Critical Role of DPP4 Inhibitors in Type 2 DM

Associate Professor Hein Yarzar Aung

Medical Ward

West Yangon General Hospital

Scenario 1

Initial Pharmacologic Approach

Scenerio 1

- A 47 year old obese gentle man
  - fasting plasma sugar level of 115mg%
    - he was anxious about the presence of diabetes mellitus after hearing that his friend recently died of DM and its complications
    - he denied osmotic symptoms like polyuria and polydypsia (asymptomatic)
  - How will you approach?

Diagnosis of Diabetes

- For decades, the diagnosis of diabetes was based on **plasma glucose** criteria

- **Hb A1C** as a diagnostic criteria
  - IDF and EASD recommended in 2009
  - ADA recommended in 2010

Criteria for the Diagnosis of Diabetes

A1C ≥6.5% (using a method that is NGSP (National Glycohemoglobin Standardization Program) certified and standardized to the DCCT assay)

or

FPG ≥126 mg/dL (7.0 mmol/L)

or

2-h plasma glucose ≥200mg/dL (11.1mmol/L) during an OGTT

or

Random plasma glucose ≥200 mg/dL (11.1 mmol/L)

Criteria for the Diagnosis of Diabetes

- **WHO**
  - In the absence of symptoms, confirm with repeat testing
- **ADA**
  - In the absence of unequivocal hyperglycaemia, confirm with repeat testing

Prediabetes

1. **IFG**

   FPG 100-125 mg/dL (5.6-6.9 mmol/L)

2. **IGT**

   2-h OGTT 140-199 mg/dL (7.8-11.0 mmol/L)

3. **Hb A1C**

   5.7-6.4%

Scenerio 1 Cont.

- after the diagnosis of prediabetes
  - he asked about the possible preventive measures not to develop diabetes mellitus in future

Prevention/Delay of Type 2 Diabetes in Patients with Prediabetes

- Referral to an effective ongoing support program
- Target **weight loss of 7%** of body weight
- Increasing physical activity
  - at least **150 min/week** of moderate activity such as walking
- At least **annual monitoring** for the development of diabetes

- RCTs have shown that **intensive lifestyle modification** programs were very effective
  - 58% reduction in development of type 2 diabetes after 3 years

Metformin for prevention of type 2 diabetes

- may be considered in those with prediabetes

- especially for those with
  - BMI >35 kg/m^2
  - Women with prior GDM
  - Age <60 years

ADA 2012 - 2020

Scenerio 1 Cont.

- He didn’t want to take any medications
- But he attended the follow up clinic regularly
- Whenever he attends the clinic, his blood sugar testing has been more or less satisfactory

Scenerio 1 Cont.

- After some years
  - this patient failed to follow the instructions to prevent the development of diabetes mellitus
  - he has developed overt diabetes mellitus
- How will you start treatment?
- His BMI was 33

Initial Evaluation

- A complete medical evaluation should be performed to …
  - classify the diabetes
  - detect diabetic complications
  - review previous medications and associated risk factors in patients with established diabetes
  - assist in formulating a management plan, and
  - provide a basis for continuing care

Management

- People with diabetes should receive medical care from a ***physician-coordinated*** team which may include
  - physicians
  - general practitioners
  - nurses
  - dietitians
  - pharmacists and
  - mental health professionals

