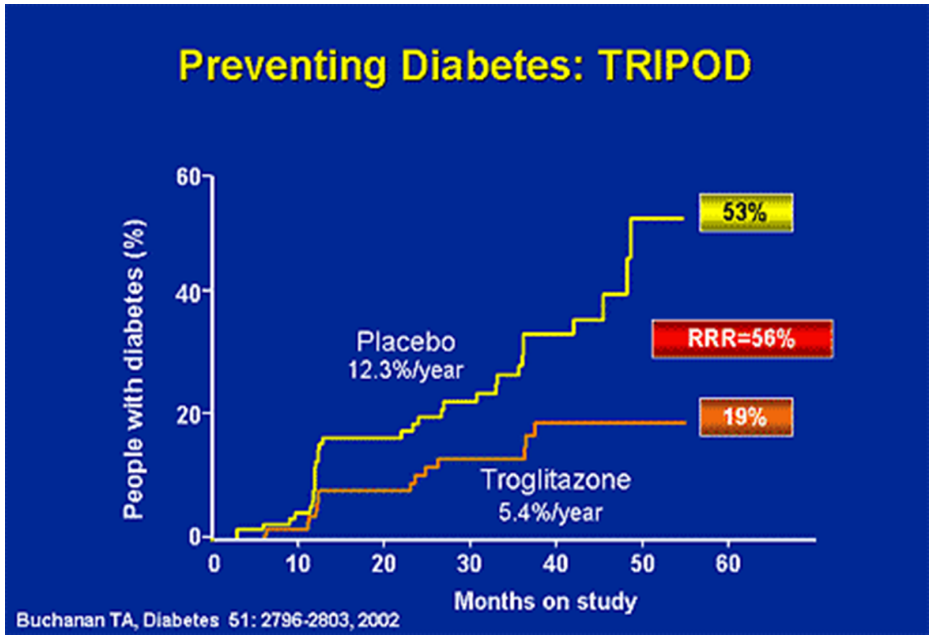


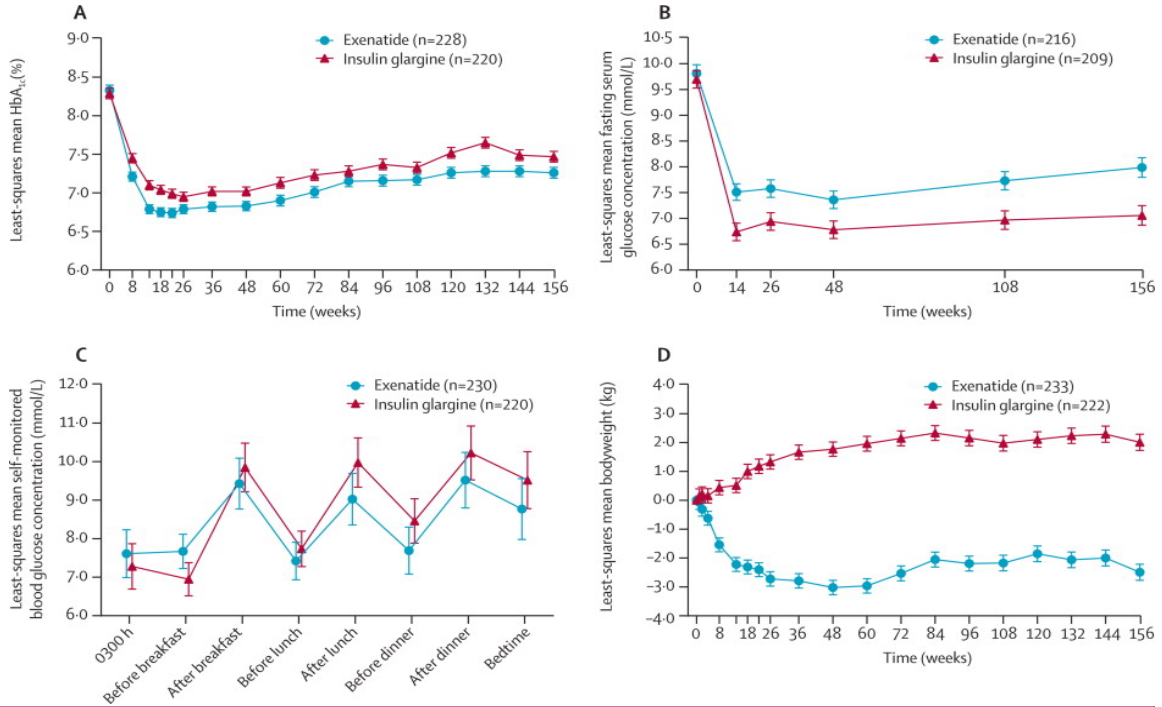
GLP-1 Receptor Agonists

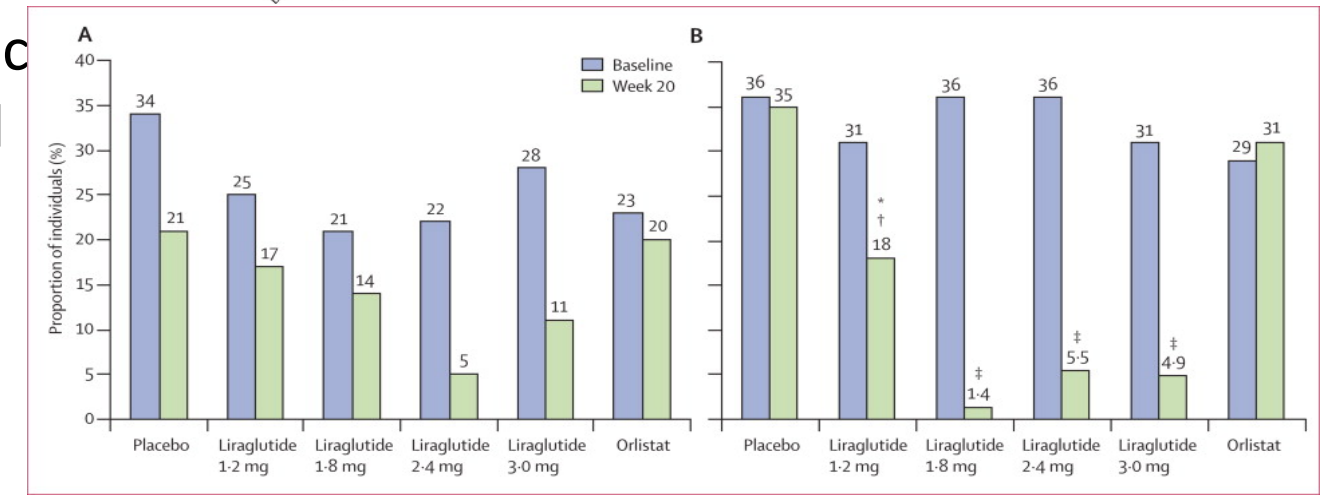
GLP-1 potentiates glucose stimulated insulin secretion, suppresses glucagon secretion, delays gastric emptying and suppresses appetite.

Studies indicate that at least 3 years of Exenatide treatment may be necessary to delineate a significant, prolonged benefit on β-cell function.

A 20-week treatment with Liraglutide (in doses ranging from 1.8 to 3 mg per day) resulted in greater weight loss and an 84 %–96 % reduc in the prevalence of prediabetes compared with placebo.

Longer term prevention trials in high-risk patients are needed to determine whether GLP-1 agonists can modify the progressive course of T2DM



