Diabetes:How To Translate guidelines into practice for general populations

KO KO
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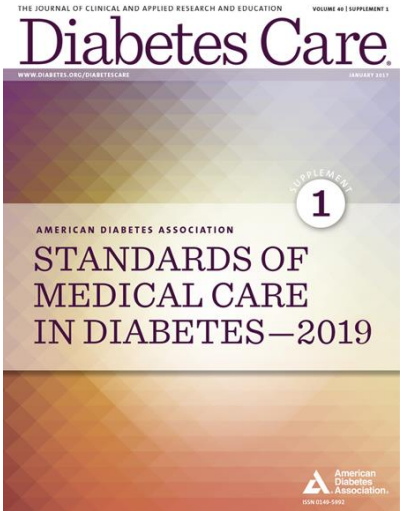
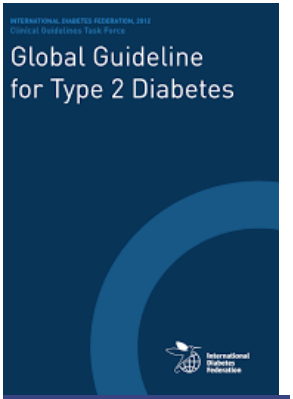
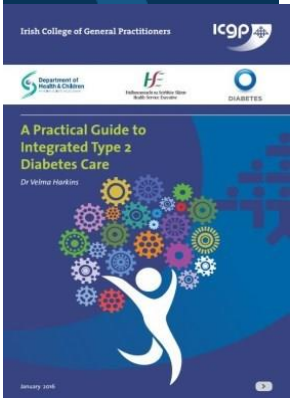
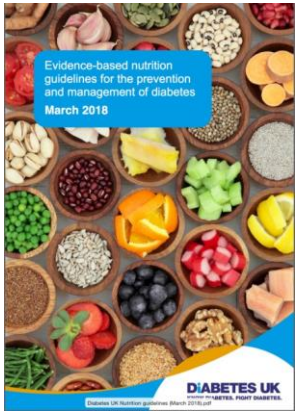
University of Medicine 2
Educational Grunt By Zifam
21.1.19,MMA,NPT

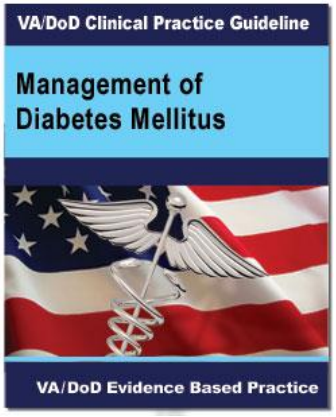

DIABETES CANADA
CLINICAL PRACTICE GUIDELINES

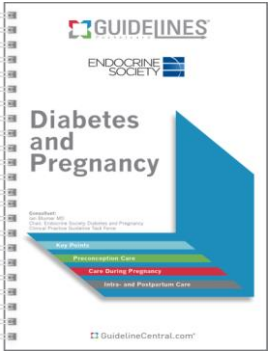

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION
VOLUME 40 | SUPPLEMENT 1
Diabetes Care
WWW.DIABETES.ORG/DIABETESCARE
JANUARY 2017
SUPPLEMENT
1
AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2019
American Diabetes Association.
ISSN 0149-5992

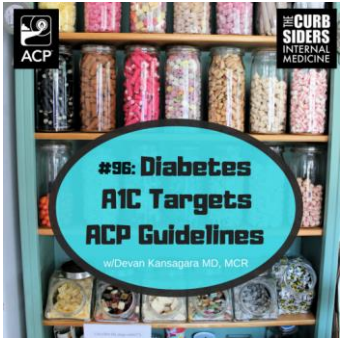

INTERNATIONAL DIABETES FEDERATION, 2012
Clinical Guidelines Task Force
Global Guideline for Type 2 Diabetes
International Diabetes Federation


Irish College of General Practitioners
icgp
Department of Health & Children
DIABETES
A Practical Guide to Integrated Type 2 Diabetes Care
Dr Velma Harkins
January 2016

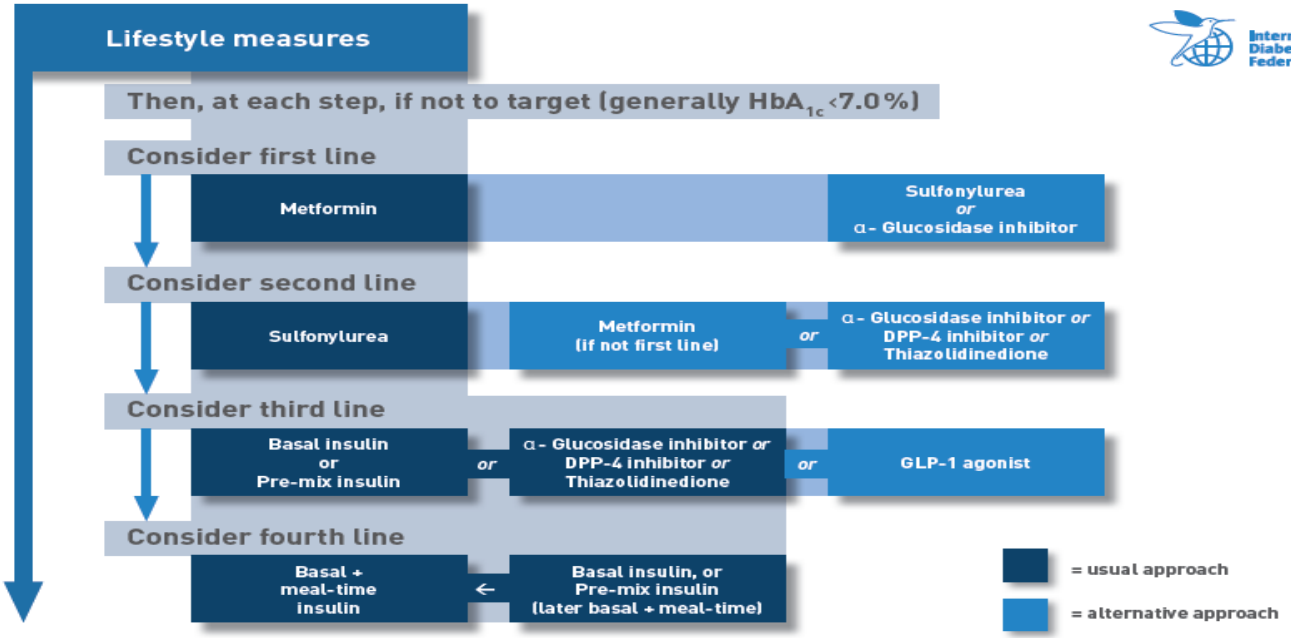

Evidence-based nutrition guidelines for the prevention and management of diabetes
March 2018
DIABETES UK


VA/DoD Clinical Practice Guideline
Management of Diabetes Mellitus
VA/DoD Evidence Based Practice


GUIDELINES
ENDOCRINE SOCIETY
Diabetes and Pregnancy
Key Points
Preconception Care
Care During Pregnancy
Intra- and Postpartum Care
GuidelineCentral.com


ACP
THE CURB SIDERS
INTERNAL MEDICINE
#96: Diabetes A1C Targets ACP Guidelines
w/Devan Kansagara MD, MCR

IDF Treatment Algorithm for People with Type 2 Diabetes



SIGN
Scottish Intercollegiate Guidelines Network
Part of NHS Quality Improvement Scotland

March 2010

1st line option in addition to lifestyle measures; start ONE OF

MET

SU (if intolerate of metformin or if weight loss/ osmotic symptoms)

Review & if not reaching target move to 2nd line

2nd line options

SU

(Usual approach)

Alternative

TZD or DPP-4 Inhibitor

Review & if not reaching target move to 3rd line

3rd line options

Oral

MET/ SU + TZD (if no HF)

Injectable

MET/ SU + Insulin (before bed)
(or)
MET/ SU + GLP -1 agonists

NICE Guideline 2015

T2DM

Metformin tolerable

Metformin

First intensification - Dual therapy

Metformin +

- DPP-4i
- Pioglitazone
- SU
- SGLT-2i

❑ **Triple therapy**

Metformin +

- DPP-4i + SU
- Pioglitazone + SU
- Pioglitazone/ SU + SGLT-2i

❑ **Insulin based therapy**

Metformin contraindicated or not tolerable

- DPP-4i/ Pioglitazone/ SU
- SGLT-2i instead of DPP-4i if SU or pioglitazone is not appropriate

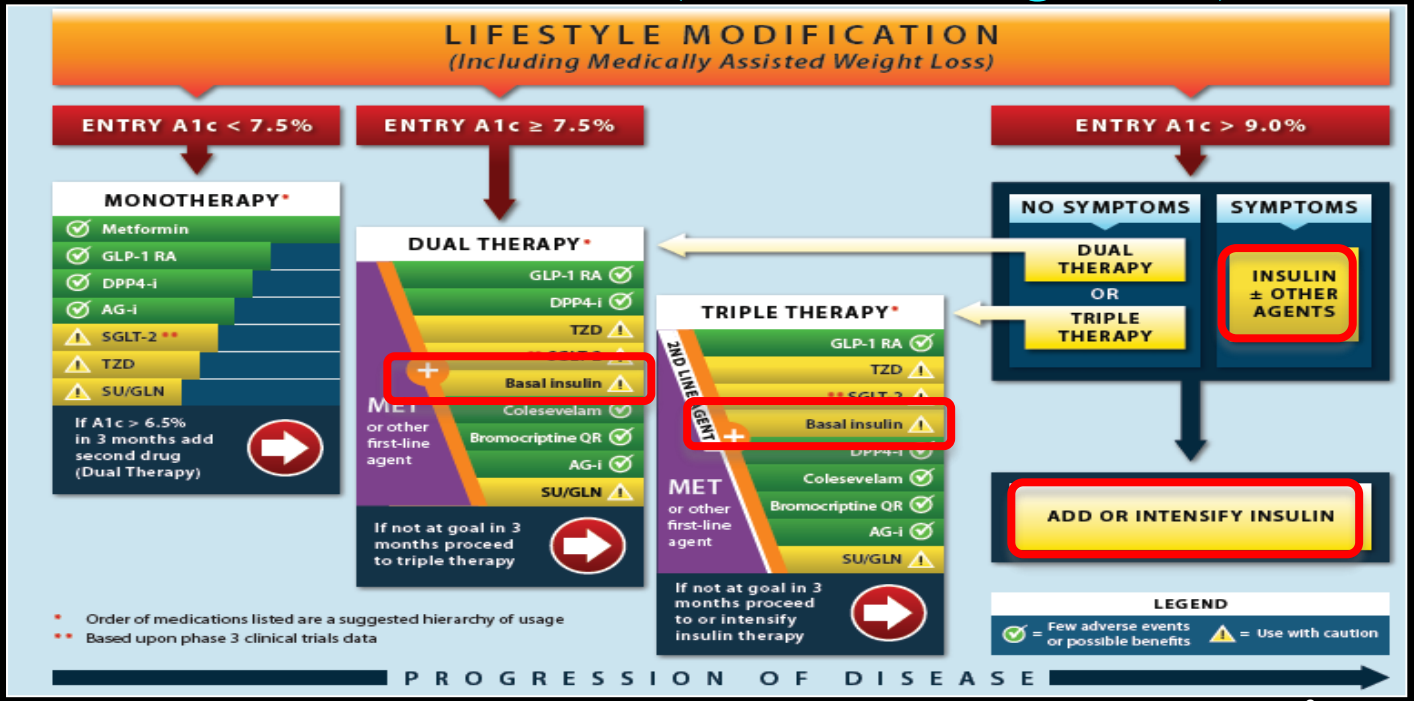
❑ **First intensification - Dual therapy**

- DPP-4i + Pioglitazone
- DPP-4i + SU
- Pioglitazone + SU

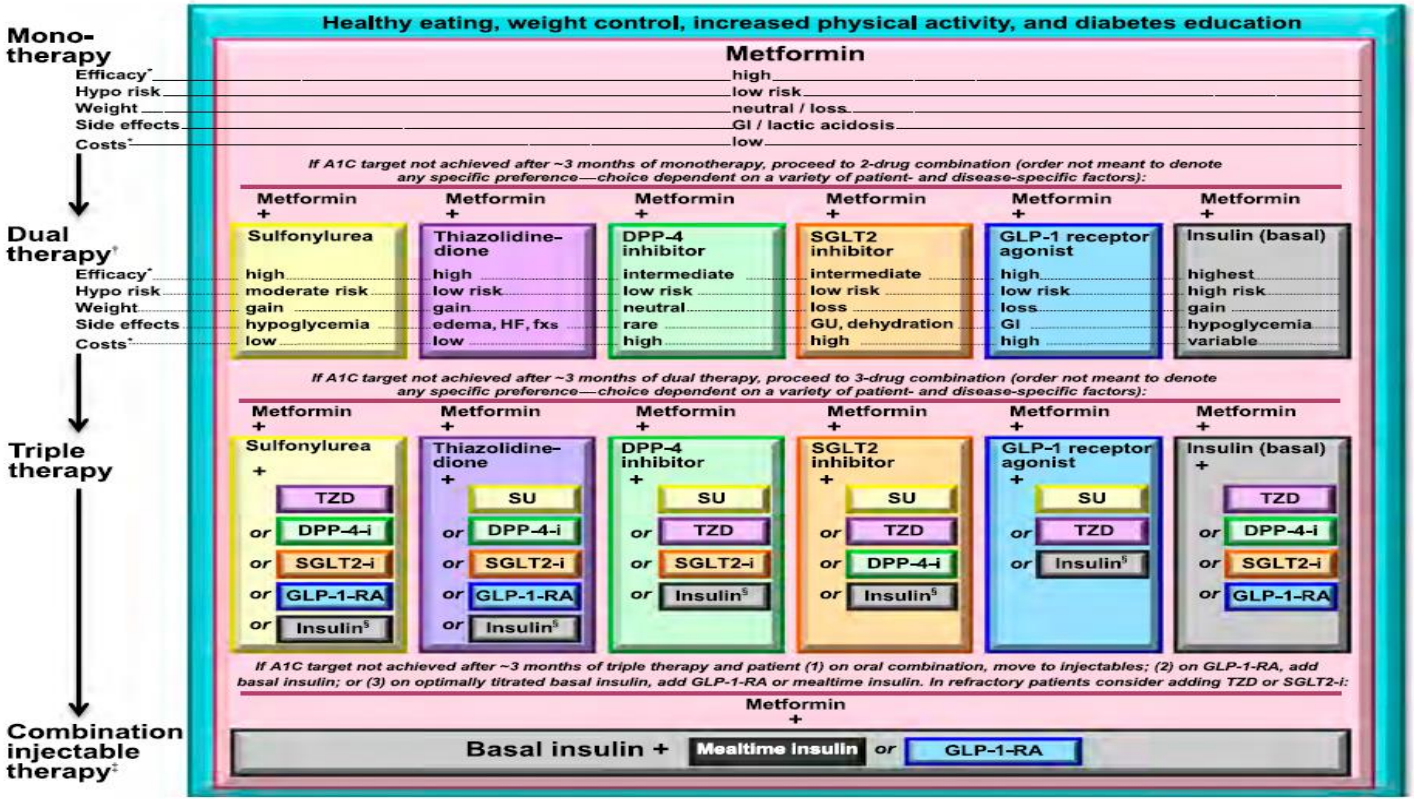
❑ **Second intensification**

- Insulin based therapy

Current Guidelines (AACE 2017Algorithm)



