



Pharmaceutical Assistance
Contract for the Elderly



Balanced information for better care

Managing type 2 diabetes:

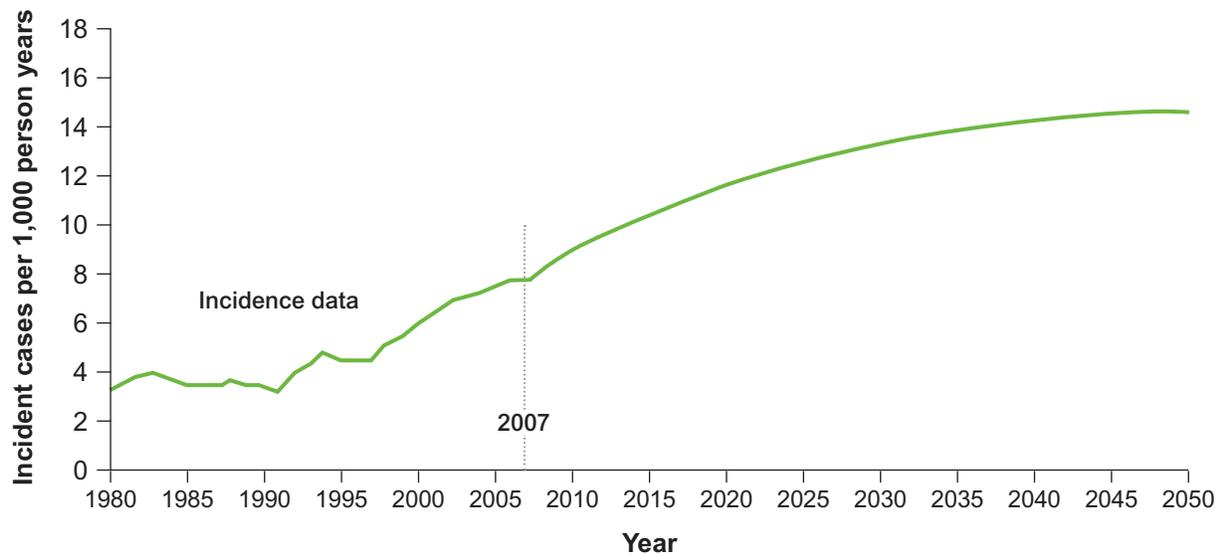
A spoonful of medicine helps the sugar go down,
but there's more to it than that



The prevalence of diabetes is rising steadily

Over 29 million Americans have diabetes,¹ and up to 1 in 3 adults will be diagnosed by 2050.²

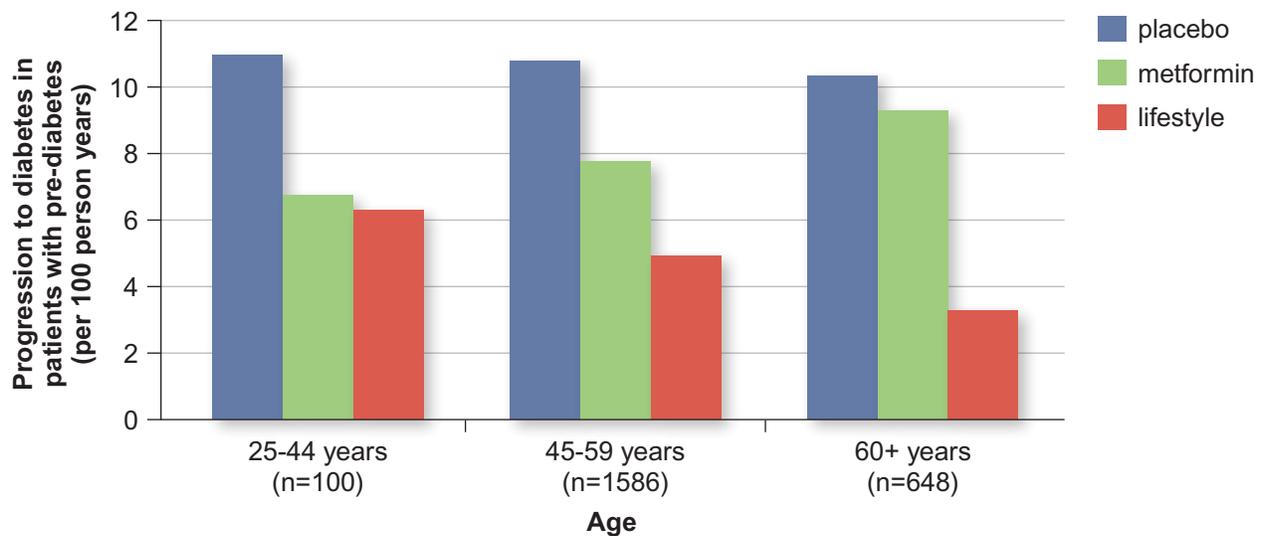
FIGURE 1. The number of new cases of diabetes diagnosed each year is increasing, and is projected to climb well into this century.²



