



New Horizons in the Treatment and Management of Type 2 Diabetes: Individualizing Therapy with Novel Options for Improved Patient Outcomes

A CME CNE Approved Activity



JOURNAL of MANAGED CARE MEDICINE 

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New Horizons in the Treatment and Management of Type 2 Diabetes: Individualizing Therapy with Novel Options for Improved Patient Outcomes

Instructions for CME/CNE: Activity is valid from June 20, 2017 to June 30, 2019.

A score of 70% must be achieved on the post-test to receive continuing education credits.

Read the monograph, answer the post-test, complete the evaluation form, and send completed post test and evaluation to:

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Learning Objectives:

1. Analyze the safety, efficacy and mechanisms of action of current and emerging therapies for achieving individualized target goals in type 2 diabetes (T2DM).
2. Apply newly released clinical data and guidelines on combination therapies to practice regarding glycemic management in patients with T2DM.
3. Examine the evidence for the use of combination regimens that include novel hyperglycemic therapies to improve glycemic control and other cardiovascular risk factors in patients with T2DM
4. Recognize the most effective place in the T2DM treatment continuum for GLP-1 agonists, newer insulins and SGLT-2 inhibitors.
5. Advance the clinician's ability to overcome clinical inertia through confident initiation of early therapy and intensification of T2DM therapy to achieve agreed upon glycemic goals.
6. Identify barriers to effective and timely combination therapy initiation and implement strategies to overcome these barriers in T2DM management.
7. Apply methods to enable optimal cost management of novel therapies to be realized by multiple T2DM stakeholders including managed care organizations.

Faculty Disclosure:

Dr. Elasy lists no relevant disclosures.

Dr. Handelsman receives research support from Amgen, AstraZeneca, BMS, BI, Grifols, Lexicon, Merck, Novo Nordisk and Sanofi. He serves as a consultant to Amarin, Amgen, AstraZeneca, BI, Eisai, Intarcia, Lilly, Janssen, Merck, Merck-Pfizer, Novo-Nordisk, Regeneron and Sanofi and serves on the speaker's bureau for Amarin, Amgen, AZ, BI-Lilly, Janssen, Merck, Novo-Nordisk, Sanofi and Regeneron.

Dr. Pratley receives research support from Lexicon, Lilly, Merck, Novo-Nordisk, Sanofi and Takeda. He serves as a consultant to AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Lilly, Merck, Novo-Nordisk, Sanofi and Takeda. All honorariums are directed toward a non-profit which supports education and research.

Dr. Reid serves as a consultant and on an advisory board for Boehringer Ingelheim, Janssen, Lilly USA, Novo-Nordisk and Sanofi.

All material has been peer reviewed for bias.

Planning Committee Disclosure

Bill Williams, MD; Jacquelyn Smith, RN, BSN, MA, CMCN; Katie Eads and Will Williams have no real or perceived financial relationships to disclose.

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Post-Test Questions

- Which of the following is an accurate statement about diabetes in the U.S.?
 - Few Americans have prediabetes.
 - 89 million have clinically evident disease.
 - \$245 billion are spent annually on diabetes.
 - Diabetes medical expenditures per patient are 10 times higher than for a patient without the disease.
- Which of the following is NOT a cardiovascular risk factor in patients with diabetes?
 - LDL-C
 - Blood pressure
 - Weight
 - Pulse rate
- Which of the following is the ADA and European Association for the Study of Diabetes (EASD) A1C target type in type 2 diabetes mellitus (T2DM) for most patients?
 - ≤ 8%
 - ≤ 7%
 - ≤ 6.5%
 - ≤ 6%
- Which of the following medications is recommended by the ADA as first-line therapy in T2DM?
 - GLP-1 receptor agonist
 - Insulin
 - DPP-4 inhibitor
 - Metformin
- Which of the following would be an appropriate choice of therapy in a patient who is overweight, has issues perceiving hypoglycemia and is currently not controlled on metformin?
 - GLP-1 RA (albiglutide)
 - Thiazolidinedione (rosiglitazone)
 - Sulfonylurea (glipizide)
 - Basal insulin (glargine)
- DPP-4 inhibitors do not increase risk of cardiovascular disease nor do they reduce risk.
 - True
 - False
- Which of the following is NOT an advantage of the SGLT-2 inhibitors in treating T2DM?
 - Weight loss
 - Low risk of hypoglycemia
 - Low risk of drug/drug interactions
 - Effectiveness in patients with severe renal impairment
- Which of the following is an accurate statement about the clinical effects of the combination formulations of basal insulin and a GLP-1 receptor agonist?
 - The combination results in similar A1C compared with insulin alone.
 - The combination results in lower rates of hypoglycemia compared with insulin alone.
 - The combination is weight neutral compared with weight gain with insulin alone.
 - The combination causes a relatively high rate of nausea compared with GLP-1 agonist alone.
- According to the ADA guidelines, which of the following should be considered for addition to a patient's regimen who already has cardiovascular disease for the purpose of cardiovascular reduction?
 - Empagliflozin or liraglutide
 - Metformin or rosiglitazone.
 - Insulin/GLP-1 receptor agonist combination.
 - Glyburide or exenatide.
- Which of the following managed care interventions can be used to increase patient concordance with therapy?
 - Prior authorization
 - Provider data analysis
 - Diabetes education referral
 - Pay for performance

Activity Evaluation and Improvement Process

*(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)*

- Based on the content presented I am better able to:
Analyze the safety, efficacy and mechanisms of action of current and emerging therapies for achieving individualized target goals in type 2 diabetes (T2DM).

4	3	2	1
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Apply newly released clinical data and guidelines on combination therapies to practice regarding glycemic management in patients with T2DM.

4	3	2	1
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Examine the evidence for the use of combination regimens that include novel hyperglycemic therapies to improve glycemic control and other cardiovascular risk factors in patients with T2DM

4	3	2	1
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Recognize the most effective place in the T2DM treatment continuum for GLP-1 agonists, newer insulins and SGLT-2 inhibitors.

4	3	2	1
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Advance the clinician's ability to overcome clinical inertia through confident initiation of early therapy and intensification of T2DM therapy to achieve agreed upon glycemic goals.

4	3	2	1
---	---	---	---

Identify barriers to effective and timely combination therapy initiation and implement strategies to overcome these barriers in T2DM management.

4	3	2	1
---	---	---	---

Apply methods to enable optimal cost management of novel therapies to be realized by multiple T2DM stakeholders including managed care organizations.

4	3	2	1
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- The activity met my expectations.

4	3	2	1
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- The activity and presenters were free of bias.

4	3	2	1
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- The activity was applicable to my position.