Endocrine Practice, 2013 March/April, 19(2)


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy* high
Hypo risk low risk
Weight neutral / loss
Side effects GI / lactic acidosis
Costs* low
If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

ADA 2018

Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 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, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

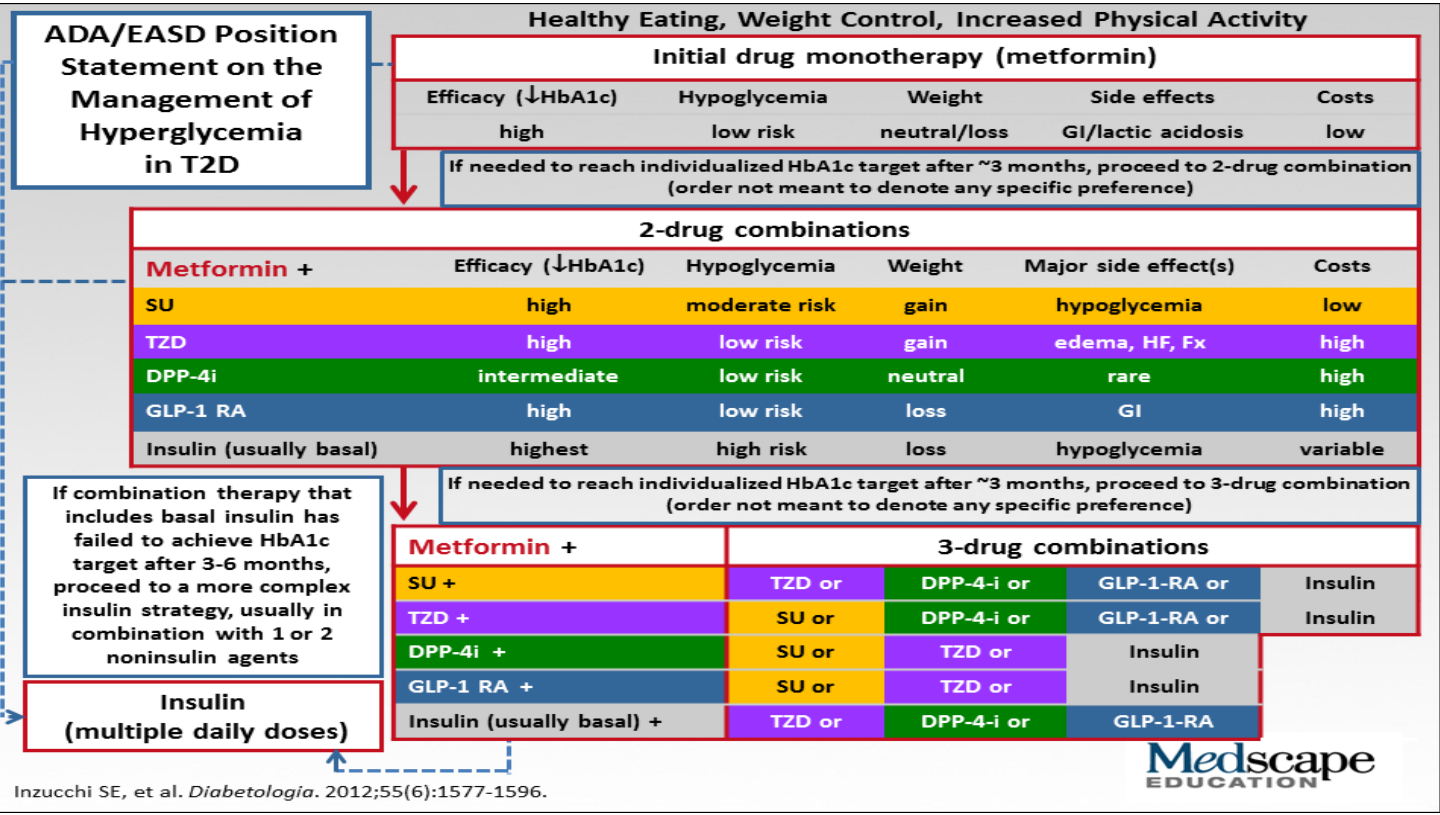
If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[‡]	or GLP-1-RA	or Insulin[‡]	or GLP-1-RA
or Insulin[‡]	or Insulin[‡]		or Insulin[‡]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

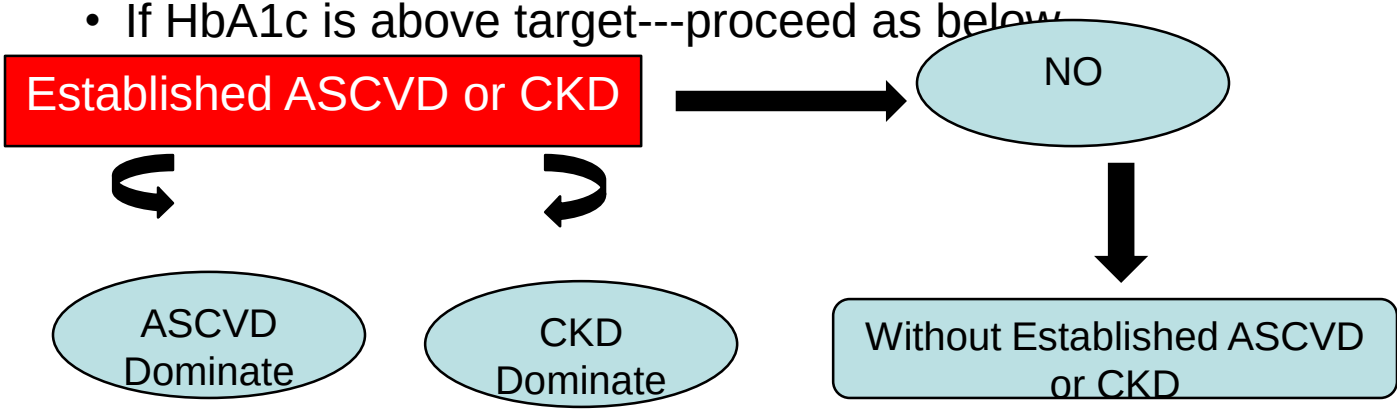


Inzucchi SE, et al. *Diabetologia*. 2012;55(6):1577-1596.

Medscape EDUCATION

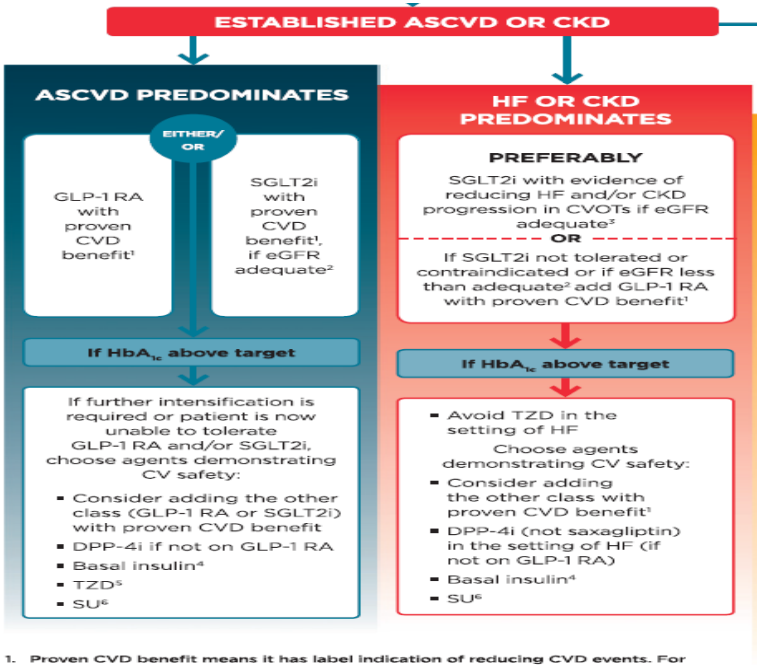
First-Line Therapy is Metformin with comprehensive life style(Including weight management and physical activity)

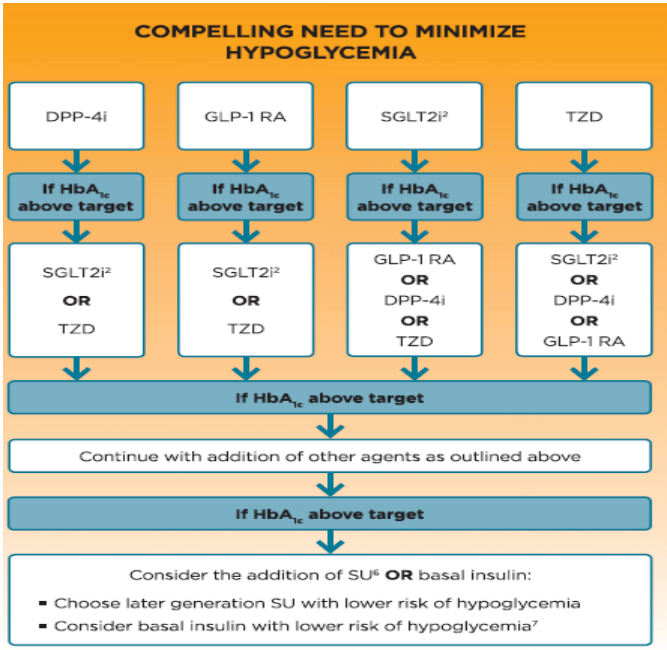
- If HbA1c is above target---proceed as below



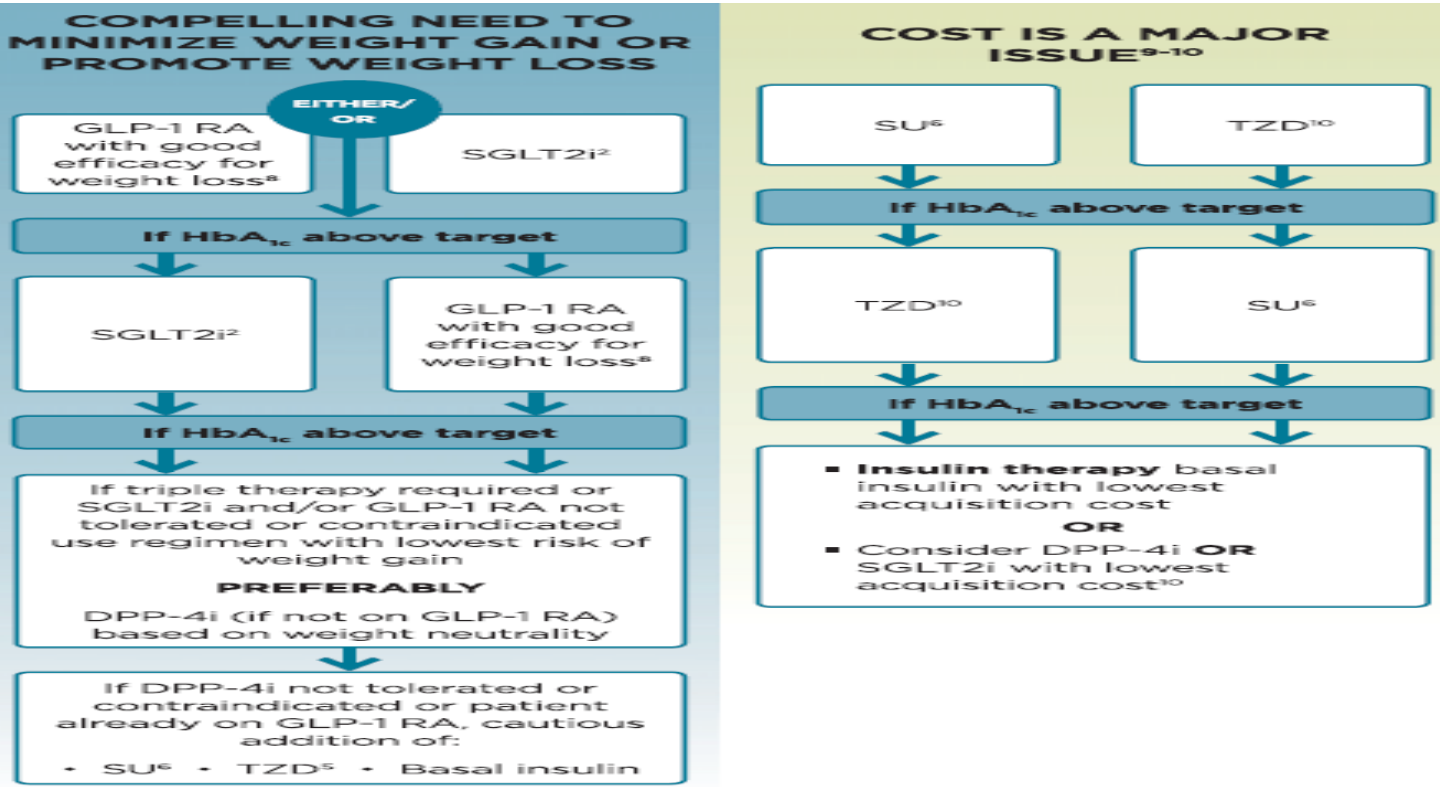
American Diabetes Association.

