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▼***Invokana®* (*canagliflozin*)** *This medicinal product is subject to additional monitoring and it is therefore important to report any suspect adverse reactions related to this medicinal product.*

Diabetes Update

what next after metformin?

Mims interactive workshop, 22nd May 2015
Euston Square, London

Dr Saqib Mahmud FRCP MRCGP
Primary Care Consultant

PHGB/VOK/0415/0028 Date of preparation: May 2015

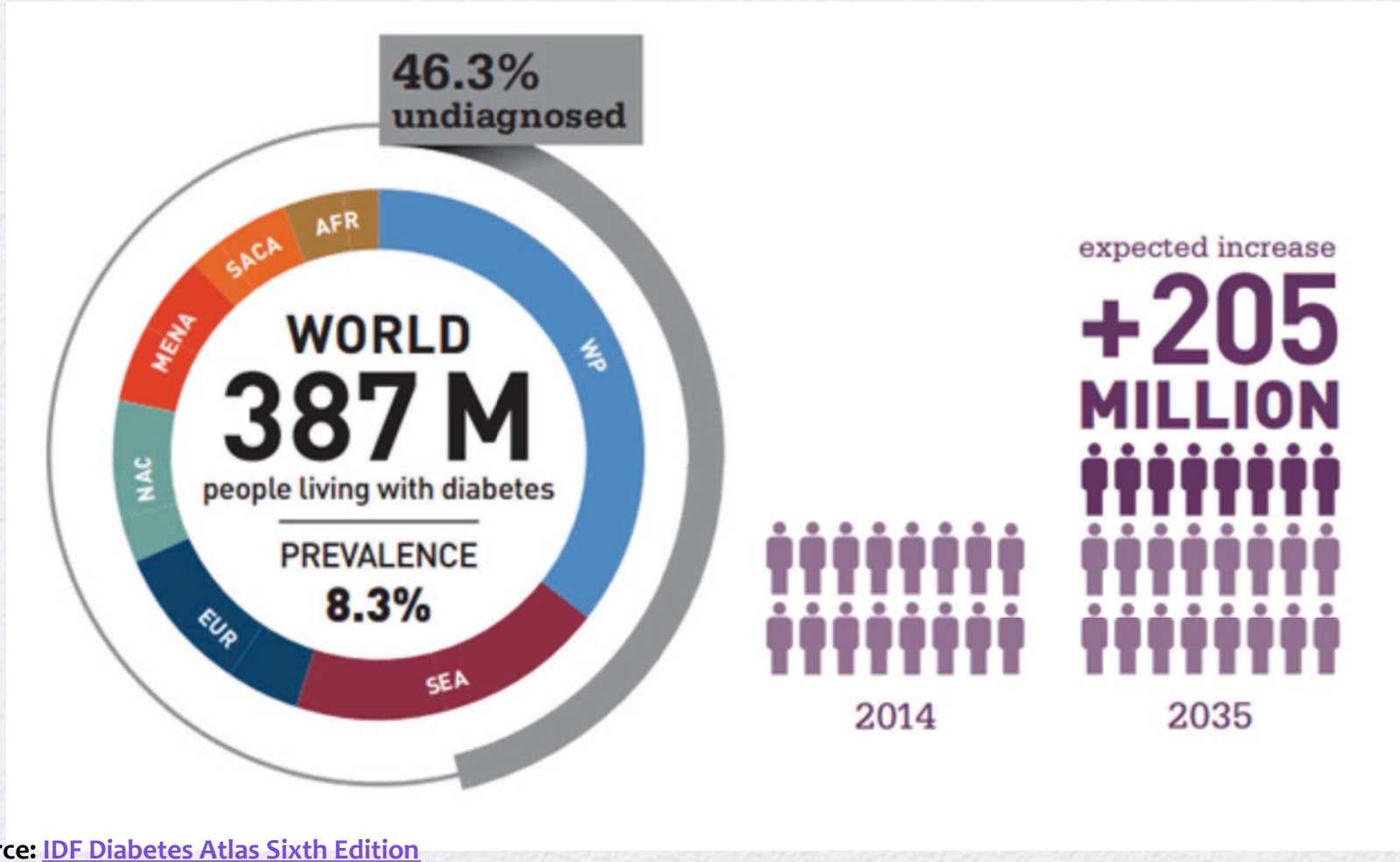
Disclosure

I have received honoraria as a speaker for

Novonordisk, Sanofi , Astra Zeneca,

Boehringer Ingleheim , GSK, Bayer and Janssen

Prevalence of DM



Source: IDF Diabetes Atlas Sixth Edition Update, International Diabetes Federation 2014

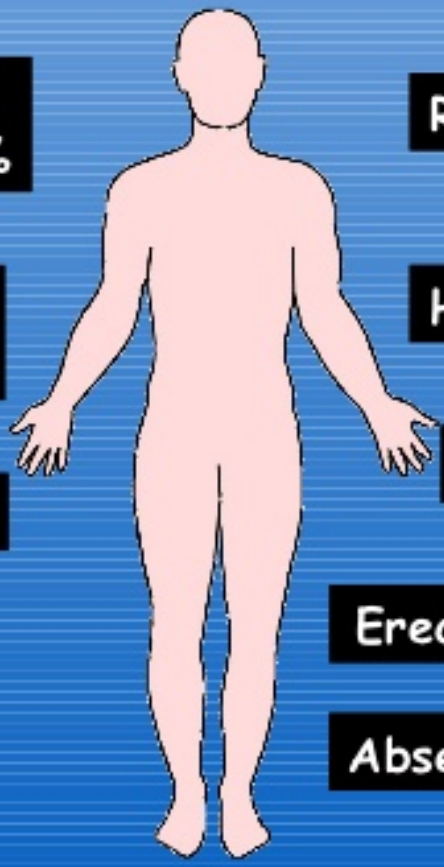
Epidemiology

- Worldwide - 387 million to date
- 46.3 million undiagnosed
- 600 million in next 20 years ….are the predictions correct? Or underestimate
- T2DM is the most rapidly rising condition in the world
- 5 million deaths per year
- 48% of deaths <60 years of age
- One person dies every 6 seconds
- 1 limb amputated every 30 seconds
- 50% of T2 Diabetics have complications at diagnosis*

*UKPDS group.Diabetologia 1991;34;877-890

Complications at Diagnosis

50% of newly presenting people with type 2 diabetes already have one or more complications at diagnosis



- Intermittent claudication: 3%
- Ischaemic skin changes to feet: 6%
- Stroke or TIA: 1%
- Plasma creatinine >120µmol/l: 3%
- Retinopathy: 21%
- Hypertension: 35%
- Abnormal ECG: 18%
- Erectile dysfunction: 20%
- Absent foot pulses: 13%

UKPDS Group. *Diabetologia* 1991; 34:877–890.

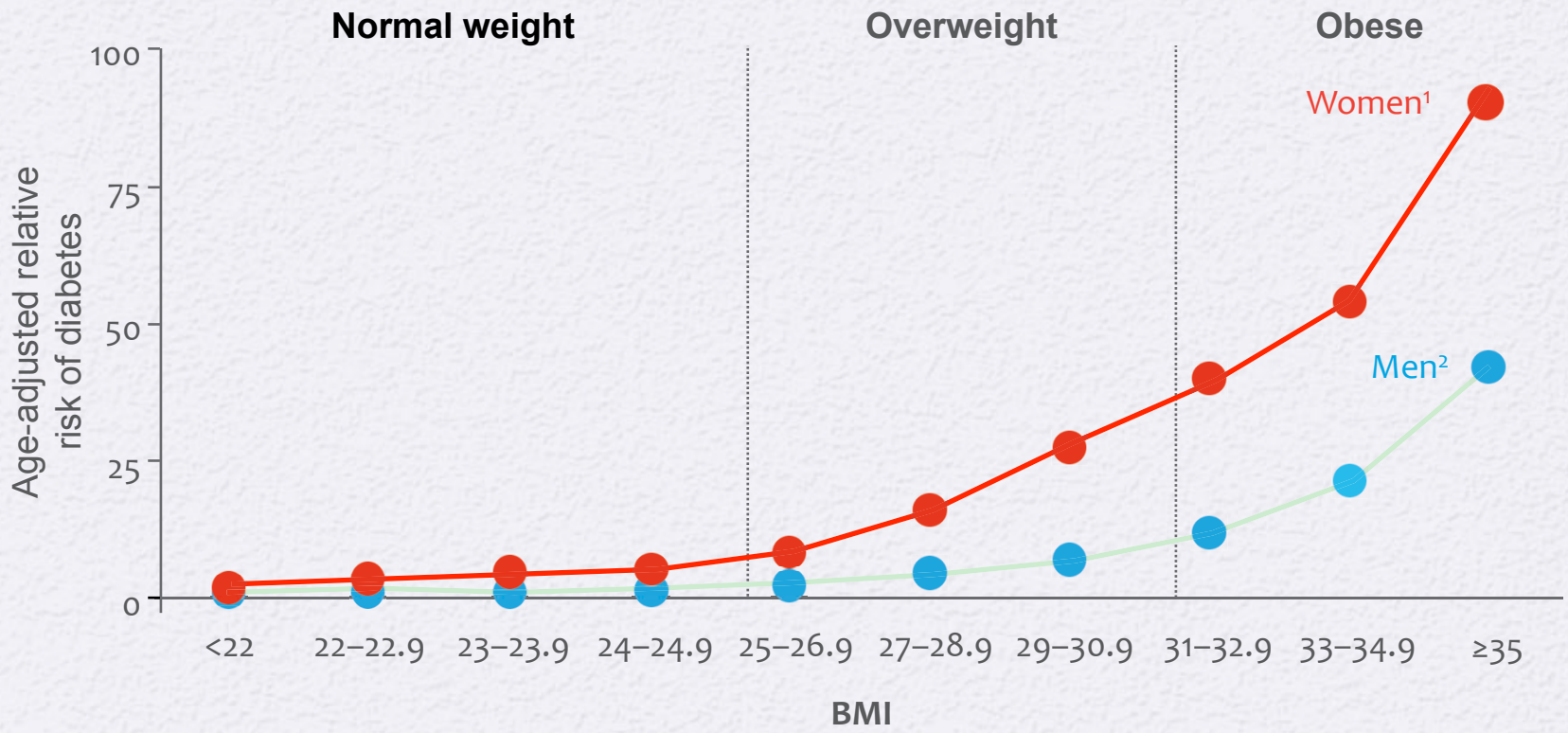
Burden of T2DM

- 3.8 million diagnosed in UK to date
- 800,000 undiagnosed
- 5 million by 2025
- 1 in 20 people in UK have T2 DM, 1 in 4 at risk
- Increased incidence of T2D at relatively young age in UK, 16% <40yrs, 20% <50yrs
- Consumes 10% NHS budget
- Obesity is a potent risk factor for type 2 diabetes.*
- In 2012, an estimated 62% of adults were overweight or obese in England (BMI ≥25), 24.7% were obese (BMI ≥30) and 2.4% were severely obese (BMI ≥40). **

*Source: National Diabetes Audit 2009-10
**Source: Health Survey for England 1993-12. Joint Health Surveys Unit (Nat Cen Social Research & UCL) 2014.

Diabetes and obesity are closely interlinked

Relationship between BMI and risk of T2DM



BMI, body mass index.
1. Colditz GA, *et al. Ann Intern Med* 1995;**122**:481–6; 2. Chan J, *et al. Diabetes Care* 1994;**17**:961–9.

