

MANAGEMENT OF COMPLICATIONS OF DIABETES MELLITUS

14/04/2021

Diagnosis- American Diabetes Association 2019

TABLE 3. Criteria for the Screening and Diagnosis of Diabetes

	Prediabetes	Diabetes
A1C	5.7–6.4%*	≥6.5%†
FPG	100–125 mg/dL (5.6–6.9 mmol/L)*	≥126 mg/dL (7.0 mmol/L)†
OGTT	140–199 mg/dL (7.8–11.0 mmol/L)*	≥200 mg/dL (11.1 mmol/L)†
RPG		≥200 mg/dL (11.1 mmol/L)‡

Classification of Complications

- Acute complications
 - 1) Hypoglycemia
 - 2) DKA, HHS
- Chronic complications
 - 1) Microvascular - Retinopathy, nephropathy, neuropathy
 - 2) Macrovascular – Coronary heart disease, Cerebrovascular disease, Peripheral arterial disease

1. Mx of Hypoglycemia

Asymptomatic (BG < 3.9mmol/L)	Ingest carbohydrate Adjust medications
Symptomatic	15-20g of fast acting carbohydrate (candy, sweetened juice, glucose tablets) Patients on alpha glucosidase-inhibitors eg. acarbose should take pure glucose (dextrose)
Severe -Bizarre behaviour -Unconscious -Convulsions	-IV 50mls 50% dextrose OR -IM/SC 1mg Glucagon

Don't forget to determine & deal with the cause of hypoglycemia....

- Excessive insulin dose
- Missed meal/fasting
- ↑d exercise
- ↓d insulin clearance ex. renal failure

2. Mx of DKA

a. Fluid replacement

- IV normal saline 1L stat, 1L over ½ hr, 1L over 1hr, 1L over 2hrs, 1l over 4hrs
- Monitor urine output!!
- Alternate with 5% dextrose once BS <13mmol/L

b. Insulin

- Soluble insulin 0.1U/kg IV bolus stat
- Then 0.1U/kg/hr infusion
- Once acidosis resolved revert to SC intermediate acting insulin

c. Potassium

- Total body K⁺ depleted usually due to both renal & GI losses

K ⁺ level	Action
4.5-5.5 mmol/L	10meq KCl
3.5- 4.4mmol/l	20meq KCl
<3.5 mmol/L	40-80 meq/L