4	3	2	1
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- Do you expect that the information you learned during this activity will help you improve your skills or judgement within the next six months? (4 definitely will change - 1 definitely will not change)

4	3	2	1
---	---	---	---
- How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

4	3	2	1
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- What other topics interest you? _____
- My goal of participating in this activity was: _____
- Did the content of the activity help in meeting your above goal?

<input type="checkbox"/> Yes	<input type="checkbox"/> No
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- Due to the content of this activity, I will change my practice patterns by:

<input type="checkbox"/> Identifying opportunities to improve treatment options for patients.
<input type="checkbox"/> Providing guidelines and resources on new therapies to providers.
<input type="checkbox"/> My practice patterns will not change.
<input type="checkbox"/> Other (specify): _____
- Will the content presented increase your abilities in any of the following areas? Please check all that apply.

<input type="checkbox"/> Management and leadership skills
<input type="checkbox"/> Business and/or financial expertise to manage the medical loss ratio.
<input type="checkbox"/> Exchange ideas and network with colleagues to improve patient outcomes.
<input type="checkbox"/> Be aware of updates of Congress, pharmaceutical, Health and Human Services and other regulatory services.
<input type="checkbox"/> Clear knowledge of practice of medicine, especially common disease.
<input type="checkbox"/> Stay updated on clinical conditions.

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Tom A. Elasy, MD, MPH; Yehuda Handelsman, MD, FACP, FACE, FNLA;
Richard E. Pratley, MD; Timothy S. Reid, MD

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease affecting millions of Americans. It is estimated that 89 million Americans have prediabetes and 29.6 million have clinically evident disease.¹ In the United States (U.S.), \$245 billion are spent annually on diabetes.² Overall, one in five health care dollars and one in three Medicare dollars are spent on this disease. Diabetes medical expenditures per patient are 2.3 times higher than for a patient without the disease.

The long-term complications of the disease drive much of the costs. These include retinopathy, nephropathy, neuropathy, and cardiovascular disease. In adults over 40 years of age with diabetes, 28.5 percent have diabetic retinopathy.³ Diabetes was the primary cause of kidney failure in 44 percent of all new cases in 2011.³ Approximately 73,000 nontraumatic lower-limb amputations are performed annually in adults over 20 years of age with diabetes.³

Diabetes doubles the risk of vascular outcomes, including coronary heart disease, myocardial infarction, and stroke.⁴ Overall, diabetes is associated with significant loss of life years. On average, a 50-year-old individual with diabetes and no history of vascular disease will die six years earlier than someone without diabetes.⁵ Diabetes is the seventh leading cause of death.⁶

Clinical Management Guidelines

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) both publish clinical management guide-

lines for T2DM.^{7,8} The ADA guidelines are widely distributed, have significant awareness among primary care providers, and are referenced by many organizations in self developed guidelines. In contrast, the AACE guidelines are well known to diabetes specialists, but not necessarily to primary care providers. The AACE guidelines are comprehensive, have detailed strength of recommendations on effectiveness and adverse effects, and take into account the progression of the disease over time in the medication recommendations. Both the ADA and AACE guidelines emphasize the comprehensive nature of diabetes management through lifestyle modifications, dietary recommendations, medication initiation and combinations, appropriate specialist referrals, and screenings.

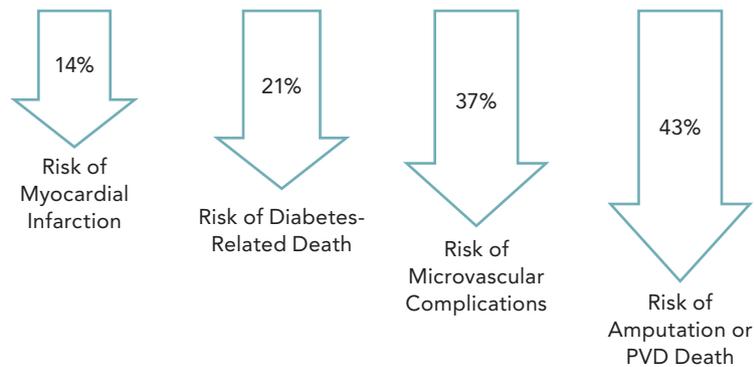
These guidelines, particularly in primary care, are used largely as a medication roadmap. Many times the charts are used but the background information is not accessed and read, so the subtleties of medication selection are missed. The guidelines are not always encultured into the actual point of care experience. A disadvantage of the guidelines is they can lead to poly-pharmacy because they do not recommend when to stop therapy. For example, a patient late in the disease process may still be on a sulfonyl-urea which no longer works because the pancreatic beta cells no longer work.

Cardiovascular Disease Risk Reduction

Because diabetes is a cardiovascular (CV) disease, risk factor reduction is important in all patients with T2DM. Aggressive low-density lipoprotein chole-

Exhibit 1: Benefits of Glycemic Control¹⁵

Every 1% decrease in A1C leads to significant reductions in complications



Decrease was statistically significant for all comparisons shown.

terol (LDL-C) lowering provides significant CV benefits in patients with DM.⁹⁻¹² Intensive blood pressure control has been shown to reduce both micro and macrovascular complications of diabetes.¹³ Weight loss and smoking cessation are additional interventions which should be implemented if indicated. Weight loss alone can reduce risk of death from CV disease and DM.¹⁴ Low-dose aspirin for secondary prevention of CV events is recommended in patients with DM and existing CVD.⁸ Clinicians may consider low-dose aspirin for primary prevention of CV events in patients with estimated 10-year CV risk greater than 10 percent.⁸ As the primary focus here is glucose control, the reader should consult the clinical guidelines for individual goals and recommended therapies for overall CV disease risk reduction.^{7,8}

Glycemic control is the last of the CV risk factors. Every 1 percent decrease in hemoglobin A1C (A1C) leads to significant reductions in diabetes complications, including CV disease (Exhibit 1).¹⁵ The ADA and the European Association for the Study of Diabetes (EASD) glycemic targets in T2DM are A1C less than 7.0 percent for most patients, pre-prandial glucose less than 130 mg/dl and post-prandial glucose of less than 180 mg/dl.^{7,16} The AACE guidelines recommend A1C less than or equal to 6.5 percent for most patients, fasting glucose less than 110 mg/dl, and post-prandial of less than 140 mg/dl.⁸ Individualization of glycemic targets is key (Exhibit 2).¹⁶ Tighter targets (6.0 - 6.5%) are suggested for younger, healthier patients. Looser targets (7.5 - 8.0%) are recommended for older patients and those

with multiple comorbidities or who are hypoglycemia prone.

