Panel Discussion:

Critical role of DPP4i in Type 2 DM:

Case Scenario approach

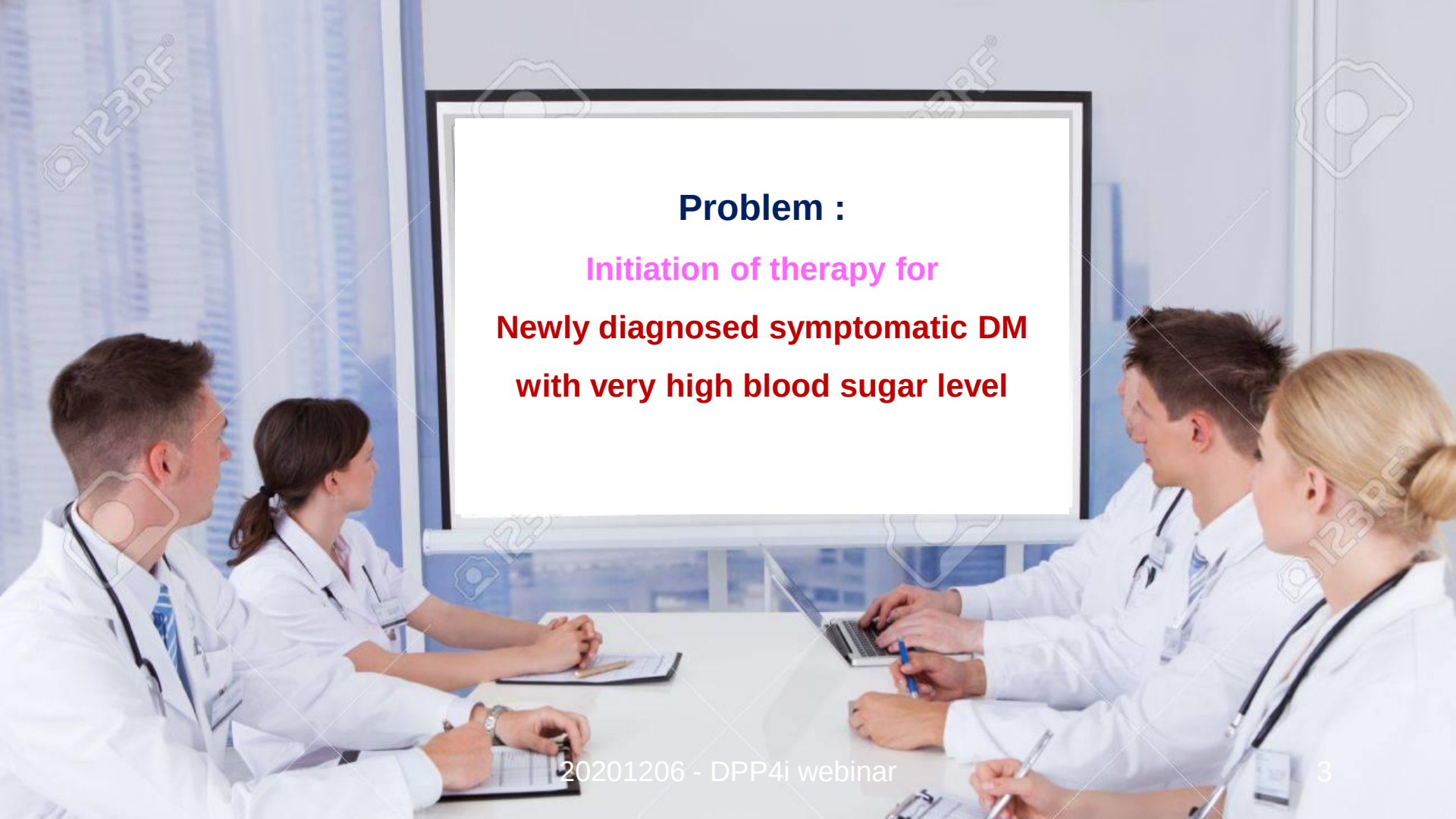
UMMG

Prof Zaw Lynn Aung

Scenario - A 35 year old male patient presents with polyuria, polydipsia and un-intentional weight loss. His casual blood sugar is 400 mg/dL. Recent HbA1C is 10.1%.