Pre-diabetes (HbA1c 5.7%–6.4%) is an important precursor to diabetes, and is even more common.³

About 86 million people in the U.S. have pre-diabetes, and many are unaware of it. Lifestyle changes can slow its progression, especially in older patients.

FIGURE 2. Metformin, dietary changes, and exercise can prevent the development of diabetes in patients with pre-diabetes.⁴



Choosing the right HbA1c target

In patients with diabetes whose HbA1c exceeds 6.5%, the right goal will depend on the clinical situation.

FIGURE 3. An appropriate goal for most patients will be $\leq 7\%$, but a tighter or less stringent target may be advisable.

Tight target: $\leq 6.5\%$	Typical target: $\leq 7\%$	Less stringent target: $\leq 8\%$
<ul style="list-style-type: none">• Younger patients with longer life expectancy• Newly diagnosed, without existing cardiovascular disease	<p>Best target for most patients</p>	<ul style="list-style-type: none">• Frail elderly• High risk of hypoglycemia• Multiple comorbidities• Limited life expectancy

Begin treatment with diet and exercise. Add metformin if medication is needed.

FIGURE 4. Lifestyle changes are central to management at all stages of the disease.^{5,6,7}

	<h3>DIET</h3> <ul style="list-style-type: none">• Reduce calories to achieve weight loss• Favor complex carbohydrates over simple carbs
	<h3>EXERCISE</h3> <ul style="list-style-type: none">• Set a goal of about 20 minutes of physical exercise each day• A combination of aerobic and resistance training is best at lowering HbA1c
	<h3>METFORMIN</h3> <ul style="list-style-type: none">• Reduces risk of major cardiovascular outcomes and HbA1c• Safe side effect profile• Low cost

Managing related conditions: a key aspect of diabetes care

Controlling hypertension and hyperlipidemia aggressively can prevent end-organ damage and is at least as important as glucose control.

FIGURE 5. Managing related conditions³

A Antiplatelet therapy	<ul style="list-style-type: none">• Use antiplatelet therapy (e.g., aspirin) in most patients with diabetes and cardiovascular disease unless contraindicated.• In primary prevention, recommend anti-platelet medication only if the ten-year risk of cardiac events is over 10%.
B Blood pressure	<ul style="list-style-type: none">• Aim for BP \leq 140/90 mmHg for most patients.• Target 130/80 mmHg in younger patients or those with albuminuria or cardiovascular risk factors.• Treatment should include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).
C Cholesterol	<p>For all patients with diabetes > 40 years of age, prescribe a statin:</p> <ul style="list-style-type: none">• Patients 40-75 years without other CV risk factors: prescribe a moderate-intensity statin regimen (e.g., atorvastatin 20mg).• Patients with CV disease or cardiovascular risk factors: prescribe a high-intensity statin regimen (e.g., atorvastatin 80mg).
S Smoking	<ul style="list-style-type: none">• Drug therapy (e.g., bupropion) or nicotine replacement can help break the habit.• Counseling programs increase the patient's chance of quitting.• Call 1-800-QUITNOW

