Management of Type 2 Diabetes: An Update and Review of Non-Injectable Pharmacological Treatment

Richard Arakaki M.D.

Endocrinologist and Clinical Consultant, IHS Division of Diabetes Treatment and Prevention; and
Professor Emeritus, University of Hawaii-Manoa

Nothing to disclose
Objectives

• Describe the prevalence and burden of diabetes mellitus across the country, specifically among AI/AN communities.
• Review the standards of care for the management of patients with diabetes.
• Discuss the current non-injectable pharmacologic treatment of hyperglycemia and complications mitigation.
Among the US population overall, crude estimates for 2019 were:

**Diabetes**
- **Total**: 37.3 million people have diabetes (11.3% of the US population)
- **Diagnosed**: 28.7 million people, including 28.5 million adults
- **Undiagnosed**: 8.5 million people (23.0% of adults are undiagnosed)

**Prediabetes**
- **Total**: 96 million people aged 18 years or older have prediabetes (38.0% of the adult US population)
- **65 years or older**: 26.4 million people aged 65 years or older (48.8%) have prediabetes
The *Diabetes Report Card* provides current information on the status of diabetes and its complications in the United States. It has been published every 2 years since 2012 by the Centers for Disease Control and Prevention (CDC).

- After almost 2 decades of continual increases, the incidence of newly diagnosed cases of diabetes in the United States decreased from 9.3 per 1,000 adults in 2009 to 5.9 per 1,000 adults in 2019.\(^\text{10}\)

- Prevalence of prediabetes among US adults remained steady from 2005–2008 to 2017–2020. However, notification of prediabetes status nearly tripled (from 6.5% to 17.4%).\(^\text{10}\)

- American Indian or Alaska Native, non-Hispanic Black, Hispanic, and non-Hispanic Asian people are more likely to be diagnosed with diabetes than non-Hispanic White people (14.5%, 12.1%, 11.8%, 9.5%, and 7.4%, respectively).\(^\text{10}\)

- During the COVID-19 pandemic, diabetes emerged as an underlying condition that increases the chance of severe illness. Nearly 4 in 10 adults who died from COVID-19 in the United States also had diabetes.\(^\text{11}\)
For the first time, diabetes prevalence in AI/AN adults has decreased—and has done so consistently for 4 years, dropping from 15.4 percent in 2013 to 14.6 percent in 2017 (Figure 2). ²
Neither the general United States (U.S.) population, nor any other U.S. racial/ethnic group has shown a decrease in prevalence. ³ Given that diabetes-related mortality has also decreased, ⁴ this improvement in prevalence appears to be driven by a reduction in new cases of diabetes in AI/AN adults.
Complications Development and Co-Morbid Conditions

- 39.2% with CKD, Stages 1-4 (CKD-EPI eGFR data), 2017-2020
  - 15.7% with moderate to severe CKD (Stage 3-4, eGFR 15-<60 ml/min)
  - Leading cause of ESRD with 62K developed ESRD in 2018; crude prevalence attributed to diabetes 38.8% (26.1% HTN, 14.9% glomerulonephritis.

- Diabetes is the leading cause of new cases of blindness among adults aged 18-64 years. 11.8% reported severe vision difficulty or blindness

- Emergency Room Visits (2018)
  - Diabetes as any listed diagnosis – 17.18 million (68.3/1000 adults), 35% admitted
  - Hyperglycemic crisis – 248 thousand (9.9/1000): DKA 223K, HHS 25K; 85.5% admitted
  - Hypoglycemia (BS<70 mg/dL)- 242 K (9.6/1000), 23% admitted

- Hospitalizations (2018)
  - Diabetes as any listed diagnosis – 8.249 million (327/1000 adults)
  - Major CVD 1.871mil (74.4/1000); Ischemic Heart Disease 440K (17.5/1000), Stroke 334K (13.3/1000)
  - Lower-extremity amputation- 154K (6.1/1000)

FIGURE 1. Number of reported incident cases of end-stage kidney disease, by primary cause — United States, 2000-2019*

