AACE Diabetes Algorithm

• Guide therapy based on A1C level
  – Focus on lifestyle intensification at all levels

• Important tenets:
  – Target A1C is ≤6.5%
    • For patients without concurrent serious illness and at low hypoglycemic risk
    • Based on associated lower risk of micro- and macrovascular complications
    • Recommend monitoring A1C quarterly, along with fasting and postprandial blood glucose, with intensification of therapy until goal A1C is achieved
    • Individualize A1C target based on comorbidities
    • Patient should monitor fasting and postprandial blood glucose levels
  – Use agents with maximal efficacy, associated with lowest risk of hypoglycemia
    • Sulfonylureas are therefore much lower in algorithm
    • Earlier use of incretin mimetics and DPP-4 inhibitors to stimulate insulin secretion without hypoglycemia

A1C = glycated hemoglobin; DPP-4 = dipeptidyl-peptidase 4

Glycemic Management of Type 2 Diabetes: Treatment Goals

Lowering A1C

Preventing Hypoglycemia

Individualized Algorithm
Risk of Hypoglycemia

• Plays a significant role in choice of agents in AACE algorithm
• For patients at highest risk of hypoglycemia, may consider close evaluation of agents chosen as well as therapeutic goal
• Patients with type 2 diabetes at highest risk of low blood glucose include those with:
  – Diabetes duration >15 years
  – Advanced macrovascular disease
  – Hypoglycemia unawareness
  – Limited life expectancy
  – Severe comorbidities

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
# Lifestyle Therapy

**Risk Stratification for Diabetes Complications**

## Intensity Stratified by Burden of Obesity and Related Complications

<table>
<thead>
<tr>
<th>Lifestyle Component</th>
<th>Strategies</th>
</tr>
</thead>
</table>
| **Nutrition**       | - Maintain optimal weight  
                      - Calorie restriction (if BMI is increased)  
                      - Plant-based diet; high polyunsaturated and monounsaturated fatty acids  
                      - Avoid trans fatty acids; limit saturated fatty acids  
                      - Structured counseling  
                      - Meal replacement |
| **Physical Activity** | - 150 min/week moderate exertion (eg. walking, stair climbing)  
                          - Strength training  
                          - Increase as tolerated  
                          - Structured program  
                          - Wearable technologies  
                          - Medical evaluation/clearance  
                          - Medical supervision |
| **Sleep**           | - About 7 hours per night  
                      - Basic sleep hygiene  
                      - Screen OSA  
                      - Home sleep study  
                      - Referral to sleep lab |
| **Behavioral Support** | - Community engagement  
                          - Alcohol moderation  
                          - Discuss mood with HCP  
                          - Formal behavioral therapy |
| **Smoking Cessation** | - No tobacco products  
                          - Nicotine replacement therapy  
                          - Referral to structured program |
Current Antihyperglycemic Medications

12 Groups with Different Mechanisms of Action

- **Sulfonylureas**
  - Generalized insulin secretagogue

- **TZDs**
  - Reduce peripheral insulin resistance

- **Biguanide**
  - Reduce hepatic insulin resistance

- **Glucosidase Inhibitors**
  - Delay CHO absorption

- **GLP-1 Analogs**
  - Stimulate \( \beta \) cells, suppress glucagon

- **Amylin Analog**
  - Suppress glucagon

- **Glinides**
  - Restore postprandial insulin patterns

- **DPP-4 Inhibitors**
  - Restore GLP-1 Level

- **-Glucosidase Inhibitors**
  - Delay CHO absorption

- **Colesevelam**
  - Bile acid sequestrant

- **Bromocriptine**
  - Hypothalamic pituitary reset

- **Insulin Replacement Therapy**
<table>
<thead>
<tr>
<th>HYPO</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
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<th>Moderate to Severe</th>
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<td>Loss</td>
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<td>Gain</td>
<td>Gain</td>
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<td>Loss</td>
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<tr>
<td>RENAL / GU</td>
<td>Contraindicated if eGFR &lt; 30 mL/min/1.73 m²</td>
<td>Exenatide Not Indicated CrCl &lt; 30</td>
<td>Not Indicated for eGFR &lt; 45 mL/min/1.73 m²</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Effective in Reducing Albuminuria</td>
<td>Neutral</td>
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<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
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<td></td>
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<td>Possible Benefit of Empagliflozin</td>
<td>Genital Mycotic Infections</td>
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<td>Possible Benefit of Empagliflozin</td>
<td>Possible Risk for Saxagliptin and Alogliptin</td>
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<td>Possible CV Benefit</td>
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<tr>
<td>KETOACIDOSIS</td>
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<td>DKA Occurring in T2D in Various Stress Settings</td>
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</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