d. Bicarbonate

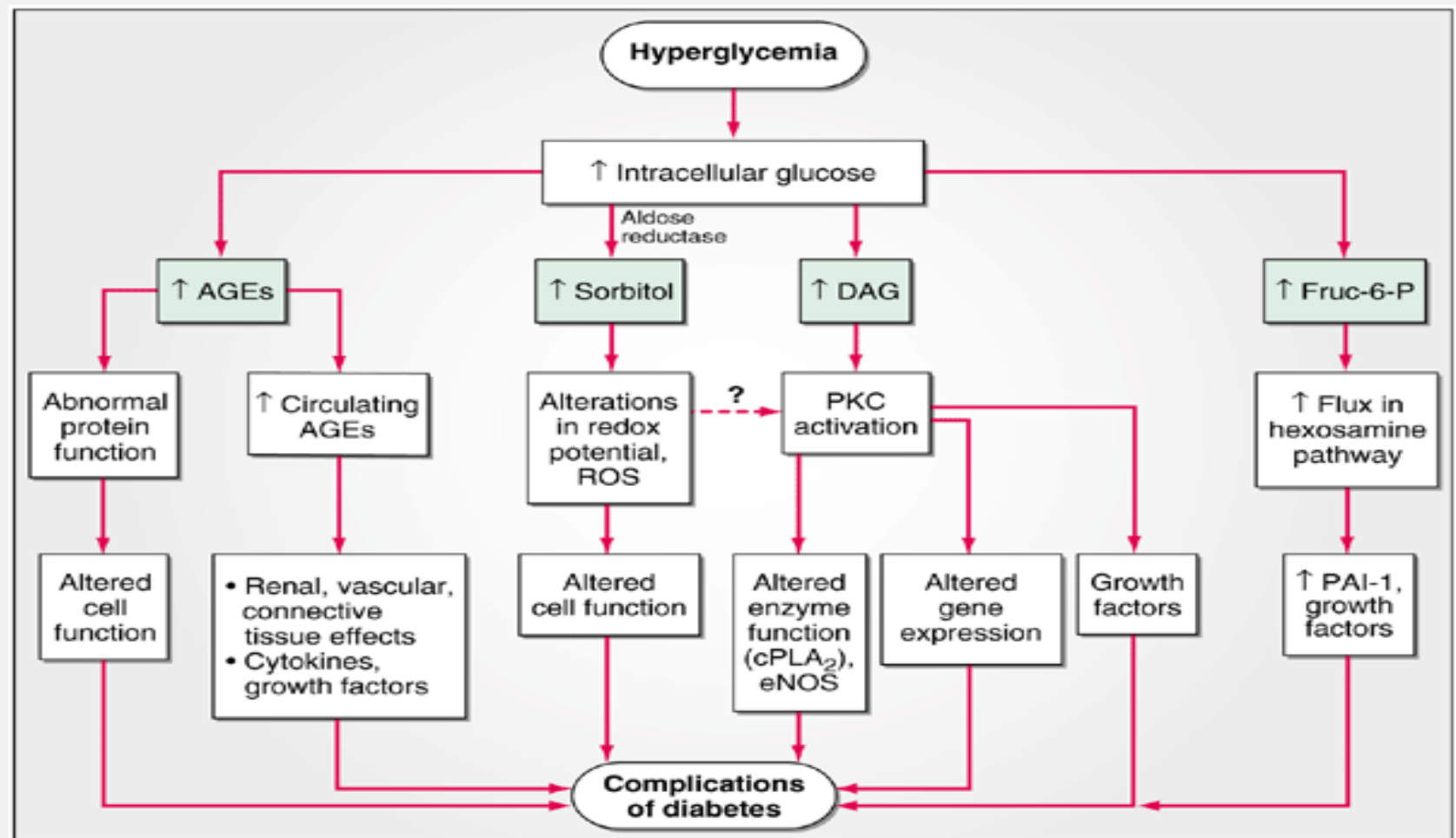
- Consider only if pH < 6.9

Determine the precipitant.....

- Infection (Pneumonia/UTI/GE/Sepsis)
 - Infarction (Myocardial/Cerebral/Mesenteric)
 - Inadequate insulin
 - Drugs eg. cocaine
 - Pregnancy
-
- ✓ Avoid complications of treatment:
 - Cerebral oedema
 - Noncardiogenic pulmonary oedema

MX OF CHRONIC COMPLICATIONS

Possible molecular mechanisms of diabetes-related complications.



PREVENTION: GOOD GLYCEMIC CONTROL!!!!

