Overview of diabetes and the most effective control of sugar

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AT THE END OF THIS PRESENTATION……..

Epidemiology of Diabetes

Current thinking of aetiopathogenesis

Advances in management for best glycemic control

Challenges preventing attainment of good glycemic control

DISCLOSURES

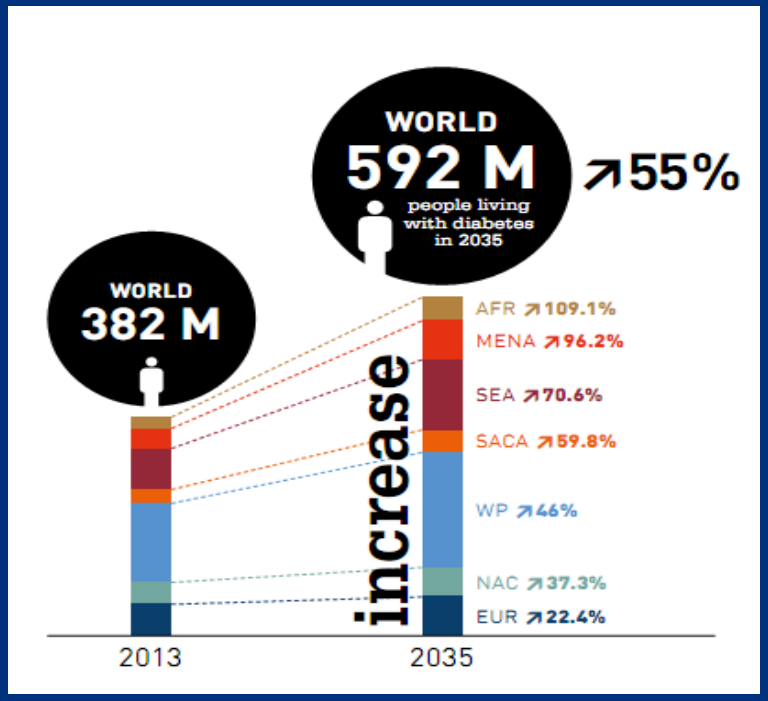
What is diabetes?

Metabolic disorder characterized by a defect in insulin secretion, insulin action resulting in hyperglycemia and associated with characteristic complications

- Type 1
- Type 2
- Gestational
- Other specific types

TYPE 2DIABETES, THE NEW EPIDEMIC

- 2010, 285 million people
- 2012 > 371 million people have DM
- By 2030, 552 million will have diabetes



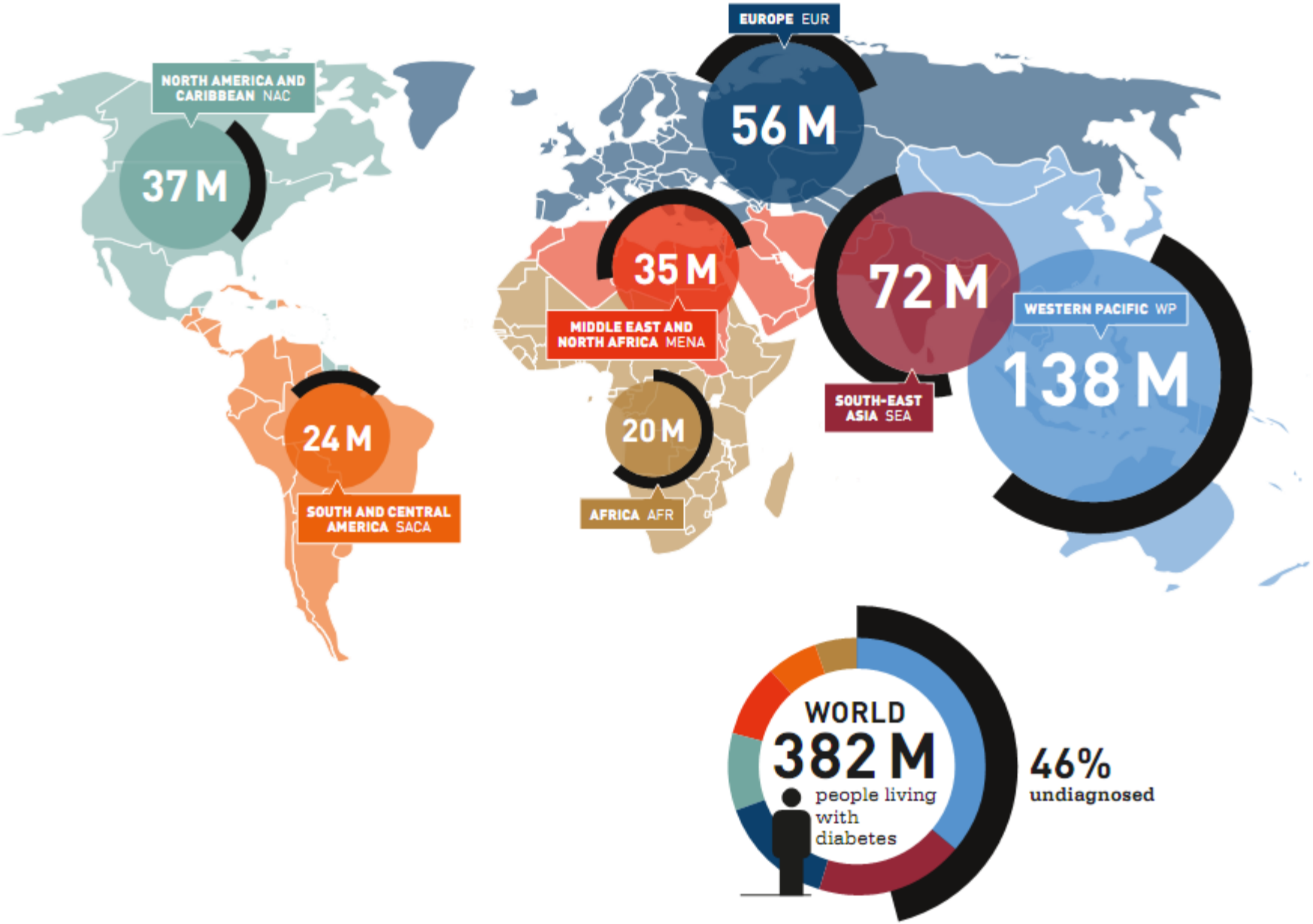
No country has been left out
Developing countries > developed countries
- Urbanization
- Westernization
- Sedentary life style
- Longevity

Double burden of disease

IDF ATLAS 5TH and 6th EDITION, 2011; Updated 2012

5

Number of people with diabetes by IDF Region, 2013



YOUNGER ONSET OF T2DM

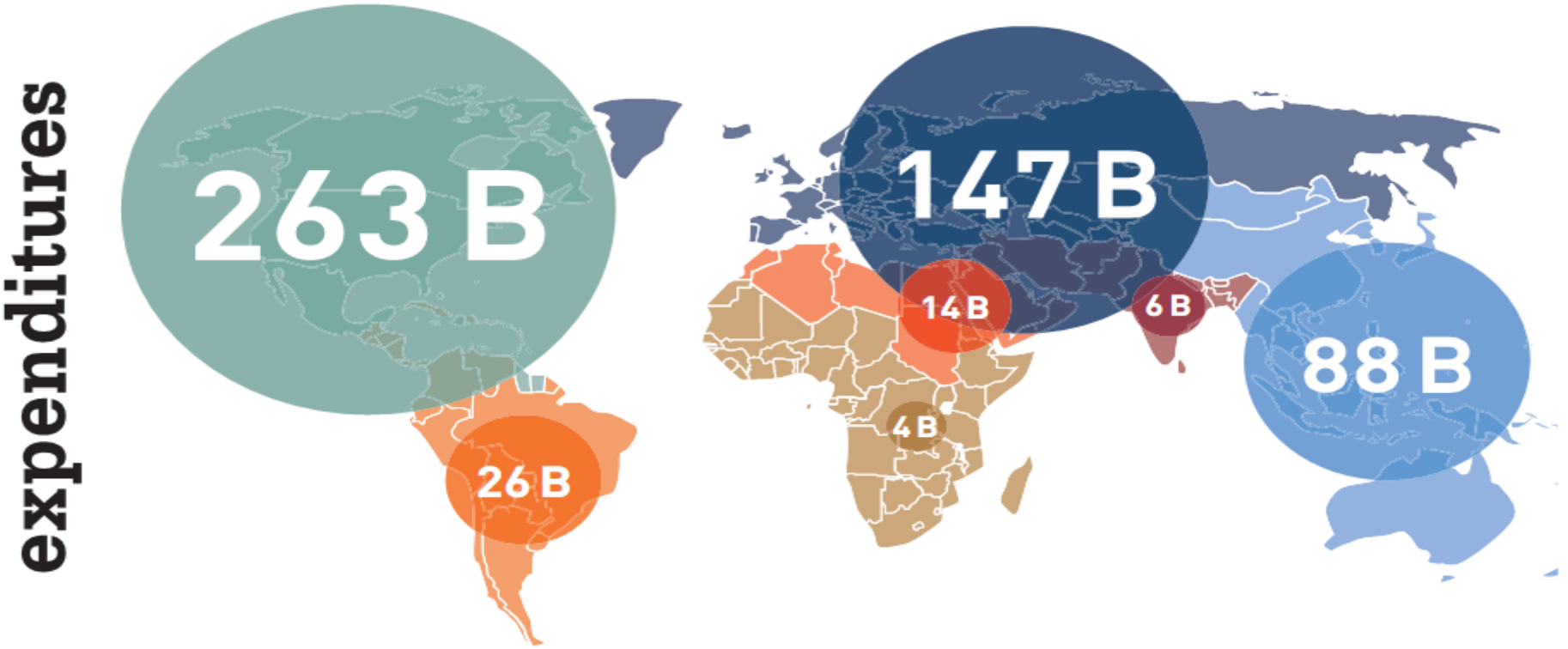
WHY?

- Sedentary lifestyle – TV, PC (“Nintendo-nization”)
- Energy dense food

Socioeconomic and Public health impact will be greater

- Premature morbidity/mortality
- Prolong exposure of the disease
  - Full gamut of complications in future

ECONOMIC BURDEN OF DIABETES



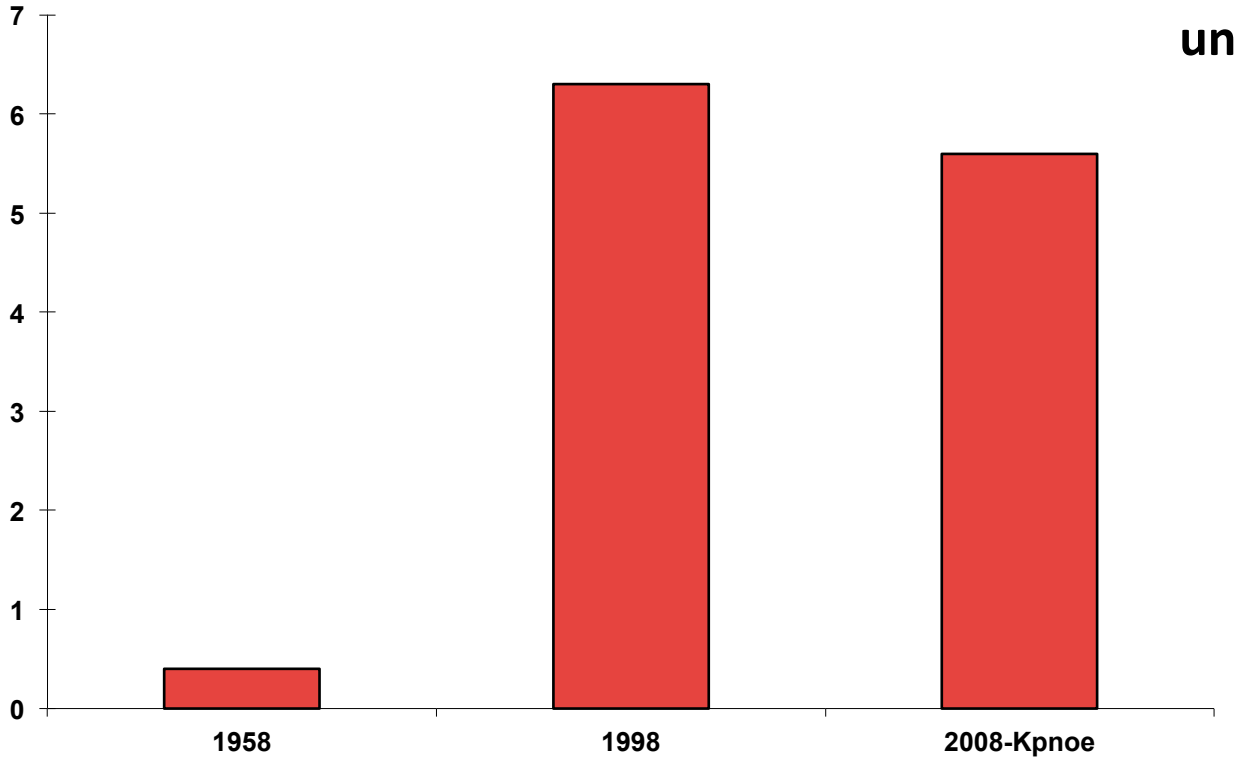
Health expenditure (USD) due to diabetes (20-79 years), 2013

4.8 million people **died** and **471 billion USD** were **spent** due to diabetes in 2012.

