

# Primary Care Case Studies

## Chart Review

VOL

1

MRS. K      DOB 8/16/53

Real World Guidance and Opinions Offered  
by Expert Colleagues to Assist in the  
Clinical Management of Type 2 Diabetes

**PATIENT NAME:**

MRS. K

**DIAGNOSIS:**

HYPERTENSION, DYSLIPIDEMIA

**REASON FOR VISIT:**

EVALUATE ELEVATED GLUCOSE SCREENING RESULTS



# Primary Care Case Studies Chart Review

## The Doctors on Call - Faculty Credentials

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### LEARNING OBJECTIVES

- List the current ADA guidelines for screening patients for diabetes
- Explain the progressive nature of diabetes and how this demands a progressive therapeutic intervention to reach goals
- List lifestyle modifications that meet an individual patient's clinical goals and lifestyle
- Describe the potential benefits and risks of currently available oral antihyperglycemic (OAH) agents and where they fit into the current treatment algorithm for type 2 diabetes
- Describe factors to consider in selecting or modifying a treatment plan to meet an individual patient's goals, concerns, and capabilities

#### Sponsor Disclosure Statement

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Medical Accuracy Reviewer, Dan Pollom, MD, disclosed that he is on the speakers' bureau for Takeda Pharmaceuticals NA, Inc.

CME Reviewer, Allan J. Wilke, MD, reported that he had no financial relationships to disclose.

#### Faculty Disclosure Statements

Dr. Barringer has disclosed that he is on the speakers' bureaus for Astra-Zeneca, GlaxoSmithKline, Pfizer, and Abbott Laboratories.

Dr. Kendall has disclosed that he is on the advisory boards for and receives educational funding from Amylin Pharmaceuticals, Bayer Diabetes Care, Daiichi-Sankyo, Eli Lilly Pharmaceuticals, HealthPartners, Intarcia, Merck, Roche, Takeda Pharmaceuticals NA, Inc. and UnitedHealth Group. He also disclosed that he has contract research with Abbott Diabetes Care, Amylin Pharmaceuticals, Bayer Diabetes Care, Dexcom, Eli Lilly Pharmaceuticals, MannKind, Medtronic/MiniMed, Merck, NIH-NHLBI, Novo Nordisk, Roche, and Sanofi-Aventis. His spouse is a current employee of Genentech (Roche).

Ms. Rodriguez de Bittner reported that she has no financial relationships to disclose.

Ms. Strock reported that she has no financial relationships to disclose.

Dr. Unger has disclosed that he receives royalty from Lippincott Publications; is on advisory boards for Novo Nordisk, Eli Lilly Pharmaceuticals, and Roche Pharmaceuticals; is on speaker bureaus for Novo Nordisk, and Eli Lilly Pharmaceuticals; and has contract research for Forest, Novo Nordisk, GlaxoSmithKline, Takeda Pharmaceuticals NA, Inc, Daiichi Sankyo, Astra-Zeneca, Ortho-McNeil Johnson, Sucampo Pharmaceuticals, Wyeth, Cephalon, MAP, Purdue, Proctor & Gamble, Arena, Amylin, Allergan, Abbott Laboratories, and Sanofi-Aventis.

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- Content peer-review by an external topic expert
- Content peer-review by an external CME reviewer
- Content validation by internal PCEC clinical editorial staff

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The Primary Care Education Consortium designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credits. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Accreditation begins on: November 1, 2009 and ends on: November 1, 2010.

This activity has been reviewed and is acceptable for up to 2.0 Prescribed credits by the American Academy of Family Physicians. Of these credits, 1.0 conforms to the AAFP criteria for evidence-based CME clinical content. CME credit has been increased to reflect 2 for 1 credit for only the EB CME portion. AAFP accreditation begins November 1, 2009. The term of approval is for 1 year from this date, with option for yearly renewal. When reporting AAFP credit, report total Prescribed and Elective credit earned for this activity. It is not necessary for members to label credit as evidence-based CME for reporting purposes.



The EB CME credit awarded for this activity was based on a current clinical question that identifies gaps in learners' knowledge, competency and/or performance in medical as identified in the current evidence available at the time this activity was approved. Since clinical research is ongoing and new evidence to supporting practice improvement is constant, the AAFP recommends that learners verify sources and review these as well as practice recommendations prior to implementation into practice.

#### Clinical Practice Recommendations for AAFP EB CME Designation

**1. Practice Recommendation:** A less stringent A1C goal than the general goal of < 7% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, or extensive comorbid conditions or those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents, including insulin.

**Evidence-Based Source:** Circulation

**Volume/Issue/Page number of Article of Supporting Evidence:** Skyler JS, et al. *Circulation*. 2009;119:351-357

**Strength of Evidence:** C. Only consensus opinion of experts, case studies, or standard-of-care

**Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy

**2. Practice Recommendation:** When adding a medication to the combination of lifestyle management and metformin, exenatide or pioglitazone is reasonable when hypoglycemia is to be especially avoided (eg., patients who have hazardous jobs).

