Diabetes Mellitus: Overview and Guidelines

Rezvan Salehidoost, M.D., Endocrinologist
IMPORTANCE?
Why is it interesting to do research in diabetes

Adults who died from diabetes, HIV/AIDS, tuberculosis, and malaria

5.0 million from diabetes
2015
IDF

1.5 million from HIV/AIDS
2013
WHO Global Health Observatory Data Repository 2013

1.5 million from tuberculosis
2013
WHO Global Health Observatory Data Repository 2013

0.6 million from malaria
2013
WHO Global Health Observatory Data Repository 2013

Executive summary
Map 3.5 Proportion (%) of people who died from diabetes before the age of 60
UKPDS 35
Each 1% Reduction in A1c Reduces the Complication Risk

Epidemiology of Type 2 Diabetes Mellitus
In 2015, IDF estimates that:

- One in 11 adults has diabetes
- One in two adults with diabetes is undiagnosed
- 12% of global health expenditure is spent on diabetes
- One in seven births is affected by gestational diabetes
- 542,000 children have type 1 diabetes
Figure 3.2 Prevalence of people with diabetes by age and sex, 2015
Map 3.1 Estimated age-adjusted prevalence of diabetes in adults (20-79), 2015
Diabetes: A global emergency

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)

- **North America and Caribbean**
  - 2015: 44.3 million
  - 2040: 60.5 million

- **Europe**
  - 2015: 59.8 million
  - 2040: 71.1 million

- **Middle East and North Africa**
  - 2015: 35.4 million
  - 2040: 72.1 million

- **South and Central America**
  - 2015: 29.6 million
  - 2040: 48.8 million

- **South East Asia**
  - 2015: 78.3 million
  - 2040: 140.2 million

- **Western Pacific**
  - 2015: 153.2 million
  - 2040: 214.8 million

- **World**
  - 2015: 415 million
  - 2040: 642 million

DM
10.2 million

Undiagnosed
5.4 million

IGT / Pre-Diabetes
13.4 million

At-Risk: 40 million

Harris et al., Diabetes Care, 1998
Two thirds of individuals do not achieve target $\text{HbA}_1\text{c}$
11.4% (95% CI, 9.9-12.9) of Iranian adults aged 25-70 yrs had diabetes.

In about one-fourth, diabetes, was undiagnosed.

The prevalence of diabetes was higher in:

- **Women (12.8%) than in men (9.9%)**
- **Urban (12.6%) than in rural (7.6%) residents**

2005 to 2011: 35% increase in the diabetes prevalence rate

The prevalence of IFG: 14.6%
What Do We Have for Treatment of T$_2$DM?
Pancreas
- Produces insulin
  - High blood glucose (after eating)

Insulin
- Cells
  - Glucose -> Energy
  - Normal blood glucose level

Liver
- Glucose -> Glycogen
  - Low blood glucose (after exercising or fasting)

Glucagon
- Pancreas
  - Produces glucagon

Liver
- Glycogen -> Glucose
### Table 2.1—Criteria for the diagnosis of diabetes

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting Plasma Glucose (FPG)</strong></td>
<td>FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*</td>
</tr>
<tr>
<td><strong>2-hour Postprandial Glucose (2-h PG)</strong></td>
<td>2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*</td>
</tr>
<tr>
<td><strong>A1C</strong></td>
<td>A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*</td>
</tr>
<tr>
<td><strong>Random Plasma Glucose</strong></td>
<td>In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).</td>
</tr>
</tbody>
</table>

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.
# Diabetes Mellitus

**Definition, Classification, Risk factors**

## Table 66-3: Etiologic Classification of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Type 1 Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-mediated (type 1a)</td>
</tr>
<tr>
<td>Idiopathic (type 1b)</td>
</tr>
</tbody>
</table>

## Type 2 Diabetes Mellitus

## Other Specific Types

- Genetic defects of beta-cell function
  - Maturity-onset diabetes of the young (MODY) and other disorders
- Genetic defects in insulin action
  - Insulin receptor mutations and other disorders
- Diseases of the exocrine pancreas
- Endocrinopathies
  - Cushing’s syndrome, acromegaly, and other disorders
- Drug- or chemical-induced
  - Glucocorticoids most common
- Infections
- Uncommon forms of immune-mediated diabetes
  - Insulin receptor–blocking antibodies and other disorders
- Other genetic syndromes sometimes associated with diabetes

## Gestational Diabetes Mellitus
Therapeutic Options

- Lifestyle interventions
- Oral agents and non-insulin injectable drugs
- Insulin
Treatment of Diabetes

No medication 14.4%
Insulin only 14.0%
Insulin and oral medication 14.7%
Oral medication only 56.9%

