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Complications-Centric Model for Care of the Overweight/Obese Patient

**STEP 1**
**Evaluation for Complications and Staging**

**Cardiometabolic Disease**
- **No Complications**
  - BMI 25–26.9, or BMI ≥ 27

**Biomechanical Complications**
- **BMI ≥ 27 with Complications**
  - Stage Severity of Complications
    - Low
    - Medium
    - High

**STEP 2**
**Select:**

(i) Therapeutic targets for improvement in complications,
(ii) Treatment modality and
(iii) Treatment intensity for weight loss based on staging

- **Lifestyle Modification:** MD/RD counseling; web/remote program; structured multidisciplinary program
- **Medical Therapy:** Phentermine; orlistat; lorcaserin; phentermine/topiramate ER
- **Surgical Therapy (BMI ≥ 35):** Lap band; gastric sleeve; gastric bypass

**STEP 3**
If therapeutic targets for improvements in complications not met, intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss

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LIFESTYLE MODIFICATION
( Including Medically Assisted Weight Loss )

OTHER CVD RISK FACTORS
- CVD Risk Factor Modifications Algorithm

ANTI-OBESITY THERAPIES
- Normal Glycemia
  - Progression
  - Overt Diabetes
    - Proceed to Hyperglycemia Algorithm

ANTIHYPERTHYGLEMIC THERAPIES
- FPG > 100 | 2 hour PG > 140
  - 1 Pre-DM Criterion
  - Multiple Pre-DM Criteria
    - Low Risk Medications
      - Metformin
      - Acarbose
      - TZD
      - GLP-1 RA
    - If glycemia not normalized, consider with caution

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Goals for Glycemic Control

A1c ≤ 6.5%
For healthy patients without concurrent illness and at low hypoglycemic risk

A1c > 6.5%
Individualize goals for patients with concurrent illness and at risk for hypoglycemia
Glycemic Control Algorithm

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

**ENTRY A1c < 7.5%**

- **MONOTHERAPY**
  - Metformin
  - GLP-1 RA
  - DPP4-i
  - AG-i
  - SGLT-2
  - TZD
  - SU/GLN

  If A1c > 6.5% in 3 months add second drug (Dual Therapy)

**ENTRY A1c ≥ 7.5%**

- **DUAL THERAPY**
  - GLP-1 RA
  - DPP4-i
  - **SGLT-2**
  - TZD
  - **AG-i**
  - **SU/GLN**

  If not at goal in 3 months proceed to triple therapy

**ENTRY A1c > 9.0%**

- **NO SYMPTOMS**
  - DUAL THERAPY
  - TRIPLE THERAPY
  - INSULIN ± OTHER AGENTS

- **SYMPTOMS**
  - DUAL THERAPY
  - TRIPLE THERAPY
  - ADD OR INTENSIFY INSULIN

**PROGRESSION OF DISEASE**

- Order of medications listed are a suggested hierarchy of usage
- Based upon phase 3 clinical trials data

**LEGEND**

- = Few adverse events or possible benefits
- ▲ = Use with caution

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**Glycemic Goal:**
- For most patients with T2D, an A1c < 7%, fasting and premeal BG < 110 mg/dL in the 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.

**Glycemic Control Not at Goal**

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

**INSENSIFY** (prandial control)

- **Add GLP-1 RA** or DPP4-i
- **Add Prandial Insulin**
  - TDD: 0.3–0.5 U/kg
  - 50% Basal Analog
  - 50% Prandial Analog
  - Less desirable: NPH and regular insulin or premixed insulin

**Insulin titration every 2–3 days to reach glycemic goal:**
- **Fixed regimen:** Increase TDD by 2 U
- **Adjustable regimen:**
  - FBG > 180 mg/dL: add 4 U
  - FBG 140–180 mg/dL: add 2 U
  - FBG 110–139 mg/dL: add 1 U
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10% – 20%
    - BG < 40 mg/dL: 20% – 40%

**Insulin titration every 2–3 days to reach glycemic goal:**
- **Fixed regimen:** Increase TDD by 2 U
- **Adjustable regimen:**
  - FBG > 180 mg/dL: add 4 U
  - FBG 140–180 mg/dL: add 2 U
  - FBG 100–139 mg/dL: add 1 U
  - Increase prandial dose by 10% for any meal if the 2-hr postprandial or next premeal glucose is > 180 mg/dL
  - Premixed: Increase TDD by 10% if fasting/premeal BG > 180 mg/dL
  - If fasting AM hypoglycemia, reduce basal insulin
  - If nighttime hypoglycemia, reduce basal and/or pre-supper or pre-evening snack short/rapid-acting insulin
  - If between meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

**Consider discontinuing or reducing sulfonylurea after basal insulin started (basal analogs preferred to NPH)**
### Dyslipidemia

#### LIPID PANEL: Assess CVD Risk

- **Statin Therapy**
  - 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

- **If TG > 500 mg/dL, fibrates, omega-3 ethyl esters, niacin**
  - Intensify therapies to attain goals according to risk levels

#### Risk Levels

<table>
<thead>
<tr>
<th></th>
<th>MODERATE</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DESIRABLE LEVELS</td>
<td>DESIRABLE LEVELS</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>&lt;3.5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
</tr>
<tr>
<td>LDL-P (nmol/L)</td>
<td>&lt;1200</td>
<td>&lt;1000</td>
</tr>
</tbody>
</table>