**Evidence-Based Source:** Diabetes Care.

**Volume/Issue/Page Number of Article of Supporting Evidence:** Nathan et al. *Diabetes Care*. 2009;32:193-203. (page 199).

**Strength of Evidence:** The recommendation is based on 2 sources:

1) clinical trials that address the effectiveness and safety of the different modalities of therapy; and 2) collective knowledge and clinical experience of the consensus panel.

**3. Practice Recommendation:** Blood pressure screening should occur at every visit and the lipid profile checked at least annually.

**Evidence-Based Source:** American Diabetes Association

**Volume/Issue/Page Number of Article of Supporting Evidence:** *Diabetes Care*. 2009;32 (Suppl 1):S13-S61.

**Strength of Evidence: C (blood pressure):** Supportive evidence from poorly controlled or uncontrolled studies. Evidence from randomized clinical trials with one or more major three or more minor methodological flaws that could invalidate the results. Or evidence from observational studies with high potential for bias (such as case series with comparison to historical controls). Or evidence from case series or case reports. Conflicting evidence with the weight of evidence supporting the recommendation.

**Strength of evidence E (lipids):** Expert consensus or clinical experience.

#### Statement of Support

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**Medium:** CME print publication

#### Method of Physician Participation

After reading the publication in its entirety, go to: [www.pceconsortium.org/PCCSNov2009TK](http://www.pceconsortium.org/PCCSNov2009TK) and complete the online evaluation and post test. Upon completing the evaluation and the post test you will be prompted to print your certificate of completion.

## Type 2 Diabetes Case Study

CASE PRESENTATION			
<b>PHYSICAL</b>		AGE: 56y	DOB: 8/16/53
HT: 5'3"	WT: 155lbs	BMI: 27.5	BP: 140/95 mm Hg
<b>LABS</b>			
A1C: 8.8%	RANDOM GLUCOSE: 250 mg/dL		
<b>MEDICATIONS</b>			
Irbesartan 300 mg daily Atorvastatin 40 mg daily			
<b>NOTES:</b>			
WD-WN Random glucose and A1C over the criteria for T2DM'			

### Type 2 Diabetes in the United States

Type 2 diabetes mellitus (T2DM) takes a huge toll on Americans by virtue of the acute and chronic complications, disability, and death it causes. Approximately 24 million people or 7.7% of the US population have diabetes, with T2DM accounting for 90-95% of all cases. A quarter of patients with diabetes (5.7 million) are undiagnosed and an estimated 57 million persons have pre-diabetes, 2 million between the ages of 12 and 19 years.<sup>2</sup> The progression to diabetes for patients with impaired glucose tolerance (IGT) is 6-10% per year, and for persons with both IGT and impaired fasting glucose (IFG) the cumulative incidence of diabetes may be as high as 60%. Conversion of IFG to diabetes increases cardiovascular mortality 2-fold, whereas IGT increases cardiovascular risk by 50%.<sup>3</sup> These sobering statistics point to the critical need for early identification, as well as the initiation and intensification of effective treatment in the primary care setting.

### Pathophysiology of T2DM

Type 2 diabetes is a multifactorial process involving insulin resistance, pancreatic beta cell dysfunction, abnormal glucose release and disposal, abnormal glucagon secretion, diminished incretin response, and decreased amylin secretion. Insulin resistance and beta cell dysfunction are thought to play early and central roles in the pathogenesis of T2DM.<sup>4,5</sup> The United Kingdom Prospective Diabetes Study (UKPDS) showed that at diagnosis, the average person such as Mrs. K has lost approximately 50% of her beta cell function.<sup>5</sup> Recent data by DeFronzo et al suggest the loss is higher, perhaps as much as 80% of beta cell function.<sup>6</sup>

Another important feature of prediabetes and diabetes is hyperglucagonemia. In persons with normal glucose tolerance, an increase in postprandial glucose is associated with a decline in the secretion of glucagon. Conversely, as the glucose level decreases below normal, the glucagon level increases leading to a 60% increase in hepatic glucose production via gluconeogenesis. The secretion of glucagon is also partly determined by the secretion of insulin, which promotes the storage of glycogen within hepatocytes. Increased glucagon secretion, which occurs in both prediabetes and T2DM leads to glycogenolysis, thereby raising ambient glucose levels. These effects are made worse in the presence of insulin resistance and insulinopenia.

Free fatty acids are also known to be involved in the pathogenesis of T2DM as they accelerate insulin resistance and impair insulin secretion by diminishing the ability of skeletal muscles to uptake glucose, hepatocytes to suppress the production of glucose, and pancreatic beta cells to secrete insulin.

