Treatment Guidelines for Type 2 Diabetes and the Role of New Agents

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Maryland Endocrine and Diabetes
Learning Objectives

1. Identify the current diagnostic criteria for diabetes.
2. Describe the current American Diabetes Association’s recommendations on treatment of type 2 diabetes.
3. List the contraindications and major side effects of the 6 major classes of non-insulin anti-diabetic agents.
DISCLOSURES

• Medical Device Companies
  – Dexcom: consulting, promotional talks, and educational grants
  – Animas: advisory board, consulting, educational grants, promotional programs
  – OmniPod: speakers bureau

• Pharma Speakers Bureau’s
  – Novo Nordisk, Lilly Diabetes, Janssen, Boehringer-Ingelheim

• Pharmaceutical Advisory Boards
  – Lilly Diabetes, Janssen
TYPE 2 DIABETES: DIAGNOSIS
Classification of Diabetes

• **Type 1 diabetes** - needs to be considered at all ages
  - β-cell destruction slower in adult onset type 1’s (LADA)
    - consider GAD-65 Ab’s at diagnosis, fasting C-peptide levels

• **Type 2 diabetes** - 90-95% of adults
  - Progressive loss of insulin secretion is the key defect
  - Insulin resistance central, also reduced GLP-1 effect, excess glucagon, abnormal kidney glucoregulation, neuroregulatory defects

• **Other specific types of diabetes**
  - Genetic defects in β-cell function or insulin action: Monogenic diabetes (aka MODY) – early presentation, non progressive
  - Diseases of the exocrine pancreas (pancreatic diabetes) – think of as a type 1 (insulin deficiency)

• **Gestational diabetes mellitus** (GDM)

• **Pre- diabetes**
Diabetes Diagnostic Criteria

A1c ≥6.5%

OR

Fasting plasma glucose ≥126 mg/dL

OR

2-h plasma glucose ≥200 mg/dL during a 75-g GTT

OR

A random plasma glucose ≥200 mg/dL with symptoms

ADA. Classification and Diagnosis. Diabetes Care 2015;38(suppl 1):S9; Table 2.1
Categories of Increased Risk (Prediabetes)*

Fasting plasma glucose 100–125 mg/dL: Impaired Fasting Glucose

OR

2-h plasma glucose in the 75-g OGTT 140–199 mg/dL: Impaired Glucose Tolerance

OR

A1C 5.7–6.4%

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

ADA. Classification and Diagnosis. Diabetes Care 2015;38(suppl 1):S10; Table 2.3
TYPE 2 DIABETES: PHYSIOLOGY AND NATURAL HISTORY
Pathophysiology of Hyperglycemia in T2D: The Ominous Octet
(Defonzo, Diabetes, April 2009 vol. 58 no. 4, 773-795)

Key organs affected by insulin resistance:

- Decreased insulin secretion
- Increased lipolysis
- Increased glucagon secretion
- Increased hepatic glucose production
- Decreased glucose uptake

Neurotransmitter dysfunction

Key organs affected by insulin resistance:
Progressive Nature of Type 2 Diabetes

Adapted from International Diabetes Center, Minneapolis, Minnesota

End stage type 2 = little insulin
DIABETES
LONG TERM
COMPLICATION PREVENTION
### 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>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC (T1D)</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

CVD and Type 2 Diabetes

- CVD: major cause of mortality for those with diabetes
- Common conditions coexisting with type 2 diabetes are clear risk factors:
  - HBP, dyslipidemia, insulin resistance, obesity
- Diabetes itself confers independent risk
  - But hyperglycemia per se is not a strong risk factor
- Benefits observed with aggressive risk factor reduction:
  - Cholesterol treatment with a statin if over 40, or if under 40 with known CAD or high risk
  - Blood pressure treatment to <140/90 (ADA) or <130/80 (AACE)
    - ADA: <130/80 if younger and can be done without undue side effects
    - AACE: <130/80 in all unless advanced age or excessive Rx burden
  - Smoking cessation
The real reason dinosaurs became extinct...
SETTING APPROPRIATE GOALS IN TYPE 2 DIABETES: EMPHASIS ON INDIVIDUALIZATION IS KEY
ADA Approach to the Management of Hyperglycemia