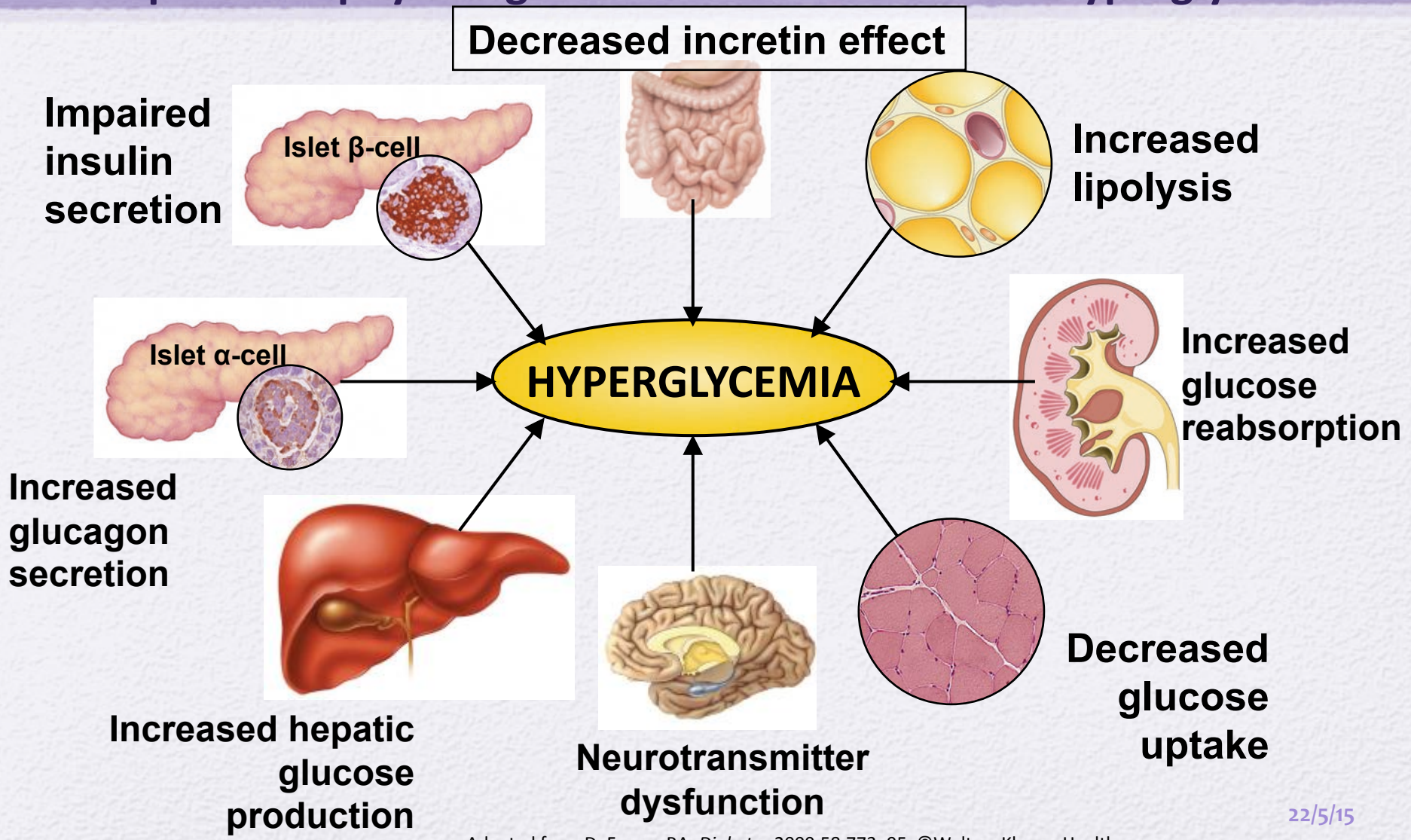

24 HOUR
FITNESS


STOP

Pathophysiology and Natural History of Type 2 Diabetes

Ominous octet

Multiple Pathophysiological Failures Contribute to Hyperglycaemia

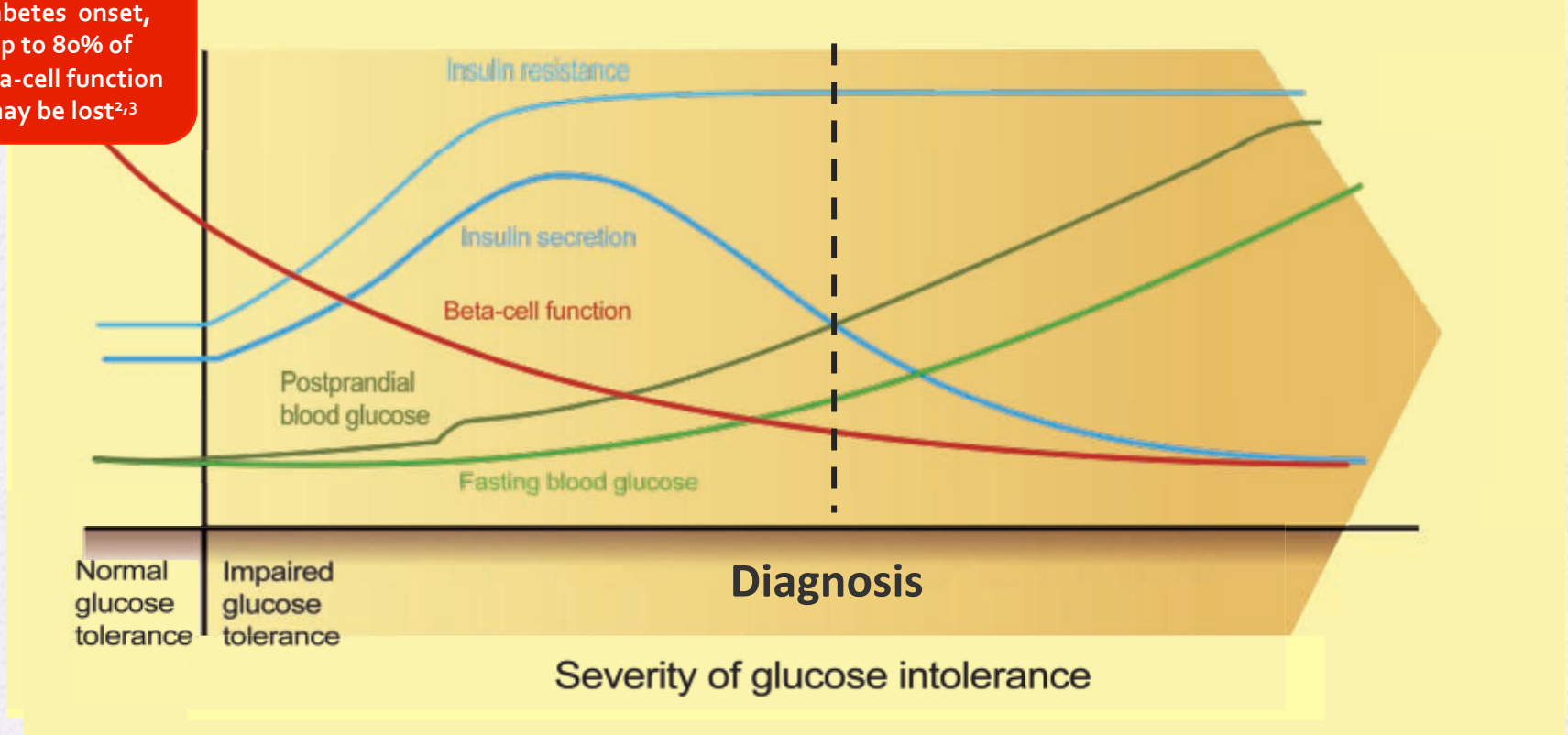


Adapted from DeFronzo RA. *Diabetes* 2009;58:773–95. ©Wolters Kluwer Health

Type 2 Diabetes Is a Complex and Progressive Metabolic Disorder

By the time of diabetes onset, up to 80% of beta-cell function may be lost[2,3]

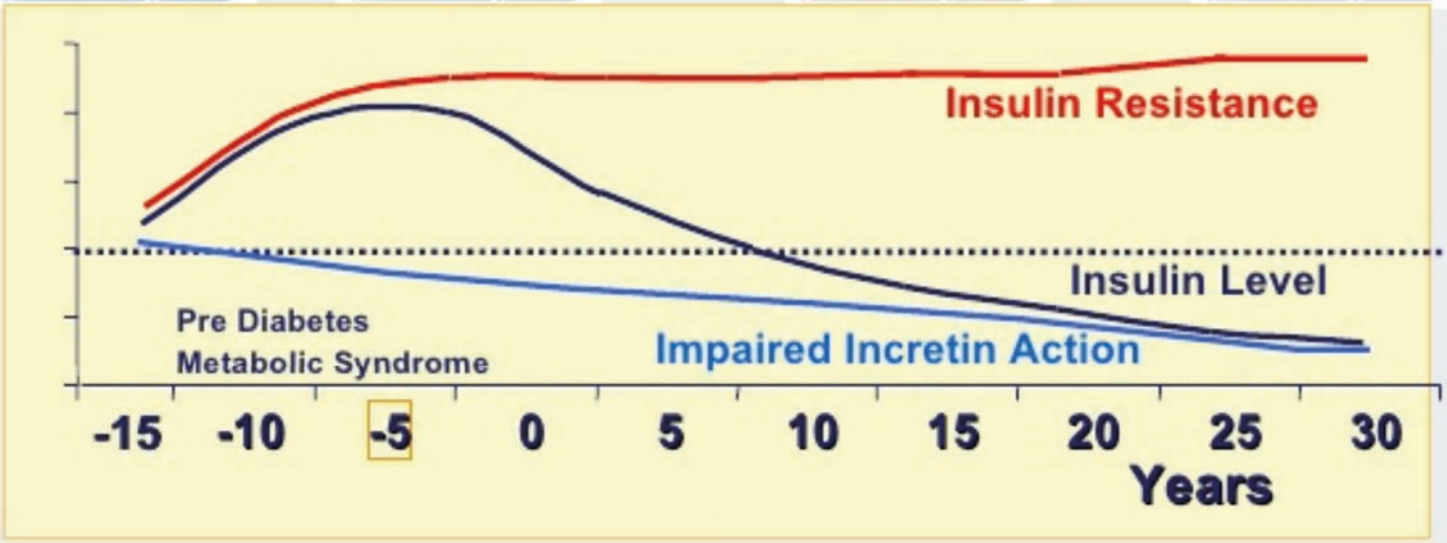
History and Progression of Type 2 Diabetes[1-3]



1. Kendall DM, et al. International Diabetes Center. 2005. 2. DeFronzo DA. *Diabetes.* 2009.
3. Fehse F, et al. *J Clin Endocrinol Metab*. 2005.

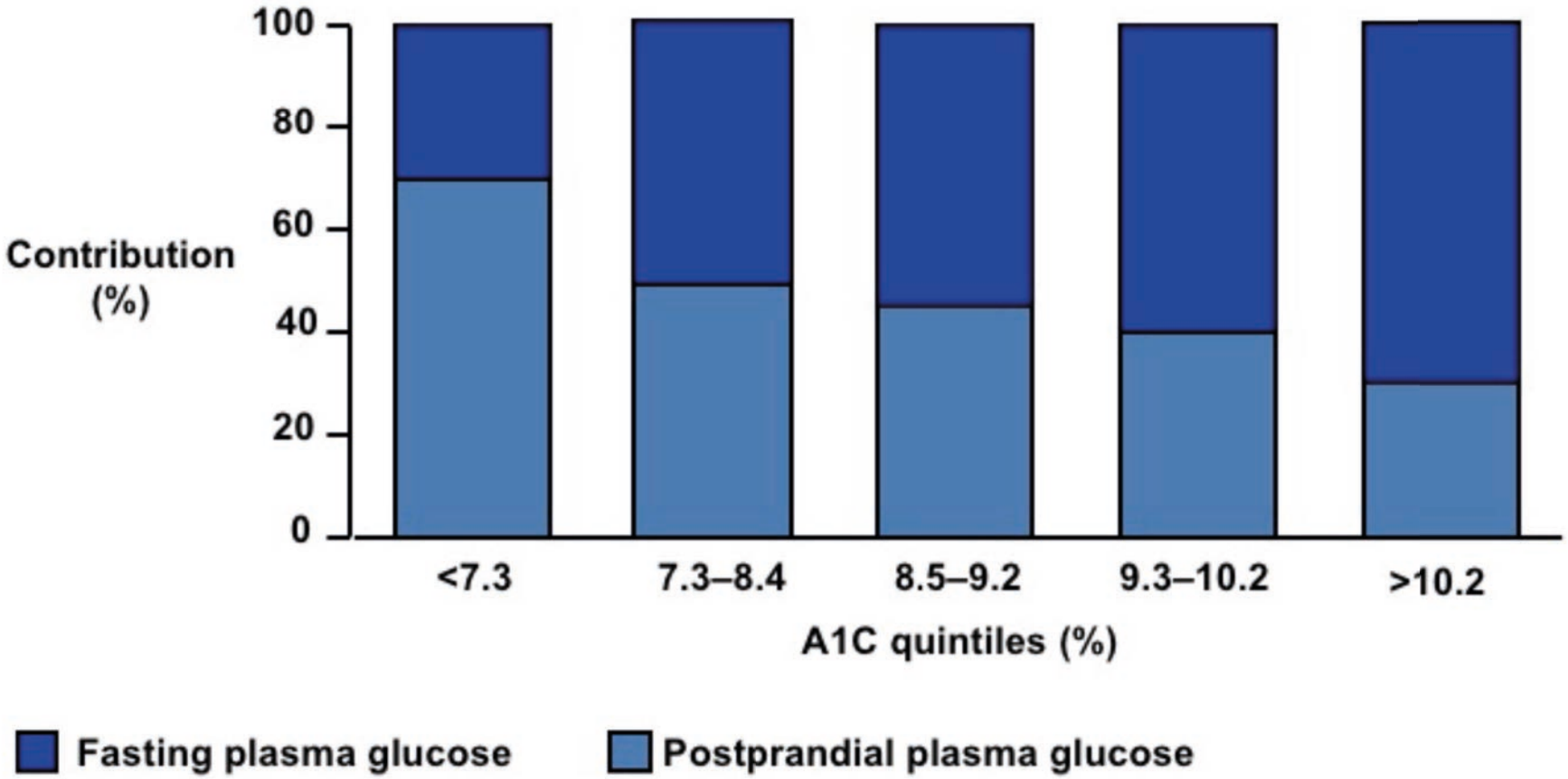
Adapted from Kendall DM, Bergenstal RM.

How does diabetes change over the years?



International Diabetes Center
Park Nicollet

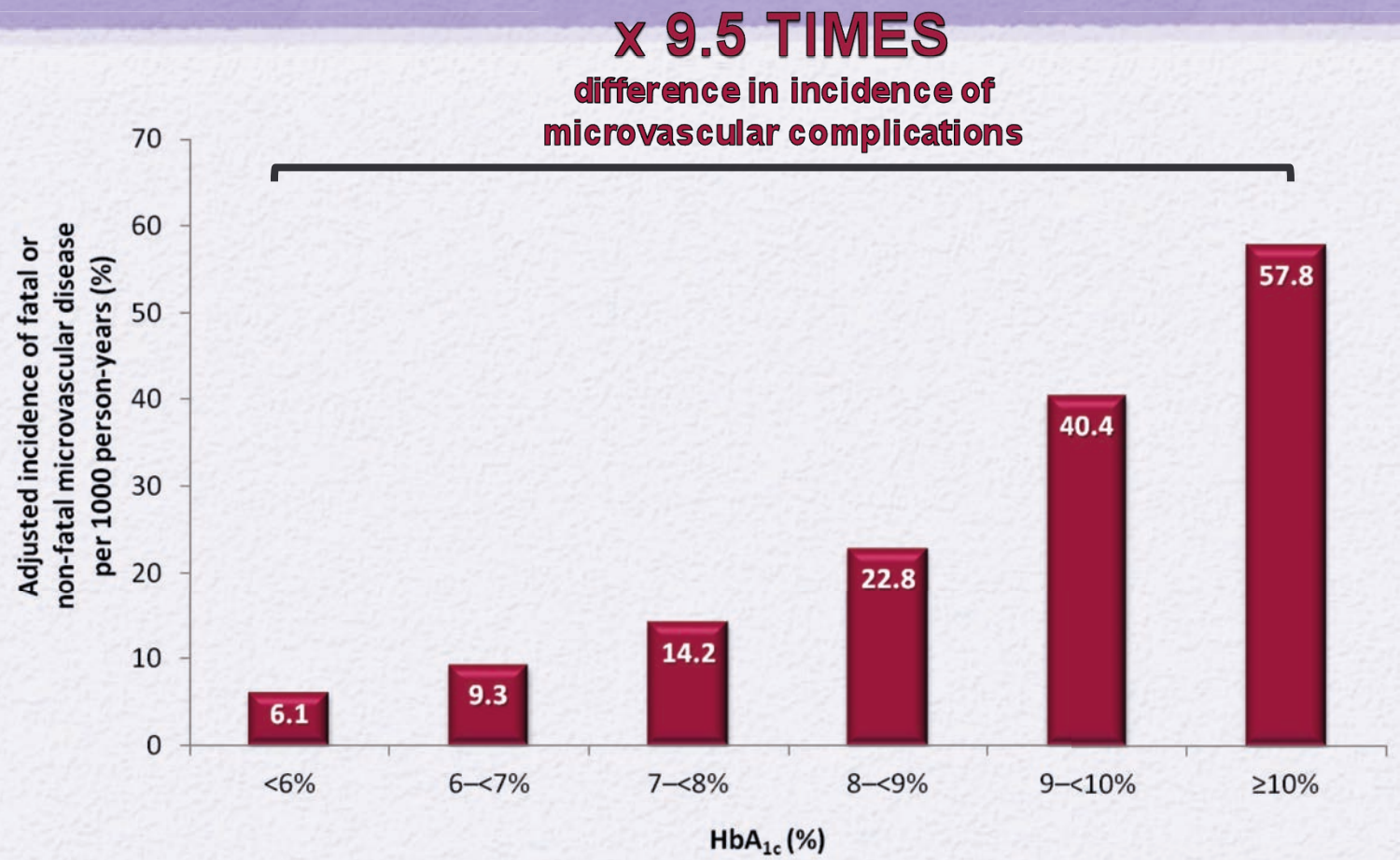
Relative contributions of postprandial glucose and FPG to A1C



Monnier L et al. *Diabetes Care*. 2003;26:881-5.

HBA1C Targets???
Why bother?