Newly Diagnosed Diabetes Mellitus

- 50% can be managed by Dietary Measure
- 25% OAD
- 25% Insulin

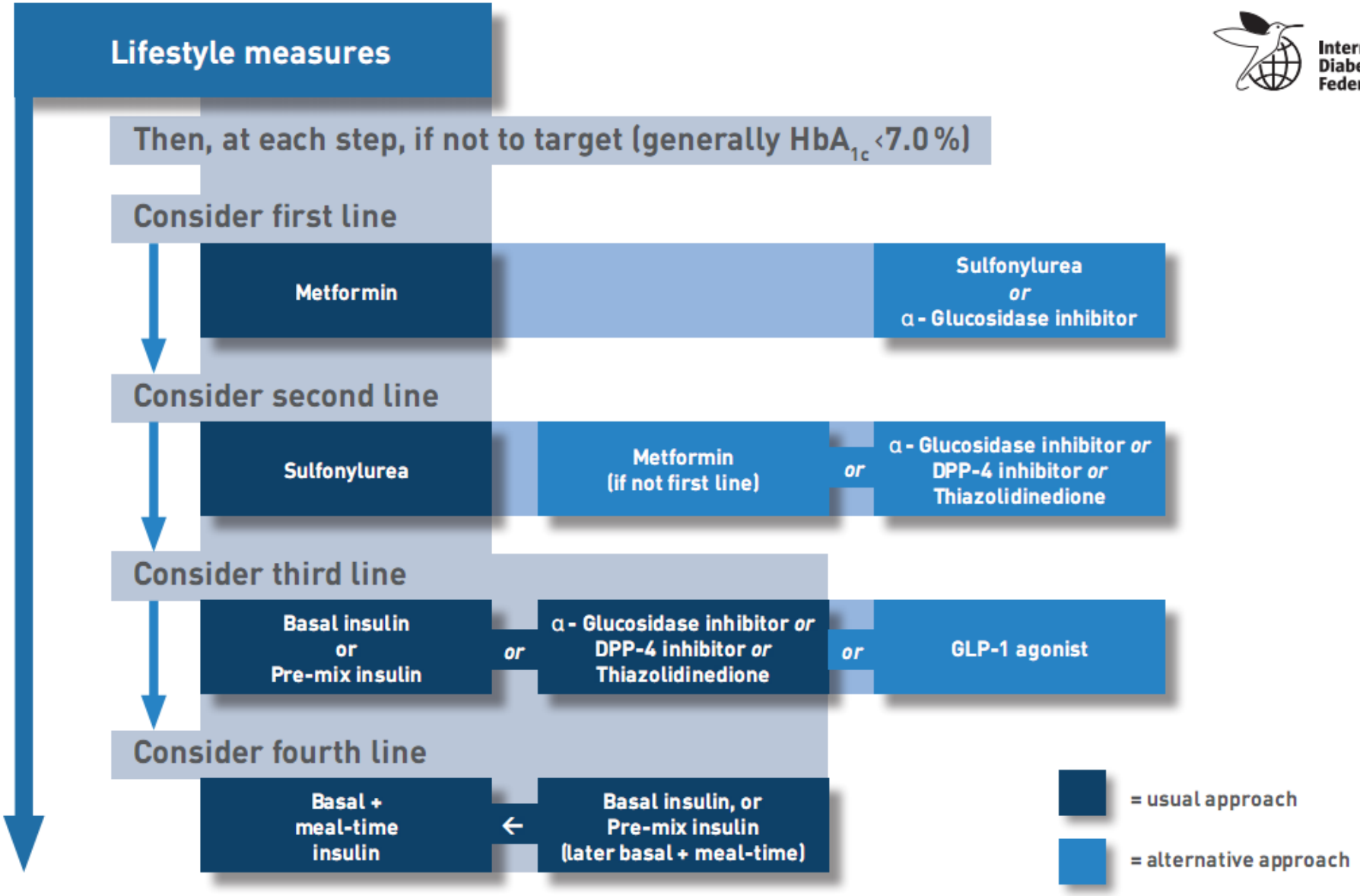
MNT – **Medical Nutrition Therapy**

– Patients with prediabetes or diabetes should receive **individualized MNT**

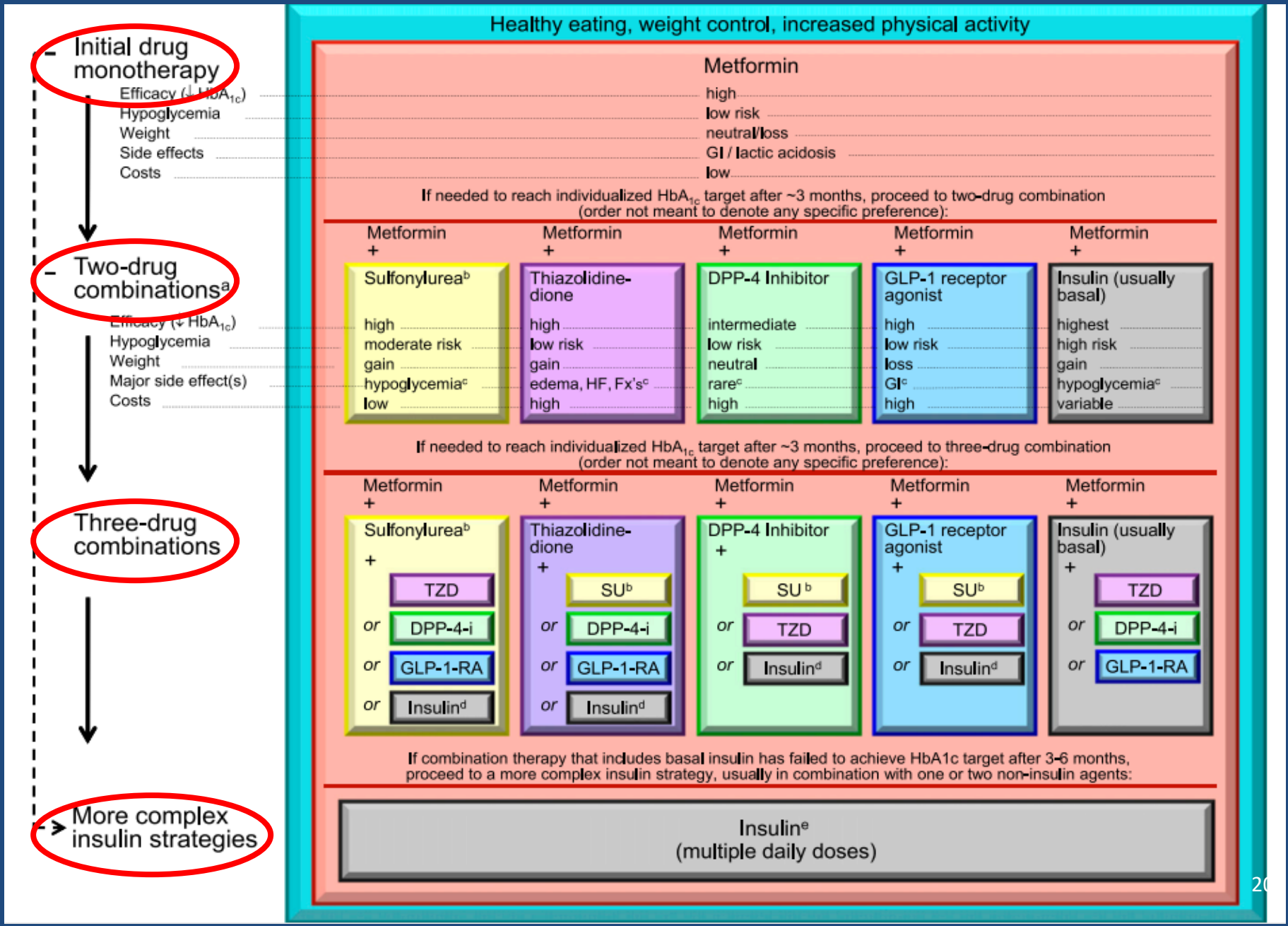
– Preferably provided by a registered **dietitian** familiar with the diabetes MNT

