What's new with type 2 diabetes care in 2021?

Use of SGLT2 inhibitors and GLP-1 agonists

Brought to you by He Ako Hiringa

Supported by PHARMAC TE PĀTAKA WHAIORANGA

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Learning Always

Declaration

- I am receiving an honorarium for this presentation
- I convened the development of the NZSSD guidance on the management of T2D
- The guidance are ‘guidelines’ and not ‘tramlines’

Introduction

- 2021 likely represents the biggest year of change ever in diabetes care in NZ
- Availability of funded SGLT2 inhibitors and GLP1 receptor agonists for the first time
- New NZSSD led national guidance on the management of T2D
- Commitment by Pharmac to reduce inequities for Māori & Pacific peoples

NZSSD guidance

- Concise pragmatic advice on aspects of diabetes management focusing on:
  - Reducing clinical inertia + inequities
  - Focusing management on reducing CV risk in addition to improving glycaemic control
  - Incorporating both current best practice and funding criteria into treatment algorithm
  - Use of the ‘new agents’ but continuing use of standard evidence-based therapy e.g. ACEi, statins
  - Targeting current clinical challenges e.g. insulin therapy
  - Acting on abnormal findings in the ‘diabetes annual review’
- To be a ‘live’ allowing updates as evidence + access to interventions changes
- To cater for the wide range of diabetes knowledge amongst health professionals
- To standardise the care of patients with type 2 diabetes across New Zealand

Organisation of the guidance

- Overarching T2D management + insulin algorithms
- Each part of the algorithm will link directly into specific section
- Further information will open in drop down text boxes
- Direct links in the guidance to relevant national documents e.g.:
  - MoH Weight Management guidelines
  - Diabetes in Pregnancy guidelines
  - Dietitian NZ resources
  - NZTA guidelines
  - Medsafe documents
- Guidance will be incorporated into health pathways + hopefully practice management systems

www.t2dm.nzssd.org.nz

Type 2 Diabetes Management Guidelines

- Screening and diagnosis of type 2 diabetes
- Glycaemic monitoring and targets for type 2 diabetes
- Lifestyle management
- Non-insulin medications
- Insulin
- Screening and management of complications of diabetes
- Management of cardiovascular risk factors in diabetes
- Management of hypoglycaemia
- Sick day management
- Diabetes in pregnancy
- Diabetes and driving
- Prediabetes

Organisation of the guidance

- Screening and diagnosis of type 2 diabetes
  - Screening for diabetes in symptomatic adults
  - Screening for diabetes in asymptomatic adults
  - Differentiating between the types of diabetes
- Glycaemic monitoring and targets for type 2 diabetes
- Lifestyle management
  - Healthy eating
  - Physical activity
  - Education + support

Organisation of the guidance

- Non-insulin glucose lowering therapies
  - Metformin
  - SGLT2 inhibitors
  - GLP1 receptor agonists
  - DPPIV inhibitors
  - Sulfonylureas
  - Acarbose
- Insulin
  - Basal insulin
  - Bolus insulin
  - Premixed insulin
  - Correction insulin
- Screening and management of complications of diabetes
  - Annual recommended screening for patients with type 2 diabetes
  - Diabetic foot disease
  - Diabetic eye disease
  - Diabetic kidney disease
  - Other complications of diabetes

Organisation of the guidance

- Management of cardiovascular risk factors in type 2 diabetes
  - Management of hypertension
  - Management of dyslipidaemia
  - Antiplatelet therapy
- Management of hypoglycaemia
- Sick day management
- Diabetes in pregnancy
- Diabetes and driving
- Prediabetes

What are the major changes in the guidance?

- Formal recommendations on when to screen for T2D
- When to consider other types of diabetes
- Reinforcing the target HbA1c for most patients with T2D is < 53 mmol/mol
- Reducing clinical inertia in the diagnosis + treatment of T2D
- Standardisation of intensification of insulin therapy
- 'Shifting the paradigm' from glycaemic control to also reducing cardiovascular + renal risk
  - Prioritising weight loss + minimising risk of hyopglycaemia
- Best practice on when & how to use SGLT2 inhibitors + GLP1 receptor agonists

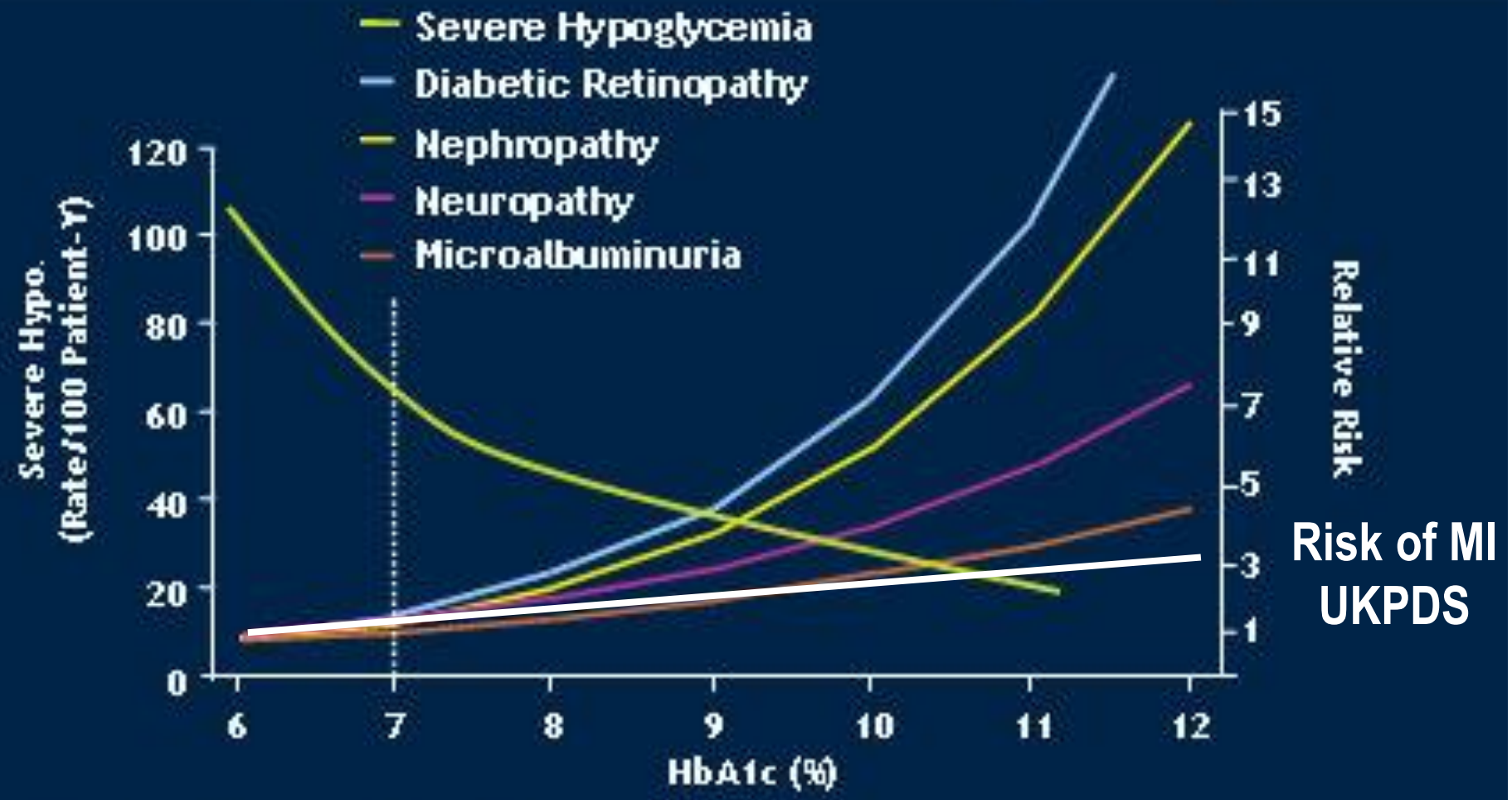
When to screen for T2D in asymptomatic adults?

- All patients with prediabetes or previous gestational diabetes should have an annual HbA1c
- All adults with ≥ 2 risk factors for diabetes should have an HbA1c performed at least 3 yearly
  - Obesity (BMI > 30 kg/m^2 or > 27 kg/m^2 if Indo-Asian OR Waist circumference > 94 cm in males or > 80 cm in women)
  - Non-European ethnicity
  - First degree relative developing T2D < 40 years of age
  - Clinical features of insulin resistance e.g. PCOS, acanthosis nigricans, hypertension, dyslipidaemia etc.
  - History of CVD
  - Current long-term corticosteroid or antipsychotic therapy
  - Post transplant
  - **Paediatric guidelines recommend screening from 10 years of age**
- Screening is always recommended immediately in symptomatic patients
- Diagnostic criteria for diabetes has not changed but confirmatory test recommended asap
  - HbA1c ≥ 50 mmol/mol
  - Fasting glucose ≥ 7 mmol/L
  - Random glucose/2 hour 75 g GTT glucose> 11 mmol/L

Establishing the target HbA1c

- HbA1c remains the most practical glycaemic target if reliable
  - The target HbA1c should be individualised + reviewed at least annually
  - If HbA1c above target → escalate therapy + repeat HbA1c 3 monthly until target
  - If HbA1c below target → repeat HbA1c 6 monthly + if above target escalate therapy + repeat HbA1c 3 monthly
- The target HbA1c for most patients with T2D is < 53 mmol/mol
- A lower HbA1c target (e.g. < 48 mmol/mol) is likely appropriate when the risk of hypoglycaemia is low (i.e. not on insulin or sulfonylureas) and the patient is either:
  - Young
  - Considering pregnancy or pregnant
  - Has microvascular and/or macrovascular complications
- A higher HbA1c target (e.g. 54 – 70 mmol/mol) may be appropriate when the risks of therapy outweigh the benefits of glycaemic control such as:
  - Life expectancy is limited by non-diabetes comorbidities
  - Previous severe hypoglycaemia and/or hypoglycaemic unawareness
  - Frail, elderly and/or cognitive impairment

Risk of Progression of Complications: DCCT Study



DCCT = Diabetes Control and Complications Trial.

