Diabetes Update 2019

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Objectives

1. Review current treatment guidelines for patients with diabetes mellitus

1. Review strategies for optimizing diabetes control using current pharmacotherapies and lifestyle modifications

1. Discuss cardiovascular and renal outcomes associated with available diabetes medications

Timothy M. Dall et al. Dia Care 2019;42:1661-1668

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Improving Care & Promoting Health In Populations

• Importance of Getting to Goal
  o NHANES Data shows ↓ in national A1c 7.6% (1999-2002) to 7.2% (2007-2010)
  o More older adults reach goal than younger adults
  o A1c < 7% leads to ↓ in end stage microvascular complications

• Cost of Diabetes
  o Annual Cost of Diagnosed Diabetes 2017:
    o $237 Billion– direct medical costs
    o $90 Billion– decreased productivity
    o Increased by >25% from 2012 to 2017

• Patient Centered Care
• Diabetes Self Care and Management

Diabetes Care 2019;42(Suppl.1):S7-S126 https://doi.org/10.2337/dc19-S001
Criteria for Diagnosis of Diabetes

Fasting Plasma Glucose $\geq 126$ mg/dL (fasting is defined as no caloric intake for at least 8 hours)

OR

2 hour Plasma Glucose $\geq 200$ during OGTT (using 75 gm test)

OR

A1c $\geq 6.5$

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis & random sugar $\geq 200$

In absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal tests from the same or separate samples
Hemoglobin A1c

- Use standardized methods for testing to prevent misdiagnosis or missed diagnosis
- Be suspicious of inconsistencies (between plasma glucose levels and A1c readings)
- Be aware of conditions affecting A1c:
  - Hemoglobinopathies
  - Pregnancy (2nd & 3rd Trimesters and Post Partum Period)
  - G6PD Deficiency
  - HIV
  - Hemodialysis
  - Recent change in blood volume (loss or transfusion)
  - Erythropoietin therapy
### Diagnostic Criteria for Prediabetes and Diabetes

<table>
<thead>
<tr>
<th>Test</th>
<th>Prediabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1c</strong></td>
<td>5.7-6.4%</td>
<td>≥ 6.5%</td>
</tr>
<tr>
<td><strong>Fasting Plasma Glucose (mg/dL)</strong></td>
<td><strong>100-125 Impaired Fasting Glucose</strong></td>
<td>≥ 126</td>
</tr>
<tr>
<td><strong>Oral Glucose Tolerance Test –</strong></td>
<td><strong>140-199 Impaired Glucose Tolerance</strong></td>
<td>≥ 200</td>
</tr>
<tr>
<td>2 hours post 75 gm OGTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Random Plasma Glucose</strong></td>
<td></td>
<td>≥ 200</td>
</tr>
</tbody>
</table>

Results should be confirmed with repeat testing on OGTT unless unequivocal hyperglycemia noted. Random blood sugars are only diagnostic with symptoms of hyperglycemia or hyperglycemic crisis. WHO & other organizations define IFG > 110.
Criteria for Testing for Diabetes/Prediabetes

1. Overweight/Obese adults with one or more of the following risk factors
   - 1st Degree Relative with Diabetes
   - High-risk Race/Ethnicity (African American, Latino, Native American, Asian American, or Pacific Islander)
   - History of CVD
   - Hypertension
   - HDL < 35 and/or a Triglyceride > 250
   - Women with Polycystic Ovarian Syndrome
   - Physical Inactivity
   - Other Clinical Conditions Associated with Insulin Resistance

2. Those with Prediabetes should be tested Q1 year
3. Women with history of GDM should be tested Q3 years
4. For all others begin testing at 45
5. If normal, retest at a minimum of 3 years or with change in health status
# Classification of Diabetes

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
<th>Autoimmune Destruction of β Cells Absolute Insulin Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes</td>
<td>Progressive Loss of β Cell Insulin Secretion Often in setting of insulin resistance</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>Diagnosed in 2nd or 3rd Trimester of Pregnancy</td>
</tr>
<tr>
<td>Specific Types</td>
<td>Monogenic Diabetes (MODY) Diseases of Exocrine Pancreatic Function Chemical/Drug Induced Diabetes - Glucocorticoids - Post Transplant Diabetes - Therapy of other Comorbidities</td>
</tr>
</tbody>
</table>
# Staging of Type 1 Diabetes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmunity</strong></td>
<td>• Normoglycemia • Presymptomatic</td>
<td>• Dysglycemia • Presymptomatic</td>
<td>• New Onset Hyperglycemia • Symptomatic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple Autoantibodies</strong></td>
<td>• No IGT or IFG</td>
<td>• Dysglycemia • FPG 100-125 • 2hPPG 140-199 • A1c 5.7-6.4% or ≥10% increase in A1c</td>
<td>• Clinical Symptoms • Diabetes by Standard Criteria</td>
</tr>
</tbody>
</table>