HEALTHCARE EXPENDITURES AND DEATHS PER 1,000 DUE TO DIABETES BY INCOME GROUP

Diabetes on the Rise in Ghana

73% undiagnosed



Dodu SRA, West Africa Med J, 1958

Amoah AG, Owusu SK, Adjei S. Diab. Res. and Clin. Pract. 2002

AETIOPATHOGENESIS OF HYPERGLYCEMIA

Role of insulin

CARBOHYDRATE

- Increases glycogen synthesis
- Decreases gluconeogenesis and glycogenolysis
- Increases glucose uptake in cells

FAT

- Clears triglyceride rich chylomicrons from blood
- Increases lipid synthesis in fat cells by re-esterification
- Inhibits lipolysis

PROTEIN

- Increases uptake of amino acids by cells
- Inhibits protein breakdown

INSULIN RESISTANCE in T2DM

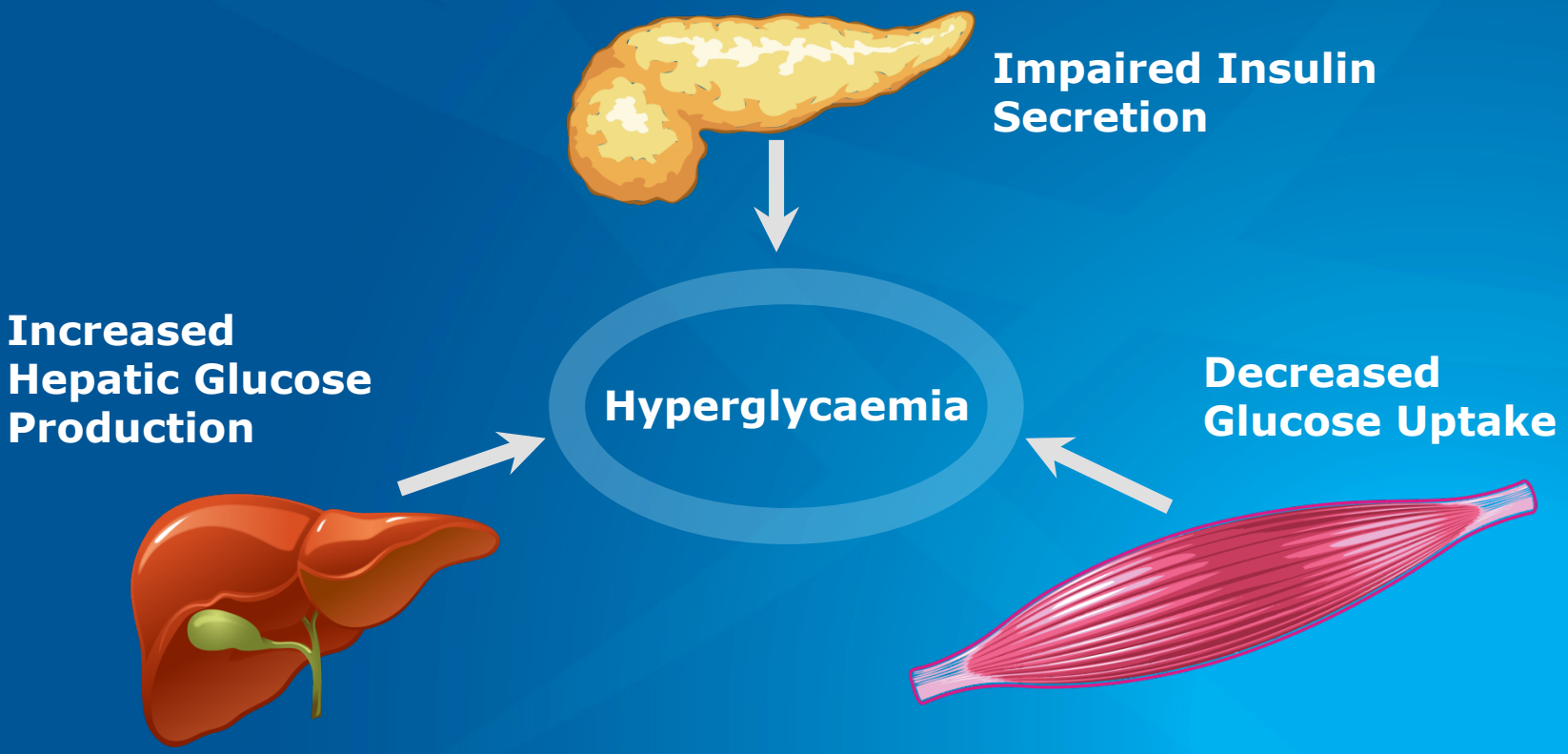
Insulin resistance(IR): A state in which a given level of insulin produces a less than expected biological effect.

Carbohydrate, Fat, protein

METFORMIN, PIOGLITAZONE

Pathogenesis of type 2 diabetes

- The triumvirate: Insulin resistance in muscle and liver and impaired insulin secretion represent the core defects in type 2 diabetes



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

Insulin secretion

Basal insulin secretion- rapid pulsatile release of insulin from pancreas

Stimulated insulin secretion- e.g. postprandially,

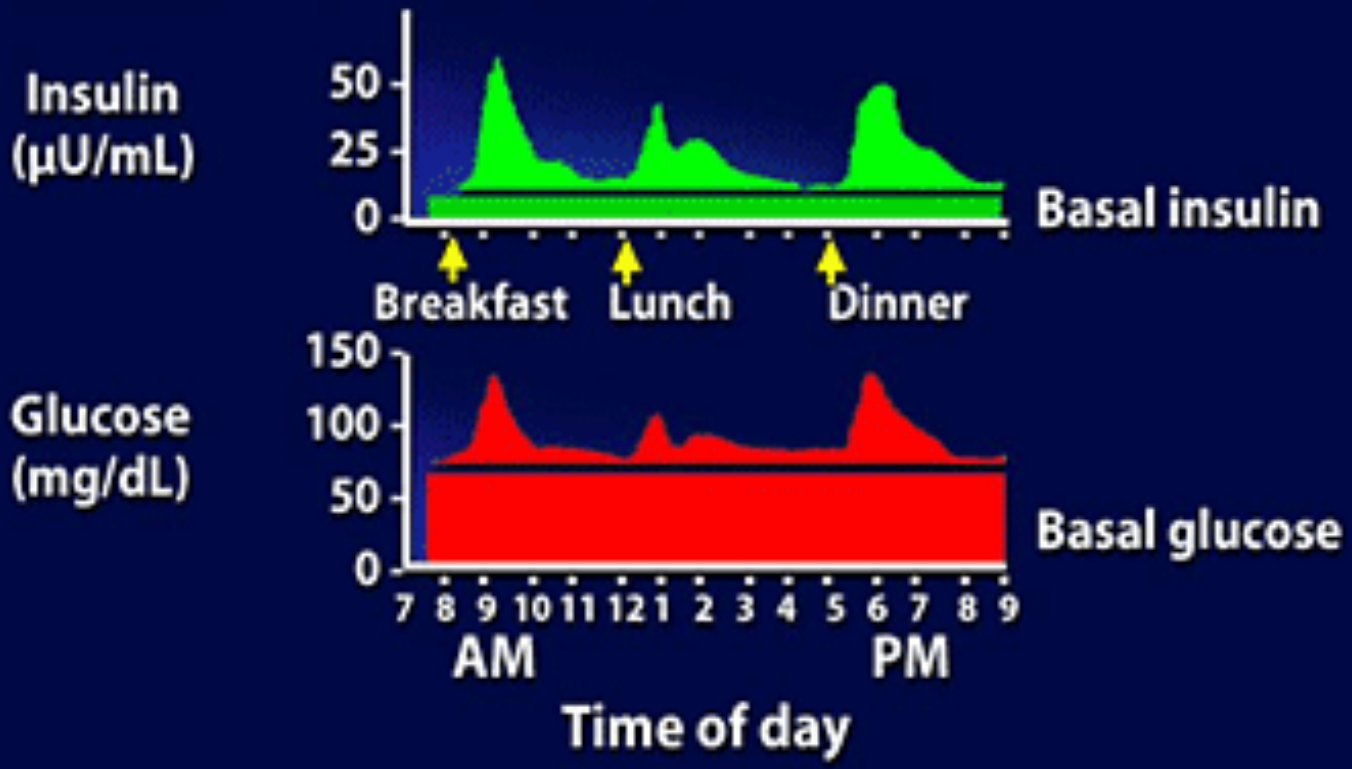
Phase 1

- **Very rapid occurs within 10 mins after eating, preformed**

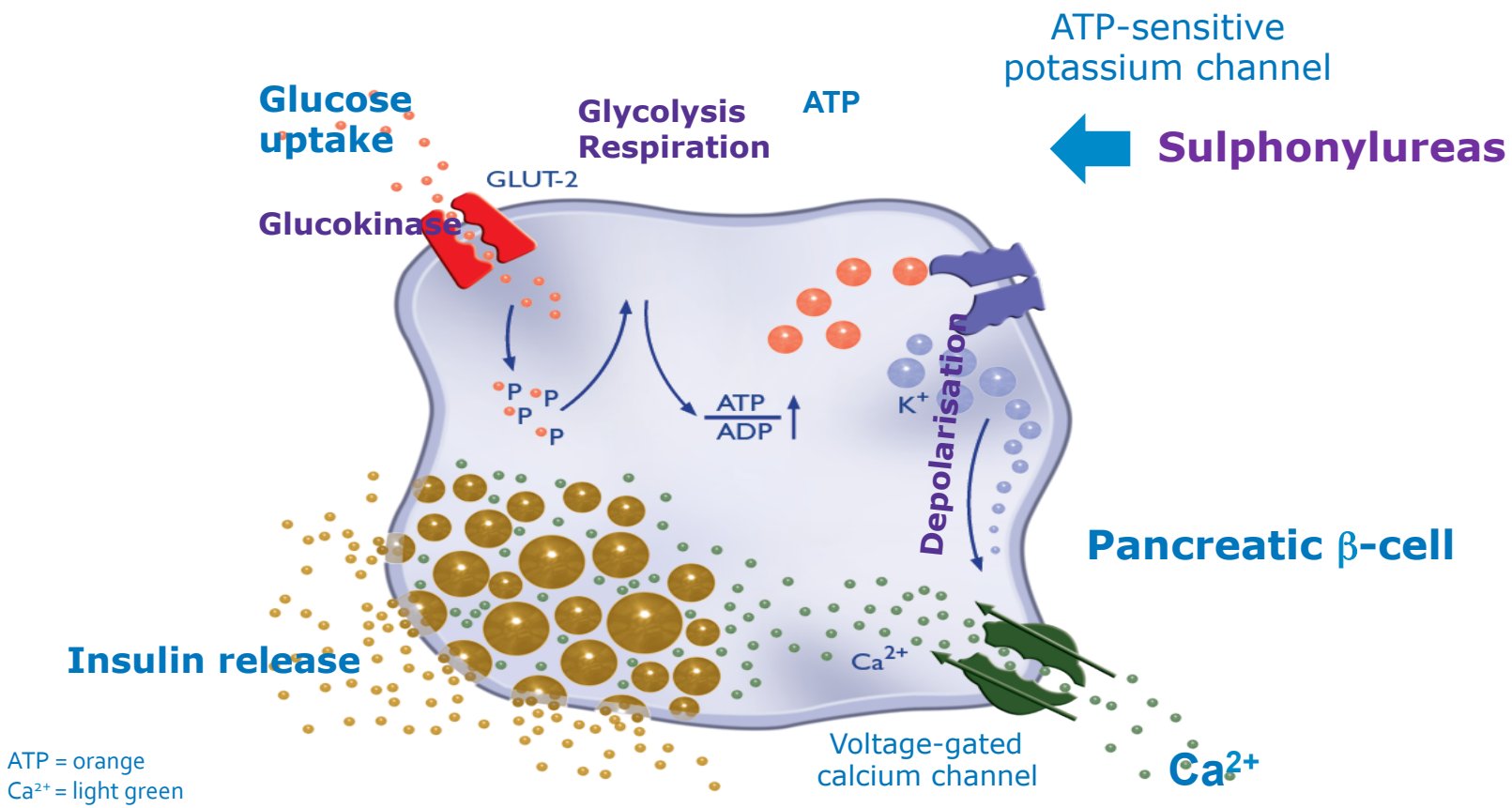
Phase 2

- **New insulin is formed, slower, lasts longer**

Physiologic Insulin Secretion: 24-Hour Profile



INSULIN SECRETION



1. Gallwitz B, Haring H-U. Diabetes Obes Metab. 2010;12:1-11. 2. Schuit FC, et al. Diabetes .2001;50:1-11.
3. Krentz AJ, Bailey CJ. Drugs. 2005;65:385-411.

Insulin secretory defect in T2DM

Basal insulin secretion

- Frequency and amplitude is reduced

Stimulated insulin secretion

- 1st phase often absent, earliest pathology in T2DM
- 2nd phase insulin secretion is impaired

- SULPHONYLUREA & MEGLITINIDE

From triumvirate to ominous octet

In addition to the well-recognised triad, others have been proven

These multiple defects are referred to as the "ominous octet"

De Fronzo RA. Am J Med. 2010;123:S38-S48.