Skyler JS. Endocrinol Metab Clin North Am. 1996;25:243-254. [Evidence Level C]

Differentiating between the types of diabetes

- Differentiating between the types of diabetes can be very difficult but important

- T1D can occur at any age with an insidious onset + consider if any of the following:
  - Age of onset < 35 years
  - Symptoms of insulin deficiency at diagnosis
  - Low C-peptide (e.g. fasting < 250 pmol/L or post-meal < 600 pmol/L with glucose > 8 mmol/L) or +ve ketones/DKA at diagnosis
  - Normal or low BMI at diagnosis
  - Personal or family history of autoimmune disease (particularly history of T1D)
  - Positive anti-GAD, anti-IA2 or anti-ZnT8 antibodies

- Consider diabetes due to loss of pancreatic function if:
  - History of pancreatitis, cystic fibrosis or pancreatic surgery, cancer or trauma
  - Diarrhoea and/or features of malabsorption
  - Low faecal elastase
  - Low C-peptide and/or ketoanaemia at diagnosis

- Also consider monogenic and secondary causes of diabetes when appropriate

Reducing clinical inertia in the diagnosis + treatment of T2D

- Confirming the diagnosis of T2D as soon as possible
- Starting lifestyle management + metformin at diagnosis
- Strongly considering 2nd line agent with metformin at diagnosis if HbA1c > 64 mmol/mol
  - If cardiovascular or renal disease → preferably SGLT2i or GLP1RA
  - If heart failure → preferably SGLT2i
  - If no renal or cardiovascular disease → preferably vildagliptin
- Repeating HbA1c 3 monthly with escalation of therapy if not to target
- Starting weight based doses of basal insulin + adding prandial insulin when doses of basal insulin reach 0.5 units/kg/day. Also starting insulin immediately if:
  - Symptoms of insulin deficiency and/or hyperglycaemia
  - HbA1c > 90 mmol/mol
  - Suspicion of type 1 diabetes

Lifestyle management

- Healthy eating, physical activity, education + support remain cornerstone of therapy of T2D at all times
  - Aim for 5-10 % loss in body weight if overweight or obese
- Nutritional education from a dietitian is recommended at diagnosis + then:
  - Annually as part of ongoing assessment or earlier if required
  - When starting prandial insulin
- Low energy low GI macronutrient dietary approaches can be as effective as bariatric surgery with achieving weight loss + remission of T2D
- There is no conclusive evidence that any one dietary approach is superior to another
  - Meta-analyses reveal no sustained reduction in weight or HbA1c with ketogenic diets
  - Dietary approach will depend on patient preference, tolerability, income, nutritional needs etc.
- Other important aspects of lifestyle management include:
  - Smoking cessation + reduction in alcohol intake
  - Screening for depression (e.g. PHQ-9) + referral for psychology input as required

Metformin

- Remains first line pharmacological agent as reduces CVD independently of glycaemic control

- Maximal recommended daily dose is 1 g twice daily
  - Starting at 250 – 500 mg od or bd often prevents development of adverse effects
  - Doses need to be reduced once eGFR < 60 mL/min
  - Maximal reduction in HbA1c ~ 16 mmol/mol so consider starting with additional agent if HbA1c > 64 mmol/mol

- Recommended to now start metformin with lifestyle management at diagnosis because:
  - Delays the progression of T2D and reduces CV risk even in those whose HbA1c returns to the 'prediabetes' range
  - Aids weight loss and likely reduces other diabetes-related complications such as cancer risk
  - Lifestyle changes difficult to sustain + even in those who achieve 'remission' metformin ↓ the chances of 'redeveloping' T2D
  - There is often a delay in months to years before any glucose lowering therapy is commenced in patients with T2D in NZ
  - Many patients with type 2 diabetes in NZ do not have access to successful funded lifestyle interventions
  - Generally well tolerated when started in low doses + will not cause hypoglycaemia

Basal insulin therapy in T2D

- Recommended if HbA1c > target on maximal other glucose lowering therapy OR immediately if:
  - Symptoms of insulin deficiency or suspicion of T1D
  - HbA1c > 90 mmol/mol at any time

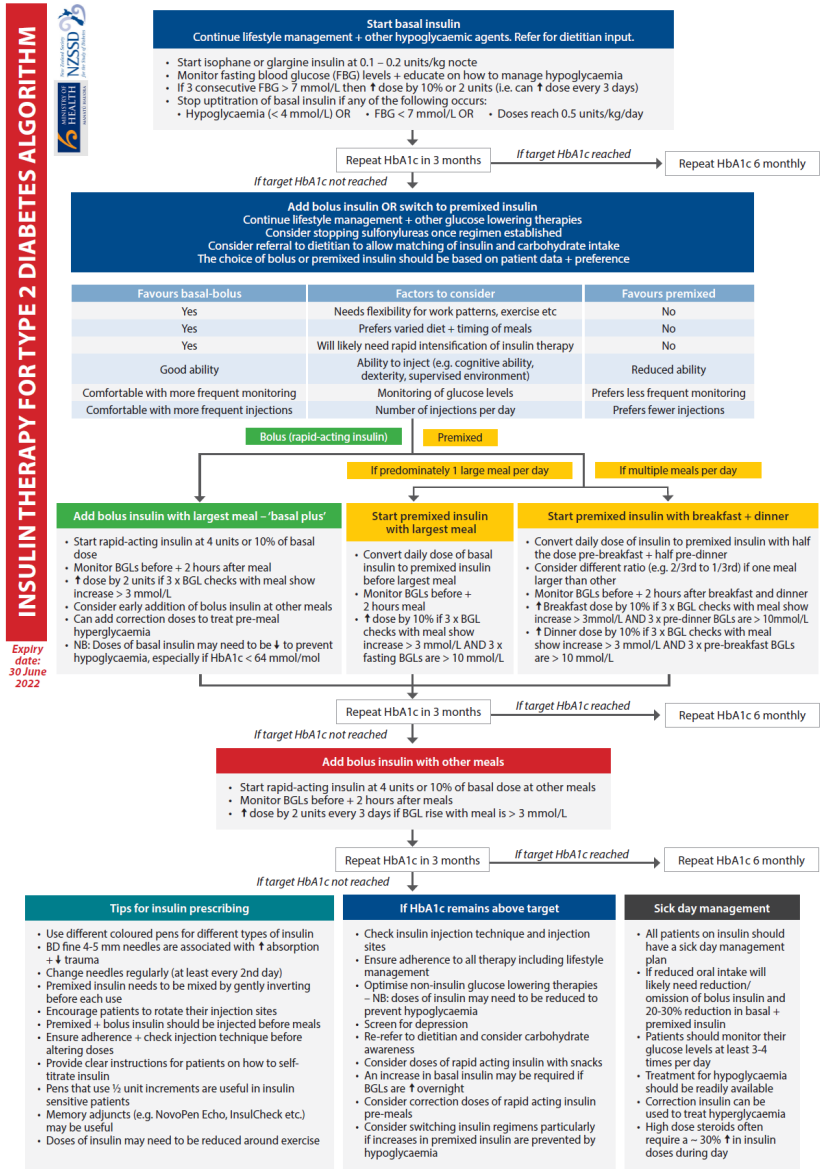
- Starting basal insulin with weight based dosing
  - 0.2 units/kg/nocte in most individuals
  - 0.1 units/kg/nocte if high risk of hypoglycaemia e.g. HbA1c < 64 mmol/mol, elderly, renal/liver disease, low BMI etc.

- Increase the dose of basal insulin by 10% or 2 units if 3 consecutive fasting BGLs > 7 mmol/L

- To stop increasing the dose of basal insulin if ANY of the following occurs:
  - Hypoglycaemia
  - Fasting BGL < 7 mmol/L
  - **Doses reach 0.5 units/kg/day**

- If HbA1c remains above target then add in prandial insulin (either premixed or bolus insulin)
  - **New algorithm to allow standard rapid intensification of insulin therapy**

NZSSD insulin algorithm in T2D



Start basal insulin
Continue lifestyle management + other hypoglycaemic agents. Refer for dietitian input.

- Start isophane or glargine insulin at 0.1 – 0.2 units/kg nocte
- Monitor fasting blood glucose (FBG) levels + educate on how to manage hypoglycaemia
- If 3 consecutive FBG > 7 mmol/L then ↑ dose by 10% or 2 units (i.e. can ↑ dose every 3 days)
- Stop uptitration of basal insulin if any of the following occurs:
  - Hypoglycaemia (< 4 mmol/L) OR
  - FBG < 7 mmol/L OR
  - Doses reach 0.5 units/kg/day