UKPDS: The incidence of microvascular disease is strongly linked to HbA1c[1]

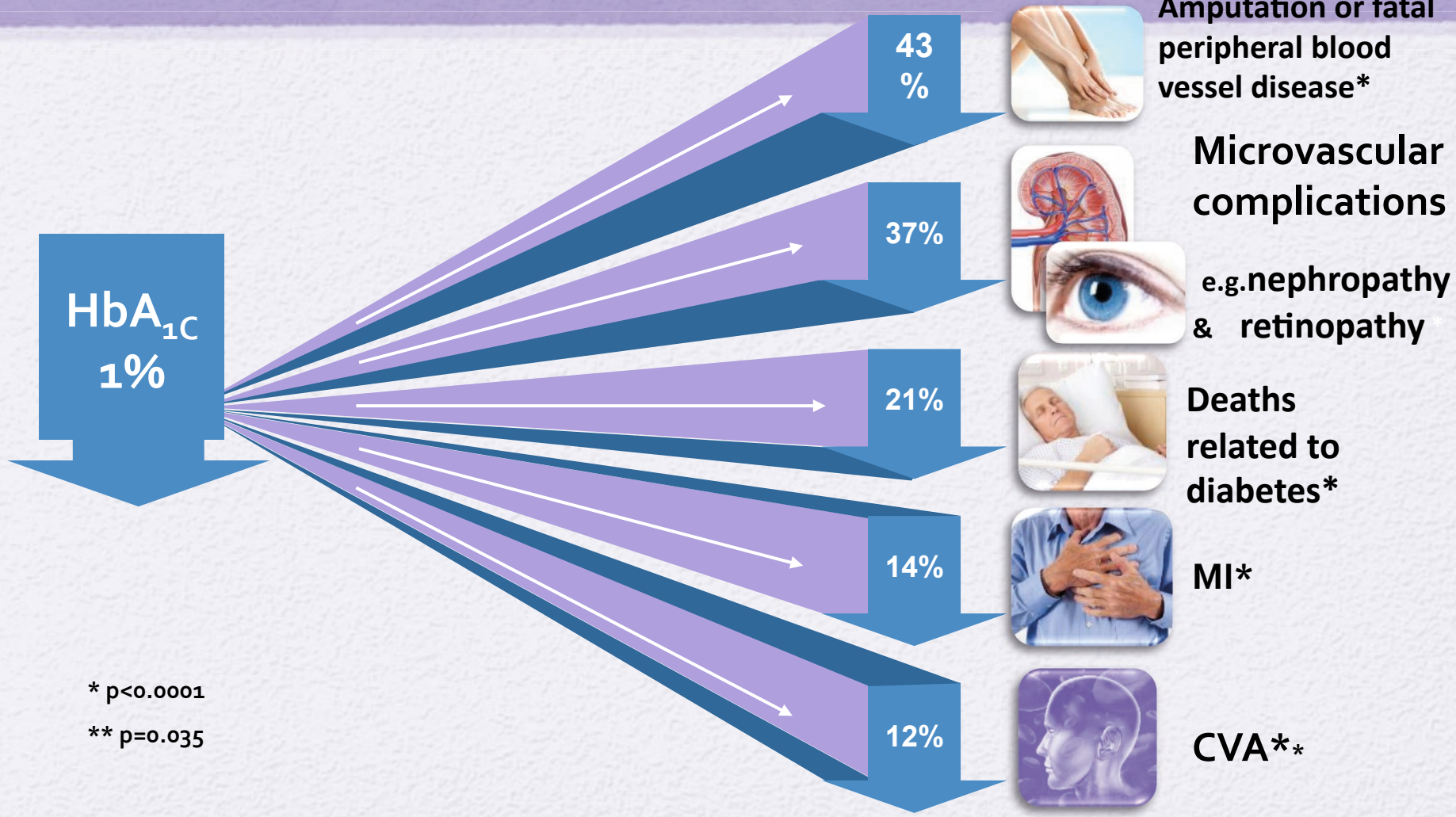


Adapted from Stratton IM, *et al. BMJ* 2000;321:405–12.

Adjusted incidence of fatal or non-fatal microvascular disease per 1000 person-years (%) by category of updated mean HbA1c concentration (%). Rates per 1000 person years' follow up adjusted in Poisson regression model to white men aged 50 to 54 years at diagnosis of type 2 diabetes and followed up for 7.5 to <12.5 years, termed "10 years" (n=4585). Microvascular events were defined as the first to occur of: retinopathy requiring photocoagulation, vitreous haemorrhage or fatal or non-fatal renal failure.

1. Stratton IM, *et al. BMJ* 2000;321:405–12.

UKPDS: A 1% decrease in HbA_{1c} is associated with a significant reduction in complications

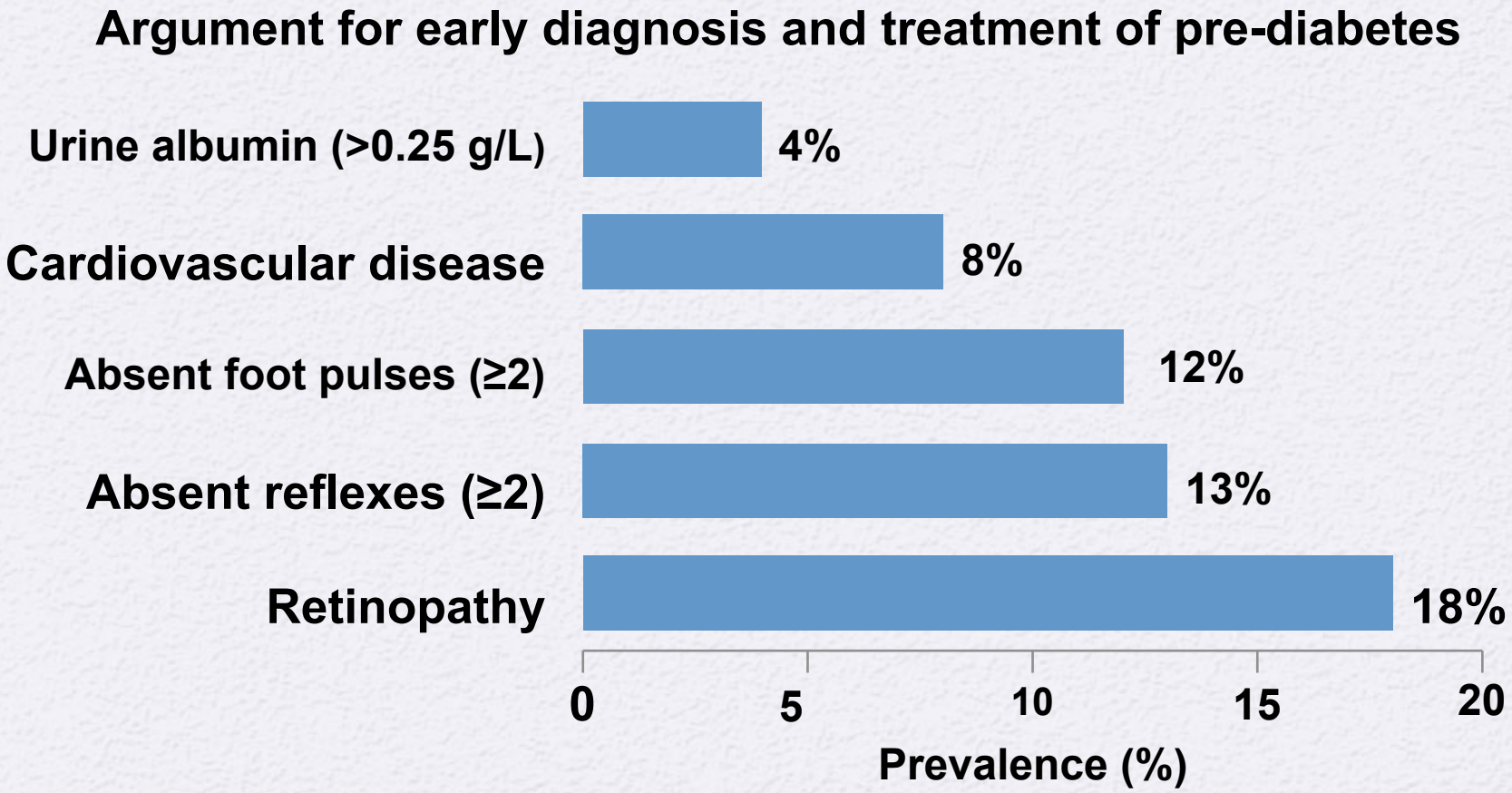


* p<0.0001

** p=0.035

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

Complications of T2D may be present prior to diagnosis



Dagogo-Jack S, Santiago JV. *Arch Intern Med* 1997;157:1802-1817.

ADA/EASD position statement: Key Points

All treatment decisions should be made in conjunction with the patient

Unless contraindicated, metformin is optimal 1st-line drug	Glycaemic targets & glucose lowering therapies must be individualised	After metformin, combination therapy is reasonable, aiming to minimise side effects where possible	Comprehensive cardiovascular risk reduction must be a major focus of therapy

Consider: Age & life expectancy, weight, sex/racial/ethnic/ genetic differences, disease duration, co-morbidities, micro/ macrovascular complications

Diet, exercise and education remain key

1. Adapted from: Inzucchi SE, *et al. Diabetes Care* 2012;35:1364–79.

ADA/EASD Recommendations for HbA_{1c}

- Long diabetes duration
- Short life expectancy
- Complications, comorbidities
- History of severe hypoglycemia

- Short diabetes duration
- Long life expectancy
- No CVD

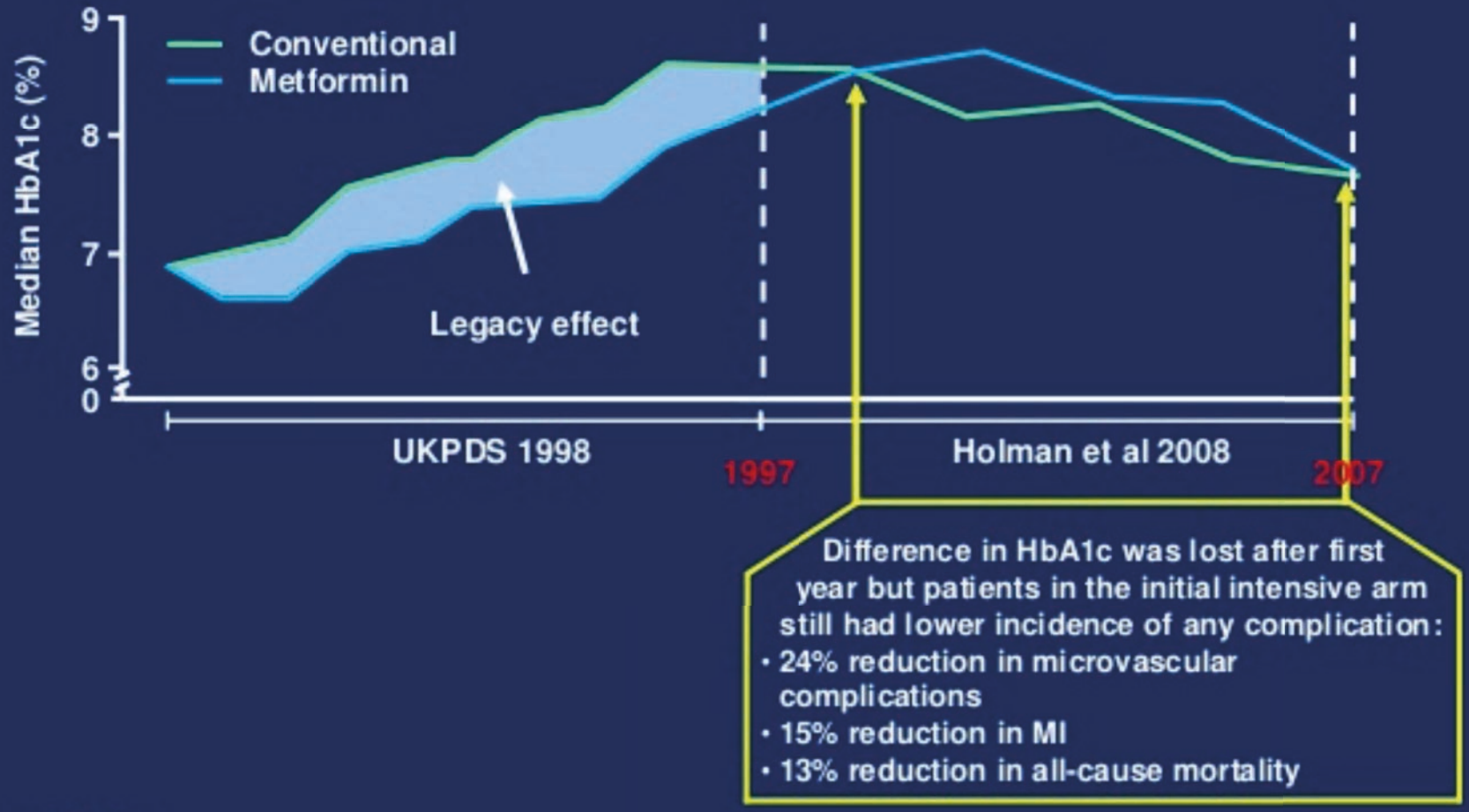
Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.[5]

The legacy effect

- Early intervention with intensification of Rx before Glycaemic window closes

- Newly diagnosed diabetics, 10yrs after the end of active trial still showed significant reduction in MI risk & all cause mortality due to "**the legacy effect**"(UKPDS)

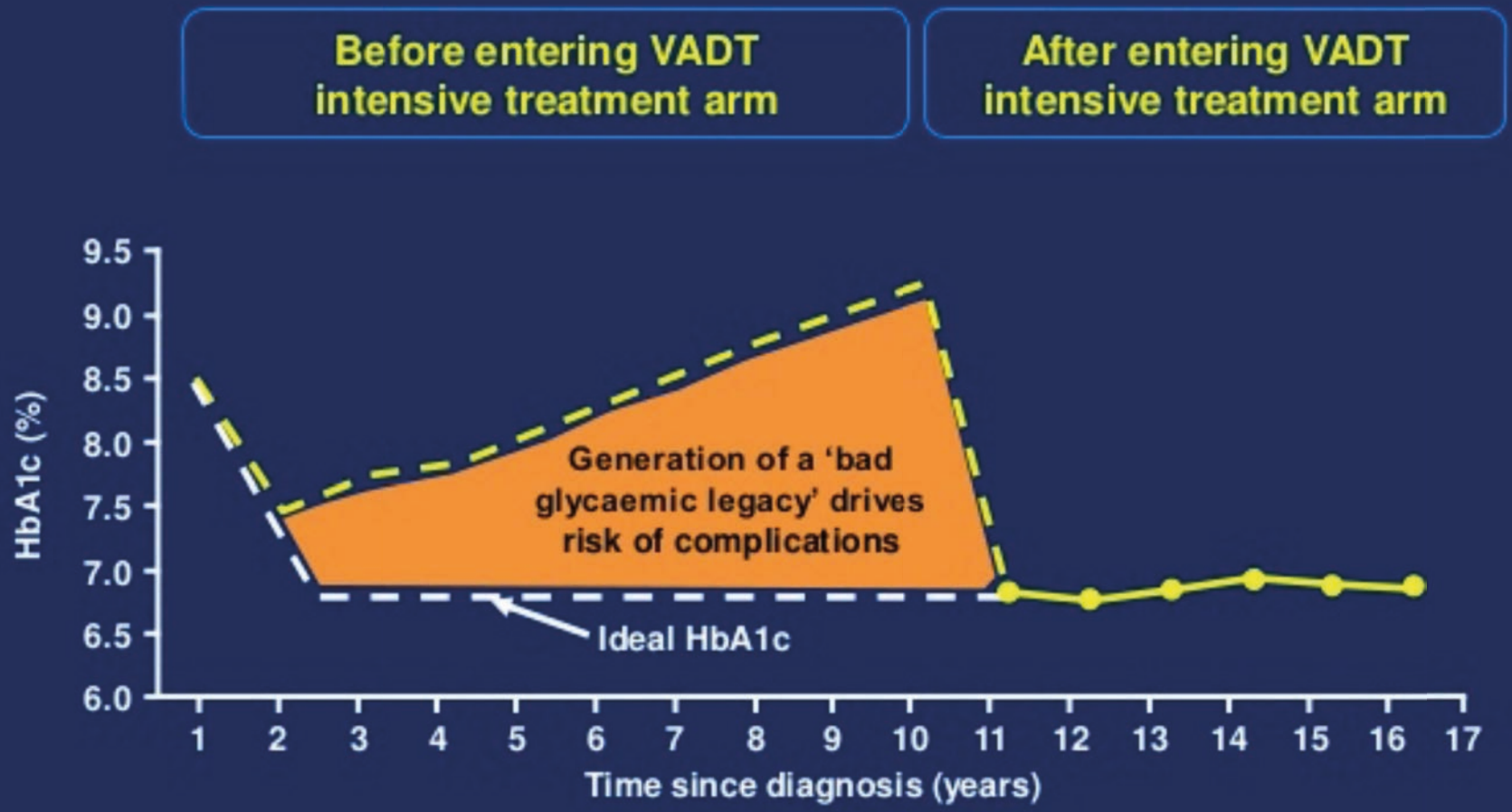
Acheiving early glycaemic control may generate a good legacy effect



HbA1c=haemoglobin A1c.

