

Common Endocrinology Problems

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GP CME November 2022

Outline

- 6 mini cases outlining common Endocrinology referrals
- Thyroid, Parathyroid, Pituitary and Adrenal
- Update on Empagliflozin and Dulaglutide
- Question Time

Case 1

- 38 year old woman come along complaining of tiredness
- Thyroid function tests show:
 - T4 28.4 pmol/l (7.0 – 16.0)
 - TSH <0.01 mIU/L (0.3 – 5.0)
- What other information might be helpful?

Relevant Thyroid history/exam

- Prior history of abnormal TFTS or thyroid disorder
 - Recent viral illness/neck pain
 - Pregnant?
 - Personal or family history of autoimmune disease
 - Iodine exposure – CT with contrast
 - Lithium, Amiodarone
-
- Signs of thyrotoxicosis
 - Eye signs
 - Goitre

What treatment do you want to start?

- If only mild Thyrotoxicosis, hold off treatment and repeat in 2 weeks
 - Asymptomatic, not compromised, T4 only mildly elevated (< 35)
- First line treatment Carbimazole
 - Half the T4 as starting dose
- Propylthiouracil
 - First trimester of pregnancy only
 - Those intolerant to carbimazole
 - Lifetime SA can be done by any practitioner
- Beta blockers if need be
 - Metoprolol CR once daily more convenient than TDS propranolol

What tests do you want to order?

- Thyroid antibodies?
- Thyroid Ultrasound?
- Thyroid Scintiscan?

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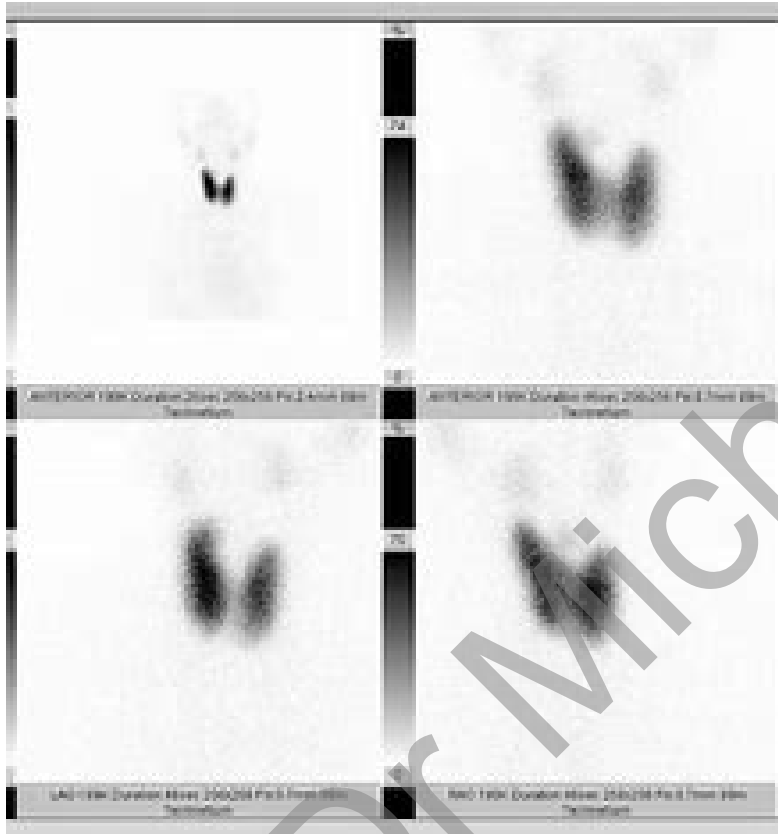
What tests do you want to order?