Glucose lowering medications

IDF Treatment Algorithm for People with Type 2 Diabetes

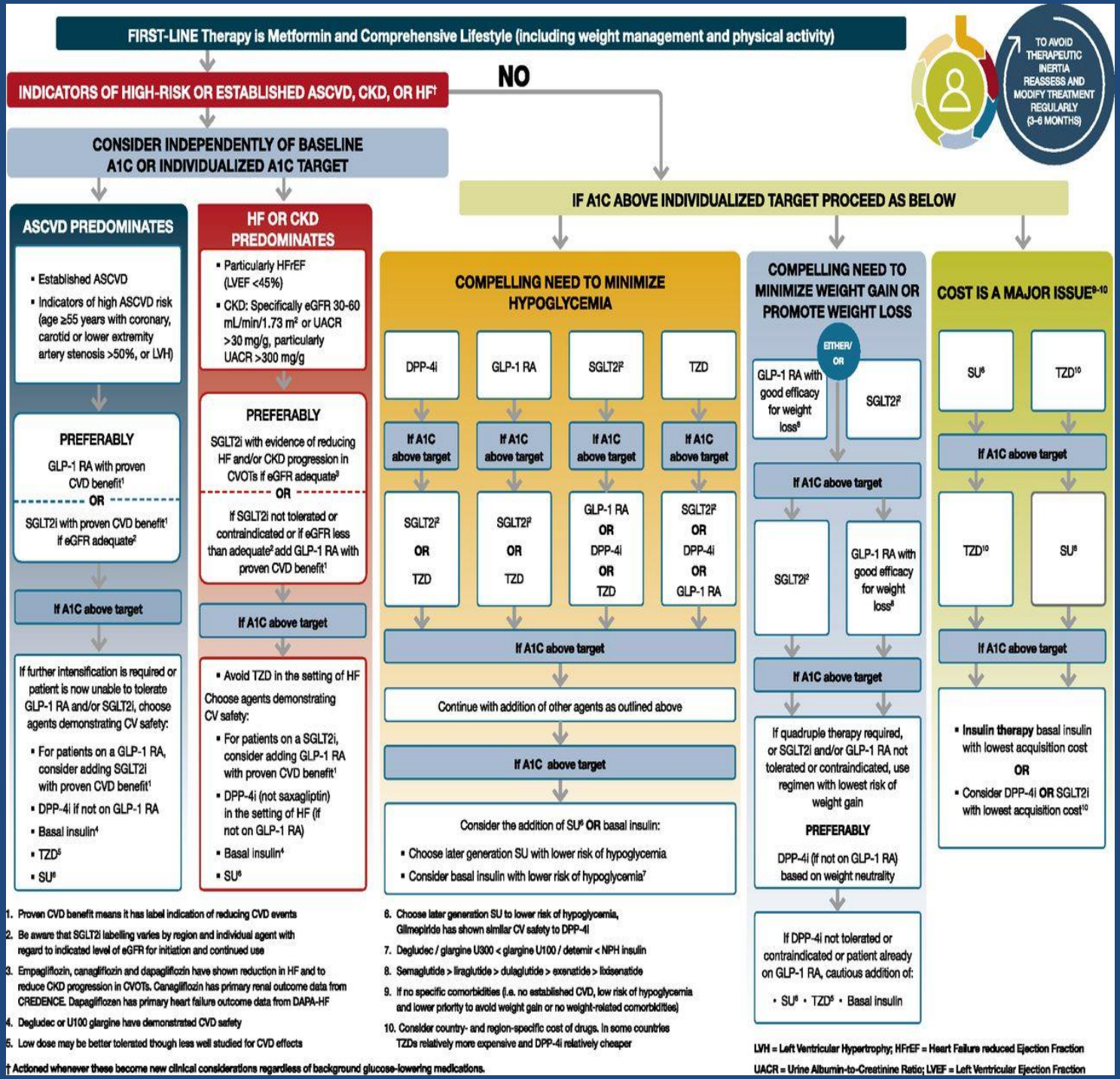


Previous ADA/EASD consensus statement



ADA 2020

Glucose-lowering Medication in Type 2 Diabetes: Overall Approach



Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2020. Diabetes Care* 2020;43(Suppl 1):S98-S110

