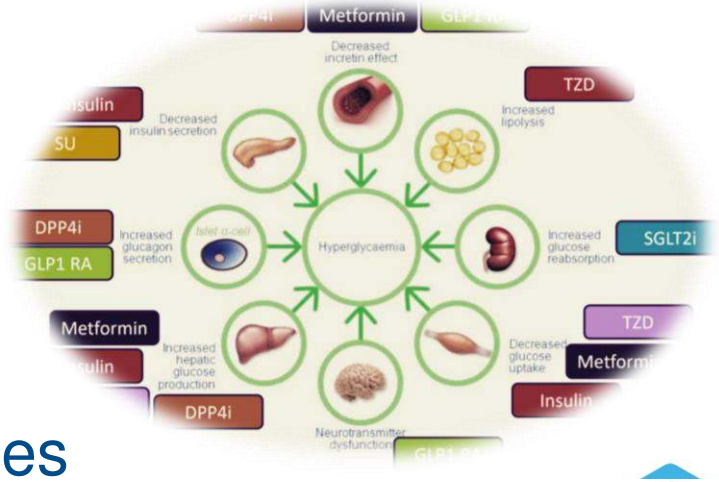
SUFFOLK
NMP MASTERCLASS
Update: Diabetes Management & Prescribing in 2021

Suffolk GP FEDERATION

NHS
East Suffolk and North Essex
NHS Foundation Trust

Pharmacology in Diabetes



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Disclosures

East Suffolk and North Essex NHS Foundation Trust

- **Research grants:**
  - Sanofi, Novo Nordisk
- **Research Trial collaborations as Principal Investigator:**
  - Boehringer Ingelheim, Sanofi, Roche, Novo Nordisk, Eli Lilly, GSK, Biogen
- **Advisory board:**
  - Novo Nordisk, Novartis
- **Speaker roles:**
  - Eli Lilly, NAPP, Sanofi, Novo Nordisk, Boehringer Ingelheim, Viatris
- **Travel grants:**
  - Novo Nordisk, Astra Zeneca, Novartis
- **Journal reviewer:**
  - Diabetologia, Diabetic medicine, Diabetes care, Journal of Diabetes research, Journal of Diabetes Science & Technology

Key learning objectives

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- The changing landscape of guidelines based on evidence
- Review the standard oral therapies used in the treatment of type 2 diabetes (metformin, sulphonylureas, thiazolidinediones, DPP-4 inhibitors)
- Emphasis on the newer drugs: SGLT-2i and GLP-1Ra
- Discuss the considerations when choosing a treatment to meet the needs and circumstances of individual patients
- Understand the sites of action for the different oral drug classes and be aware of the prescribing considerations including renal function and hepatic disease
- Consider different goals of treatment and evaluate how different oral therapies can help to achieve these goals
- Basics of insulin treatment in both Type1 and Type 2 diabetes
- Patient cases

DPP-4: dipeptidyl peptidase-4; SGLT2: sodium–glucose co-transporter 2

Adam…47 years old

Male age 47

Diagnosed 2 years ago with type 2 diabetes

- **Commenced metformin 18 months ago**
  - maximum tolerated dose: 1g BD
- **BMI: 31 kg/m^2**
- **Smoker**
- **HbA1c: 58 mmol/mol (7.5%)**
- **BP: 190/85 mmHg**
  - losartan 50 mg OD
- **LDL: 4.2 mmol/L**
  - atorvastatin 10 mg OD
- **eGFR: 78 mL/min/1.73 m^2**
- **uACR: 12.4 mg/mmol**
- **Cholesterol: 5.4 mmol/L**
- **Bilateral background retinopathy**

Thinking about patients in your own practice, where might Adam be in 5–10 years time?

Agenda

East Suffolk and North Essex NHS Foundation Trust

- **Guidelines relevant to pharmacological treatment of diabetes**
  - NICE / EASD / ADA
- **Overview of various therapies**
  - SGLT-2i
  - GLP-1Ra
- **Class Comparison**
- **Individualising Treatment**
- **Principles of Insulin initiation**
- **Patient cases**

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Updated national and international guidelines position SGLT2 inhibitors ahead of DPP-4 inhibitors and sulphonylureas for many patients

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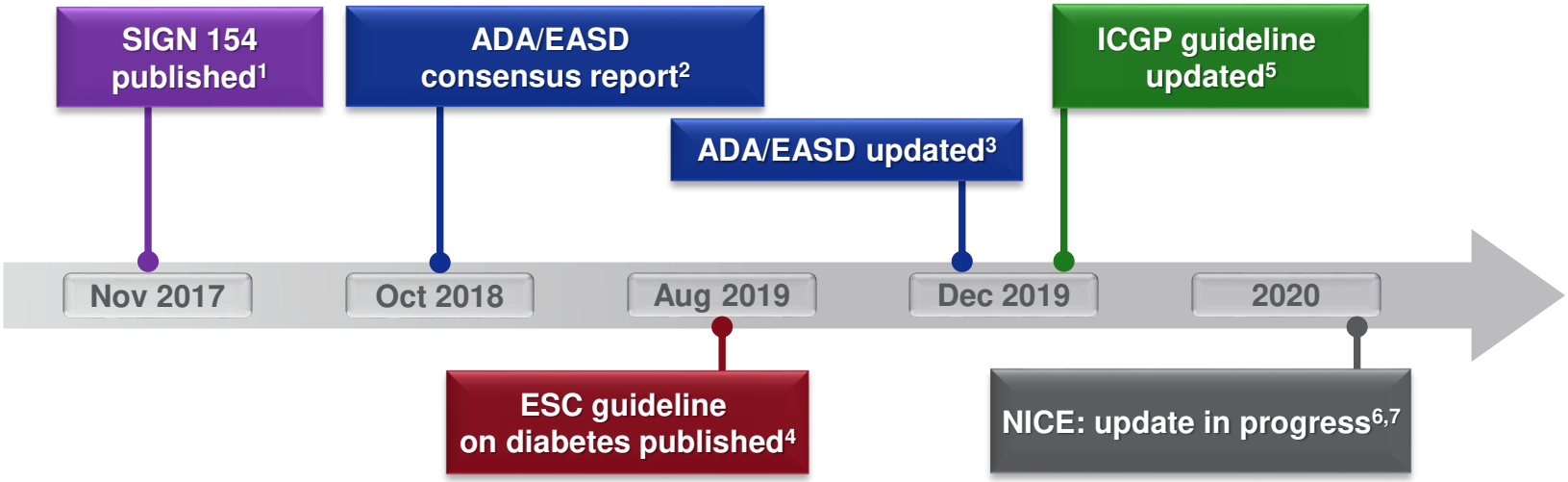


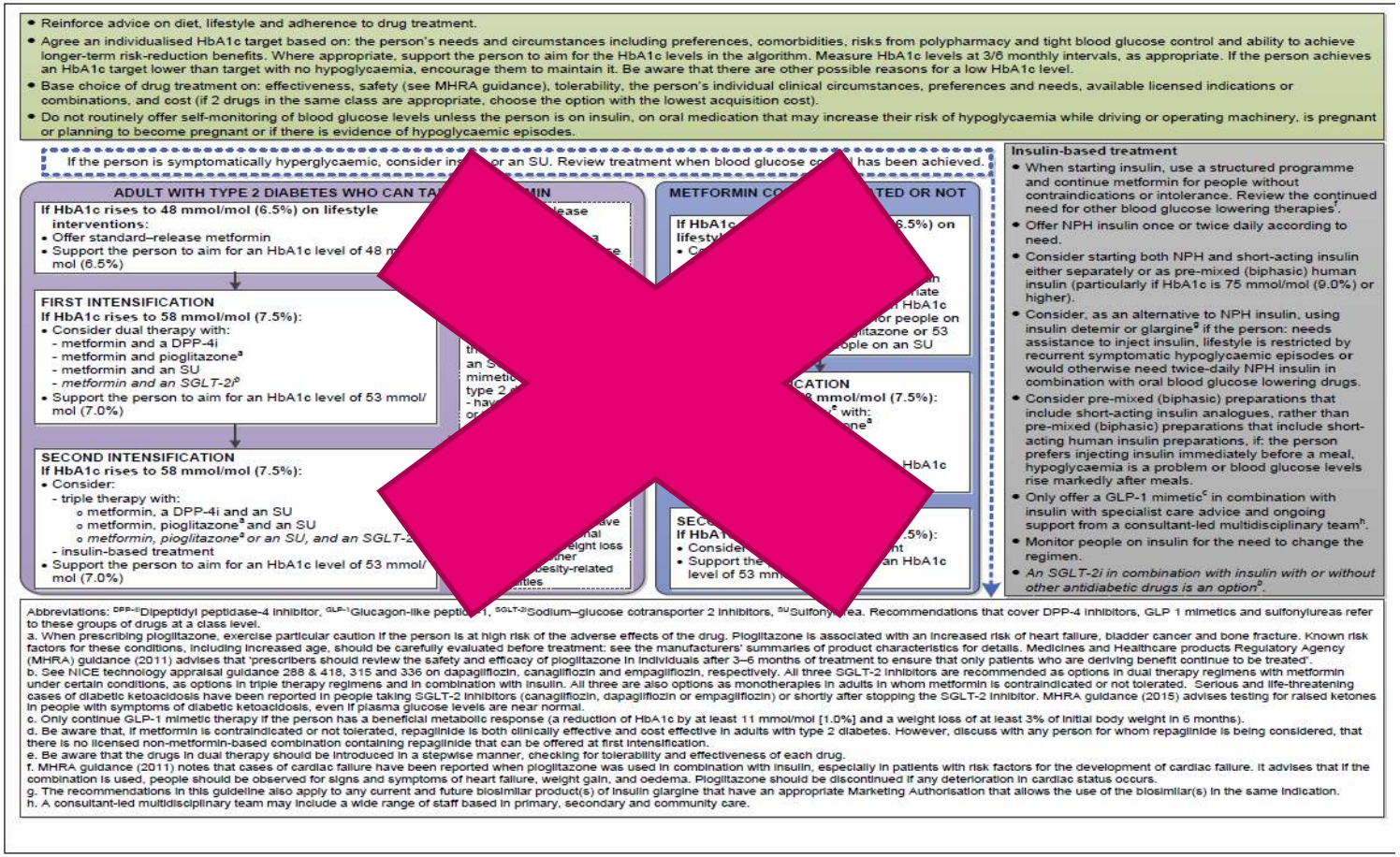
Are your local guidelines updated with the latest evidence?

ADA: American Diabetes Association; DPP-4: dipeptidyl peptidase-4; EASD: European Association for the study of diabetes; ESC: European Society of Cardiology; ICGP: Irish College of General Practitioners; NICE: National Institute for Health and Care Excellence; SGLT2: sodium–glucose co-transporter 2; SIGN: Scottish Intercollegiate Guidelines Network

1. SIGN 154. *Pharmacological management of glycaemic control in people with type 2 diabetes.* November 2017. Available at: www.sign.ac.uk (accessed October 2020);
2. Davies MJ *et al. Diabetologia.* 2018;61:2461–2498; 3. Buse JB *et al. Diabetologia.* 2019;63:221–228; 4. Cosentino F *et al. Eur Heart J.* 2020;41:255–323;
5. ICGP. *Diagnosis and management of uncomplicated type 2 diabetes in adults (T2DM): A succinct practical guide for Irish General Practice.* December 2019. Available at: www.icgp.ie (accessed October 2020); 6. NICE. *2019 surveillance of diabetes (NICE guidelines NG17, NG18, NG19 and NG28).* July 2019. Available at: www.nice.org.uk (accessed October 2020);
7. NICE. *Guidance and advice list.* Available at: www.nice.org.uk (accessed October 2020).

Guidelines: from theory to practice

NICE ng28



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Guidelines: from theory to practice[1]

ADA/EASD 2019

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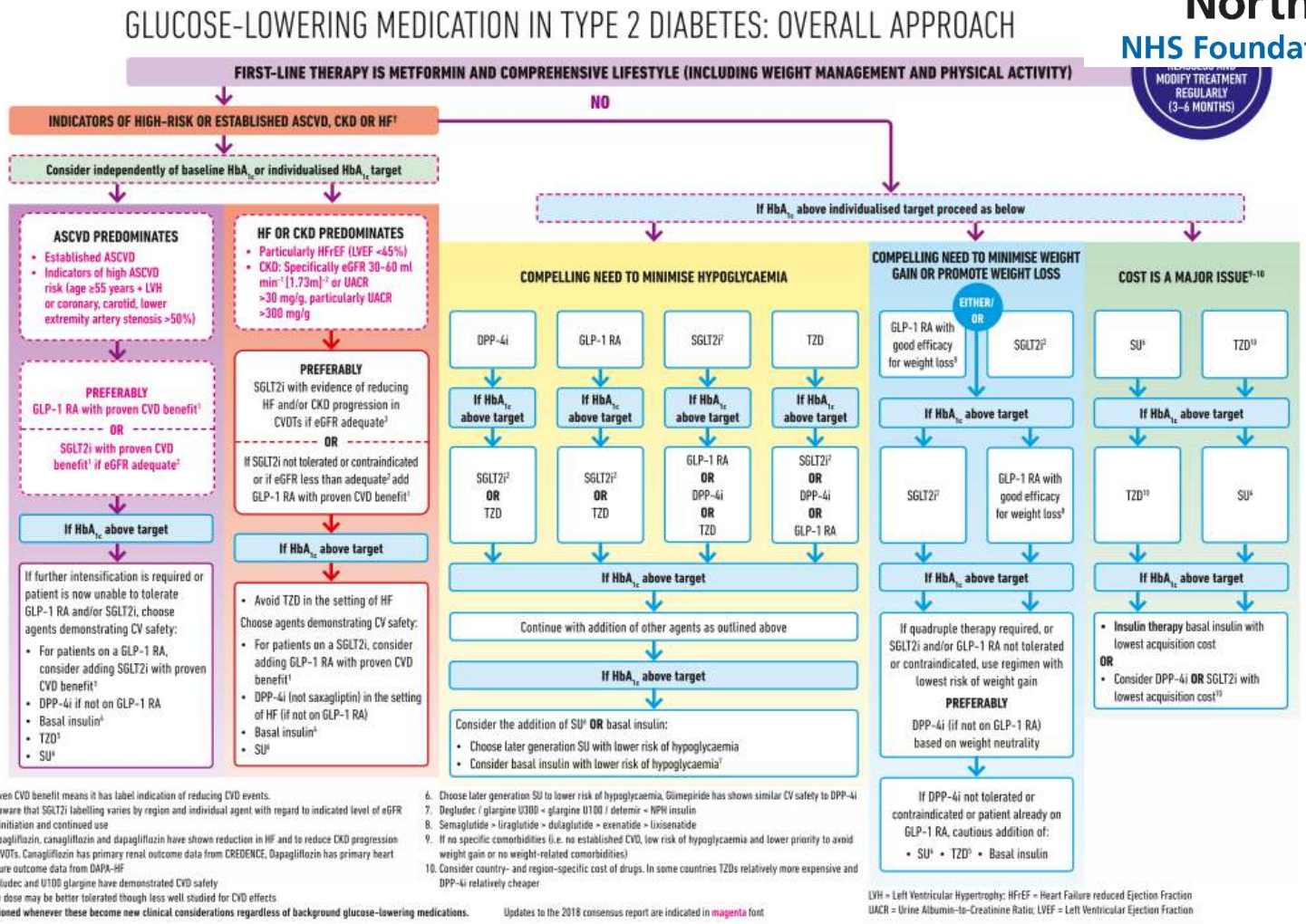
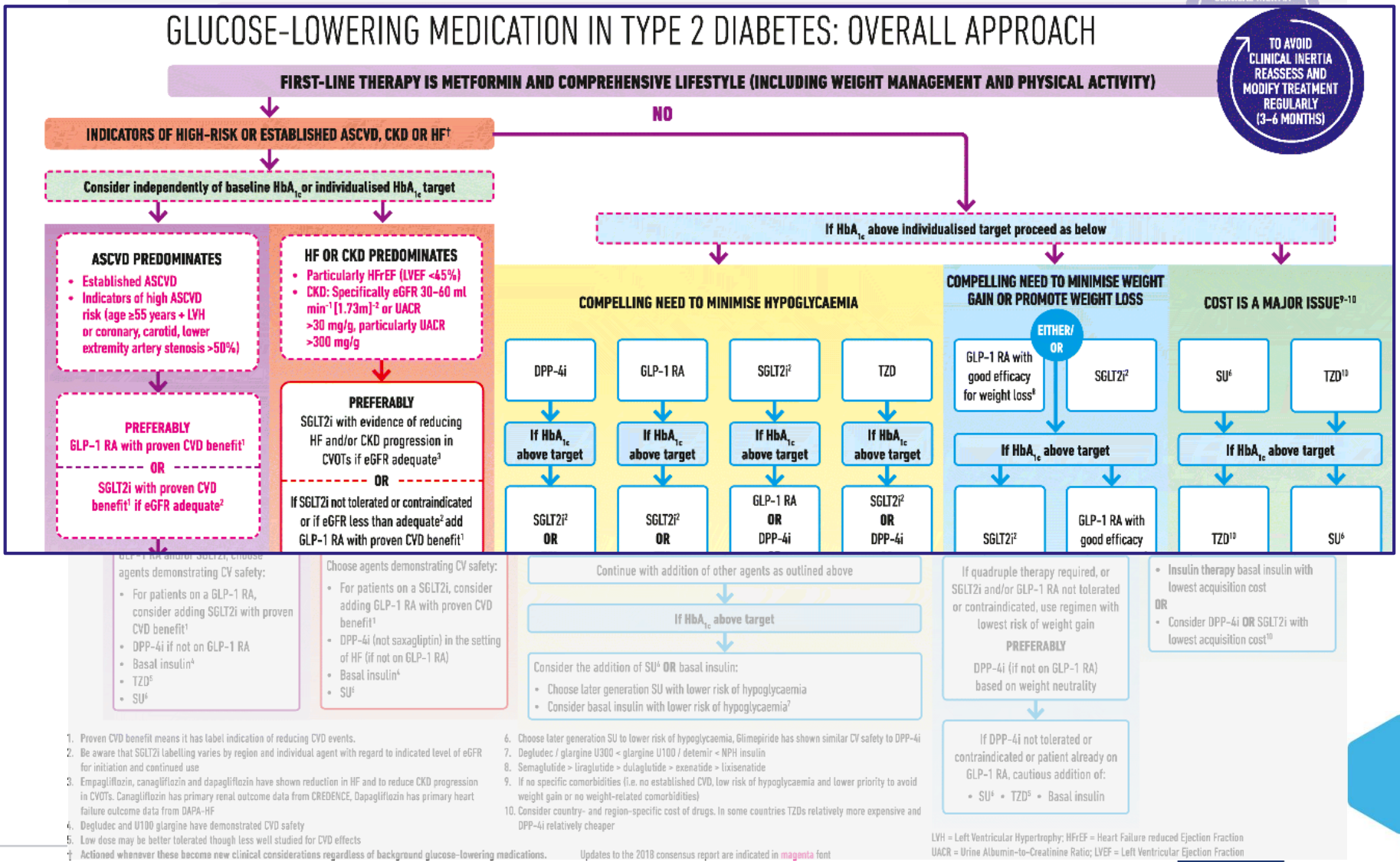


Fig. 1 Glucose-lowering medication in type 2 diabetes: overall approach. CV, cardiovascular; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonsist; AGLT2i, SGLT2 inhibitor; SU, sulfonylurea

1. Buse JB, et al. Diabetes Care. 2020; 43(2):487–493

The 2019 ADA/EASD consensus report update has incorporated Cardiovascular Outcome Trial Data

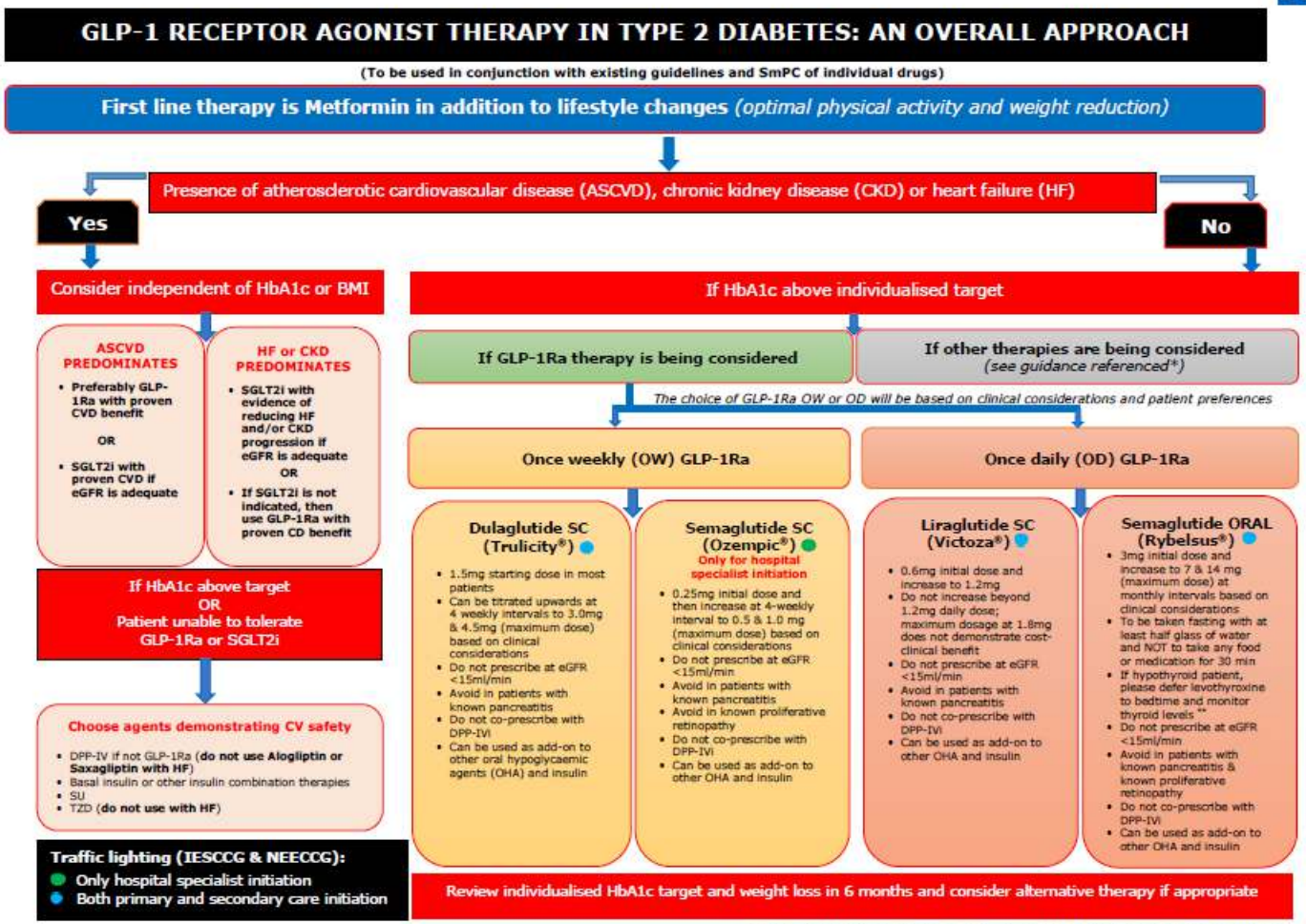


Glucose-lowering medication in type 2 diabetes: overall approach. Modified from [2] with permission from Springer.

