



Maine Independent Clinical Information Service
Balanced Data About Medications

GOAL: To improve clinical outcomes by delivering up-to-date, evidence-based prescribing information, using data and guidelines developed by non-commercial sources

FUNDING: MICIS mandated by Maine Legislature, funded by fees collected from pharmaceutical companies as a cost of doing business in the state.

Legislature's Primary Goal

To assist providers in aligning their prescribing patterns with the best scientific evidence

- Improve health care quality and outcomes;
- Decreasing complications;
- Reducing costs

**Academic detailing has no
commercial bias toward any given
drug or approach to care.**

The goal is better outcomes.

**Just a spoonful of medicine
helps the sugar go down:**

*IMPROVING THE MANAGEMENT OF
TYPE 2 DIABETES*

Diabetes: >20 million Americans

Successful Management requires:

- Patient education, lifestyle modification, self-monitoring
- Ongoing clinical contact
- Treatment of related conditions such as hypertension and hypercholesterolemia

Patients with diabetes do not control their blood sugar well enough to reduce the risk of complications.

Why?

Contributing Factors:

- Patients have difficulty making necessary lifestyle adjustments
- Physicians lack time and/or resources

Making the Diagnosis

- Presents with symptoms:
 - Polyuria
 - Polydipsia
- Single random blood glucose $>200\text{mg/dL}$
- Asymptomatic
- “Pre-diabetes”
 - Impaired fasting glucose or impaired glucose tolerance
 - Can be managed with diet and exercise alone

Diagnosis of Diabetes (p. 2)

Patient Presentation	Test and threshold	Notes
Symptomatic: e.g., polyuria, polydipsia, weight loss	Random plasma glucose ≥ 200 mg/dL	
Asymptomatic	Fasting plasma glucose ≥ 126 mg/dL	Repeat on a second day to confirm; Fasting glucose 100-125 mg/dL indicates pre-diabetes
	Oral glucose tolerance test (OGTT); plasma glucose	Used less often due to inconvenience; Glucose 140-199 mg/dL indicates pre-diabetes; repeat test recommended for clinical confirmation

Screening for Diabetes

Hemoglobin A1c is currently not recommended for use as a screening or diagnostic test due to inadequate sensitivity

Age	BMI	Other Risk	Notes
≥ 45	Any	None required	Repeat at 3 year intervals
< 45	≥ 25	<ul style="list-style-type: none">• Family history of diabetes• Physically inactive• High-risk ethnic group• History of gestational diabetes• Hypertension• Polycystic ovary syndrome• Low HDL/high triglycerides• Vascular disease• Pre-diabetes on previous testing	For patients with multiple risk factors, consider screening more frequently (every 1-2 years)

Goals of Care

- Optimize the plasma glucose level
- Reduce the risk of macrovascular disease

Goals of Care (cont.)

- A1c levels
 - Checked twice per year
 - Every three months in patients who are not meeting their goals or with ongoing adjustments in the medical regimen
 - Close to 7% is considered adequate control
- Blood glucose
 - Fasting 70-130 mg/dL
 - Postprandial >180 mg/dL

Hypoglycemia

- Plasma glucose <70 mg/dL
- Symptoms
 - Sweating
 - Anxiety
 - Palpitations
 - Hunger
 - Tremor
 - Confusion
- Treatments
 - Milk
 - Glucose-containing foods
 - Glucagon

Weight Management, Diet and Exercise

Working with Patients..

- Structured program
 - Reduce overall caloric intake
 - Reduce the calories from fat and saturated fat
- Structured exercise program
 - Combined aerobic-resistance programs most effective

Lifestyle modification, diet change, and increased exercise can:

- Improve glycemic control
- Slow progression from pre-diabetes to diabetes
- Offer multiple other health benefits

Prevention or Delay of Diabetes

- Lifestyle interventions can delay the development of diabetes significantly

Finnish Diabetes Prevention Study

- Lifestyle modification reduced the incidence of diabetes by 58%

Diabetes Prevention Program (DPP)

- Lifestyle modification group had a lower rate of diabetes development than the metformin group.

Medication Trials in Pre-diabetes

- STOP-NIDDM
 - Treatment with acarbose reduced the development of diabetes by 25% (gastrointestinal symptoms)
- DREAM
 - Treatment with rosiglitazone reduced the development of diabetes by 62% (cardiovascular toxicity)

Treatment to Prevent Development of Diabetes

Treatment	Reduction in diabetes (compared to placebo)	Notes
Lifestyle modification <ul style="list-style-type: none">•Weight loss•Decreased saturated fat•Exercise	58%	Results over 3-4 years; at 3-year follow-up reduction was 43%
Metformin 850 mg b.i.d.	31%	Cost-effectiveness of treatment unclear
Acarbose 100 mg t.i.d.	25%	GI side effects limit acceptability to patients
Rosiglitazone 8 mg q.i.d.	62%	Cardiac toxicity/CHF limits use

Bottom Line

Intensive lifestyle modification, including weight loss (5% or more), reduced saturated fat intake, and increased exercise (30 minutes 5 times weekly) can reduce the incidence of diabetes in pre-diabetic patients by over 50%. Oral medication can also reduce the incidence of diabetes, but the benefits must be weighed carefully against side effects and costs.

Non-insulin Treatment of Diabetes

Class	Examples (brand names)	Principal mechanisms of action
Sulfonylureas	Glyburide (Diabeta, Micronase), glipizide (Glucotrol), glimepiride (Amaryl)	Increase insulin secretion
Biguanides	Metformin (Glucophage)	Decrease hepatic glucose production (major), increase uptake of glucose from blood into the tissues (minor)
Glitazones (thiazolidinediones)	Pioglitazone (Actos), rosiglitazone (Avandia)	Increase insulin-mediated glucose uptake into adipose tissues and skeletal muscles (major), decrease hepatic glucose production (minor)
A-glycosidase inhibitors	Acarbose (Precose), miglitol (Glyset)	Reduce rate of glucose production from dietary carbohydrates in the intestine
Meglitinides	Repaglinide (Prandin), nateglinide (Starlix)	Increase insulin secretion
Dipeptidyl pdptidase 4 inhibitors (DPP4)	Sitagliptin (Januvia)	Increase incretin hormones, which augment glucose-dependent insulin secretion and decrease glucagon release
Incretin mimetics	Exenatide (Byetta)	Mimic naturally occurring incretin hormones which stimulate insulin production and the response to elevated blood glucose; inhibit release of glucagons after meals, slows nutrient absorption.