Most hypoglycemics lower HbA1c by about a percentage point

Metformin is the best first-line agent.⁸

FIGURE 6. HbA1c reduction with selected non-insulin hypoglycemic agents⁹⁻¹¹

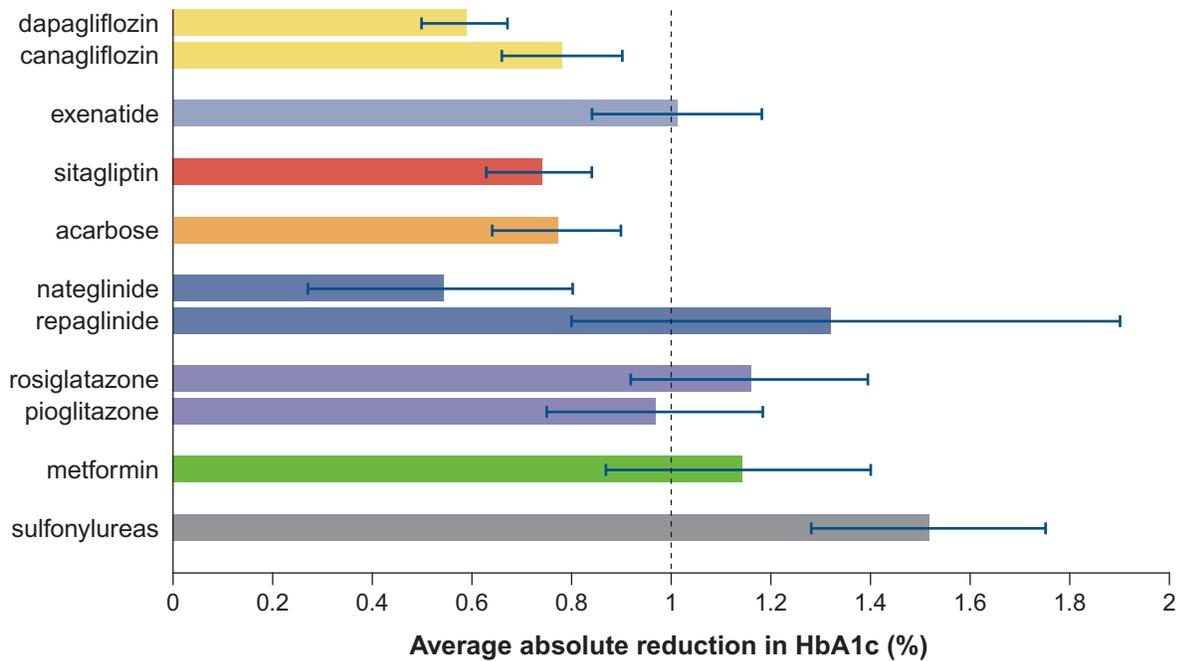
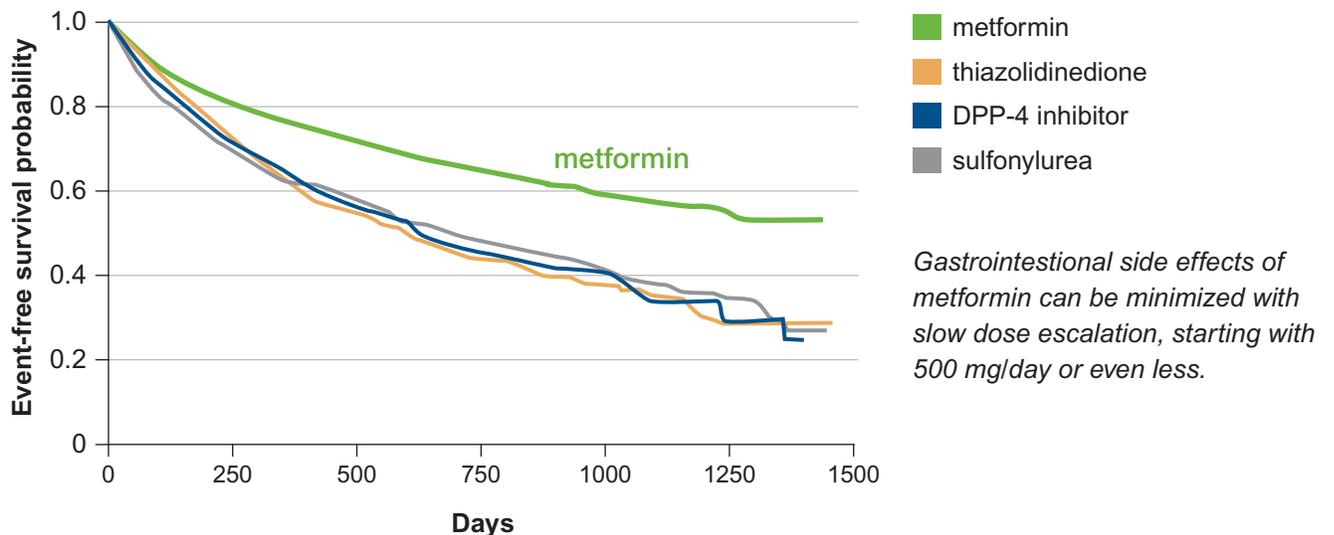