<table>
<thead>
<tr>
<th></th>
<th>Met</th>
<th>GLP1RA</th>
<th>SGLT2I</th>
<th>DPP4I</th>
<th>TZD</th>
<th>AGI</th>
<th>Coles</th>
<th>BCR-QR</th>
<th>SU/Glinide</th>
<th>Insulin</th>
<th>Pram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight</strong></td>
<td>Slight loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td><strong>Hypo-glycemia</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mod to severe</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>FPG lowering</strong></td>
<td>Mod</td>
<td>Mild to mod*</td>
<td>Mod</td>
<td>Mild</td>
<td>Mod</td>
<td>Neutral</td>
<td>Mild</td>
<td>Neutral</td>
<td>SU: mod</td>
<td>Mod to marked (basal insulin or premixed)</td>
<td>Mild</td>
</tr>
<tr>
<td><strong>PPG lowering</strong></td>
<td>Mild</td>
<td>Mod to marked</td>
<td>Mild</td>
<td>Mod</td>
<td>Mild</td>
<td>Mod</td>
<td>Mild</td>
<td>Mild</td>
<td>Mod</td>
<td>Mod to marked (short/rapid-acting insulin or premixed)</td>
<td>Mod to marked</td>
</tr>
<tr>
<td><strong>Renal impairment/ GU</strong></td>
<td>Contra-indicated in stage 3B, 4, 5 CKD</td>
<td>Exenatide contra-indicated</td>
<td>CrCl &lt;30 mg/mL</td>
<td>GU infection risk</td>
<td>Dose adjustment (except linaagliptin)</td>
<td>May worsen fluid retention</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Increased hypo-glycemia risk</td>
<td>Increased risks of hypo-glycemia and fluid retention</td>
</tr>
<tr>
<td><strong>GI adverse effects</strong></td>
<td>Mod</td>
<td>Mod*</td>
<td>Neutral</td>
<td>Neutral*</td>
<td>Neutral</td>
<td>Mod</td>
<td>Mild</td>
<td>Mod</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mod</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td>Possible benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Safe</td>
<td>?</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Bone loss</td>
<td>Neutral</td>
<td>Mod bone loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>NAFLD benefit</strong></td>
<td>Mild</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mod</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>
Available Treatment Algorithms for T₂DM
Lifestyle measures

Then, at each step, if not to target (generally HbA$_{1c}$ < 7.0%)

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2016

TASK FORCE
Alan J. Garber, MD, PhD, FACE, Chair

Martin J. Abrahamson, MD
Joshua I. Barzilay, MD, FACE
Lawrence Blonde, MD, FACP, FACE
Zachary T. Bloomgarden, MD, MACE
Michael A. Bush, MD
Samuel Dagogo-Jack, MD, DM, FRCP, FACE
Ralph A. DeFronzo, MD
Daniel Einhorn, MD, FACP, FACE
Vivian A. Fonseca, MD, FACE
Jeffrey R. Garber, MD, FACP, FACE
W. Timothy Garvey, MD, FACE
George Grunberger, MD, FACP, FACE
Yehuda Handelsman, MD, FACP, FNLA, FACE
Robert R. Henry, MD, FACE
Irl B. Hirsch, MD
Paul S. Jellinger, MD, MACE
Janet B. McGill, MD, FACE
Jeffrey I. Mechanick, MD, FACP, FACE, FACN, ECNU
Paul D. Rosenblit, MD, PhD, FNLA, FACE
Guillermo Umpierrez, MD, FACP, FACE
LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%
Entry A1C ≥ 7.5%
Entry A1C > 9.0%
Diabétologia
DOI 10.1007/s00125-012-2534-0

POSITION STATEMENT

Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

S. E. Inzucchi · R. M. Bergenstal · J. B. Buse · M. Diamant · E. Ferrannini · M. Nauck · A. L. Peters · A. Tsapas · R. Wender · D. R. Matthews
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)


Diabetes Care 2015;38:140–149
Diabetologia 2015;58:429–442
There is a call for a move toward more **patient-centred care**.

Treatment for T₂DM should consider the **needs, preferences and tolerances**, as well as **age** and **disease progression**, of each patient.

These factors makes it difficult to prescribe a single treatment regimen designed to work for everyone.

