1. Pathophysiologically based therapeutic options in T2DM

2. ADA-EASD Statements

3. AACE & Other Guidelines

4. Considerations in Choosing Drugs

5. A Look to the Future
Multiple Complex Pathophysiological Abnormalities in T2DM

- Peripheral glucose uptake
- Hepatic glucose production
- Pancreatic insulin secretion
- Pancreatic glucagon secretion
- Gut carbohydrate delivery & absorption
- Incretin effect
- Renal glucose excretion
- Hepatic glucose production
- Peripheral glucose uptake

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
Multiple Pathophysiologically-Based Therapies for T2DM

GLP-1R agonists
DPP-4 inhibitors
Amylin mimetics
Insulin
Glinides
SUs
DA agonists
TZDs
Metformin
Bile acid sequestrants
SGLT-2 inhibitors

HYPERGLYCEMIA

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
2 + 2 + 2 + 1

- **GLP-1R agonists**
- **DPP-4 inhibitors**
- **Insulin**
- **SU s**
- **SGLT-2 inhibitors**
- **Metformin**
- **TZD s**

"incretin enhancers"

"insulin providers"

"insulin sensitizers"

"glucose excreter"
## Glucose Lowering Drugs Classes

<table>
<thead>
<tr>
<th>Classes</th>
<th>Generic Names</th>
<th>↓ A1c</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Degludec, Glargine, Detemir, NPH, Regular, Lispro, Aspart, Glulisine</td>
<td>No limit</td>
<td>Hypo, weight gain, injections</td>
</tr>
<tr>
<td>SU’s</td>
<td>Glyburide, Glipizide, Glimepiride</td>
<td>1-1.5%</td>
<td>Hypo, weight gain</td>
</tr>
<tr>
<td>Metformin</td>
<td>Metformin</td>
<td>1-1.5%</td>
<td>GI, lactic acidosis, B-12 deficiency</td>
</tr>
<tr>
<td>TZD’s</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>1-1.5%</td>
<td>Weight gain, edema, HF, bone fx’s, ?bladder ca</td>
</tr>
<tr>
<td>DPP-4 i’s</td>
<td>Sitagliptin, Saxagliptin, Alogliptin, Linagliptin</td>
<td>0.5-1%</td>
<td>Urticaria, ?pancreatitis</td>
</tr>
<tr>
<td>GLP-1 RA’s</td>
<td>Exenatide, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide</td>
<td>1-1.5%</td>
<td>GI, ?pancreatic disease, injections</td>
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<tr>
<td>SGLT2-i’s</td>
<td>Canagliflozin, Dapagliflozin, Empagliflozin</td>
<td>0.5-1%</td>
<td>Polyuria, GU infections, DKA, ?bone fx’s</td>
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<tr>
<td>Classes</td>
<td>Generic Names</td>
<td>↓ A1c</td>
<td>Costs</td>
</tr>
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</table>
Half-Century of HTN & T2DM Medications in U.S.

Type 2 DM Management Guidelines
Diabetes Mellitus (125)

Narrow: Diabetes Complications (38)
Diabetes Mellitus, Type 1 (21)
Diabetes Mellitus, Type 2 (42)

View all...
‘Guideline’ vs. ‘guideline’

“Clinical Practice Guidelines”

“statements that include recommendations intended to optimize patient care . . . informed by a systematic review of evidence and an assessment of the benefits and harms of care options.”