Adapted from Table 2.1 Staging of Type 1 Diabetes ADA Standards of Medical Care in Diabetes 2019
Autoantibodies in T1DM

- Islet Cell
- GAD65
- Insulin
- Tyrosine Phosphatases
  - IA-2
  - IA-2β
Type 1 Risk Assessment
Clinical Research Study

www.trialnet.org
Idiopathic Type 1 Diabetes

- No association with HLA linkage but strongly heritable
- No evidence of B cell autoimmunity
- Most often seen in African/Asian ancestry
- Insulinopenic
- Prone to DKA
- May only have intermittent insulin requirements
Type 2 Diabetes

• 90-95% of all cases of Diabetes
• Relative insulin deficiency with insulin resistance
• Spontaneous DKA RARE, but can be seen with stress/drugs:
  o Infection
  o Concomitant Meds: Corticosteroids, Antipsychotics, SGLT2 inhibitors
• Usually undiagnosed for many years due to gradual presentation of hyperglycemia
Mechanisms of Hyperglycemia in T2DM

- Beta Cell Dysfunction
- Insulin Resistance (liver, fat, & muscle)
- Increased Sympathetic Tone
- Increased SGLT2 Effect
- Alpha Cell Dysfunction (increased glucagon)
- Decreased Amylin
- Decreased Incretin
- Immune Dysregulation/Inflammation
- Microbiome Changes

Prevention/Delay of T2DM

• Annual Monitoring in Prediabetes
• Lifestyle Modifications
  o Diabetes Prevention Program
    • Weight loss 7%
    • Increase Physical Activity to 150 min/week
    • Nutrition Counseling/Calorie Reduction
    • Utilization of Technology (Apps)
    • Tobacco Cessation
• Pharmacologic Therapies
  o Some drugs approved for DM have been show to help decrease conversion to DM but none explicitly approved for Prediabetes
  o Reasonable to recommend Metformin in prediabetes with high risk for progression to Diabetes
• Assessment and Treatment of CV Risks
• Education
Evaluation & Assessment of Comorbidities

- BMI
- BP/Vitals
- Eye Evaluation
- Skin Exam
  - Insulin Resistance Markers—Acanthosis Nigricans & Acrochordans
  - Lipodystrophy
  - Necrobiosis Lipoidica Diabeticorum
- Foot Exam
- Lab Assessment
- Immunizations
- Hyperglycemia/Hypoglycemia
Acanthosis Nigricans

From: www.medicinenet.com
Insulin-Mediated Lipohypertrophy
# A1c Goals in Diabetes

<table>
<thead>
<tr>
<th>&lt; 6.5%</th>
<th>&lt; 7%</th>
<th>&lt; 8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stricter goals for:</td>
<td>Reasonable goal for many non-pregnant adults</td>
<td>Looser goals for:</td>
</tr>
<tr>
<td>- otherwise healthy</td>
<td></td>
<td>- Complicated medical histories,</td>
</tr>
<tr>
<td>- few other comorbidities</td>
<td></td>
<td>- significant hypoglycemia risk</td>
</tr>
<tr>
<td>- lower hypoglycemia risk</td>
<td></td>
<td>- limited life expectancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- advanced microvascular or macrovascular complications</td>
</tr>
</tbody>
</table>
The ABC’s of A1c Trials

A1c Reduction < 7%

- **T1DM**
  - DCCT
  - EDIC
- **T2DM**
  - UKPDS
  - Kumamoto
Finding the Perfect Fit

• ACCORD, ADVANCE, and VADT Trials
  o Too low is not always best
  o Increase Mortality from Risk of Hypoglycemia
  o Trials suggested no significant reduction in CVD outcomes with intensive glucose control
<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent</th>
<th>A1C 7%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>few / mild</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mild</td>
<td>severe</td>
</tr>
<tr>
<td>Patient preference</td>
<td>highly motivated, excellent self-care capabilities</td>
<td>preference for less burdensome therapy</td>
<td></td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
</tr>
</tbody>
</table>