The incretin system is also involved in the pathogenesis of T2DM. The incretin hormone glucagon-like peptide-1 (GLP-1) is released

by L-cells in the distal ileum and colon as food is ingested. The actions of GLP-1 are glucose-dependent. In the presence of hyperglycemia, GLP-1 suppresses glucagon secretion from pancreatic alpha cells, while stimulating the secretion of insulin from pancreatic beta cells. As glucose levels fall towards normal, glucagon and insulin levels also normalize, thereby preventing hypoglycemia.

TREATMENT PLAN
<p>Metformin 500 mg daily with meals x 3 days            Increase to 500 mg twice daily with meals            Referral to dietician for weight loss regimen</p>
<p><b>NOTES:</b></p> <p>Discussed diagnosis of T2DM - progressive disease that needs her involvement for successful management. Reviewed importance of nutrition and exercise.</p>

### Treatment Strategies

The care of patients with T2DM requires the collaboration and coordinated care of all members of the health care team as it is impossible for a single provider to be able to address all of the needs of a patient with T2DM. The patient-centered plan should include the prevention and/or treatment of glucose and non-glucose-related diseases<sup>7</sup> (Refer to Table 1). Large randomized, double-blind studies have found that intensive management of all risk factors, including lipids, blood pressure, and glycemia, have significant beneficial effects on cardiovascular-related events and that these interventions can be cost-effective.<sup>8-13</sup>

Table 1: Recommended Goals for Patients with Type 2 Diabetes

LEVEL	GOAL
<b>Glucose</b>	
A1C	< 7.0% <sup>1</sup>
Preprandial	70-130 mg/dL
Postprandial	< 180 mg/dL <sup>2</sup>
<b>Blood Pressure</b>	< 130/80 mm Hg
<b>Lipids</b>	
LDL-cholesterol	< 100 mg/dL [ $< 70$ mg/dL overt CVD]
HDL-cholesterol	> 50 mg/dL (female); > 40 mg/dL (male)
Triglyceride	< 150 mg/dL

<sup>1</sup> Referenced to a non-diabetic range of 4.0-6.0% using a DCCT assay  
<sup>2</sup> Measurement should be made 1-2 h after the beginning of the meal, generally peak levels in patients with diabetes.

The American Diabetes Association recommends that most patients have a targeted A1C level less than 7%.<sup>7</sup> However, achieving a higher A1C in patients with advanced microvascular or macrovascular complications, known coronary artery disease, hypoglycemic unawareness, or shortened life expectancy may be more prudent.<sup>14</sup> A philosophical approach to pharmacologic management in most patients should be to treat as: 1) low as possible; 2) soon as possible; 3) long as possible; 4) safely as possible; and 5) rationally as possible.

Because overweight and sedentary lifestyle are major risk factors for T2DM and interventions that reverse or improve them have beneficial effects on glycemic control,<sup>16</sup> lifestyle management is a cornerstone of therapy. For this reason, the 2009 American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus panel emphasizes the importance of weight loss, noting that weight loss as little as 4 kg (approximately 8.8 lbs) will often ameliorate hyperglycemia.<sup>16</sup>

FOLLOW UP - 3 MONTHS			
PHYSICAL		AGE: 56y	DOB: 8/16/53
HT: 5'3"	WT: 148 lbs	BMI: 26.5	BP: 135/90 mm Hg
LABS			
A1C: 6.5-6.9%	FPG:	PPG:	
MEDICATIONS			
Irbesartan 300 mg daily Atorvastatin 40 mg daily Metformin 1000 mg twice daily			
NOTES:			
* 7lb weight loss from 300 cal reduction daily plus 45 min kickboxing 4x week! * Feeling energetic; Proud of accomplishments * Continues to SMBG FPG and PPG			

Evolving evidence continues to demonstrate the benefits of lifestyle management. The Look AHEAD study is an on-going, randomized, controlled trial examining the outcomes of lifestyle intervention programs designed to produce intentional weight loss in patients with T2DM over 11 years.<sup>15</sup> The study randomized 5,145 overweight patients (BMI > 25 kg/m<sup>2</sup>) into two cohorts. The intensive lifestyle intervention (ILI) group will have access to individual and group lifestyle educational sessions with weekly meetings for 6 months; the frequency of the visits will decrease over time. If needed, weight loss medications can be used. The control group receives educational sessions about nutrition and physical activity, as well as social support. Both groups receive comparable diabetes education. The goal of Look AHEAD is to reduce baseline body weight by 7% in order to determine whether ILI can reduce cardiovascular risk.<sup>15</sup> This study is of critical importance because observational studies do not separate intentional from unintentional weight loss (ie., weight loss due to illness) nor do they control for pre-existing illness or confounding factors such as cancer or mental illness which can only be addressed through randomized trials.

Preliminary results, after 1-year, of the Look AHEAD study show that the average weight loss from baseline in the ILI group was 8.6% compared with 0.7% in the control group.<sup>15</sup> The weight loss in the ILI group resulted in significantly greater reductions in A1C and blood pressure compared with the control group (Refer to Table 2). LDL-cholesterol was reduced in both groups compared with baseline, but the difference between the two groups was not statistically significant. These results show that moderate weight loss reduces cardiovascular risk within the first year. What is unknown is whether successful weight loss and metabolic improvement can be maintained over time or if the initial weight loss, even if short-lived, might be associated with long-term benefits in terms of cardiovascular risk.

