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New ADA-EASD Guidelines: The Patient Centered Approach to Therapy in Type 2 Diabetes

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Hypertension & Diabetes: Drug Classes* in the U.S. over the Past Half-Century

The Complex Pathogenesis of T2DM

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
2008 ADA / EASD Consensus Algorithm

**STEP 1**

At Diagnosis: Lifestyle + Metformin

**STEP 2**

Tier 1: Well-validated therapies

- Lifestyle + Metformin
- Lifestyle + Metformin + Sulfonylurea
- Lifestyle + Metformin + Basal Insulin
- Lifestyle + Metformin + Intensive Insulin
- Lifestyle + Metformin + Pioglitazone
- Lifestyle + Metformin + GLP-1 agonist

**STEP 3**

Tier 2: Less well-validated therapies

- Lifestyle + Metformin + Sulfonylurea
- Lifestyle + Metformin + Basal Insulin
- Lifestyle + Metformin + Pioglitazone
- Lifestyle + Metformin + GLP-1 agonist

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.

Reasons for a New Guideline

1. Increasing number & variety of anti-hyperglycemic agents.
2. New data re: benefits vs. risks of tight glycemic control.
3. Increasing concerns about drug safety.
4. Increasing discourse about personalized medicine and 'patient-centered' care.
5. Prior guidelines were consensus documents – not official 'position statements.' ADA & EASD requested that a more formal process be followed - leading to review / endorsement by their respective Professional Practice & Executive Committees.

Management of Hyperglycemia 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)
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>▼</td>
<td></td>
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<tr>
<td>DCCT/EDIC*</td>
<td>▼</td>
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<td>ADVANCE</td>
<td>▼</td>
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<td>VADT</td>
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* in T2DM

Survival as a Function of HbA1c in T2DM after Treatment Intensification: Insights from UK’s GPRD

- Age>50
- During 1986-2008

ANTI-HYPERGLYCEMIC 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.
  > Avoidance of hypoglycemia

PG = plasma glucose
Figure 1

**Glycemic Control Efforts**

- **Patient attitude & expected treatment efforts**
  - Highly motivated, adherent, excellent self-care capacities
  - Less motivated, non-adherent, poor self-care capacities

- **Risks potentially associated with hyperglycemia, other adverse events**
  - Low
  - High

- **Disease duration**
  - Brief
  - Long-standing
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options:
  - **Oral agents & non-insulin injectables**
    - Metformin
    - Sulfonylureas
    - Thiazolidinediones
    - DPP-4 Inhibitors
    - GLP-1 receptor agonists
    - Meglitinides
    - α-glucosidase inhibitors
    - Bile acid sequestrants
    - Dopamine-2 agonists
    - Amylin mimetics
### Table 1. Properties of anti-hyperglycemic agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (Metformin)</td>
<td>• Activates AMP-kinase, ↓ Hepatic glucose production</td>
<td>• Extensive experience</td>
<td>• Gastrintestinalal experience</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No hypoglycemia</td>
<td>• B-12 deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weight neutral</td>
<td>• Contraindications</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↑↑ ↑↑ CVD events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUs / Meglitinitides</td>
<td>• Activates PPAR-γ, ↓ insulin secretion</td>
<td>• No hypoglycemia</td>
<td>• Hypoglycemia</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Durability</td>
<td>• Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↑↑ ↑↑ TG, ↑ HDL-C</td>
<td>• Low durability</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ CVD events (pio)</td>
<td>• ↑↑ ↑↑ Ischemic preconditioning</td>
<td></td>
</tr>
<tr>
<td>TZDs</td>
<td></td>
<td>• Activates PPAR-γ, ↑ satiety</td>
<td>• Weight gain, ↑ HDL-C</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No hypoglycemia</td>
<td>• Edema / heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ TG, ↓ HDL-C</td>
<td>• Bone fractures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ CVD events (pio)</td>
<td>• ↓ MI (rou)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Bladder ca (pio)</td>
<td></td>
<td></td>
</tr>
</tbody>
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<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 Inhibitors</td>
<td>• Inhibits DPP-4, ↑ increases GLP-1, GIP</td>
<td>• No hypoglycemia</td>
<td>• Modest ↑ A1c</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Well tolerated</td>
<td>• ↑ Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>• Activates GLP-1 receptor, ↓ Insulin, ↓ glucagon</td>
<td>• Weight loss</td>
<td>• GI</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ No hypoglycemia</td>
<td>• ↑ Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Gastric emptying</td>
<td>• Medullary ca (pio)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ ↑ satiety</td>
<td>• Injectable</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>• Activates insulin receptor, ↓ Glucose disposal</td>
<td>• Universally effective</td>
<td>• Hypoglycemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Hepatic glucose production</td>
<td>• Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Microvascular risk</td>
<td>• ↑ ↑ ↑ ↑ Mitogenicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Injectable</td>
<td>• Training requirements</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &quot;Stigma&quot;</td>
<td>• &quot;Stigma&quot;</td>
<td></td>
</tr>
</tbody>
</table>

### ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

**ANTI-HYPERGLYCEMIC THERAPY**

- **Therapeutic options: Insulin**
  - Human Neutral protamine Hagedorn (NPH)
  - Human Regular
  - Basal analogues (glargine, detemir)
  - Rapid analogues (lispro, aspart, glulisine)
  - Pre-mixed varieties
### AHRQ: Comparative Effectiveness & Safety of T2DM Medications: EFFICACY

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Drug 1 vs. Drug 2</th>
<th>Studies (N)</th>
<th>Mean Difference (95% CI)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met vs. Pi</td>
<td>3 (386)</td>
<td>0.7</td>
<td>0.67 (-0.17 to 0.30)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Met vs. SU</td>
<td>53 (406)</td>
<td>1.2</td>
<td>0.77 (0.13 to 0.45)</td>
<td>High</td>
</tr>
<tr>
<td>Met vs. Mig</td>
<td>7 (345)</td>
<td>-0.2</td>
<td>0.67 (0.05 to 0.28)</td>
<td>High</td>
</tr>
<tr>
<td>Met vs. TZD</td>
<td>16 (385)</td>
<td>-1</td>
<td>0.67 (0.08 to 0.18)</td>
<td>Moderate</td>
</tr>
<tr>
<td>TZD vs. SU</td>
<td>53 (406)</td>
<td>0.0</td>
<td>0.67 (0.02 to 0.10)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Met vs. Met + SU</td>
<td>3 (106)</td>
<td>1.3</td>
<td>0.67 (0.28 to 0.86)</td>
<td>Low</td>
</tr>
<tr>
<td>Met vs. Met + SU</td>
<td>6 (275)</td>
<td>-0.0</td>
<td>0.66 (0.38 to 0.94)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Met + SU vs. TZD</td>
<td>9 (104)</td>
<td>-1.1</td>
<td>0.66 (1.98 to 0.08)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Favors Drug 1: Favor Drug 2

Pooled Between-Group Difference in 140 head-to-head trials + 26 observational studies