Inzucchi et al. *Diabetes Care* 2015;38:140-149
Approach to the Management of Hyperglycemia

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. *Diabetes Care* 2017; 40 (Suppl. 1): S48-S56
### 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**

<table>
<thead>
<tr>
<th>Efficacy*</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo Risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>Neutral/loss</td>
<td></td>
</tr>
<tr>
<td>Side Effects</td>
<td>GI/lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Costs*</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

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 +**

<table>
<thead>
<tr>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 Inhibitor</th>
<th>SGLT2 Inhibitor</th>
<th>GLP-1 Receptor Agonist</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>High</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>Moderate risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Gain</td>
<td>Neutral</td>
<td>Loss</td>
<td>Loss</td>
<td>Gain</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>Hypoglycemia</td>
<td>Edema, HF, FXs</td>
<td>Rare</td>
<td>GI, dehydration, FXs</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>COSTS*</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

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 +**

<table>
<thead>
<tr>
<th>Sulfonylurea +</th>
<th>Thiazolidinedione +</th>
<th>DPP-4 Inhibitor +</th>
<th>SGLT2 Inhibitor +</th>
<th>GLP-1 Receptor Agonist +</th>
<th>Insulin (basal) +</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZD</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>or Insulin*</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
</tbody>
</table>

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)
## ADA 2017: Pharmacologic Therapy in T2DM

**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**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>GI/lactic acidosis</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
</tr>
</tbody>
</table>

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):

---

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. *Diabetes Care* 2017; 40 (Suppl. 1): S64-S74
Target organs and action mechanism of anti-diabetic drugs

- **Metformin**
  - ↑ Glucose uptake
  - ↓ Gluconeogenesis
  - ↓ Insulin sensitivity

- **TZDs**
  - ↑ Glucose uptake
  - ↑ Insulin sensitivity

- **Meglitinides, Sulphonylureas**
  - ↑ Insulin release
  - ↓ Glucagon secretion

- **DPP-4i, GLP-1RA**
  - ↓ Glucagon secretion
  - ↑ Insulin secretion

- **TZDs**
  - ↑ Gastric emptying

- **GLP-1RA**
  - ↑ GLP-1

- **DPP-4i**
  - ↑ GLP-1

- **Metformin**
  - ↑ GLP-1
  - ↓ Glucose absorption

- **SGLT-2i**
  - ↑ Renal glucose excretion

Zhou K, et al. doi:10.1038/nrendo.2016.51
Treat 1000 patients for 1 year with Metformin in addition to diet there will be 5 fewer deaths.

Treat 1000 patients for 1 year with Metformin in place of SUs or Insulin there will be 3 fewer deaths.

Support for Metformin: 1957–2009

- First used in clinical practice: 1957
- UGDP findings for Phenformin: 1968
- Lactic Acidosis withdrawal of Phenformin from US: 1978
- Approval of Metformin in US: 1995
- License revised in Europe 2001 “Risk of complications reduced”
- Use in children: 2002
- NICE
- IDF
- ADA
- EASD
- New Millennium
- UKPDS ↓ mortality/morbidity in Metformin treated patients
- Diabetes Prevention
- New Millennium
Contraindications:

- **Hypersensitivity** to metformin or any component of the formulation
- **Any potentially hypoxemic conditions:**
  - shock state
  - acute MI
  - renal disease with GFR < 30 ml/min
  - decompensated heart failure
  - respiratory failure
  - liver failure (synthetic failure)
  - septicemia
  - acute or chronic metabolic acidosis with or without coma

Warnings, precautions:

- **Iodinated contrast:** temporarily withdraw for 3 days after contrast medium containing iodine has been given, and start it again only after renal function has been checked.
- **Surgical procedures:** therapy should be suspended 2 days before general anaesthesia for any surgical procedures (resume only after normal oral intake resumed and normal renal function is verified).
- **Elderly:** GFR should be calculated. *Do not start Metformin if 30 < GFR < 50 ml/min.*
- **Ethanol use:** instruct patients to avoid excessive acute or chronic ethanol use; it may potentiate metformin's effect on lactate metabolism.
ADA 2017: Pharmacologic Therapy in T2DM

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):

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonlurea</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
<td>gain-neutral</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>intermediate</td>
<td>loss</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>intermediate</td>
<td>loss</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>high</td>
<td>gain</td>
</tr>
<tr>
<td>Insulin (basal)</td>
<td>highest</td>
<td>highest</td>
</tr>
</tbody>
</table>