How would you manage his blood sugar?

Prof Thein Myint


Problem :
Initiation of therapy for
Newly diagnosed symptomatic DM
with very high blood sugar level

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2020

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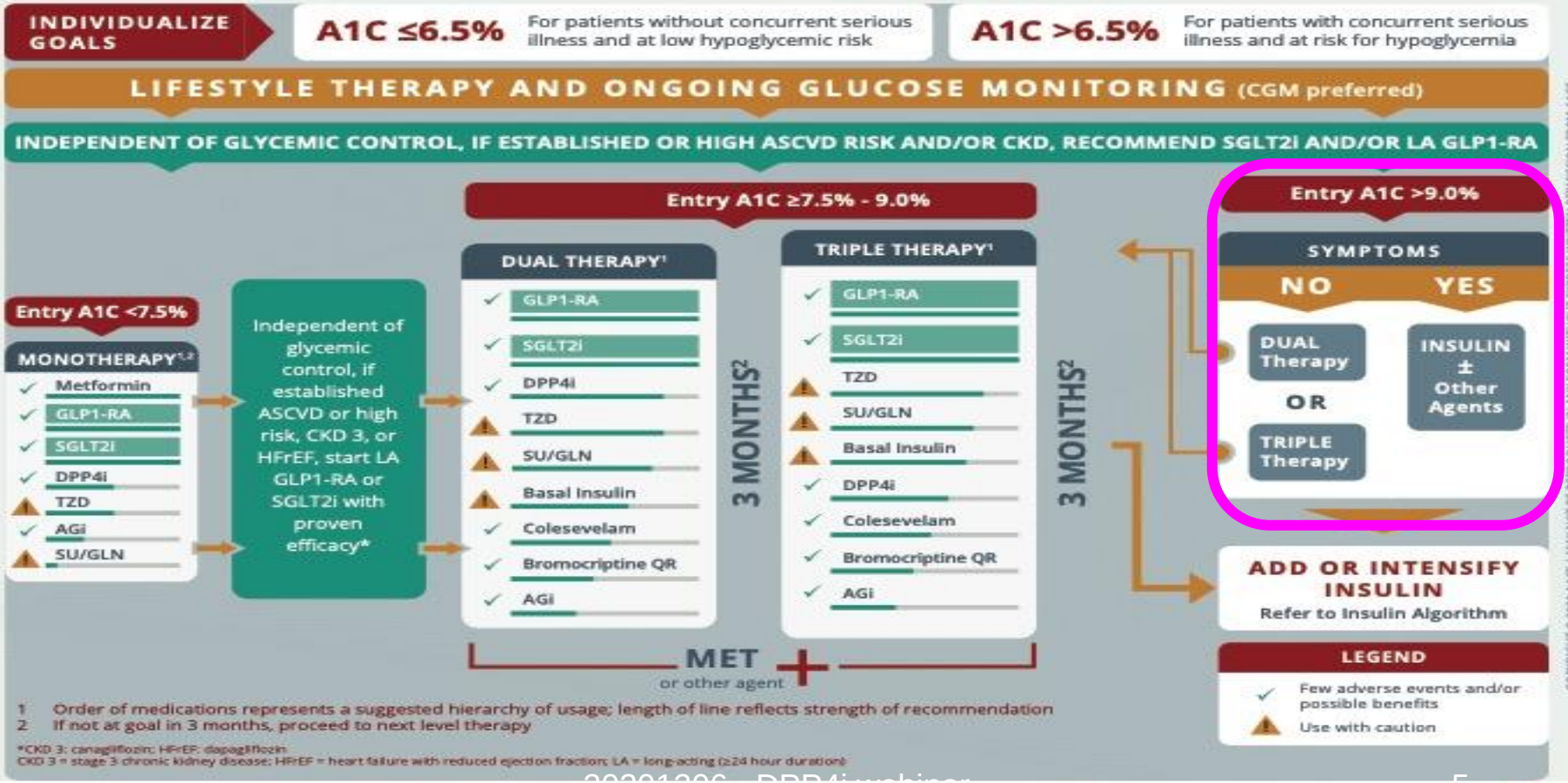
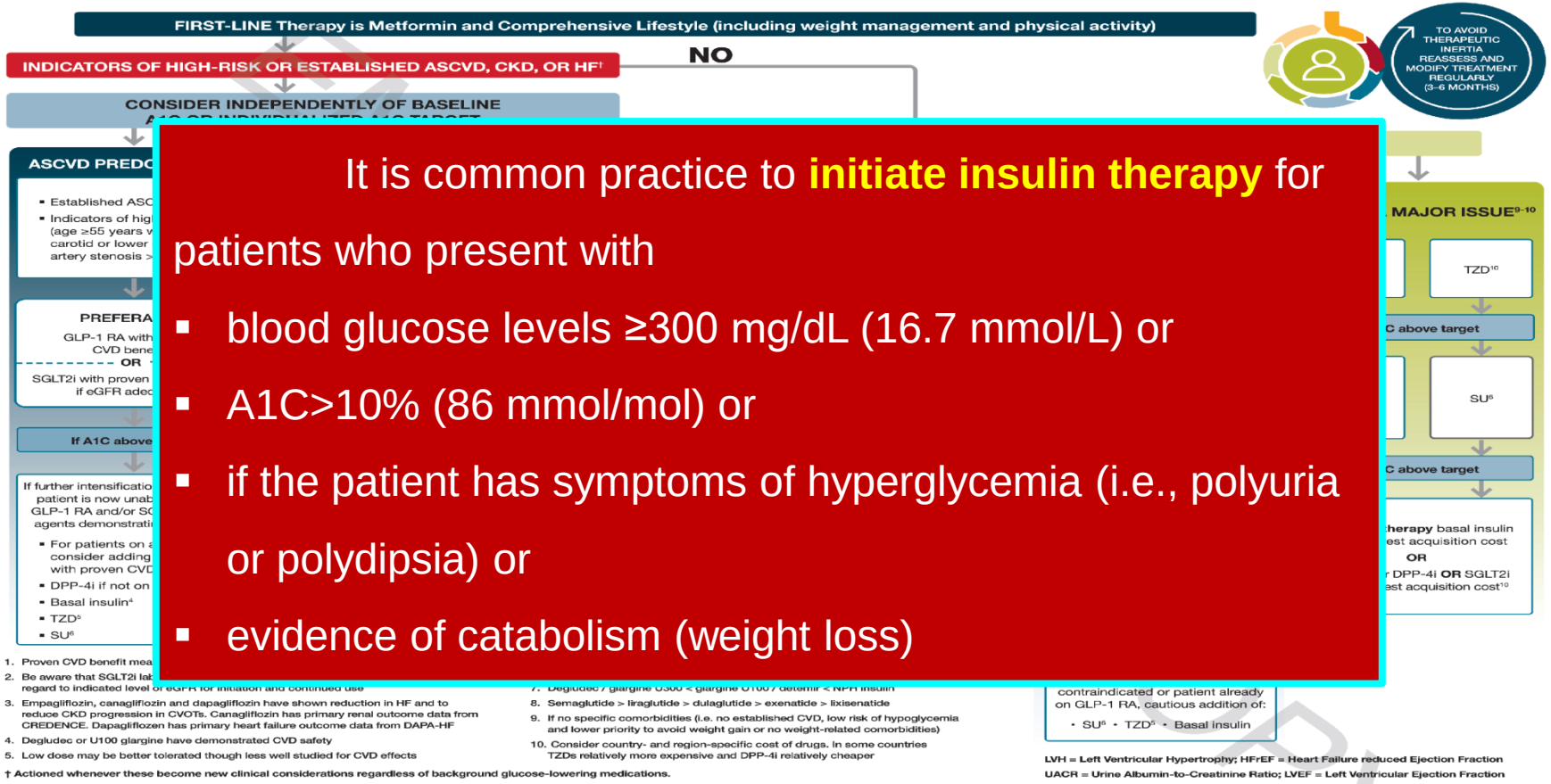
GLYCEMIC CONTROL ALGORITHM