- Thyroid antibodies
 - Need to request TSH receptor antibodies specifically
 - Thyroid peroxidase antibodies not sensitive or specific enough to diagnose Autoimmune Hyperthyroidism (Graves)
 - TSH receptor antibodies = sensitivity 97% and specificity of 99%
- Only if TSH receptor antibodies are negative should a scintiscan be ordered
 - An Endocrinologist will usually have to order this
- Do not order a Thyroid Ultrasound in a hyperthyroid patient

Thyroid Scintiscans

- Diffuse Uptake
 - Autoimmune
- Nodular uptake
 - Autonomous nodule or multinodular goitre
- No uptake
 - Thyroiditis

Graves



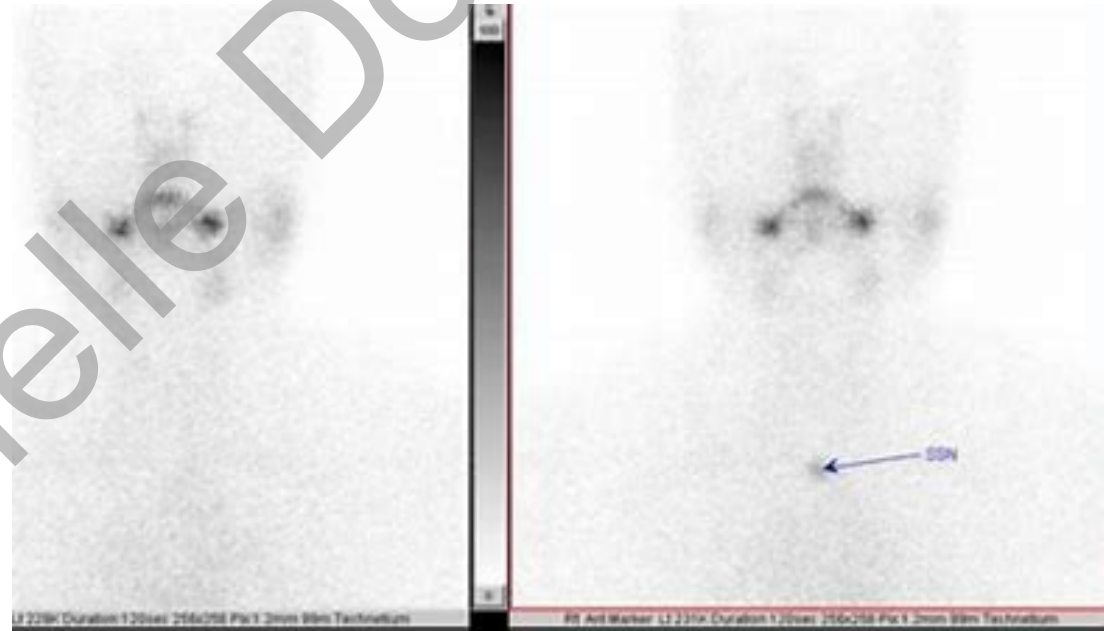
MNG



“Hot” Nodule



Thyroiditis



Longer term treatment

- Autoimmune Hyperthyroidism (Graves)
 - Carbimazole for 12-18 months
- Nodule or MNG
 - Definitive treatment with RAI usually required
- Thyroiditis
 - Symptomatic treatment, watch for hypothyroidism

Case 2

- A 23 year old woman comes to see you with ongoing hyperemesis. She is currently 9/40 pregnant.
- She is found to have the following TFTS:
 - T4 18.4 pmol/l (7.0 – 16.0)
 - TSH <0.01 mIU/L (0.3 – 5.0)
- What else do you want to know?

Gestational Hyperthyroidism

- Common, especially with hyperemesis gravidarum
- BHCG acts on TSH receptor to stimulate
- Initial response should be check thyroid antibodies including TSH receptor antibodies, and repeat TFTs in 2 weeks
- Should be discussed with an Endocrinologist about whether treatment is required
 - Generally hold off treatment, may be different if history of Thyroid disorders or very toxic
- Usually resolves by second trimester

Subclinical Hyperthyroidism

- All the same causes as overt hyperthyroidism
- No need to start medical treatment straight away
- Repeat in a month, then 3 monthly
- Check TSH receptor antibodies
- Thyroid scintiscan if these are negative
- Leave off treatment and refer to Endocrinology outpatients
- Reasons for treating long term?