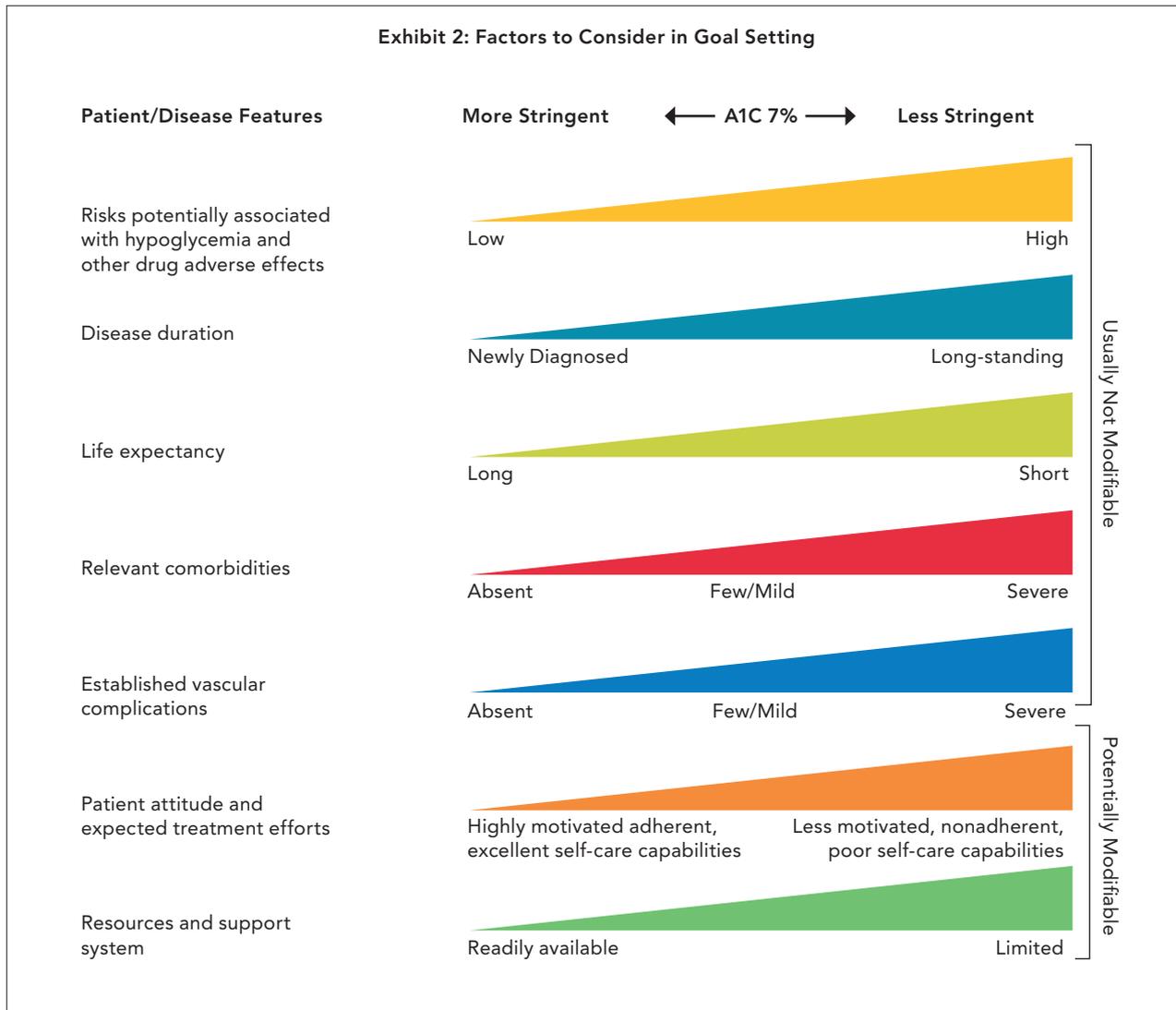
Achieving glycemic targets, particularly strict ones, typically requires multiple interventions. In a trial of standard therapy compared with a multiple-factor interventional treatment for T2DM patients, intensive therapy resulted in significantly lower rates of all the major complications.¹⁷

Individual Anti-diabetic Agents

An extensive array of non-insulin anti-diabetic agents are available for treatment of T2DM (Exhibit 3). Each class targets different metabolic defects that contribute to hyperglycemia in T2DM (Exhibit 4). To take advantage of the differing but complementary mechanisms of action, various classes are available in preset combinations or individual agents can be combined (Exhibit 5).

Metformin is the typical agent of first choice for treating T2DM because it is potent, inexpensive, does not cause hypoglycemia when used as monotherapy, and can cause modest weight loss. Initially, nausea, vomiting, and diarrhea occur in approximately 20 percent of patients; these effects wane with continued therapy. Long-term use of metformin is associated with vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. There is little disagreement that metformin is first-line medication therapy in T2DM unless contraindicated because of significant renal dysfunction (estimated glomerular filtration rate [eGFR] < 30

Exhibit 2: Factors to Consider in Goal Setting



ml/min) or not tolerated.

For many years the sulfonylureas were the therapy of first choice. Although initially effective, the sulfonylureas do not continue to have efficacy long term.¹⁸ This is likely due to pancreatic beta cell failure as T2DM progresses. The sulfonylureas have fallen out of favor because this class causes the highest rate of hypoglycemic events of the oral agents and modest weight gain (~ 2-4 kg). The advantages of the sulfonylureas are extensive clinical experience and low cost. Similar in action to the sulfonylureas, the meglitinides (repaglinide, nateglinide) have also fallen out of favor for similar reasons.

In T2DM, there is substantial impairment of about 40 percent of normal response in secretion of insulin in response to a meal or oral glucose load.¹⁹ The spike in insulin secretion in response to an oral glucose load is termed the incretin effect. Overall, this impairment is because of a decreased response to glucagon-like peptide 1 (GLP-1) which is secreted

from L cells in the gut in response to food. This can be overcome by achieving higher than physiologic GLP-1 levels.

GLP-1 infusions that achieve supra-physiologic levels are effective at enhancing insulin secretion and suppressing glucagon in a glucose-dependent manner, but these infusions are not practical as a treatment. The effort to identify effective forms of GLP-1 administration was challenged by its extremely short half-life; GLP-1 is rapidly metabolized by dipeptidyl peptidase 4 (DPP-4) following its release from gut cells.