FIGURE 7. In one large study of routine care, only about half of patients were treated with metformin first, even though it was the best agent in delaying the need to intensify therapy.⁸



Benefits and risks vary by class and by drug

Some hypoglycemic agents have been shown to reduce cardiovascular events, but one increases the risk. It remains unstudied for many more.

TABLE 1. Cardiovascular outcomes and adverse effects of hypoglycemic drugs^{6,12-17}

Class	CV outcomes	Weight change	Hypoglycemia	LDL	Precautions
biguanide metformin (Glucophage)	32% reduction	loss	low risk	lowers	avoid in renal disease or insufficiency
sulfonylureas chlorpropamide (Diabinese) glyburide (DiaBeta, Glynase)	16% reduction	gain	high risk	*	hypoglycemia
glipizide (Glucotrol)	*				
glitazones rosiglitazone (Avandia)	64% increase	gain	low risk	raises	heart failure, fracture
pioglitazone (Actos)	18% reduction				
meglitinides nateglinide (Starlix)	*	gain	high risk	*	caution with impaired liver function
repaglinide (Prandin)					
gliptins (DPP-4 inhibitors) alogliptin (Nesina) saxagliptin (Onglyza) sitagliptin (Januvia)	neutral	*	*	*	? pancreatitis
linagliptin (Tradjenta)	*				
GLP-1 receptor agonists liraglutide (Victoza) [†]	neutral	loss	*	*	? pancreatitis
albiglutide (Tanzeum) dulaglutide (Trulicity) exenatide (Byetta, Bydureon)	*				
flozins (SGLT-2 inhibitors) empagliflozin (Jardiance)	24% reduction	loss	low risk	raises	UTI, ketoacidosis, genital infections, hypotension
canagliflozin (Invokana) dapagliflozin (Farxiga)	*				