• multidisciplinary expert panel
• systematic review
• rate quality of evidence and strength of recommendations
• transparent process to minimize biases and COI’s
• consider patient subgroups and patient preferences
• discuss alternative care options
• revised when new information available

guideline

noun guide·line \ˈgīd-ˌlīn\ Definition: “a rule or instruction that shows or tells how something should be done”
1. Pathophysiologically based therapeutic options in T2DM

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5. A Look to the Future
American Diabetes Assoc (ADA) - European Assoc for the Study of Diabetes (EASD): 2006 Consensus Statement

Diagnosis → Lifestyle interventions + metformin

No → A1C ≥ 7%

Yes* →

Add basal insulin - most effective

No → A1C ≥ 7%

Yes* → Intensify insulin

No → A1C ≥ 7%

Yes* → Add glitazone†

No → A1C ≥ 7%

Yes* → Add sulfonylurea†

No → A1C ≥ 7%

Yes* →

Add basal insulin

Yes* → Add sulfonylurea†

No → A1C ≥ 7%

Yes* →

Add glitazone†

No → A1C ≥ 7%

Yes* →

Add basal or intensify insulin

Add intensive insulin + metformin ± glitazone

* Check A1C every 3 months until < 7% and then at least every 6 months.
† Although 3 oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.

At Diagnosis:
Lifestyle + Metformin

Tier 1: Well-validated therapies

Lifestyle + Metformin + Basal Insulin

Lifestyle + Metformin + Sulfonylurea\(^a\)

Lifestyle + Metformin + Pioglitazone

Lifestyle + Metformin + GLP-1 agonist\(^b\)

Tier 2: Less well-validated therapies

Lifestyle + Metformin + Pioglitazone + Sulfonylurea\(^a\)

Lifestyle + Metformin + Basal Insulin

STEP 1

STEP 2

STEP 3

Reinforce lifestyle changes at every visit and check A1C every 3 months until < 7.0%, then at least every 6 months thereafter. Change interventions whenever A1C ≥ 7.0%.

\(^a\)Sulfonylureas other than glibenclamide (glyburide) or chlorpropamide.
\(^b\)Insufficient clinical use to be confident regarding safety.

Nathan DM, et al. *Diabetes Care.* 2008;31:1
GLUCOSE-LOWERING THERAPY

• Glycemic targets
  - HbA1c < 7.0% (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - Individualization is key:
    - Tighter targets (6.0 - 6.5%) - younger, healthier
    - Looser targets (7.5 - 8.0%+) - older, comorbidities, hypoglycemia prone, etc.

• Pharmacological options
  - Individualize drug choice
  - Minimize adverse effects, especially hypoglycemia
  - Patient-centered care

PG = plasma glucose
Figure 1

Approach to management of hyperglycemia:

- **Patient attitude and expected treatment efforts**
  - more stringent: highly motivated, adherent, excellent self-care capacities
  - less stringent: less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hypoglycemia, other adverse events**
  - low
  - high

- **Disease duration**
  - newly diagnosed
  - long-standing

- **Life expectancy**
  - long
  - short

- **Important comorbidities**
  - absent
  - few / mild
  - severe

- **Established vascular complications**
  - absent
  - few / mild
  - severe

- **Resources, support system**
  - readily available
  - limited
Clinical Assessment of Individualized Glycemic Goals in T2DM: Formulation of an Algorithm Based on a Survey Among Leading Worldwide Diabetologists.

N=57 global diabetes experts

Cahn A et al. Diabetes Care 2015;38:2293–2300
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

*Diabetes Care* 2015;38:140–149 | DOI: 10.2337/dc14-2441

Silvio E. Inzucchi,¹ Richard M. Bergenstal,² John B. Buse,³ Michaela Diamant,⁴ Ele Ferrannini,⁵ Michael Nauck,⁶ Anne L. Peters,⁷ Apostolos Tsapas,⁸ Richard Wender,⁹,¹⁰ and David R. Matthews¹¹,¹²,¹³
PATIENT / DISEASE FEATURES

- Risks potentially associated with hypoglycemia and other drug adverse effects
- Disease duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient attitude and expected treatment efforts
- Resources and support system

Approach to the management of hyperglycemia

- more stringent
- HbA1c 7%
- less stringent

- low
- high
- newly diagnosed
- long-standing
- long
- short
- absent
- few / mild
- severe
- absent
- few / mild
- severe
- highly motivated, adherent, excellent self-care capacities
- less motivated, non-adherent, poor self-care capacities
- Readily available
- limited