United Kingdom Prospective Diabetes Study (UKPDS) Results

*Insulin vs. Sulfonylurea vs. Diet alone
in Non-overweight Patients*

Intensive drug therapy with either regimen was:

- More effective than diet for lowering A1c
- Reducing the risk of microvascular complications
- Only small reduction in the risk of myocardial infarction

United Kingdom Prospective Diabetes Study (UKPDS) Results

*Metformin vs. Sulfonylurea vs. Diet alone
in Overweight Patients*

Metformin:

- Significantly reduced the risk of diabetes-related death
- Significantly reduced death from all causes

A Diabetes Outcome Progression Trial (ADOPT) Results

Rosiglitazone vs. Metformin vs. Glyburide

Rate of serious cardiovascular events:

- Glyburide: 1.8%
- Metformin: 3.2%
- Rosiglitazone: 3.4%

Due to rates

- Congestive heart failure
- Non-fatal myocardial infarction

The glitazone controversy

2007 meta-analysis of 42 randomized controlled trials showed that use of rosiglitazone increased risk of:

- Myocardial infarction by 43%, and
- Cardiovascular causes by 64%

Pioglitazone

2007 meta-analysis of 19 randomized controlled trials showed that use of pioglitazone reduced the relative risk of a primary end-point of death, myocardial infarction or stroke by 18%

Bottom Line

No one class of oral hypoglycemic agents is more effective in reducing cardiovascular events. Trials find benefits from: metformin, sulfonylureas and pioglitazone.

Bottom Line (cont.)

Pioglitazone vs. rosiglitazone both cause:

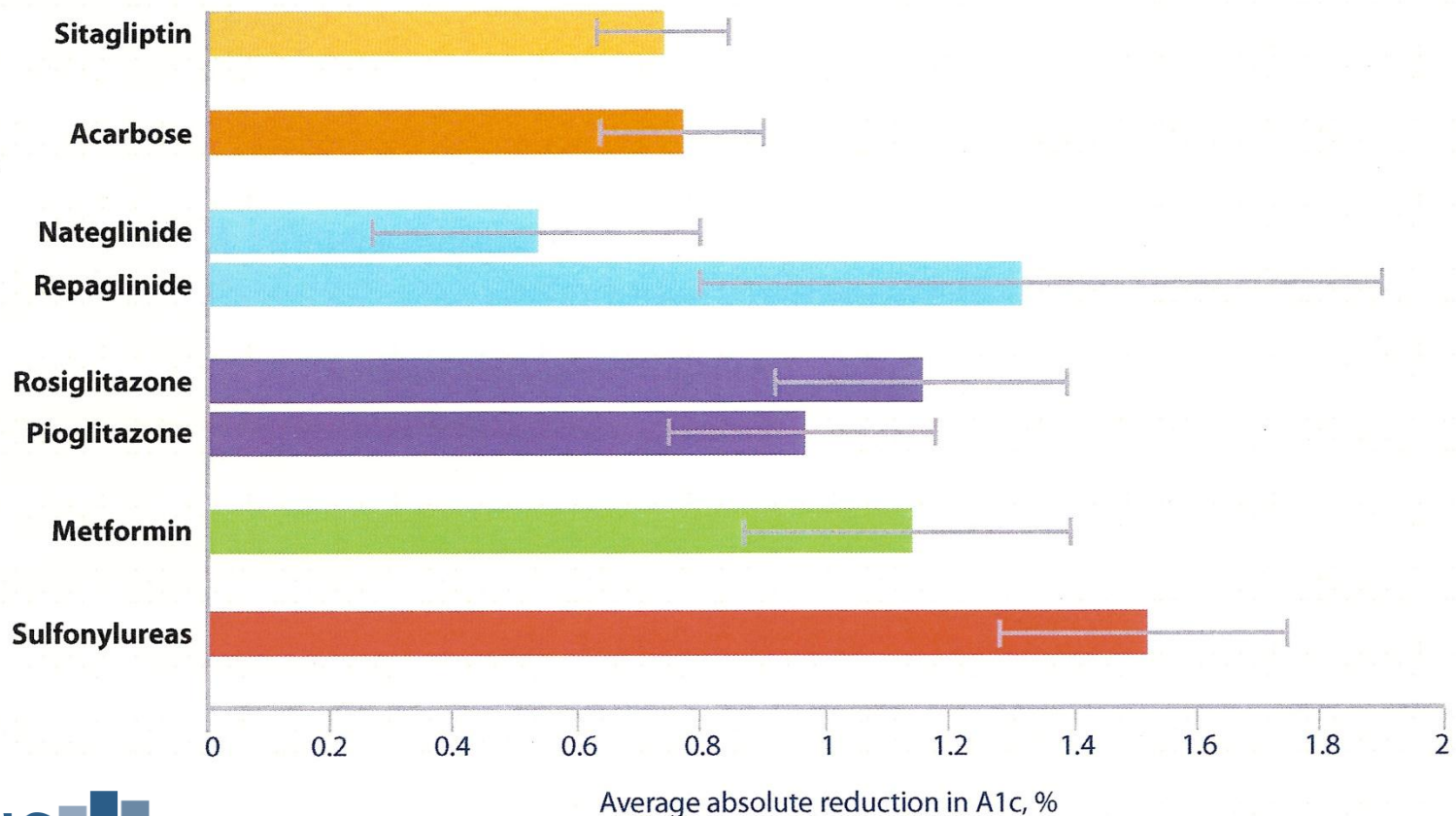
- Congestive heart failure
- Increased fractures

Rosiglitazone increases risk of:

- Cardiovascular events

Reductions in hemoglobin A1c

Figure 2. Expected reductions in A1c from indirect comparisons of different oral hypoglycemic agents. Derived from Bolen et al.³¹, Amori et al.³⁷

