August 31, 2020

Clinical Review: 2020 Standards of Care for Treatment of Type 2 Diabetes

Learning Objectives:

- Review recommendations provided in the American Diabetes Association (ADA) Standards of Medical Care – 2020 addressing the pharmacologic approach to glycemic control for patients with type 2 diabetes
- Describe patient factors to consider when prescribing antihyperglycemic agents
- Understand the boxed warnings for antihyperglycemic agents

Key Points:

- Diabetes is a complex illness requiring continuous chronic care. Glycemic control is one aspect of comprehensive care for patients with diabetes.
- The ADA recently published their annual Standards of Medical Care in Diabetes - 2020, which reviews the current evidence surrounding diabetes care, general treatment goals, and tools to evaluate the quality of care.
- Recent evidence demonstrates a benefit of adding sodium-glucose cotransporter 2 inhibitors (SGLT-2i) or glucagon-like peptide 1 receptor agonists (GLP-1 RA) to metformin in patients with preexisting cardiovascular disease (secondary prevention) or who are at increased cardiovascular risk.
- The Medi-Cal Fee-for-Service List of Contract Drugs includes therapy options from all categories of antihyperglycemic medications, including oral agents, combination products, non-insulin injectable products, and insulin vials and pens.

Background

Diabetes is a complex, chronic illness requiring continuous care in order to achieve glycemic control. In 2018, an estimated 8.2% of the population of the United States and 12.8% of adults between 18 and 64 years of age in the Medicaid population had a diagnosis of diabetes.[1,2] Uncontrolled diabetes can lead to poor general health, microvascular and macrovascular complications, hospital admissions, as well as higher out-of-pocket health care costs.[3]

Approximately 90 – 95% of people diagnosed with diabetes have type 2 diabetes, which most often develops in people over 45 years of age.[1] A type 2 diabetes diagnosis is based on the presence of classic symptoms of hyperglycemia (such as polydipsia or polyuria) and:

- a random plasma glucose ≥ 200 mg/dL, or
- fasting plasma glucose ≥ 126 mg/dL, or
- 2-hour postprandial glucose ≥ 200 mg/dL, or
- A1C ≥ 6.5%, which is the more common screening test.

Two abnormal test results are required if the patient does not present with documented hyperglycemia. Glycemic targets for patients with type 2 diabetes include A1C values from < 6.5% to < 8%.[3] Each 1% drop in A1C down to 7% has been shown to reduce microvascular complications.[4,5] More stringent A1C goals are recommended in individuals with low risk for hypoglycemia, longer life expectancy, early diagnosis, fewer comorbidities, and existence of good support systems. Less stringent A1C goals may be considered for patients who have advanced vascular complications, history of severe hypoglycemia, limited life expectancy or when treatment risks outweigh the benefits. Individualized A1C goals must be a shared decision based on clinician judgement and patient motivation to adhere to the treatment regimen. The frequency of A1C testing may vary from quarterly to biannual measurements depending on treatment efficacy and patient ability to reach target A1C.[3]

The ADA annually publishes its Standards of Medical Care in Diabetes. This document provides clinicians, patients, researchers, payers, and other interested individuals with an overview of care for diabetes, general treatment goals, and tools to evaluate quality of care.[3] The sections on the pharmacologic approach to glycemic control and cardiovascular risk and management offer guidance on the use of medications. As shown in Table 1, the Medi-Cal Fee-for-Service List of Contract Drugs includes therapy options from all categories of antihyperglycemic medications, including oral agents, combination products, non-insulin injectable products, and insulin vials and pens.