4. Disharmonious quartet (fat cells)

Fat cells are insulin resistant

- Elevated plasma free fatty acid concentrations and increased levels of toxic lipid metabolites, and thus lipotoxicity

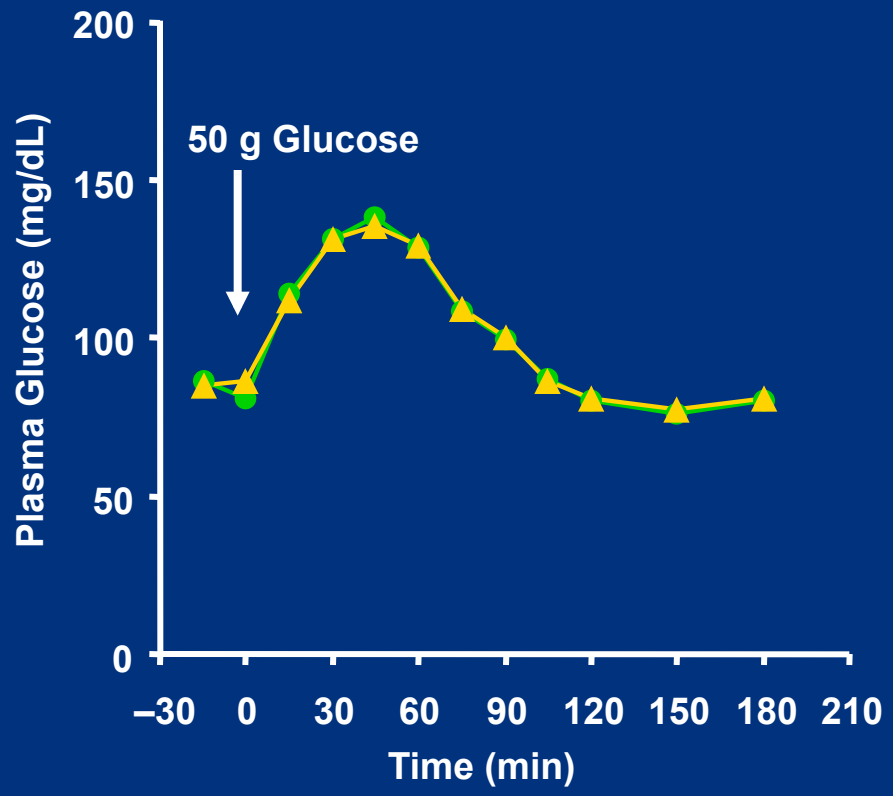
- These toxic lipid metabolites worsen insulin resistance in muscle and liver and promote beta-cell failure

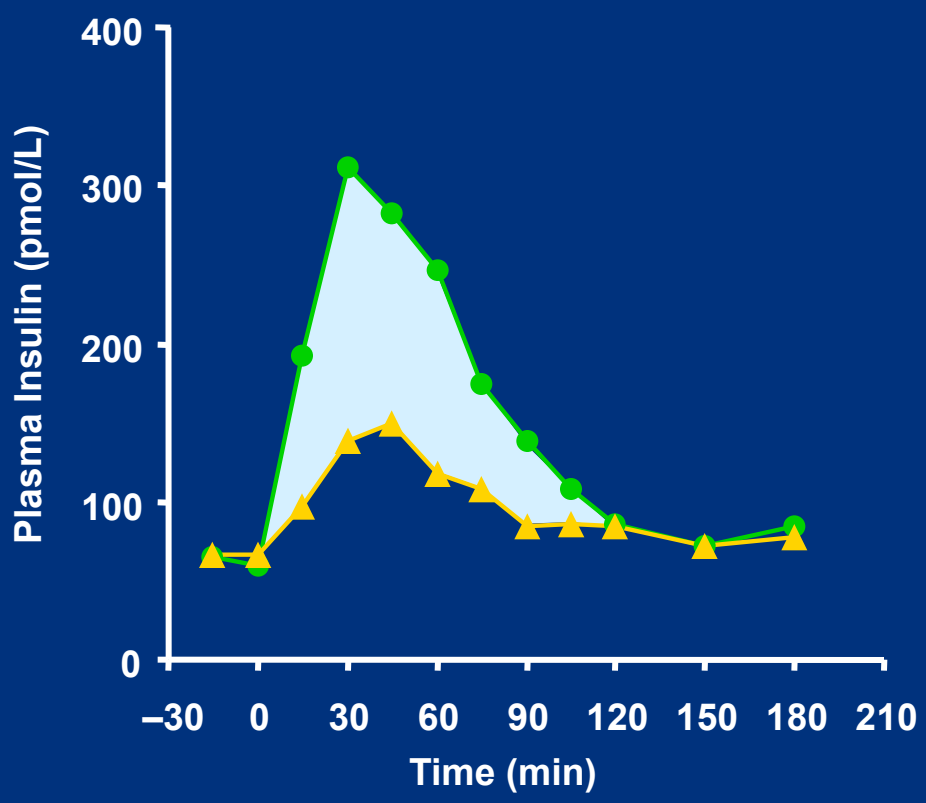
- METFORMIN, PIOGLITAZONE

De Fronzo RA. Am J Med. 2010;123:S38-S48.

5.INCRETIN EFFECT

Oral Glucose Tolerance Test and Matched IV Infusion





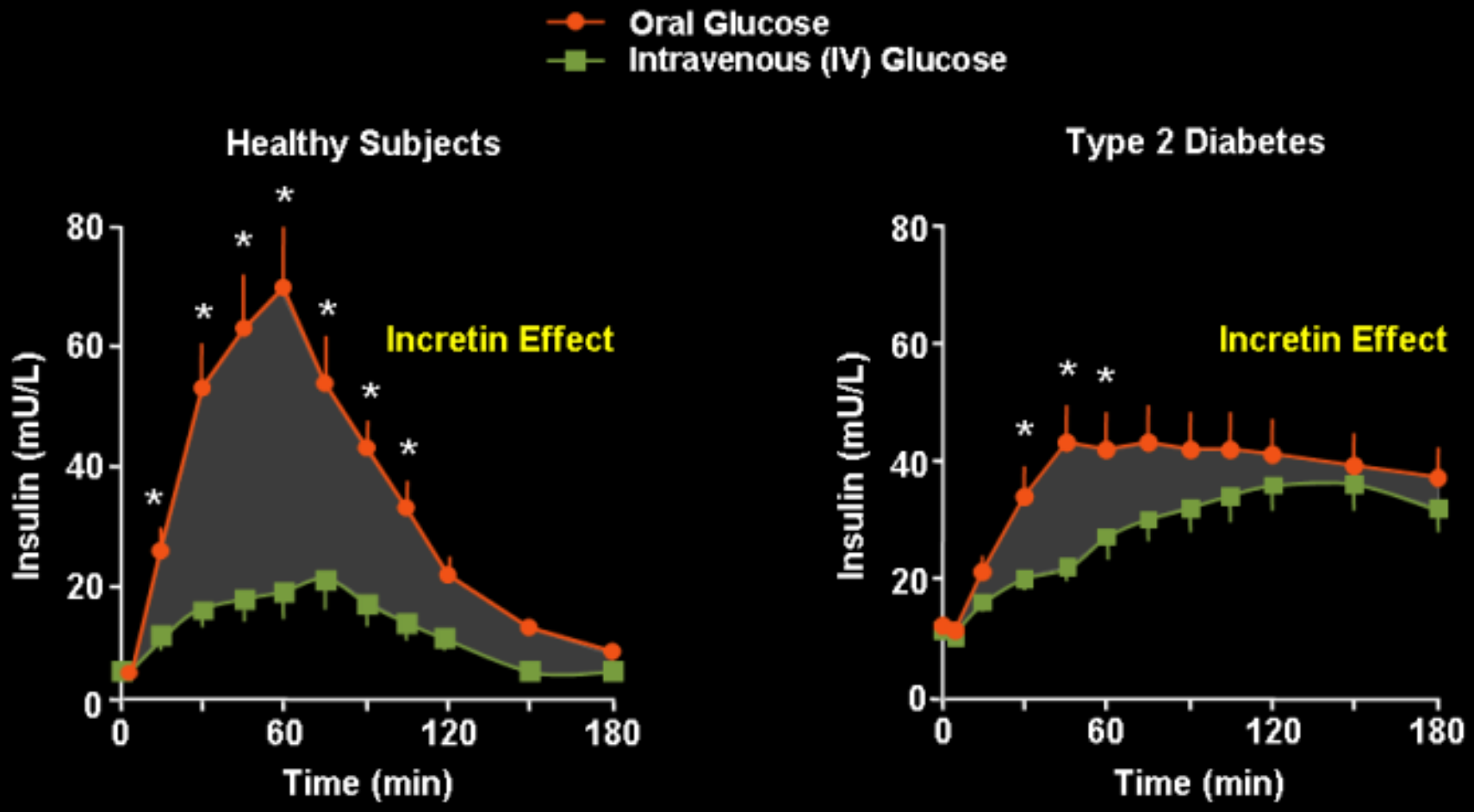
N=6

● Oral ▲ IV

IV=intravenous

Adapted from Nauck MA, et al. *J Clin Endocrinol Metab*. 1986; 63: 492–498.

The Incretin Effect Is Reduced in Type 2 Diabetes



N = 22; Mean (SE); *$P \leq 0.05$

Data from Nauck M, et al. *Diabetologia*. 1986;29:46-52

Definition of Incretins

"Gut-derived factors that increase glucose-stimulated insulin secretion"

In·cre·tin

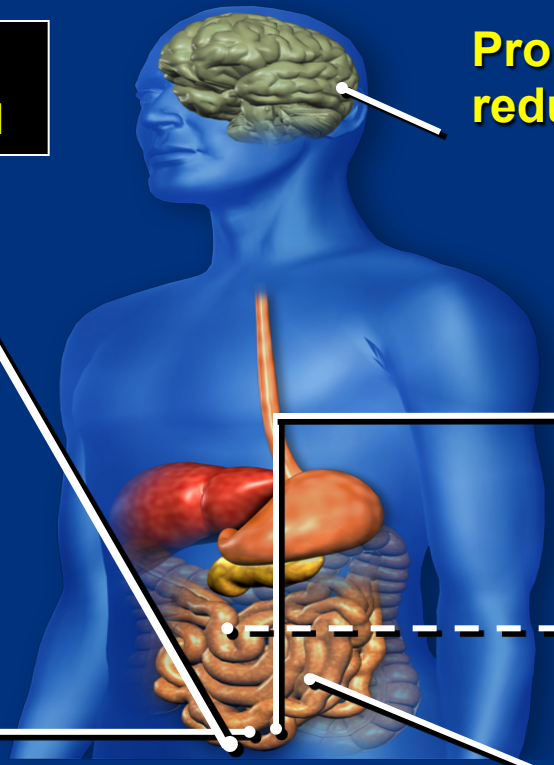
Intestine Secretion Insulin

Creutzfeldt. *Diabetologia*. 1985;28:5645.

GLP 1- GLUCAGON LIKE PEPTIDE-1

GIP- GLUCOSE INSULININOTROPHIC PEPTIDE

GLP-1 Modulates Numerous Functions in Humans



GLP-1: Secreted upon the ingestion of food

GLP ANALOGUES
DPP4 INHIBITORS

Promotes satiety and reduces appetite

Alpha cells:
↓ Postprandial glucagon secretion

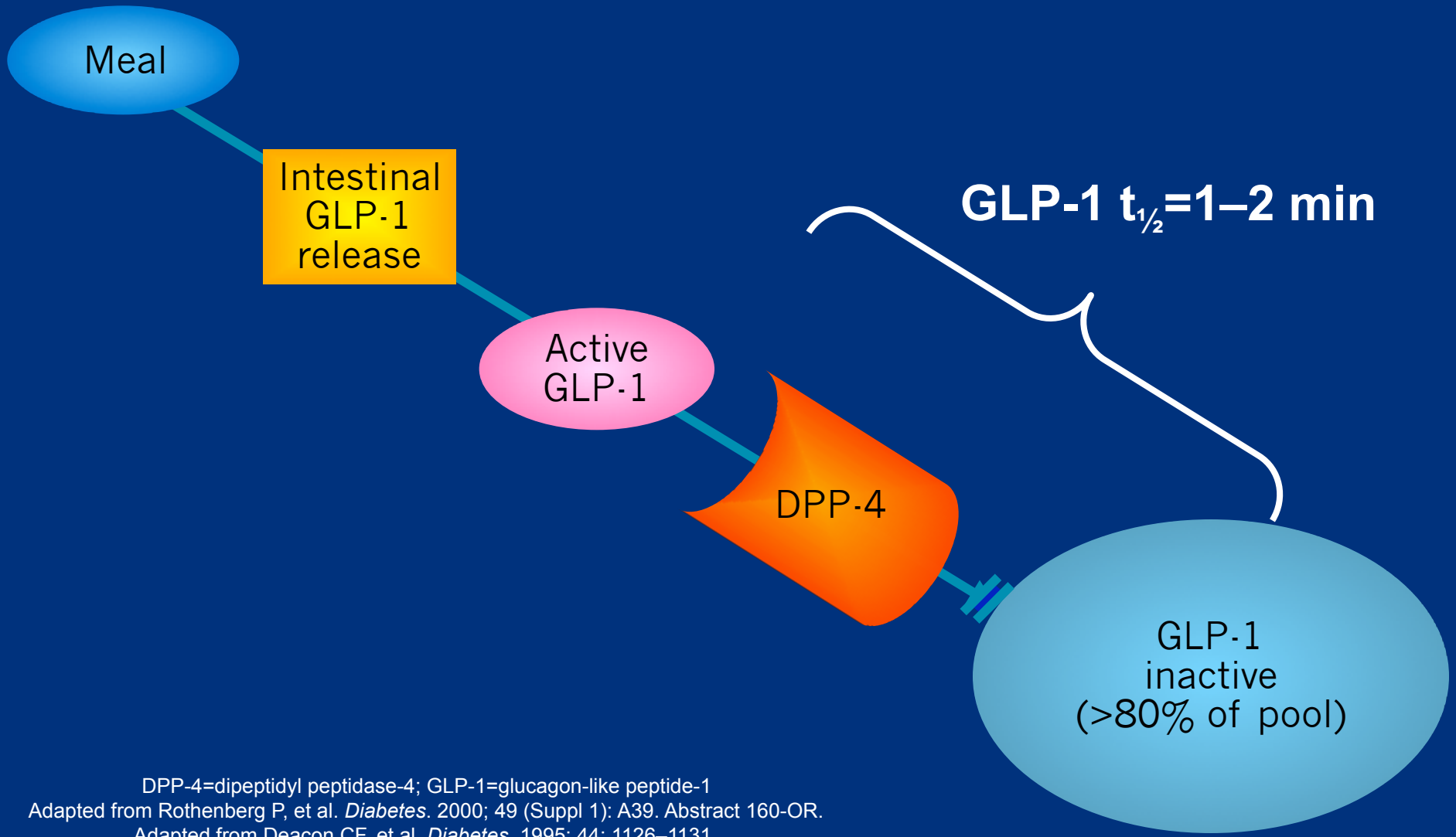
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