1. Buse J.B et al. Diabetologia. 2020; 63:221-228.

IESCCG/NEECCG/WSCCG GLP-1Ra guideline

https://ipswichandeastsuffolkccg.nhs.uk/GPpracticememberarea/Clinicalarea/Medicinesmanagement/Medicalconditions/Diabetes.aspx



GLP-1 RECEPTOR AGONIST THERAPY IN TYPE 2 DIABETES: AN OVERALL APPROACH

(To be used in conjunction with existing guidelines and SmPC of individual drugs)

First line therapy is Metformin in addition to lifestyle changes *(optimal physical activity and weight reduction)*

Presence of atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD) or heart failure (HF)

Yes

Consider independent of HbA1c or BMI

ASCVD PREDOMINATES

- Preferably GLP-1Ra with proven CVD benefit

OR

- SGLT2i with proven CVD if eGFR is adequate

HF or CKD PREDOMINATES

- SGLT2i with evidence of reducing HF and/or CKD progression if eGFR is adequate

OR

- If SGLT2i is not indicated, then use GLP-1Ra with proven CD benefit

If HbA1c above target OR Patient unable to tolerate GLP-1Ra or SGLT2i

Choose agents demonstrating CV safety

- DPP-IV if not GLP-1Ra (**do not use Alogliptin or Saxagliptin with HF**)
- Basal insulin or other insulin combination therapies
- SU
- TZD (**do not use with HF**)

No

If HbA1c above individualised target

If GLP-1Ra therapy is being considered

If other therapies are being considered *(see guidance referenced*)*

The choice of GLP-1Ra OW or OD will be based on clinical considerations and patient preferences

Once weekly (OW) GLP-1Ra

Dulaglutide SC (Trulicity®) ●

- 1.5mg starting dose in most patients
- Can be titrated upwards at 4 weekly intervals to 3.0mg & 4.5mg (maximum dose) based on clinical considerations
- Do not prescribe at eGFR <15ml/min
- Avoid in patients with known pancreatitis
- Do not co-prescribe with DPP-IVi
- Can be used as add-on to other oral hypoglycaemic agents (OHA) and insulin

Semaglutide SC (Ozempic®) ●

Only for hospital specialist initiation

- 0.25mg initial dose and then increase at 4-weekly interval to 0.5 & 1.0 mg (maximum dose) based on clinical considerations
- Do not prescribe at eGFR <15ml/min
- Avoid in patients with known pancreatitis
- Avoid in known proliferative retinopathy
- Do not co-prescribe with DPP-IVi
- Can be used as add-on to other OHA and insulin

Once daily (OD) GLP-1Ra

Liraglutide SC (Victoza®) ●

- 0.6mg initial dose and increase to 1.2mg
- Do not increase beyond 1.2mg daily dose; maximum dosage at 1.8mg does not demonstrate cost-clinical benefit
- Do not prescribe at eGFR <15ml/min
- Avoid in patients with known pancreatitis
- Do not co-prescribe with DPP-IVi
- Can be used as add-on to other OHA and insulin

Semaglutide ORAL (Rybelsus®) ●

- 3mg initial dose and increase to 7 & 14 mg (maximum dose) at monthly intervals based on clinical considerations
- To be taken fasting with at least half glass of water and NOT to take any food or medication for 30 min
- If hypothyroid patient, please defer levothyroxine to bedtime and monitor thyroid levels **
- Do not prescribe at eGFR <15ml/min
- Avoid in patients with known pancreatitis & known proliferative retinopathy
- Do not co-prescribe with DPP-IVi
- Can be used as add-on to other OHA and insulin

Review individualised HbA1c target and weight loss in 6 months and consider alternative therapy if appropriate

Traffic lighting (IESCCG & NEECCG):

- ● Only hospital specialist initiation
- ● Both primary and secondary care initiation

* Adapted from EASD/ADA T2DM 2020 guidelines: Buse J.B et al. Diabetologia. 2020; 63:221-228

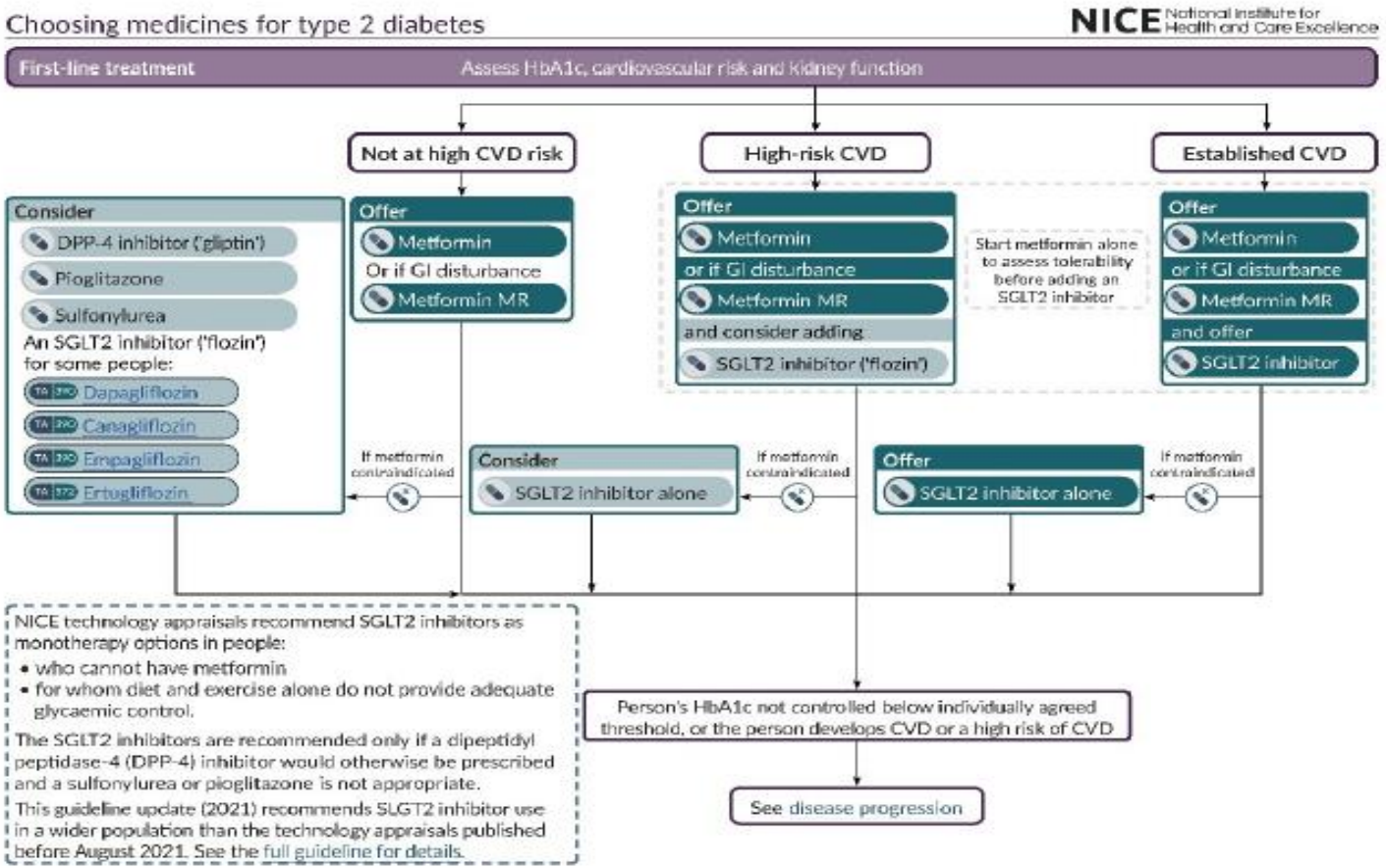
** Based on advice from local diabetes centre at ESNEFT

East Suffolk and North Essex NHS Foundation Trust (ESNEFT)
NHS Ipswich and East Suffolk CCG
NHS North East Essex CCG

Ver. 2.0 25th Feb 2021 – Diabetes and Endocrine departments (Ipswich & Colchester hospitals: ESNEFT)

NICE 2021 draft guideline

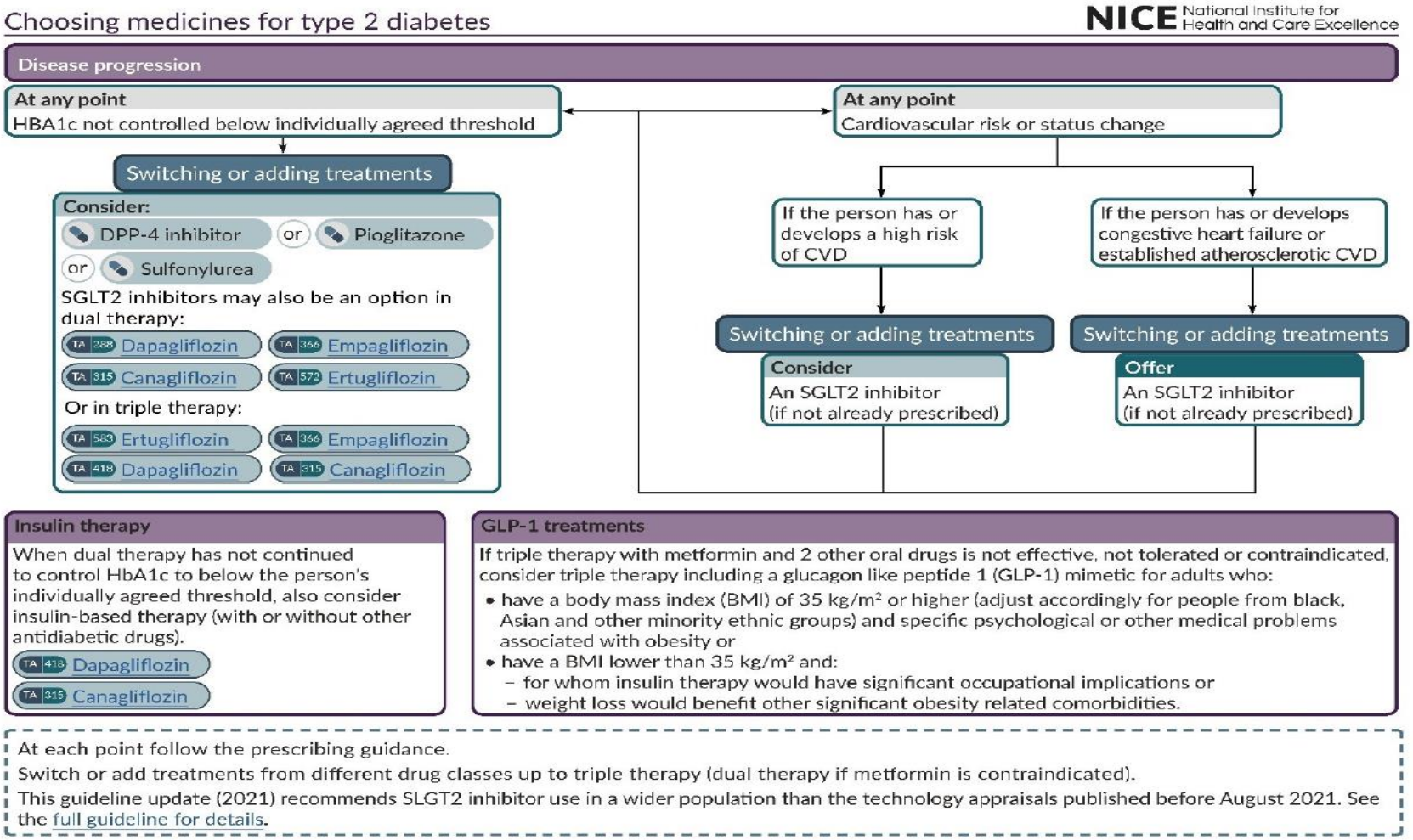
1 **Visual summary 2. First-line treatment**



2

NICE 2021 draft guideline

Visual summary 3. Disease progression



NICE 2021 draft guideline

The committee did not look at clinical and cost-effectiveness evidence for the use of GLP-1 mimetics to control blood glucose levels. As a result, the committee were unable to update the 2015 GLP-1 mimetic recommendations. However, the committee were concerned that, as written, the 2015 recommendation on GLP1-mimetics would mean that people taking newer drugs with proven cardiovascular benefit, such as SGLT2 inhibitors, would have to switch to a combination of metformin, a sulfonylurea and a GLP-1 mimetic. They agreed that this might be clinically inappropriate and not in keeping with current clinical practice, so they amended recommendation 1.7.22 to remove the requirement for this specific combination of treatment options. The rest of the recommendation and the other recommendations for GLP-1 mimetics were out of scope for this update, so the criteria for accessing a GLP-1 mimetic remain unchanged. These recommendations set tight limits on who should be offered a GLP-1 mimetic, based on the lack of cost effectiveness of this treatment for most people in the 2015 guideline.

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Type 2 diabetes therapies: an overview

Oral therapies

- Metformin
- Sulphonylureas
- DPP-4 inhibitors
- SGLT2 inhibitors
- Thiazolidinediones (i.e. pioglitazone)
- ?

Injectables

- GLP-1 receptor agonists*
- Insulin

*As of October 2020 there is one oral GLP-1 receptor agonist with a European marketing authorisation; Rybelsus▼ (oral semaglutide).
DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium–glucose co-transporter 2

Type 2 diabetes therapies: an overview

Oral therapies

- Metformin
- Sulphonylureas
- DPP-4 inhibitors
- SGLT2 inhibitors
- Thiazolidinediones (i.e. pioglitazone)
- GLP-1 receptor agonists (i.e. oral semaglutide)*
- Acarbose

Injectables

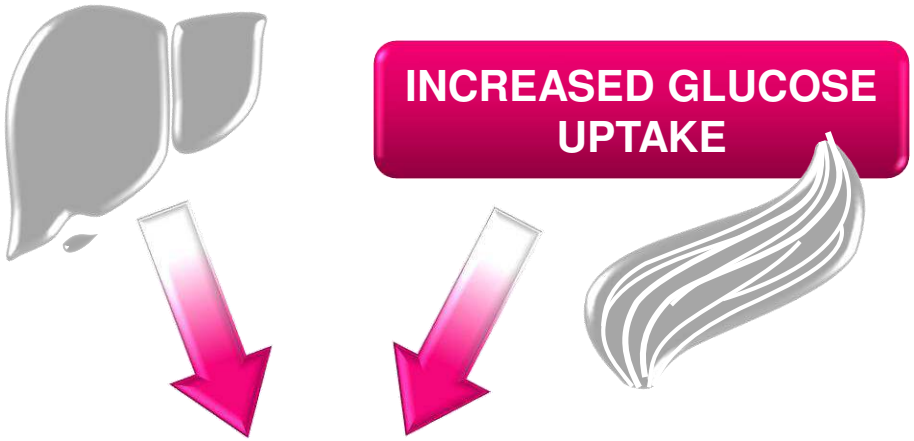
- GLP-1 receptor agonists*
- Insulin

*As of October 2020 there is one oral GLP-1 receptor agonist with a European marketing authorisation; Rybelsus ▼ (oral semaglutide).
DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium–glucose co-transporter 2

Metformin

Mode of action:

SUPPRESSION OF HEPATIC GLUCONEOGENESIS



INCREASED GLUCOSE UPTAKE

Lower blood glucose

BENEFITS

- Established efficacy[1] HbA1c reduction 1.0–1.5%[4]
- Extensive real-world experience[1]
- Weight reduction (some patients)[1]
- Reduced MIs in UKPDS[1–3]
- Consistently reduced the risk of diabetic adverse events, including microvascular disease, in UKPDS[3]

CONSIDERATIONS

- Caution in renal impairment[1,2]
- GI side effects[1,2]
- Lactic acidosis with CKD[1,2]

Refer to the full Summary of Product Characteristics for detailed safety information

CKD: chronic kidney disease; GI: gastrointestinal; MI: myocardial infarction; UKPDS: UK Prospective Diabetes Study

1. Boyle JG *et al. Br J Cardiol.* 2010;17:231–234; 2. Metformin (metformin hydrochloride) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/medicine/23244/; 3. Holman RR *et al. N Engl J Med.* 2008;359:1577–1589; 4. Inzucchi SE *et al. Diabetologia.* 2012;55:1577–1596.

Clinical Tip 1: Metformin: dosing in renal impairment

	Degree of renal impairment				
	Normal function (eGFR ≥ 90 ml/min/1.73 m^2)	**Mild impairment** (eGFR 60–89 ml/min/1.73 m^2)	**Mild to moderate impairment** (eGFR 45–59 ml/min/1.73 m^2)	**Moderate to severe impairment** (eGFR 30–44 ml/min/1.73 m^2)	**Severe impairment /ESRD** (eGFR <30 ml/min/1.73 m^2)
Maximum total daily dose	**3000 mg**	**3000 mg**	**2000 mg**	**1000 mg**	**Metformin contraindicated**
Additional considerations		**Consider dose reduction in relation to declining renal function**	**Before initiating, review factors that may increase the risk of lactic acidosis Starting dose is ≤50% maximum dose**		

Patients with renal impairment

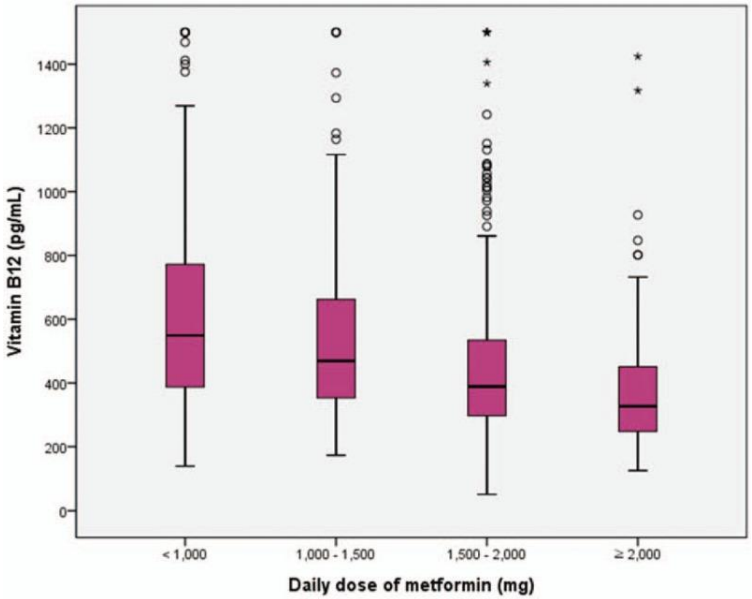
- Assess eGFR before initiation and at least annually thereafter
- Assess more frequently (e.g. every 3–6 months) in the elderly and patients at increased risk of further decline

eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease

Metformin (metformin hydrochloride) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/medicine/23244/.

Clinical Tip 2 (IR vs SR)

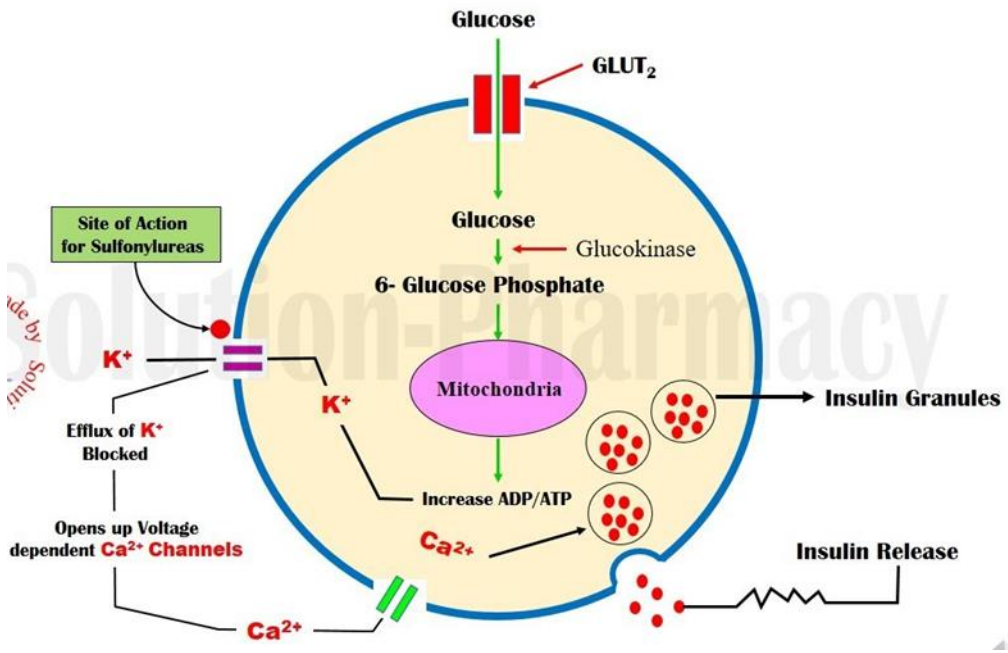
- **Compliance**
- **Cost** (£0.80 vs £1.8-2.8)
- **B12 deficiency**
  - Myth or hype?
  - 6-30%
  - Tissue (MMA) vs plasma level



Jiwoon K et al. Medicine (Baltimore). 2019 Nov; 98(46): e17918.

Sulphonylureas

Mode of action:



BENEFITS

- Established efficacy HbA1c reduction 1.0–1.5%[1]
- Evidence of reduced microvascular risk in UKPDS[2]

CONSIDERATIONS

- Weight gain[3]
- Hypoglycaemia[3]
- No dedicated cardiovascular outcome trial
- Contraindicated in severe renal or hepatic impairment

Refer to the full Summary of Product Characteristics for detailed safety information.

UKPDS: UK Prospective Diabetes Study

1. Inzucchi SE *et al. Diabetologia.* 2012;55:1577–1596; 2. Holman RR *et al. N Engl J Med.* 2008;359:1577–1589 3. Davies MJ *et al. Diabetologia.* 2018;61:2461–2498.

