

Diabetes: When Behavior Modification is Not Enough

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Summary

The incidence and prevalence of diabetes has been increasing dramatically, and is not just a problem in the United States. Although few patients achieve nationally accepted glycemic control goals, there are many effective treatment options available. All the antidiabetic medications have advantages and disadvantages with no one agent standing out as best for all patients.

Key Points

- Good glycemic control matters in type 2 diabetes.
- Few patients reach appropriate goals.
- There are many effective treatments for type 2 disease.
- None appears to be a superior agent.
- All have adverse effects that need to be considered.
- The amount of decrease in A1C with oral medication is proportional to the starting A1C.

IN 2005, APPROXIMATELY 11 PERCENT OF the U.S. adult population had glycemia.¹ The incidence and prevalence of diabetes has been increasing dramatically, particularly among the more than 65 age group.² Exhibit 1 shows the projected rate of diabetes around the world in 2030.³ The global cardiovascular burden of diabetes has been estimated to be 959,000 deaths directly from diabetes.⁴ Additionally, over a million deaths from coronary heart disease and 700,000 from strokes related to diabetes occur each year.⁴ One point eight of 2.2 million cardiovascular deaths in low or middle income people are the result of diabetes.⁴

Although there are many aspects of diabetes management, this article will focus on glycemic control. In patients with type 2 diabetes, there appears to be an increase in blood glucose over time even with treatment (Exhibit 2).⁵ Because treatments are not added or increased to maintain control, relatively few people with diabetes in the United States are at appropriate glycemic goals (Exhibit 3).^{6,7} In one study, 73 percent of patients on diet alone were at goal, 38 percent on oral agents, and 45 percent on insulin.⁸

An interesting study from Kaiser found that physicians initiated additional therapy in patients with hemoglobin A1C (A1C) greater than 8 percent, less in patients already on more aggressive therapy.⁹ In this study, the average time to initiate additional

therapy in patients with A1C greater than 8 percent was 14 months in patients on metformin monotherapy, and 20.5 months in those on sulfonylureas.⁹ The average person had about five years of poor control before being placed on appropriate therapy.

There is an abundance of data that good glycemic control matters in both type 1 and type 2 diabetes (Exhibit 4).¹⁰⁻¹³ The recent publication of the Accord Trial has generated some controversy as to how tight control should be in type 2 diabetes.¹⁴ We are far from understanding the optimal approach to diabetes. Based on the UKPDS study data, there is clearly a linear relationship between A1C and microvascular endpoints and heart attack rates - the higher the A1C, the worse the outcome. In a meta-analysis, there is on average a 13 percent reduction in CV disease for each 1 percent decrease in A1C.¹⁵

Exhibit 5 lists the medication classes that can be used to treat type 2 diabetes. There are a lot of good treatments now available, but each agent or class has disadvantages that also must be considered.

A large Veterans Administration trial examined the difference in outcome with several treatment approaches.¹⁶ When adjusted for various other risk factors present in the population, treatment with metformin, metformin plus a sulfonylurea, sulfonylureas alone, or thiazolidinediones with or without other treatments result in similar relative risk of mortality.

Exhibit 1: Diabetes Projections: 2000-2030

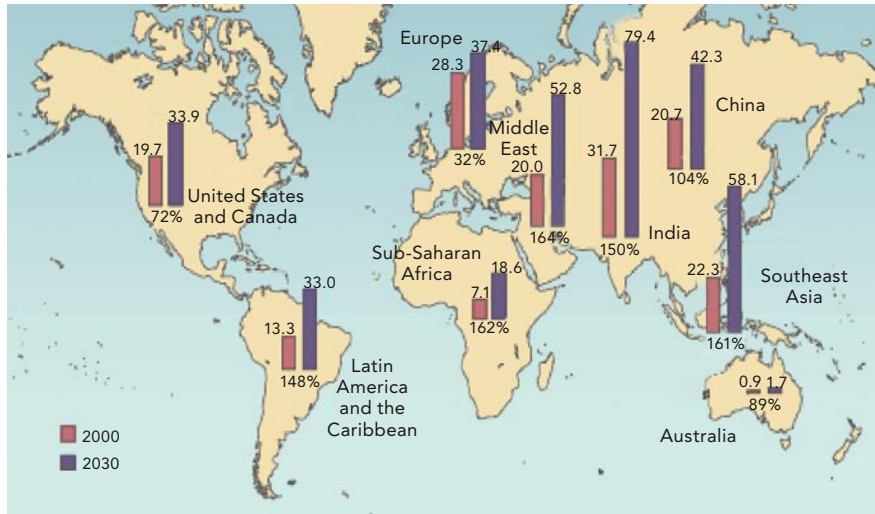
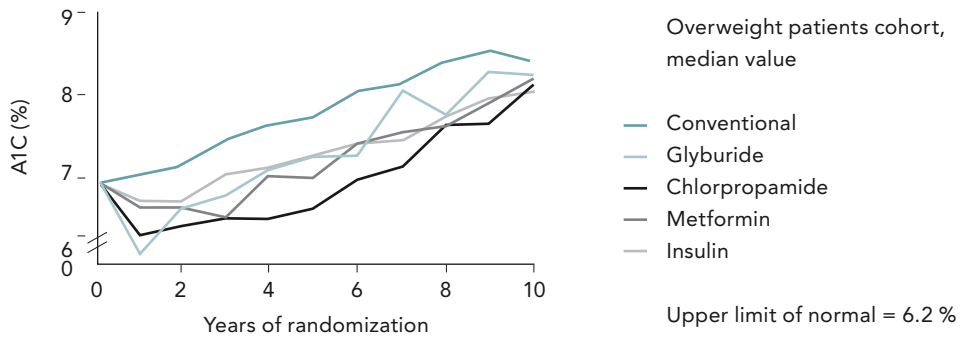


