MMDA
Myanmar Diabetes Association

MYANMAR SOCIETY OF ENDOCRINOLOGY AND METABOLISM
MSEM

New Guidelines;

Implications on Clinical Practice

1. **Diabetes in Children – What are the possibilities?**

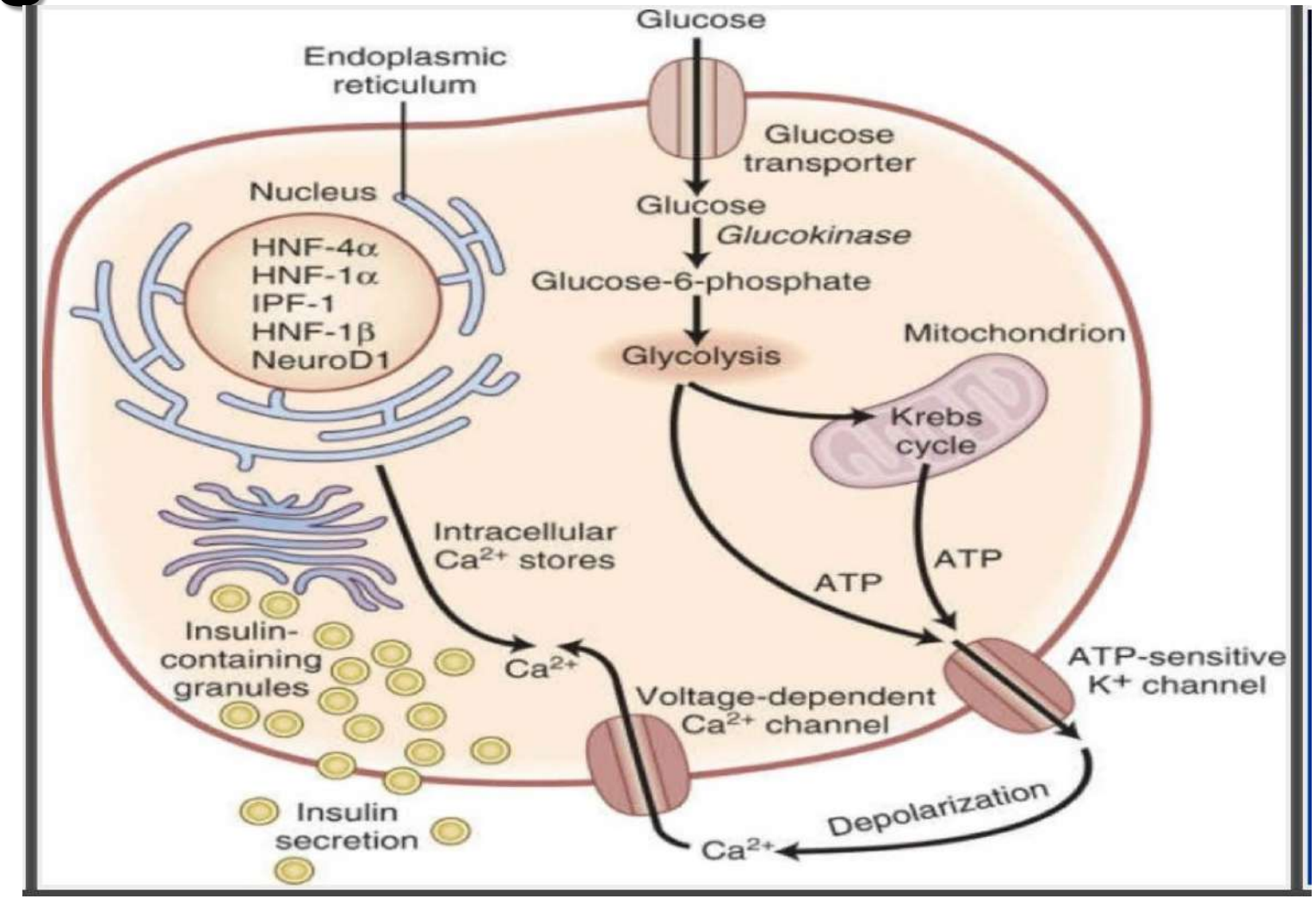
   How would you differentiate each types from others?

Diabetes in children
Monogenic diabetes

Monogenic diabetes

- Inheritance of mutation in single gene
- Dominant, recessive or denovo
- Mutation in genes which regulate beta cell function
- Rare cases due to insulin resistance(I Receptor Leprechaunism, Rabson Mendenhall)
- Can mimic type 1 or type 2 diabetes
- Diagnosis is important to elucidate the pathophysiology , change the treatment and find the affected family screening

How beta cell functions are governed by genes



Mechanism of beta cell function

- Reduce beta cell number
- Pancreatic aplasia

- Reduce beta cell development
- Reduce metabolism
- Reduce glucose sensing

- Failure to depolarize memb
- Failure to close KATP channel

Gene mutation

- IPF1homozygous
- HNF1β

- GCK
- HNF1B
- HNF1α
- HNF4α
- IPF1 heterozygous

- KCNJ11
- ABCC8

When to suspect

- Neonatal diabetes and diabetes associated within the first 6 months of life
- Familial diabetes with an affected parent
- Mild (5.5-8.5 mmol/L) fasting hyperglycemia especially if young or familial
- Diabetes associated with extra pancreatic features

  Renal cysts & developmental kidney disease

How to diagnose

- Molecular testing for mutations - Costly
- Careful patient selection for C peptide level and autoantibody testing
- Genetic testing is recommended if
- Diabetes is diagnosed within first 6months of age
- Diabetes is diagnosed in children and young adults, with strong family history of diabetes, who do not have typical features of type 1 or type 2 diabetes –autoantibodies, metabolic features
- A person has stable, mild fasting hyperglycemia especially when obesity is not present

Neonatal Diabetes

- Rare form of diabetes , usually diagnosed in children under 6 months of age
- 1 in 300,000 to 400,000 births
- Due to genetic mutation , so can described as monogenic form of diabetes
- 2 main types - Transient Neonatal diabetes mellitus(TNDM)

  - Permanent Neonatal diabetes mellitus(PNDM)
- Caused by defects in insulin secretions

  beta cell development

Salient features of NDM

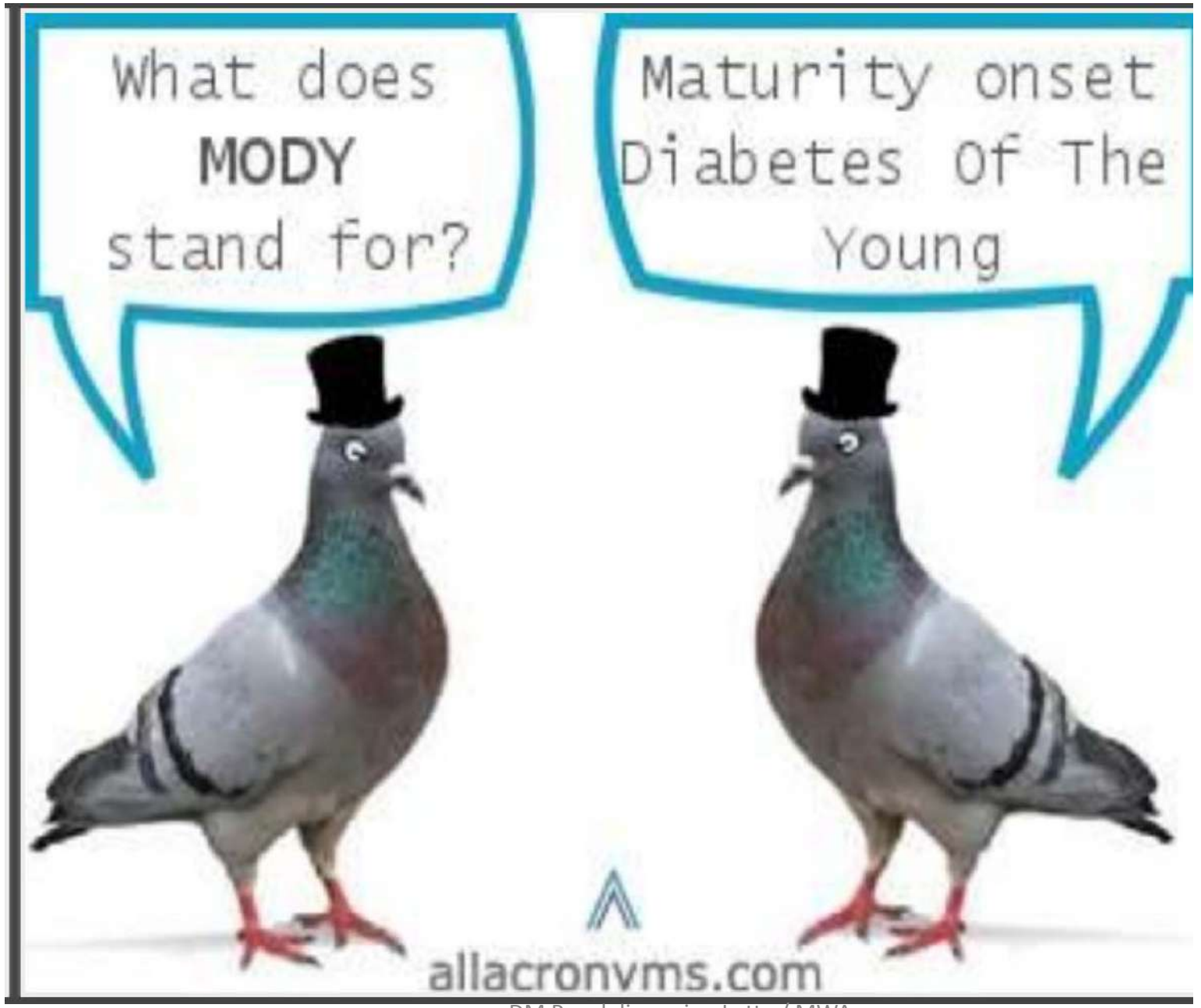
- Hyperglycemia occurs within the first month of life
- requiring management with insulin at diagnosis as pancreas fail to produce insulin
- Lasting weeks to months
- Presents with IUGR , volume depletion, glycosuria, polyuria, profound hyperglycemia ,ketonuria, ketoacidosis
- Half of NDM can be treated with sulphonylurea, some may need insulin

TNDM

- Accounts for 50%of NDM cases
- 60 to 80% of TNDM patients, display
- Genetic mutations mostly on chromosome 6q abnormalities
- Course of TNDM is highly variable
- TNDM resolution within first several weeks or months (12 weeks)
- Reappearance of diabetes in adolescence and later years

PNDM

- Accounts for remaining half of all cases of NDM
- Mutation in K channels on pancreatic beta cells
- ABCC8 & KCJN11
- Leads to decreased insulin secretions
- Long term sequelae of either type : developmental delay, cardiac abnormalities, seizures, poor weight gain


What does MODY stand for?
Maturity onset Diabetes Of The Young
allacronyms.com

Maturity Onset Diabetes of the Young

- Early onset diabetes (<25 years) – misdiagnosed as T1D
- Non insulin dependent
- Autosomal dominant inheritance
- Caused by single gene defect altering beta cell function
- Obesity unusual , no features of insulin resistance

- Primary defect in insulin secretion
- First degree relative with similar degree of glycemia
- Low renal threshold (glycosuria) with mild hyperglycemia
- Absence of positive autoantibodies
- Evidence of endogenous insulin production past the “ honeymoon” phase – c peptide normal

How to D/D MODY with Type 1 DM?

- C peptide is normal
- GAD 65 negative (Glutamic Acid Decarboxylase)
- ICAs negative (Islet cell antibody)
- IA2 negative (Insulin Antibody)

How to D/D MODY with Type 2 DM?

Almost similar to Type 2 DM except:

- Young age
- Running in Family and
- Molecular genetic to identify defective gene.

MODY TYPE	MUTATION	GENE defect	Treatment
MODY1	Chromosome 12	HNF 1α	SU (40%) , insulin (20%)
MODY2	Chromosome 7p	GCK	Diet , physical activities
MODY3	Chromosome 20	HNF 4α	1/3 SU, 1/3 insulin
MODY4	Chromosome 13	IPF 1	SU mostly
MODY5	Chromosome 17	HNF 1β	Atrophy of pancreas & renal cyst-insulin only
MODY6	Chromosome 2	Neuro D1	Insulin

MODY 3 is commonest type (70%), MODY 2 is second commonest (14%) , MODY 1 (5%) ,MODY 4 <1%

Treatment for MODY

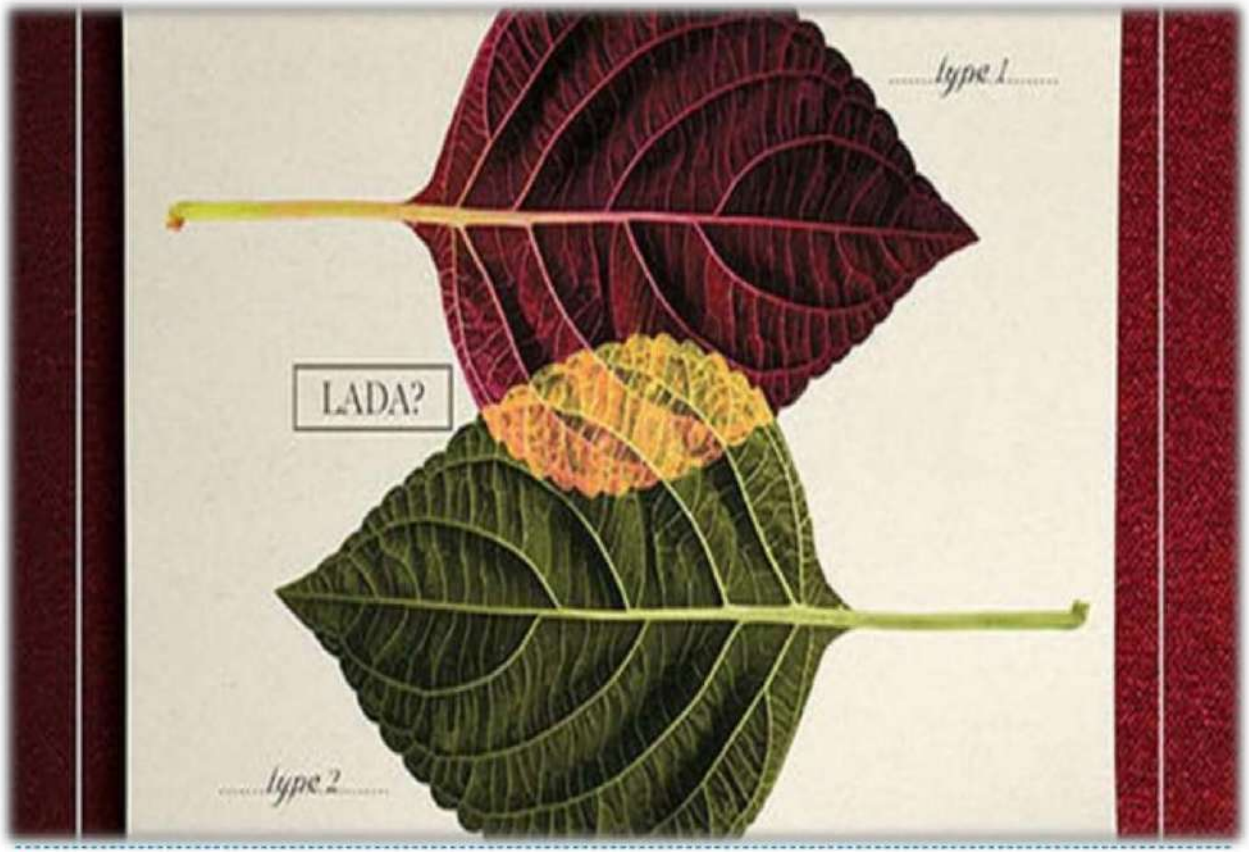
- Therapy depend on involved gene and severity
- MODY 1 & 3 can be initially treated with sulphonylureas which prompts the body to produce insulin , a few will need insulin in late stage
- MODY 2 may be treated with diet only and no medications required
- MODY 5 & 6 need insulin treatment

Diabetes in the Early Adulthood

Youth onset Type 2 DM

- Clearly differ from Type 1
- More closely resemble the pathophysiology in adult : Insulin resistance & non auto immune Beta cell failure
- Rapidly progressive beta cell decline
- Accelerated development of diabetes complications
- Treatment options: insulin & metformin and promotion of healthy life style

Diabetes 1.5



Latent Autoimmune Diabetes of Adulthood (LADA)

- Late autoimmune diabetes of adult is a form of autoimmune (Type 1 DM) which is diagnosed in individuals who are older than usual age of onset of T1DM
- Slow onset Type 1 DM in adulthood
- Also called Type 1.5 diabetes
- Mistakenly diagnosed as Type 2 DM
- Progress to insulin requirement within years

Characteristics of LADA

- Age of onset – 30 years or older (30 to 50)
- May initially appear to be non obese T2 diabetes
- Initially treated with nutrition and exercise and free from insulin for first 6 months after diagnosis
- OHA don’t help much (some worsen autoimmunity)
- Positive for at least one of the autoantibodies found in type 1 – GAD antibodies commonly positive
- Low levels of C Peptide Vs high levels in Type 2DM
- Present with symptoms of hyperglycemia
- Ketosis prone
- May become insulin dependent later due to gradual destruction of beta cells (after 6 years)

ADA Recommendations: Monogenic Diabetes Syndromes

- All children diagnosed with diabetes in the first 6 months of life should have genetic testing for neonatal diabetes. A

- Children and adults, diagnosed in early adulthood, who have diabetes not characteristic of T1D or T2D that occurs in successive generations should have genetic testing for MODY. A

Distinct Etiologies and Characteristics

	T1D	'LADA'	T2D	MODY
Typical Age of Onset	All Ages	Usually Age >30	Adults	Usually Age <25
% of all Diabetes	10%	10%	75%	5%
Typical BMI	Mostly Normal or Thin	Mostly Normal or Overweight	Mostly Overweight or Obese	Mostly normal
Ethnicity	All	All	All	All
Progression to insulin Dependence	Fast (Days/Week)	Latent (Months/Years)	Slow (Years)	Depends on MODY type
Insulin Resistance	Mostly no; ~10% ,yes	Some	Yes	Depends on MODY type
Presence of Autoantibodies	Yes (ICA, IA2, GAD65, IAA)	Yes (mostly GAD65), Some not	Some	No
T cell Reponses to islet proteins	Yes	Yes	No	No
Insulin/ C-peptides Level at diagnosis	Undectable or extermely low	Low	Normal to High	Normal
Ketoacidosis	Yes	Yes, many not all	Rare	Rare
Insulin Secretion	Low/null	Varies	Varies	Varies
Islet Inflammation	Chronic Inflammation	Chronic Inflammation	Chronic Inflammation	None
HLA Link	High	Low	None	None
TCF7L2 Link	None	In some pop'n, stronger link than T2D	25%	None
Other Genes Involved	*PTPN22; INS; CTLA4; CCR5; FOXP3;CLEC16a HNF1A; IL2RA; IL6; ITPR3; OAS1; SUMO4*	*PTPN22; INS*	*PPARG; JAZF1; KCNJ11; NOTCH2; WFS1; IGF2BP2; FTO; SLC30A8; HHEX*	*HNF4A; GCK; HNF1A; IPF1; HNF1B; NEUROD1*
Early Treatment	Insulin required, diet & exercise helpful	Non-Insulin or insulin, diet & exercise helpful	Non-Insulin, diet & increased activity	Gene Specific
Late Treatment	Insulin, diet, exercise	Insulin, pills, diet, exercise	Insulin, pills, diet, exercise	Gene Specific

Diabetes and the Elderly : Points to ponder

- Diabetes mellitus (DM) frequency is a growing problem worldwide, because of long life expectancy and life style modifications. In old age (>65 years old), DM is becoming an alarming public health problem in developed and even in developing countries

- People with diabetes have higher incidence of all-cause dementia, Alzheimer's disease and vascular dementia than people with normal glucose tolerance

ADA Recommendation

- Hypoglycemia should be avoided in older adults with diabetes. It should be assessed and managed by adjusting glycemic targets and pharmacologic interventions. C

- Healthy older adults with few coexisting chronic illness and intact cognitive function and good functional status. A1C <7.5(58mmol/mol). C

- Those with multiple coexisting chronic illness, cognitive impairment and poor functional status.A1C <8.0 to 8.5% (64-69mmol/mol) .C

- Treatment of hypertension to individualized target level is indicated in most older adults. C

- Treatment of other cardiovascular risk factors should be individualized in older adults considering the time frame of benefit. C.

- There is less evidence for lipid lowering therapy and aspirin therapy

- For patients receiving palliative care and end-of-life care, the focus should be to avoid symptoms and complications from glycemic management.

- In older adults at increased risk of hypoglycemia, medication classes with low risk of hypoglycemia are preferred. B

- Overtreatment of diabetes in older adults is common and should be avoided. B

- the fundamental rule is “go slowly and individualize” to avoid interaction with poly medicated elder persons and fatal iatrogenic hypoglycemias in those treated with sulfonylureas or insulin.

- **Depression** screening in the elderly population with diabetes is of great importance, as elderly patients with diabetes experience more isolation, less support, and more feeling of hopelessness

- The elderly with diabetes who are capable of activities of daily living without assistance, and who have no cognitive impairment should have A1C and blood sugar goals similar to that of a younger person.

Choice of therapy

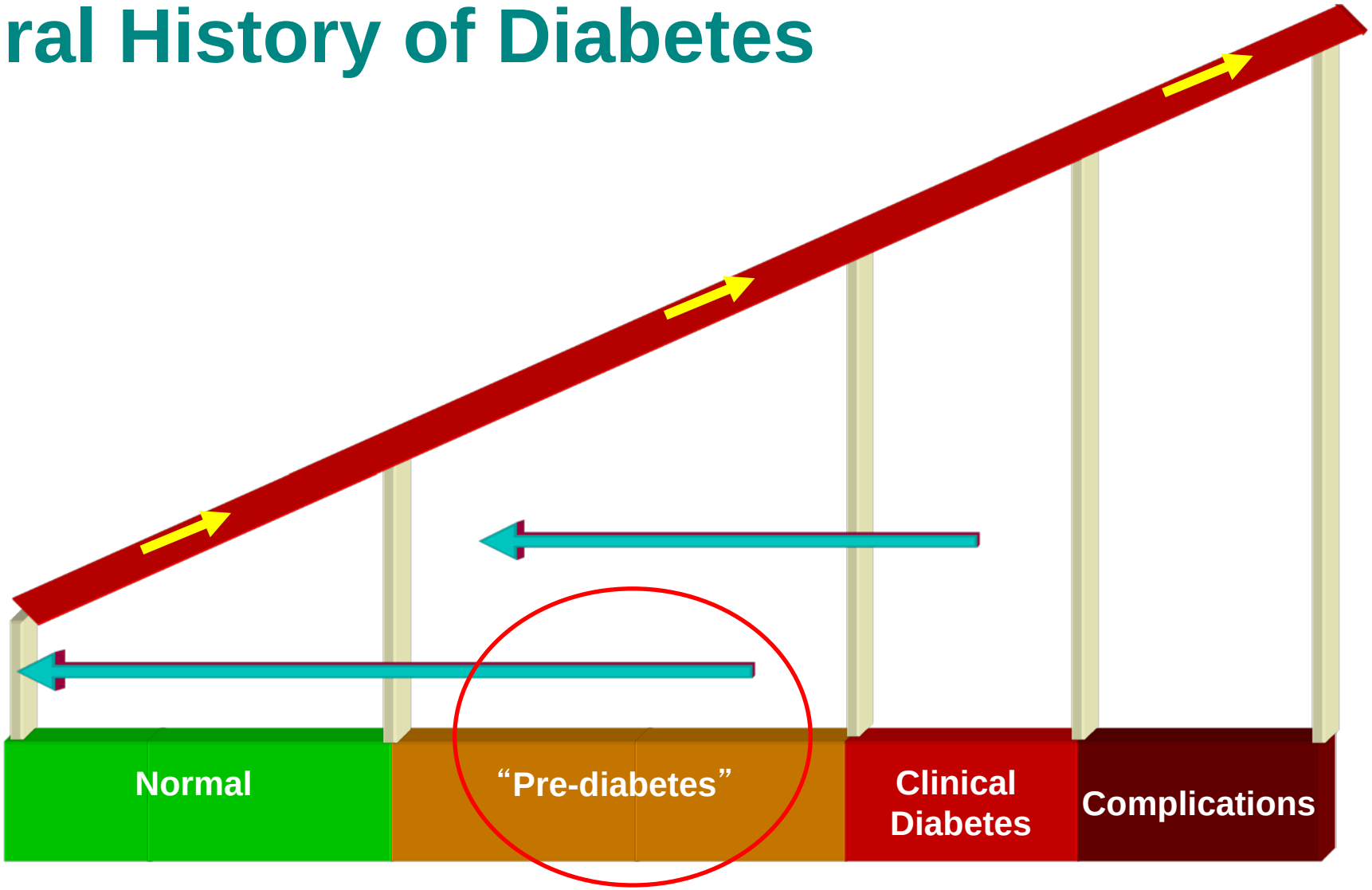
- Metformin – first line agent for older people with DM, can safely used until GFR > or = 30ml/min
- Thiazolidinediones – not a good choice with risk of falls and fractures, contraindicated in CHF
- Insulin secretogauges – sulphonylureas and others should be used with caution as risk of hypoglycemia, short acting ones are preferably used
- Incretin based therapies –oral DPP4 inhibitor has few side effects and minimal hypoglycemia, but cost may be barrier to some older patients
- SGLT2 inhibitors may be convenient for older adults but risk of genital fungal infections and UTI, euglycemic DKA, as well as long term experience is limited

Injectable therapy

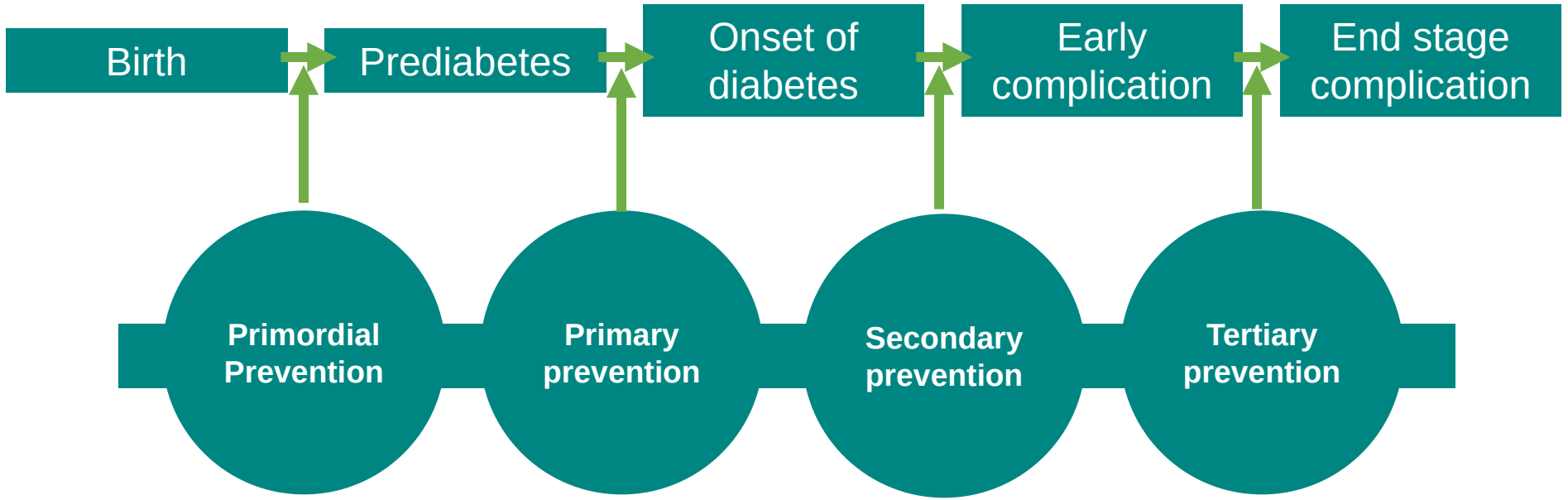
- Multiple injections are complex and limited to the older adults who has reduced visual, motor and cognitive skills, even burden to the care givers
- Once daily basal injections may be useful of simplicity and low risk of hypoglucemia
- Well structured regime, timing and adjustment scheme should be educated to the care givers
- GLP1 agonists can cause nausea, vomiting and pancreatic side effects, so not a good choice for older adults with diabetes
- Successful diabetes care in aging population needs multidisciplinary approach

CAN WE PREVENT TYPE 2 DIABETES ?

Natural History of Diabetes



Prevention Strategies Do Not End Once The Person Develops Diabetes!



Risk-Based Screening in Asymptomatic Children and Adolescents

Table 2.5—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents in a clinical setting*

Criteria

- Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height) A

Plus one or more additional risk factors based on the strength of their association with diabetes as indicated by evidence grades:

- Maternal history of diabetes or GDM during the child's gestation A
- Family history of type 2 diabetes in first- or second-degree relative A
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) A
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) B

*Persons aged <18 years.

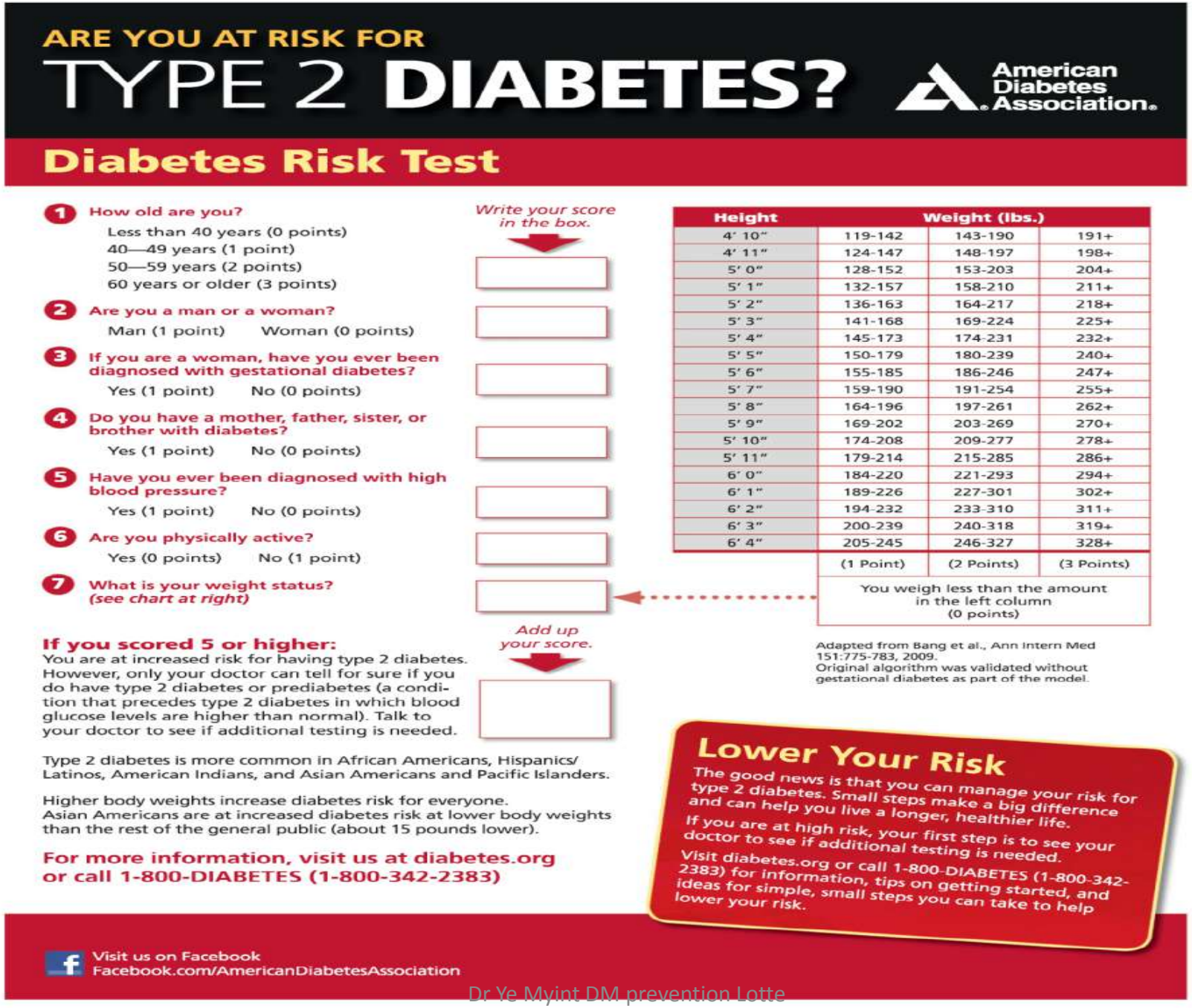


Figure 2.1—ADA risk test.

Testing for Diabetes or Prediabetes in Asymptomatic Adults

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

Categories of Increased Risk for Diabetes (Prediabetes)

Table 2.4—Categories of increased risk for diabetes (prediabetes)*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

To Whom Should Prevention Strategies Be Aimed?

"Pre-diabetic" states viz. IGT and IFG are known to be associated with an increased risk of progression to diabetes

Hence these individuals are ideal candidates for application of prevention strategies

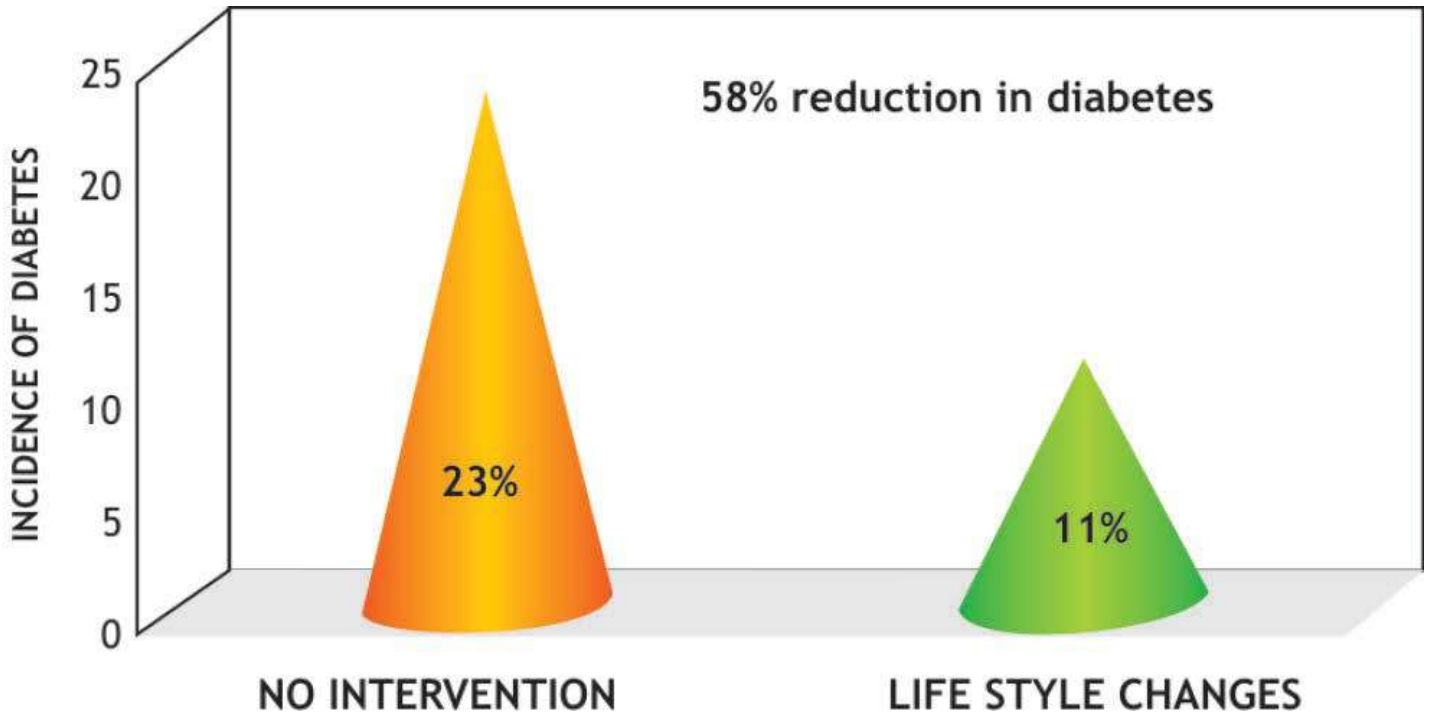
A fasting plasma glucose or an oral glucose tolerance test can be used to detect these individuals

How Best Can Diabetes Prevention Be Achieved?