Glucose lowering medication in type 2 DM

Overall approach

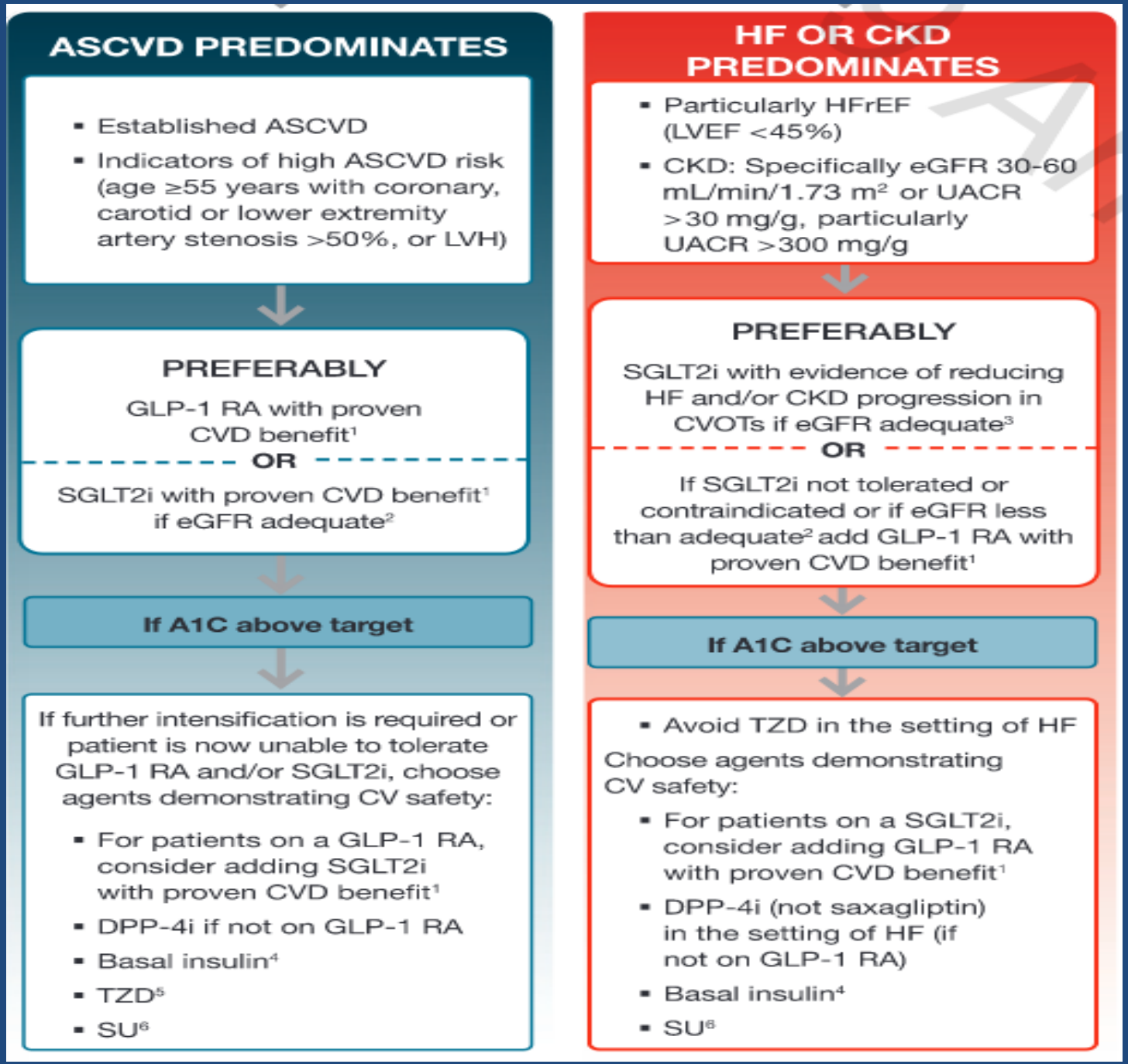
ADA 2020

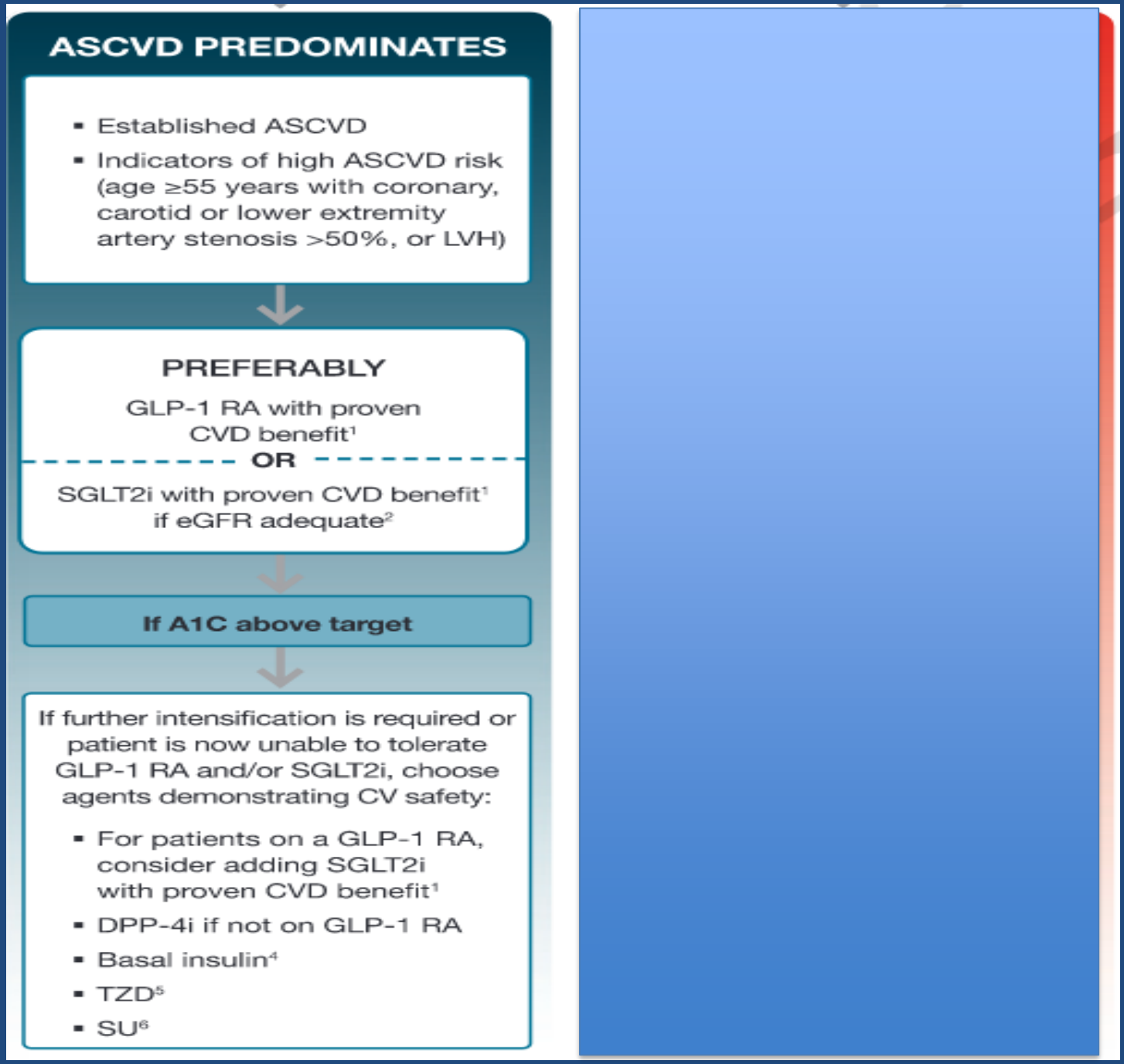
First line therapy

- Metformin and
- Comprehensive Lifestyle
  - Weight management
  - Physical activity

Next step

- To assess
  - indicators of high-risk or established ASCVD, ESRD or Heart failure