Diabetes Trials Unit. UKPDS Post Trial Monitoring. UKPDS 80 Slide Set. Available at: http://www.dtu.ox.ac.uk/index.php?maindoc=/ukpds/. Accessed 12 September, 2008; Holman RR, et al. *N Engl J Med*. 2008; 359: 1577–1589; UKPDS 33. *Lancet*. 1998; 352: 837–853.

Achieving late glycaemic control may generate a bad legacy effect increasing risk of complications



- Hypothetical representation of the natural history of diabetic patients in the VADT study: initial poor glycaemic control increases risk of complications later in disease course

HbA1c=haemoglobin A1c; T2DM=type 2 diabetes mellitus.
Adapted from Del Prato S. *Diabetologia*. 2009; 52: 1219–1226.

Hypoglycemia

Hypoglycaemia – the hidden problem

- Hypoglycaemia -common in T2 D (38% pts)
- In the UK, the estimated cost £7.4 million
- Even mild hypoglycaemia induces impaired awareness
- Impaired awareness predisposes to six-fold increase in the frequency of severe hypoglycaemia
- Only 15% of patients reported Hypoglycemic event to their GP
- Can cause severe morbidity and mortality and lowers quality of life and poor Rx adherence
- Sulphonylureas & Insulin are associated with the highest risk of hypoglycaemia*

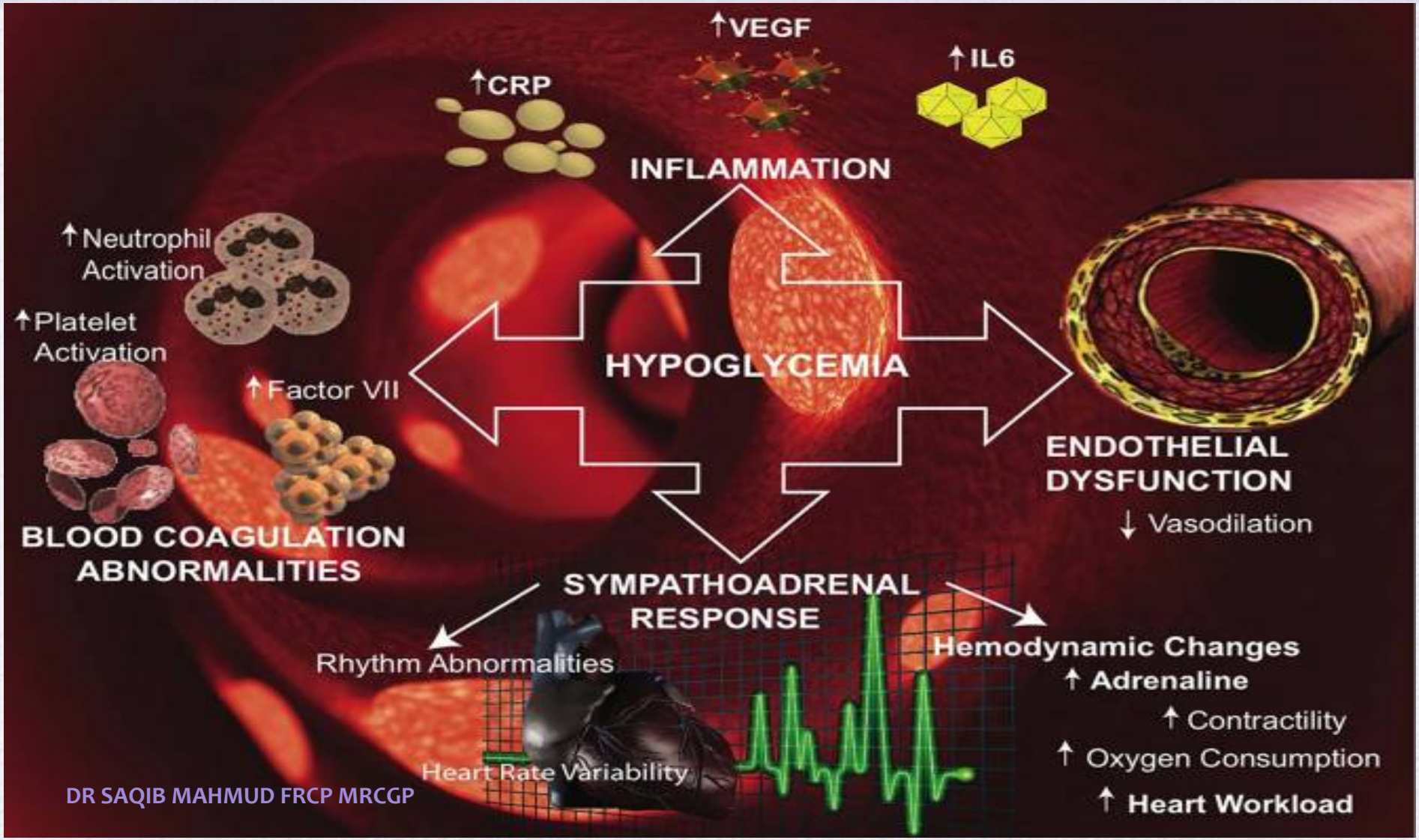
*Rates of hypoglycemia associated with intensive glycemic control.
: Patel A, et al[24]; Gerstein HC, et al[25]; UK Prospective Diabetes Study (UKPDS) Group[57]; Duckworth W, et al.

Consequences of hypoglycemia

- ↑ risk of falls / fractures in elderly
- Weight gain by defensive eating
- ↑risk of car accidents
- Hospitalization costs
- ↑risk of dementia* – 1 hypo / year - ↑risk by 25% in 7-10yrs
- ↑CV complications

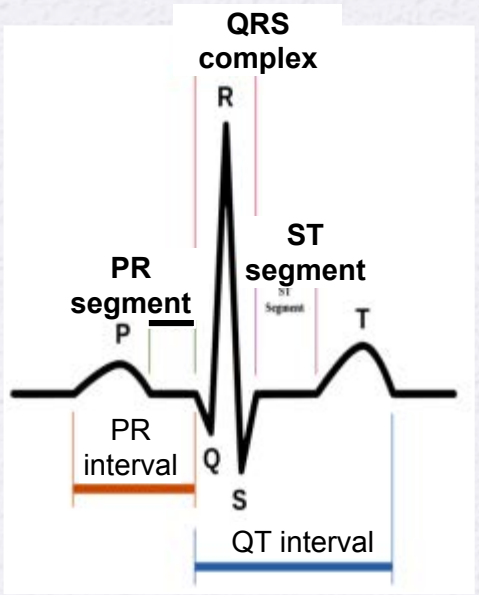
***RA Whitmer, AJ Karter, K Yaffe, CP Quesenberry… - Jama, 2009 - jama.jamanetwork.com**
Research from JAMA — Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus.

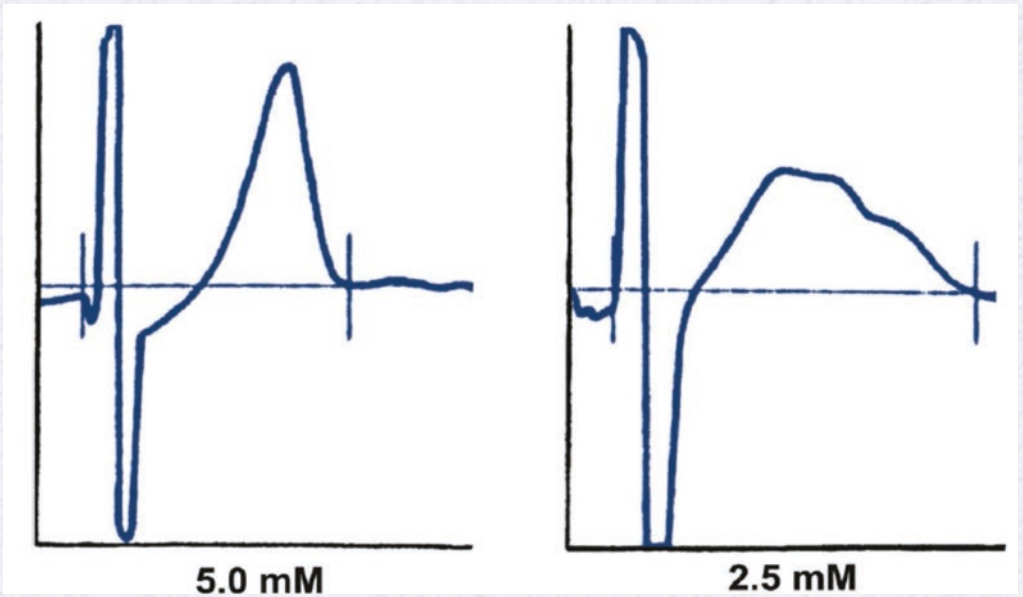
Pathophysiological CV consequences



DR SAQIB MAHMUD FRCP MRCGP

Increased risk of cardiac arrhythmia





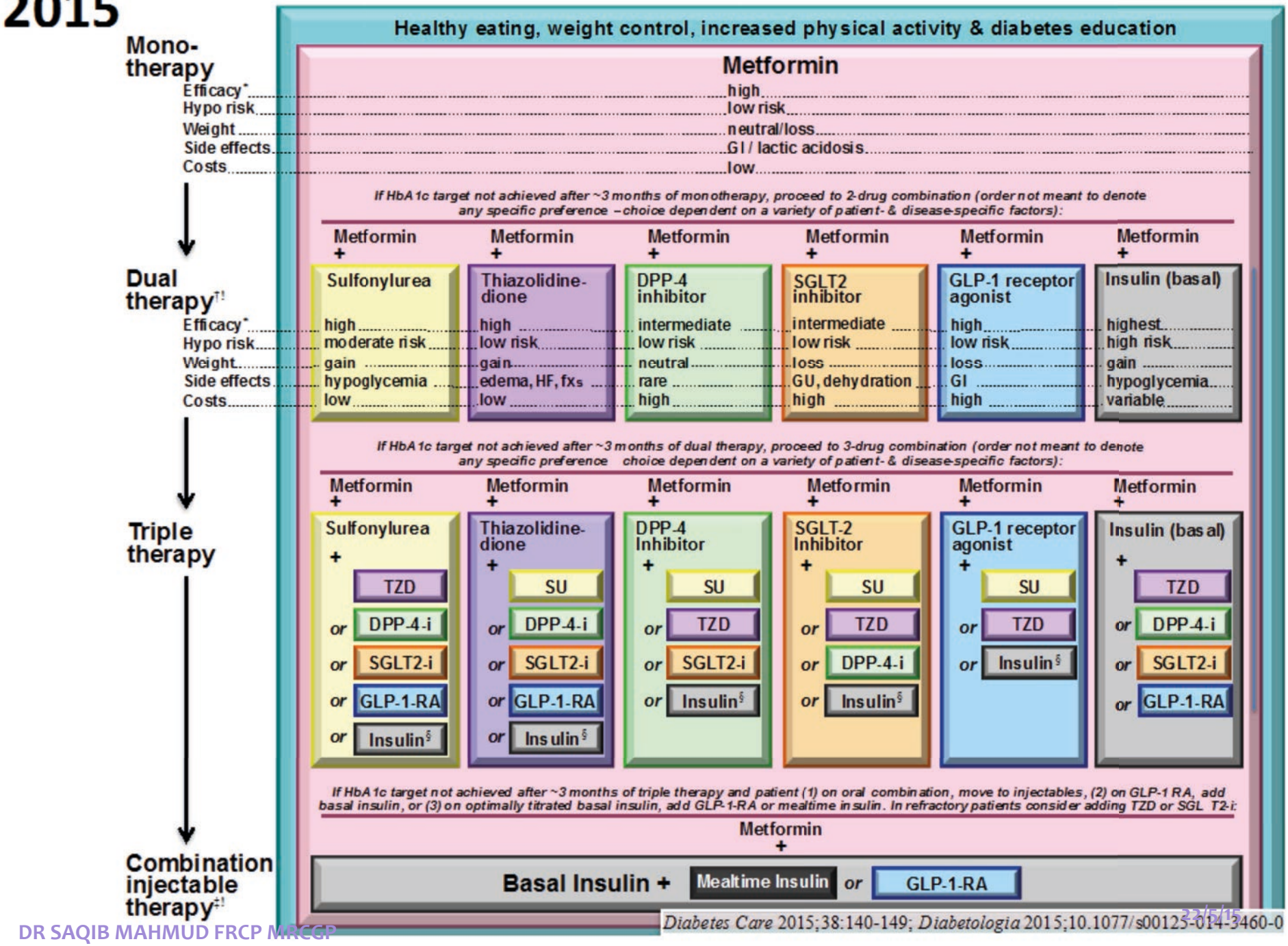
Hypoglycaemia is known to prolong both the QT interval and cardiac repolarisation

Drug/class	Main effects	Hypoglycaemia risk
Metformin	Decreases hepatic glucose output	Low
α-Glucosidase inhibitor	Reduces rate of polysaccharide digestion in the proximal small intestine	Low
Meglitinides	Stimulates insulin secretion	High*
Sulphonylurea	Enhances insulin secretion	High
Thiazolidinedione	Increases sensitivity of muscles, fat, and liver to endogenous and exogenous insulin	Low
GLP-1 agonist	Potentiates glucose-stimulated insulin secretion	Low
DPP-4 inhibitor	Enhances effects of GLP-1, increases glucose-mediated insulin secretion and suppressed glucagon secretion	Low
SGLT2 inhibitor	Glucose excretion from kidneys …insulin independent mechanism	Low
Insulin	Insulin replacement	High

Reference to speakers own experience

What are the options for optimal glycaemic control after metformin?

2015



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

Guidelines are not railway lines

Guidelines are better described as hand rails..

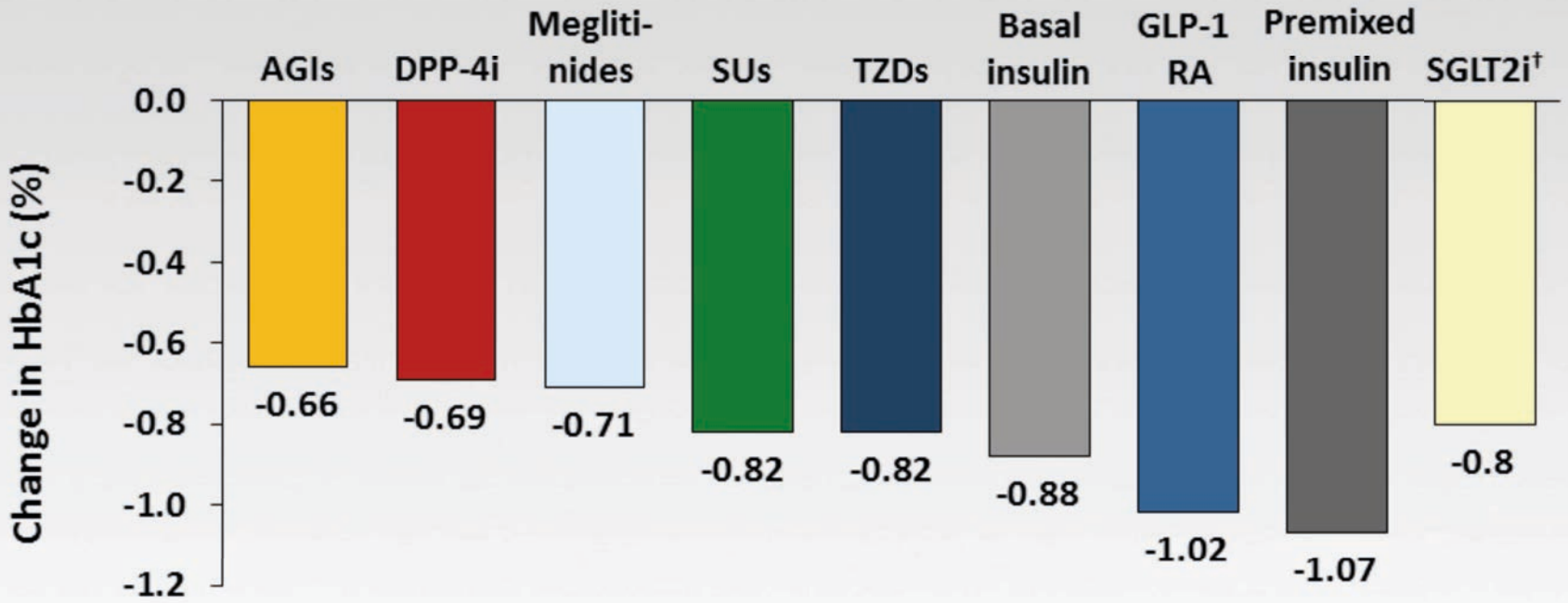
What would be an ideal drug for T2DM Rx?

