Medicines Individualisation in Diabetes

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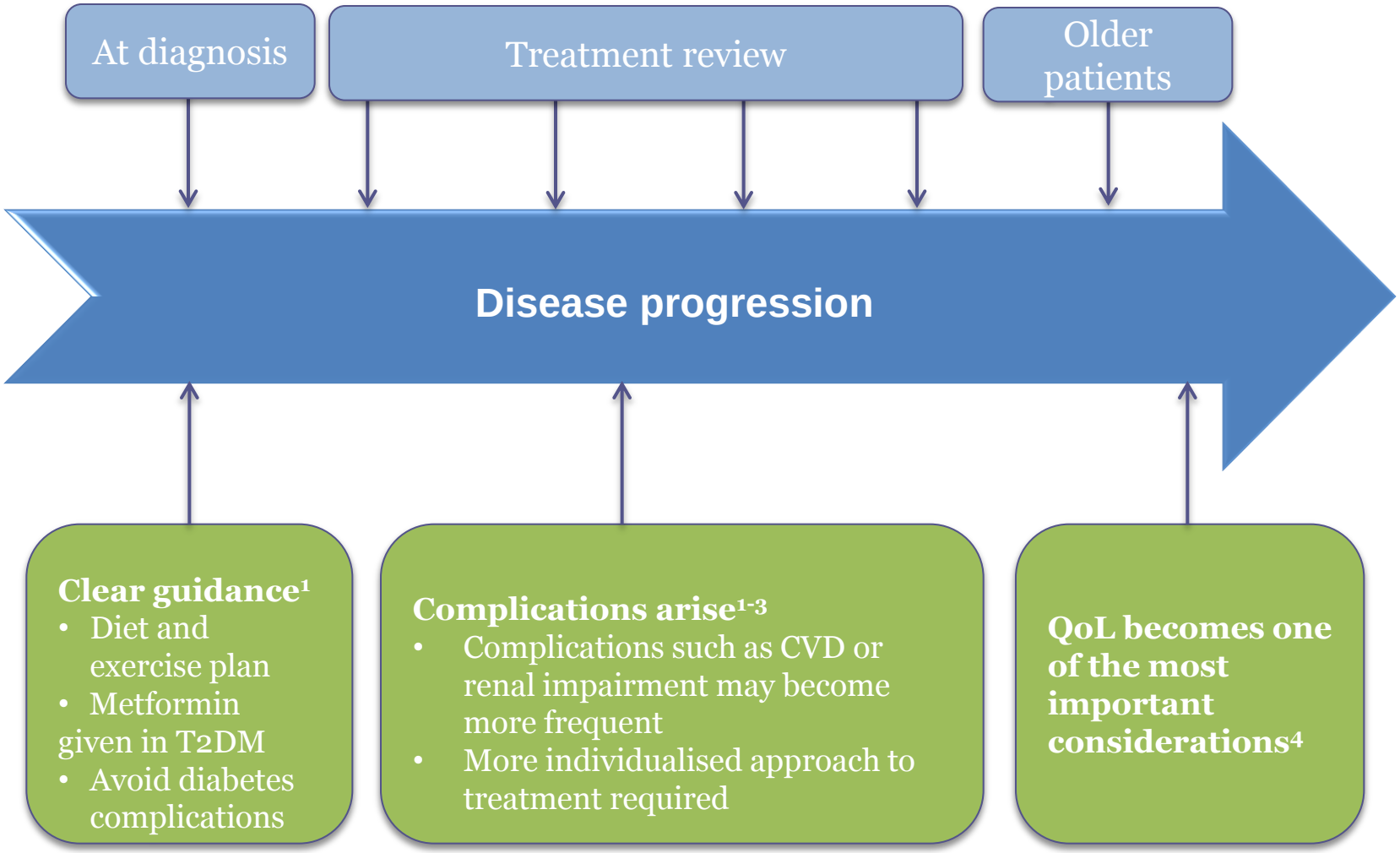
Objectives

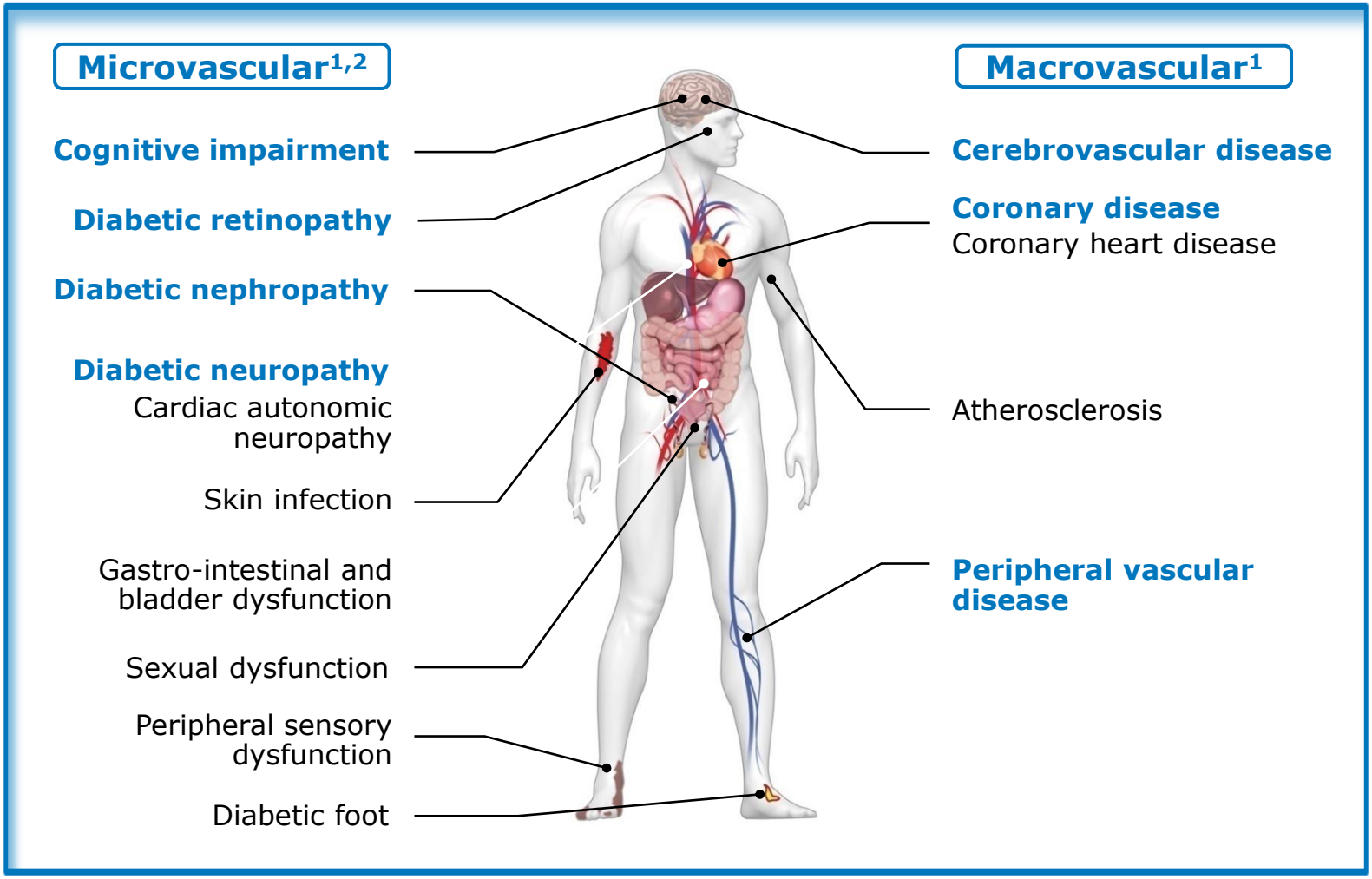
- List the current treatments available in type 2 diabetes
- Identify the patient factors that influence treatment decisions
- Use this information to identify the most suitable treatment for your patient

Diabetes becomes more complex over time



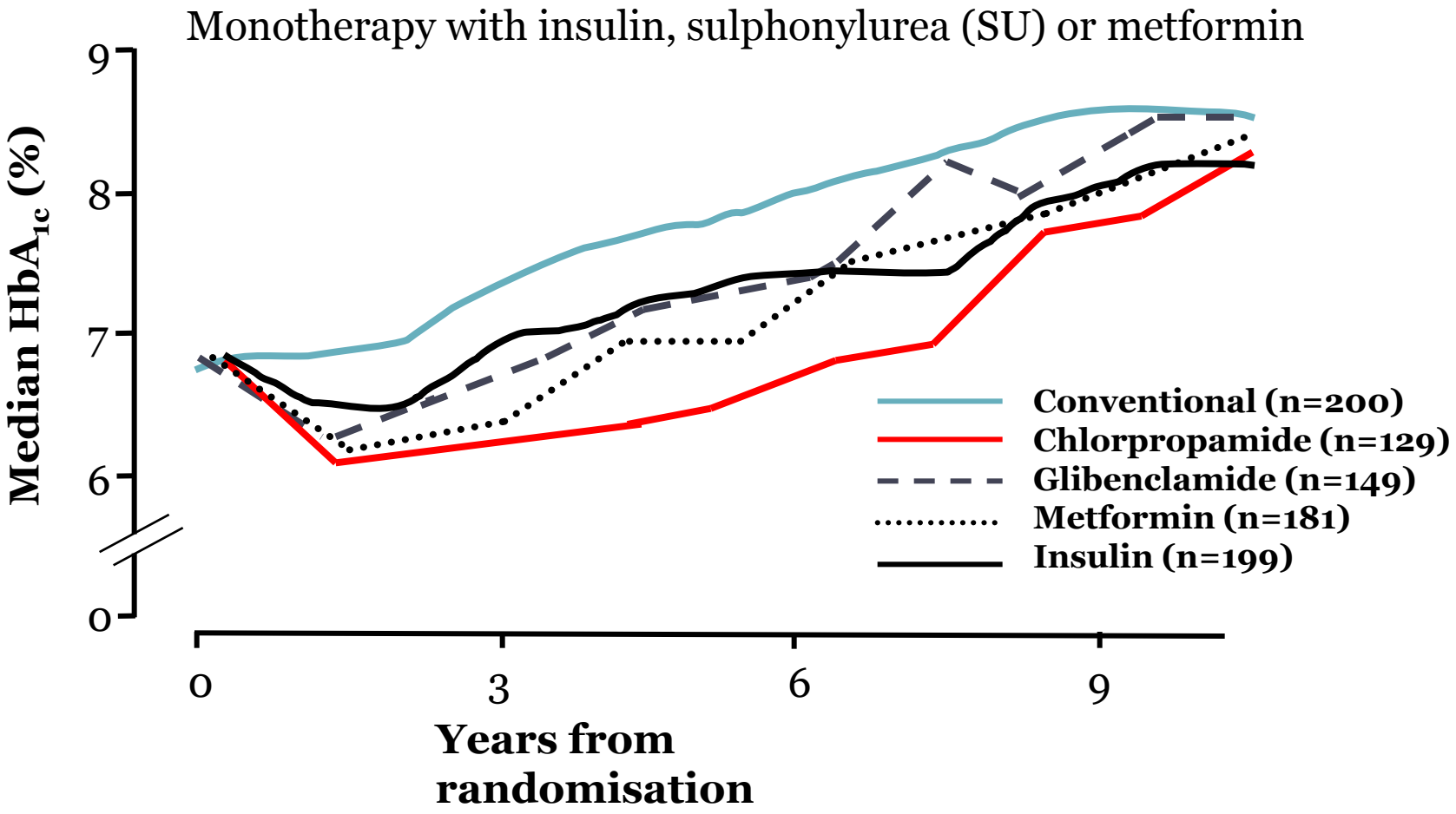
1. Adapted from National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide.
2. NICE clinical guideline 66: Type 2 Diabetes Management. Available at: http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf (last accessed January 2013).
3. Go AS, et al. N Engl J Med 2004;351:1296-1305; 4. John E. Morley. Diabet Med 1998;15 (Suppl. 4): S41–S46.