- Hypertension
- Other cause
- Diabetes


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident cases</th>
<th>Prevalent cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>92,660 (100.0)</td>
<td>131,422 (100.0)</td>
</tr>
<tr>
<td>Age group, yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>14,194 (15.3)</td>
<td>16,230 (12.3)</td>
</tr>
<tr>
<td>45-64</td>
<td>32,370 (34.9)</td>
<td>48,874 (37.2)</td>
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<tr>
<td>65-74</td>
<td>23,494 (25.4)</td>
<td>35,744 (27.2)</td>
</tr>
<tr>
<td>≥75</td>
<td>22,602 (24.4)</td>
<td>30,574 (23.3)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>49,500 (53.4)</td>
<td>76,631 (58.3)</td>
</tr>
<tr>
<td>Women</td>
<td>43,160 (46.6)</td>
<td>54,791 (41.7)</td>
</tr>
<tr>
<td>Race and Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>51,156 (55.2)</td>
<td>67,919 (51.7)</td>
</tr>
<tr>
<td>Black</td>
<td>25,917 (28.0)</td>
<td>33,700 (25.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11,297 (12.2)</td>
<td>20,790 (15.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>2,507 (2.7)</td>
<td>6,256 (4.8)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1,041 (1.1)</td>
<td>1,299 (1.0)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>742 (0.8)</td>
<td>1,455 (1.1)</td>
</tr>
<tr>
<td>Primary cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>41,458 (44.7)</td>
<td>61,522 (46.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23,384 (25.2)</td>
<td>37,539 (28.6)</td>
</tr>
<tr>
<td>Other cause</td>
<td>27,818 (30.0)</td>
<td>32,361 (24.6)</td>
</tr>
</tbody>
</table>

† Percentages might not sum to 100% because of rounding.

Burden of Diabetes: ESRD

- Incident and prevalent ESRD cases was slower in AI/AN than other populations from 2000-2019.
- “Population health and team-based approach to diabetes care including kidney disease testing and case management...supported by SDPI funding ... may explain the lower percentage change”
- Goal of Advancing American Kidney Health Initiative of US HHS is to reduce incidence of ESRD by 25% by 2030.
- Need to address HTN and Diabetes management

Incidence of Microvascular Complications

Retinopathy

- Incidence of any diabetic retinopathy 69.6/1000 patient-years assessed through the JVN Tele-ophthalmology Program from 2015 to 2016-2019.
- Low DR incidence rate compares to other populations and similarly associated with duration of diabetes, higher A1C levels, and insulin therapy (w/wo oral meds)
- The low incidence rates support the ADA recommendation of biennial retinal examinations among patients with diabetes served by IHS.

Incidence of Microvascular Complications

Nephropathy: CKD

- Incidence of DKD (new eGFR<60 or UACR >30 or UPCR > 150) from 2015-2016 was 81.6/1000 P-Y, 2017-2018 was 73.7/1000 P-Y, and 2019-2020 was 64/1000 P-Y
- The incidence rates of DKD varied among ethnic groups in the cohort compared to White Americans; higher rates among NH/Pacific Islanders, African American, AI/AN, and Hispanic Americans; lower rate among Asian Americans.
- Higher Incidence rates associated with longer duration of diabetes, higher A1C levels, and HTN

Comprehensive Assessment and Treatment

• Patient-centered care
  • “providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patients values guide all clinical decisions”.

• Health literacy and numeracy

• Self-management resources and affordability

• Consideration of other comorbid conditions that impact self-care
  • Depression, cognitive impairment
  • Periodontal Disease
  • Sensory loss; hearing or vision or sensations
  • Arthritis; frailty
  • Liver disease and other gastrointestinal problems

Diabetes Self-Management Education and Support (DSMES)

• Self-Management (self-care)
  • Practice healthy eating and physical activity
  • Use medication properly; knowing efficacy and adverse effects
  • Monitor and track changes
  • Learn to cope with stress and setbacks; problem solve
  • Teach self-advocacy; navigate health systems; assess SDOH
  • Achieve target goals

• Evaluation of self-management needs (professional services)
  • Four critical times- 1) at diagnosis, 2) annually and/or not meeting treatment goals, 3) when complicating factors develop, 4) when transitions in life and care occur.
  • Who, when, and where?