Clinical Tip 1: Post prandial hyperglycaemia

Second generation sulfonylureas

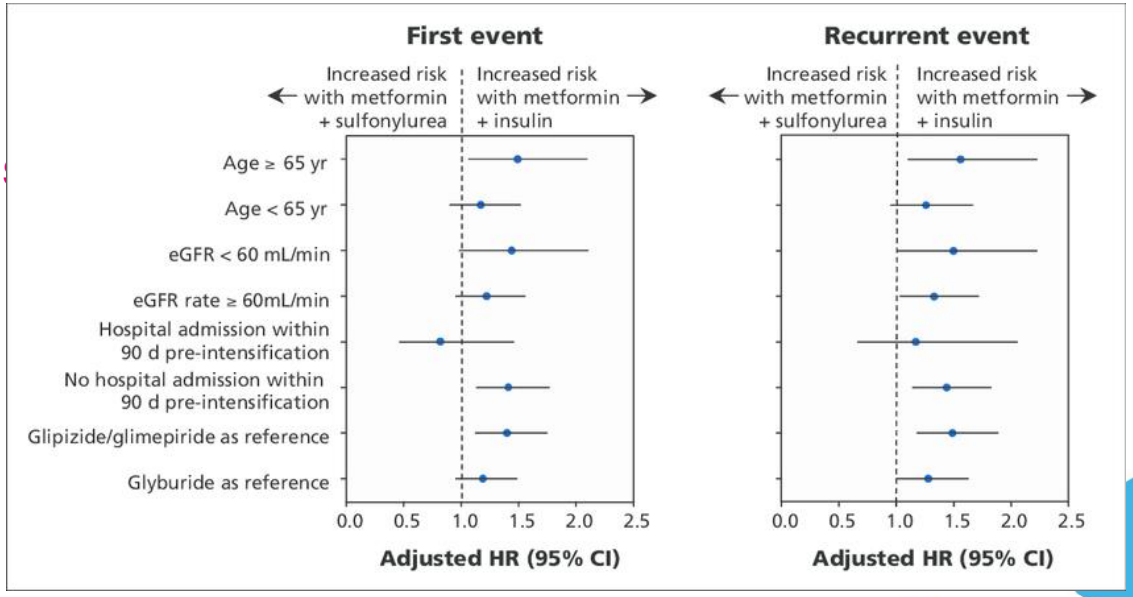
	Glipizide	Glibenclamide (Glyburide)	Glimepiride
Absorption	Well	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Inactive	Inactive
Half-life	2 – 4 hrs	Less than 3 hrs	5 - 9 hrs
Duration of action	10 – 16 hrs	12 – 24 hrs	12 – 24 hrs
	short	long	long
Doses	Divided doses 30 min before meals	Single dose	Single dose
Excretion	Urine	Urine	Urine

Meglitinides Summary

Medication (A1C reduction)	Mechanism of Action	Comments
Repaglinide Nateglinide (0.5% to 1%)	Stimulates the release of insulin from the β-cells of the pancreas	• Shorter acting than the SUs • Taken with meals • The dose should be skipped if the meal is skipped • Lower risk of hypoglycemia than with SUs • May cause weight gain

Clinical Tip 2: SU & hypoglycaemia

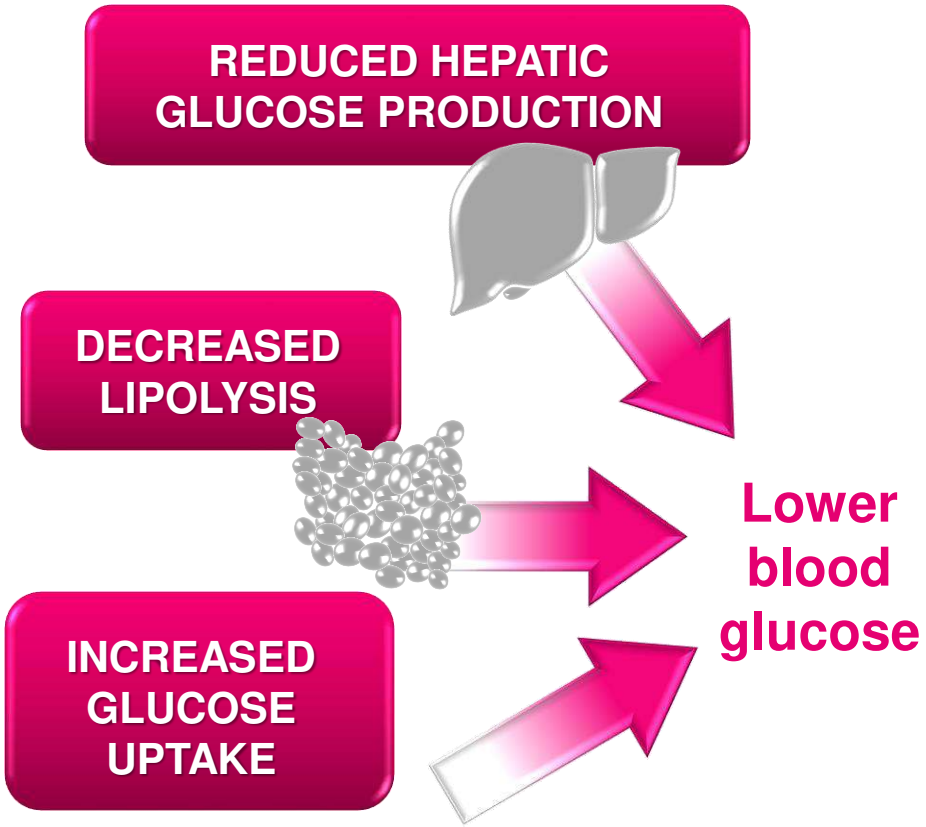
- Incidence of **hypoglycaemia** in the first 3 years of treatment is the same as initiating insulin
  - *Wilding J et al 2016*
- Beware of **short-term escalations** due to
  - Hospital stay
  - Concomitant meds
- **Fluctuating renal function**



Roumie C et al. Canadian Medical Association Journal. 188. 10.1503/cmaj.150904.

Pioglitazone

Mode of action:



BENEFITS

- Established efficacy HbA1c reduction 1.0–1.5%[1]
- Low risk of hypoglycaemia[2]
- Possible reduction in non-fatal myocardial infarction and all-cause mortality based on PROactive study*[3,4]

CONSIDERATIONS

- Weight gain[2]
- Fluid retention exacerbating heart failure[2]
- Fractures[2]
- Cases of bladder cancer[2]
- Possible macular oedema[2]

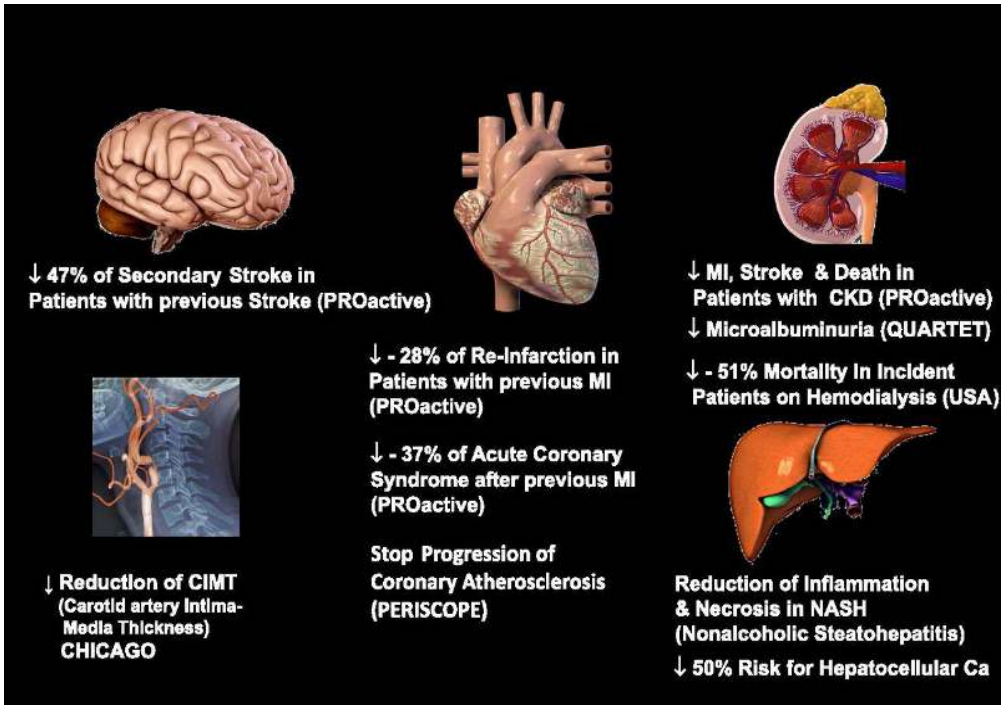
Refer to the full Summary of Product Characteristics for detailed safety information.

***Significant difference was recorded for the main secondary endpoint only (death from any cause, non-fatal myocardial infarction [excluding silent myocardial infarction], or stroke). The primary endpoint was death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg. No significant difference was recorded for the primary endpoint.**

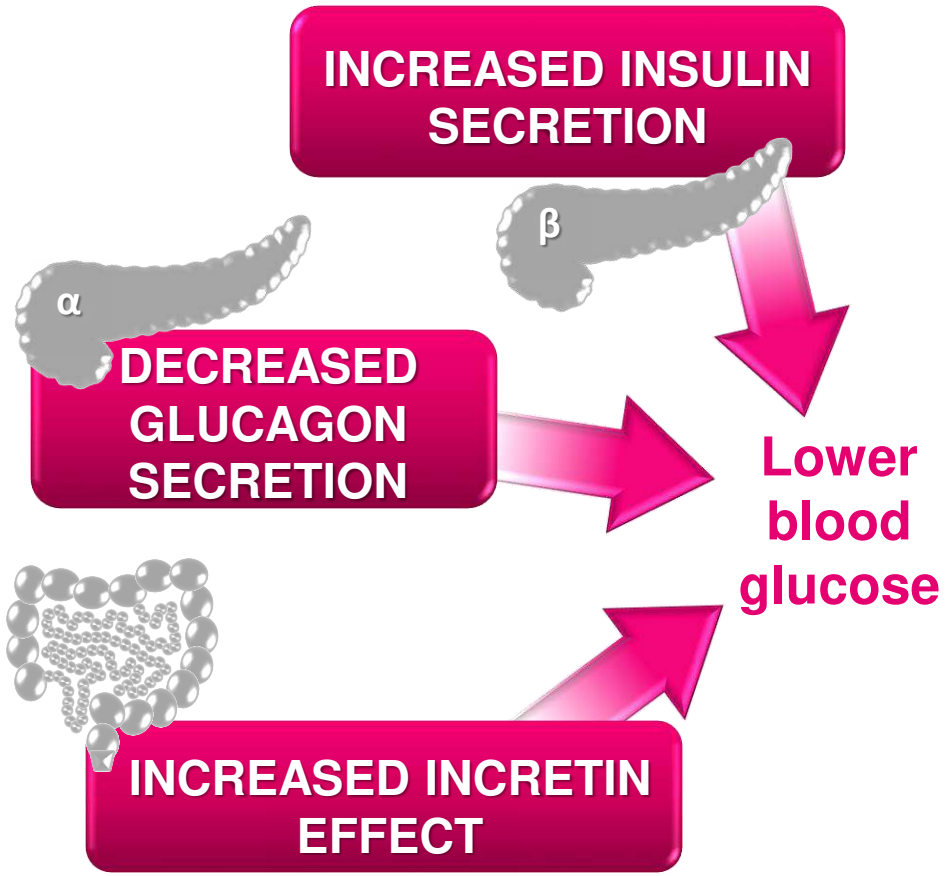
1. Inzucchi SE *et al. Diabetologia.* 2012;55:1577–1596; 2. Davies MJ *et al. Diabetologia.* 2018;61:2461–2498;
3. McGrane D *et al. Br J Cardiol.* 2011;18:24–27; 4. Dormandy JA *et al. Lancet.* 2005;366:1279–1289.

Clinical tips

- Hypersensitivity to pioglitazone
- Heart failure – any stage (initiation/during therapy)
- Pregnancy
- Breast-Feeding: the safety of pioglitazone during breast-feeding has not yet been established
- Serious hepatic impairment
- Active bladder cancer; history of bladder cancer; uninvestigated macroscopic hematuria



DPP-4 inhibitors



BENEFITS

- HbA1c reduction 0.5–1.0%[1]
- Well tolerated[2]
- Weight neutral[2]
- Low risk of hypoglycaemia[2]
- No increase in ischaemic events in cardiovascular outcome trials[3–6]

CONSIDERATIONS

- Acute pancreatitis[2]
- Dose adjustment may be required in renal impairment (agent dependent)[2]
- Increased risk of hospitalisation for heart failure observed with saxagliptin[3]
- Rare cases of bullous pemphigoid[6]

Refer to the full Summary of Product Characteristics for detailed safety information.

DPP-4: dipeptidyl peptidase-4

1. Inzucchi SE *et al. Diabetologia.* 2012;55:1577–1596; 2. Davies MJ *et al. Diabetologia.* 2018;61:2461–2498; 3. Scirica BM *et al. N Engl J Med.* 2013;369:1317–1326; 4. White WB *et al. N Engl J Med.* 2013;369:1327–1335; 5. Green JB *et al. N Engl J Med.* 2015;373:232–242; 6. Rosenstock J *et al. JAMA.* 2019;321:69–79.

Incretin Therapy: application[1]

East Suffolk and North Essex
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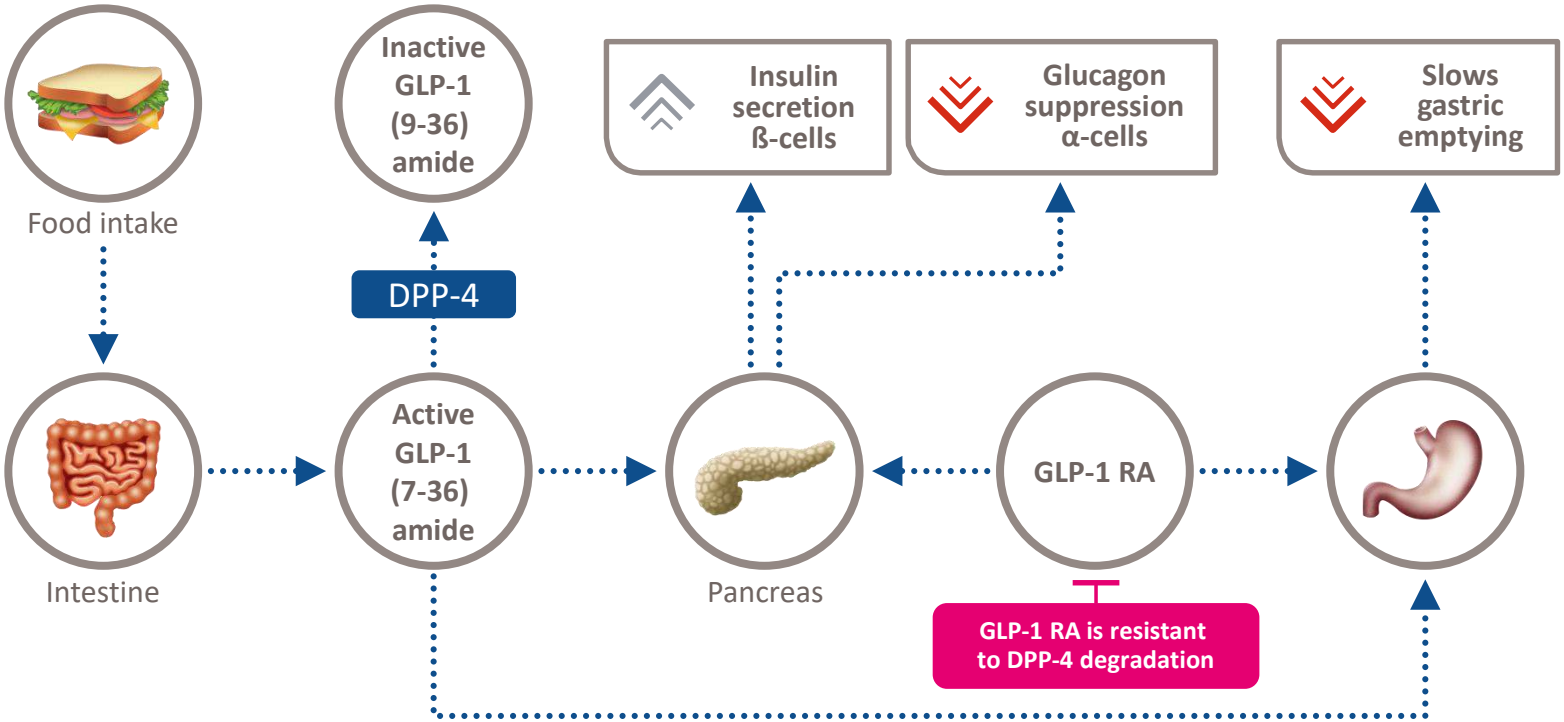


DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide-1.

1. Baggio LL, et al. Gastroenterology. 2007;132:2131-2157.

Clinical Tip 1: Most DPP-4 inhibitors require dose adjustment based on renal function

Dosing adjustment based on renal function as defined by SmPC

	Normal function	Mild impairment	Moderate impairment		Severe impairment/ESRD
Alogliptin*†[1]	25 mg OD	CrCl >50 to ≤80 ml/min 25 mg OD	CrCl ≥30 to ≤50 ml/min 12.5 mg OD		CrCl <30 ml/min Limited experience in renal dialysis. Not studied in peritoneal dialysis 6.25 mg OD
Linagliptin[2]	5 mg OD				
Saxagliptin*[3]	5 mg OD	GFR ≥60 to <90 ml/min 5 mg OD	GFR ≥45 to <60 ml/min 5 mg OD	GFR ≥30 to <45 ml/min 2.5 mg OD	GFR <30 ml/min ESRD on haemodialysis: not recommended 2.5 mg OD
Sitagliptin*[4]	100 mg OD	GFR ≥60 to <90 ml/min 100 mg OD	GFR ≥45 to <60 ml/min 100 mg OD	GFR ≥30 to <45 ml/min 50 mg OD	GFR ≥15 to <30 ml/min; ESRD (GFR <15 ml/min) including on haemodialysis or peritoneal dialysis 25 mg OD
Vildagliptin[5]	50 mg BD 50 mg OD with an SU	CrCl 50 to <80 ml/min 50 mg BD 50 mg OD with an SU	CrCl 30 to <50 ml/min 50 mg OD		CrCl <30 ml/min ESRD on haemodialysis: use with caution 50 mg OD

For individual guidance on DPP-4 inhibitor dosing in renal impairment please refer to the individual product SmPC.

*Assessment of renal function is recommended prior to initiation and periodically thereafter. †Not indicated as monotherapy.

BD: twice daily; CrCl: creatinine clearance (based on Cockcroft-Gault formula); DPP-4: dipeptidyl peptidase 4; ESRD: end-stage renal disease; GFR: glomerular filtration rate; OD: once daily; SmPC: Summary of Product Characteristics; SU: sulphonylurea

1. Vipidia (alogliptin) SmPC; 2. Trajenta (linagliptin) SmPC; 3. Onglyza (saxagliptin) SmPC; 4. Januvia (sitagliptin) SmPC; 5. Galvus (vildagliptin) SmPC. All SmPCs available at www.medicines.org.uk/emc.

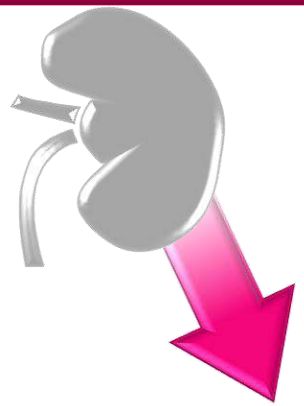
Clinical Tip 2

- **STOP when initiating GLP-1Ra's**
- **Caution with Heart failure**
  - Alogliptin, Saxagliptin and Vildagliptin contradicted in HF
  - **Linagliptin safe**
- **No cardiovascular outcome data**
- **Special clinical consideration in elderly/frail**
  - Linagliptin (Trajenta®)

SGLT2 inhibitors

Mode of action:

DECREASED GLUCOSE REABSORPTION



Lower blood glucose

BENEFITS

- Established efficacy HbA1c reduction 0.5–1.0%[1]
- Weight reduction[2]
- Low risk of hypoglycaemia[2]
- Reduction in blood pressure[2]
- Reduce cardiovascular risk*[3,4]

CONSIDERATIONS

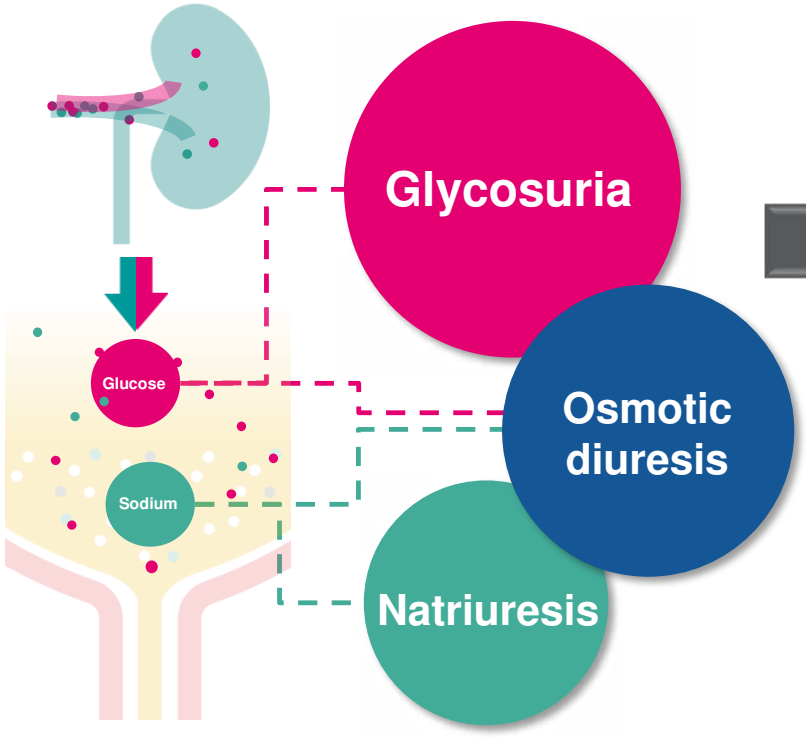
- Glycaemic efficacy dependent on renal function[2]
- GTIs/UTIs can be common†[5]
- Risk of volume depletion (uncommon)[5]
- Warnings/precautions:[5–8]
  - DKA (rare)
  - Fournier's gangrene (unknown incidence)
  - Lower-limb amputation‡

Refer to the full SmPCs for detailed safety information.
Empagliflozin is not indicated for weight loss, blood pressure reduction or reducing cardiovascular risk.
***Empagliflozin and canagliflozin have been shown to reduce cardiovascular events vs placebo in patients with type 2 diabetes and cardiovascular disease in dedicated cardiovascular outcome trials. †Side effect frequency shown as per Jardiance SmPC. ‡Observed In long-term studies of ertugliflozin and canagliflozin.[6,8]**
DKA: diabetic ketoacidosis; LLA: lower-limb amputation; SGLT2: sodium–glucose co-transporter 2

1. Inzucchi SE *et al. Diabetologia.* 2015;58:429–442; 2. Davies MJ *et al. Diabetologia.* 2018;61:2461–2498; 3. Zinman B *et al. N Engl J Med.* 2015;373:2117–2128; 4. Neal B *et al. N Engl J Med.* 2017; 377:644–657; 5. Jardiance (empagliflozin) SmPC; 6. Invokana (canagliflozin) SmPC; 7. Forxiga (dapagliflozin) SmPC; 8. Steglatro (ertugliflozin) SmPC. All SmPCs available at: www.medicines.org.uk.

Due to their mode of action, SGLT2 inhibitors have multiple benefits for people with type 2 diabetes

SGLT2 inhibitors promote excretion of sodium and glucose from the kidneys into the urine



Glycosuria

Osmotic diuresis

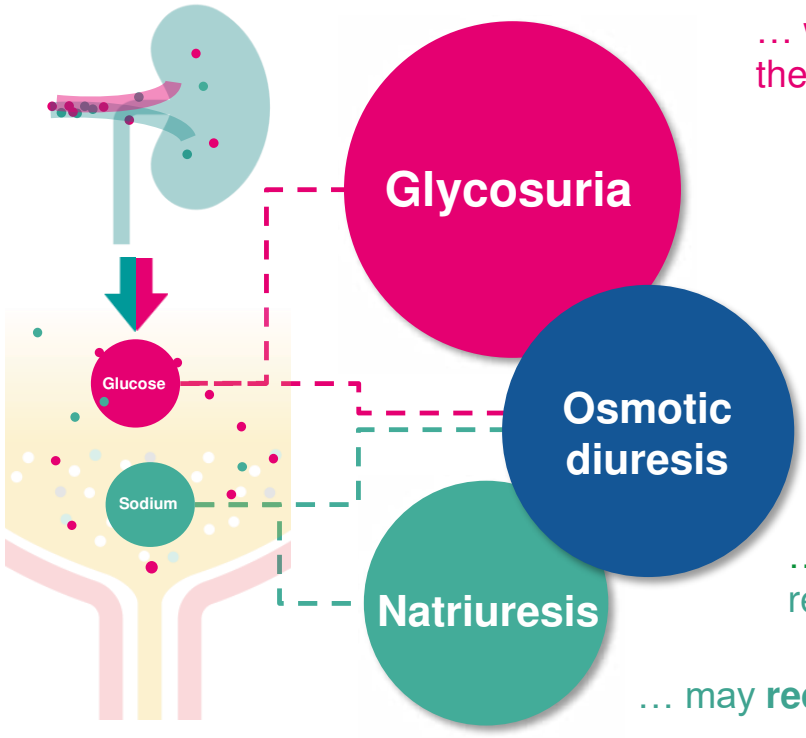
Natriuresis

Reductions in HbA1c, weight and blood pressure vs placebo with a low risk of hypoglycaemia

Empagliflozin is not indicated for blood pressure reduction, weight loss, the treatment of heart failure or kidney disease, the prevention of death or the reduction of cardiovascular risk. Please refer to the SmPC for full details of the licensed indication before prescribing.

Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441/smpc.

The glycosuria, natriuresis and osmotic diuresis observed with SGLT2 inhibitors may contribute to improvements in cardiovascular outcomes



… which lowers plasma glucose, therefore **reduces HbA1c**[1] and glucose toxicity[2]

… which causes a caloric loss, resulting in **weight loss**[1,3] and reduction in fat mass[1,4]

… which reduces plasma volume, leading to **reduction in blood pressure** and cardiac preload[1,5]

… which **alters tubular–glomerular feedback** and reduces glomerular hyperfiltration[6]

… may **reduce arterial pressure**,[7] which improves cardiac afterload[5]

Empagliflozin is not indicated for blood pressure reduction, weight loss, the treatment of heart failure or kidney disease, the prevention of death or the reduction of cardiovascular risk. Please refer to the SmPC for full details of the licensed indication before prescribing.

1. Jardiance (empagliflozin) Summary of Product Characteristics; 2. Torimoto K *et al. Diabetol Metab Syndr.* 2017;9:60; 3. Ferrannini G *et al. Diabetes Care.* 2015;38:1730–1735; 4. Ridderstråle M *et al. Lancet Diabetes Endocrinol.* 2014;2:691–700; 5. Garg V *et al. Prog Cardiovasc Dis.* 2019;62:349–357; 6. Wanner C *et al. N Engl J Med.* 2016;375:323–334; 7. Chilton R *et al. Diabetes Obes Metab.* 2015;17:1180–1193.

Cardiovascular benefits seen with SGLT2 inhibitors

	EMPA-REG OUTCOME Empagliflozin[1–3] >99% cardiovascular disease	CANVAS Program Canagliflozin[4] 65.6% cardiovascular disease 34.4% multiple risk factors	DECLARE-TIMI 58 Dapagliflozin[5] 40.6% cardiovascular disease 59.4% multiple risk factors	VERTIS CV Ertugliflozin[6,7] 99.9% cardiovascular disease
Primary endpoint:				
3P-MACE: non-inferiority	✓	✓	✓*	✓
3P-MACE: superiority	✓	✓	-	not tested
CV death	✓	-	-	-
Non-fatal MI	-	-	-	-
Non-fatal stroke	-	-	-	-
Other pre-specified outcomes:				
HHF	✓	✓	✓	✓
Renal composite (most comparable)	✓†	✓	✓	- did not include albuminuria
All-cause mortality	✓	-	-	-

Empagliflozin is not indicated for the treatment of heart failure or kidney disease, the prevention of death or the reduction of cardiovascular risk. Please refer to the relevant SmPCs for full details of licensed indications before prescribing. For illustration only, due to differences in study design, inclusion criteria and population direct comparisons cannot and should not be made.

***Co-primary endpoint. †Component of the pre-specified microvascular outcome. Unless marked 'non-inferiority', ✓ indicates demonstrated superiority over placebo.**

CV: cardiovascular; HHF: hospitalisation for heart failure; MACE: major adverse cardiovascular events; SGLT2: sodium–glucose co-transporter-2

1. Zinman B *et al. N Engl J Med.* 2015;373:2117–2128; 2. Zinman B *et al. Cardiovasc Diabetol.* 2014;13:102. Supplementary appendix; 3. Wanner C *et al. N Engl J Med* 2016;375:323; 4. Neal B *et al. N Engl J Med.* 2017;377:644–657; 5. Wiviott SD *et al. N Engl J Med.* 2019;380:347–357; 6. Cannon CP *et al. Am. Heart J.* 2018;206:11–23; 7. Pratley RE *et al.* American Diabetes Association (ADA) Virtual 88th Scientific Sessions. June 2020. Oral presentation.

Clinical Tip 1: What should we discuss with patients when initiating an SGLT2 inhibitor?

Reinforce lifestyle messages when intensifying therapy

- SGLT2 inhibitors can help patients lose weight and causes a modest reduction in blood pressure, which may motivate patients to reach and maintain lifestyle targets
- SGLT2 inhibitors should be used with caution in patients aged ≥75 years and in those patients for whom a drop in blood pressure could pose a risk

Highlight the need to maintain good personal hygiene

- Genital and urinary tract infections can be common when using SGLT2 inhibitors (approximately 1–10% of patients)
- Post-marketing cases of Fournier's gangrene (outside clinical trials) have been reported with unknown incidence; patients should be advised to seek medical attention if they experience pain, tenderness, or swelling in the genital or perineal area, with fever or malaise

Empagliflozin is not indicated for weight loss or the reduction of blood pressure. Please refer to the SmPC for full details of the licensed indication before prescribing.

SGLT2: sodium–glucose co-transporter 2

Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441/smpc.

Clinical Tip 2: What should we discuss with patients when initiating an SGLT2 inhibitor?

Counsel patients on sick day rules

- SGLT2 inhibitors should be discontinued during any dehydrating illness, along with other medications such as metformin and ACE inhibitors – they can be restarted when the patient is feeling better[1]
- Rare cases of diabetic ketoacidosis (DKA) have been reported in patients treated with SGLT2 inhibitors; before initiating an SGLT2 inhibitor, factors in the patient history that may predispose to ketoacidosis such as low β-cell function reserve should be considered. Discontinue treatment immediately if DKA is suspected[2]

Consider the risk of hypoglycaemia

- SGLT2 inhibitors are associated with a low risk of hypoglycaemia when used as monotherapy or in combination with metformin due to its mechanism of action[2]
- Hypoglycaemia is a very common side effect when SGLT2 inhibitors are used in combination with a sulphonylurea or insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia[2]

ACE: angiotensin converting enzyme; DKA: diabetic ketoacidosis; SGLT2: sodium-glucose co-transporter 2

1. Down S. *Diabetes Prim. Care.* 2018;20:15-16; 2. Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441/smpc.

Clinical Tip 3: During treatment with an SGLT2 inhibitor

MONITOR

- Have systems in place to measure blood ketones when patients are feeling unwell or not eating
- Reinforce education about DKA

SUSPEND TREATMENT

- Acute medical admission
- Admission for elective surgery or procedure requiring starvation
- Vomiting or dehydration

STOP TREATMENT

- Stop and do not restart treatment in people who develop DKA unless there was a clear precipitant that has been resolved

RESTART TREATMENT

- When the potential precipitant of DKA is no longer a threat
- This may range from 24 hours to several days
- Consider the need for alternative diabetes treatment in the interim

DKA: diabetic ketoacidosis; SGLT2: sodium–glucose co-transporter 2

Association of British Clinical Diabetologists. *SGLT-2 inhibitors in people with type 2 diabetes: an educational resource for health professionals.* Available at: https://abcd.care/sites/abcd.care/files/site_uploads/Resources/Position-Papers/SGLT2-inhibitors-ABCD.pdf (accessed October 2020).

Clinical Tip 4: SGLT2 inhibitors: dosing in renal impairment

	Degree of renal impairment*			
	Normal function (eGFR ≥90 ml/min/1.73 m^2)	**Mild** im…	**Moderate to** …ere	**Severe impairment /ESRD** (eGFR ≤29 ml/min/1.73 m^2)
Canagliflozin Max. daily dose[1]	**300 mg**			**100 mg†, ‡, § Do not initiate if eGFR** …**ml/min/1.73 m^2**
Dapagliflozin Max. daily dose[2]	**10 mg**			…**ndicated**
Empagliflozin Max. daily dose[3]	**25 mg**			…**ntraindicated**
Ertugliflozin ▼ Max. daily dose[4]	**15 mg**			…**rtugliflozin contraindicated**

***Assessment of renal function is recommended prior to initiation or periodically thereafter; †If further glycaemic control is needed, the addition of other anti hyperglycaemic agents should be considered; ‡With urinary albumin/creatinine ratio >300 mg/g; §Continue dosing until dialysis or renal transplantation.**
eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; OD: once daily; SGLT2: sodium–glucose co-transporter 2

1. Invokana (canagliflozin) Summary of Product Characteristics; 2. Forxiga (dapagliflozin) Summary of Product Characteristics; 3. Jardiance (empagliflozin) Summary of Product Characteristics.
4. Steglatro (ertugliflozin) Summary of Product Characteristics. All SmPCs available at: www.medicines.org.uk/emc.

Clinical Tip 4:

Clinical Tip 4: eGFR cut offs

Diabetes

- All drugs
  - Start at eGFR ≥60
  - Continue till 45

Heart failure

- Empa: eGFR 20
- Dapa: eGFR no limit
- Cana: no license
- Ertu: no license

Nephropathy

- Empa: no license
- Dapa: eGFR no limit
- Cana: eGFR ≥ 30 if ACR >300mg/g
- Ertu: no license

Clinical Tip 5: SmPC Empagliflozin (Jardiance)

Special populations

Renal impairment

In patients with type 2 diabetes mellitus, the glycaemic efficacy of empagliflozin is dependent on renal function. For dose adjustment recommendations according to eGFR or CrCL refer to Table 1.

Table 1: Dose adjustment recommendations[a]

Indication	eGFR [ml/min/1.73 m²] or CrCL [ml/min]	Total daily dose
Type 2 diabetes mellitus	≥60	Initiate with 10 mg empagliflozin. In patients tolerating 10 mg empagliflozin and requiring additional glycaemic control, the dose can be increased to 25 mg empagliflozin.
	45 to <60	Do not initiate empagliflozin. Continue with 10 mg empagliflozin in patients already taking Jardiance.
	<45	Empagliflozin is not recommended.
Heart failure (with or without type 2 diabetes mellitus)	≥20	Recommended daily dose is 10 mg empagliflozin.
	<20	Empagliflozin is not recommended.

[a] See sections 4.4, 4.8, 5.1 and 5.2

Due to the mechanism of action, the glycaemic efficacy of empagliflozin is dependent on renal function. No dose adjustment is required for patients with an eGFR ≥60 ml/min/1.73 m^2 or CrCl ≥60 ml/min.

For treatment of type 2 diabetes mellitus, empagliflozin should not be initiated in patients with an eGFR <60 ml/min/1.73 m^2 or CrCl <60 ml/min. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m^2 or CrCl below 60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m^2 or CrCl persistently below 45 ml/min (see sections 4.4, 4.8, 5.1, and 5.2).

For treatment of heart failure in patients with or without type 2 diabetes mellitus, empagliflozin 10 mg may be initiated or continued down to an eGFR of 20 ml/min/1.73 m^2 or CrCl of 20 ml/min.

https://www.medicines.org.uk/emc/product/5441/smpc#gref (accessed 1st Nov 2021)

Clinical Tip 5: SmPC Dapagliflozin

4. Clinical particulars

4.1 Therapeutic indications

Type 2 diabetes mellitus

Forxiga is indicated in adults for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.

- in addition to other medicinal products for the tre The glycosuria, natriuresis and ...

For study results with respect to combination of therapies, effects on glycaemic control, cardiovascular and renal events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Heart failure

Forxiga is indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

Chronic kidney disease

Forxiga is indicated in adults for the treatment of chronic kidney disease.

4.2 Posology and method of administration

Posology

Type 2 diabetes mellitus

The recommended dose is 10 mg dapagliflozin once daily.

When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

https://www.medicines.org.uk/emc/product/5441/smpc#gref (accessed 1st Nov 2021)

Clinical Tip 5: SmPC Canagliflozin

For treatment of diabetic kidney disease as add on to standard of care (eg ACE-inhibitors or ARBs), a dose of 100 mg canagliflozin once daily should be used (see table 1). Because the glycaemic lowering efficacy of canagliflozin is reduced in patients with moderate renal impairment and likely absent in patients with severe renal impairment, if further glycaemic control is needed, the addition of other anti-hyperglycaemic agents should be considered. For dose adjustment recommendations according to eGFR refer to table 1.

Table 1: Dose adjustment recommendations[a]

eGFR (mL/min/1.73 m^2) or CrCl (mL/min)	**Total daily dose of canagliflozin**
≥ 60	Initiate with 100 mg. In patients tolerating 100 mg and requiring additional glycaemic control, the dose can be increased to 300 mg.
45 to < 60[b]	Initiate with 100 mg. Continue 100 mg for patients already taking Invokana.
30 to < 45[b, c]	Initiate with 100 mg. Continue 100 mg for patients already taking Invokana.
< 30[b, c]	Continue 100 mg for patients already taking Invokana[d]. Invokana should not be initiated.

[a] See sections 4.4, 4.8, 5.1, and 5.2.

[b] If further glycaemic control is needed, the addition of other anti hyperglycaemic agents should be considered

[c] With urinary albumin/creatinine ratio > 300 mg/g

[d] Continue dosing until dialysis or renal transplantation.

uACR: 33.9 mmol/mol

Hepatic impairment

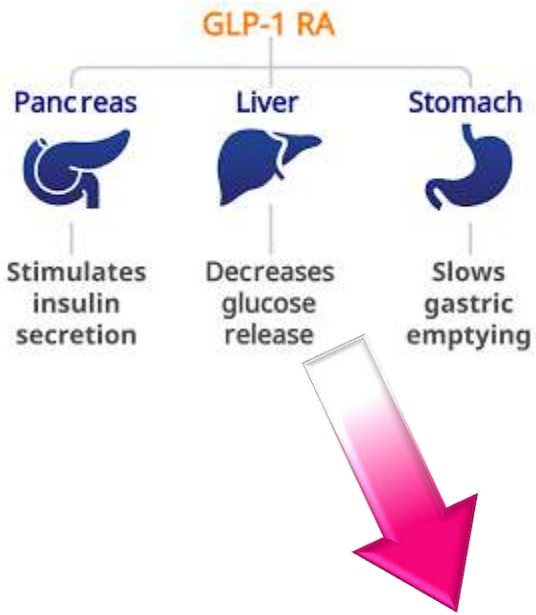
For patients with mild or moderate hepatic impairment, no dose adjustment is required.

Canagliflozin has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients (see section 5.2).

https://www.medicines.org.uk/emc/product/5441/smpc#gref (accessed 1st Nov 2021)

Oral GLP-1Ra (Rybelsus)[1,2,3]

Mode of action:



Lower blood glucose

BENEFITS

- Established efficacy HbA1c reduction 0.6–1.4%[1]
- Weight reduction[2]
- Low risk of hypoglycaemia[2]
- Reduction in blood pressure[2]
- Cardiovascular safe – no CV outcome data*[3,4]

CONSIDERATIONS

- 30 minutes prior to breakfast once daily
- Levothyroxine interaction
- CV safety data but no outcome data
- 3 doses – 3mg, 7mg, 14mg
- Real world retinopathy data awaited

Refer to the full SmPCs for detailed safety information.

[1]RYBELSUS® [package insert]. Plainsboro, NJ: Novo Nordisk Inc; April 2021.
[2]Bain SC, Mosenzon O, Arechavaleta R, et al. Cardiovascular safety of oral semaglutide in patients with type 2 diabetes: Rationale, design and patient baseline characteristics for the PIONEER 6 trial. Diabetes Obes Metab. 2019;21(3):499-508.
[3]Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841-851.

East Suffolk and North Essex NHS Foundation Trust

Patient cases

Case study: Adam, 47 years old

Diagnosed 2 years ago with type 2 diabetes

Male age 47

- **Commenced metformin 18 months ago**
  - Maximum tolerated dose: 1 g BD
- **HbA1c: 58 mmol/mol (7.5%)**
- **BP: 190/85 mmHg**
  - Losartan 50 mg OD
- **LDL: 4.2 mmol/L**
  - Atorvastatin 10 mg OD
- **BMI: 31 kg/m$^{2;}$ smoker**
- **eGFR: 78 mL/min/1.73 m^2**
- **Cholesterol: 5.4 mmol/L**

What would you do?

Not an actual patient.

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Case study: Adam, 47 years old

Diagnosed 2 years ago with type 2 diabetes

Male age 47

- **Commenced metformin 18 months ago**
  - Maximum tolerated dose: 1 g BD
- **HbA1c: 58 mmol/mol (7.5%)**
- **BP: 190/85 mmHg**
  - Losartan 50 mg OD
- **LDL: 4.2 mmol/L**
  - Atorvastatin 10 mg OD
- **BMI: 31 kg/m$^{2;}$ smoker**
- **eGFR: 78 mL/min/1.73 m^2**
- **Cholesterol: 5.4 mmol/L**
- **Stable angina**

What would you do?

Not an actual patient.

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Case study: Brian, 62 years old

Diagnosed 3 years ago with type 2 diabetes

Male age 62

- **Diabetes medications:**
  - Metformin 1 g BD
  - Sitagliptin 100 mg OD
- **HbA1c: 51 mmol/mol (6.8%)**
- **BP: 152/93 mmHg**
- **LDL: 3.6 mmol/L**
  - Atorvastatin 20 mg OD
- **BMI: 38 kg/m^2**
- **eGFR: 78 mL/min/1.73 m^2**
- **Delivery driver, previously struggled with hypoglycaemia on gliclazide; needle phobic**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Case study: Brian, 62 years old

Diagnosed 3 years ago with type 2 diabetes

Male age 62

- **Diabetes medications:**
  - Metformin 1 g BD
  - Sitagliptin 100 mg OD
- **HbA1c: 51 mmol/mol (6.8%)**
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  - Atorvastatin 20 mg OD
- **BMI: 38 kg/m^2**
- **eGFR: 58 mL/min/1.73 m^2**
- **Delivery driver, previously struggled with hypoglycaemia on gliclazide; needle phobic**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Case study: Martha, 73 years old

Diagnosed 5 years ago with type 2 diabetes

Female age 73

- **Diabetes medications:**
  - Metformin 500 mg BD (maximum tolerated dose)
  - Alogliptin 25mg OD
- **HbA1c: 60.7 mmol/mol (7.7%)**
- **BP: 142/80 mmHg**
  - Ramipril 2.5 mg OD
- **LDL: 2.7 mmol/L**
  - Atorvastatin 20 mg OD
- **BMI: 30 kg/m^2**
- **eGFR: 58 mL/min/1.73 m^2**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Case study: Martha, 73 years old

Diagnosed 5 years ago with type 2 diabetes

Female age 73

- **Diabetes medications:**
  - Metformin 500 mg BD (maximum tolerated dose)
- **HbA1c: 60.7 mmol/mol (7.7%)**
- **BP: 142/80 mmHg**
  - Ramipril 2.5 mg OD
- **LDL: 2.7 mmol/L**
  - Atorvastatin 20 mg OD
- **BMI: 30 kg/m^2**
- **eGFR: 58 mL/min/1.73 m^2**
- **Heart failure with reduced EF**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Universal Definition and Classification of Heart Failure (HF)

Definition

HF is a *clinical syndrome* with current or prior

- ***Symptoms and or signs caused by a structural and/or functional cardiac***

And corroborated by at least one of the following:

- ***Elevated natriuretic peptide levels***
- ***Objective evidence of cardiogenic pulmonary or systemic congestion***

Stages

AT RISK *(STAGE A)*	**Patients at risk for HF, but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease**
PRE-HF *(STAGE B)*	**Patients without current or prior symptoms or signs of HF with evidence of one of the following:** • *Structural Heart Disease* • *Abnormal cardiac function* • *Elevated natriuretic peptide or cardiac troponin levels*
HF *(STAGE C)*	**Patients with current or prior symptoms and/or signs of HF caused by a structural and/or functional cardiac abnormality**
ADVANCED HF *(STAGE D)*	**Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT, requiring advanced therapies transplantation, mechanical circulatory support, or palliative care**

Classification By EF

HF with reduced EF (HFrEF)
- *HF with **LVEF < 40%***

HF with mildly reduced EF (HFmrEF)
- *HF with **LVEF 41-49%***

HF with preserved EF (HFpEF)
- *HF with **LVEF > 50%***

HF with improved EF (HFimpEF)
- *HF with a baseline LVEF of < 40%, a 10-point increase from baseline LVEF, and a second measurement of LVEF of > 40%*

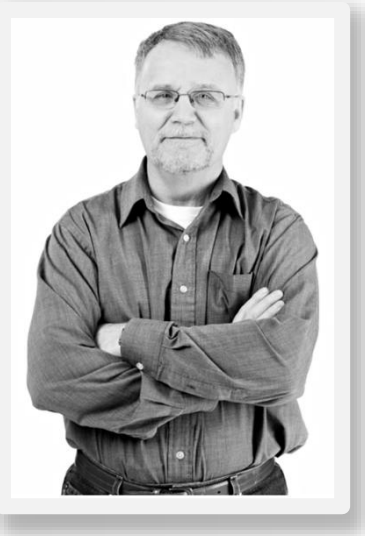
Language matters! The new universal definition offers opportunities for *more precise communication* and description with terms including ***persistent HF*** instead of "stable HF," and ***HF in remission*** rather than "recovered HF."

Case study: Philip, 65 years old

Diagnosed 6 years ago with type 2 diabetes

Male age 65

- **Diabetes medications:**
  - Metformin 500 mg BD (maximum tolerated dose)
  - Gliclazide 80 mg BD
- **HbA1c: 67.2 mmol/mol (8.3%)**
- **BP: 140/90 mmHg**
  - Ramipril 2.5 mg OD
- **LDL: 3.9 mmol/L**
  - Atorvastatin 20 mg OD
- **BMI: 27 kg/m^2**
- **eGFR: 69 mL/min/1.73 m^2**
- **Recently presented with a diabetic foot ulcer for which he is under the diabetes foot clinic**



What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Case study: Miriam, 59 years old

Diagnosed 9 months ago with type 2 diabetes

Female age 59

- **Diabetes medications:**
  - Metformin 1 g BD
  - Pioglitazone 45mg
- **HbA1c: 59 mmol/mol (7.5%)**
- **BP: 150/85 mmHg**
  - Ramipril 5 mg OD
- **LDL: 2.8 mmol/L**
  - Atorvastatin 20 mg OD
- **BMI: 29 kg/m^2**
- **eGFR: 75 mL/min/1.73 m^2**
- **6-month history of worsening breathlessness**
- **Echo showing mild-to-moderate LVSD**
  - LVEF 43%
- **NtProBNP: 700 pg/ml (N:0-400)**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; NtProBNP: N-terminal portion of the precursor of brain natriuretic peptide; OD: once daily

Case study: Dan, 45 years old

Diagnosed 1.5 years ago with type 2 diabetes

Male age 45

- **Commenced metformin 1 year ago**
  - Maximum tolerated dose: 1 g BD
- **HbA1c: 65 mmol/mol (8.1%)**
- **BP: 145/85 mmHg**
- **LDL: 2.6 mmol/L**
  - Atorvastatin 20 mg OD
- **BMI: 29 kg/m^2**
- **eGFR: 87 mL/min/1.73 m^2**
- **Regular smoker (26 pack-year history)**
- **Father suffered a fatal MI at 54 years old**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; MI: myocardial infarction; OD: once daily

Case study: Arnold, 66 years old

Diagnosed 12 months ago with type 2 diabetes

Male age 66

- **Diabetes medications:**
  - Metformin 1 g BD (maximum tolerated dose)
  - Gliclazide 160mg BD
- **HbA1c: 77 mmol/mol (9.2%)**
- **BP: 165/92 mmHg**
  - Ramipril 5 mg OD
- **LDL: 3.0 mmol/L**
  - Atorvastatin 20 mg OD
- **BMI: 33 kg/m^2**
- **eGFR: 62 mL/min/1.73 m^2**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Case study: Ethel, 85 years old

Diagnosed 12 years ago with type 2 diabetes

Female age 85

- **Diabetes medications:**
  - Metformin 1 g BD
  - Gliclazide 80 mg OD
- **HbA1c: 75 mmol/mol (9.0%)**
- **BP: 163/70 mmHg**
  - Ramipril 2.5 mg OD
- **LDL: 2.6 mmol/L**
  - Atorvastatin 10 mg OD
- **BMI: 21 kg/m^2**
- **eGFR: 70 mL/min/1.73 m^2**
- **Osteoarthritis medications:**
  - Ibuprofen 200 mg OD
  - Lansoprazole 15 mg OD
- **Limited mobility, relies on carers**

What would you do?