Diabetes Care 2019 Jan; 42(Supplement 1): S61-S70.  
https://doi.org/10.2337/dc19-S006
**Recommended Glycemic Goals for Most Non-Pregnant Adults**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>&lt; 7.0%</td>
</tr>
<tr>
<td>Preprandial Glucose</td>
<td>80-130 mg/dL</td>
</tr>
<tr>
<td>Peak Postprandial Glucose</td>
<td>&lt; 180 mg/dL</td>
</tr>
</tbody>
</table>
Hypoglycemia

- Assess at risk individuals at every visit for symptomatic and asymptomatic low sugars
- Hypoglycemia Unawareness indicates need for treatment reevaluation/de-intensification
- Review Treatment Plans with Patient and Family
  - Glucose always preferred if able to take PO
    - 15-15-15 Rule
  - Glucagon
    - IM
    - Intranasal
## Classification of Hypoglycemia

<table>
<thead>
<tr>
<th>Level of Hypoglycemia</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Glucose &lt; 70 and glucose ≥ 54</td>
</tr>
<tr>
<td>Level 2</td>
<td>Glucose &lt; 54</td>
</tr>
<tr>
<td>Level 3</td>
<td>Severe event with altered mental/physical status and requiring assistance</td>
</tr>
</tbody>
</table>

From Diabetes Care 2019; 42(Suppl.1 ):S61-S70
Lifestyle Management

Critical Times to Address

1. Diagnosis
2. Annually
3. Complications
4. Life Transitions
Goals of Nutrition Therapy

• Promote healthy eating patterns
  o Higher quality nutrients
  o Emphasis on appropriate portion size

• Approach ideal body weight
  o Weight loss
  o Maintenance

• Achieve metabolic goals
  o A1c
  o Blood Pressure
  o Lipids

• Delay/prevent complications of diabetes
• Maintain pleasure and social nature of eating
• There is no single best way to eat
Medical Nutrition Therapy

- Individualized Diet Plan
  - Eating Patterns
  - Macronutrient Distribution
- Energy Balance
- Carbohydrates
- Protein
- Fat
- Dietary Supplements
- Alcohol
- Sodium
- Nonnutritive Sweeteners
Nonnutritive Sweeteners

- May be useful at reducing overall ingested calories and carbohydrates
- Avoid excess
- Potential influence on microbiome
- May lead to further “sweets” cravings
Physical Activity

- Most adults should participate in 150 minutes or more of moderate to vigorous intensity aerobic activity each week
- Resistance Exercise for 2-3 sessions/week on non-consecutive days
- Avoid prolonged sitting
- Flexibility and balance training 2-3 times/week for older adults
How Exercise Helps?

- Glycogen used for fuel in early exercise
- As blood sugars decrease → insulin secretion decreases
- Glucagon rises → stimulates TG use for muscle fuel
- Increased GLUT4 expression → increased glucose sensitivity in peripheral tissues
Pharmacologic Therapies

Type 1 Diabetes

• Basal/Bolus Insulins
  o Basal Dose ~ 50% TDD
  o Prandial Dose Based on Pre Meal Sugar + Ingested CHO
• Multiple Daily Injections
• Insulin Pump Therapy
• Non Insulin Treatments
  o Pramlintide
• Pancreas/Islet Transplants

Type 2 Diabetes

• Oral Hypoglycemics
• Non Insulin Injectables
  • Insulins
    o Basal
    o Prandial
Non Insulin Therapies for Diabetes

- Biguanides (Metformin)
- Sulfonylureas
- Meglitinides
- Alpha Glucosidase Inhibitor
- Thiazolidinediones
- GLP-1 Receptor Agonists
- DPP-4 Inhibitors
- SGLT2 Inhibitors
- Dopamine 2 Agonists
- Amylin Mimetics
- Bile Acid Sequestrants
Where do they work?

- **Insulin secretion**
  - ↑ Sulfonyureas
  - ↑ Meglitinides
  - ↑ Incretins

- **Glucagon secretion**
  - ↓ Incretins
  - ↓ Amylin

- **GI**
  - Incretins
  - α glucosidase inhibitors
  - Amylin
  - Bile acid sequestrant

- **Hepatic glucose output**
  - ↓ Metformin
  - ↓ Thiazolidinediones

- **Lipotoxicity**
  - Thiazolidinediones
  - Salicylates

- **Glucose uptake and utilization**
  - ↑ Thiazolidinediones
  - ↑ Metformin

- **Glucose reabsorption**
  - ↓ SGLT2 inhibitors

- **Appetite control**
  - Incretins
  - Amylin

- **Hyperglycemia**
Galega officinalis (French Lilac)
Gila Monster (*Heloderma suspectum*)
Effects of GLP-1 Agonists

