1. STRATEGIES FOR IMPROVING DIABETES CARE
Recommendations: Strategies for Improving Diabetes Care (1)

- Care should be aligned with components of the Chronic Care Model to ensure productive interactions between a prepared proactive practice team and an informed activated patient.

- When feasible, care systems should support team-based care, community involvement, patient registries, and embedded decision support tools to meet patient needs.

Recommendations: Strategies for Improving Diabetes Care (2)

- Treatment decisions should be timely, based on evidence-based guidelines tailored to individual patient preferences, prognoses, and comorbidities.

- A patient-centered communication style should be employed that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care.
Diabetes Care Concepts

The American Diabetes Association highlights three themes that are woven throughout the Standards of Care in Diabetes that clinicians, policymakers, and advocates should keep in mind:

a) **Patient-Centeredness**: The science and art of medicine come together when the clinician is faced with making treatment recommendations for a patient who would not have met eligibility criteria for the studies on which guidelines were based.

b) **Diabetes Across the Lifespan**: There is a need to improve coordination between clinical teams as patients pass through different stages of the life span or the stages of pregnancy (preconception, pregnancy, and postpartum.)

Objective 1: Optimize Provider and Team Behavior

- Care team should prioritize timely, appropriate intensification of lifestyle and/or pharmaceutical therapy
  - Patients who have not achieved beneficial levels of blood pressure, lipid, or glucose control

- Strategies include
  - Explicit goal setting with patients
  - Identifying and addressing barriers to care
  - Integrating evidence-based guidelines
  - Incorporating care management teams
Objective 2: Support Patient Behavior Change

- Implement a systematic approach to support patient behavior change efforts
  a) Healthy lifestyle: physical activity, healthy eating, nonuse of tobacco, weight management, effective coping
  b) Disease self-management: medication taking and management, self-monitoring of glucose and blood pressure when clinically appropriate
  c) Prevention of diabetes complications: self-monitoring of foot health, active participation in screening for eye, foot, and renal complications, and immunizations

2. CLASSIFICATION AND DIAGNOSIS OF DIABETES
Classification of Diabetes

- Type 1 diabetes
  - β-cell destruction
- Type 2 diabetes
  - Progressive insulin secretory defect
- Other specific types of diabetes
  - Genetic defects in β-cell function, insulin action
  - Diseases of the exocrine pancreas
  - Drug- or chemical-induced
- Gestational diabetes mellitus (GDM)

Criteria for the Diagnosis of Diabetes

- A1C ≥6.5%
  - OR
- Fasting plasma glucose (FPG) ≥126 mg/dL
  - OR
- 2-h plasma glucose ≥200 mg/dL during an OGTT
  - OR
- A random plasma glucose ≥200 mg/dL
Criteria for the Diagnosis of Diabetes

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL

Categories of Increased Risk for Diabetes (Prediabetes)*

FPG 100–125 mg/dL: IFG

OR

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

OR

A1C 5.7–6.4%

*For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.
**Recommendations: Testing for Diabetes in Asymptomatic Patients**

- Consider testing overweight/obese adults (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) with one or more additional risk factors for type 2 diabetes; for all patients, particularly those who are overweight, testing should begin at age 45 years.
- If tests are normal, repeat testing at least at 3-year intervals is reasonable.
- To test for diabetes/prediabetes, the A1C, FPG, or 2-h 75-g OGTT are appropriate.
- In those with prediabetes, identify and, if appropriate, treat other CVD risk factors.

**Criteria for Testing for Diabetes in Asymptomatic Adult Individuals (1)**

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) and have additional risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - Women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovarian syndrome (PCOS)
   - A1C ≥5.7%, IGT, or IFG on previous testing
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - History of CVD
2. In the absence of criteria (risk factors on previous slide), and particularly in those who are overweight or obese, testing for diabetes should begin at age 45 years.

3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly), and risk status.
A complete medical evaluation should be performed to
- Classify the diabetes
  - Detect presence of diabetes complications
  - Review previous treatment, risk factor control in patients with established diabetes
  - Assist in formulating a management plan
  - Provide a basis for continuing care
- Perform laboratory tests necessary to evaluate each patient’s medical condition

Screening Recommendation
- Consider screening those with type 1 diabetes for other autoimmune diseases (thyroid, vitamin B12 deficiency, celiac) as appropriate

Medical history (1)
- Age and characteristics of onset of diabetes (e.g., DKA, asymptomatic laboratory finding
- Eating patterns, physical activity habits, nutritional status, and weight history; growth and development in children and adolescents
- Diabetes education history
- Review of previous treatment regimens and response to therapy (A1C records)
Medical history (2)
• Current treatment of diabetes, including medications, adherence and barriers thereto, meal plan, physical activity patterns, readiness for behavior change
• Results of glucose monitoring, patient’s use of data
• DKA frequency, severity, cause
• Hypoglycemic episodes
  – Hypoglycemic awareness
  – Any severe hypoglycemia: frequency, cause