Exhibit 2: Loss of Glycemic Control in the UKPDS



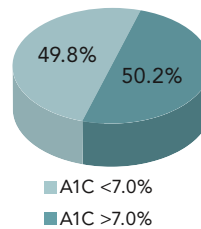
Thus, no one agent is better or worse for this long-term outcome.

During the first six months of therapy, patients will have a great response to sulfonylureas, which subsequently wears off. The mechanism for this is not understood. Most patients will require combination therapy for adequate glycemic control. The addition of metformin to sulfonylureas has been shown to be more effective than either agent alone.¹⁷ Metformin also is effective in combination with rosiglitazone or pioglitazone. Other effective combinations are sulfonylurea-glitazone and acarbose-sulfonylurea, insulin, or metformin. Unfortunately, even on combination therapy, patients will experience increasing A1C over time. In one four-year study, 50 percent of patients receiving metformin-sulfonylurea and 31.5 percent of patients receiving metformin-thiazolidinedione experienced secondary failure (A1C increasing more than 7 percent).¹⁸

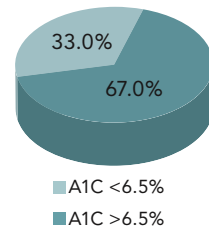
There has been much publicity recently about a possible increase in cardiovascular events with the

Exhibit 3: The Majority of US Patients Fail to Achieve A1C Goals

50.2% fail to meet American Diabetes Association goal of <7.0%¹



67.0% fail to meet American Association of Clinical Endocrinologists goal of <6.5%²



Reference: 6,7

use of rosiglitazone. Exhibit 6 shows data on the difference in cardiovascular events.¹⁹ This data must be interpreted somewhat cautiously. There are several weaknesses in this analysis, which have been noted

Exhibit 4: Randomized Controlled Trials Complications Risk per 1%↓HbA1c

Study	Patients	Complication	Risk Reduction
DCCT	Type 1 diabetes n=1440	Retinopathy, nephropathy, neuropathy	30%-35% decrease
Kumamoto	Type 2 diabetes n=110	Retinopathy, nephropathy, neuropathy	30%-38% decrease
UKPDS	Type 2 diabetes n=4209	Retinopathy, CVD	28% decrease

DCCT=Diabetes Control and Complications Trial

Reference: 10-13

by several authorities.²⁰ The absolute rate of myocardial ischemia is actually higher in the control group versus the rosiglitazone group, which makes it difficult to understand how the odds ratio was then higher for the rosiglitazone group. Selective data rather than a complete literature search were used for this analysis. Additionally, there was a failure to define the hypothesis to be tested. Also, a fixed effects rather than random effects model was used for the meta-analysis. The fixed effects model assumes all the subjects came from the same type of study, which is not true. It appears that subjects in some of the studies had much higher rates of events, which may be explained by something other than the particular medication used. The Nissen analysis used the number of events rather than time to first event, which may be a particular issue with longer follow-up on rosiglitazone. Lastly, studies not reporting events were excluded. It is uncertain whether rosiglitazone actually increases the rate of cardiovascular events.

Other effective treatment approaches include adding bedtime or twice-daily NPH to oral agents (sulfonylurea, metformin, or combination), or adding

Exhibit 5: Approaches to Type 2 Diabetes Treatment

- **Insulin sensitizers**
 - Metformin
 - Thiazolidinediones
- **Alpha glucosidase inhibitors acarbose, miglitol**
- **Insulin secretagogues**
 - Sulfonylureas
 - GLP-1-related treatments
 - GLP-1 receptor agonist: exenatide
 - DPP-4 inhibitor: sitagliptin
- **Insulin**

another long acting insulin such as insulin glargine to oral agents.²¹⁻²³ With aggressive titration of long acting insulin in combination with metformin, the majority of patients can reach goal. Another insulin approach in type 2 is to give a mixed insulin solution (short + long acting) twice daily in combination with oral agents. Hypoglycemia is the major adverse effect of any approach, which includes insulin.