How can we choose the suitable anti-hyperglycaemic drug

American Diabetes Association. 2020

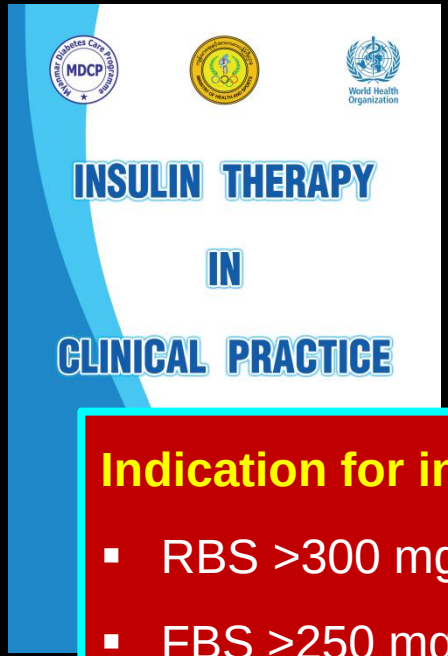


It is common practice to **initiate insulin therapy** for patients who present with

- blood glucose levels ≥300 mg/dL (16.7 mmol/L) or
- A1C>10% (86 mmol/mol) or
- if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia) or
- evidence of catabolism (weight loss)

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

Myanmar Guideline ?



SUMMARY OF INSULIN THERAPY ALGORITHM

Indications for Insulin Therapy in Type 2 Diabetes

(1) Newly diagnosed patients with RBS > 300mg/dl or **FBS >250mg/dl** or HbA1C of > 10% with severe osmotic symptoms such as polyuria, polydipsia, dehydration

(2) Type 2 DM patients with OAD failure (Poor glycemic control with two or three OAD over three months, without getting target HbA1C or HbA1C >7%

Indication for insulin therapy for newly diagnosed T2D

- RBS >300 mg/dL (16.7 mmol/L) or
- FBS >250 mg/dL
- A1C>10% (86 mmol/mol)
- With Severe osmotic symptoms (i.e., polyuria or polydipsia, dehydration)

Approach to clinical problem

- 35 year old patient with newly diagnosed DM
- RBS 400 mg/dL
- HbA1C – 10.1%
- Osmotic symptoms (+)
- Evidence of catabolism (+)

Initiation of pharmacological therapy

- Should start with insulin

Further consideration

- Insulin for life ? OR change to OADs later ?
- Type of DM ? – T2D OR other type ?

Approach to clinical problem

Further consideration

- Type of DM ? – T2D OR other type ?
- **LADA** - *latent autoimmune diabetes in adults*
  - 4% – 14% of newly diagnosed T2D are LADA
- **When should we consider LADA**
  - Age of diagnosis >30 years
  - Not obese
  - unable to manage their diabetes symptoms with oral medications or lifestyle and dietary changes.
  - test positive for at least one of the antibodies found in T1D (e.g., GAD Ab)
  - ↓ c-peptide

Initiation of insulin in newly diagnosed DM

- **Initiation of insulin in newly diagnosed DM**
  - A1C > 10 [OR]
  - RBS > 300 mg/dL [OR]
  - FBS >250 mg/dL
  - **With symptoms**
- **Further consideration**
  - T2D? OR LADA?

Thank You

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Prof Zaw Lynn Aung

Scenario - A 60 year old male patient with known T2DM come to your clinic for glycaemic control. He is taking Gliclazide MR 60 mg OD and metformin 500 mg bid. He lost follow-up for two years. His recent HbA1C is 8.5% and his serum creatinine is 350 µmol/L (eGFR = 16.6 ml/min/1.73m^2)

How would you manage his blood sugar?