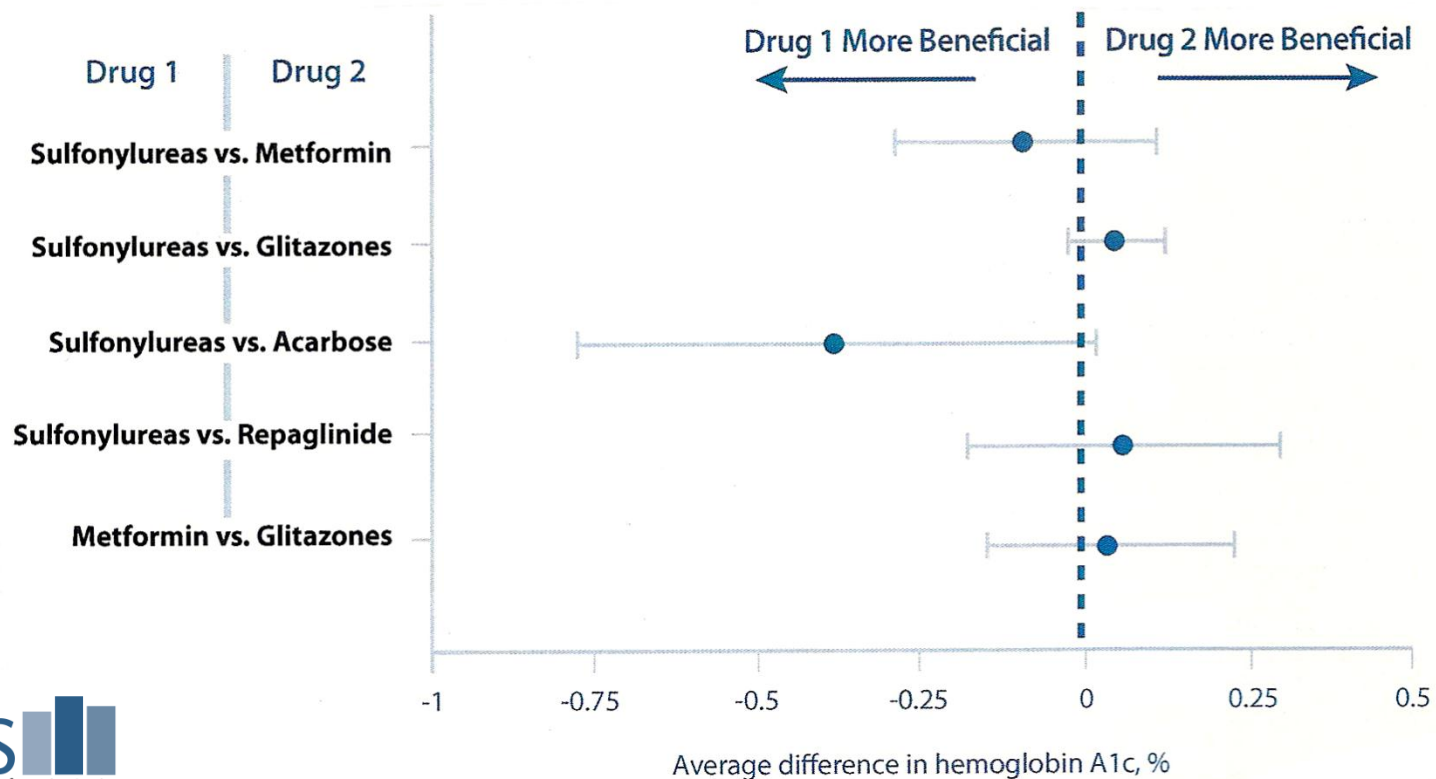


Comparisons of Oral Hypoglycemic Agents

Most drug classes produce similar reductions in A1c.

Figure 3. Direct comparisons of different oral hypoglycemic agents.

Derived from Bolen et al.³¹ Differences were modest across all drug classes.

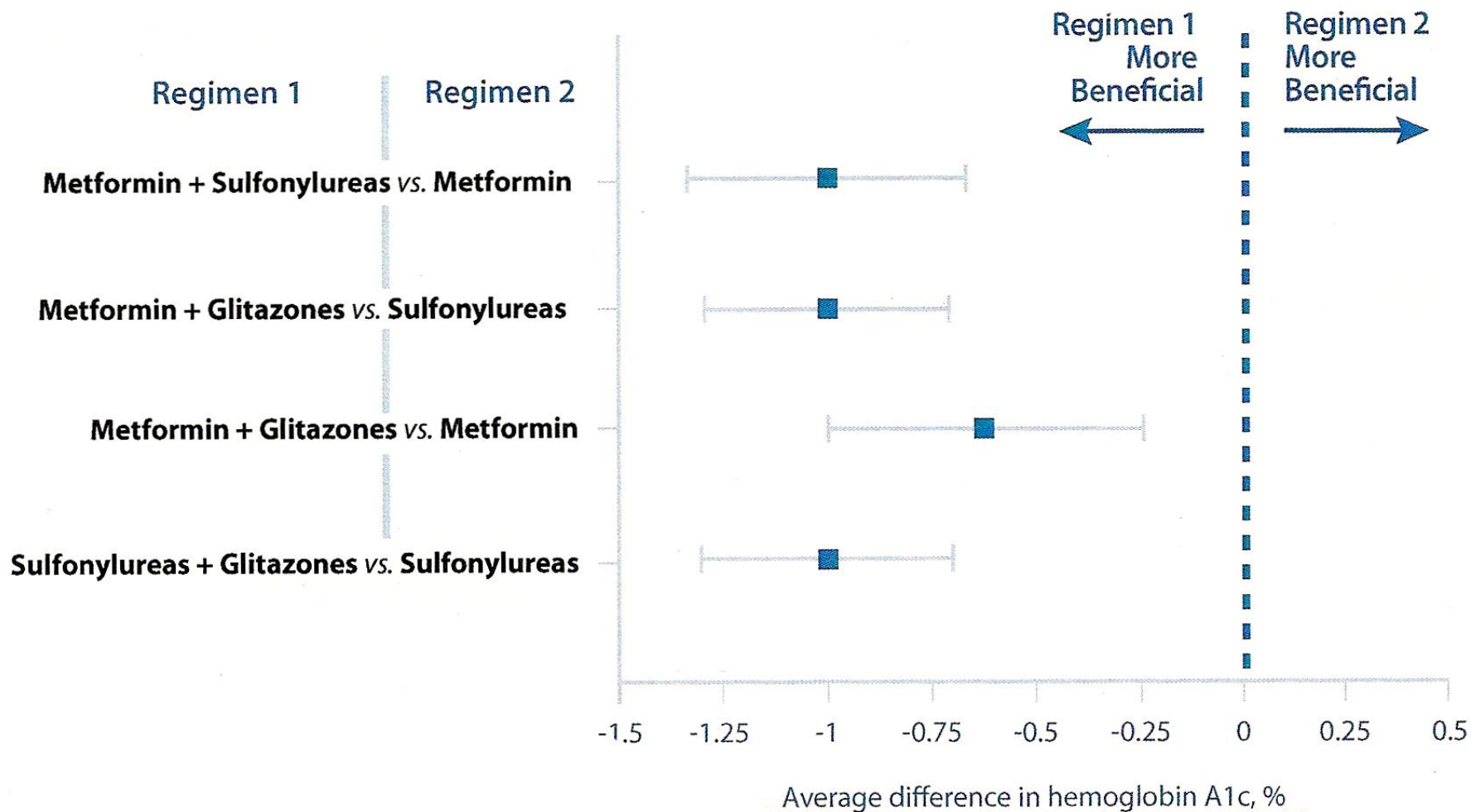


Combination Therapy

The addition of a second oral agent from a different class lowers A1c by an additional 1% over treatment with maximum doses of a single agent.