- Dietary modification
- Increasing physical activity
- Drugs
- A combination of the above

Finnish Diabetes Prevention Study

STUDY SUBJECTS - 522
FOUR YEARS OF FOLLOW-UP OF PROGRESSION TO DIABETES



Tuomilehto J et al, N Engl J Med 2001; 344: 1343-1350

Lifestyle Modification

Found to be more effective than metformin in the DPP

Recommendations:

- Modest weight loss (5 to 10% of weight)
- Modest physical activity (30 minutes per day)

- Higher intakes of nuts ,berries,yogurt ,coffee, and tea are associated with reduced diabetes risk.
- Conversely, red meats and sugar-sweetened beverages are associated with an increased risk of type 2 diabetes

Lifestyle Modification – Advantages

Advantages

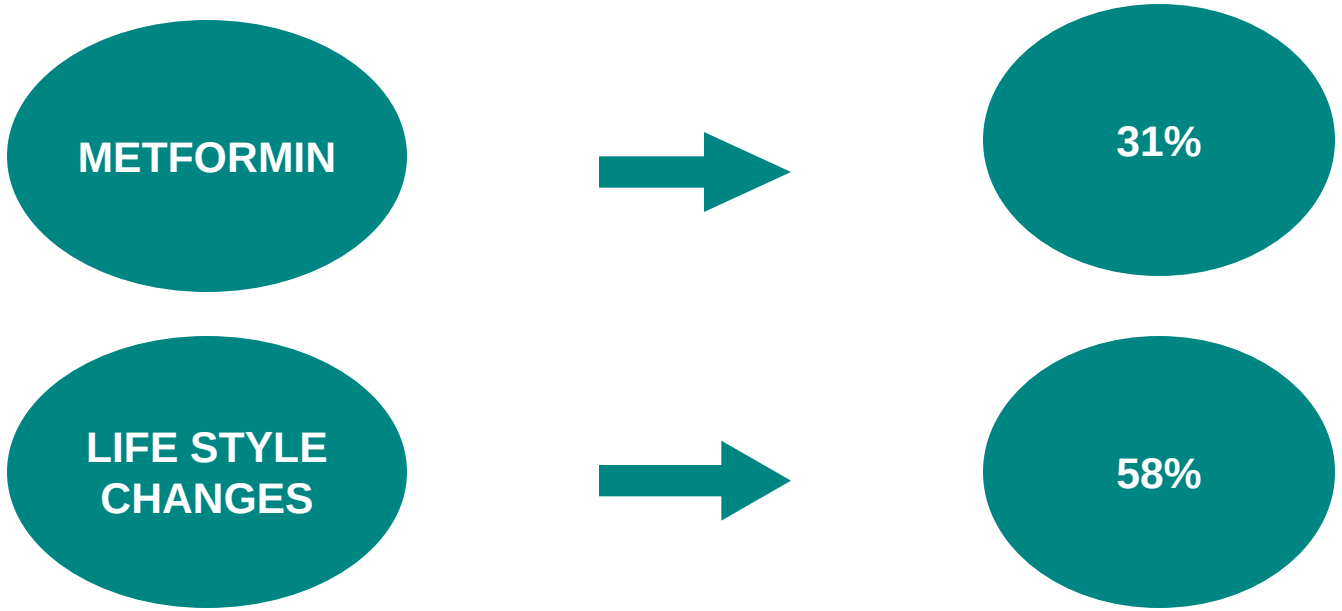
- Safe
- Effective
- Inexpensive
- Can be advised for almost anyone
- Has additional benefits - on lipids, BP, CV health etc

Evidence For Effectiveness of Pharmacological Interventions In Prevention of Diabetes

DIABETES PREVENTION PROGRAM (DPP)

STUDY SUBJECTS – 3234
THREE YEARS OF FOLLOW-UP

The risk for diabetes reduced by



Knowler WC et al, N Engl J Med. 2002; 346:393 - 403

Pharmacologic Interventions for Prevention: Recommendations

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m^2, those aged <60 years, and women with prior GDM. A
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

Prevention of Diabetes – Major Trials

Study	Results (Risk Reduction)	Year
DIABETES PREVENTION PROGRAM Life style modifications & drugs (n=3200)	Metformin – 31% Life style changes – 58%	1996
FINNISH DIABETES PREVENTION STUDY Life style modifications (n=522)	Diet + exercise – 58%	1993
DA QING IGT AND DIABETES STUDY Life style modifications (n=577)	Diet – 31% Exercise – 46%	1986
STOP NIDDM Acarbose (n=1429)	Acarbose – 36%	1998
INDIAN DIABETES PREVENTION PROGRAM Life style modifications & drugs (n=531)	Metformin – 26.4% Lifestyle – 28.5% Met + Lifestyle – 28.2%	2006
DREAM Rosiglitazone & Ramipril (n=5269)	Rosiglitazone – 70% (IFG) 55% (IGT) Ramipril – NS	2006
NAVIGATOR Nateglinide & Valsartan (n=9306)	Nateglinide – NS Valsartan – 14%	2010

Secondary Prevention

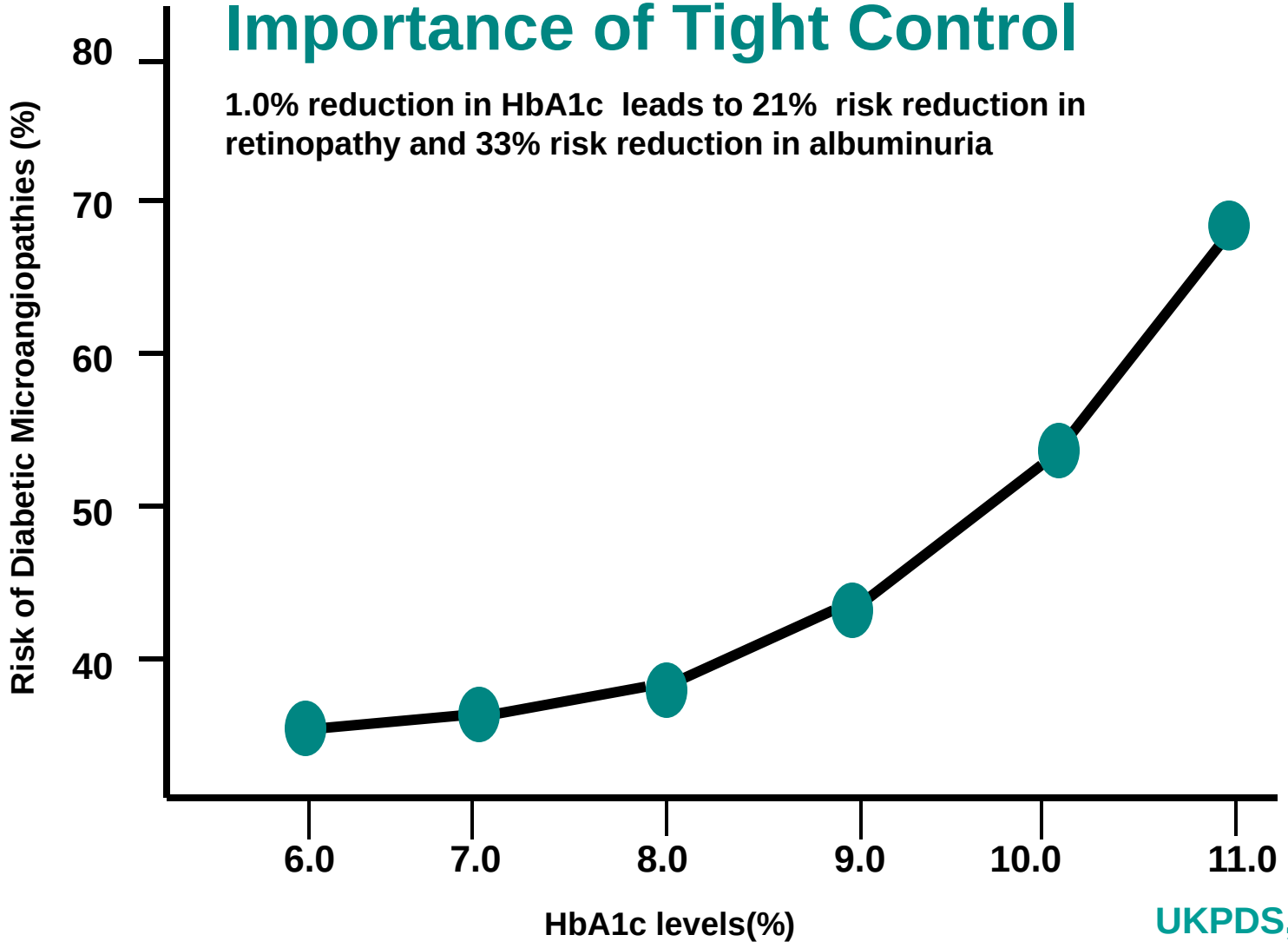
Preventing micro and macrovascular complications by good diabetes control

THREE MAIN APPROACHES

- Control of hyperglycaemia
- BP control
- Correction of hyperlipidemia

Importance of Tight Control

1.0% reduction in HbA1c leads to 21% risk reduction in retinopathy and 33% risk reduction in albuminuria



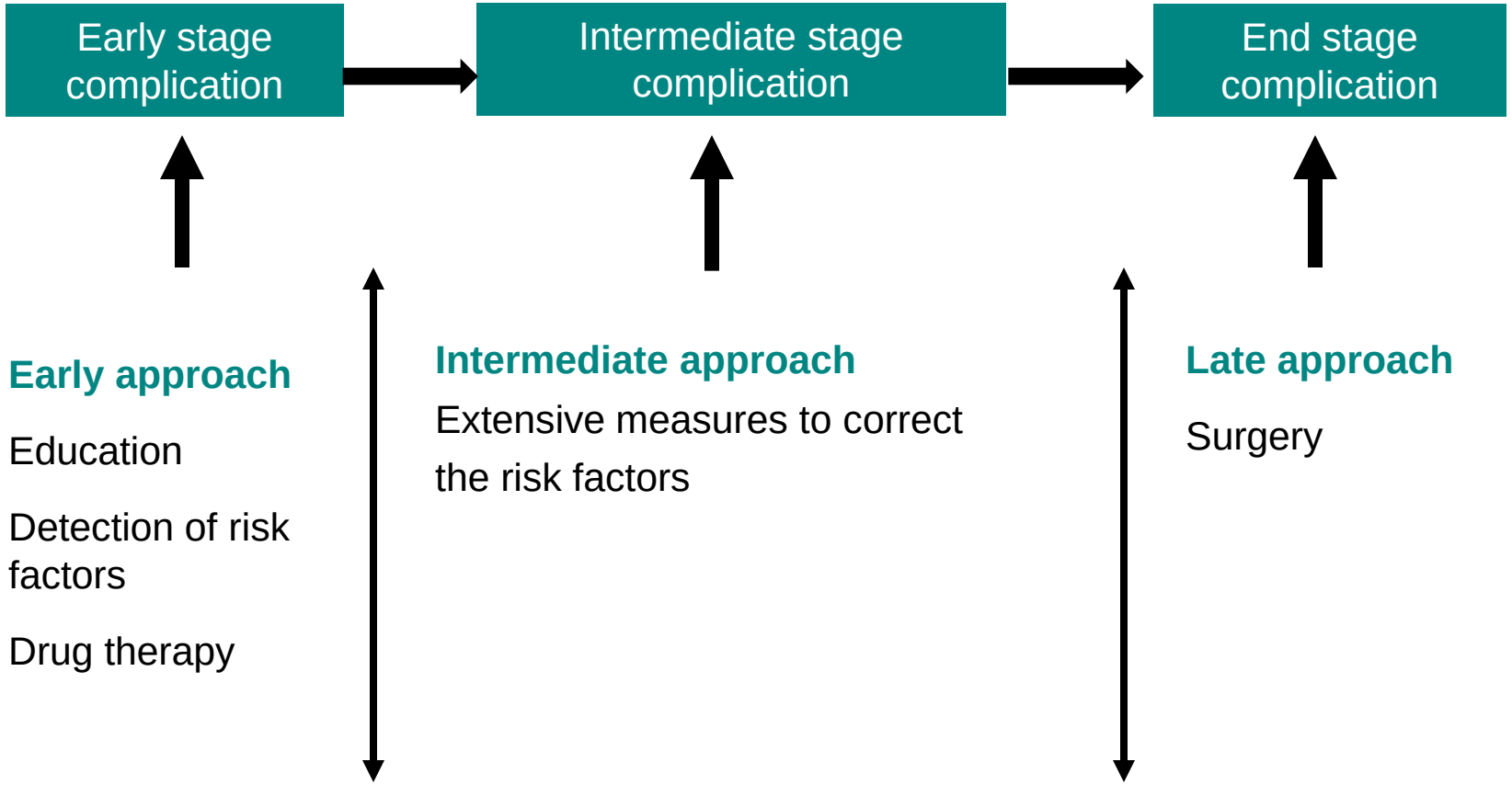
UKPDS, 1998

Strategies For Prevention of Diabetes Complications

Complication	Early approach	Intermediate approach	Late approach
Diabetic retinopathy	Glycemic control, Blood pressure control, Lipid control	Photocoagulation	In vitreo-retinal surgery
Diabetic nephropathy	Glycemic control, Blood pressure control, Lipid control	ACE inhibitors	Dialysis Transplantation
Peripheral neuropathy	Glycemic control, Foot wear	Management of neuropathic pain? neuroprotective agents	Prompt intervention (antibiotics, surgery), Custom made foot wear, Corrective surgery
Macrovascular disease	Glycemic control, Blood pressure control, Lipid control	Antiplatelet drugs	Revascularisation Surgery

Tertiary Prevention

Limiting physical disability and rehabilitation measures in those who have already developed diabetic complications

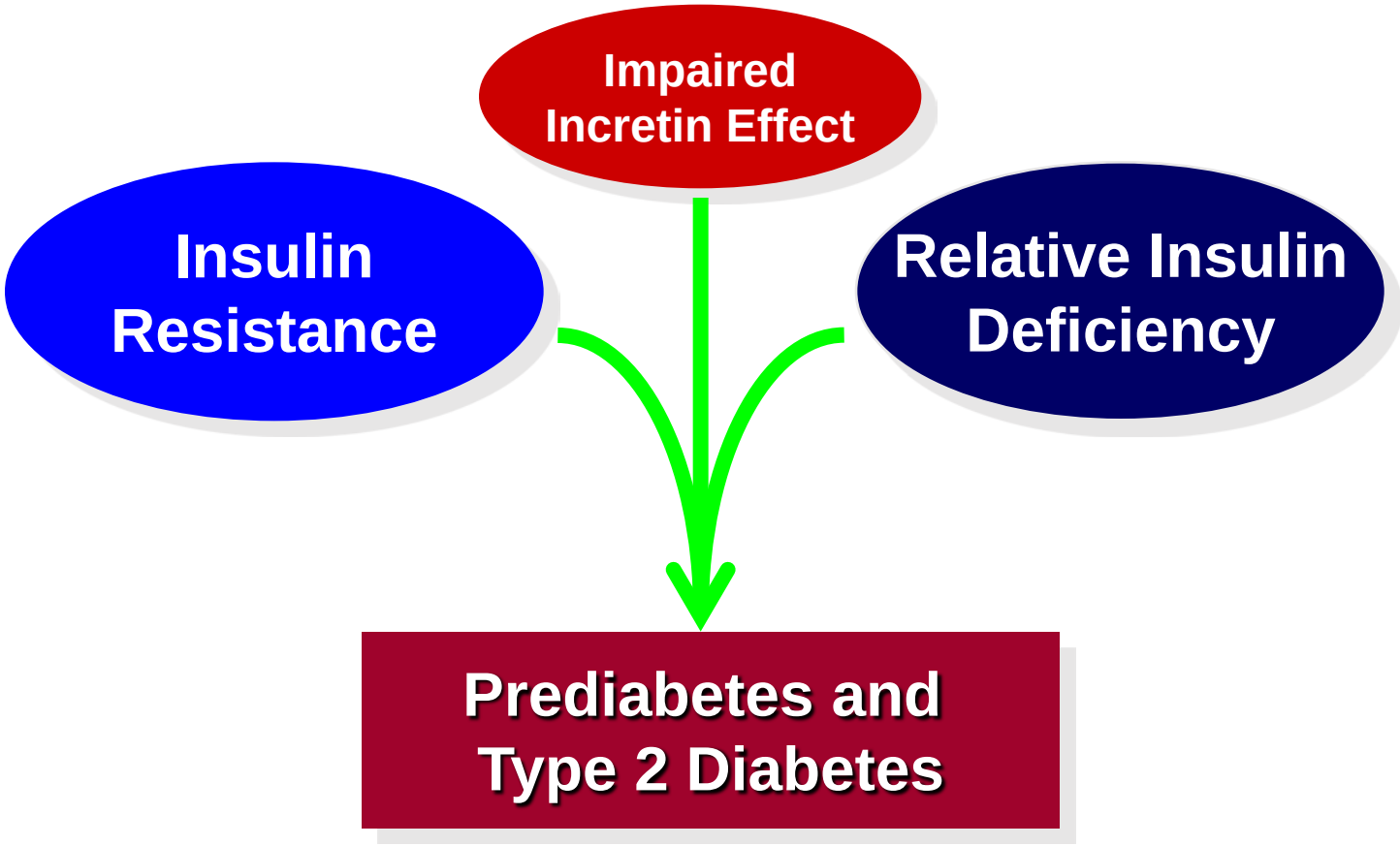


Conclusions

- Type 2 diabetes is preventable
- Detect individuals with IGT and IFG and direct prevention strategies to them
- Lifestyle modification is the key to prevent diabetes
- Drugs may have a role in some cases
- Even after diabetes develops, good control of glucose, lipids and BP can prevent complications

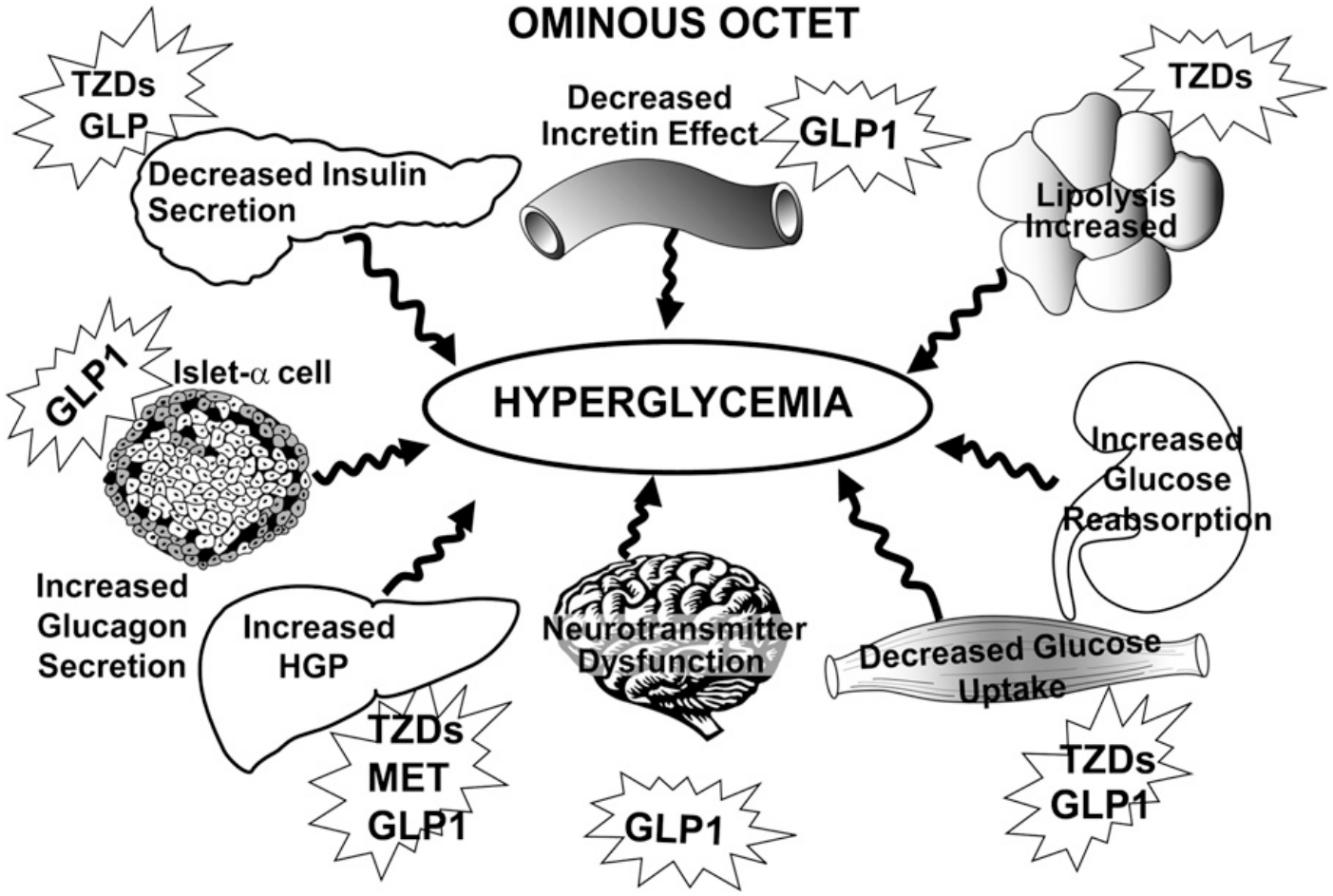
Current Understanding on the pathogenesis of Type 2 Diabetes?

Multiple Defects Underlie the Pathophysiology of Type 2 Diabetes



Ominous Octet

Pathophysiology of T2 Diabetes & General Therapeutic approach

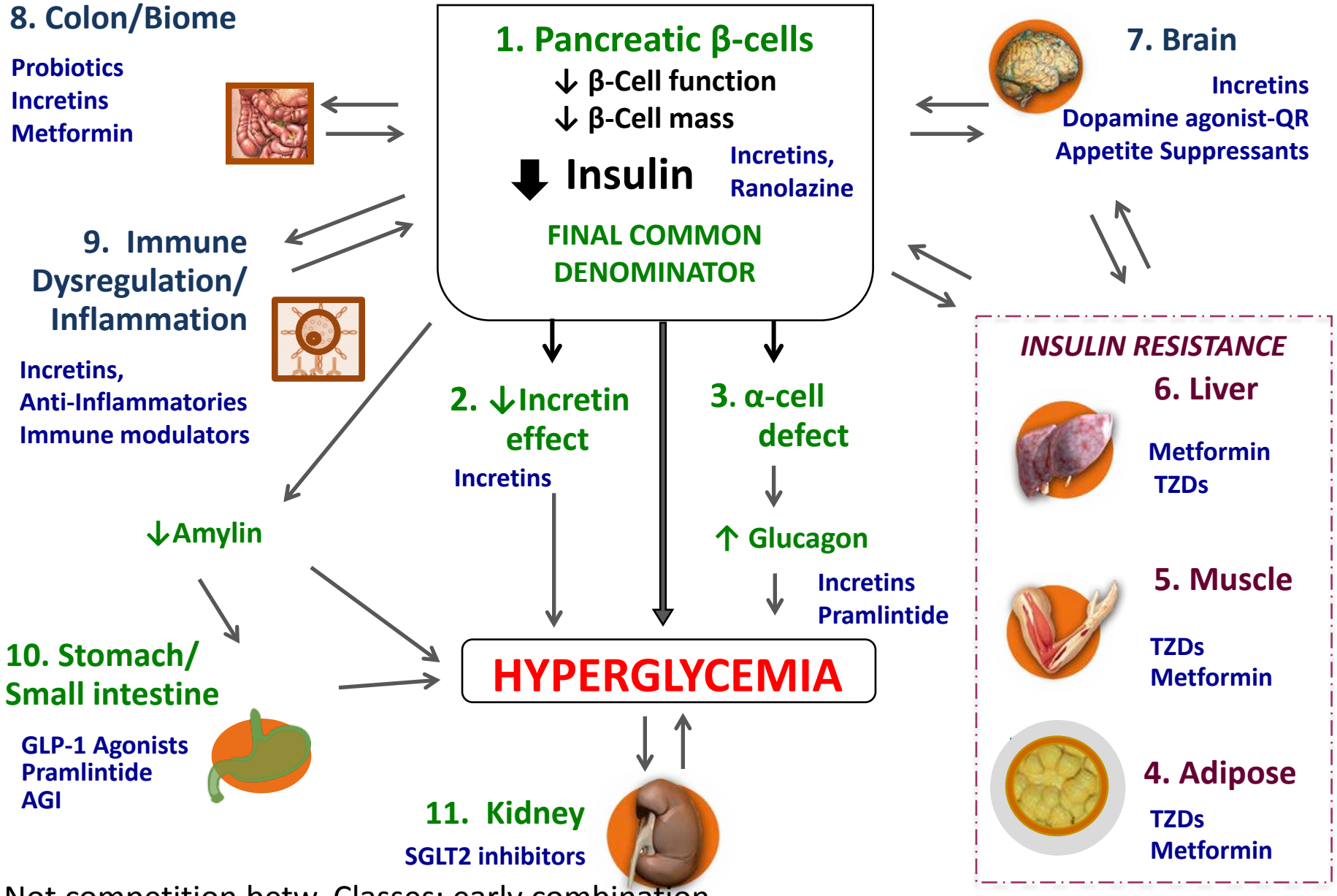


Therapeutic options as they relate to key pathophysiological derangements in T2DM

Diabetes. 2009 April; 58(4): 773–795.

B. β-*Cell-Centric Construct: Egregious Eleven*

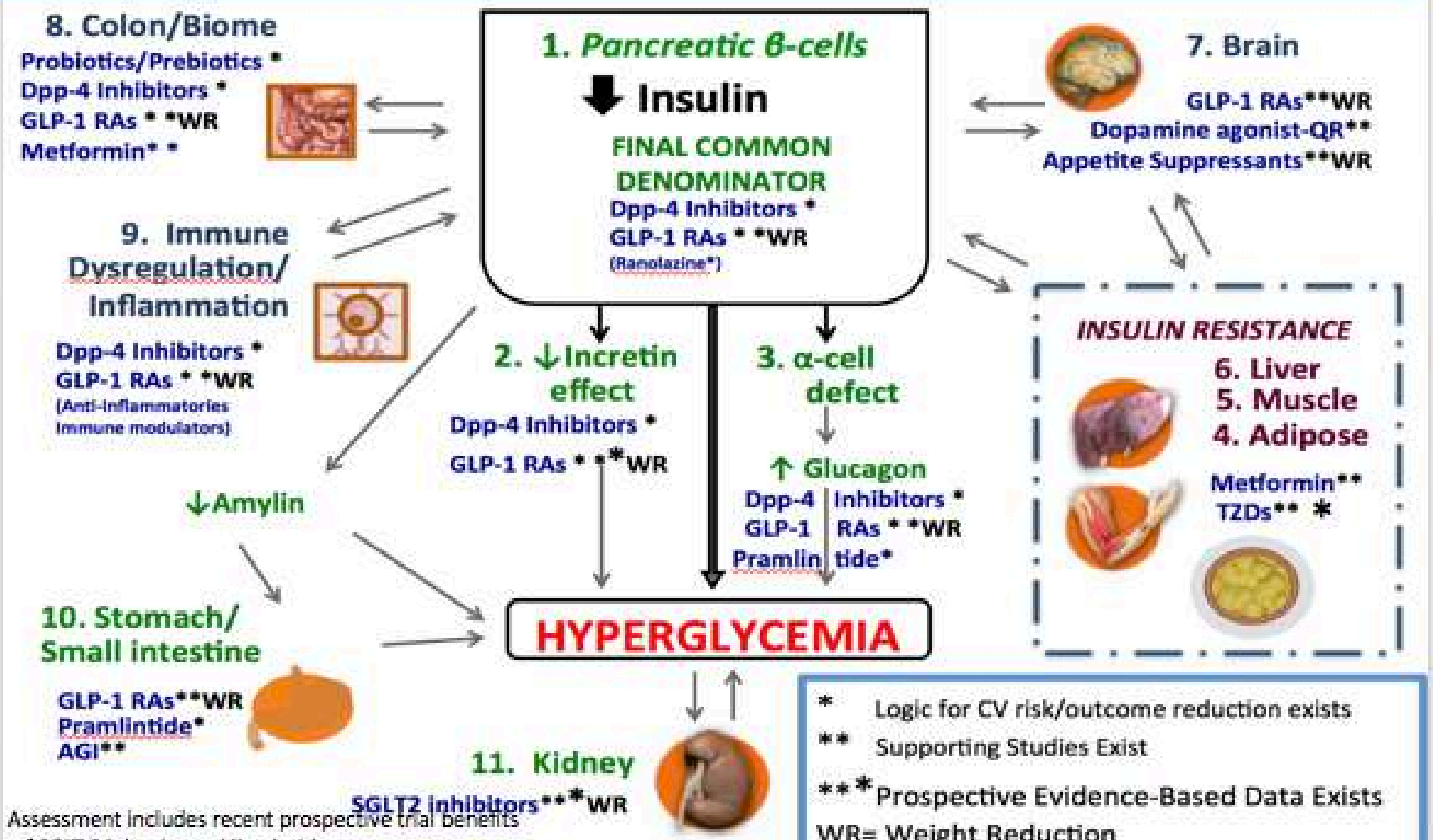
Targeted Treatments for Mediating Pathways of Hyperglycemia



Not competition betw. Classes; early combination

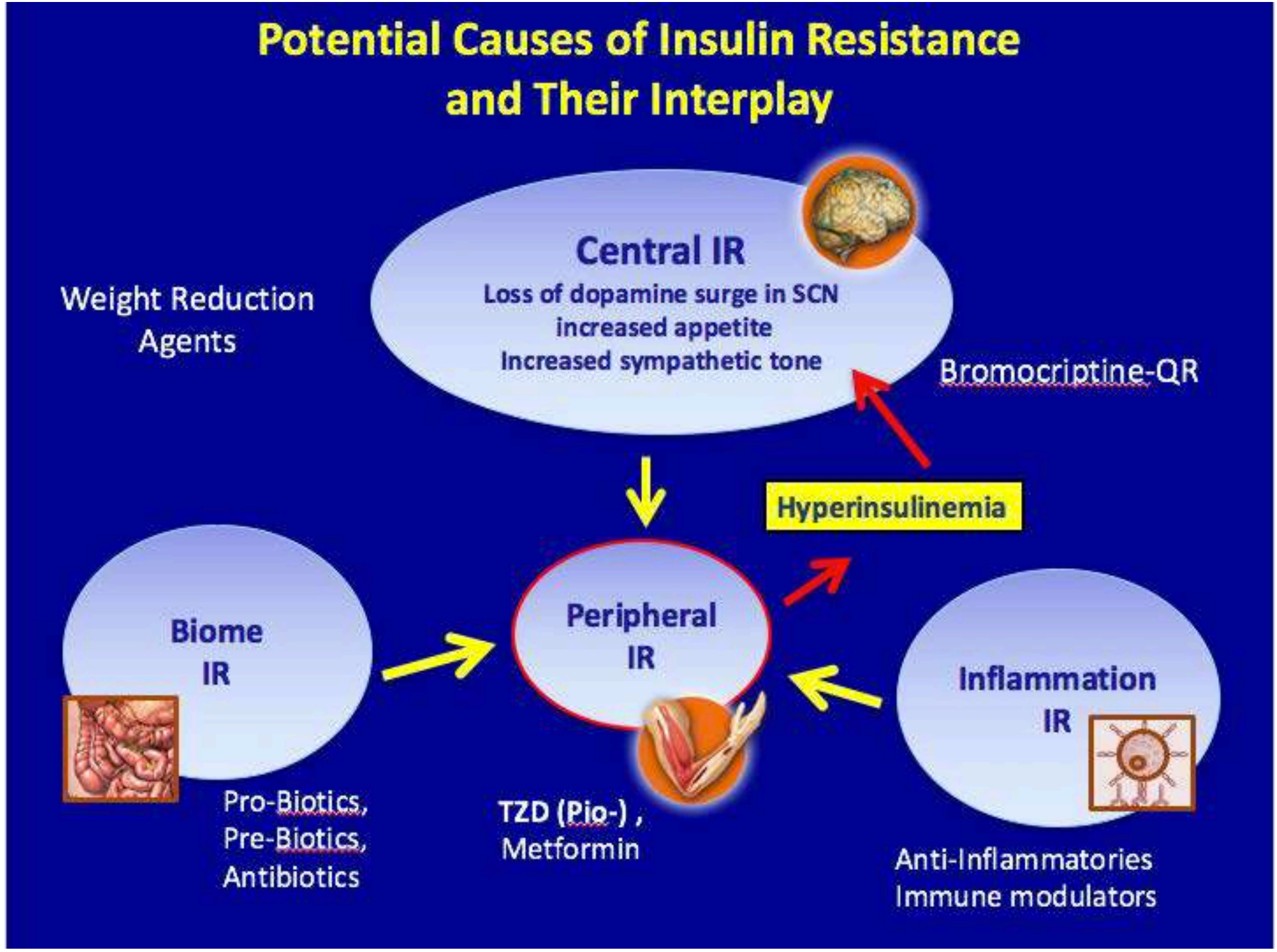
Least # meds, Rx most # mechanisms of Htperglycemia-
Preserve b-cells, rather than destroy them

***Implications for New Guidelines



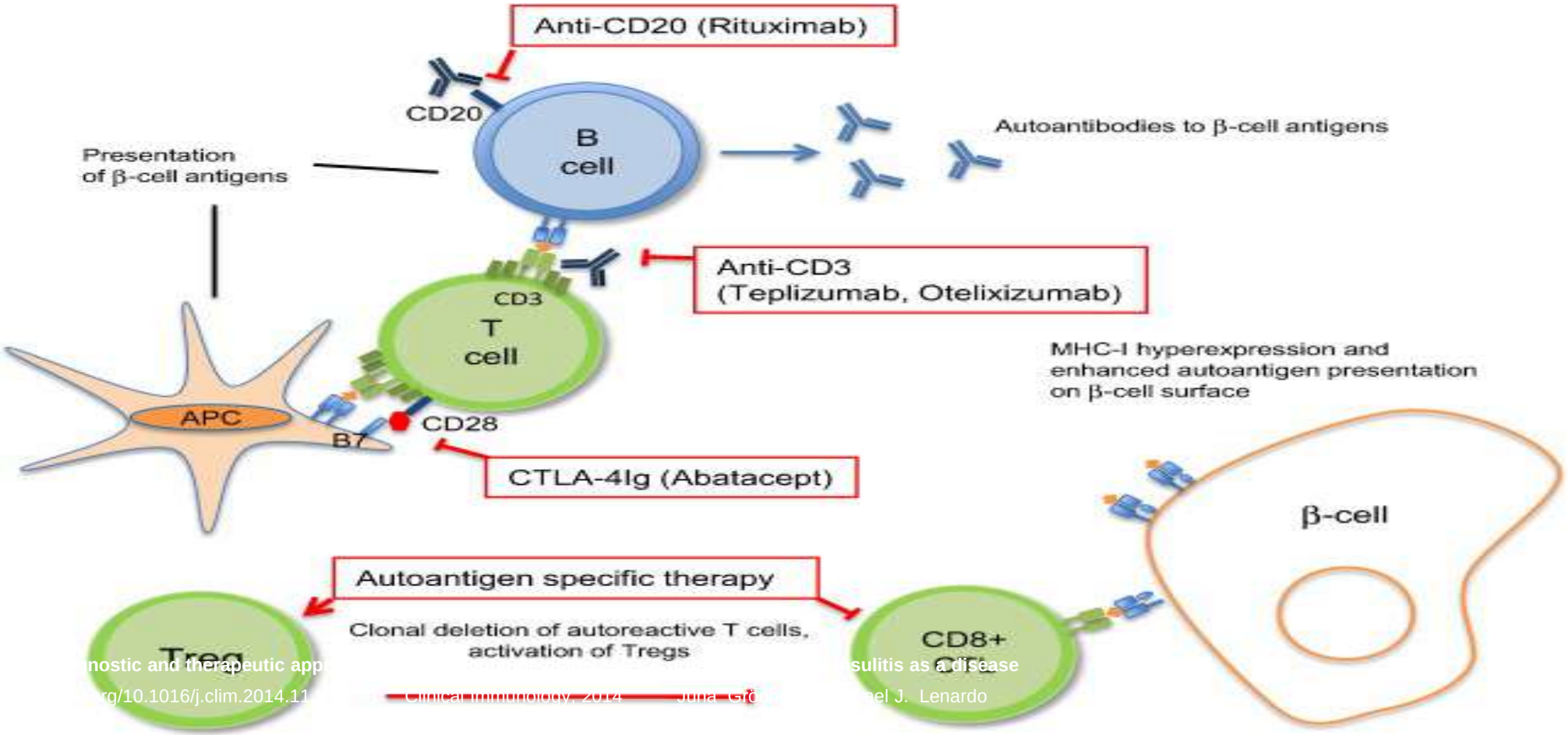
Assessment includes recent prospective trial benefits of SGLT-2 inh, pio, and liraglutide

Potential Causes of Insulin Resistance and Their Interplay



Pathogenesis and biological interventions in T1DM- LIKE autoimmune diabetes- Insulitis

The class I MHC molecules are hyperexpressed on the β-cell surface in T1D patients making β-cells more susceptible to cytotoxic lymphocyte (CTL)-mediated destruction.

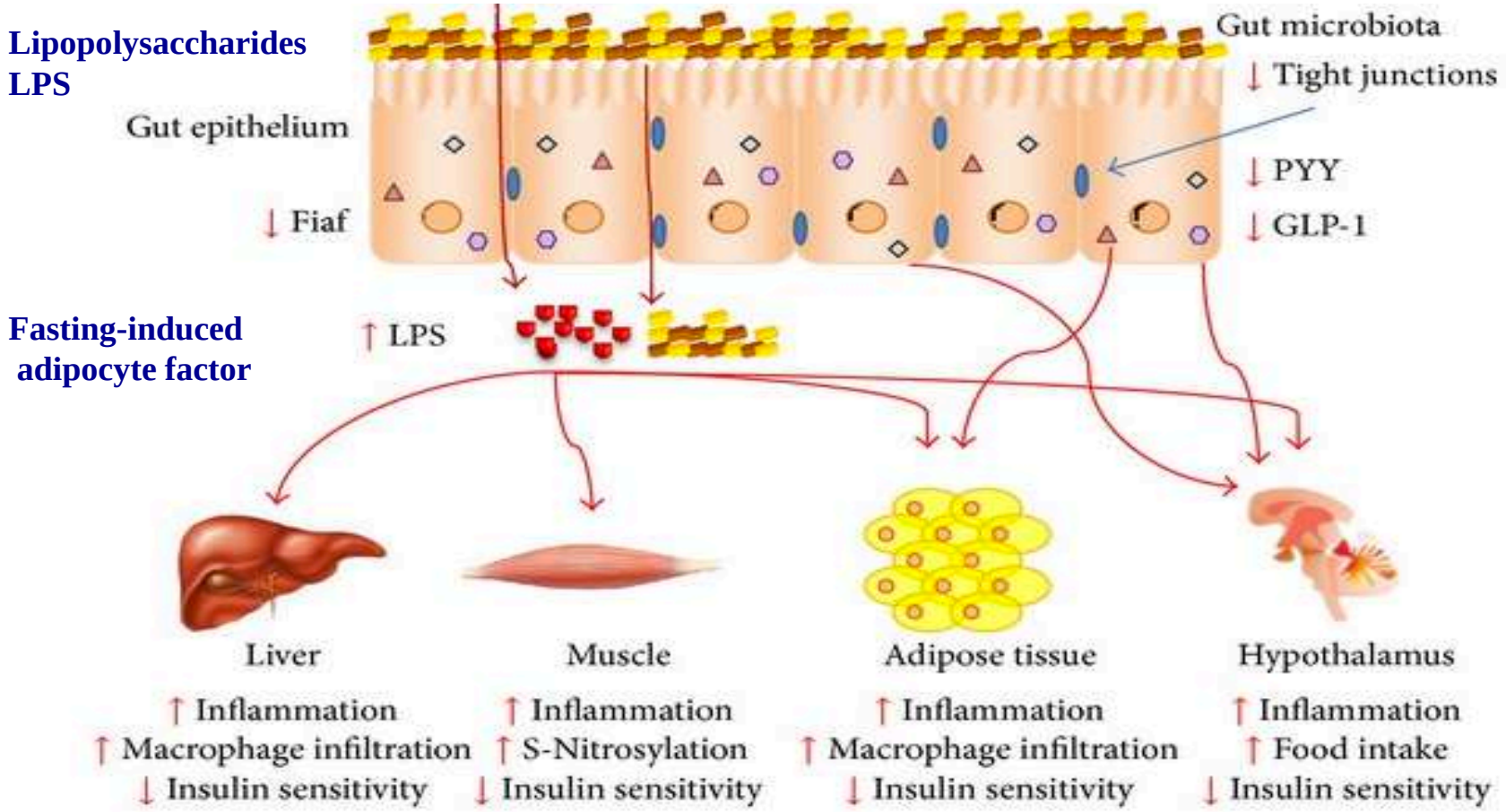


nostic and therapeutic app sulitis as a disease

rg/10.1016/j.clim.2014.11 Clinical Immunology, 2014 Juna Sc el J. Lenardo

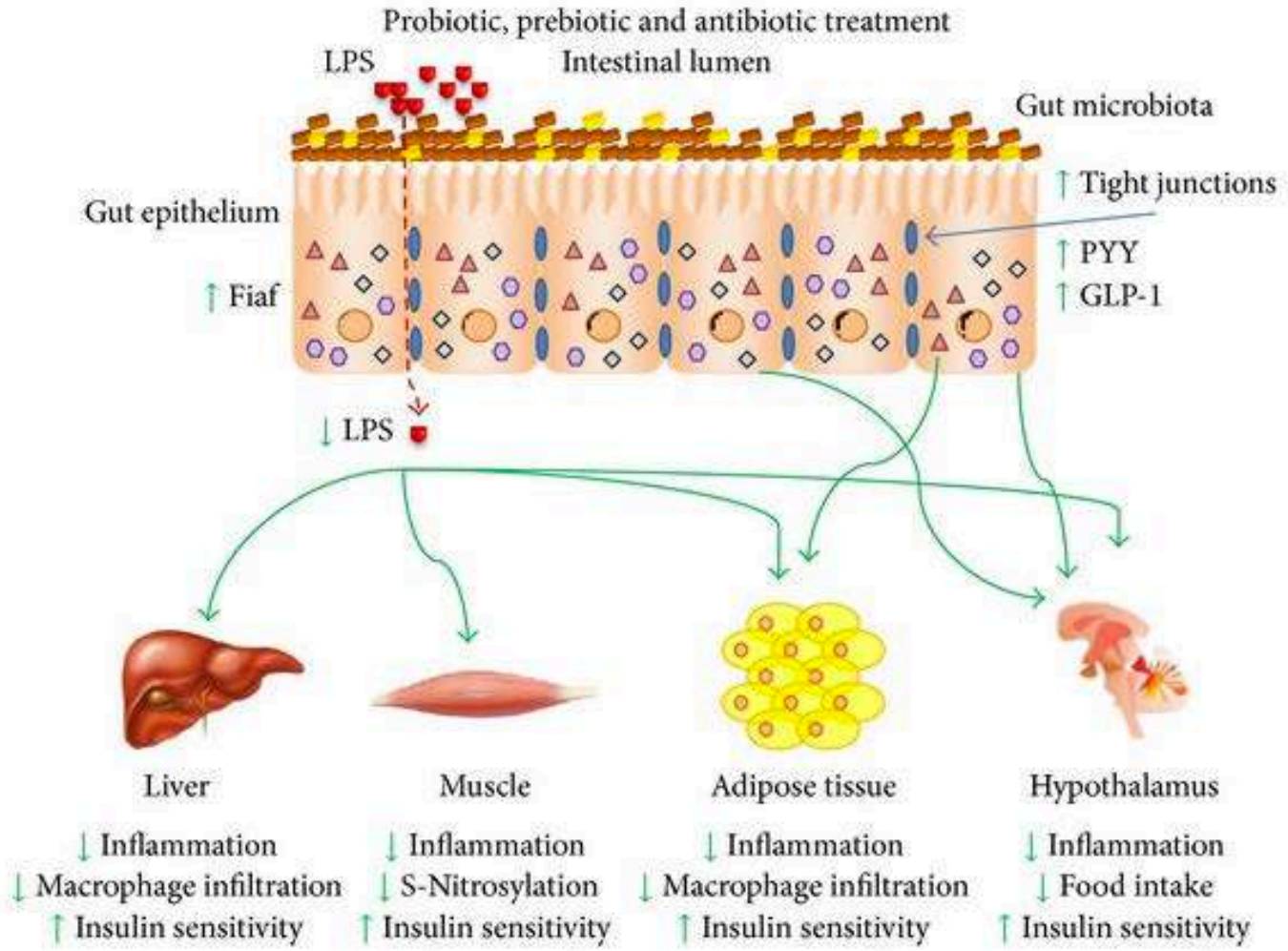
Figure 1

Metabolic Derangement, and Insulin Resistance Associated with Microbiome



Pioglitazone Treats Secondary Adverse Effects of Abnormal Biome

Probiotic, Prebiotic and Antibiotic Treatment of Abnormal Gut Biome



RANOLAZINE CAN BE USED IN PATIENTS WITH CAD AND DIABETES

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- Ranolazine affects Na+ channel function in cardiomyocytes,
  and is likely to do the same in beta-cells
- Ranolazine is approved for treatment of ischemic anginal-equivalents
- Ranolazine significantly and dose- dependently reduces HbA1c.
- The magnitude of HbA1c lowering by ranolazine is correlated with the levels of HbA1c and FPG at baseline.
- Ranexa does not increase the incidence of hypoglycemia compared with placebo
- Ranexa does not increase the incidence of:
  - Weight gain
  - Cardiovascular adverse events
  - Dyslipidemia (LDL, HDL, total cholesterol, and triglycerides)
  - No Clinically relevant changes in blood pressure or heart rate