Glycemic

- Corrects deficient GLP-1 state of T2DM (and likely T1DM)
- Promotes insulin secretion in glucose dependent fashion
- Decreases Glucagon Levels
- Slows Gastric Emptying

Non-Glycemic

- Slows Gastric Emptying
- Natriuresis
- Vasodilation
  - ↓ BP
  - ↑ HR
- Increase Satiety
- Improves Lipid Profiles
- Weight Loss
# Differences in Available GLP Agonists

## Short Acting Agents
- Greater effect on Gut-delays gastric emptying
- Reduce post prandial hyperglycemia
  - Exenatide
  - Lixisenatide

## Long Acting Agents
- Greater effect at pancreatic level:
  - ↓ Glucagon
  - ↑ Insulin
- Targets fasting hyperglycemia
  - Liraglutide
  - Exenatide ER
  - Dulaglutide
  - Semaglutide

SGLT-2 Inhibitors

- Phlorizin isolated in 1835 from apple tree bark
- Use as hypoglycemic was limited due to non selectivity and side effects
- Approved in US in 2013
- Associated with weight loss
  - Diuretic properties
  - Glucosuria leading to loss of 100-300 calories/day

Adapted from [www.diabetesincontrol.com](http://www.diabetesincontrol.com) “History of the SGLT2 Inhibitor Drug Class.” Jan. 17, 2014
Concentrated Insulins

Prescribe for your Patients

‘Wellcome’ Insulin

The Insulin of outstanding purity, activity and reliability

Trade ‘WELLCOME’ Brand Insulin
Issued in rubber-capped amber-glass phials containing 100 units in 5 c.c. and 200 units in 5 c.c.; also in rubber-capped bottles containing 200 units in 10 c.c.

Burroughs Wellcome & Co., London (Eng.)

Associated Houses: New York, Montreal, Sydney, Cape Town, Milan, Bombay, Shanghai, Buenos Aires

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Benefits of Concentrated Insulins

- Decreased Hypoglycemia
  - Nocturnal
  - Severe
  - Overall
- Increased flexibility in dosing due to longer duration of action
- Less need for frequent adjustments
- Less variability in activity
- Less risk of “stacking”
- Equivalent or less weight gain

Currently Used Basal Insulins

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Concentration</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>U100</td>
<td>16 hours</td>
</tr>
<tr>
<td>Glargine</td>
<td>U100</td>
<td>~24 hours</td>
</tr>
<tr>
<td>Detemir</td>
<td>U100</td>
<td>~24 hours</td>
</tr>
<tr>
<td>Glargine</td>
<td>U300</td>
<td>&gt; 36 hours</td>
</tr>
<tr>
<td>Degludec</td>
<td>U100 or U200</td>
<td>&gt; 42 hours</td>
</tr>
</tbody>
</table>
Glucose-lowering medication in type 2 diabetes: overall approach.

FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA1c above target proceed as below

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

COST IS A MAJOR ISSUE

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > exenatide > semaglutide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.

2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use

3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs

4. Degludec or U300 glargine have demonstrated CVD safety

5. Low dose may be better tolerated though less well studied for CVD effects

6. Choose later generation SU with lower risk of hypoglycemia

7. Degludec or glargine U300 < glargine U100 / detemir < NPH insulin

8. Semaglutide > liraglutide > dulaglutide > exenatide > exenatide

9. If no specific comorbidities (i.e., low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities) consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

10. Consider dual use - GLP-1 RA and metformin. In patients with weight loss and no risk factors for CVD, consider use of GLP-1 RA alone.

American Diabetes Association Dia Care 2019;42:S90-S102
Intensifying to injectable therapies.

- **INITIATION FOR GLP-1 RA**
  - Initiate starting dose (varies across class)

- **TITRATION FOR GLP-1 RA**
  - Gradual titration to maintenance dose (varies across class)

- **INITIATION FOR BASAL**
  - Start 10 IU a day OR 0.1-0.2 IU/kg a day

- **TITRATION FOR BASAL**
  - Patient self titration is more effective
  - Set FPG target that correlates to HbA1c target
  - Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
  - For hypoglycemia determine causes, if no clear reason lower dose by 10-20%

- **INITIATION FOR PRANDIAL**
  - 4 IU a day or 10% of basal dose
  - If HbA1c >6.4 mmol/mol (45%) consider lowering the total dose by 10% a day or 10% of basal dose

