Novedades en el Tratamiento de la Diabetes tipo 2?
Guias ADA and AACE

Guillermo E. Umpierrez, MD, CDE, FACP, FACE
Professor of Medicine
Director Clinical Research, Diabetes & Metabolism Center
Emory University School of Medicine

Chief, Endocrinology Section,
Grady Health System
<table>
<thead>
<tr>
<th>Relationships</th>
<th>Company Name(s)</th>
<th>Role</th>
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<tbody>
<tr>
<td>Equity, stock, biomedical industry</td>
<td>• BMJ Open Diabetes Research &amp; Care</td>
<td>Editor-in-Chief</td>
</tr>
<tr>
<td>• ADA Professional Practice Recommendation Committee</td>
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<tr>
<td>• AACE Diabetes Council and Guidelines Writing Committee</td>
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<tr>
<td>• Chairman National AACE Primary care Diabetes Education</td>
<td>Fast National Board ADA and Endocrine Society</td>
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<tr>
<td>Industry funds to Emory University for my research</td>
<td>Merck, Sanofi, Novo Nordisk Astra Zeneca, Boehringer Ingelheim</td>
<td>Investigator-Initiated Research Projects</td>
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<tr>
<td>Industry Advisory/Consultant activities</td>
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Type 2 DM Management Guidelines
The ADA Professional Practice Committee reviews and revises the Standards of Medical Care in Diabetes each year.

A Medline search is performed for human studies published in the prior calendar year.

Revisions are made to reflect new evidence, changes in the strength of evidence, and for clarity.
AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2017

TASK FORCE

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Novedades Guias de la ADA, 2018

Agenda

• Diagnosis of Diabetes
• Prevention of Type 2 Diabetes
• Glycemic Targets
• Pharmacological Approaches to Glycemic Treatment
• Cardiovascular Disease and Risk Management
### Criteria for the Diagnosis of Diabetes

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)</td>
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<tr>
<td><strong>OR</strong></td>
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<tr>
<td>2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT</td>
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<td><strong>OR</strong></td>
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<td>A1C ≥6.5%</td>
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<tr>
<td><strong>OR</strong></td>
</tr>
<tr>
<td>Classic diabetes symptoms + random plasma glucose ≥200 mg/dL (11.1 mmol/L)</td>
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</tbody>
</table>

*American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. Diabetes Care 2018*
Criteria for the Diagnosis of Diabetes

- A1C ≥6.5%
- OR
- Fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l)
  - OR
- Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT
  - OR
- A random plasma glucose ≥200 mg/dl (11.1 mmol/l)

ADA. I. Classification and Diagnosis. Diabetes Care 2012;34(suppl 1):S13. Table 2.
Prediabetes

FPG 100–125 mg/dL
(5.6–6.9 mmol/L): IFG

OR

2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

Estimated HbA1c Levels by Mean Glucose Concentrations and Race in Type 1 DM

<table>
<thead>
<tr>
<th>Mean Glucose Concentration</th>
<th>Estimated Hemoglobin A1c Level (95% CI), %</th>
<th>Difference (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black Participants</td>
<td>White Participants</td>
</tr>
<tr>
<td>100 mg/dL</td>
<td>6.5 (6.2 to 6.8)</td>
<td>6.0 (5.7 to 6.3)</td>
</tr>
<tr>
<td>150 mg/dL</td>
<td>7.9 (7.7 to 8.1)</td>
<td>7.5 (7.3 to 7.6)</td>
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<tr>
<td>200 mg/dL</td>
<td>9.3 (9.2 to 9.5)</td>
<td>8.9 (8.8 to 9.1)</td>
</tr>
<tr>
<td>250 mg/dL</td>
<td>10.8 (10.5 to 11.0)</td>
<td>10.4 (10.1 to 10.6)</td>
</tr>
<tr>
<td>300 mg/dL</td>
<td>12.2 (11.8 to 12.5)</td>
<td>11.8 (11.4 to 12.2)</td>
</tr>
<tr>
<td>350 mg/dL</td>
<td>13.6 (13.1 to 14.1)</td>
<td>13.3 (12.7 to 13.8)</td>
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</tbody>
</table>