Table 2: Patient Response After 1 Year of Intensive Lifestyle Intervention

PARAMETER	INTENSIVE LIFESTYLE INTERVENTION (N=2,463)	CONTROL GROUP (N=2,496)	P VALUE
Weight loss from baseline	8.6% (7.6% in insulin users)	0.7% (0.3% in insulin users)	P=0.001
Patients achieving A1C < 7%	26.4%	5.4%	P< 0.001
Patients who met all 3 ADA goals (A1C, BP, LDL-cholesterol)	12.8%	6.5%	P< 0.001

Since weight regain is common, lifestyle management must be continued throughout the course of T2DM. Lifestyle modifications that reduce caloric intake, saturated and trans fatty acids, cholesterol, and sodium, and increase physical activity are encouraged.<sup>17</sup> The means by which these modifications are achieved should be individualized. This is generally best accomplished through the involvement of a certified diabetes educator or dietitian with experience in the care of patients with T2DM. A multitude of resources for patients regarding lifestyle management are available from credible sources (Refer to Table 3).

Table 3: Credible Sources of Lifestyle Management Information for Patients with Type 2 Diabetes

<p><b>American Diabetes Association</b>  <a href="http://www.diabetes.org/food-nutrition-lifestyle/lifestyle-prevention/weight-loss.jsp">www.diabetes.org/food-nutrition-lifestyle/lifestyle-prevention/weight-loss.jsp</a>  <a href="http://www.diabetes.org/food-nutrition-lifestyle/nutrition.jsp">www.diabetes.org/food-nutrition-lifestyle/nutrition.jsp</a>  <a href="http://www.diabetes.org/food-nutrition-lifestyle/fitness.jsp">www.diabetes.org/food-nutrition-lifestyle/fitness.jsp</a></p> <p><b>American Dietetic Association</b>  <a href="http://www.eatright.org/cps/rde/xchg/ada/hs.xsl/nutrition.html">www.eatright.org/cps/rde/xchg/ada/hs.xsl/nutrition.html</a></p>	<p><b>National Institute of Diabetes and Digestive and Kidney Diseases</b>  <a href="http://diabetes.niddk.nih.gov/treatments/index.htm">http://diabetes.niddk.nih.gov/treatments/index.htm</a></p> <p><b>US Centers for Disease Control and Prevention</b>  <a href="http://www.cdc.gov/diabetes/consumer/index.htm">www.cdc.gov/diabetes/consumer/index.htm</a>  <a href="http://www.cdc.gov/diabetes/ndep/index.htm">www.cdc.gov/diabetes/ndep/index.htm</a></p>
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Although lifestyle intervention is considered to be a safe and cost-effective means to reduce hyperglycemia, pharmacotherapy is often required to maintain targeted goals. Metformin is recommended by the ADA/EASD panel as initial therapy in combination with lifestyle management. Metformin is considered an insulin sensitizing agent with the following proposed mechanisms of action: 1) decreases hepatic glucose production, 2) improves peripheral glucose uptake in skeletal muscles and adipocytes, and 3) decreases appetite and caloric intake in the gut, and 4) may improve pancreatic insulin secretion. Metformin also reduces free fatty acids, improves endothelial function and decreases LDL-C levels. Additional benefits of metformin include a low risk of hypoglycemia with monotherapy, low cost, and generally good tolerability. Most patients treated with metformin will either lose weight or experience no weight gain.

FOLLOW UP - 16 MONTHS	
<b>LABS</b>	
A1C: <b>7.8%</b>	FPG: PPG: <b>170-195 mg/dL</b>
<b>NOTES:</b>	
Presents because her FPG and PPG levels have been higher - No symptomatic complaints Neuro exam: loss of vibratory sensation in feet - probable neuropathy	

## Intensifying Treatment

### **How often or at what trigger points should treatment be reevaluated?**

The ADA/EASD consensus statement<sup>15</sup> suggests that an A1C level > 7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level < 7% in most patients. Intensification of therapy should be individualized and should take into account factors such as anticipated life expectancy, risk of hypoglycemia, and the severity of co-existing microvascular and macrovascular complications. Patients whose A1C is at or below target should have their A1C repeated biannually. Patients for whom intensification of therapy is ongoing should have A1C levels performed every 3 months or more until they have achieved their targeted goal.<sup>7</sup>

Reevaluation of therapy should also be considered when patients complain of symptomatic hyperglycemia or experience hypoglycemia. If severe or frequent hypoglycemia occurs, there may be a need to set higher glycemic goals.<sup>7</sup> Any patient who becomes pregnant or who is contemplating pregnancy should have intensification of their diabetes regimen while targeting A1C levels of 6.0%, provided that

this can be done without excessive hypoglycemia.<sup>7</sup> Treatment should also be re-evaluated if the patient has issues related to drug side effects, cost, or adherence.