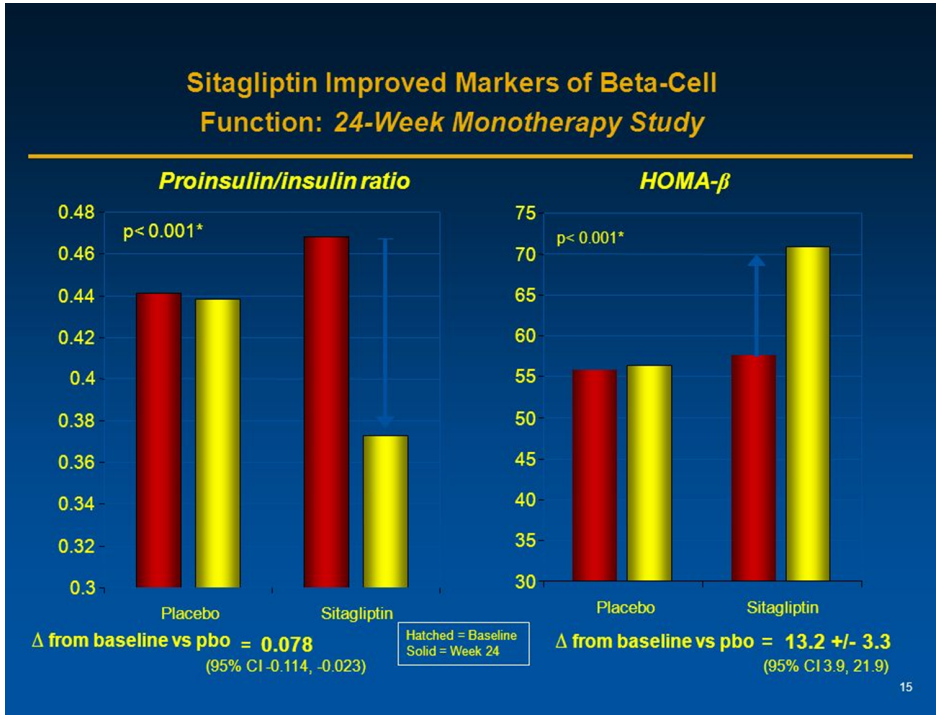


DPP-4 inhibitors

The incretin receptor signaling is associated with activation of protein kinase A, induction of gene transcription, enhanced levels of insulin biosynthesis, and stimulation of β-cell proliferation. Both GLP-1R and GIP receptor activation also promote resistance to apoptosis and enhanced β-cell survival, in human islets cells.

In preclinical studies, DPP-4 inhibitors mimic many of the actions ascribed to GLP-1R agonists, including stimulation of insulin and inhibition of glucagon secretion, and preservation of β-cell mass through stimulation of cell proliferation and inhibition of apoptosis.

Long-term clinical data assessing the durability and efficacy of these agents in the treatment of type 2 diabetes are not yet available



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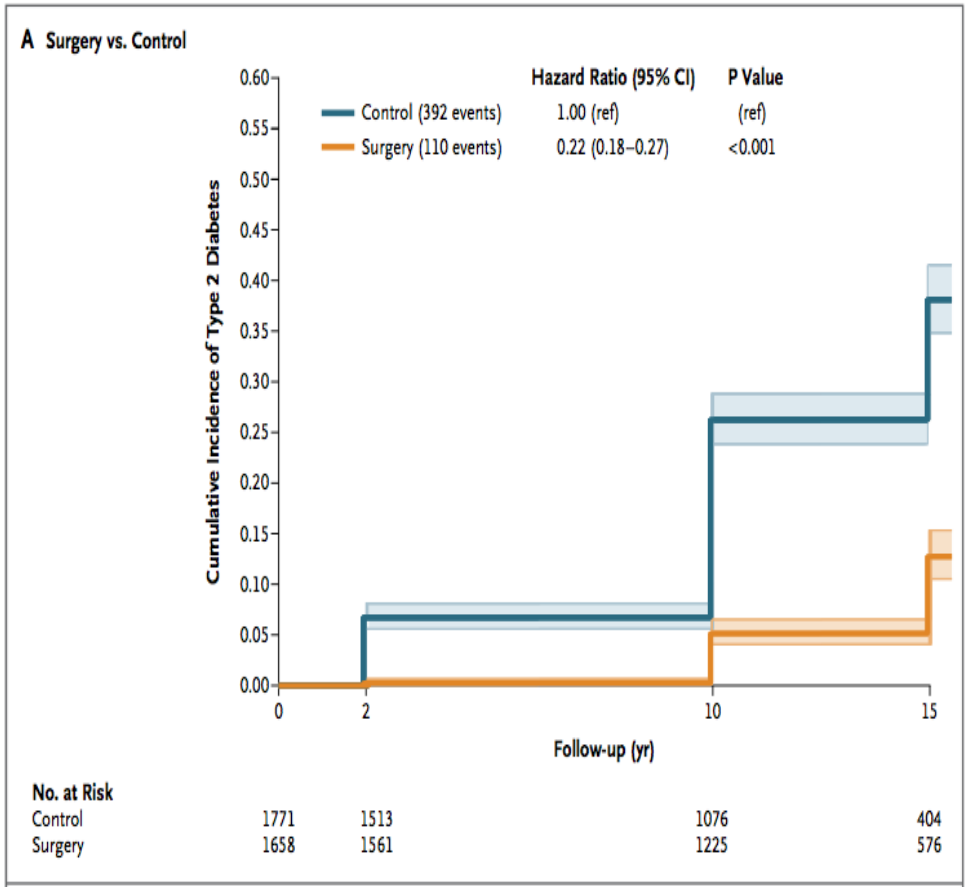
Bariatric Surgery