**EFFICACY**
- high
- moderate risk
- gain
- hypoglycemia
- low

**HYPO RISK**
- high
- low risk
- gain
- edema, HF, fx
- rare
- GI

**WEIGHT**
- neutral
- neutral
- neutral
- neutral
- high

**SIDE EFFECTS**
- hypoglycemia
- edema, HF, fx
- rare
- GU, dehydration, fx
- GI

**COSTS**
- low
- low
- high
- high
- high
Thiazolidinediones
Target organs and action mechanism of anti-diabetic drugs

Metformin
- ↑ Glucose uptake

TZDs
- ↑ Glucose uptake

Meglitinides, Sulphonylureas
- ↑ Insulin release

DPP-4i, GLP-1RA
- ↓ Glucagon secretion
- ↑ Insulin secretion

TZDs
- ↑ Insulin sensitivity

Metformin
- ↓ Gluconeogenesis

SGLT-2i
- ↑ Renal glucose excretion

TZDs
- ↑ GLP-1

GLP-1RA
- ↓ Gastric emptying

DPP-4i
- ↑ GLP-1

Metformin
- ↑ GLP-1
- ↓ Glucose absorption

Zhou K, et al. doi:10.1038/nrendo.2016.51
Thiazolidinediones (TZDs)

- The TZDs increase insulin sensitivity by acting on adipose, muscle, and liver to increase glucose utilization and decrease glucose production.

- When used as monotherapy, they reduce HbA$_{1c}$ values by 1-1.5%.

- Although in some cases metformin and TZDs may have similar efficacy as monotherapy, the cost and side effects of the later make them less appealing as initial therapy.
TZDs: Pros & Cons

**Positive points:**
- Efficacy
- No hypo
- Once daily dose
- Use in renal CKD
- Targeting insulin resistance
- Positive effect on NAFLD

**Negative points:**
- Edema & weight gain
- Heart failure
- Fracture
- Bladder CA
- Ischemia (Rosi)
Clinical Use of TZDs

- A TZD may be considered in patients with lower initial HbA$_{1c}$ values or if there are specific contraindications to other OADs.

- If a thiazolidinedione is to be used as initial therapy, Pioglitazone is preferred.

- The TZDs have also been studied in combination with metformin, SUs, and insulin.

- It is not recommended to use TZDs with a goal of prevention, even in patients felt to be at high risk of developing diabetes.
Dosing: Adult **Diabetes mellitus, type 2:**

- **Oral:** Initial: 15 to 30 mg once daily; patients with heart failure (NYHA Class I or II) should initiate therapy with 15 mg once daily. **Note:** Not recommended in patients with symptomatic heart failure.

**Dosage titration:** Based on HbA$_1c$, the dosage may be increased in 15 mg increments up to a maximum of 45 mg once daily; monitor closely during titration for adverse effects (eg, weight gain, edema, signs/symptoms of heart failure).
- **Dosing: Renal Impairment**  No dosage adjustment necessary.
- **Dosing: Hepatic Impairment**
  - Hepatic impairment prior to initiation: No dosage adjustment necessary; use with caution if baseline liver tests are abnormal
  - Hepatic impairment during therapy: If liver injury is suspected (eg, fatigue, jaundice, dark urine): Interrupt therapy, measure serum liver tests, and investigate possible etiologies:
    - If an alternative etiology is not identified and ALT >3 x ULN: Do not reinitiate therapy.
    - If an alternative etiology is identified and ALT elevated (but <3 x ULN) or total bilirubin elevated (but <2 x ULN): May reinitiate with caution.
SGLT$_2$ Inhibitors
Target organs and action mechanism of anti-diabetic drugs

- **Metformin**
  - ↑ Glucose uptake
- **TZDs**
  - ↑ Glucose uptake
- **Meglitinides, Sulphonylureas**
  - ↑ Insulin release
- **DPP-4i, GLP-1RA**
  - ↓ Glucagon secretion
  - ↑ Insulin secretion
- **TZDs**
  - ↑ Insulin sensitivity
- **Metformin**
  - ↓ Gluconeogenesis
- **SGLT-2i**
  - ↑ Renal glucose excretion
- **TZDs**
  - ↑ Glucose uptake
- **GLP-1RA**
  - ↓ Gastric emptying
- **DPP-4i**
  - ↑ GLP-1
- **Metformin**
  - ↑ GLP-1
  - ↓ Glucose absorption

Zhou K, et al. doi:10.1038/nrendo.2016.51
Renal glucose re-absorption in healthy individuals

Filtered glucose load 180 g/day

SGLT2
~ 90%

SGLT1
~ 10%

When blood glucose increases above the renal threshold (~180 mg/dL), the capacity of the transporters is exceeded, resulting in urinary glucose excretion.
Loss of ~80 g of glucose/day (~240 cal/day)

SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

*Loss of ~ 80 g of glucose/day (~ 240 cal/day)

Current FDA approved SGLT$_2$ inhibitors

- **Canagliflozin** *(Invokana, 100 & 300 mg)*

- **Dapagliflozin** *(Forxiga, 5 & 10 mg)*

- **Empagliflozin** *(Jardiance, 10 & 25 mg)*

All may be used as once daily tablets in the morning.
SGLT$_2$i therapy: Clinical benefits