Prof Thein Myint


Problem :
Glycaemic management in CKD

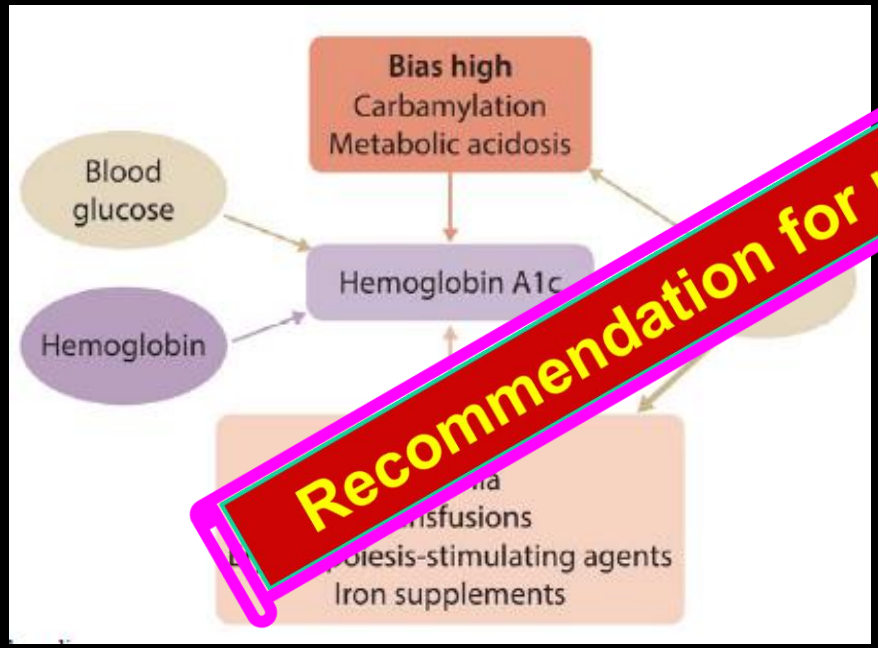
Glycaemic management in CKD

Mainly four components

1. Monitoring
2. Glycaemic target
3. anti-hyperglycaemic intervention
4. Others – lifestyle, self management and optimal models of care

Monitoring of glycaemic control

- **Recommendation 2.1.1.** We recommend hemoglobin A1[illegible] to monitor glycemic control in patients with diabetes and CKD *(1[illegible]*



Recommendation for monitoring - HbA1C

Alt[illegible] – Glycated albumin and [illegible]mine

- [illegible]eflect glycemia in 2-4 weeks
  - Evidence – (observational studies) glycated albumin is associated with all-cause and cardiovascular mortality in patients with hemodialysis.
  - However, the glycated albumin and Fructosamine levels are biased by hypoalbuminemia, a common condition in patients with CKD

Monitoring of glycaemic control

Practice Point

- Frequency of Monitoring by HbA1c – twice per year (four times per year if the glycemic target is not met or after change in anti-hyperglycemic therapy)
- Accuracy and precision of HbA1c measurement - low reliability with advanced CKD, particularly among patients treated by dialysis
- A continuous glucose management indicator (CGMI) – can be used when HbA1c is discordant with directly measured blood glucose levels or clinical symptoms.
- Daily SMBG or CGM – may help to prevent hypoglycemia and improve glycemic control when anti-hyperglycemic therapies associated with risk of hypoglycemia are used.
- For patients with CKD and T2DM without daily SMBG or CGM - anti-hyperglycemic agents with a lower risk of hypoglycemia are preferred (in doses appropriate for the level of eGFR)
- CGM devices with multiple functionalities (e.g., CGMI, real-time and flash glycemia monitoring)- advantages for certain patients, depending on their values, goals, and preferences.