#### Intensify TLC
- (weight loss, physical activity, dietary changes) and glycemic control; Consider additional therapy

#### To lower LDL-C:
- Intensify statin, add ezetimibe &/or colesuveralam &/or niacin
- Intensify statin &/or add OM3EE &/or fibrates &/or niacin

#### To lower Non-HDL-C, TG:
- Intensify statin &/or ezetimibe &/or colesuveralam &/or niacin

#### To lower Apo B, LDL-P:
- Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

### Hypertension

#### GOAL: SYSTOLIC ~130, DIASTOLIC ~80 mm Hg

- For initial blood pressure >150/100 mm Hg:
  - Dual therapy
  - ACEi or ARB
  - If not at desirable levels:
    - To lower LDL-C: Intensify statin, add ezetimibe &/or colesuveralam &/or niacin
    - To lower Non-HDL-C, TG: Intensify statin &/or add OM3EE &/or fibrates &/or niacin
    - To lower Apo B, LDL-P: Intensify statin &/or ezetimibe &/or colesuveralam &/or niacin
  - If not at goal (2–3 months)
    - Add ß-blocker or calcium channel 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, spironolactone)
  - Achievement of target blood pressure is critical

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* even more intensive therapy might be warranted

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# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
<th>TZD</th>
<th>AGI</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>SU</th>
<th>GLN</th>
<th>INSULIN</th>
<th>SGLT-2</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</td>
<td>Neutral</td>
<td>Moderate/Severe</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>Slight Loss</td>
<td>Neutral</td>
<td>Loss</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Loss</td>
<td>Loss</td>
<td></td>
</tr>
<tr>
<td><strong>RENAL/GU</strong></td>
<td>Contraindicated Stage 3B,4,5</td>
<td>Dose Adjustment May be Necessary (Except Linagliptin)</td>
<td>Exenatide Contraindicated CrCl &lt; 30</td>
<td>May Worsen Fluid Retention</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>More Hypo Risk &amp; Fluid Retention</td>
<td>Infections</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>CHF</strong></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>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td>Benefit</td>
<td>Neutral</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>Neutral</td>
</tr>
<tr>
<td><strong>BONE</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Bone Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Bone Loss</td>
</tr>
</tbody>
</table>

- **Few adverse events or possible benefits**
- **Use with caution**
- **Likelihood of adverse effects**

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1) Lifestyle optimization is essential for all patients with diabetes. This is multifaceted, ongoing, and engages the entire diabetes team. However, such efforts should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on the response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it.

2) The A1c target must be individualized, based on numerous factors, such as age, co-morbid conditions, duration of diabetes, risk of hypoglycemia, patient motivation, adherence, life expectancy, etc. An A1c of 6.5% or less is still considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate and may change in a given individual over time.

3) Glycemic control targets include fasting and postprandial glucose as determined by self blood glucose monitoring.

4) The choice of therapies must be individualized based on attributes of the patient (as above) and the medications themselves (see Profiles of Anti-Diabetic Medications). Attributes of medications that affect their choice include: risk of inducing hypoglycemia, risk of weight gain, ease of use, cost, and safety impact of kidney, heart, or liver disease. This algorithm includes every FDA-approved class of medications for diabetes. This algorithm also stratifies choice of therapies based on initial A1c.

5) Minimizing risk of hypoglycemia is a priority. It is a matter of safety, adherence, and cost.

6) Minimizing risk of weight gain is a priority. It too is a matter of safety, adherence, and cost.

7) The algorithm provides guidance to what therapies to initiate and add, but respects individual circumstances that would make different choices.

8) Therapies with complementary mechanisms of action must typically be used in combinations for optimum glycemic control.

9) Effectiveness of therapy must be evaluated frequently until stable (e.g. every 3 months) using multiple criteria including A1c, SMBG records including both fasting and post-prandial data, documented and suspected hypoglycemia, and monitoring for other potential adverse events (weight gain, fluid retention, hepatic, renal, or cardiac disease), and monitoring of co-morbidities, relevant laboratory data, concomitant drug administration, diabetic complications, and psycho-social factors affecting patient care.

10) Safety and efficacy should be given higher priorities than initial acquisition cost of medications per se since cost of medications is only a small part of the total cost of care of diabetes. In determining the cost of a medication, consideration should be given to monitoring requirements, risk of hypoglycemia and weight gain, etc.

11) The algorithm should be as simple as possible to gain physician acceptance and improve its utility and usability in clinical practice.

12) The algorithm should serve to help educate the clinician as well as to guide therapy at the point of care.

13) The algorithm should conform, as nearly as possible, to a consensus for current standard of practice of care by expert endocrinologists who specialize in the management of patients with type 2 diabetes and have the broadest experience in outpatient clinical practice.

14) The algorithm should be as specific as possible, and provide guidance to the physician with prioritization and a rationale for selection of any particular regimen.

15) Rapid-acting insulin analogs are superior to Regular because they are more predictable.

16) Long-acting insulin analogs are superior to NPH insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency both between subjects and within subjects, with a corresponding reduction in the risk of hypoglycemia.

This document represents the official position of the American Association of Clinical Endocrinologists and the American College of Endocrinology. Where there were no RCTs or specific FDA labeling for issues in clinical practice, the participating clinical experts utilized their judgment and experience. Every effort was made to achieve consensus among the committee members. Many details that could not be included in the graphic summary (Figure) are described in the text.