2019





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


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 HbA1c above target
SGLT2i[2]
GLP-1 RA with good efficacy for weight loss[8]
If HbA1c above target
If triple 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:
• SU[6] • TZD[5] • Basal insulin
COST IS A MAJOR ISSUE[9-10]
SU[6]
TZD[10]
If HbA1c above target
TZD[10]
SU[6]
If HbA1c above target
▪ Insulin therapy basal insulin with lowest acquisition cost
OR
▪ Consider DPP-4i OR SGLT2i with lowest acquisition cost[10]

2018 Diabetes Canada CPG – Chapter 13. Pharmacologic Glycemic Management of Type 2 Diabetes

Initial choice of therapy

A1C **<**1.5% over target → Initiate healthy behavior interventions and **start metformin** if not at target in 3 months

OR

Start metformin with healthy behavior interventions

A1C **≥** 1.5% over target → **Start metformin** with healthy behavior interventions

AND

Consider second concurrent agent

CASE 1

- 45 male with newly diagnosed DM,school teacher
- RBS 240mg%,FBS 140mg%,
- HbA1c 7.4%
- BP 120/80mm Hg
- BMI 26
- Smoking (+),social drinker

Target?
Treatment start?
Which Medication?
What are you looking for ?
Investigations?

- Management?
- Problem—1.Newly Diagnosed DM
  2.Overweight
  3.smoking

A. Theapeutic life style
B. TLY +Metformin 500 BD
C. Gliclazide 80 mg BD
D. Pioglitazone 30 mg od
E. Sitagliptin 50 mg bd

Choice?

Management

- Stop smoking
- Reduce weight
- Metformin 500 mg BD
- Atovastatin 20mg od
- Therapeutic life style
- A1c 6,5 to 7%
- Looking for complications and comorbid conditions

What a Doctor should do for medical care of patient with DM?

- Diagnosis
- Screening
- Evaluation of diabetes complications-macro and microvascular
- Detection of comobidities
- Reducting the risk of microvascular complications

  Glycemic control
- Reducting the risk of Macrovascular complications

  smoking cessation

  control of **BP,Lipid,asprin**
- Monitoring of complications
- Prevention of Diabetes
- DSME (Diabetes self management education)

Principle

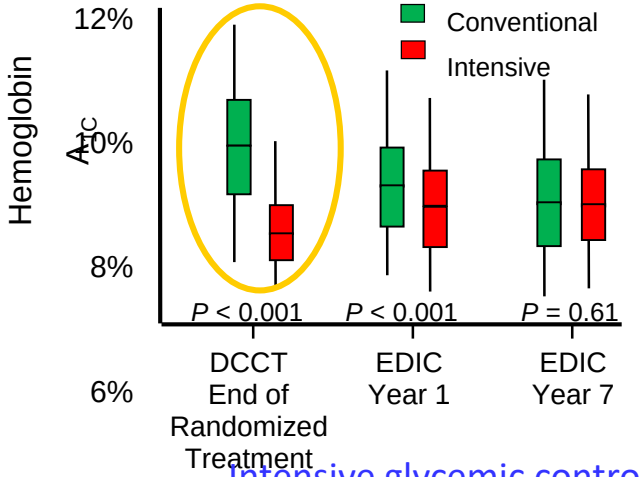
- Set the Target.
- Monitoring and prevention of complication
- Combination Treatment
- Multisectorial Treatment-glucose,lipid,BP
- Patient centred apporach
- Therapeutic inertia
- Drugs according to pathogenesis
- Self medical education
- Choosing drugs(avoid impact on weight,hypoglycemia and cardiovascular risk

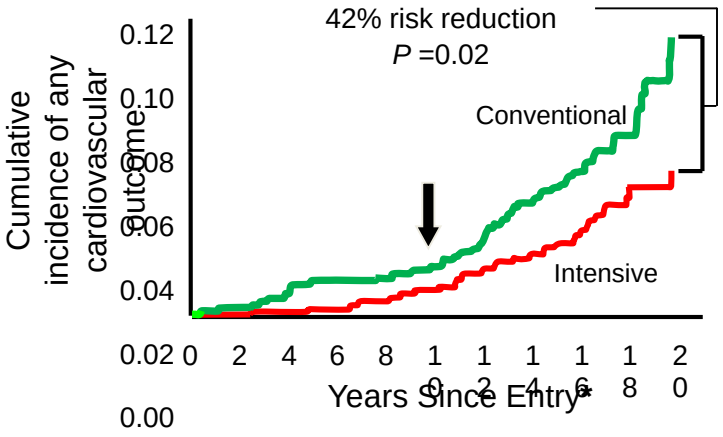
Current Trends

1. Early Combination Therapy
2. Multidirectional aggressive Treatment
3. Good Glycemic Control
    1. As low as possible
    2. As early as possible
    3. As safe as possible
4. Target to treat Pathogenesis
    1. Newer Drugs for newer pathogenesis

Diabetes Mellitus (Type I): Effect of Intensive Glycemic Control

Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC)

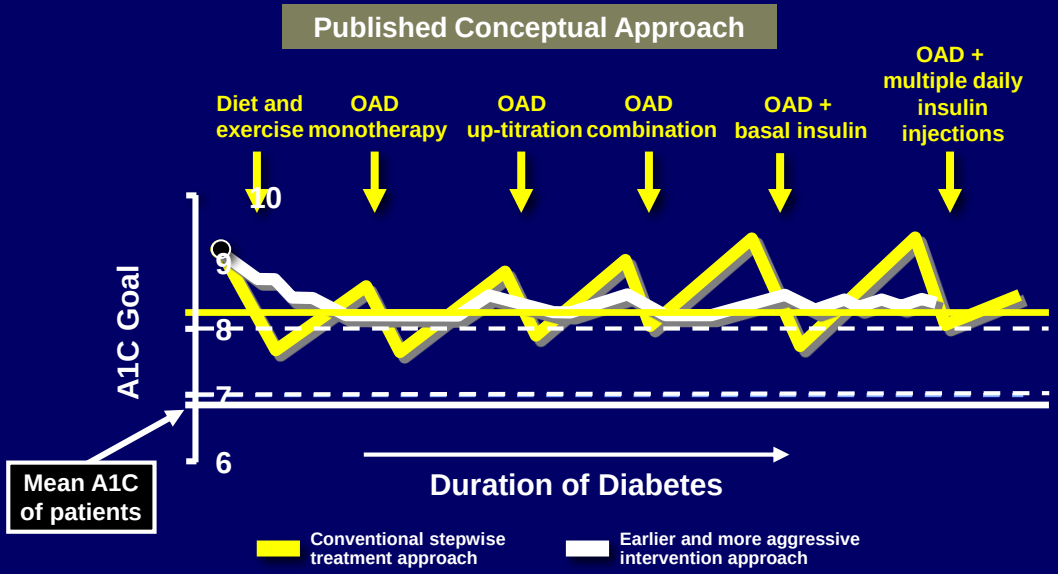




Intensive glycemic control in DM reduces long-term CV risk

Sources:
DCCT/EDIC Research Group. *JAMA* 2002;287:2563-2569
DCCT/EDIC Research Group. *NEJM* 2005;353:2643-2653

Earlier and More Aggressive Intervention May Improve Patients' Chances of Reaching Goal



OAD=oral antidiabetic agent.

Adapted from Del Prato S et al. *Int J Clin Pract*. 2005;59(11):1345–1355. Permission pending.

Logic for Combination therapy- Use least number of Agents that treat most number of mechanisms of hyperglycemia

Table 3. Beta-Cell-Centric Model: Mediating Pathways of the Egregious Eleven Targeted by Individual Pharmacologic Treatments

	Targeted Mediating Pathway of Hyperglycemia										
Pharmacologic Agents	Incretin Regulation			Insulin Resistance			Kidney	Brain	Colon/ Biome	Stomach/ Small Intestine	Immune Dysregulation/ Inflammation
	BetaCe ll	AlphaCe ll	Incretin Defect	Muscle	Liver	Adipose					
GLP-1RA	√	√	√					√	√	√	√
DPP4-I	√	√	√						√		√
TZD / Pioglitazone	√			√	√	√					
SGLT2-I							√				
Metformin				√					√		
Dopamine-A								√			
Pramlintide		√								√	
Ranolazine	√										
AGI										√	

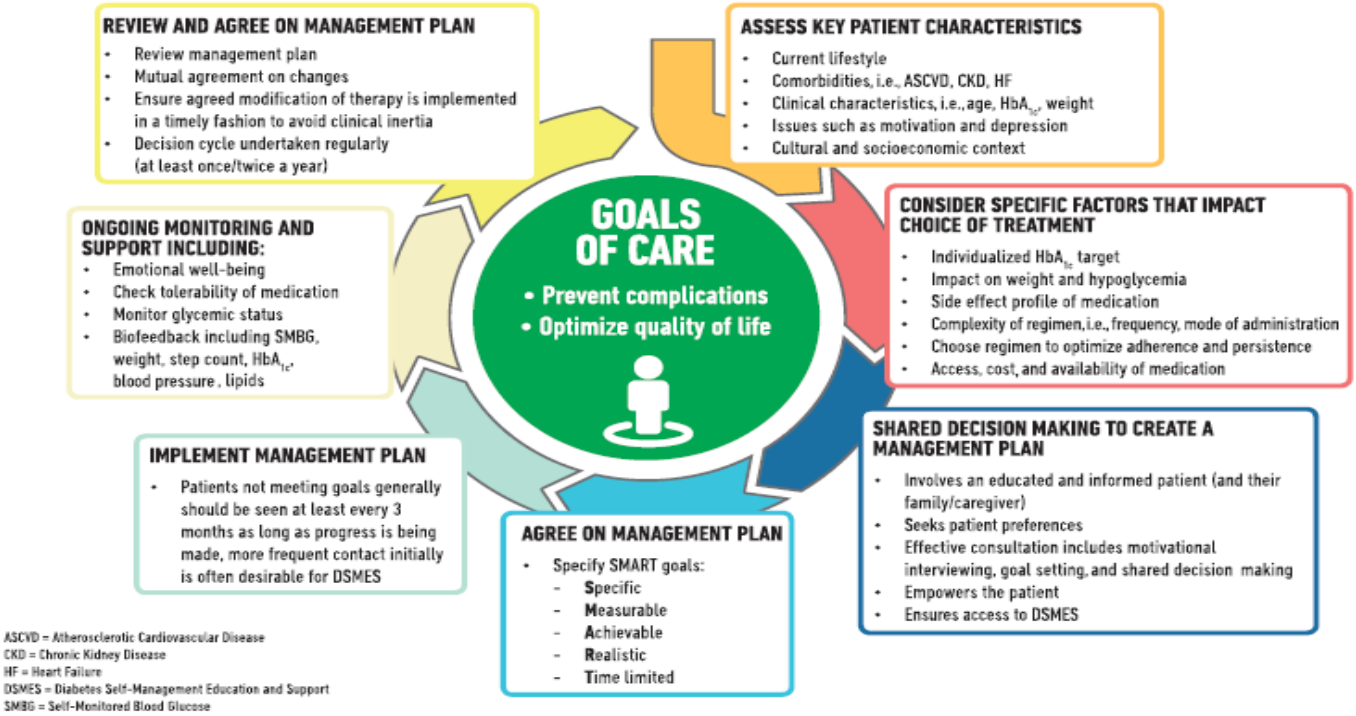


Figure 4.1—Decision cycle for patient-centered glycemic management in type 2 diabetes. Adapted from Davies et al. (119).

Table 4.1 – Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment regimens and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Macrovascular and microvascular	✓		✓
	▪ Common comorbidities (e.g., obesity, OSA)	✓		
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ Presence of hemoglobinopathies or anemias	✓		
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam	✓		✓
	▪ Visits to specialists	✓	✓	✓
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓

LIFESTYLE FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication regimen	✓	✓	✓
	▪ Medication-taking behavior	✓	✓	✓
	▪ Medication intolerance or side effects	✓	✓	✓
	▪ Complementary and alternative medicine use	✓	✓	✓
	▪ Vaccination history and needs	✓		✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc.	✓		✓
	▪ Glucose monitoring (meter/CGM): results and data use	✓	✓	✓
	▪ Review insulin pump settings and use	✓	✓	✓
BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS	**Psychosocial conditions**			
	▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓		✓
	▪ Identify existing social supports	✓		
	▪ Consider assessment for cognitive impairment*	✓		✓
	Diabetes self-management education and support			
	▪ History of dietician/diabetes educator visits/classes	✓	✓	✓
	▪ Assess diabetes self-management skills and barriers	✓		✓
	▪ Assess familiarity with carbohydrate counting (type 1 diabetes)	✓		
	Pregnancy planning			
	▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

Table 4.1 (cont.)– Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)**	✓		✓
	• Screen for PAD (pedal pulses–refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year	✓		✓
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides#	✓		✓^
	• Liver function tests#	✓		✓
	• Spot urinary albumin–to–creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate+	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes#	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		✓
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics+	✓		✓

Diabate TYPE 2 DIABETES

Table 4.2—Assessment and treatment plan*

Assess risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors (see **Table 10.2**) and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (**Table 4.3**)

Goal setting

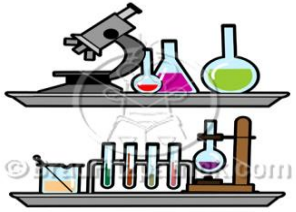
- Set A1C/blood glucose target
- If hypertension present, establish blood pressure target
- Diabetes self-management goals (e.g., monitoring frequency)

Therapeutic treatment plan

- Lifestyle management
- Pharmacologic therapy (glucose lowering)
- Pharmacologic therapy (cardiovascular disease risk factors and renal)
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. *Assessment and treatment planning is an essential component of initial and all follow-up visits.