Timmis AD, et al. Eur Heart J 2006;27:42-48

Bromocryptine QR: Proposed mechanism of action

Morning administration (within 2 hours of waking) of AGENT

Corrects

Low dopaminergic tone in hypothalamus in early morning in diabetes

Restoration of morning peak in dopaminergic activity (via D2 receptor-mediated activity)

⬆Sympathetic tone
⬆HPA axis tone
⬆ Hepatic gluconeogenesis
⬆ FFA and TG
⬆ Insulin resistance
⬆ Inflammation/hypercoagulation

⬇Sympathetic tone
⬇HPA axis tone
⬇ Hepatic gluconeogenesis
⬇ FFA and TG
⬇ Insulin resistance
⬇ Inflammation/hypercoagulation

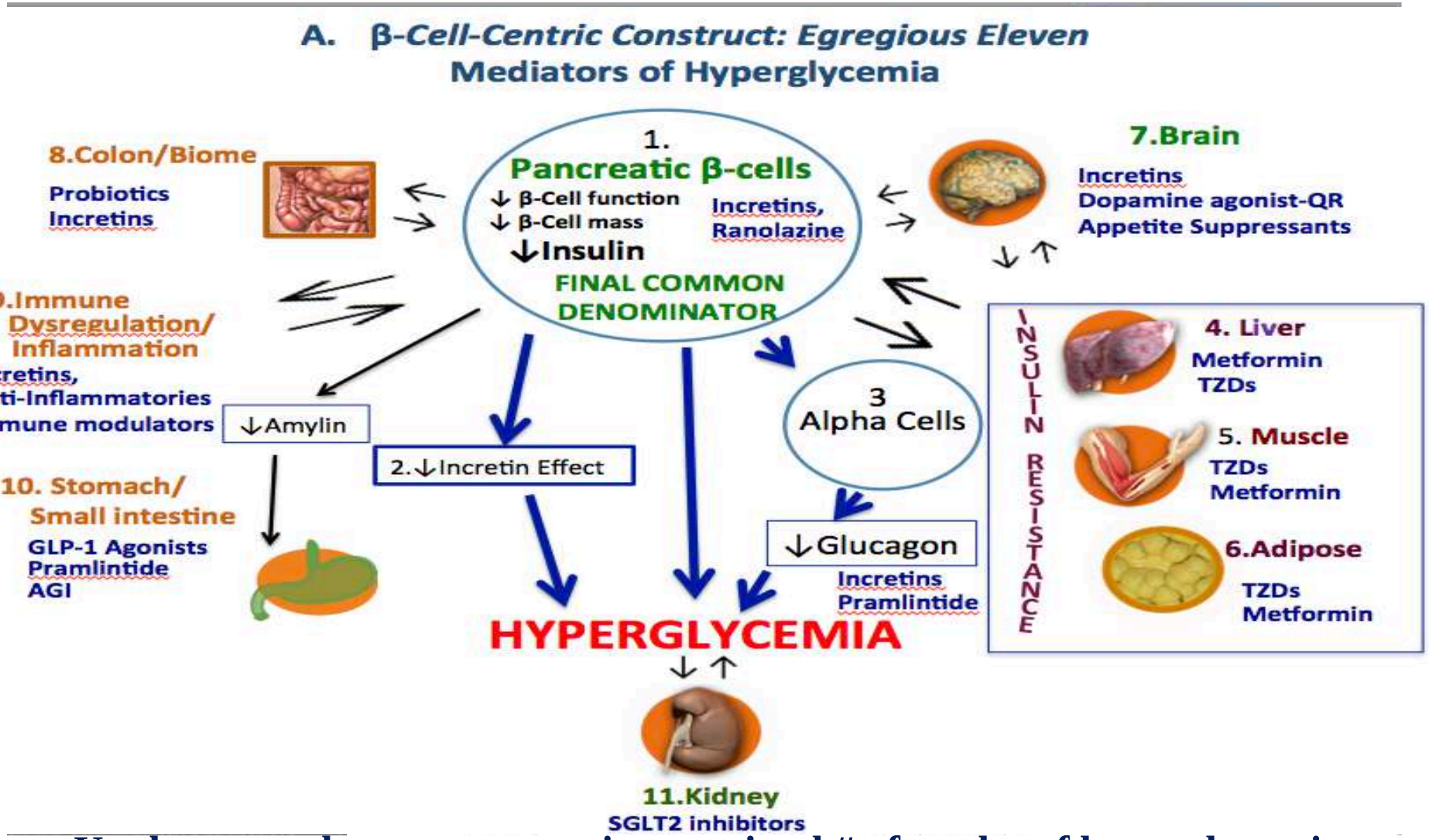
Impaired glucose metabolism, hyperglycemia and insulin resistance
Adverse cardiovascular pathology

Decreased postprandial glucose levels
Reduction in insulin resistance
Day-long reduction in plasma glucose, TGs and FFAs

Fonseca. Use of Dopamine agonists in Type-2-Diabetes. Oxford American Pocket Cards. OUP, 2010
Cincotta. Hypothalamic role in Insulin Resistance and insulin Resistance Syndrome. Frontiers in Animal Diabetes Research Series. Taylor and Francis, Eds Hansen, B Shafrir, E London, pp 271-312, 2002

Therapeutic Logic of SGLT-2 Inhibitors to Fulfill Unmet Needs; Can Tell Patient :

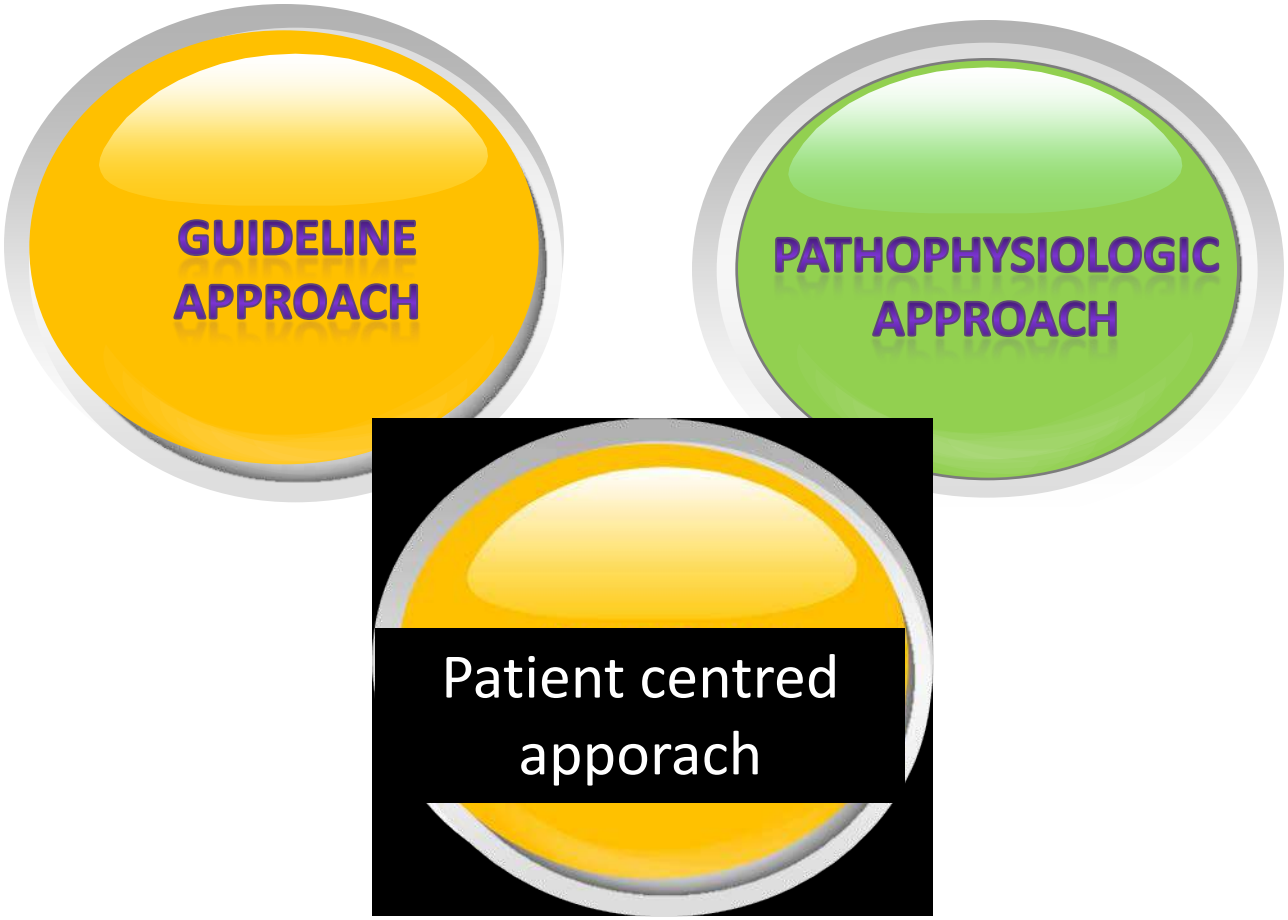
- Effective Glycemic Control with No undue risk for hypoglycemia (unless combined with Insulin or Insulin Secretagogue Therapy) Durable- (2 yr data)
- Reduces HgA1c, Fasting and Postprandial Hyperglycemia, variability
- Additive benefits with incretins, esp. GLP-RA's
- Weight Loss, Modest BP reduction
- Minimal GI side effects (with volume depletion)
- No edema,, decreases modest existing edema; decreases/obviates edema of pioglitazone
- Durable long-term glycemic control
- Acceptable side effect profile - minimize by quality pro-active care- volume depletion, UTI, yeast infections
- Delay, prevent need for basal insulin; and fast-analog insulin
- Works with FIRST DOSE- patients love to see QUICK benefit



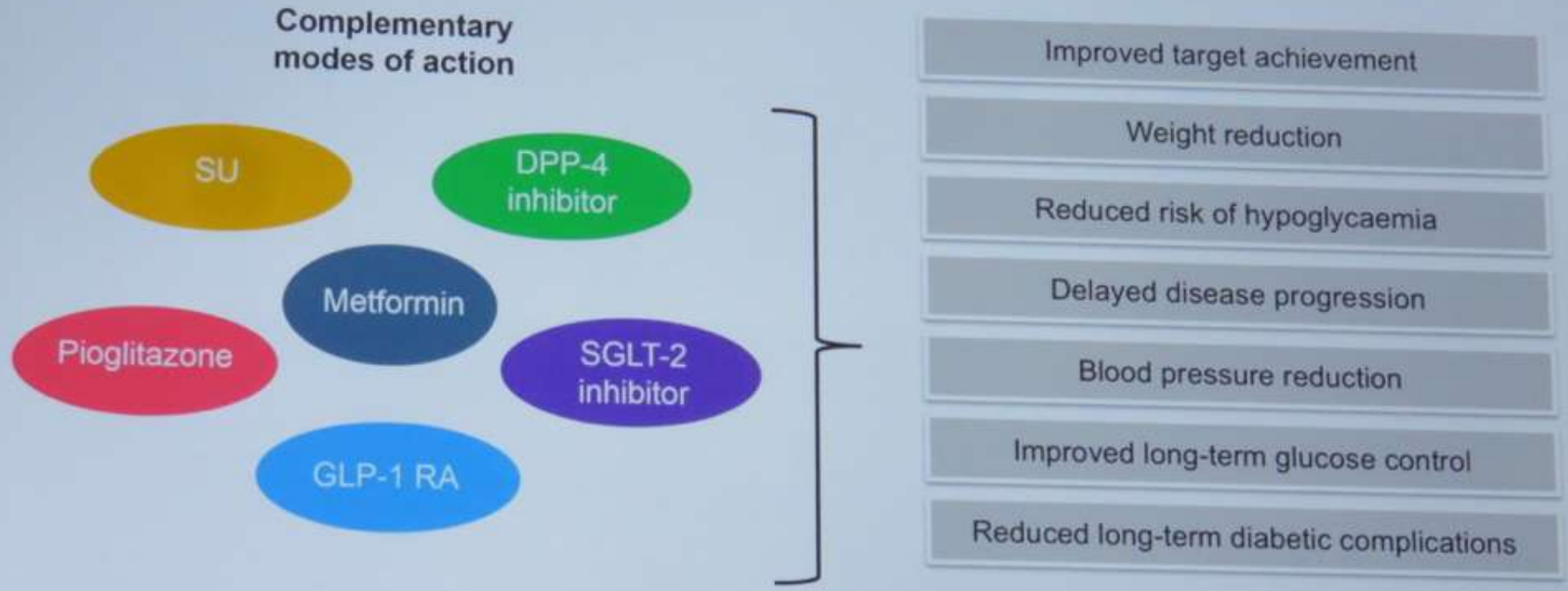
Use least number agents treating maximal # of modes of hyperglycemia

SGLT-2 Inhibition addresses 5 of these Mechanisms of Hyperglycemia

Three approaches to the Initial Treatment of Type 2 Diabetes Mellitus



Combining treatments with complementary modes of action may demonstrate clinical benefits in the treatment of type 2 diabetes



Phung OJ, *et al. Diabetes Obes Metab* 2014;16:410–17.

UNIVERSITÄTS KLINIKUM

Diabetes Self Management Education (DSME)

What issues/elements need to be touched in Patient education?

What is DSME ?

The **ongoing process** of facilitating the knowledge, skill, and ability necessary for **diabetes self-care**.

AADE 7 self-care behaviors

Peros J (2016)DSME program for glycemic control,*Integr Obesity Diabetes*,, Volume 2(3): 239-244

Diabetes Self-Management Education (DSME)

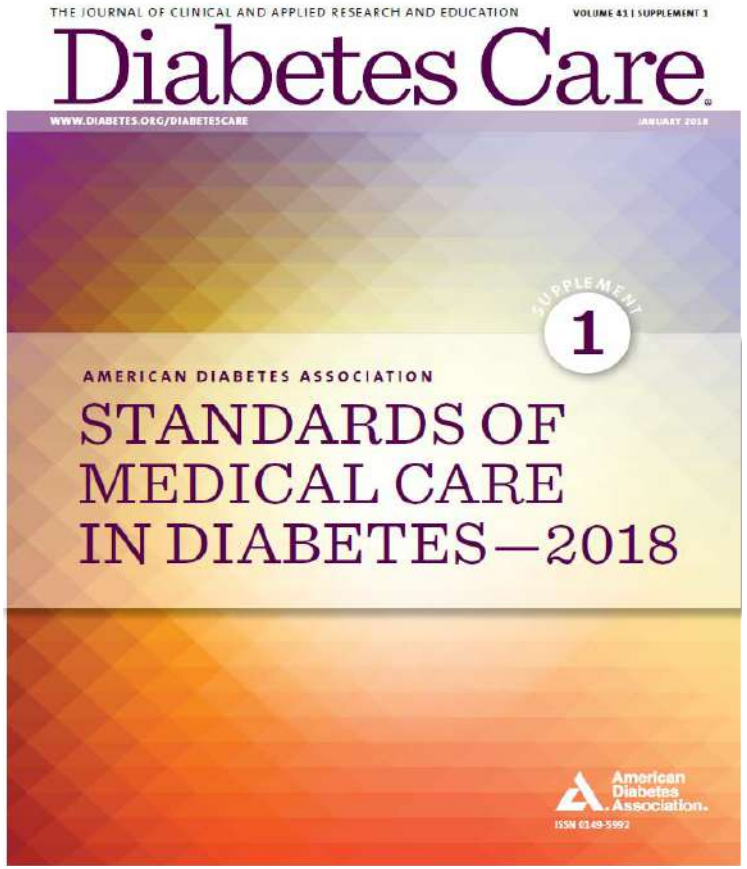
- **DSME teaches life style intervention**
- **Diabetes education focuses on the Self-Care Behaviors that are essential for improved health status and greater quality of life**
  - Healthy Eating
  - Being Active
  - Monitoring
  - Taking Medication
  - Problem Solving
  - Healthy Coping
  - Reducing Risk

Self-Management Education for Adults With Type 2 Diabetes

A meta-analysis of the effect on glycemic control

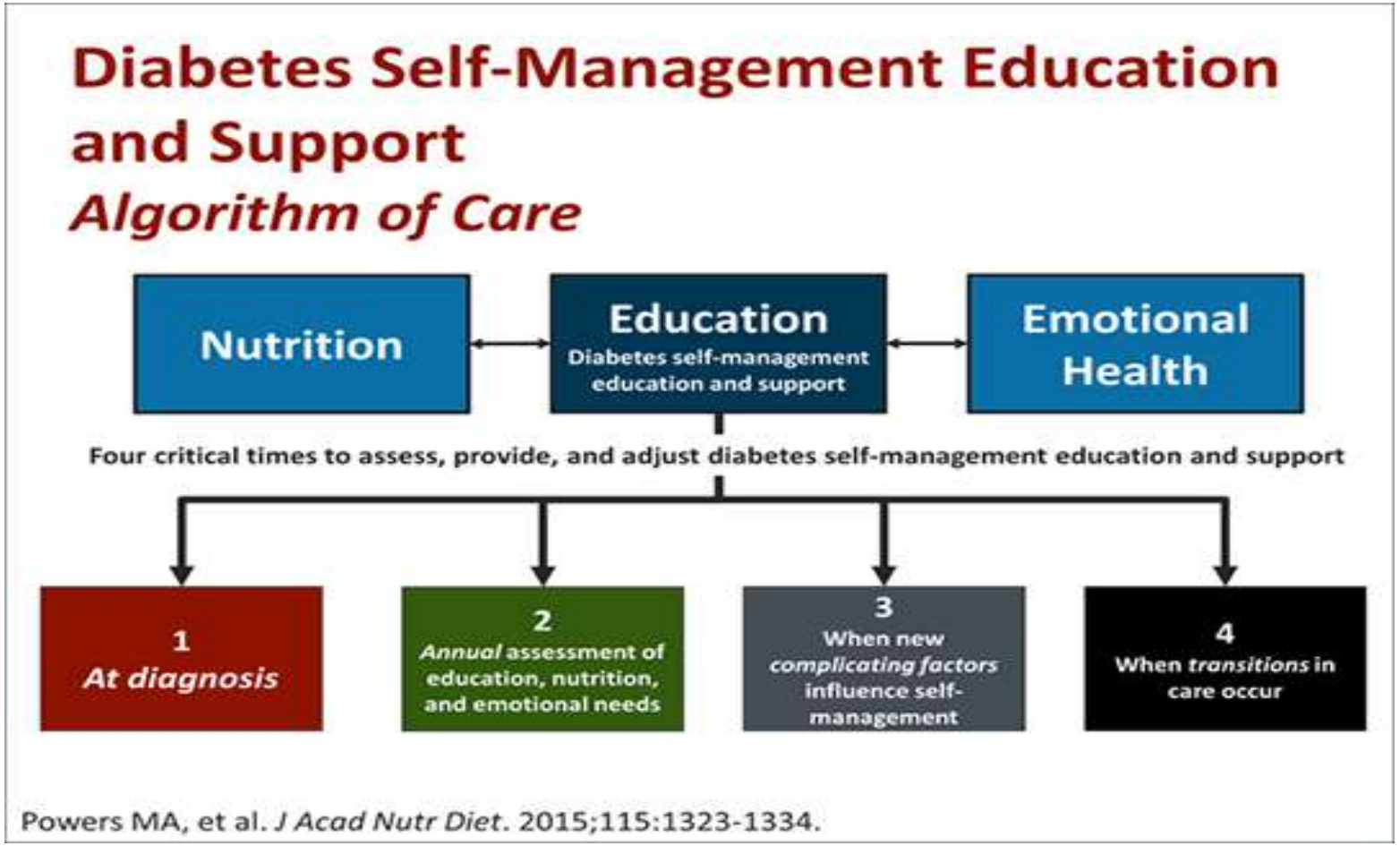
Norris 2002 *Diabetes Care* 25:1159–1171, 2002

Diabetes Self-Management Education and Support: Component of Standard Diabetes Care



"… Ongoing patient self-management education and support are critical to **preventing acute complications and reducing the risk of long-term complications** …"

When to deliver DSME



Diabetes Self-management Education and Support for Adults with Type 2 Diabetes: **ALGORITHM of CARE**

ADA *Standards of Medical Care in Diabetes* recommends all patients be assessed and referred for:

NUTRITION
Registered dietitian for medical nutrition therapy

EDUCATION
Diabetes self-management education and support

EMOTIONAL HEALTH
Mental health professional if needed

FOUR CRITICAL TIMES TO ASSESS, PROVIDE, AND ADJUST DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

1 AT DIAGNOSIS

- ☐ Newly diagnosed. All newly diagnosed individuals with type 2 diabetes should receive DSME/S
- ☐ Ensure that both nutrition and emotional health are appropriately addressed in education or make separate referrals

2 ANNUAL ASSESSMENT OF EDUCATION, NUTRITION, AND EMOTIONAL NEEDS

- ☐ Needs review of knowledge, skills, and behaviors
- ☐ Long-standing diabetes with limited prior education
- ☐ Change in medication, activity, or nutritional intake
- ☐ HbA_{1c} out of target
- ☐ Maintain positive health outcomes
- ☐ Unexplained hypoglycemia or hyperglycemia
- ☐ Planning pregnancy or pregnant
- ☐ For support to attain or sustain behavior change(s)
- ☐ Weight or other nutrition concerns
- ☐ New life situations and competing demands

3 WHEN NEW **COMPLICATING FACTORS** INFLUENCE SELF-MANAGEMENT

CHANGE IN:

- ☐ Health conditions such as renal disease and stroke, need for steroid or complicated medication regimen
- ☐ Physical limitations such as visual impairment, dexterity issues, movement restrictions
- ☐ Emotional factors such as anxiety and clinical depression
- ☐ Basic living needs such as access to food, financial limitations

4 WHEN **TRANSITIONS** IN CARE OCCUR

CHANGE IN:

- ☐ Living situation such as inpatient or outpatient rehabilitation or now living alone
- ☐ Medical care team
- ☐ Insurance coverage that results in treatment change
- ☐ Age-related changes affecting cognition, self-care, etc.

WHEN PRIMARY CARE PROVIDER OR SPECIALIST SHOULD CONSIDER REFERRAL:

American Diabetes Association. | AADE American Association of Diabetes Educators | eat right. Academy of Nutrition and Dietetics

What is Self-Management ?

"The **individual's ability** to manage the **symptoms, treatment, physical and social consequences**, and **lifestyle changes** inherent in **living with a chronic illness."**

Barlow et al. (2002) Patient Education & Counseling 48:177

My diabetes self-management goal

Standards of Medical Care in Diabetes - 2018

Medical Nutrition Therapy

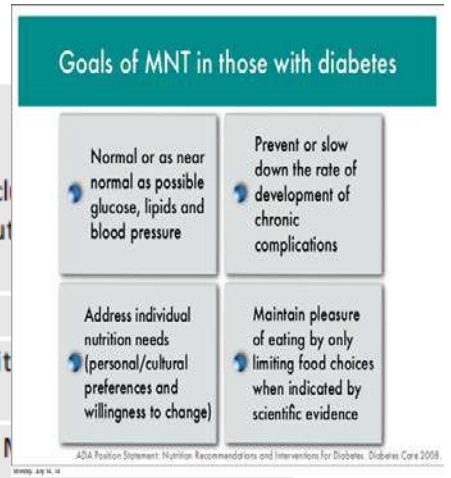
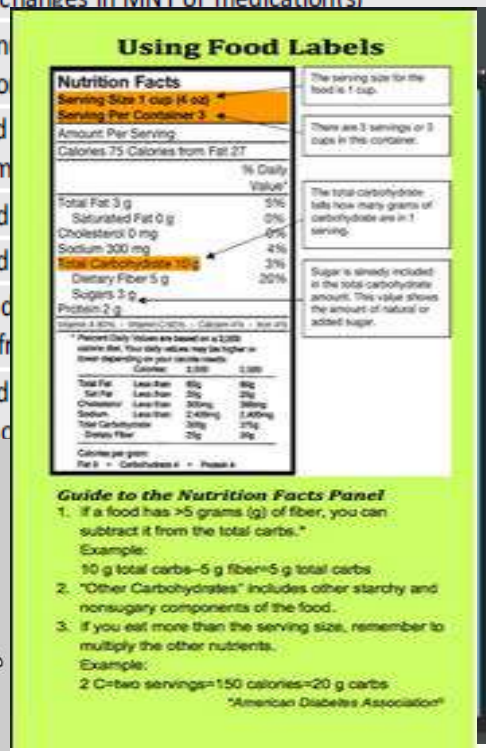
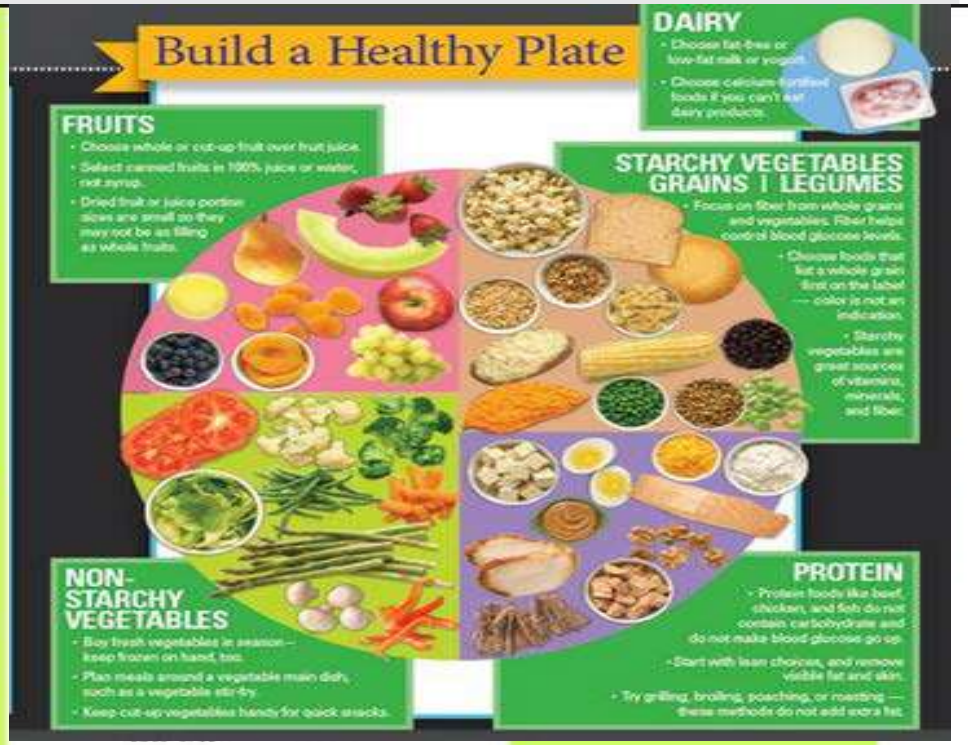


Table 5—Overview of MNT

MNT is an evidence-based application of the nutrition care process provided by the registered dietitian nutritionist. It incl
nutrition assessment, nutrition diagnosis, intervention and monitoring, and evaluation and is the legal definition of nut
a registered dietitian nutritionist practicing in the U.S. (8).

1. Characteristics of MNT reducing HbA_{1c} by 0.5–2% for type 2 diabetes:
   - Series of three to four encounters with a registered dietitian nutritionist lasting from 45 to 90 min; the registered dietit
   determine if additional encounters are needed
   - Series of encounters should begin at diagnosis of diabetes or at first referral to a registered dietitian nutritionist for M
   should be completed within 3–6 months
   - At least one follow-up encounter is recommended annually to reinforce lifestyle changes and to evaluate and monitor outcomes that indicate the need for changes in MNT or medication(s)
2. MNT provides n
plan and suppo
   - Individualized
   overall glycem
   - Individualized
   - Individualized
   - Education and
   eating away fr
   - Individualized
   disorders/disc





the food exchange

Standards of Medical Care in Diabetes - 2018

Being Active and Exercise

Medication


Repaglinide
0.5mg
tablets
Repaglinide
1mg
Repaglinide
2mg
tablets
Glipizide
Tablets USP
5 mg
100 Tablets
Metformin STADA
1000 mg Filmtabl
Wirkstoff: Metforminhydrochlorid
Glimepiride
3
mg
Glimepiride
2
mg
8mg
AVANDIA
4mg
AVANDIA
Metformin
500
mg
Saxenda
liraglutide injection
6 mg/mL (5×3 mL pre-filled pen)
Trajenta
5 mg
film-coated
tablets
Linagliptin
Oral use
30 film-coated
tablets
Boehringer
Ingelheim
METFORMIN
METFORMIN
METFORMIN

Taking Care of your Feet

Diabetes

Healthy Habits:

- ✔ Exercise Daily
- ✔ Don't Smoke
- ✔ Control Blood Sugar Levels
- ✔ Proper Daily Care

6 reasons you are at risk for foot infections

1. Nerve damage - the feeling of pins & needles
2. Poor blood circulation
3. High blood sugar feeds fungus growth on toes and toenails
4. Dry or cracked skin
5. Distorted foot share
6. Extra body weight

Risks:

High blood sugar can cause a variety changes to our feet that put you at ris for foot infections.

Low Risk Foot:
- Intact protective sensation
- No severe deformity
- No prior foot ulcer
- No Amputation
- Podial pulses present

High Risk Foot:
- Loss of protective sensation
- Severe foot deformity
- History of foot ulcer
- Absent pedal pulses
- High blood sugar

Foot Care Dos & Don'ts

Do

Check feet for cuts, bruises, and swelling
Wear comfortable shoes and socks that fit well
Wash feet with warm water and soap
Apply lotion or cream to feet
Keep toenails trimmed and filed

Don't

Don't soak feet, it can dry them out, causing cracks and cuts
Don't walk barefoot
Don't wear shoes that are too tight
Don't apply lotion or cream between the toes

Foot Screening Tool

Foot Assessment

☐ Toe deformations ☐ Foot drop
☐ Bunions ☐ Toenail fungus

Skin Assessment

☐ Redness ☐ Warmth ☐ Dryness
☐ Swelling ☐ Ulcers ☐ Lesions

Footwear Assessment

	y	n
Do you wear appropriate shoes	☐	☐
Do you wear orthotics or inserts	☐	☐

If you answered yes to 1 or more questions, please seek physician support.

NCES www.NCEScatalog.con | NCES, Inc. | 800.888.8888

Head-to-head comparison of the benefits of DSME vs. metformin

Scorecard: DSME vs Metformin		
Criteria	Benefits Rating	
	DSME	Metformin
Efficacy	High	High
Hypoglycemia risk	Low	Low
Weight	Neutral/Loss	Neutral/Loss
Side effects	None	GI
Cost	Low/Savings	Low
Psychosocial benefits	High	N/A

Margaret A. Powers Dia Care 2016;39:2101-2107

American Diabetes Association.

Barriers for Persons with Diabetes

- Lack of awareness of:
  - Risk factors for diabetes.
  - Signs and symptoms related to diagnosis.
  - Self-care for prevention of complications.
- Minimal skills for self-management.
- Costs of monitoring equipment & supplies.
- Lack of support for physical activity and nutrition behaviors.
- Long waits for care.
- Fatalism and hopelessness.

Jenkins, C, Todd, E. Diabetes. 1997; 46 (Suppl 2), 37A

Barriers for Healthcare Providers

- Time
- Disorganized records
- Too little help
- Not enough resources
- Reimbursement concerns
- Office time consumed by acute non-diabetes issues (Episodic Care)
- Patients inability to understand treatment plan

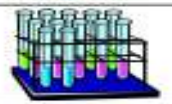
Jenkins, C, Todd, E. Diabetes. 1997; 46 (Suppl 2), 37A

Systems Barriers

- Lack of diabetes education programs
- Few materials for low literacy persons
- Few materials culturally appropriate
- Lack of reimbursement for diabetes care and education.

Jenkins, C, Todd, E. Diabetes. 1997; 46 (Suppl 2), 37A

DIABETES SELF MANAGEMENT GOALS

#		Goal
1		I will exercise to increase my heart rate for at least 30 minutes a day, 5 days a week.
2		I will follow my low fat, low salt and low sugar diabetic diet. I will control my portion sizes.
3		I will check my blood sugar as directed by my doctors.
4		I will complete a lab test to check for my Hemoglobin A1C (HbA1c) levels at least once a year or twice a year and 3 months apart.
5		I will complete a lab test to check for my LDL levels at least once a year.
6		I will check my feet daily. If I find sores or an irritation, I will go see my doctor.
7		I will visit the eye specialist once a year or as suggested by my doctor.
8		I will see my dentist once a year for a comprehensive exam or as suggested by my doctor.
9		I will follow my doctors' instructions and take the medications my doctors prescribe.
10		I will keep my appointments and regularly see my doctor for diabetic management.
11		I will stop smoking.

Reducing Risks

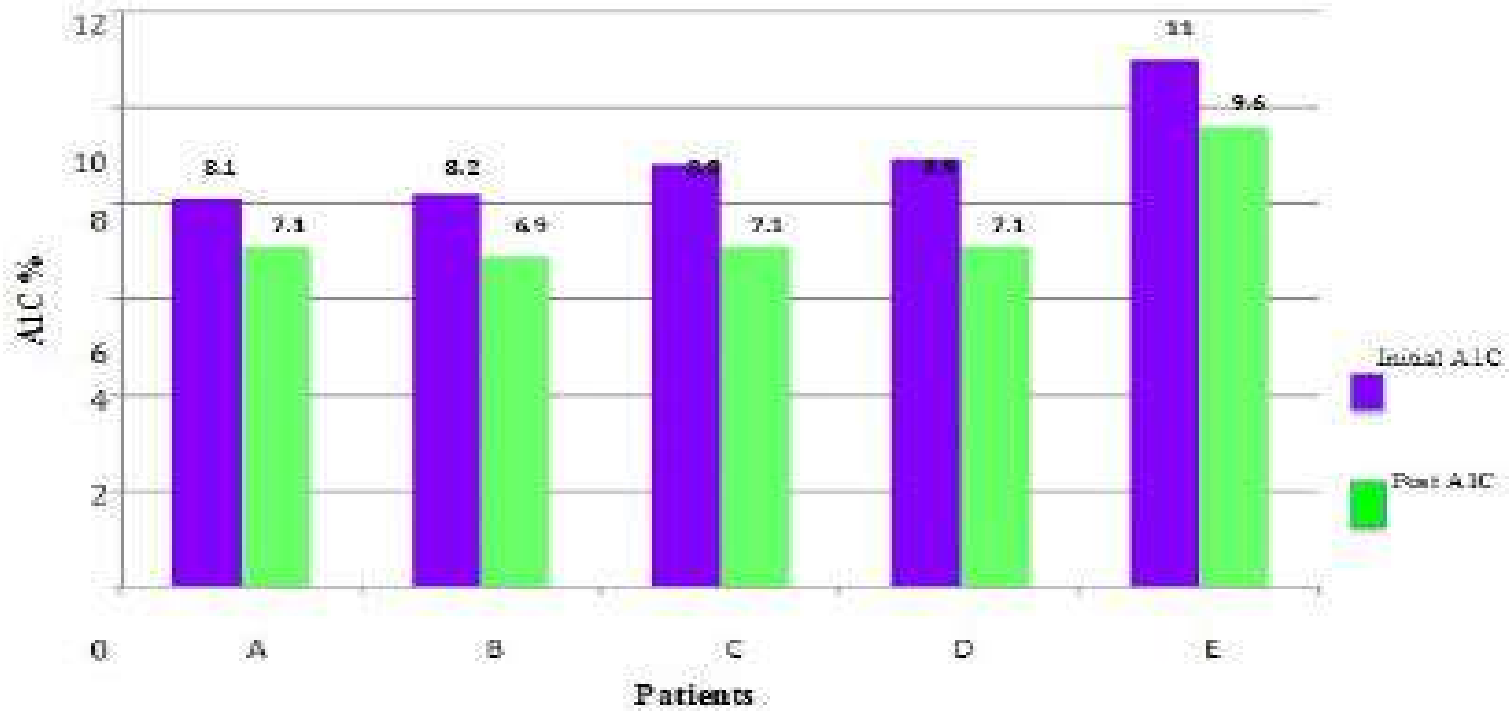
- Hypoglycaemia
- Hyperglycaemia
- Sick Days
- CVD
- Feet
- Eyes (visual chart vs dilated)
- Kidneys
- Sex

Benefits Associated with DSME/S

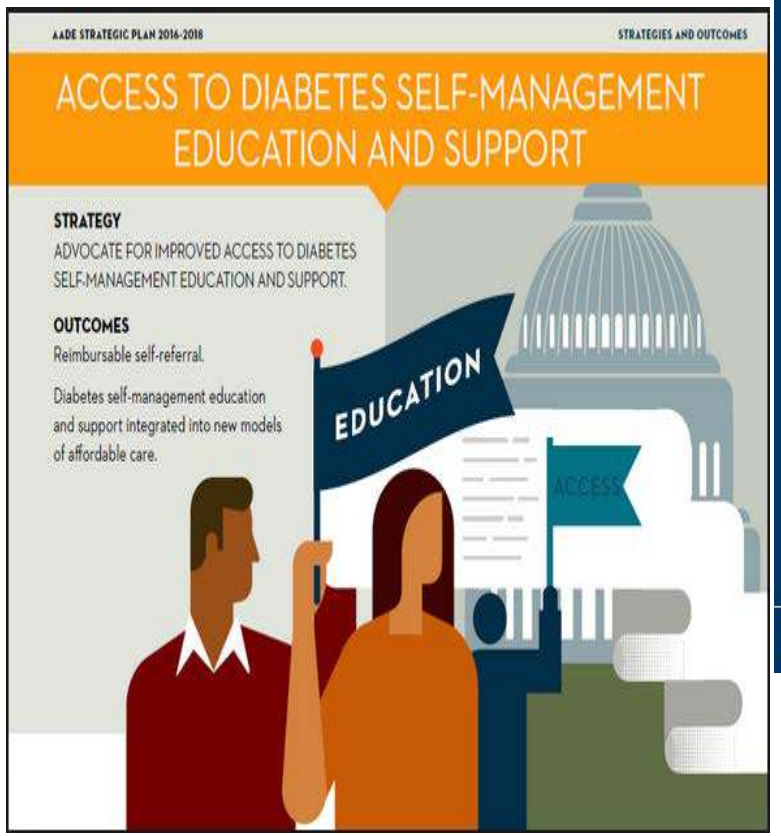
- **Improved health outcomes**
  - Reduced A1c
  - Reduced onset and/or advancement of complications
  - Reduced hospital admissions and readmissions
- **More healthful eating patterns and regular activity**
- **Enhanced self-efficacy and empowerment**
  - Increased healthy coping
  - Improved quality of life

Diabetes Care, The Diabetes Educator, Journal of Academy of Nutrition and Dietetics
Norris SL, et al. Diabetes Care 2001

Impact of Diabetes on Self-Management Education Program on A1C for Glycaemic Control



American Diabetes Association.