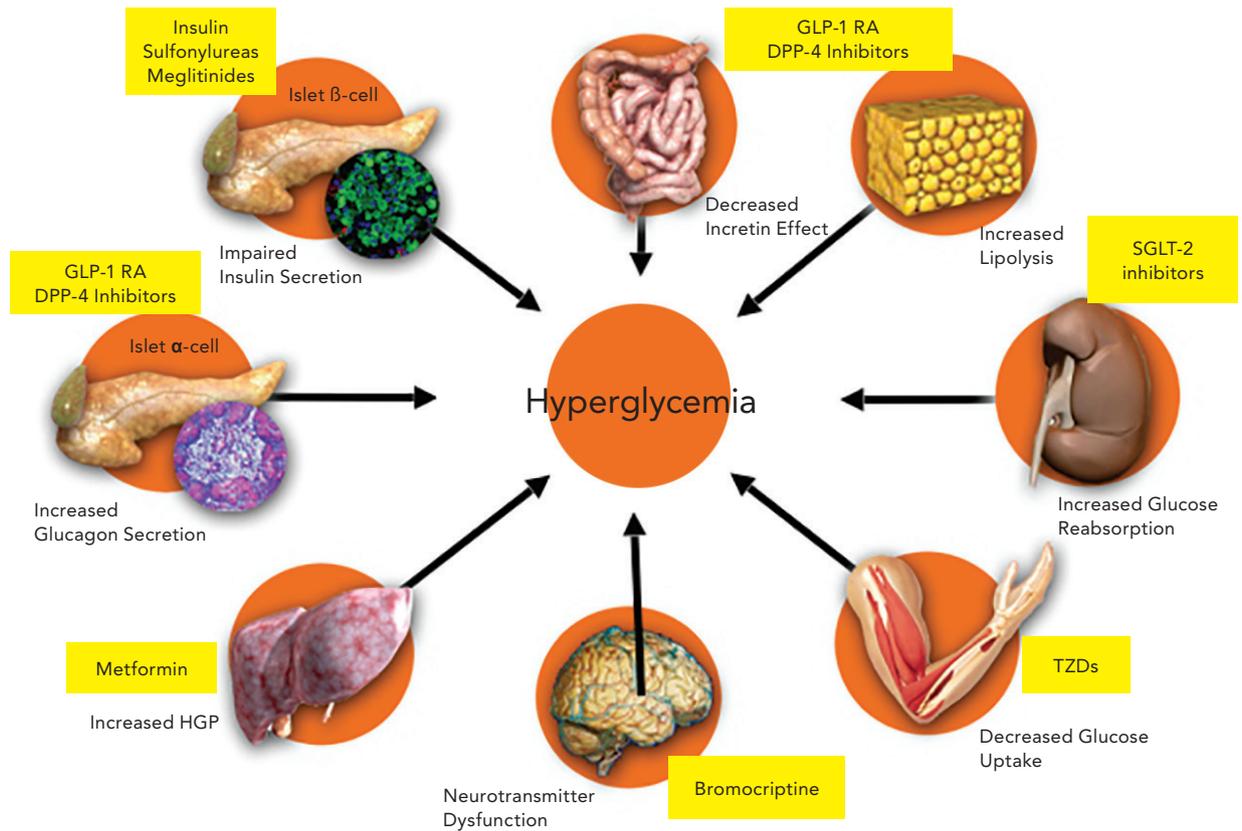
Much research has focused on compounds with molecular structures and incretin activity that are similar to GLP-1, but which have longer half-lives because they are not degraded by DPP-4 or are resistant to DPP-4. Exendin-4 derived GLP-1 receptor agonists (GLP-1 RAs) include exenatide twice daily (Byetta[®]), exenatide once weekly (Bydureon[®]), and lixisenatide (Adlyxin[®]). Human-based GLP-1 RAs

Exhibit 3: Noninsulin Agents for Treatment of Type 2 Diabetes

Class	Primary Mechanism of Action	Agent	Available as
α-Glucosidase inhibitors	<ul style="list-style-type: none"> • Delay carbohydrate absorption from intestine 	Acarbose	Precose or generic
		Miglitol	Glyset
Amylin analogue	<ul style="list-style-type: none"> • Decrease glucagon secretion • Slow gastric emptying • Increase satiety 	Pramlintide	Symlin
Biguanide	<ul style="list-style-type: none"> • Decrease HGP • Increase glucose uptake in muscle 	Metformin	Glucophage or generic
Bile acid sequestrant	<ul style="list-style-type: none"> • Decrease HGP • Increase incretin levels? 	Colesevelam	Welchol
DPP-4 inhibitors	<ul style="list-style-type: none"> • Increase glucose-dependent insulin secretion • Decrease glucagon secretion 	Alogliptin	Nesina
		Linagliptin	Tradjenta
		Saxagliptin	Onglyza
		Sitagliptin	Januvia
Dopamine-2 agonist	<ul style="list-style-type: none"> • Activates dopaminergic receptors 	Bromocriptine	Cycloset
Glinides (Meglitinides)	<ul style="list-style-type: none"> • Increase insulin secretion 	Nateglinide	Starlix or generic
		Repaglinide	Prandin
GLP-1 receptor agonists	<ul style="list-style-type: none"> • Increase glucose-dependent insulin secretion • Decrease glucagon secretion • Slow gastric emptying • Increase satiety 	Exenatide	Byetta
		Exenatide Weekly	Bydureon
		Liraglutide	Victoza
		Liraglutide Weekly	Saxenda
		Albiglutide	Tanzeum
		Dulaglutide	Trulicity
SGLT2 inhibitor	<ul style="list-style-type: none"> • Increase urinary excretion of glucose 	Dapagliflozin	Farxiga
		Canagliflozin	Invokana
		Empagliflozin	Jardiance
		Ipraflozin	Suglat
Sulfonylureas	<ul style="list-style-type: none"> • Increase insulin secretion 	Glimepiride	Amaryl or generic
		Glipizide	Glucotrol or generic
		Glyburide	DiaBeta, Glynase, Micronase or generic
Thiazolidinediones	<ul style="list-style-type: none"> • Increase glucose uptake in muscle and fat • Decrease HGP 	Pioglitazone	Actos
		Rosiglitazone	Avandia

HGP = hepatic glucose production

Exhibit 4: Multiple Metabolic Defects in T2DM and Mechanism of Action of Anti-diabetic Agents



GLP-1 RA = glucagon like peptide receptor agonist
 DPP-4 = dipeptidyl peptidase four
 SGLT-2 = sodium-glucose co-transporter two
 TZDs = thiazolidinedione
 HGP = hepatic glucose production

are liraglutide (Victoza[®], Saxenda[®]), albiglutide (Tanzeum[®]), and dulaglutide (Trulicity[®]). Semaglutide, injected once weekly, and ITCA 650, an implanted osmotic mini-pump of exenatide changed every six months, have been submitted to the FDA for approval. An oral formulation of semaglutide is in Phase II trials.