↓

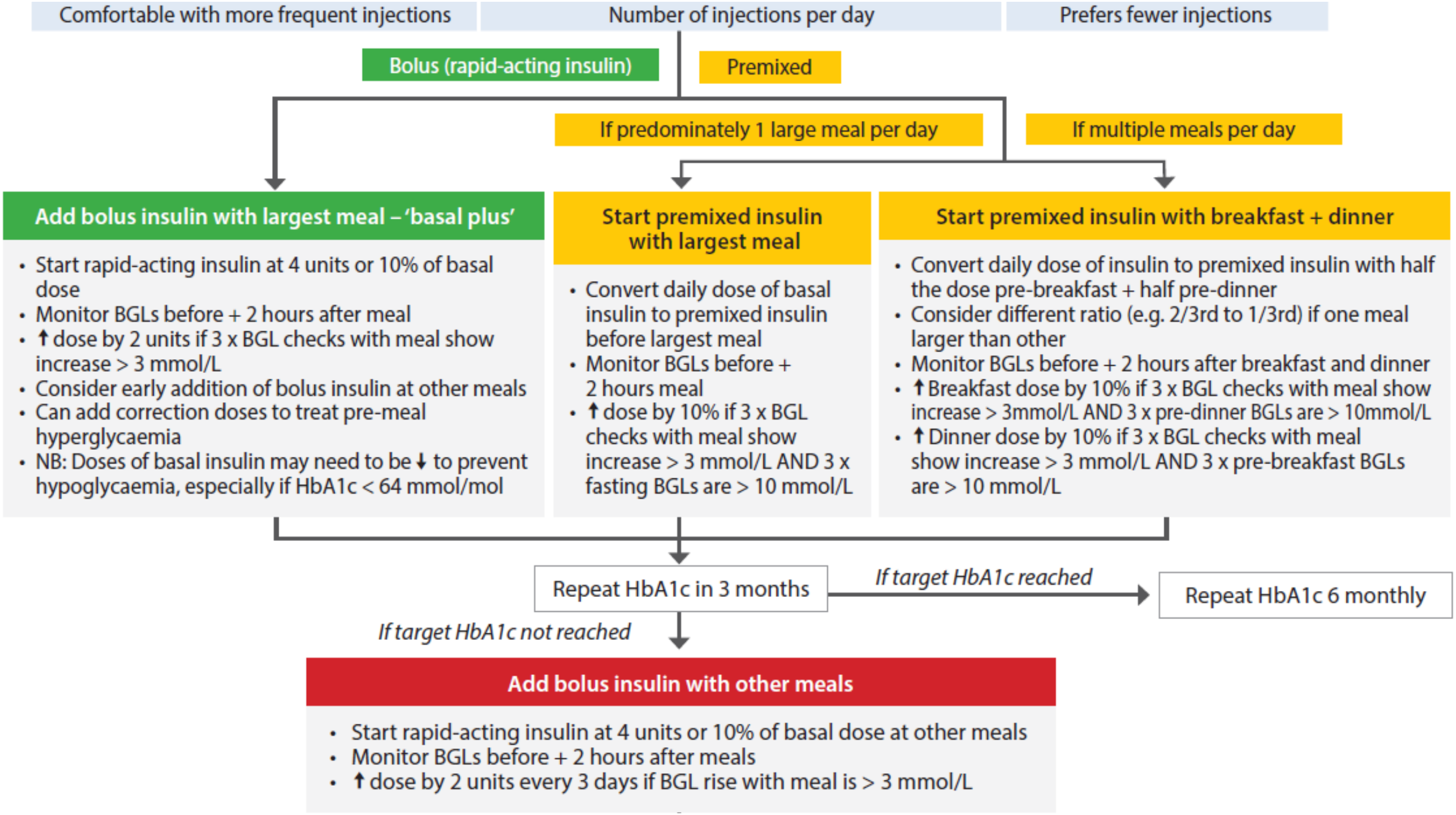
Repeat HbA1c in 3 months

If target HbA1c reached → Repeat HbA1c 6 monthly

If target HbA1c not reached ↓

Add bolus insulin OR switch to premixed insulin
Continue lifestyle management + other glucose lowering therapies
Consider stopping sulfonylureas once regimen established
Consider referral to dietitian to allow matching of insulin and carbohydrate intake
The choice of bolus or premixed insulin should be based on patient data + preference

Favours basal-bolus	Factors to consider	Favours premixed
Yes	Needs flexibility for work patterns, exercise etc	No
Yes	Prefers varied diet + timing of meals	No
Yes	Will likely need rapid intensification of insulin therapy	No
Good ability	Ability to inject (e.g. cognitive ability, dexterity, supervised environment)	Reduced ability
Comfortable with more frequent monitoring	Monitoring of glucose levels	Prefers less frequent monitoring
Comfortable with more frequent injections	Number of injections per day	Prefers fewer injections


Comfortable with more frequent injections
Number of injections per day
Prefers fewer injections
Bolus (rapid-acting insulin)
Premixed
If predominately 1 large meal per day
If multiple meals per day
Add bolus insulin with largest meal – 'basal plus'
• Start rapid-acting insulin at 4 units or 10% of basal dose
• Monitor BGLs before + 2 hours after meal
• ↑ dose by 2 units if 3 x BGL checks with meal show increase > 3 mmol/L
• Consider early addition of bolus insulin at other meals
• Can add correction doses to treat pre-meal hyperglycaemia
• NB: Doses of basal insulin may need to be ↓ to prevent hypoglycaemia, especially if HbA1c < 64 mmol/mol
Start premixed insulin with largest meal
• Convert daily dose of basal insulin to premixed insulin before largest meal
• Monitor BGLs before + 2 hours meal
• ↑ dose by 10% if 3 x BGL checks with meal show increase > 3 mmol/L AND 3 x fasting BGLs are > 10 mmol/L
Start premixed insulin with breakfast + dinner
• Convert daily dose of insulin to premixed insulin with half the dose pre-breakfast + half pre-dinner
• Consider different ratio (e.g. 2/3rd to 1/3rd) if one meal larger than other
• Monitor BGLs before + 2 hours after breakfast and dinner
• ↑ Breakfast dose by 10% if 3 x BGL checks with meal show increase > 3mmol/L AND 3 x pre-dinner BGLs are > 10mmol/L
• ↑ Dinner dose by 10% if 3 x BGL checks with meal show increase > 3 mmol/L AND 3 x pre-breakfast BGLs are > 10 mmol/L
Repeat HbA1c in 3 months
If target HbA1c reached
Repeat HbA1c 6 monthly
If target HbA1c not reached
Add bolus insulin with other meals
• Start rapid-acting insulin at 4 units or 10% of basal dose at other meals
• Monitor BGLs before + 2 hours after meals
• ↑ dose by 2 units every 3 days if BGL rise with meal is > 3 mmol/L

Add bolus insulin with other meals

- Start rapid-acting insulin at 4 units or 10% of basal dose at other meals
- Monitor BGLs before + 2 hours after meals
- ↑ dose by 2 units every 3 days if BGL rise with meal is > 3 mmol/L

↓

Repeat HbA1c in 3 months

If target HbA1c reached → Repeat HbA1c 6 monthly

If target HbA1c not reached ↓

Tips for insulin prescribing

- Use different coloured pens for different types of insulin
- BD fine 4-5 mm needles are associated with ↑ absorption + ↓ trauma
- Change needles regularly (at least every 2nd day)
- Premixed insulin needs to be mixed by gently inverting before each use
- Encourage patients to rotate their injection sites
- Premixed + bolus insulin should be injected before meals
- Ensure adherence + check injection technique before altering doses
- Provide clear instructions for patients on how to self-titrate insulin
- Pens that use ½ unit increments are useful in insulin sensitive patients
- Memory adjuncts (e.g. NovoPen Echo, InsulCheck etc.) may be useful
- Doses of insulin may need to be reduced around exercise

If HbA1c remains above target

- Check insulin injection technique and injection sites
- Ensure adherence to all therapy including lifestyle management
- Optimise non-insulin glucose lowering therapies – NB: doses of insulin may need to be reduced to prevent hypoglycaemia
- Screen for depression
- Re-refer to dietitian and consider carbohydrate awareness
- Consider doses of rapid acting insulin with snacks
- An increase in basal insulin may be required if BGLs are ↑ overnight
- Consider correction doses of rapid acting insulin pre-meals
- Consider switching insulin regimens particularly if increases in premixed insulin are prevented by hypoglycaemia

Sick day management

- All patients on insulin should have a sick day management plan
- If reduced oral intake will likely need reduction/ omission of bolus insulin and 20-30% reduction in basal + premixed insulin
- Patients should monitor their glucose levels at least 3-4 times per day
- Treatment for hypoglycaemia should be readily available
- Correction insulin can be used to treat hyperglycaemia
- High dose steroids often require a ~ 30% ↑ in insulin doses during day

‘Shifting the paradigm’ from glycaemic control to also reducing CVD/renal risk

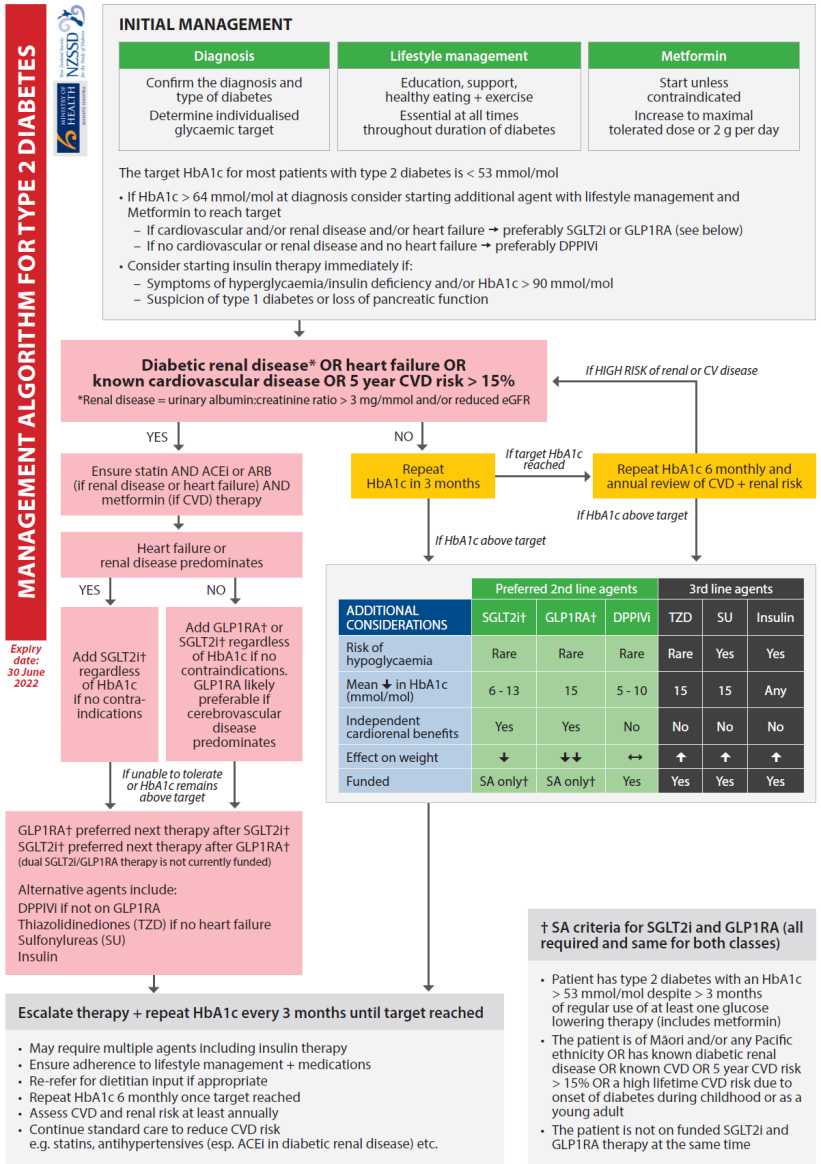
- Previous management algorithms have all been focused on glycaemic control
  - I.e. escalation of therapy based on HbA1c
- However, most morbidity + mortality in T2D is from CVD + renal disease
  - Māori + Pacific peoples 4-5 times more likely to develop diabetic renal disease + 1.5 times more likely to die from CVD
- Many current glucose lowering therapies offer no additional CVD/renal benefit to improved glycaemic control
  - DPPIV inhibitors e.g. vildagliptin
  - Acarbose
  - Sulfonylureas + insulin
- Focus is now on agents that ↓ CVD and/or renal disease independently of glycaemic control
  - Metformin → ↓ CVD
  - SGLT2i e.g. empagliflozin → ↓ CVD + renal disease
  - GLP1 receptor agonists e.g. dulaglutide → ↓ CVD (including stroke) + likely renal disease
- **NB**: We should not forget about the other agents particularly in those without CVD or renal disease
  - Vildagliptin only agent currently known agent when in combination with metformin to delay the need for insulin therapy
  - But sulfonylureas + insulin are now at least 3rd/4th line agents due to risk of hypoglycaemia + weight gain