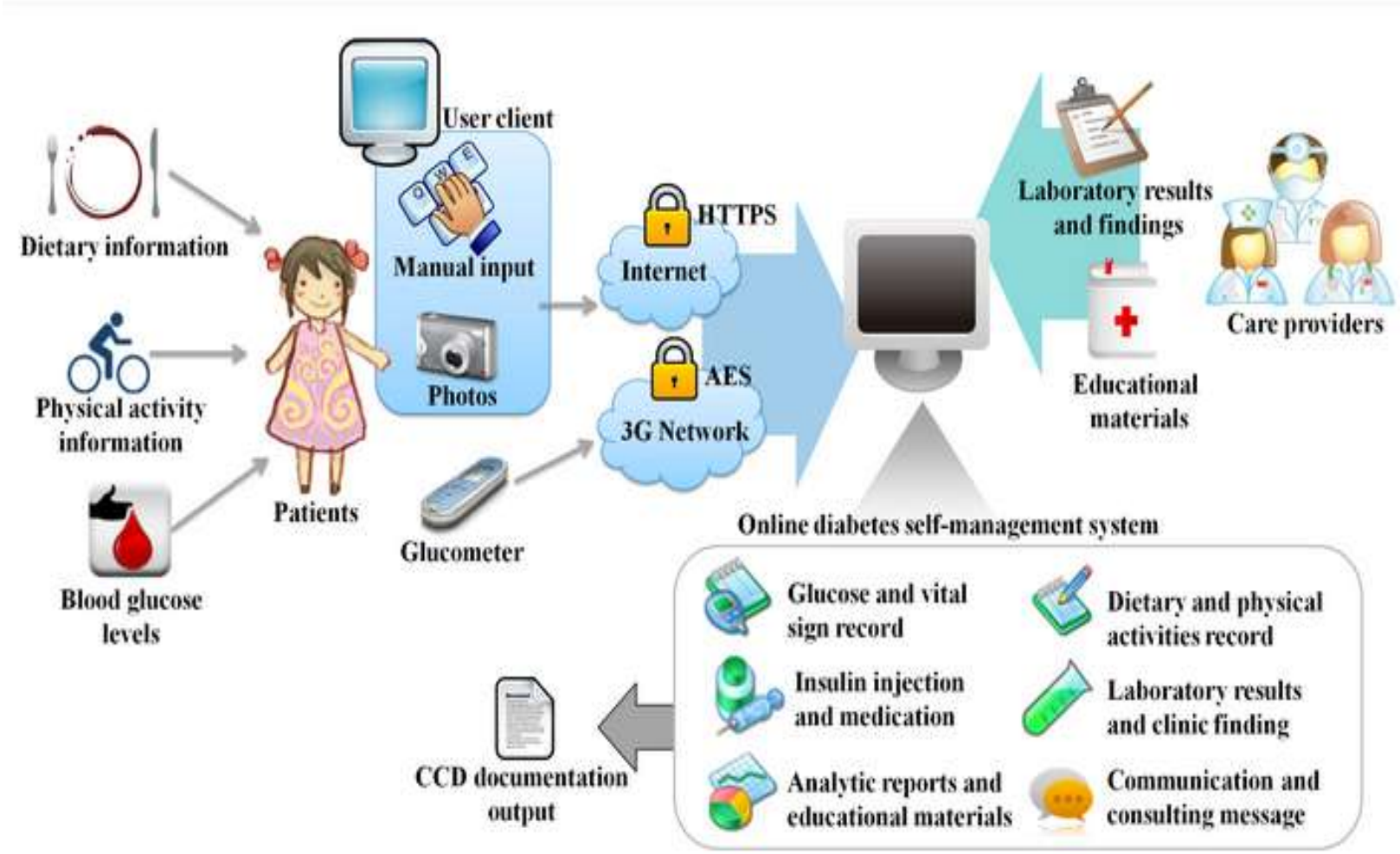
Recommendations: Diabetes Self-Management Education, Support

- DSME/DSMS programs are appropriate venues for people with prediabetes to receive education and support to develop and maintain behaviors that can prevent or delay the onset of diabetes **C**
- Because DSME/DSMS can result in cost-savings and improved outcomes **B**, DSME/DSMS should be adequately reimbursed by third-party payers **E**

American Diabetes Association.

ADA. 4. Foundations of Care. Diabetes Care 2015;38(suppl 1):S20

Updated DSME (2018)
(Technology Enable Self Management)



AACE in Practice Jan, 2018

What is SMBG?

Could you elaborate on SMBG?

Method of assessment of glycaemic control

- SMBG – Self-monitoring of blood glucose
- CGM – Continuous glucose monitoring
- HbA1C

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SMBG – Self-monitoring of blood glucose

Recommendations

- **Patients with intensive insulin regimens**
  - prior to meals and snacks (3 main meals + 3 snacks - total 6 times / day)
  - at bedtime,
  - **occasionally** postprandially,
  - prior to exercise and critical tasks such as driving
  - When suspect and after treating low blood glucose until they are normoglycemic

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SMBG – Self-monitoring of blood glucose

Recommendations

- **T2DM using oral agents and/or basal insulin**
  - Insufficient evidence for when and how often SMBG
- **T2DM using basal insulin**
  - fasting glucose →to inform dose adjustments
- **T2DM with less intensive insulin therapy**
  - more frequent SMBG (e.g., fasting, before/after meals)

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SMBG – Self-monitoring of blood glucose

Less frequent insulin injections or non-insulin Rx

- **help guide**
  - treatment decisions and/or
  - self-management for patients
- **SMBG allows patients to**
  - evaluate their individual response to therapy and
  - assess whether glycemic targets are being achieved.
- **Integrating SMBG results into diabetes management can be a useful tool for**
  - guiding medical nutrition therapy and physical activity,
  - preventing hypoglycemia, and
  - adjusting medications (particularly prandial insulin doses)
- **Type 1 diabetes,**
  - greater SMBG frequency → lower A1C

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SMBG – Self-monitoring of blood glucose

Recommendations

Less frequent insulin injections or non-insulin Rx

- **When prescribing SMBG, ensure that**
  - patients receive ongoing instruction and
  - regular evaluation of
    - SMBG technique,
    - SMBG results, and
    - their ability to use SMBG data to adjust therapy

Which one first ?– FBS or 2HPP

- Importance
- Contribution to A1C

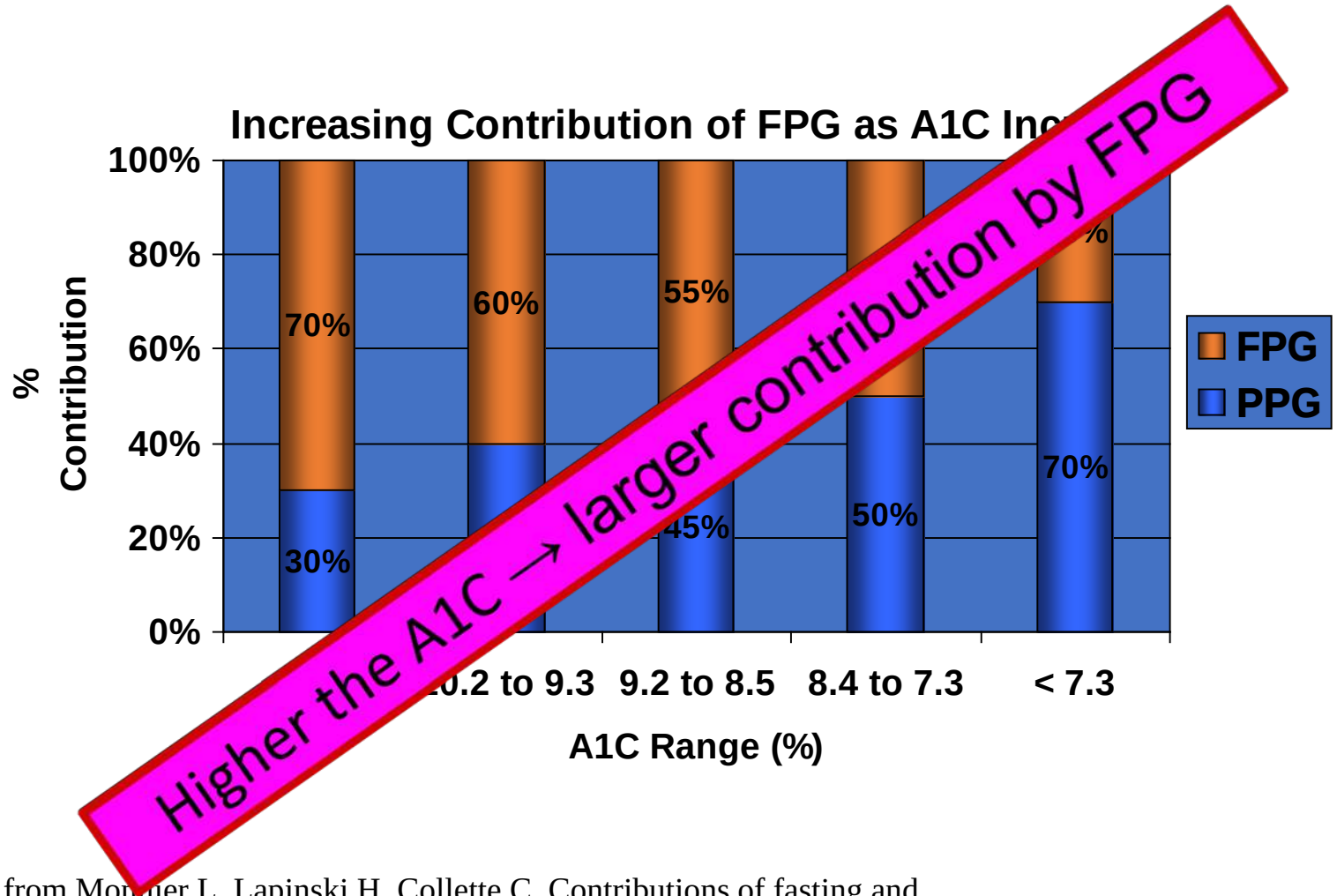
- Which one is important?

- FPG ------for microvascular complication

- 2HPP ----for macrovascular complication (mainly CVS)

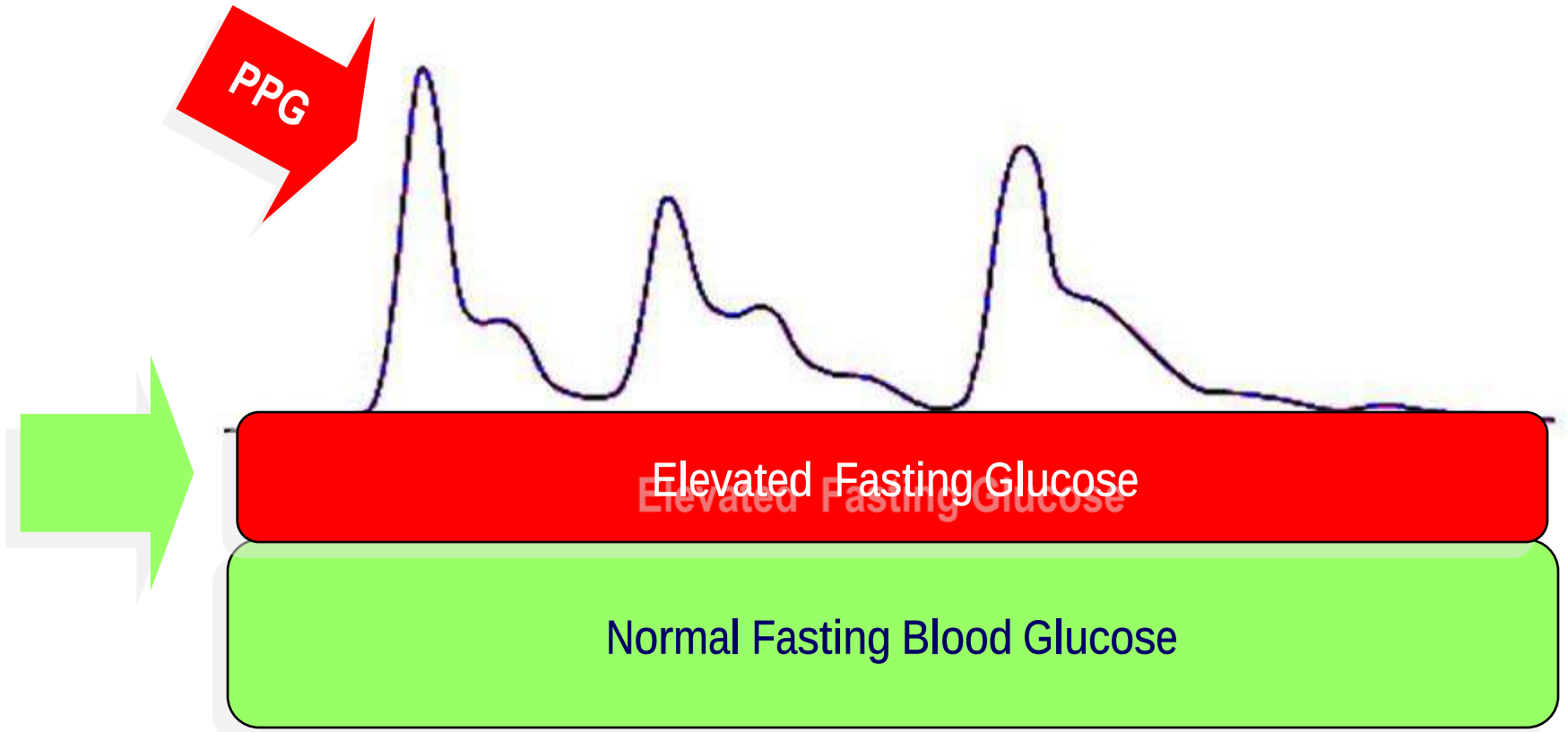
Both are important

Contributions of FPG and PPG On Glycosylated Haemoglobin



Adapted from Monnier L, Lapinski H, Collette C. Contributions of fasting and postprandial plasnma glucose increments to the overall diurnal hyper glycemia of Type 2 diabetic patients: variations with increasing levels of HBA(1c). *Diabetes Care.* 2003;26:881-885.

Fix Fasting First



[Lowering FPG first will lower all PG values throughout the day and thus will also reduce PPG and may be sufficient.]

Hence, there is a need to fix the fasting first.

Which one first ?– FBS or 2HPP

Why

- Safer
- Simpler

SMBG Summary

- Patient should have **well validated Glucometer**
- **Regular SMBG** – an integral part of DM Management
- Regular **recording** of SMBG
- Regular **reviewing** of SMBG by patient and health care provider
- Patients should be taught how to **use SMBG data** to adjust food intake, exercise, or pharmacologic therapy to achieve specific goals *
- important **to monitor for and prevent** asymptomatic hypoglycemia and hyperglycemia*

- *** To be useful, the information must be integrated into clinical and self-management plans**

What are the different set of Glycemic Targets in different settings?

Glycemic Targets for different settings

1. Non-pregnant adults
2. Pregnancy
3. In-patient
4. Special population
   - Children
   - Elderly

Glycemic Targets

for

Non-pregnant adults

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Glycemic Recommendations for Non-pregnant 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)

- * Goals should be individualized.
- † Postprandial glucose → 1–2 hours after the **beginning of the meal**.
- **Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals.**

- **Preprandial glycemic target - 70–130 mg/dL → to → 80–130 mg/dL (2015 ADA)**
- *(ADAG Study – A1C-Derived Average Glucose Study-2008)*
- Raising the lower range of the glycemic target → to limit overtreatment and
  → provide a safety margin

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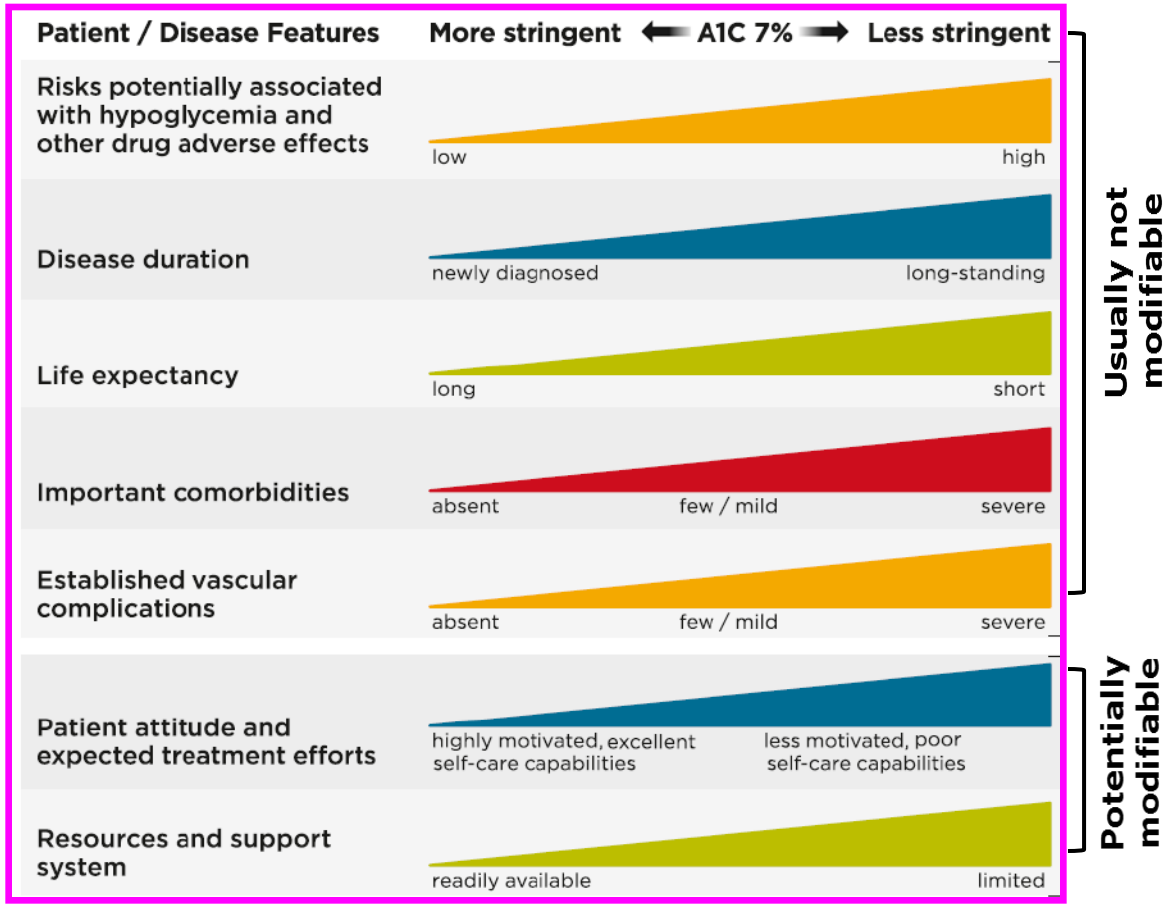
A1C Goals



Recommendations

- **A reasonable A1C goal**
  - <7% (53 mmol/mol).
- **more stringent A1C goals**
  - (<6.5% [48 mmol/mol])
- **Less stringent A1C goals**
  - (<8% [64 mmol/mol])

Diabetes Care 2018;41(Suppl. 1):S55–S64 | https://doi.org/10.2337/dc18-S006c

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A1C Goals (Recommendations)

More stringent A1C goals (<6.5% [48 mmol/mol])

- [if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy)].
- **Appropriate patients** might include those with
  - short duration of diabetes,
  - type 2 diabetes treated with lifestyle or metformin only,
  - long life expectancy, or
  - no significant cardiovascular disease.

Diabetes Care 2018;41(Suppl. 1):S55–S64 | https://doi.org/10.2337/dc18-S006c

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A1C Goals (Recommendations)

Less stringent A1C goals (such as <8% [64 mmol/mol])

may be **appropriate** for patients with

- a history of severe hypoglycemia,
- limited life expectancy,
- advanced micro- or macrovascular complications,
- extensive comorbid conditions, or
- long-standing diabetes in whom the goal is difficult to achieve

(despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.)

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Mean Glucose Levels for Specified A1C Levels

	Mean Plasma Glucose*		Mean Glucose			
			Fasting	Premeal	Postmeal	Bedtime
A1C%	mg/dL	mmol/L	mg/dL	mg/dL	mg/dL	mg/dL
6	126	7.0				
<6.5			122	118	144	136
6.5-6.99			142	139	164	153
7	154	8.6				
7.0-7.49			152	152	176	177
7.5-7.99			167	155	189	175
8	183	10.2				
8-8.5			178	179	206	222
9	212	11.8				
10	240	13.4				
11	269	14.9				
12	298	16.5				

professional.diabetes.org/eAG

Diabetes Care 2018;41(Suppl. 1):S55–S64 | https://doi.org/10.2337/dc18-S006c

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Glycaemic Targets -(Hypoglycaemia)

Level	Glycemic criteria	Description
Hypoglycaemia alert value (level 1)	≤70 mg/dL (3.9 mmol/L) (**~4 mmol/L**)	Sufficiently low for **treatment with fast-acting carbohydrate** and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dL (**3.0 mmol/L**)	Sufficiently low to **indicate serious, clinically important hypoglycemia**
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with **severe cognitive impairment requiring external assistance for recovery**

the International Hypoglycaemia Study Group,

Glycemic Targets for Pregnancy

Diabetes Care 2018;41(Suppl. 1):S137–S143 | https://doi.org/10.2337/dc18-S013

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GLYCAEMIC targets in pregnancy

Preconception counseling

- Ideally **A1C = 6.5% (48 mmol/mol)** (to ↓ the risk of congenital anomalies)

GLYCAEMIC targets in pregnancy

	Women with type 1 or type 2 diabetes or Gestational diabetes mellitus (GDM)
Fasting	≤ 95 mg/dL (5.3 mmol/L)
1-hr postprandial	≤ 140 mg/dL (7.8 mmol/L)
2-hr postprandial	≤ 120 mg/dL (6.7 mmol/L)
A1C	▪ 6.0 – 6.5 % (42 – 48 mmol/mol) recommended ▪ < 6.0% may be optimal if this can be achieved without significant hypoglycaemia ▪ Relax <7% (53 mmol/mol) to prevent hypoglycaemia

Postprandial monitoring - associated with better glycemic control and lower risk of preeclampsia.

Glycemic Targets for In-patient

Diabetes Care 2018;41(Suppl. 1):S137–S143 | https://doi.org/10.2337/dc18-S013

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Glycaemic targets for In-Patient

Recommendations

Perform an A1C on all patients with diabetes or hyperglycemia (blood glucose >140 mg/dL) admitted to the hospital if not performed in the prior 3 months.

Insulin - preferred method for diabetes care in the hospital

Recommendations

- Initiate insulin starting at ≥180 mg/dL (10.0 mmol/L)
- target glucose range - 140-180 mg/dL (7.8-10.0 mmol/L)

More stringent goals

- 110 -140 mg/dL (6.1 - 7.8 mmol/L)
- may be appropriate for selected patients, if this can be achieved without significant hypoglycemia.

Higher glucose ranges may be acceptable in terminally ill patients, in patients with severe comorbidities, and in inpatient care settings where frequent glucose monitoring or close nursing supervision is not feasible.

Peri-operative

Target – 80 -180 mg/dL (4.4-10.0 mmol/L)

Diabetes Care 2018;41(Suppl. 1):S137–S143 | https://doi.org/10.2337/dc18-S013

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ADA 2018

Glycemic Targets for Children and Adolescents With T1DM

Consider a risk-benefit assessment, including hypoglycemia risk, when individualizing glycemic targets	
A1C target	▪ <7.5% (58 mmol/mol) – for all ▪ <7.0% - reasonable if it can be achieved without excessive hypoglycemia
Plasma glucose (preprandial)	90-130 mg/dL(5.0-7.2 mmol/L)
Plasma glucose at bedtime and overnight	90-150 mg/dL (5.0-8.3 mmol/L)

Diabetes Care 2018;41(Suppl. 1):S137–S143 | https://doi.org/10.2337/dc18-S013

American Diabetes Association®

ADA 2018

Glycaemic targets for Older Patient (>65 year)

Status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)
Coexisting chronic illnesses ▪ conditions serious enough to require medications or lifestyle management ▪include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke.				

Diabetes Care 2018;41(Suppl. 1):S137–S143 | https://doi.org/10.2337/dc18-S013

American Diabetes Association®

ADA 2018

Glycaemic targets for Older Patient (>65 year)

Status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose
Complex/ intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to moderate Cognitive Impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	< 8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L

*"multiple," - mean at least three, but many patients may have five or more
ADL – Activities of Daily living

Diabetes Care 2018;41(Suppl. 1):S137–S143 | https://doi.org/10.2337/dc18-S013

American Diabetes Association®

ADA 2018

Glycaemic targets for Older Patient (>65 year)

Status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	< 8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)

**The presence of a single end-stage chronic illness, such as stage 3–4 CCF or oxygen-dependent lung disease, CKD requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.

Diabetes Care 2018;41(Suppl. 1):S137–S143 | https://doi.org/10.2337/dc18-S013

American Diabetes Association®

ADA 2018

Glycaemic targets for Older Patient (>65 year)

Status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose
Healthy	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)
Complex/ intermediate	Intermediate remaining life expectancy,	< 8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L
Very complex /poor health	Limited remaining life expectancy	< 8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)

- What are the main unique features of 2018 ADA Guideline?

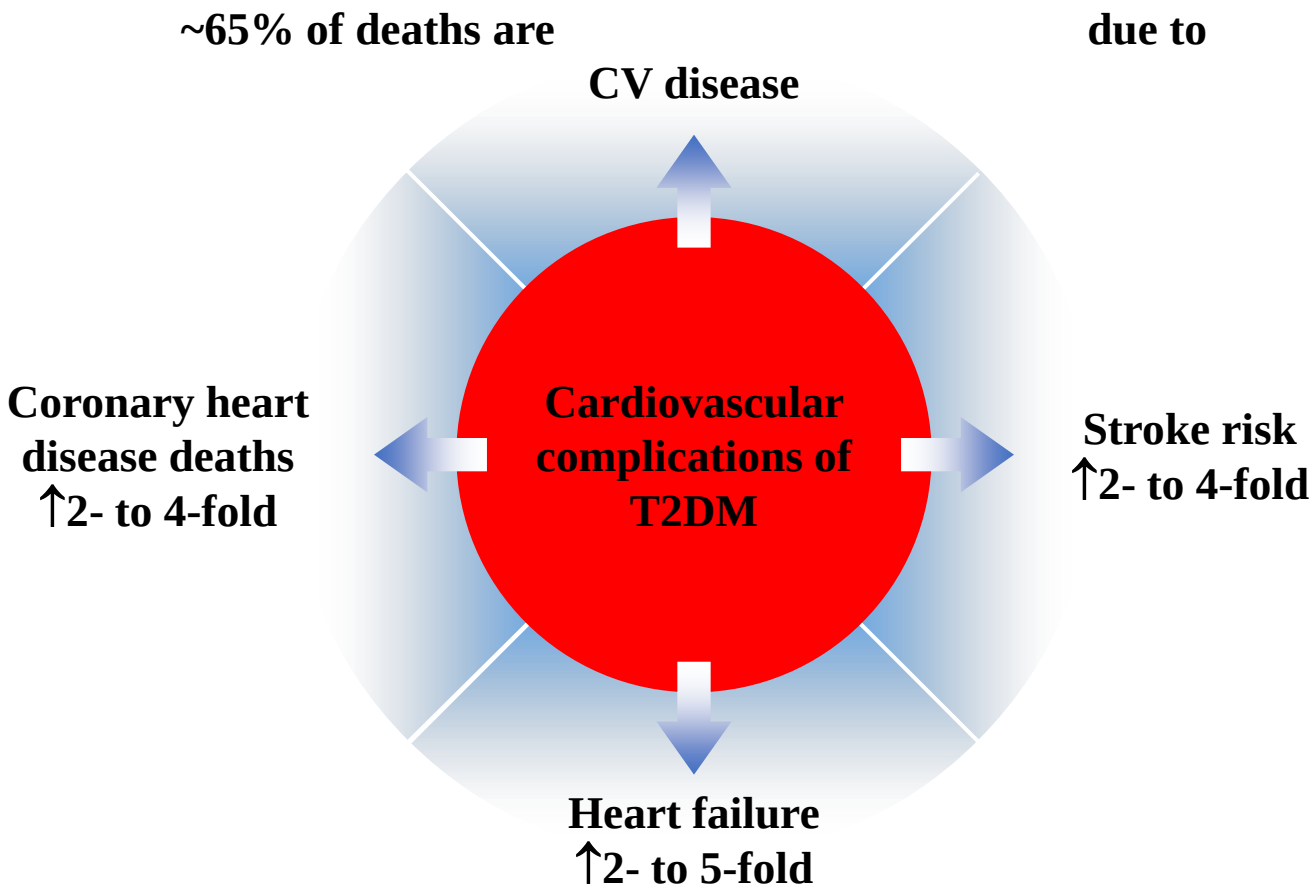
- What are the findings of CVOT on GLP1-RA, SGL2 i, DPP4 i?

- Feasibility of new 2018 ADA Guideline in Myanmar? What is your suggestion?

Macrovascular disease in diabetes

- The **main cause of death** in type 1 and type 2 diabetes
- Excess mortality is seen in all age groups, especially the young
- Premenopausal women lose their protection against macrovascular disease
- Disease is **diffuse, distal, and affects many vessels**
- **Reocclusion and reinfarction** rates are higher after thrombolysis
- **Restenosis** rates are higher after angioplasty, although drug eluting stenting may help
- Five year survival after coronary artery bypass grafting is lower than in non-diabetic patients

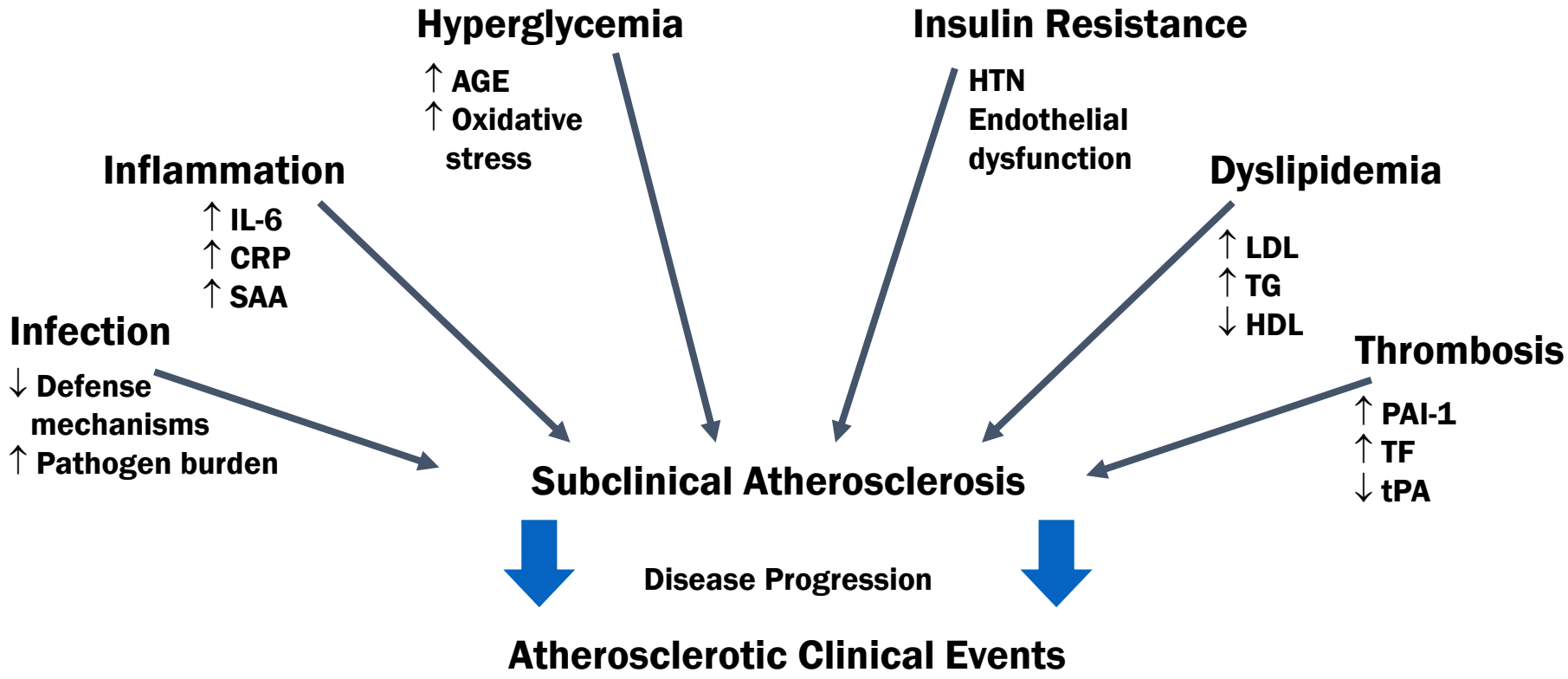
Cardiovascular disease and diabetes



T2DM = type 2 diabetes mellitus

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

Mechanisms by which Diabetes Mellitus Leads to Coronary Heart Disease



AGE=Advanced glycation end products, CRP=C-reactive protein, CHD=Coronary heart disease HDL=High-density lipoprotein, HTN=Hypertension, IL-6=Interleukin-6, LDL=Low-density lipoprotein, PAI-1=Plasminogen activator inhibitor-1, SAA=Serum amyloid A protein, TF=Tissue factor, TG=Triglycerides, tPA=Tissue plasminogen activator

Source: Biondi-Zoccai GGL et al. *JACC* 2003;41:1071-1077

Cardiometabolic Risk

A patient with diabetes

=

Normal person with MI

Consider yourself having a heart attack already, when you develop diabetes

Strategies

- Good glycaemic control(Early treatment)

(To use drugs which reduce CV mortality or cardiovascular safe)

GLP1 agonist and SGLT2 inhibitors(reduce CVD motality)

Metformin and DPP4 inhibitors –CVD safe

- Treatment of Hypertension
- Reductions of Lipids
- Smoking cessation
- Obesity reduction

Glucose Control and CV reduction

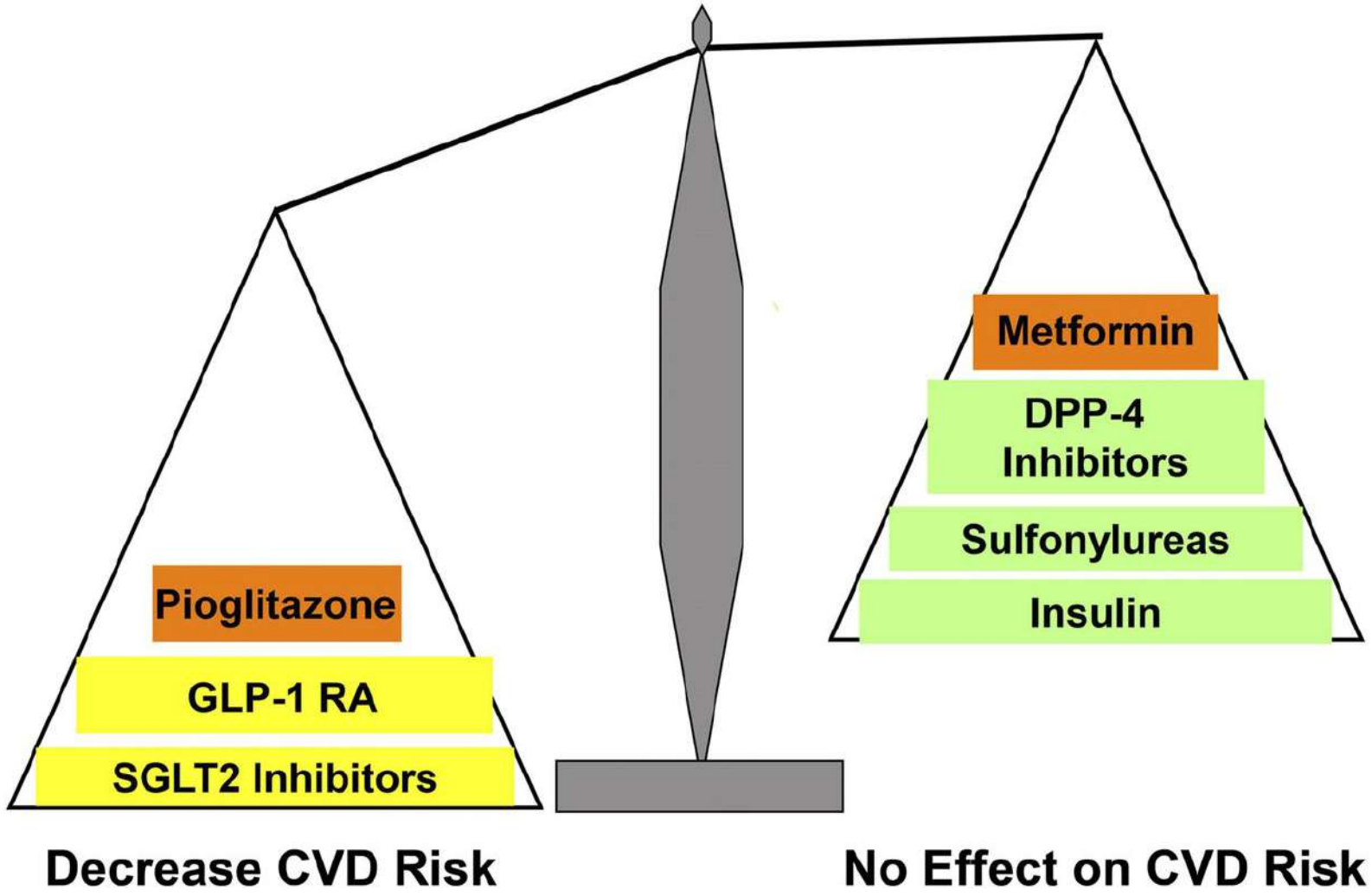
STUDY	Duration of DM at inclusion for tight control	CV REDUCTION
UKPDS 20 year f/u	New	Yes
ADVANCE	8 Yrs	No
ACCORD	10 Yrs	Increase
VADT	12 Yrs	No

Metabolic Memory: The Legacy

Early *vs* late glycaemic intervention: UKPDS enrolled newly diagnosed patients

	UKPDS[1] (n=3867)	ADVANCE[2] (n=11,140)	ACCORD[3] (n=10,251)	VADT[4] (n=1791)
	Disease progression			
Duration of diabetes (years)	0*	8	10	11.5
Mean baseline HbA_{1c} (%)	7.1	7.5	8.3	9.4
Mean baseline FPG (mmol/L)	8.0	8.5	9.7	11.4
Mean age (years)	53	66	62	60

Not all antidiabetes agents are equal in their ability to reduce cardiovascular risk.