* Estimated A1c levels are adjusted for age (intercept and slope) and model-estimated values are for a 31-year old person (the mean age in the data set).
Novedades Guías de ADA, 2018

Agenda

• Diagnosis of Diabetes
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• Patients with prediabetes should be referred to an intensive diet and physical activity behavioral counseling program adhering to the tenets of the DPP targeting a loss of 7% of body weight, and should increase their moderate physical activity to at least 150 min/week. A
Prevention or Delay of T2DM: Metformin

- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with:
  - BMI $>35$ kg/m$^2$,
  - Age $< 60$ years,
  - Women with prior gestational diabetes (GDM),
  - Rising A1C despite lifestyle intervention. A

American Diabetes Association Standards of Medical Care in Diabetes. Prevention or delay of type 2 diabetes. Diabetes Care 2018
Diabetes Prevention Program: Progression to Type 2 Diabetes

- Placebo (n=1082)
- Metformin (n=1073, p<0.001 vs. Placebo)
- Lifestyle (n=1079, p<0.001 vs. Metformin, p<0.001 vs. Placebo)

**Risk reduction**
- 31% by metformin
- 58% by lifestyle

DPP Research Group. NEJM. 2002;346:393-403.
The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1)

**Indian Diabetes Prevention Programme (IDPP)**
Native Asian Indians with IGT
Primary outcome: development of diabetes by OGTT
Median follow-up: 30 months
- Control group (n= 136)
- Lifestyle modification (LSM) (n= 133)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>LSM</th>
<th>MET</th>
<th>LSM + MET</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>133</td>
<td>120</td>
<td>128</td>
<td>121</td>
</tr>
<tr>
<td>Cumulative incidence of diabetes at year 3, % (95% CI)</td>
<td>55.0 (46.0–63.5)</td>
<td>39.3 (30.4–48.5)</td>
<td>40.5 (32.0–49.7)</td>
<td>39.5 (30.9–48.9)</td>
</tr>
<tr>
<td>Absolute risk reduction, %</td>
<td>–</td>
<td>15.7</td>
<td>14.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Relative risk reduction, % (95% CI)</td>
<td>–</td>
<td>28.5 (20.5–37.3)</td>
<td>26.4 (19.1–35.1)</td>
<td>28.2 (20.3–37.0)</td>
</tr>
<tr>
<td>p value vs control group (Cox’s regression equation)</td>
<td>–</td>
<td>0.018</td>
<td>0.029</td>
<td>0.022</td>
</tr>
<tr>
<td>Number needed to treat for 3 years to prevent diabetes in one case</td>
<td>–</td>
<td>6.4</td>
<td>6.9</td>
<td>6.5</td>
</tr>
</tbody>
</table>
The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1)

Cumulative incidence of diabetes

- Control group (n= 136)
- Lifestyle modification (LSM) (n= 133)
- Metformin (n= 133)
- LSM + Metformin (n=129)
Prevention or Delay of T2DM

New Recommendation

• Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B
• Open-label, cluster-randomized trial (DiRECT) at 49 primary care practices in Scotland and England.

• Study population: age 20–65 years, T2D within the past 6 years, BMI 27–45 kg/m2, not receiving insulin.

• Intervention: withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks), and structured support for long-term weight loss maintenance.

• Co-primary outcomes: weight loss of 15 kg or more, and remission of diabetes, defined as HbA1c of <6.5% after at least 2 months off all antidiabetic medications, from baseline to 12 months.
Change in weight of participants who remained in the trial and those who dropped out during each phase of the intervention

N= 306 individuals, 24% lost > 15 kg vs none in the control group.
Counterweight-Plus weight management programme
Weight loss of 15 kg or more, and remission of diabetes (HbA1c < 6.5%) from baseline to 12 months (DiRECT)

www.thelancet.com Published online December 5, 2017
Recovery from Diabetes, Lipid Disturbances, Hypertension, and Hyperuricemia over 2 and 10 Years in Surgically Treated Subjects and Their Obese Controls
Novedades Guias de ADA, 2018

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### ADA vs. AACE: HbA1c Targets