Components of the Comprehensive Diabetes Evaluation (3)

Medical history (3)
• History of diabetes-related complications
  – Microvascular: retinopathy, nephropathy, neuropathy
    • Sensory neuropathy, including history of foot lesions
    • Autonomic neuropathy, including sexual dysfunction and gastroparesis
  – Macrovascular: CHD, cerebrovascular disease, PAD
  – Other: psychosocial problems,* dental disease*

*See appropriate referrals for these categories.
Components of the Comprehensive Diabetes Evaluation (4)

Physical examination (1)
- Height, weight, BMI
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination
- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)

Components of the Comprehensive Diabetes Evaluation (5)

Physical examination (2)
- Comprehensive foot examination
  - Inspection
  - Palpation of dorsalis pedis and posterior tibial pulses
  - Presence/absence of patellar and Achilles reflexes
  - Determination of proprioception, vibration, and monofilament sensation
**Components of the Comprehensive Diabetes Evaluation (6)**

**Laboratory evaluation**
- A1C, if results not available within past 3 months
- If not performed/available within past year
  - Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides
  - Liver function tests
  - Test for urine albumin excretion with spot urine albumin-to-creatinine ratio
  - Serum creatinine and calculated GFR
  - TSH in type 1 diabetes, dyslipidemia, or women over age 50 years

**Components of the Comprehensive Diabetes Evaluation (7)**

**Referrals**
- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for MNT
- Diabetes self-management education/support
- Dentist for comprehensive periodontal examination
- Mental health professional, if needed
Diabetes Care: Management

• People with diabetes should receive medical care from a team that may include
  – Physicians, nurse practitioners, physician’s assistants, nurses, dietitians, pharmacists, mental health professionals
  – In this collaborative and integrated team approach, essential that individuals with diabetes assume an active role in their care

• Management plan should recognize diabetes self-management education (DSME) and on-going diabetes support

Recommendation: Assessment of Common Comorbid Conditions

• Consider assessing for and addressing common comorbid conditions that may complicate the management of diabetes

• Common comorbidities
  Depression                                Cognitive impairment
  Obstructive sleep apnea                   Low testosterone in men
  Fatty liver disease                       Periodontal disease
  Cancer                                    Hearing impairment
  Fractures
6. GLYCEMIC TARGETS

**Diabetes Care: Glycemic Control**

- Two primary techniques available for health providers and patients to assess effectiveness of management plan on glycemic control
  - Patient self-monitoring of blood glucose (SMBG), or interstitial glucose
  - A1C
**Recommendations: Glucose Monitoring (1)**

- Patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG
  - Prior to meals and snacks
  - Occasionally postprandially
  - At bedtime
  - Prior to exercise
  - When they suspect low blood glucose
  - After treating low blood glucose until they are normoglycemic
  - Prior to critical tasks such as driving

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**Recommendations: Glucose Monitoring (3)**

- When used properly, CGM in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥ 25 years) with type 1 diabetes.

- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.
**Recommendations: A1C**

- Perform the A1C test at least two times a year in patients meeting treatment goals (and have stable glycemic control)

- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals

- Use of point-of-care (POC) testing for A1C provides the opportunity for more timely treatment changes

**Mean Glucose Levels for Specified A1C Levels**

<table>
<thead>
<tr>
<th>A1C%</th>
<th>Mean Plasma Glucose*</th>
<th>Mean Fasting Glucose</th>
<th>Mean Premeal Glucose</th>
<th>Mean Postmeal Glucose</th>
<th>Mean Bedtime Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/dL</td>
<td>mmol/L</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
</tr>
<tr>
<td>6</td>
<td>126</td>
<td>7.0</td>
<td>122</td>
<td>118</td>
<td>144</td>
</tr>
<tr>
<td>&lt;6.5</td>
<td>142</td>
<td>8.6</td>
<td>152</td>
<td>152</td>
<td>176</td>
</tr>
<tr>
<td>6.5-6.99</td>
<td>167</td>
<td>10.2</td>
<td>185</td>
<td>179</td>
<td>206</td>
</tr>
<tr>
<td>7</td>
<td>183</td>
<td>11.8</td>
<td>212</td>
<td>13.4</td>
<td>240</td>
</tr>
<tr>
<td>8</td>
<td>269</td>
<td>14.9</td>
<td>298</td>
<td>16.5</td>
<td></td>
</tr>
</tbody>
</table>

*These estimates are based on ADA data of ~2,700 glucose measurements over 1 month per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92. A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dL or mmol/L, is available at http://professional.diabetes.org/eAG.*
• Lowering A1C to below or around 7% has been shown to reduce microvascular complications and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease.