- Minimal or no side effects / well tolerated
- No weight gain / promote weight loss
- Easy regime for compliance
- Preferably oral
- No hypoglycaemia risk
- Durability of glycaemic control & efficacy
- Possible physiological benefits & counteracts pathophysiological mechanisms
- Cost effective

Meta-analysis: HbA1C Reductions With Antihyperglycemic Agents Added to Metformin[a]

Network meta-analysis comparing antihyperglycemic drugs as add-on to metformin*

Mean difference from placebo



AGI = α glucosidase inhibitor; SGLT2i = sodium glucose cotransporter-2 inhibitor

*All antihyperglycemic classes were significantly different vs placebo.

†An estimate of HbA1c reduction; SGLT2 inhibitors were not included in the network meta-analysis.[b]

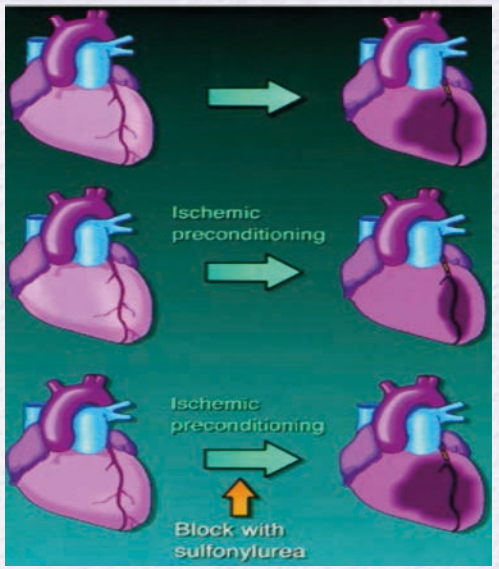
a. Liu SC, et al. *Diabetes Obes Metab.* 2012;14:810-820.

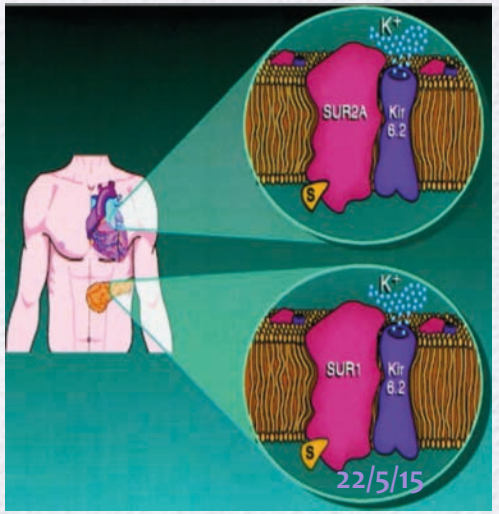
b. Fujita Y, et al. *J Diabetes Investig*. 2014;5:265-275.

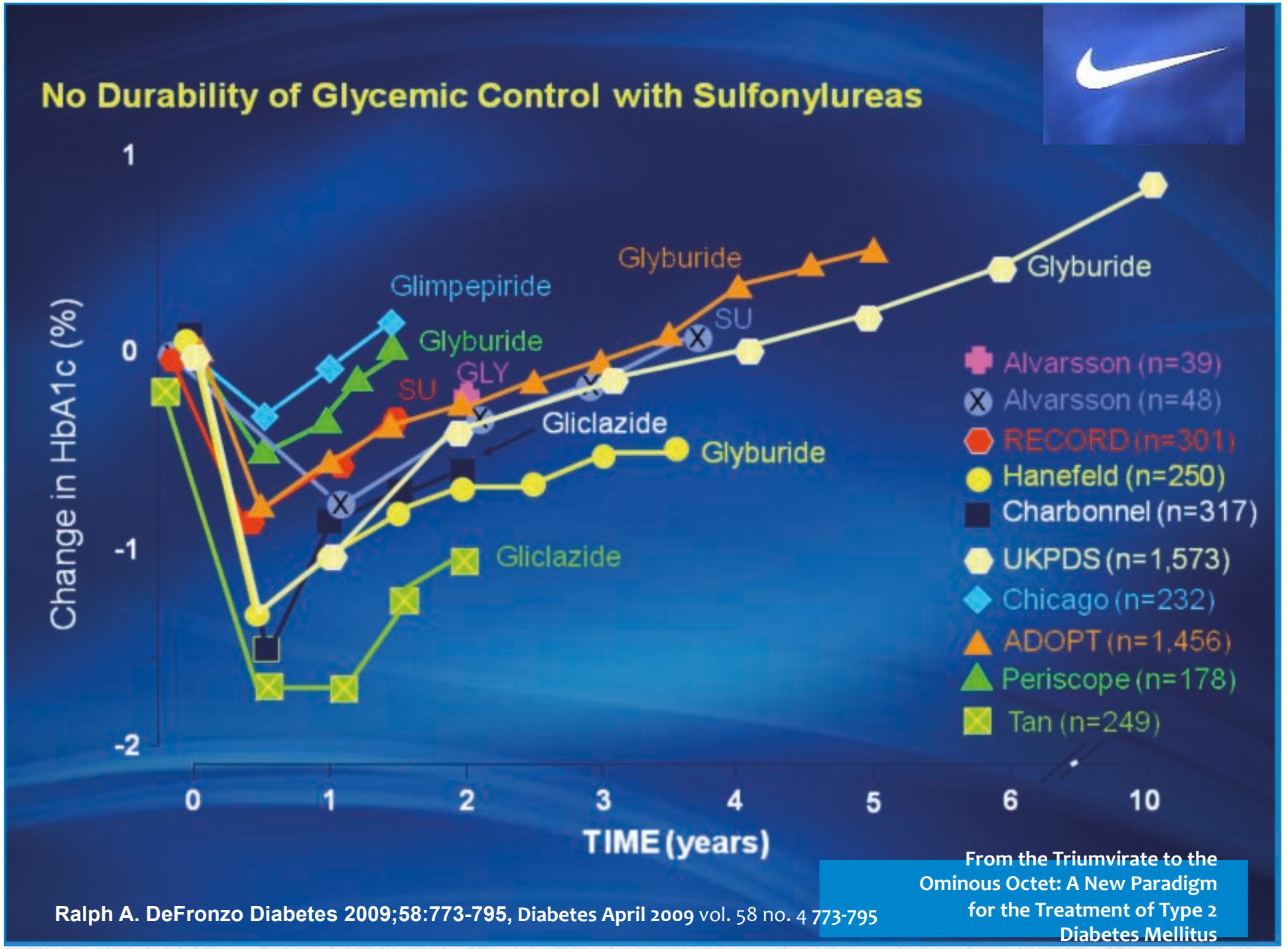
22/5/15

SUs

- Effective in controlling acute symptoms of T2DM in newly diagnosed but decreased response in long duration of disease
- Very low cost
- Hypoglycaemia risk - high
- Weight gain
- No evidence of CV benefit
- Potential adverse CV effects, ↑risk of CV death (su receptors →myocardium)
- Poor durability →tonic stimulation of beta cells→ promote beta cell failure
- Would SUs pass CV safety by FDA in current day ?







Ralph A. DeFronzo Diabetes 2009;58:773-795, Diabetes April 2009 vol. 58 no. 4 773-795

From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

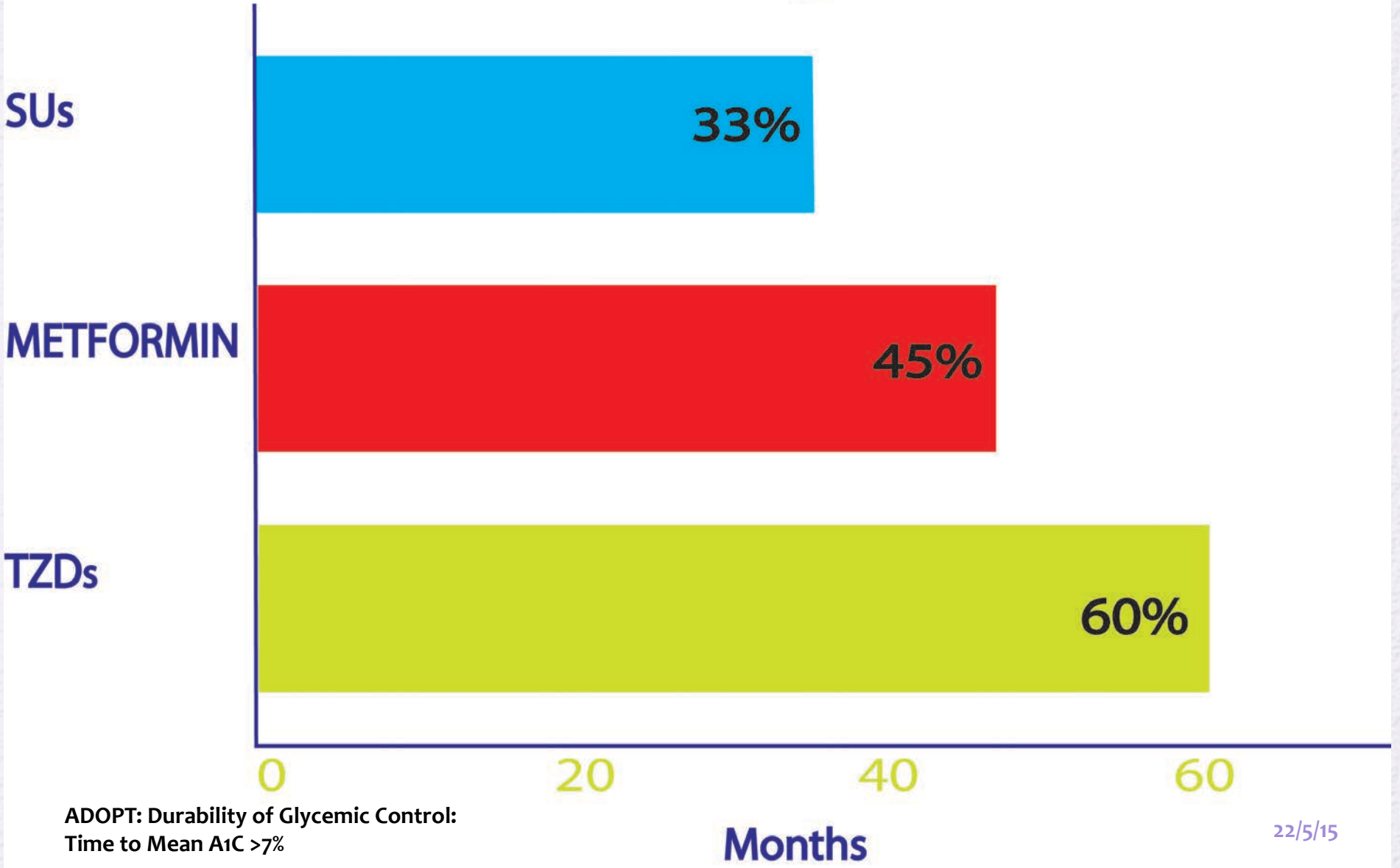
Pioglitazone

- Benefits exceed risks in many patients especially with insulin resistance *1*
- Potential ability to modify natural Hx of T2DM by beta cell preservation
- Inhibit hepatic gluconeogenesis & enhance insulin sensitivity in muscle and adipose tissue
- Low risk of hypos
- Cardio protective beyond glucose lowering →lipids(↑HDL,↓LDL), ↓inflammation*, ↓BP (post MI&CVA), ↓atherosclerosis* & CVD
- Fluid retention, weight gain, oedema →HF
- Bone demineralization….UL #
- Concerns re risk of bladder ca???

1, speaker's own experience

*Antiinflammatory and Antiarteriosclerotic Effects of Pioglitazone ..*Hypertension.* 2002;40:687-693

Durability of Glycaemic Control: Time to Mean HbA_{1c} >7%



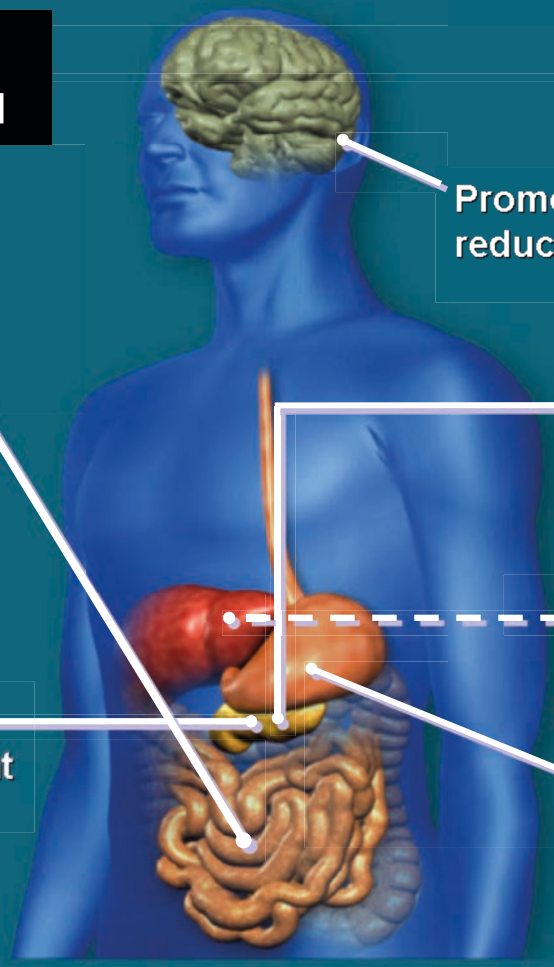
ADOPT: Durability of Glycemic Control: Time to Mean A1C >7%