Subclinical Hyperthyroidism

- Reasons for treating long term ?
 - Increased risk of osteopenia/osteoporosis and AF
 - To save ongoing monitoring of TFTS forever!

Case 3

- A 73 year old man complains of tiredness. His Thyroid function tests are below:
- T4 6.5 pmol/l (7.0 – 16.0)
- TSH 0.2 mIU/l (0.3 – 5.0)
- What should you do?

Central Hypothyroidism

- Repeat for confirmation
- Undertake rest of anterior pituitary hormone panel
- Refer to an Endocrinologist
 - Will need Pituitary MRI

Case 4

- A 65 year old woman reports tiredness and constipation. Amongst other things you check a calcium which is slightly high and then you repeat this alongside a PTH.
- Results are as follows:
 - Corrected calcium 2.75 mmol/l (2.15 – 2.65 mmol/l)
 - PTH level 12.9 pmol/l HIGH
- What next?

Primary Hyperparathyroidism

- **What you want to know:**

- Has it been high in the past?
- Kidney Stones?
- Fractures?
- Other family members?
- Vitamin D status?
- Thiazides?
- Calcium supplements?

- **What you want to do:**

- Check renal function
- Ideally check Vitamin D level
- Spot Urine Calcium:Creatinine Ratio
 - To Exclude FHH
- DEXA
- Stop Thiazides

Primary Hyperparathyroidism

- Indications for referral for consideration of definitive treatment with Surgery
 - Age < 50 years
 - Corrected Calcium $\geq 2.9 - 3.0$ mmol/L
 - Renal Calculi
 - ? Significant Osteoporosis – debateable
- Otherwise just monitoring of serum calcium, Vitamin D supplementation, avoidance of thiazides and dehydration, serial DEXA monitoring +/- Bisphosphonates as indicated

Case 5

- A 42 year old woman has an MRI Brain done as part of an ACC assessment for a prolonged concussion syndrome. The MRI shows an incidental 11mm pituitary adenoma.
- What do you want to know?
- What should you do?

History

- Change in vision
- Symptoms or signs suggestive of Cushing's, Acromegaly, Prolactinoma
- Galactorrhoea, amenorrhoea and erectile dysfunction can be most helpful

Pituitary Incidentaloma

- Anterior Pituitary Hormones
 - 9am cortisol
 - T4 and TSH
 - LH, FSH – either oestradiol or testosterone
 - IGF1
 - Prolactin
 - Macroprolactin if elevated
- Serum osmolarity and Na
- Formal Visual Field testing
- Refer to Endocrinology
- Surgery if: Cushing's, Acromegaly, Non functioning adenoma with visual field compromise
- Cabergoline for all prolactinomas

Case 6

- A 54 year old man undergoes a trauma series CT scan after a moderate impact MVA. This demonstrates a 32mm left adrenal lesion and the surgical house surgeon asks you to follow this up.
- What should you do?

Adrenal Incidentaloma

- **Is it functional?**
 - Plasma Metanephrines
 - Plasma Renin:Aldosterone ratio
 - Beware interfering medications
 - Switch to Doxazocin or Verapamil for 2 weeks before testing
 - Stop spironolactone 4 weeks before
 - 1mg overnight Dexamethasone suppression test
 - Preferred
 - Following the above on a different day
 - OR 24 hour urine cortisol
 - COCP, very high BMI
- **Is it benign radiologically?**
 - CT usually best modality.
 - Endocrine team can usually have this reviewed to see whether needs a dedicated Adrenal CT
 - Looks at Hounsfield units and contrast washout
 - Low Hounsfield units < 10 usually benign adenomas
 - Rapid washout of contrast with adenomas

Adrenal Incidentaloma

- If non functional, radiologically benign and less than 4cm
 - No further follow up at all required

The not so new Diabetes Medications....

New to New Zealand but not the world...