• Therefore, a reasonable A1C goal for many nonpregnant adults is <7%

**Recommendations:** Glycemic Goals in Adults (1)

**Recommendations:** Glycemic Goals in Adults (2)

• Providers might reasonably suggest more stringent A1C goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment.

• Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD
Recommendations: Glycemic Goals in Adults (3)

- Less stringent A1C goals (such as <8%) may be appropriate for patients with
  - History of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions
  - Those with longstanding diabetes in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin

Approach to the Management of Hyperglycemia

- Table showing the relationship between patient/disease features and A1C goals.
  - More stringent care needed for high-risk patients.
  - Less stringent care needed for low-risk patients.

Source:
ADA. 6. Glycemic Targets. Diabetes Care 2015;38(suppl 1):S37. Figure 6.1; adapted with permission from Inzucchi SE, et al. Diabetes Care, 2015;38:140-149
**Glycemic Recommendations for Nonpregnant Adults with Diabetes (1)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt;7.0%*</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>80–130 mg/dL*  (4.4–7.2 mmol/L)</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose†</td>
<td>&lt;180 mg/dL*  (&lt;10.0 mmol/L)</td>
</tr>
</tbody>
</table>

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

**Glycemic Recommendations for Nonpregnant Adults with Diabetes (2)**

- Goals should be individualized based on
  - Duration of diabetes
  - Age/life expectancy
  - Comorbid conditions
  - Known CVD or advanced microvascular complications
  - Hypoglycemia unawareness
  - Individual patient considerations
Recommendations: Hypoglycemia (1)

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter

- Glucose (15–20 g) preferred treatment for conscious individual with hypoglycemia

- Glucagon should be prescribed for all individuals at significant risk of severe hypoglycemia and caregivers/family members instructed in administration

7. APPROACHES TO GLYCEMIC TREATMENT
Recommendations: Pharmacological Therapy For Type 1 Diabetes

Most people with type 1 diabetes should:

• Be treated with MDI injections (3–4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII)

• Be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity

• Use insulin analogs to reduce hypoglycemia risk

Recommendations: Pharmacological Therapy For Type 2 Diabetes (1)

• Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes

• In patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy (with or without additional agents)
**Recommendations: Therapy for Type 2 Diabetes (2)**

- If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or insulin.

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**Recommendations: Therapy for Type 2 Diabetes (3)**

- A patient-centered approach should be used to guide choice of pharmacological agents:
  - Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences.

- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
The Present

- Metformin
- Thiazolidinediones (TZD's) (pioglitazone)
- Sulfonlyureas/glinder (glyburide, glipizide, glimepiride)
- Glucagon-like peptide-1 (GLP-1) agonists
  - Exenatide (Byetta, LAR-Bydureon)
  - Linglutide (Victoza)
  - Dulaglutide (Trulicity)
  - Albiglutide (Tanzeum)

- Dipeptidiyl peptidase 4 (DPP-4) inhibitor
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Linagliptin (Tradjenta)
  - Alogliptin (Nesina)

- Alpha glucosidase inhibitors
  - acarbose

- Sodium glucose co-transporter 2 (SGLT2) inhibitor
  - Canagliflozin (Invokana)
  - Empagliflozin (Jardiance)
  - Dapagliflozin (Farxiga)
The Ominous Octet

- Islet β-cell
  - Impaired Insulin Secretion
- Islet α-cell
  - Increased Glucagon Secretion
  - Increased HGP
- Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

Hyperglycemia
Current Oral Therapies Do Not Address the Multiple Defects in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Glucose influx from GI tract</th>
<th>Impaired insulin action</th>
<th>Inadequate glucagon suppression (α-cell dysfunction)</th>
<th>Acute β-cell dysfunction</th>
<th>Chronic β-cell decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>TZDs²</td>
<td>unmet need</td>
<td>Sultfonylureas</td>
<td>unmet need</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td>Glinides</td>
<td></td>
</tr>
</tbody>
</table>

↑ Plasma glucose and disease progression

1 Gastrointestinal
2 Thiazolidinedione
DeFronzo RA. Br J Diabetes Vasc Dis. 2003;3(suppl 1):S24–S40

Action of glucagon

Low blood glucose promotes glucagon release from α-cells of pancreas

Glucagon stimulates breakdown of glycogen

Raises blood glucose
Insulin and glucagon dynamics in response to meals in normal subjects and Type 2 diabetes