Newer agents include the dipeptidyl peptidase 4 (DPP-IV) inhibitors and exenatide. Sitagliptin is the

Exhibit 6: Rates of Myocardial Ischemia and Death from Cardiovascular Causes

Study	Rosiglitazone Group no. of events/total no. (%)	Control Group	Odds Ratio (95% CI)	P Value
Myocardial ischemia				
Small trials combined	44/10,280 (0.43)	22/6105 (0.36)	1.45 (0.88-2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74-3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.44)	1.33 (0.80-2.21)	0.27
Overall	86/14371=0.60%	72/11634=0.62%	1.43 (1.03-1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,557 (0.38)	7/3700 (0.19)	2.40 (1.17-4.91)	0.02
DREAM	12/2,365 (0.51)	10/2634 (0.38)	1.20 (0.52-2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2854 (0.18)	0.80(0.17-3.86)	0.78
Overall			1.64 (0.98-2.74)	0.06

Adapted from reference 18

Note: Table in original publication used myocardial infarction instead of myocardial ischemia as heading. Events were really myocardial ischemia and not necessarily myocardial infarction

Exhibit 7: Comparison of DPP-4 Inhibitors Exenatide

	DPP-4 inhibitor	Exenatide
Mechanism of action	Increase endogenous incretin	GLP-1 receptor agonist
A1c reduction	Yes	Yes
Effect on weight	Neutral	Decrease
Hypoglycemia	When administered with SU	
Mode of administration	Oral	Parenteral
Gastrointestinal adverse events	No	Yes
N	4190	1228
Change in A1C	-0.74% (-0.85, -0.62)	-1.01 (-1.18, -0.84)
Baseline A1C	8.02%	8.38%

Reference: 26

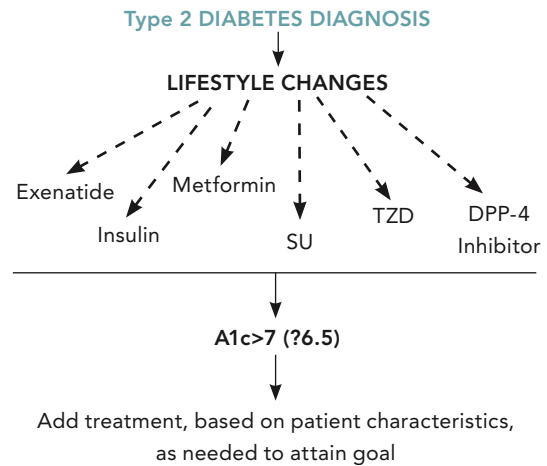
first approved DPP-IV inhibitor. Vildagliptin is another, which is not yet available in the United States. The DPP-IV inhibitors can be used in combination with metformin or sulfonylureas.

Exenatide is a GLP-1 receptor antagonist. This agent decreases both A1C and weight. There appears to be a central effect of GLP-1 on appetite but long-term outcomes are needed to prove this. Exenatide has been compared with mixed insulin (70/30 as part).²⁴ Throughout the course of a year with these two agents, A1C fell and rose in a similar pattern but weight was significantly lower in exenatide group. Weight increased in the insulin group and decreased in the exenatide group for a mean difference of 12.1 lbs. This is probably clinically meaningful. A similar pattern was seen in comparing exenatide and insulin glargine.²⁵ Exenatide can be combined with a sulfonylurea but the weight loss is not as great as that of exenatide alone and the rate of hypoglycemia is relatively high. The combination of sitagliptin plus sulfonylurea and/or metformin will increase the likelihood of hypoglycemia. Exhibit 7 compares exenatide and the DPP-IV inhibitors.²⁶ The slightly higher baseline A1C in the exenatide trials may account for the difference in A1C reduction between the two groups.

The amount of decrease in A1C with oral medication is proportional to the starting A1C (i.e., the higher the A1C, the higher the drop with oral medications). A patient with an A1C greater than 9 will have about a 1.4 percent drop in A1C with oral medication. A patient with an A1C of less than 8 will have about a 0.6 percent decrease.

Exhibit 8 presents an algorithm for managing patients with type 2 diabetes. Although the American Diabetes Association suggests metformin as the

Exhibit 8: Algorithm for Type 2 Diabetes Treatment: Metformin as 1st Among Equals



initial medication choice for most patients, other agents also can be considered.

Achievement of the A1C goal needs to be monitored and therapy adjusted appropriately. In patients who have an A1C less than 6.5 percent, no additional pharmacologic therapy is needed. Continued lifestyle and medication adherence are needed to maintain the A1C level. If patients are slightly above goal (6.5 to 7.3), additional therapy can be added. The patient may need reinforcement of lifestyle issues. Above 7.4, an additional agent can be added. At well above goal (>8 percent), initial combination therapy, including insulin, is useful.

Conclusion

Achieving good glycemic control is an important goal and only one aspect in type 2 diabetes management. There are numerous effective treatment options with no one treatment standing out as the ideal agent for all patients. The effect of various anti-diabetic agents on A1C reduction varies depending on the starting A1C. Each agent or class has disadvantages, which also must be considered. **JMCM**

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