Complications of diabetes



Adapted from: 1. International Diabetes Foundation. Time to Act: Type 2 diabetes, the metabolic syndrome and cardiovascular disease in Europe. 2006. Available at: www.idf.org/webdata/docs/IDF_T2D_slides_final_aug06.ppt Last accessed February 2013.
2. Seaguist ER. *Diabetes* 2010;**59**:4-6.

UKPDS (T2DM): Glycaemic control worsens over time

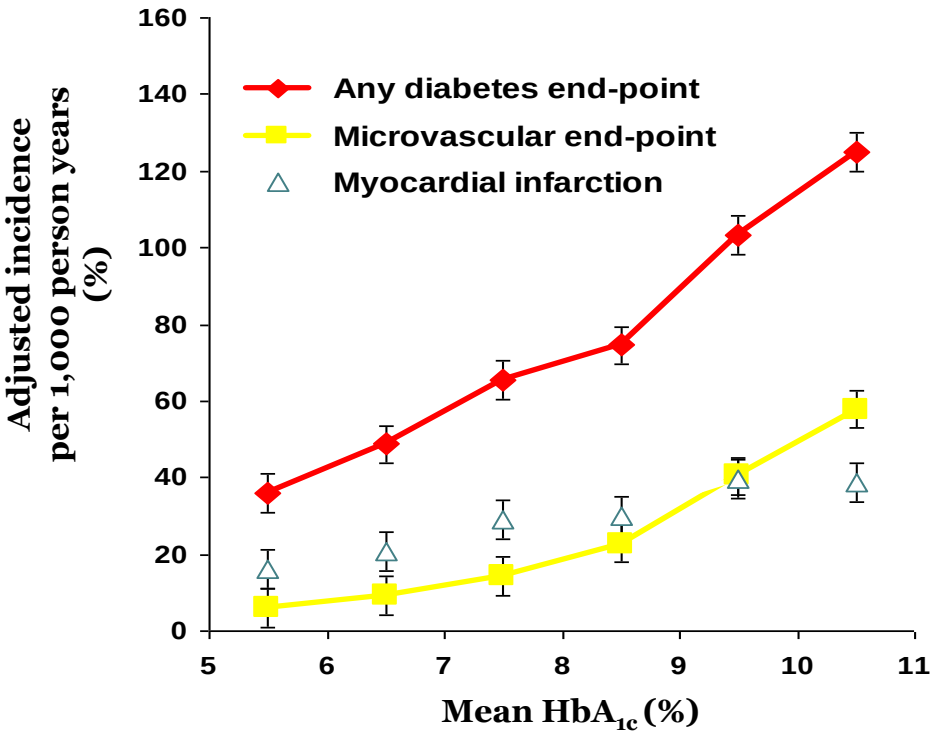


UKPDS Group. *Lancet* 1998;352:854-865.

UKPDS: Improving HbA_{1c} control reduces diabetes-related complications

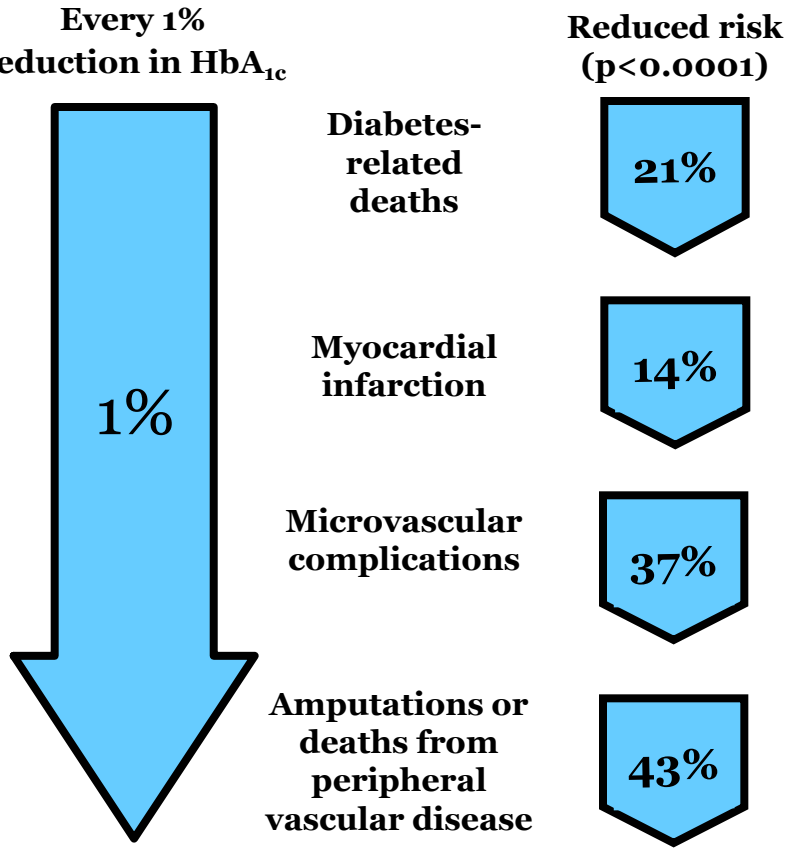
Incidence of complications

n=4,585



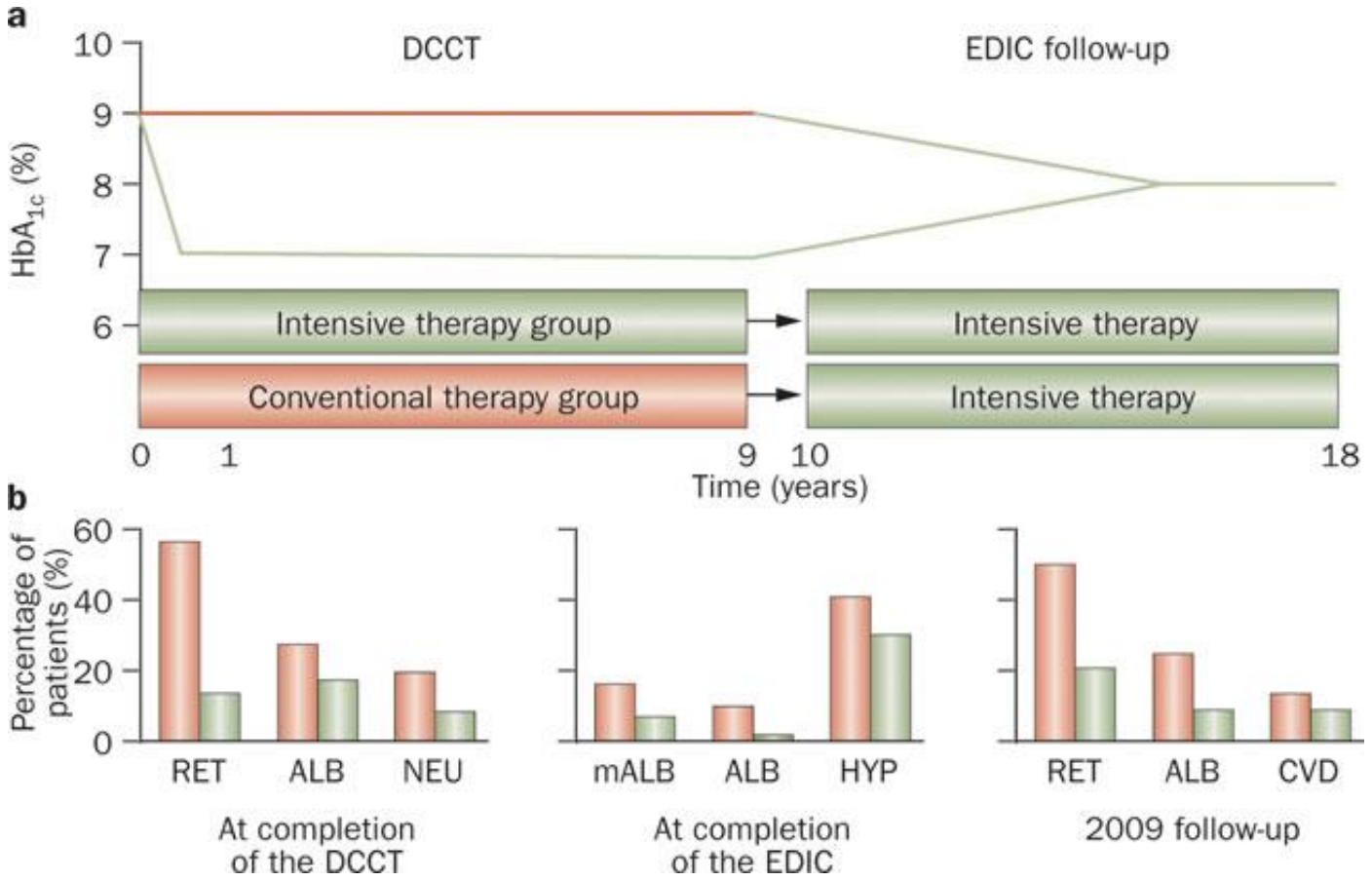
Relative risk

n=3,642



Stratton IM et al. *BMJ* 2000;321:405-412.