- **TITRATION FOR PRANDIAL**
  - Increase dose by 1-2 IU or 10-15% twice weekly
  - For hypoglycemia determine causes, if no clear reason lower corresponding dose by 10-30%

- **INITIATION OF STEPSWIZE PRANDIAL**
  - Stepwise addition of prandial insulin every 3 months if HbA1c >6.4 mmol/mol (45%)
  - Stepped add of prandial insulin every 3 months if HbA1c >6.4 mmol/mol (45%) and risk of hypoglycemia and increase patient satisfaction compared with immediate introduction of full basal-bolus regimen

- **TITRATION FOR PRANDIAL**
  - Proceed to FULL basal-bolus regimen (i.e., basal insulin and prandial insulin with each meal)

- **Consider GLP-1 RA in most prior to insulin**
  - Consider: INITIATION + TITRATION

- **Consider insulin as first injectable**
  - HbA1c very high >97 mmol/mol (17%)
  - Symptom or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
  - If type 1 diabetes is a possibility

- **Add basal insulin**
  - For patient on GLP-1 RA and basal insulin
  - Consider IRC of GLP-1 RA and insulin (Dexi, lis, or EliLan)
  - But note max dose of insulin in the IRCs

- **If above HbA1c target**
  - Titrated to FPG target and tolerability

- **If already on GLP-1 RA or if GLP-1 RA not appropriate or insulin preferred**
  - If on GLP-1 RA use 10-15 dose steps (Dexi, lis) or 10-15 units (EliLan, Lan)
  - Titrated to FPG target and tolerability

- **If above HbA1c target**
  - Add prandial insulin
  - Usually one dose with the largest meal or meal with greatest PPG excursion
  - Consider: INITIATION + TITRATION

- **If above HbA1c target**
  - Additional basal insulin or additional prandial insulin
  - Consider twice or three times daily premix insulin regimen

- **If above HbA1c target**
  - Caution higher risk of hypoglycemia and/or weight gain
  - Consider: INITIATION + TITRATION

- **If above HbA1c target**
  - Individual dose adjustment depends on type of basal insulin
  - More complex if on three times daily regimen

1. When selecting GLP-1 RA, consider: patient preference, HbA1c lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.
Diabetes Technology

The first insulin pump created by Dr. Arnold Kadish in California in 1963 which delivered both insulin and glucagon.

From: www.medscape.org
Continuous Glucose Monitoring Sensors
CGM-based targets for different diabetes populations.
Ambulatory Glucose Profile

AGP Report

GLUCOSE STATISTICS AND TARGETS

26 Feb 2019-10 Mar 2019 13 days
% Time CGM is Active 99.9%

Glucose Ranges Targets [% of Readings (Time/Day)]
Target Range 70–180 mg/dL Greater than 70% (16h 48min)
Below 70 mg/dL Less than 4% (58min)
Below 54 mg/dL Less than 1% (140min)
Above 180 mg/dL Less than 25% (6h)
Above 250 mg/dL Less than 5% (1h 12min)
Each 5% increase in time in range (70–180 mg/dL) is clinically beneficial.

Average Glucose 173 mg/dL
Glucose Management Indicator (GMI) 7.6%
Glucose Variability 49.5%
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

Very High (<280 mg/dL) 20% (4h 48min)
High (181–250 mg/dL) 23% (5h 31min)
Target Range (70–180 mg/dL) 47% (11h 17min)
Low (54–99 mg/dL) 4% (58min)
Very Low (<54 mg/dL) 6% (1h 26min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.

DAILY GLUCOSE PROFILES

Each daily profile represents a midnight-to-midnight period.

Tadej Battelino et al. Dia Care 2019;42:1593-1603
Obesity Management for the Treatment of T2DM

• Lifestyle
  o Dietary Goals → >5% weight loss and maintained
  o Intense Behavioral Therapy
    • Focus on diet, exercise, and behavioral strategies
    • ≥ 16 sessions in 6 months