‘Shifting the paradigm’ from glycaemic control to also reducing CVD/renal risk

- **NB: Do not to forget traditional evidence based treatment to reduce CVD/renal risk**
  - Statins 1st line agent to reduce CVD/CV risk + indicated in all patients with renal disease → target LDLc < 1.8 mmol/L
  - ACEi/ARBs 1st line agents to reduce progression of renal disease
    - NB: ACEi/ARBs do not prevent diabetic renal disease
    - If no renal disease can treat BP with thiazide, calcium channel blocker or ACEi/ARB
    - Target BP is < 130/80 mmHg if CVD/5 year CVD risk > 15% or renal or eye disease
    - Target BP is < 140/90 mmHg if no complications + 5 year CVD risk < 5%
  - Aspirin should be used for all patients for secondary prevention unless contraindicated
    - Now generally not recommended for primary prevention as ↓ benefits + ↑ bleeding risk versus people without diabetes

- There is no current evidence that SGLT2i or GLP1RA prevent diabetic renal disease or CVD
  - Escalation of therapy in this group based on glycaemic control not reducing CVD or renal disease
  - Vildagliptin useful 2nd line agent in this group as funded for all but weight neutral
  - But SGLT2i or GLP1RA likely preferable in overweight/obese due to weight loss
    - GLP1RA likely more effective than SGLT2i in reducing HbA1c + weight

NZSSD Management Algorithm for T2D



ALGORITHM FOR TYPE 2 DIABETES

INITIAL MANAGEMENT

Diagnosis	Lifestyle management	Metformin
Confirm the diagnosis and type of diabetes Determine individualised glycaemic target	Education, support, healthy eating + exercise Essential at all times throughout duration of diabetes	Start unless contraindicated Increase to maximal tolerated dose or 2 g per day

The target HbA1c for most patients with type 2 diabetes is < 53 mmol/mol

- If HbA1c > 64 mmol/mol at diagnosis consider starting additional agent with lifestyle management and Metformin to reach target
  - If cardiovascular and/or renal disease and/or heart failure → preferably SGLT2i or GLP1RA (see below)
  - If no cardiovascular or renal disease and no heart failure → preferably DPPIVi
- Consider starting insulin therapy immediately if:
  - Symptoms of hyperglycaemia/insulin deficiency and/or HbA1c > 90 mmol/mol
  - Suspicion of type 1 diabetes or loss of pancreatic function

Diabetic renal disease* OR heart failure OR known cardiovascular disease OR 5 year CVD risk > 15%

*Renal disease = urinary albumin:creatinine ratio > 3 mg/mmol and/or reduced eGFR

MANAGEMENT ALGORI

Expiry date: 30 June 2022

Diabetic renal disease* OR heart failure OR known cardiovascular disease OR 5 year CVD risk > 15%

*Renal disease = urinary albumin:creatinine ratio > 3 mg/mmol and/or reduced eGFR

YES

Ensure statin AND ACEi or ARB (if renal disease or heart failure) AND metformin (if CVD) therapy

Heart failure or renal disease predominates

YES

Add SGLT2i† regardless of HbA1c if no contra-indications

NO

Add GLP1RA† or SGLT2i† regardless of HbA1c if no contraindications. GLP1RA likely preferable if cerebrovascular disease predominates

If unable to tolerate or HbA1c remains above target

GLP1RA† preferred next therapy after SGLT2i†
SGLT2i† preferred next therapy after GLP1RA†
(dual SGLT2i/GLP1RA therapy is not currently funded)

Alternative agents include:
DPPIVi if not on GLP1RA
Thiazolidinediones (TZD) if no heart failure
Sulfonylureas (SU)
Insulin

NO

Repeat HbA1c in 3 months

If target HbA1c reached

Repeat HbA1c 6 monthly and annual review of CVD + renal risk

If HIGH RISK of renal or CV disease

If HbA1c above target

If HbA1c above target

	Preferred 2nd line agents			3rd line agents		
ADDITIONAL CONSIDERATIONS	SGLT2i†	GLP1RA†	DPPIVi	TZD	SU	Insulin
Risk of hypoglycaemia	Rare	Rare	Rare	Rare	Yes	Yes
Mean ↓ in HbA1c (mmol/mol)	6 - 13	15	5 - 10	15	15	Any
Independent cardiorenal benefits	Yes	Yes	No	No	No	No
Effect on weight	↓	↓↓	↔	↑	↑	↑
Funded	SA only†	SA only†	Yes	Yes	Yes	Yes

Escalate therapy + repeat HbA1c every 3 months until target reached

- May require multiple agents including insulin therapy
- Ensure adherence to lifestyle management + medications
- Re-refer for dietitian input if appropriate
- Repeat HbA1c 6 monthly once target reached
- Assess CVD and renal risk at least annually
- Continue standard care to reduce CVD risk
  e.g. statins, antihypertensives (esp. ACEi in diabetic renal disease) etc.

SGLT2 inhibitors + GLP1 receptor agonists

- SGLT2 inhibitors (SGLT2i) + GLP1 receptor agonists (GLP1RA) are 'new' classes of glucose lowering medications that became funded in NZ from 1st Feb 2021
  - GLP1RA + SGLT2i have been used worldwide since 2005 + 2011, respectively

- SGLT2i + GLP1RA are the preferred 2nd line agents after metformin in most patients with T2D because:
  - Reduce glucose levels by novel mechanisms and do not cause hypoglycaemia in or of themselves
  - Typically lead to weight loss
  - Reduce mortality from CVD and slow progression of diabetic renal disease independent of effects on glycaemic control

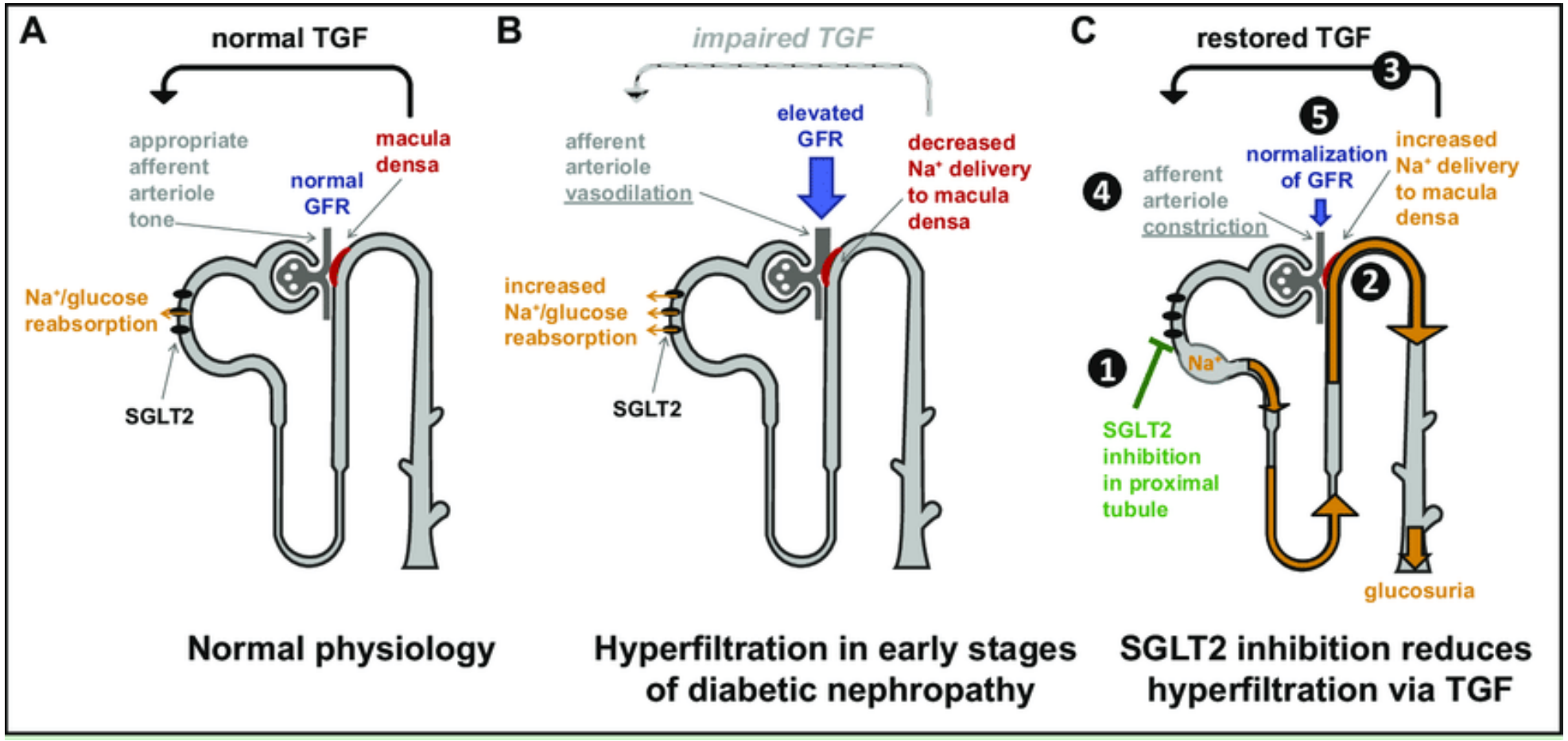
- Empagliflozin (SGLT2i) + dulaglutide (GLP1RA) will be funded under special authority criteria
  - More than 1/3rd of New Zealanders with T2D meet the funding criteria
  - Funding criteria differs slightly from best clinical practice

NB: Dulaglutide unlikely to be approved by Medsafe until July/August

How do SGLT2i work?