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Patients</td>
<td>&lt;7.0%</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>Young, no hypoglycemia, low</td>
<td>&lt;6.5%</td>
<td>&lt;6.5%</td>
</tr>
<tr>
<td>comorbidities or complications</td>
<td></td>
<td>Avoid hypoglycemia</td>
</tr>
<tr>
<td>Hx. hypoglycemia, +comorbidities</td>
<td>&lt;8.0%</td>
<td>&gt;6.5%</td>
</tr>
<tr>
<td>or complications, hard to control</td>
<td></td>
<td>Avoid hypoglycemia</td>
</tr>
</tbody>
</table>
Management of Type 2 Diabetes

Prevention of Microvascular Complications
Driven by A1C reduction irrespectively of treatment regimen

Prevention of Cardiovascular Disease
Driven by drug strategy (agents) more than A1c reduction
Glycemic Control and Complications

DCCT: Type 1 DM

A1C and Microvascular Complications: DCCT

UKPDS: Type 2 DM

UKPDS: Risk Reductions With Intensive Therapy (Median HbA$_{1c}$ = 7.0%)

Glycemic Control and Macrovascular Complications

**ACCORD: Treatment Effect on All-Cause Mortality**

- **Patients with events (%)**
- **HR 1.22 (1.01-1.46)**
  - **P = 0.04**

**Time to nonfatal outcome**

- **Proportion free of nonfatal outcome**
  - **Hazard Ratio and CL**
    - **0.845 (0.704, 1.016) p=0.0725**

**ADVANCE: Treatment Effect on Primary Macrovascular Outcome**

- **HR 0.94 (0.84-1.06)**
  - **P = 0.32**

**VADT: Effects of Recent Severe Hypoglycemia**

- **Predictor of CV death**
  - HR 4.04 p≤0.008
- **Predictor of all cause mortality**
  - Standard HR 5.89 p=0.001
  - Intensive HR 1.28 p=0.68

**References**

Hypoglycemia and Annualized Mortality Rates Within Treatment Groups: ACCORD

Mortality Rate (n=451 deaths)

- Requiring Any Assistance, Medical or Non-medical (HA)†
  - Standard: 1.0%
  - Intensive: 3.7%

- Requiring Medical Assistance (HMA)‡
  - Standard: 1.0%
  - Intensive: 4.9%

- Person-years: *
  - Standard: 1.7297
  - Intensive: 5.64

- * Person-years
  † p = .076 for interaction between history of hypoglycemia requiring any assistance and glycemia intervention
  ‡ p = .009 for interaction between history of hypoglycemia requiring medical assistance and glycemia intervention

Individualization of Care is needed for the Management of Patients with Diabetes

Novedades Guias de ADA, 2018

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ADA 2017 Antihyperglycemic Therapy in T2DM

If A1C 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- and disease-specific factors):
New Recommendation
ADA Standards of Medical Care in Diabetes - 2018

Monotherapy

A1C not at goal

Dual therapy

ASCVD?

Yes

Add agent with evidence of CV risk reduction:
- SGLT2-I (empagliflozin or canagliflozin)
- GLP1-RA (liraglutide)

No

Metformin

- Sulfonylurea
  - high risk
  - moderate risk
  - low risk
  - gain
  - hypoglycemia
- Thiazolidinedione
- DPP-4 inhibitor
  - intermediate risk
  - low risk
  - neutral
  - rare
  - low
- SGLT2 inhibitor
  - intermediate risk
  - low risk
  - neutral
  - low
- GLP-1 receptor agonist
  - high
  - high risk
  - loss
  - GI
  - high
- Insulin (basal)
  - highest
  - high risk
  - loss
  - gain
  - hypoglycemia
  - variable
Start Basal Insulin (NPH, Glargine, Detemir, Degludec):

- Initial therapy (+ metformin) if symptoms of hyperglycemia
- A1C > 9-10%
- ADD-ON to 1-3 oral agents if A1c not at goal

**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%
What to do when Oral Antidiabetic drugs (OAD) fail in patients with type 2 diabetes

- Prandial insulin (Basal Bolus)
- Incretin Agents (GLP1 RA)
- Basal Insulin
Lixilan-O: Lixilan vs Lixi vs Glargine