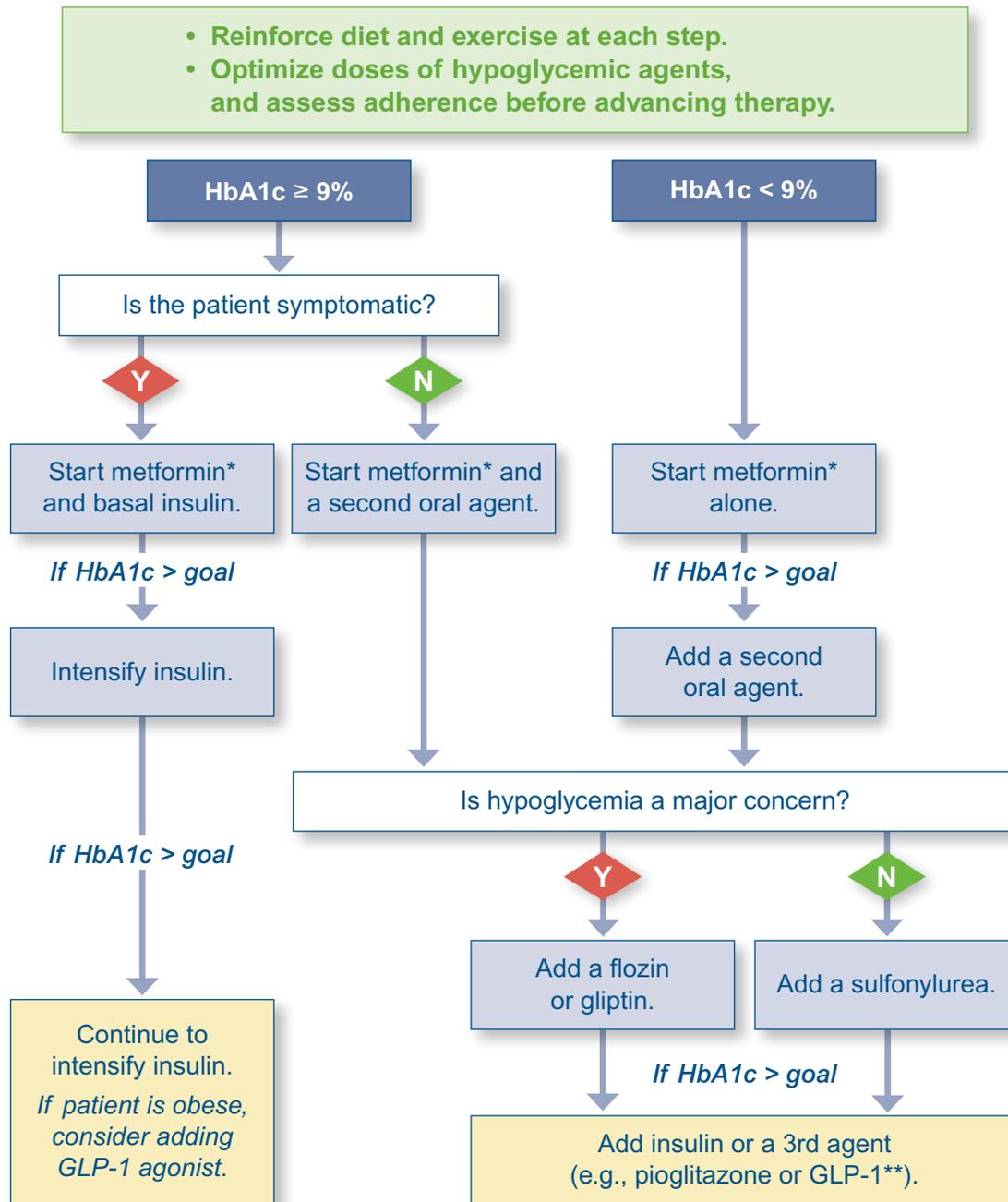
* No data available.

[†] New CV outcome data on liraglutide pending.

When lifestyle and metformin are not enough

The patient's clinical situation and data on end-organ protection can help determine which drug to add to the regimen.

FIGURE 8. Algorithm for selecting treatment



* If contraindicated or not tolerated, go to the next step.

** GLP-1 can be added when a gliptin is not selected as the second agent.

References and rationale for these recommendations are detailed in the evidence document provided at AlosaHealth.org.

The other ‘resistance’: starting insulin

Many patients can successfully achieve their HbA1c target with basal insulin combined with non-insulin agents.

FIGURE 9. Initiate basal insulin first, adding a mealtime dose at the main meal of the day. If needed, additional doses can then be added before other meals.