BD: twice daily; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; OD: once daily

Type 2 diabetes therapies: an overview

Oral therapies

- Metformin
- Sulphonylureas
- DPP-4 inhibitors
- SGLT2 inhibitors
- Thiazolidinediones (i.e. pioglitazone)
- GLP-1 receptor agonists (i.e. oral semaglutide)*
- Acarbose

Injectables

- GLP-1 receptor agonists*
- Insulin

*As of October 2020 there is one oral GLP-1 receptor agonist with a European marketing authorisation; Rybelsus ▼ (oral semaglutide).
DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium–glucose co-transporter 2

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Pharmacology: GLP-1 RA

The Incretin Effect[1]

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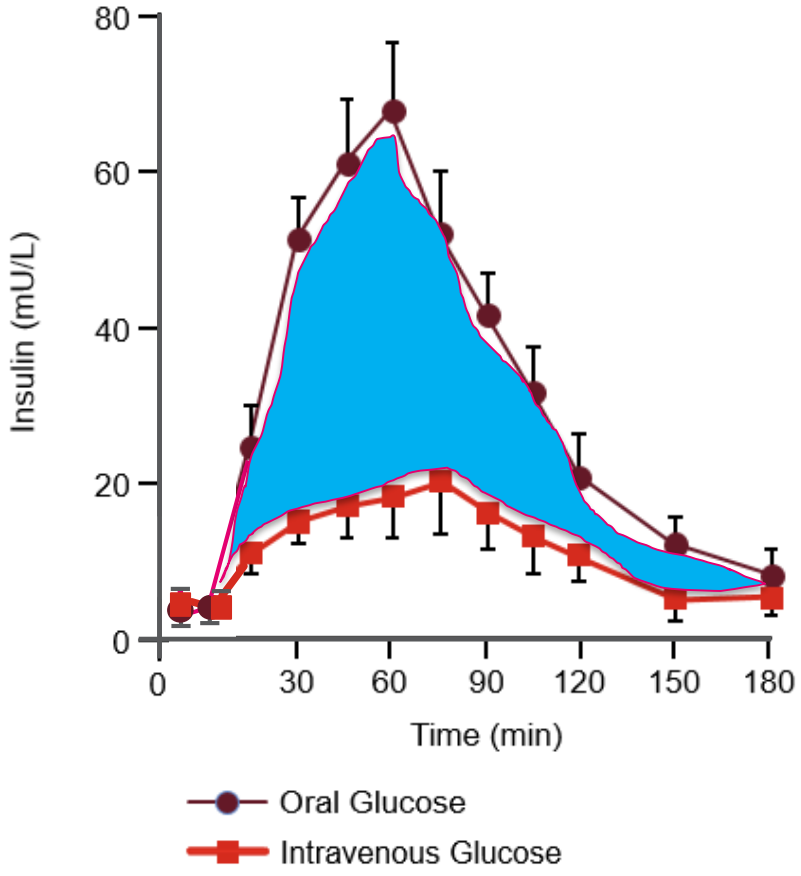
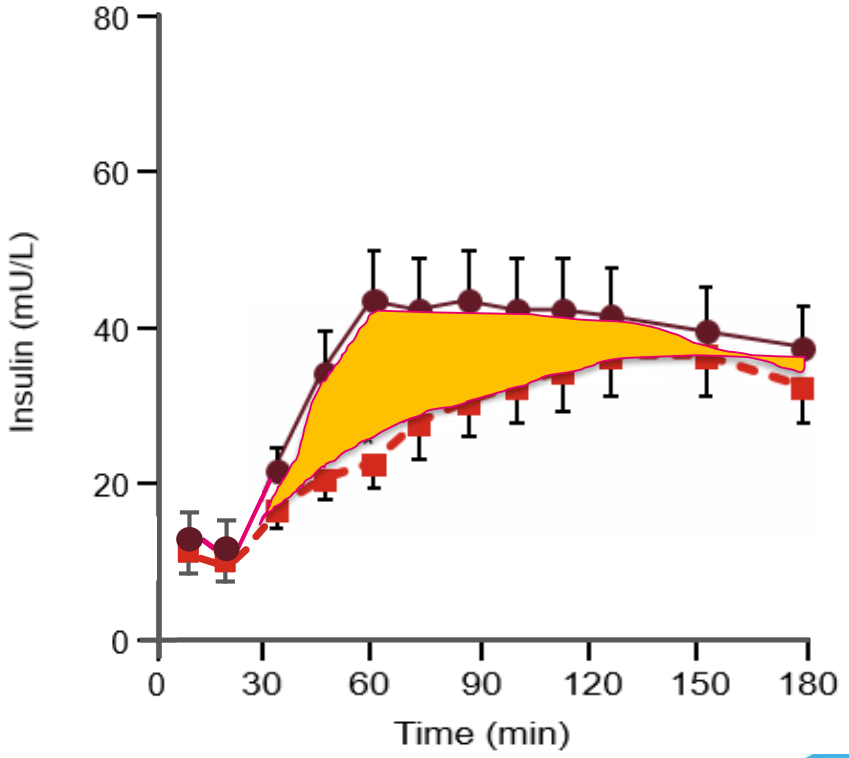
Control subjects (n=8)



Subjects with type 2 diabetes (n=14)



***p≤0.05**

1. Nauck M et al. Diabetolgia. 1986; 29:46–52.

What are Incretin Hormones?

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- Gut-derived hormones, secreted in response to nutrient ingestion[1]
- The two predominant incretin hormones are GLP-1 and Glucose-dependent insulinotropic peptide (GIP)[2]
- GLP-1 is the main incretin hormone targeted in the treatment of T2DM[2]

1. Meier JJ and Nauck MA. Diabetes Metab Res Rev. 2005; 21:91–117.
2. Holst JJ and Orskov C. Diabetes. 2004; 53:s197–s204.

GLP-1 effects in humans: Understanding the glucoregulatory role of incretins

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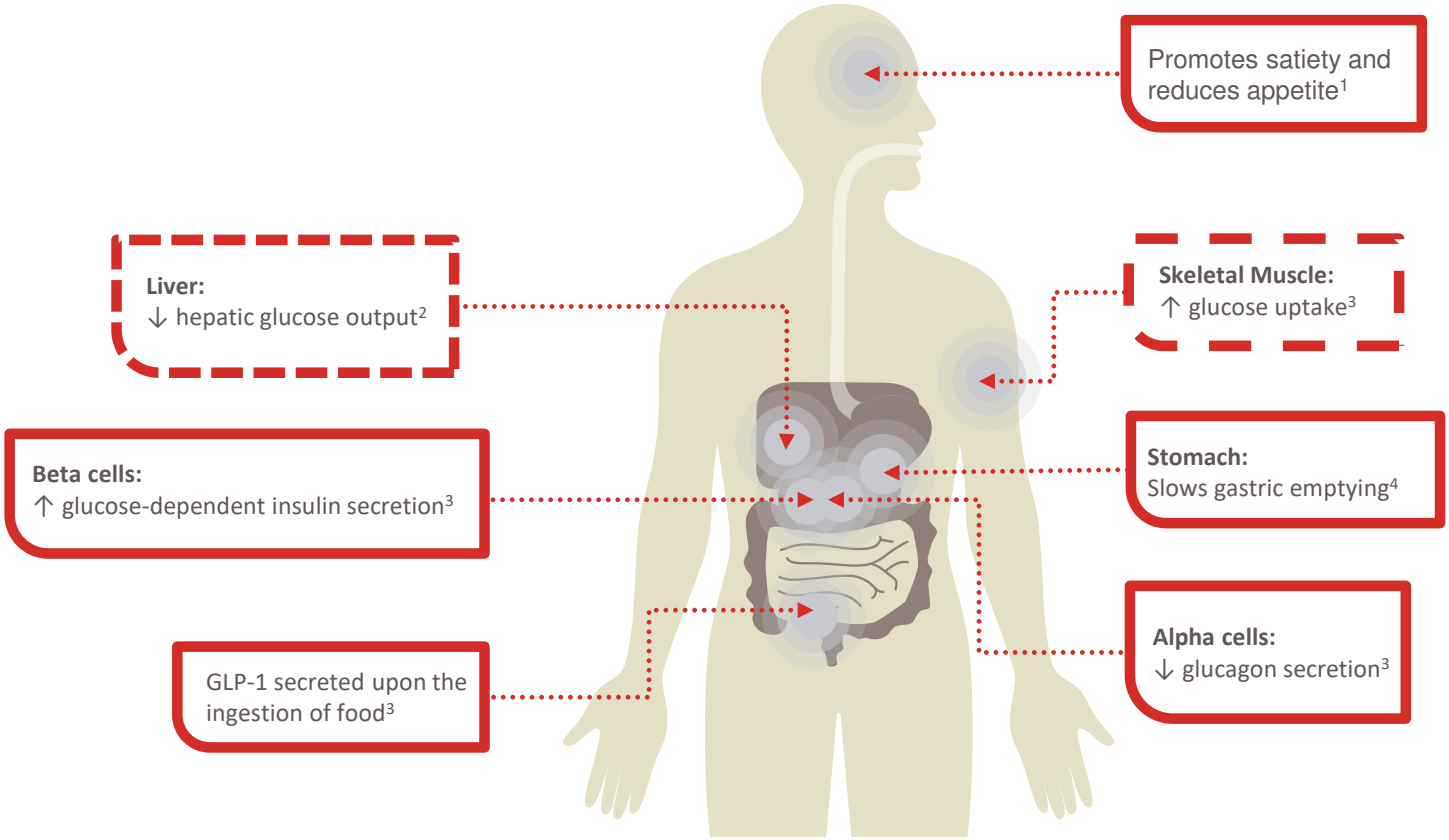

1. Flint A *et al.* J Clin Invest. 1998; 101:515–520. 2. Larsson H *et al.* Acta Physiol Scand. 1997; 160:413–422. 3. Drucker DJ. Diabetes. 1998; 47:159–169. 4. Nauck MA *et al.* Diabetologia. 1996; 39:1546–1553.

Frequently reported side effects

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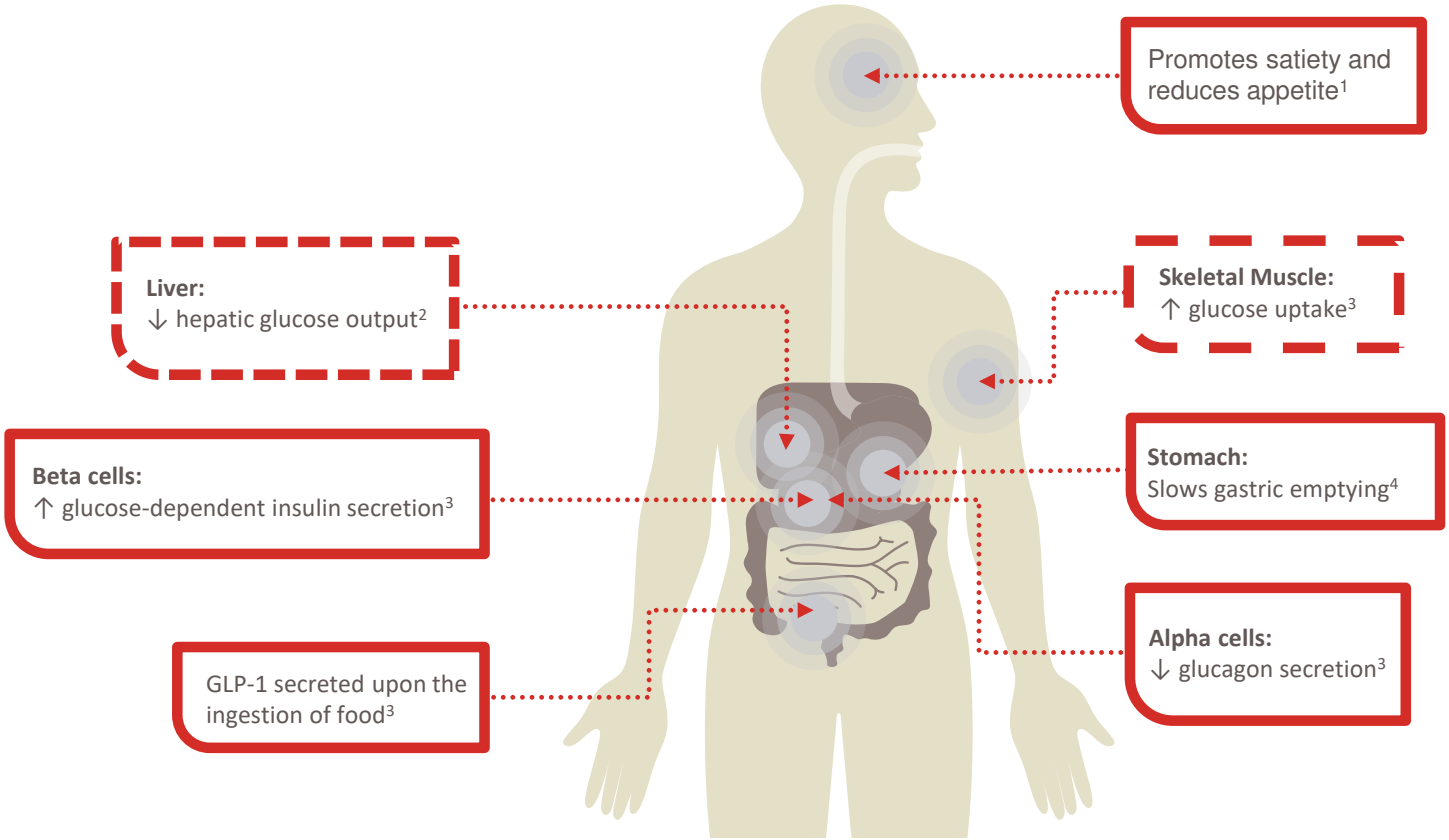

Refer to individual product SmPC (Summary of Product Characteristics) for further details on specific side effects

1. Flint A *et al.* J Clin Invest. 1998; 101:515–520. 2. Larsson H *et al.* Acta Physiol Scand. 1997; 160:413–422. 3. Drucker DJ. Diabetes. 1998; 47:159–169. 4. Nauck MA *et al.* Diabetologia. 1996; 39:1546–1553.

Frequently reported side effects

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Increased risk of hypoglycaemia* if combined with a therapy which has a *non-glucose-dependent* mechanism

Liver:
↓ hepatic glucose output[2]

Beta cells:
↑ glucose-dependent insulin secretion[3]

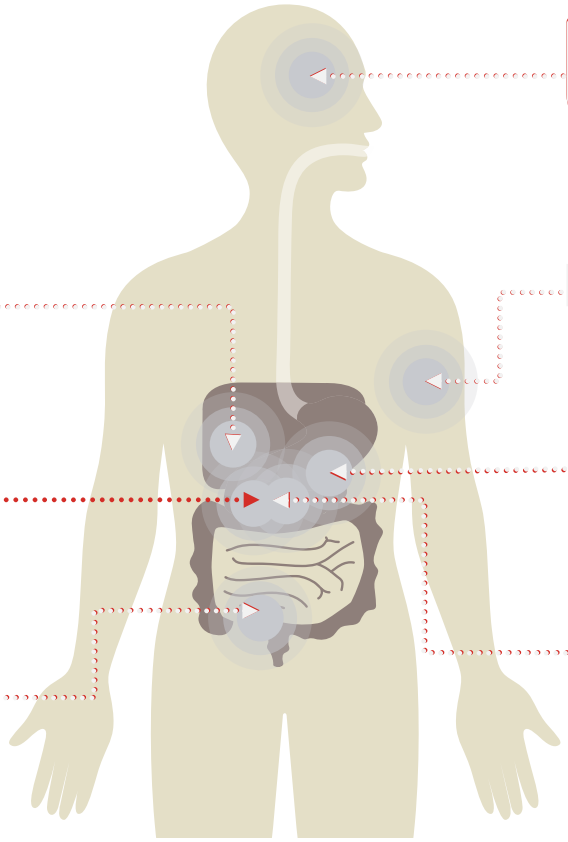
GLP-1 secreted upon the ingestion of food[3]

Promotes satiety and reduces appetite[1]

Skeletal Muscle:
↑ glucose uptake[3]

Stomach:
Slows gastric emptying[4]

Alpha cells:
↓ glucagon secretion[3]



*Frequency >1/10 (very common).
All other side effects occurred at a frequency of >1/100 (common)

Refer to individual product SmPC (Summary of Product Characteristics) for further details on specific side effects

1. Flint A *et al.* J Clin Invest. 1998; 101:515–520. 2. Larsson H *et al.* Acta Physiol Scand. 1997; 160:413–422. 3. Drucker DJ. Diabetes. 1998; 47:159–169. 4. Nauck MA *et al.* Diabetologia. 1996; 39:1546–1553.

Frequently reported side effects

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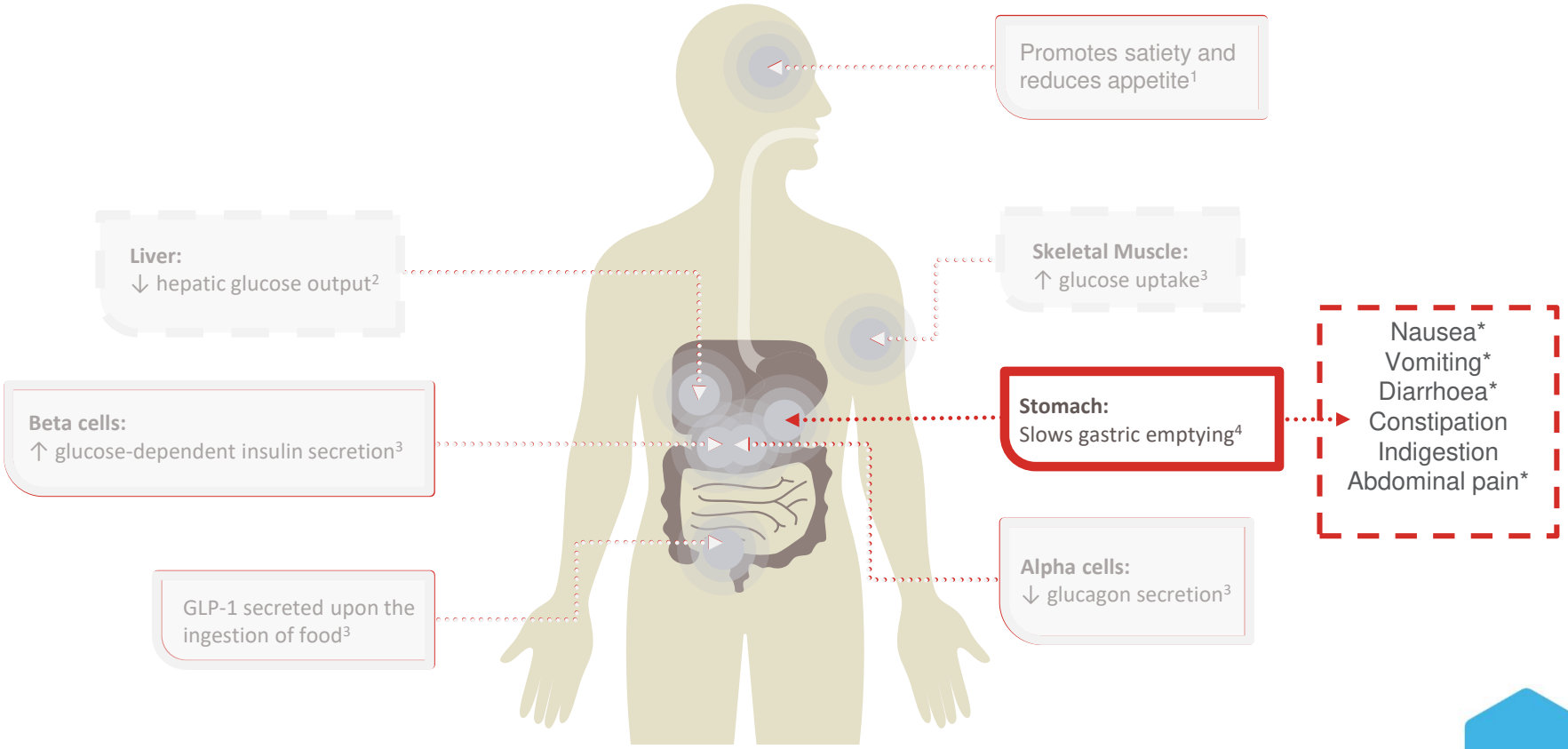

*Frequency >1/10 (very common).
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Refer to individual product SmPC (Summary of Product Characteristics) for further details on specific side effects

1. Flint A *et al.* J Clin Invest. 1998; 101:515–520. 2. Larsson H *et al.* Acta Physiol Scand. 1997; 160:413–422. 3. Drucker DJ. Diabetes. 1998; 47:159–169. 4. Nauck MA *et al.* Diabetologia. 1996; 39:1546–1553.