DCCT-EDIC (T1DM): Complications continue to rise even if glucose control is improved

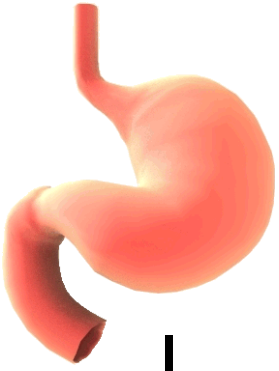


Pirola, L. *et al.* (2010) Epigenetic phenomena linked to diabetic complications *Nat. Rev. Endocrinol.*

How do we choose a treatment?

- Follow a guideline?
- Pick a favourite?
- Read all of the evidence?
- Think about cost?
- Listen to the patient?

Drug treatments for Type 2 diabetes

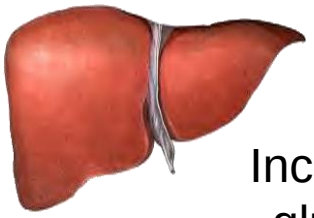


Biguanides
GLP-1 agonists
DPP-4 inhibitors

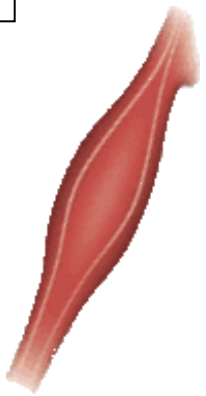
Acarbose

Glucose absorption

Biguanides
Thiazolidinediones



Hyperglycaemia

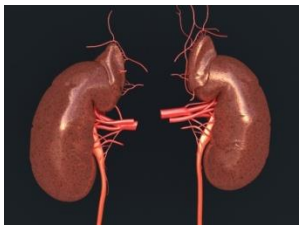


Increased glucose production

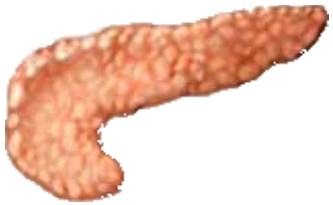
Decreased glucose uptake

Insulin
Sulfonylureas
Meglitinides
GLP-1 agonists
DPP-4 inhibitors

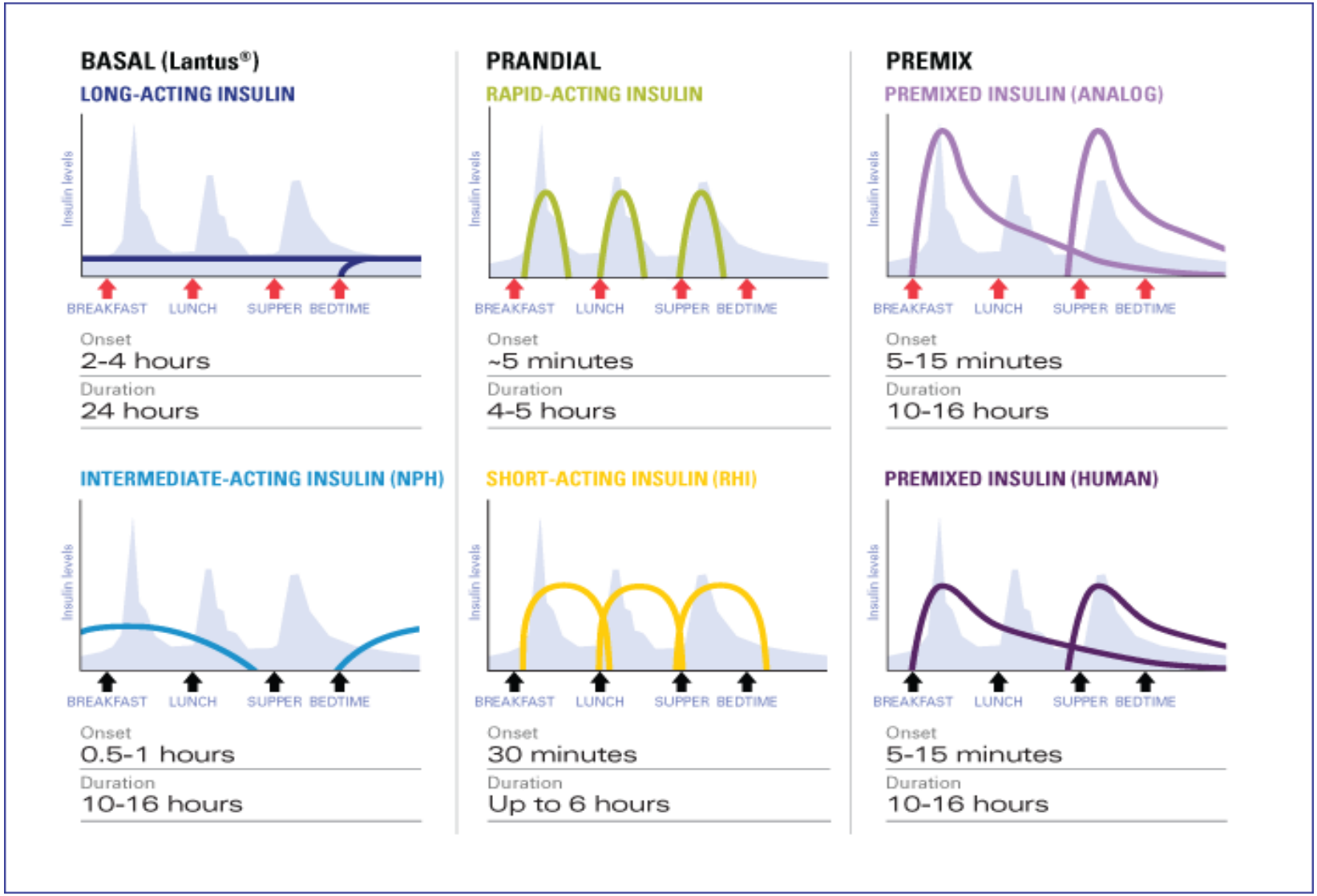
Impaired Insulin secretion



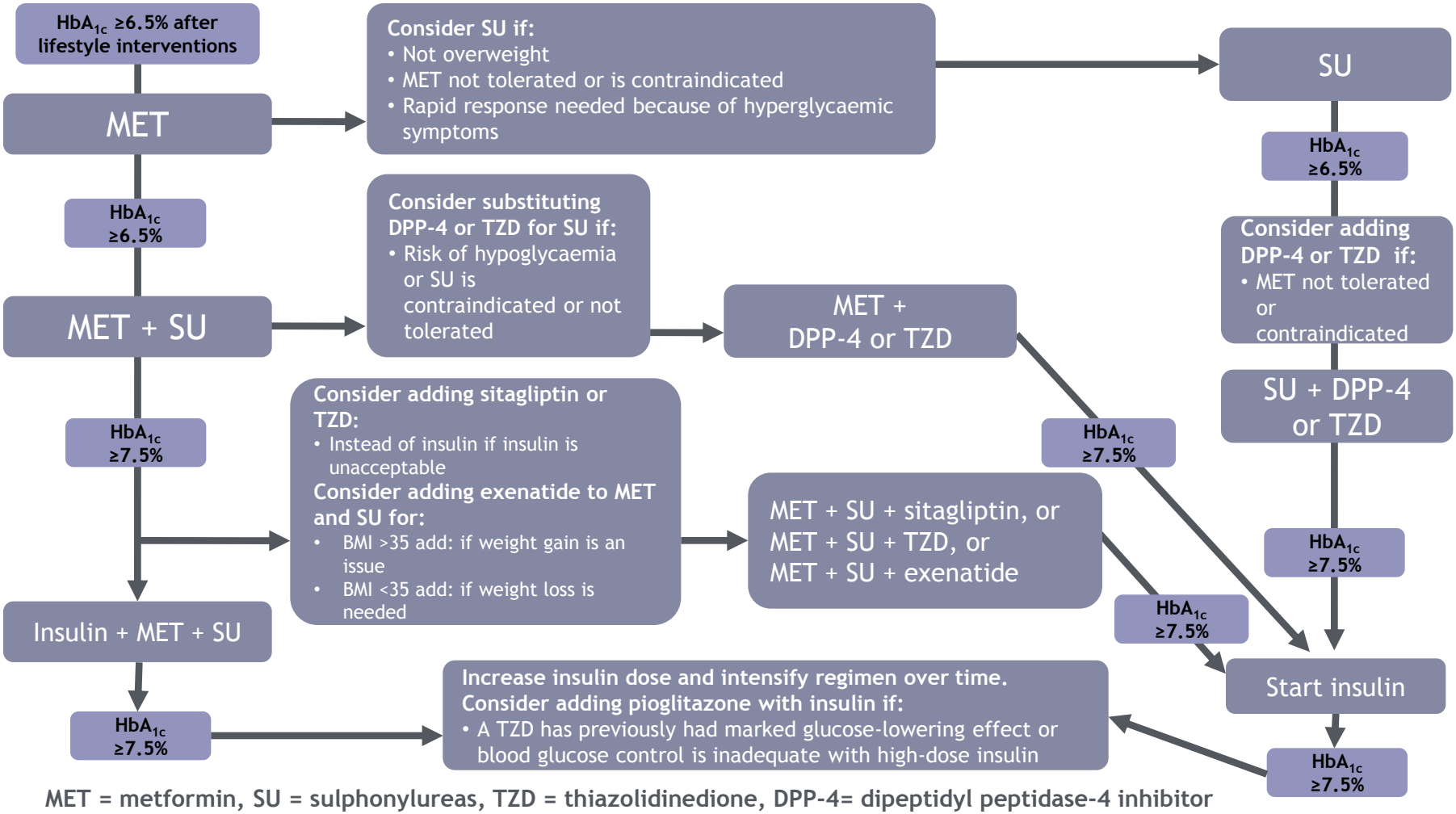
SGLT-2 inhibitors



Drug treatment for Type 1 Diabetes: Insulin



National Institute for Health and Clinical Excellence (NICE): T2D treatment algorithm



MET = metformin, SU = sulphonylureas, TZD = thiazolidinedione, DPP-4= dipeptidyl peptidase-4 inhibitor

Adapted from: National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes - newer agents (a partial update of CG66): quick reference guide. Available at: http://www.nice.org.uk/nicemedia/pdf/CG87ShortGuideline.pdf (last accessed January 2013).