Potentially modifiable

Usually not modifiable

Figure 1. Modulating intensive-ness of A1c lowering in T2DM
Healthy eating, weight control, increased physical activity & diabetes education

**Metformin**

<table>
<thead>
<tr>
<th>Efficacy'</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
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<tbody>
<tr>
<td>high</td>
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<td>neutral/loss</td>
<td>GI / lactic acidosis</td>
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If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

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Sulfonylurea + Thiazolidinedione + DPP-4 inhibitor + SGLT2 inhibitor + GLP-1 receptor agonist + Insulin (basal)

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<td>low</td>
</tr>
<tr>
<td>high</td>
<td>low risk</td>
<td>intermediate</td>
<td>loss</td>
<td>rare neutral</td>
</tr>
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2015 ADA-EASD Position Statement on Management of Hyperglycemia in T2DM

*†‡§*
**Healthy eating, weight control, increased physical activity & diabetes education**

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<td>or</td>
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</tr>
<tr>
<td>DPP-4-i</td>
<td>SU</td>
<td>TZD</td>
<td>SU</td>
<td>Insulin</td>
</tr>
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<td>or</td>
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<tr>
<td>GLP-1-Ra</td>
<td>or</td>
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<td>or</td>
</tr>
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<td>or</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

**Combination injectable therapy**

| Metformin + | Basal Insulin + | Mealtime Insulin | or | GLP-1-RA |

---

*Efficacy*, Hypo risk, Weight, Side effects, Costs

- **Mono-therapy**
  - HbA1c ≥9%
- **Dual therapy**
  - HbA1c ≥9%
- **Triple therapy**
  - Uncontrolled hyperglycemia (catabolic features, BG ≥300-350 mg/dl, HbA1c ≥10-12%)
- **Combination injectable therapy**

---

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
Anti-hyperglycemic therapy in T2DM: General recommendations

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
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<tr>
<td>Efficacy*</td>
<td>High</td>
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</tr>
<tr>
<td>Hypo Risk</td>
<td>Low risk</td>
<td></td>
</tr>
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<td></td>
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<tr>
<td>Costs*</td>
<td>Low</td>
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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):

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
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<tr>
<td>Sulfonylurea</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>Low Risk</td>
<td></td>
</tr>
<tr>
<td>SGLT2 Inhibitor</td>
<td>Low Risk</td>
<td></td>
</tr>
<tr>
<td>GLP-1 Inhibitor agonist</td>
<td>Low Risk</td>
<td></td>
</tr>
<tr>
<td>Insulin (basal)</td>
<td>Highest</td>
<td></td>
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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):

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<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
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<tbody>
<tr>
<td>Sulfonylurea +</td>
<td>High</td>
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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).
Figure 3. Approach to starting & adjusting insulin in T2DM

Basal Insulin (usually with metformin +/- other non-insulin agent)

- **Start:** 10U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine & address cause; ↓ dose by 4 units or 10-20%.

If not controlled after FBG target is reached (or if dose > 0.5 U/kg/day), treat PPG excursions with meal-time insulin. (Consider initial GLP-1-RA trial.)

Change to premixed insulin* twice daily

- **Start:** Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

Add 1 rapid insulin* injections before largest meal

- **Start:** 4U, 0.1 U/kg, or 10% basal dose. If A1c<8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

Add ≥2 rapid insulin* injections before meals ('basal-bolus')

- **Start:** 4U, 0.1 U/kg, or 10% basal dose/meal.‡ If A1c<8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly to achieve SMBG target.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.