**What considerations should be taken into account when choosing therapy after metformin?**

When intensifying therapy for patients with T2DM, the following factors should be considered:

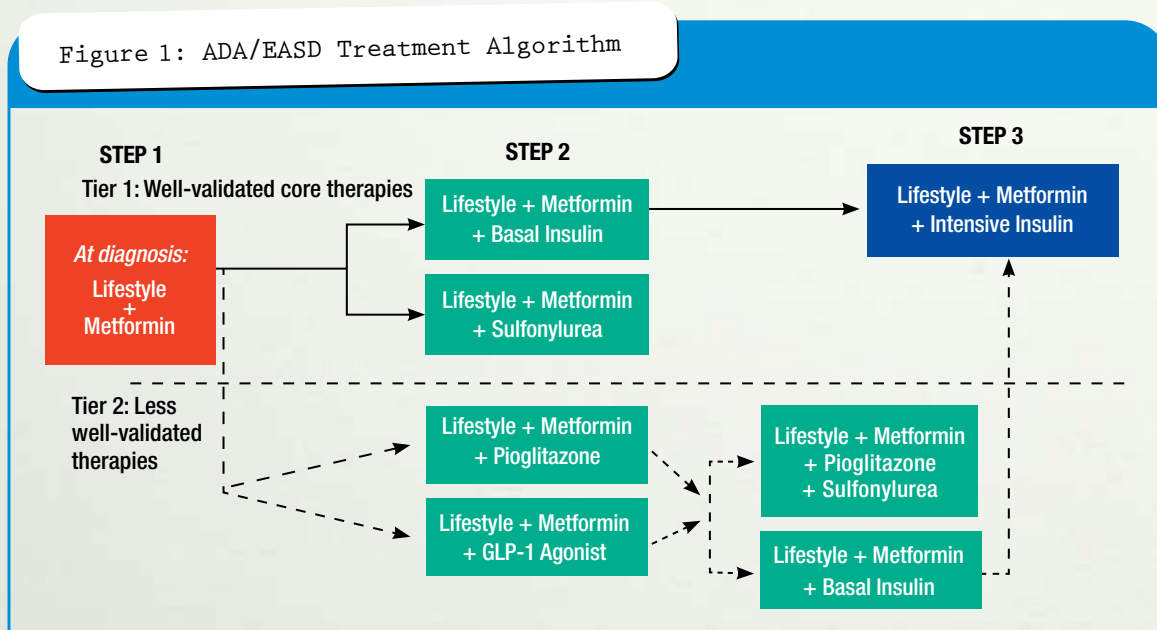
- The efficacy (likelihood) that the chosen agent will allow the patient to successfully achieve the target glycemic goals.
- The durability (anticipated length of time) the drug will remain effective at reducing hyperglycemia and allowing the patient to maintain the target glycemic goals.
- Long-term safety of the chosen agent with respect to induction of hypoglycemia, cardiovascular risk, and long bone fractures.
- Tolerability and ease of use. Is the patient willing and able to use injections? Is the patient willing to sacrifice slight weight gain and edema for improvement in insulin resistance and cardiovascular markers? What are the risks and benefits of more expensive drugs vs. generic drugs? Do the newer and more expensive drugs offer any non-glycemic advantages (reduction in cardiovascular markers, blood pressure, visceral fat, and beta cell preservation) over the generic agents?

Body weight and A1C level are important factors to consider since they affect the magnitude of the response to treatment. Generally, the higher the body weight, the smaller the reduction in A1C level; conversely, the higher the A1C level, the greater the A1C level is reduced with treatment. Thought should also be given to patient comorbidities such as history of cardiovascular disease, severe liver disease, or kidney disease as patient safety and tolerability can be affected.

**What treatment options are recommended for patients who no longer achieve glycemic control with lifestyle management and metformin?**

The ADA/EASD consensus panel grouped the antihyperglycemic agents into 3 tiers according to the criteria as described below<sup>16</sup> (Refer to Figure 1). The tier 1 therapies include lifestyle management and metformin as step 1 or initial therapy. The tier 1, step 2 therapies are insulin or a sulfonylurea. Tier 2 therapies are the thiazolidinediones or GLP-1 agonist.