The GLP-1 RAs have five important actions. They upregulate beta-cell activity (insulin), down-regulate α -cell activity (glucagon), slow liver production of glucose, slow gastric emptying, and have a central hypothalamic satiety action.

The GLP-1 RAs are currently all injectable and available in pen-based delivery devices. Short-acting GLP-1 RAs include exenatide (Byetta[®] twice daily), liraglutide (once daily) and lixisenatide (once daily). The others are long-acting (once weekly dosing). The short-acting agents have greater impact on post-prandial glucose and less impact on fasting

glucose. The opposite occurs with the long-acting agents. The long-acting agents have more impact on A1C values. A1C reduction varies from 0.6 to 1.5 percent when GLP-1 RAs are used as monotherapy or as add-on therapy.²⁰⁻²⁵ Each leads to a similar degree of modest weight loss.

GLP-1 RAs have been compared with basal insulin and found to be noninferior and in some cases superior to basal insulin.²⁶⁻³³ There is less of a burden of treatment with the GLP-1 RAs compared with basal insulin because of less required monitoring, lower rate of hypoglycemia, and weight loss compared to weight gain. When used in combination with basal insulin, albiglutide once weekly results in similar A1C reductions to those observed with lispro insulin injections three times a day with meals.³⁴ Thus, the GLP-1 RAs are an attractive alternative to prandial short-acting insulin to improve glucose control.

Exhibit 5: Non-Insulin Combinations for the Treatment of Type 2 Diabetes

Class	Added Agents	Available as
DPP-4 inhibitor + SGLT-2 inhibitor	Linagliptin/Empagliflozin	Glyxambi
Metformin + DPP-4 inhibitor	Alogliptin	Kazano
	Linagliptin	Jentadueto
	Saxagliptin	Kombiglyze XR
	Sitagliptin	Janumet & XR
Metformin + glinide	Repaglinide	Prandimet
Metformin + SGLT-2 inhibitor	Canagliflozin	Invokamet & XR
	Dapagliflozin	Xigduo XR
	Empagliflozin	Synjardy & XR
Metformin + sulfonylurea	Glipizide	Metaglip and generic
	Glyburide	Glucovance and generic
Metformin + thiazolidinedione	Pioglitazone	Actoplus Met
	Rosiglitazone	Avandamet
Thiazolidinedione + DPP-4 inhibitor	Pioglitazone + alogliptin	Oseni
Thiazolidinedione + sulfonylurea	Pioglitazone + glimepiride	Duetact
	Rosiglitazone + glimepiride	Avandaryl

In terms of adverse effects, nausea, vomiting, and diarrhea are relatively common when therapy is started with a GLP-1 RA; these effects tend to be mild and improve with continued therapy. Albiglutide appears to cause the lowest rate of nausea. Liraglutide causes the next lowest level. Hypersensitivity, renal impairment, and pancreatitis can also occur. Medullary thyroid carcinoma nodules have been seen in rat and mice studies but have not been reported in humans. Patients at high risk for developing medullary thyroid carcinoma based on a history of multiple endocrine neoplasia or familial medullary thyroid carcinoma should not receive GLP-1 RAs.³⁸

When GLP-1 RAs are given alone, the rate of hypoglycemia is very low. Another benefit of GLP-1 RAs is modest reduction in blood pressure, total cholesterol, and LDL-cholesterol. In head-to-head trials, BP reductions averaged 3.57 mm Hg and were similar for individual GLP-1 RAs. Total cholesterol reductions ranged from 3 to 12 mg/dL. LDL-cholesterol changes ranged from 17 mg/dL reduction to 1 mg/dL increase. Triglyceride reductions ranged from 8 mg/dL to 36 mg/dL.

Because of unproven concerns about increased CV risk from thiazolidinediones, the FDA has been requiring CV outcomes studies with anti-diabetic

agents. There are now three CV outcomes studies with the GLP-1 RAs. One trial found that treatment with a GLP-1 RA resulted in a 13 percent reduction in deaths from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke.³⁵ CV death was reduced by 24 percent in patients treated with liraglutide.³⁶ There were trends for MI and stroke rates to be improved. In a preregistration trial, semaglutide reduced major cardiovascular events by 26 percent and nonfatal stroke by 39 percent.³⁷ In these trials, the majority of subjects already had CV disease or were at high risk for developing CV disease.

Advantages of the GLP-1 RAs include enhancement of insulin secretion, decreased glucagon, glucose-dependent action and thus low risk of hypoglycemia, quick onset, superior efficacy, weight loss, and CV disease safety/benefit. Disadvantages include cost, injectable only formulation, gastrointestinal adverse effects at treatment onset, possibility of pancreatitis and medullary thyroid cancer, and unknown long-term safety and durability.

Basal insulin-GLP-1 RA fixed-ratio co-formulations are the newest improvement in lowering glucose. Lixisenatide/insulin glargine (Soliqua[®]) and liraglutide/insulin degludec (Xultophy[®]) are both given once daily. The combinations result in better reductions in A1C (0.5% more) with lower rates

of hypoglycemia than with basal insulin alone.³⁹⁻⁴⁰ Weight loss also still occurs with the combination compared with weight gain, with insulin alone (1.4 kg – 3.2 kg average loss).

Patient selection for basal insulin/GLP-1 RA combination therapy may be limited as this is a new combination therapy. It is well known that the individual components work well together. Clinicians can consider these combination products for patients not at goal with either GLP-1 RAs or basal insulin therapy. Benefits of giving the combination products versus the individual components would be adherence (1 versus 2 or more injections) and one copay compared with two copays. Patients will need to be monitored closely when starting one of these combination products because glucose control can worsen during the titration period. To prevent hypoglycemia, if the patient is also receiving a secretagogue, the dose of the secretagogue should be reduced or it can be discontinued when making the transition to the combination product.

Another approach to altering the incretin effect in T2DM was to develop compounds that inhibit the activity of DPP-4, thus prolonging the half-life of naturally occurring GLP-1. Oral DPP-4 inhibitors are alogliptin (Nesina[®]), linagliptin (Tradjenta[®]), saxagliptin (Onglyza[®]), and sitagliptin (Januvia[®]). The DPP-4 inhibitors are effective as monotherapy and primarily have been compared with sulfonylureas. The typical A1C reduction with these agents is 0.5 percent to 0.8 percent. Studies have found the DPP-4 inhibitors to be noninferior or, in the case of alogliptin, superior to sulfonylurea in terms of A1C effect. These agents are also effective when combined with metformin or sulfonylureas.⁴¹⁻⁴⁵ The combination of a DPP-4 inhibitor and metformin results in modest weight loss over two years and a low rate of hypoglycemia. The DPP-4 inhibitors are well tolerated with low risk of adverse effects, including hypoglycemia. They can cause nausea, vomiting, and diarrhea when initially started. Pancreatitis has also rarely been reported.