- GLP1RA agonists available since as far back as 2005
- Commonly used in clinical practice since approximately 2009
- Empagliflozin in use since 2011
 - Landmark EMPA REG 2015
- Dulaglutide in use since 2014

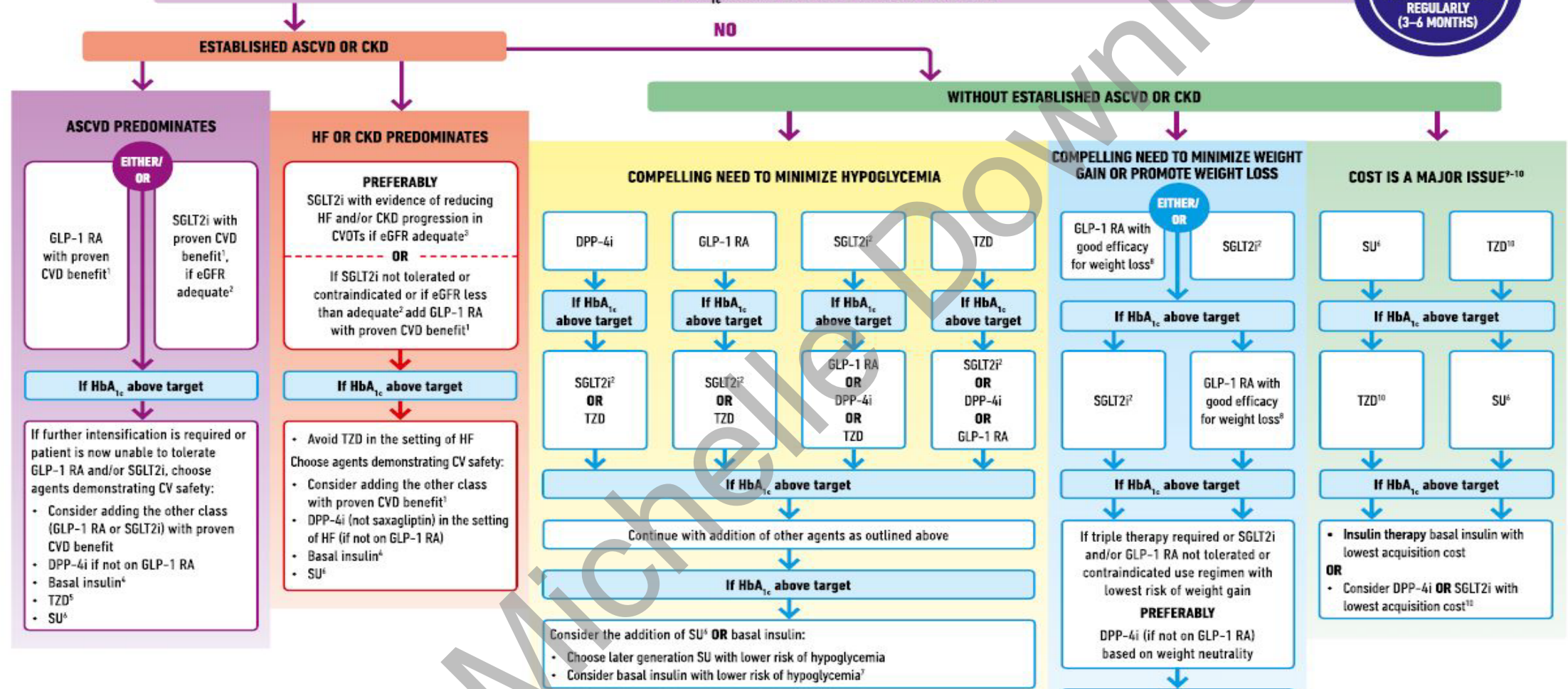
Benefits

- Reduction in cardiovascular disease, stroke and renal disease independent of glycaemic control
- Weight loss
- No Hypoglycaemia when used as monotherapy