• Pharmacotherapy
• Metabolic Surgery
<table>
<thead>
<tr>
<th>Drug</th>
<th>% Weight Loss</th>
<th>Side Effects</th>
<th>Safety Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>5.5-6.1</td>
<td>Dry Mouth</td>
<td>Severe HTN CI with MAOI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Irritability</td>
<td></td>
</tr>
<tr>
<td>Orlistat</td>
<td>5.6-9.6</td>
<td>Abdominal Pain</td>
<td>Malabsorption Cholelithiasis Nephrolithiasis Liver Injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gas</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Fecal Urgency</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Back Pain</td>
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<tr>
<td></td>
<td></td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>4.5</td>
<td>Headache</td>
<td>Serotonin &amp; Neuroleptic Malignant Syndrome Worsening HTN</td>
</tr>
<tr>
<td></td>
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<td>Nausea</td>
<td>CI with uncontrolled HTN or Seizures Acute Angle Glaucoma</td>
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<td>Fatigue</td>
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<td></td>
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<td>Dizziness</td>
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<td>Phentermine/Topiramate ER</td>
<td>7.8-9.8</td>
<td>Constipation</td>
<td>Birth Defects Cognitive Impairment Acute Angle Glaucoma</td>
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<td>Paresthesia</td>
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<td>Insomnia</td>
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<td>Xerostomia</td>
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<tr>
<td>Naltrexone/Bupropion ER</td>
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<td>GI Symptoms</td>
<td>CI with uncontrolled HTN or Seizures Acute Angle Glaucoma</td>
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<td></td>
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<td>Headache</td>
<td>BLACK BOX: SI</td>
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<tr>
<td></td>
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<td>Xerostomia</td>
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<td></td>
<td></td>
<td>Insomnia</td>
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</tr>
<tr>
<td>Liraglutide</td>
<td>2.0-6.0</td>
<td>Hypoglycemia</td>
<td>Acute pancreatitis BLACK BOX: Risk of thyroid C cell tumors</td>
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<tr>
<td></td>
<td></td>
<td>GI Symptoms</td>
<td>&amp; CI with h/o MTC or MEN 2</td>
</tr>
</tbody>
</table>
Metabolic Surgery Recommendations

• Metabolic surgery should be recommended as an option to treat T2DM in appropriate candidates with BMI ≥ 40 & in adults with BMI 35-39.9 who do not achieve durable weight loss and improvement in comorbidities with reasonable nonsurgical methods.

• Metabolic surgery may be considered as an option for adults with T2DM and BMI 30-34.9 who do not achieve durable weight loss and improvement in comorbidities with reasonable nonsurgical methods.

From: Obesity Management for the Treatment of T2DM: Standards of Medical Care in Diabetes— 2019. Diabetes Care 2019;42(Suppl.1):S81-89
CV Disease & Risk Management

• Achieve BP goals:
  o _DM +HTN with higher ASCVD risk /10 yr atherosclerotic CVD risk > 15% consider target BP < 130/80
  o DM + HTN with lower risk for CVD.10 yr atherosclerotic risk < 15% use goal BP < 140/90
  o Antihypertensive therapy reduces risk of CVA, retinopathy & albuminuria

• Lifestyle Interventions
  o DASH Diet
  o Mediterranean Diet
  o Physical Activity

• Lipids
  o High Intensity Statin- DM + ASCVD or 10 year risk > 20%
  o Moderate Intensity Statin- DM Age > 40 without additional CV RF
  o No Statin Age < 40 without ASCVD or risk < 20%
  o Consider PCSK9 or Ezetimibe if LDL remains ≥ 70
High & Moderate Intensity Statin Therapies

**High Intensity**
- Atorvastatin 40-80 mg
- Rosuvastatin 20-40 mg

**Moderate Intensity**
- 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

From: verywellhealth.com
CV Outcome Trial Summary

- EMPA-REG
  - Empagliflozin reduced risk of MI, CVA and CV death by 14% & CV death by 38%

- CANVAS
  - Canagliflozin reduced risk of CV death, MI, & CVA vs Placebo
  - Increased risk of lower limb amputation with Canagliflozin

- LEADER
  - Liraglutide reduced risk of MI, CVA or CV death as compared to placebo

- SUSTAIN-6
  - Semaglutide results consistent with LEADER

- ELIXA
  - Lixisenatide was non-inferior to placebo but not superior at reducing CV outcomes

- EXSCEL
  - Exenatide Qweek showed non-inferiority but not superior to primary end point

From: Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes–2019. Diabetes Care 2019;42(Suppl.1):S103-S123
Microvascular Complications-- CKD

- Assess spot urine/creatinine ratio annually
- Optimize glycemic & BP control (< 140/90)
- Consider SGLT2i or GLP1 agonist in T2DM as may reduce progression of CKD
- Consider ACE/ARB in patients with albumin/Cr > 30 (strongly encouraged if > 300)
- Periodically monitor K and Cr
- Refer for renal evaluation when needed

**ACE/ARB therapy not recommended for primary prevention of CKD in patients with DM with normal BP and normal eGFR and normal microalbumin/creatinine ratio**