Frequently reported side effects

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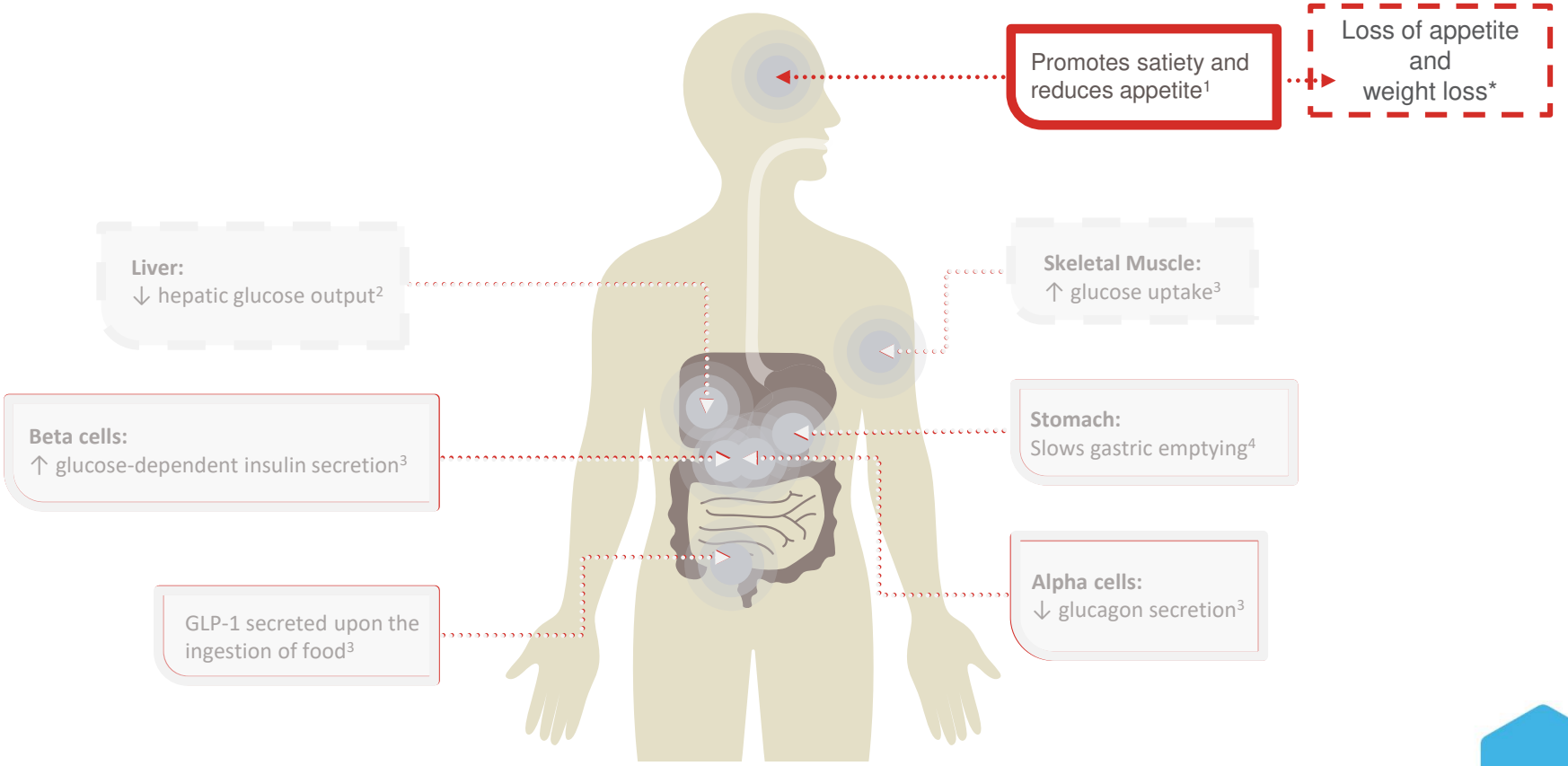

*GLP-1 RAs are not indicated for weight loss, apart from liraglutide, which is approved as a weight loss agent at a 3 mg dose.

Refer to individual product SmPC (Summary of Product Characteristics) for further details on specific side effects

1. Flint A *et al.* J Clin Invest. 1998; 101:515–520. 2. Larsson H *et al.* Acta Physiol Scand. 1997; 160:413–422. 3. Drucker DJ. Diabetes. 1998; 47:159–169. 4. Nauck MA *et al.* Diabetologia. 1996; 39:1546–1553.

Overview of approved administered GLP-1 RAs

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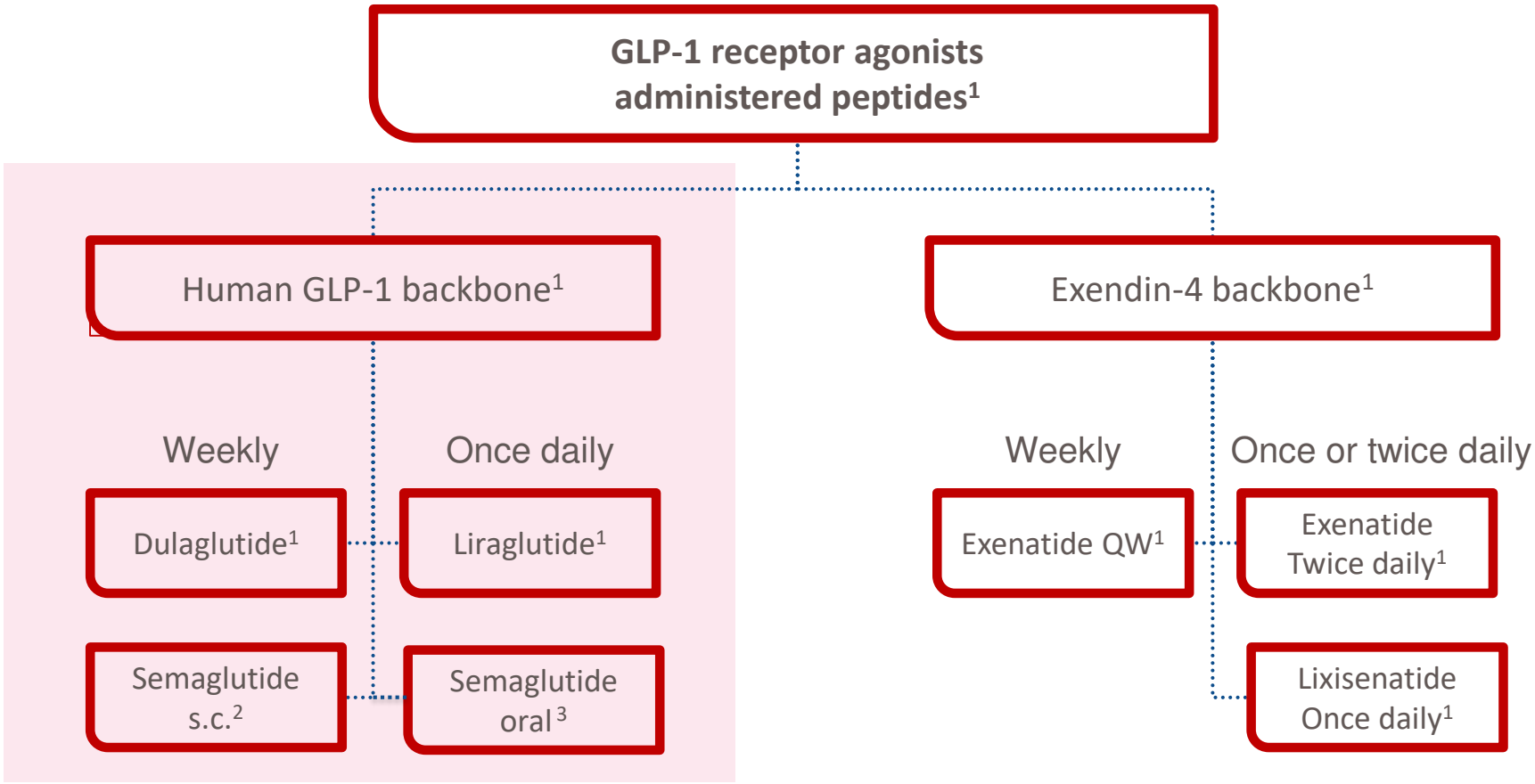

Trulicity is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise
-As a monotherapy when metformin is considered inappropriate due to intolerance or contraindications
-In addition to other medicinal products for the treatment of diabetes.

1. Madsbad et al. Diabetes Obes Metab. 2016; 18:317-332; 2. Novo Nordisk Semaglutide s.c SmPC 3. Novo Nordisk Oral Semaglutide SmPC

Summary table for each compound

East Suffolk and North Essex NHS Foundation Trust

	Liraglutide[1]	Trulicity[2]	Semaglutide s.c.[3]	Oral Semaglutide[4]
Therapeutic doses available	1.2mg, 1.8mg	0.75mg, 1.5mg, 3mg, 4.5mg	0.5mg, 1mg	7mg, 14mg
Efficacy				
Glucose lowering	✓	✓	✓	✓
Weight loss*	✓	✓	✓	✓
MACE benefit in established CVD **(doses studied)**	✓ **(1.8mg)**	✓ **(1.5mg)**	✓ **(0.5mg and 1mg)**	✘
MACE benefit in CV risk factors **(doses studied)**	✘	✓ **(1.5mg)**	✘	✘
Patient and HCP factors				
Weekly	✘	✓	✓	✘
Oral	✘	✘	✘	✓
S.C. Device: ready to use with no need to handle needles	✘	✓	✘	**N/A**
No need for titration to therapeutic dose at initiation	✘	✓	✘	✘
Independent of meals, other meds	✓	✓	✓	✘
Safety monitoring considerations				
No compound-specific safety monitoring requirements	✓	✓	✘	✘

* Dulaglutide and semaglutide are not indicated for weight loss. Liraglutide has an indication for weight management at a 3mg dose

1. Novo Nordisk Liraglutide Summary of Product Characteristics. 2. Trulicity (dulaglutide) Summary of Product Characteristics 3. Novo Nordisk Semaglutide s.c. Summary of Product Characteristics. 4. Novo Nordisk Oral Semaglutide Summary of Product Characteristics.

Special considerations

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- **Drivers on GLP-1 RAs should consider[1]:**
  - Group 1 (car and motorcycles) drivers do **not** need to inform DVLA.
  - Group 2 (bus and lorry) drivers **must** inform DVLA.
- **People on sulphonylureas and/or insulin should consider:**
  - Increased blood glucose monitoring in the initial weeks to determine if sulphonylurea or insulin dose needs revising.
  - A stepwise approach to insulin dose reduction is recommended, as diabetic ketoacidosis has been reported in insulin-dependent patients after rapid discontinuation or dose reduction of insulin.
  - Revisit hypoglycaemia management.
- **Local initiation and monitoring guidelines if applicable**

1. GOV.UK. Diabetes and driving. (2020) Available at: https://www.gov.uk/diabetes-driving [Last accessed: January 2021].

Agenda

East Suffolk and North Essex NHS Foundation Trust

- **Guidelines relevant to pharmacological treatment of diabetes**
  - NICE / EASD / ADA
- **Overview of various therapies**
  - SGLT-2i
  - GLP-1Ra
- **Class Comparison**
- **Individualising Treatment**
- **Principles of Insulin initiation**
- **Patient cases**

Summary of clinical effects of oral antidiabetic therapies

Benefit	Metformin	Pioglitazone	Sulphonylureas	DPP-4 inhibitors	SGLT2 inhibitors	Oral GLP-1Ra	Inj GLP-1Ra
Reduce HbA1c	✓	✓	✓	✓	✓	✓	✓
Reduce weight	✓ (or neutral)	–	–	–	✓	✓	✓
Reduce blood pressure	–	–	–	–	✓	✓	✓
Low risk of hypoglycaemia (when used as monotherapy)	✓	✓	–	✓	✓	✓	✓
Cardiovascular benefit	✓	Likely benefit	–	–	✓*	Likely benefit	✓

SGLT2i/GLP-1Ra have multiple benefits beyond glycaemic control

Empagliflozin is not indicated for blood pressure reduction, weight loss, the treatment of heart failure, the prevention of cardiovascular death or the reduction of cardiovascular risk. Please refer to the SmPC for full details of the licensed indication before prescribing.

These are not head-to-head trials and comparisons should be interpreted with caution due to differences in study design, populations and methodology.

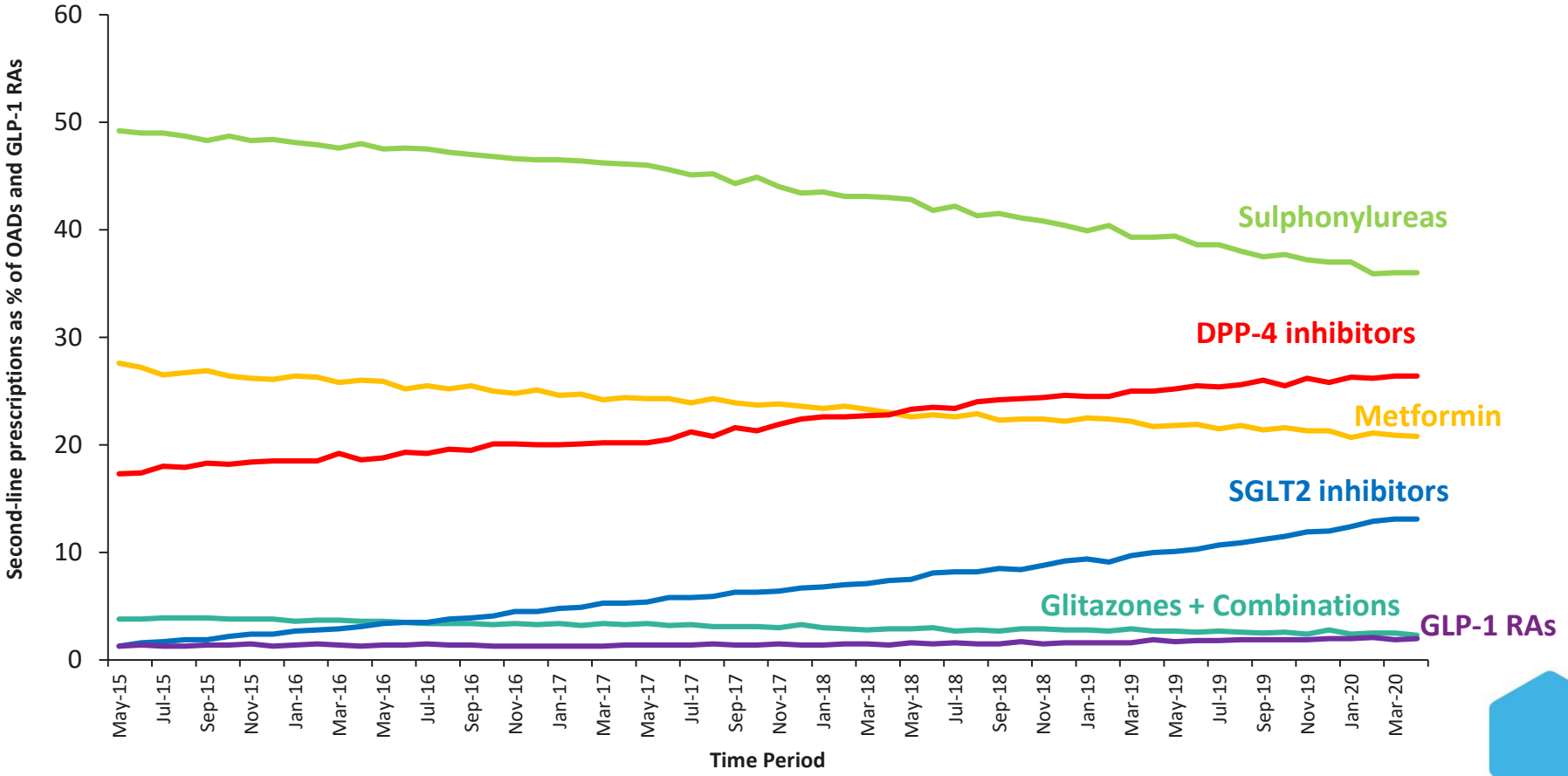
Owing to the breadth and conflicting nature of the data available for the sulphonylurea class, it is difficult to determine exact benefit/risk for these specific parameters.

*Empagliflozin and canagliflozin have been shown to reduce cardiovascular events vs placebo in patients with type 2 diabetes and cardiovascular disease in dedicated cardiovascular outcome trials.

DPP-4: dipeptidyl peptidase-4; SGLT2: sodium–glucose co-transporter 2. Davies MJ *et al. Diabetologia*. 2018;61:2461–2498.

Evidence is emerging and guidance is being updated – are prescribing patterns changing?

Second-line prescriptions as % of OADs and GLP-1 RAs in the UK, May 2015 to April 2020



DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; OAD: oral antidiabetic drug; SGLT2: sodium–glucose co-transporter 2

Boehringer Ingelheim Data on File EMP 20-06, July 2020.

Agenda

East Suffolk and North Essex NHS Foundation Trust

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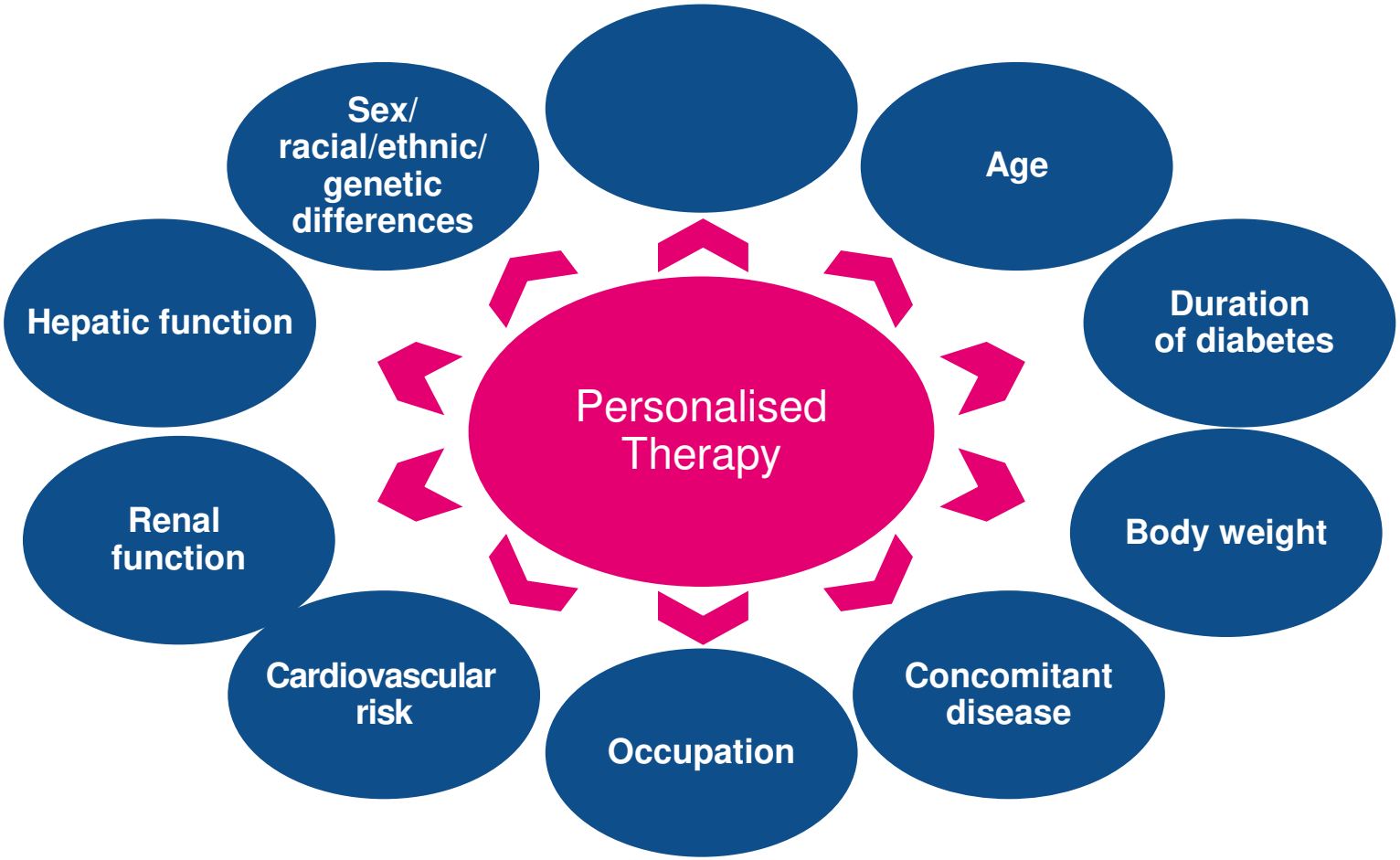
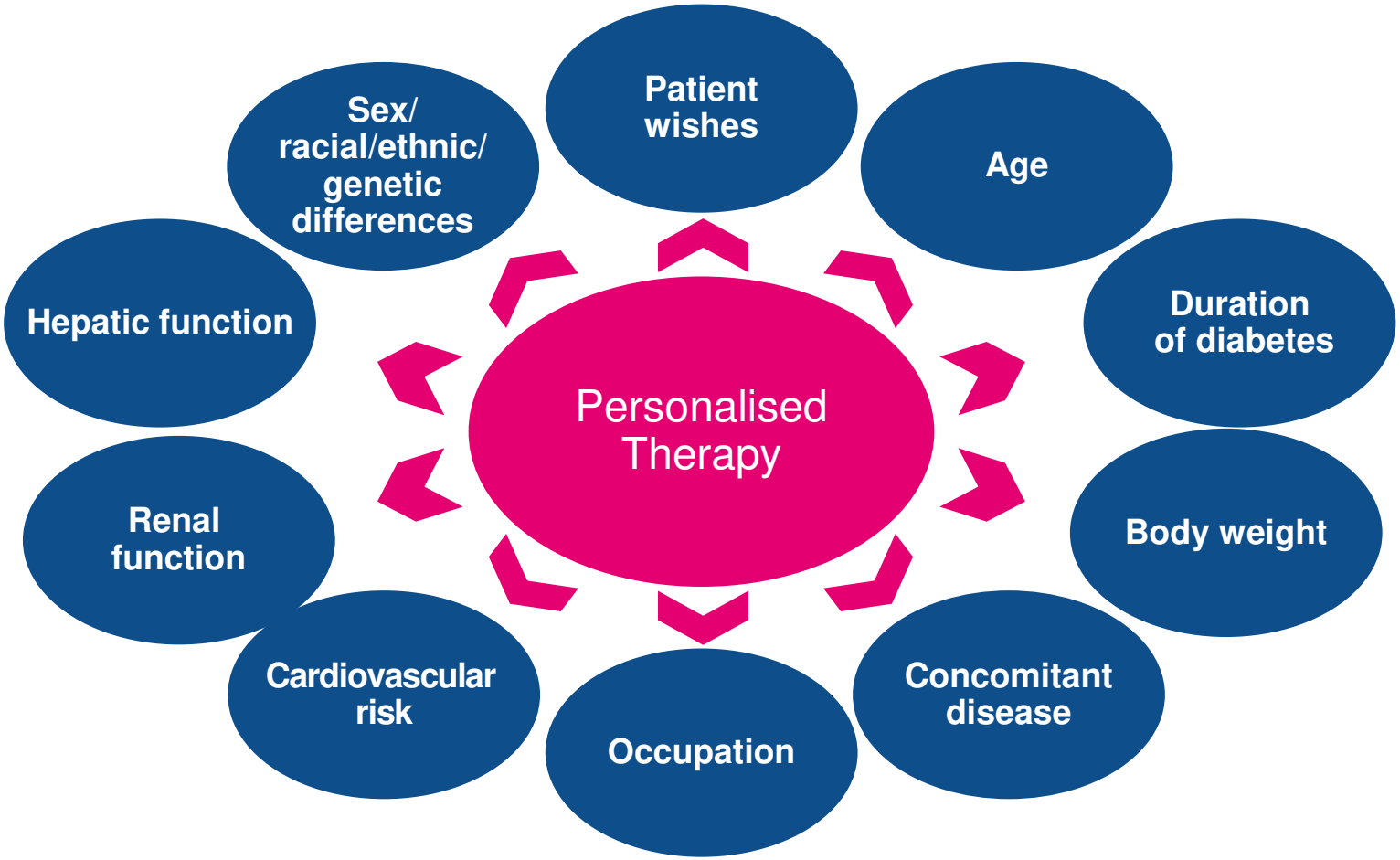
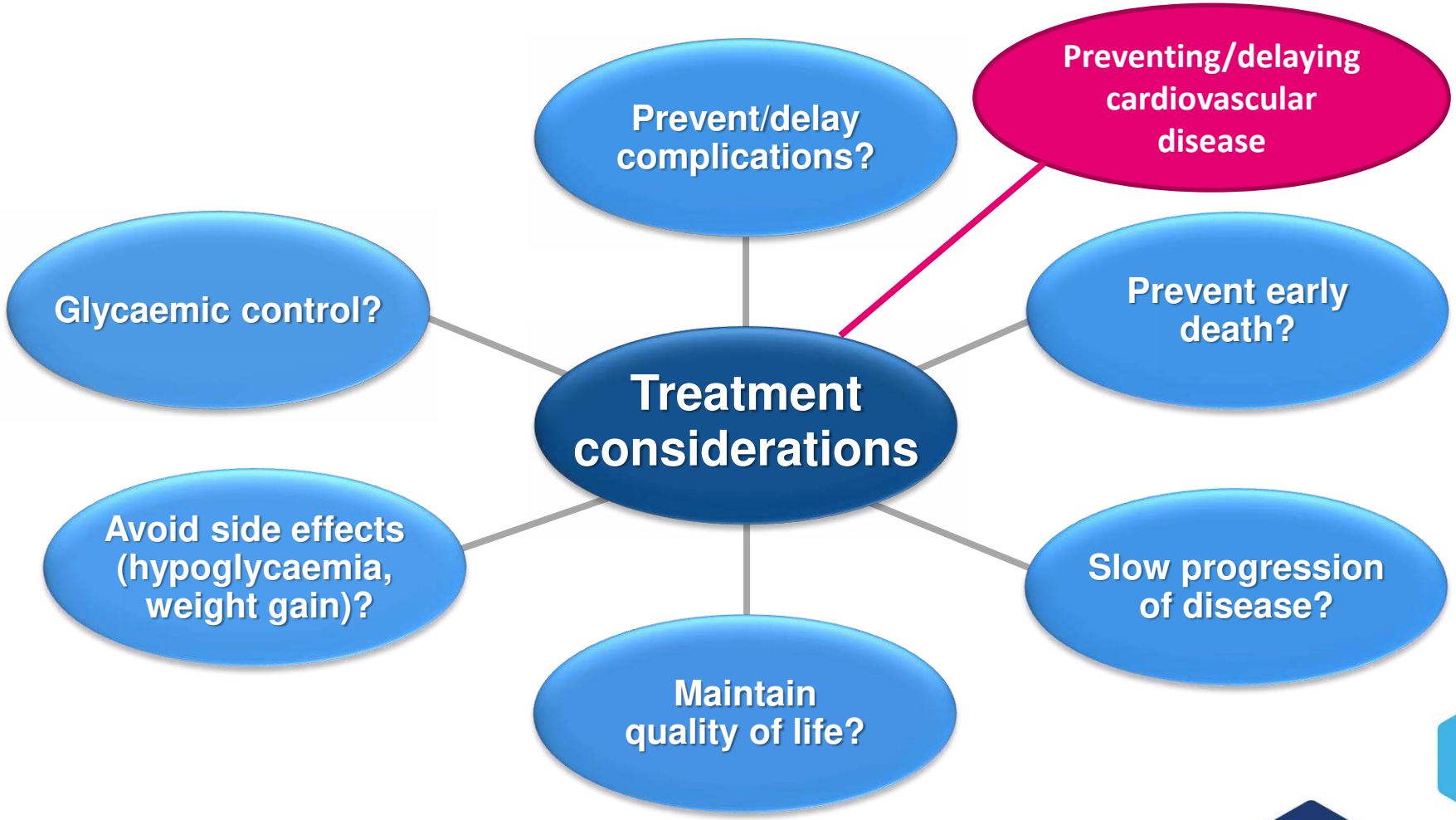
Therapy should be individualised to meet the needs and circumstances of the patient