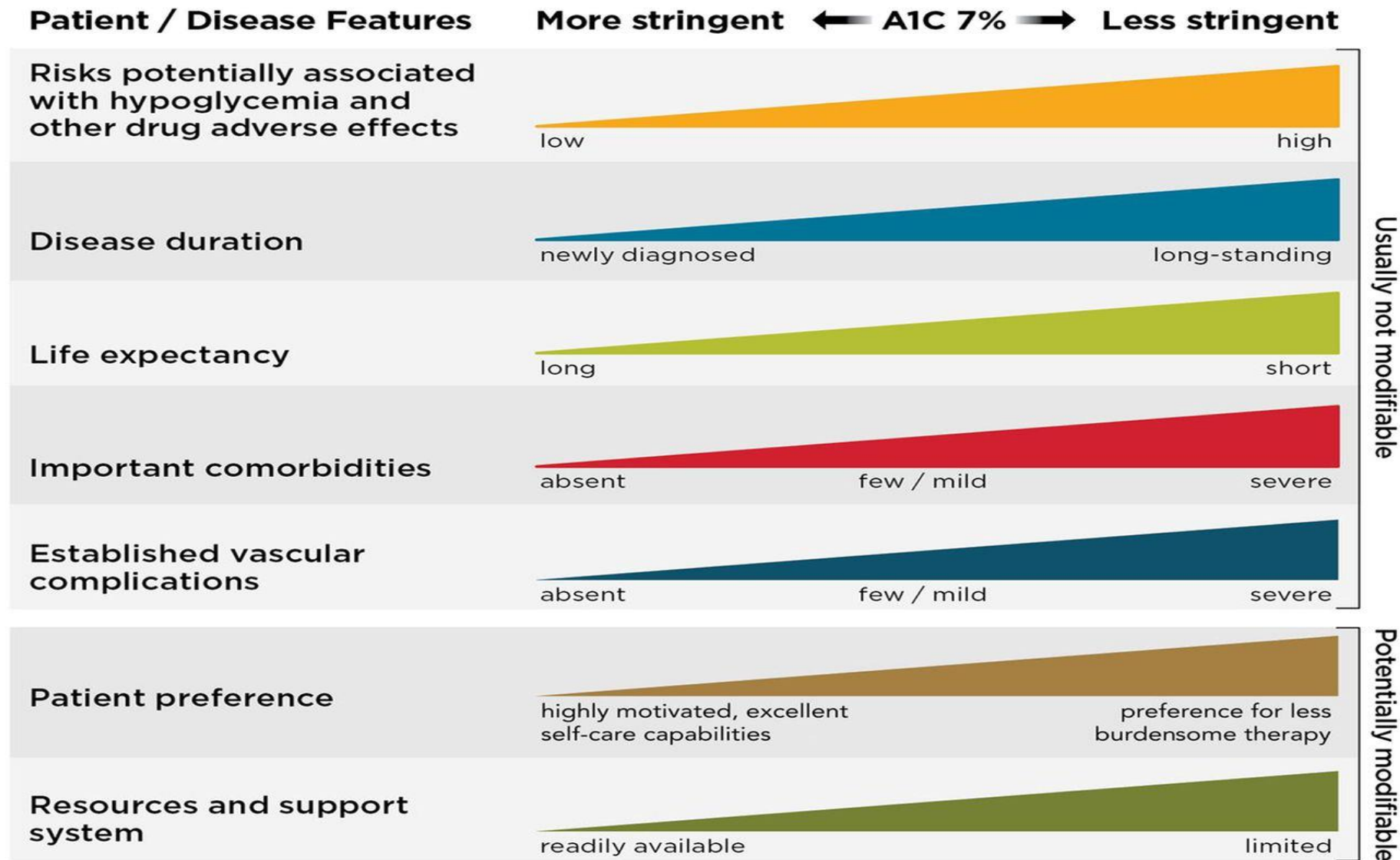
What is good glycaemic control?

TABLE 4. Summary of Glycemic Recommendations for Many Nonpregnant Adults With Diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

**More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals*

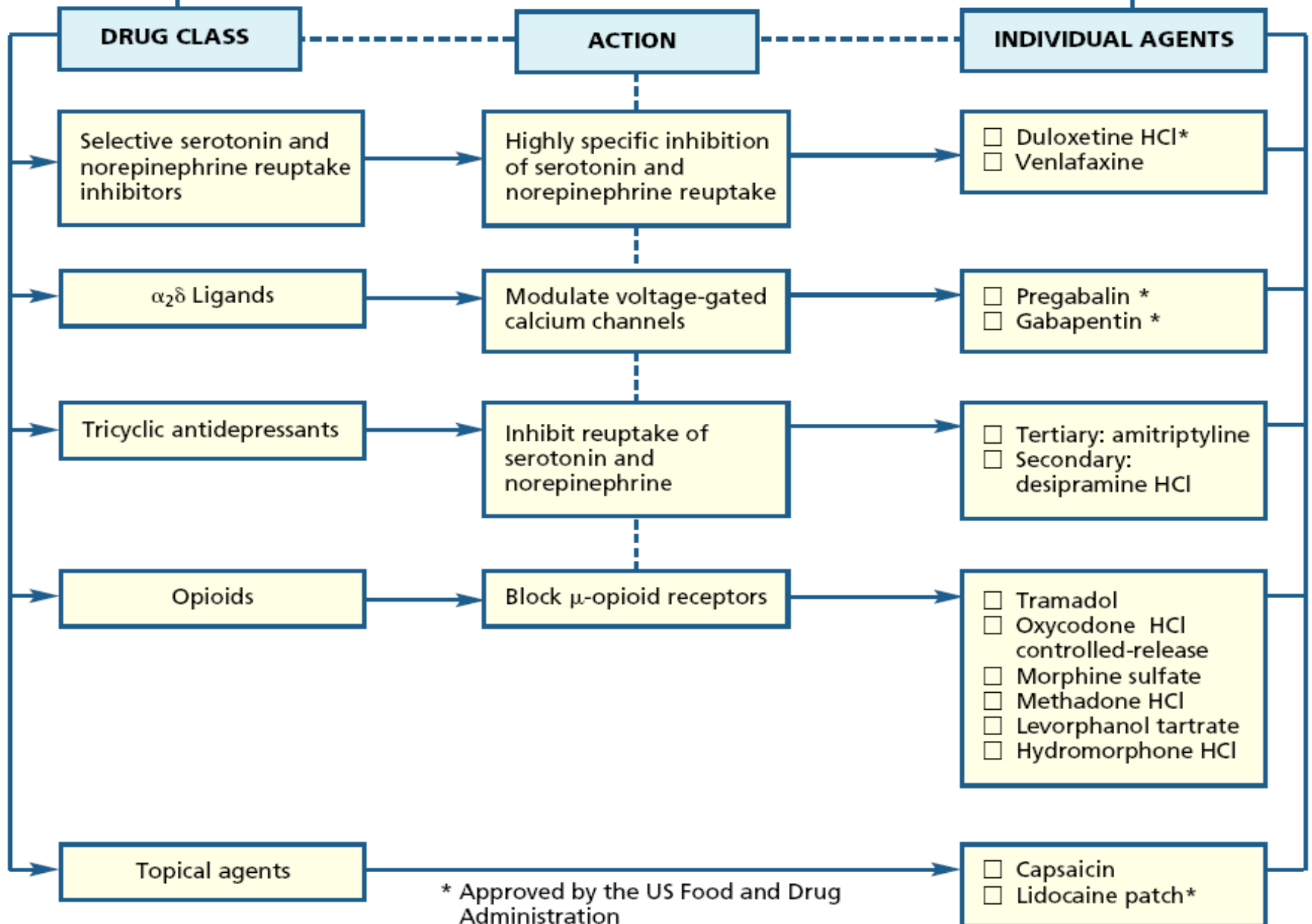
Approach to Individualization of Glycemic Targets