- 90% of glucose is reabsorbed by sodium/glucose co-transporter-2 (SGLT2) in the proximal renal tubule
  - Glucose is reabsorbed with Na^+ & H_2O
- There is increased expression of SGLT2 channels in T2D
  - Results in hyperglycaemia + increased fluid volume → ↑ blood pressure, heart + renal disease
- SGLT2i ↑ urinary glucose + Na^+ loss → ↓ blood glucose levels + volume
  - Reduction in blood glucose levels is independent of insulin so does not cause hypoglycaemia alone
    - Associated decrease in insulin secretion likely contributes towards weight loss
  - Reduction in circulating volume likely major mechanism for ↓ heart disease (esp. heart failure)
  - Restoration of tubuloglomerular feedback likely major mechanism for ↓ renal disease
- SGLT2i may have other potential benefits such as altered glucagon secretion etc.

SGLT2i in the diabetic kidney



TGF = tubuloglomerular feedback

Fioretto et al. Diabetes Care 2016; 39(S2):S165

What are the benefits of SGLT2i?

- Mean reductions in HbA1c of 6 – 13 mmol/mol (range 4 – 21 mmol/mol)
  - Effects of SGLT2i on glycaemic control ↓with ↓renal function (CVD + renal benefits maintained)
  - Improvements in glycaemic control are additive to all other glucose lowering therapies
  - Hypoglycaemia is very rare unless used in combination with sulfonylureas and/or insulin
- Modest sustained weight loss with mean weight loss of 1 – 3 kg at 2 years
- Mean reductions in systolic + diastolic blood pressure of 1 – 6 mmHg
- Reduced development of renal failure – NNT ~ 26 for 5 years if high risk (BMJ 2021;372:m4573)
  - Associated with ↓ renal replacement therapy + death from renal disease
  - Benefits are additive to those from ACE inhibitors (ACEi)/Angiotensin II receptor blockade (ARB)

What are the benefits of SGLT2i cont…?

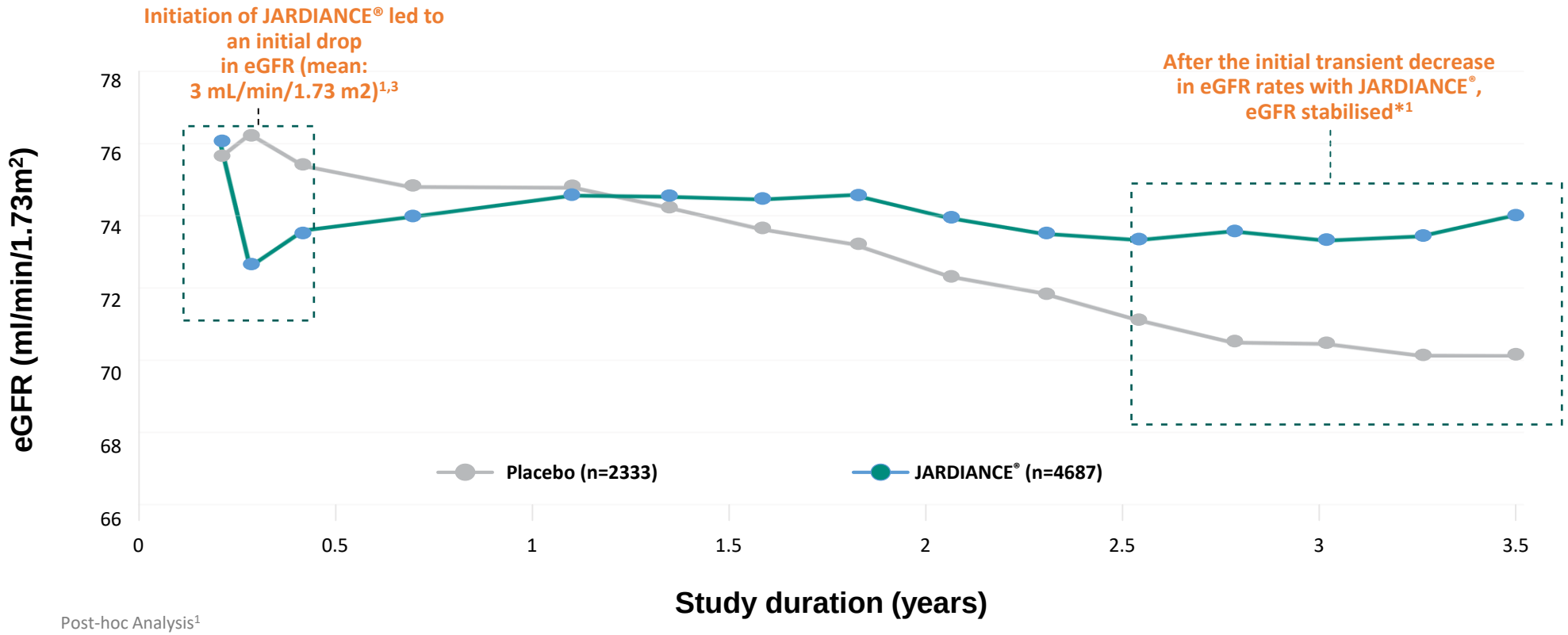
- Reduced cardiovascular events (MI + CVD death) - NNT ~ 23 for 5 years if high risk
  - Benefit confined to those with known atherosclerotic CVD + no clear effect on non-fatal stroke
- Reduced hospitalisation + death from heart failure – NNT ~ 17 for 5 years if high risk
  - Benefits seen in those with and without known heart failure
  - Benefits predominantly in HFrEF + associated with reduced incidence of atrial fibrillation + flutter
- Reduced mortality in known CVD or renal disease - NNT ~ 21 for 5 years if high risk
  - Studies were performed to assess safety so effects in those without CVD or renal disease still awaited
- **NB: There is no current evidence that SGLT2i prevent diabetic renal disease or CVD**
  - i.e: The benefits are confined to secondary prevention + not primary prevention
  - There is also no evidence that SGLT2i are more or less effective in Māori or Pacific peoples

What are the adverse effects of SGLT2i?

- Predominantly due to glycosuria + associated osmotic diuresis
- Polyuria - typically transient + mild to moderate intensity only (worse with higher glucose levels)
- Volume depletion + hypotension
  - Greatest risk is in those > 75 years of age and/or on diuretics and/or on ACE inhibitors/ARBs
  - May be associated with up to a 25% transient decrease in eGFR + symptomatic hypotension
  - Consider reducing dose of diuretics and/or antihypertensives when starting SGLT2i
- Increased risk of genitourinary infections
  - More common in females + those with recurrent genitourinary infections → discuss good genital hygiene
    - E.g. Women to wash +/- change pads ≥ twice per day & uncircumcised men wash ≥ once per day
  - Approximately 3 fold increase in mycotic genitourinary infections e.g. vulvovaginitis, balantis etc.
  - Associated with mild ↑ in UTIs → rarely associated with urosepsis/pyelonephritis
  - Rarely associated with necrotising fasciitis of the perineum (Fournier's gangrene)
    - Suspect if significant genital or perineal pain, erythema or swelling, particularly if fever + malaise

Impact on eGFR*

*JARDIANCE is not indicated to prevent renal decline.[2]



Post-hoc Analysis[1]
Adapted from Wanner *et al.* 2016.[1]

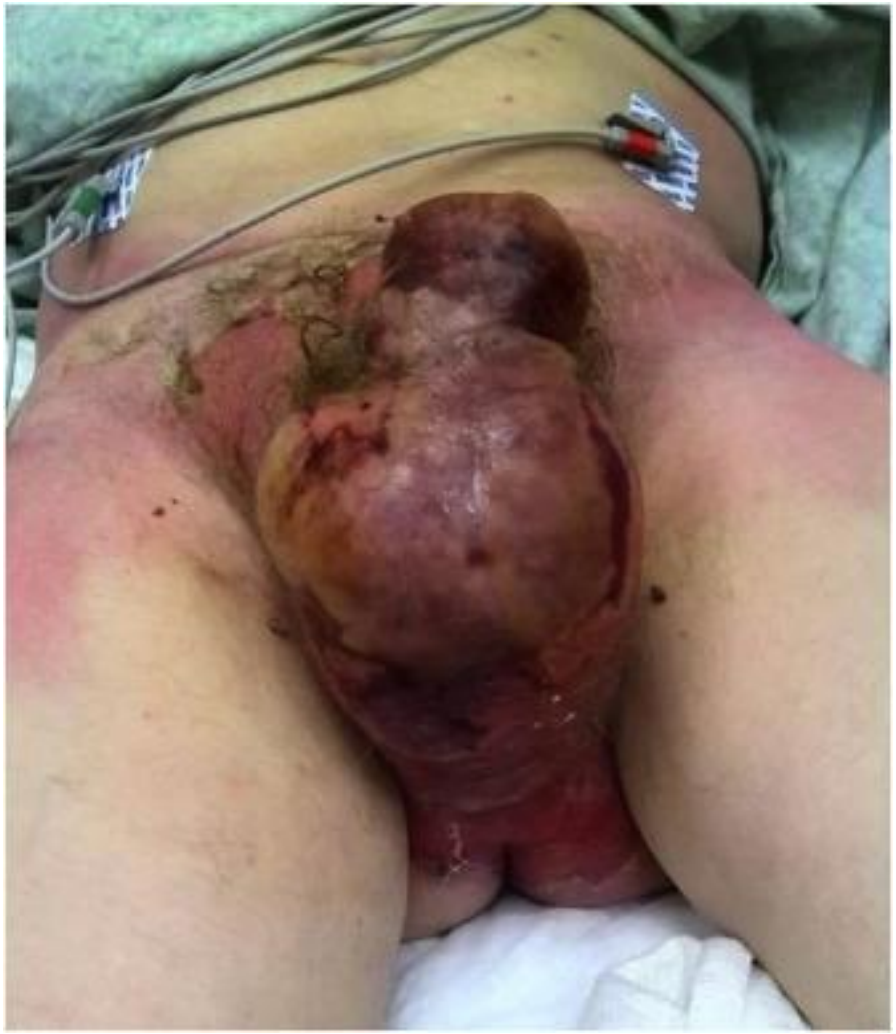
Pre-specified mixed model repeated measures analysis in all patients treated with ≥1 dose of study drug who had a baseline and post-baseline measurement.[1]
Overall, 26% of patients in EMPA-REG OUTCOME had an eGFR <60 mL/min/1.73m² at baseline. Primary endpoint of 3P-MACE was met (HR 0.86; 95% CI: 074–0.99; p=0.04).[3]
Definition: eGFR, estimated glomerular filtration rate

References: 1. Wanner C *et al. N Engl J Med* 2016; 373:323–34. **2.** JARDIANCE® Data Sheet 2019. **3.** Zinman B *et al. N Engl J Med* 2015; 373:2117–28.