Therapy should be individualised to meet the needs and circumstances of the patient



What are we trying to achieve when we decide on a treatment option for our patient?



Management of type 2 diabetes needs to consider more than just HbA1c

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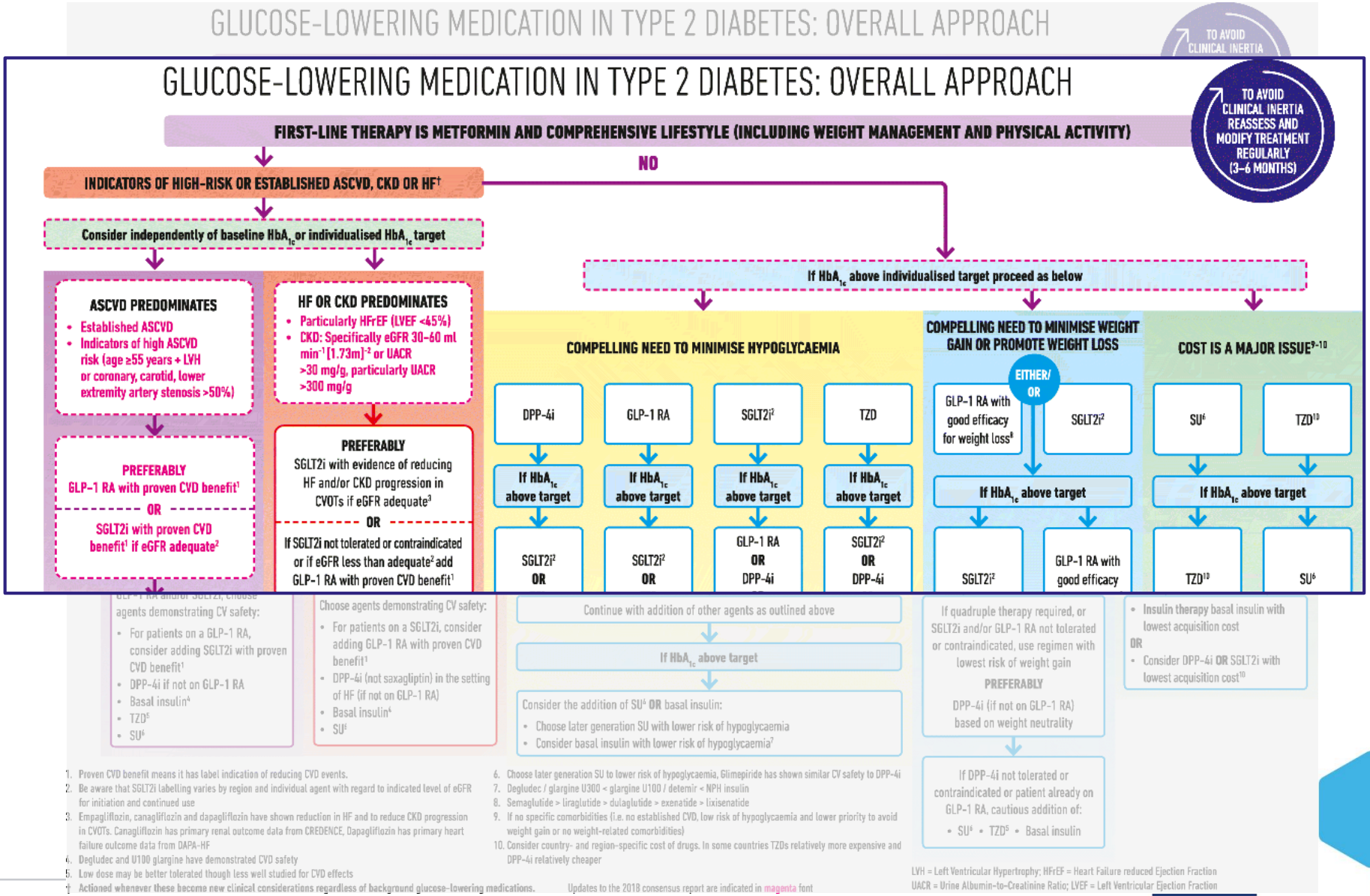
Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes[1-3]

1. Jardiance (empagliflozin) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/5441/smpc;
2. Davies MJ *et al. Diabetologia.* 2018;61:2461–2498; 3. Cosentino F *et al. Eur Heart J.* 2020;41:255–323.

The 2019 ADA/EASD consensus report update has incorporated Cardiovascular Outcome Trial Data



Glucose-lowering medication in type 2 diabetes: overall approach. Modified from [2] with permission from Springer.
©European Association for the Study of Diabetes and American Diabetes Association 2018

1. Buse J.B et al. Diabetologia. 2020; 63:221-228.

Summary

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- There are many different oral agents available to consider for patients with type 2 diabetes – all with benefits and considerations
- Understanding how oral therapies target underlying pathophysiology may support decision making
- National and international clinical guidelines are being updated and position SGLT2 inhibitors ahead of SUs and DPP-4 inhibitors for their multiple benefits, including cardiovascular benefits

DPP-4: dipeptidyl peptidase-4; SGLT2: sodium–glucose co-transporter 2; SU: sulphonylureas

Key objectives and learning

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- To recall the different considerations when choosing oral treatments for patients with type 2 diabetes
- Therapy choice should be individualised to achieve treatment goals that are tailored to the needs and circumstances of the patient
- To explore the need for individualised treatment targets and goals, and the impact that this has on choosing the right treatment, for the right patient, at the right time
- To use case studies to bring theory to life

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Agenda

East Suffolk and North Essex NHS Foundation Trust

- **Guidelines relevant to pharmacological treatment of diabetes**
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  - GLP-1Ra
- **Class Comparison**
- **Individualising Treatment**
- **Principles of Insulin initiation**
- **Patient cases**

Objectives

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- To understand the difference between Human and Analogue Insulins.
- To understand the variety of insulins available and their associated profiles.
- To discover appropriate rationale for initiating insulin.
- To be able to identify which patients would benefit from insulin therapy
- To explore factors that impact insulin initiation

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Type 1 diabetes in adults: diagnosis and management

NICE guideline [NG17] Published: 26 August 2015 Last updated: 21 July 2021

Insulin

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- Insulin is used for the management of Type 1 diabetes mellitus and for Type 2 diabetes mellitus when other glucose-lowering agents are insufficient to maintain individualised HbA_{1c}.

- There are many different insulins in the market and choice depends on patient characteristics.

- Insulins can be categorised into Human insulin and Analogue insulin. Within these categories there are three different types.

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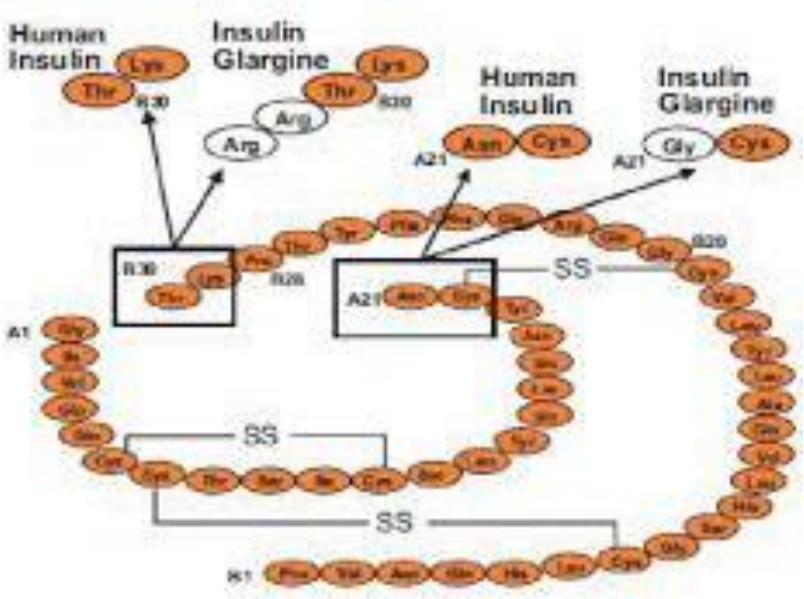

- Analogue insulin is based on endogenous human insulin.
- **Different chemical groups or amino acids** are added to the endogenous insulin molecule.
- The chemical groups added differ between the different insulin analogues.

1. Tibaldi JM. Am J Med. 2014; 127:S25–38.

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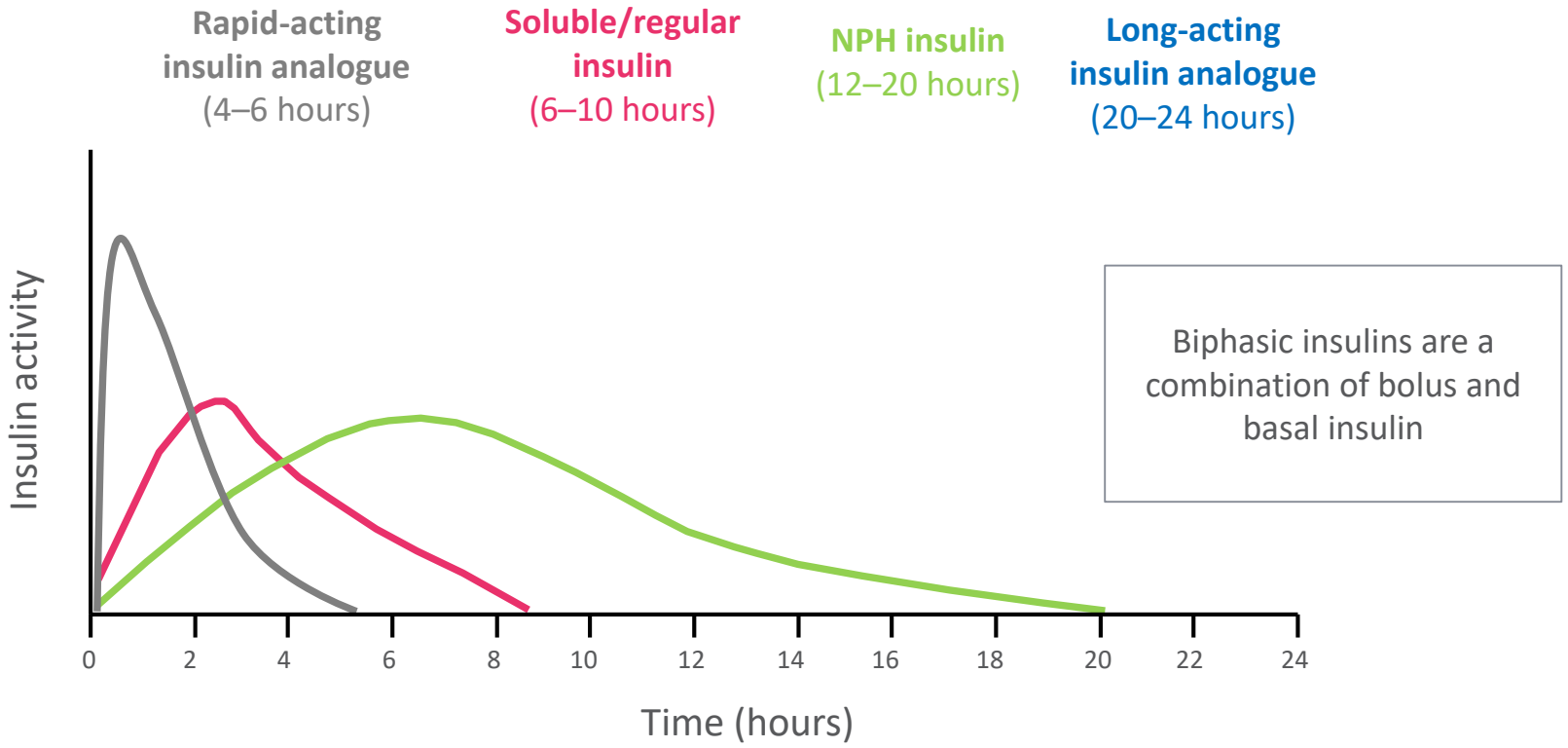
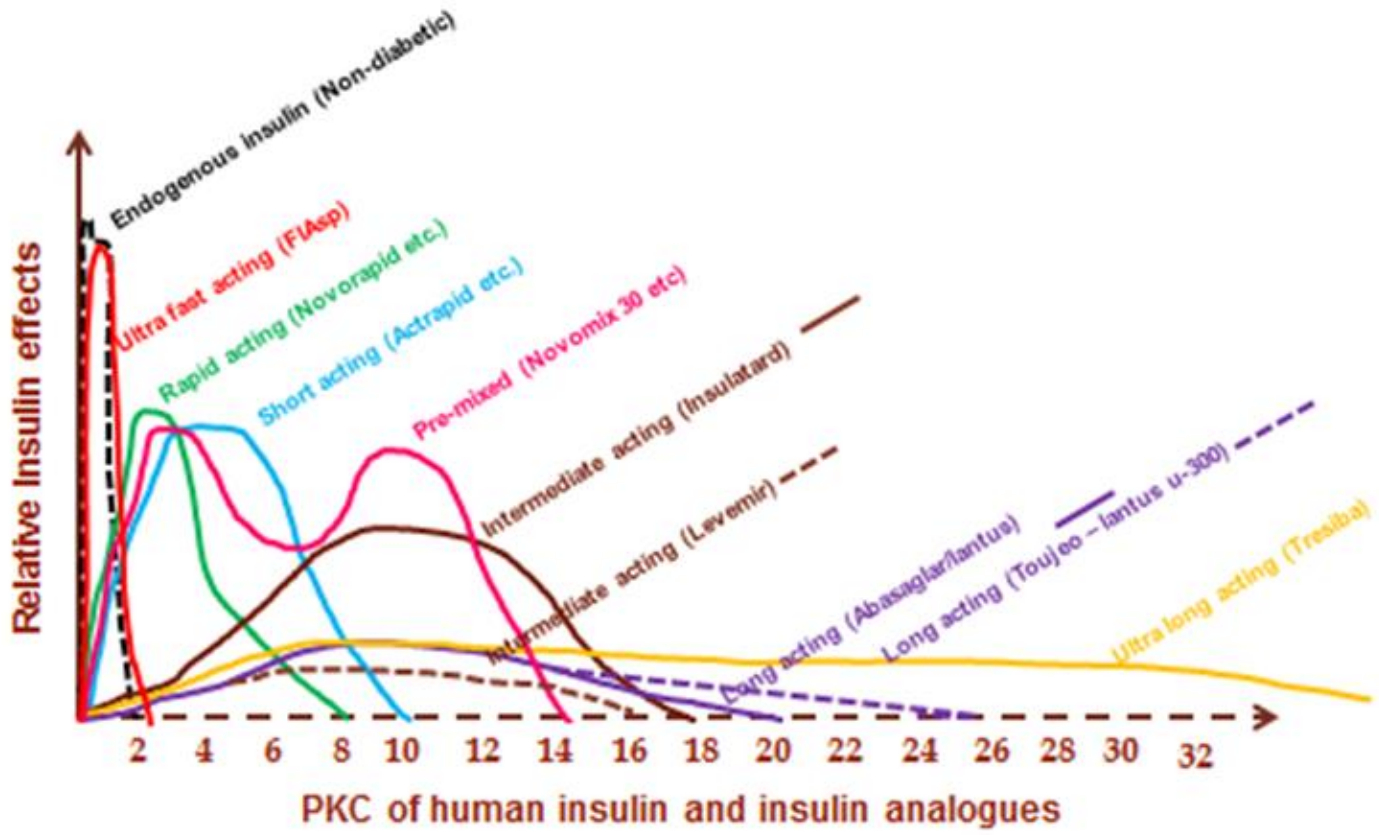


Biphasic insulins are a combination of bolus and basal insulin

NPH, neutral protamine hagedorn.
These diagrams are theoretical representations based on known pharmacological profiles

1. Diabetes Education Online. Types of Insulin. Available at: http://dtc.ucsf.edu/types-of-diabetes/type2/treatment-of-type-2-diabetes/medications-and-therapies/type-2-insulin-rx/types-of-insulin [Accessed: June 2020].

Commonly used insulin pharmacology



Sharma S et al. Diabetes & Endocrinology. Medical Masterclass RCP London 2020

Types of treatment – T1DM

Bilous R et al. **Handbook of Diabetes, 4th Edition, Excerpt #4: Normal Physiology of Insulin Secretion and Action. 2014**

What is a biosimilar?

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A biosimilar medicine is a biological medicine which has been shown not to have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy. Where NICE has already recommended the originator biological medicine, the same guidance will normally apply to a biosimilar of that originator.[1]

1. NHS England. Biosimilar medicines. Available from: https://www.england.nhs.uk/medicines/biosimilar-medicines/ [Accessed: June 2020]

Initiating basal insulin

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- Basal insulins such as human NPH insulin, insulin glargine, insulin detemir and insulin degludec are designed to work throughout the day.
- An example regimen:
  - Initiate at low fixed-dose (e.g. 10 units) and titrate upwards (2–4 unit increments) over 3-7 days to achieve target fasting glucose level.[1]
- If given at bedtime, pre-breakfast (fasting) blood glucose levels give a good indication of efficacy.[1]

NPH, neutral protamine hagedorn.

1. Royal College of Nursing. Starting injectable treatment in adults with type 2 diabetes, 3rd edition. Available at: https://www.rcn.org.uk/-/media/royal-college-of-nursing/documents/publications/2019/november/007-758.pdf?la=en [Accessed: June 2020]

Initiating bolus insulin

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- Bolus insulins are designed to work with carbohydrate consumption, administered pre-meal.[1]
- Usually used in combination with a basal insulin when HbA_{1c} is elevated but fasting is optimised. [2]
- Typical starting dose:
  - 4 units or alternatively, 10% of basal dose[1]
- If glucose levels are above target after meals (2 hours) or before next meal for 3 - 4 days, up-titrate mealtime dose by 10%.[1]
- If given with a meal, testing glucose levels 2 hours after eating gives a good indication of efficacy.

1. Peters K R & Paulsen T. Clinical Diabetes. 2017; 35:108-111
2. Royal College of Nursing. Starting injectable treatment in adults with type 2 diabetes, 3rd edition. Available at: https://www.rcn.org.uk/-/media/royal-college-of-nursing/documents/publications/2019/november/007-758.pdf?la=en [Accessed: June 2020]

Initiating pre-mixed insulins – Human

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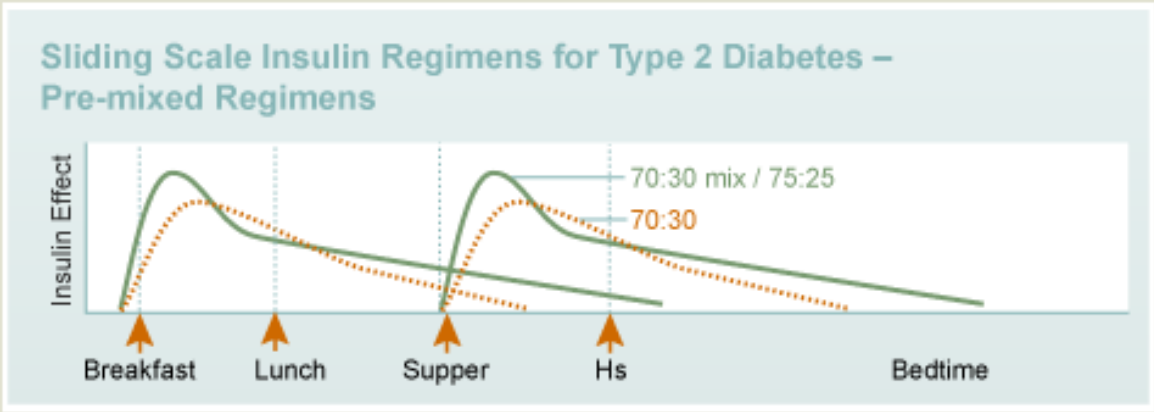
A commercially produced combination of two different types of insulin

- Long-acting insulin component manages glucose levels between meals
- Human soluble insulin component manages glucose load from the meals

For a 30/70 premixed insulin analogue this is how units break down



These diagrams are theoretical representations based on known pharmacological profiles

1. Diabetes Education Online. Types of Insulin. Available at: http://dtc.ucsf.edu/types-of-diabetes/type2/treatment-of-type-2-diabetes/medications-and-therapies/type-2-insulin-rx/types-of-insulin [Accessed: June 2020].