Figure 1: ADA/EASD Treatment Algorithm



Although this tiered approach to therapy is helpful, the lack of head-to-head comparisons of combinations, especially with regard to impact on complications, necessitates that the choice of which agent to add to the combination of lifestyle management and metformin be based on the best match of the profile of each drug with the characteristics of the individual patient<sup>16,18-22</sup> (Refer to Table 4). The goal is to achieve and subsequently maintain the A1C level at the target goal, generally < 7.0%, by modifying treatment at as rapid a pace as titration allows.<sup>16</sup>

Table 4: Characteristics of Antihyperglycemic Medications

CLASS	MECHANISM	↓ A1C	EXTRAGLYCEMIC EFFECTS				SAFETY & TOLERABILITY	ADMINISTRATION	COST <sup>1</sup>
			Weight	Blood Pressure	Lipids	Beta Cell			
<b>TIER 1- STEP 1</b>									
Metformin	↓ hepatic glucose output ↑ insulin sensitivity	1.1-3	↔↓	↔	Imp	↔	diarrhea; lactic acidosis (rare)	oral; 1-2/d	\$
<b>TIER 1- STEP 2</b>									
Insulin	↑ insulin	1.5-3.5	↑	↔	Imp	Imp	hypoglycemia	injection; 1-4/d; rapidly effective; no dose limit; SMBG needed	\$
Sulfonylurea	↑ insulin release	1-2	↑	↔	↔	↔	hypoglycemia	oral; 1-2/d; rapidly effective	\$
<b>TIER 2</b>									
Thiazolidinedione	↑ insulin sensitivity	0.5-1.4	↑	↓	Imp(P)	Imp	fluid retention; CHF; fractures; risk of MI: ↑ (R), ↓ (P)	oral; 1-2/d; monitor hepatic function	\$\$
GLP-1 Agonist	↑ insulin secretion; ↓ glucagon secretion; ↑ insulin sensitivity	0.5-1.5	↓	↓(SBP)	Imp	Imp <sup>2</sup>	low incidence of mild/ moderate hypoglycemia; nausea; diarrhea; acute pancreatitis (E)	injection; 2/d (E), 1/d (L); not for use if CrCl < 30 mL/min; lower SU dose when used in combination	\$\$\$
<b>OTHER</b>									
Alpha-Glucosidase Inhibitor	delays CHO absorption	0.6-1.3	↔	↔	↔	↔	diarrhea, abdominal pain, flatulence	oral; 3/d	\$
DPP-4 Inhibitor	↑ insulin secretion; ↓ postprandial glucagon secretion; ↑ insulin sensitivity	0.5-0.8	↔	↓(SBP)	Imp	Imp <sup>2</sup>	low incidence of mild/ moderate hypoglycemia; severe allergic and hypersensitivity reactions (Si)	oral; 1/d; lower dose if CrCl < 50 mL/min; lower SU dose when used in combination	\$\$\$
Glinide	↑ insulin secretion	1-1.5 <sup>3</sup>	↑	↔	↔	↔	hypoglycemia	oral; 3/d	\$\$
Pramlintide	↓ postprandial	0.4-0.6	↔	↔	↔	↔	hypoglycemia, nausea, headache	injection; use with bolus insulin	\$

Noteworthy benefits. Noteworthy limitations.

<sup>1</sup>Based on an average daily maintenance dose of available products.  
\$ = ≤\$3.00/day; \$\$ = \$3.01-\$5.00/day; \$\$\$ = \$5.01-\$10.00/day.  
Source: drugstore.com. Cost to the patient depends on health insurance  
and formulary coverage of each patient. Accessed August 4, 2009.

<sup>2</sup>In vitro and rodent data; limited human data.

<sup>3</sup>Repaglinide more effective than nateglinide.

CHF = congestive heart failure; Imp=improve;  
MI = myocardial infarction; P = pioglitazone; R = rosiglitazone;  
E = exenatide; Si = sitagliptin; L = liraglutide; CrCl = creatinine clearance;  
SMBG = self-monitoring of blood glucose; SBP=systolic blood pressure

### SULFONYLUREAS

Although inexpensive, sulfonylureas have short-term durability in controlling blood glucose such that after initial improvement in glycemic control, they are associated with a progressive loss of beta cell function and rise of the A1C.<sup>23</sup> The ADA/EASD consensus statement does not include the use of chlorpropamide or glyburide as these drugs appear to increase the risk of hypoglycemia and cardiovascular events.<sup>16</sup>

### INSULIN

Insulin is the most effective agent for lowering blood glucose, with hypoglycemia its primary limitation. The availability of different types of insulin, human and analog, and different onset and duration of activity allow individualization of therapy to meet patients' needs and capabilities. Although the injection route of administration has been a major barrier to the use of insulin, the availability of fine-gauge needles and a variety of injection devices should minimize this concern.

**FOLLOW UP NOTES - 16 Month**

Based on the results of the neurologic exam, which reveals diabetic neuropathy, and the point of care A1C level of 7.8%, discuss with Mrs. K the available options for intensifying treatment. Also discuss the importance of maintaining her lifestyle changes. Although weight regain is a concern, you and the patient agree to add pioglitazone given her promises to maintain her lifestyle changes. Adding a basal insulin is also an option, but weight gain is a concern. Another consideration is a DPP-4 inhibitor. However, patient is unlikely to achieve her glycemic target of < 7% with the use of a DPP-4 inhibitor. A GLP-1 agonist, such as exenatide, can also be used in combination with metformin and pioglitazone however self-injection is a concern.