Jardiance® (empagliflozin)

TAPS MR7257 PC-NZ-100144. February 2021.

Fournier’s gangrene



Joury et al. Urology Case Reports 2019; 26:100943

What are the adverse effects of SGLT2i cont…?

- Hypoglycaemia
  - Extremely rare unless SGLT2i used in combination with insulin and/or sulfonylureas
  - When starting SGLT2i consider ↓ total daily dose of insulin by 15-20% and sulfonylureas by 50% if tight glycaemic control (e.g. HbA1c < 64 mmol/mol)

- Diabetic ketoacidosis (DKA) including normoglycaemic DKA
  - SGLT2i ↑ production of ketones so can lead to DKA even in those with normal glucose levels
  - DKA is rare (1:3000) but patients and health professionals should be aware of sick day management
    - To stop SGLT2i when acutely unwell or 2 days before an elective procedure
    - SGLT2i ↓ urinary excretion of ketones so cannot use urinary ketones as marker of DKA
    - To have capillary ketone levels checked at practice or hospital if symptoms of DKA e.g. nausea, vomiting or abdo pain
    - Capillary ketone levels > 1.5 mmol/L warrant urgent medical attention
  - SGLT2i should not be used in those high risk for DKA:
    - Type 1 diabetes or diabetes due to pancreatic insufficiency
    - Previous DKA
    - Insulin deficiency with low carbohydrate diet and/or significant alcohol use

When should SGLT2i not be used?

- Pregnancy/breast feeding
- Youth (< 18 years of age)
- eGFR < 30 mL/min
- Previous severe or recurrent genitourinary infections
- Nephrolithiasis/recurrent renal calculi
- High risk for volume depletion (e.g. > 85 years of age, symptomatic hypotension)
- High risk for DKA
  - Type 1 diabetes or diabetes due to loss of pancreatic function
  - Low carbohydrate diets and/or significant alcohol intake
  - Previous episodes of DKA

GLP1RA- Introduction

- GLP1RA are self-administered subcutaneously + have been used worldwide since 2005
  - GLP1RA pens are very similar to insulin pens

- Three GLP1RA will be available in NZ:

  - Dulaglutide (Trulicity) – funded under SA criteria but awaiting Medsafe approval (likely mid-2021)
    - Only 1.5 mg pens for weekly use will be available in NZ (also available in 0.75 mg, 3 mg + 4.5 mg pens overseas)
    - Available in easy use single-use pens with hidden needle

  - Exenatide – non-funded + costs approximately $280 per month
    - Available in short-acting (Byetta) 5 – 10 µg s/c bd + extended release (Bydureon) 2 mg s/c weekly formulations
    - Bydureon will be shortly withdrawn from the NZ market

  - Liraglutide (Saxenda) – non-funded + currently approved for obesity only (costs approx. $500 per month)

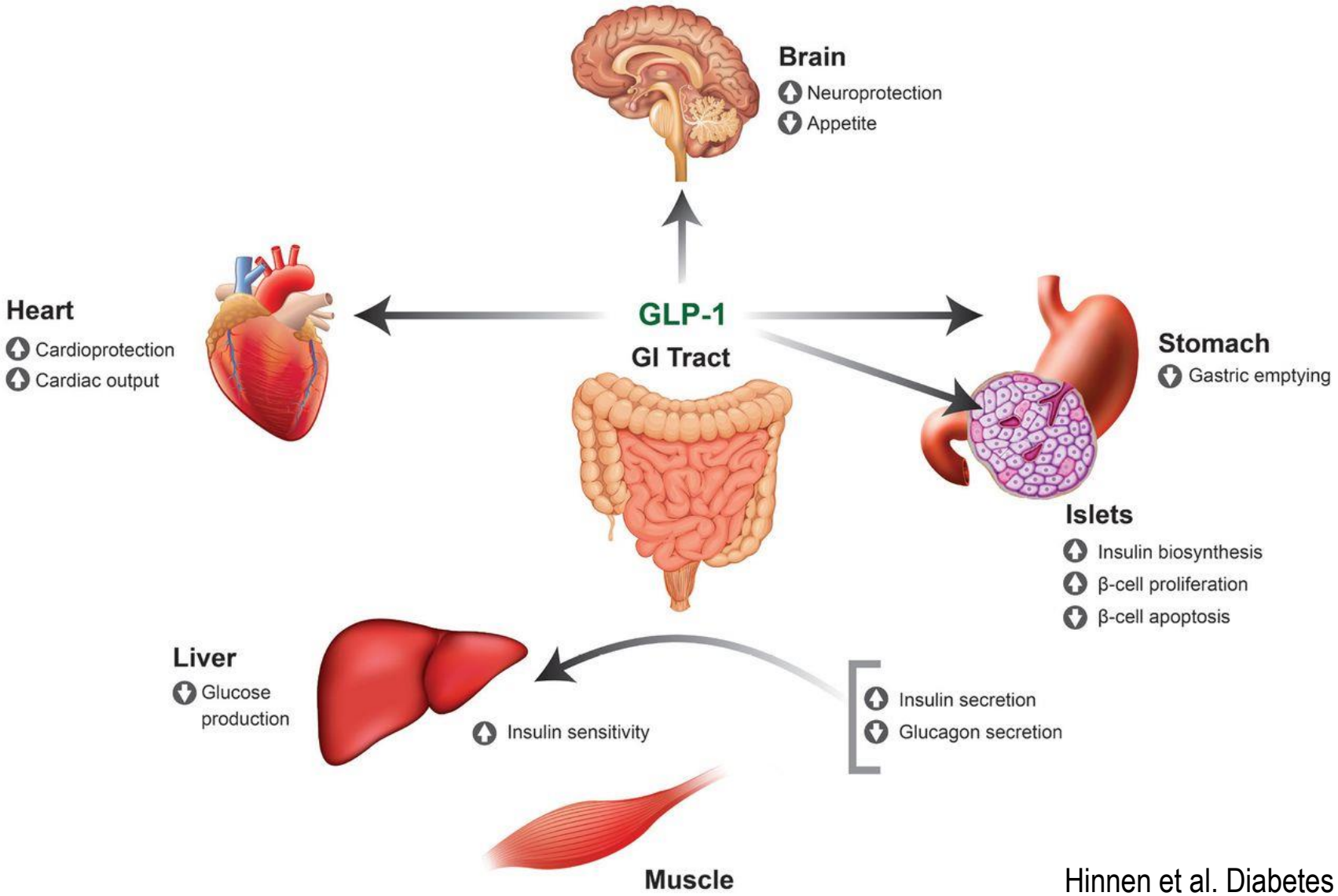
- Other GLP1RA are not available in NZ at present e.g. lixisenatide + semaglutide etc.

Dulaglutide single use pens

Mechanism of action of GLP1RA

- Glucagon-like peptide-1 (GLP-1) is the main incretin produced by L cells in small bowel in response to nutrients
- Main mechanism of action of GLP-1 is acting directly on pancreatic islet cells via to:
  - ↑ glucose-dependent insulin secretion→ as glucose-dependent does not cause hypoglycaemia alone
  - ↓glucagon secretion
  - ↑ β-cell proliferation + ↓ β-cell apoptosis (animal studies only at present)
  - ↑ insulin + ↓ glucagon secretion results in ↓ hepatic gluconeogenesis (glucose production)
- GLP1 also has beneficial actions on other target organs:
  - Stomach → ↓ gastric emptying
  - Brain → ↓appetite
  - Heart → ↑ cardiac output + cardioprotection
  - Kidney → ↑ natriuresis
- Endogenous GLP1 is normally rapidly deactivated by the enzyme dipeptidyl peptidase IV (DPPIV)
- Patients with T2D have decreased action of GLP-1 due to ↓ GLP-1 production + ↑ DPPIV activity
  - GLP1RA act via endogenous GLP1 receptors to mimic actions of GLP-1 + are resistant to degradation
  - GLP1RA result in greater actions of GLP-1 than DPPIV inhibitors (DPPIVi) e.g. vildagliptin

Mechanism of action of GLP1RA



Hinnen et al. Diabetes Spectrum 2017; 30(3):202

Clinical benefits of GLP1RA

- Benefits are typically a ‘class effect’ unless mentioned
- Mean reductions in HbA1c of 15 mmol/mol
  - Reductions in HbA1c are additive to other glucose lowering therapies except for DPPIVi
  - GLP1RA likely lead to greater improvements in glycaemic control than SGLT2i or DPPIVi
  - Hypoglycaemia is very rare unless used in combination with sulfonylureas and/or insulin
- Mean sustained weight loss of 1.5 – 3 kg at 6 – 12 months
- Mean reductions in systolic blood pressure of 2 – 3 mmHg
- Mean reductions in LDL cholesterol of 0.08 mmol/L

Clinical benefits of GLP1RA

- Reduced cardiovascular events (MI, stroke + CVD death)
  - Benefit confined to those with known atherosclerotic CVD disease
  - Benefits likely greater for dulaglutide than for exenatide
  - Dulaglutide reduce non-fatal strokes (unlike exenatide + SGLT2i)
  - Unlike SGLT2i, GLP1RA do not appear to reduce hospitalisations with heart failure
  - **No data to date for a role for GLP1RA in primary prevention of CVD**