Figure 4. Comparisons of combined versus monotherapy.

Derived from Bolen et al.³¹



Bottom Line

- Sulfonylureas, metformin, and repaglinide all appear to lower A1c by roughly equivalent amounts. Glitazones may be about as effective in lowering A1c.
- Combining oral hypoglycemic agents from different classes has an additive effect on glycemic control.

Are These Agents All Equally Safe?

Table 5. Summary of comparative efficacy, safety, and cost of non-insulin agents.

Drug	Risk of death, and/or major CV events	Control of A1c	Weight gain or loss	Hypo-glycemia	Heart failure and edema	LDL	GI	Cost	Overall
metformin	Green	Green	Green	Green	Green	Green	Red	Green	Green
sulfonylureas	Yellow	Green	Red	Red	Green	Yellow	Yellow	Green	Yellow
glitazones	pioglitazone	Green	Yellow	Red	Green	Red	Yellow	Red	Yellow
	rosiglitazone	Red	Green	Red	Green	Red	Yellow	Red	Red
α-glucosidase inhibitors		Yellow	Green			Yellow	Red	Yellow	
meglitinides	repaglinide		Green	Red	Red		Yellow	Yellow	
	nateglinide		Yellow	Yellow	Yellow		Yellow	Yellow	
DPP4 inhibitors		Yellow						Red	
exenatide		Yellow	Green	Yellow			Red	Red	

GI = gastrointestinal intolerance; LDL = LDL cholesterol level



Initiation of therapy: Which drug to choose?

Hypoglycemia

- Diet Therapy Alone
 - .7% (major episodes)
 - 7.9% (minor episodes)
- Metformin, glitazones
 - Do not appear to increase the risk of hypoglycemia
- Sulfonylureas, meglitinides
 - Increase absolute risk by 4-9%
- Longer-acting sulfonylureas, glyburide
 - Increase absolute risk by 2%

Bottom Line

Sulfonylureas and repaglinide increase the risk of hypoglycemia while other classes of agents appear not to. Longer-acting sulfonylureas (e.g., glyburide) are more likely to cause hypoglycemia than short-acting agents (e.g., glipizide).

The glitazones substantially increase the risk of congestive heart failure and peripheral edema compared with sulfonylureas and metformin.

Metformin and acarbose frequently cause some gastrointestinal intolerance

- Up to 60% of Pts on Metformin
- Start with 500mg QD or BD
 - Increase dose in 5-7 days if tolerated
- Symptoms usually diminish over time.

Incretin mimetics (exenatide)

1. Potentiates glucose-mediated insulin secretion
2. Suppresses glucagon secretion
3. Slows gastric motility

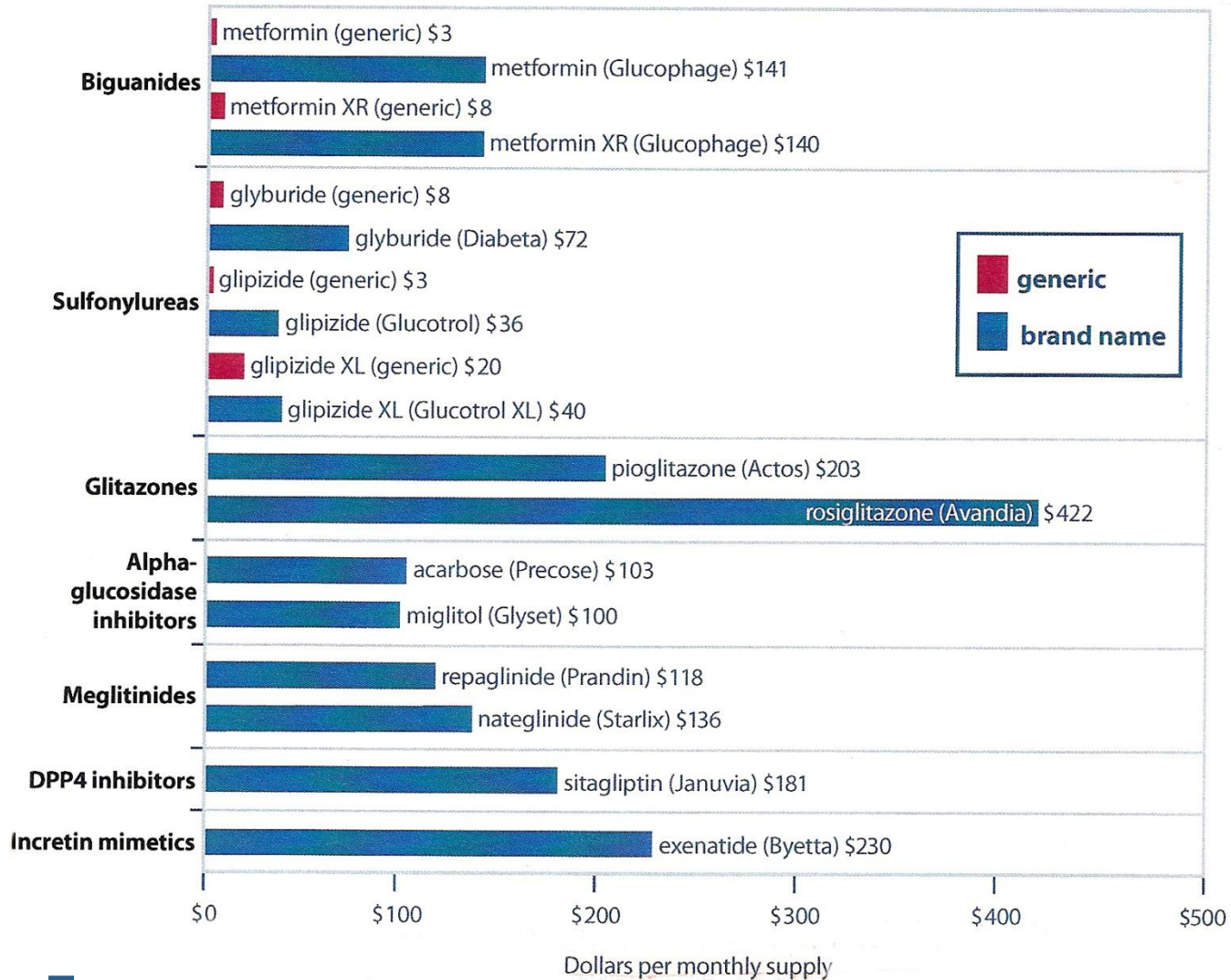
Side effects

- Half of patients complained of nausea
- Vomiting and diarrhea also common
- Significant increase in risk of pancreatitis
- Weight loss

Bottom line

- Exenatide is not recommended:
 - High rates of side effects
 - Need for daily injections
 - Scant long-term data
 - Use should be limited
 - Obese patients
 - Patients with occupational restrictions prohibiting insulin

Figure 6. Costs for monthly supplies of equivalent doses of non-insulin agents.