ASCVD PREDOMINATES
Established ASCVD
Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)
PREFERABLY
GLP-1 RA with proven CVD benefit[1]
OR
SGLT2i with proven CVD benefit[1] if eGFR adequate[2]
If A1C above target
If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit[1]
DPP-4i if not on GLP-1 RA
Basal insulin[4]
TZD[5]
SU[6]
HF OR CKD PREDOMINATES
Particularly HFrEF (LVEF <45%)
CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g
PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]
OR
If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]
If A1C above target
Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin[4]
SU[6]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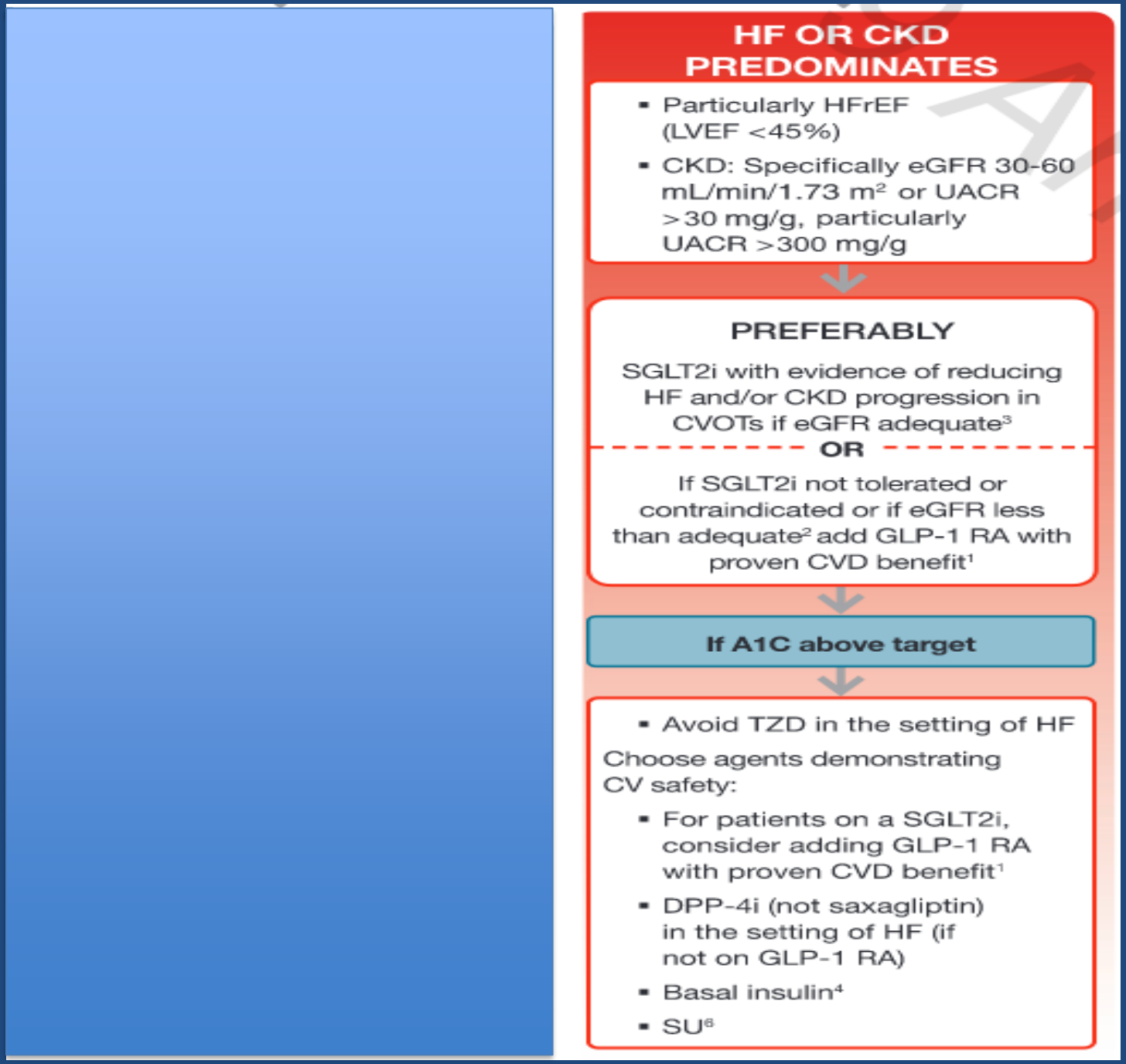
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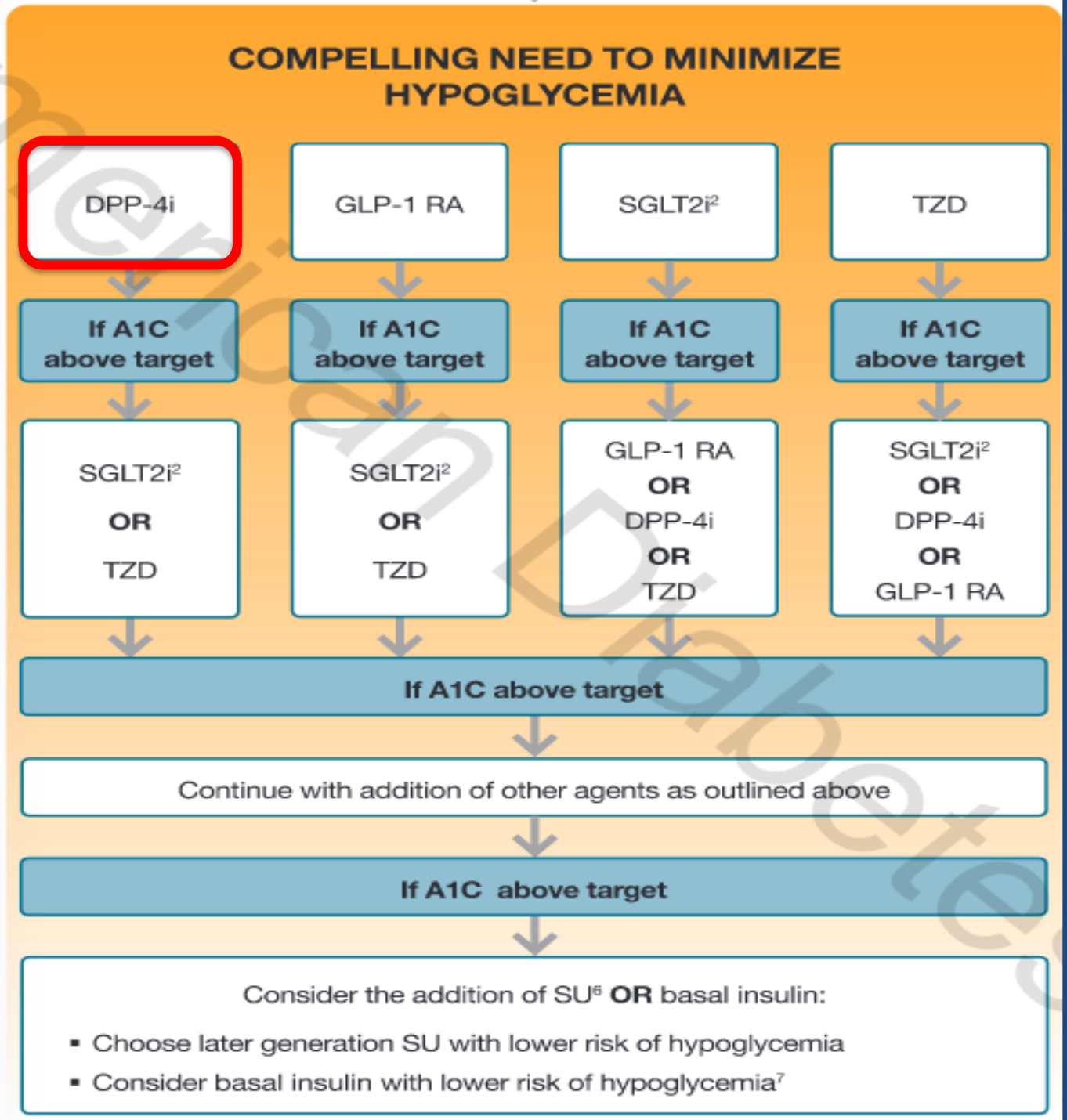
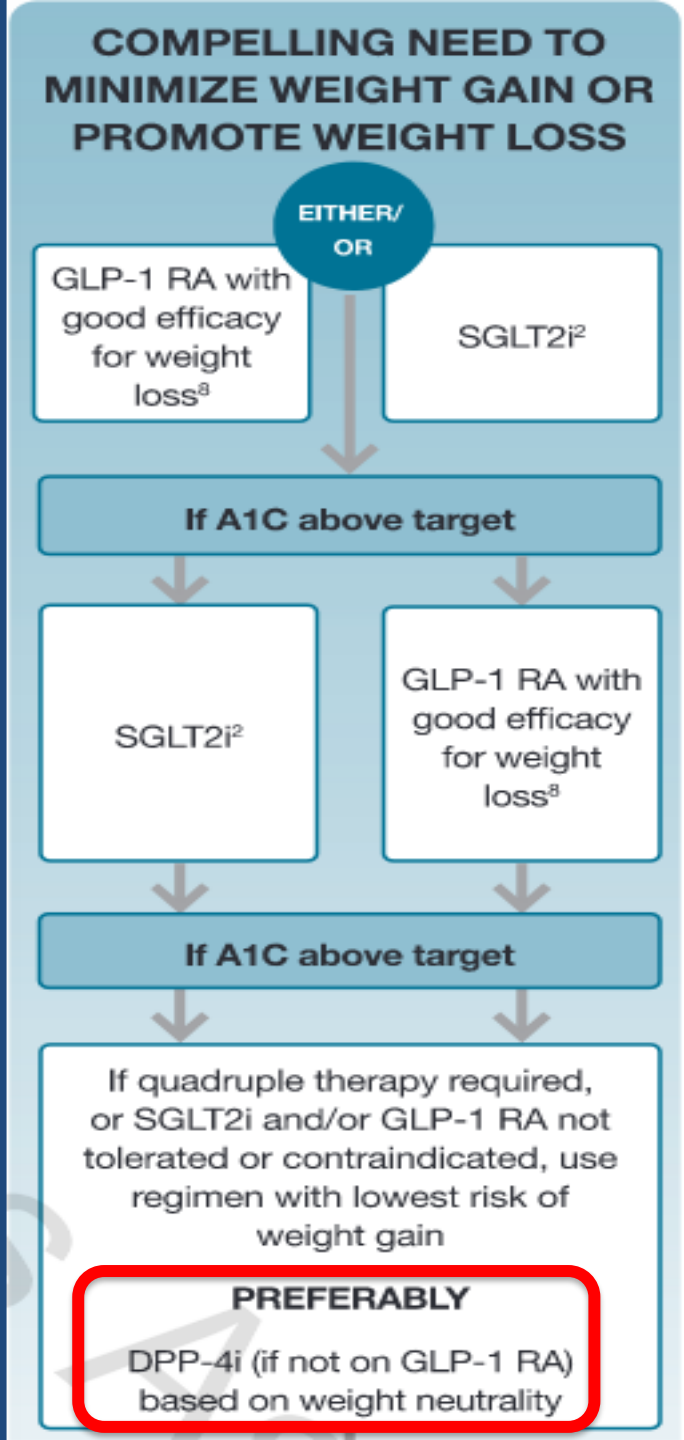
Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit[1]
DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
Basal insulin[4]
SU[6]