- Likely reduced progression of diabetic renal disease
  - Studies designed to assess safety in CVD have shown GLP1RA ↓ macroalbuminuria
  - These studies have not shown a ↓ in decline of eGFR, renal replacement therapy or renal death
  - Results from studies designed to investigate effects of GLP1RA on hard renal outcomes awaited
  - **No convincing evidence to date for GLP1RA in primary prevention of diabetic renal disease**

- Associated with reductions in all-cause mortality in those with known CVD disease

Adverse effects of GLP1RA

- Gastrointestinal e.g. nausea, vomiting + diarrhoea
  - Occur in 25-60% of patients, but typically mild + dissipate over a few weeks despite continued treatment
  - Less common with long-acting formulations + rarely leads to cessation of treatment
  - Patients should be instructed to stop eating when they feel full + maintain adequate hydration
    - Vomiting with GLP1RA has been associated with acute kidney injury in patients also on ACE inhibitors/ARBs + diuretics
- Injection site reactions e.g. redness, nodules
  - Occur in < 10% of patients and are usually mild + transient and resolve despite continued treatment
  - More common with exenatide than other formulations
- Antibody formation to GLP1RA
  - May develop in up to 50% of patients but does not alter efficacy
- Pancreatitis
  - Although rare in initial studies, meta-analyses have revealed no clear link between GLP1RA + pancreatitis
  - Caution is still recommended if previous pancreatitis + consider if severe abdominal pain
- Medullary thyroid hyperplasia + carcinoma in rodent studies (no case reports in humans to date)

Contraindications/precautions for use of GLP1RA

- Given lack of safety data GLP1RA not recommended for use in:
  - Pregnancy/breast feeding
  - Youth (< 18 years of age)
  - Type 1 diabetes or diabetes due to loss of pancreatic function (unless specialist approval)
  - eGFR < 30 mL/min
    - Dulaglutide is registered for use if eGFR > 15 mL/min in USA but Medsafe eGFR cut off awaited

- Be cautious using GLP1RA if:
  - Significant gastrointestinal disease – especially gastroparesis or severe gastroesophageal reflux
  - High risk of volume depletion e.g. elderly patients on ACE inhibitors/ARBs and diuretics
  - Previous pancreatitis
  - History of medullary thyroid carcinoma or multiple endocrine neoplasia 2 (MEN2) syndrome

Special authority criteria for SGLT2i + GLP1RA

- Single SA criteria for both empagliflozin + dulaglutide, but only one agent can be funded for use at any time (i.e. patients will have to self-fund one agent to be on dual therapy)
  - **Lack of funding for dual therapy is due to financial constraints + is not evidence based**
  - Patients may choose to self-fund other available SGLT2i + GLP1RA e.g. dapagliflozin, exenatide etc.
  - Addition of ethnicity + age criteria is designed to reduce barriers to access + not ↑ inappropriate use in these groups

- SA criteria:
  - Patient has type 2 diabetes with an HbA1c > 53 mmol/mol despite > 3 months of regular use of metformin and/or an alternative glucose lowering therapy **AND** any of the following:
    - Māori or Pacific ethnicity **OR**
    - Diabetic renal disease (urinary albumin:creatinine ratio > 3 mg/mmol and/or eGFR < 60 mL/min) **OR**
    - Known cardiovascular disease (any IHD, cerebrovascular event, peripheral vascular disease, congestive heart failure, or familial hypercholesterolaemia) **OR**
    - 5 year cardiovascular disease risk > 15% **OR**
    - A high lifetime CVD risk due to onset of diabetes in childhood or as a young adult

Clinical indications for use of SGLT2i + GLP1RA

- Lifestyle management + metformin remain 1st line management for all patients with T2D but either SGLT2i or GLP1RA may be preferred 2nd line agents depending on clinical scenario:

:

  - All patients with either diabetic renal disease (UACR > 3 mg/mmol and/or ↓ eGFR) **OR** heart failure **OR** known CVD disease **OR** high CVD risk (esp. 5 year CVD risk > 15%) **regardless of HbA1c + other glucose lowering therapies**
    - **SGLT2i preferred 2nd line agent after metformin if renal disease and/or heart failure predominates**
      - GLP1RA preferred next therapy after SGLT2i
    - **GLP1RA preferred 2nd line agent after metformin if cerebrovascular disease predominates**
      - SGLT2i preferred next therapy after GLP1RA
    - **Otherwise either SGLT2i or GLP1RA after metformin based on precautions, tolerability + patient preference etc.**
      - SGLT2i preferred next therapy after GLP1RA + vice versa
  - **Overweight or obese patients with an HbA1c above target** despite regular use or intolerability of metformin
    - Either SGLT2i or GLP1RA preferred 2nd line agent after metformin but GLP1RA associated with greater weight loss + reduction in HbA1c
    - SGLT2i preferred next therapy after GLP1RA + vice versa
  - **All other patients with an HbA1c above target** despite regular use or intolerability of metformin **AND** vildagliptin
    - Either SGLT2i or GLP1RA preferred 3rd line agent

Mismatch between SA criteria + clinical indications for use of SGLT2i + GLP1RA

- The SA criteria ensures access for high risk patients for SGLT2i + GLP1RA but there is a mismatch with best clinical practice

- For best practice, patients with T2D should be offered to **self-fund SGLT2i and/or GLP1RA** in the following situations where the **SA criteria does not apply**:
  - Patients with diabetic renal disease and/or known CVD and/or 5 year CVD risk > 15% with an HbA1c < 53 mmol/mol
  - Patients with diabetic renal disease and/or known CVD and/or 5 year CVD risk > 15% on either funded empagliflozin or dulaglutide
  - Overweight or obese patients with an HbA1c above target despite regular use or intolerability of metformin
  - All other patients with an HbA1c above target despite regular use or intolerability of metformin + vildagliptin
  - All other patients with an HbA1c to target where a SGLT2i or GLP1RA is preferable to limit adverse effects of thiazolidinedione, sulfonylurea and/or insulin therapy (e.g. weight gain + hypoglycaemia)

Self funding SGLT2i or GLP1RA

- Empagliflozin costs ~ $85/month + dulaglutide cost awaited (likely $300–500/month)
  - Cost of empagliflozin + dapagliflozin very similar
  - Marked variance in mark ups by pharmacies (online pharmacies often cheapest)
- Given SA encompasses both empagliflozin + dulaglutide patients are best to receive funded dulaglutide + self-fund empagliflozin or dapagliflozin if able
- Should not assume whether patients can afford self-funding or not
- Patients that previously self-funded SGLT2i and/or GLP1RA

How to use a SGLT2i

- Start empagliflozin 10 mg daily (funded) or dapagliflozin 10 mg daily (non-funded)
  - For empagliflozin either 10 mg once daily or 5 mg twice daily if combined with metformin (5mg/500mg or 5mg/1000mg)
- Continue to provide ongoing education + support for lifestyle management
- Continue metformin + other evidence based therapies e.g. GLP1RA, ACEi/ARBs/statins
- Continue other glucose lowering therapies if required for glycaemic control
  - Most patients will not require alteration of other glucose lowering regimen
  - But if on insulin and/or sulfonylureas + high risk for hypoglycaemia (e.g. HbA1c < 64 mmol/mol) consider reducing total daily dose of insulin by 15 – 20% and/or dose of sulfonylureas by 50%
- Consider reducing diuretics and/or antihypertensives as required
  - If possible continue to optimise ACEi/ARB if diabetic renal disease

How to use a SGLT2i cont…

- Warn patients of adverse effects + provide sick day management plan
  - To stop SGLT2i if acutely unwell or 2 days before an elective procedure
  - To present to GP practice or hospital to measure capillary ketones if nausea, vomiting, or abdo pain
  - Encourage adequate hydration + discuss hygiene to prevent genitourinary infections
  - Encourage early treatment of genitourinary infections + seek medical attention if severe symptoms

- Repeat BP, HbA1c + eGFR in 3 months
  - Increase empagliflozin to 25 mg daily if well tolerated + HbA1c above target
  - Can increase dose after a few weeks if clinically indicated e.g. persistently high blood glucose levels
  - If combined with metformin, will need to switch to 12.5 mg/500 mg or 12.5 mg/1000 mg tablets
  - If on dapagliflozin + HbA1c above target → escalate other glucose lowering therapy
  - If diabetic renal disease + BP remains above target → maximise ACEi/ARB + then other antihypertensives
  - If no diabetic renal disease + BP remains above target → maximise antihypertensive therapy

- If above targets then repeat BP, HbA1c + eGFR in 3 months
  - Escalate glucose-lowering therapy if HbA1c above target + antihypertensives if BP above target
  - Continue to optimise other management e.g. statin therapy if indicated, weight loss, feet cares etc.

How to use a GLP1RA

- Start dulaglutide 1.5 mg s/c weekly (funded) or exenatide 5 µg bd (non-funded)
  - Dulaglutide can be injected at any time of day
  - Exenatide should be injected < 60 mins before main meals with both doses > 6 hours apart
  - Will need to provide education on injection technique
- Continue to provide ongoing education + support for lifestyle management
- Continue metformin + other evidence based therapies e.g. SGLT2i, ACEi/ARBs/statins
- Stop DPPIV inhibitors e.g. vildagliptin
- Continue other glucose lowering therapies if required for glycaemic control
  - Most patients will not require alteration of other glucose lowering regimen
  - But if on insulin and/or sulfonylureas + high risk for hypoglycaemia (e.g. HbA1c < 64 mmol/mol) consider reducing total daily dose of insulin by 15 – 20% and/or dose of sulfonylureas by 50%

How to use a GLP1RA cont…

- Warn patients of adverse effects + that nausea will likely occur
  - Reassure patients that GI adverse effects are typically mild + dissipate on continued treatment
  - Encourage adequate hydration (especially if on ACEi/ARBS and/or diuretics)
  - Dietary modifications may minimise GI adverse effects such as:
    - Eating smaller meals + stopping eating when feeling full
    - Avoiding fatty or spicy foods
    - Reducing smoking + alcohol intake
    - Not eating within 2 hours before bed
  - Encourage patients to contact practice if significant adverse effects persist

- Repeat BP, HbA1c + eGFR in 3 months
  - If HbA1c above target on dulaglutide → escalate other glucose lowering therapy
  - If on exenatide 5 µg bd + HbA1c above target → can increase dose to 10 µg bd
  - If diabetic renal disease + BP above target → maximise ACEi/ARB + then other antihypertensives
  - If no diabetic renal disease + BP above target → maximise antihypertensive therapy

How to use a GLP1RA cont…

- If above HbA1c + BP targets then repeat BP, HbA1c + eGFR in 3 months
  - Escalate glucose-lowering therapy if HbA1c above target + antihypertensives if BP above target
  - Continue to optimise other management e.g. statin therapy if indicated, weight loss, feet cares etc.