Muhammad Abdul-Ghani, and Ralph A. DeFronzo Dia Care 2017;40:1121-1127

American Diabetes Association.

ADA 2017

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):

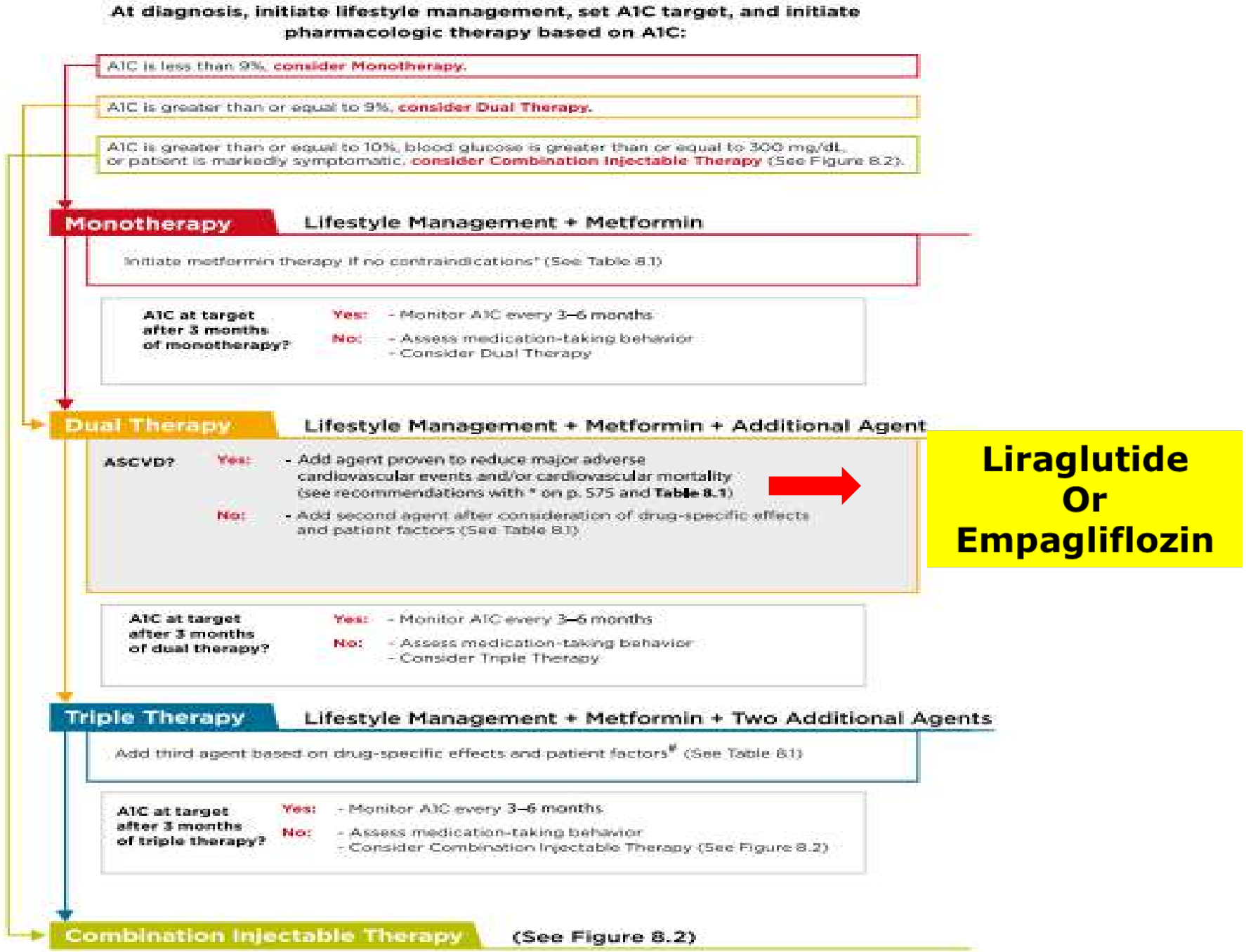
Triple Therapy — Metformin + — Lifestyle Management

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)

Antihyperglycemic Therapy in Adults with Type 2 Diabetes



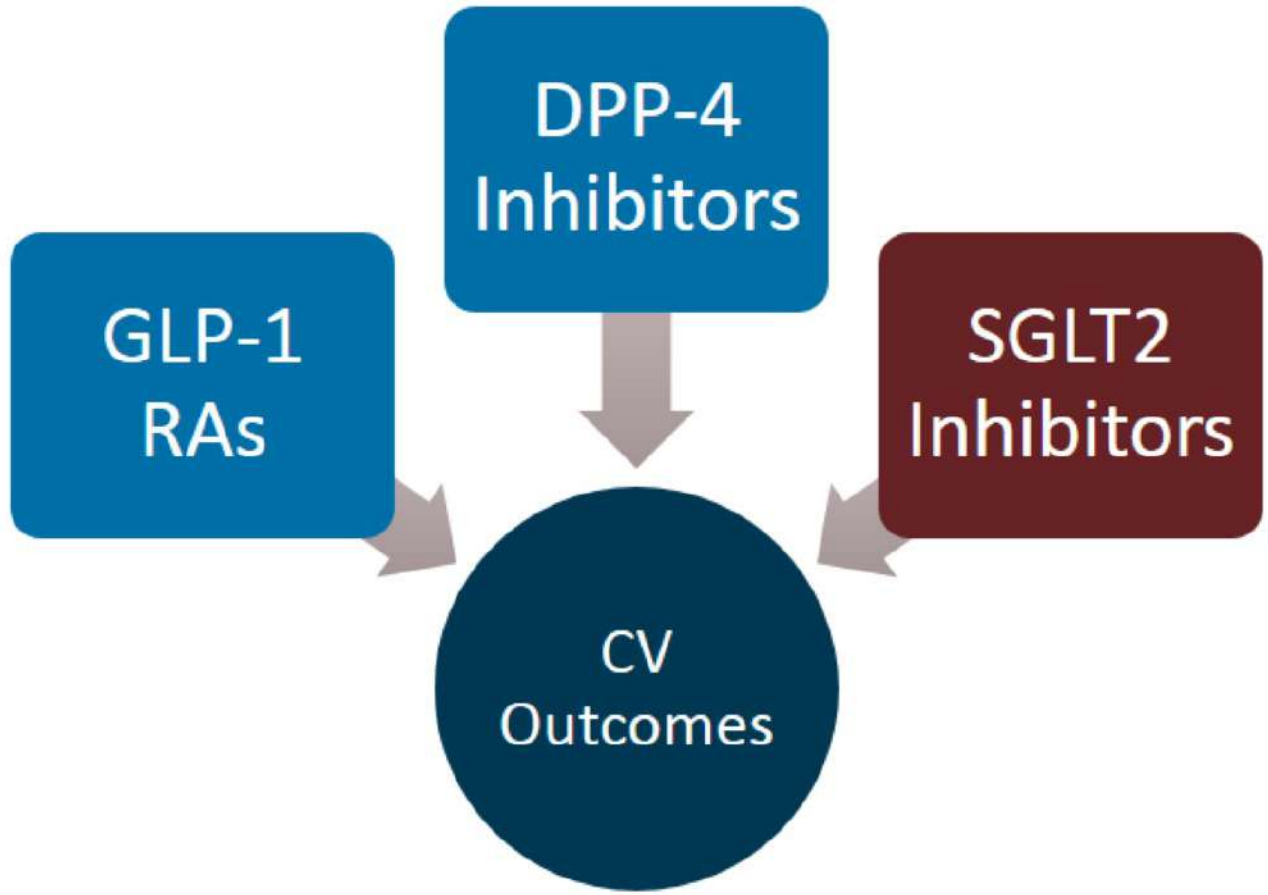
Liraglutide Or Empagliflozin

Table 8.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Dos/SQ	Renal Effects		Additions/Considerations
				ASCVD	CHF			Progression of CKD	Dosing/Use considerations	
Metformin	High	No	Neutral Potential for Modest Loss	Potential Benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects comm (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin not recommended with eGFR <45 • Dapagliflozin not recommended with eGFR <60; contraindicated with eGFR <30 • Empagliflozin: contraindicated with eGFR <30	• **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
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	• Exenatide not indicated with eGFR <30 • Lixisenatide: caution with eGFR <30 • Increased risk of side effects in patients with renal impairment	• **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; can be used in renal impairment	• Potential risk of acute pancreatitis • Joint pain
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 • Glyburide & glimepiride: initiate concomitantly 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
Insulin: Analogs						High	SQ			

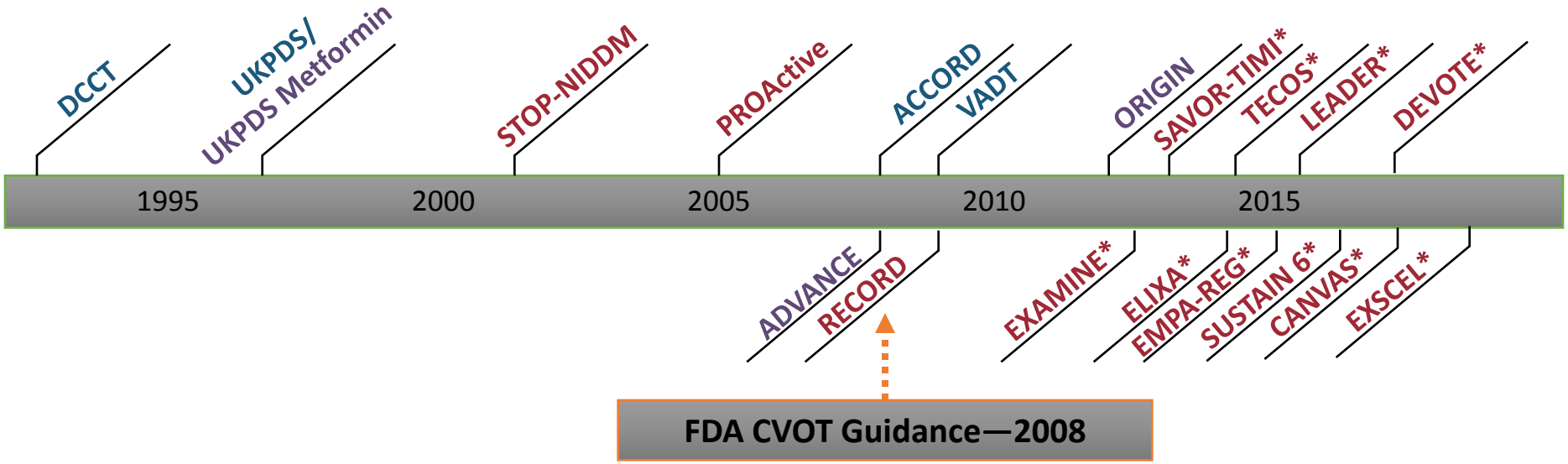
*See ref., 31 for description of efficacy. †FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes.

CVOTs With Glucose-Lowering Agents



Cheng JWM, et al. *Curr Med Res Opin*. 2017;33:985-992.

Timeline of Major Diabetes Outcomes Trials



Blue = Intensive vs standard control using same set of glucose-lowering agent(s)
Purple = Intensive control with a specific agent vs standard care
Red = Placebo- or active-controlled study
* = FDA-mandated cardiovascular safety trial

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; DCCT, Diabetes Control and Complications Trial; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, EMPA-REG OUTCOME trial; Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PROActive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Cardiovascular Outcomes Trials: A Brief History

- 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
  - Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
    - Some study designs tested for superiority if noninferiority criteria were met
  - Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
    - Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.

FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf.

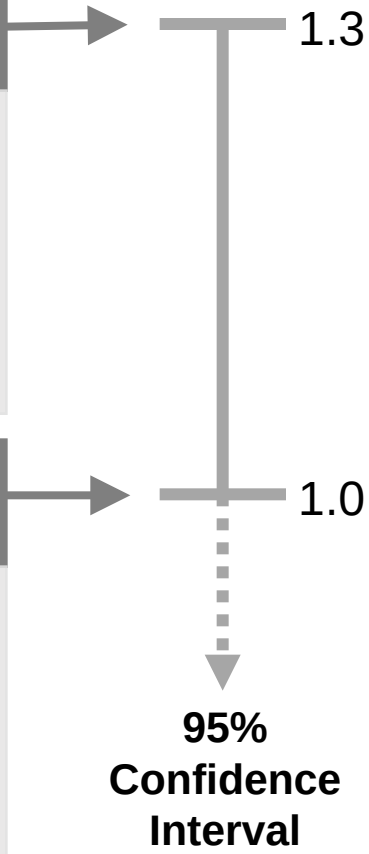
Noninferiority and Superiority Criteria in CVOTs

Noninferiority

- Upper bound of the confidence interval for the primary endpoint is less than a prespecified threshold (often 1.3, but criteria vary with study design)
- **Means study drug performed no worse than comparator and is <u>safe</u>**

Superiority

- Upper bound of confidence interval for the primary endpoint is typically less than 1 (criteria may vary with study design)
- Tested after noninferiority criteria are met
- **Means study drug reduced CV outcomes relative to comparator**



Agents Shown to Have CV Safety:
All antihyperglycemic agents evaluated in CVOTs to date

Agents Shown to Reduce CV Outcomes:
Canagliflozin
Empagliflozin
Liraglutide

CV Improvements and Novel Glucose-Lowering Agents

The CV and renal benefits observed with long-acting GLP-1 RAs and SGLT2 inhibitors may be the result of an entire milieu of improvements, eg,

- HbA1c reduction
- Improvements in insulin resistance
- Weight loss
- Blood pressure reduction
- Improvements in lipids
- Improvements in CV function

GLP-1 RAs and Cardiac Function

- **Treatment with GLP-1 RAs has been associated with SBP reduction. Potential mechanisms include vasodilation and natriuresis[a]**
- **Treatment with liraglutide 1.2 or 1.8 mg/day has reduced SBP, ranging from 2.1 to 6.7 mmHg among across LEAD studies[a]**
- **The decrease in SBP appears to be independent of weight loss and occurs before weight loss[a]**
- **In a hypertensive and heart failure-prone rat, GLP-1 improved survival and preserved left ventricular function[b]**
- **Liraglutide decreased left ventricular structural remodeling and improved cardiac output in mice after occlusion of the left anterior descending coronary artery[c]**
  - Similar results have been shown for the GLP-1 analogue, exenatide[d]

a. Lorber D. *Cardiovasc Ther*. 2013;31:238-249.
b. Poornima I, et al. *Circ Heart Fail*. 2008;1:153-160.
c. Noyan-Ashraf, MH, et al. *Diabetes*. 2009;58:975-983.
d. Liu et al. *Cardiovascular Diabetology* 2010;9:76.

CVOTs With GLP-1 RAs (cont)

CVOT	Agent	Established CV Safety	Demonstrated Beneficial Effects on CV Endpoints
LEADER[a]	Liraglutide	Yes	Yes
ELIXA[b]	Lixisenatide	Yes	No
SUSTAIN-6[c]	Semaglutide	Yes	Yes
EXSCEL[d]	Exenatide once weekly	Yes	No

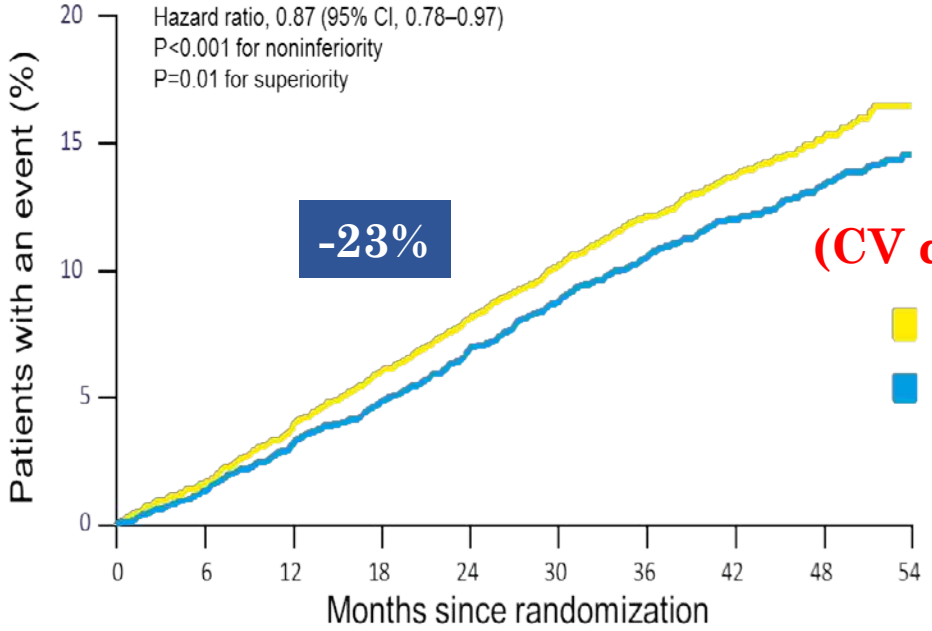
a. Marso SP, et al. *N Engl J Med*. 2016;372:311-322.
b. Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.
c. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.
d. AstraZeneca website, 2017. Primary safety objective.

Do Differences in GLP-1 RA Half-Life Explain Differences in Clinical Outcomes?

Agent	Half-Life[a]	CVOT	Primary Outcome Measure	Primary Outcome Result
Lixisenatide	3-4 h	ELIXA[b]	Composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA	HR 1.02; 95% CI: 0.89,1.17
Liraglutide	13 h	LEADER[c]	Composite of CV death, nonfatal MI, or nonfatal stroke	HR 0.87; 95% CI: 0.78, 0.97 *P* < .001 for noninferiority *P* = .01 for superiority
Semaglutide	165-184 h	SUSTAIN-6[d]	Composite of CV death, nonfatal MI, or nonfatal stroke	HR 0.74; 95% CI: 0.58,0.95 *P* < .001 for noninferiority *P* = .02 for superiority
Exenatide once weekly	4.7 days	EXSCEL [e]	Composite of CV death, nonfatal MI, or nonfatal stroke	*P* = NS for superiority

a. Dalsgaard NB, et al. *Expert Opin Drug Saf*. 2017;16:351-363.
b. Pfeffer MA, et al. *N Engl J Med*. 2015;33:2247-2257.
c. Marso SP, et al. *N Engl J Med*. 2016;372:311-322.
d. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844.
e. AstraZeneca website, 2017. Primary safety objective.

LEADER(Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results)

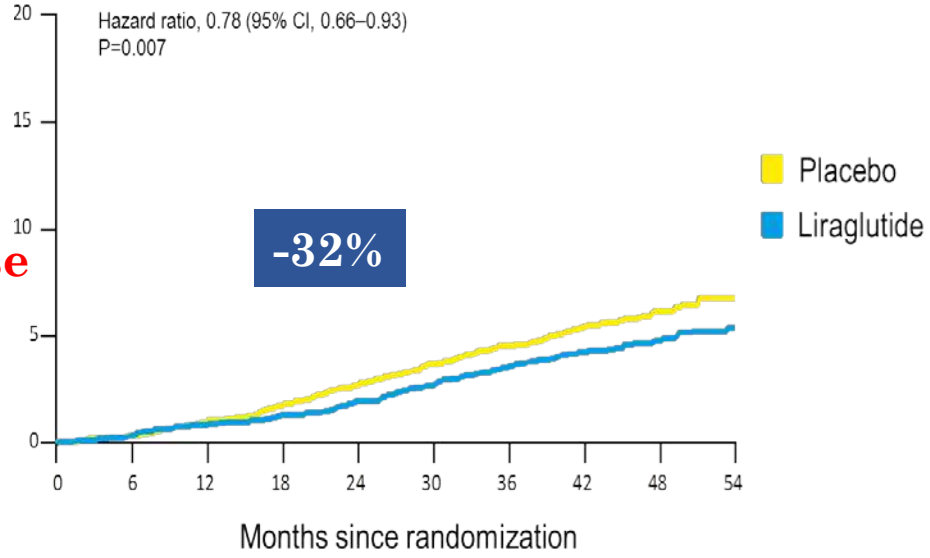


(CV death, nonfatal MI, or nonfatal stroke)

Placebo

Liraglutide

Death from Cardiovascular Cause

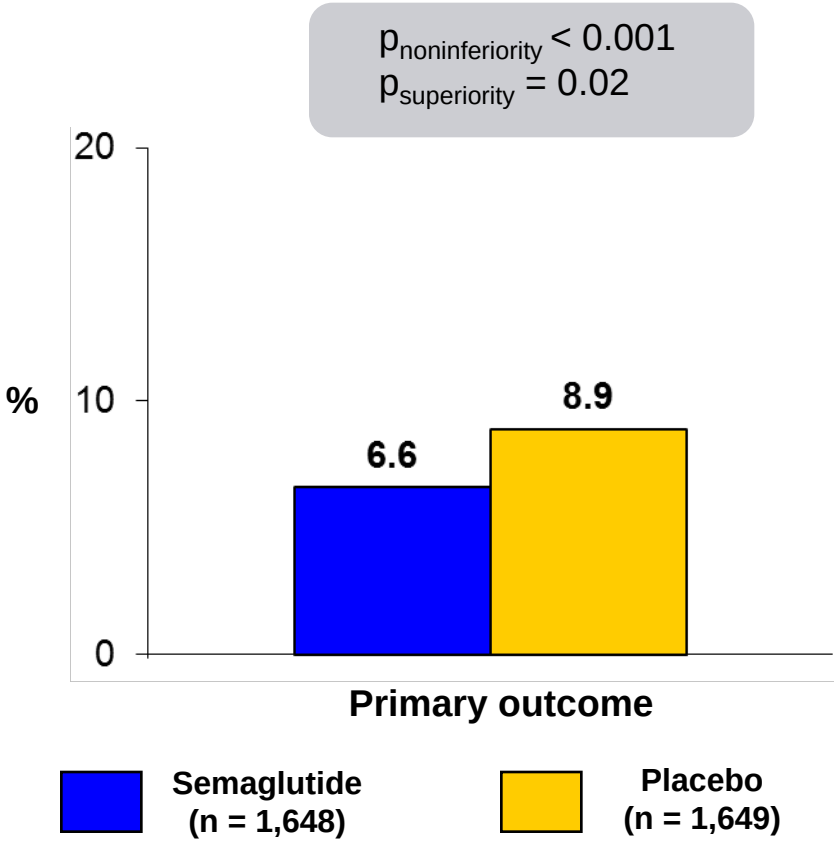


Placebo

Liraglutide

SUSTAIN-6(Semaglutide in Subject with Type2 diabetes

Trial design: Patients with DM2 at high risk for CV events were randomized in a 1:1:1:1 fashion to either semaglutide 0.5 mg, semaglutide 1 mg, or matching placebo. They were followed for a median of 2.1 years.



Results

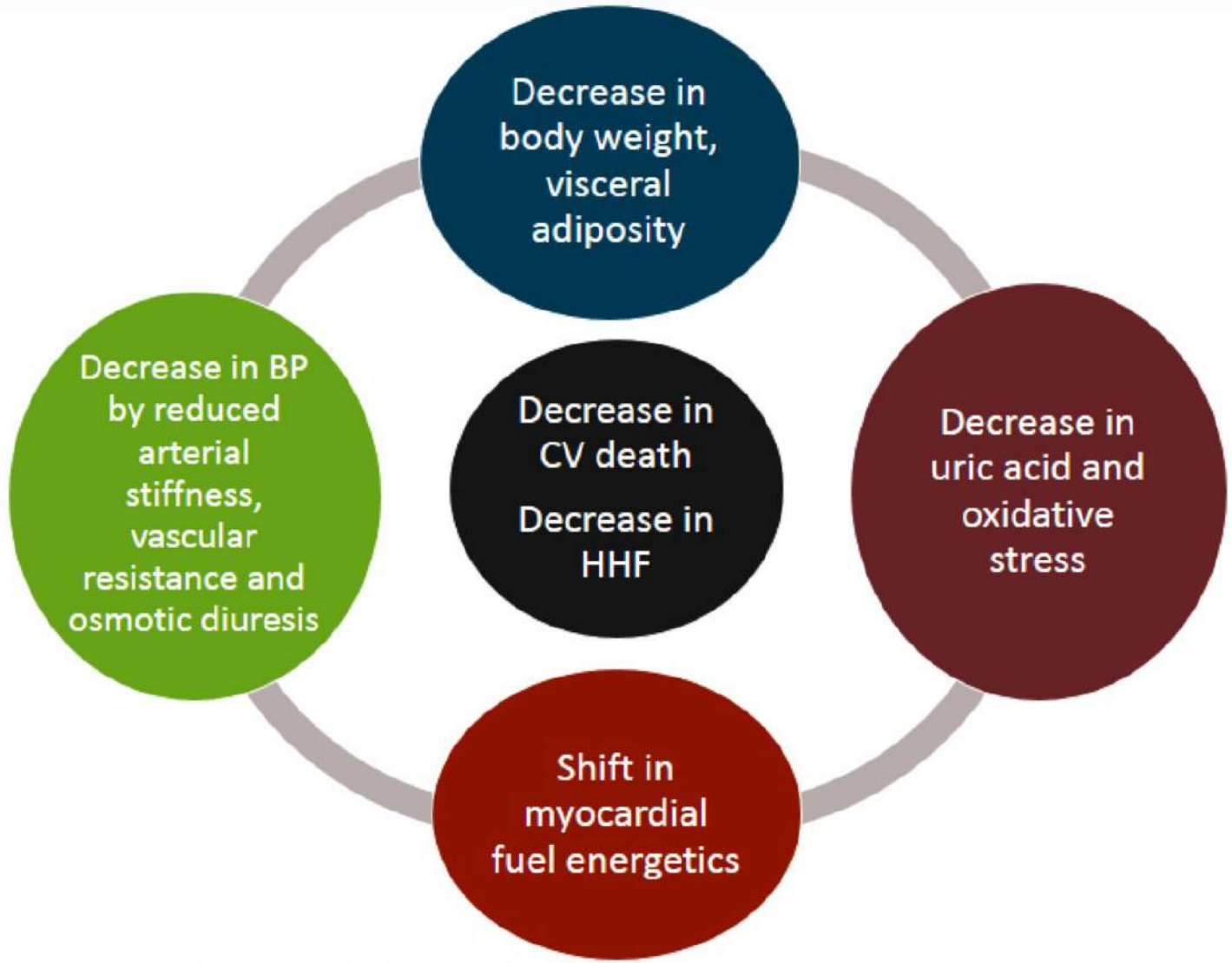
- Primary outcome, CV death/MI/stroke: semaglutide vs. placebo: 6.6% vs. 8.9%, HR 0.74, 95% CI 0.58-0.95, p < 0.001 for noninferiority; p = 0.02 for superiority
- CV death: 2.7% vs. 2.8%, p = 0.92; all MI: 2.9% vs. 3.9%, p = 0.12; all stroke: 1.6% vs. 2.7%, p = 0.04
- HbA1c at week 104: 7.6% vs. 7.3% vs. 8.3%

Conclusions

- Injectable once a week semaglutide (GLP-1 agonist) was superior to placebo in improving glycemic control and ↓ CV events in high-risk patients with diabetes
- There is also a significant reduction in stroke and new or worsening nephropathy with semaglutide, perhaps related to a concomitant reduction in BP, and also a reduction in body weight

Marso SP, et al. N Engl J Med 2016;375:1834-44

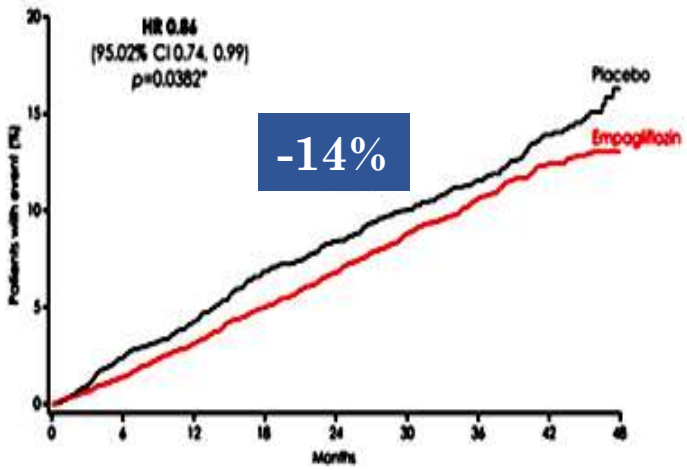
Potential Mechanisms of SGLT2 Inhibitors Resulting in CV Outcomes



Cheng JWM, et al. *Curr Med Res Opin*. 2017;33:985-992.

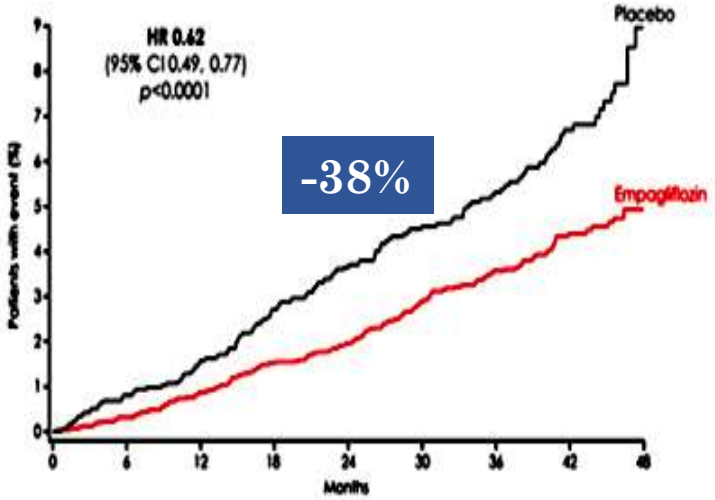
EMPA-REG - CV Outcomes

Primary outcome: 3-point MACE



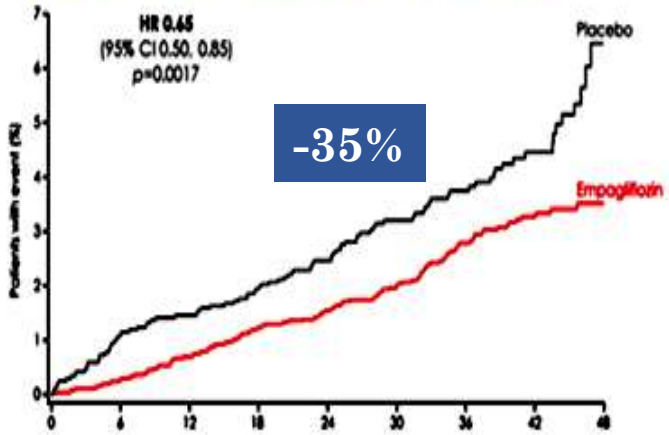
-14%

CV Death



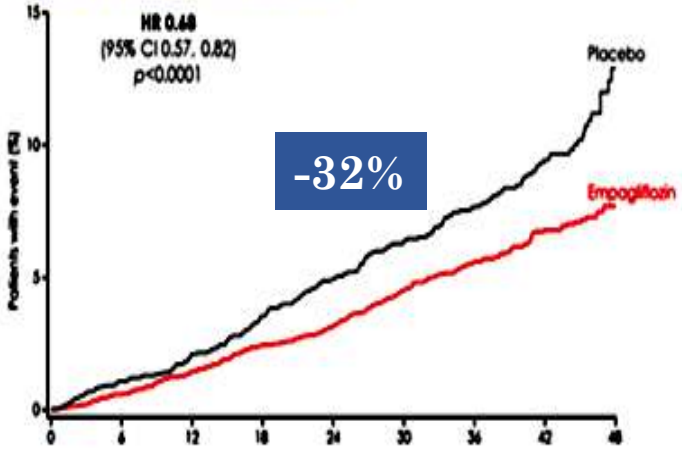
-38%

Hospitalization for heart failure



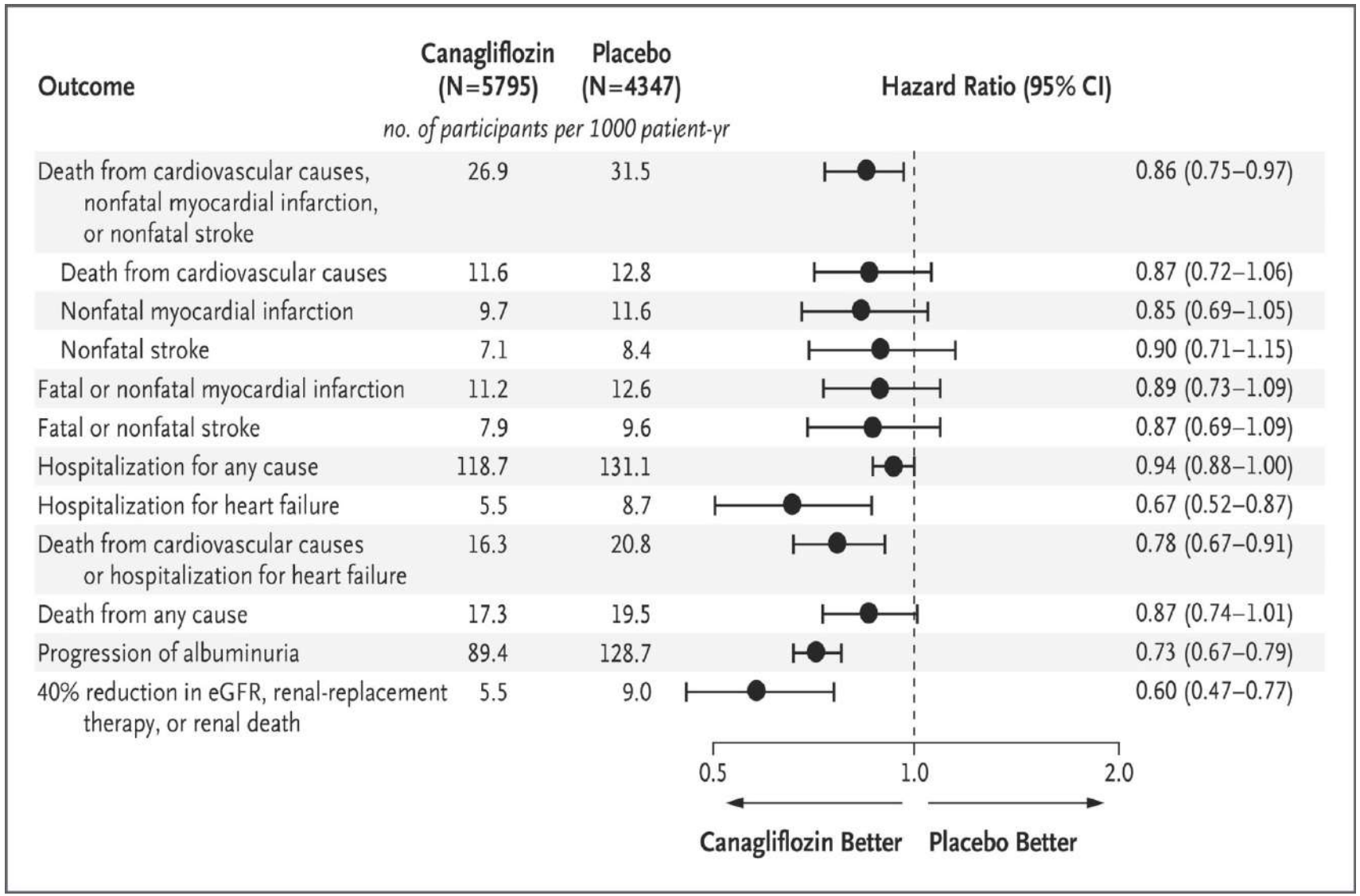
-35%

All-cause mortality

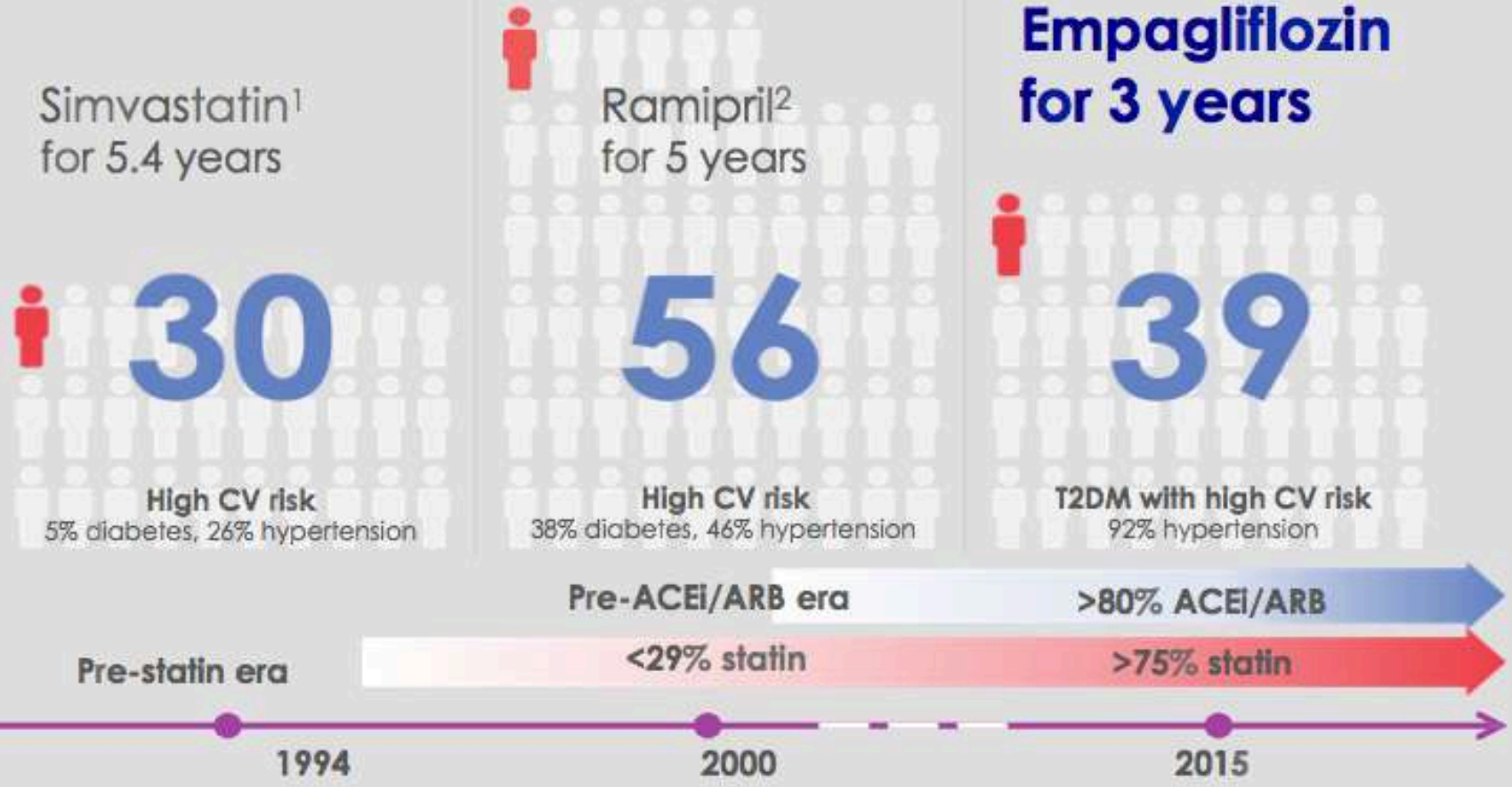


-32%

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS)



Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk



1.4S Investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2.HOPE Investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

SAVOR-TIMI, EXAMINE, TECOS: Primary Outcome Measure

No CV benefit vs placebo observed with either saxagliptin, alogliptin, or sitagliptin[a-c]

CVOT	Agent	Primary Endpoint	HR (95% CI)
SAVOR-TIMI 53[a]	Saxagliptin	CV death, nonfatal MI, or nonfatal stroke	1.00 (0.89, 1.12) *P* = .99
EXAMINE[b]	Alogliptin	CV death, nonfatal MI, or nonfatal stroke	0.96 (upper boundary of 1-sided repeated CI: 1.16) *P* = .315
TECOS[c]	Sitagliptin	CV death, nonfatal MI, or nonfatal stroke CV death, nonfatal MI, nonfatal stroke, or UA requiring hospitalization	0.99 (0.89, 1.10) *P* = .84 (superiority) 0.98 (0.88, 1.09) *P* = .645 (superiority)

a. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.
b. White W, et al. *N Engl J Med*. 2013;369:1327-1335.
c. Green JB, et al. *N Engl J Med*. 2015;373:232-242.

