PACE Pharmaceutical Assistance Contract for the Elderly

Alosa Health

Balanced information for better care

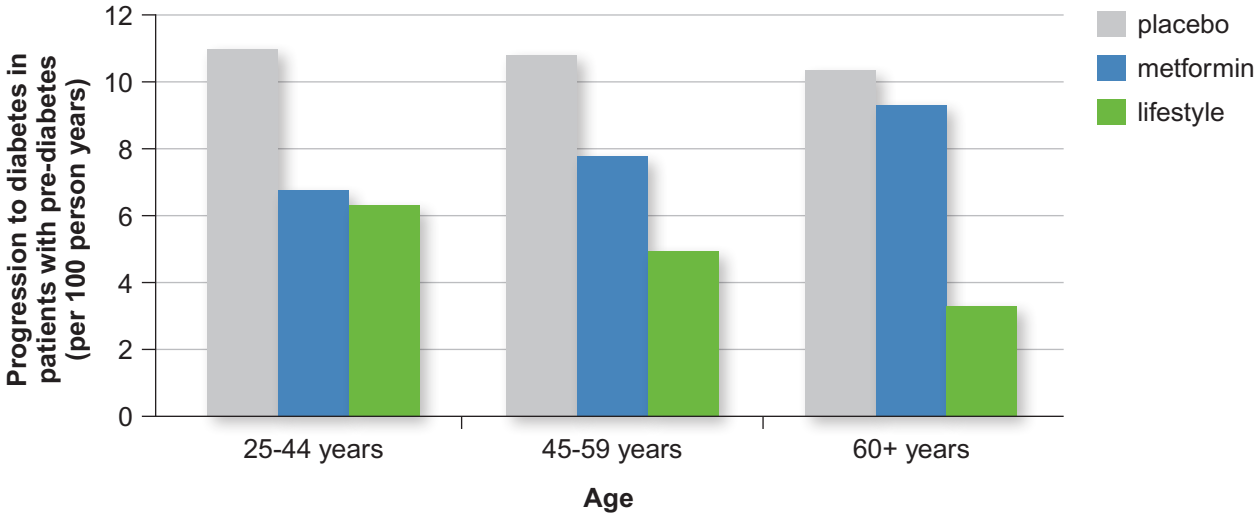
Managing type 2 diabetes

New trials and guidelines are transforming medication use

Type 2 diabetes is common, but its risk can be reduced with lifestyle changes

Prediabetes (HbA1c 5.7-6.4%) affects more than 80 million people.[1]

FIGURE 1. Diet and exercise can reduce or delay the progression from prediabetes to diabetes, especially in older adults.[2]



Diabetes Prevention Programs

DPP support lifestyle changes in patients with prediabetes through exercise and wellness programs certified by the CDC. To learn more about referring patients and to find programs in your area, visit **AlosaHealth.org/Prediabetes**.

Over 30 million Americans have diabetes (HbA1c ≥6.5%),[1] including more than 10% of adult Pennsylvanians.[3]

Select HbA1c goal based on patient characteristics

FIGURE 2. For most adults, the HbA1c target is <7%. But the proper goal can change as patients age, especially in older adults with comorbidities, cognitive decline, or frailty.[4]

HbA1c goal

<6.5%	<7%	<8%	<8.5%
Tighter target	**Typical**	**Relaxed target**	**Looser target**
Newly diagnosed, younger patients without cardiac disease	Best target for most patients	Older patients with other comorbidities (or reduced functional status)	Older patients with frailty, end-stage disease, or limited life expectancy

Begin with lifestyle changes, adding metformin if needed.

FIGURE 3. Diet and exercise are a central component of management; medications such as metformin will be needed if greater HbA1c lowering is required.

DIET

- Reduce calories to achieve weight loss.
- Favor whole grains, nuts, fruits, and vegetables over refined and processed foods.

+

EXERCISE

- Set a goal of 150 minutes of physical activity per week.
- A combination of aerobic and resistance training is best at lowering HbA1c.

+

METFORMIN

- Safe side effect profile
- Low cost
- Start at a low dose to reduce GI side effects, then increase dose.

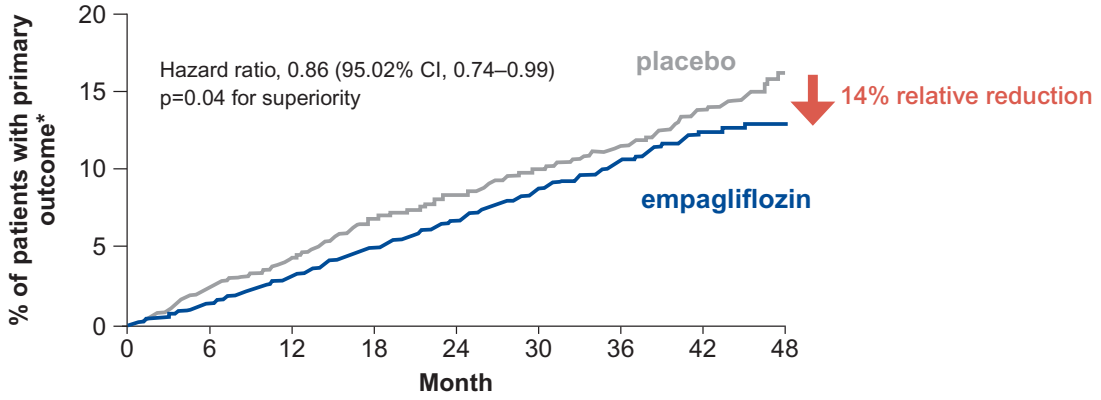
Diabetes self-management programs can help patients make lifestyle changes. So can other members of the healthcare team, including diabetes educators, nurses, pharmacists, and nutritionists. Links to diabetes education resources are at **AlosaHealth.org/Diabetes**.