Table 1. Antihyperglycemic Medications Available On The Medi-Cal List Of Contract Drugs

Drug Therapeutic Category	Mechanism of Action	Drug *
Alpha-glucosidase inhibitors	Inhibits intestinal alpha-glucosidase enzyme to delay carbohydrate digestion and glucose absorption in the gut	acarbose miglitol
Amylin analogs	Affects the rate of postprandial glucose appearance through hypothalamic medicated anorectic effects, slows gastric emptying, and suppresses glucagon secretion not normalized by insulin alone	pramlintide
Biguanides	Multiple mechanisms of action: • decrease hepatic glucose production • decease intestinal absorption of glucose • increase peripheral glucose uptake and utilization	metformin
Dipeptidyl peptidase-4 inhibitors (DPP-4i)	Decreases the degradation of incretin hormones (GLP-1 and GIP), which are responsible for decreasing glucagon release, increasing glucose-dependent insulin secretion, decreasing gastric emptying, and decreasing blood glucose levels	alogliptin linagliptin saxagliptin sitagliptin
Glucagon-like peptide 1 receptor agonists (GLP-1 RA)	Analogs of endogenous incretin hormones that promote glucose-dependent insulin secretion, decreasing postprandial glucagon release, decreasing rate of gastric emptying, and increasing satiety	exenatide exenatide ER dulaglutide
Insulins	Stimulates peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production	aspart protamine/aspart glargine lispro lispro protamine/lispro NPH human/regular NPH human isophane regular, human
Meglitinides	Acts on ATP-sensitive potassium channels on pancreatic beta-cells to close stimulate glucose-dependent the insulin release	nateglinide
Sodium-glucose cotransporter 2 inhibitors (SGLT-2i)	Inhibits SGLT-2 co-transporter located in the proximal renal tubules to reduce glucose reabsorption and increase urinary excretion	dapagliflozin empagliflozin
Sulfonylureas (SU)	Binds to sulfonylurea receptors on functioning pancreatic beta-cells to stimulate insulin release	chlorpropamide glimepiride glipizide glyburide tolbutamide
Thiazolidinediones (TZD)	Activates peroxisome proliferator-activated receptor gamma (PPAR-γ) nuclear receptors to decrease insulin resistance of tissues in skeletal muscles, adipocytes, and liver to promote glucose utilization	pioglitazone

* Some medications may have restrictions to use. For current information on covered combination medications and insulin products, visit the online Medi-Cal Formulary search tool available on the Search Medi-Cal Formulary page of the Department of Health Care Services (DHCS) website.

Published in January of 2020, the ADA's *Standards of Medical Care in Diabetes – 2020* recommends metformin in conjunction with lifestyle modifications as the preferred first-line medication for the treatment of type 2 diabetes, when the estimated glomerular filtration rate (eGFR) is > 30 mL/min/1.73m^2 and there are no other contraindications.[3] For individuals with heart failure, established atherosclerotic cardiovascular disease (ASCVD), high ASCVD risk or chronic kidney disease (CKD), addition of an SGLT-2i or GLP-1 RA to metformin should be considered as a second-line agent.[3] Selected agents in these classes of medications have a demonstrated reduction in cardiovascular events (as secondary prevention in most cases), hospitalization for heart failure, and reduction in the risk of CKD progression.[3] Three GLP-1 RAs (dulaglutide, liraglutide, and semaglutide) currently have an indication by the U.S. Food and Drug Administration (FDA) for risk reduction of major cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. All SGLT-2i medications currently have an FDA indication to reduce the risk of cardiovascular death in adult patients with type 2 diabetes and established cardiovascular disease, while both dapagliflozin and canagliflozin also have an FDA indication to reduce the risk of hospitalization in adults with heart failure with reduced ejection fraction. Dosage adjustment of SGLT-2i is recommended for eGFR < 45 – 60mL/min/1.73m^2 (varies by agent).

In patients diagnosed with type 2 diabetes who do not have notable cardiovascular risk factors or chronic kidney disease, additional oral or injectable pharmacological agents may be added to metformin based on patient-specific factors (see Table 2). In general, if oral agents do not decrease glucose and A1C to desired target level, a GLP-1 RA should be tried prior to insulin initiation, when possible.[3]

Table 2. Treatment Algorithm for Choosing Additional Antihyperglycemic Agents[3] : What is the primary concern for the individual patient?