Discuss

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What would you do with current hypoglycaemic agents?

Are you aware of any specific warnings associated with the drug combinations?

How would you manage insulin doses if hypoglycaemic events occur?

Which classes of oral agents are licensed for use with insulin?

At what speed should you titrate insulin?

What are we going to choose for our patients?

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Let's discuss

What do your local guidelines recommend regarding the prescribing of insulin in type 2 diabetes?

NICE NG28: algorithm for blood glucose - lowering therapy in adults with type 2 diabetes

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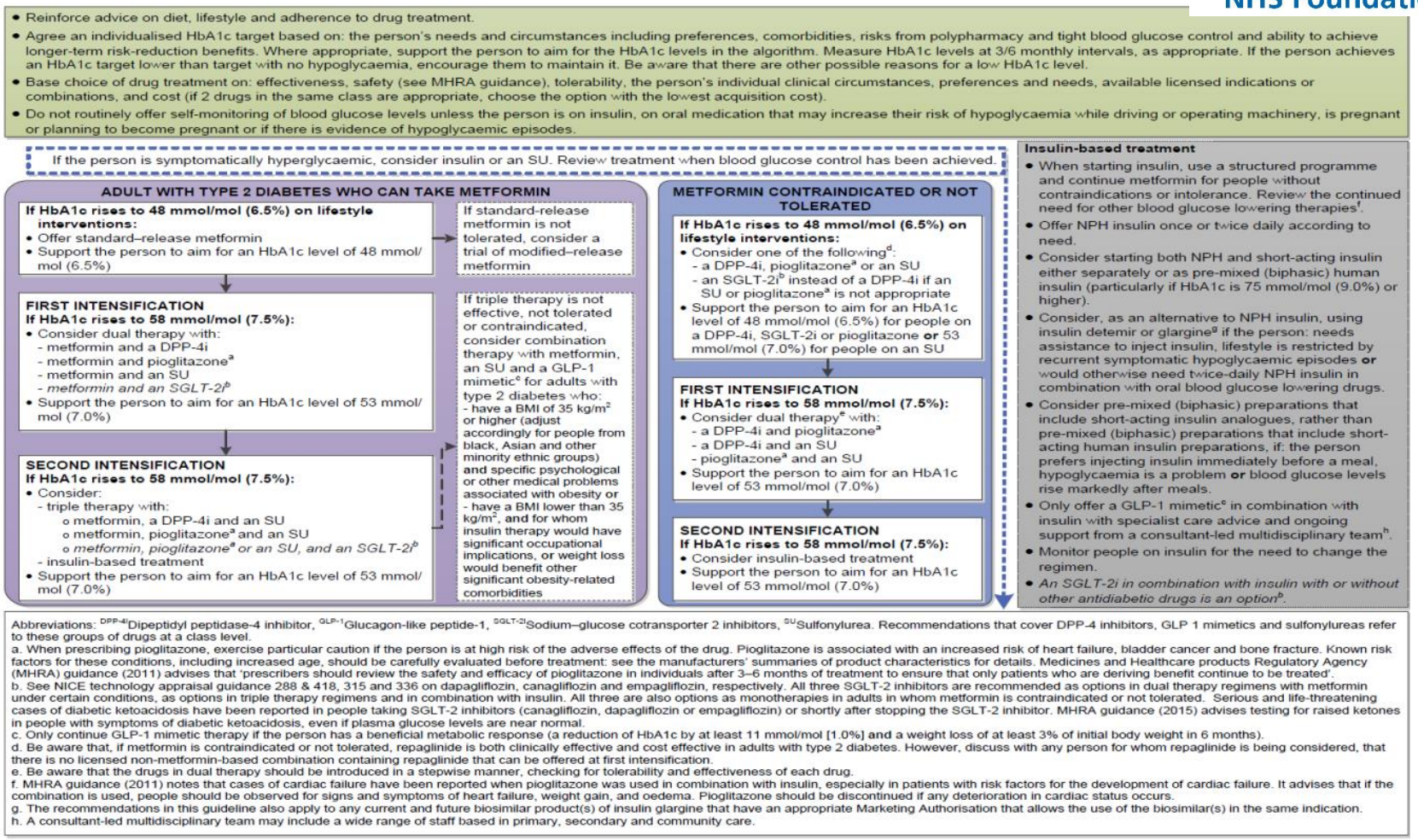

Abbreviations: [DPP-4i]Dipeptidyl peptidase-4 inhibitor, [GLP-1]Glucagon-like peptide-1, [SGLT-2i]Sodium–glucose cotransporter 2 inhibitors, [SU]Sulfonylurea. Recommendations that cover DPP-4 inhibitors, GLP 1 mimetics and sulfonylureas refer to these groups of drugs at a class level.

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. See NICE technology appraisal guidance 288 & 418, 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, as options in triple therapy regimens and in combination with insulin. All three are also options as monotherapies in adults in whom metformin is contraindicated or not tolerated. 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 NG28: algorithm for blood glucose – lowering therapy in adults with type 2 diabetes

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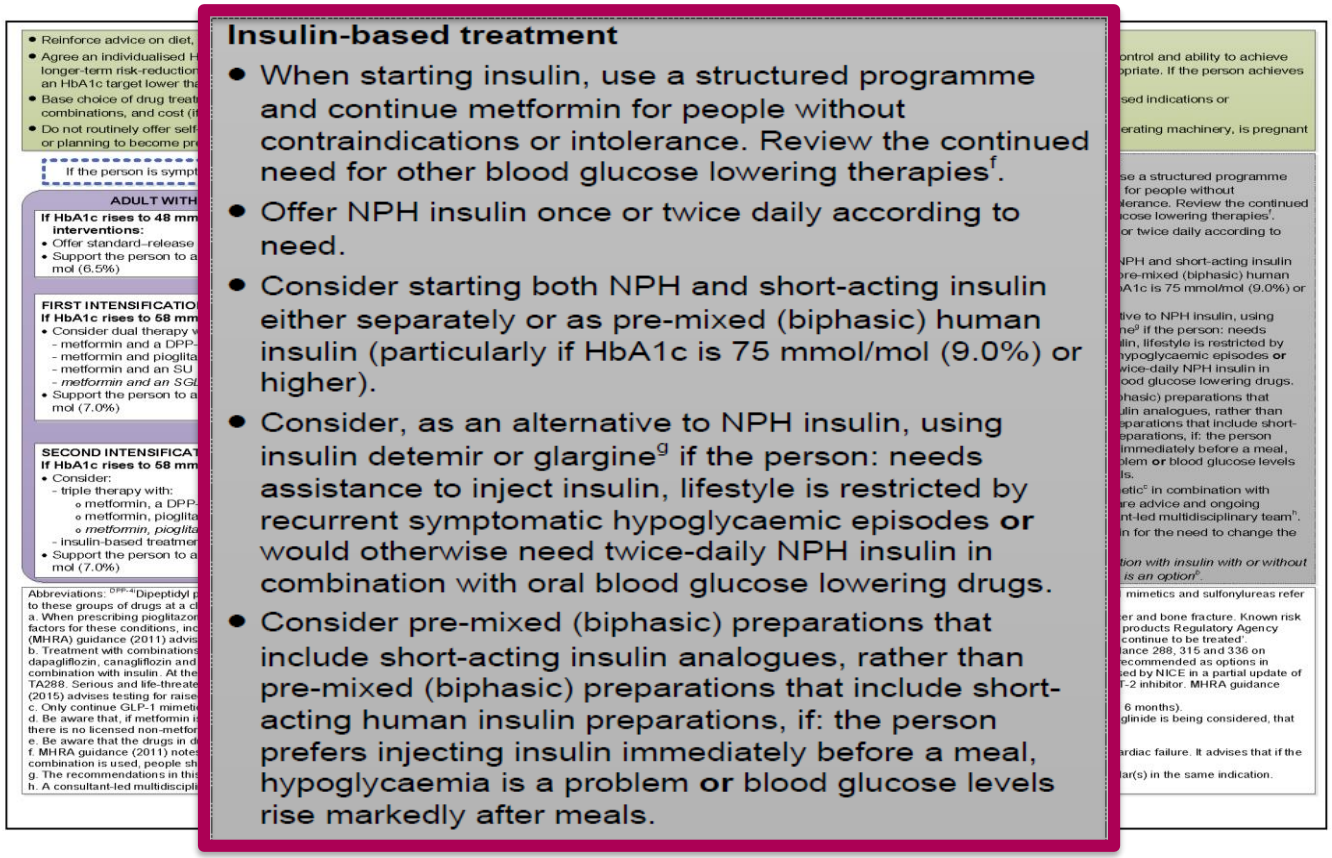

Insulin-based treatment

- 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.

What is the main reason why you would initiate a basal insulin analogue over an NPH?

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- Does a basal insulin analogue have a better efficacy compared with an NPH?
- Is there a reduced risk of hypoglycaemia compared with other insulins?
- Does the patient have a preference of one over another?
- Are there local guideline recommendations?

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Patient cases

Case Study No. 1

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Tom

55 year-old man with 6-year history of type 2 diabetes

- BMI: 31 kg/m^2
- Normal renal function
- Past medical history of heart failure
  Current medications:
  - Biguanide
  - Thiazolidinedione
  - SGLT-2 inhibitor OD
  - Statin
  - Anti-hypertensives
- HbA_{1c} 64 mmol/mol (8%)

BMI, body mass index; OD, once-daily; HbA_{1c}, glycated haemoglobin.

Tom's discovery sheet

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	Blood glucose before breakfast	Breakfast foods eaten	Blood glucose 1-2 hrs after breakfast	Blood glucose before lunch	Lunch foods eaten	Blood glucose 1-2 hrs after lunch	Blood glucose before evening meal	Evening meal foods eaten	Blood glucose 1-2 hrs after evening meal	Blood glucose before bedtime	Snacks	Exercise and general comments
Day 1	13.1	2x boiled eggs 2x slices of toast	12.9	10.9	Cheese sandwich packet of crisps, apple, bottled water	13.0	11.1	Chilli con carne and rice sugar free mousse	13.9	10.8	Plain biscuit before bed	Glass of white wine with meal
Day 2	12.8	2x Weetabix, semi skimmed milk	13.7	11.0	Two small ham rolls, mini cheddar, diet coke	12.3	10.7	Roast chicken, carrots, peas and broccoli, roast pot. x3 baked apple and custard	12.1	9.9	/	
Day 3	13.9	Poached eggs + 2 slices of toast	13.3	10.6	Pasta Salad, small roll, cup of tea	13.4	11.4	Shepherd's pie and peas and carrots, strawberry ice cream	12.7	11.8		Glass of white wine with meal

This table is a representation of the use of a discovery sheet.

What would you recommend for Tom?

Case Study No. 2

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Elsie

- 79 year-old woman with a 14-year history of type 2 diabetes.
- She lives alone.
- She is experiencing recurrent urinary tract infections, feels lethargic and lacks energy for her usual daily tasks.
- Eats regularly: decent breakfast, lunch (meals on wheels) and a light tea.
- BMI 28 kg/m^2
- Normal renal function
- HbA_{1c} 81 mmol/mol (7.7%)
- Current blood glucose: 13–16 mmol/L
- Past medical history of TIA
- Current medications:
  - Metformin 1000 mg BD
  - Gliclazide 60mgs SR OD

OD, once daily; BD, bi-daily; BMI, body mass index; $HbA_{1c,}$ glycated haemoglobin; TIA, Transient ischemic attack; SR, Sustained release

Elsie's discovery sheet

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	Blood glucose before breakfast	Breakfast foods eaten	Blood glucose 1-2 hrs after breakfast	Blood glucose before lunch	Lunch foods eaten	Blood glucose 1-2 hrs after lunch	Blood glucose before evening meal	Evening meal foods eaten	Blood glucose 1-2 hrs after evening meal	Blood glucose before bedtime	Snacks	Exercise and general comments
Day 1	10.2	Porridge slice of toast			Sausage mash peas cake and custard			Egg on toast		18.5	2 rich tea biscuits	
Day 2	11.7	Porridge slice of toast		13.0	Cod parsley sauce boiled potato and green beans			Cheese on toast		15.1	Mr Kipling Bakewell tart	
Day 3	10.8	Porridge, English muffin			Jacket potato, beans, fairy cake		16.0	Ham sandwich, tomato				

This table is a representation of the use of a discovery sheet.

Bearing her past medical history in mind, how would you manage Elsie's elevated HbA_{1c}?

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A. Continue all agents?

B. Stop biguanide?

C. Stop sulphonylureas?

D. Initiate an insulin regimen? Which?

Case Study No. 3

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Margaret

46-year-old woman with 3-year history of type 2 diabetes.
Now very symptomatic, HbA_{1c} has progressively deteriorated.

Past medical history: Hypertension

Current medications:

- biguanide
- sulphonylurea
- basal analogue insulin
- statin
- ramipril 10 mg od
- indapamide 2.5 mg od

O/E: BMI= 27 kg/m^2, background retinopathy and microalbuminuria.

Ix: HbA_{1c} = 77 mmol/mol (9.2%)

BMI, body mass index; HbA_{1c}, glycated haemoglobin; OD, once a day; O/E, on examination; Ix, investigations

Discovery sheet

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	Blood glucose before breakfast	Breakfast foods eaten	Blood glucose 1-2 hrs after breakfast	Blood glucose before lunch	Lunch foods eaten	Blood glucose 1-2 hrs after lunch	Blood glucose before evening meal	Evening meal foods eaten	Blood glucose 1-2 hrs after evening meal	Blood glucose before bedtime	Snacks	Exercise and general comments
Day 1	11.4	2 slices toast + jam, cup of tea	13.7	12.9	Pork chop, peas, sweetcorn, mash & gravy, low-fat yogurt	15.3	13.2	Ham sandwich, Tomato soup, cup of tea	16.6	14.1	Banana, coffee	
Day 2	12.1	2 slices toast, boiled eggs x2, cup of tea	13.2	11.8	Portion lasagne, small slice garlic bread, salad, apple	16.1	14.3	2 slices bread, slice cheese, salad, pickle, cup of tea	15.9	13.4	Digestive biscuit, cup of coffee	Walked to buy paper (10 mins – bit breathless)
Day 3	10.9	2 slices toast jam, cup of tea	12.6	10.9	Chicken curry, small rice, fruit salad with yoghurt	14.7	12.4	Scrambled egg on toast (x2) piece of fruit cake	14.3	12.9	Little bit of fruit cake, cup of coffee	

This table is a representation of the use of a discovery sheet.

Bearing in mind that Margaret is symptomatic, how would you manage her HbA_{1c}?

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A. Change the basal insulin regimen?
   - switch to twice-daily pre-mixed insulin
   - add prandial insulin with the largest meal od (basal +)
   - add prandial insulin with meals tds (basal +++)

B. Adjust the basal insulin regimen?
   - up-titrate the dose
   - reduce the dose
   - change the timing of the od injection
   - inject twice daily

C. If you change Margaret's insulin regimen, what is an appropriate course of action with the oral agents?
   - continue all agents
   - stop biguanide
   - stop oral anti-hyperglycaemic agents

OD, once daily; tds, three times daily

Summary

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- Eventually oral therapy will be insufficient to control blood glucose levels in Type 2 diabetes and it will become necessary to add insulin to return HbA_{1c} to target levels.
- The physiology of insulin in normal subjects helps to inform the understanding of both pre- and post-prandial insulin requirements
- The different insulin types vary in their:
  - action, peak and duration.
  - timing and administration.
  - prescription regimens.
  - combination with oral agents.

Which patients need insulin?

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What do you need to consider?

Questions to consider for an individualised clinical evaluation

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What is the indication?	*Increase in HbA_{1c}/symptoms relating to T2DM*
What is the goal?	*HbA_{1c} or plasma glucose targets/risk factor reduction/symptom reduction*
What is the 'metabolic milieu'?	*Baseline weight/weight change*
Are there relevant co-morbidities?	*Cardiac/renal/central nervous system*
What are the personal habits of the individual?	*Eating pattern, exercise, etc.*
Are there specific barriers to insulin?	*Employment/driving/needle anxiety/psychological insulin resistance/preconceptions of insulin*
Has the individual expressed preferences?	*Device/regimen*
What is the blood glucose experience of the individual?	*Capillary blood glucose patterns related to the fasting and/or post prandial state*

Risks and limitations of insulin therapy

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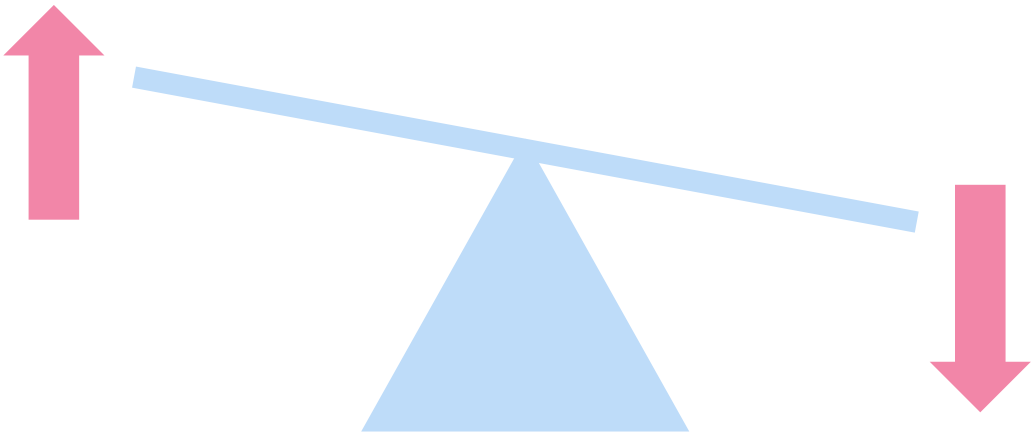

Benefits

- *Achieve tight glycaemic control*
- *Avoid long-term disease complications*
- *Relieve osmotic symptoms*

Risks/ limitations

- *Hypoglycaemia*
- *Weight gain*
- *Regular glucose monitoring*
- *Increased patient involvement*

Considerations

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If mean glucose levels (HbA_{1c}) are rising and unresponsive to current diabetes treatments, consider initiation of insulin especially if:

- Concordance with therapy is good[1]
- Lifestyle measures are realistically optimised[2]
- There is an acute medical event causing acute metabolic deterioration or planned surgical intervention[2]
- There are osmotic symptoms[1]

Situations in which to be cautious when considering insulin initiation:

- Rising weight alongside rising HbA_{1c} (likely dietary indiscretion), because weight gain is likely to be exacerbated with insulin, resulting in minimal benefit[2]
- As insulin therapy is a risk factor for hypoglycaemia, patients with impaired cognitive function may have delayed recognition of the symptoms of hypoglycaemia[3]

1. Scottish Intercollegiate Guidelines Network. 116 Management of diabetes: A national clinical guideline. 2010 (updated September 2013). Available from: http://www.sign.ac.uk [Accessed November 2019]
2. Home P et al. Diabetes Care. 2014; 37:1499–1508.
3. Yaffe K et al. JAMA Intern Med. 2013; 173 (14):1300–1306.

Diabetes Masterclass series

Date	Time	Format	Topic	Discussion
8th Sept '21 (Wed)	1300-1400	Webinar	Anatomy/physiology and aetiology of diabetes	• Pancreatic functions • Physiology of insulin secretion • Risk factors for T1 & T2DM • Less common forms of diabetes
22nd Sept '21 (Wed)	1300-1400	Webinar	Diagnosis and Monitoring of diabetes Mellitus	• Determining the diagnosis with blood tests • Monitoring trends in glycaemic control • Optimising treatment with monitoring • Atypical scenarios
6th Oct '21 (Wed)	1300-1400	Webinar	Overview of diabetes	• Determining review the pathophysiology of type 2 diabetes • To explore the impact of clinical inertia on patient outcomes and the importance of early treatment optimisation • To recognise the differences between compliance, adherence and concordance and to understand the features of concordant patient consultations
20th Oct '21 (Wed)	1300-1400	Webinar	Complications of diabetes	• Identifying short and long-term complications of diabetes • Exploring micro and macro vascular complications • Understanding monitoring guidelines for management of complications • Reviewing evidence-based outcomes
3rd Nov '21 (Wed)	1900-2100	Face to face workshop	Oral therapies in diabetes and practicalities for starting treatment	• Discuss the considerations when choosing a treatment to meet the needs and circumstances of individual patients • Review the standard oral therapies used in the treatment of T1 & T2DM • Understand the sites of action for the different oral drug classes and be aware of the prescribing considerations including renal function and hepatic disease • Consider different goals of treatment and evaluate how different oral therapies can help to achieve these goals • To use case studies to bring theory to life
17th Nov '21 (Wed)	1900-2100	Face to face workshop	Thinking beyond HbA1c: Managing cardiovascular risk in patients with type 2 diabetes	• To explore complications associated with type 2 diabetes • To consider the unmet clinical need related to cardiovascular morbidity and mortality in patients with type 2 diabetes • To understand how clinical guidance for type 2 diabetes has been updated to reflect the results of positive cardiovascular outcome trials
1st Dec '21 (Wed)	1900-2100	Face to face workshop	GLP-1Ra therapy in diabetes	• When and how to start GLP-1Ras • To explore differences between the GLP-1 Receptor Agonists with a human GLP-1 backbone • To examine existing guidelines and their application to practice • To explore the impact of cardiovascular data on evolving guidance • To use case studies to illustrate key points
15th Dec '21 (Wed)	1900-2100	Face to face workshop	Insulin in the management of T1DM and T2DM	• Types of insulin therapy • To differentiate between basal and bolus therapy • Identifying patients who would benefit from insulin therapy • Switching patients already on insulin to more appropriate regimens • Case studies to illustrate the above

Speaker: *Dr Sanjeev Sharma*
Consultant – Diabetes & Endocrinology
Ipswich Hospital (ESNEFT)

NHS East Suffolk and North Essex NHS Foundation Trust

Registration: *Email cobbold_matthew@network.Lilly.com or*
Call at mobile: 07393 244151

This meeting has been organised and funded by Eli Lilly and Company

Lilly

Strategy 5 HCP was authoritarian

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Over 53% of initially reluctant people with T2D felt that it helped moderately or a lot when their HCP:

- Warned them that **he / she could not be responsible** for what might happen if they did not start insulin soon (60%)
- Said that **he / she could not continue to treat them** if they refused to start insulin (64%)
- **Repeatedly** over many visits, **tried to convince them** to get started on insulin (**53%**)

1. Polonsky WH et al. J diabetes Complicat. 2019; 33(4):307-314.

Summary

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- Type 2 diabetes is a progressive condition. Insulin therapy is clinically indicated when mean glucose levels (HbA_{1c}) are rising and are unresponsive to current glucose-lowering treatment.
- Assessing the factors that influence sub-optimal glycaemic control is essential.
- The most appropriate insulin regimen should be selected through a process of clinical evaluation.
- Involve the patient in the decision to start insulin.

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Patient cases

Summary

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- Individualising care is the cornerstone of good type 2 diabetes management – the right treatment must be selected for the right patient at the right time

- Management of type 2 diabetes should consider more than just glycaemic control; reducing cardiovascular morbidity and mortality is an essential part of treatment

- Treatment choice should balance improvements in glycaemic efficacy and reducing cardiovascular risk with minimising weight gain and the risk of hypoglycaemia