Medical Nutrition Therapy (MNT)

• Foundation of type 2 diabetes management: beyond hyperglycemia
• Ideally, provided by Registered Dietitian/Registered Dietitian Nutritionist
  • At the time of diagnosis and as needed
  • MNT shown to reduce A1C, 0.5 to 2.0 % similar to some medication effectiveness
  • Covers nutrition assessment, individualized interventions, and evaluation with ongoing followup to support long-term lifestyle changes

• MacroNutrients
  • Fats: minimize trans fat, choose mono or polyunsaturated fats (limit saturated fat to < 10% daily consumption)
  • Carbohydrates: eat variety of fruits and vegetables, choose high-fiber foods (25-30 gm per day); limit added sugars and avoid sugar-sweetened beverages
  • Proteins: choose low-fat animal and plant based proteins
  • Other: Sodium-2300 mg/day, alcohol, fluids- water and other low calorie beverages

• Physical Activity: At least, 150 minutes of moderate intensity activity per week.

NIDDK. Guiding Principles for the Care of People with or at Risk for Diabetes
Summary of glycemic recommendations for many nonpregnant adults with diabetes (Table 6.3)

A1C                          <7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose           80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose† <180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients.
#CGM may be used to assess glycemic target as noted in Recommendation 6.5b and Fig. 6.1. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per Fig.6.2).
†Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Diabetes Type 2: Hyperglycemia Development

- The hyperglycemia in type 2 diabetes appears to result from a progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance.
  - β-cell secretory dysfunction is related to genetics, inflammation, or metabolic stress
  - Insulin resistance is related to obesity and/or visceral adiposity
  - Glucose toxicity (hyperglycemia begets hyperglycemia)
- Progressive dysglycemia occurs for many years starting with prediabetes
  - Interventions may delay or prevent diabetes development
  - Fasting and post-prandial hyperglycemia result from worsening β-cell failure

## Oral Anti-Diabetes Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Efficacy (% Δ A1C)</th>
<th>Other Benefits</th>
<th>Side effects; Caution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin (biguanide)</td>
<td>Decrease Hepatic glucose production</td>
<td>1.0-2.0%</td>
<td>CVD; Dementia; Use in Youth</td>
<td>GI symptoms; eGFR&gt;30 ml/min</td>
<td>B12 deficiency Lactic Acidosis</td>
</tr>
<tr>
<td>Sulfonylurea/Glinides (glipizide, glimepiride, glyburide, repaglinide, nateglinide)</td>
<td>Stimulate insulin secretion-SUR/K+ATPase</td>
<td>1.0-2.0%</td>
<td>Rapid effect; neutral/worsening CVD</td>
<td>Hypoglycemia; Weight Gain; Accelerates β-cell failure</td>
<td>cost</td>
</tr>
<tr>
<td>Thiazolidinediones (pioglitazone, rosiglitazone)</td>
<td>Reduce insulin resistance by activating PPARγ nuclear receptor</td>
<td>1.0-2.0%</td>
<td>CVD; NAFLD and NASH; No hypoglycemia</td>
<td>Weight gain; Edema; HF hospitalization</td>
<td>Slow activation and glycemic effects, 2-4 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Efficacy (↓ A1C)</th>
<th>Other Benefits</th>
<th>Side effects; Caution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 Inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)</td>
<td>Increase GLP-1; insulin/decrease glucagon</td>
<td>0.5-1.0%</td>
<td>CVD neutral; Weight neutral</td>
<td>HF hospitalization – saxagliptin, alogliptin</td>
<td>All indications; renal dose adjustment</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, bexagliflozin)</td>
<td>Inhibits Sodium Glucose Co-transporter 2; increase glycosuria</td>
<td>0.5-1.0%</td>
<td>CVD, CVD death; HF Hospitalization; Nephropathy; Weight loss; SBP</td>
<td>Need eGFR &gt; 45 UTI &amp; genital mycotic; acute kidney injury; DKA; Fournier’s gangrene</td>
<td>Cost; Monitor renal function (stop if eGFR &lt; 30)</td>
</tr>
<tr>
<td>GLP-1 RA (oral semaglutide)</td>
<td>Stimulates GLP-1 receptors; Increase insulin, decrease glucagon/appetite</td>
<td>1.0-2.0%</td>
<td>Weight loss; CVD trend lower</td>
<td>GI problems; Pancreatitis; MTC</td>
<td>Cost; nausea; vomiting</td>
</tr>
</tbody>
</table>