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

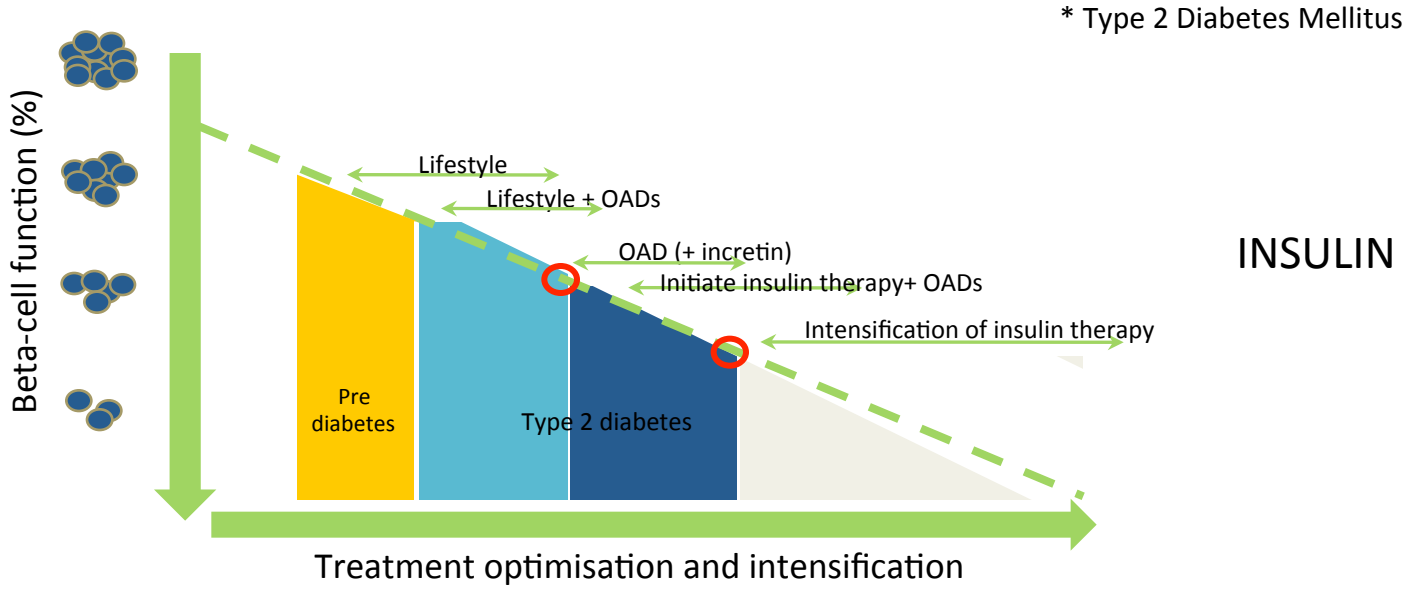
Inhibition of DPP-4 Increases Active GLP-1



DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1
Adapted from Rothenberg P, et al. *Diabetes*. 2000; 49 (Suppl 1): A39. Abstract 160-OR.
Adapted from Deacon CF, et al. *Diabetes*. 1995; 44: 1126–1131.

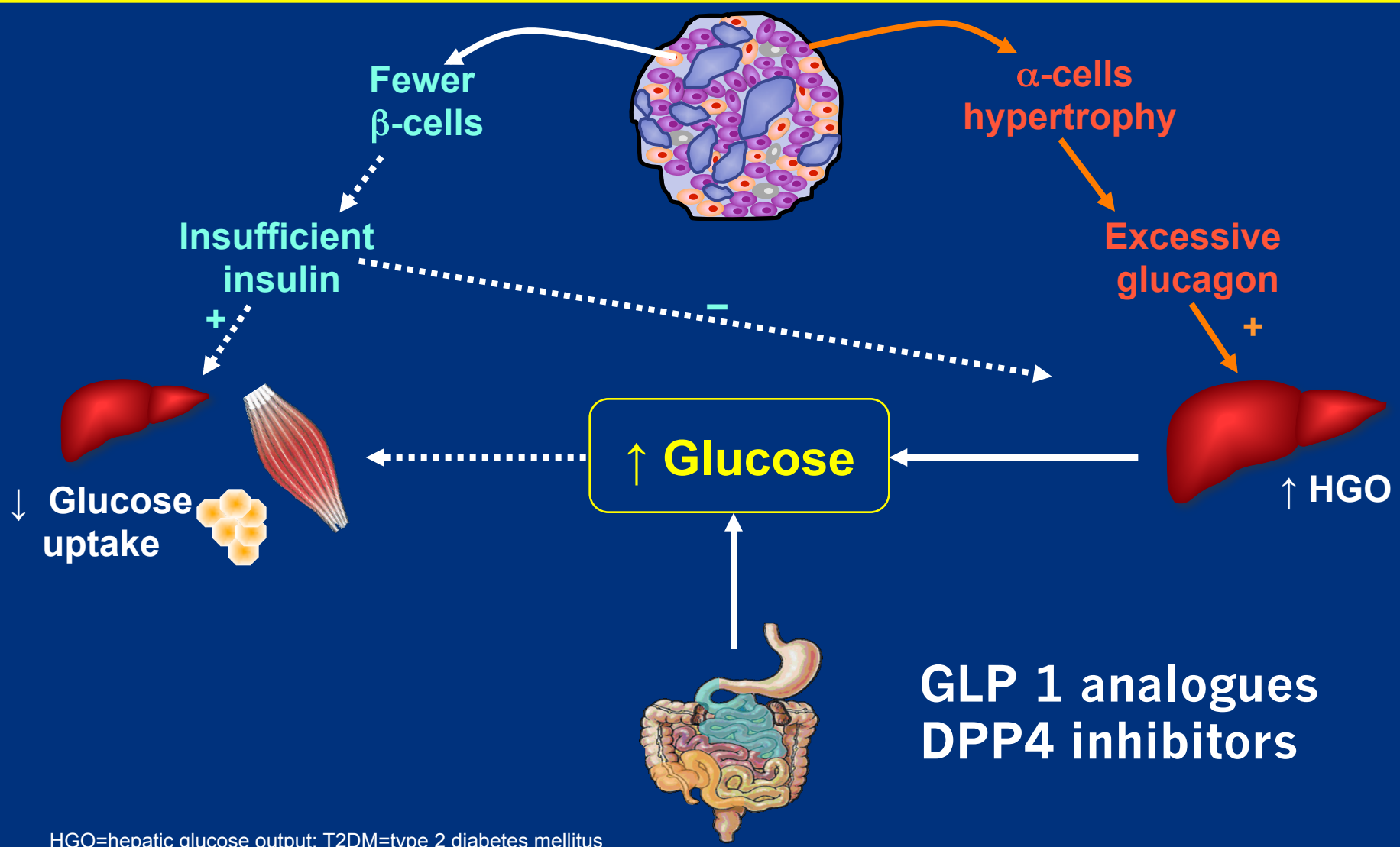
Progressive loss of ß-cell function

- T2DM progression is characterised by decline in ß-cell function and worsening insulin resistance[1]



1. Fonseca VA. Br J Diab Vasc Dis 2008;8:S3; 2. Nathan DM, et al. Diabetes Care 2009;32:193-203; 3. Shimoda M, et al. Diabetologia 2011; 54:1098-1108; 4. Inzucchi et al. Diabetes Care 2012; Published online 19Apr2012; 5. IDF Treatment Algorithm. International Diabetes Federation 2011

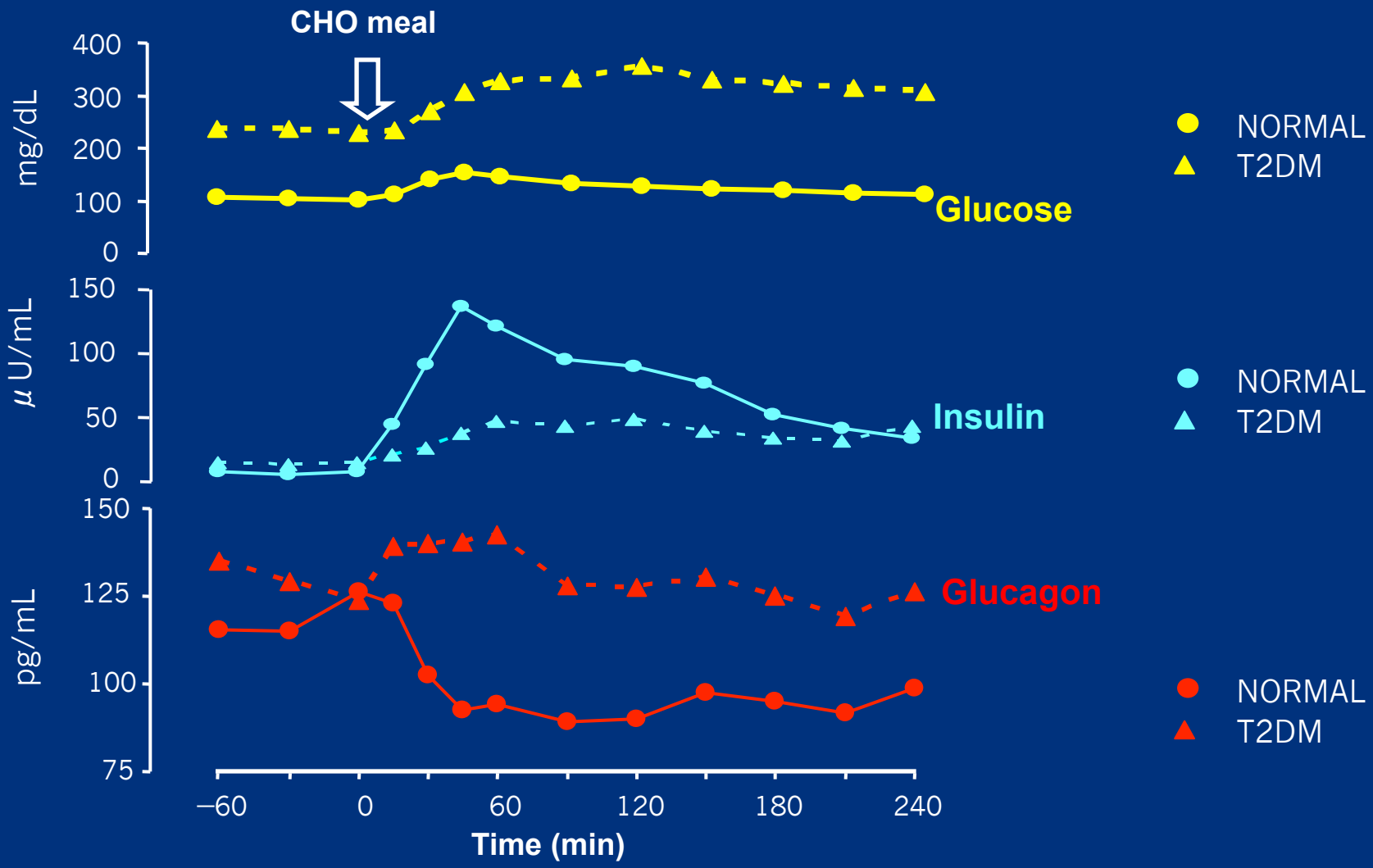
6. Pancreatic Islet Dysfunction in T2DM



HGO=hepatic glucose output; T2DM=type 2 diabetes mellitus

Adapted from Ohneda A, et al. *J Clin Endocrinol Metab.* 1978; 46: 504–510; Gomis R, et al. *Diabetes Res Clin Pract*. 1989; 6: 191–198.

Hyperglucagoneamia



CHO=carbohydrate; NGT=normal glucose tolerance; T2DM=type 2 diabetes mellitus
Adapted from Müller WA, et al. *N Engl J Med*. 1970; 283: 109–115.

7. INCREASED RENAL ABSORPTION OF GLUCOSE

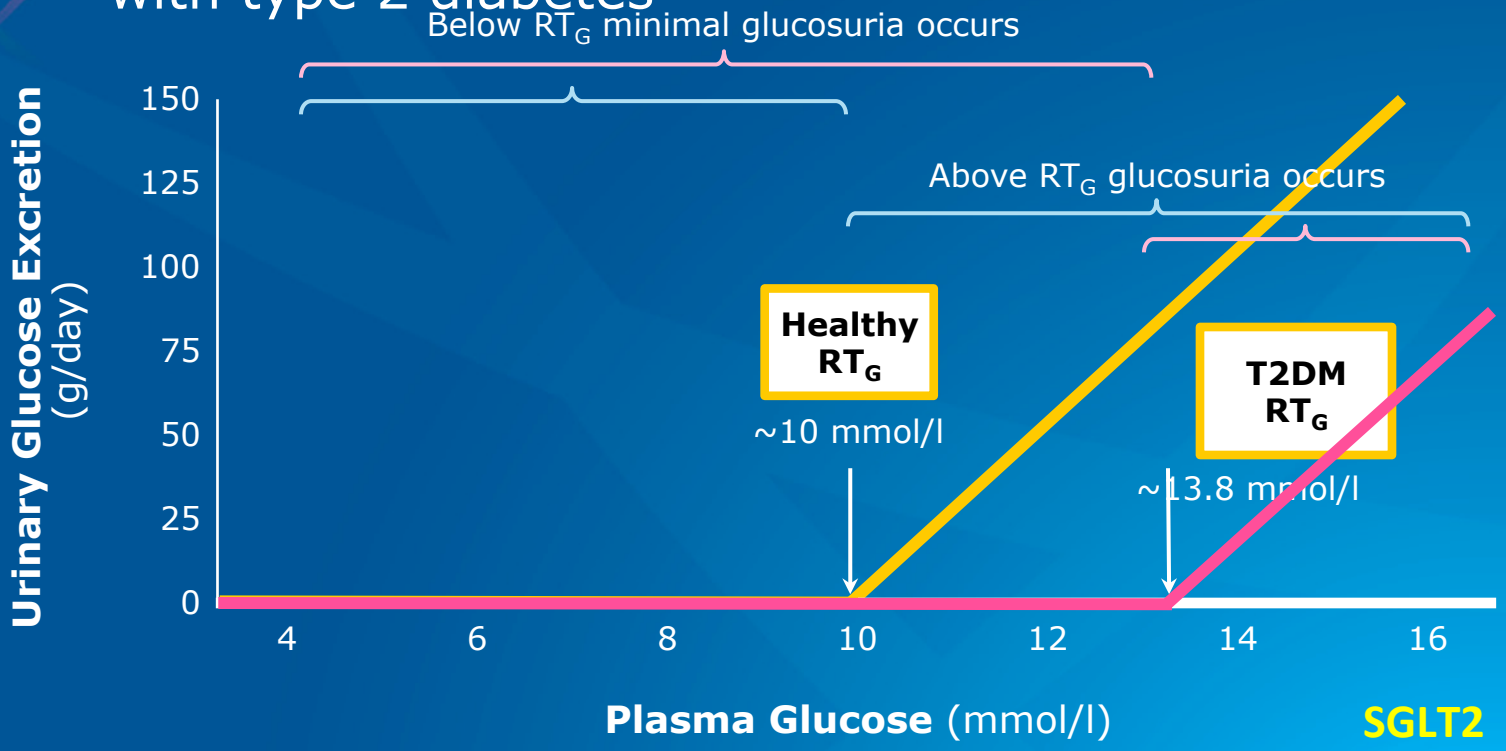
180g of glucose is filtered and reabsorbed by the kidneys daily

90% by sodium glucose co-transporter 2 (SGLT2)

10% of this by sodium glucose co-transporter 1 (SGLT 1)

Septicidal septet (the kidney)

The renal glucose threhold (RT_G) is increased in subjects with type 2 diabetes



SGLT2 INHIBITORS

- Renal glucose reabsorption is increased in diabetes, which could contribute to further increasing plasma glucose levels

RT_G, renal threshold for glucose excretion.