- Can switch to 6 monthly monitoring once HbA1c + BP to target

Case 1

- 65 year old Samoan woman with a background of:
  - Type 2 diabetes for > 20 years
  - IHD with 2 x previous MI
  - Diabetic renal disease - eGFR 45 mL/min with UACR 85 mg/mmol

- HbA1c is 56 mmol/mol + BP 112/76 mmHg on current regimen that includes:
  - Metformin 1 g tds
  - Vildagliptin 50 mg bd
  - Glipizide 10 mg bd
  - Lantus 35 units nocte
  - Accupril 20 mg bd
  - Felodipine 5 mg od
  - Frusemide 80 mg od

- How will you optimise the management of her diabetes?

Learning points

- All patients with T2D + diabetic renal disease and/or CVD/high CVD risk should ideally be on a SGLT2i and/or GLP1RA regardless of glycaemic control + other therapies

- Choosing between a SGLT2i + GLP1RA can be a difficult decision but:
  - SGLT2i likely preferable if renal disease or heart failure predominates
  - GLP1RA likely preferable if cerebrovascular disease predominates
  - Co-morbidities (e.g. previous UTIs, GI disease etc.) + patient preference may influence decision

- Little benefit in > 2 g per day of metformin + dose needs to be reduced with ↓eGFR
  - Dose of vildagliptin also needs to be ↓ to maximum of 50 mg daily once eGFR < 50 mL/min

- You ↓ her metformin to 500 mg bd + vildagliptin to 50 mg od+ start empagliflozin 10 mg od
  - Would you make any other changes to her medication regimen + what advice do you give?

Learning points

- If starting a SGLT2i or GLP1RA - patients on insulin and/or sulfonylureas may need a reduction in doses if high risk of hypoglycaemia (e.g. HbA1c < 64 mmol/mol)
  - 15-20% ↓ in total daily dose of insulin + 50% ↓ in dose of sulfonylureas useful starting point
  - Monitoring of glucose levels provides best guide to ongoing changes in regimen

- If starting a SGLT2i – patients on antihypertensives and/or diuretics may need a reduction in doses to prevent hypotension + volume depletion
  - Will likely only require reduction in antihypertensives if BP low
    - Aim to continue ACEi/ARB if renal disease or heart failure e.g. would stop felodipine in this case
  - Will likely only require reduction in diuretics if not fluid overloaded
    - Consider stopping low doses (e.g. frusemide 20 mg od) or reducing higher doses (e.g. frusemide 80 mg to 40 mg od)

- Warn patients of adverse effects + provide advice on sick day management
  - To stop their SGLT2i if they are acutely unwell or 2 days before an elective procedure
  - To present to practice or hospital if nausea, vomiting or abdo pain to ensure ketones low
  - To advise on hygeine + contact practice if significant genitourinary symptoms

Case 1 cont…

- She continues to do well but 1 year later her HbA1c is 70 mmol/mol despite:
  - Metformin 500 mg bd
  - Empagliflozin 10 mg od
  - Vildagliptin 50 mg od
  - Glipizide 10 mg bd
  - Lantus 50 units nocte
- Her eGFR remains 45 mL/min with a weight of 100 kg + BP of 120/80 mmHg
- Fasting blood glucose levels 10 mmol/L
- How will you optimise the management of her diabetes now?

Learning points

- Increasing empagliflozin to 25 mg daily beneficial but patient won't reach HbA1c target
- The SA criteria does not allow funded dual GLP1RA/SGLT2i therapy at present
- But GLP1RA next best recommended therapy so should be offered to patient
  - SGLT2i + GLP1RA are under a shared SA criteria with funding of only one at any time
  - Recommend patients self-fund SGLT2i as > 3-fold cheaper than any GLP1RA
    - Either empagliflozin or dapagliflozin cost approximately $85-90 per month at present
  - Encourage patients to 'shop around' as mark-up varies significantly between pharmacies
- If she cannot afford to self-fund then the next best therapy is prandial insulin
  - **NB:** Indicated when HbA1c above target + doses of basal insulin reach 0.5 units/kg/day
  - Will need to stop sulfonylureas at meals with prandial insulin once regimen established

Case 2

- 48 year old fit and well Māori man attends for CVD risk assessment
  - HbA1c 68 mmol/mol + 5 year CVD risk 10%
  - BMI 35 kg/m^2
  - BP150/95 mmHg
- Random glucose in practice is 12 mmol/L
- UACr 2.2. mg/mmol with eGFR > 90 mL/min
- He is keen for the ‘new medications’ after being informed of diagnosis of T2D
- How will you manage his diabetes?

Learning points

- Lifestyle management + metformin remains first line management of T2D

- Continue to address other cardiovascular risk factors (e.g. BP, LDLc, smoking etc.)
  - ACEi/ARBs first line antihypertensive if diabetic renal disease
  - Either ACEi/ARB, thiazide or Ca^{++} channel blocker first line if no diabetic renal disease
    - NB: ACEi/ARBs do not prevent diabetic renal disease

- If no diabetic renal disease or CVD/ high CVD risk then escalation of glucose lowering therapy is based on HbA1c – in this situation:
  - SGLT2i or GLP1RA are recommended 2nd line agents if patient is overweight/obese
    - GLP1RA more effective than SGLT2i for weight loss + glycaemic control
    - Could use empagliflozin as alternative or until dulaglutide available
  - Vildagliptin is likely best 2nd line agent in all other patients

- His repeat HbA1c is 58 mmol/mol so you start funded dulaglutide 1.5 mg weekly. What instructions do you give?

Learning points

- The target HbA1c for most patients with T2D is < 53 mmol/mol
  - Monitor HbA1c 3 monthly if not to target + escalate therapy as required
  - Monitor HbA1c 6 monthly if to target + escalate therapy as required
  - Review target HbA1c annually

- Discuss adverse effects with GLP1RA + provide instructions on how to self-titrate
  - Nausea will occur in ~ 50% of patients, but mild + generally resolves despite continued treatment
  - Vomiting, diarrhea + injection site reactions each occur in ~ 10% of patients
    - Will also typically resolve despite continued treatment
  - Gastrointestinal side effects can be limited by:
    - Eating smaller meals, not eating within 2 hours of bed + stopping eating when feeling full
    - Avoiding fatty or spicy foods+ reducing smoking + alcohol intake
    - Ensuring adequate hydration (will also reduce risk of volume depletion)

- Despite weight loss (BMI 30 kg/m^2) & good adherence to his dulaglutide + metformin his HbA1c ↑ to 60 mmol/mol 2 years later?
  - How will you manage his T2D now?

Learning points

- SGLT2i next best therapy but patient will need to self-fund
- Vildagliptin cannot be used in combination with GLP1RA
- If unable to afford then alternatives include:
  - Pioglitazone
    - Beneficial in that it won't cause hypoglycaemia + will likely be well tolerated in this patient
    - Beware of adverse effects that preclude use in others e.g. fluid retention, osteoporosis etc.
  - Sulfonylureas
  - Insulin

Case 3

- 28 year old NZ European man with T2D. ‘Intolerant’ of metformin
- HbA1c 75 mmol/mol despite lifestyle management + gliclazide 80 mg bd
- UACr 2.2. mg/mmol with eGFR > 90 mL/min
- LDL cholesterol 4.5 mmol/L + BP 155/95 mmHg
- BMI 38 kg/m^2 with 5 year CVD risk < 5%
- How will you manage his diabetes?

Learning points

- Most patients 'intolerant' to metformin will tolerate metformin when started low + slow
  - E.g. metformin 250 mg od with food + gradually ↑ dose
- He will almost certainly not reach an HbA1c < 53 mmol/mol on metformin alone
  - Mean maximal ↓ in HbA1c with metformin is ~ 16 mmol/mol
- Current CVD risk calculators do not account for family history + underestimate risk in young adults
  - Young adults with T2D will have a low 5 year CVD risk but an extremely high lifetime CVD risk
  - Consider aggressive management of CVD risk factors (e.g. statins, antihypertensives) despite low CVD risk
- Remember all patients with T2D diagnosed in childhood or a young adult qualify for funded SGLT2i or GLP1RA therapy
  - GLP1RA likely next best therapy given obesity but dulaglutide currently not available
  - **NB:** Start on funded empaglifozin until dulaglutide available then switch over

Learning points

- Sulfonylureas are no longer preferred 2nd line agents due to risk of hypoglycaemia + weight gain
  - Would ideally stop sulfonylureas in this case if able to get HbA1c to target

- If this patient had a normal BMI then vildagliptin would likely be best 2nd line agent
  - Vildagliptin in combination with metformin is the only regimen been shown to delay the need for insulin therapy
  - There is no good evidence at present that SGLT2i and/or GLP1RA prevent diabetic renal disease or CVD
  - However, a SGLT2i or GLP1RA would be the best 3rd line therapy in this situation if required

- Vildagliptin also best alternative to SGLT2i/GLP1RA in diabetic renal disease and/or CVD/high CVD risk and/or obesity when SA criteria not met and cannot self-fund SGLT2i/GLP1RA OR SGLT2i/GLP1RA not tolerated/contraindicated (e.g. renal failure)

- Escalation of therapy should be based on best practice + not funding of medications
  - All patients should be offered SGLT2i or GLP1RA when clinically appropriate
  - Assumptions should not be made on whether the patient can or cannot afford SGLT2i or GLP1RA therapy

Discussion

The introduction of the 'new' agents and the NZSSD national guidance provide the ideal opportunity to improve the care of all New Zealanders with type 2 diabetes and the inequalities therein.

Implementation and reducing clinical inertia are the key