Addition to Metformin	ASCVD predominates	Heart failure or CKD	Hypoglycemia	Minimize weight gain/ promote weight loss
1st addition	• GLP-1 RA (*preferred)* • SGLT-2i	• SGLT-2i (*preferred)* • GLP-1 RA	• DPP-4i **or** GLP-1 RA • SGLT-2i • TZD	• GLP-1 RA • SGLT-2i
2nd addition *	• DPP-4i • Basal insulin • TZD • SU	• DPP-4i • Basal insulin • SU	• Basal insulin • SU	• DPP-4 *(preferred)* • Basal insulin • TZD • SU

* Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥ 1.5% (12.5mmol/mol) above their glycemic target

Cardiovascular comorbidities

The 2020 Standards of Care recommend addition of a GLP-1 RA to metformin for individuals with established ASCVD or high ASCVD risk who do not achieve blood glucose target on metformin alone.[3] Factors indicating high ASCVD risk include age ≥ 55 years with coronary, carotid, or lower-extremity artery stenosis >50% or left ventricular hypertrophy. The recommendation is based on results from trials of SGLT-2i and GLP-1 RA in patients with type 2 diabetes with or at high risk for cardiovascular disease. The SGLT-2i trials showing a positive benefit included approximately 27,800 patients and the GLP-1 RA trials included approximately 22,400 patients.[6-13] More than 70% of patients were taking concomitant metformin. Cardiovascular benefit was defined in clinical trials as a reduction in a composite endpoint (myocardial infarction, stroke or cardiovascular death).

If a GLP-1 RA does not provide adequate glycemic control or cannot be tolerated, then an SGLT-2i with proven cardiovascular benefits should be initiated. If A1C is still above the target value, the following classes of medications may be added sequentially to the current drug regimen: DPP-4i (if not on GLP-1 RA), basal insulin, TZD, and/or SU.[3]

In individuals for whom heart failure or chronic kidney disease is the primary concern, the 2020 Standards of Medical Care recommend that an SGLT-2i shown to reduce heart-failure-related hospitalization be added to metformin, given adequate eGFR and no contraindications to therapy.[3] At eGFR ≤ 45, the effect on glucose lowering may be less, but a benefit at reducing heart-failure-related hospitalizations may still be seen.[3] This regimen is especially beneficial in patients with left ventricular ejection fraction <45%. If SGLT-2i cannot be tolerated (e.g., due to side effects) or is not adequate to reach target A1C, then a GLP-1 RA should be initiated.[3] If A1C is still above the target, the following classes of medications may be added sequentially to their drug regimen: DPP-4i (except saxagliptin, due to an association with increased hospitalization for heart failure) if not already on a GLP-1 RA, basal insulin, and SU.[3] Avoid TZD because these medications have been shown to worsen heart failure.[3]

Renal Complications
In individuals with type 2 diabetes and CKD, an SGLT-2i is the preferred agent to add to metformin. SGLT-2i appears to reduce the progression of kidney disease in patients with established ASCVD, high ASCVD risk, or diabetic kidney disease. SGLT-2i is especially beneficial in individuals with eGFR 30 – 60 mL/min/1.73 m^2 or when the urine-albumin-to-creatinine ratio is greater than 30 mg/g.[3] Therefore, the selection of specific agents may depend on comorbidity and CKD stage. If use of SGLT-2i is contraindicated or not tolerated, a GLP-1 RA should be considered because several studies have shown to reduce risk of CKD progression, cardiovascular events, or both. If A1C is still above the target value, the following classes of medications may be added sequentially to their drug regimen: basal insulin and SU.[3]