Incretins

DPP4 inhibitors & GLP 1 RA

GLP-1 Effects in Humans

Understanding the Natural Role of Incretins



GLP-1 secreted upon the ingestion of food

↓ Beta-cell workload

Promotes satiety and reduces appetite

↑ Beta-cell response

Alpha cells:
↓ Postprandial glucagon secretion

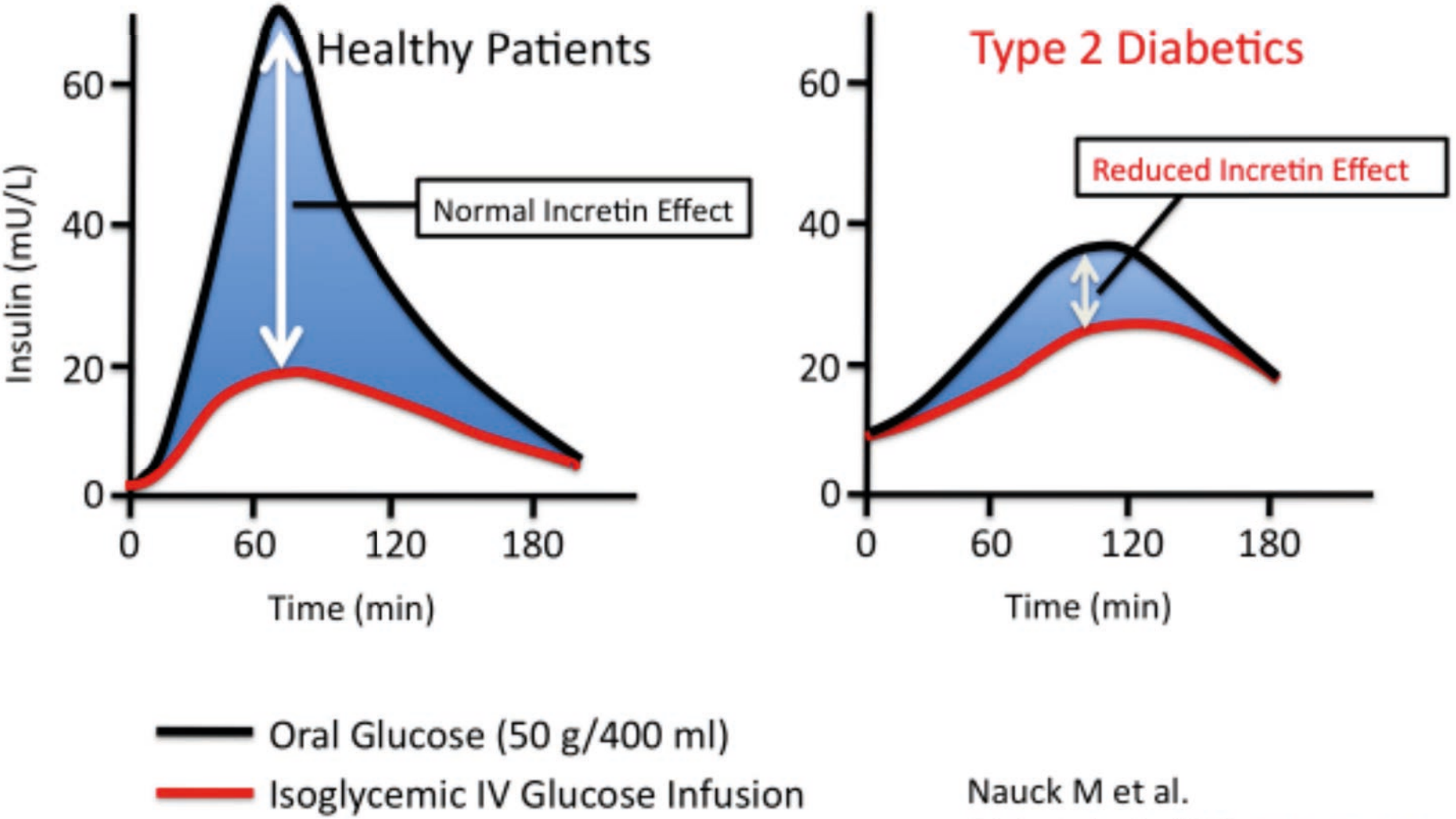
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

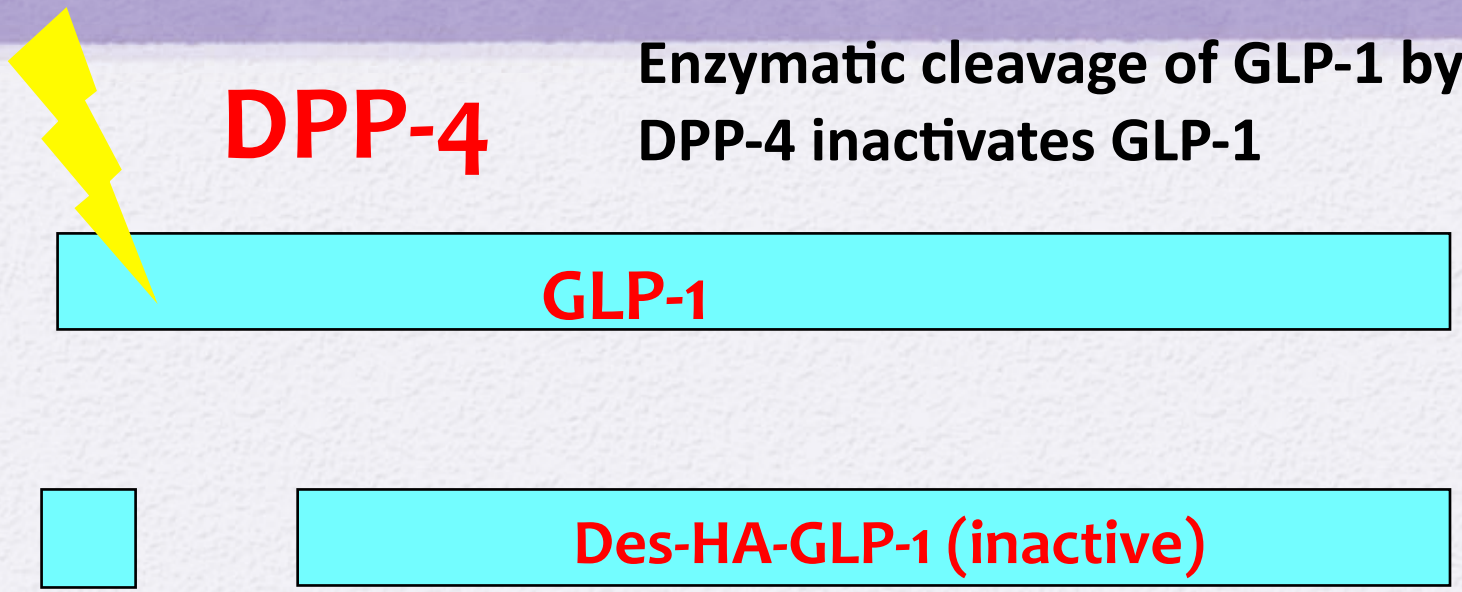
Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520
Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422
Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553
Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169

Diabetes & The "Incretin Effect"



Nauck M et al.
Diabetologia (1986) 29:46-52

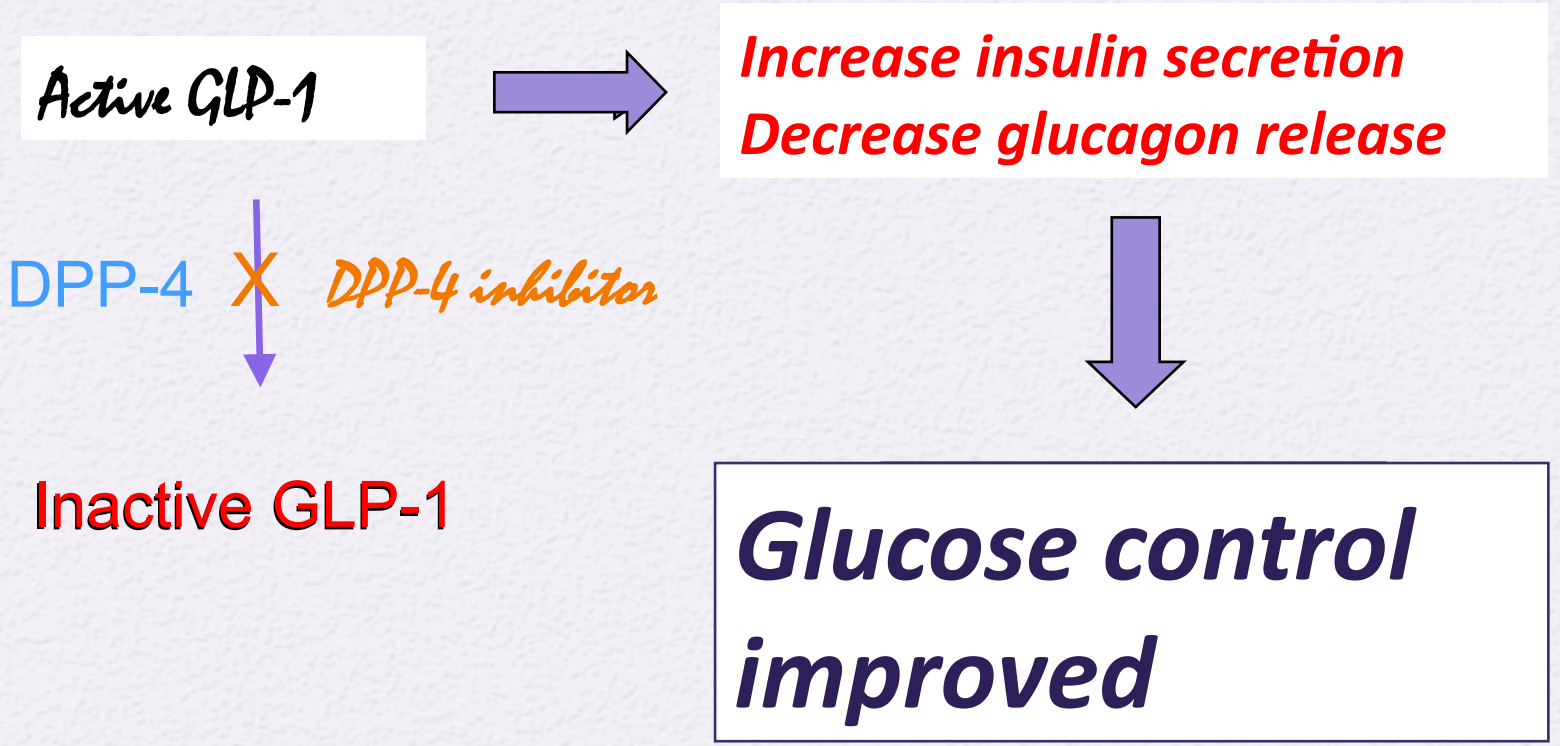
Degradation of GLP-1
half life 1-2 min



Two possible solutions to utilize GLP-1 action therapeutically:

1) Long-acting DPP-4-resistant GLP-1 analogues / incretin mimetics
2) DPP-4 inhibitors / incretin enhancers

Diagram of how DPP-4 inhibition might be expected to improve blood glucose control



DPP4 inhibitors

- Increase half life of GLP-1 by inhibiting DPP-4
- low risk of hypoglycaemia
- Weight neutral
- Oral, well tolerated,
- Reduces FPG & PPG
- HBA1C ↓ by 1 %
- Improves LVEF in AMI & LV function in CCF
- Favourable CV effects and BP reduction reported
- s/e nasopharyngitis

Cardiovascular effects of the DPP-4 inhibitors ,Tessey Jose and Silvio E Inzucchi
Diabetes & Vascular Disease Research 9(2) 109–116

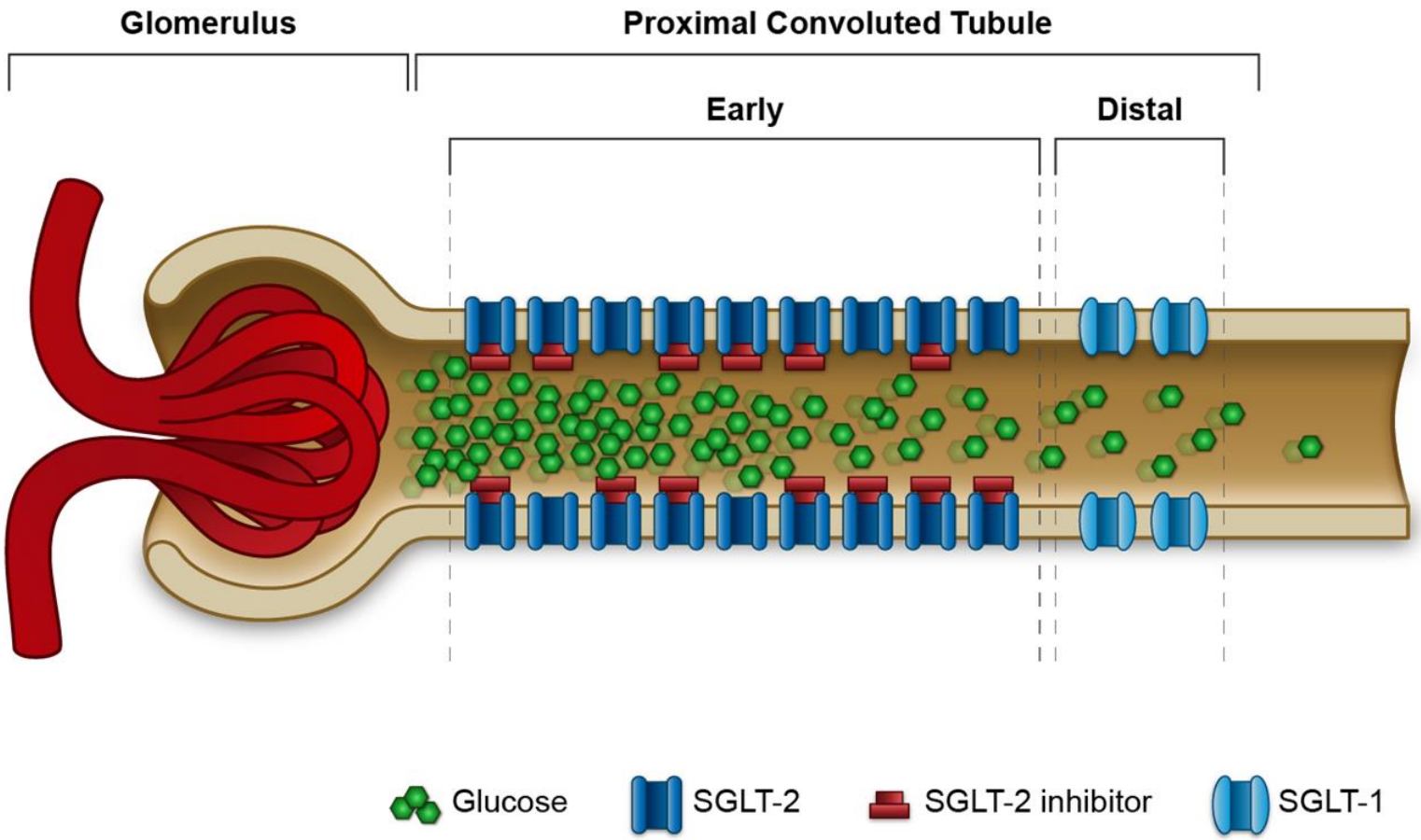
GLP1 RA

- Not degraded by DPP-4
- Given by s/c injection
- Principal advantage over insulin – facilitate weight loss and reduce appetite, increase satiety
- Low risk of hypoglycaemia
- 4 generations ; short acting – exenatide (BD), long acting-liraglutide (OD), Lixisenatide, Longer-acting once weekly Exenatide QW (Bydureon), dulaglutide
- s/e – Nausea, Vomiting, Diarrhoea