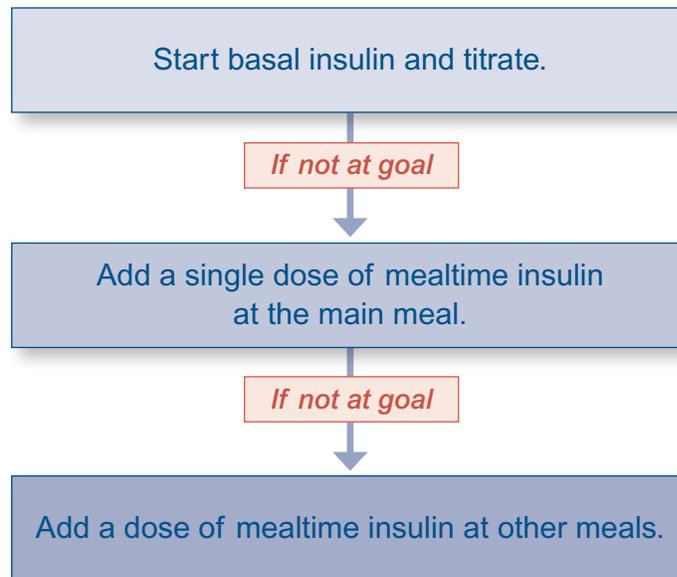
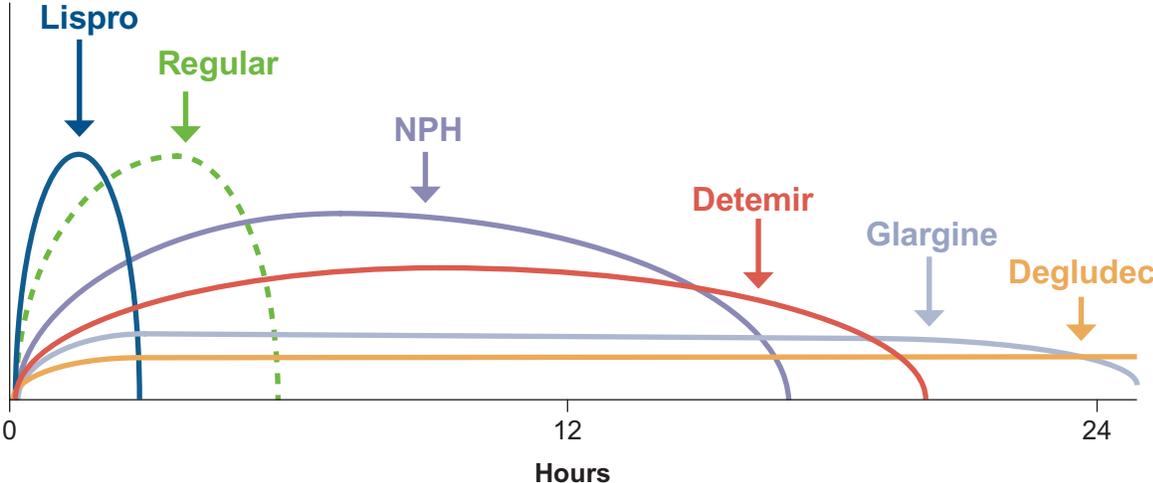


TABLE 2. The “Treat to Target” criteria provide a pragmatic way to increase insulin doses.¹⁸

<ul style="list-style-type: none"> • Start with 10 units of basal insulin (either intermediate or long-acting insulin) at bedtime. • Adjust insulin dose every week, based on the mean self-monitored fasting blood glucose (FBG) values from the previous 2 days. 	
If mean FPG is:	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

Choosing among insulin products

FIGURE 10. Duration of action of insulin formulations



More concentrated insulin products can be useful in managing higher dose requirements.