American Diabetes Association Clin Diabetes 2020;38:10-38

1. DIABETIC NEUROPATHY

Pharmacologic Treatment of Diabetic Peripheral Neuropathic Pain



TCA_s

- Amitriptyline 25-100mg usually used
- Onset of analgesia is in 1-4wks
- Administered nocte
- Has anticholinergic side effects: constipation, dry mouth, urinary hesitancy

Gabapentin

- Dose: 300mg day 1, 600mg day 2, 900mg day 3
 - Advantage: No significant drug interactions
 - Disadvantages: Can cause significant peripheral oedema
- : Req. dose adjustment in renal impairment

Pregabalin

- Better bioavailability compared to gabapentin
- Starting dose 25-50mg PO
- Side effects: Dizziness, somnolence, oedema

AUTONOMIC NEUROPATHY

Autonomic Neuropathy

Symptomatic

Postural hypotension
Gastroparesis
Diabetic diarrhea
Neuropathic bladder
Erectile dysfunction
Charcot arthropathy
Gustatory sweating

Subclinical abnormalities

Abnormal pupillary reflexes
Esophageal dysfunction
Abnormal cardiovascular
reflexes
Blunted counter-regulatory
responses to hypoglycemia

Management

- **Gastroparesis:**

1. Metoclopramide PO 10mg QID, 30 mins before meals
 - Increases gut motility through indirect cholinergic stimulation of gut muscle
 - A/e: tardive dyskinesia
2. Domperidone
3. Cisapride
4. Erythromycin
 - Interacts with motilin receptors, increasing gut motility
5. Eat smaller, more frequent meals

Mx of Sexual dysfunction

- ED in males: Phosphodiesterase 5 inhibitors
- Females: Vaginal lubricants, Rx of vaginal infections, local or systemic oestrogen replacement

Mx of Diabetic Diarrhoea

- Loperamide or octreotide

Mx of Diabetic Cystopathy

- Timed voiding or self catheterization +/- bethanechol

Mx of Orthostatic Hypotension

- Fludrocortisone, midodrine, octreotide

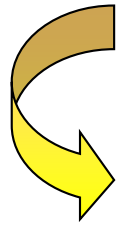
2. DIABETIC NEPHROPATHY

Interventions to Slow the Progression of Renal Disease in DM

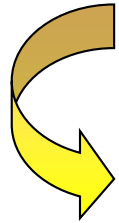
INTERVENTION	TARGET
Blood-pressure control	<130/80 mm Hg
Inhibition of renin–angiotensin system	Urinary protein excretion, <0.3 g/24 hr
Correction of dyslipidemia	LDL cholesterol, <100 mg/dl (2.6 mmol/liter)
Glycemic control	Glycosylated hemoglobin, <7%

*Cessation of smoking, loss of weight, exercise, and reduction of protein, salt, and alcohol intake are also recommended, as appropriate. LDL denotes low-density lipoprotein.