Guidelines' Changes as a Result of CV Outcomes Trial Findings

Changes to NICE guidelines May 2017[a]

- SGLT2 inhibitors are listed much more prominently as second-line therapy options, along with DPP-4 inhibitors, pioglitazone, or SUs to be used on treatment intensification when HbA1c rises above 7.5% on metformin. They are also listed prominently for use in triple therapy once HbA1c rises above 7.5% on dual therapy
- In addition, SGLT2 inhibitors can be considered as a first-line therapy option if metformin is contraindicated or cannot be tolerated and "a sulfonylurea or pioglitazone is not appropriate"

Changes to Canadian Diabetes Association Guidelines[b]

- GLP-1 RAs added to medications' list to be prescribed second line after monotherapy with metformin

ADA 2018,if ASCVD (+) next to metformin is liraglutide or Empagliflozin

a. NICE website. Type 2 Diabetes in Adults: Management.
b. Canadian Diabetes Association website. Guidelines.

Old(Met/SU/Pioz) or New?(GLP1 /SGLT2 inhibitors/DPP4 inhibitors)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Time to Change the Treatment Paradigm for Type 2 Diabetes?
Silvio E. Inzucchi
Author Affiliations
Corresponding author: Silvio E. Inzucchi, silvio.inzucchi@yale.edu.
Diabetes Care 2017 Aug; 40(8): 1128-1132. https://doi.org/10.2337/dc16-2372
Previous
Next
Article
Figures & Tables
Info & Metrics
PDF
Abstract
Most treatment guidelines, including those from the American Diabetes Association/European Association for the Study of Diabetes and the International Diabetes Federation, suggest metformin be used as the first-line therapy after diet and exercise. This recommendation is based on the
Diabetes Care
Current Issue
About the Cover
Index by Author
Masthead (PDF)
Search this issue
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Print
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Article Alerts
Email Article
Share
Request Permissions
Altmetric 40
Tweet

How much have to spend to Reduce 1%Hba1c in Australia

Drug class and agent #	Cost/day (AUD) per 1% ↓ in HbA1c *
Sulfonylureas	**0.95** (938 Kyats)
TZD (Pioglitazone)	**0.83** (813 Kyats)
SGLT2 (Empagliflozin)	**2.53** (2,477 Kyats)
DPP4i (Sitagliptin)	**2.70** (2,643 Kyats)
GLP 1(Exenatide LAR)	**3.07** (3,005 Kyats)
GLP 1 (Liraglutide)	**5.11** (5,002 Kyats)
Insulin (NPH)	**0.56** (548 Kyats)
Insulin (Glargine)	**1.33** (1,302 Kyats)

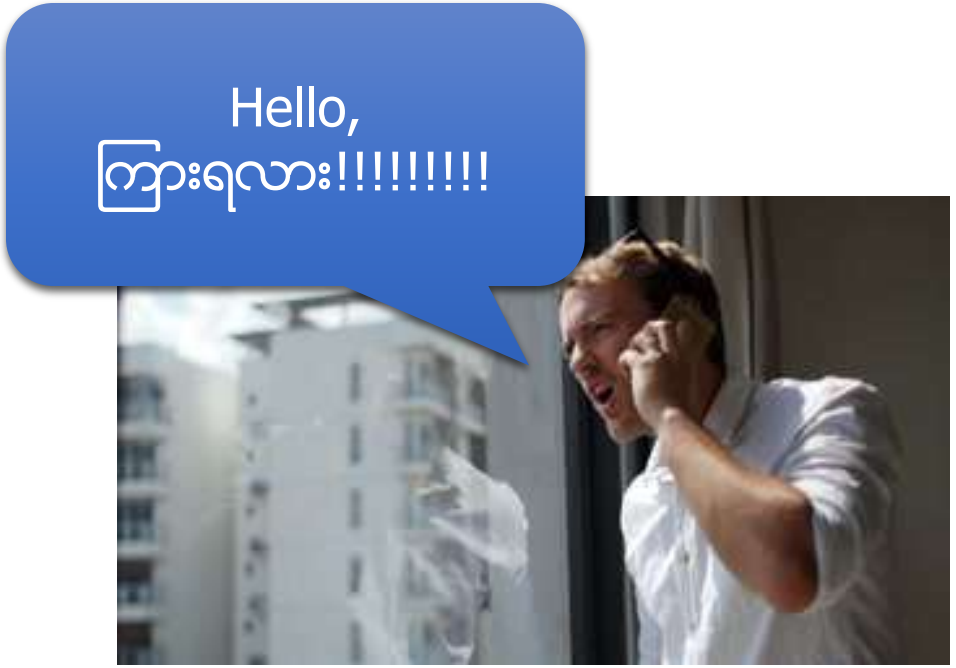
Australian published product information , * Yki-Jarvinen H et al. Diabetes Care 23:1130-1136, 2000 (Insulin dose 23 units/day)

Costs of diabetes care have dramatically increased

Between 1987 and 2011,

- per person medical spending attributable to diabetes X 2
- **≥ 50%of the increase was due to prescription drug spending**

No need to change old drugs



Myanmar Guideline(2018)

Treatment Algorithm (Table)

HbA1c < 9% - Consider Monotherapy Metformin

↓ Not well controlled (After 3 months)

HbA1c(9-10)

Metformin + SU or
Metformin + TZD or
Metformin + DPP4 Inhibitor or
Metformin + SGLT2 Inhibitor

↓ Not well controlled (After 3 months)

HbA1c. >10

Metformin + SU + TZD/ DPP4-I/ SGLt2-I
Metformin + TZD+ SU/ DPP4-I/SGLT2-I
Metformin + DPP4-I+ SU/ TZD/ SGLT2-I
Metfomin+ SGLT2-I + SU/ TZD/ DPP4-I

↓ Not well controlled (After 3 months)

Oral triple therapy + Basal insulin

Current understanding of role of Metformin in the management of diabetes?

Metformin

in the management of

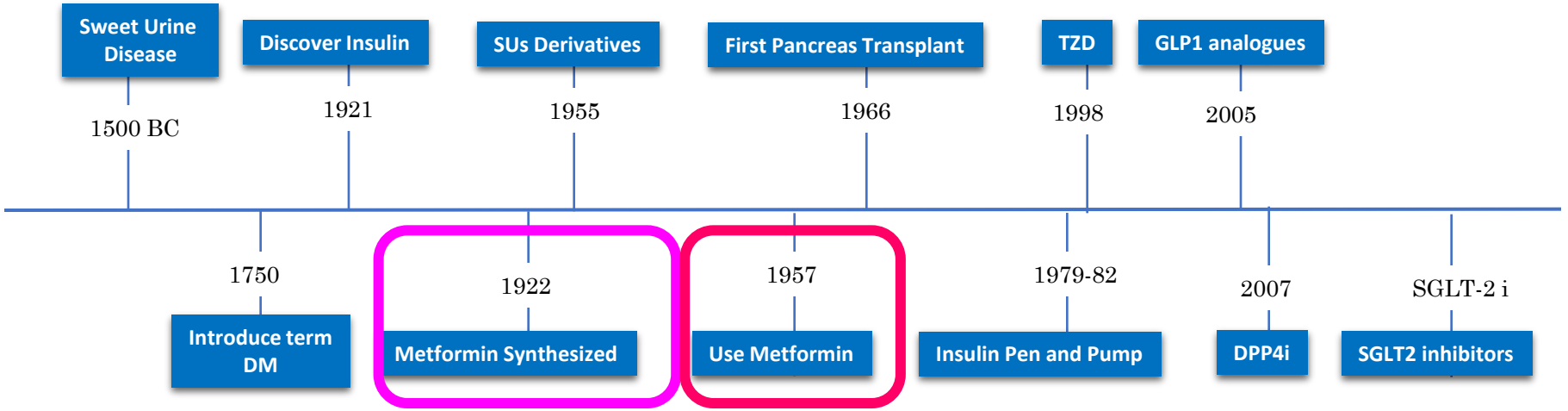
- T2DM
  - CV Safety
  - Renal insufficiency
- T1DM
- Prevention of DM
- Pregnancy
- Beyond DM – in PCOS and aging

Galega officinalis

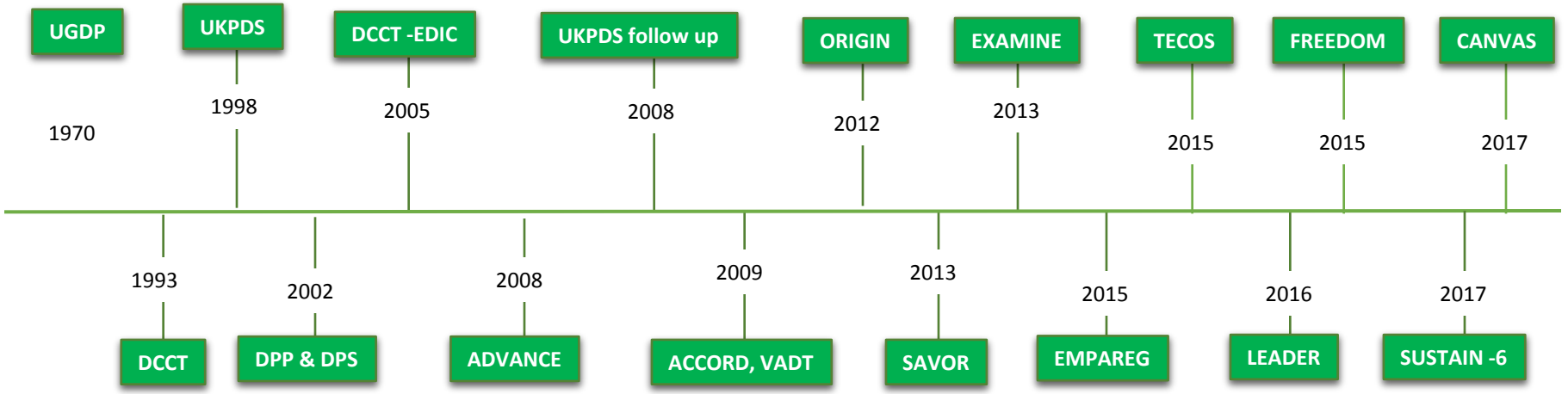
also known as

- goat's rue,
- French lilac,
- Italian Fitch,
- Spanish sainfoin or
- professor weed.

- ❑ used as a traditional medicine in medieval Europe
- ❑ it is now classed as a noxious weed in many states of the USA.

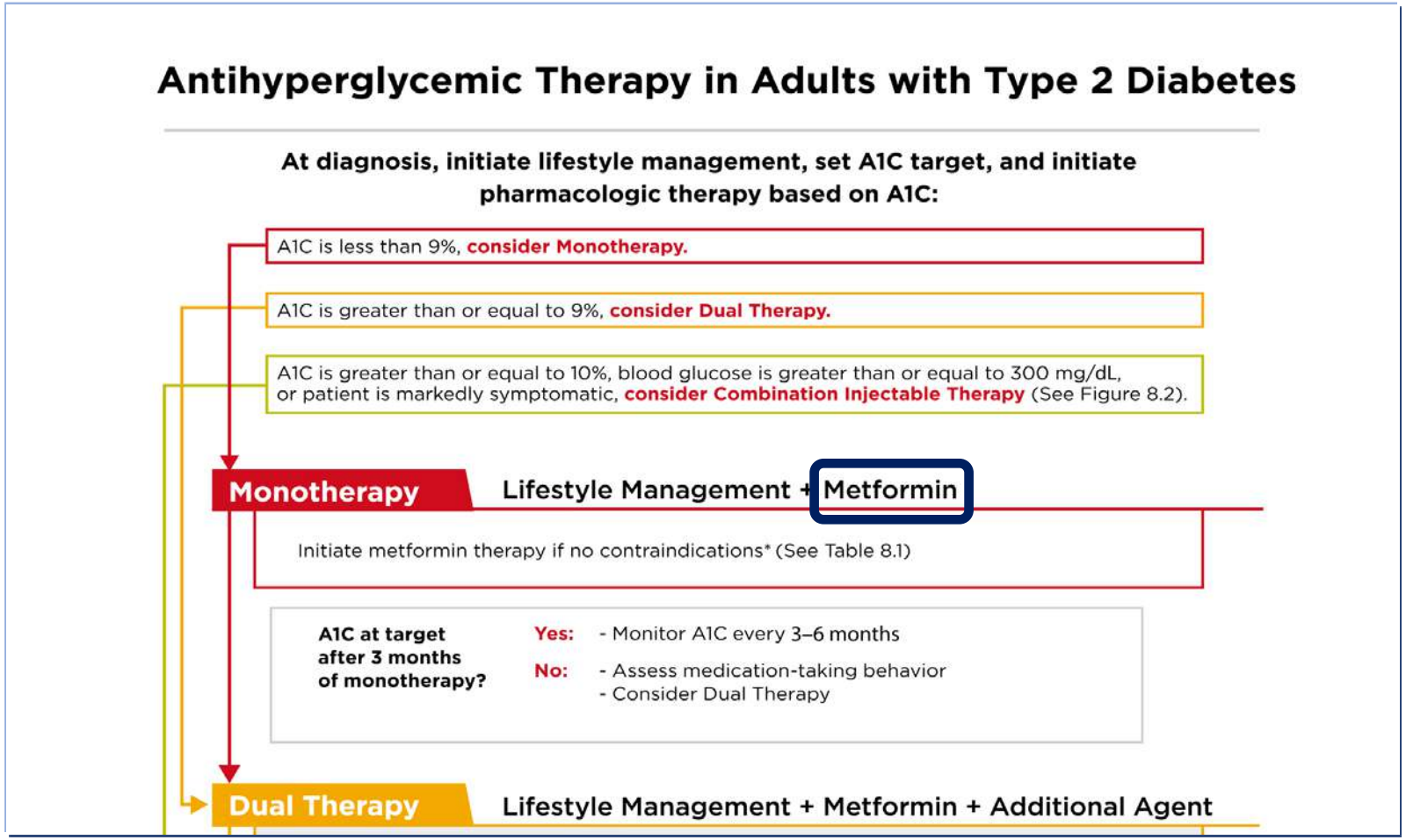


> 6 decades of metformin



Metformin – for type 2 DM

American Diabetes Association.
2018

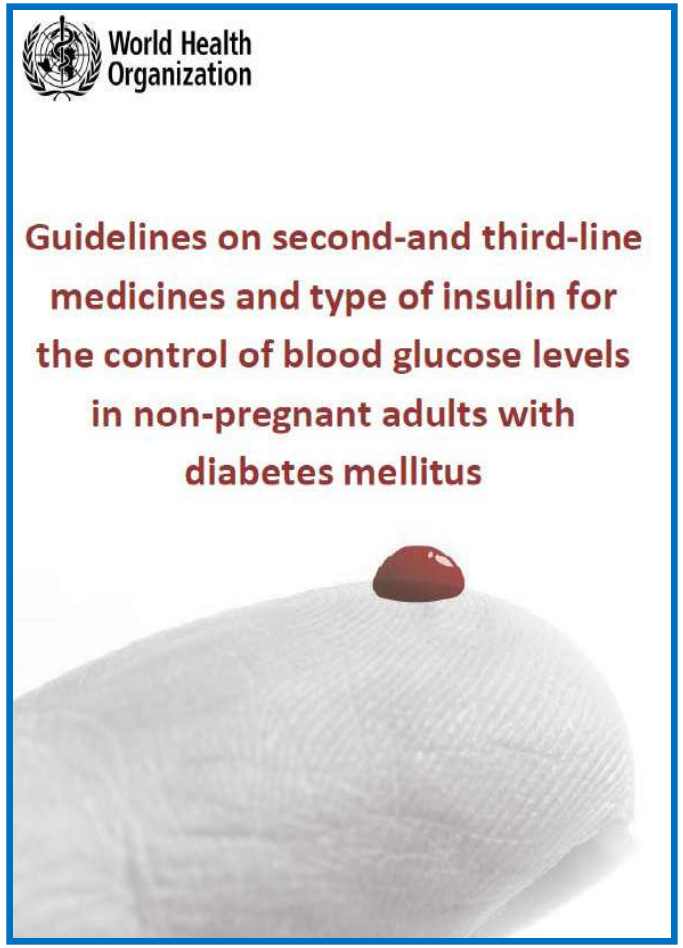


PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES
Metformin

American Diabetes Association 2018

- if not contraindicated and if tolerated → the **preferred initial pharmacologic agent**
- Long-term use of metformin → **vitamin B12 deficiency** → periodic measurement of vitamin B12 levels should be considered (especially in those with anemia or peripheral neuropathy)

[Diabetes Prevention Program Outcomes Study (DPPOS)]



2018

The WHO–PEN recommendations for control of glycaemia in people with type 2 diabetes include

- diet,
- physical activity and
- **metformin** as first-line treatment

The WHO–PEN recommendations for control of glycaemia in people with type 2 diabetes include diet, physical activity and metformin as first-line treatment; sulfonylurea as second-line treatment (or first-line treatment if metformin is contraindicated); and insulin as third line treatment. In the

Guideline Development Group

Name	Area of expertise	Affiliation
Amanda Adler	Health technology assessment, health economics, guideline development	Addenbrooke's Hospital, Cambridge, UK
David Beran	Health systems research, access to insulin, access to diabetes care in low-resource settings	Geneva University Hospitals and University of Geneva, Switzerland
Catherine Cornu	Pharmacology of diabetes medicines, evidence synthesis and appraisal, guideline development	Hospices Civils de Lyon, INSERM Clinical Investigation Centre, Lyon, France
Pamela Donggo	Diabetes management, diabetes and infectious diseases co-morbidities	Lira Hospital, Lira, Uganda
Adel El Sayed	Diabetes management, cardiovascular complications	Sohag Faculty of Medicine, Sohag, Egypt
Edwin Gale	Management of diabetes, clinical epidemiology, qualitative evidence	University of Bristol, United Kingdom
Molly Lepeska	Person with diabetes, access to insulin in low-resource settings	Health Action International, Amsterdam, The Netherlands
Naomi Levitt	Pathophysiology of diabetes, acute and chronic complications of diabetes	Diabetic Medicine and Endocrinology, Department of Medicine at Groote Schuur Hospital and University of Cape Town, South Africa
Jianhong Li	Public health, policy-making, epidemiology of noncommunicable diseases, programme implementation, primary health care	National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China
Manuel Vera Gonzalez	Diabetes management in young people, community health	Diabetes Care Centre in Havana National Institute of Endocrinology
Tint Swe Latt	**Management of noncommunicable diseases, primary health care**	**University of Medicine , Yangon, Myanmar**
Adil Zurumova	Policy-making, clinical pharmacology, essential medicines for noncommunicable diseases	Ministry of Health, Kyrgyz Republic; Kyrgyz Russian Slavic University, Bishkek, Kyrgyz Republic

Why Metformin?

All the Guidelines Strongly recommended Metformin as First line

Pros	Cons
Strong Efficacy (↓ HbA1c-1.5%)	GI Side Effects
No Hypoglycemia	Can't use in severe renal, Cardiac and Liver Failure
Weight Neutrality	
Cardiovascular Safe	
Cheap	
Time-Tested Drugs (>60 yrs)	
Long Term Evidence	
Easily & Widely available	
Reduce Insulin Resistance	
Lipid Neutral and reduce LDL	
Reduce Cancer	

Metformin – Evidences of CVD outcome

Table 2–Randomized clinical trials involving metformin and CVD outcomes

Trial/year	Comparison	Study population	*N*	Main CVD outcome(s)	HR (95% CI)	*P*
UKPDS 34 (4) (1998)	Metformin vs. diet Metformin vs. SU/insulin	Overweight, newly diagnosed T2D patients	1,704	All-cause mortality Myocardial infarction	0.64 (0.45, 0.91) 0.61 (0.41, 0.89)	NR 0.010
HOME (6) (2009)	Metformin vs. placebo	T2D patients on insulin	390	Expanded MACE*	0.61 (0.40, 0.94)	0.02
SPREAD-DIMCAD (7) (2013)	Metformin vs. glipizide	T2D patients with CAD	304	Expanded MACE†	0.54 (0.30, 0.90)	0.026

CAD, coronary artery disease; MACE, major adverse cardiovascular events; NR, not reported; SU, sulfonylurea. *Myocardial infarction, acute coronary syndrome, coronary or peripheral revascularization, electrocardiogram changes, heart failure, stroke/transient ischemic attack. †Cardiovascular cause, death from any cause, nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization.

Metformin – in Renal insufficiency

US FDA Drug Safety Communication:

FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

- may be safely used in patients with mild to moderate renal impairment.
- the measure of kidney function → use glomerular filtration rate estimating equation (eGFR)

  (because of additional parameters that are important, such as the patient's age, gender, race and/or weight)

Metformin – in Renal insufficiency

US FDA Drug Safety Communication:

- **Starting of metformin**
  - **obtain** eGFR before starting metformin
  - **contraindicated** when eGFR <30 mL/min/1.73 m^2 .
  - **not recommended** for starting metformin when eGFR 30-45 mL/minute/1.73 m^2
- **Obtain an eGFR**
  - **at least annually** in all patients
  - **more frequently** →In patients at increased risk for the development of renal impairment such as the elderly

Metformin – in Renal insufficiency

US FDA Drug Safety Communication:

- **In patients taking metformin**
  - eGFR < 45 mL/min/1.73 m^2 → assess the benefits and risks of continuing treatment.
  - eGFR < 30 mL/min/1.73 m^2 → Discontinue metformin
- **Discontinue metformin** at the time of or before an **iodinated contrast imaging procedure** in patients with
  - an eGFR between 30 and 60 mL/minute/1.73 m^2 ;
  - a history of liver disease, alcoholism, or heart failure; or
  - intra-arterial iodinated contrast
- Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

Metformin in T1DM

Overall, studies suggest that metformin use

- ↓ insulin dose requirement
- ↓ weight and
- potentially, ↓ LDL-cholesteol.
- ↓ atherosclerosis progression
- does not lead to sustained improvements in glycaemic control
- Hence, there appears to be potential for this drug to have glucose-independent effects that may be beneficial for those with type 1 diabetes.

[Reducing with Metformin Vascular Adverse Lesions (REMOVAL) study].

Metformin in Prevention of Diabetes

- The Diabetes Prevention Program (DPP) / DPP Outcomes Study (DPPOS) - the largest and longest clinical trial of metformin for the prevention of diabetes
- **metformin**
  - ↓ diabetes incidence by 31% vs. placebo after 2.8 years follow-up,
  - ↓ risk (18%) still being observed over 10 and 15 years post-randomisation.
  - favorable effects on several cardiovascular risk factors (+)

- Hence, the findings from the DPP/DPPOS show promise for metformin use for the prevention of type 2 diabetes, with additional benefits extending to its cardiovascular complications.

Metformin in pregnancy

- Important insight into metformin use in pregnancy has been gained from studies of its use in PCOS.
- **Metformin has been used in pregnancy for over 40 years.**
- The drug crosses the placental barrier, and the proposed increased lactic acidosis risk and relatively hypoxic fetal environment have raised concerns about its use in pregnancy.
- However, studies in PCOS suggested that **metformin does not increase congenital malformations or miscarriage.**

Metformin and PCOS

- PCOS has metabolic consequences
  - insulin resistance
  - impaired glucose tolerance and
  - type 2 diabetes.
- Metformin was first shown to ameliorate hyperandrogenism in women with PCOS in the 1990s and,
- mechanism of action - not fully understood
  - ↓ hepatic glucose output,
  - ↑ muscle glucose uptake and
  - regulate androgen production by the ovary.

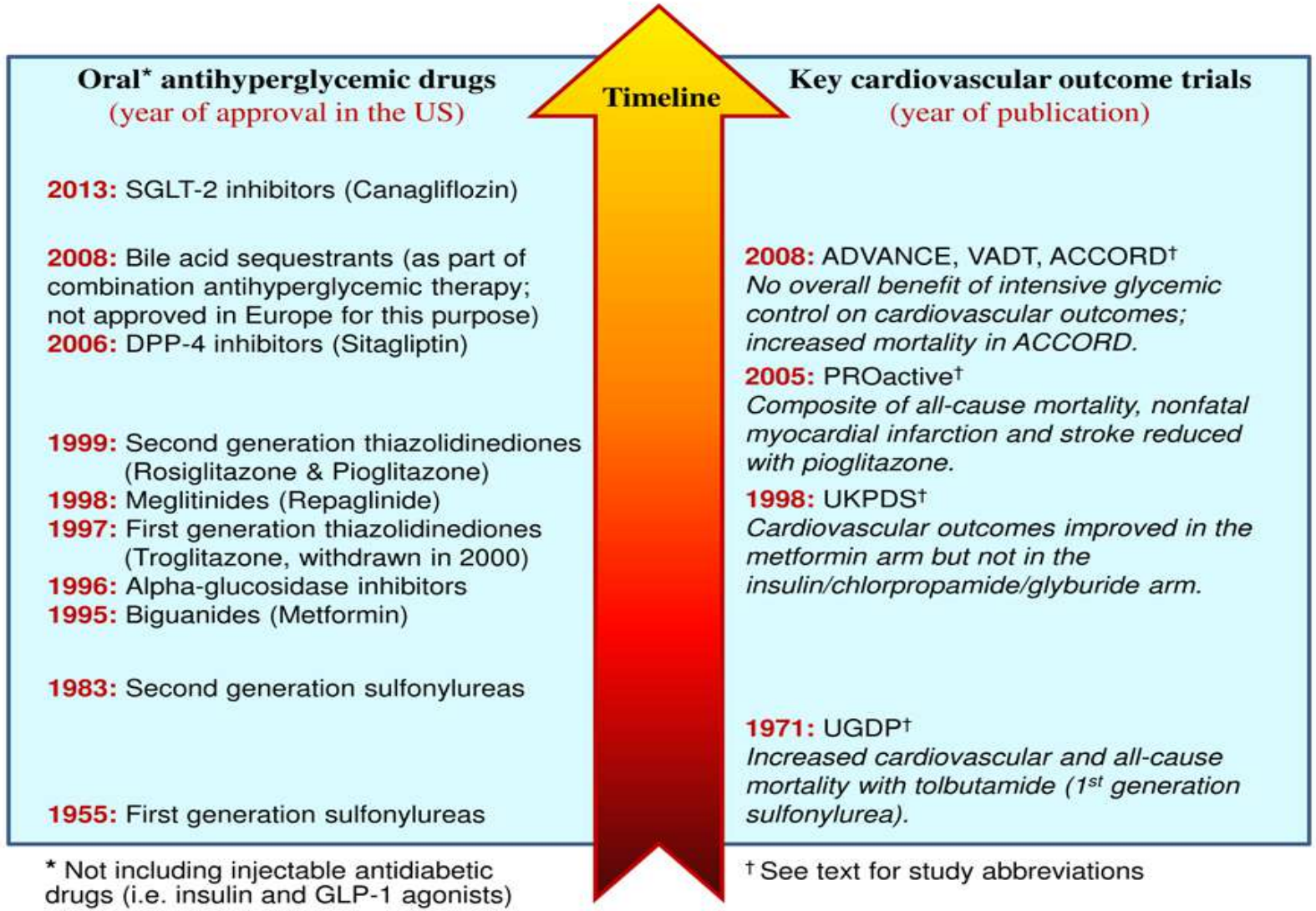
Metformin and ageing

- **metformin can reduce**
  - diabetes risk in those aged ≥60 years
  - ageing outcomes – e.g., frailty and impaired physical and cognitive function
- **potential mechanisms** (independent of blood glucose regulation)
  - ↓ inflammation and reactive oxygen species → reduce DNA damage
  - effects on ceramides (which contribute to ↓ myoblast numbers in the elderly) may also help to improve tissue health and function.
  - Furthermore, cardio- and neuroprotective roles of metformin, and the impact of metformin on psychological health and cognitive function may also promote healthy ageing and increase lifespan.

[Valencia et al]

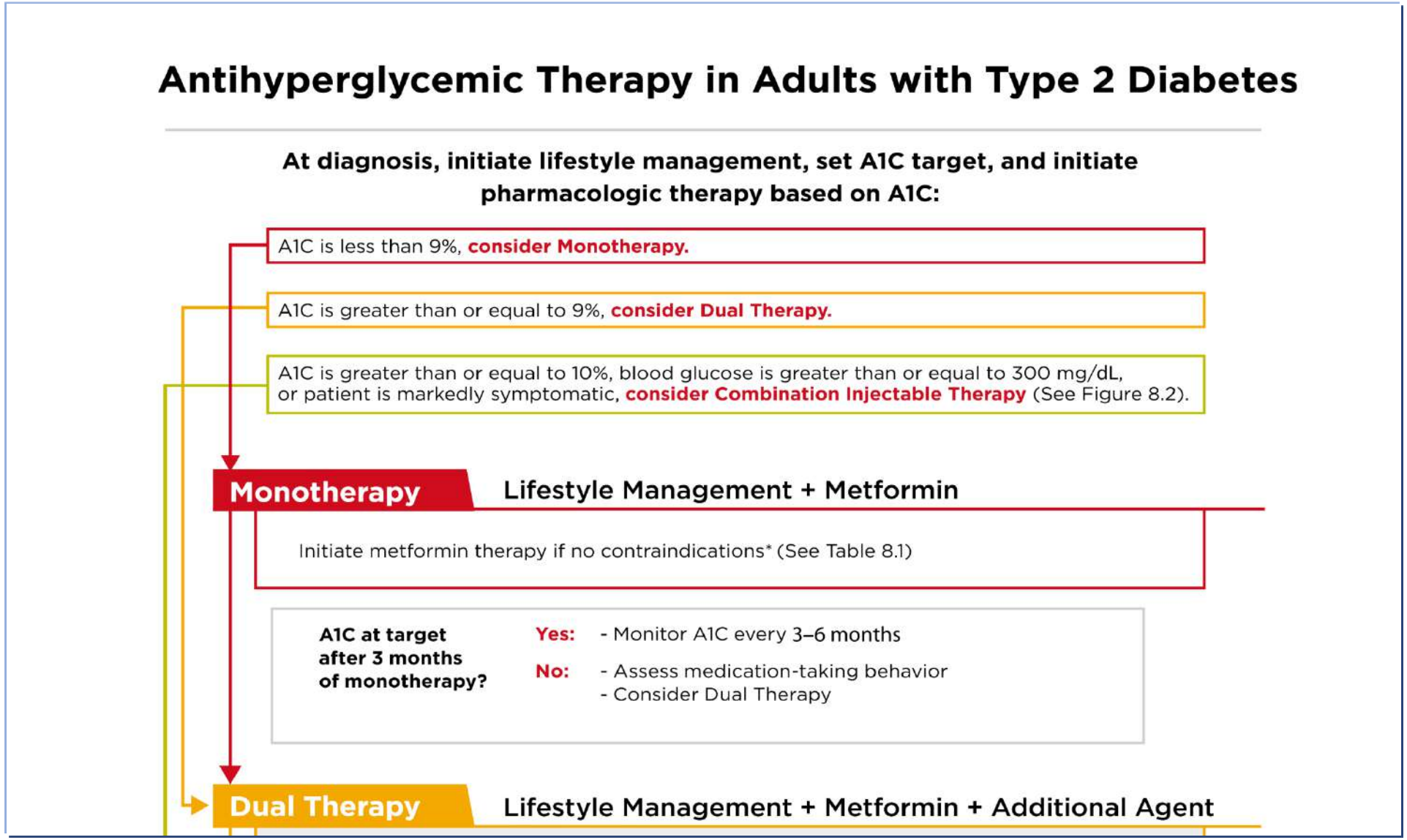
Role of Sulphonylurea in the current era of CVOT?

Over 60 years History of Sulphanylurea



AMERICAN DIABETES ASSOCIATION

American Diabetes Association.
2018



WHAT IS NEXT AFTER METFORMIN

American Diabetes Association.

2018

ASCVD ?

Yes - Add agent proven to reduce major adverse Cardiovascular events and/or cardiovascular mortality (see recommendation with * on p.$75 and Table 8.1)

No - Add second agent after consideration of drug-specific effects and patient factors (See table 8.1)

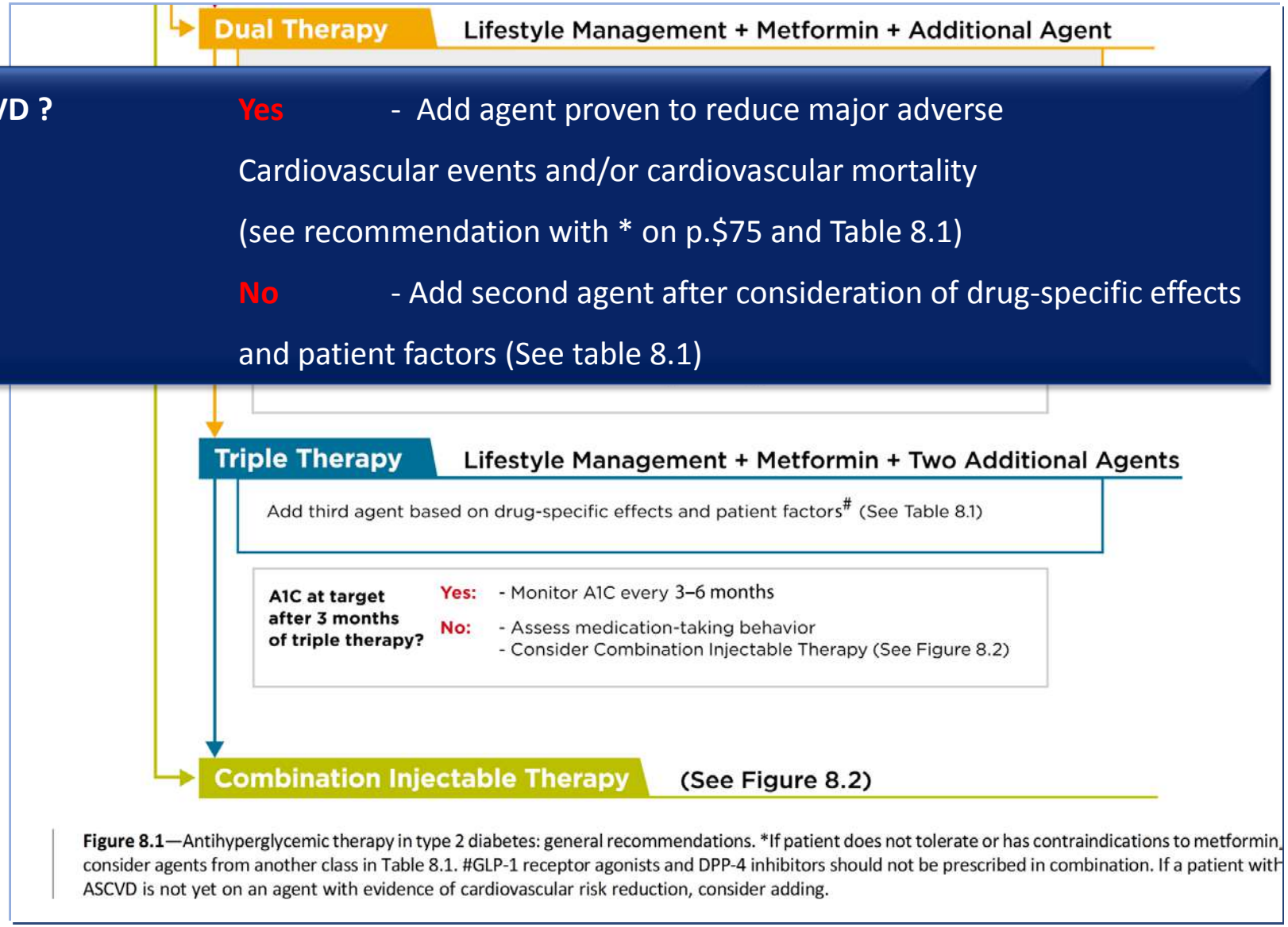


Figure 8.1—Antihyperglycemic therapy in type 2 diabetes: general recommendations. *If patient does not tolerate or has contraindications to metformin, consider agents from another class in Table 8.1. #GLP-1 receptor agonists and DPP-4 inhibitors should not be prescribed in combination. If a patient with ASCVD is not yet on an agent with evidence of cardiovascular risk reduction, consider adding.

SUMMARY OF CVOT TRIALS

	SGLT2 inhibitors		GLP-1 receptor agonists				DPP4 inhibitors		
	EMPA-REG 2015	**CANVAS** June 2017	**ELIXA** 2015	**LEADER** 2016	**SUSTAIN** 2016	**EXSCEL** Sep 2017	**SAVOR** 2013	**EXAMINE** 2016	**TECOS** 2015
	Empagliflozin	Canagliflozin	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Saxagliptin	Alogliptin	Sitagliptin
	SYNJARDY/ Glyxambi	FORXIGA/ XIGDUO	LYXUMIA	VICTOZA/ saxenda	NOT YET FDA APPROVED	BYDUREON	ONGLYZA/ Kombiglyze XR	Vipdomet/ Incresync	JANUVIA/ Janumet XR
	Boeh Ingelh	Janssen	Sanofi	Novo Nordisk	Novo Nordisk	AstraZeneca	AstraZeneca	Takeda	MSD
3-point MACE	**-14%** HR 0.86* 0.74-0.99	**-14%** HR 0.86* 0.75-0.97 p<0.001 for non-inferiority; p=0.02 for superiority	**+2%** HR 1.02 0.89-1.17	**-13%** HR 0.87* 0.78-0.97	**-26%** HR 0.74* 0.58-0.95	**-9%** HR 0.91 0.83-1.00	**Neutral** HR 1.0 0.89-1.12	**-4%** HR 0.96 upper ≤1.16	**-2%** HR 0.98 0.89-1.08 (4-point MACE including hospitalization for unstable angina)
CV death	**-38%** HR 0.62* 0.49-0.77	**-13%** HR 0.87 0.72-1.06	**-2%** HR 0.98 0.78-1.22	**-22%** HR 0.78* 0.66-0.93	**-2%** HR 0.98 0.65-1.48	**-12%** HR 0.88 0.76-1.02	**+3%** HR 1.03 0.87-1.22	**-21%** HR 0.79 0.60-1.04	**+3%** HR 1.03 0.89-1.19
NF MI	**-33%** HR 0.67* 0.70-1.09	**-15%** HR 0.85 0.69-1.05	**+3%** HR 1.03 0.87-1.22	**-12%** HR 0.88 0.75-1.03	**-26%** HR 0.74 0.51-1.08	**-3%** HR 0.97† 0.85-1.10	**-5%** HR 1.95 0.80-1.12	**+8%** HR 1.08 0.88-1.33	**-5%** HR 0.95 0.81-1.11
NF stroke	**+24%** HR 1.24 0.92-1.67	**-10%** HR 0.90 0.71-1.15	**+12%** HR 1.12 0.79-1.58	**-11%** HR 0.89 0.72-1.11	**-39%** HR 0.61* 0.38-0.99	**-15%** HR 0.85† 0.70-1.03	**+11%** HR 1.11 0.89-1.39	**-9%** HR 0.91 0.55-1.50	**-3%** HR 0.97 0.89-1.08
Hospitalization HF	**-35%** HR 0.65* 0.50-0.85	**-33%** HR 0.67* 0.52-0.87	**-4%** HR 0.96 0.75-1.23	**-13%** HR 0.87 0.73-1.05	**+11%** HR 1.11 0.72-1.61	**-6%** HR 0.94 0.78-1.13	**+27%** HR 1.27* 1.07-1.51	**+7%** HR 1.07 0.78-1.15	**Neutral** HR 1.00 0.83-1.20
All-cause death	**-32%** HR 0.68* 0.57-0.82	**-13%** HR 0.87 0.74-1.01	**-6%** HR 0.94 0.78-1.13	**-15%** HR 0.85* 0.74-0.97	**+5%** HR 1.05 0.74-1.50	**-14%** HR 0.86* 0.77-0.97	**+11%** HR 1.11 0.96-1.27	**-12%** HR 0.88 0.71-1.09	**+1%** HR 1.01 0.90-1.14
EMA warning	**Amputation risk**	**Amputation risk**							
FDA warning		**Amputation risk**					**HF risk**	**HF risk**	

CVOT – focus only on patients with High CV risk

	EMPA-REG	LEADER	SUSTAIN-6
Vs	Placebo		
Patients	**Pre Existing CVD**	≥50 years + preexisting CVD, CKD, HF; ≥60 years + CVD risk factors	≥50 years + preexisting CVD; ≥60 years + CVD risk factors
Mean Age	63.1	64.3	64.6
Hypertension	94%	90%	93%
CVD	99%	81%	83%
Stroke/TIA	47/23	31/16	47/23
Statin Use	77%	72%	73%
Met Patients	74%	73%	76%

CV EFFECT OF DIFFERENT OADS (ADA 2018)

	ASCVD	CHF
SGLT2 inhibitors	Benefits • Canagliflozin • Empagliflozin	Benefits : • Canagliflozin • Empagliflozin
GLp1 Agonist	Benefits: Liraglutide Neutral : • Lixisentide • Exenatide Extended Release	Neutral
Metformin	Potential Benefits	Neutral
Sulfonylureas	Neutral	Neutral
Dpp4 inhibitors	Neutral	Potential Risk • Saxagliptin • Alogliptin
Pioglitazone	Potential Benefit : Pioglitazone	Increased Risk

Myanmar
- Availability ?
- Price ?