National Institute for Health and Clinical Excellence (NICE): T1D treatment algorithm

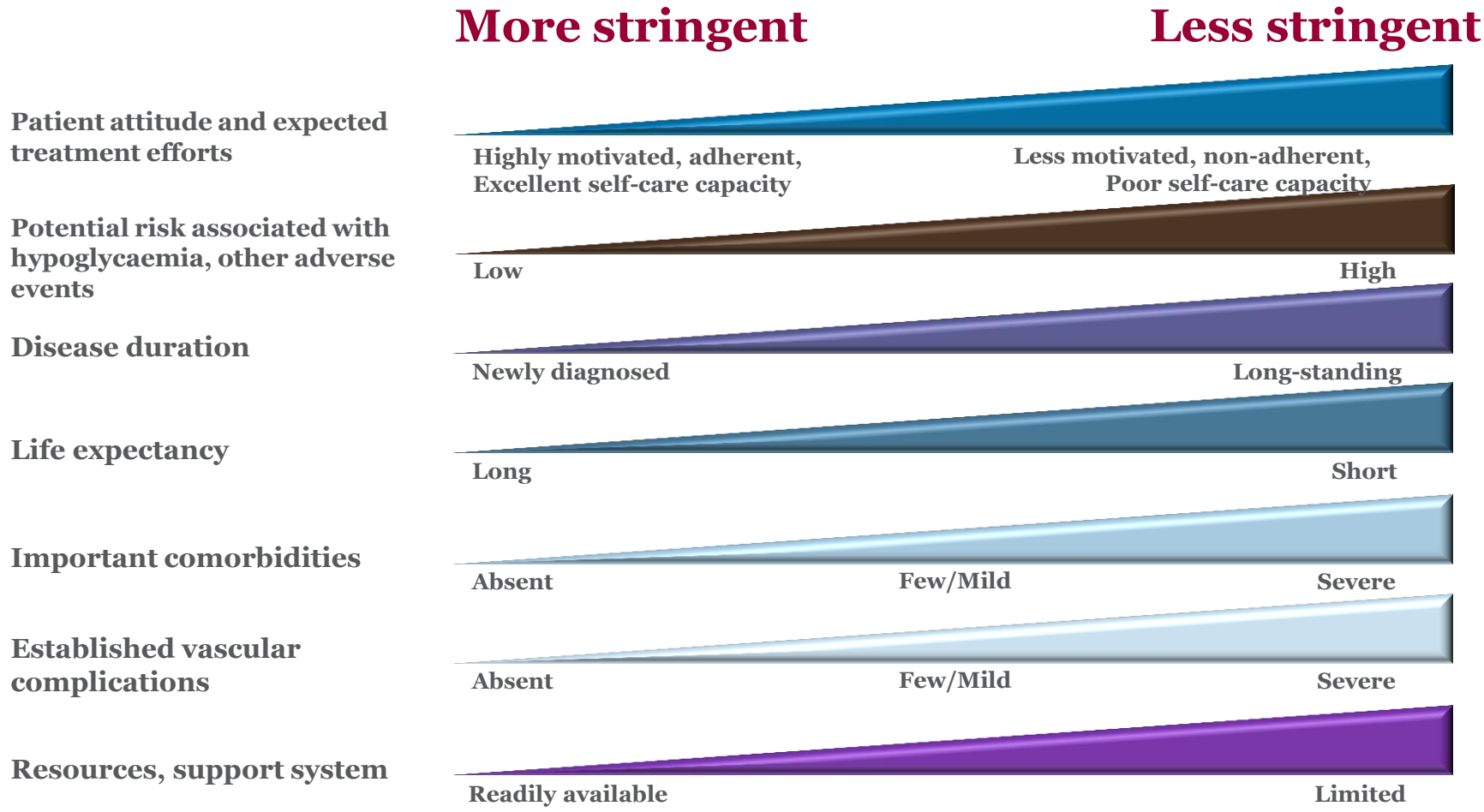
- Prescribe the type of insulin that allows optimal well-being
- Use multiple insulin injection regimens in an integrated package with education, food, skills training and appropriate self-monitoring.
- Other options include twice-daily insulin regimens (although newer evidence no longer recommends this)
- Avoid the general use of oral glucose-lowering drugs in people with type 1 diabetes.
- Provide the device that allows optimal well-being

Adapted from: National Institute for Health and Clinical Excellence. Clinical Guideline 815 Type 1 diabetes : Diagnosis and managements of children, young people and adults Available at: http://publications.nice.org.uk/type-1-diabetes-cg15/guidance (last accessed May 2014).

Follow the guideline – find the treatment?

- Guidelines are published based on 'averaged' population data
- Treatments with the best evidence form the backbone of all recommendations
- No consideration given to special populations unless identified during guideline protocol

The EASD and ADA recommend an individualised approach to manage hyperglycaemia (T2DM)



Adapted from Inzucchi SE, et al. Diabetes Care 2012;35:1364–1379 and Ismail-Beigi F, et al. Ann Intern Med 2011;154:554–9.

Figure depicts elements to consider when making decisions about HbA1c targets for specific patients. The scale is not designed to be applied rigidly but to serve as a broad framework to assist in determining glycaemic targets.

Adapted from: Inzucchi SE, et al. Diabetes Care 2012;35:1364–1379.

The ADA / EASD 2012 supports the individualised treatment approach

All treatment decisions should be made in conjunction with the patient

- Unless contraindicated, metformin is the optimal 1st-line drug (T2DM)
- Glycaemic targets and glucose-lowering therapies must be individualised
- After metformin, combination therapy is reasonable, aiming to minimise side effects where possible
- Comprehensive cardiovascular (CV) risk reduction must be a major focus of therapy

Consider: age, weight, sex / racial / ethnic / genetic differences and co-morbidites

Diet, exercise and education remain key

Adapted from Inzucchi SE et al. *Diabetes Care* 2012 ; 35: 1364-1379.

Inzucchi SE, et al. *Diabetes Care* 2012;35:1364–1379.

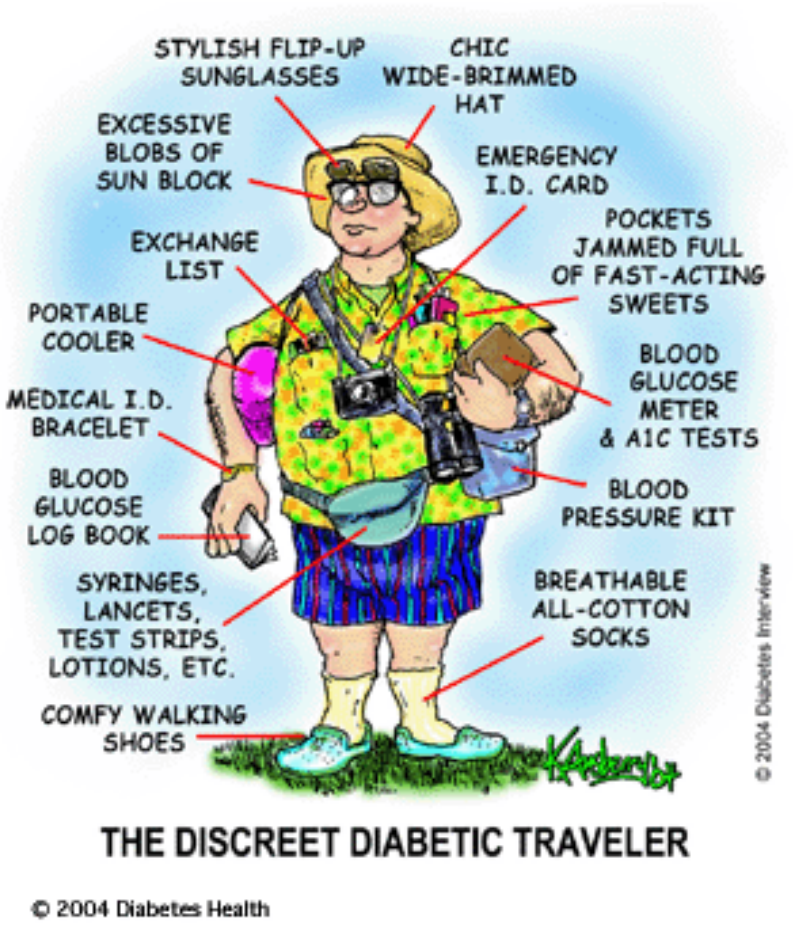
What patient factors affect diabetes control?

Factors affecting Diabetes Control

- Food
- Alcohol
- Exercise
- Travel
- Medication
- Illness
- Complications and co-morbidities
- Menstruation and menopause
- Stress

Some personal stories….

Travel



Preparation is KEY!

Consider:

- Food (and alcohol)
- Activity
- Temperature
- Medication
- Current control
- Ability to adjust treatment?

Food

Carb counting
Portion size
Fat content
Reference points
Blood glucose monitoring
Lactose / gluten intolerance
Individual reaction