**Combined use of ACE and ARB not recommended**
Microvascular Complications-- Retinopathy

- Optimize lipids, BP, and glycemic control
- Refer to ophthalmologist
- Women planning pregnancy should be followed closely

Treatments include:
  - Laser Photocoagulation
  - anti-VEGF Therapies

Microvascular Complications-- Neuropathy

- Begin assessing at diagnosis in T2DM
  - Small fiber function with temperature/pin prick sensation
  - Large fiber function with tuning fork
  - Protective sensation with 10 gm Monofilament

- Optimize glucose control to delay diagnosis and prevent progression of neuropathy in T2DM

- Pharmacologic options:
  - Pregabalin
  - Duloxetine
  - Gabapentin

From webmd.com
Diabetic Autonomic Neuropathy

- Hypoglycemia Unawareness
- Tachycardia at Rest
- Orthostatic Hypotension
- Gastroparesis
- Constipation/Diarrhea
- Fecal Incontinence
- Erectile Dysfunction
- Neurogenic Bladder
- Sudomotor dysfunction

From: www.skillscommons.org
Foot Care in Diabetes

• Perform annual comprehensive foot exam
  o Skin Inspection
  o Foot Deformities
  o Neurological Testing (monofilament + one more test)
  o Vascular Assessment - check pulses

• Inspect those with sensory loss or prior ulceration or amputation at EVERY visit

• Encourage Tobacco Cessation

• Educate on self foot care

From: Diabetes Care 2011 Sep; 34(9): 2123-2129. https://doi.org/10.2337/dc11-0844
Insulin Resistance in NAFLD

Leite, NC et al Non-alcoholic fatty liver disease and diabetes: from physiopathological interplay to diagnosis and treatment. World J Gastroenterology July 2014;20(26): 8377-8392
Diabetes in Older Adults

• Prevalence of Diabetes in Older Adults
  o ¼ of all Adults > 65 years have Diabetes
  o ½ of all older adults have Prediabetes
• Assess Diabetes Self Management Skills
• Hypoglycemia Risk
• Consider Adjustment of Glycemic/Lipid/BP Goals:

<table>
<thead>
<tr>
<th>Healthy Individuals</th>
<th>A1c &lt; 7.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex Comorbidities</td>
<td>A1c &lt; 8.0%</td>
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<tr>
<td>Mild to Moderate Impairment of Cognition</td>
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<tr>
<td>and Effects on ADL</td>
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<tr>
<td>Complex Health Issues and Functional</td>
<td>A1c &lt; 8.5%</td>
</tr>
<tr>
<td>Status</td>
<td></td>
</tr>
</tbody>
</table>
Diabetes in Older Adults

- **Metformin**
  - OK for GFR > 30 but not to be used with ESRD and should be used cautiously with CHF or impaired hepatic function

- **Thiazolidinediones**
  - Use caution (if at all) with or at risk for CHF or high falls/fracture

- **Sulfonylureas**
  - Use caution due to increase hypoglycemia risk
  - Glyburide contraindicated in older adults (due to longer duration)

- **Incretins (DPP4/GLP agents)**
- **SGLT2 agents**
- **Insulins**
# Patients Perceptions on Need for Aggressiveness of DM Therapy

<table>
<thead>
<tr>
<th>Hypothetical Patient Factor</th>
<th>Study Participant Perception Relative to Guideline Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Duration of DM</td>
<td></td>
</tr>
<tr>
<td>- 5 years</td>
<td>Discordant</td>
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<tr>
<td>- 15 years</td>
<td></td>
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<tr>
<td>DM Complications</td>
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<tr>
<td>- None</td>
<td>Discordant</td>
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<tr>
<td>- Severe</td>
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<tr>
<td>Comorbidities</td>
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</tr>
<tr>
<td>- None</td>
<td>Discordant</td>
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<tr>
<td>- Many</td>
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</tr>
<tr>
<td>Life Expectancy</td>
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</tr>
<tr>
<td>- 5 years</td>
<td>Concordant</td>
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<tr>
<td>- 15 years</td>
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<tr>
<td>Adverse Event Risk</td>
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<tr>
<td>- High Risk</td>
<td>Concordant</td>
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<tr>
<td>- Low Risk</td>
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</tbody>
</table>

Summary of Revisions: Standards of Medical Care in Diabetes-2019

- **Diagnosis**
  - Inclusion of 2 abnormal test results from the SAME sample
  - Additions to conditions affecting A1c accuracy