The lowest daily costs for these medications are based on several websites, including www.drugstore.com, www.target.com, and www.samsclub.com. Prices obtained January 2009.

Initiation of therapy: Which drug to choose?

- Metformin best as initial therapy
 - Therapeutic profile
 - Relative safety
 - Low cost

Contraindications and required dose-adjustments for various agents as indicated on the FDA-approved product labels

Class	Examples	Contraindications and Warnings
Sulfonylureas	Glyburide, glipizide	<ul style="list-style-type: none"> •Glyburide generally not recommended for patients with CrCl < 50mL/min •Glipizide generally not recommended for patients with CrCl < 10mL/min
Biguanides	Metformin	<ul style="list-style-type: none"> •Renal disease or dysfunction (Cr ≥ 1.5 mg/dL inmailes, 1.4 mg/dL in females, or abnormal CrCCI) •Acute or chronic metabolic acidosis
Glitazones (thiazolidnediones)	Pioglitazone, rosiglitzaone	<ul style="list-style-type: none"> •Symptomatic heart failure including established Class III or IV heart failure; rosiglitazone associated with increase MI risk
A-glucosidase inhibitors	Acarbose, miglitol	<ul style="list-style-type: none"> •Cirrhosis •Inflammatory bowel disease, colonic ulceration, partial intestinal obstruction (or predisposition to obstruction), chronic intestinal disease associated with disorders of digestion or absorption
Meglitinides	Repaglinide, nateglinide	<ul style="list-style-type: none"> •Patients with severe renal insufficiency should initiate therapy with reduced doses; use with caution in patients with impaired liver function
Dipeptidyl peptidase 4 inhibitors (DPP4)	Sitagliptin	<ul style="list-style-type: none"> •Patients with severe renal insufficiency should initiate therapy with reduced doses
Incretin mimetics	Exenatide (Byetta)	<ul style="list-style-type: none"> •Monitor for hypoglycemia when used with sulfonylureas •Not tested in patients with gastroparesis or severe gastrointestinal disease •Acute pancreatitis can occur •Not recommended in patients with severe renal impairment

What is the most appropriate therapeutic goal?

1. Action to Control Cardiovascular Risk in Diabetes (ACCORD)
2. Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)
3. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes (VADT)

	ACCORD	ADVANCE	VADT
Number of patients	10,251	11,140	1,791
Mean age, years	62	66	60
Duration of diabetes, years	10	8	11
History of CVD, %	35	32	40
BMI, kg/m ²	32	28	31
Median baseline HbA1c	8.1%	7.2%	9.4%
Target HbA1c	< 6.0% vs. 7.0-7.9%	< 6.5%	< 6.0% vs. a planned difference of 1.5% between groups
Median follow-up	3.5 years (trial stopped early)	5 years	5.6 years
Outcomes (intensive glycemic control compared to standard control)			
HbA1c achieved	6.4% vs. 7.5%	6.5% vs. 7.3%	6.9% vs. 8.4%
Macrovascular events	No significant difference	No significant difference	No significant difference
Microvascular events	Not measured	Significant reduction	No significant difference
Death (CV)	Significant increase	No significant difference	No significant difference
Death (all causes)	Significant increase	No significant difference	No significant difference

Possible causes of the higher death rate in the intensive treatment group of ACCORD compared to ADVANCE and VADT

- Large magnitude of the reduction in HbA1c (under 6%)
- Speed of the reduction in HbA1c (reductions of approximately 1.4% in the intensive therapy group and 0.6% in the standard-therapy group within the first 4 months after randomization)
- Differences in drug regimens
- Rates of hypoglycemia
- Undetected adverse interactions among the various drug classes used at high doses.

- The lack of significant reduction in CVD events with intensive glycemic control in these studies should not lead to an abandonment of the general target of an HbA1c < 7.0%
- Lowering HbA1c to approximately 7% or less reduces the microvascular complications of diabetes.
- The UKPDS trial suggests that treating to a target HbA1c of 7% or less soon after diabetes is diagnosed may cause long-term reduction in risk of cardiovascular disease.

Bottom Line

The greatest clinical benefit of good glycemic control may occur early in the course of the disease. A reasonable HbA1c target is 7% for most patients.

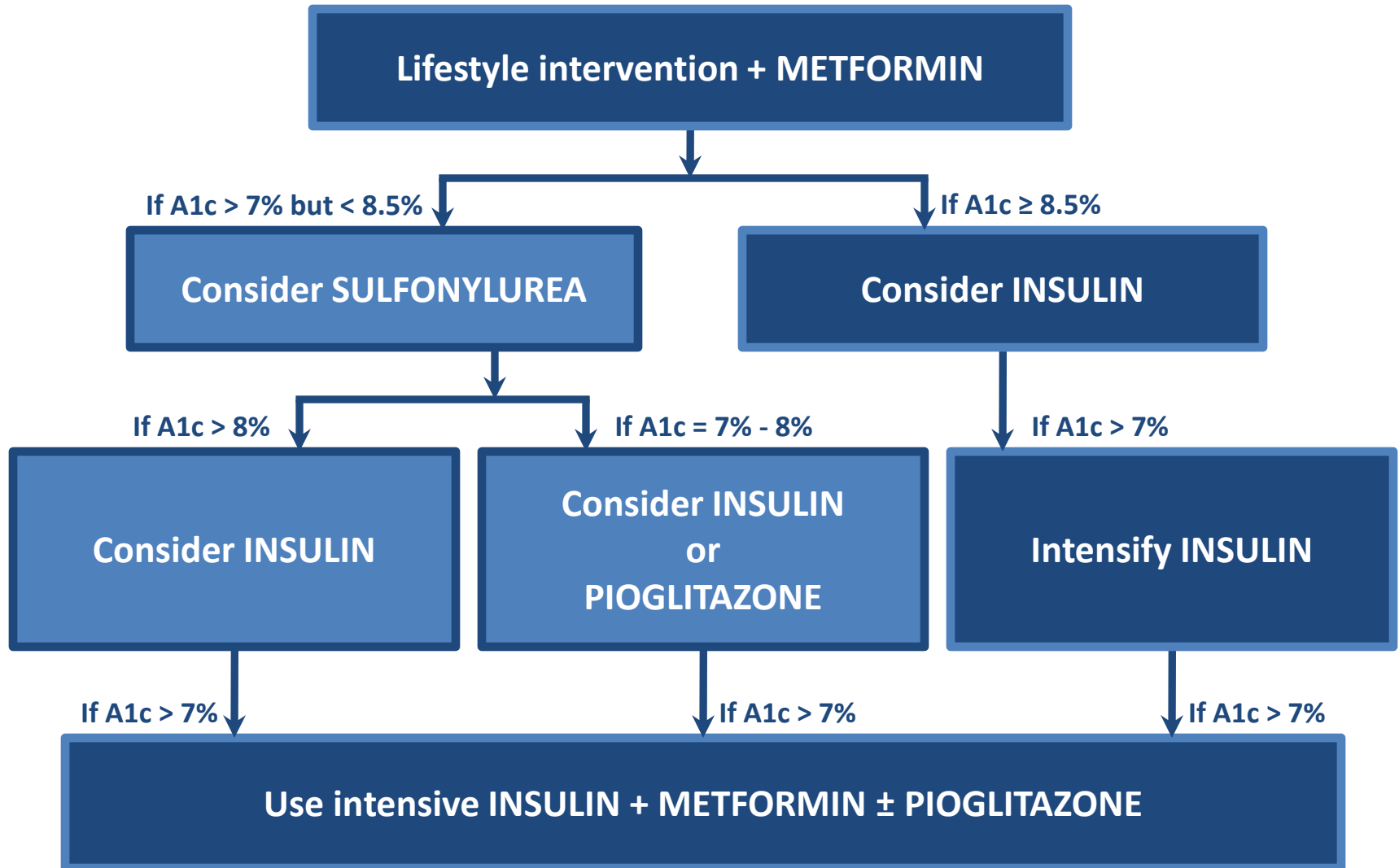
Goal should be individualized in selected patients such as the:

- Frail elderly
- Pregnant women

Monitoring

- After initiation of therapy, the ADA recommends measuring hemoglobin A1c
 - Every 3 months until a level of 7% is achieved
 - Every 6 months thereafter

Figure 7. Treatment algorithm for the management of type 2 diabetes (p.31)



Optimizing the Use of Insulin

- Patients in the UKPDS trial failed oral therapy at a rate of 5-10% per year.
- 50% required the addition of a second drug after three years
- 75% needed multiple therapies by nine years
- Only 37% of patients with diabetes reach a goal of A1c < 7%

Barriers to Insulin Therapy

Patient-based:

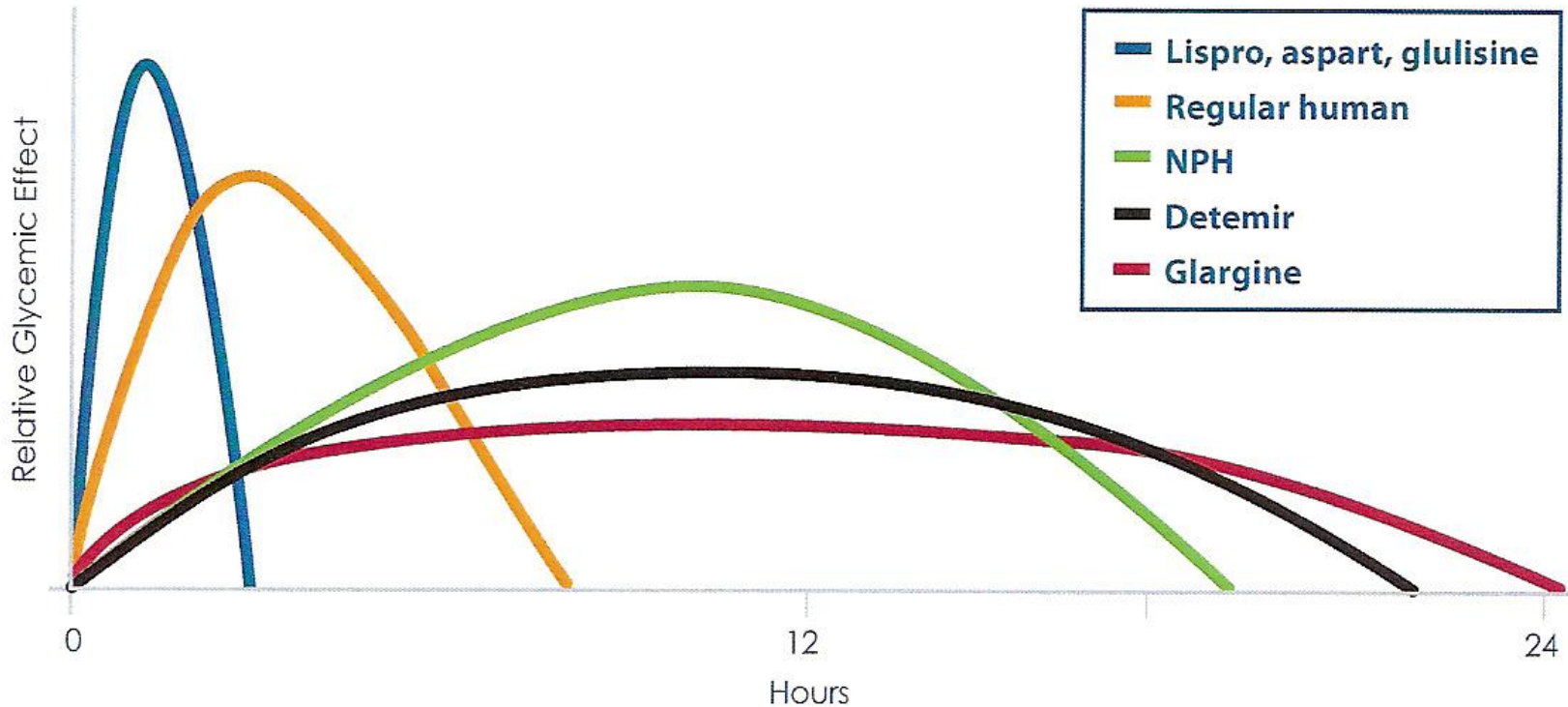
- Fear of injections
- Associated discomfort
- Low perceived efficacy
- Belief that adding insulin therapy is a sign of treatment and lifestyle failure

Barriers to Insulin Therapy

Physician-based:

- Hypoglycemia
- Lack of time to adequately instruct patients
- Sense of failure
- Belief that insulin should only be started when “absolutely essential”

Figure 8. Comparison of Human Insulin Preparations and Insulin Analogs. Reproduced with permission from McMahon and Dluhy, *NEJM*, 2007.⁶³



Used with permission, McMahon GT, Dluhy RG. Intention to treat - initiating insulin and the 4-T study. *NEJM* 2007;357(17):1759-61.¹⁵

Type 2 diabetes

No benefit of rapid acting insulin over regular insulin in managing A1c or in reducing hypoglycemic episodes.