Kidney

- Increased glucose excretion
  - Reduced fasting and postprandial glycemia
    - 0.6 to $\sim$1\% HbA$_1c$ reduction$^{a,b}$

- Loss of energy

- Increased sodium excretion
  - Reduced sodium load
    - Mild $\sim$3 to 5 mm Hg reduction in blood pressure$^{d,e}$
  - Modest $\sim$2 to 3 kg weight loss$^c$

References:

### Points in using SGLT₂ inhibitors

#### Pros
- Action is **independent of insulin**
- Easy to use, once daily in the morning
- Efficacious as dual and triple therapy and combination with insulin
- Lack of hypoglycemia
- Weight reduction
- SBP reduction
- Reduction of CVD mortality
- Reduction of all cause mortality
- Slowing progression of nephropathy

#### Cons
- Modest improvement in glycemia
- Lower efficacy with decreasing eGFR
- Increased genital mycotic infection
- DKA
- Mild LDL elevation
- Mild volume depletion
- Bone loss (*Canagliflozin*)
- Bladder Cancer (*Dapagliflozin*)
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).
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,
drops 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%

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

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%

Change to premixed insulin twice daily (before breakfast and supper)
Start: Divide current basal dose into ½ AM, ½ PM or ⅛ AM, ⅛ 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 basal-bolus

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%

If A1C not controlled, advance to 3rd injection

If goals not met, consider changing to alternative insulin regimen
ADA 2017: Pharmacologic Therapy in T2DM
Never miss Metformin

Start with Monotherapy unless:
- AIC is greater than or equal to 9%, **consider Dual Therapy**.
- AIC 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

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>GI/lactic acidosis</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
</tr>
</tbody>
</table>

If AIC 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

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>high</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>intermediate</td>
</tr>
<tr>
<td>SGLT2 inhibitor</td>
<td>intermediate</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>high</td>
</tr>
<tr>
<td>insulin (basal)</td>
<td>highest</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>moderate risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>gain</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>edema, HF, fx</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
</tr>
</tbody>
</table>

If AIC 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

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea +</td>
<td>high</td>
</tr>
<tr>
<td>Thiazolidinedione +</td>
<td>high</td>
</tr>
<tr>
<td>DPP-4 inhibitor +</td>
<td>intermediate</td>
</tr>
<tr>
<td>SGLT2 inhibitor +</td>
<td>intermediate</td>
</tr>
<tr>
<td>GLP-1 receptor agonist +</td>
<td>high</td>
</tr>
<tr>
<td>insulin (basal) +</td>
<td>highest</td>
</tr>
<tr>
<td>or TZD</td>
<td></td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td></td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td></td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td></td>
</tr>
<tr>
<td>or insulin*</td>
<td></td>
</tr>
</tbody>
</table>

If AIC 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)*
### ADA 2017: Pharmacologic Therapy in T2DM

#### Dual Therapy

<table>
<thead>
<tr>
<th></th>
<th>Sulfonlurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 inhibitor</th>
<th>SGLT2 inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>gain</td>
<td>gain</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>hypoglycemia</td>
<td>edema, HF, fxs</td>
<td>rare</td>
<td>GU, dehydration, fxs</td>
<td>GI</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If AIC 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

<table>
<thead>
<tr>
<th></th>
<th>Sulfonlurea +</th>
<th>Thiazolidinedione +</th>
<th>DPP-4 inhibitor +</th>
<th>SGLT2 inhibitor +</th>
<th>GLP-1 receptor agonist +</th>
<th>Insulin (basal) +</th>
</tr>
</thead>
<tbody>
<tr>
<td>or</td>
<td>TZD</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>DPP-4-i or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGLT2-i or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1-RA or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin⁶ or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If AIC 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 otheroral 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)

**HbA1c ≥ 9%**

**Markedly symptomatic hyperglycemia,**

HbA1c ≥ 10%

BG ≥ 300 mg/dl,
Conclusion
Important Practical Points

- **Education:**
  - structured program, experienced educators
  - Discuss the fundamental principals in each visit

- Not only glucose centric (HTN, HLP)

- Management of DM patients must be individualized.

- Avoid combination therapy with drugs that have same pathophysiologic mechanism.
In the era of growing number of diabetes medications and new data, we should consider the below factors to select the proper component for each individual patient:

- Effectiveness
- Safety profiles
- Side effects
- Extra-glycemic effects
- Cardiovascular effects
- Our experience in handling
- Availability
- Patient preference
- Cost
Thanks for your attention