The role of the kidney in T2D and SGLT2 inhibition

Mechanism of Action

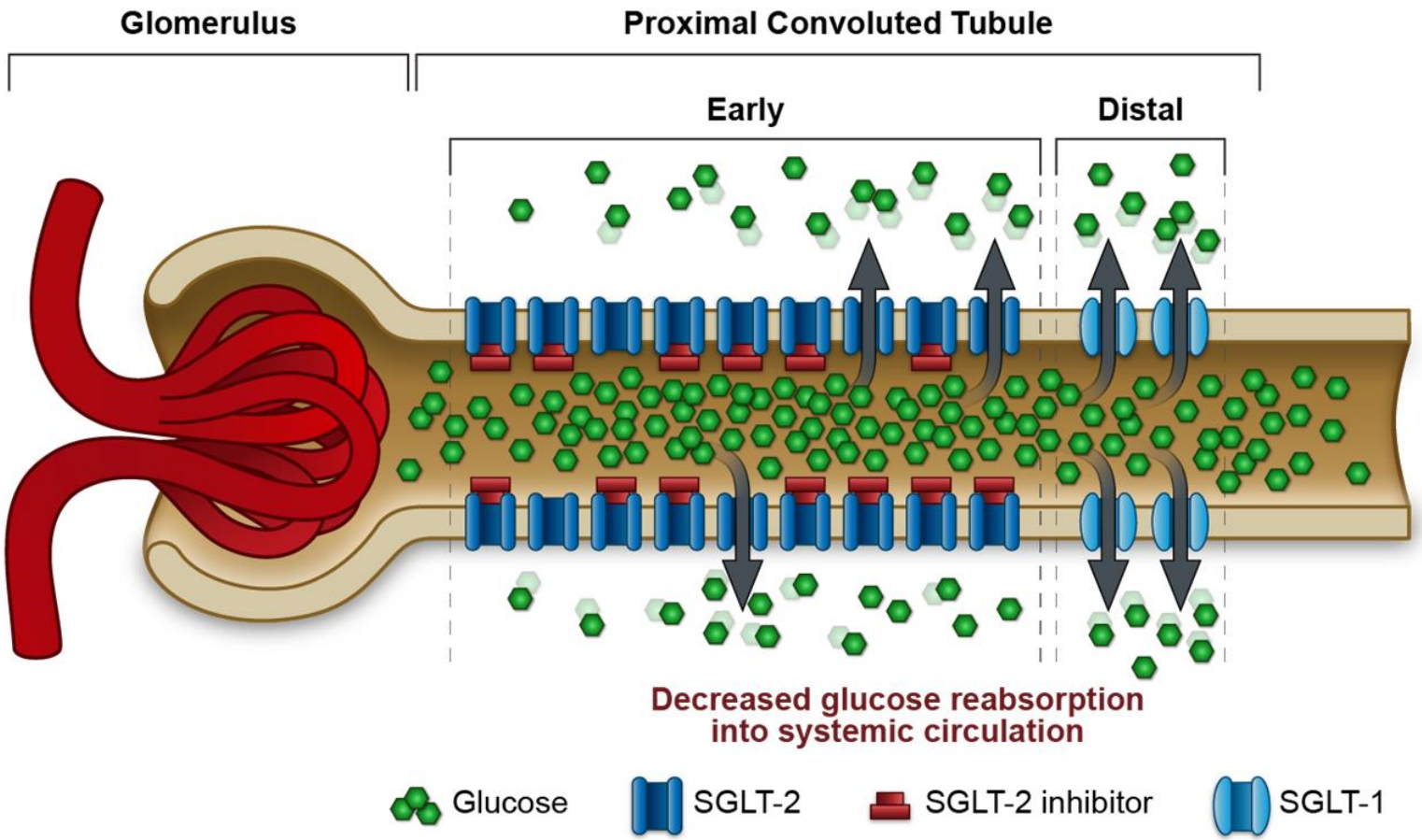
Increase the removal of glucose via SGLT2 inhibitors



Kanai Y, et al. *J Clin Invest*. 1994;93:397-404[18]; You G, et al. *J Biol Chem*. 1995;270:29365-29371[19]; Rothenberg PL, et al. EASD 2010:Abstract 876.[20]

Mechanism of Action (cont)

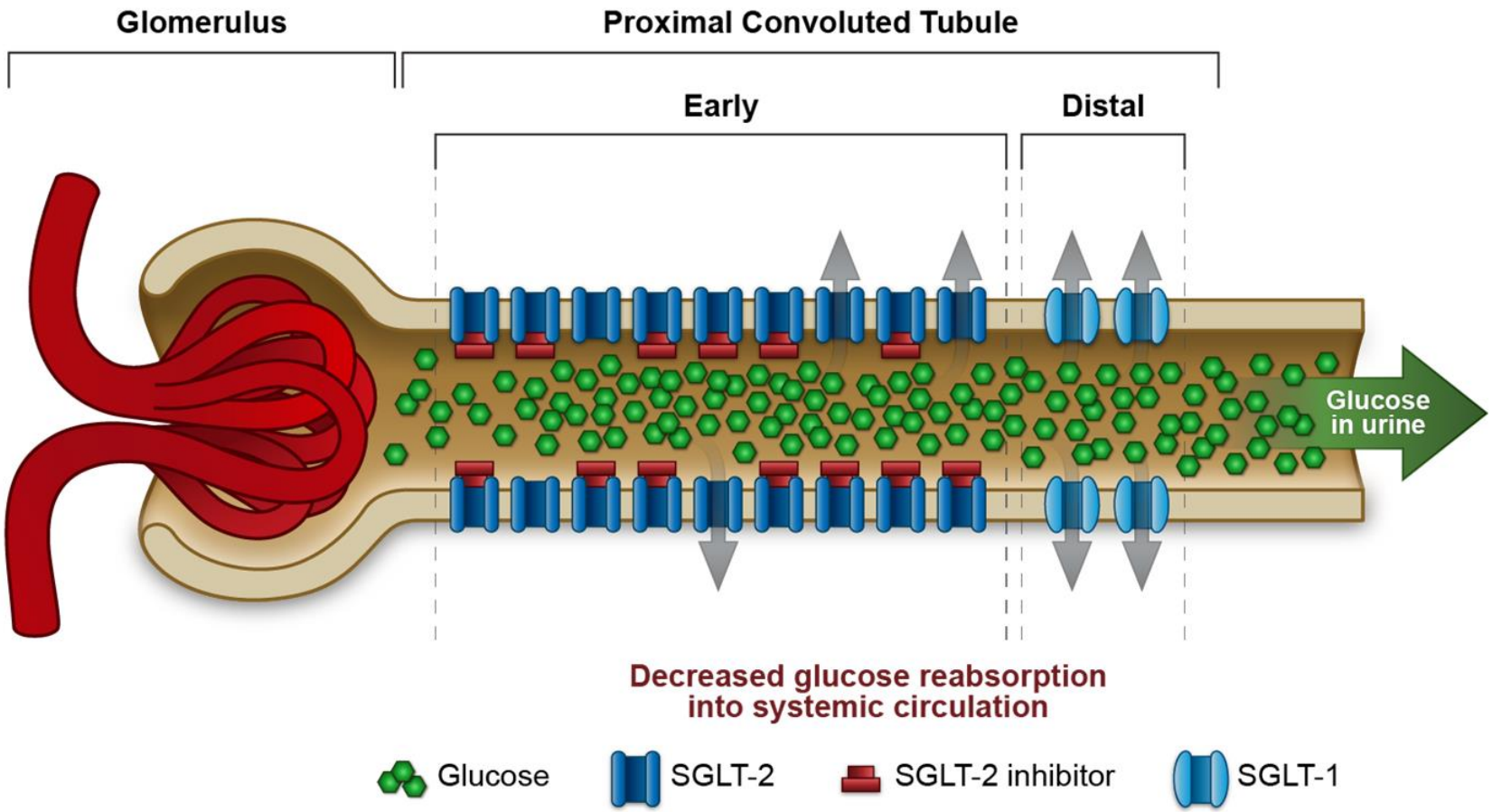
Increase the removal of glucose via SGLT2 inhibitors



Kanai Y, et al. *J Clin Invest*. 1994;93:397-404[18]; You G, et al. *J Biol Chem*. 1995;270:29365-29371[19]; Rothenberg PL, et al. EASD 2010:Abstract 876.[20]

Mechanism of Action (cont)

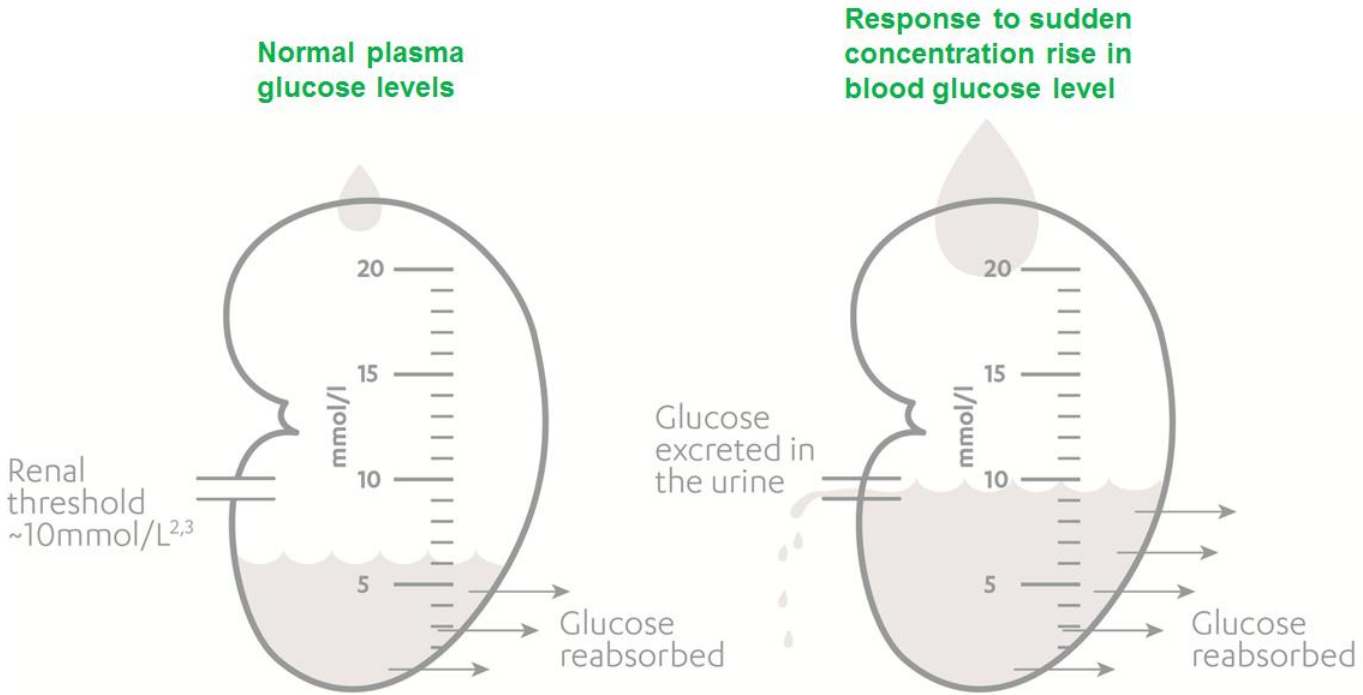
Increase the removal of glucose via SGLT2 inhibitors



Kanai Y, et al. *J Clin Invest*. 1994;93:397-404[18]; You G, et al. *J Biol Chem*. 1995;270:29365-29371[19]; Rothenberg PL, et al. EASD 2010:Abstract 876.[20]

Glucose reabsorption, renal threshold and hyperglycaemia in healthy individuals

The renal threshold is the 'tipping point' where the capacity of the SGLT2 inhibitors is exceeded, and excess glucose starts to be excreted in the urine [1]



Stylised representations of renal glucose reabsorption and urinary glucose excretion in healthy individuals [2,3]

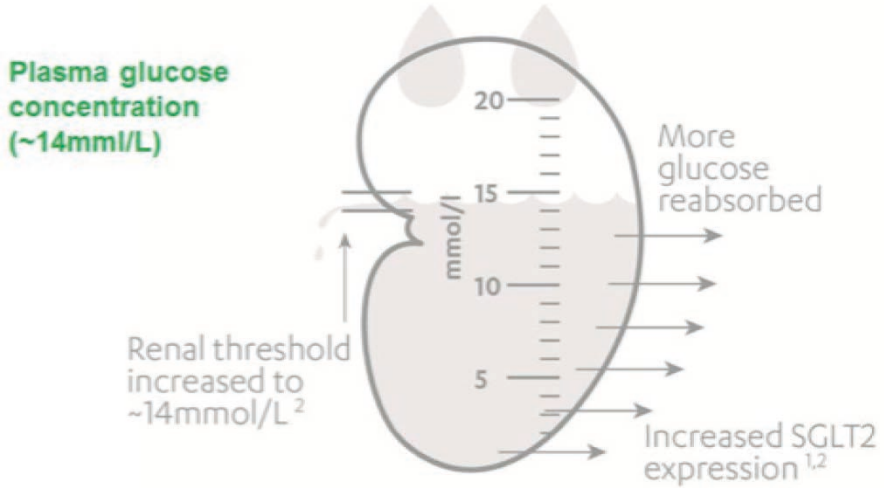
References: 1. [GERICH 2010] Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med. 2010 Feb;27(2):136-42.**2.** [DEFRONZO 2012] DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab. 2012 Jan;14(1):5-14. **3.** [NAIR WILDING 2010] Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab. 2010 Jan;95(1):34-42.

Glucose reabsorption, renal threshold and hyperglycaemia in poorly controlled T2DM

In T2DM, prolonged exposure to high levels of blood glucose cause the kidneys to adapt;

- Increased expression of SGLT2 transporters = increased glucose reabsorption into the blood [1,2]
- Renal threshold increases to ~14mmol/L [2]

Consequently more glucose is reabsorbed back into the blood, potentially causing further hyperglycaemia [1,2]

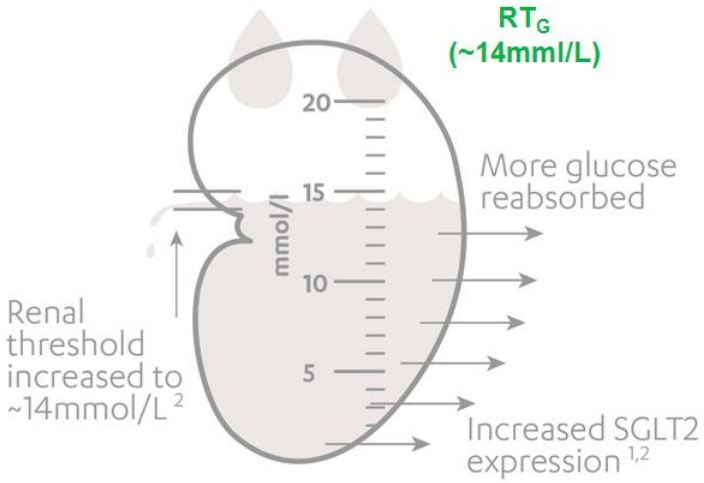


Renal glucose reabsorption and urinary glucose excretion in individuals with T2DM.
Adapted from Nair S and Wilding JP 2010 [1,2]

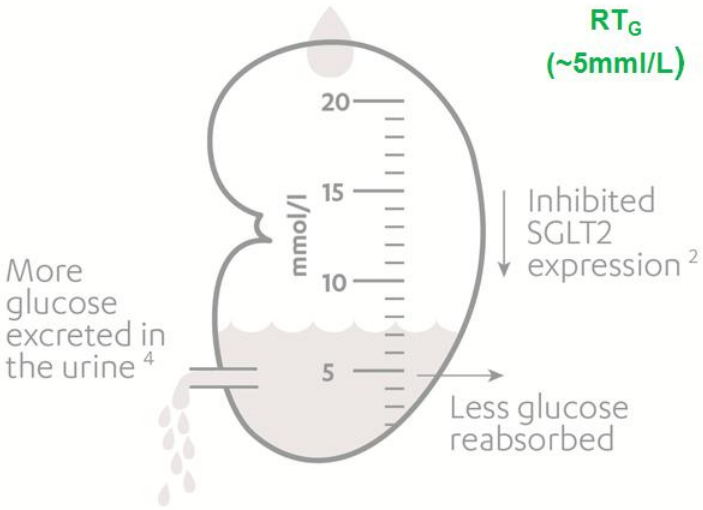
References: 1. [DEFRONZO 2012] DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab. 2012 Jan;14(1):5-14. **2.** [NAIR WILDING 2010] Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab. 2010 Jan;95(1):34-42.