Diabate
TYPE 2 DIABETES



Doctors (Service Provider)

- Continuous Professional Development (Update Guideline)
- Good communication
- Cost-containment strategy
- Referral in time
- No clinical inertia

Process indication

- Periodic HbA1c testing
- Periodic lipid testing
- Periodic creatinine testing
- ECG

Patient

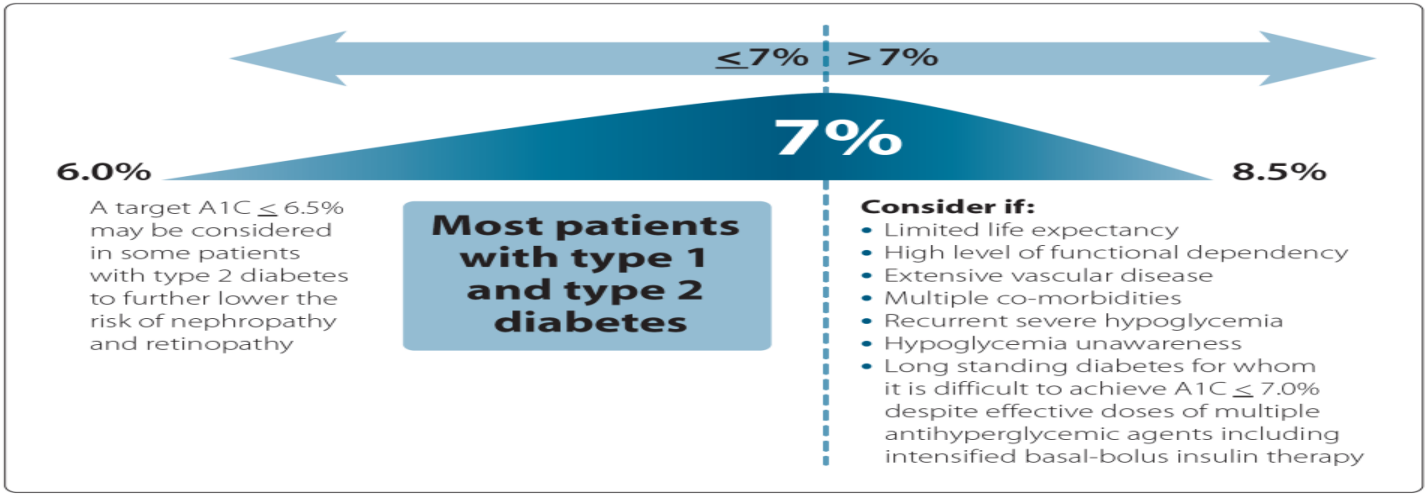
- Trust
- Adherence
- Satisfaction

Health outcome

- Glycaemic control
- Blood pressure control
- Lipid control

Target

- Target HbA1c 7%(6.5% if tolerated)-(Intensive control is better than conventional control
- individualized



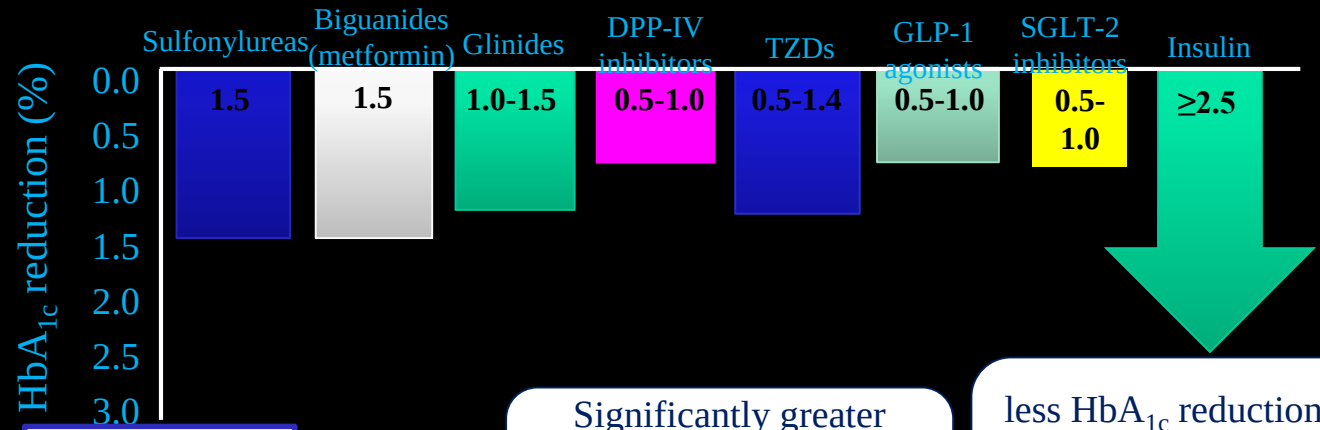
Summary of glycemic recommendations for non-pregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Pre-prandial capillary plasma glucose	80 –130 mg/dL* (4.4 –7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10 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 are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Effecacy of anti-diabetic agent



Efficacy as mono therapy

Significantly greater HbA_{1c} reductions on insulin,SU and Metformin

less HbA_{1c} reductions on GLP1, DPP4Inhibitors and SGLT2 Inhibitors

Initial Choice of Therapy Depends on Glycemia (ADA 2018)

MONOTHERAPY

A1c < 9%
FBS <150
RBS<250

DUAL THERAPY

A1c ≥ 9%
FBS 150-200
RBS 250-350

COMBINATION INJECTABLE THERAPY

A1c ≥ 10%
BG ≥ 300 mg/dl
Markedly symptomatic
FBS >200

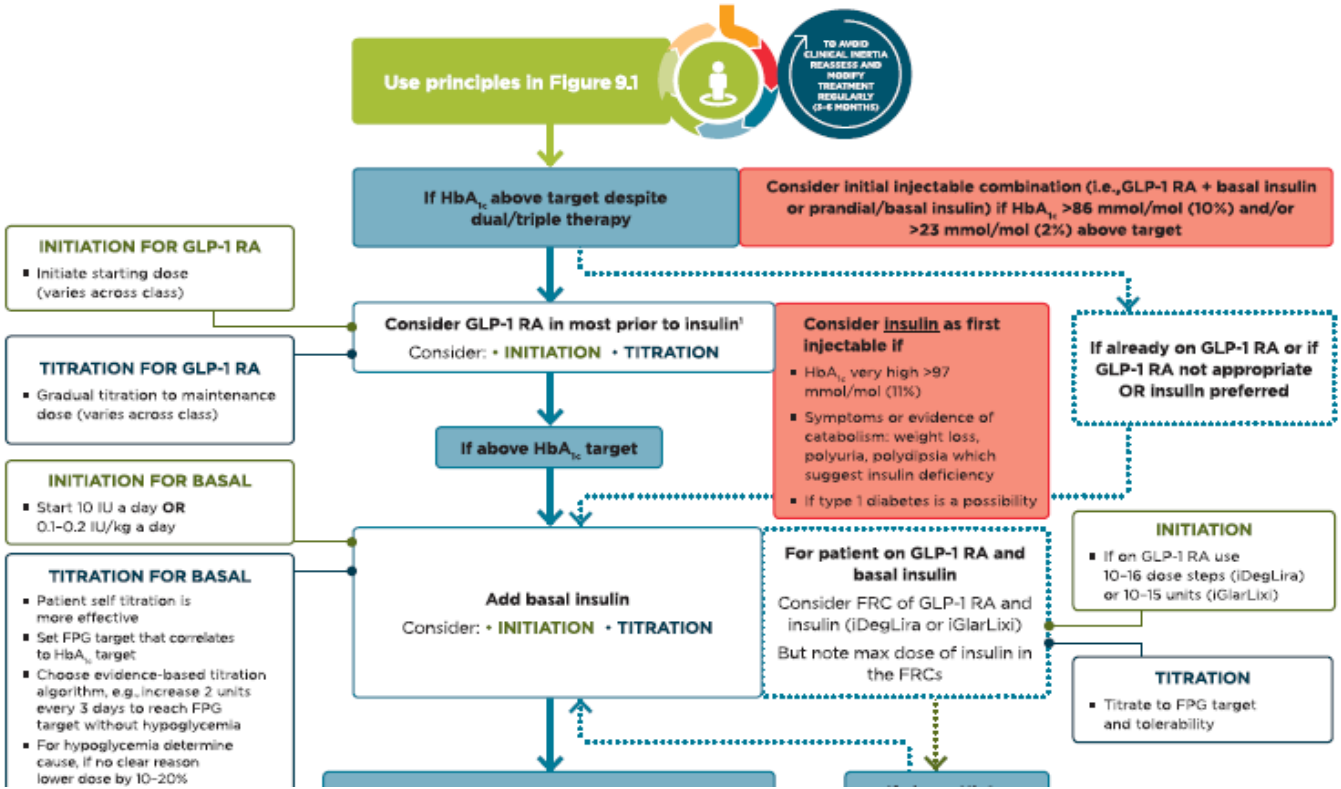
Uncontrol DM

- 54 male ,On Metformin 1 G BD+Glicalzide MR 120 mg od+sitagliptin 100mg OD ,HbA1c 9.5%

What is next STEP? Check

- Drug Compliance
- Diet
- Stress
- Diabetogenic drugs –Steroid,indigenous medicine

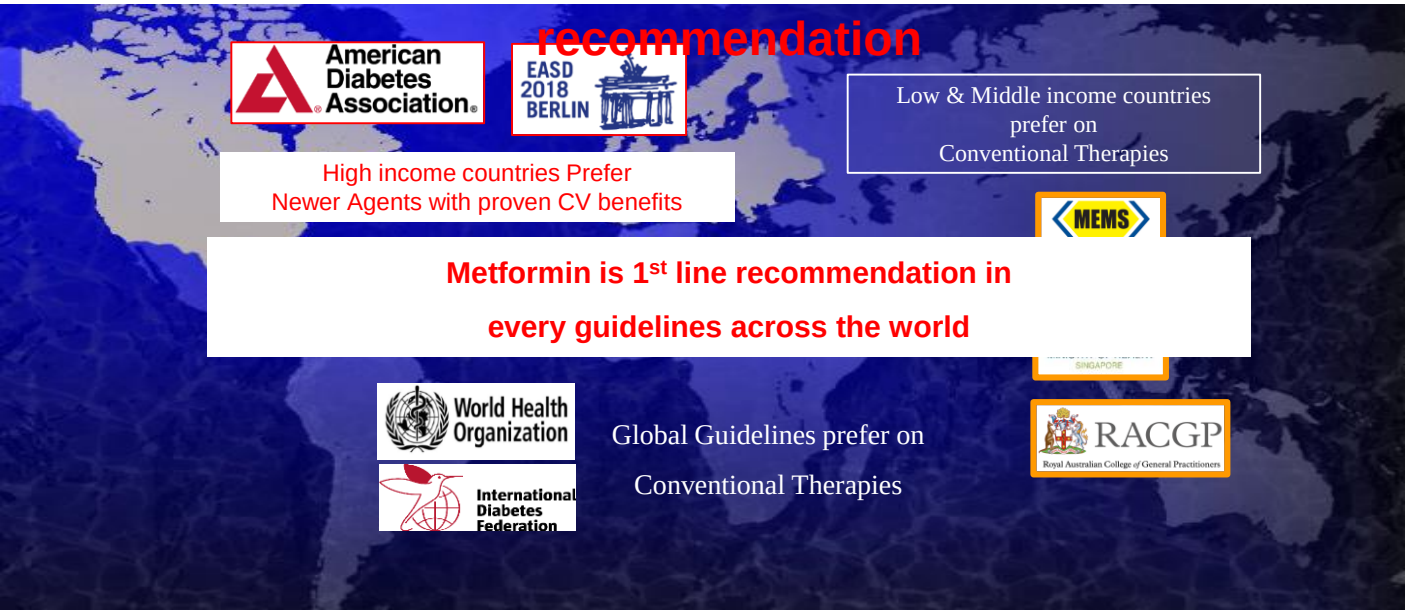
Basal insulin or GLP 1


Use principles in Figure 9.1
TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If HbA1c above target despite dual/triple therapy
Consider initial injectable combination (i.e., GLP-1 RA + basal insulin or prandial/basal insulin) if HbA1c >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target
INITIATION FOR GLP-1 RA
Initiate starting dose (varies across class)
TITRATION FOR GLP-1 RA
Gradual titration to maintenance dose (varies across class)
Consider GLP-1 RA in most prior to insulin[1]
Consider: • INITIATION • TITRATION
Consider insulin as first injectable if
HbA1c very high >97 mmol/mol (11%)
Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
If type 1 diabetes is a possibility
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above HbA1c target
INITIATION FOR BASAL
Start 10 IU a day OR 0.1–0.2 IU/kg a day
TITRATION FOR BASAL
Patient self titration is more effective
Set FPG target that correlates to HbA1c target
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Add basal insulin
Consider: • INITIATION • TITRATION
For patient on GLP-1 RA and basal insulin
Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi)
But note max dose of insulin in the FRCs
INITIATION
If on GLP-1 RA use 10–16 dose steps (iDegLira) or 10–15 units (iGlarLixi)
TITRATION
Titrate to FPG target and tolerability


lower dose by 10–20%
INITIATION FOR PRANDIAL
4 IU a day or 10% of basal dose
If HbA1c <64 mmol/mol (8%) consider lowering the total dose by 4 IU a day or 10% of basal dose
TITRATION FOR PRANDIAL
Increase dose by 1–2 IU or 10–15% twice weekly
For hypoglycemia determine cause, if no clear reason lower corresponding dose by 10–20%
INITIATION OF STEPWISE PRANDIAL
Stepwise addition of prandial insulin every 3 months if HbA1c > target is associated with lower risk of hypoglycemia and increases patient satisfaction compared with immediate introduction of full basal-bolus regimen
TITRATION FOR PRANDIAL
If above HbA1c target
Despite adequately titrated basal insulin OR once basal dose >0.7–1.0 IU/kg OR FPG at target
Add prandial insulin
Usually one dose with the largest meal or meal with greatest PPG excursion
Consider: • INITIATION • TITRATION
If above HbA1c target
Stepwise additional injections of prandial insulin
(i.e., two, then three additional injections)
Consider: • INITIATION • TITRATION
If above HbA1c target
INITIATION FOR PRANDIAL
TITRATION FOR PRANDIAL
Proceed to FULL basal-bolus regimen, i.e., basal insulin and prandial insulin with each meal
Consider:
• INITIATION • TITRATION
IF HbA1c DOES NOT IMPROVE REVIEW ONGOING NEED FOR BASAL-BOLUS REGIMEN. CONSIDER ADDITIONAL DSMES
If above HbA1c target
Additional basal insulin or additional prandial insulin
Consider twice or three times daily premix insulin regimen
Caution higher risk of hypoglycemia and/or weight gain
Consider:
• INITIATION
• TITRATION
INITIATION
In insulin-naive patients 10–12 IU or 0.3 IU/kg
If on existing insulin regimen usually unit to unit at the same total insulin dose but may require adjustment to individual needs
TITRATION
Individual dose adjustment depends on type of biphasic insulin
More complex if on three times daily regimen