Safety
Some classes of antihyperglycemic medications have a boxed warning for potentially life threatening or permanent side effects.[6-13] These include metformin, SGLT-2i, GLP-1 RA and TZD. Post-marketing cases of lactic acidosis have been reported with metformin. All GLP1-RA (including exenatide ER but not exenatide) have a boxed warning for increased risk of thyroid C-cell tumor and are contraindicated in patients with history of medullary thyroid carcinoma. Canagliflozin has a boxed warning for the risk of limb amputation. Although other SGLT-2i do not contain a boxed warning for this potential side effect, the FDA recommends that providers consider risk factors for amputation prior to prescribing, however this is likely a class effect and recent studies show no increased risk compared to other agents. Risk factors include prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Patients should be counseled regarding the important of preventative foot care and discontinue therapy if any of the following occur: signs and symptoms of new infection (including osteomyelitis), new pain or tenderness, or sores/ulcers involving the lower limbs. TZD may cause or exacerbate heart failure and are not recommended for use in patients with symptomatic heart failure.

Although not included in the boxed warning, metformin has a warning regarding the potential risk for vitamin B12 deficiency. All SGLT-2i medications have warnings regarding the risk of acute kidney injury, diabetic ketoacidosis, genitourinary infections, hypotension due to volume depletion, and Fournier's gangrene. Some of these were identified during post-marketing surveillance from 2015-2018.[14-17] An increased risk of bone fractures has been observed for some SGLT-2i medications.

Pancreatitis and gall bladder disease and worsening kidney disease are risks described for all GLP-1 RA medications, with certain agents having the potential risk for psychiatric effects. Providers should review the most recent product prescribing information or a reputable drug information resource for current information on boxed warnings, warnings, and precautions for all medications.

Use of Antihyperglycemic Medications in the Medi-Cal Population
A retrospective cohort study was conducted to evaluate utilization of antihyperglycemic medications in the Medi-Cal population. The study population included all certified, continuously eligible Medi-Cal beneficiaries between 18 and 64 years of age throughout the duration of the measurement year (between April 1, 2019, and March 31, 2020) with a documented diagnosis of type 2 diabetes at any time during or preceding the measurement year. Beneficiaries that were dually eligible for Medicare were excluded, in order to ensure complete medical and pharmacy claims data.

All paid pharmacy claims for antihyperglycemic medications with dates of service from April 1, 2019, through March 31, 2020, were included. Demographic characteristics, including gender, age, race/ethnicity, and geographic region of residence, were reviewed for all beneficiaries in the study population (Table 3). Both pharmacy and medical claims data were reviewed to assess the clinical characteristics of the study population, including comorbidities, risk factors, and concomitant medication use. The study population was stratified by beneficiary enrollment in either the Medi-Cal fee-for-service (FFS) program or a Medi-Cal managed care plan, in order to assess if there were any differences between the programs.

Table 3. Demographic and Clinical Characteristics of the Study Population

Study population	FFS	MCP	Overall
Overall	**71,365 (15%)**	**436,095 (90%)**	**485,508 (100%)**
Gender			
• Male	30,651 (43%)	190,680 (44%)	209,606 (43%)
• Female	40,714 (57%)	245,415 (56%)	275,902 (57%)
Age			
• 18 – 44 years of age	24,987 (35%)	113,949 (26%)	132,792 (27%)
• 45 – 64 years of age	46,378 (65%)	322,146 (74%)	352,716 (73%)
Race/ethnicity			
• Hispanic	46,344 (65%)	219,096 (50%)	254,936 (53%)
• All other races/ethnicities	25,021 (35%)	216,999 (50%)	230,572 (47%)
California region of residence			
• Los Angeles	21,446 (30%)	133,683 (31%)	150,158 (31%)
• All other regions	49,919 (70%)	302,412 (69%)	335,350 (69%)
Paid Claims for insulin during measurement year	39,691 (56%)	144,514 (33%)	161,090 (33%)