- **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

- **More Stringent**
- **A1C 7%**
- **Less Stringent**

- **Usually not modifiable**
- **Potentially modifiable**

ADA Glycemic Targets. Diabetes Care 2015;38(suppl 1):S37. Figure 6.1; adapted with permission from Inzucchi SE, et al. Diabetes Care, 2015;38:140-149
ADA Glycemic Recommendations for Nonpregnant Adults with Diabetes

**A1C**

<7.0%*  
(AACE 6.5% or lower)

Preprandial capillary plasma glucose

80–130 mg/dL*  
(AACE <110 mg/dL)

Peak postprandial capillary plasma glucose†

<180 mg/dL*  
(AACE < 140 mg/dL)

*Goals should be individualized.
†Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.
Mean Glucose Levels for Specified A1C

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

These estimates are based on ADAG (A1c Derived Average Glucose) data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92. A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dL or mmol/L, is available at http://professional.diabetes.org/eAG.

ADA Glycemic Targets. Diabetes Care. 2015;38(suppl 1):S35; Table 6.1
Lifestyle and diet matters...
Metformin, if not contraindicated and if tolerated, is the preferred initial agent for type 2 diabetes **at the time of diagnosis**

- AACE rates desirability of alternates, in order: GLP-1 RA, SGLT-2i, DPP-4i, TZD, AGi, SU/GLN

In patients with newly diagnosed type 2 diabetes who are symptomatic or with markedly elevated blood glucose levels or A1C, insulin therapy (with or without additional agents) is the initial Rx of choice.

Combinations should be with agents with different and/or complementary mechanisms

- AACE guidelines emphasize initial combinations if well above goal
Oral agents & non-insulin injectables

- Metformin
- Sulfonylureas/meglitinides
- Thiazolidinediones
- DPP-4 inhibitors
- GLP-1 receptor agonists
- SGLT-2 inhibitors
- $\alpha$-glucosidase inhibitors
- Bile acid sequestrants
- Dopamine-2 agonists
- Amylin mimetics
### ADA-EASD Antihyperglycemic Rx in Type 2 Diabetes

**Monotherapy**
- **Efficacy**
- **Hypoglycemia risk**
- **Weight change**
- **Side effects**
- **Costs**

**Dual therapy**
- **Efficacy**
- **Hypoglycemia risk**
- **Weight change**
- **Side effects**
- **Costs**

**Triple therapy**
- **Combination injectable therapy**

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

### Metformin
- **Efficacy** high
- **Hypoglycemia risk** low
- **Weight change** neutral/loss
- **GI/lactic acidosis risk** low

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

<table>
<thead>
<tr>
<th>Metformin</th>
<th>+</th>
<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>high</td>
<td></td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td></td>
<td>low 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>gain</td>
<td></td>
<td>gain</td>
<td>edema, HF, fxs</td>
<td>neutral</td>
<td>low risk</td>
<td>loss</td>
<td>gain</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td></td>
<td>low</td>
<td>high</td>
<td>rare</td>
<td>high</td>
<td>GU, dehydration</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>low</td>
<td></td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>variable</td>
<td>variable</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Metformin</th>
<th>+</th>
<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>high</td>
<td></td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td></td>
<td>low 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>gain</td>
<td></td>
<td>gain</td>
<td>edema, HF, fxs</td>
<td>neutral</td>
<td>low risk</td>
<td>loss</td>
<td>gain</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td></td>
<td>low</td>
<td>high</td>
<td>rare</td>
<td>high</td>
<td>GU, dehydration</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>low</td>
<td></td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>variable</td>
<td>variable</td>
</tr>
</tbody>
</table>

**If A1C target not achieved after ~3 months of triple therapy and patient (1) on one 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>Metformin</th>
<th>+</th>
<th>Basal insulin</th>
<th>Mealtime insulin</th>
<th>GLP-1-RA</th>
</tr>
</thead>
</table>

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ADA. Approaches to Glycemic Treatment. Diabetes Care 2015;38(suppl 1):S43. Figure 7.1; adapted with permission from Inzucchi SE, et al. Diabetes Care, 2015;38:140-149
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGI
- SU/GLN

Monotherapy

Entry A1C ≥ 7.5%
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AGI
- SU/GLN

Dual Therapy

Entry A1C > 9.0%
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AGI
- SU/GLN