**THIAZOLIDINEDIONES (TZDs)**

Both of the TZDs currently available, pioglitazone and rosiglitazone, are ligands of peroxisome proliferator-activated receptor (PPAR)-gamma. They increase insulin sensitivity in muscle, fat, and peripheral tissue. In clinical trials of patients with T2DM, TZDs improve beta cell function, improve glycemic control, exert antiinflammatory effects, and decrease fatty liver. Pioglitazone and rosiglitazone have comparable glycemic efficacy. However, pioglitazone monotherapy reduces postprandial glucose (PPG) levels, which may help to reduce the risk of macrovascular events in patients with T2DM. In addition, pioglitazone has a greater effect on the PPG level when compared with rosiglitazone.<sup>24</sup>

Robust published clinical trial evidence demonstrates that TZDs decrease the likelihood of progression from prediabetes to diabetes. The use of pioglitazone in the ACT NOW trial has been demonstrated to reduce the progression from impaired glucose tolerance to diabetes by 81% compared with placebo when taken over a mean follow-up of 2.6 years.<sup>6</sup> The use of rosiglitazone in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, for example, reduced the progression from impaired glucose tolerance to diabetes by 62% over 3 years when compared with placebo.<sup>25</sup> These studies suggest that TZDs preserve pancreatic beta cell function in patients with impaired glucose regulation. Currently, no medications have received FDA approval for the management of prediabetes.

The benefits of the thiazolidinediones are countered with their limitations. An average weight gain of 4.8 kg over 5 years has been observed in patients treated with rosiglitazone. Edema was observed in 14% of patients.<sup>23</sup> The major limitation of the thiazolidinediones is their associated cardiovascular risks. The risk of heart failure is 1.2 to more than two-fold higher with a thiazolidinedione than with placebo, metformin, glyburide, or various combinations of antihyperglycemic medications.<sup>23,26-28</sup> Although the data are inconsistent, there appears to be a 40% increase in the relative risk for myocardial infarction with the use of rosiglitazone.<sup>29,30</sup> On the other hand, pioglitazone lowers the risk of myocardial infarction,<sup>28,31</sup> possibly because of its ability to improve the atherogenic lipid profile, whereas rosiglitazone has the opposite effect.<sup>23,32</sup> However, a recent retrospective cohort study involving nearly 40,000 patients observed no difference in the risk of acute myocardial infarction with pioglitazone and rosiglitazone (hazard ratio 0.95); however, the risk of death (hazard ratio 0.86) and heart failure (hazard ratio 0.77) were higher in the rosiglitazone group.<sup>33</sup> Side effects of edema and congestive heart failure can be minimized by appropriate patient selection and avoidance of undue salt intake. Weight gain can be prevented by caloric control or prevented/managed with exenatide coadministration. TZDs appear to be safe when used as indicated in patients who have T2DM who do not have clinical evidence of New York Heart Association Class III or IV cardiac disease.<sup>28,34</sup>

An increased risk of fractures also occurs with both pioglitazone and rosiglitazone. The hip and wrist are predominantly affected with a more than 2-fold risk after 12-18 months of use. Women are at greater risk of fractures than men, but the risk is independent of age or dose.<sup>23,35,36</sup>

Because of the risk-benefit profile of rosiglitazone and the availability of other antihyperglycemic treatment options, the ADA/EASD consensus panel does not recommend rosiglitazone for T2DM.<sup>16</sup>

**GLUCAGON-LIKE PEPTIDE-1 AGONISTS**

The GLP-1 agonist exenatide is also recommended as a tier 2 therapy because of its effectiveness in lowering fasting and postprandial glucose through several novel mechanisms (Refer to Table 5). Two other GLP-1 agonists, liraglutide and a long-acting form of exenatide, are currently under review by the US Food and Drug Administration. Because of the contribution of obesity to T2DM and the rising prevalence of obesity, an especially important attribute of the GLP-1 agonists is promotion of weight loss. A weight loss of up to 4.4 kg over 82 weeks has been reported.<sup>37,38</sup> GLP-1 agonists are also associated with a low incidence of mild to moderate hypoglycemia.<sup>38-40</sup> In addition, the GLP-1 agonists have several extraglycemic effects, including a modest reduction of the systolic blood pressure,<sup>38,40,41</sup> improvement of the lipid profile,<sup>40,41</sup> and improvement of pancreatic beta cell function.<sup>42-44</sup>