During the measurement year there were a total of 485,508 Medi-Cal beneficiaries meeting the study population inclusion/exclusion criteria. There were 21,952 beneficiaries (4.5% of the study population) with enrollments in both programs throughout the measurement year. Within the study population, Medi-Cal FFS enrollees were more likely to be younger (35% were between 18 and 44 years of age vs. 26% of MCP enrollees) and have paid claims for insulin during the measurement year (56% vs. 33% of MCP enrollees). As metformin is the preferred first-line medication for the treatment of type 2 diabetes if eGFR is adequate (>30 mL/min/1.73m^2) and patient has no other contraindication for use, pharmacy claims data were analyzed to determine what percentage of the study population was taking metformin, either as monotherapy or with an additional antihyperglycemic agent (Table 4). Beneficiaries with concomitant paid claims for insulin were excluded from these results. Beneficiaries with enrollments in both programs during the measurement year were included in each column only if they met the listed criteria during enrollment.

Table 4. Antihyperglycemic Medication Use in the Study Population

Drug Therapeutic Category	FFS n = 71,365	MCP n = 436,095	Overall n = 485,508
Biguanide monotherapy (no insulin)	25,871 (36%)	155,631 (36%)	173,195 (36%)
Biguanide + SGLT-2i (no insulin)	1,717 (10%)	22,407 (5%)	23,721 (5%)
Biguanide + GLP-1 RA (no insulin)	368 (< 1%)	8,615 (2%)	8,916 (2%)
Biguanide + DPP4i (no insulin)	4,879 (7%)	37,892 (9%)	41,681 (9%)
Biguanide + TZD (no insulin)	2,478 (3%)	19,610 (4%)	21,435 (4%)

While there were more Medi-Cal FFS beneficiaries in the study population with a paid claim for insulin during the measurement year, the proportion of the study population taking only metformin was identical across programs, at 36%. Use of concomitant metformin and SGLT-2i (without insulin) was nearly twice as common in the FFS population (10% vs. 5% among MCP enrollees), while concomitant metformin use with other antihyperglycemic agents, including GLP-1 RA, DPP4i, and TZD, was slightly higher in the MCP population.

Conclusion/Discussion

Diabetes is a complex illness requiring continuous chronic care. Glycemic control is one aspect of comprehensive care for patients with diabetes. Recent evidence demonstrates a benefit of adding SGLT-2i or GLP-1 RA to metformin in patients with preexisting cardiovascular disease (secondary prevention) or who are at increased cardiovascular risk, prior to the initiation of insulin, when possible. The ADA's Standards of Medical Care in Diabetes is a comprehensive resource that can help guide health care providers when considering a pharmacologic approach to glycemic control.

Clinical Recommendations:

- For a comprehensive update on diabetes treatment guidelines, please review the *Standards of Medical Care in Diabetes – 2020* published by the ADA. The ADA Standards of Care App is also a helpful resource, which is available as a web-based tool and also as an application for either iOS and Android platforms.
- The 2020 Standards of Medical Care recommend the following:
    - Metformin is the preferred first-line medication for the treatment of type 2 diabetes if eGFR is adequate (>30 mL/min/1.73m^2) and patient has no other contraindication for use.
    - SGLT-2i or GLP-1 RA are recommended add-on agents for individuals with heart failure, established or high ASCVD risk, or kidney disease.
    - Some SGLT-2i or GLP-1 RA have demonstrated cardiovascular disease benefit.
    - SGLT-2i are recommended for use in individuals with eGFR ≥30 mL/min/1.73 m^2.
    - In patients diagnosed with type 2 diabetes and without notable cardiovascular risk factors or chronic kidney disease, DPP-4i, TZD, and/or SU may be added based on patient-specific factors (hypoglycemia risk, minimize weight gain/promote weight loss).
    - TZDs should be avoided in patients with heart failure.
    - If oral agents do not decrease glucose and A1C to desired target level, GLP-1 agonists should be tried prior to insulin.
- Metformin, SGLT-2i, GLP-1 RA and TZD have boxed warnings for potentially life threatening or permanent side effects. Counsel patients on the potential risk vs benefit for these agents.

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