Polidori D et al. 2010. Abstract 2186-PO. American Diabetes Association. June 25-29, 2010; Orlando, Florida.
Polidori D et al. 2010. Presented at: European Association for the Study of Diabetes. September 20-24, 2010; Stockholm, Sweden.
Nair S, Wilding JPH. J Clin Endocrinol Metab.2010;95(1):34-42

8. Ominous octet (the brain)

- Satiety center dysfunction.

??? Reduced GLP levels

Adipokines

- Obese individuals, both diabetic and non-diabetic, are more insulin resistant with hyperinsulineamia.

- Despite hyperinsulinaemia in IGT, obese Insulin resistant people continue eat more, indicating that the appetite centres must be resistant to insulin

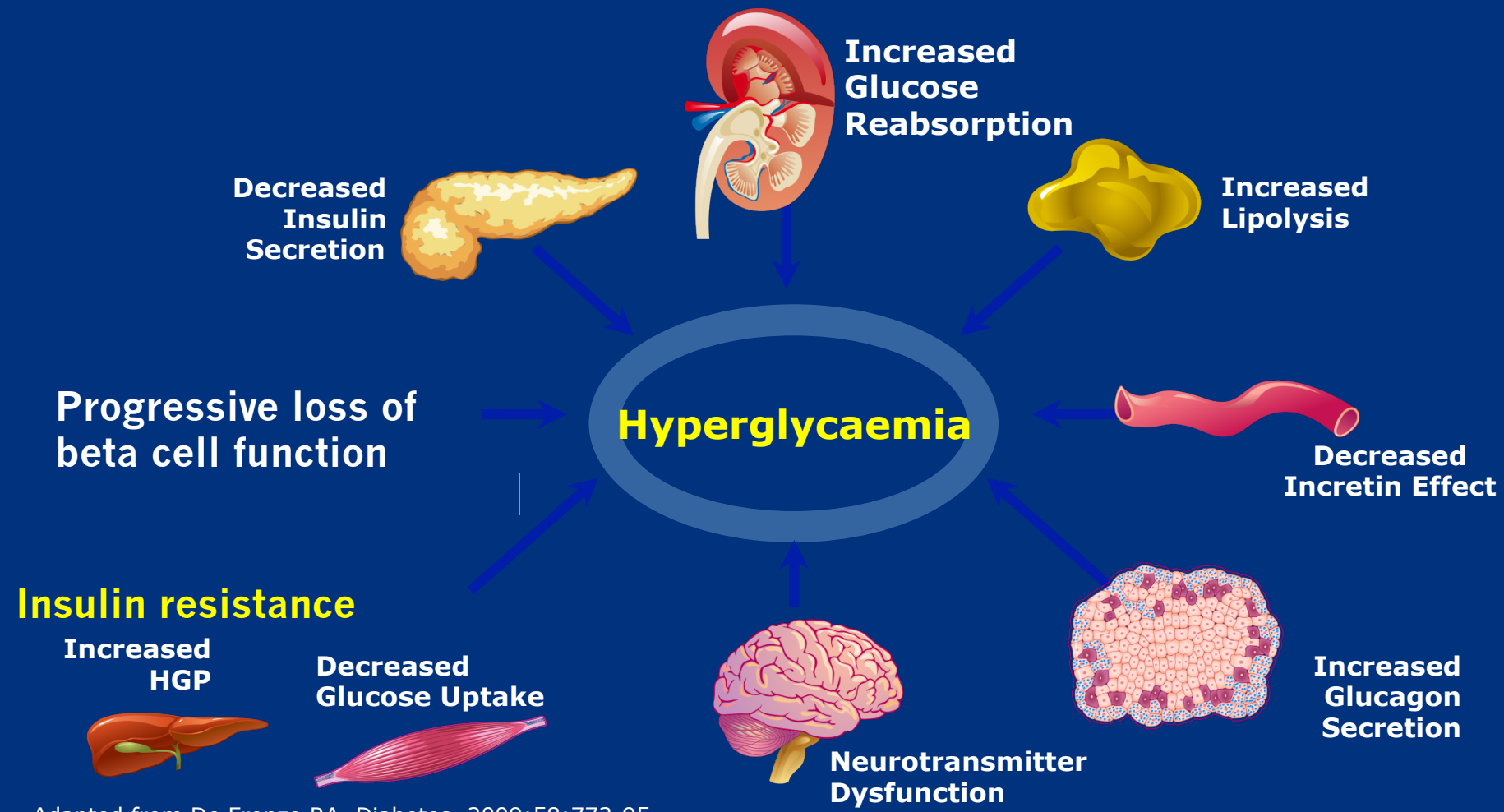
??metformin, pioglitazone

??GLP1 Analogues, DPP4 inhibitors

De Fronzo RA. Am J Med .2010;123:S38-S48.

Pathophysiology of T2DM summary

- Multiple defects contribute to the progression of type 2 diabetes mellitus

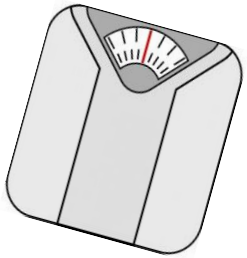


Adapted from De Fronzo RA. Diabetes. 2009;58:773-95.

ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options: Lifestyle**

  - **Weight optimization**



  - **Healthy diet**

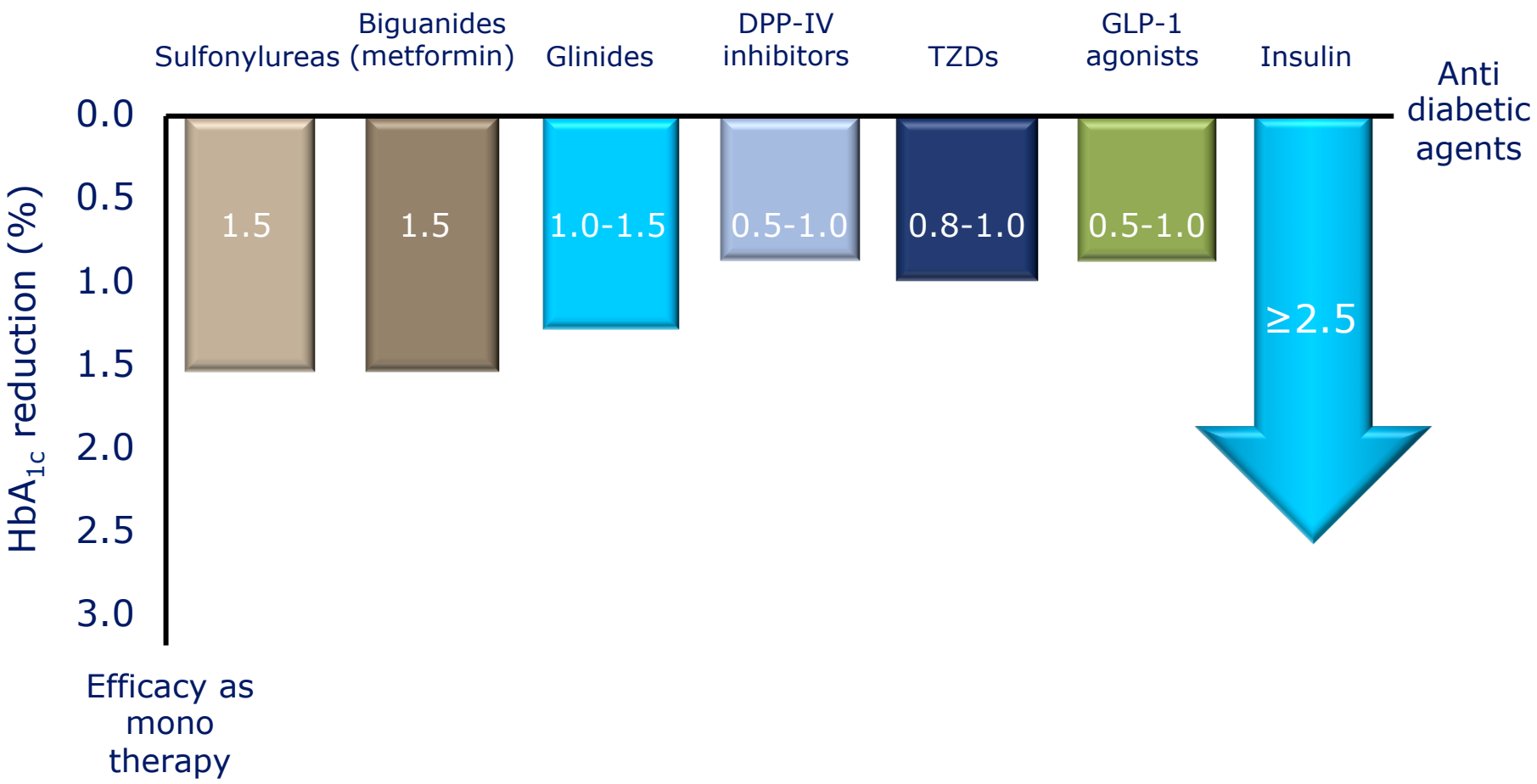
  - **Increased activity level**

Diabetes Care 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596

Classes of diabetes medications

1. Insulin (1920)
2. Biguanides (1950s)
3. Sulfonylureas (1950s)
4. Thiazolidinediones (TZDs) (1980s, 1990s)
5. a- glucosidase inhibitors (1980s, 1990s)
6. Dipeptidyl peptidase 4 inhibitors (2007, 2008)
7. Meglitinide derivatives (1980s)
8. Amylininomimetics (2005)
9. Glucagon like peptide -1 analogues (2005)
10. Bile acid sequesterants(2008)
11. Dopamine agonists (2009)
12. Selective sodium glucose transporter2 inhibitors(2013)

HBA1c reduction of DM drugs



Adapted from Nathan DM. N Engl J Med. 2007;356:437-40
and Nathan et al. Diabetes Care. 2009;32:193-203