Results of RCTs (Sulphanylureas)

Title of study/treatment	Patient numbers/study duration	Impact on CV morbidity (individual or composite end points)
Studies utilizing both first-generation and second-generation SUs		
UKPDS 33 Conventional glucose-lowering versus intensive insulin versus intensive SU (chlorpropamide, glyburide or glipizide)	*n* = 3867; of whom, 1573 received SU, 1156 insulin and 1138 conventional treatment – median of 10-year FU Analysis restricted to *n* = 3041 from first 15 centres; of whom, 619 received chlorpropamide, 615 glibenclamide, 911 insulin and 896 conventional treatment – median 11.1 (IQR = 9.0–13.0) years FU	No difference in any CV outcome with individual drugs Combined SU/insulin reduced the risk of MI by 16% (p = 0.052) versus conventional treatment
UKPDS 80 Conventional glucose-lowering versus intensive insulin versus intensive SU (chlorpropamide or glibenclamide)	*n* = 2998; of whom, 2118 originated from the 2729 of the UKPDS, 33 receiving SU/insulin and 880 from the 1138 receiving conventional treatment – median 16.8-year FU (8.5-year FU after UKPDS 33)	Combined SU/insulin reduced risk for MI by 15% (p = 0.01) versus conventional treatment

UKPDS: "Legacy Effect" of Insulin/Sulfonylurea Therapy

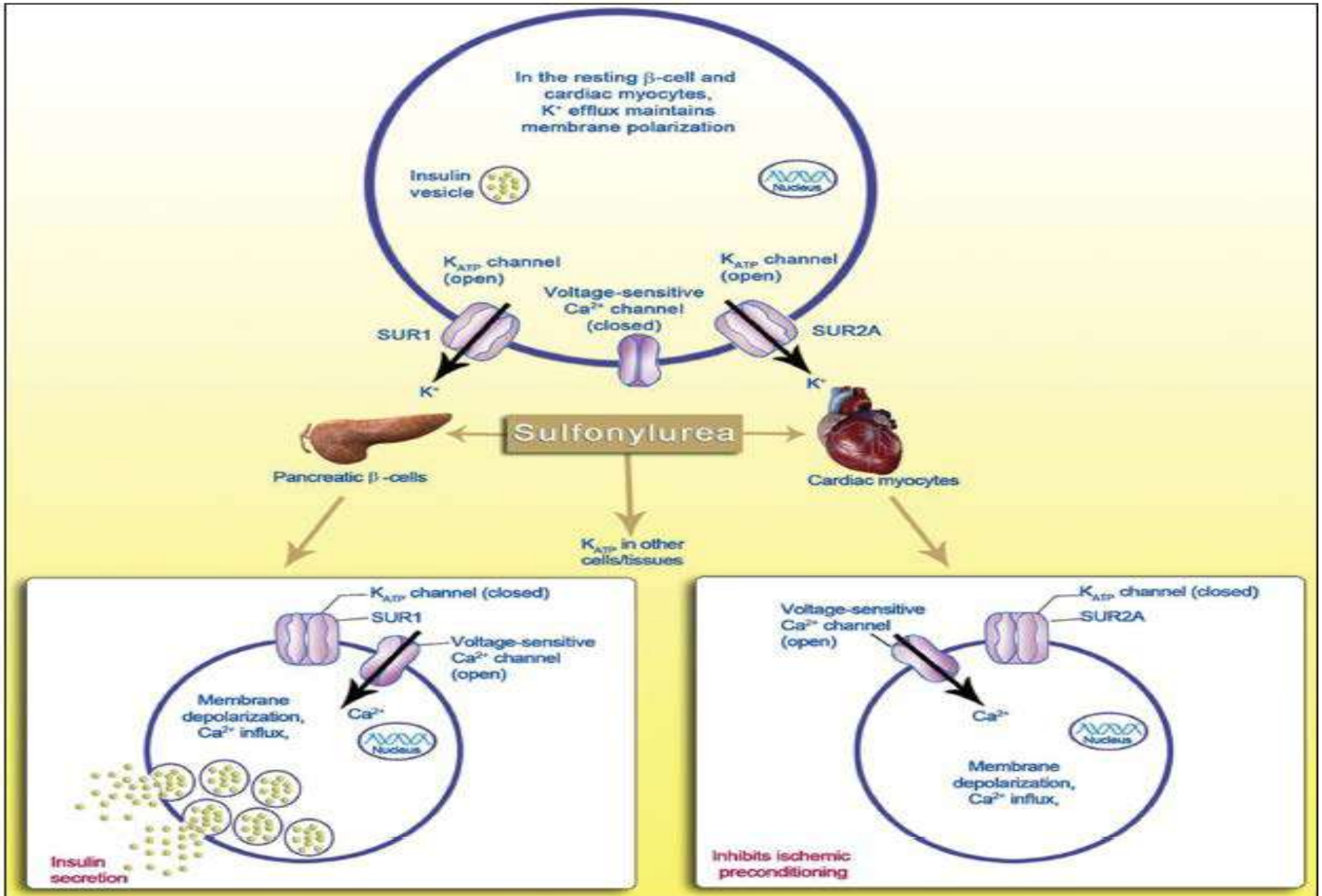
After median 8.8 years post-trial follow-up

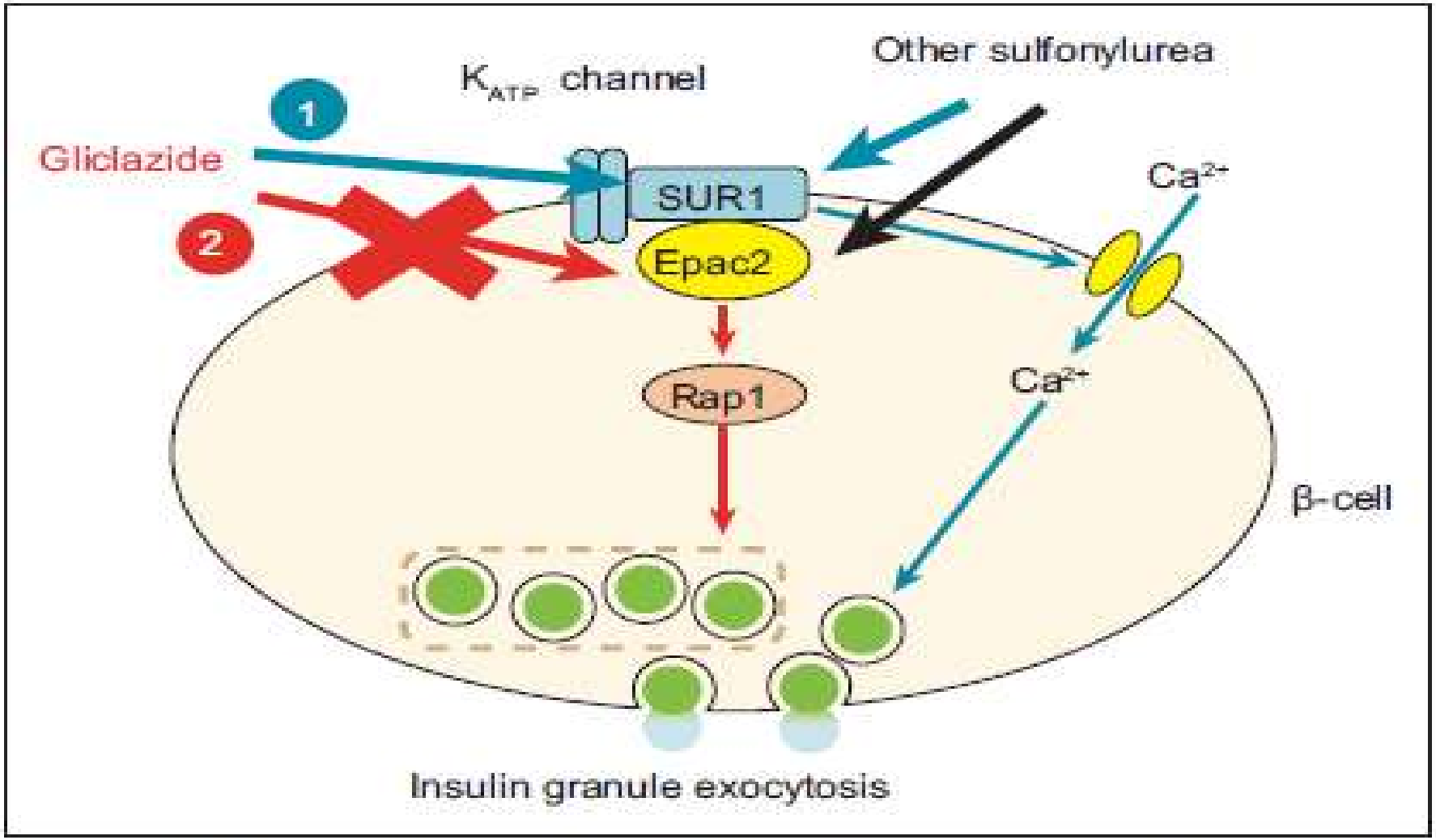
Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	9%
	P:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	P:	0.009	0.001
Myocardial infarction	*RRR:*	16%	15%
	P:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	P:	0.44	0.007

RRR = Relative Risk Reduction P = Log Rank

Holman RR, et al. *New England Journal of Medicine* 2008; 359:1577-1589

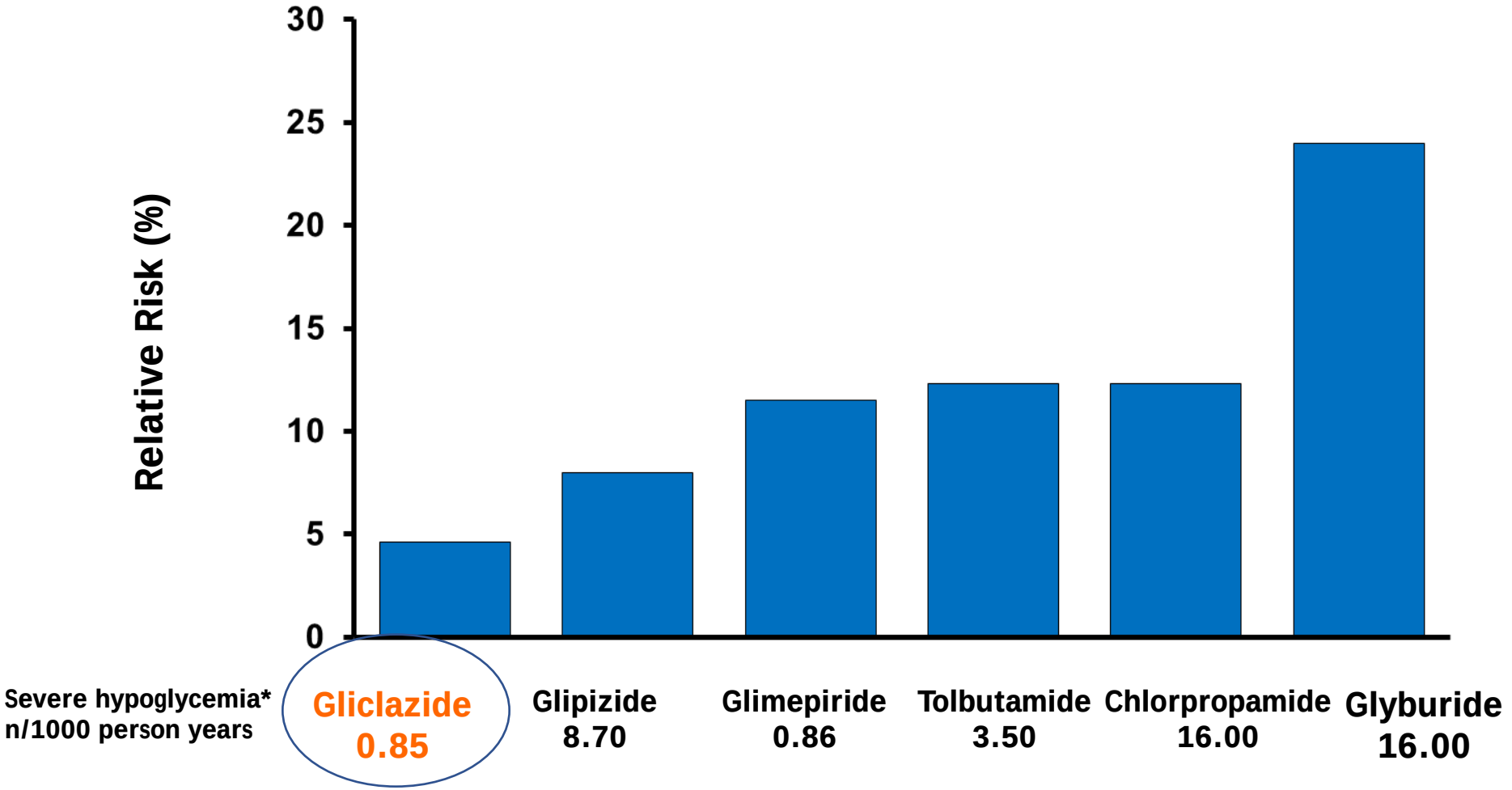
Mechanism of action of sulfonylureas on pancreatic β-cells and cardiomyocytes





Mechanism of action of gliclazide on pancreatic β-cells (SUR: Sulfonylurea receptor)

Hypoglycaemia with different Sulfonylureas



*<50 mg/dL.

Tayek J. *Diabetes Obes Metab.* 2008; 10: 1128–1130.

HbA1C Reduction with different OAD

Class/Drug	Suggested Dosing	Mechanism of Action	Expected ΔHbA1c (%)	Cost/ Month (US$)
Biguanide				
Metformin	500–2000 mg/d	↓Gluconeogenesis	−1 to −2	4 (generic)
Sulfonylureas				
Glipizide	2.5–10 mg/d	↑Insulin release	−1 to −2	4 (generic)
Glimepiride	1–4 mg/d			4 (generic)
Glinides				
Repaglinide	0.5–2 mg TID with meals	—	—	200 (generic)
Nateglinide	60–120 mg TID with meals	—	—	120
TZDs				
Rosiglitazone	2–4 mg/d	↓FFA release	−1 to −2	130
Pioglitazone	15–30 mg/d	↑Insulin sensitivity		45 (generic)
SGLT2s				
Canagliflozin	100–300 mg/d	↑Glycosuria	−1 to −1.5	290
Dapagliflozin	5–10 mg/d			290
Alpha-glucosidase Inhibitors				
Acarbose	25–100 mg TID with meals	↓Carbohydrate absorption	−0.5 to −1	45 (generic)
Bile Acid Sequestrants				
Colesevelam	3750 mg/d	Unclear	−0.5 to −1	335
Bromocriptine mesylate	1.6–4.8 mg/d	↑CNS dopamine	−0.5	120

Place of SUs in diabetes therapy

Placement	Approach	Indication
Initial therapy	Monotherapy	Contraindication to metformin Intolerance to metformin
	Combination therapy with metformin	High blood glucose levels at presentation
2nd line therapy	Add on therapy	Inadequate glycemic control with metformin
Subsequent add on therapy	Add on to combination	Inadequate glycemic control with existing oral therapy
Special consideration	Biological factors	Age >60
		Renal impairment
		Neonatal diabetes
		MODY-3
	Psychosocial factors	Ramadan*
	Glucophenotype	Fasting hyperglycemia
		Postprandial hyperglycemia

*Preferred SUs include modern SUs like glipizide MR, gliclazide, gliclazide MR, glimepiride. MR: Modified release, SUs: Sulfonylureas, MODY: Maturity-onset diabetes of the young

Kalra *et al* (2015)Indian J Endocr Metab;19:577-96

Table 10: Use of different SUs in renal impairment

Class	Drug	CKD (stage 3-5)	Dialysis	Complications
Conventional SUs	Chlorpropamide	Reduce dose by 50% if GFR: 50-70 ml/min/1.73 m^2 Avoid if GFR <50 ml/min/1.73 m^2	Avoid	Hypoglycemia
	Tolbutamide	Avoid	Avoid	Hypoglycemia
	Glibenclamide	Avoid	Avoid	Hypoglycemia
Modern SUs	Glimepiride	Start at low dose: 1 mg/day	Avoid	Hypoglycemia
	Gliclazide	No dose adjustment (ref. NKF 2012 guidelines)	Avoid/low dose and careful monitoring	Hypoglycemia
	Glipizide	No dose adjustment	No dose adjustment	Hypoglycemia
	Gliclazide MR	No dose adjustment (ref. NKF 2012 guidelines)	Avoid/low dose and careful monitoring	Hypoglycemia

GFR: Glomerular filtration rate, CKD: Chronic kidney disease, MR: Modified release, SUs: Sulfonylureas

Kalra *et al* (2015)Indian J Endocr Metab;19:577-96

World Health Organization

Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus

- Give a sulfonylurea* to patients with type 2 diabetes who do not achieve glycaemic control** with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence).

- ***Glibenclamide*** *should be avoided in patients aged 60 years and older. Sulfonylureas with a better safety record for hypoglycaemia (e.g. gliclazide) are preferred in patients for whom hypoglycaemia is a concern*

Review Article

Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement

Clinical issues associated with the use of SUs are agent-specific. Careful choice of SU, appropriate dosage, timing of administration, adequate patient counseling and considering their efficacy, safety, pleiotropic benefits, and low cost of therapy, SUs should be considered as recommended therapy for the treatment of diabetes in South Asia.

Kalra S, Aamir AH, Raza A, Das AK, Azad Khan AK, *et al* (2015)Indian J Endocr Metab;19:577-96.

"SAFE & Smart"
Use of Sulfonylureas

- Practice Points for optimal use of this essential class of drugs in T2DM
  - Place of SU in current diabetes management
  - **Addressing concerns with SU treatment**
  - Hypoglycemia, Weight changes, Durability, CV risk, etc
  - Choosing among the SUs
  - Translating evidence into practice
  - Patient selection, drug selection, dose selection, patient empowerment & physician empowerment
- Executive Summary released at the 2nd SAFES Summit, Dhaka on 24 April, 2015

Kalra S, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab. 2015 Sep-Oct;19(5):577-96.

A: Indications of SUs

A1. SUs are an **effective, safe, well tolerated, affordable & convenient therapeutic option** in the management of T2DM.

A2. SUs are effective second line agents after metformin, in the management of T2DM. SU monotherapy as first line may be considered in Type 2 Diabetes with metformin intolerance/ contraindication and in patients with **MODY**.

A3. **Modern SUs should be initiated early in the course of T2DM,** to achieve maximum glycemic benefits and obtain the benefits of metabolic memory.

A4. SU - containing dual or triple FDCs, if available, (with drugs that have complementary modes of action) reduce cost, offer convenience, and improve patient adherence.

Kalra S, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab. 2015 Sep-Oct;19(5):577-96.

B. Preferred SUs

B1. **Modern SUs should be preferred** over conventional SUs in view of the **reduced mortality, better CV outcomes, and renal protection.**

B2. **Modern SUs** should be preferred over conventional SUs in T2DM **patients at increased risk of hypoglycemia.**

B3. **Modern SUs** should be the preferred choice of SU in **overweight/obese** T2DM patients.

B4. **Modern SUs** should be preferred over conventional SUs in patients **at increased risk of CVD or with CVD.**

Kalra S, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab. 2015 Sep-Oct;19(5):577-96.

To Conclude…

- This initiative by SAFES aims to encourage rational, safe and smart prescription of SUs
- Considering **their efficacy, safety, pleiotropic benefits, and low cost of therapy,** SUs should be considered as recommended therapy for the treatment of diabetes in South Asia.
- **Modern SUs (gliclazide MR, Glimepiride)** are backed by a large body of evidence, experience, and most importantly, outcome data, which supports their role in managing patients with diabetes.
- Person-centred care, **i.e., careful choice of SU, appropriate dosage, timing of administration, and adequate patient counseling,** will ensure that deserving patients are not deprived of the advantages of this well-established class of anti-diabetic agents

Kalra S, et al. Place of sulfonylureas in the management of type 2 diabetes mellitus in South Asia: A consensus statement. Indian J Endocrinol Metab. 2015 Sep-Oct;19(5):577-96.

American Diabetes Association.

SULPHANYLUREA					
Efficay	Hypo-glycemia	Weight changes	CV effects		COST
			ASCVD	CHF	
High	**Yes**	**Gain**	Neutral	Neutral	**Low**

Current concepts and practice of Insulin Therapy?

If RBS control is difficult

- Always ask about other medications
  - Steroids
  - Thiazide
  - Beta-blockers

- Always check diets

- Always check sepsis and stress
  - Skin – carbuncle, abscess, gan
  - Foot – ulcer
  - Lungs – TB, Pneumonia
  - Renal – UTI, pylonephritis
  - Stroke/MI

Compliance of drugs

Clinical inertia

clinical inertia', defined as 'failure of healthcare providers to initiate or intensify therapy when indicated)

Maximum dose of 3 drugs
Not control for 3 months
Drugs failure
Time for insulin

Progression of type 2 diabetes:

Impairment of beta cell function

- Hyperglycaemia
  - HbA_{1c}
  - Fasting glucose
  - Postprandial glucose

Present therapeutic options frequently cause

- Weight gain
- Hypoglycaemia

Poor metabolic control causes

- Diabetic late complications

Is there a solution?

Is earlier insulin therapy

the solution?

World Health Organization

Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus

2018

Metformin
Metformin +SU
Metformin+SU+insulin

If insulin not available

DPP4 inhibiors ,SGLT 2 inhibitor or TZD can be added

Key recommendations of the guidelines are:

Hypoglycaemic agents for second and third-line treatment in type 2 diabetes
1. Give a sulfonylurea* to patients with type 2 diabetes who do not achieve glycaemic control** with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence). *Remarks* ** Glibenclamide should be avoided in patients aged 60 years and older. Sulfonylureas with a better safety record for hypoglycaemia (e.g. gliclazide) are preferred in patients for whom hypoglycaemia is a concern (people who are at risk of falls, people who have impaired awareness of hypoglycaemia, people who live alone, people who drive or operate machinery*

as part of their job). *** The WHO PEN protocol recommends a target fasting blood glucose of <7 mmol/L (126 mg/dl). However, an individualized approach is encouraged in setting the patient's target level for glycaemic control, taking into account their comorbidities, risks from medication side-effects and their likely benefit from tight glycaemic control in view of life expectancy.*
2. Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence).
3. If insulin is unsuitable*, a DPP-4 inhibitor, SGLT-2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence). *Remark* ** Insulin treatment could be unsuitable when circumstances make its use difficult (e.g. persons who live alone and are dependent on others to inject them with insulin).*

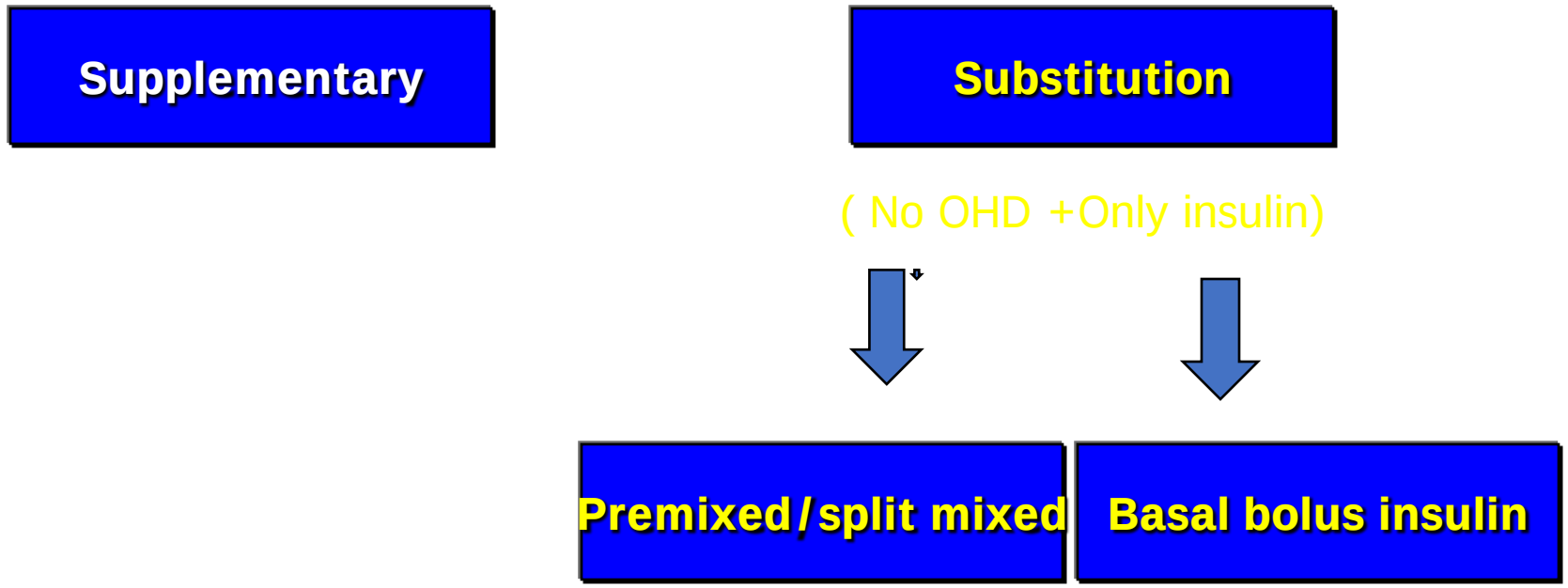
When to start Insulin in Type 2 DM?

- At onset:
  - If the blood glucose values are very high
    - Fasting > 250 mg/dl
    - postprandial > 300 mg/dl
    - HbA1C >9%
    - (Osmotic Symptoms , Sign & Symptoms of major organ decompensation)
  - Type 2 DM with major stress
    - Major medical illnesses (e.g., MI, Stroke)
    - Severe infection (e.g., Extensive Koch's Lung, Lobar Pneumonia, Severe Bronchopneumonia, Curbuncles)
    - Major Operation (e.g., Laprotomy, Hystrectomy)
  - Diabetes in Pregnancy (GDM or Pre-GDM)
  - Diabetes Emergency (e.g., DKA, HHS (HONK), Lactic Acidosis, Hypoglycaemia)

When to start Insulin in Type 2 DM?

- Poor glycemic control in spite of optimal dose of two or three OADs
  - Fasting >150 mg/dl
  - Random or Postprandial >200 mg/dl
  - HbA1C >9%
- Diabetic Kidney Disease/CKD/
- Chronic Liver Disease
- Steroid Therapy
- Proliferative retinoipathy,maculopathy & painful neuropathy

TWO basic INSULIN REGIMENS

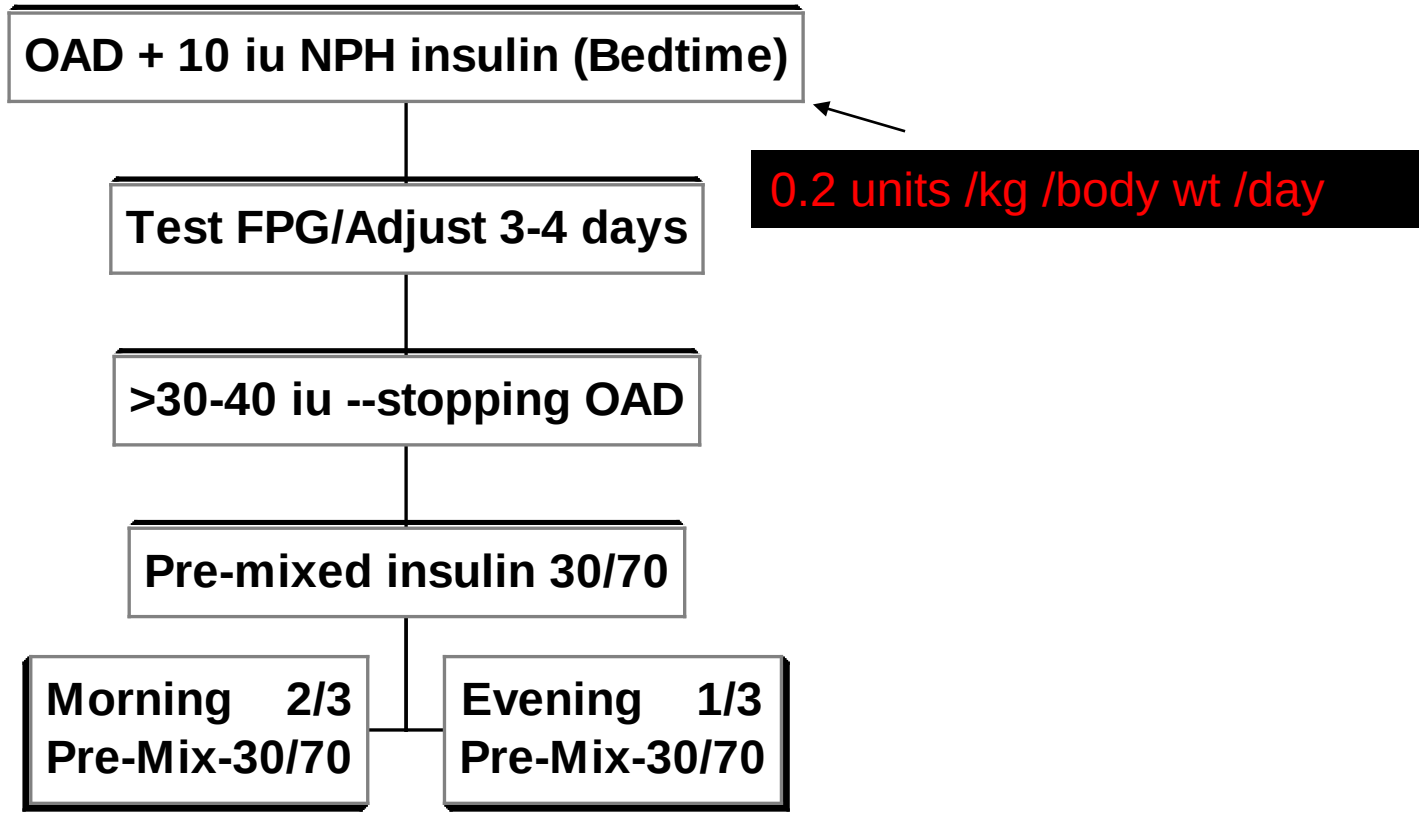


Insulin Regimen for Type 2 Diabetes Mellitus

Guidelines for initiating insulin

Chart Guidelines for Starting Insulin Therapy

(Asia Pacific Type 2 Diabetes Policy group)

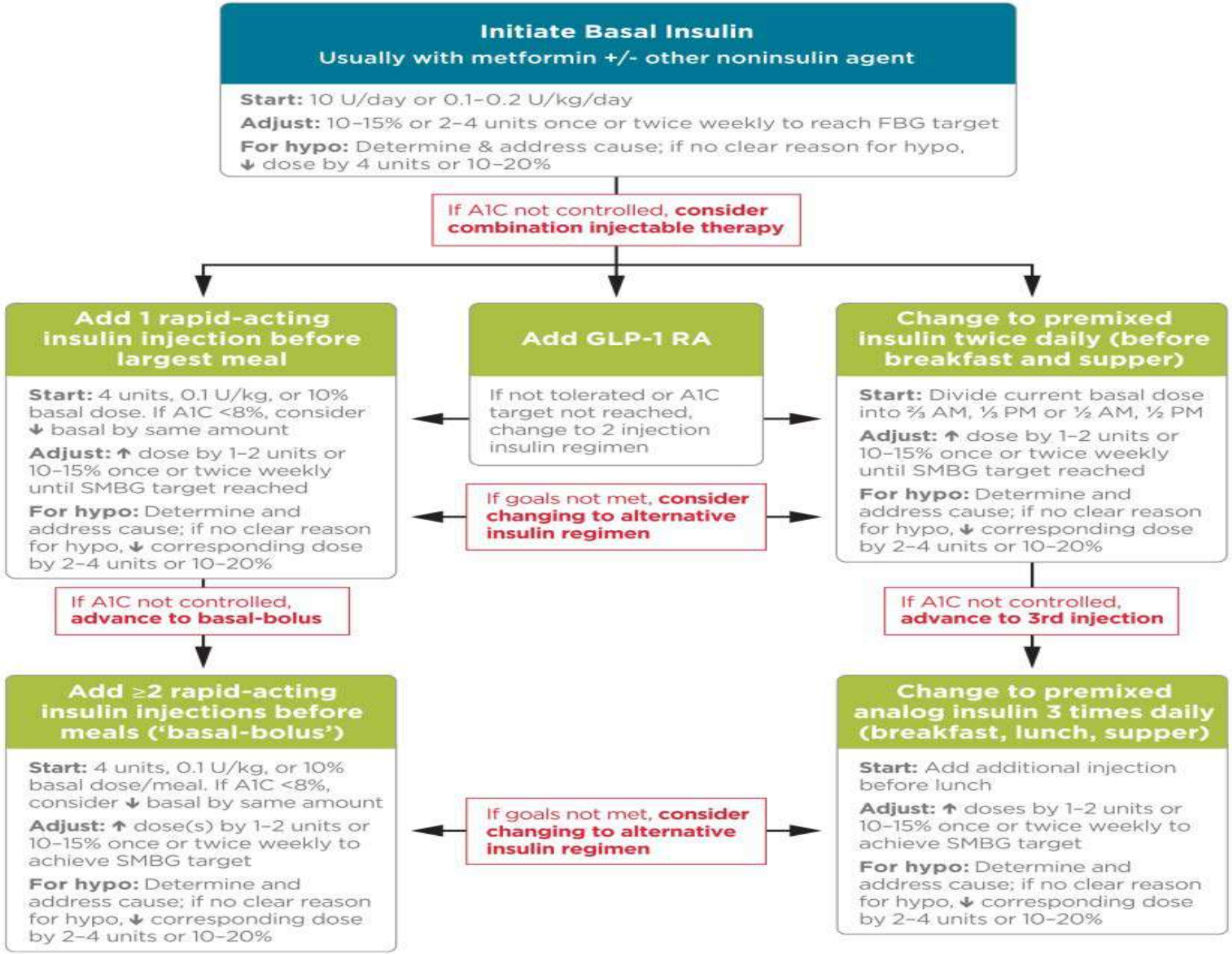


Insulin practicalities

Storage

- One month in fridge or at room temperature once the vial has been opened
- Must never be frozen
- Store away from source of heat
- If refrigeration not available store in clay pot or hole in ground
- May be damaged by direct sunlight or vigorous shaking

Combination Injectable Therapy in T2DM


Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent
Start: 10 U/day or 0.1–0.2 U/kg/day
Adjust: 10–15% or 2–4 units once or twice weekly to reach FBG target
For hypo: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10–20%
If A1C not controlled, consider combination injectable therapy
Add 1 rapid-acting insulin injection before largest meal
Start: 4 units, 0.1 U/kg, or 10% basal dose. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to basal-bolus
Add ≥2 rapid-acting insulin injections before meals ('basal-bolus')
Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1C <8%, consider ↓ basal by same amount
Adjust: ↑ dose(s) by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
Add GLP-1 RA
If not tolerated or A1C target not reached, change to 2 injection insulin regimen
If goals not met, consider changing to alternative insulin regimen
If goals not met, consider changing to alternative insulin regimen
Change to premixed insulin twice daily (before breakfast and supper)
Start: Divide current basal dose into ⅔ AM, ⅓ PM or ½ AM, ½ PM
Adjust: ↑ dose by 1–2 units or 10–15% once or twice weekly until SMBG target reached
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%
If A1C not controlled, advance to 3rd injection
Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)
Start: Add additional injection before lunch
Adjust: ↑ doses by 1–2 units or 10–15% once or twice weekly to achieve SMBG target
For hypo: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2–4 units or 10–20%

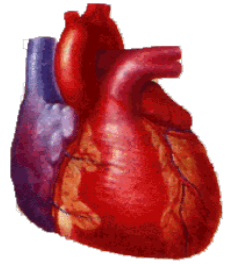
How to prevent cardiovascular diseases in Diabetes?

Macrovascular Damage Affects Large Arteries - Atherosclerosis

Coronary artery disease (CAD)

Subjects with diabetes have 2-4 times higher risk of CAD

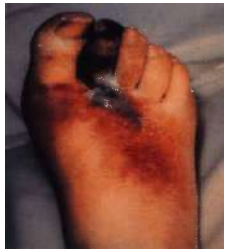
Haffner et al, 1998



Peripheral vascular disease (PVD)

Subjects with diabetes have 2- 3 times higher risk of PVD

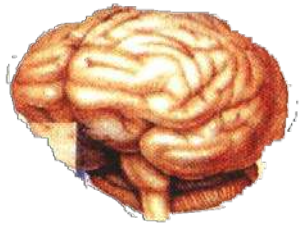
-Becks et al, 1995



Stroke / Cerebrovascular disease (CVD)

Subjects with diabetes have 2- 4 times higher risk of CVD

Malmberg et al, 2000



The Ticking Clock Hypothesis

For microvascular complications, the clock starts ticking only at the onset of hyperglycemia (i.e. once diabetes develops)

For macrovascular disease, the clock starts ticking even at the stage of pre-diabetes

Haffner SM, JAMA, 1990

CORONARY ARTERY DISEASE

Indications for CAD Screening in Asymptomatic Patients with Diabetes

Routine screening of asymptomatic individuals not recommended, since it does not improve outcomes (ADA, 2013)

Screening may be useful in the presence of

- Other atherosclerotic vascular disease
- Resting ECG suggestive of ischemia or MI
- Renal disease
- Presence of other diabetes complications
- Male sex; age >65;
- Presence of other risk factors
- Hypertension
- Dyslipidemia
- Smoking habit
- Physical inactivity
- Abdominal obesity

ADA. Diabetes Care. 2007; 30:2729-2736.

Prevention of CVD in Prediabetes: Recommendation

- Screening for and treatment of modifiable risk factors for cardiovascular disease is suggested for those with prediabetes. B

Primary Prevention-Role of Aspirin

Consider low dose (75 to 162 mg/day) aspirin in all patients with diabetes and no previous history of vascular disease who are at increased CVD risk and who are not at increased risk of bleeding.