Monitoring of glycaemic control

Recommendation – HbA1c

Practice Point

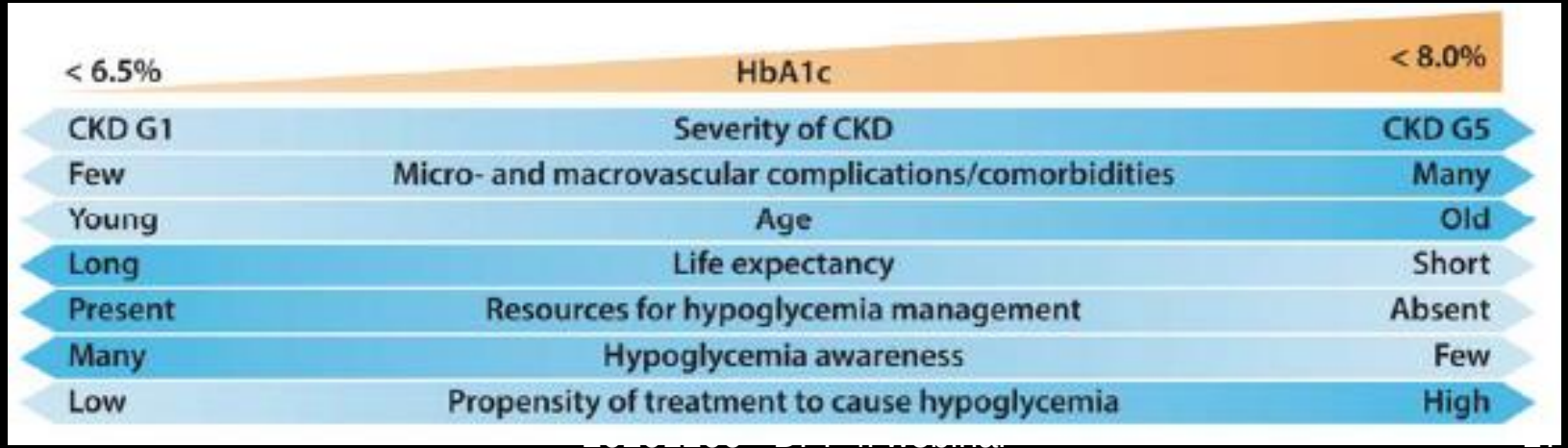
- **HbA1c frequency** → 2/ year (4/year if the target is not met or change in therapy)
- If **A1C discordant** with BG or clinical symptoms (esply in dialysis) → use CGM or daily SMBG
- **Daily SMBG or CGM** → helpful for anti-hyperglycemic therapies with risk of hypoglycemia
- **without daily SMBG or CGM** → anti-hyperglycemic agents with a lower risk of hypoglycemia are preferred (in doses appropriate for the level of eGFR)

Antihyperglycemic agents	Risk of hypoglycemia	Rationale for SMBG / CGM
Insulin/ SU/ meglitinides	Higher	Higher
Metformin / SGLT2i/ GLP-1RA/ DPP-4i	Lower	Lower

Glycaemic Target

Recommendation : individualized HbA1c target (from <6.5% to <8.0%) in patients with diabetes and non-dialysis dependent CKD *(1C)*.

- *For patients where prevention of complications is the key goal, **a lower HbA1c target (e.g., <6.5% or <7.0%)** might be preferred,*
- *while for those with multiple co-morbidities or increased burden of hypoglycemia, **a higher HbA1c target (e.g., <7.5% or <8.0%)** might be preferred.*



Choice of anti-hyperglycemic agents

Antihyperglycemic agents	Risk of hypoglycemia	Rationale for SMBG / CGM
Insulin/ SU/ meglitinides	Higher	Higher
Metformin / SGLT2i/ GLP-1RA/ DPP-4i	Lower	Lower

Insulin

- renal failure advances → insulin clearance ↓→ dose ↓ to prevent hypoglycemia.
- Dose adjustment - (independent of the insulin type)
  - GFR >50 mL/min → no dose adjustment
  - GFR is between 10 and 50 mL/min → insulin ↓ to 75% of the total daily dose
  - GFR of <10 mL/min → insulin ↓ to 50%
- Type
  - All types of insulin can be used
  - Analogues – better control

Relationship among the drugs, dose and creatinine clearance

Drugs	Dose Adjustment Based on eGFR
Metformin	US FDA: CI – serum creatinine >1.5 mg/dL (for men) and >1.4 mg/dL (women) UK guideline - allows when eGFR >30 mL/min/1.73 m^2 KDIGO - recommends when eGFR >45 mL/min/1.73 m^2
Sulfonylureas	
Glipizide	No dose adjustment required
Glimepiride	Initiate conservatively at 1 mg daily Avoid use if eGFR <60
Gliclazide	↓ dose if eGFR <30 ; Not recommended if eGFR <15
Glyburide or glibenclamide	Avoid if eGFR <60

Risk of hypoglycaemia

- ❑ Glyburide or glibenclamide > Glimepiride > Gliclazide

Relationship among the drugs, dose and creatinine clearance

Drugs	Dose Adjustment Based on eGFR
Meglitinides	
Repaglinide	Initial dose of 0.5 mg before meals when eGFR <30
Nateglinide	Caution when used with eGFR <30 ; Initiate with 60 mg before meals
α-Glucosidase inhibitors	
Acarbose/ Miglitol	▪ Avoid if eGFR <30
TZDs	
Pioglitazone	▪ No dose adjustment required ▪ Use with caution in patients with CKD and hypervolemia