The effect of bariatric surgery (LAGB, VBG, RYGB) on the prevention of T2DM in obese adults was examined in the SOS study which followed surgically treated and matched controls for 15 years. Bariatric surgery compared with standard care reduced the long-term relative risk of T2DM by 78 % in obese adults, and in IFG it reduced the relative risk of by 82 %. The postoperative mortality was 0.2 %, and 2.8 % of patients had complications that required a reoperation. These findings indicate that bariatric surgery has effective and durable effects on the prevention of T2DM in obese adults, particularly among those with IFG. RCTs are needed to confirm whether bariatric surgery is an effective and safe approach for preventing T2DM in high-risk individuals.



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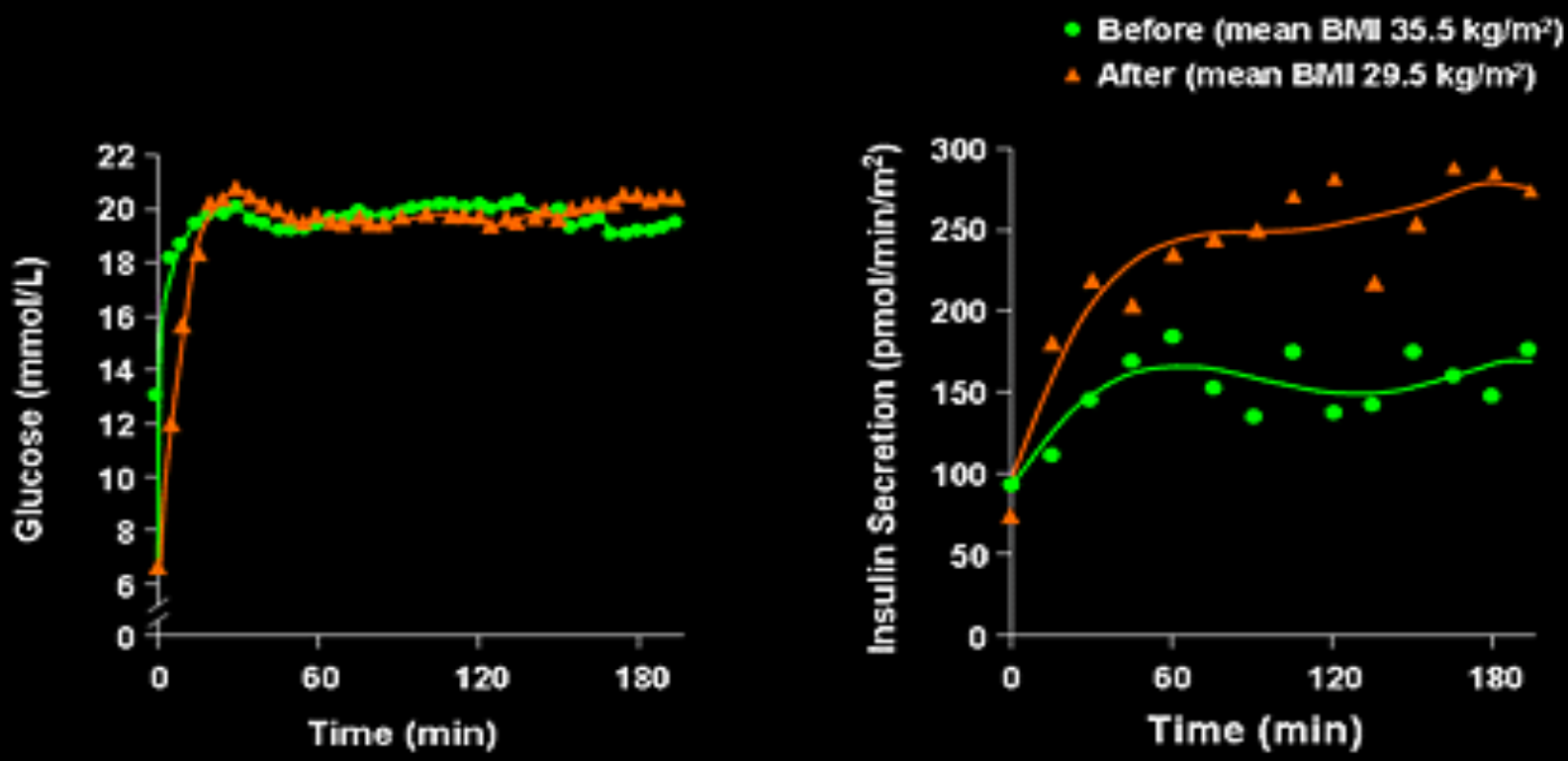
Effect of Weight Loss on β-cell Function in Obese Patients With Type 2 Diabetes