Effects of SGLT2 inhibition on glucose reabsorption

In both healthy individuals and those with T2DM, inhibition of SGLT2 lowers the renal threshold (RT_G) at which glucose starts to be excreted in the urine [1-3]



Renal glucose reabsorption in individuals with T2DM [1, 2]

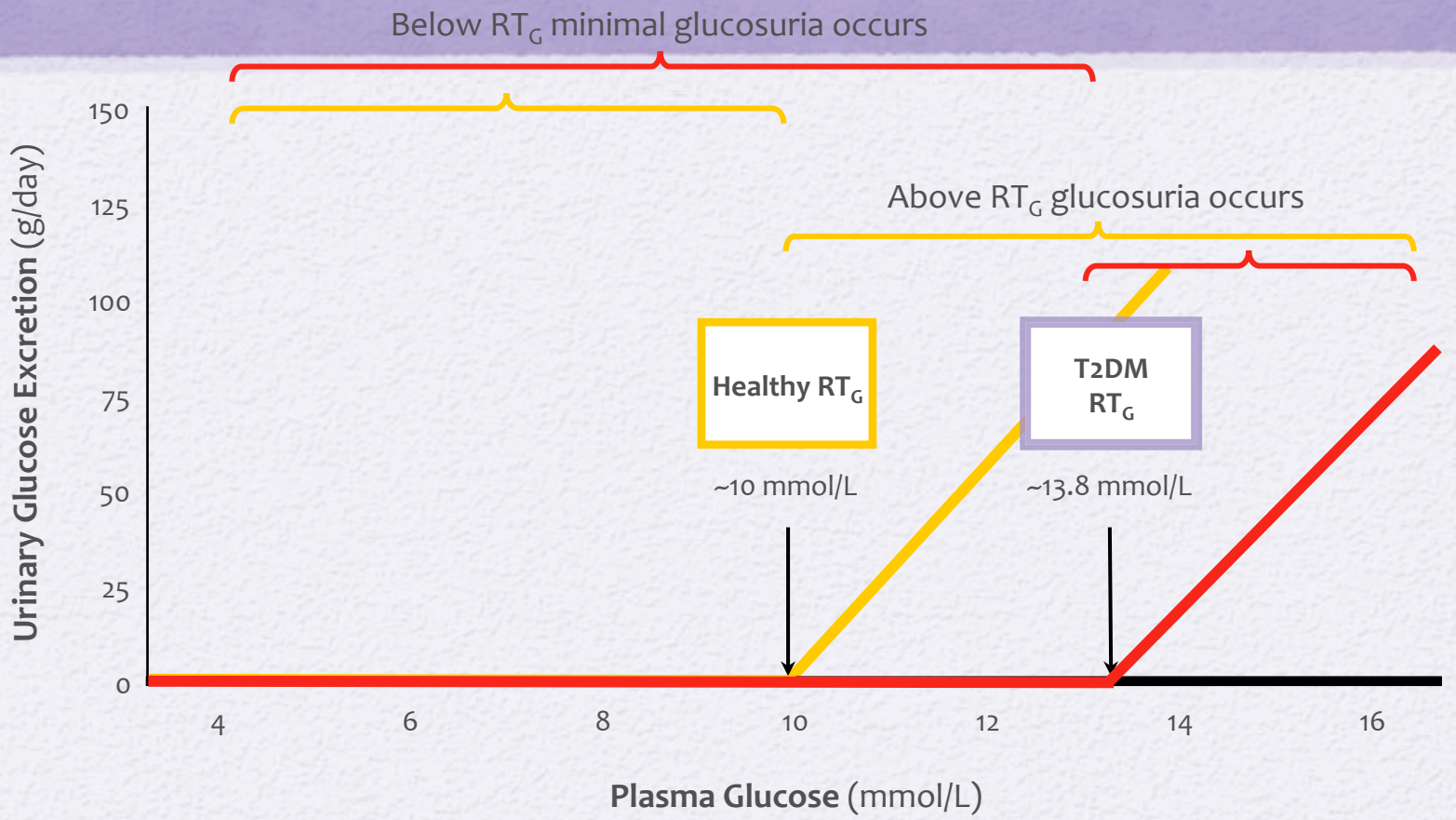


Renal glucose reabsorption in individuals with T2DM treated with an SGLT2 inhibitor [2]

In subjects with T2DM, treatment with an SGLT2 inhibitor lowers the mean RT_G from ~14mmol/L to ~5mmol/L[2]

References: 1. [DEFRONZO 2012] DeFronzo RA, Davidson JA, Del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab. 2012 Jan;14(1):5-14. **2.** [NAIR WILDING 2010] Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab. 2010 Jan;95(1):34-42. **3.** [MARSENIC 2009] Marsenic O. Glucose control by the kidney: an emerging target in diabetes. Am J Kidney Dis. 2009;53:875-83. **4.** [CHAO 2010] Chao EC and Henry RR. SGLT2 inhibition — a novel strategy for diabetes treatment. Nature Reviews Drug Discovery. AOP, published online 28th May 2010; doi: 10.1038/nrd3180.

The Renal Glucose Threshold (RT_G) is Increased in Subjects with Type 2 Diabetes

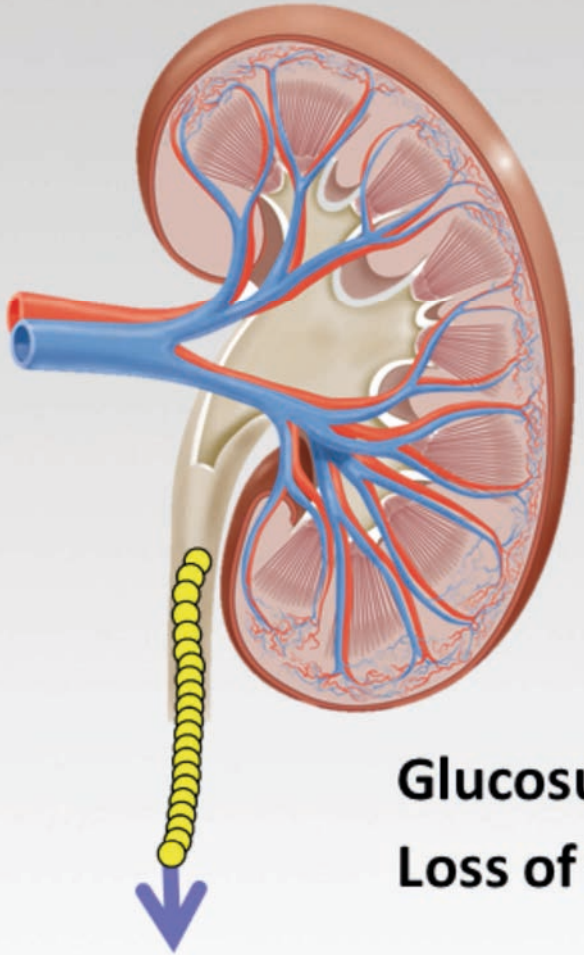


- Renal glucose reabsorption is increased in diabetes, which could contribute to further increasing plasma glucose levels

Polidori D et al. Poster presented at ADA 2010; Orlando, Florida.
Polidori D et al. Poster presented at EASD 2010; Stockholm, Sweden.

Effects of SGLT2 Inhibition

- Insulin-independent
- HbA1c Reduction
- Reduction of
  - FPG
  - PPG
  - Weight
- Reduction of blood pressure



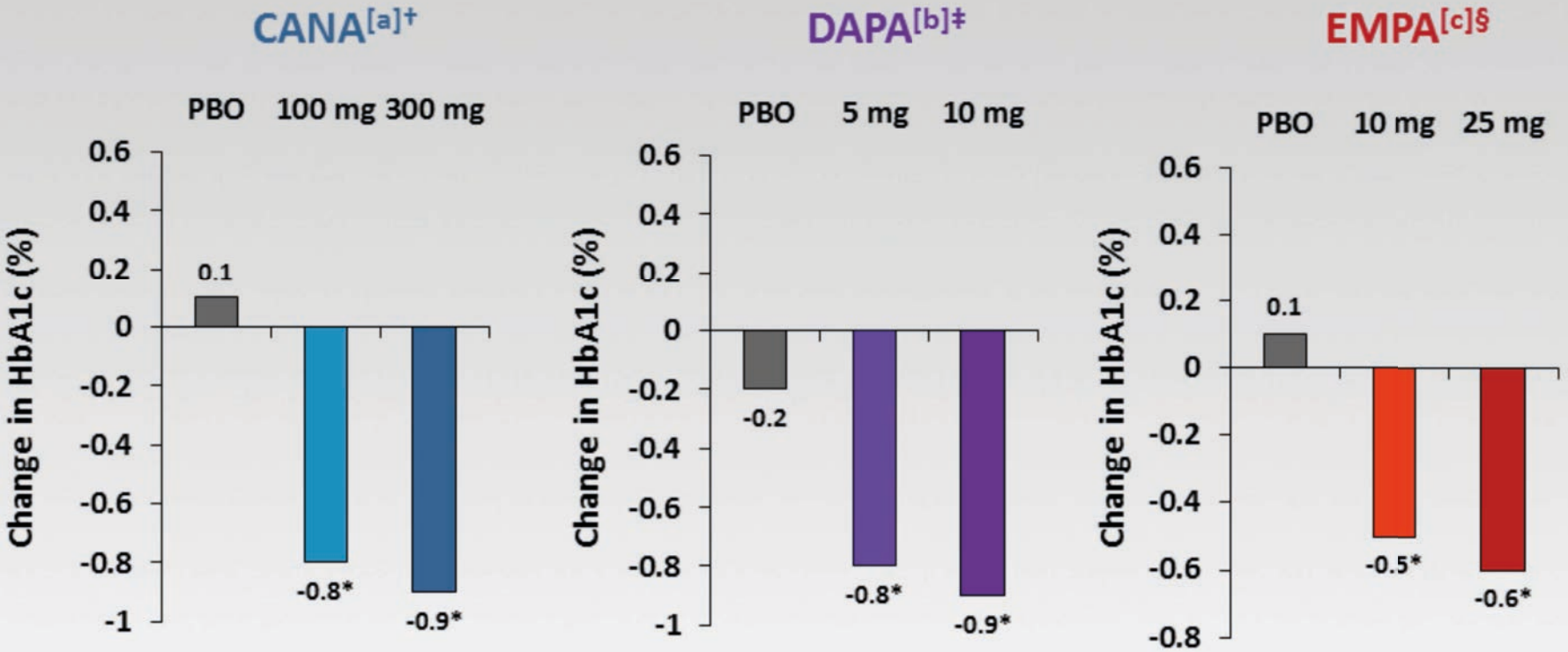
Glucosuria

Loss of Calories

Glucosuria

FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; PPG = postprandial glucose

SGLT2 Inhibitors: Glycemic Efficacy as Monotherapy



*P<.05 vs PBO

†12 weeks; baseline HbA1c = 8.1%

‡24 weeks; baseline HbA1c = 7.8%-8.0%

§ 12 weeks; baseline HbA1c = 7.9%

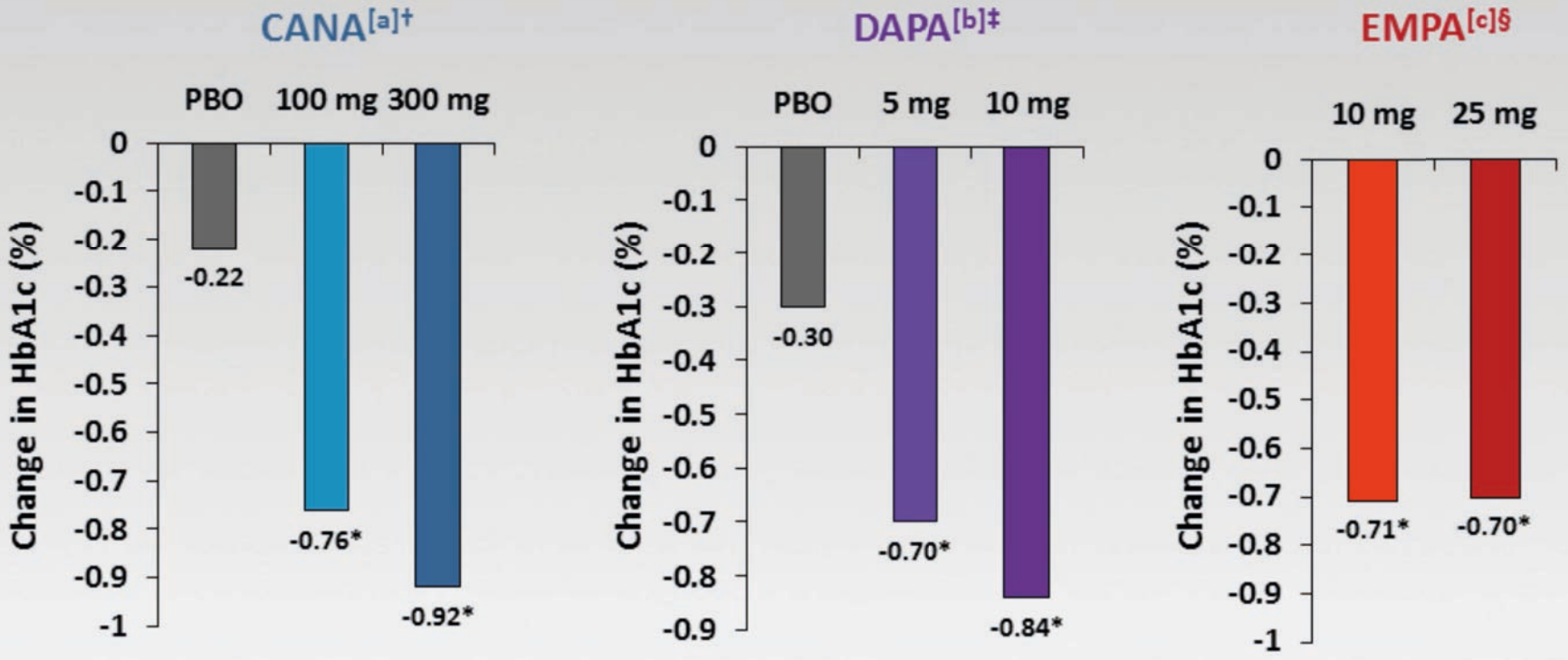
CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; PBO = placebo

a. Inagaki N, et al. *Diabetes.* 2011;60(Suppl 1):999-P.

b. Ferrannini E, et al. *Diabetes Care.* 2010;33:2217-2224.

c. Ferrannini E, et al. *Diabetologia.* 2010;53(Suppl 1):877.

SGLT2 Inhibitors: Glycemic Efficacy When Added to MET



*P<.05 vs PBO

†12 weeks; baseline HbA1c = 7.75%

‡24 weeks; baseline HbA1c = 7.9%-8.2%

§ 12 weeks; baseline HbA1c = 7.9%; mean PBO-subtracted change from baseline

MET = metformin

a. Rosenstock J, et al. *Diabetes Care*. 2012;35:1232-1238.

b. Bailey C, et al. *Lancet*. 2010;375:2223-2233.

c. Seman L, et al. *Diabetologia*. 2011;54(Suppl 1):147.

Role of SGLT2-Inhibition in Diabetes Management

SGLT2-inhibitors

- Improve glycemic control without increasing risk of hypoglycemia
- Are associated with weight reduction
- Are associated with reduction of blood pressure
- Are suitable for combination therapies with other therapeutic options

SGLT2 = sodium-glucose cotransporter 2

Takeaways……..

- Aggressive Rx must be started early in disease to achieve the legacy effect and prevent progressive beta cell failure
- CV risk reduction → focus of diabetes care beyond glucose management
- Treatments must be individualized according to age, life expectancy, disease duration and complications
- Hypoglycaemia must be avoided at all costs
- Personalized care should be the cornerstone of good diabetes management