Triple Therapy

If not at goal in 3 months proceed to Dual Therapy
If not at goal in 3 months proceed to Triple Therapy
If not at goal in 3 months proceed to or intensify insulin therapy

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND

- Few adverse events and/or possible benefits
- Use with caution

PROGRESSION OF DISEASE
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<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| Biguanides: metformin | ↓Hepatic glucose production ↑GLP-1?? | • Extensive experience  
• No hypoglycemia  
• Weight neutral  
• ? ↓ CVD | • Gastrointestinal-diarrhea common, onset may be delayed  
• Lactic acidosis-*rare*  
• B-12 deficiency-not uncommon  
• Contraindications: eGFR <30-40 | Low   |

**Keys:** good place to start and in combination, cheap, but not sufficient as monotherapy for long; OK if GFR > 40, limit dose 30-40, stop < 30; be aware of delayed diarrhea, watch vit B 12.
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors</td>
<td>• Inhibits DPP-4</td>
<td>• No hypoglycemia</td>
<td>• Modest ↓ A1c</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• Increases GLP-1, GIP</td>
<td>• Well tolerated</td>
<td>• ?? Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral once daily</td>
<td>• Urticaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Weight neutral</td>
<td>• Arthralgias (recent reports)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Keys:</strong> generally well tolerated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>to start but not highly potent;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>pancreatitis rare in cardiac safety studies</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 receptor agonists:

• Activates GLP-1 Receptor
• ↑ Insulin, ↓ glucagon
• ↓ gastric emptying
• ↑ satiety
• Potent A1c reduction
• Weight loss
• No hypoglycemia
• ? Beta cell mass

GI side effects
• ? Beta cell mass
• Medullary ca

SGLT-2 inhibitors:

• Partial inhibition of proximal tubule glucose resorption
• Secondary increase in glucagon
• No hypoglycemia
• Weight loss
• Lower SBP by 3-5 mmHg
• Independent of insulin sensitivity
• Moderate potency
• Dec CV death in sec prevention (empa)
• GMI's, UTI's
• Orthostasis possible, esp older
• Requires eGFR >45 (or 60 dapa.)
• euglycemic DKA
• ?inc toe amputation (Cana)
<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| Amylin mimetics      | • Activates amylin receptor  
|                      |  • ↓ glucagon  
|                      |  • ↓ gastric emptying  
|                      |  • ↑ satiety                                                   | • Weight loss  
|                      |  • ↓ PPG                                                      | • GI  
|                      |  • Modest ↓ A1c  
|                      |  • Injectable  
|                      |  • Hypo w/ insulin  
|                      |  • Dosing TID                                                 | High |
| Bile acid sequestrants | • Bind bile acids  
|                      |  • ↓ Hepatic glucose production                                    | • No hypoglycemia  
|                      |  • Nonsystemic  
|                      |  • ↓ Post-prandial glucose  
|                      |  • ↓ CVD events                                                 | • GI  
|                      |  • Modest ↓ A1c  
|                      |  • Dosing frequency                                             | High |
| Dopamine-2 agonists  | • Activates DA receptor  
|                      |  • Modulates hypothalamic control of metabolism  
|                      |  • ↑ insulin sensitivity                                         | • No hypoglycemia  
|                      |  • ? ↓ CVD events                                              | • Modest ↓ A1c  
|                      |  • Dizziness/syncope  
|                      |  • Nausea  
|                      |  • Fatigue                                                    | High |
| α-GIs                | • Inhibits α–glucosidase  
|                      |  • Slows carbohydrate absorption                                  | • No hypoglycemia  
|                      |  • Nonsystemic  
|                      |  • ↓ Post-prandial glucose  
|                      |  • ? ↓ CVD events                                              | • Gastrointestinal  
|                      |  • Dosing frequency                                            | • Modest ↓ A1c  
|                      |  • Modest ↓ A1c  
|                      |  • Dosing frequency                                            | Mod. |
**Insulin Pharmacokinetics (ADA)**

- **Note:** AACE recommends preferential use of insulin analogues due to more physiologic profiles.
ADA Sequential Insulin Strategies in T2DM

*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]*
“Give it to me straight, Doc. How long do I have to ignore your advice?”
• Good control reduces microvascular complications, but glycemic targets & therapies must be individualized.