### AHRQ: Comparative Effectiveness & Safety of T2DM Medications: WEIGHT

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Drug 1 vs. Drug 2</th>
<th>Studies (N)</th>
<th>Mean Difference (95% CI)</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU vs. GLP-1</td>
<td>13 (1310)</td>
<td>-0.7</td>
<td>-0.7 (-0.54 to -0.20)</td>
<td>Moderate</td>
</tr>
<tr>
<td>TZD vs. SU</td>
<td>5 (385)</td>
<td>1.9</td>
<td>1.9 (0.60 to 1.9)</td>
<td>Low</td>
</tr>
<tr>
<td>SU vs. Mig</td>
<td>6 (183)</td>
<td>-0.1</td>
<td>0.6 (-0.01 to 1.8)</td>
<td>High</td>
</tr>
<tr>
<td>Met vs. Pi</td>
<td>3 (106)</td>
<td>-0.3</td>
<td>0.6 (-0.90 to 0.39)</td>
<td>Low</td>
</tr>
<tr>
<td>Met vs. TZD</td>
<td>11 (406)</td>
<td>-0.9</td>
<td>0.6 (-0.18 to 0.31)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Met vs. SU</td>
<td>3 (345)</td>
<td>-1.1</td>
<td>0.6 (-0.24 to 0.68)</td>
<td>Low</td>
</tr>
<tr>
<td>Met vs. Met + SU</td>
<td>6 (275)</td>
<td>-0.9</td>
<td>0.6 (-0.17 to 0.96)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Met vs. Met + SU</td>
<td>5 (104)</td>
<td>-1.1</td>
<td>0.6 (-0.19 to 0.81)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Favors Drug 1: Favor Drug 2

Pooled Between-Group Difference in Weight, kg

### AHRQ: Comparative Effectiveness & Safety of T2DM Medications: HYPOGLYCEMIA

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Drug 1 vs. Drug 2</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met vs. Pi</td>
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<td>Moderate</td>
</tr>
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<td>5 (385)</td>
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</tr>
<tr>
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<td>3 (345)</td>
<td>Low</td>
</tr>
<tr>
<td>Met vs. Met + SU</td>
<td>6 (275)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Met vs. Met + SU</td>
<td>5 (104)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

• Most medications decreased A1c level by ≥1%.

• Evidence supports metformin as a first-line agent...

• Most 2-drug combinations similarly reduce A1c levels, but some increased risk for hypoglycemia and other adverse events.

• Evidence on long-term clinical outcomes (e.g., mortality, CV disease, nephropathy, and neuropathy) was...insufficient.

Favors Drug Z: Favor Drug Z

Pooled Odds Ratio (95% CI) for Mild-Moderate Hypoglycemia
4. OTHER CONSIDERATIONS

• Age: Older adults
  - Reduced life expectancy
  - Higher CVD burden
  - Reduced GFR
  - At risk for adverse events from polypharmacy
  - More likely to be compromised from hypoglycemia

  ✓ Less ambitious targets
  ✓ HbA1c <7.5–8.0% if tighter targets not easily achieved
  ✓ Focus on drug safety

4. OTHER CONSIDERATIONS

• Weight
  - Majority of T2DM patients overweight/obese
  - Intensive lifestyle program
  - Metformin
  - GLP-1 receptor agonists
  - ? Bariatric surgery
  - Consider LADA in lean patients
4. OTHER CONSIDERATIONS

- Sex/ethnic/racial/genetic differences
  - Little is known!
  - MODY & other monogenic forms of diabetes
  - Latinos: more insulin resistance
  - East Asians: more beta cell dysfunction
  - Gender may drive concerns about adverse effects (e.g., bone loss from TZDs)

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia
  - Metformin: May use unless condition is unstable or severe

- Avoid TZDs
- Pioglitazone & ↓↓ ↓↓ CVD events
- Effects of incretin therapies
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

4. OTHER CONSIDERATIONS

- Comorbidities
  - Coronary Disease
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - Hypoglycemia

Increased risk of hypoglycemia
- Metformin & lactic acidosis
  - US: stop if SCR ≥ 1.5 (1.4 women)
  - UK: half-dose if GFR < 45 & stop if GFR < 30
- Caution with SUs (esp. glyburide)
- DPP-4 i's – dose adjust for most
- Avoid exenatide if GFR < 30

Most drugs not tested in advanced liver disease
- Pioglitazone may help steatosis
- Insulin best option if disease severe