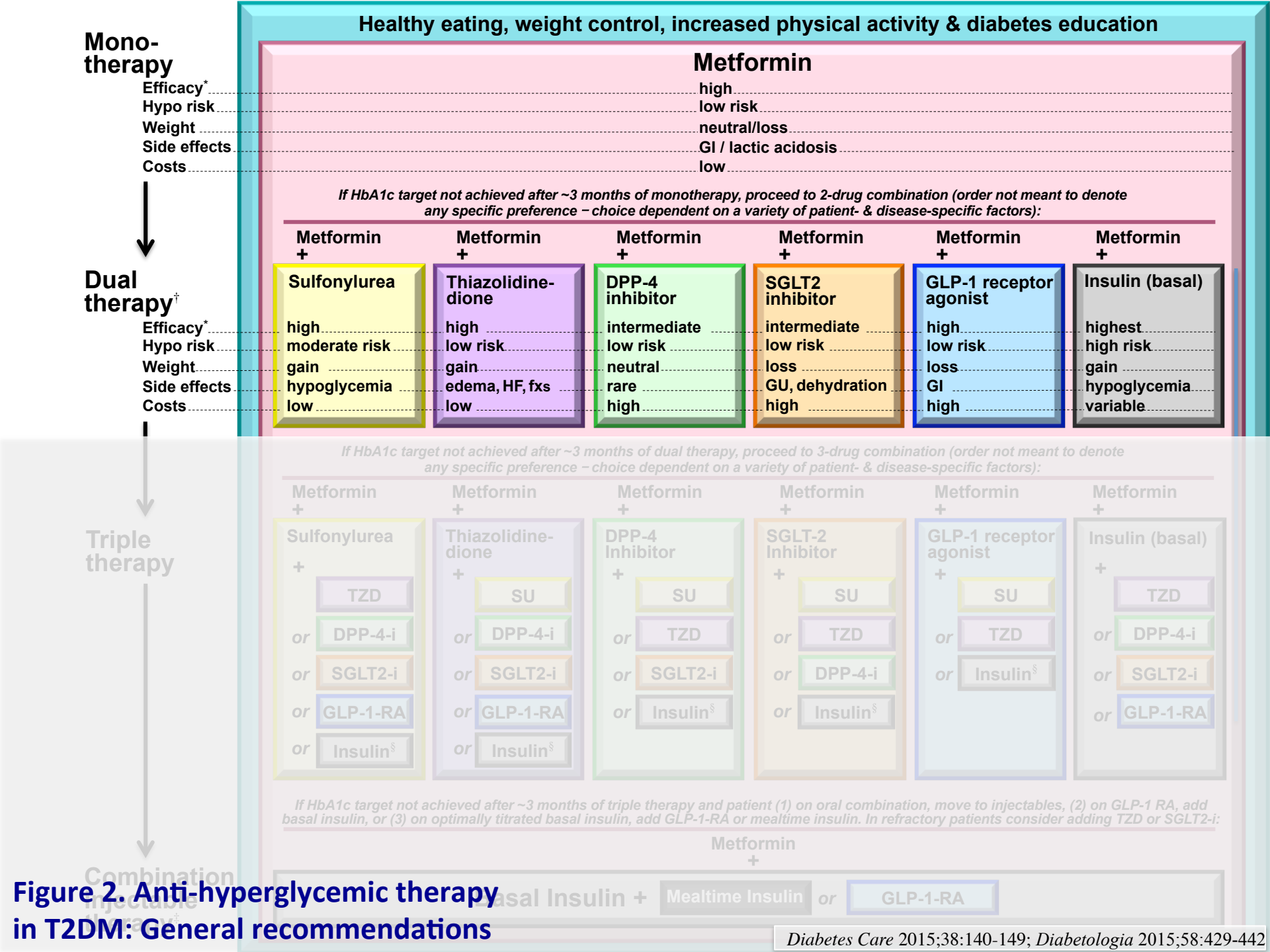
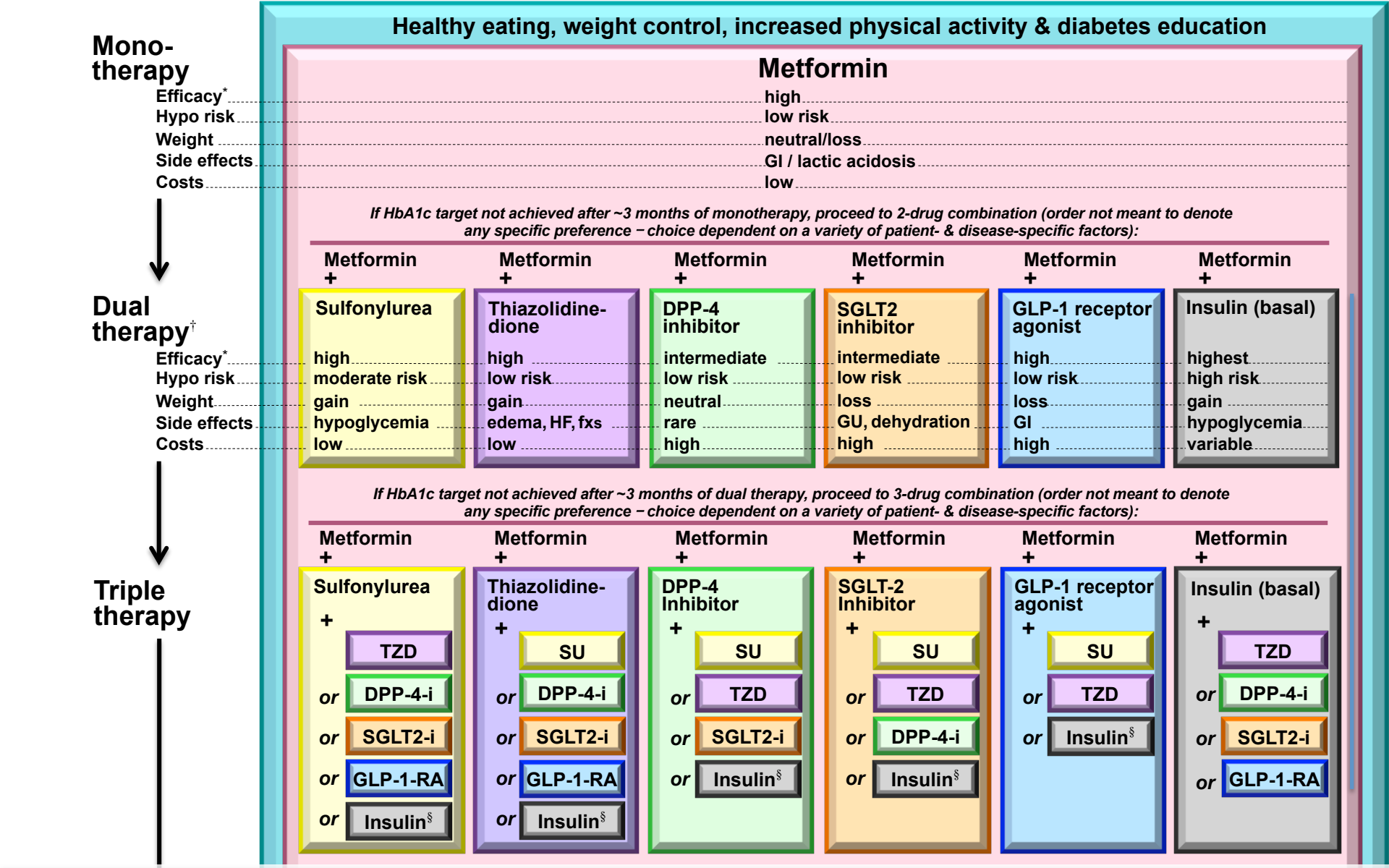


Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations

Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442



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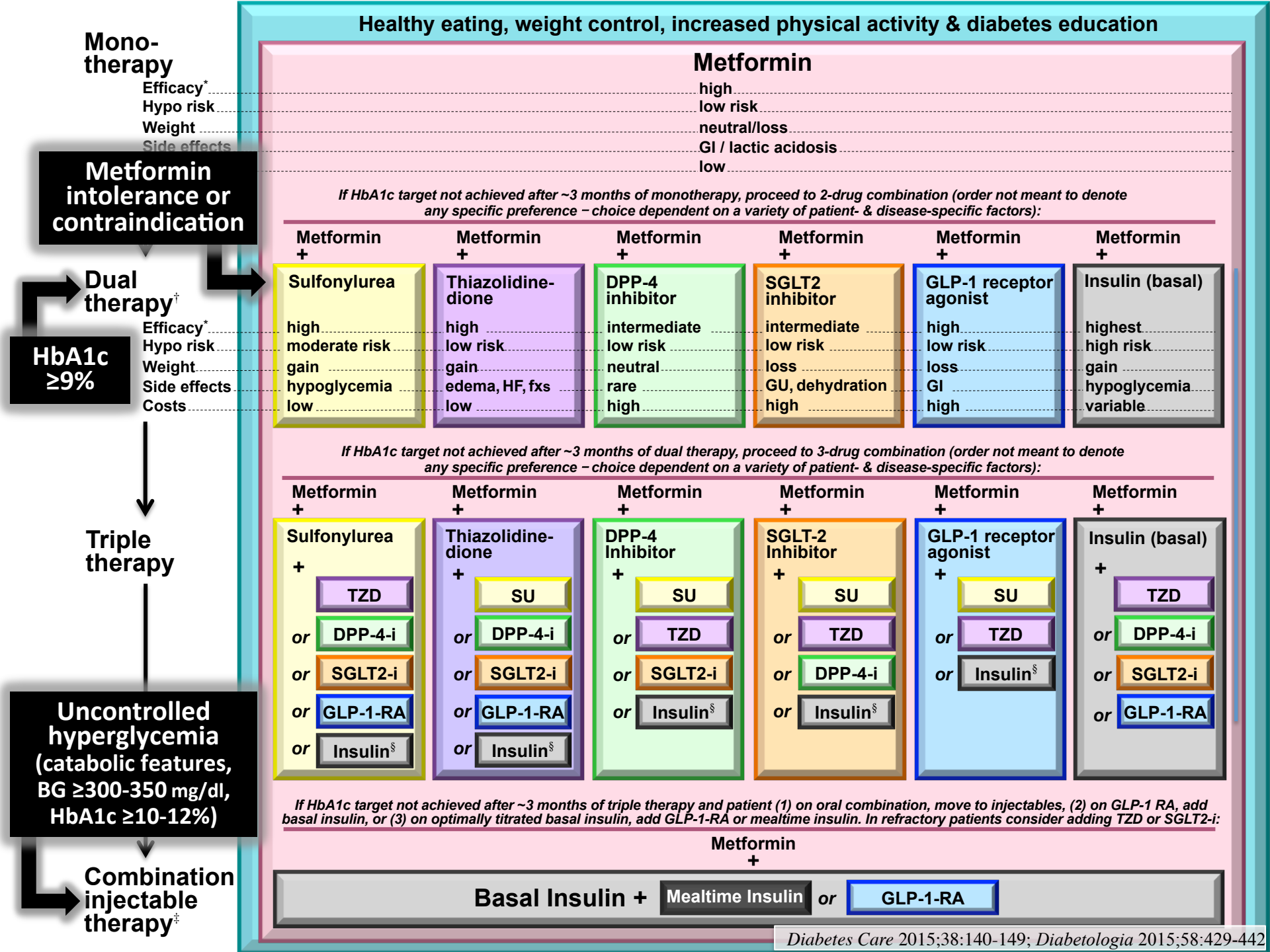
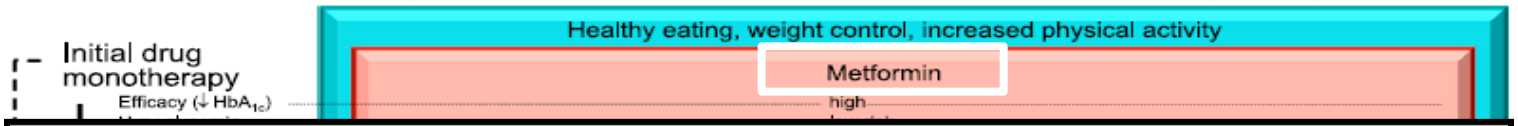


Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

Antihyperglycaemic therapy in type 2 diabetes : general recommendations



In choosing your 2nd option, your clinical judgement considering:

Risk of Weight gain

Risk of Hypoglycaemia

Severity of co-morbidities

Long-term safety of new agents

Cost of medications to the patient

Predominant pathophysiologic defect

Metformin

596

Poor glucose control is associated with increased risk

Microvascular

Retinopathy and blindness

After 15 years:

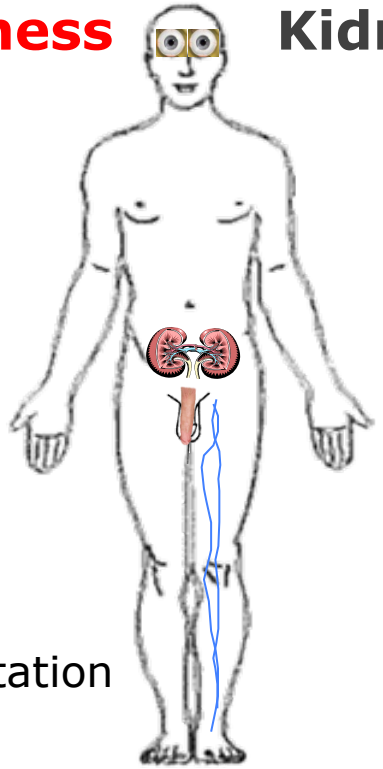
- ~40% develop retinopathy
- 2% become blind

Erectile dysfunction

- Up to 75% of male patients

Diabetic foot disease

- 15-40 times more likely to require lower limb amputation



Kidney disease (nephropathy)

- Up to ~1/3 of patients

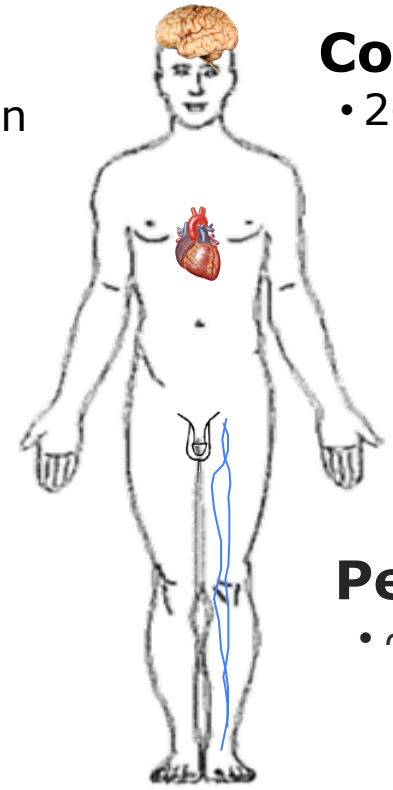
Neuropathy

- Up to 50% of patients

Poor glucose control is associated with increased risk

Macrovascular

Stroke
- Occur twice as often



Coronary heart disease
- 2-4 times more likely

Peripheral vascular disease
- ~1/3 of patients

THE EVIDENCE FOR GOOD GLYCEMIC CONTROL

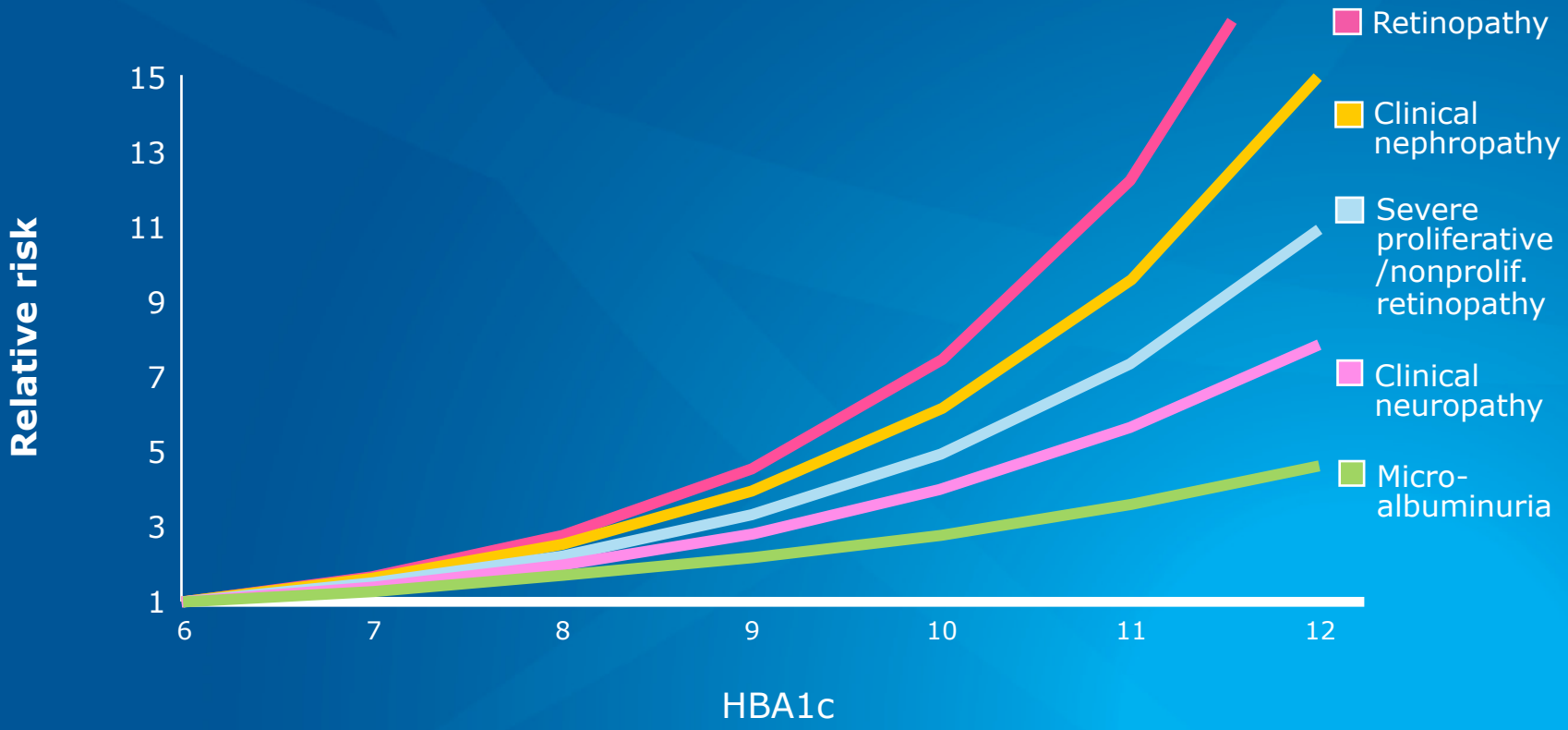
Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions and Complications (EDIC) for T1DM