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

**FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA_{1c} ABOVE TARGET PROCEED AS BELOW**

TO AVOID CLINICAL INERTIA
REASSESS AND
MODIFY TREATMENT
REGULARLY
(3–6 MONTHS)



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety

5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

<https://t2dm.nzssd.org.nz/>

MANAGEMENT ALGORITHM

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 (for all) 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 contraindications

(HbA1c needs to be >53 mmol/mol for funding)

NO

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

(HbA1c needs to be >53 mmol/mol for funding)

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

ADDITIONAL CONSIDERATIONS

Risk of hypoglycaemia

Mean ↓ in HbA1c (mmol/mol)

Independent cardiorenal benefits

Effect on weight

Funded

Preferred 2nd line agents

SGLT2i[†]

GLP1RA[†]

DPPiVi

3rd line agents

TZD

SU

Insulin

Rare

Rare

Rare

Rare

Yes

Yes

6 - 13

15

5 - 10

15

15

Any

Yes

Yes

No

Yes

No

No

↓

↓↓

↔

↑

↑

↑

SA only[†]

SA only[†]

Yes

Yes

Yes

Yes

[†]SA criteria for SGLT2i and GLP1RA (all required and same for both classes)

- Patient has type 2 diabetes with an HbA1c > 53 mmol/mol despite > 3 months

NNT for 5 years for Benefits

	Empagliflozin	Dulaglutide
Primary Prevention of CVD	No conclusive evidence to date	60 (predominantly stroke)
Secondary Prevention of CVD/MACE	23	18
Primary Prevention of renal failure	No evidence to date	No evidence to date
Secondary prevention of renal failure	26	Reduced progression only to date
Heart failure hospitalisation and death	17 (if high risk)	No evidence to date