- If indicators for high-risk or established ASCVD, ESRD or HF absent,
  - Option 1
    - compelling need to minimize hypoglycemia
  - Option 2
    - compelling need to minimize weight gain or promote weight loss
  - Option 3
    - if cost is a major issue

Option 1

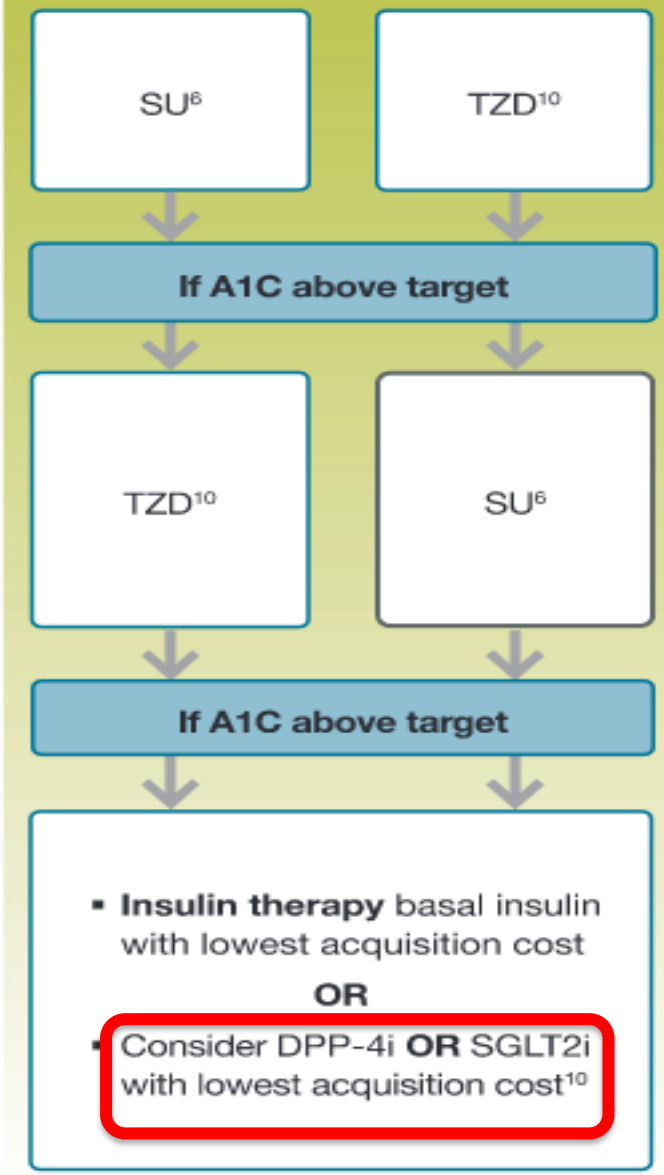

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i[2]
TZD
If A1C above target
If A1C above target
If A1C above target
If A1C above target
SGLT2i[2] OR TZD
SGLT2i[2] OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i[2] OR DPP-4i OR GLP-1 RA
If A1C above target
Continue with addition of other agents as outlined above
If A1C above target
Consider the addition of SU[6] OR basal insulin:
Choose later generation SU with lower risk of hypoglycemia
Consider basal insulin with lower risk of hypoglycemia[7]

Option2


COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
EITHER/ OR
GLP-1 RA with good efficacy for weight loss[8]
SGLT2i[2]
If A1C above target
SGLT2i[2]
GLP-1 RA with good efficacy for weight loss[8]
If A1C above target
If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality

COST IS A MAJOR ISSUE[9-10]

Option 3



Role of DPP-4i
in newly diagnosed T2DM

- ASCVD predominates
  - Metformin +
    - Preferably GLP-1RA or
    - SGLT 2i
  - If HbA1C above target,
    - Metformin + SGLT 2i + DPP-4i

Role of DPP-4i
in newly diagnosed T2DM

- HF or CKD predominates
  - ? Metformin +
    - Preferably SGLT 2i or
    - GLP-1RA
  - If HbA1C above target,
    - ? Metformin + SGLT 2i + DPP-4i (not Saxagliptin)

Role of DPP-4i
in newly diagnosed T2DM

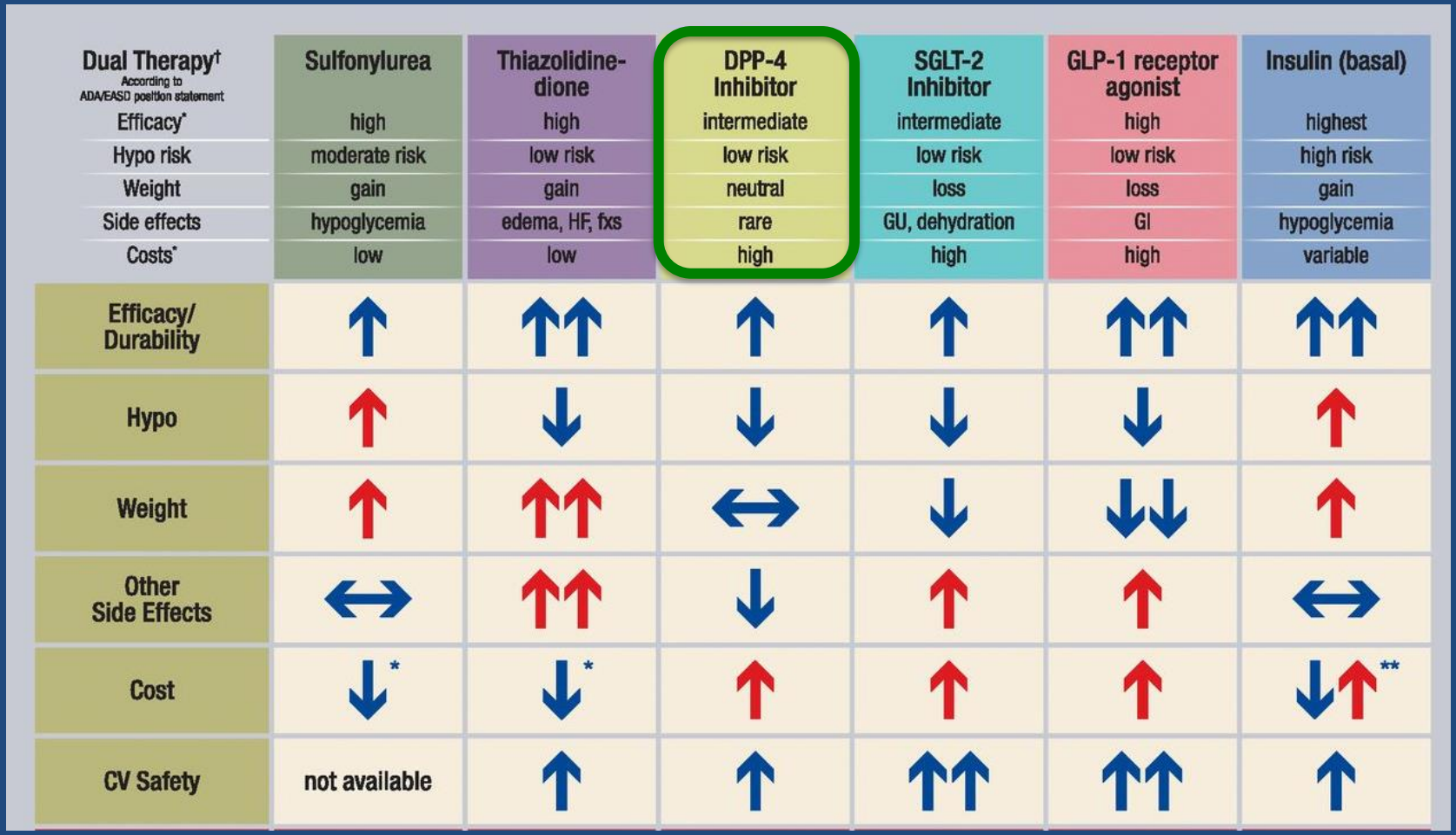
- Patients with no ASCVD risk, HF or ESRD
  - Weight neutral effect
  - 2 drug combination (if HbA1C above target)
    - Metformin + DPP-4i
    - SGLT 2i + DPP-4i
    - TZD + DPP-4i

Role of DPP-4i
in newly diagnosed T2DM

- If cost is a major issue
  - Metformin + SU + TZD/ DPP-4i

All are good players!

Glucose lowering medications



Dual Therapy† According to ADA/EASD position statement	Sulfonylurea	Thiazolidine-dione	DPP-4 Inhibitor	SGLT-2 Inhibitor	GLP-1 receptor agonist	Insulin (basal)
Efficacy*	high	high	intermediate	intermediate	high	highest
Hypo risk	moderate risk	low risk	low risk	low risk	low risk	high risk
Weight	gain	gain	neutral	loss	loss	gain
Side effects	hypoglycemia	edema, HF, fxs	rare	GU, dehydration	GI	hypoglycemia
Costs*	low	low	high	high	high	variable
Efficacy/ Durability	↑	↑↑	↑	↑	↑↑	↑↑
Hypo	↑	↓	↓	↓	↓	↑
Weight	↑	↑↑	↔	↓	↓↓	↑
Other Side Effects	↔	↑↑	↓	↑	↑	↔
Cost	↓*	↓*	↑	↑	↑	↓↑**
CV Safety	not available	↑	↑	↑↑	↑↑	↑

Thank you

Critical Role of DPP4 Inhibitors in Type 2 DM (Case Scenario Approach)

Moderator
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Panelist
Prof. Thein Myint

Professor
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Magway

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Time : 7:30 - 9:00 PM

zoom WEBINAR

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Scenario 3

Diabetic emergency

Scenario

- 71-year-old obese lady
  - 12 year history of T2DM
  - family members found patient confused after a fall at home
  - On PO Metformin and Gliclazide since diagnosis, inadequate diabetic control
  - Refused Insulin therapy (needle phobia)
  - No self monitoring of blood sugar at home
  - Last HbA1C was 11.2% - 1.5 years ago
  - Family members observed urinary and fecal incontinence
  - How will you manage?