Diabetes divide the world in TWO

Different Guidelines : different recommendation



Types of Oral Anti-Diabetes Agents (Available in Myanmar)

1. Biguanides (Metformin, Metformin SR)
2. Sulphonylureas (SU) (Gliclazide, Gliclazide MR, Glimepride, Glipizide)
3. Thiazolidinediones (TZDs) (Pioglitazone)
4. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors (Sitagliptin, Linagliptin, Vildagliptin)
5. Sodium-glucose Co-transporter 2 (SGLT-2) Inhibitors (Canagliflozin is available now,Empagliflozin will be available soon)
6. α-Glucosidase Inhibitors (AGIs) (Acarbose, Voglibose)
7. Meglitinides (Repaglinide)
8. Quick-release dopamine receptor agonist bromocriptine mesylate (Dibor)

Maximum Daily Dose for OHAs

OHAs	Maximum daily dose
Metformin	3 g
Gliclazide	320 mg
Glimepiride	6-8 mg
Glipizide	20 mg
Glibenclamide	15 mg
Acarbose	600 mg
Pioglitazone	45 mg
Rosiglitazone	8 mg
Novonorm	4 mg/meal, 16 mg/day

Why Metformin?

- **Pros** **cons**

- weight neutral
- safe(long record)
- reduce insulin resistance
- cardiovascular safe
- lipid neutral and reduce LDL
- can reduce cancer
- cheap
- durable
- widely available

GI SE:N,V,D

Can't use in severe renal cardiac and liver failure

Table 3—Recommended dose adjustments for noninsulin antihyperglycemic agents in DKD

Medication	In patients with impaired GFR	In dialysis patients
Biguanides		
Metformin	U.S. prescribing information states "do not use if serum creatinine ≥1.5 mg/dL in men, ≥1.4 mg/dL in women" British National Formulary and the Japanese Society of Nephrology recommend cessation if eGFR <30 mL/min/1.73 m^2	Contraindicated

Table 4—Recommended dose adjustments for metformin based on eGFR

eGFR (mL/min/1.73 m^2)	Proposed action
≥60	No contraindication to metformin Monitor kidney function annually
<60 and ≥45	Continue use Increase monitoring of renal function (every 3–6 months)
<45 and ≥30	Prescribe metformin with caution Use lower dose (e.g., 50%, or half-maximal dose) Closely monitor renal function (every 3 months) Do not start new patients on metformin
<30	Stop metformin

Adapted with permission from ADA (83).

Why Sulfonylureas?

- Most of the guidelines Endorse as in 1st and 2nd-line therapy except AACE
- At least 25% of patients with type 2 diabetes are using sulfonylureas

Pros	Cons
Strong Efficacy (↓ HbA1c-1.5%)	Hypoglycemia
Prompt HbA1c reduction	Weight Gain
Effective Symptom Control	CV Safety
Cardiovascular Safe	Beta Cell Fatigue
Cheap	Need to use in early treatment
Time-Tested Drugs	
Long Term Evidence	
Easily & Widely available	
Can be use in Renal, heart failure	

Sulfonylureas: How to Choose?

- Cardiac patients: Glimepiride/GLICLAZIDE
- Elderly patients: Glimepiride/GLICLAZIDE
- Economy: Glibenclamide
- Mild renal insufficiency: Glimepiride
- Severe Renal : Gliclazide and glipizide
- Require high potency: Glibenclamide
- Relatively younger patients: Glibenclamide

Dipeptidyl Peptidase-4 Inhibitors

Efficacy : modest improvement in A1C (0.5-0.74 %)
Low Risk Of Hypoglycemia
Favorable Adverse-effect Profile
Weight Neutral
Easy Dosing
Appear to have the potential, at least experimentally, to decrease β-cell apoptosis and increase β-cell survival

DPP-4 Inhibitor–Related Pancreatitis: Rare but Real!

Diabetes Care 2017;40:161–163 | DOI: 10.2337/dci16-0035

Drugs	Formulation	Minimum Dose	Maximum Dose
Sitagliptin	25 mg / 50 mg / 100 mg	25 mg OD	100 mg OD
Vildagliptin	50 mg	25 mg BD	50 mg BD
Saxagliptin	2.5 mg / 5 mg	2.5 mg OD	5 mg OD
Linagliptin	5 mg	5 mg OD	5 mg OD
Alogliptin	6.25 mg / 12.5 mg / 25 mg	6.25 mg OD	25 mg OD

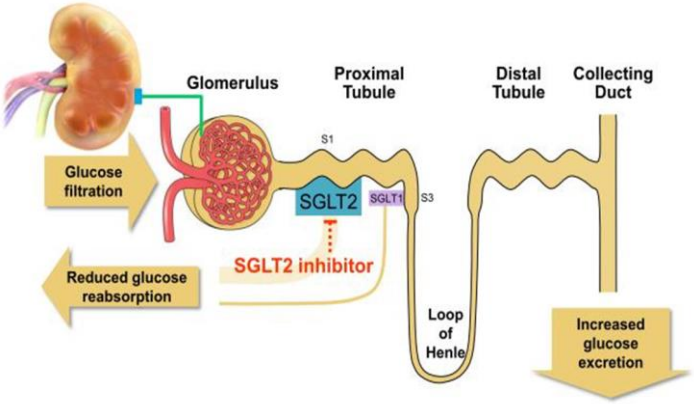
- For fixed combination formulations, please refer to specific product inserts.

SGLT2 inhibitors

Pros	Cons
• No Hypoglycemia • Weight loss • Benefits in ASCVD and also HF • Benefits in Progression of DKD	▪ FDA black box : Risk of amputation (Canaglipflozin) ▪ Intermediate efficacy ▪ High Cost ▪ Risk of Bone Fractures (Canaglipflozin) ▪ DKA risk (all agents, Reae in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion (Hypotension) ▪ Increase LDL cholesterol
	Contraindicated in eGFR < 60 – Dapagliflozin eGFR < 45 – Canagliflozin eGFR < 30 – Dapagliflozin, Empagliflozin

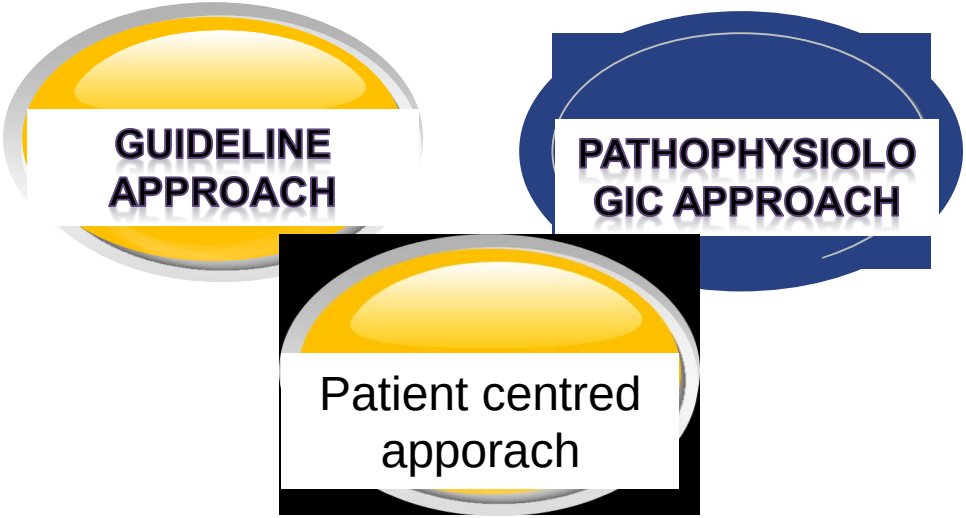
Drugs	Formulation	Minimum Dose	Maximum Dose
Dapagliflozin	5 mg / 10 mg	5 mg OD	10 mg OD
Canagliflozin	100 mg / 300 mg	100 mg OD	300 mg OD
Empagliflozin	10 mg / 25 mg	10 mg OD	25 mg OD

- This class of drugs selectively inhibits SGLT2, a transporter in the proximal tubule, thus reducing glucose reabsorption leading to an increase in urinary glucose excretion.
- It reduces A1c by 0.2% to 0.8%.
- This is accompanied by
- weight loss (2.5 to 3.0 kg)
- modest blood pressure reduction
- lower risk of hypoglycaemia.



4

Three approaches to the Initial Treatment of Type 2 Diabetes Mellitus



MSEM ,MMDA

Treatment Algorithm

Metformin or Gliclazide

↓ **Not well controlled**

Metformin + Gliclazide

↓ **Not well controlled**

Metformin + Gliclazide + Pioglitazone

Or

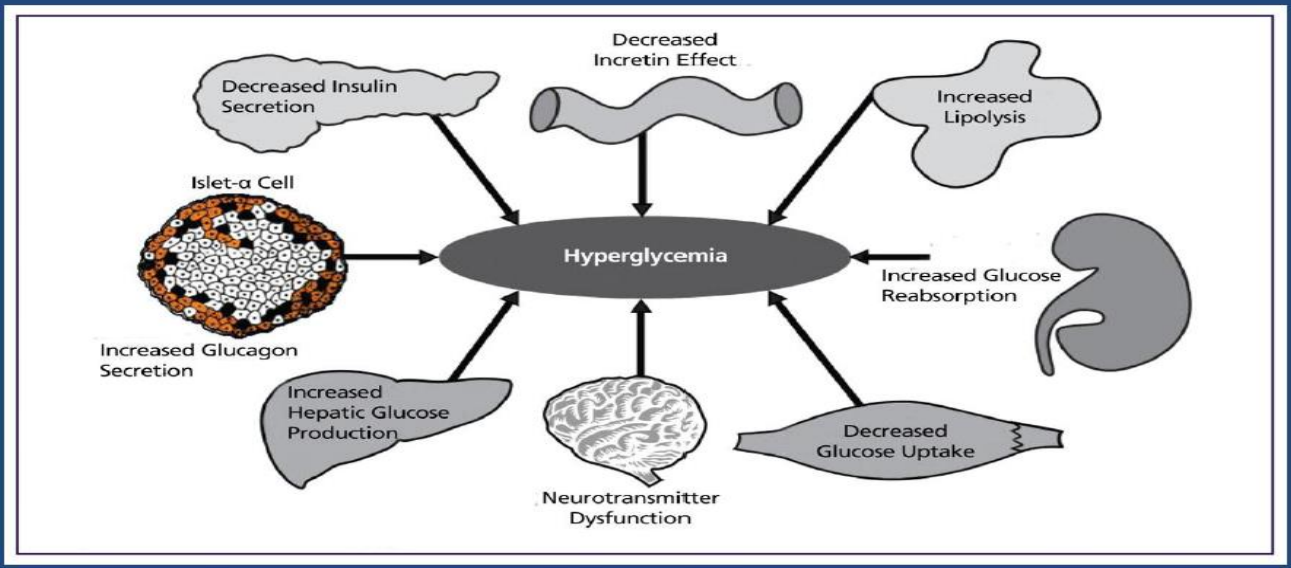
Metformin + Gliclazide + Sitagliptin

Not well controlled

↓

Oral triple therapy + Basal insulin

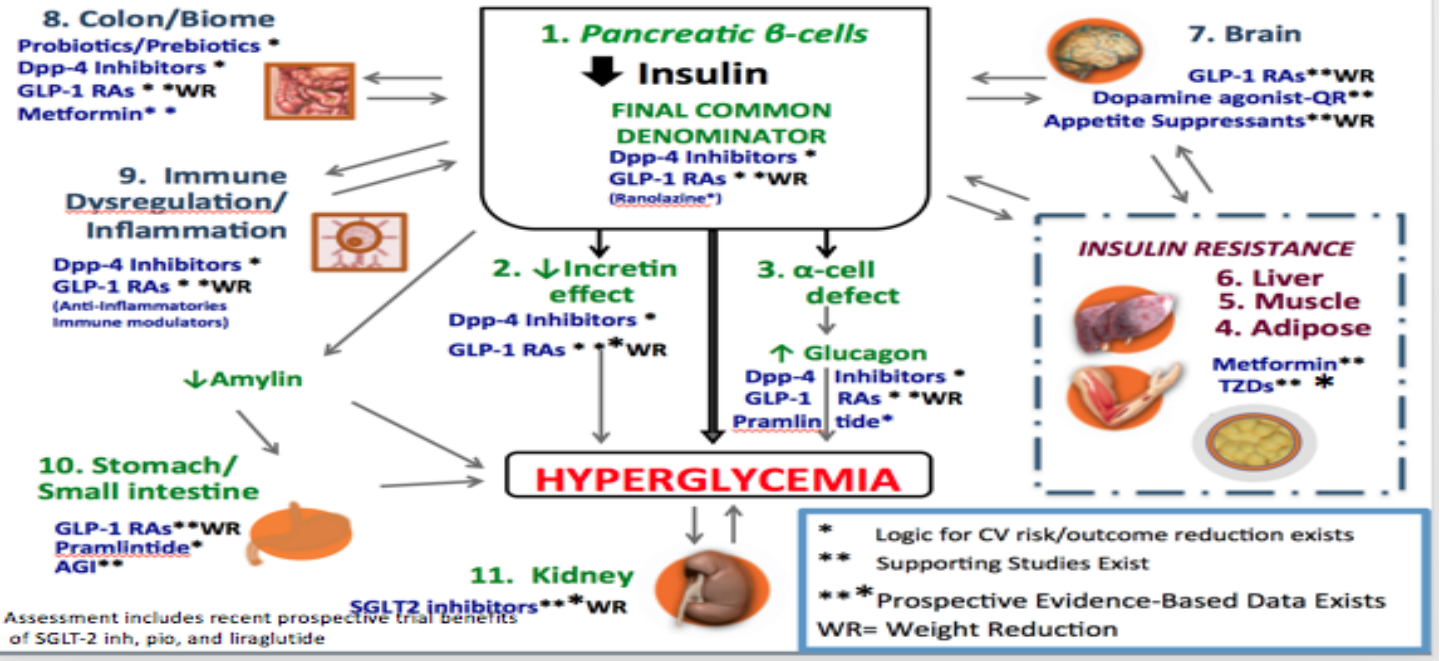
Our Belief And Knowledge Regarding Type 2 Diabetes Pathogenesis Has Evolved To Include Multiple Organ Defects Known As The "Ominous Octet"