Other FDA-approved oral anti-diabetes medications include α-glucosidase inhibitors (acarbose, miglitol), bile acid sequestrant (colesevelam), and dopamine-2 agonist (bromocriptine).

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

Healthy Lifestyle Behaviors; Diabetes Self-Management Education and Support (DSMES); Social Determinants of Health (SDOH)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

- ASCVD†
  - Defined differently across CVFs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure).
  - Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

- Indicators of high risk
  - While definitions vary, most comprise ≤55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

- HF
  - Current or prior symptoms of HF with documented HFREF or HFrEF

- CKD
  - eGFR < 60 mL/min per 1.73 m² OR albuminuria (ACR ≥ 30 mg/mmol (30 mg/g))
  - Measurement may vary over time; thus, a repeat measure is required to document CKD.

- SGLT2i
  - With proven HF benefit in this population

- PREFERABLY
  - SGLT2i with primary evidence of reducing CKD progression
    - Use SGLT2i in people with an eGFR ≥ 20 mL/min per 1.73 m²; once initiated should continue until initiation of dialysis or transplantation
    - GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

- If A1C above target
  - For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
  - TZD

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

- Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
  - Metformin or Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
  - Consider avoidance of hypoglycemia a priority in high-risk individuals

- In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

- Efficacy for glucose lowering
  - Very High: Dulaglutide (high dose), Semaglutide, Tirzepatide
  - Intermediate: GLP-1 RA (not listed above), Metformin, SGLT2i, Sufonylurea, TZD
  - Minimal: DPP-4i

- Efficacy for weight loss
  - Very High: Semaglutide, Tirzepatide
  - High: Dulaglutide, Liraglutide
  - Intermediate: GLP-1 RA (not listed above), SGLT2i
  - Neutral: DPP-4i, Metformin

- Identify barriers to goals:
  - Consider DSMES referral to support self-efficacy in achievement of goals
  - Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
  - Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.† A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details. § Low-dose TZD may be better tolerated and similarly effective. ¶ For SGLT2i, CV renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HF, and renal outcomes in individuals with T2D with established high risk of CVD.

§ For GLP-1 RA, CV safety data demonstrate their efficacy in reducing composite MACE at 3 years, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/ high risk of CVD.

Guidance for initiating oral anti-diabetes medication use

Assess glycemia and complications (emphasis on cardiorenal protection- CVD, HF, and CKD)

• At glycemic goal*
  • No CVD or HF and/or CKD – consider metformin
  • CVD or HF and/or CKD - prescribe SGLT-2 inhibitors

• Not at glycemic goal*
  • No CVD or HF and/or CKD – prescribe metformin
  • CVD or HF and/or CKD - prescribe SGLT-2 inhibitors

Reassess glycemia and complications, 3-6 month intervals

* A1C <7.0 % for most people with diabetes; consider more or less stringent consideration based on patient-centered approach.
Guidance for advancing oral anti-diabetes medication use

Reassess glycemia and complications (CVD, HF, and CKD)