Rosenstock J, Diabetes Care, Aug 2016
IDegLira (Dual 1): HbA$_{1c}$ over time

Mean values (±SEM) based on FAS and LOCF-imputed data; EOT = end of trial; p-values are from an ANCOVA

- ADA/EASD HbA$_{1c}$ target <7.0%; AACE HbA$_{1c}$ target ≤6.5%

* $p<0.0001$ vs. IDeg and vs. Liraglutide

Gough, Bode et al, Lancet Diab Endo 2014
What to do when Oral Antidiabetic drugs (OAD) fail in patients with type 2 diabetes

Combination of 2 or 3 OADs

Basal Plus → Basal Bolus

Basal Insulin

Basal + Incretin Agents

Incretin Agents

Lifestyle changes plus metformin
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Efficacy*</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>CV Effects</th>
<th>Cost</th>
<th>Renal Effects</th>
<th>Additional Considerations</th>
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<td>ADRG</td>
<td>CPF</td>
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<td></td>
<td>Progress of DM</td>
<td>Dosing/Use considerations</td>
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<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral (Potential for Moderate Level)</td>
<td>Potential Benefit</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
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<td>• Gastrointestinal side effects common (abdominal, nausea)</td>
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<td>• Potential for B12 deficiency</td>
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<td>SGLT-2 Inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Loss</td>
<td>Benefit: canagliflozin, empagliflozin</td>
<td>Benefit: canagliflozin, empagliflozin</td>
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<td>• Na+ loss fracture risks</td>
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<td>• DKA risk (all agents, rare in SGLT2s)</td>
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<td>• Risk of volume depletion, hyperkalemia</td>
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<td>GLP-1 RAs</td>
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<td>DPP-4 inhibitors</td>
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<td>Thiazolidinediones</td>
<td>High</td>
<td>No</td>
<td>Gain</td>
<td>Potential Benefit: pioglitazone</td>
<td>Increased Risk</td>
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<tr>
<td>Sulfonylureas (2nd Generation)</td>
<td>High</td>
<td>Yes</td>
<td>Gain</td>
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<tr>
<td>Insulin Human Insulin Analogs</td>
<td>Highest</td>
<td>Yes</td>
<td>Gain</td>
<td>Neutral</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<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 GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
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</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate/Severe</td>
<td>Mild</td>
<td>Neutral</td>
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<td>Moderate to Severe</td>
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<td>WEIGHT</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>
</tr>
<tr>
<td>RENAL / GU</td>
<td>Contraindicated if eGFR &lt; 30 mL/min/1.73 m^2</td>
<td>Exenatide Not Indicated CrCl &lt; 30</td>
<td>Not Indicated for eGFR &lt; 45 mL/min/1.73 m^2</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Effective in Reducing Albuminuria</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>More Hypo Risk</td>
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<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
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<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Possible Benefit of Linagliptide</td>
<td>Possible Benefit of Empagliflozin</td>
<td>Possible Risk for Saxagliptin and Alogliptin</td>
<td>Moderate</td>
<td>More CHF Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More CHF Risk</td>
<td>Neutral</td>
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<tr>
<td>CARDIAC*</td>
<td>Neutral</td>
<td>Possible CV Benefit</td>
<td>Possible CV Benefit</td>
<td>Moderate</td>
<td>May Reduce Stroke Risk</td>
<td>?</td>
<td>Benefit</td>
<td>Safe</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td>ASCVD</td>
<td>Neutral</td>
<td>Possible CV Benefit</td>
<td>Possible CV Benefit</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Canagliflozin Warning</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<td>Neutral</td>
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<td>KETOACIDOSIS</td>
<td>Neutral</td>
<td>Neutral</td>
<td>DKA Occurring in T2D in Various Stress Settings</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

* Few adverse events or possible benefits
* Use with caution
* Likelihood of adverse effects
* Uncertain effect
* FDA indication to prevent CVD death in diabetes plus prior CVD events

Novedades Guias de ADA, 2018

Agenda

• Diagnosis of Diabetes
• Prevention of Type 2 Diabetes
• Glycemic Targets
• Pharmacological Approaches to Glycemic Treatment
• Cardiovascular Disease and Risk Management
Hypertension/ Blood Pressure Control

Systolic Targets:

• People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. A

• Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals at high risk of CVD, if they can be achieved without undue treatment burden. C

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2018
Hypertension/ Blood Pressure Control

Diastolic Targets:

• Patients with diabetes should be treated to a diastolic blood pressure <90 mmHg. A

• Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals at high risk for CVD if they can be achieved without undue treatment burden. C

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2018
Hypertension/ Blood Pressure Treatment (3)

• Treatment for hypertension should include A
  – ACE inhibitor
  – Angiotensin II receptor blocker (ARB)
  – Thiazide-like diuretic
  – Dihydropyridine calcium channel blockers

• Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2018
Patients with diabetes should be treated to a goal of 130/80 mmHg

Treatment for hypertension should include A

- ACE inhibitor
- Angiotensin II receptor blocker (ARB)
- Thiazide-like diuretic
- Dihydropyridine calcium channel blockers

Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.

Achievement of target blood pressure goal is critical
Lipid Management

• In adults not taking statins, a screening lipid profile is reasonable (E):
  – At diabetes diagnosis
  – At the initial medical evaluation
  – And every 5 years, or more frequently if indicated

• Obtain a lipid profile at initiation of statin therapy, and periodically thereafter. E
## Recommendation for Statin Treatment in People with Diabetes

ASCVD risk factors include LDL cholesterol ≥100 mg/dL, high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Statin intensity</th>
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</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
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<tr>
<td></td>
<td>ASCVD risk factor(s)*</td>
<td>Moderate or high</td>
</tr>
<tr>
<td>40-75 years</td>
<td>None</td>
<td>Moderate</td>
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<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
</tbody>
</table>

*ASCVD risk factor(s)* include LDL cholesterol ≥100 mg/dL, high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.
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 therapies to attain goals according to risk levels

High-Intensity Statin Therapy
Lowers LDL by ≥50%
Atorvastatin 40-80 mg
Rosuvastatin 20-40 mg

Moderate-Intensity Statin Therapy
Lowers LDL by 30 - <50%
Atorvastatin 10-20 mg
Rosuvastatin 5-10 mg
Simvastatin 20-40 mg
Pravastatin 40-80 mg
Lovastatin 40 mg
Fluvastatin XL 80 mg
Pitavastatin 2-4 mg
Consider aspirin therapy (75–162 mg/day) C

- As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk
- Includes most men or women with diabetes age ≥50 years who have at least one additional major risk factor, including:
  - Family history of premature ASCVD
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria
Antiplatelet Agents

• Use aspirin therapy (75–162 mg/day) as secondary prevention in those with diabetes and history of ASCVD. A

• For patients w/ ASCVD & aspirin allergy, clopidogrel (75 mg/day) should be used. B

• Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. B

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2018
Management of Type 2 Diabetes: 2017

Efficacy
- Lowering HgA1c

Safety
- Hypoglycemia Prevention

Trials with + CVD Prevention
- GLP1-RA:
  - Leader (Liraglutide)
  - Duration (Semaglutide)
- SGLT2-I
  - EMPA-REG (Empagliflozin)
  - CANVAS (Canagliflozin)
Criteria for the Diagnosis of Diabetes

A1C ≥6.5%

OR

Fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l)

OR

Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/l)

ADA. I. Classification and Diagnosis. Diabetes Care 2012;34(suppl 1):S13. Table 2.

A1C ≥6.5%
LEADER: Liraglutide and Cardiovascular Outcomes in T2D

Trial Design: 9,340 patients with T2D and high CV risk, CVD: (81.3%), HbA1c >7% receiving OADs with or without insulin. Median follow-up: 3.5 years

Primary outcome: CV death, nonfatal MI, nonfatal stroke

LEADER Trial
Primary Outcomes

**CV Death, Non-fatal MI or Non-fatal Stroke**

- **Placebo**
  - HR = 0.87
  - 95% CI = 0.78-0.97
  - \( P < 0.001 \) for noninferiority
  - \( P = 0.01 \) for superiority

- **Liraglutide**

**CV Death**

- **Placebo**
  - HR = 0.78
  - 95% CI = 0.66-0.93
  - \( P = 0.007 \)