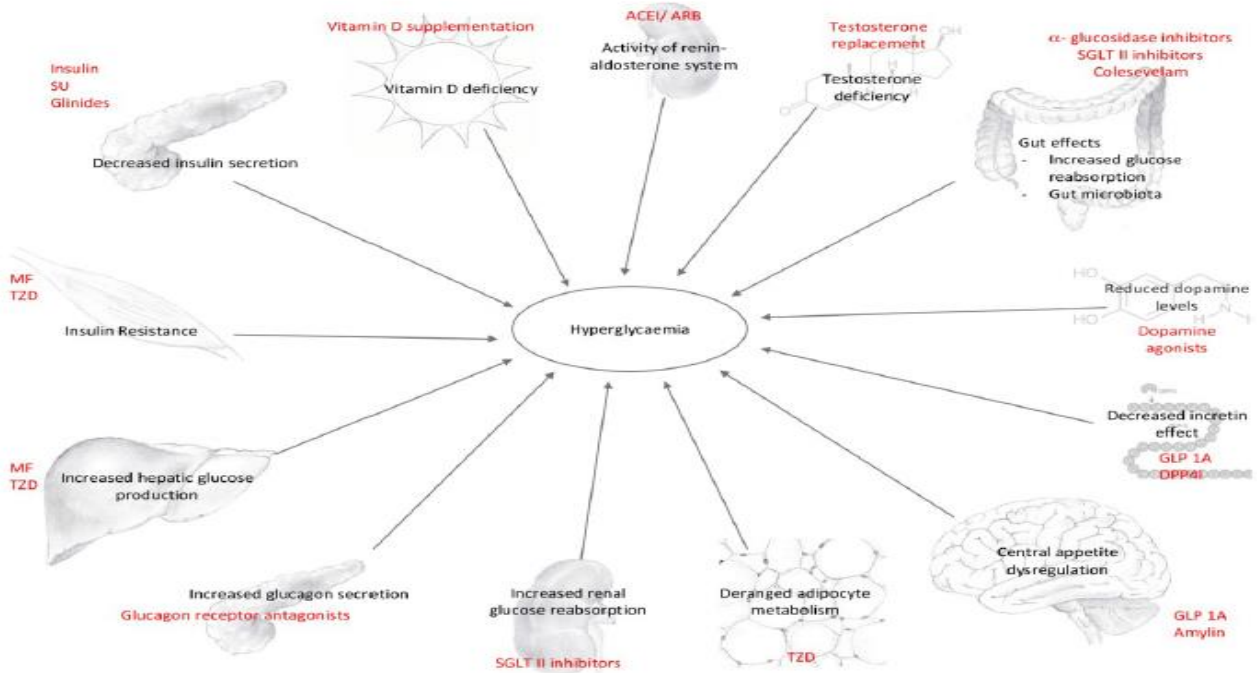


DeFronzo RA. *Diabetes*. 2009. 58 (4): 773-795.

Precision Medicine Approach to DM/ CV Therapy: Algorithms should Assess not only Glycemic benefits of agents/classes but CV/weight benefits

***Implications for New Guidelines





ıre 1. Unlucky Thirteen in Diabetes SU, sulfonylurea; MF, metformin; TZD, thiazolidinediones; SGLT, sodium glucose co transporter; 1A, glucagon like peptide 1 agonists; DPP4i, dipeptidyl peptidase 4 inhibitors; ACEi, angiotensin converting enzyme inhibitor; ARB, iotensin II receptor blockers

Current Guidelines Emphasize the Value of Individualized Treatment to Improve Glycemic Control While Considering Side Effect Profiles

- Glycemic control remains a challenge for many people with diabetes[1]
  - NHANES data: 48% of adults with diabetes are uncontrolled*
- To achieve glycemic control, current guidelines recommend evaluating therapeutic options using 5 key considerations[2,3]:

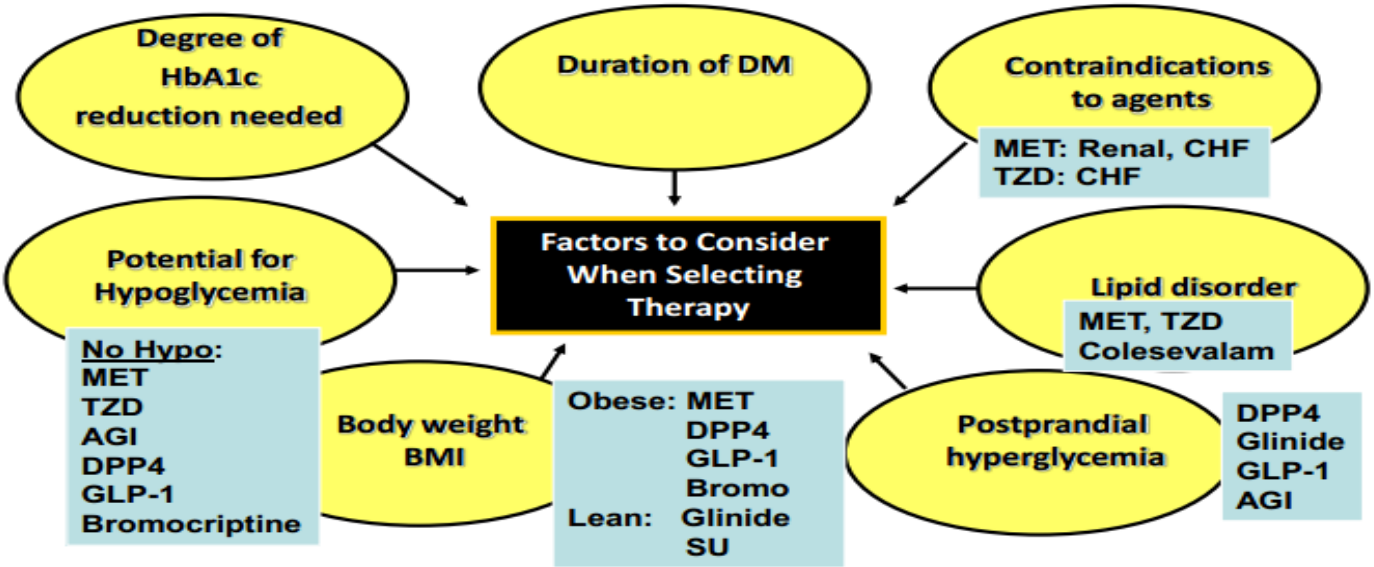
Pathophysiology and individual patient needs must also be considered when developing a type 2 diabetes disease management strategy[2,3]

* Data from NHANES 2007–2010 included 1444 adults aged 18 years or older who reported having received a diagnosis of diabetes from a health care professional.[1]
NHANES=National Health and Nutrition Examination Survey.

1. Ali MK et al. *N Engl J Med*. 2013;368:1613-1624. 2. Inzucchi SE et al. *Diabetes Care*. 2012;35:1364-1379.
3. Garber AJ et al. *Endocr Pract*. 2013;19:536-557.

AstraZeneca

Factors to Consider When Selecting Therapy in Type 2 Diabetes



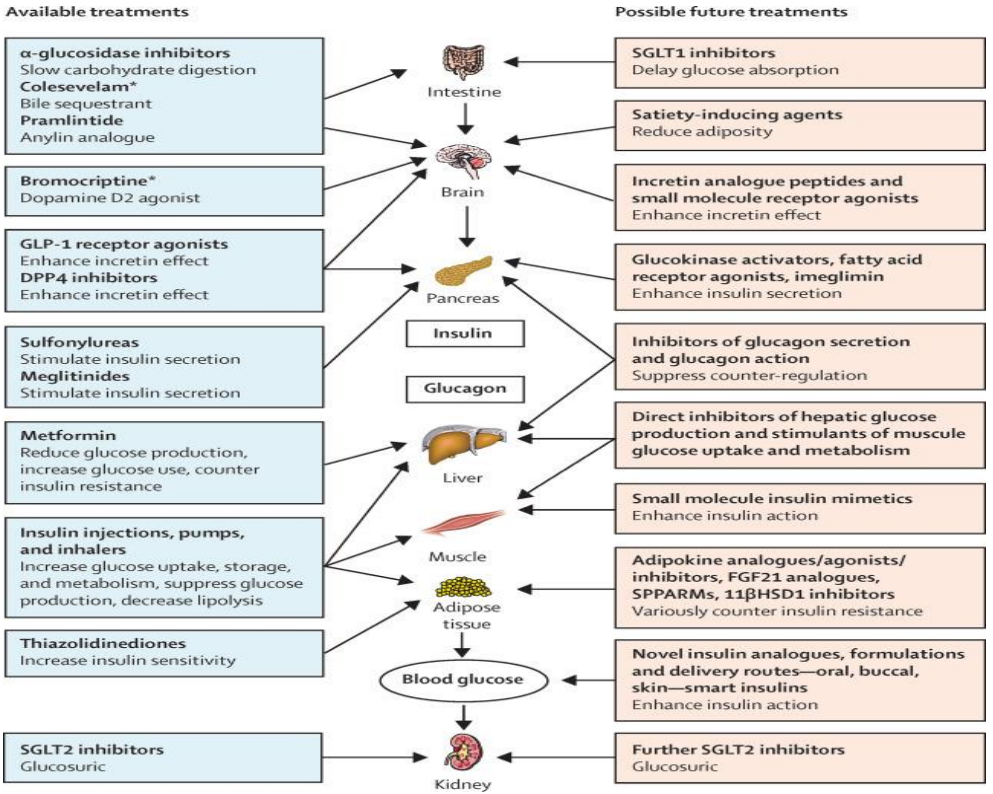
Internal Medicine Board Review 2010

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide† > semaglutide > exenatide extended release	Neutral	High	SQ	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Potential risk of acute pancreatitis ▪ Joint pain

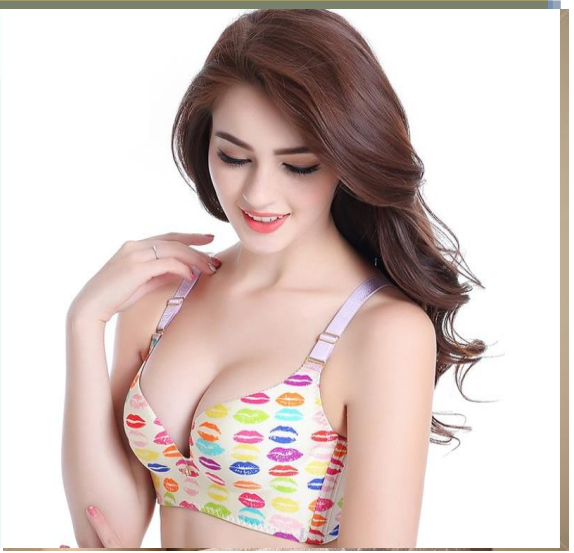
		Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
					ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Thiazolidinediones		High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)		High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin	Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
	Analogs						High	SQ			

*For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.


Available treatments
α-glucosidase inhibitors
Slow carbohydrate digestion
Colesevelam*
Bile sequestrant
Pramlintide
Anylin analogue
Bromocriptine*
Dopamine D2 agonist
GLP-1 receptor agonists
Enhance incretin effect
DPP4 inhibitors
Enhance incretin effect
Sulfonylureas
Stimulate insulin secretion
Meglitinides
Stimulate insulin secretion
Metformin
Reduce glucose production, increase glucose use, counter insulin resistance
Insulin injections, pumps, and inhalers
Increase glucose uptake, storage, and metabolism, suppress glucose production, decrease lipolysis
Thiazolidinediones
Increase insulin sensitivity
SGLT2 inhibitors
Glucosuric
Intestine
Brain
Pancreas
Insulin
Glucagon
Liver
Muscle
Adipose tissue
Blood glucose
Kidney
Possible future treatments
SGLT1 inhibitors
Delay glucose absorption
Satiety-inducing agents
Reduce adiposity
Incretin analogue peptides and small molecule receptor agonists
Enhance incretin effect
Glucokinase activators, fatty acid receptor agonists, imeglimin
Enhance insulin secretion
Inhibitors of glucagon secretion and glucagon action
Suppress counter-regulation
Direct inhibitors of hepatic glucose production and stimulants of muscule glucose uptake and metabolism
Small molecule insulin mimetics
Enhance insulin action
Adipokine analogues/agonists/ inhibitors, FGF21 analogues, SPPARMs, 11βHSD1 inhibitors
Variously counter insulin resistance
Novel insulin analogues, formulations and delivery routes—oral, buccal, skin—smart insulins
Enhance insulin action
Further SGLT2 inhibitors
Glucosuric

Which Drugs ?Old or New?