When should insulin therapy be initiated?

Diabetic patient has:

- A1c > 8.0% on maximal dose oral hypoglycemic monotherapy
- A1c > 8.0% on two oral hypoglycemic agents

Figure 9. ADA consensus algorithm for initiating and intensifying insulin (p.36)

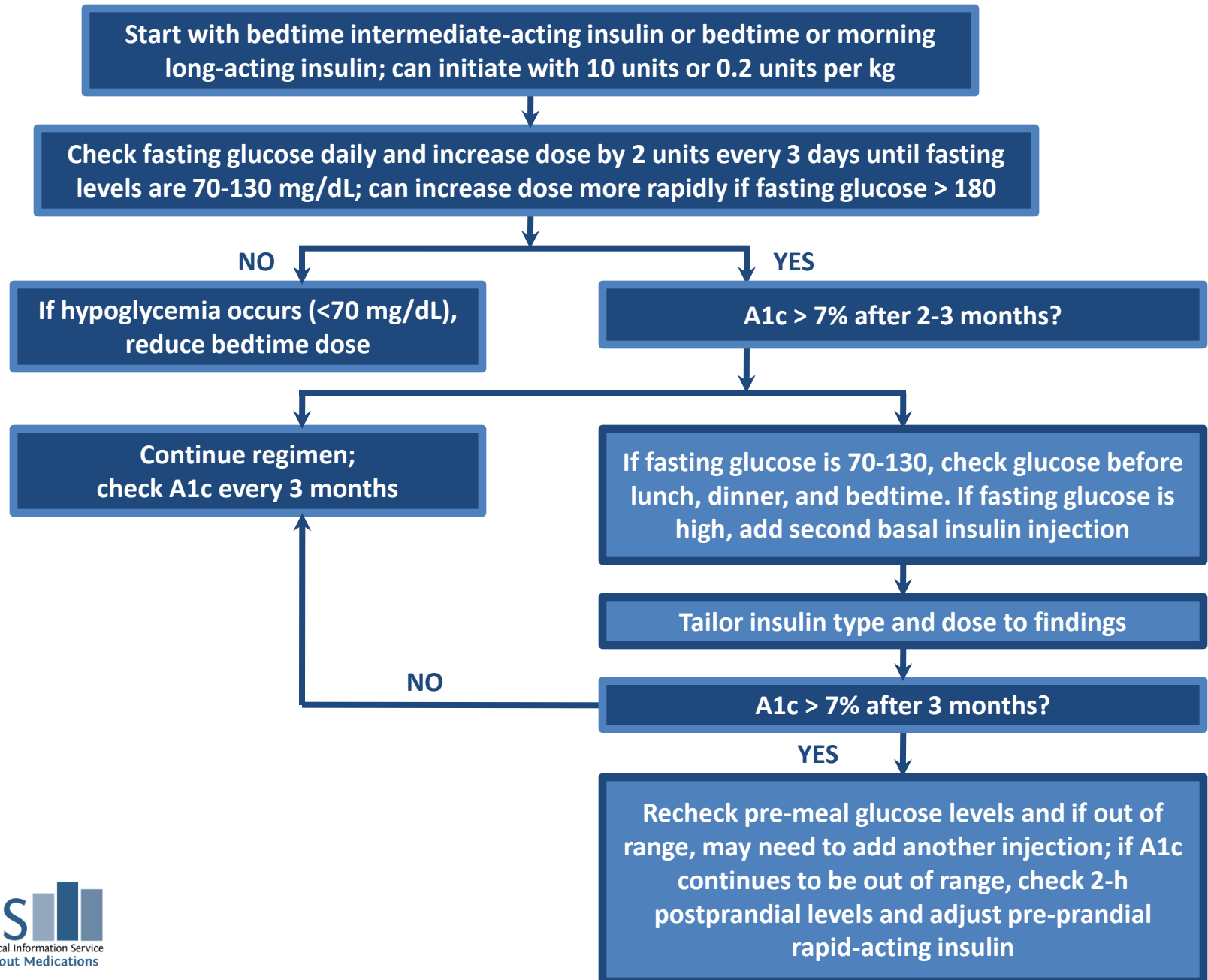


Table 7. Insulin initiation or titration

(p.37)

- Start with 10 units per day of bedtime basal insulin.
- Adjust insulin every week. To adjust, calculate the mean self-monitored fasting blood glucose (FBG) values from the previous 2 days.

Mean FBG	Increase insulin by
100-120 mg/dL	2 units
120-140 mg/dL	4 units
140-180 mg/dL	6 units
≥ 180 mg/dL	8 units

Which Insulin to Pick?

NPH vs. glargine or detemir

Treat to Target Trial

- Mean fasting blood glucose levels and A1c levels achieved were similar
- More nocturnal hypoglycemic events occurred in the NPH group

LANMET Study

- Treatment with glargine and metformin vs. treatment with NPH and metformin
 - Glucose control was similar in both groups
 - Fewer hypoglycemic events in the first 12 weeks in the glargine group
 - At 36 weeks, investigators found no significant differences in hypoglycemic events

Bottom Line

- Long-acting insulin, intermediate-acting insulin have equivalent effects on glucose control in type 2 diabetes
- Long-acting insulins may be associated with modest reductions in overnight hypoglycemic events

Biphasic or Prandial Insulin vs. Basal Insulin Alone

- Biphasic and prandial formulations produce more side effects
- More difficult for patients to manage
- Biphasic and Prandial formulations were more likely to get patients to goal