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

SUSTAIN-^ Trial: Semaglutide and Cardiovascular Outcomes in Patients with T2D

Trial Design: 3,297 patients with T2D and high CV risk, CVD: (83%), HbA1c >7% receiving OADs with or without insulin.
Median follow-up: 3.5 years
Primary outcome: CV death, nonfatal MI, nonfatal stroke

Change in HbA1c

Change in Body Weight

SUSTAIN 6: Semaglutide

CV Outcomes


**A) Primary Outcome**

- **HR (95% CI) = 0.74 (0.58-0.95)**
- **P < 0.001 noninferiority**
- **P = 0.02 superiority**

**B) Nonfatal Myocardial Infarction**

- **HR (95% CI) = 0.74 (0.51-1.08)**
- **P = 0.12**

**C) Nonfatal Stroke**

- **HR (95% CI) = 0.61 (0.38-0.99)**
- **P = 0.04**

**D) Death from Cardiovascular Causes**

- **HR (95% CI) = 0.98 (0.65-1.48)**
- **P = 0.92**
Primary outcome

- 3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

EMPAS-REG OUTCOMES
Empagliflozin and CV Outcomes

Death from any cause

- HR = 0.68 (95% CI: 0.57, 0.82)
- P < 0.001

Hospitalization for heart failure

- HR = 0.65 (95% CI: 0.50, 0.85)
- P = 0.002

No. at risk

- Empagliflozin:
  - Month 0: 4687
  - Month 6: 4651
  - Month 12: 4568
  - Month 18: 4556
  - Month 24: 4128
  - Month 30: 3079
  - Month 36: 2617
  - Month 42: 1722
  - Month 48: 414

- Placebo:
  - Month 0: 2333
  - Month 6: 2303
  - Month 12: 2280
  - Month 18: 2243
  - Month 24: 2012
  - Month 30: 1503
  - Month 36: 1281
  - Month 42: 825
  - Month 48: 177

No. at risk

- Empagliflozin:
  - Month 0: 4687
  - Month 6: 4614
  - Month 12: 4523
  - Month 18: 4427
  - Month 24: 3988
  - Month 30: 2950
  - Month 36: 2487
  - Month 42: 1634
  - Month 48: 395

- Placebo:
  - Month 0: 2333
  - Month 6: 2271
  - Month 12: 2226
  - Month 18: 2173
  - Month 24: 1932
  - Month 30: 1424
  - Month 36: 1202
  - Month 42: 775
  - Month 48: 168

Cl, confidence interval; CV, cardiovascular; HR, hazard ratio

EMPA-REG and CANVAS: Renal Outcomes


CANVAS: CANagliflozin cardioVascular Assessment Study

• T2DM ~14 years
  – Study medication in addition to standard of care
  – HbA1c ≥7.0% to ≤10.5%

• High CV risk
  – eGFR ≥30 mL/min/1.73 m²
  – Age ≥30 years and history of prior CV event
  – Age ≥50 years with ≥2 CV risk factors

CANVAS: CANagliflozin cardioVascular Assessment Study

Under Consideration:
ADA Standards of Medical Care in Diabetes - 2018

Monotherapy ➔ Metformin

A1C not at goal ➔ Dual therapy

ASCVD?

Yes ➔ Add agent with evidence of CV risk reduction:
- SGLT2-I (empagliflozin or canagliflozin)
- GLP1-RA (liraglutide)

No ➔ Continue Metformin

---

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
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<th>Metformin +</th>
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<tbody>
<tr>
<td><strong>Sulfonylurea</strong></td>
<td><strong>Thiazolidinedione</strong></td>
<td><strong>DPP-4 inhibitor</strong></td>
<td><strong>SGLT2 inhibitor</strong></td>
<td><strong>GLP-1 receptor agonist</strong></td>
<td><strong>Insulin (basal)</strong></td>
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<td>high, moderate risk gain hypo/hypoglycemia low</td>
<td>high, low risk gain edema, HF, fxs low</td>
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<td>intermediate, low risk</td>
<td>high</td>
<td>highest</td>
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<td>loss</td>
<td>high</td>
<td>low risk</td>
<td>high</td>
</tr>
</tbody>
</table>

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STANDARDS OF MEDICAL CARE IN DIABETES—2017

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