Limitations of treatment with a GLP-1 agonist include the injectable route of administration. Nausea is common, but transient generally peaking within 6-8 weeks. Dose titration over the first few weeks when initiating therapy reduces the incidence of nausea.<sup>19,38,45</sup> Some concern over the safety of GLP-1 agonists first arose in 2007 following the reports of 30 cases of acute pancreatitis in patients taking exenatide. However, the diagnosis of acute pancreatitis (based on the presence of nausea, vomiting, and abdominal pain, which are also known side effects of this drug class) was confirmed by laboratory tests in only 17 cases. Twenty-seven cases had at least one risk factor for pancreatitis (severe clinical obesity, gallstones, alcohol abuse, or hypertriglyceridemia). In August 2008, the FDA reported six new cases of hemorrhagic or necrotizing pancreatitis in patients using exenatide, as well as death in six patients who had experienced pancreatitis, although other confounding factors were noted in each case.<sup>46</sup> The association of pancreatitis with other causes, including medications, is complicated in type 2 diabetes because of the approximately 3-fold higher incidence of pancreatitis in patients with diabetes than in the normoglycemic population.<sup>47</sup> No cases of hemorrhagic or necrotizing pancreatitis have been reported in any patients exposed to liraglutide in phase-3 clinical trials.<sup>48</sup>

Based on the risk-benefit profile of these medications, a thiazolidinedione or GLP-1 agonist may be preferred to a tier 1, step 2 medication in certain circumstances. For example, when hypoglycemia is to be especially avoided (eg., patients who have hazardous jobs), the addition of exenatide or pioglitazone to metformin and lifestyle management is reasonable. If weight loss is particularly desirable and the A1C level is less than 8.0%, exenatide is a good option.<sup>16</sup>

#### DIPEPTIDYL PEPTIDASE-4 INHIBITORS

In preclinical studies, DPP-4 inhibitors mimic many of the actions ascribed to GLP-1 agonists, including glucose dependent stimulation of insulin secretion, inhibition of glucagon secretion by the pancreatic alpha cell, and preservation of beta cell mass. However, DPP-4 inhibitors are not associated with slowing of gastric emptying or weight loss. The difference in pharmacologic actions between the DPP-4 inhibitors and the GLP-1 agonists are likely due to their different mechanisms of action. Due to their high affinity for the GLP-1 receptor, GLP-1 agonists can increase the levels of GLP-1 much more than DPP-4 inhibitors, which simply inhibit the breakdown of endogenous GLP-1.

Two DPP-4 inhibitors are currently available for clinical use in the US, sitagliptin and saxagliptin. Data from an 18 week study of sitagliptin monotherapy showed placebo-corrected decreases in A1C with 100 mg (-0.6%) and 200 mg (-0.5%) doses. Patients with higher baseline A1C had the greatest reductions.<sup>49</sup> Based on post-marketing reports of 88 cases of acute pancreatitis, including 2 cases of hemorrhagic or necrotizing pancreatitis, the prescribing information for sitagliptin has been revised to include the recommendation of careful monitoring for the development of pancreatitis.<sup>50</sup>

### Comprehensive Management

In addition to lowering blood glucose with lifestyle management and medications, the comprehensive management of patients with T2DM involves the prevention and management of diabetes complications. Among these, cardiovascular diseases such as hypertension and dyslipidemia are the most important. Consequently, blood pressure readings should occur at every visit and the lipid profile checked at least annually.<sup>7</sup> Treatment should be implemented as appropriate and lifestyle management intensified. Antiplatelet therapy, generally with low-dose aspirin, is important for secondary prevention of cardiovascular disease.<sup>7</sup> The benefit of using low-dose aspirin for primary prevention of cardiovascular events is less certain. Recent evidence suggests no benefit in reducing a composite endpoint (death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischemia) compared with placebo in patients with type 1 or type 2 diabetes and asymptomatic peripheral arterial disease.<sup>51</sup> Smoking cessation is also essential.

Although cardiovascular disease is a major risk of T2DM, there are other risks as well. These include nephropathy, retinopathy, neuropathy, and skin breakdown. Consequently, ongoing assessment is needed to reduce these risks and begin treatment at the earliest stage.<sup>7</sup>

In summary, the management of patients with T2DM must be comprehensive, addressing the risks of other complications, and must be individualized based on the goals, concerns, and capabilities of the patient. As these change over time, the plan also must be dynamic.

Finally, among all of the issues to consider in initiating or modifying lifestyle management as well as medications, patient adherence is important. Since numerous factors can affect patient adherence, identifying these at the time of diagnosis and as part of an overall plan for patient self-management is vital. Indeed, an educated, empowered patient supported by a multidisciplinary health care team and family is necessary for successful long-term management of patients with T2DM.

★ Go to [www.pceconsortium.org/PCCSNov2009TK](http://www.pceconsortium.org/PCCSNov2009TK) to complete the online post-test and evaluation to receive your certificate of completion.

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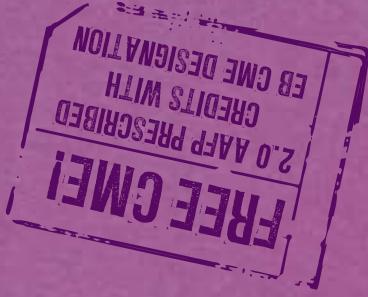
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