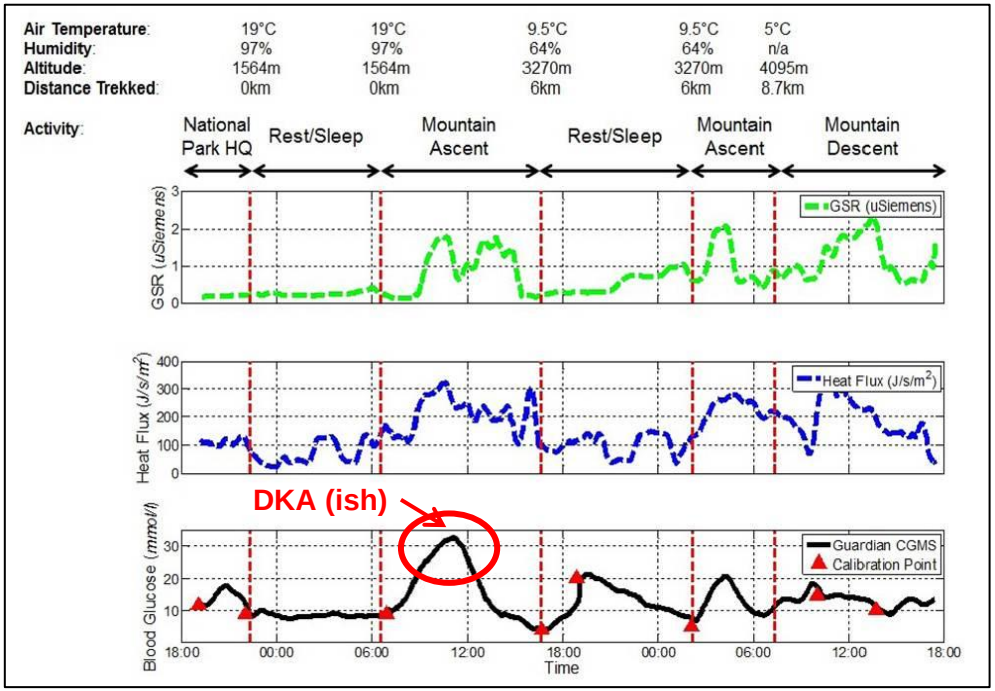
Alcohol

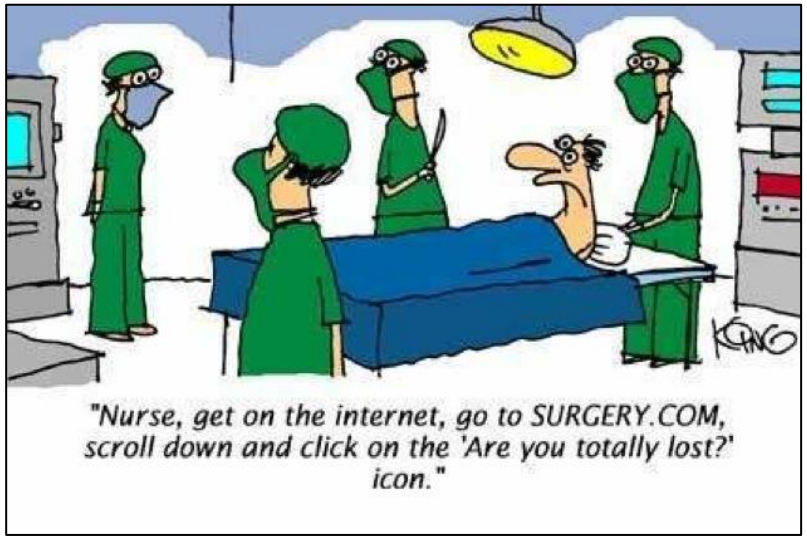
Effect on blood glucose
Effect on liver
Calories
Delayed hypoglycaemia

Exercise

Type of exercise
Timing of exercise
Food
Delayed effects

Illness





Sick Day Rules:

- Continue to give insulin
- Maintain high fluid levels
- Monitor blood glucose
- Test for ketones
- Stop metformin, continue other meds

Admission for surgery:

- Lack of understanding
- Starvation Period
- ‘Forced’ to eat

Hypoglycaemia

Symptoms of hypos
Timing of hypos
Hypo awareness
Fear of hypos
Driving

Rule of thirds:

- >3.0 mmol/l – 1/3 bottle of 380ml Lucozade
- 2.0-2.0 mmol/l – 2/3 bottle of 380ml Lucozade
- <2.0 mmol/l – whole bottle of 380ml Lucozade

Or a glass of juice, 6 jelly beans or 3-5 dextrose tablets

T2DM on tablets: Treat the same HOWEVER high risk of prolonged hypos

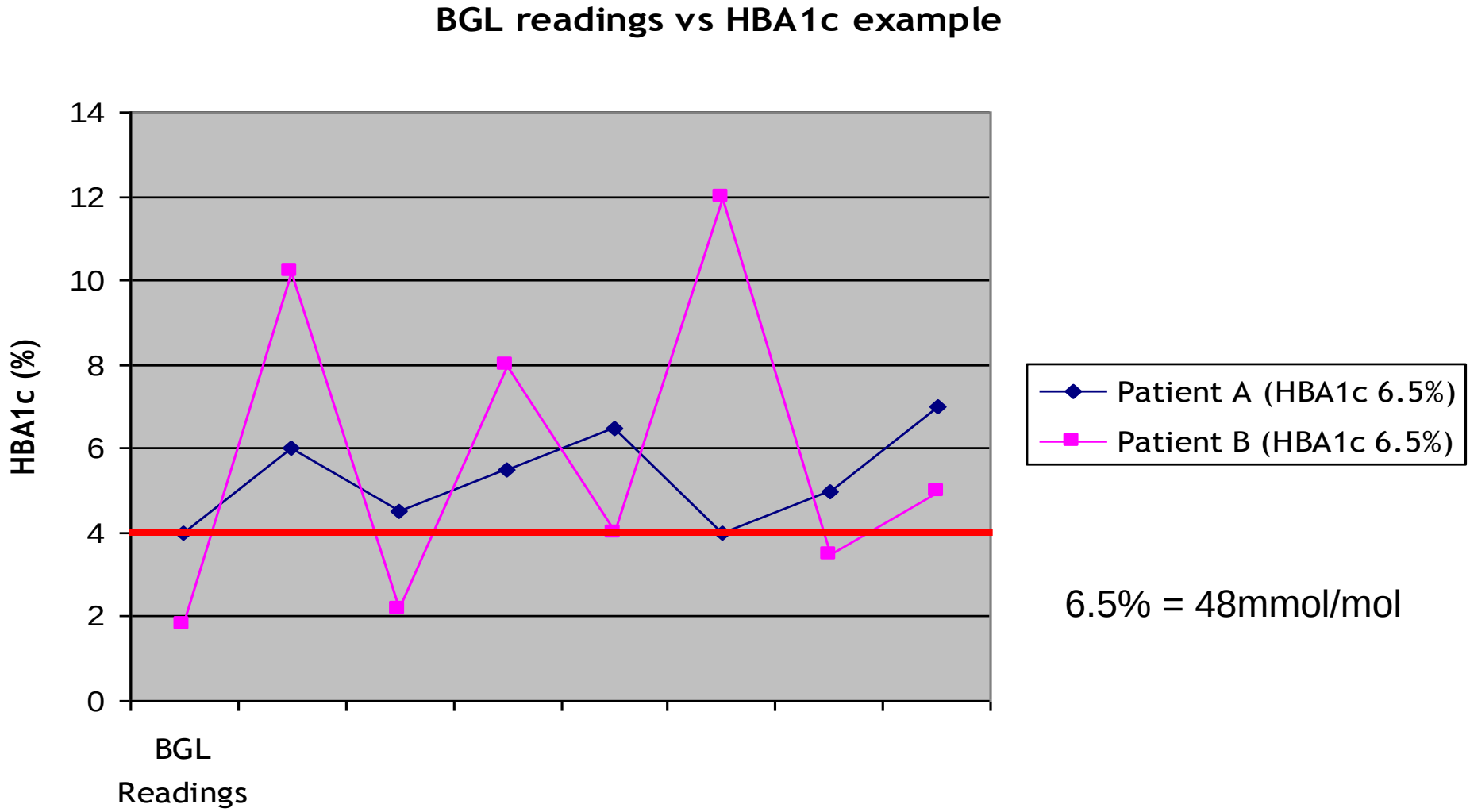
Hypoglycaemia risk with T2D treatments

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	Moderate
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 and GIP; increases glucose-mediated insulin secretion and suppressed glucagon secretion	Low
SGLT-2 antagonist	Reduces renal glucose reabsorption	Low
Insulin	Insulin replacement	High

*May be less frequent with nateglinide; GIP, glucose-dependent insulinotropic polypeptide.

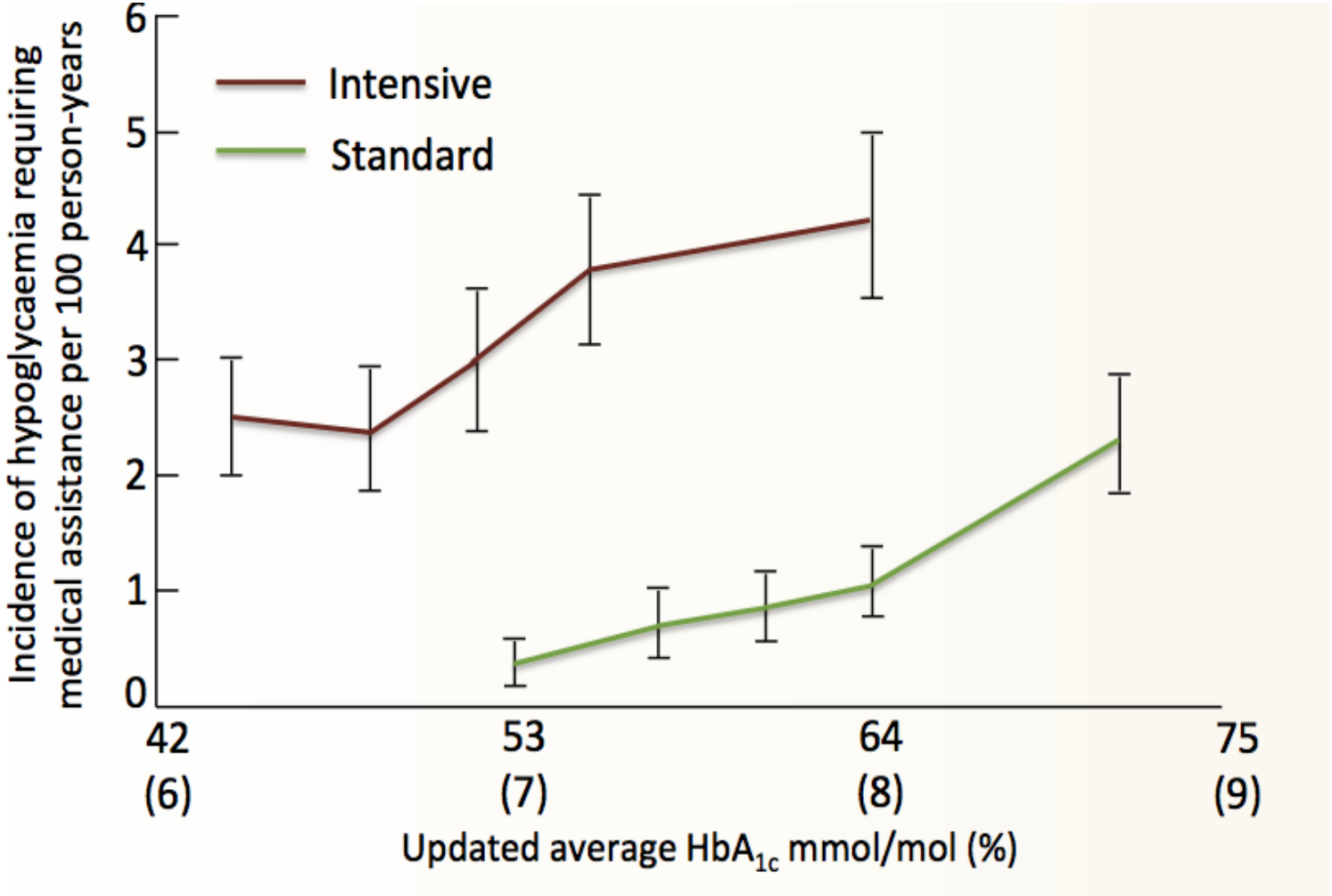
Adapted from Kushner P. *Diabetes Metab Syndr Obes* 2010;3:49-53.