• **Diet, exercise, & education**: foundation of any T2D therapy program

• Unless contraindicated, **metformin** usually a good 1st drug, but not effective as monotherapy long term.

• **Combination therapy** with adding 1-2 other oral / injectable agents is reasonable and usually necessary; minimize side effects, especially hypoglycemia.

• Ultimately, many patients will require **insulin** therapy, best given along with insulin sparing agents.

• Comprehensive **CV risk reduction** is crucial
Questions?
Supplementary slides

More on AACE Guidelines and CV risk reduction trials in T2D
**INDIVIDUALIZE GOALS**

**A1C ≤ 6.5%**
For patients without concurrent serious illness and at low hypoglycemic risk

**A1C > 6.5%**
For patients with concurrent serious illness and at risk for hypoglycemia
### Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPO</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral/Severe</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
<td></td>
</tr>
<tr>
<td><strong>RENAL/GU</strong></td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Not Effective with eGFR &lt; 45</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<td></td>
</tr>
<tr>
<td><strong>ASCVD</strong></td>
<td>Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Safe</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
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<tr>
<td><strong>BONE</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
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<td>Neutral</td>
<td>Neutral</td>
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</tr>
</tbody>
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**Legend:**
- Green: Few adverse events or possible benefits
- Yellow: Use with caution
- Orange: Likelihood of adverse effects
- ?: Uncertain effect

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**ASCVD RISK FACTOR MODIFICATIONS ALGORITHM**

**DYSLIPIDEMIA**

**LIFESTYLE THERAPY** (Including Medically Assisted Weight Loss)

**LIPID PANEL: Assess ASCVD Risk**

**STATIN THERAPY**
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C-lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapiest to attain goals according to risk levels

**RISK LEVELS**

**HIGH**
- DM but no other major risk and/or age <40

**VERY HIGH**
- DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking) or ASCVD*

<table>
<thead>
<tr>
<th><strong>DESI RABLE LEVELS</strong></th>
<th><strong>DESIRABLE LEVELS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
</tr>
<tr>
<td>LDL-P (nmol/L)</td>
<td>&lt;1200</td>
</tr>
</tbody>
</table>

**IF NOT AT DESIRABLE LEVELS:**

Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

**TO LOWER LDL-C:**
- Intensify statin, add ezetimibe, PCSK9i, colesve lamin, or niacin

**TO LOWER Non-HDL-C, TG:**
- Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin

**TO LOWER Apo B, LDL-P:**
- Intensify statin and/or add ezetimibe, PCSK9i, colesve lamin, and/or niacin

**TO LOWER LDL-C in FH:**
- Statin + PCSK9i

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED ** FAMILIAL HYPERCHOLESTEROLEMIA

**HYPERTENSION**

**GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg**

**ACEi or ARB**

For initial blood pressure >150/100 mm Hg:

**DUAL THERAPY**

ACEi or ARB + Calcium Channel Blocker

β-blocker

Thiazide

If not at goal (2–3 months)

Add calcium channel blocker, β-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

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Algorithm for Adding/Intensifying Insulin

**Start Basal** (Long-Acting Insulin)

- **A1C < 8%**
  - TDD 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD 0.2–0.3 U/kg

**Insulin titration every 2–3 days to reach glycemic goal:**
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10%–20%
  - BG < 40 mg/dL: 20%–40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

**Glycemic Control Not at Goal**

**Intensify** (Prandial Control)

- **Add GLP-1 RA**
  - Or SGLT-2i
  - Or DPP-4i

- **Add Prandial Insulin**
  - Basal Plus 1, Plus 2, Plus 3
    - Begin prandial insulin before largest meal
    - If not at goal, progress to injections before 2 or 3 meals
    - Start: 10% of basal dose or 5 units
  - Basal Bolus
    - Begin prandial insulin before each meal
    - 50% Basal / 50% Prandial
    - TDD 0.3–0.5 U/kg
    - Start: 50% of TDD in three doses before meals

**Insulin titration every 2–3 days to reach glycemic goal:**
- Increase prandial dose by 10% or 1–2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10%–20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20%–40%

*Glycemic Goal:
- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk
Required language in package inserts of diabetes drugs per FDA:

• “there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with drug X or any other antidiabetic drug”
Reducing CV risk in type 2 diabetes