If not controlled after FBG target is reached (or if dose > 0.5 U/kg/day), treat PPG excursions with meal-time insulin. (Consider initial GLP-1-RA trial.)
Combination injectable therapy for type 2 diabetes

Diabetes Care
2017;40:S67
1. Pathophysiologically based therapeutic options in T2DM

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GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

**Entry A1C < 7.5%**
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- **AGI**

**Entry A1C ≥ 7.5%**

**MONOTHERAPY**
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- **AGI or other 1st-line agent**

**DUAL THERAPY**
- **AGI**
- **Bromocriptine QFi**
- Coleselvam

**TRIPLE THERAPY**
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal insulin
- **AGI or other 2nd-line agent**

**Entry A1C > 9.0%**
- **SYMPTOMS**
  - **NO**
    - DUAL Therapy
  - **YES**
    - INSULIN ± Other Agents
    - **TRIPLE Therapy**

**ADD OR INTENSIFY INSULIN**
- Refer to Insulin Algorithm

**PROGRESSION OF DISEASE**

*Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation.*

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## DM GUIDELINES: ADA-EASD vs. AACE

<table>
<thead>
<tr>
<th>Focus</th>
<th>ADA-EASD</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glycemia</td>
<td>Comprehensive (CV risk, weight, preDM)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A1c target</th>
<th>ADA-EASD</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;7.0%</td>
<td>&lt;6.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>ADA-EASD</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>metformin</td>
<td>various</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>ADA-EASD</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>@ A1c 9.0%</td>
<td>@ A1c 7.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapeutic choices</th>
<th>ADA-EASD</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More narrow</td>
<td>More broad</td>
</tr>
</tbody>
</table>
Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone
  - metformin and an SU
  - metformin and an SGLT-2i
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone and an SU
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If standard-release metformin is not tolerated, consider a trial of modified-release metformin

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic for adults with type 2 diabetes who:
- have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups)
- have a BMI lower than 35 kg/m², and for whom insulin therapy would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
Oral Pharmacologic Treatment of T2DM: A Clinical Practice Guideline from the American College of Physicians

The American College of Physicians Guideline on Oral Medications for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target audience</td>
<td>Internists, family physicians, other clinicians</td>
</tr>
<tr>
<td>Target patient population</td>
<td>Adults with type 2 diabetes</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral pharmacologic treatment for hyperglycemia in type 2 diabetes</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular morbidity and mortality</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular morbidity</td>
<td></td>
</tr>
<tr>
<td>Neuropathy, nephropathy, retinopathy</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A₁c levels</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Plasma lipid levels</td>
<td></td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations

1. ...add orals when lifestyle (has) failed...
2. ...monotherapy with metformin...
3. ...add a second agent...

Clinical Considerations

- Good management of type 2 diabetes with pharmacologic and nonpharmacologic therapies is important and includes patient education, evaluation, and self-management, for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors.
- Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss.
- Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss and/or lifestyle modification fails.
- Metformin monotherapy was more effective in decreasing glycemic levels than other monotherapies, as well as in combination therapy with a second agent. In addition, metformin has the advantage of reducing body weight and improving plasma lipid profiles (in most cases).
- Although combination therapy more effectively reduces hemoglobin A₁c levels, it is also associated with more adverse events.

Oral Pharmacologic Treatment of T2DM: A Clinical Practice Guideline *Update* from the American College of Physicians

1. ...add orals when lifestyle (has) failed...

2. ...monotherapy with metformin...

3. ...add a second agent...

1. Pathophysiologically based therapeutic options in T2DM

2. ADA-EASD Statements

3. AACE & Other Guidelines

4. Considerations in Choosing Drugs

5. A Look to the Future
6 *P’s of Personalizing of Diabetes Care*

1. **Pathophysiology**
   - Insulin resistance vs. deficiency?
   - Stage of disease?

2. **Potency**
   - Distance from A1c target?

3. **Precautions**
   - Side effects, contraindications?
     (GI, renal, CV)

4. **Pluses**
   - Added benefits beyond glucose control?
     (weight, BP, CV events)

5. **Practicalities**
   - Pills vs. injections? Frequency?
   - Need for BG monitoring?