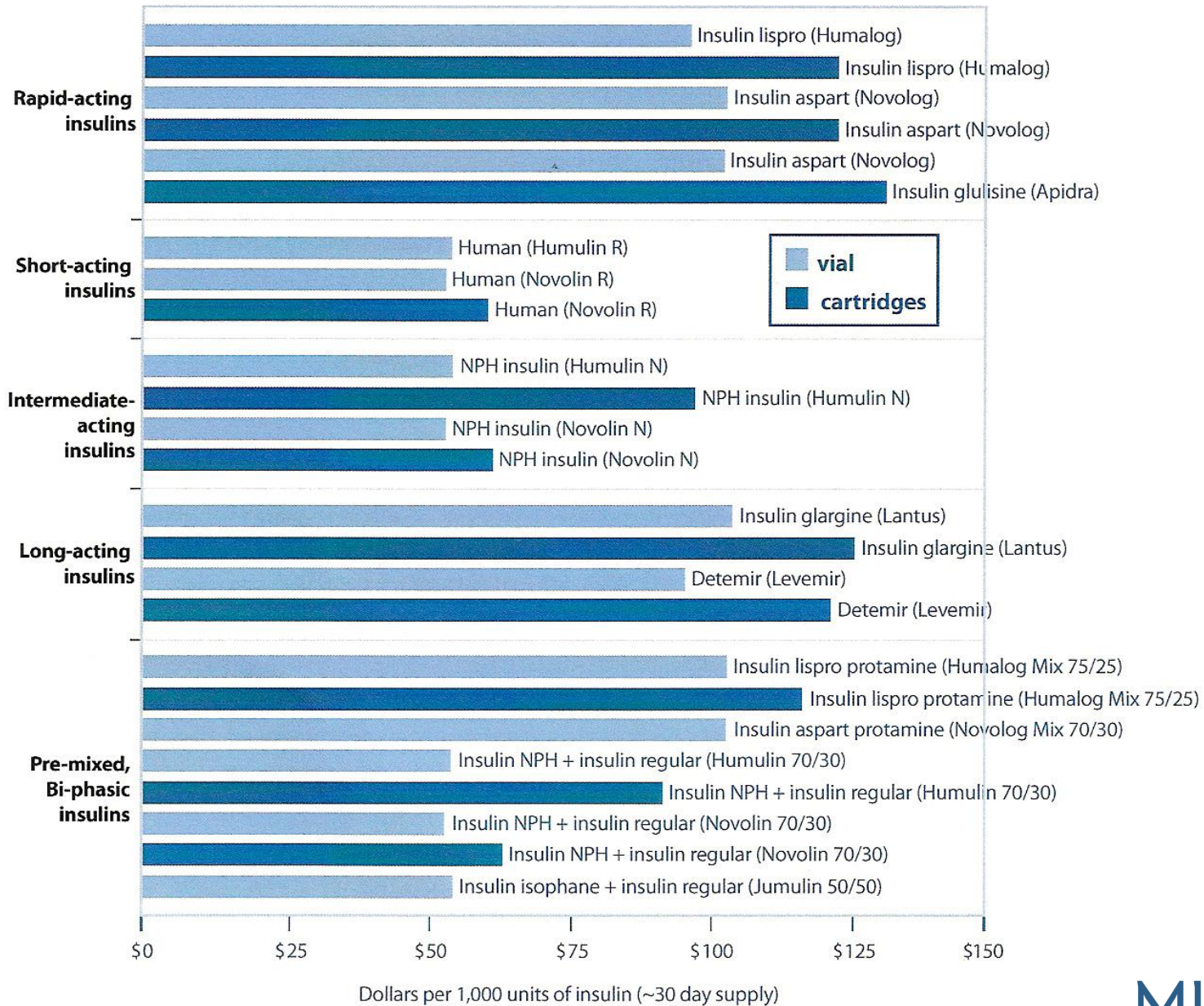
Recommendations are still to start with intermediate or long-acting insulin at night and titrate as needed, based on individual response.

Combining insulin with oral hypoglycemic agents

Combination therapy with oral hypoglycemic agents and insulin can produce improved glucose control and less weight gain than therapy with insulin alone. Insulin combined with metformin offers the offers the greatest synergy for clinical effect and the lowest risk of adverse events.

- Produces improved glucose control
- Less weight gain

Figure 10. Costs* of insulin preparations per 5,000 units.



*Prices obtained from www.drugstore.com or www.cvs.com, January 2009.

Bottom Line

1. The new insulin analogs differ substantially in price from conventional insulins but not necessarily in efficacy.
2. Preparations that are used with insulin pens add significant additional costs.

Setting blood glucose goals in the elderly

- Risks of hypoglycemia, polypharmacy, and drug interactions may outweigh the value of intensive therapy in some frail patients.
- Elderly patients in relatively good health, good functional status
 - Target A1c should be $< 7\%$
- Frail older adults, patients with life expectancy < 5 years, others for whom risks outweigh benefits
 - Target A1c $< 8\%$ more acceptable

Bottom Line

In frail elderly patients, glycemic goals should be tailored to balance the risks and benefits of treatment.

Potential Complications of diabetes

- First evaluation after a patient is diagnosed
 - Fundoscopic exam, referral to an ophthalmologist for periodic dilated eye exams
 - Control of blood pressure with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker
 - Management of cholesterol levels
 - Annual screening for microalbuminuria and serum creatinine measurement to estimate glomerular filtration rate
 - Good foot care, patient education about foot care, referral to a podiatrist as needed.

Treatment of related conditions

Condition	Identification	Goal of therapy	Recommended Interventions
Hypertension	Check BP at all visits	SBP \leq 130 mmHg DBP \leq 80 mmHg	<ul style="list-style-type: none"> • Begin with lifestyle modification • Drug therapy should include ACE-I (ARB if ACE-I not tolerated) • Thiazide-type diuretic if second agent is needed
Hyperlipidemia	Check fasting lipids	LDL $<$ 100 mg/dL (LKL $<$ 70 mg/dL if CAD)	<ul style="list-style-type: none"> • Treat with statins for elevated LDL
Antiplatelet therapy	Assess for cardiac risk factors	Risk reduction	<ul style="list-style-type: none"> • Aspirin for patients with coronary artery disease
Smoking	Inquire about tobacco use	Smoking cessation	<ul style="list-style-type: none"> • Nicotine replacement • Bupropion/varenicline • Counseling programs

Hypertension

Blood pressure $> 130/80$ mm/Hg should be treated aggressively in patients with diabetes

ACE inhibitors should be first-line treatment, with ARBs reserved for patients who cannot tolerate ACE-I

Hyperlipidemia

All patients with diabetes should have their cholesterol checked at least once per year.

Target levels:

- LDL cholesterol <100 mg/dL
- Triglycerides <150 mg/dL
- HDL cholesterol >40 mg/dL (men); >50 mg/dL (women)

If not met:

- Lifestyle intervention including diet modification and exercise is warranted
- For high-risk patients, more aggressive treatment to drive LDL below 70 mg/dL

Statins

- Most patients with diabetes requiring cholesterol reduction should be treated with a statin.
 - Generic for most patients
 - Atorvastatin or rosuvastatin if LDL must be lowered by 50% or more.

Antiplatelet medication

- Diabetes generally considered a coronary artery disease “risk equivalent”
- POPADAD and JPAD trials
 - Aspirin for primary prevention of cardiovascular disease in patients with diabetes offers little to no benefit with possible increase in risk of adverse events.

Bottom Line

The benefit of aspirin for the primary prevention of cardiovascular events in patients with diabetes is unclear. An individual clinical decision must be made weighing the degree of cardiovascular risk and the risk of bleeding.

Smoking

All patients with diabetes should be encouraged not to smoke.

Several effective interventions are available:

- Nicotine replacement therapy
- Bupropion (Zyban)
- Varenicline (Chantix)

Questions?