These include most patients above age 50 who have one or more of the following:

- Hypertension
- Dyslipidemia
- Smoking
- Family history of premature CVD
- Albuminuria

ADA, 2017

Primary Prevention

- **Achieve lipid goals**

  Consider moderate to high intensity statin for all patients

  Achieve non-HDL and HDL- cholesterol goal

- **Achieve BP goal**

Secondary Prevention

- Antiplatelet therapy
- Beta-blockers
- ACEI
- Statins

Antiplatelet Agents: Recommendations

- Use aspirin therapy (75-162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. A
- For patients with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B
- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome A and may have benefits beyond this period. B

Modalities for CAD Screening

Exercise stress test (TMT) - may not be useful in asymptomatic patients

Cardiac CT - A coronary calcium score >400 is indication for further testing

PET scanning/stress echo/cardiac MRI

Use clinical judgment to decide on advanced cardiac evaluation

Key Management

When medical therapy fails, invasive procedures are required

- PTCA: flattening the plaque with a balloon-tipped catheter to open the artery

  Stents: tubes inserted after angioplasty that prop open a once-clogged artery

- CABG: grafting vessels to bypass lesions

Long-term outcome in patients with diabetes is worse than in those without ***BARI,2000***

There do not appear to be long-term differences in outcome between PTCA and CABG in patients with diabetes

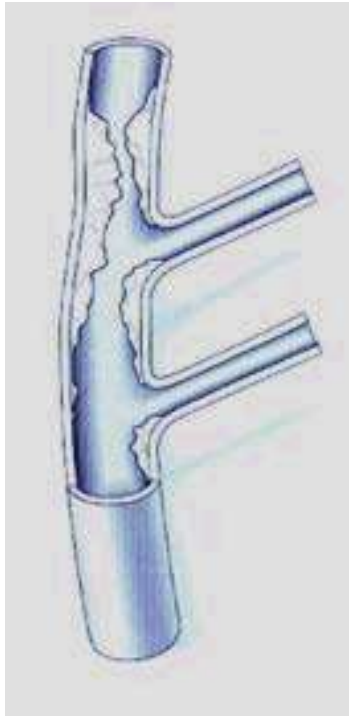
FREEDOM trial, 2014

PERIPHERAL VASCULAR DISEASE

Peripheral Vascular Disease

Peripheral vessels affected are

- The Iliac arteries (lower abdomen leading to the legs)
- The femoral and popliteal arteries (legs)
- The tibial and peroneal arteries (legs)
- The renal arteries (kidneys)
- The subclavian arteries (arms)



Differences in Diabetic and Non-diabetic PVD

	DIABETIC	NON-DIABETIC
CLINICAL	More common Younger patient More rapid Progression	Less common Older patient Less rapid progression
MALE:FEMALE	M = F	M > F
OCCLUSION	Multisegmental	Single Segment
VESSELS ADJACENT TO OCCLUSION	Involved	Not Involved
COLLATERALS	Involved	Usually normal
LOWER EXTREMITIES	Both	Unilateral
VESSELS INVOLVED	Tibials, Peroneals	Aortaliac, Femoral

Levin ME, Bowker JH, 1993

Signs and Symptoms of PVD

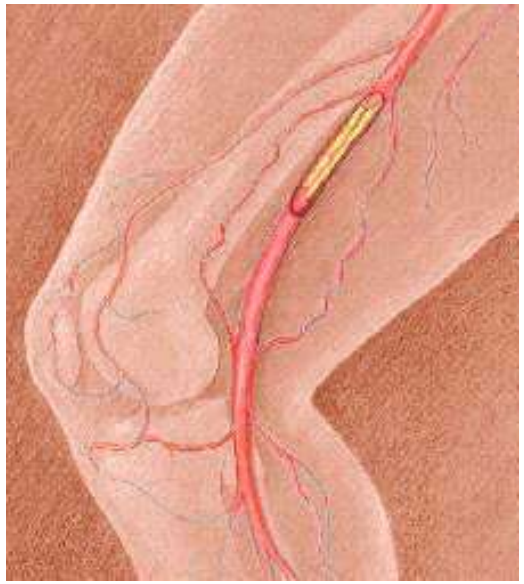
- Intermittent claudication
- Nocturnal / rest pain
- Non-healing ulcer in the most distal part of the foot
- Cold legs or feet - Absent pulses
- Color change in skin of legs or feet - Gangrene
- Loss of hair on legs
- Shiny atrophic skin
- Thick toenails
- Calcification of blood vessels

Diagnosis of PVD

- Ankle brachial index (less than 0.9 indicates PVD)
- Arterial duplex colour doppler
- Magnetic resonance angiography
- Spiral CT/Multislice CT
- Peripheral digital subtraction angiography

Management of Peripheral Vascular Disease

- Drugs like cilostazol can provide symptomatic relief of claudication
- For clots, a thrombolytic drug such as coumadin or heparin may be used
- Angioplasty [Balloon catheters, stents, stent-grafts, atherectomy, laser assistance]
- Bypass surgery

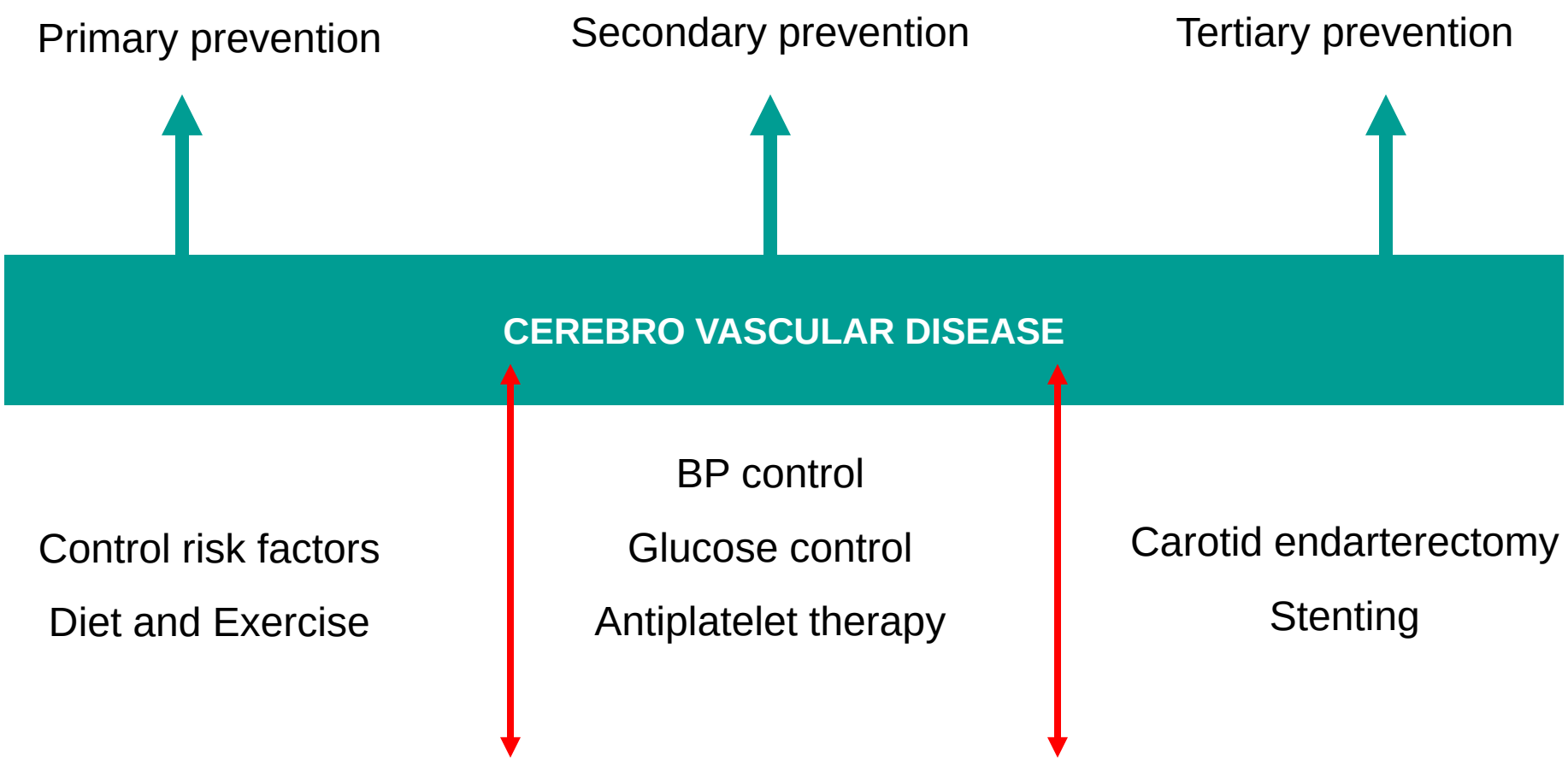


CEREBROVASCULAR DISEASE

Clinical Classification of Stroke

- Completed stroke
  - Major
  - Minor
- Evolving stroke
- Transient Ischaemic Attack (TIA)

Prevention


Primary prevention
Secondary prevention
Tertiary prevention
CEREBRO VASCULAR DISEASE
Control risk factors
Diet and Exercise
BP control
Glucose control
Antiplatelet therapy
Carotid endarterectomy
Stenting

Management - Infarction

- Persistent hyperglycemia is an indicator of poor prognosis
- Insulin therapy should be considered if glucose levels are high (>140 mg/dl)
- Ideal to maintain blood glucose levels between 140-180 mg/dl.
- BP, if high, should be reduced cautiously
- BP >185/110 mm Hg is a contraindication for thrombolysis

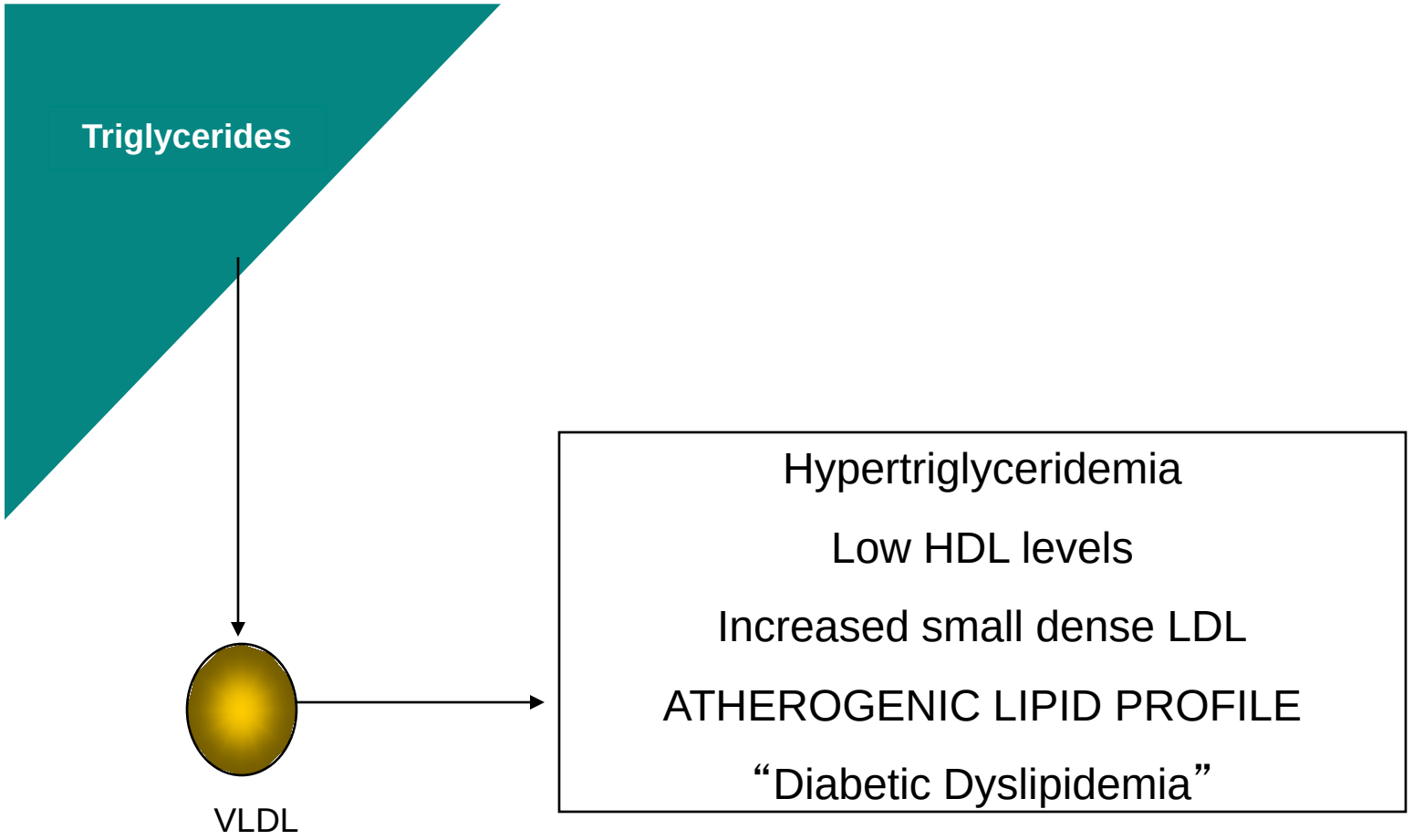
Strategies for CAD Risk Reduction in Patient with Diabetes

TEN POINT FORMULA

1. Early Identification of diabetes
2. Good control of diabetes
3. Control of hyperlipidemia
4. BP control
5. Aspirin where indicated
6. Dietary modification
7. Exercise
8. Weight reduction
9. Quit smoking
10. Relaxation techniques

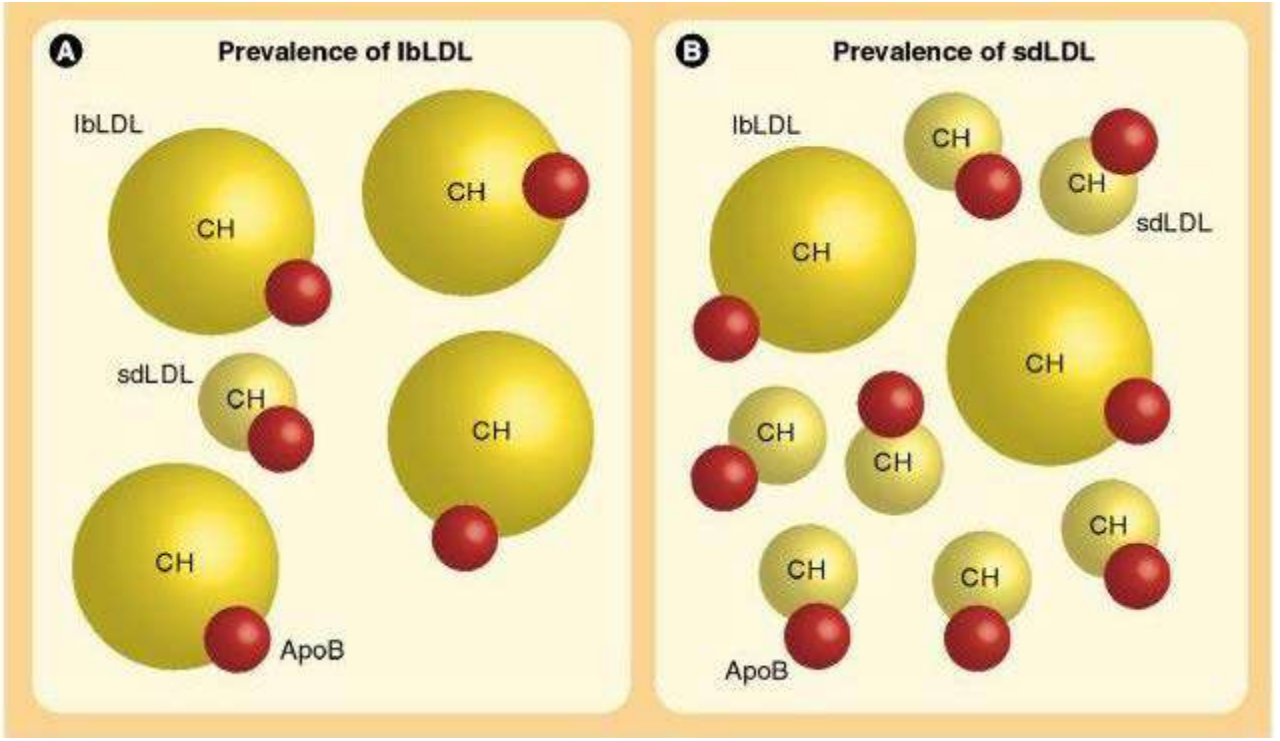
Current Lipid Guidelines: Practical Highlight?

Pathogenesis of Diabetic Dyslipidemia



Contd…

Predominance of Small Dense LDL



For any given LDL concentration, the *number* of particles will be more if there is a preponderance of small dense LDL

CV risk depends on the *number* of atherogenic lipoprotein particles rather than the cholesterol concentration per se

Recommendations for Statin Use in Diabetes

(ACC/AHA- recommended by ADA)

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
<40 years	None	None	Annually or as needed to monitor for adherence
	CVD risk factor(s)**	Moderate or high	
	Overt CVD***	High	
40–75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	High	
	Overt CVD	High	
>75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	Moderate or high	
	Overt CVD	High	

**** In addition to lifestyle therapy.***
***** CVD risk factors include LDL cholesterol ≥ 100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.***
****** Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.***

Moderate vs High Intensity Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Lowers LDL-C by ~≥ 50% Atorvastatin 40-80 mg Rosuvastatin 20 mg (40 mg)	**Lowers LDL-C by ~ 30% to <50%** Atorvastatin 10 mg (20 mg) Rosuvastatin 5 mg (10 mg) Simvastatin 20-40 mg Pravastatin 40 mg (80 mg) Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg

Doses in parentheses have not been evaluated in randomised trials

NCEP ATP III Classification of Lipid Levels

Lipid profile to be obtained after 9 to 12 hour fast

Risk	LDL Cholesterol (mg/dl)	HDL Cholesterol (mg/dl)		Triglyceride (mg/dl)	Cholesterol (mg/dl)
		Males	Females		
High	≥ 160	< 40	< 50	≥ 200	≥ 240
Borderline	≥ 130 - 159	40 - 59	50 - 69	150 - 199	200 - 239
Desirable	100 - 129	> 60	> 70	< 150	< 200
Optimal	< 100	-	-	-	-

In individuals at very high risk for CAD, an LDL target of <70 mg/dl may be an option

How Often To Test ?

- Screen patients with diabetes with a fasting lipid profile at the time of first diagnosis, at the initial medical evaluation and/or at age of 40 years
- Repeat screening periodically thereafter (e.g. every 1 to 2 years)

ADA Standards of Care, 2015

If the patient's blood glucose levels are very high at the time of first evaluation, lipid profile should be repeated after euglycemia is achieved

Approach To Management

- Therapeutic lifestyle change
- Improvement of glycemic control
- Drugs

Therapeutic Lifestyle Change

Weight loss

Reduces TGL and increases HDL-C

Modest effects on LDL-C

Diet

Saturated fat restricted to <7% of total fat

Cholesterol <200 mg/day

Increased dietary fibre

Increased physical activity

Patients on TLC should be reviewed every 3 to 6 months and considered for pharmacotherapy if needed

Improvement in Glycemic Control

Can modestly reduce TGL levels

Usually no effect on HDL or LDL

Metformin, SU and acarbose reduce TGL levels

Pioglitazone reduces TGL levels, but increases both HDL and LDL levels

SGLT2 inhibitors have been shown to increase both LDL and HDL levels

Drug Therapy

Indications

- Simultaneously with TLC (most patients with diabetes will come under this category)
- If TLC fails to achieve targets after 3 months

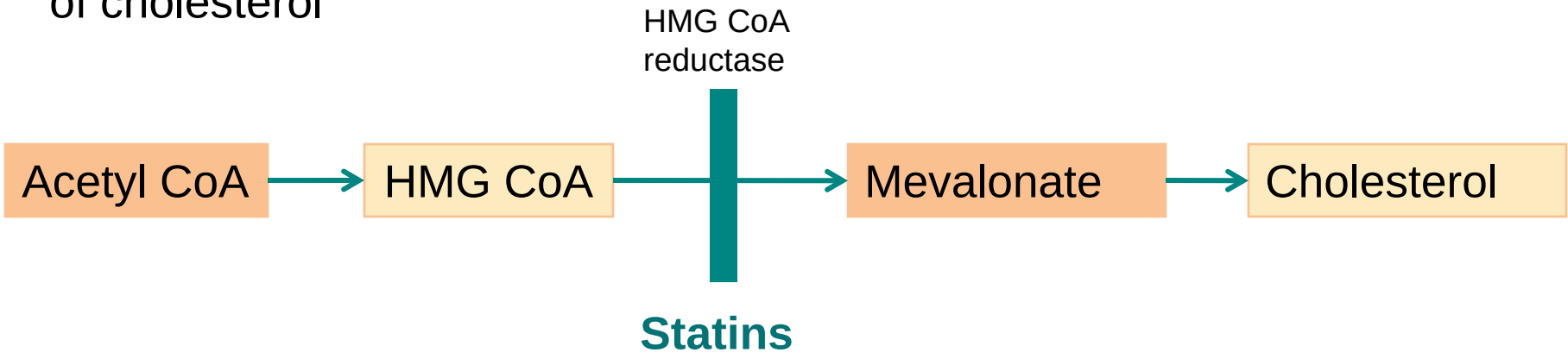
Options

HMG CoA reductase inhibitors (“statins”) are the drug of choice for dyslipidemia in diabetes

Other agents such as fibrates and ezetimibe may be useful in selected situations

Statins

Inhibit HMG CoA reductase, a key enzyme in the biosynthetic pathway of cholesterol



Significantly reduce LDL-C; more modest effects on HDL and TGL

e.g. Simvastatin, atorvastatin, rosuvastatin

Pleiotropic Effects of Statins

- Regression of atheroma
- Plaque stabilisation
- Antiinflammatory effect
- Antithrombotic effect
- Improve endothelial function

Statin & ASCVD

- Meta-analyses, including data from over 18,000 patients with diabetes from14 randomized trials of statin therapy (mean follow-up 4.3 years), demonstrate a
- 9% proportional reduction in all-cause mortality and
- 13% reduction in vascular mortality for each mmol/L (39 mg/dL) reductionin LDL cholesterol

Adverse Effects of Statins

- Myopathy- ranging from nonspecific myalgias to frank rhabdomyolysis
- GI side effects- nausea, flatulence
- CNS side effects- insomnia, nightmares
- New onset of diabetes and worsening of hyperglycemia have been reported but these are rare and should not preclude use of statin (benefit far outweighs the risk)

Contraindicated in pregnancy

Measure liver enzymes before starting treatment, subsequent measurements only on clinical indication; levels >3 times ULN warrant discontinuation of statin

Statin& Risk of DM

- The absolute risk increase was small
- (over 5 years of follow-up,**1.2%** of participants on placebo developed diabetes and **1.5%** on rosuvastatin developed diabetes)
- A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes,
- so that(on average) treatment of **255** patients with statins for 4 years resulted in **one** additional case of diabetes while simultaneously preventing **5.4** vascular events among those 255 patients

Statins and the Liver

- Elevations in transaminase levels do not reflect hepatic injury per se; the best indicator of true liver injury is the serum bilirubin level.1
- Meta-analyses of randomized placebo controlled trials demonstrate that low to moderate dosages of statins are not associated with clinically significant (i.e., greater than three times the upper limit of normal) elevations in transaminase levels.2,8
- Maximal recommended dosages of lovastatin (Mevacor), 9 pravastatin (Pravachol),10 simvastatin (Zocor),11 atorvastatin (Lipitor),8 and rosuvastatin (Crestor)8 were associated with modest but notable increases in transaminase levels.
- Many of these elevations will resolve with continued therapy.1

Considerations for Safe Use of Statins: Liver Enzyme Abnormalities and Muscle Toxicity

- R. CLARK GILLETT, JR., MD, and ANGELICA NORRELL, PharmD, *Columbus Regional Healthcare System, The Medical Center, Columbus, Georgia*

- Clinically important drugs that interact with statins and increase the risk of adverse effects include **fibrates, diltiazem, verapamil, and amiodarone.**
- (*Am Fam Physician. 2011;83(6):711-716. Copyright © 2011 American Academy of Family Physicians.)*

SORT: KEY RECOMMENDATIONS FOR PRACTICE

- Elevated transaminase levels and nonalcoholic fatty liver disease are not contraindications to statin use. C
- Stable hepatitis C infection is not an absolute contraindication to statin use. C
- Statin-induced myopathy is dose-related and may occur with all statins. C
- Baseline levels of creatine kinase need to be obtained only in patients at high risk of muscle toxicity. C

C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series.

Ezetimide

Table 9.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

*In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

PCSK 9 inhibitors

Effect of PCSK9 Inhibitors on Clinical Outcomes in Patients With Hypercholesterolemia: A Meta-Analysis of 35 Randomized Controlled Trials

Aris Karatasakis, MD; Barbara A Danek, MD; Judit Karacsonyi, MD; Bavana V Rangan, BDS, MPH; Michele K Roesle, RN, BSN; ThomasKnickelbine, MD; Michael D Miedema, MD, MPH; Houman Khalili; MD; Zahid Ahmad, MD; Shuaib Ab**d**ullah, MD; Subhash Banerjee, MD;Emmanouil S. Brilakis, MD, PhD

- **Conclusions-**—Treatment with a PCSK9 inhibitor is well tolerated and improves cardiovascular outcomes. Although no overall benefit was noted in all-cause or cardiovascular mortality, such benefit may be achievable in patients with higher baseline low density lipoprotein cholesterol.

(J Am Heart Assoc. 2017;6:e006910. DOI: 10.1161/JAHA.117.006910.)

Fibrates

Activate PPAR-α in liver, muscle and adipose tissue leads to

- Activation of lipoprotein lipase
- Increased fatty acid oxidation
- Increased HDL synthesis
- Increased clearance of remnant lipoproteins

Net effects- reduce TGL, raise HDL, modestly reduce LDL

Examples- gemfibrozil, fenofibrate, bezafibrate

Side effects- myopathy, hepatotoxicity, raised serum creatinine (fenofibrate)

Large clinical trials have not shown improvement in CV endpoints with fibrate use; however, in the FIELD trial, there was a reduction in microvascular complications

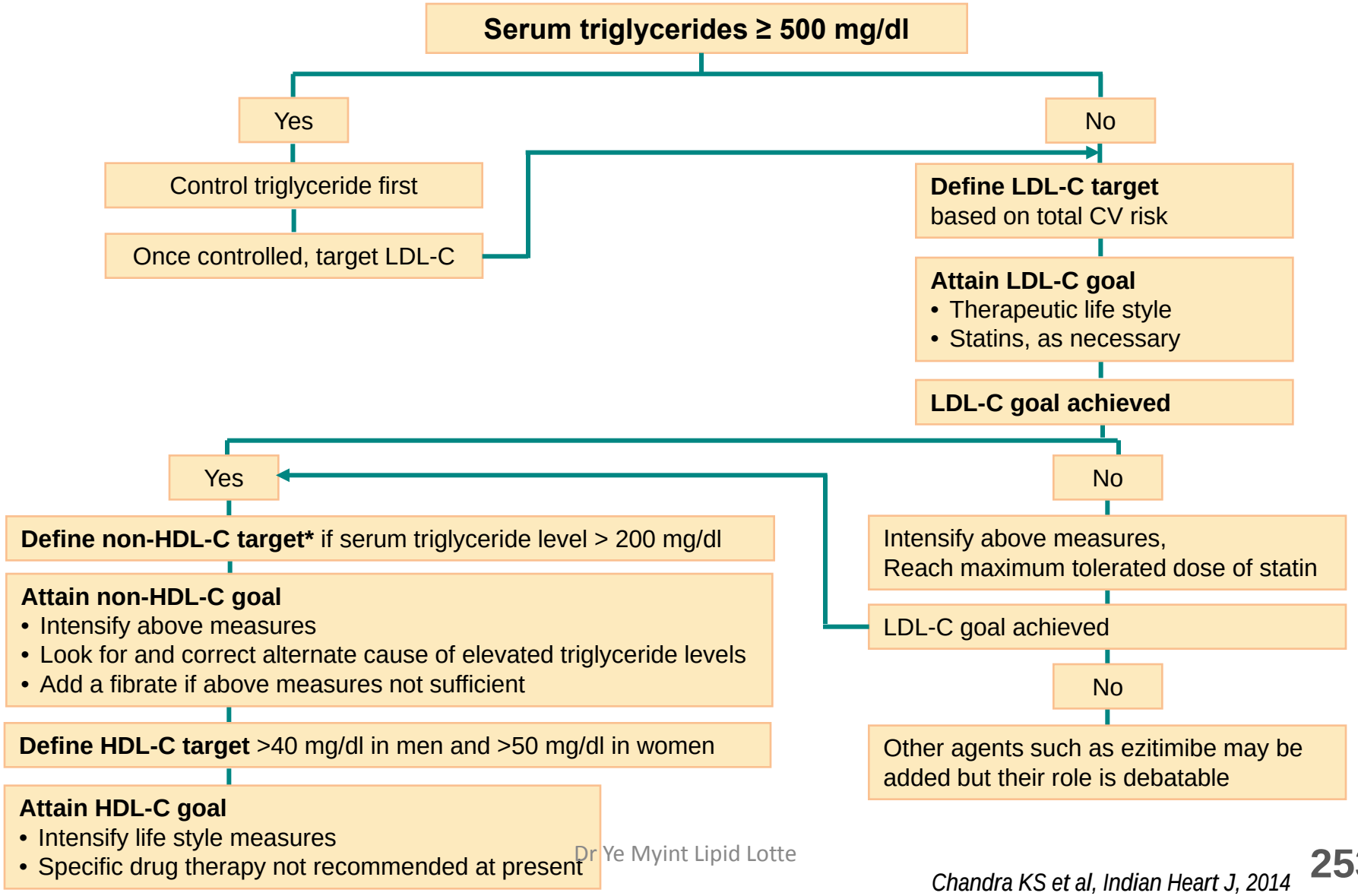
Finofibrate & Specific role

- Prespecified subgroup

  analyses suggested heterogeneity in treatment effects with possible benefit for men with both a triglyceride level >204 mg/dL (2.3 mmol/L) and an HDL cholesterol level <34 mg/dL (0.9 mmol/L)

- Ginsberg HN, Elam MB, Lovato LC, et al.;ACCORDStudy Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574

Conclusion



Chandra KS et al, Indian Heart J, 2014

- **Current Guidelines on Hypertension and its implication in Diabetes Management?**

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Recommendation 5

- In the population age **≥18 years with diabetes**, initiate pharmacologic treatment at
  - SBP ≥ 140 mmHg or
  - DBP ≥ 90 mmHg and
- treat to a
  - goal SBP ≤ 140 mmHg and
  - goal DBP ≤ 90 mmHg

(E)

Diabetes Mellitus

COR	LOE	Recommendations for Treatment of Hypertension in Patients With DM
I	SBP: B-R[SR]	In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg.
	DBP: C-EO	
I	A[SR]	In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective.
IIb	B-NR	In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria.

SR indicates systematic review.

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Whelton PK, et al.
2017 High Blood Pressure Clinical Practice Guideline

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

American Heart Association®
life is why™

Hypertension in Patients With Comorbidities

	Target	Initial (first-line)
DM	<130/80	all first-line classes of antihypertensive agents (i.e., diuretics, ACEIs, ARBs, and CCBs)
DM + albuminuria		ACEI / ARB

American Diabetes Association.

ADA 2018

MANAGEMENT OF BLOOD PRESSURE

Screening & Dx	Measure BP at every visit, confirm ↑BP with multiple readings including that on separate day
Monitoring	Should monitor BP at home
Goals	DM + HTN → **<140/90 mmHg** DM + HTN + high risk of CVD → **<130/80 or <120/80 mmHg** (if they can be achieved without undue treatment burden) DM + HTN + Pregnancy → **<120–160/ 80–105 mmHg** **(in 2016 ADA -** BP targets - 110–129/65–79 mmHg)

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MANAGEMENT OF BLOOD PRESSURE

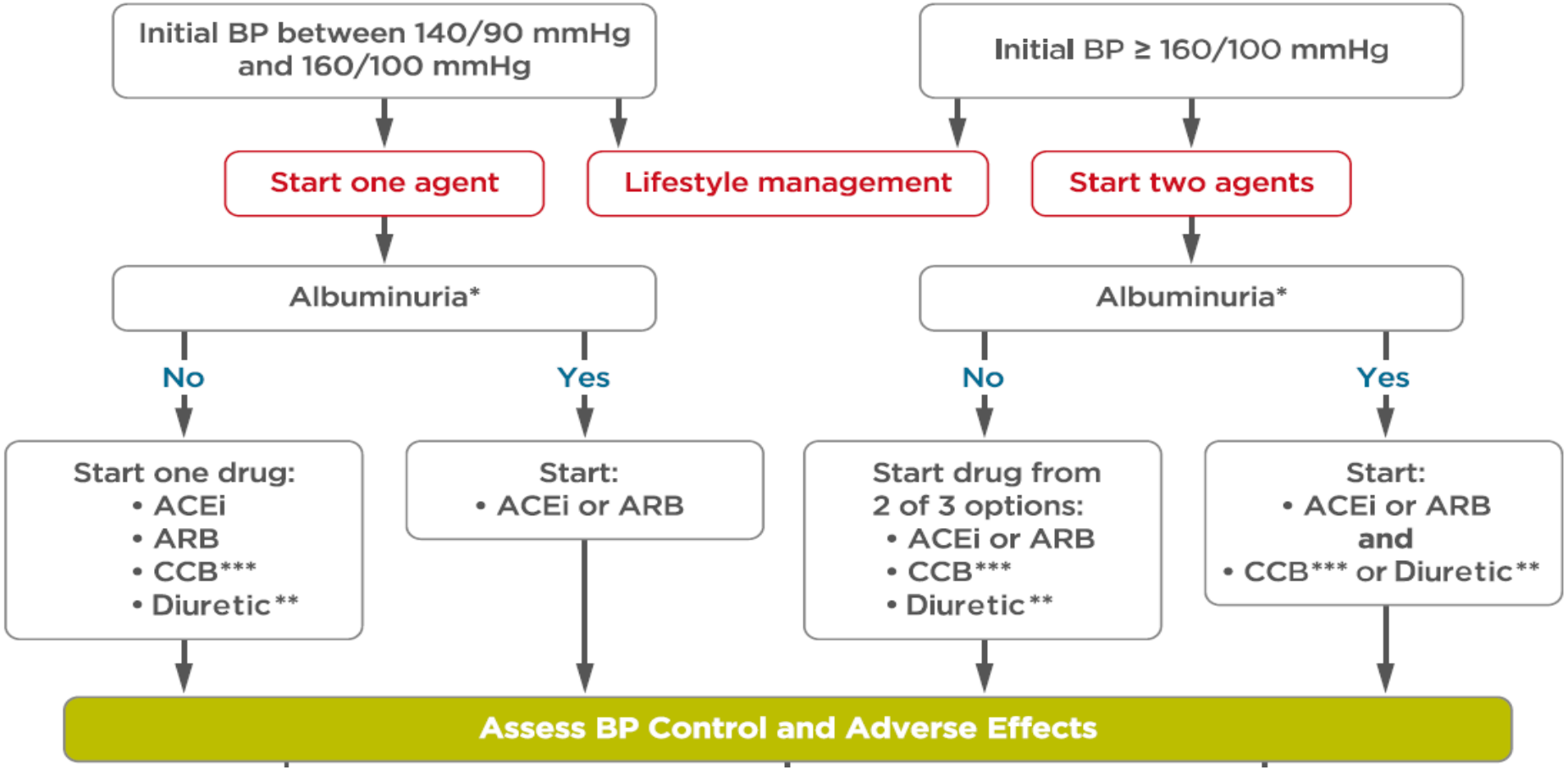
Lifestyle intervention	▪ Indication → **>120/80** ▪ Weight ↓ → if overweight or obese ▪ DASH (Dietary Approaches to Stop Hypertension) ▪ ↑ physical activity
Pharmacologic intetrventions	▪ Indication → **≥140/90** ▪ **≥160/100** → initiate with 2 drugs or single-pill combination
Drug choices	▪ ACEI, ARB, thiazide-like diuretics, dihydropyridine CCB ▪ Generally – multiple drug therapy is required ▪ **NOT recommend** – ACEI + ARB or ACEI + ARB + direct Renin Inhibitor ▪ DM + HTN + **UACR ≥300 mg/g or 30-299 mg/g** → ACEI or ARB ▪ **Resistant Hypertension –** mineralocorticoid receptor antagonist

American Diabetes Association®

ADA 2018

MANAGEMENT OF BLOOD PRESSURE

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes



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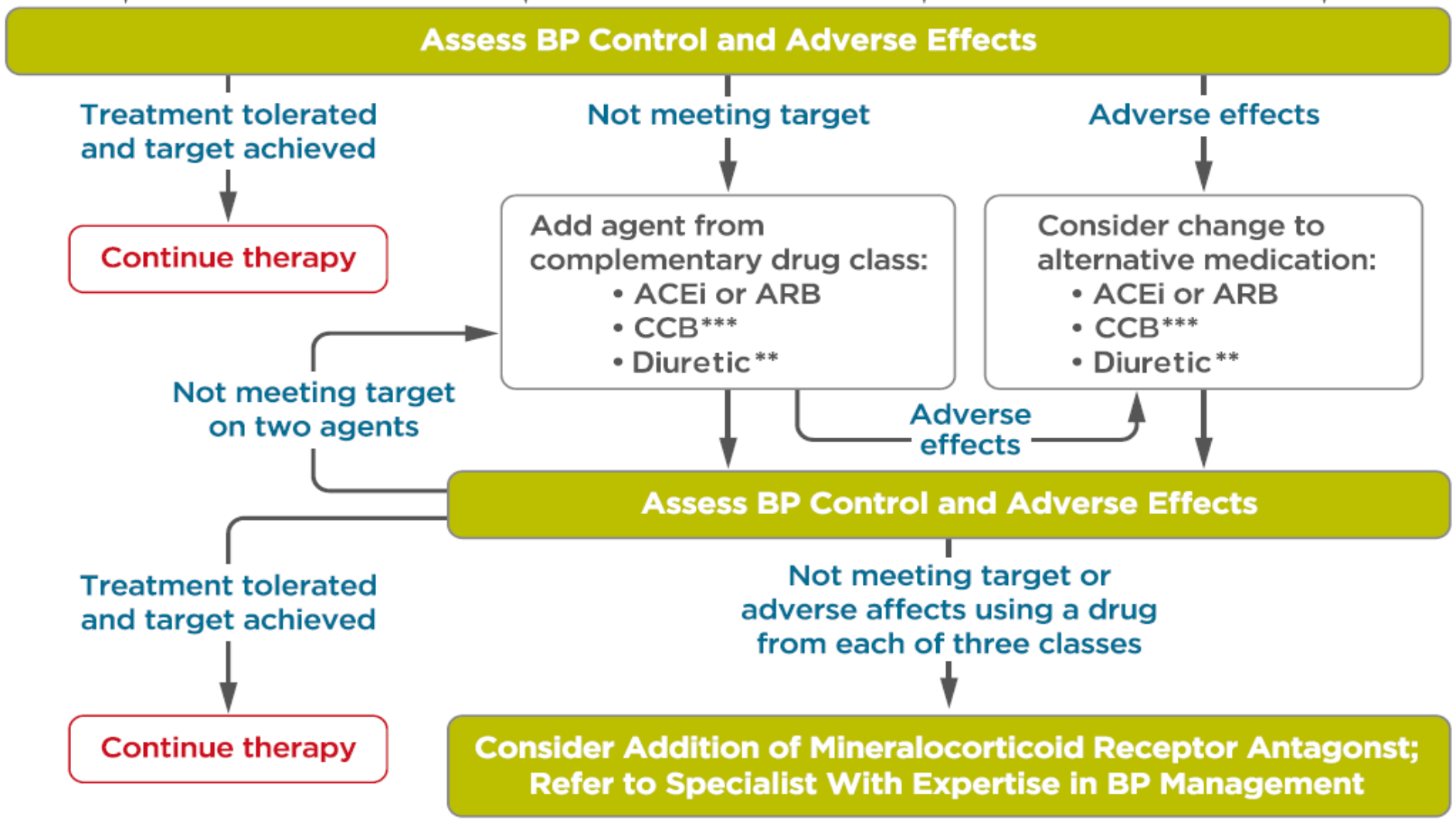
ADA 2018

MANAGEMENT OF BLOOD PRESSURE



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Thank You