Cardiovascular outcome trials of DPP-4 inhibitors, for safety purposes, have also been required by the FDA. All of these studies enrolled patients with CV disease or at high risk. All the trials found no difference between DPP-4 inhibitors and placebo in terms of CV outcomes; thus, the DPP-4 inhibitors do not increase risk of CV disease, nor do they reduce risk.⁴⁶⁻⁴⁸ Heart failure exacerbation has been reported with saxagliptin.

Advantages of the DPP-4 inhibitors include enhanced insulin secretion, decreased glucagon, glucose-dependent action, once daily oral, superior tolerability compared to other oral agents, weight

neutral, and no apparent CV risk. Disadvantages include cost, lower efficacy than other orals, unknown long-term safety (beyond 3 years), possible risk of pancreatitis, and unknown durability of efficacy.

Sodium-glucose cotransporter -2 (SGLT-2) inhibitors are the newest class of anti-diabetic agents. They remove excess glucose from circulation by blocking the reuptake of glucose at the nephron. These agents can remove up to 100 gm of glucose daily from circulation; the body typically filters 180 gm per day and reabsorbs the majority of it. SGLT-2 inhibition leads to insulin-independent reversal of glucotoxicity. Dapagliflozin (Farxiga[®]), canagliflozin (Invokana[®]), and empagliflozin (Jardiance[®]), each given once a day, are the three agents FDA approved in the U.S. Because the SGLT-2 inhibitors do not enhance insulin secretion, there is a low risk of hypoglycemia. These agents have comparable efficacy to sulfonylureas and DPP-4 inhibitors and reduce A1C 0.4 percent to 1.4 percent as monotherapy or in combination.⁴⁹ They are effective in combination with metformin, with a much lower rate of hypoglycemia and better impact on weight than a sulfonylurea/metformin combination.⁵⁰⁻⁵¹ The SGLT-2 inhibitors and DPP-4 inhibitors cause similar rates of hypoglycemia.⁵²⁻⁵³ The SGLT-2 inhibitors do result in more weight loss than the DPP-4 inhibitors. SGLT-2 inhibitors modestly decrease blood pressure, but also can increase LDL cholesterol slightly (-1% to 4.5%, depending on agent and dose). These agents lead to a 3 to 4 kg weight loss.

Empagliflozin has been shown to reduce CV events.⁵⁴ Treatment with this agent decreased the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 14 percent compared with placebo and CV death by 38 percent; this degree of risk reduction is similar to what is seen with statin therapy. Treatment with the SGLT-2 inhibitor also led to a 35 percent reduction in hospitalization rates. Some of the CV benefit of the SGLT-2 inhibitor may be explained by the mild diuresis that occurs early in therapy. Given that the benefit was sustained during the trial suggests that the mechanism of action of the CV benefit is more complicated than simple diuresis during early therapy. Postulated mechanisms are improvements in cardiac metabolism, cardiac function, or cardiac oxygen demand; reduced oxidative stress; or glucagon effects. This agent would be suggested to be added to a patient's regimen if the patient already has CV disease and is already on combination therapy because that is the population which has been studied. Adverse effects that have been reported with SGLT-2 inhibitors include bladder infections, genital yeast infections,

dehydration, impaired renal function, long bone fractures, hypersensitivity, and euglycemic diabetic ketoacidosis.

From March 2013 to May 2015, 73 cases of ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT-2 inhibitors were reported to the FDA, leading to revised package labeling for these agents.⁵⁵ In one case series, 13 cases of euglycemic DKA in patients with type one DM (9 cases, used off-label) or T2DM (4 cases) were reviewed.⁵⁶ Most patients were women and most cases were linked to reduced insulin doses. Possible precipitating factors were increased activity, recent illness, alcohol use, and decreased food intake. Some patients had no identifying cause. All patients responded to intravenous rehydration and insulin.

Several mechanisms have been proposed for why DKA occurs with SGLT-2 treatment. When SGLT-2 inhibitors are combined with insulin, the insulin dose is often decreased to avoid hypoglycemia. The lower dose of insulin may be insufficient to suppress lipolysis and ketogenesis.⁵⁷ Two other mechanisms may be increased glucagon secretion and volume depletion.^{56,57}

SGLT-2 inhibitors have several advantages including good efficacy, decreased glucotoxicity, weight loss, lower BP, low risk of hypoglycemia, quick onset, low risk of drug- drug interactions, and possible

CV benefits. Disadvantages of this class include cost, ineffectiveness in patients with moderate to severe renal impairment, polyuria, volume depletion, genital mycotic infections, risk of DKA, and unknown long-term safety and durability.

Patients selected to receive a SGLT-2 inhibitor should be selected wisely. Given the risk of adverse effects, this class should not be the first oral medication to consider. Patients will need to be encouraged to increase water intake and maintain good genital hygiene. These are not effective in patients with very low renal function and must be used cautiously with volume-fragile patients. The elderly are especially at risk for adverse effects because of lowered kidney function and the effects of dehydration.

Thiazolidinedione (TZD) use dramatically fell when trials suggesting increased risk of CV outcomes were published. Pioglitazone and rosiglitazone may be coming back into favor because there are some data to suggest that cardiovascular outcomes are reduced by this class.^{58,59}

Insulin therapy is the most appropriate choice for many patients with T2DM, particularly in the later stages of the disease. Its major advantages are nearly universal response with unlimited efficacy, the ability to finely tune doses, and many years of clinical use. The disadvantages are hypoglycemia, weight gain, need for injection and associated training, and

Exhibit 6: Insulins Available for the Treatment of Type 2 Diabetes

Class	Agent	Available as
Basal	Detemir U100	Levemir
	Glargine U100	Lantus, Basaglar
	Degludec U100 and U200	Tresiba
	Glargine U300	Toujeo
	Neutral protamine Hagedorn (NPH)	Generic
Prandial	Inhaled insulin	Afrezza
	Aspart	NovoLog
	Glulisine	Apidra
	Lispro U100 and U200	Humalog U100, U200
	Regular human	Humulin, generic
	Regular U500	Humulin 500 and Pen
Premixed	Biphasic aspart 70/30	NovoMix
	Biphasic lispro 75/25 50/50	Humalog Mix
Basal + Prandial	Degludec + Aspart	Ryzodeg

patient and clinician fears. Although inhaled rapid-acting insulin is available, its use is not extensive.