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Therapeutic approaches for maintaining β-cell function and mass in animal and human data

Agents	Mode of action in β-cell	Animal data	Human data
PPARγ agonists	Upregulate Pdx-1 expression [25] Increase insulin gene transcription, GLUT2, and glucokinase [26] Reverse lipotoxicity [27]	Reduced oxidative stress [28] Inhibited β-cell apoptosis [29] Increased β-cell mass and function [28,29]	Slow the rate of loss of β-cell function and improve insulin sensitivity in ADOPT trial [23], ACT NOW study [30], PIPOD, and TRIPOD study [31]
GLP-1 analogues	Enhance glucose-stimulated insulin secretion [33] Act as a growth factor by promoting β-cell proliferation and inhibiting β-cell apoptosis [33] Stimulate insulin gene expression and biosynthesis [34] Attenuate ER stress [35]	Increased β-cell mass [36] Modulated the expression of β-cell specific genes [37] Inhibited β-cell apoptosis [38]	Improved insulin secretory capacity and insulin sensitivity [39] Reduced proinsulin to insulin ratio [40] Restore 1st and 2nd phase insulin secretion [41]
DPP-4 inhibitors	Inhibit the incretin degrading enzyme DPP-4 [32] Increase the bioavailability of active GLP-1 [42]	Increased β-cell mass and pancreatic insulin content [42,43] Enhanced insulin secretion [42]	Improved β-cell function [44,45]
GSK3β inhibitors	Regulate glycogen metabolism by inhibiting glycogen synthase [48] Inhibit ER stress induced β-cell apoptosis [51] Improve β-cell function by preserving β-cell transcriptional factor Pdx1 [52]	Enhanced insulin signaling [53] Improved insulin resistance [53] Increased β-cell mass [54]	–
GPR40 agonists	Induce insulin secretion by modulating G protein-coupled receptor involved in free fatty acid [55]	Enhanced glucose-dependent insulin secretion with elevation of Ca^{2+} [57] Decreased glucose and insulin level [58]	Increased insulin secretion [59]

Jung KY, Kim KM, Lim S. Therapeutic Approaches for Preserving or Restoring Pancreatic β-Cell Function and Mass. Diabetes & Metabolism Journal. 2014;38(6):426-436. doi:10.4093/dmj.2014.38.6.426.


Thank
You