• Emphasis should be on aggressive treatment of traditional CV risk factors
• The following are some interesting studies looking at reducing CV risk in type 2 diabetes in addition to traditional CV risk reduction modalities
Leader Trial: liraglutide use in high risk T2D patients (NEJM available ahead of print)

- Prospective, multicenter, double blind, randomized trial, with adjudicated endpoints, n= 9340, mean FU 3.8 years
- Patients >50 yo, had established CAD or CKD level 3 or higher, or > 60 yo and multiple risk factors
- Primary outcome- time to first occurrence of 3-point major adverse cardiac event (CV death, nonfatal MI or nonfatal stroke); secondary outcomes included time to first occurrence of expanded composite CV outcome, which included coronary revascularization, unstable angina or hospitalization for heart failure, as well as all-cause death and each individual component of CV outcome
LEADER trial continued

- Fewer patients in the liraglutide group experienced a primary CV outcome vs. those assigned placebo (13% vs. 14.9%), for an HR of 0.87 (95% CI, 0.78-0.97) and a 1.9% absolute risk reduction.

- Fewer patients in the liraglutide group died from CV causes (4.7% vs. 6%), for an HR of 0.78 (95% CI, 0.66-0.93). In addition, rate of death from any cause was lower in the liraglutide group vs. placebo (8.2% vs. 9.6%), for an HR of 0.85 (95% CI, 0.74-0.97).

- Fewer myocardial infarctions vs. placebo (6.3% vs. 7.3%) for a 14% relative risk reduction.

- Fewer strokes- 14% relative risk reduction (3.4% vs. 3.8%). Hospitalization for heart failure was also lower in the liraglutide group, with a rate of 4.7% vs. 5.3%.
EMPA-REG Trial: Cardiovascular Outcomes and Death from Any Cause (n= 7020, 3.1 yrs median fu, empagliflozin 10 mg or 25 mg vs placebo on background of aggressive CVD risk factor treatment, T2D patients with macrovascular disease)

A Primary Outcome

- Hazard ratio, 0.86 (95% CI, 0.74−0.99)
- P=0.04 for superiority

B Death from Cardiovascular Causes

- Hazard ratio, 0.62 (95% CI, 0.49−0.77)
- P<0.001

C Death from Any Cause

- Hazard ratio, 0.68 (95% CI, 0.57−0.82)
- P<0.001

D Hospitalization for Heart Failure

- Hazard ratio, 0.65 (95% CI, 0.50−0.85)
- P=0.002
Limitations of the application of EMPA-REG

- Tested secondary prevention only (81% had already manifest macrovascular disease, others with very high risk)

- **Mechanism is unclear**- because SGLT-2 inhibitors have multiple benefits which might have helped:
  - Reduced SBP, weight, blood glucose
  - Reduced several markers of increased risk: uric acid and urine microalbumin

- The benefit was driven by reduced death and CHF outcomes
  - Possible improved cardiac energy metabolism in a compromised heart (common in T2D)

- **Unclear if class effect**, other CV safety trials ongoing with canagliflozin and dapagliflozin
  - While many experts believe it is, this is speculative at this time
Other diabetes agents showing CV reduction

- IRIS: Pioglitazone in Insulin resistance patients (not diabetic) as secondary prevention after CVA
  - Reduced second CVA or MI after CVA or TIA, HR 0.76
  - Published on line ahead of print NEJM 2-17-2016, DOI: 10.1056/NEJMoa1506930
Figure 1. Primary Outcome.

By 5 years, the primary outcome (fatal or nonfatal stroke or fatal or nonfatal myocardial infarction) had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group. The inset shows the same data on an enlarged y axis. The numbers at risk were the numbers of patients who were alive without an event and still being followed at the beginning of each time point.
• Did not achieve primary outcome: composite of all-cause mortality, non fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle (HR 0.90, p not significant, 0.095)

• Not significant primarily due to increase in leg amputations, an outcome not generally part of CV outcomes, and time of exposure was relatively short (3.4 years) due to more rapid recruitment than expected and end of study pre-specified by number of events

• Did achieve pre specified secondary outcome of reduced non fatal MI, non fatal CVA, and CV death (HR 0.84, p = 0.027)

• Since did not achieve primary outcome, secondary indicators generally not considered significant