There are a large number of insulin products available in the U.S. (Exhibit 6). Several of the insulin products are available as concentrated formulations (higher than 100 units per ml). These result in smaller volumes infused with changing pharmacokinetic and pharmacodynamics properties, including flatter action curves and longer durations of action, compared with the non-concentrated forms. For the patient, the concentrated insulins typically have a more predictable effect, which may allow more dosing flexibility, but may require more total units of insulin for similar results. For example, 10 percent more glargine U-300 is required compared with glargine U-100. The concentrated insulins are used for patients who require very high doses, which is common in the U.S. because of our obesity and insulin resistance epidemic. Other insulins which may be coming to market include fast-acting insulin aspart (Fiasp), which has been submitted to the FDA for approval and a 70/30 combination of insulin degludec and fast-acting insulin aspart.

Treatment Selection

Treatment selection should be patient-tailored. The ADA recommends a patient-centered approach of “providing care that is respectful of and responsive to individual patient preferences, needs, and values — ensuring that patient values guide all clinical decisions.”⁷ The clinician should gauge the patient’s preferred level of involvement and should explore, where possible, therapeutic choices with the patient. The clinician should also utilize decision aids and have shared decision-making for final treatment.

Considerations for selecting therapies are numerous. Current A1C levels and magnitude of reduction needed to reach goal, potential effects on body weight, and potential for hypoglycemia are all important considerations. For example, a given patient may have a lack of awareness of hypoglycemia or disordered eating habits which would need to be considered in selecting an anti-diabetic therapy. Effect on weight is a significant issue given that most patients with T2DM are already overweight. Insulin, sulfonylureas and TZDs lead to weight gain over time. Metformin, GLP-1 RAs, and SGLT-2 inhibitors all lead to modest weight loss, and the DPP-4 inhibitors are weight neutral.

Effects on other CV disease risk factors, including blood pressure and lipids, and current comorbidities, including coronary heart disease, heart failure, chronic kidney disease, and liver dysfunction, also need to be considered (Exhibit 7). Patient factors to be considered include adherence to medications

and lifestyle changes, preference for oral or injected therapy, and economic considerations.

For all patients, treatment includes lifestyle changes including healthy eating, weight control, and increased physical activity. Unless contraindicated, metformin should be added at diagnosis or soon after.⁷ If metformin is contraindicated or it is not tolerated, a medication from one of the classes appropriate for combination therapy may be substituted as initial therapy. The AACE guidelines recommend initial monotherapy with metformin, GLP-1 RA, SGLT-2 inhibitor, or DPP-4 inhibitor.⁸ The AACE guidelines also recommend initial combination therapy with metformin as the base for those who have starting A1C greater than or equal to 7.5 percent because one agent is not likely to achieve the A1C goal.⁸ Clinicians should consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed T2DM who are symptomatic and/or have A1C greater than or equal to 10 percent and/or blood glucose levels greater than or equal to 300 mg/dL.⁷

Overall, the efficacy of non-insulin agents depends on the baseline A1C; the higher the baseline A1C, the greater the reduction with a given medication. On average, non-insulin anti-diabetic agents produce a 1 to 2 percent reduction. Monotherapy fails in the majority of patients either initially to achieve goal A1C or in the long-term given the progressive nature of the disease. Whether for biological or behavioral reasons (or both), combination therapy will often be needed.

If non-insulin monotherapy at the maximum tolerated dose does not achieve or maintain the A1C target after three months, a second agent (oral agent, GLP-1 RA, or basal insulin) should be added. Exhibit 8 compares the options. For patients with T2DM who are not achieving glycemic goals, insulin therapy should not be delayed. If after an additional three months, two agents are not effective, a third can be added to the regimen.

In patients with long-standing, suboptimally controlled T2DM and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered, as they have been shown to reduce CV and all-cause mortality when added to standard care.⁷ This is a new recommendation in the ADA guidelines. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.

Managed Care Issues

Because of the large population of patients with diabetes in the U.S. and the enormous costs of caring for this chronic and progressive disease state, it is a

Exhibit 7: How do Comorbidities Affect Anti-Hyperglycemic Therapy in T2DM?

Coronary Disease	Heart Failure	Renal Disease	Liver Dysfunction	Hypoglycemia
<ul style="list-style-type: none"> ▶ CVD benefit ▶ Metaformin ▶ Empagliflozin ▶ Liraglutide ▶ Avoid hypoglycemia 	<ul style="list-style-type: none"> ▶ Metaformin - may use unless condition is unstable or severe ▶ Avoid TZDs ▶ Saxagliptin may exacerbate 	<ul style="list-style-type: none"> ▶ High risk of hypoglycemia ▶ Metformin and lactic acidosis <ul style="list-style-type: none"> • Stop @ Scr \geq 1.5 (1.4 women) ▶ Caution with SUs (esp. glyburide) ▶ DPP-4 inhibitors - dose adjust for most ▶ Avoid exenatide if GFR < 30 	<ul style="list-style-type: none"> ▶ Most drugs not tested in advanced liver disease ▶ Pioglitazone may help steatosis ▶ Insulin best option if disease severe 	<ul style="list-style-type: none"> ▶ Emerging concerns regarding association with increased morbidity/mortality ▶ Proper drug selection is key in hypoglycemia prone

SCr = serum creatinine
 GFR = glomerular filtration rate
 GLP-1 RA = glucagon like peptide receptor agonist
 DPP-4 = dipeptidyl peptidase four
 SGLT-2 = Sodium-glucose co-transporter two
 TZDs = thiazolidinedione
 SU = sulfonylurea

major focus for managed care. Although it is expensive to treat T2DM effectively, it is even more expensive to not treat or suboptimally treat the disease. Best practices to optimize outcomes in T2DM require a hands-on approach for both providers and managed care organizations.

Diabetes is one of the significant focus areas for the Medicare program with value-based and quality payment initiatives. The goal of the value-based programs is better health care for individuals, better health for populations, and lower cost. The quality payment program includes advanced alternative payment models and a merit-based incentive payment system (MIPS). In the merit-based program, there are eight diabetes-specific measures including the percentage of patients who have A1C greater than 9 percent.⁶⁰ There are also obesity and hypertension measures that are applicable to the diabetes population.

Commercial managed care approaches to diabetes management have been to implement case management, physician education and incentives, and formulary management. Case management has used a chronic care model which includes self-management support, decision support, delivery system design, clinical information systems, organization of health care, and community.⁶¹ To be successful, any case

management has to focus on the patient being the center of all the activities.