• Not at glycemic goal*, consider
  • Metformin: start or optimize treatment
  • DPP-4 inhibitor: useful in older patients, mild side effects, HF
  • SGLT-2 inhibitor: low hypoglycemia risk, multiple side effects
  • Oral GLP-1 RA: weight loss, low hypoglycemia risk
  • TZDs: improves fatty liver, weight gain, edema, HF
  • Secretagogues (SU/glinides): hypoglycemia and weight gain

• Newly identified CVD, HF, and/or CKD
  • Prescribe SGLT-2 inhibitor (injectable GLP-1 RA is unable to use)

* A1C <7.0 % for most people with diabetes; consider more or less stringent consideration based on patient-centered approach.
<table>
<thead>
<tr>
<th>Medication (Study/# Pts)</th>
<th>Type of Patients</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin- (EMPA-REG 7,020)</td>
<td>Known CVD (99%)</td>
<td>3.1 yrs</td>
<td>MACE</td>
</tr>
<tr>
<td>Canagliflozin- (CANVAS 10,142)</td>
<td>Known CVD 71%</td>
<td>2.4 yrs</td>
<td>MACE</td>
</tr>
<tr>
<td>Dapagliflozin- (DECLARE 17,160)</td>
<td>Known CVD 40%; CVD Risk Factors 60%</td>
<td>4.2 yrs</td>
<td>MACE</td>
</tr>
<tr>
<td>Ertugliflozin- (VERTIS CV 8,246)</td>
<td>Known CVD</td>
<td>3.0 yrs</td>
<td>MACE</td>
</tr>
<tr>
<td>Canagliflozin- (CREEDENCE 4,401)</td>
<td>Known CKD 100%; HF 17%</td>
<td>2.6 yrs</td>
<td>CKD</td>
</tr>
<tr>
<td>Dapagliflozin- (DAPA-CKD 4304)</td>
<td>Known CKD</td>
<td>2.4 yrs</td>
<td>CKD</td>
</tr>
<tr>
<td>Empagliflozin- (EMPEROR- R 3,730; EMPEROR- P 5,988)</td>
<td>Known HFReducedEF Known HFpreservedEF (40% w DM)</td>
<td>1.5 yrs  2.2 yrs</td>
<td>HHF, CV Death</td>
</tr>
<tr>
<td>Dapagliflozin- (DAPA-HF 4,744)</td>
<td>Known HFReducedEF Known HFpreservedEF (40% w DM)</td>
<td>1.5 yrs</td>
<td>HHF, CV Death</td>
</tr>
<tr>
<td>Sotagliflozin- (SCORED 10,584)</td>
<td>Known CKD</td>
<td>1.5 yrs</td>
<td>HHF, CV Death</td>
</tr>
<tr>
<td>Sotagliflozin- (SOLOIST-WHF 1,222)</td>
<td>Known HF</td>
<td>0.75 yrs</td>
<td>HHF, CV Death</td>
</tr>
</tbody>
</table>

**MACE:** CVD death, Nonfatal MI, Nonfatal stroke; **HHF:** Hospitalization for Heart Failure and CVD Death; **CKD:** doubling creatinine, renal replacement, progressing or incident albuminuria, sustained eGFR decrease >40 % to < 60 ml/min
SGLT-2 Inhibitors: Cardiovascular Outcomes Trials

MACE: CVD death, Nonfatal MI, Nonfatal stroke

SGLT-2 Inhibitors: HHF/CV Mortality Outcomes Trials

SGLT-2 Inhibitors: CKD Outcomes Trials

SGLT-2 inhibitors provide robust reduction in Heart Failure in people with and without diabetes (RRR 32%)
  • A class effect- absence of heterogeneity among studies
  • Reduced risk of HHF is > 25% among all studies
  • Narrow confidence interval (27% - 39% CI)

Provide strong evidence for reduction in renal outcomes (RRR 35%)
  • CVOT showed heterogeneity of outcomes
  • Greater effects seen in patients with HFrEF; a potential secondary effect

Mild reduction in CV death and MACE (RRR 16%)

Thank you for your attention

Any Questions? Comments?