A Graph to show HBA1c in relation to Blood glucose level readings



6.5% = 48mmol/mol

Lower HbA_{1c} does NOT predict hypoglycaemia risk in T2DM



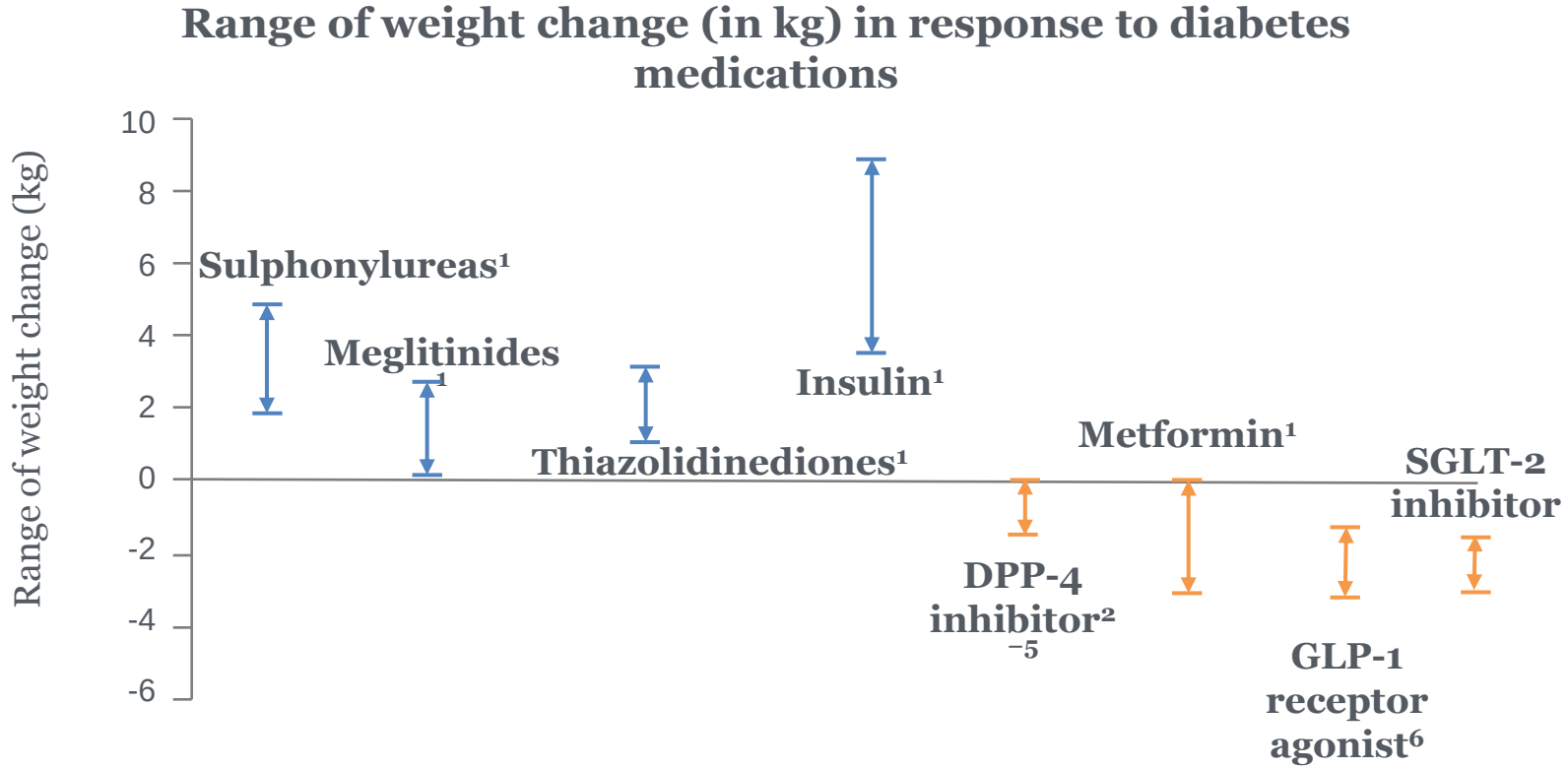
Adapted from Miller ME *et al. Br Med J* 2009;**339**:b5444.

Co-morbidities and Concurrent Disease

- CV risk (weight, BP, lipids)
- Nephropathy
- Retinopathy
- Neuropathy

- Infection
- Steroids

Glucose-lowering medications and weight profile



Weight change (Kg): -1.39 (linagliptin vs glimepiride) [2], -0.6 (sitagliptin vs glipizide)[3], -1.5 (sitagliptin vs glipizide)[3], -0.3 (vildagliptin vs rosiglitazone)[4], -0.2 (vildagliptin vs glimepiride), +0.1 (vildagliptin vs gliclazide)[4], -1.1 (saxagliptin vs glipizide)[5], -1.0 to -2.8 (liraglutide in combination with metformin, metformin + glimepiride and metformin + rosiglitazone).[6]

Reproduced from 1. Mitri J, Hamdy O. *Expert Opin Drug Saf* 2009; 8:573–8; 2. Boehringer Ingelheim and Eli Lilly and Company Limited. Trajenta (linagliptin) Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/25000/SPC/ Oct 2012 (accessed January 2013); 3. MSD Januvia (sitagliptin) Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/19609/SPC/ Mar 2012 (accessed January 2013); 4. Novartis Galvus (vildagliptin) Summary of Product Characteristics http://www.medicines.org.uk/EMC/medicine/20734/SPC/Galvus+50+mg+Tablets/ Oct 2012 (accessed January 2013); 5. AstraZeneca Onglyza (saxagliptin) Summary of Product Characteristics. http://www.medicines.org.uk/emc/medicine/22315/SPC/ Jan 2012 (accessed January 2013); 6. Novo Nordisk Limited. Victoza (liraglutide) Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/21986/SPC/Victoza+6+mg+ml+solution+for+injection+in+pre-filled+pen/ July 2012 (accessed January 2013).

Weighing the balance: Treatment options in T2D*

Drug/Class	Effect on			Adverse effects[4*]
	Weight[1,2]	Lipids[1,2]	Blood pressure[1–3]	
Metformin	Neutral or slightly decreased	Improved	Neutral	Anorexia, nausea, vomiting, diarrhoea, abdominal pain, taste disturbance
Acarbose	Suggested decrease	Poorly quantified	Poorly quantified	Flatulence, soft stools, diarrhoea, abdominal distention, pain
Meglitinides	Neutral (poorly quantified)	Poorly quantified	Poorly quantified	Hypoglycaemia, hypersensitivity reactions, abdominal pain, diarrhoea, constipation, nausea, vomiting
Sulphonylureas	Increased	Small improvements, mainly in TG	Poorly quantified	Increased hypoglycaemia risk; gastrointestinal disturbances; hyponatraemia (glimepiride and glipizide)
Pioglitazone	Increased	Improved HDL and TG	Small improvements	Gastrointestinal disturbances, oedema, anaemia, headache, visual disturbances, dizziness, arthralgia, hypoaesthesia, haematuria, impotence
GLP-1 receptor agonists	Decreased	Improved	Lowers systolic pressure	Gastrointestinal disturbances; GORD, weight loss, headache, dizziness, agitation, asthenia, hypoglycaemia, increased sweating, injection-site reactions
DPP-4 inhibitors	Neutral	Poorly quantified	Small improvements in non-diabetics	Vomiting, dyspepsia, gastritis; peripheral oedema; headache, tremor, dizziness, fatigue; upper respiratory tract infection, UTI; hypoglycaemia, myalgia (saxagliptin)
SGLT-2 inhibitors	Decreased	Improved	Small improvements	Constipation, thirst, nausea, dyslipidaemia, UTI, genital infection, polyuria, raised haematocrit; postural hypotension, dizziness, dehydration, hypovolaemia, rash
Insulin	Increased	Improved	Neutral	Transient oedema; local reactions and fat hypertrophy at injection site

Table adapted from 1. Kurukulasuriya LR, Sowers JR. *Cardiovasc Diabetol* 2010;9:45; 2. Inzucchi SE, McGuire DK. *Circulation* 2008;117(4):574-84; 3. Unger JR, Parkin CG. Diabetes Ther. 2011; 2(1):29–39. 4. *British National Formulary. Available at www.bnf.org (last accessed May 2014.

Overview of cautions and contraindications related to renal function for commonly prescribed[a] oral antidiabetic therapies

	Metformin	SU	Meglitinides	Acarbose	Pioglitazone	DPP4-inhibitors	GLP-1 agonists	SGLT-2 antagonists
Mild renal impairment		Gliclazide Glimepiride Glipizide Tolbutamide	Nateglinide Repaglinide			Sitagliptin Vildagliptin Saxagliptin Linagliptin	Exenatide Liraglutide Lixisenatide	Dapagliflozin Canagliflozin
Moderate renal impairment		Gliclazide Glimepiride Glipizide Tolbutamide	Nateglinide Repaglinide			Sitagliptin Vildagliptin Saxagliptin Linagliptin	Exenatide Liraglutide Lixisenatide	Dapagliflozin Canagliflozin
Severe renal impairment		Gliclazide Glimepiride Glipizide Tolbutamide	Nateglinide Repaglinide			Sitagliptin Vildagliptin Saxagliptin Linagliptin	Exenatide Liraglutide Lixisenatide	Dapagliflozin Canagliflozin
End-stage renal impairment		Gliclazide Glimepiride Glipizide Tolbutamide	Nateglinide Repaglinide			Sitagliptin Vildagliptin Saxagliptin Linagliptin	Exenatide Liraglutide Lixisenatide	Dapagliflozin Canagliflozin

Contraindicated/not recommended

Dose adjustment/caution required

No dose adjustment required

[a]As described in the British National Formulary.
SPCS all available at: www.medicines.org.uk (last accessed May 2014)
No SPC available for glibenclamide