Clinicians see heroism, determination, and persistence from their patients on a daily basis. The salient question for managed care and clinicians is “are we doing everything we can to support their heroism in a meaningful way.” Clinicians do not want to be getting in the way of the patient. The community, workplace, providers, government, and family should all be working to support patients with diabetes. The ADA guidelines now focus more on the individual rather than just achieving a particular goal A1C with such things as taking into account how well a given person tolerates hypoglycemia and life expectancy when selecting therapy and goals. When taking care of a diabetic population, clinicians and managed care need to both make sure they are improving the whole patient and not just looking at hitting some particular A1C target.

When discussing chronic disease treatment, several terms (adherence, compliance, and concordance) get thrown around without everyone truly understanding what they mean. Adherence is how well a patient’s behavior corresponds to a health care provider’s recommendation.⁶² Compliance is the proportion of administered doses or prescribed doses over a period to time. Both of those terms

Exhibit 8: Choice of Therapy After Metformin¹⁶

	SU	TZD	DPP-4i	GLP-1RA	SGLT-2i	Basal Insulin
Efficacy (↓ HbA _{1c})	+++	+++	++	+++	+++	++++
Hypo risk	++	+	+	+	+	+++
Weight effect	↑	↑	↔	↓	↓	↑
Major side-effects	Hypo	Edema, Heart failure, Bone fractures	Rare	GI	Urinary and genital infections	Hypo

DPP-4i = dipeptidyl peptidase-4 inhibitor
 GI = gastrointestinal
 GLP-1RA = glucagon-like peptide-1 receptor agonist
 HbA_{1c} = glycosylated haemoglobin
 SU = sulphonylurea
 TZD = thiazolidinedione
 SGLT-2i = sodium glucose co-transporter 2 inhibitors
 ↑ = weight gain
 ↓ = weight loss
 ↔ = weight neutral
 + = low
 ++ = moderate/intermediate
 +++ = high
 ++++ = highest

are predicated on the providers' desires and decisions rather than the patients' and the providers' perceived greater knowledge about what is best for the patient. But, patients bring with them their own knowledge base and understanding. Clinicians can learn from their patients by listening to them and educating them about how the clinician can help the patient achieve their particular goals. Concordance is the involvement of patients in decision-making to improve patient adherence/compliance with medical advice. Much better results are achieved when the patient is involved in the decision-making

Adherence is important with medications, lifestyle, exercise, and diet. Based on electronic medical record data, oral anti-diabetic medication adherence has been found to be 61 to 85 percent, with 39.6 percent of patients being persistent with therapy at 24 months.⁶² Importantly, 4 percent of patients never filled their initial prescription.⁶² Retrospective studies of insulin adherence found that 62 percent of long-term users were adherent, 64 percent of new users were adherent, 4.5 percent never filled the

initial prescription, and 25.5 percent never refilled their prescription.⁶² A prescribed medication that is not taken is wasting resources. There are many factors which impact adherence, including age, culture, perception, duration of disease, dosing complexity, poly-therapy, psychological factors, safety, tolerability, and cost.⁶² Not all of these factors are modifiable, but several are. Long-term adherence and concordance is an area where clinicians and managed care can focus and have an impact in making sure scarce health care dollars are used appropriately.

Clinical inertia is primarily a clinician barrier to optimal outcomes in T2DM. Clinicians tend to delay changing therapy for many months, especially when intensifying insulin.⁶³ Clinicians need to move faster to get patients to goal and keep them at goal. Managed care can intervene with programs to try to overcome clinical inertia. Case manager contact with clinicians can be used to increase provider concordance with management guidelines.

Physician incentives and education interventions have also been used by managed care to steer popu-

lations of patients with diabetes. Pay for performance is somewhat tricky because the incentives need to be enough to get physicians to participate, but there also needs to be enough money for those who care for complicated patients to still make a living.

Since the mid-1990s, there has been an explosion in the number of classes of medication available and recommended for managing diabetes. The majority of the new diabetes medications have become available since the majority of practicing physicians completed their training. It is challenging for clinicians to keep up to date on all the available medications. Education on appropriate use of newer medications can help clinicians upgrade their practices.

Cost containment interventions of formulary management and prior authorizations for prescribing are commonly used by managed care. Formulary management has focused primarily on reducing medication costs but, of course, reducing medication costs may increase other costs, such as for complications or hospitalizations. The total costs of therapy have to be considered when developing formulary guidelines. Medication that is purchased and never used, insulin or other medications that are used sub-therapeutically, medication used for the wrong patient type, and medication that is not given to a patient that needs it due to clinician inattention or unfamiliarity will all result in costs to the health care system. Targeting these issues is another way to reduced overall costs of care.

Prior authorization restriction or non-formulary designations restrict access to higher cost medications and are possibly cost saving for a health plan. These interventions potentially redirect patients to less costly alternatives. The disadvantages include interference with patients receiving necessary medication and fostering of distrust in the patient/physician relationship. Navigating the whole process of getting patient access to medications that the clinician thinks is appropriate contributes to physician stress, burnout, adds burden to patient care staff, and can lead to providers not choosing appropriate medication because of administrative burden.

Managed care needs to understand the wisdom of the clinical practice guidelines and recommendations. The wisdom of the treating physician also needs to be acknowledged when they deviate from the guidelines. The patient's well-being should be central to managed care decision-making.

Managed care should use the data available to them. Provider data includes meeting recommended process goals (eye exams, foot exams, measurement of A1C, etc.), how frequently at risk patients are seen, what medications are being used, appropriateness of referrals, and outcomes. It is difficult cur-

rently to identify provider-specific outcomes given different acuity mixes. Sharing data with a provider is beneficial, but the format in which it is presented can impact what the provider does with the information. It is important to present the feedback as opportunities for improvement.

Instead of prior authorization, one intervention that managed care could consider is requiring a diabetes education referral before the patient can be prescribed an expensive therapy. Essentially, diabetes education would be part of step therapy and can help improve patient concordance with therapy.

Conclusion

Diet, exercise, and education are the foundation of therapy. Diabetes therapy should be personalized using patient factors and preferences, comorbid conditions, and life expectancy. CV risk reduction should be a major focus of therapy. Metformin is usually first-line therapy for T2DM, and there are multiple options for improving glycemic control after monotherapy failure. Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain control. All treatment decisions should be made in conjunction with the patient with a focus on preferences, needs, and values. Managed care plays a significant role in diabetes management. Managed care has access to data that can help all parties understand better how diabetes care is being delivered and where care delivery can be improved.

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