TABLE 3. Newer insulin concentrations and packaging

Insulin type	Brand name	Concentration (per mL)	Packaging
regular	Humulin R	500 units	vial, pen
lispro	Humalog	200 units	pen
glargine	Basaglar Toujeo	300 units 300 units	pen pen
degludec	Tresiba	200 units	pen

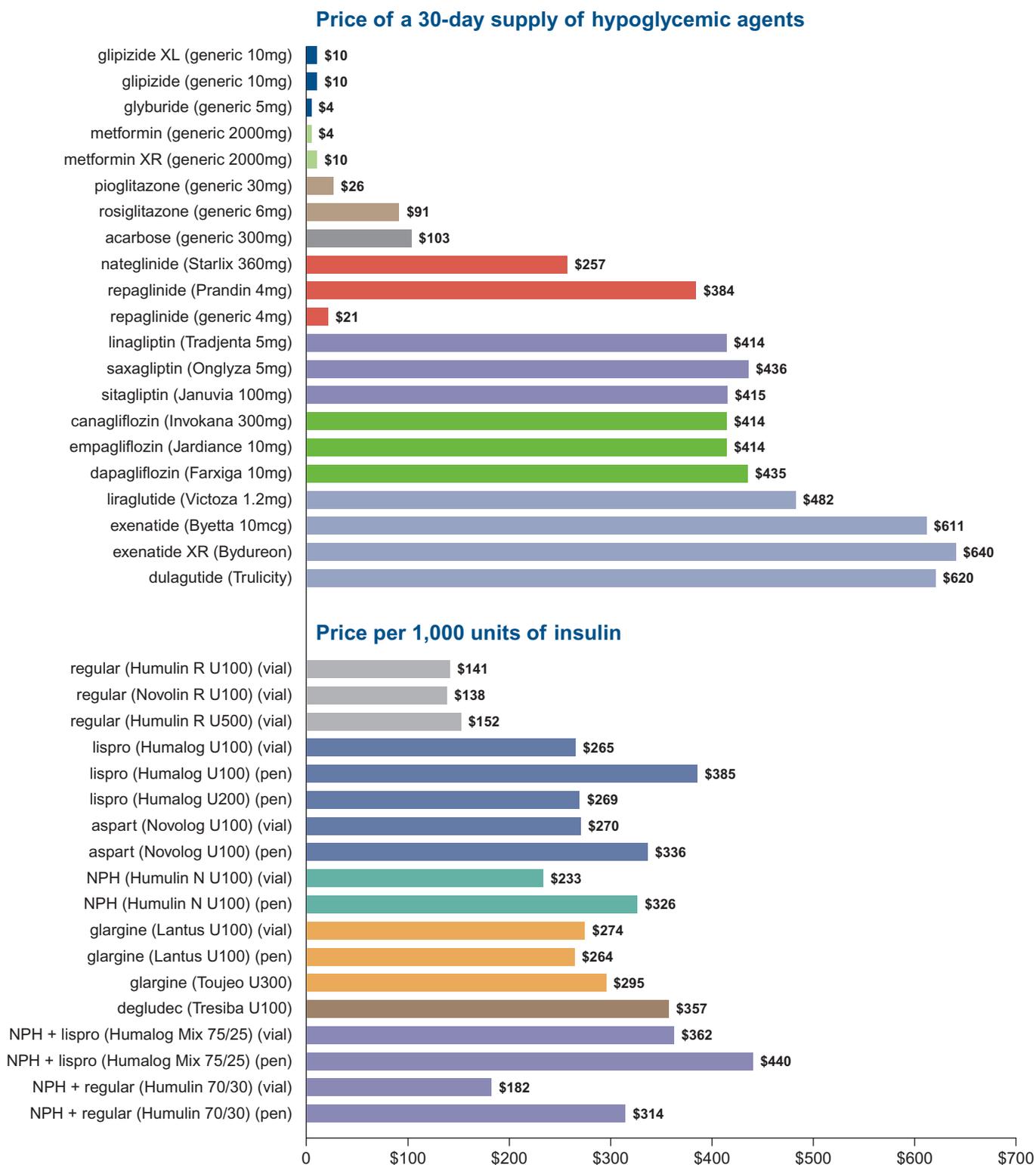


U-500 preparations of regular insulin in vials requires careful calculation of volume and caution in drawing up individual doses.