Relationship among the drugs, dose and creatinine clearance

Drugs	Dose Adjustment Based on eGFR
GLP-1RA	

			Primary outcome		Kidney outcomes		
Drug	Trial	Kidney-related eligibility criteria	Primary outcome	Effect on primary outcome	Effect on albuminuria or albuminuria-containing composite outcome	Effect on GFR loss*	Adverse effects
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	↓	ND	None notable
Liraglutide	LEADER	eGFR ≥ 15 ml/min/1.73 m²	MACE	↓	↓	ND	GI
Semaglutide	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER-6	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	None notable
Albiglutide	HARMONY	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	NA	NA	None notable
Dulaglutide	REWIND	eGFR ≥ 15 ml/min/1.73 m²	MACE	↓	↓	↓	GI

Relationship among the drugs, dose and creatinine clearance

Drugs	Dose Adjustment Based on eGFR
SGLT2i	

			Primary outcome		Kidney outcomes		
Drug	Trial	Kidney-related eligibility criteria	Primary outcome	Effect on primary outcome	Effect on albuminuria or albuminuria-containing composite outcome	Effect on GFR loss*	Adverse effects
SGLT2 inhibitors							
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
Canagliflozin	CANVAS trials	eGFR ≥ 30 ml/min/1.73 m²	MACE	↓	↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR > 300 mg/g and eGFR 30–90 ml/min/1.73 m²	Progression of CKD[†]	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥ 60 ml/min/1.73 m²	MACE composite of HF and cardiovascular death[‡]	ND/↓	↓	↓↓	Genital mycotic infections, DKA

Relationship among the drugs, dose and creatinine clearance

Drugs	Dose Adjustment Based on eGFR
DPP-4i	Sitagliptin and saxagliptin dose adjustment required based on eGFR
Sitagliptin	eGFR >50 → 100 mg/day; eGFR 30–50 → 50 mg/day; eGFR <30 →25 mg/day
Linagliptin	No dose adjustment required

Drug	Trial	Kidney-related eligibility criteria	Primary outcome	Effect on primary outcome	Effect on albuminuria or albuminuria-containing composite outcome	Effect on GFR loss*	Adverse effects
DPP-4 inhibitors							
Saxagliptin	SAVOR-TIMI 53	eGFR ≥ 15 ml/min/1.73 m²	MACE	ND	↓	ND	HF
Alogliptin	EXAMINE	Patients treated with dialysis excluded	MACE	ND	NA	NA	None notable
Sitagliptin	TECOS	eGFR ≥ 30 ml/min/1.73 m²	MACE	ND	NA	NA	None notable
Linagliptin	CARMELINA	eGFR ≥ 15 ml/min/1.73 m²	Progression of CKD†	ND	↓	ND	None notable

Approach to clinical problem

- 60 year old patient with type 2 DM
- Uncontrolled – (HbA1C - 8.5%)
- CKD – (eGFR – 16.6)
- Current medications
  - Gliclazide + metformin