- **Glucose (mmol/l)**
  - Type 2 diabetes
  - Normal subjects

- **Insulin (mU/l)**
  - Delayed/depressed insulin response
  - Normal subjects

- **Glucagon (ng/l)**
  - Nonsuppressed glucagon
  - Normal subjects

<table>
<thead>
<tr>
<th>Meal Time (min)</th>
<th>-60</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/l)</td>
<td>18.3</td>
<td>16.6</td>
<td>15.0</td>
<td>13.3</td>
<td>6.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>120</td>
<td>90</td>
<td>60</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glucagon (ng/l)</td>
<td>140</td>
<td>130</td>
<td>120</td>
<td>110</td>
<td>100</td>
<td>90</td>
</tr>
</tbody>
</table>

Normal subjects n=11; Type 2 diabetes n=12

**β-Cell function and glucagon in Type 2 diabetes**

- Loss of β-cell function and glucagon over-secretion both play key roles in Type 2 diabetes development
  - Progressive β-cell decline is coupled with inadequate insulin secretion
  - Glucagon is not suppressed during the postprandial period
  - Hepatic glucose production is increased during the fasting period and is not suppressed during the postprandial period
GLP-1: effects in humans

GLP-1 is secreted from L-cells of the jejunum and ileum

After food ingestion...

- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Leads to a reduction of food intake
- Improves insulin sensitivity

That in turn...

Long-term effects in animal models:
- Increase of β-cell mass and improved β-cell function

Drucker. Mol Endocrinol. 2003

Incretin effect on insulin secretion

Control subjects (n=8)  People with Type 2 diabetes (n=14)

Incretin effect

Oral glucose load
Intravenous glucose infusion

Nauck et al. Diabetologia. 1986
Postprandial GLP-1 levels are decreased in people with IGT and Type 2 diabetes

Toft-Nielsen et al. J Clin Endocrinol Metab. 2001

GLP-1 (pmol/l)

*P<0.05 T2DM vs NGT

Nauck et al. Diabetologia. 1993

Therapeutic effect of GLP-1 in people with Type 2 diabetes
GLP-1 enhancement

- GLP-1 secretion is impaired in Type 2 diabetes
  - Natural GLP-1 has extremely short half-life

Add GLP-1 analogues with longer half-life:
- Injectables

Block DPP-4, the enzyme that degrades GLP-1:
- Oral agents

---

The Kidneys Play an Important Role in Glucose Control

Normal Renal Glucose Physiology

- 180 g of glucose is filtered each day
- Virtually all glucose reabsorbed in the proximal tubules & reenters the circulation
- SGLT2 reabsorbs about 90% of the glucose
- SGLT1 reabsorbs about 10% of the glucose
- Virtually no glucose excreted in urine

---

Targeting the Kidney

Renal Glucose Transport
SGLT2 Inhibitors

- Canagliflozin (Invokana)
- Empagliflozin (Jardiance)
- Dapagliflozin (Farxiga)

Canagliflozin

Metformin + Canagliflozin Dose-Ranging Study

Mean Baseline A1C (%)

<table>
<thead>
<tr>
<th>Dose</th>
<th>A1C</th>
<th>ΔA1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>7.71</td>
<td>-0.22%</td>
</tr>
<tr>
<td>50 mg</td>
<td>8.01</td>
<td>-0.79%</td>
</tr>
<tr>
<td>100 mg</td>
<td>7.81</td>
<td>-0.76%</td>
</tr>
<tr>
<td>200 mg</td>
<td>7.57</td>
<td>-0.70%</td>
</tr>
<tr>
<td>300 mg</td>
<td>7.70</td>
<td>-0.92%</td>
</tr>
<tr>
<td>300 mg BID</td>
<td>7.71</td>
<td>-0.95%</td>
</tr>
<tr>
<td>SITA 100 mg</td>
<td>7.62</td>
<td>-0.74%</td>
</tr>
</tbody>
</table>


*P<.001 vs. placebo calculated using LS means
Canagliflozin Trials

- Symptomatic genital infections in 3-8% canagliflozin arms
  - 2% placebo
  - 2% SITA

- Urinary tract infections in 3-9% canagliflozin arms
  - 6% placebo
  - 2% SITA

- Hypoglycemia in 0-6% canagliflozin arms
  - 2% placebo
  - 5% SITA
Summary

• Type 2 diabetes is marked by several core defects that lead to development and progression of disease

• A number of Novel agents offer alternative treatments that not only improve glycemic control, but also target some of the core defects causing the disease

Summary

• Incretin based therapy has a role early in treatment of Type 2 diabetes

• SGLT2 inhibitors offer a new, novel therapy that can also offers promise in respect to improved glycemic control