Emerging concerns regarding association with increased morbidity/mortality
- Proper drug selection is key in the hypoglycemia prone
Since We Can’t Yet use Patient *Genotype*, We Often Use Patient *Phenotype* to Personalize Therapy

**MEDICATION CHOICE**

### What Phenotypic Features Might Guide Optimal Drug Selection?

<table>
<thead>
<tr>
<th>Patient Features</th>
<th>Disease Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Stage of disease</td>
</tr>
<tr>
<td>Race / ethnicity / sex</td>
<td>Degree of hyperglycemia</td>
</tr>
<tr>
<td>Body weight</td>
<td>Fasting vs. postprandial hyperglycemia</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Insulin deficiency vs. insulin resistance</td>
</tr>
<tr>
<td>Anticipated propensity for or tolerance of side effects</td>
<td>Special circumstances: MODY, LADA, pancreatic</td>
</tr>
<tr>
<td>‘Psycho-social-economic’ context of the patient</td>
<td></td>
</tr>
</tbody>
</table>
Examples:
- "A glitazone will be highly effective in this patient because he appears to be very insulin resistant."
- "Exenatide is a good option here because of large PPG spikes."
- "Insulin is the only alternative due to her severe degree of hyperglycemia."
- "I just need to drop A1c by about 0.7% ... a glibtin would be a perfect choice!"

Examples:
- "I will use a GLP-1 receptor agonist; she has so much weight to lose."
- "That LDL is stubborn! Colesevelam might be a great choice for him."
- "He has CAD (but good LV function); let's try some pio."
- "Chronic constipation? I have just the fix for you!"
Anticipation of Drug Efficacy

Concerns of Adverse Effects

Desire for Added Benefits

MEDICATION CHOICE

Examples:
• “Her bowels are always loose; I will have to avoid metformin.”
• “She had a hypoglycemic event a few years ago when her husband was alive. He’s passed on and she now lives alone - let’s avoid SUs.”
• “A recent echo shows severe diastolic dysfunction; even though he is without symptoms, I don’t feel comfortable using a TZD.”
• “He already has gastroparesis; a GLP-1 agonist is a horrible choice for him!”

Patient Phenotype...Personalized Treatment?

GEDICATION CHOICE

MEDICATION CHOICE

MEDICATION CHOICE

...But What to Do in the Complex Patient?

Example:
68 y/o MH w/ T2DM x14 yrs on metformin / glimepiride. CAD, OSA, prostate ca, 7 h/o pancreatitis 6 yrs ago. He smokes and his brother has carcinoma of the bladder. Exam: BMI 41.3, 2+ edema, but no heart failure. FBG 150-170mg/dl (8-10mmol/L), HbA1c 9.8%, eGFR 44; LVEF 52%, TG 358, HDL 31, on atorvastatin 40 mg.

What are his options at this stage of disease? Target? Strategies?

ADA-EASD Position Statement:
Management of Hyperglycemia in T2DM

KEY POINTS
• Glycemic targets & BG-lowering therapies must be individualized.
• Diet, exercise, & education: foundation of any T2DM therapy program
• Unless contraindicated, metformin = optimal 1st-line drug.
• After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable; minimize side effects.
• Ultimately, many patients will require insulin therapy alone / in combination with other agents to maintain BG control.
• All treatment decisions should be made in conjunction with the patient (focus on preferences, needs & values.)
• Comprehensive CV risk reduction, a major focus of therapy.

Diabetes Care 2012;35:1364–1379
Diabetologia 2012;55:1577–1596
For Discussion....

- How often should such guidelines be rewritten?
- What key data will be needed to inform future guidelines?
- What impact will the large incretin/CVD trials (if positive) have on future guidelines?
- Where will emerging drugs fit in (e.g. SGLT-2 inhibitors)?
- Where does bariatric surgery fit in?
- Where do anti-obesity drugs fit in?

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

- Screening
  - T2DM on metformin alone
  - HbA1c ≥ 7% at screening
  - < 5 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