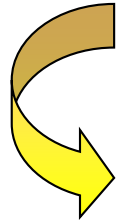
Intensive blood pressure control in diabetic patients



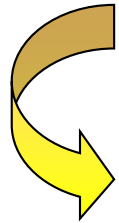
Step 1 Low sodium diet (100 mEq/day), body weight control, physical exercise, stop smoking



Step 2 ACE-inhibitors or Ang-II antagonists



Step 3 Diuretics, CCBs



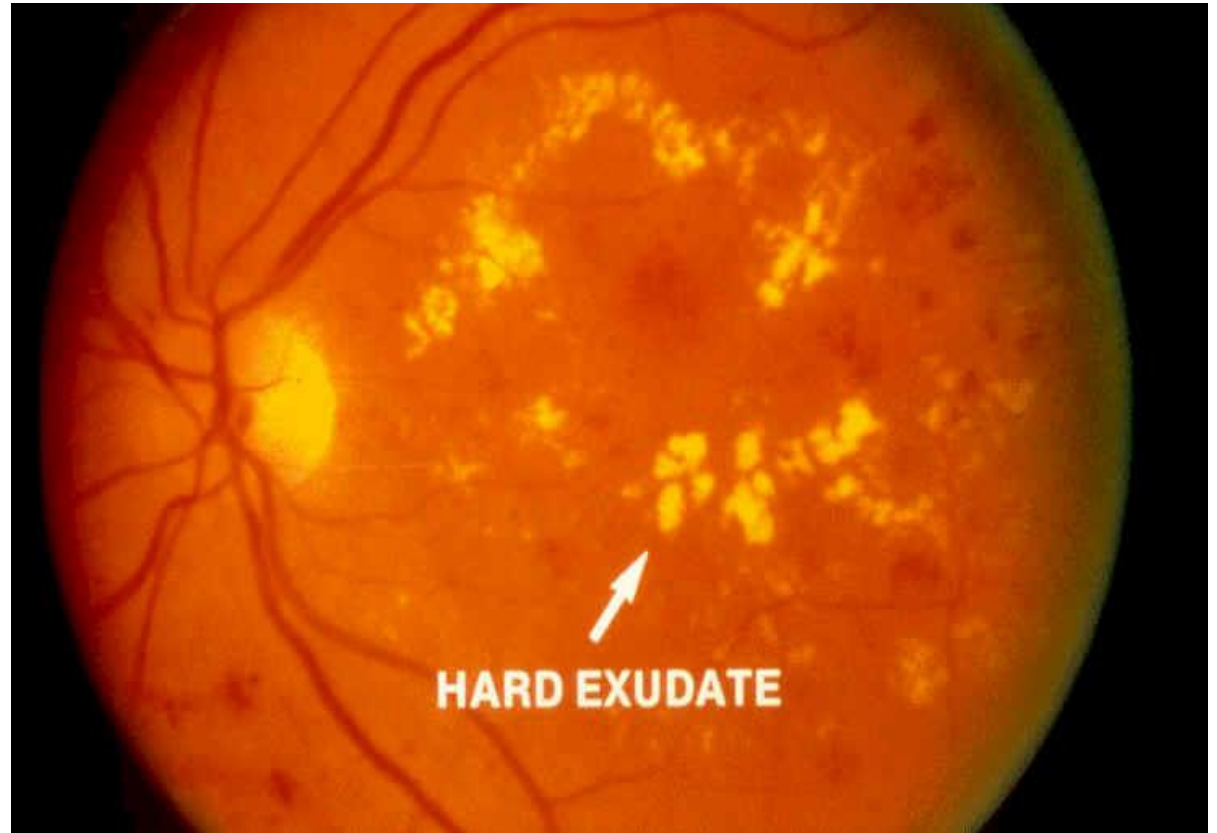
Step 4 β -blockers

Step 5 Vasodilators, α -blockers

Goal of Treatment of Hypertension

Lower target for diabetic patients than non-diabetic patients:

130/80 vs. 140/90



3. DIABETIC RETINOPATHY

Mx

- Most effective therapy is prevention
- Annual ophthalmology review for fundoscopy
- Proliferative retinopathy- treated with panretinal laser photocoagulation
- Macular oedema- focal laser photocoagulation, intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF)

4. CARDIOVASCULAR AND CEREBROVASCULAR DISEASE

Additional risk factors- deal with these as well....