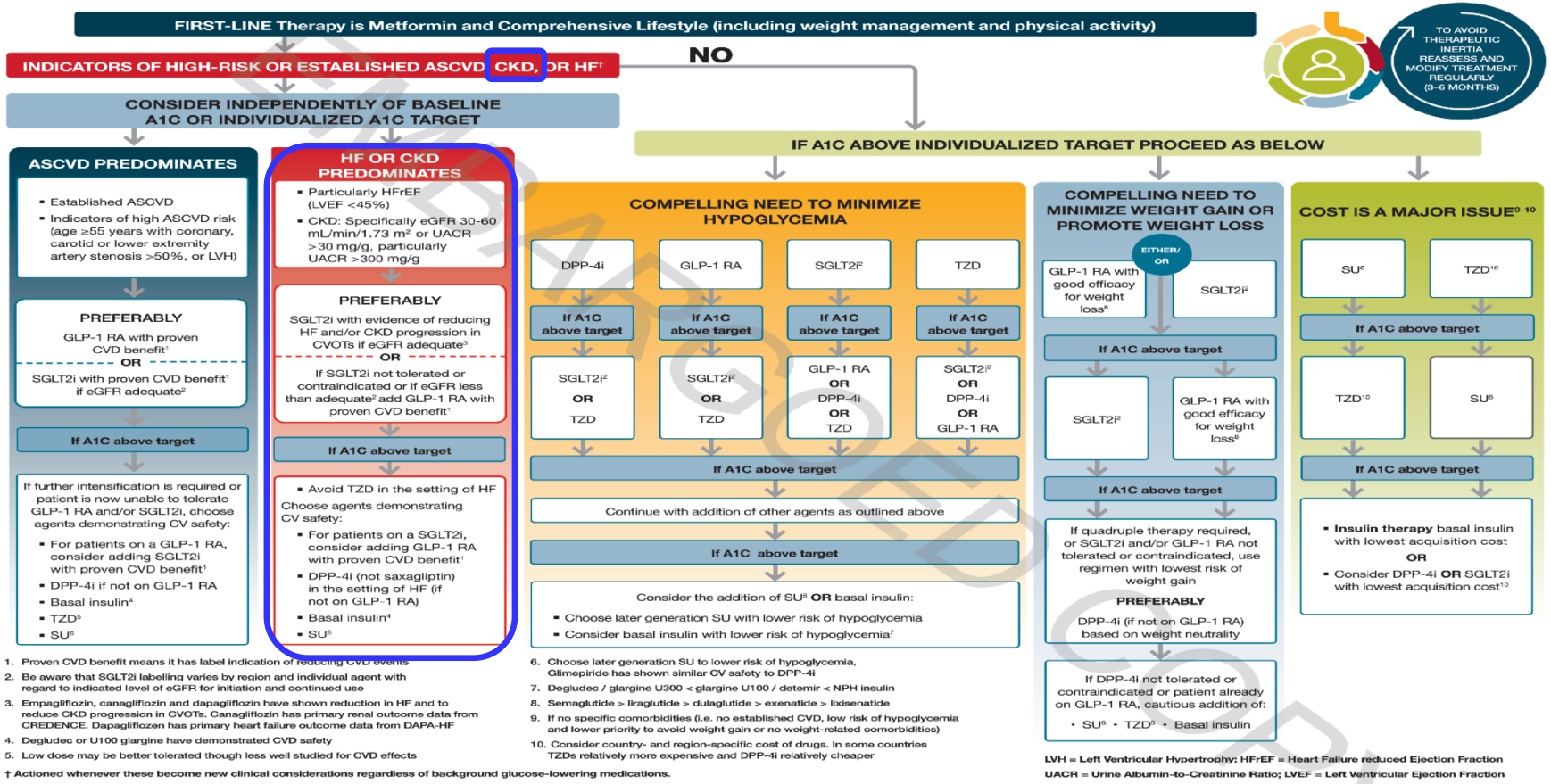
Target
- HbA1C - 6.5 – 8
- Now – 8.5%
- Need to adjust

Monitoring
- CGM? or daily SMBG?

Drug choice
- Depends on availability of CGM / daily SMBG

How can we choose the suitable anti-hyperglycaemic drug

American Diabetes Association 2020



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
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 to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
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

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Figure 9.1—Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies and colleagues (33,34).

Rational choice of anti-hyperglycaemic agent

First

- eGFR < 30 → omit metformin

Next

For SU (Gliclazide)

- If patient can follow daily SMBG → can continue
- If patient cannot follow daily SMBG → change to drugs withh low risk of hypoglycaemia

Rational choice of anti-hyperglycaemic agent

Next drug

- for SGLT-2i → eGFR is NOT adequate (<30)
- If possible – **GLP-1RA** → suitable
- → BUT feasibility ? (injection?/ cost?/ SE?)
- **TZD ?** → if fluid overload (+) → NOT suitable
- → risk of oedema (+)
- **DPP4i ?** → most suitable (low risk of hypo/ oral)
  - which DPP4i ?
    - DPP4i with renal safety and renal evidence if possible
    - **Linagliptin – my choice**
    - → no dose adjustment, has renal evidence (CARMELINA)

Management of DM with CKD

- Monitoring by HbA1C
- Target – individualized

  [<6.5% - <8.0%]
- Drug choice depends on
  - eGFR
  - Risk of hypoglycaemia
  - Feasibility – price, route etc

Thank You

Professor Thein Myint

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