Other concentrated insulins are available in ‘pen’ form, which enables the patient to dial in the prescribed dose to be injected.

Costs

FIGURE 11. Retail price of commonly used agents to treat diabetes



Prices are from goodrx.com as of February 2016. The WHO defined daily dose was used to define doses. Insulin prices are standardized to 1,000 units. Regular U-500 insulin is available only in a 20mL vial at a total price of over \$1,500.

Key messages

- Diet and exercise can have a major impact on glucose control, and can slow the progression of prediabetes to diabetes.
- Aim for a target HbA1c of 7% for most patients. Modify the goal (e.g., 8% or higher) for frail older patients in whom overtreatment can pose its own risk.
- Use metformin as first-line treatment for the vast majority of patients who require drug treatment.
- Focus on adherence before titrating doses or adding a new drug.
- Intensify treatment with a second oral agent for patients not controlled on metformin; tailor the second-line treatment based on patient characteristics.
- Add insulin promptly when oral agents are not sufficient to achieve A1c goal.
- Manage hypertension and hyperlipidemia aggressively and focus on smoking cessation where necessary to prevent diabetes-related complications.
- Continuously promote weight control, exercise, and adherence to medications.

Extensive documentation of these recommendations and additional materials for prescribers and patients is available at AlosaHealth.org/modules/diabetes

References:

(1) Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States. 2014. (2) Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality and prediabetes prevalence. *Population Health Metrics*. 2010;8(2):29. (3) American Diabetes Association. Standards of medical care in diabetes. *Diabetes care*. 2016;39 (Suppl 1). (4) Crandall J, Schade D, Ma Y, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A: Biol Sci Med Sci*. 2006;61(10):1075-1081. (5) Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589. (6) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):854-865. (7) Church TS, Blair SN, Cocroham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010;304(20):2253-2262. (8) Berkowitz SA, Krumme AA, Avorn J, et al. Initial choice of oral glucose-lowering medication for diabetes mellitus: A patient-centered comparative effectiveness study. *JAMA Intern Med*. 2014;174(12):1955-1962. (9) Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med*. 2007;147(6):386-399. (10) Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA*. 2007;298(2):194-206. (11) Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159(4):262-274. (12) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-853. (13) Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-2471. (14) Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA*. 2007;298(10):1180-1188. (15) White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327-1335. (16) Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326. (17) Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-2128. (18) Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes care*. 2003;26(11):3080-3086.

About this publication

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition. More detailed information on this topic is provided in a longer evidence document at AlosaHealth.org.



The **Independent Drug Information Service (IDIS)** is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.



This material is provided by **Alosa Health**, a nonprofit organization which is not affiliated with any pharmaceutical company. IDIS is a program of Alosa Health.

This material was produced by Marie McDonnell, M.D., endocrinologist and Director of the Brigham Diabetes Program at the Brigham and Women's Hospital and Lecturer in Medicine at Harvard Medical School; Jerry Avorn, M.D., Professor of Medicine (principal editor); Michael A. Fischer, M.D., M.S., Associate Professor of Medicine; Niteesh K. Choudhry, M.D., Ph.D., Associate Professor of Medicine; and Dae Kim, M.D., M.P.H., Sc.D., Assistant Professor of Medicine, all at Harvard Medical School; and Ellen Dancel, PharmD, MPH, Director of Clinical Material Development, Alosa Health. Drs. Avorn, Choudhry, Fischer, and McDonnell are physicians at the Brigham and Women's Hospital, and Dr. Kim practices at the Beth Israel Hospital, both in Boston. None of the authors accepts any personal compensation from any drug company.

Medical writer: Stephen Braun.



Pharmaceutical Assistance
Contract for the Elderly