- Accelerated atherosclerosis/dyslipidemia
- Smoking
- Obesity
- Hypertension
- Reduced physical activity
- Micro- and macroalbuminuria
- Abnormal platelet function
- Insulin resistance

Dyslipidemia Mx in DM

- DM usually associated with ***hypertriglyceridemia*** & reduced HDL.
- +/- raised LDL
- Initial treatment- dietary changes:
 - ✓ ↑ monounsaturated fat
 - ✓ ↓ saturated fats & cholesterol
- Drug of choice: HMG CoA reductase inhibitors (Statins)
 - ✓ Pleiotropic effects
 - ✓ Antiinflammatory, antioxidant, plaque stabilizing effects

Antiplatelet therapy

Primary prevention

DM1 and DM2 patients ≥ 30 years with high CV risk

- ✓ CAD family history
- ✓ Smoking
- ✓ Hypertension
- ✓ Obesity
- ✓ Dislipidemia
- ✓ Albuminuria (micro or macro)

Secondary prevention

DM1 and DM2 patients with clinical history of cardiovascular disease

- ✓ myocardial infarction or angina
- ✓ Stroke or TIA
- ✓ Peripheral vascular disease
- ✓ By-pass surgery

aspirin (tablets)
75-100mg/day

Contraindications

- ✓ Allergy
- ✓ Bleeding tendency
- ✓ Anticoagulation treatment
- ✓ Recent gastro-intestinal bleeding
- ✓ Clinically active liver disease
- ✓ Age ≤ 21 years ($\uparrow$ Reye's syndrome)

clopidogrel
ticlopidine



5. DIABETIC FOOT ULCERS

Prevention- Do's and Don'ts of foot care



Patient should

- check feet daily
- Wash feet daily
- Keep toenails short
- Protect feet
- Always wear shoes
- Look inside shoes before putting them on
- Always wear socks
- Break in new shoes gradually
- Use moisturizing lotions

Treatment of diabetic foot ulcers

1. Off-loading: complete avoidance of weight bearing on the ulcer, which removes the mechanical trauma that retards wound healing
2. Debridement
3. Appropriate antibiotics
 - ✓ Mixed infections (G +ve, G –ve & anaerobes)
 - ✓ Cephalosporin/Augmentin/Clindamycin/Metronidazole/Fluoroquinolone
4. Wound dressing

SUMMARY OF TREATMENT CHOICES IN DM

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF[†]

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

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 benefit¹

OR

SGLT2i with proven CVD benefit¹ if eGFR adequate²

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 benefit¹
- DPP-4i if not on GLP-1 RA
- Basal insulin⁴
- TZD⁶
- SU⁸

HF OR CKD PREDOMINATES

- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >3 mg/g, particularly UACR >30 mg/g

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate³

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate² add GLP-1 RA with proven CVD benefit¹

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 benefit¹
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin⁴
- SU⁸

NO

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i

GLP-1 RA

SGLT2i²

TZD

If A1C above target

If A1C above target

If A1C above target

If A1C above target

SGLT2i²

SGLT2i²

GLP-1 RA

SGLT2i²

OR

OR

OR

OR

TZD

TZD

DPP-4i

GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU⁸ OR basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia⁷

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss⁹

OR

SGLT2i²

If A1C above target

SGLT2i²

GLP-1 RA with good efficacy for weight loss⁹

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

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

• SU⁸ • TZD⁶ • Basal insulin

COST IS A MAJOR ISSUE⁹⁻¹⁰

SU⁸

TZD¹⁰

If A1C above target

TZD¹⁰

SU⁸

If A1C above target

- Insulin therapy basal insulin with lowest acquisition cost
- OR
- Consider DPP-4i OR SGLT2i with lowest acquisition cost¹⁰



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. Dapagliflozin 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

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

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 > lraglutide > 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

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction

UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

.

THE END