- **Prevention/Delay**
  - Nutritional Updates
  - Tobacco Cessation

- **Comorbidity Assessment**
  - Avoidance of Clinical Inertia
  - Hypoglycemia Risk Assessment
  - ASCVD Risk
  - Fatty Liver

- **Lifestyle Management**
  - Macronutrient Patterns to be Individualized
  - Decrease Sweetened and Artificially Sweetened Beverages
  - Sodium Consumption

- **Glycemic Targets**
  - Fluidity of A1c Goals

- **Diabetes Technology**

- **Obesity Management for Treatment of T2DM**
  - Health Trackers
  - Recommendations for Metabolic Surgery

- **Pharmacologic Therapies**

- **CV Disease & Risk**

- **Microvascular Complications & Foot Care**

- **Older Adults**

- **Diabetes in the Hospital**

Diabetes Care 2019;42(Suppl.1):S4-S6 https://doi.org/10.2337/dc19-srev01
**Gut Microbiome**

- **Important Microbial Roles in Gut:**
  - Breakdown of indigestible fibers
  - Biosynthesis of amino acids and vitamins
  - Neurotransmitter/Hormone Production

- **Therapeutic Targets for Diabetes and Obesity**
  - Alterations in microbiome composition
  - Genetic alteration to bacteria
  - Targeting specific regions of colonic delivery
  - Pro/Pre Biotics and Personalized Nutrition

- **Changes in microbiome composition following bariatric surgery**

Changes to Gut Microbiome in Diabetes

- **↓ Butyrate** producing bacteria seen in DM
  - may be improved with metformin treatment
- **↑ Branched Chain Amino Acids** associated with increase in Insulin Resistance
- **Akkermansia muciniphil** = a potential biomarker of Glucose Intolerance
- **Prevotella** genus is associated with **↑ fiber diets**
  - May enhance digestion of complex polysachharides
Inpatient Diabetes Care

• **A1c Status**

• **Treat persistent hyperglycemia ≥ 180 with insulin**
  - Glucose Targets on Insulin 140-180
  - More stringent goals (110-140) for select patients if low risk of hypoglycemia

• **Preferred Therapies for Hyperglycemia in Hospital:**
  - Basal/Prandial/Correction Doses of Insulin
  - Discourage “sliding scale” as sole treatment
  - Restart PO agents prior to D/C when patient is eating normally

• **Avoid Hypoglycemia**
  - Begin treating < 70
  - Recognize common triggers
    - ↓ PO intake, ↓ corticosteroids, NPO status
Simplification of Complex Insulin Therapy

Patient on basal (long- or intermediate-acting) and/or mealtime (short- or rapid-acting) insulins

- **Basal insulin**
  - Change timing from bedtime to morning
  - Titrate dose of basal insulin based on fasting fingerstick glucose test results over a week
    - Fasting Goal: 90–150 mg/dL (4.9–8.3 mmol/L)
      - May change goal based on overall health and goals of care
    - If 50% of the fasting fingerstick glucose values are over the goal:
      - ↑ dose by 2 units
    - If ≥2 fasting fingerstick values/week are <80 mg/dL (4.4 mmol/L):
      - ↓ dose by 2 units

- **Mealtime insulin**
  - If mealtime insulin >10 units/dose:
    - ↓ dose by 50% and add noninsulin agent
    - Titrate mealtime insulin doses down as noninsulin agent doses are increased with aim to discontinue mealtime insulin
  - If mealtime insulin ≤10 units/dose:
    - Discontinue mealtime insulin and add noninsulin agent(s)

Patient on premixed insulin

- Use 70% of total dose as basal only in the morning

**Additional Tips**
- Do not use short-acting insulin at bedtime
- While adjusting mealtime insulin, may use simplified sliding scale, for example:
  - Premeal glucose >250 mg/dL (13.9 mmol/L), give 2 units of short- or rapid-acting insulin
  - Premeal glucose >350 mg/dL (19.4 mmol/L), give 4 units of short- or rapid-acting insulin
- Stop sliding scale when not needed daily

Using patient and drug characteristics to guide decision making, as depicted in Fig. 9.1 and Table 9.1, select additional agent(s) as needed:
- Every 2 weeks, adjust insulin dose and/or add glucose-lowering agents based on fingerstick glucose testing performed before lunch and before dinner
- Goal: 90–150 mg/dL (4.9–8.3 mmol/L) before meals; may change goal based on overall health and goals of care
- If 50% of premeal fingerstick values over 2 weeks are above goal, increase the dose or add another agent
- If >2 premeal fingerstick values/week are <90 mg/dL (4.9 mmol/L), decrease the dose of medication

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