Metformin
SU
PIOGLITAZONE
INSULIN



DPP4 inhibitors
GLP1
SGLT2 inhibitors

Individualizing Antihyperglycemic Therapy

Glycemic efficacy

Adverse effects

Cost

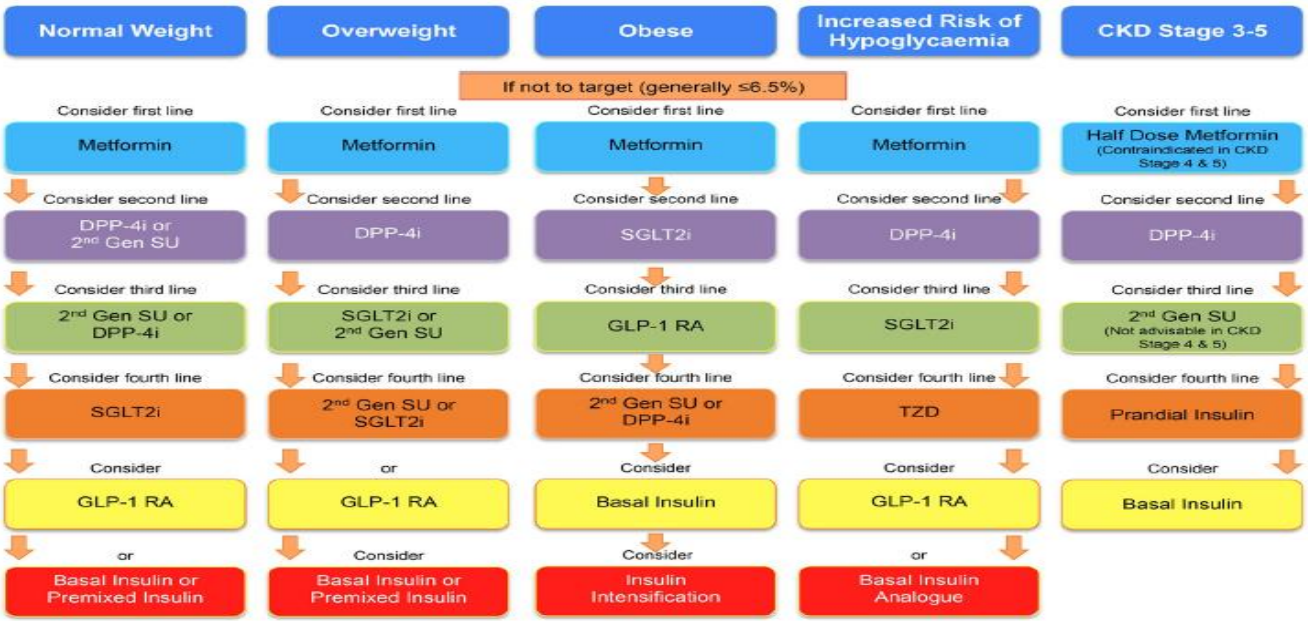
Hypoglycemia risk

Effect on weight

There is no "one size fits all"

Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

Suggested Treatment Approach for Specific Patient Profiles



2nd Gen SU: selected 2nd generation sulphonylurea (gliclazide); DPP-4i: dipeptidyl peptidase-4 inhibitor; SGLT2i: sodium-glucose cotransporter 2 inhibitor; GLP-1 RA: glucagon-like peptide-1 receptor agonist. DPP-4i should be stopped once GLP-1 RA is introduced.

Different types of patient with Different NEEDs

Diabetes in Elderly

Target HbA1c 8
Avoid hypoglycemia,
Polypharmacy

Diabetes in young

Target HbA1c 6.5
Avoid hypoglycemia,
Adherence to drugs
lifestyle

Diabetes Nephropathy

Target HbA1c 7
Avoid hypoglycemia,
Anaemia

Diabetes & obesity

Target HbA1c 7
Choose drug to
reduce
body weight,
Co mobidity

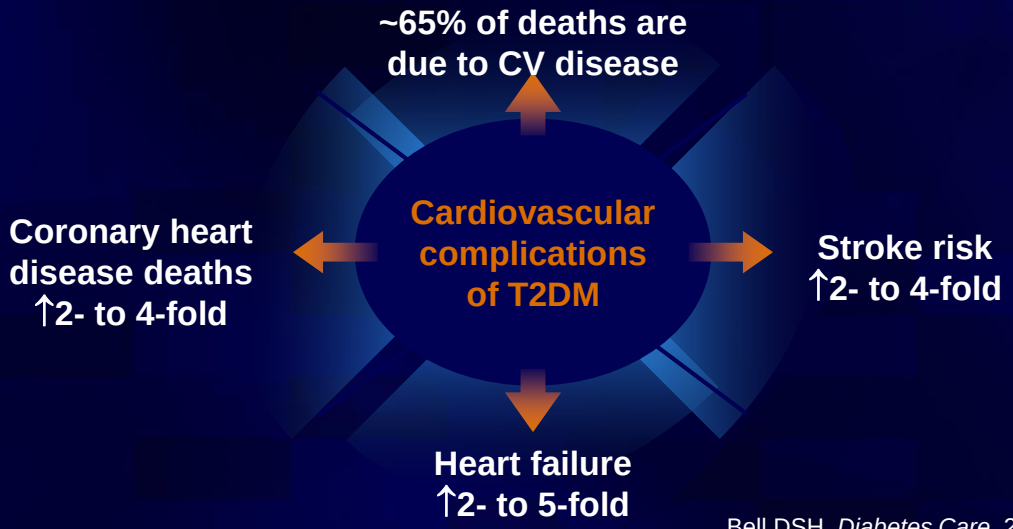
Uncontrolled Diabetes

Target HbA1c 6.5--7
Choose efficient drug
to reduce A1c

Poor Diabetes

Target HbA1c 7
Choose drug with low cost
to reduce A1c
Minimal care

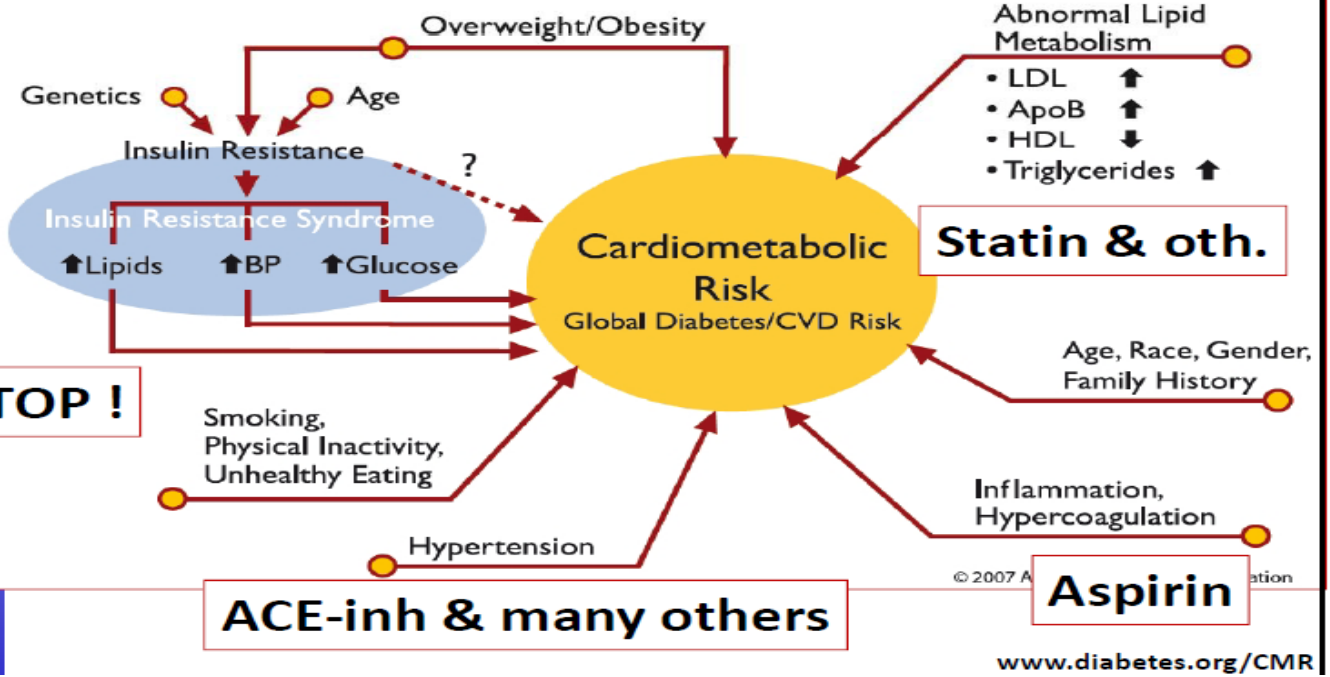
Cardiovascular disease and diabetes

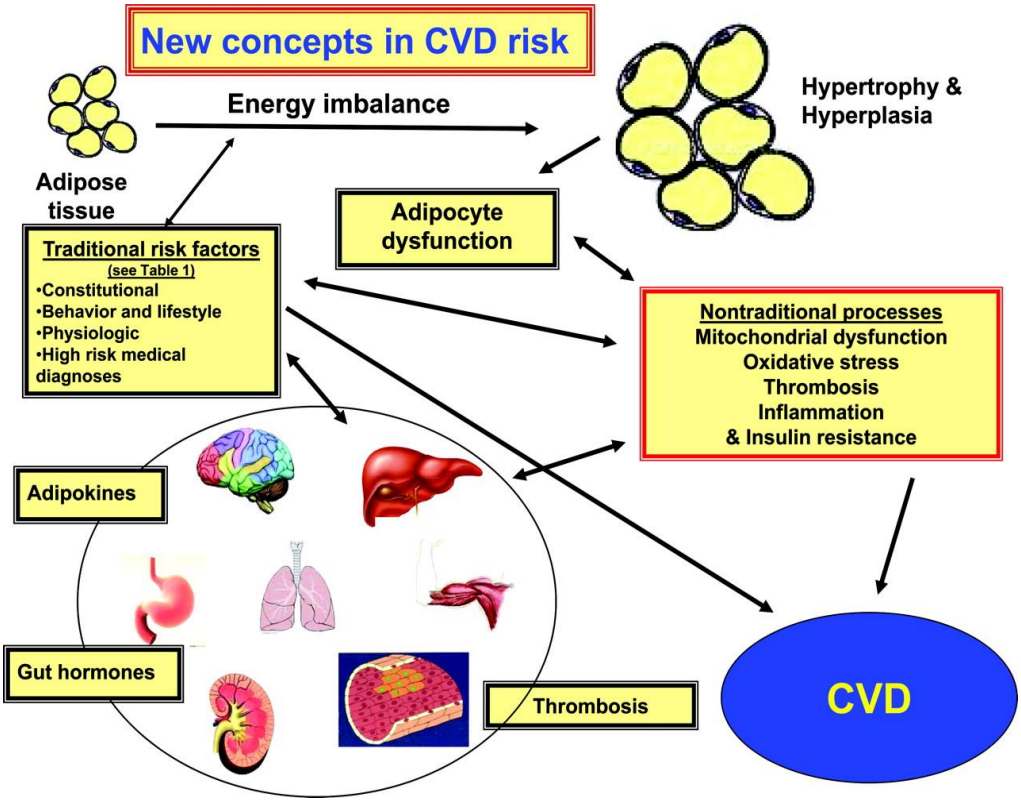


T2DM = type 2 diabetes mellitus

Bell DSH. *Diabetes Care*. 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.