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## Effect of Glucose-lowering Drugs on Patient Weight

<table>
<thead>
<tr>
<th>Therapeutic Options</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>TZD&lt;sup&gt;3,4&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>↑</td>
</tr>
<tr>
<td>Metformin&lt;sup&gt;7&lt;/sup&gt;</td>
<td>⇔</td>
</tr>
<tr>
<td>DPP-4 inhibitor&lt;sup&gt;8&lt;/sup&gt;</td>
<td>⇔</td>
</tr>
<tr>
<td>GLP-1 receptor agonist&lt;sup&gt;9&lt;/sup&gt;</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors&lt;sup&gt;10&lt;/sup&gt;</td>
<td>↓</td>
</tr>
</tbody>
</table>

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium glucose co-transporter-2; TZD = thiazolidinedione

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*
- GLP-1 RA
- SGLT-2i
- Basal Insulin
- DPP-4i
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

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

Entry A1C > 9.0%

SYMPTOMS
NO
- DUAL Therapy
OR
- TRIPLE Therapy
YES
- INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

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

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

PROGRESSION OF DISEASE

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Algorithm To Achieve Glycemic Goals

Baseline A1C 6.5% - 7.5%

• Monotherapy may be effective in this range
  – Metformin first choice for monotherapy if no contraindications
  – Consider DPP-4 if PP and FPG, GLP-1 if PP, TZD if metabolic syndrome or NAFLD, AGI if PP
  – Do not recommend secretagogue (SU or glinide) in this range due to risk of hypoglycemia; short-lived effect

• If monotherapy is unsuccessful, move on to dual oral rx; often need to augment reduction in PP BG to get to goal in this A1C range

DPP-4=dipeptidyl peptidase-4; PP=post-prandial; FPG=fasting plasma glucose; GLP-1 = glucagon-like peptide-1; TZD=thiazolidinedione; NAFLD=non-alcoholic fatty liver disease; AGI=alpha-glucosidase inhibitor; SU=sulfonylurea; A1C=glycated hemoglobin; SGLT-2=sodium glucose transport-2

Algorithm To Achieve Glycemic Goals
Baseline A1C 7.6% - 9.0%

- Dual therapy with metformin provides superior glycemic control over metformin alone.
- If dual oral rx is unsuccessful, consider triple therapy
- If triple oral rx fails to achieve A1C goal, initiate insulin

GLP-1 RA = glucagon-like peptide-1 receptor agonist
DPP4-i=dipeptidyl peptidase 4 inhibitor
TZD=thiazolidinedione
SGLT-2=sodium glucose cotransporter 2 inhibitor
QR=quick-release
AG-i=alpha-glucosidase inhibitor
SU=sulfonylurea
GLN=glinide

Inzucchi S et al. Diabetes Care 2015;38:140-149.
If patient is asymptomatic with recent onset of disease and drug naïve, may consider starting with dual or triple oral regimens.

Once A1C has improved to <7.5%, consider initiation of dual oral therapy with tapering and possible discontinuation of insulin rx.

If symptomatic, start insulin.

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

**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
  - Basal Bolus
    - Begin prandial insulin before each meal
    - 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

**Glycemic Control Not at Goal**

- 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 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

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Add/Intensify 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:
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*Glycemic Goal:
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- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

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

# 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 therapies to attain goals according to risk levels

<table>
<thead>
<tr>
<th>Risk Levels</th>
<th>Desirable Levels</th>
<th>Very High</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;70</td>
<td>&lt;55</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
<td>&lt;70</td>
</tr>
</tbody>
</table>

**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, CHD3,4
- **EXTREME:** DM plus established clinical CVD

**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, colesvelam, 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, colesvelam, 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**

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## Hypertension

**Goal:** Systolic <130, Diastolic <80 mm Hg

**ACEi or ARB**
- For initial blood pressure >150/100 mm Hg:
  - DUAL THERAPY
    - Calcium Channel Blocker
    - β-blocker
    - Thiazide