6. **Price**
   - Branded vs. generic?
   - Formulary coverage?
Costs of 30 Days of Diabetes Medications

- Metformin 1000mg QD: $4
- Glipizide 10mg BID
- Pioglitazone 45mg QD
- NPH 50U QD (vials)
- Sitagliptin 100mg QD
- Glargine 50U QD (pen)
- Canagliflozin 300mg QD
- Liraglutide 1.8mg QD

www.GoodRx.com/, accessed June 18, 2016, (lowest price for New Haven, CT 06510)
1. Pathophysiologically based therapeutic options in T2DM

2. ADA-EASD Statements

3. AACE & Other Guidelines

4. Considerations in Choosing Drugs

5. A Look to the Future
Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

“...sponsors should demonstrate that the therapy will not result in an unacceptable increase in CV risk.”

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2008
Clinical/Medical

Pre-marketing Analyses
Upper CL of 95% CI <1.8
For a HR=1.0 ➔ ≈122 events

Post-marketing Analyses
Upper CL of 95% CI <1.3
For a HR=1.0 ➔ ≈611 events

• Meta-analysis strategy using Phase 2/3 data
• Blinded central adjudication of CVD events
• Inclusion of high-risk subjects: advanced CVD, elderly, CKD
• Minimum exposure of 2 years in large CVOT
• Approximately 15,000 pt-yrs

Courtesy, Darren McGuire, UTSW Medical Ctr, 2015
# Large CV Outcomes Trials in Diabetes (Non-Insulin)

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP4-i</strong></td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>sulfonylurea</td>
<td>placebo</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>5,400</td>
<td>14,000</td>
<td>6,000</td>
<td>8,300</td>
<td></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2017</td>
<td>2017</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLP1-RA</strong></td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>16,500</td>
<td>14,000</td>
<td>6,000</td>
<td>5,400</td>
<td>8,300</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
<td>2019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>NCT01986881</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SGLT-2-i</strong></td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagli flozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>7300</td>
<td>4300</td>
<td>22,200</td>
<td>3900</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
</tbody>
</table>
# New Clinical Trial Data Influencing Treatment Decisions in T2DM

## 1. EMPA-REG Outcome

The SGLT2 inhibitor, empagliflozin, ↓’d 3-point MACE by 14%, driven by a 38% ↓ in CV death in 7020 T2DM patients with overt CVD. Also, 35% ↓ in HF hospitalization.

## 2. IRIS

The TZD, pioglitazone, ↓’d fatal/non-fatal stroke & MI by 24% (and 52% ↓ progression to DM) in 3895 insulin resistant patients with stroke or TIA. (Supports MACE results from 2005’s PROactive study.)

## 3. LEADER

The GLP-1 RA, liraglutide, ↓’d MACE by 13% in 9340 T2DM patients at high CVD risk. (22% ↓ CV death and 15% ↓ all-cause death.)

## 4. SUSTAIN 6

The weekly GLP-1 RA, semaglutide, ↓’d MACE by 26% in 3297 T2DM patients at high CVD risk. (↓ 61% stroke)