Physical examination

- T - 38.6 C
- BP 84/52 mmHg
- PR 126 bpm
- RR 24 breaths / min
- SaO2 on air 100%
- RBS – high

Physical examination cont.

- Drowsy, dysphasic, unable to swallow
- oral mucosa dry
- skin turgor diminished
- Lungs – decrease air entry right lower zone with coarse crepts
- JVP not raised
- Abd – NAD
- Right sided hemiparesis

Hyperglycemic emergency

DKA or HHS?

Investigation results

Serum glucose 59.8 mmol/L

Renal profile

- Urea 14.6 mmol/L
- sodium 154 mmol/L
- potassium 5.4 mmol/L
- chloride 110 mmol/l
- creatinine 176 µmol/L

Arterial blood gases: pH 7.4, bicarbonate 20 mmol/L

Investigation results

- Urine FEME
    - Cloudy, ketone 1+, nitrites and leucocytes present

- Full blood count
    - WBC 19 X 10^9/L (80% polymorphonuclears)
    - RBS and platelet counts were normal

- C-reactive protein: 134 mg/L (normal < 5)

- ESR 85 mm/1st hour

Investigation results

ECG

- Sinus tachycardia, no ischaemic changes or right ventricular strain pattern

CXR:

- Consolidation right lower zone

More tests?

Serum osmolality

Formula : (2 x serum [Na]) + [glucose] + [urea] (all in mmol/L)
Or **laboratory measured value**

(2 x [154]) + [59.8] + [14.6] = **382.4**
Normal range 275-295 mosmol/kg

Anion gap

$([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$

(154 + 5.4) – (110 + 20) = **69.4**
Normal range 8 – 16 mmol/l

Others

Septic workup
Urine for culture and sensitivity
Blood culture

Stroke workup
Including swallowing test and CT brain

What is the diagnosis?

This patient	• **Dehydration** - tachycardia, bp 84/52, dry mucosa and diminished skin turgor, confusion • **Blood glucose 59.8 mmol/l** • Urine ketones minimal • Bicarbonate 20 mmol/l – no acidosis
Criteria for Hyperglycaemic Hyperosmolar State	• Hypovolemia – dehydration, • Marked hyperglycaemia > 33.3 mmol/l • pH > 7.3, bicarbonate > 15 mmol/l • Urine or blood ketones nil or minimal • Serum osmolality > 320 mOsm/kg
Diagnosis	• **Hyperglycaemic Hyperosmolar State**

What are the precipitating factors?

Precipitating factors	This patient
• Infection and sepsis • Thrombotic stroke • Intracranial haemorrhage • Silent myocardial infarction • Pulmonary infarction	Stroke Sepsis

What happen if treatment is delayed or not properly carried out? (HHS)

- Vascular complications
  - myocardial infarction, stroke or peripheral arterial thrombosis are common
- Seizures, cerebral oedema and osmotic demyelination uncommon
- Rapid changes in osmolality - precipitant of osmotic demyelination syndrome
- Mortality higher than DKA

What are the management goals?

Gradually and safely:

1. Normalise the osmolality
2. Replace fluid and electrolyte losses
3. Normalise blood glucose
4. Prevention of complications

Treat the underlying/ associating/ precipitating cause: stroke management and aspiration pneumonia

Care in high dependency ward

What is the immediate management?

- Hydration
- Insulin
- Electrolytes balance

Hydration

- Intravenous (IV) 0.9% saline solution
- Monitor serum osmolality regularly - prevent harmful rapid changes in osmolality
- The rate of rehydration - assessing the combination of initial severity and any pre-existing comorbidities
- Rapid rehydration - heart failure
- Insufficient rehydration - fail to reverse acute kidney injury

Hydration cont.

- An initial rise in sodium is expected and is not in itself an indication for hypotonic fluids
- Thereafter, the rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours
- The fall in blood glucose should be no more than 5 mmol/L/hr

Insulin

- Low dose IV insulin (0.05 units/kg/hr) commenced
  - once blood glucose is no longer falling with IV fluids alone or
  - immediately if there is significant ketonaemia (β-hydroxy butyrate >3 mmol/L)

Electrolytes

- Hyperkalaemia
- Hypokalaemia
- Hypophosphataemia and
- Hypomagnesaemia
  - common and should be corrected accordingly

Other issues

- In acutely ill patients, pyrexia may not be present
  - If sepsis is highly suspicious, the source of infection should be sought and treated

- Discharge planning
  - diabetes education
  - dietitian referral
  - education on medication and insulin administration (if patient is on insulin) to reduce the risk of recurrence and prevent long-term complications

Continuing
Glucose lowering medication

after HHS

DKA vs HHS

Hyperglycemic Emergencies

- DKA = Diabetic Ketoacidosis
- HHS = Hyperosmolar Hyperglycemic State

- Common features
  - Insulin deficiency → hyperglycemia → urinary loss of water and electrolytes

    → **Volume depletion + electrolyte deficiency + hyperosmolarity**

  - Insulin deficiency (absolute) + increased glucagon

    → **Ketoacidosis** (in DKA)

Suspect DKA or HHS in an ill patient with Hyperglycemia (usually)

DKA

- Ketoacidosis
- ECFV contraction
- Milder hyperosmolarity
- Normal to high glucose
- May have ↓LOC
- Beware hypokalemia
- Must use insulin
- Absolute insulin deficiency + increased glucagon

HHS

- Minimal acid-base problem
- ECFV contraction
- Hyperosmolarity
- Marked hyperglycemia
- Marked ↓↓LOC
- Beware hypokalemia
- May need insulin
- Relative insulin deficiency

DKA, diabetic ketoacidosis; *ECFV*, extracellular fluid volume; *HHS*, hyperosmolar hyperglycemic state; *LOC*, level of consciousness

post HHS

- Continuing Glucose lowering medication
  - usually do not need to stick on long term Insulin
  - can switch back to OAD

post HHS

- In this particular patient
  - Patient is not keen on Insulin therapy since the start of the story (needle phobia)
  - Stroke with dysphasia
    - hypoglycemic awareness?
    - Sulphonylurea - ?
  - Persistent renal impairment
    - Metformin – ?

What will be the most suitable OAD
for this patient?

Thank you

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