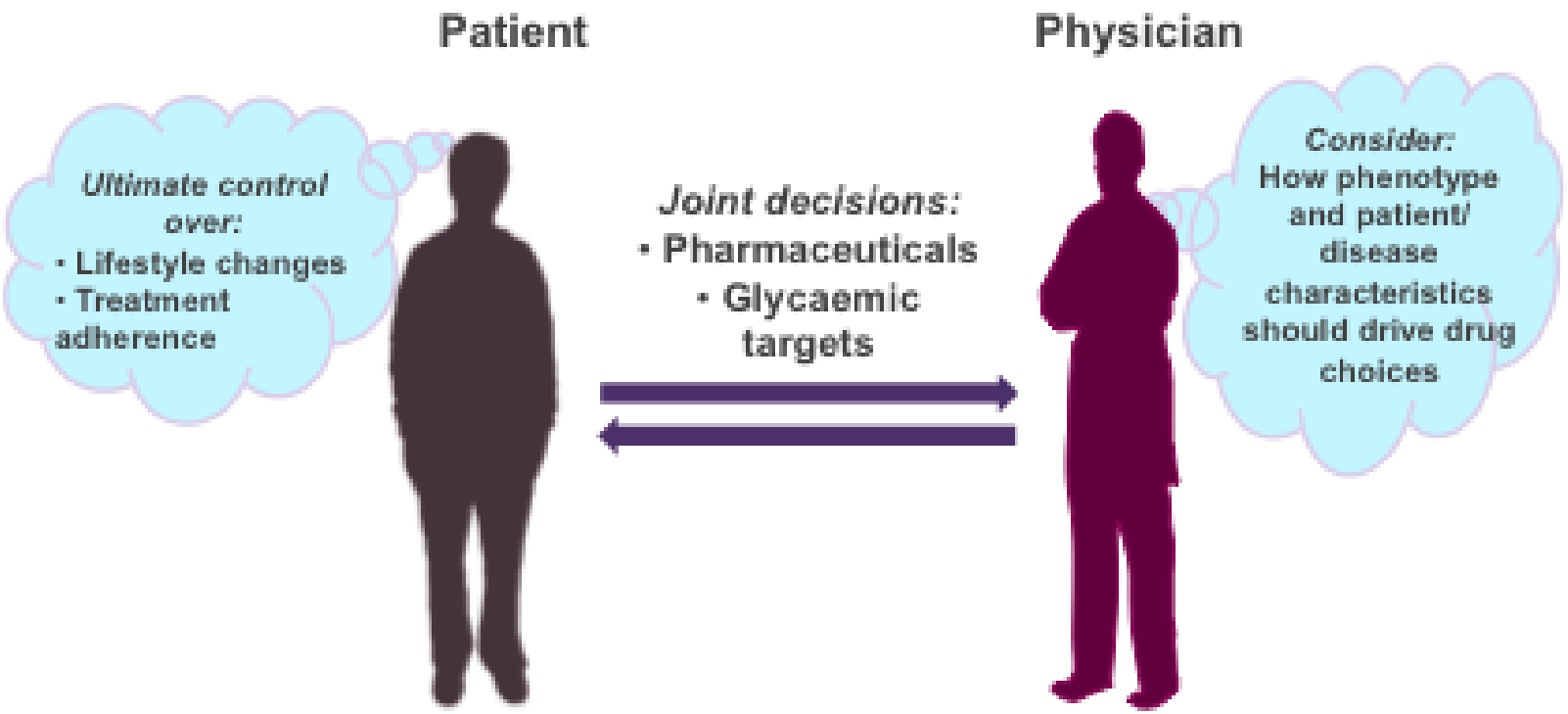
What is cost effective?

- If treatment is not having a benefit to HbA1c or weight loss – combination or monotherapy is expensive
- There needs to be adequate mechanisms by which prescribers take the responsibility of stopping oral medication with no benefit
- This will mean more money to enable early treatment of more patients to prevent weight gain / keep HbA1c lower.

Setting the scene for a consultation

- What is their agenda?
- How well is their diabetes currently controlled?
- Are they taking their medicines?
- What will their diabetes “journey” look like?

Patient-HCP interactions are key to individualising care



There is good evidence that sharing decision-making between HCPs and patients is effective and may enhance adherence to therapy

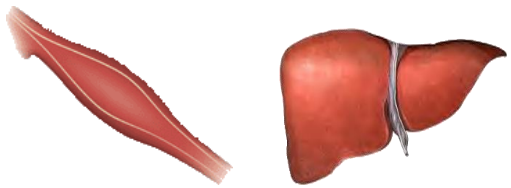
Adapted from: Inzucchi SE, et al. Diabetes Care 2012;35:1364–1379.

Summary

- Therapy targeting must be individualised for those with co-morbidity / complications
- Consultation and agreed goals are key to effective individualised targets
- Structured consideration of patient agenda can assist in the process
- Treatment type as well as target must be individualised and regularly reviewed

Thank you
Any Questions??

Biguanides

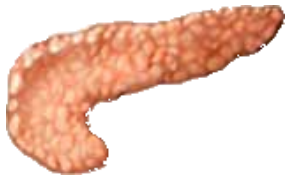


- Metformin (Glucophage)
- Decreases gluconeogenesis and increases peripheral utilisation of glucose
- Acts only in the presence of insulin
- Does not cause hypoglycaemia or weight gain
- Side-effects: most commonly GI effects such as diarrhoea & abdominal pain
  - incidence minimised by starting with a low dose (500mg od), taking with food and titrating slowly
  - modified-release preparation may help

Lactic acidosis with metformin

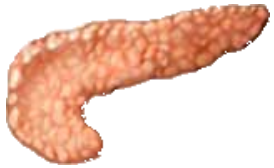
- A rare, but potentially fatal, side-effect of metformin
- Occurs because metformin reduces hepatic uptake of lactate
- Risk reduced by avoiding metformin use in patients with:
  - renal impairment (Cr > 150μmol/L or eGFR < 60mL/min/1.72m^2)
  - a risk of tissue hypoxia (sepsis, severe heart failure or significant hepatic impairment)
  - patients receiving iodinated contrast (as this can reduce renal function)

Sulfonylureas



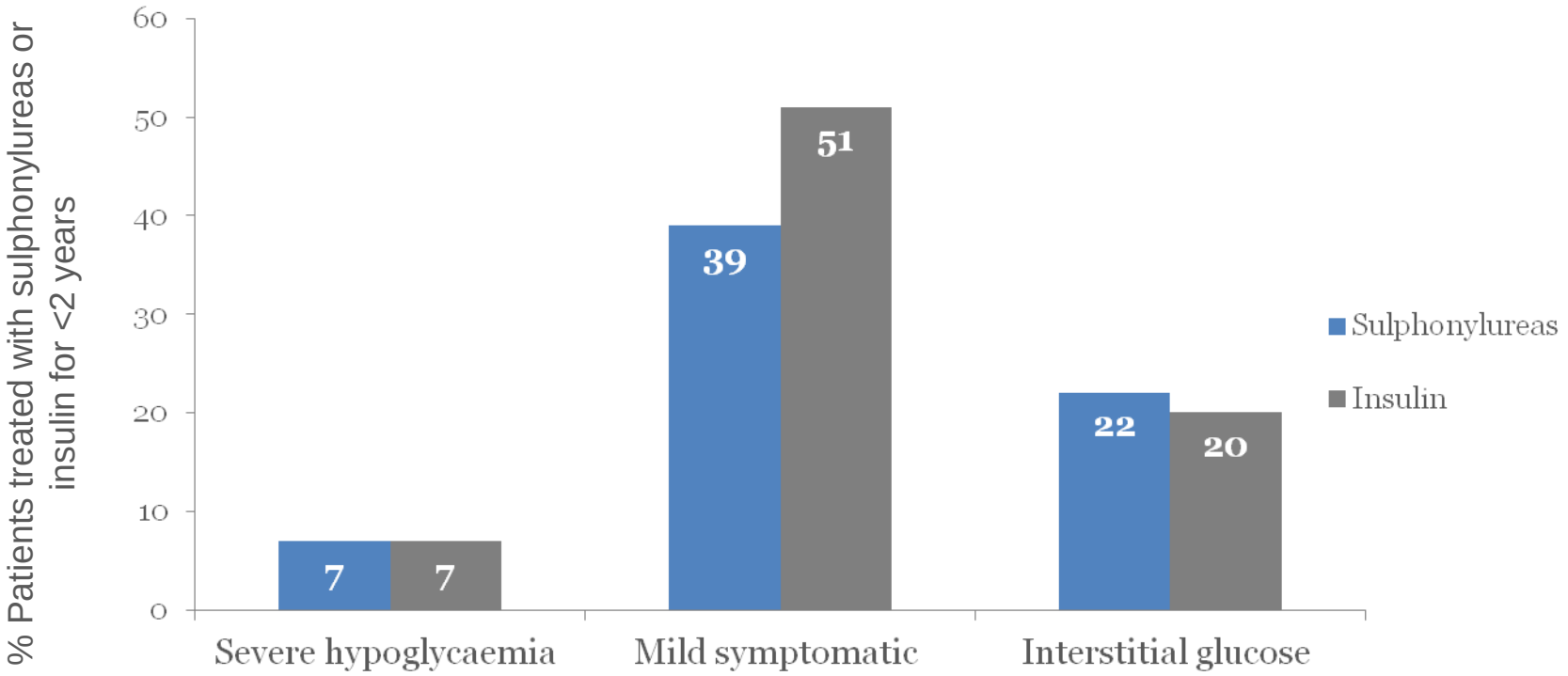
- Tolbutamide, gliclazide (Diamicron), glipizide, glimepiride (Amaryl)
- Stimulate insulin release by the beta cells of the pancreas
  - require functioning beta cells to work
  - “insulin secretagogues”
- Need to be taken with meals to prevent hypoglycaemia
- Risk of accumulation and hypo’s in renal impairment

Meglitinides



- Repaglinide & nateglinide
- Stimulate insulin secretion but only in the presence of food
- Rapid onset and short duration of action
  - more physiological insulin release then SUs
- Lower risk of hypoglycaemia compared to sulfonylureas

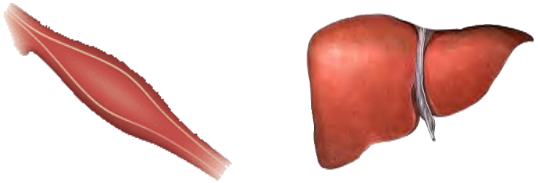
Hypoglycaemia in T2D: Sulphonylureas vs Insulin



No annual differences were observed between the two groups

UK Hypoglycaemia Study Group. *Diabetologia* 2007 50:1140-1147.