**Healthy eating, weight control, increased physical activity & diabetes education**

### Metformin

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low risk</td>
<td>neutral/loss</td>
<td>GI / lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<th>2-Drug Combination</th>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Metformin</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>neutral/loss</td>
<td>low</td>
</tr>
<tr>
<td>Metformin + Sulfonylurea</td>
<td>high/high</td>
<td>high/moderate</td>
<td>low/gain</td>
<td>hypoglycemia</td>
<td>low/low</td>
</tr>
<tr>
<td>Metformin + DPP-4 inhibitor</td>
<td>intermediate</td>
<td>low</td>
<td>neutral</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Metformin + SGLT2 inhibitor</td>
<td>intermediate</td>
<td>low</td>
<td>neutral</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Metformin + GLP-1 receptor agonist</td>
<td>high</td>
<td>high risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<th>3-Drug Combination</th>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Metformin + Sulfonylurea</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>neutral/loss</td>
<td>low</td>
</tr>
<tr>
<td>Metformin + Metformin + Thiazolidinedione</td>
<td>high</td>
<td>high</td>
<td>low</td>
<td>neutral/loss</td>
<td>low</td>
</tr>
<tr>
<td>Metformin + Metformin + DPP-4 inhibitor</td>
<td>intermediate</td>
<td>low</td>
<td>neutral</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Metformin + Metformin + SGLT2 inhibitor</td>
<td>intermediate</td>
<td>low</td>
<td>neutral</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Metformin + Metformin + GLP-1 receptor agonist</td>
<td>high</td>
<td>high risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:

<table>
<thead>
<tr>
<th>Triple Therapy</th>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Metformin + Insulin (basal)</td>
<td>highest</td>
<td>high</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
<tr>
<td>Metformin + Metformin + DPP-4-i</td>
<td>or</td>
<td>high</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
<tr>
<td>Metformin + Metformin + SGLT2-i</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2015 ADA-EASD Position Statement on Management of Hyperglycemia in T2DM

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
At diagnosis of type 2 diabetes
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

- **A1C <8.5%**
  - If not at glycemic target (2-3 mos)
    - Start/Increase metformin
- **A1C ≥8.5%**
  - Start metformin immediately
    - Consider initial combination with another antihyperglycemic agent
    - If not at glycemic targets
- **Symptomatic hyperglycemia with metabolic decompensation**
  - Initiate insulin +/- metformin

Add another agent best suited to the individual by prioritizing patient characteristics:

<table>
<thead>
<tr>
<th>PATIENT CHARACTERISTIC</th>
<th>CHOICE OF AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Priority: Clinical Cardiovascular Disease</strong></td>
<td>SGLT2 inhibitor with demonstrated CV outcome benefit</td>
</tr>
<tr>
<td>Degree of hyperglycemia</td>
<td>Consider relative A1C lowering</td>
</tr>
<tr>
<td>Risk of hypoglycemia</td>
<td>Rare hypoglycemia</td>
</tr>
<tr>
<td>Overweight or obesity</td>
<td>Weight loss or weight neutral</td>
</tr>
<tr>
<td>Cardiovascular disease or multiple risk factors</td>
<td>Effect on cardiovascular outcome</td>
</tr>
<tr>
<td>Comorbidities (renal, CHF, hepatic)</td>
<td>See therapeutic considerations, consider eGFR</td>
</tr>
<tr>
<td>Preferences &amp; access to treatment</td>
<td>See cost column; consider access</td>
</tr>
</tbody>
</table>
Screening
T2DM on metformin alone
HbA1c $>6.8\%$ at screening
< 10 years duration at randomization

Metformin run-in
Titrate metformin to 1000 (min) – 2000 (goal) mg/day

HbA1c 6.8-8.5% at final run-in visit

Randomization
n=5000 eligible subjects

- Sulfonylurea (glimepiride) n=1250
- DPP-IV inhibitor (sitagliptin) n=1250
- GLP-1 analog (liraglutide) n=1250
- Insulin (glargine) n=1250

https://portal.bsc.gwu.edu/web/grade
GUIDELINES FOR DIABETES MANAGEMENT

1. Increasing T2DM prevalence & complexity of therapeutic options have led to the need for treatment “guidelines.”

2. These tend not to be based on high-quality evidence but instead on expert opinion and/or cost concerns.

3. Most begin quite similarly (“Lifestyle...then metformin...”), but differ to varying degrees on what to do next.

4. Emerging data from recent CVOT trials should lead to some modifications in guidelines - particularly in those patients with overt CVD.

5. There will also always be a need for the wise and skilled physician to choose the optimal therapeutic regimen for (and with) each patient.