Type 2 diabetes: a complicated way to get cardiovascular disease and die young




New concepts in CVD risk
Energy imbalance
Adipose tissue
Hypertrophy & Hyperplasia
Adipocyte dysfunction
Traditional risk factors
(see Table 1)
•Constitutional
•Behavior and lifestyle
•Physiologic
•High risk medical diagnoses
Nontraditional processes
Mitochondrial dysfunction
Oxidative stress
Thrombosis
Inflammation
& Insulin resistance
Adipokines
Gut hormones
Thrombosis
CVD

How to prevent CVD in DM

THERAPEUTIC LIFESTYLE

GOOD GLYCEMIC CONTROL

TREATMENT OF HYPERTENSION

REDUCTIONS OF LIPIDS

SMOKING CESSATION

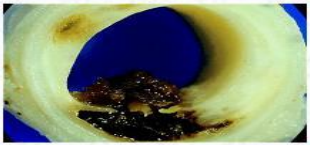
OBESITY REDUCTION

ASPIRIN

Principles for multifactorial management of people with diabetes

Life style modification

- Glycaemic control
- Antiplatelet therapy
- Blood pressure control
- Lipid control



www.escardio.org/guidelines

Full text: European Heart Journal 2013;34(39):3035-3087
Summary: ESC web site & Diabetologia 2013;56(12)

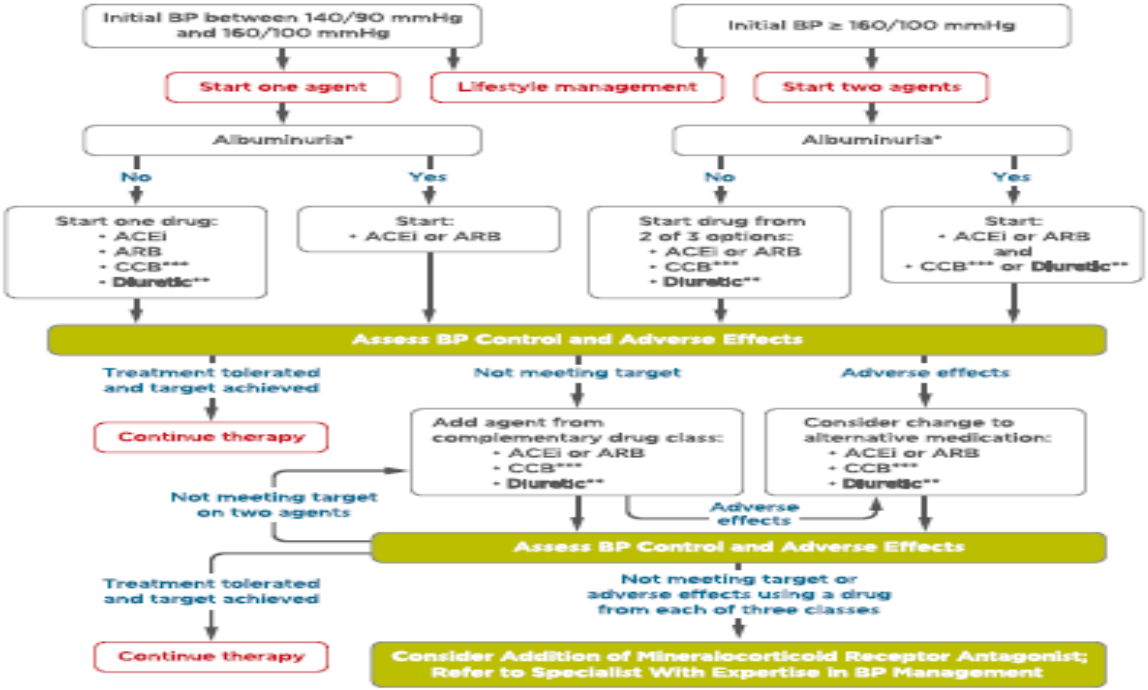
EUROPEAN SOCIETY OF CARDIOLOGY®

Treating the ABCs Reduces Diabetic Complications

Strategy	Complication	Reduction of Complication
Blood glucose control	• Heart attack	↓ **37%**[1]
Blood pressure control	• Cardiovascular disease	↓ **51%**[2]
	• Heart failure	↓ **56%**[3]
	• Stroke	↓ **44%**[3]
	• Diabetes-related deaths	↓ **32%**[3]
Lipid control	• Coronary heart disease mortality	↓**35%**[4]
	• Major coronary heart disease event	↓**55%**[5]
	• Any atherosclerotic event	↓**37%**[5]
	• Cerebrovascular disease event	↓**53%**[4]

[1] UKPDS Study Group (UKPDS 33). *Lancet*. 1998;352:837-853.
[2] Hansson L, et al. *Lancet*. 1998;351:1755-1762.
[3] UKPDS Study Group (UKPDS 38). *BMJ*. 1998;317:703-713.
[4] Grover SA, et al. *Circulation*. 2000;102:722-727.
[5] Pyörälä K, et al. *Diabetes Care*. 1997;20:614-620.

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



ADA 2017 Guidelines

Glycemic, Blood Pressure, and Lipid Targets

A1C : < 7.0% (53 mmol/mol)

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

Blood pressure : < 140/90 mm HG

Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden.

Lipids: LDL-C <100 mg/dL (<2.6 mmol/L)

A lower LDL-C target of <70 mg/dL, using a high dose of a statin, may be appropriate in persons with overt CVD

CVD=cardiovascular disease; SBP=systolic blood pressure

AMERICAN DIABETES ASSOCIATION, STANDARDS OF MEDICAL CARE IN DIABETES—
January 2017 Volume 40, Supplem

Aggressive medical therapy in diabetes-ADD

SGLT-2 Inh.
Bromocriptine QR
Pioglitazone
Incretins,
Metformin
Ranolazine

→ **Hyperglycemia/ Insulin resistance**

ACE inhibitors
ARBs
β-blockers
CCBs
Diuretics

→ **Hypertension**

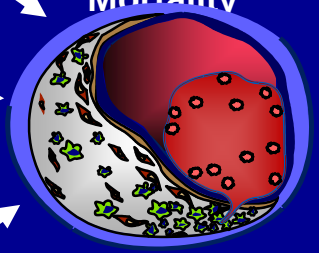
Statins
Fibric acid derivatives
Colsevalam
PCSK-9 Inh

→ **Dyslipidemia**

ASA
Clopidogrel
Ticlopidine

→ **Platelet activation and aggregation**

Atherosclerosis,
CV Outcomes,
CV Risk Factors,
Mortality

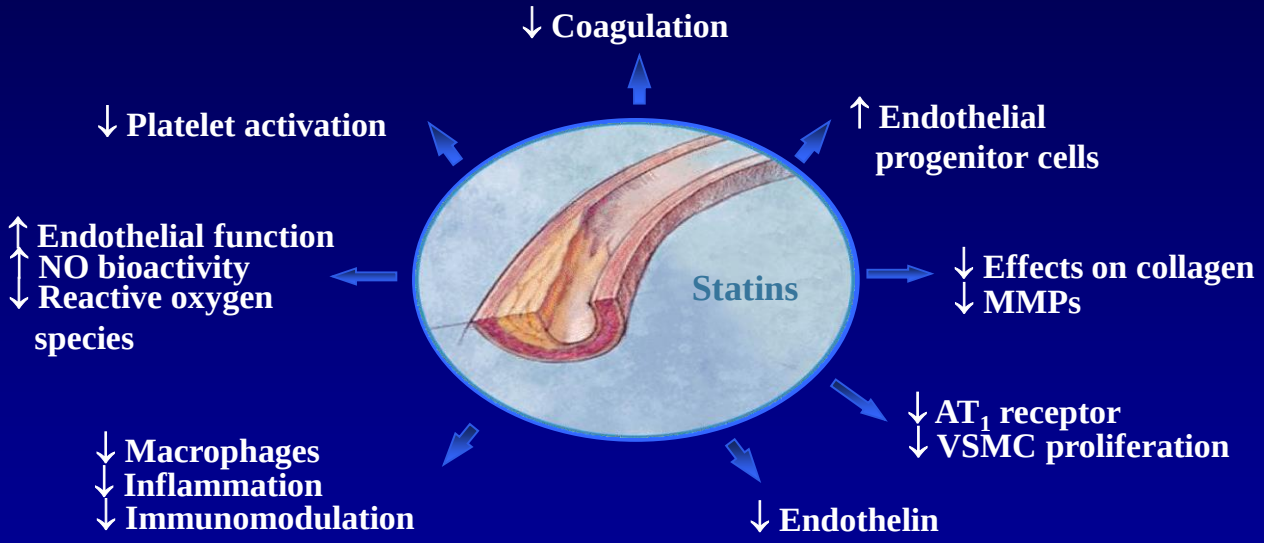


dapted from Beckman JA et al. *JAMA*. 2002;287:2570-81.

Recommendations for Statin Treatment in People with Diabetes

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe

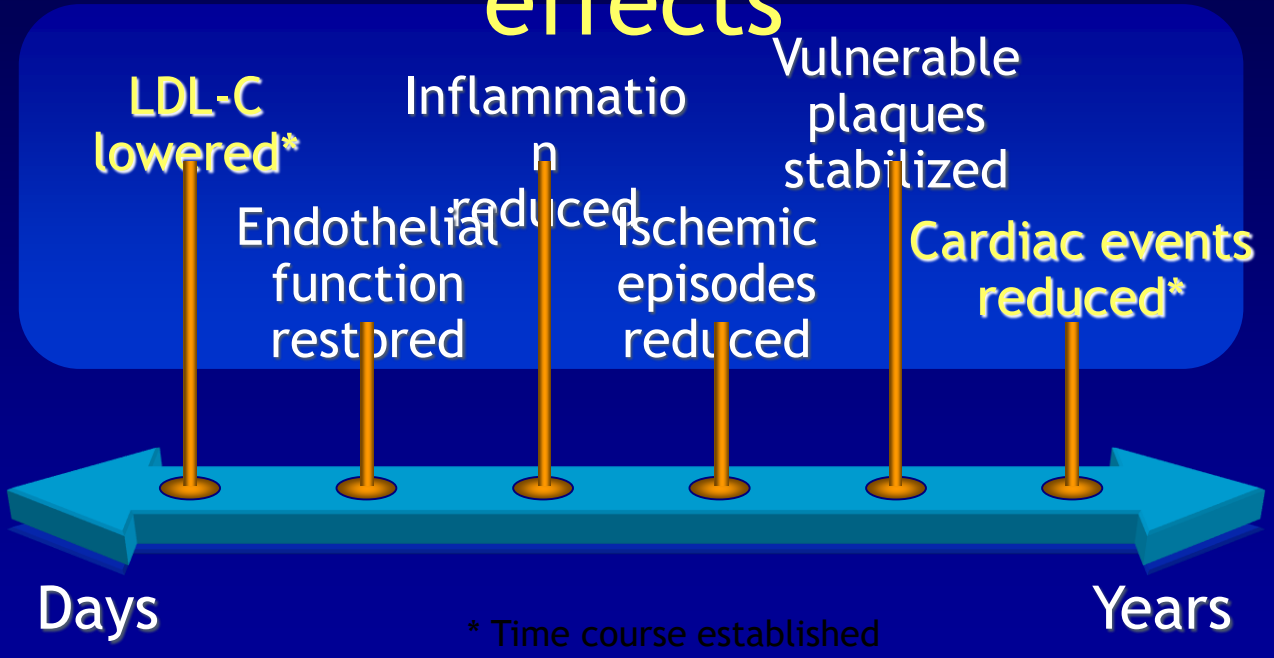
Pleiotropic effects of statins



MMPs = matrix metalloproteinases

Liao JK. *Am J Cardiol*. 2005;96(suppl 1):24F-33F.

Time course of Statin effects



* Time course established

Recommendations: Antiplatelet Agents (3)

- Use aspirin therapy (75–162 mg/day) as secondary prevention in those with diabetes and history of ASCVD. A
- For patients w/ ASCVD & aspirin allergy, clopidogrel (75 mg/day) should be used. B
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. B

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Antiplatelet Agents (2)

- Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effects from bleeding likely offset potential benefits. C
  - Low risk: such as in men or women with diabetes aged <50 years with no major additional ASCVD risk factors)
- In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. E

American Diabetes Association Standards of Medical Care in Diabetes.
Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75-S87

Recommendations: Smoking Cessation

- Advise all patients not to smoke (A)
- Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care (B)

*If not contraindicated.

ADA. VI. Prevention, Management of Complications. *Diabetes Care* 2011;34(suppl 1):S32.

Treat obesity for health benefits

21st century Mona Lisa

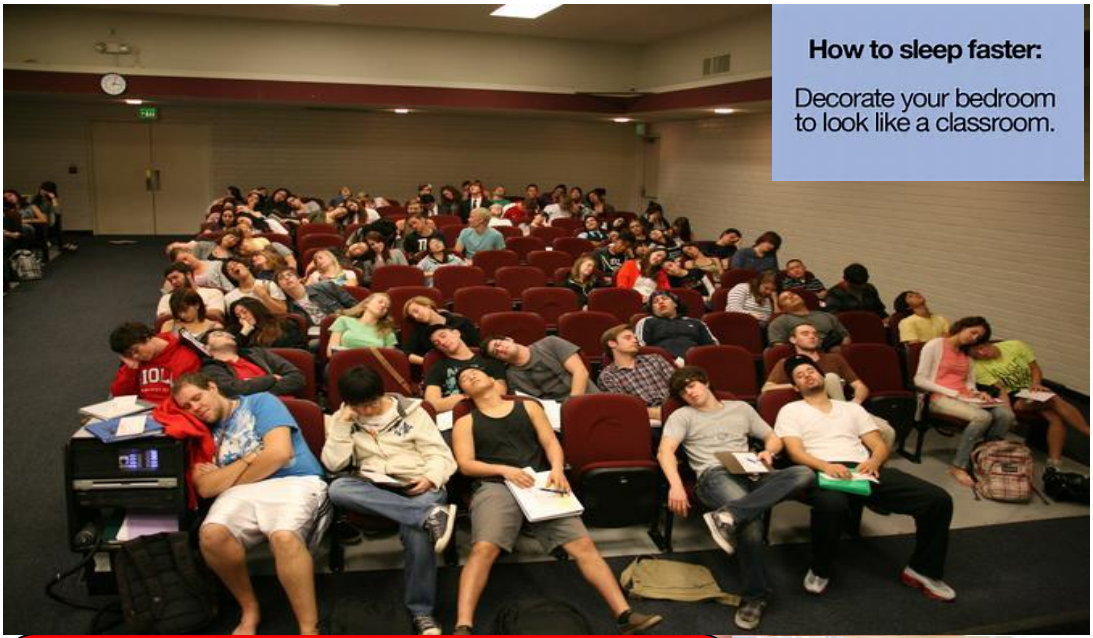
Do not forget Hidden issue in DM

- Nonalcoholic Fatty Liver Disease
- Vaccination(Influenza,Pneumococcal ,Hepatitis B vaccine(<60)
- Fractures(Age-specific hip fracture risk is significantly increased)
- Hearing Impairment(both in high frequency and low/midfrequency ranges, is more common in DM)
- HIV
- Low Testosterone in Men
- Anxiety Disorders
- Depression

- Obstructive Sleep Apnea(The prevalence may be as high as 23%)
- Periodontal Disease(Current evidence suggests that periodontal disease adversely affects diabetes outcomes)
- Psychosocial/Emotional Disorders
- Disordered Eating Behavior
- Serious Mental Illness
- Cancer(increased risk of cancers of the liver, pancreas,endometrium, colon/rectum, breast,and bladder)

Diabetes And Glycemic Control: A Rational Approach

- A = Advice – Diet, Exercise, Stop smoking
- B = BP – 130/80 mm Hg
- C = Cholesterol – LDL 70 mg/dl
- D = Diabetes – FBG, PP BG, HbA1c
- E = Eye checkup regularly
- F = Foot examination daily
- G = Guardian Drugs – Aspirin, Statin, ACE-I



Thank you
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