UK Prospective Diabetes Study (UKPDS) for T2DM*

- **Newly diagnosed patients were recruited in the study, intensive vrs conventional**

Relationship between glycaemic control and progression of diabetic complications (DCCT)

DCCT: relative risk of progression of diabetic complications by mean HbA1c



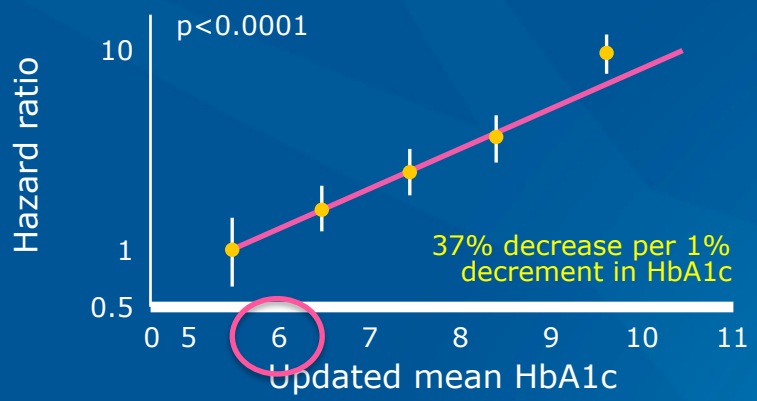
NB: stylised graph in which the RR of each complication has been set to 1.0 at an HbA1c of 6%

Skyler JS. Endocrin Metab Clin N Am. 1996;25:243-54.

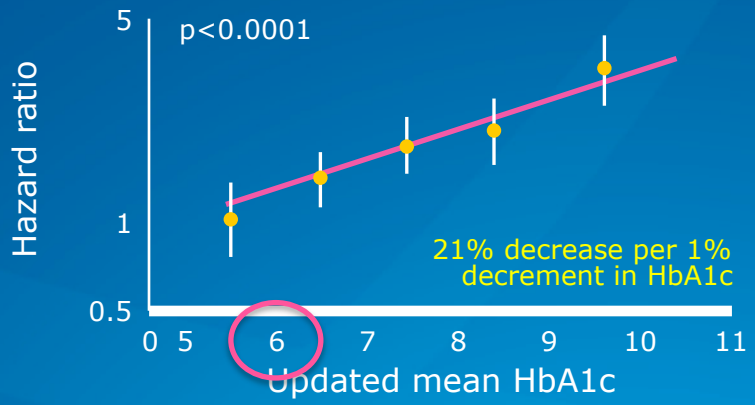
UKPDS

There is a clear epidemiological relationship between HbA_{1c} level and complications in type 2 diabetes,

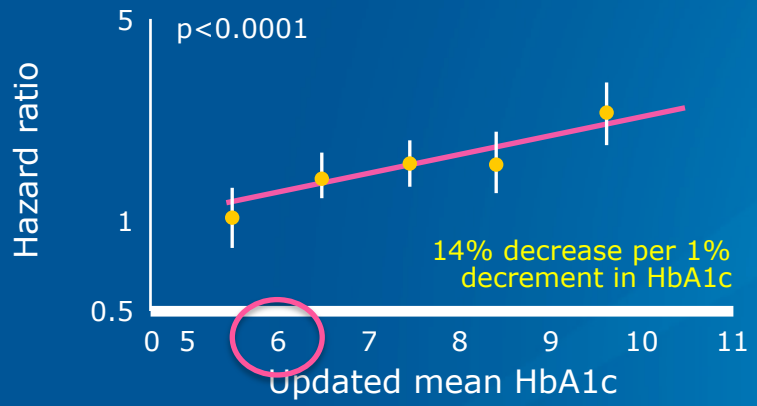
Microvascular endpoints



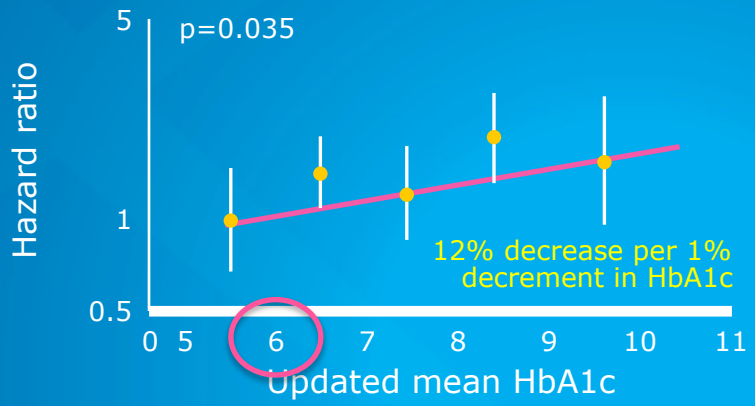
Diabetes-related deaths



Fatal and non-fatal myocardial infarction



Fatal and non-fatal stroke



Stratton IM, et al. BMJ. 2000;321:405-12.

WHAT HAPPENS YEARS AFTER BEING IN THE INTENSIVE ARM?

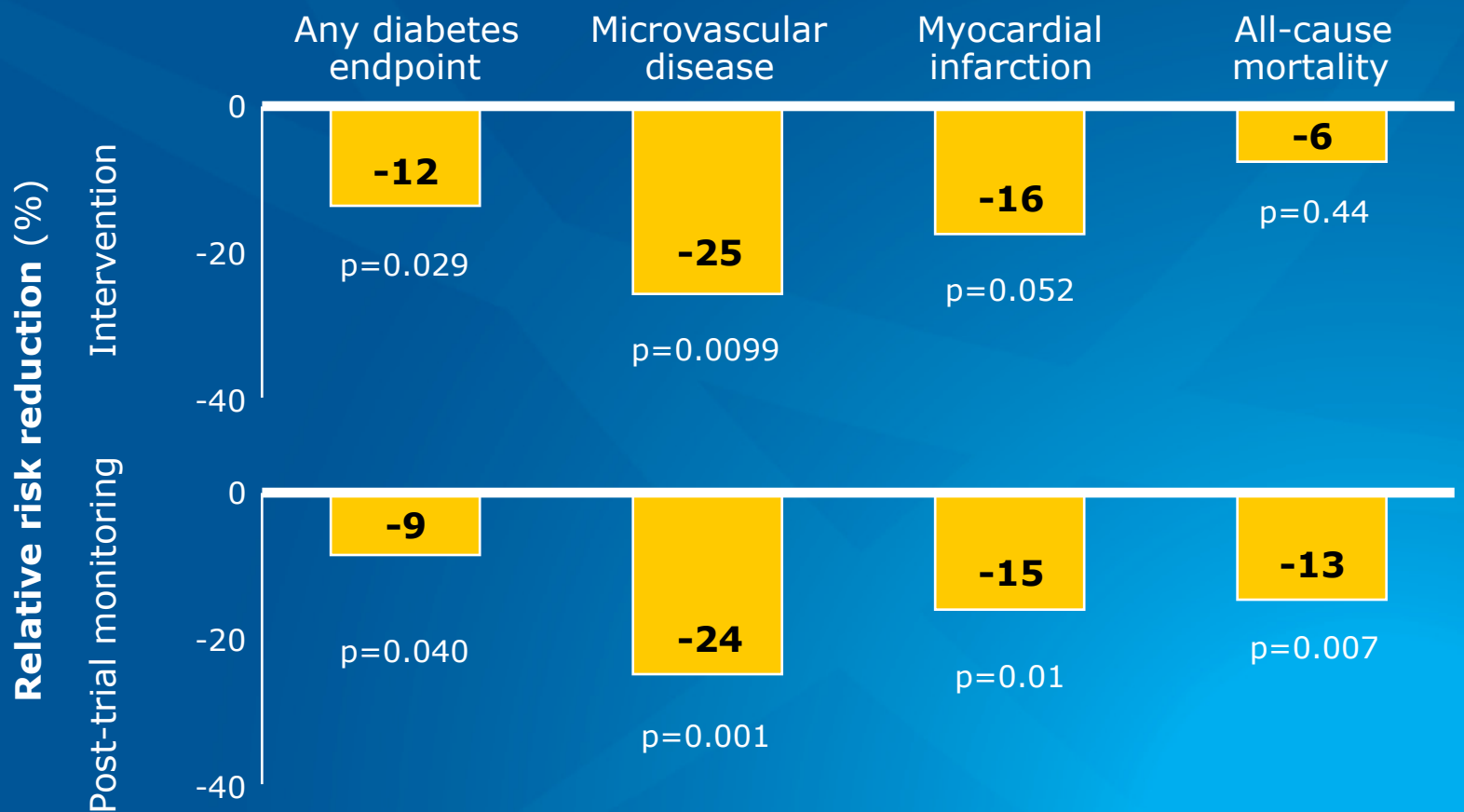
After the UKPDS and DCCT patients were now taken care of by GPs with normal follow up. Even with subsequent deterioration in glycemic control.

UKPDS- Benefits of "earlier intensive" control continued up to 8.5 years after the trial

DCCT-EDIC – benefits of earlier control continued up to 14 years after the trials.

Holmann RR et al. N Engl J Med 2008;359:1577-1589

UKPDS showed "THE LEGACY EFFECT"



1. Holman RR, et al. N Engl J Med. 2008;359:1577-89.
2. UKPDS Study Group. Lancet. 1998;352:837-53.

For glycemic control:

- **Intensive** treatment was better
- **Early intensive** treatment was preferred

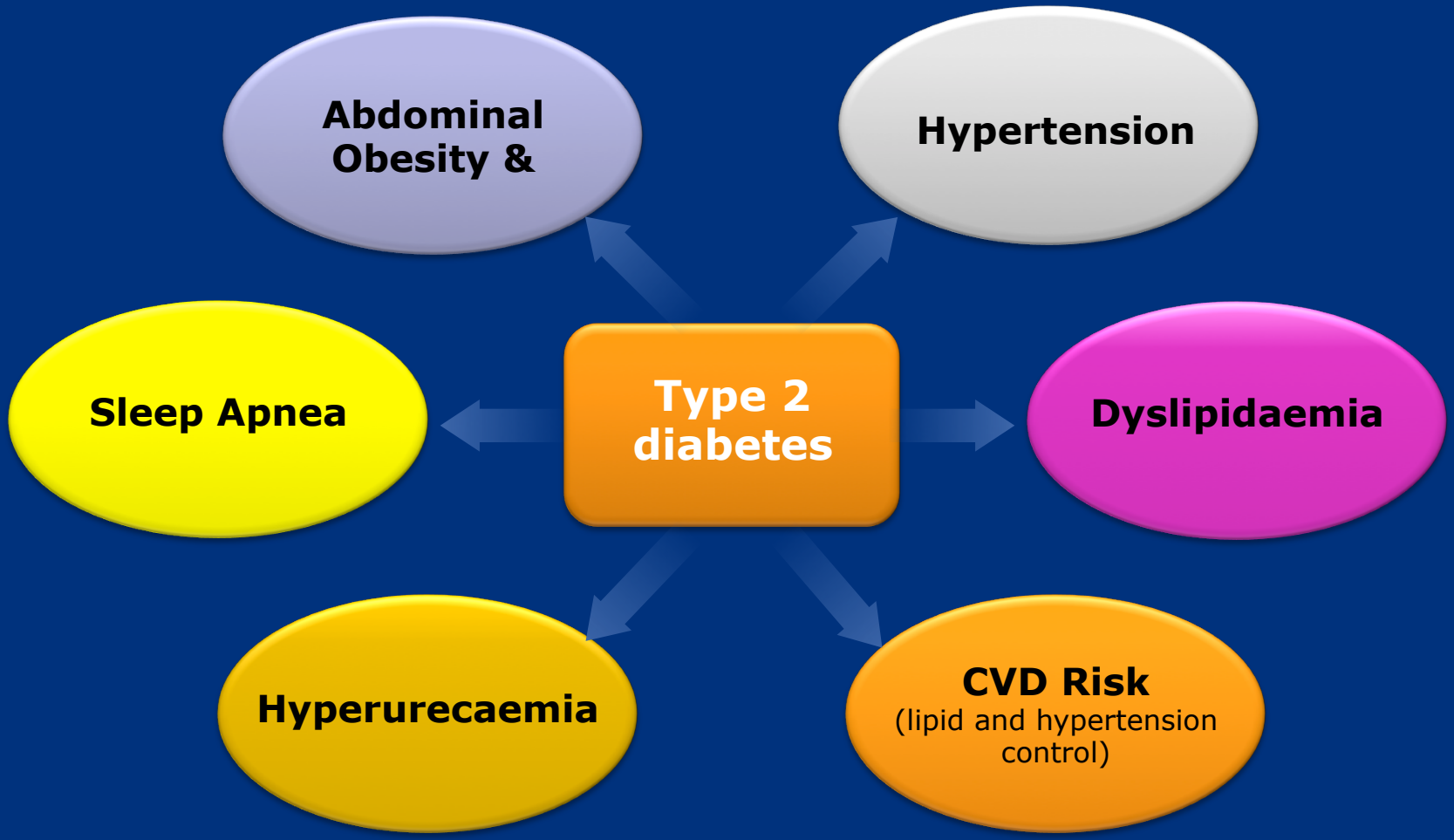
Glycemic targets were revised- FBG, PPG, HBA1c

LEGACY EFFECT/ METABOLIC MEMORY

Early intensive glycemic control confers extended reduction in complications, even when control deteriorates later on

Akalin S et al. Int J Clin Pract. 2009;63:1421-5.
MacIsaac RJ & Jerums G. Heart Lung Circ. 2011;20:647-54.