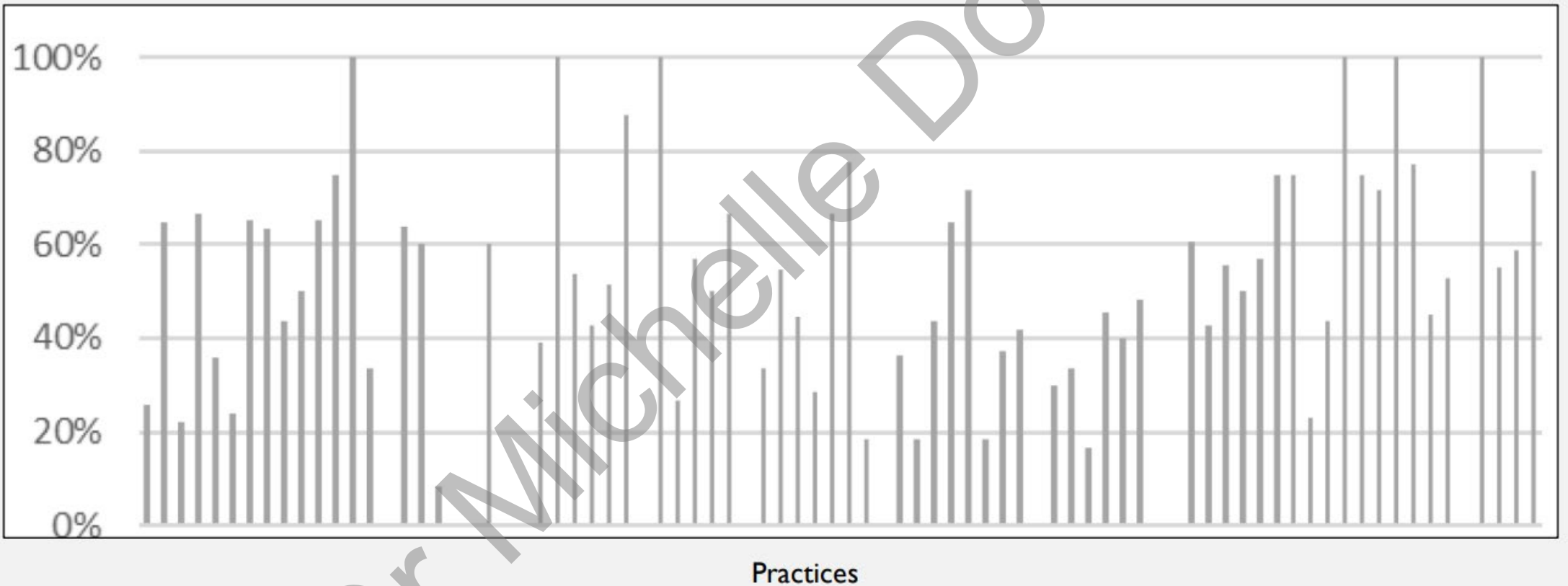
Risk of DKA with Empagliflozin

- 40, 523 dispensed Empagliflozin between 1 Feb – 31 Oct 2021
 - 15,673 European
 - 10,888 Maori
 - 8157 Pacific peoples
 - 4724 Asian
- 94 admissions with DKA temporally associated with Empagliflozin use
 - Overall incidence 0.23% = 1 in 500
 - More common in Europeans and those aged < 30 years
- **DO NOT prescribe SGLT2 inhibitors to those with Type 1 Diabetes/insulin deficiency. If in doubt, a c –peptide can be useful.**

What has uptake been like?

- Up to date Waikato Data courtesy Dr Ryan Paul
- Over about 80 practices
 - 66.5% of those with renal disease/CVD/ or CV risk > 15%
 - 6 practices have 100% of those eligible prescribed
 - 12 practices have no patients been prescribed
- No increase in those reaching HbA1c < 53 mmol/mol
 - Average 38.5%
- Prescribing in Maori and Pacific about 10% higher than in European

What has uptake been like?



Update on the evidence

- Evidence for secondary prevention of CV events by SGLT2i and/or GLP 1RA has strengthened
- Conclusive evidence of either agent in primary prevention trials still awaited
- Real world analysis suggest may be just as effective in primary prevention
- Dulaglutide safe and effective in 10-17 year olds
- SGLT2i (particularly empagliflozin) now one of the four pillars of heart failure management both in people with Diabetes and without

Update to the NZSSD Guidance

- Empagliflozin can be used if eGFR > 20 ml/min as per KDIGO guidance
- Dulaglutide will be preferred second line treatment in 10-17 year olds
- A 2nd 1.5 mg dulaglutide injection can be added if HbA1c above target and tolerating well
 - Works best in twice weekly split dose
 - No extra costs to patients and pharmacies get reimbursed for both injections
 - Wording will be that this is off-label but consistent with best practice

Dulaglutide Supply

- Likely global shortage of GLP1RA due to increasing off-label use for obesity
- Aotearoa NZ vulnerable due to small market and sole supplier
- Lilly have assured NZ and Australia will be prioritised and currently no supply issues
 - Likely to be though by early next year
- Widespread messaging from Pharmac to consider not prescribing and use SGLT2i instead
 - Wholesalers are limiting supplies to individual pharmacies
- NZSSD stance to continue with best practice
- NZSSD Working with Pharmac to consider options
- Reasonable to dispense monthly

Clinical Pearls

- Offer people the choice of self funding one of the newer agents second line
 - Empagliflozin cheaper for better to use SA for GLP1 RA
 - Cheaper if patients can split a 25 mg tablet in half
 - Patients should shop around pharmacies if self funding
- Decrease sulfonylurea dose by 50% and insulin dose by 20% if HbA1c < 75 mmol/mol when starting
- Significant adverse effects from GLP1 RA more common than reported but still probably up to 10%
 - Antiemetics and anti-diarrhoeals work well short term
- No apparent difference in side effects between 10mg and 25 mg per day of SGLT2i
- Limited HbA1c lowering effect so still a need for other options often
 - SGLT2i 7-9 mmol/mol, GLP1RA 6- 15 mmol/mol
- Remember education re symptoms of DKA and peri-procedures for SGLT2i

Question Time