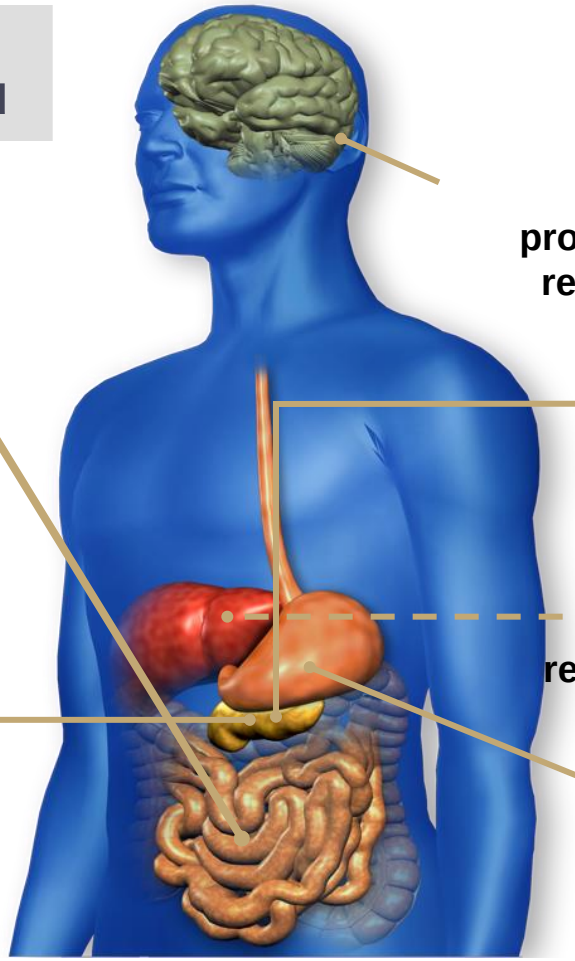
Thiazolidinediones



- Pioglitazone (Actos)
- Enhance tissue sensitivity to insulin
- Contraindications/ adverse effects:
  - heart failure
  - hepatic impairment
  - bladder cancer
  - osteoporosis

GLP-1 effects

GLP-1 secreted upon the ingestion of food



Brain:
promotes satiety and reduces appetite[4,5]

Alpha-cell:
suppresses postprandial glucagon secretion[1]

Liver:
reduces hepatic glucose output[2]

Beta-cell:
enhances glucose-dependent insulin secretion in the pancreas[1]

Stomach:
slows the rate of gastric emptying[3]

Adapted from [1]Nauck MA, et al. *Diabetologia* 1993;36:741–744; [2]Larsson H, et al. *Acta Physiol Scand* 1997;160:413–422; [3]Nauck MA, et al. *Diabetologia* 1996;39:1546–1553; [4]Flint A, et al. *J Clin Invest* 1998;101:515–520; [5]Zander et al. *Lancet* 2002;359:824–830.

Incretin-based therapies

DPP-4 inhibitors
Protect native GLP-1 from inactivation by DPP-4

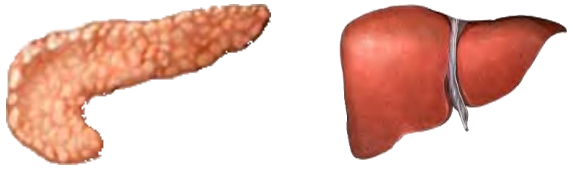
- Sitagliptin
- Vildagliptin
- Saxagliptin
- Linagliptin

GLP-1 receptor agonists
Mimic native GLP-1

- Exenatide
  (Exendin-based therapy)
  BD – 'Byetta'
  OW – 'Bydureon'
- Lixisenatide
- Liraglutide
  (Human GLP-1 analogue)

Drucker DJ, Nauck MA. Lancet 2006;368:1696–1705

GLP-1 analogues



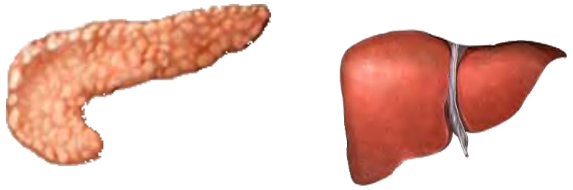
- Exenatide (Byetta) & liraglutide (Victoza) & lixisenatide (Lyxumia)
- These are given by subcutaneous injection but are NOT insulins
- Resistant to DPP-4 inactivation

- Most common side-effect is nausea
  - tolerability improved by starting at low doses and gradually titrating
- Rare reports of pancreatitis, excludes further use
  - persistent, severe abdominal pain

- Low risk of hypoglycaemia except in combination with sulfonylureas

- Benefit of weight loss

DPP-4 inhibitors



- Sitagliptin, vildagliptin, saxagliptin, linagliptin
- Prevent the breakdown of endogenous GLP-1
- Weight neutral
- Low risk for causing hypoglycaemia

Dangerous??

- Dispatches / BMJ
- Recent meta-analysis showed DPP-4's 48% reduction in CV events (Patil Am J Cardiol 2012)
- Think about the patient and concomitant conditions.

SGLT2 inhibitors – Dapagliflozin/Canagliflozin

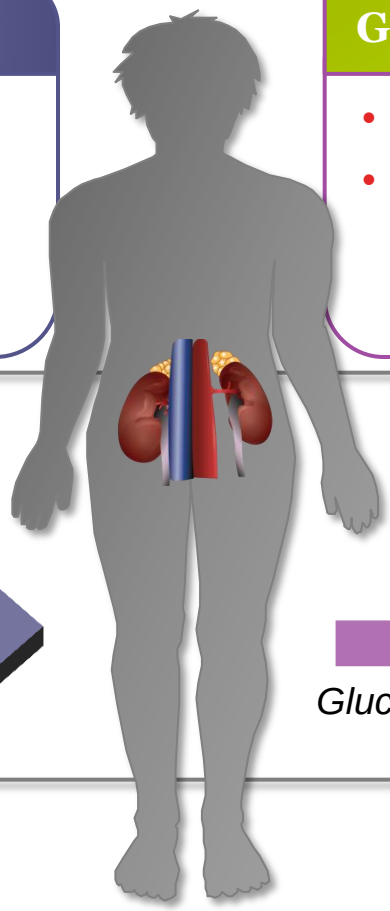
Glucose Homeostasis: Net balance ~0 g/day

Glucose input ~250 g/day:

- Dietary intake ~180 g/day
- Glucose production ~70 g/day
  - Gluconeogenesis
  - Glycogenolysis

Glucose uptake ~250 g/day:

- Brain ~125 g/day
- Rest of the body ~125 g/day



The kidney filters circulating glucose

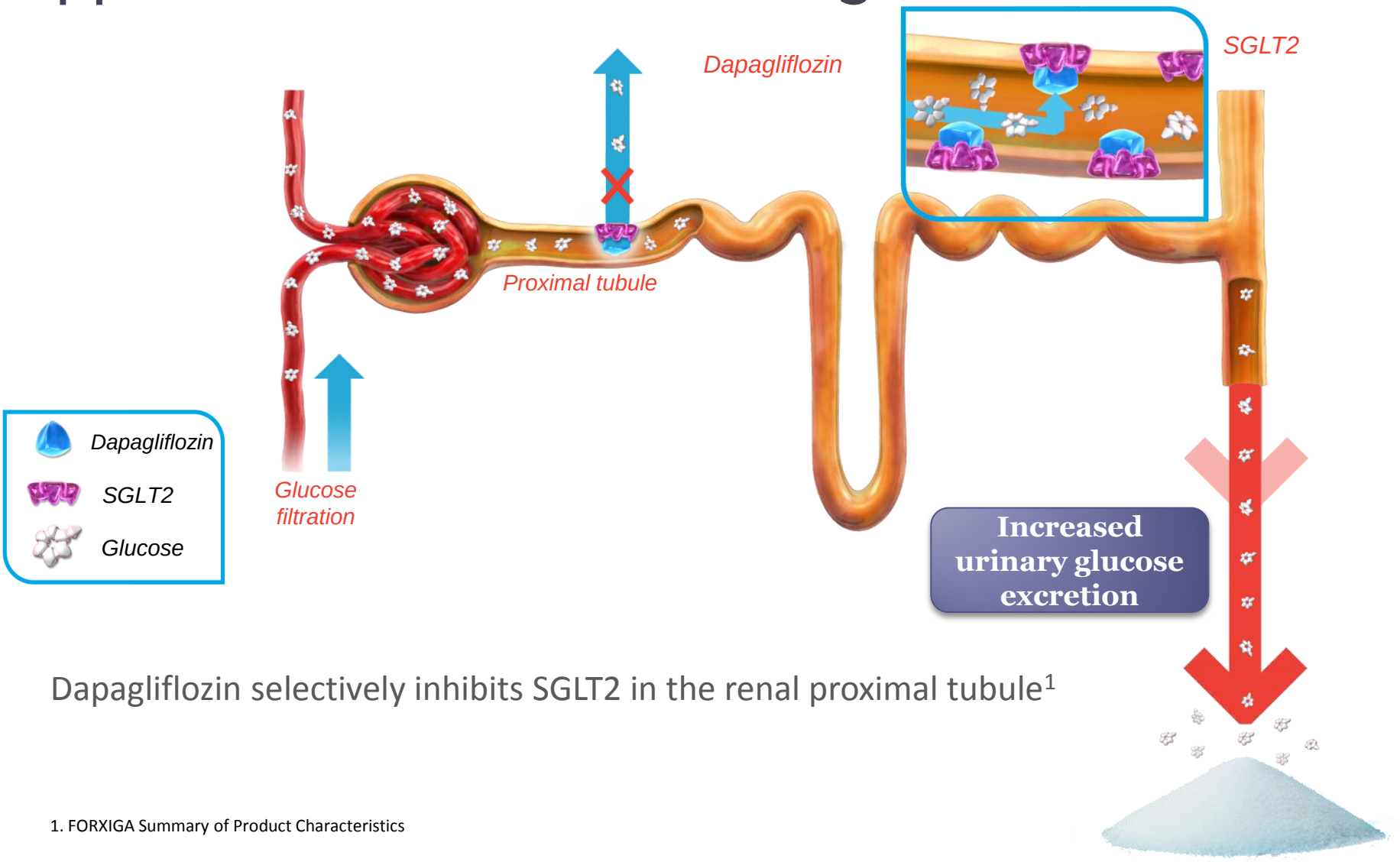
Glucose filtered ~180 g/day

The kidney reabsorbs and recirculates glucose

Glucose reabsorbed ~180 g/day

1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18.
2. Gerich, JE. *Diabetes Obes Metab* 2000;**2**:345–50.

Dapagliflozin: A novel insulin-independent approach to remove excess glucose



Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule[1]

1. FORXIGA Summary of Product Characteristics

Insulin

- Removes glucose from circulation
- Helps tissue (muscles) to uptake glucose
- Promotes glucose to be stored as glycogen
- Helps body to make fat and protein