PRESENTING THE EVIDENCE - MACROVASCULAR



Postgrad Med. 2009 May;121(3 Suppl 1):7-12

WHAT DO WE MEAN BY INTENSIVE?

TIGHT CONTROL

GETTING TO TARGET

FBG, PPG, HBA1c

HBA1c as a Monitoring tool

Hb + glucose react non enzymatically to form glycated derivatives , levels are dependent on average glucose levels

- It indicates the average blood glucose over the past 120 days

Glycemic Targets

	ADA[1]	ACE[2]	IDF[3]
HbA1c	<7.0% *(general goal)*	≤6.5%	<6.5%
Preprandial capillary plasma glucose	70–130 mg/dL (3.9–7.2 mmol/L)	<110 mg/dL (<6.0 mmol/L)	<110 mg/dL (<6.0 mmol/L)
Peak postprandial capillary plasma glucose	<180 mg/dL (<10.0 mmol/L)	<140 mg/dL (<7.7 mmol/L)	<145 mg/dL (<8.0 mmol/L)

ACE=American College of Endocrinology; ADA=American Diabetes Association; IDF=International Diabetes Federation

Adapted from: [1]ADA / EASD consensus statement: Nathan DM, et al. *Diabetes Care*. 32:193–203;
[2]American Association of Clinical Endocrinologists, American College of Endocrinology. *Endocr Pract.* 2002; 8 (Suppl 1): 5–11;
[3]International Diabetes Federation. *Global Guideline for Type 2 Diabetes*. Brussels: International Diabetes Federation; 2005.

Global targets for glycaemic control

FPG	HbA_{1c}	PPG
<110 mg/dL (6.0 mmol/L)	<7.0%	< 145 mg/dL (8.0 mmol/L)

- Less stringent targets:
  - In older population could be less stringent
  - Comorbid cardiac disease

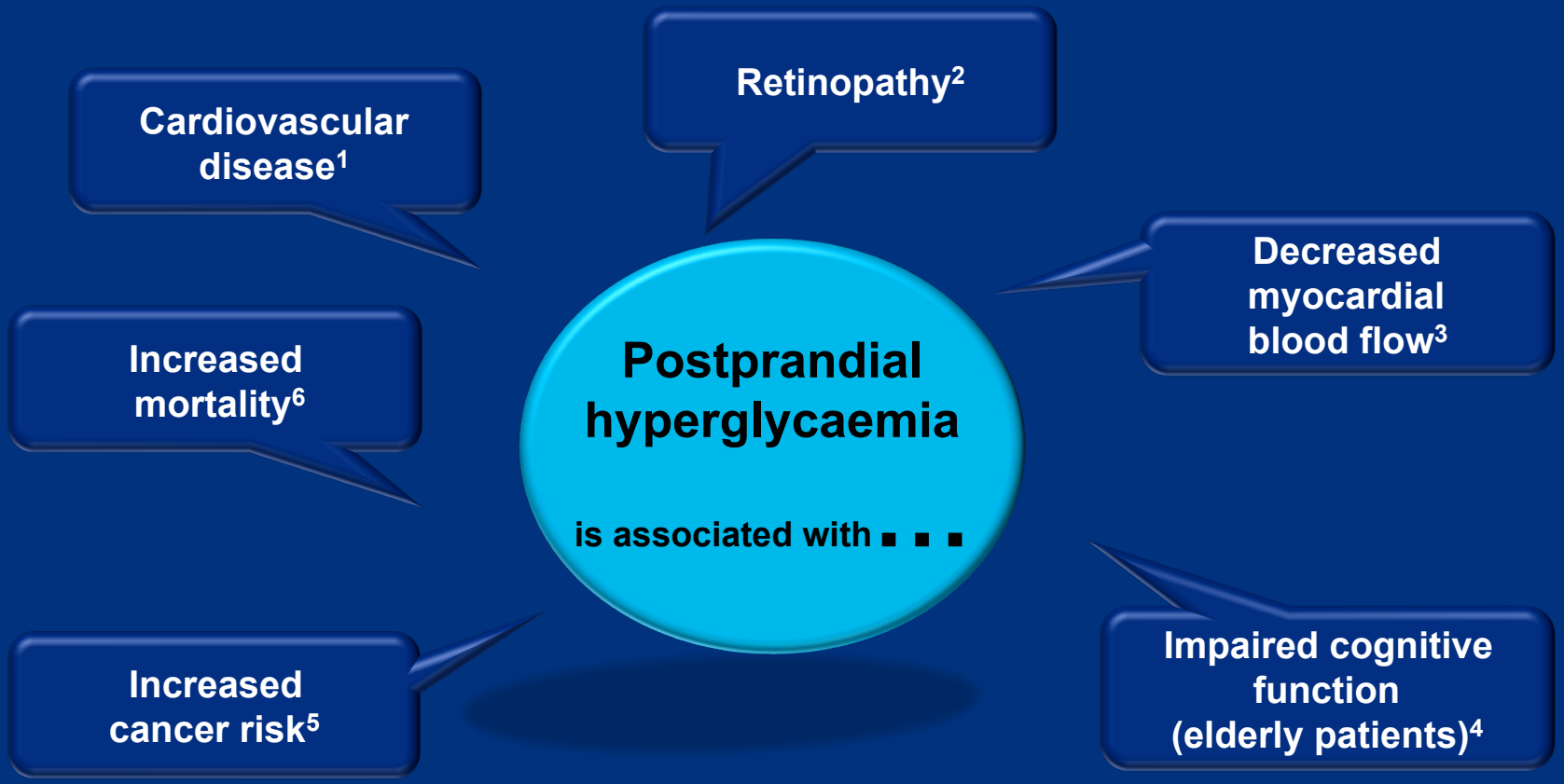
American Diabetes Association Diabetes Care 2009;32 (Suppl 1):S13-S61
Nathan et al. ADA/EASD Consensus guideline. Diabetes Care 2009;32(1): 193-203
IDF Treatment Algorithm for People with Type 2 Diabetes. 2011
IDF Clinical Guidelines Task Force. International Diabetes Federation 2005

POSTPRANDIAL HYPERGLYCEMIA

- 36yr male patient
- HBA1c-10%

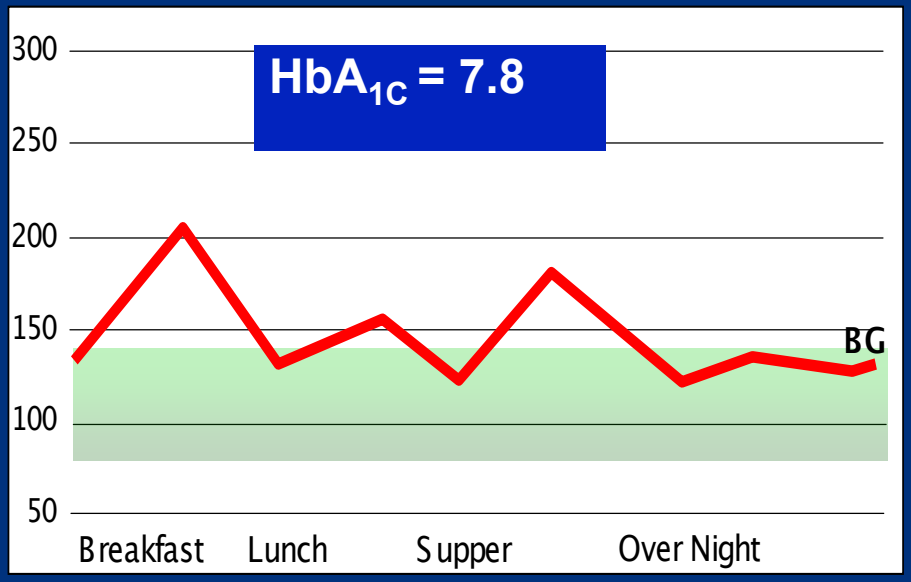
FPG	PRE LUNCH	2HPP	PRE SUPPER	2HPOST SUPPER
6.8	10.7	14.3	13.4	11.2

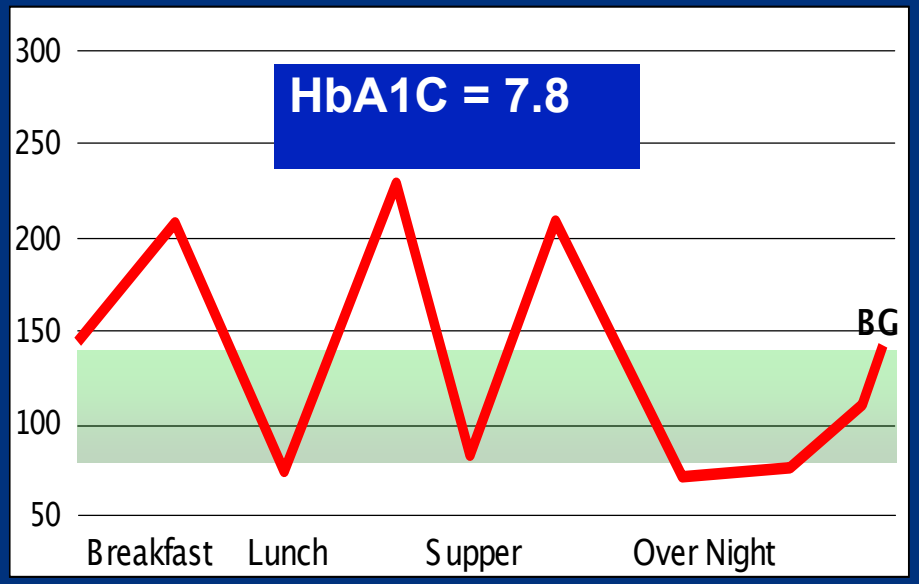
Risks of postprandial hyperglycaemia



1. Cavalot F et al. J Clin Endocrn Metab 2006; 91:813–819
2. Shiraiwa T et al. Diabetes Care 2005;28:2806-2807
3. Scognamiglio R et al. Circulation 2005; 112(2):179-184
4. Abbatecola AM et al. Neurology 2006; 67(2):235-240
5. Stattin P et al. Diabetes Care 2007; 30:561-567
6. Hanefeld M et al. Diabetologia 1996;39:1577–83

Same HbA_{1C}s are really not the same





- There is a variable relationship between fasting glucose, postprandial glucose and HbA_{1C}
- Hypothetically on the same dose of diabetes medications

Source: Diabetes Care, Bonora yr:2001 vol:24 iss:12 pg:2023 -2029

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Summary of management

- Individualized treatment and involve patients
- (Lifestyle +metformin) + (any other) depending on patient and pathhophysiology at play
- Ultimately, patients will require insulin
- Comprehensive risk management

CHALLENGES IN DIABETES/ GLYCEMIC CONTROL

When to convince the patient to shift from orals to insulin-2

Difficulty in convincing patients to accept/switch to insulin injections-3

Initiation of insulin/understanding proper use of insulin-2

Storage of insulin 2

DUMSOR affecting insulin storage-

Compliance to medication-25

Default to follow up

Adhering to nutritional recommendations-5

CHALLENGES IN DIABETES/ GLYCEMIC CONTROL

Insulin marks the beginning of the end

Effective medication-for individuals

What drug to start with-2

What to add on

Medication choice

Medication choice when a1c is out of control but FBS is normal

Medication choice in elderly

Medication choice in renal complication

CHALLENGES IN DIABETES/ GLYCEMIC CONTROL

- Literacy level of patients
- Managing DKA 2
- Patients Prefer herbal
- Lack of evidence based data
- Lack of management protocols in Ghana
- Diagnostic criteria
- Cost of a1c
- Cost of SMBG
- Complications

CHALLENGES IN DIABETES/ GLYCEMIC CONTROL

Obesity

Unavailability of dietician

Diet not well understood-4

Adhering to physical activity recommendations-4

Financial constraints-13/cost of medications

When to intensify treatment-2

Achieving good glycaemic control-5

CHALLENGES IN DIABETES/ GLYCEMIC CONTROL

Diabetic nephropathy

Management of hypertension and dyslipidaemia

Patient misinformation 3

Poor education on diabetes-4

Pill burden

What is a suitable well controlled point for T2DM patients (TARGETS)

Challenges in reaching desires glycaemic targets-4

Challenges ……my opinion

Cost

Provider education

Lack of guidelines

Clinical inertia in intensification

AT THE END OF THIS PRESENTATION……..

Epidemiology- its an epidemic now

Current thinking of aetiopathogenesis- diabetic octet

Advances in management for best glycemic control-

- Individualize
- Treat to target
- Insulin for all (if they live long enough)

Challenges preventing attainment of good glycemic control-

THANK YOU

Questions?