**If not at goal (2–3 months):**
- Add calcium channel blocker, β-blocker or thiazide diuretic
- 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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Complications-Centric Model for Care of the Patient with Overweight/Obesity

**Step 1: Evaluation for Complications and Staging**

**Cardiometabolic Disease**

- **BMI < 25**
  - No Complications
    - BMI ≥ 25
      - Overweight or Obesity
        - Stage 0

**Biomechanical Complications**

- **BMI ≥ 25**
  - Complications
    - Mild to Moderate
      - Stage 1
      - Treatment modality
    - Severe
      - Stage 2
      - Treatment intensity based on staging

**Step 2: Select**

- Therapeutic targets for improvement in complications
  - Lifestyle Therapy: Physician/RD counseling, web/remote program, structured multidisciplinary program
  - Medical Therapy (BMI ≥ 27):
    - Individualize care by selecting one of the following based on efficacy, safety, and patients' clinical profile: phentermine, orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg
  - Surgical Therapy (BMI ≥ 35):
    - Gastric banding, sleeve, or bypass

**Step 3**

If therapeutic targets for complications not met, intensify lifestyle, medical, and/or surgical treatment modalities for greater weight loss. Obesity is a chronic progressive disease and requires commitment to long-term therapy and follow-up.
### Impaired Fasting Glucose (IFG):
FPG 100-125 mg/dL (5.6-6.9 mmol/l)

or

### Impaired Glucose Tolerance (IGT):
2-h plasma glucose in the 75-g OGTT
140-199 mg/dL (7.8-11.0 mmol/l)

or

**A1C 5.7% to 6.4%**

A1C = glycated hemoglobin; FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.

Handelsman Y et al. *Endocrine Practice* 2015;21 (Suppl 1)
Increased risk for both microvascular and macrovascular disease begins early \textbf{in the prediabetic state}

- Insulin resistance is already present in patients with NGT who later develop T2DM
- Patients with prediabetes already have insulin resistance and significantly decreased beta-cell function
- Diabetic retinopathy, peripheral neuropathy, and nephropathy occur in patients with prediabetes
- Patients with prediabetes have a 2- to 3-fold increase in CHD risk, similar to patients with diabetes

CHD = coronary heart disease; NGT = normal glucose tolerance; T2DM = type 2 diabetes mellitus
Prediabetes Treatment Algorithm

- Weight-loss agents orlistat, lorcaserin, phentermine/topiramate and liraglutide can prevent progression to T2DM
  - Improve BP, triglycerides, and insulin sensitivity
- Metformin and acarbose can reduce progression to T2DM by 25% - 30%
  - Use for prediabetes is off-label
  - Both are safe, confer CVD risk benefit; metformin is well tolerated
- TZDs prevented progression to T2DM in 60% - 75% of patients in clinical trials
  - Associated with adverse outcomes
- GLP-1 receptor agonists may be as effective as TZDs
  - Promote weight loss, but inadequate safety data

T2DM = type 2 diabetes mellitus
BP = blood pressure
CVD = cardiovascular disease
TZD = thiazolidinedione
GLP-1 RA = glucagon-like peptide-1 receptor agonist

### Principles of the AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

1. Lifestyle therapy, including medically supervised weight loss, is key to managing type 2 diabetes.

2. Weight loss should be considered as a lifelong goal in all patients with prediabetes and T2D who also have overweight or obesity, utilizing behavioral interventions and weight loss medications as required to achieve chronic therapeutic goals.

3. The A1C target must be individualized.

4. Glycemic control targets include fasting and postprandial gluoses.

5. The choice of therapies must be individualized on basis of patient characteristics, impact of net cost to patient, formulary restrictions, personal preferences, etc.

6. Minimizing risk of hypoglycemia is a priority.

7. Minimizing risk of weight gain is a priority.

8. Initial acquisition cost of medications is only a part of the total cost of care which includes monitoring requirements, risk of hypoglycemia, weight gain, safety, etc.

9. This algorithm stratifies choice of therapies based on initial A1C.

10. Combination therapy is usually required and should involve agents with complementary actions.

11. Comprehensive management includes lipid and blood pressure therapies and related comorbidities.

12. Therapy must be evaluated frequently until stable (e.g., every 3 months) and then less often.

13. The therapeutic regimen should be as simple as possible to optimize adherence.

14. This algorithm includes every FDA-approved class of medications for diabetes.