In patients with cardiac disease, newer glucose lowering drugs prevent CV events

All these studies were conducted in patients already taking metformin.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors or 'flozins'

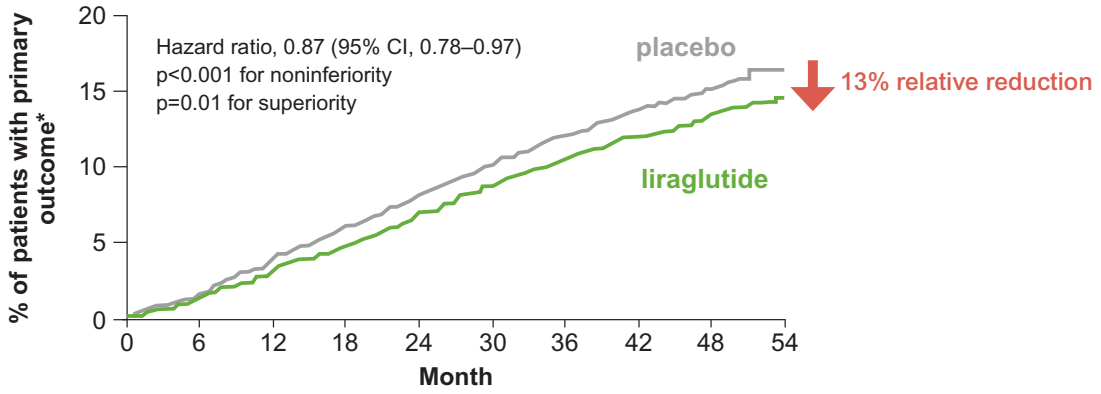
FIGURE 4. The EMPA-REG trial showed that empagliflozin (Jardiance) reduced the risk of cardiovascular events more than placebo.[5]



Canagliflozin (Invokana) also provided CV benefit over placebo. The effect of dapagliflozin (Farxiga) was mixed.[6,7]

Glucagon-like peptide-1 receptor agonists (GLP-1)

FIGURE 5. Liraglutide (Victoza) reduced the relative risk of CV outcomes 13% more than placebo in the LEADER trial.[8]



Not all GLP-1s have been shown to reduce CV outcomes. Semaglutide (Ozempic) reduced CV events more than placebo (relative reduction, 26%), but exenatide weekly (Bydureon) was no better than placebo in doing so.[9,10]

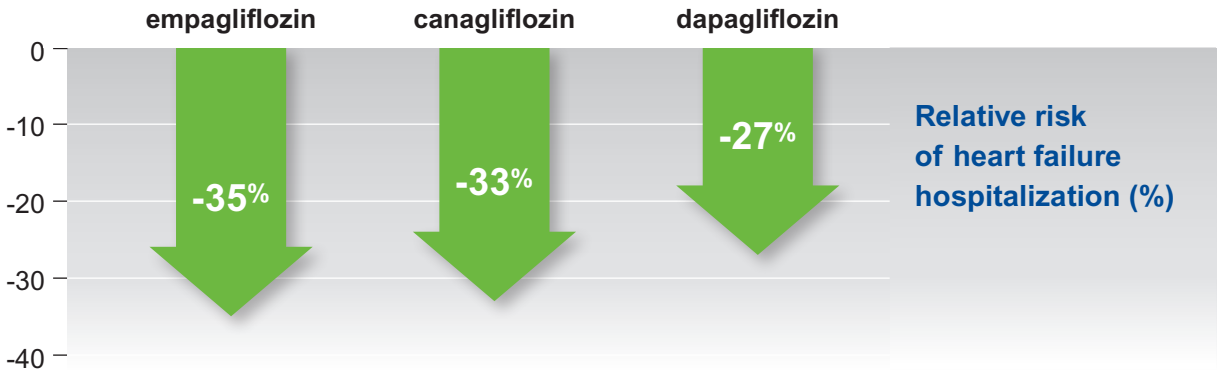
Management of hypertension and cholesterol can also reduce CV risk.

* Primary outcomes were CV death, non-fatal myocardial infarction, and non-fatal stroke.

Newer medications can also reduce heart failure and renal damage

Hospitalization for heart failure

FIGURE 6. All SGLT-2 inhibitors (flozins) studied significantly reduced the risk of heart failure hospitalization compared to placebo.[5-7]



However, GLP-1s did not differ from placebo in preventing heart failure outcomes.

Progression of nephropathy

TABLE 1. GLP-1s and SGLT-2 inhibitors (flozins) significantly slowed decline in renal function compared to placebo.[6-9,11]

Class	Drug	% with worsening renal function		Relative risk reduction
		On Medication	On Placebo	
SGLT-2 inhibitors	empagliflozin (Jardiance)	13%	19%	**39%**
	canagliflozin (Invokana)	0.5%	0.9%	**40%**
	dapagliflozin (Farxiga)	4%	6%	**24%**
GLP-1	liraglutide (Victoza)	1.5%	1.9%	**22%**
	semaglutide (Ozempic)	4%	6%	**36%**

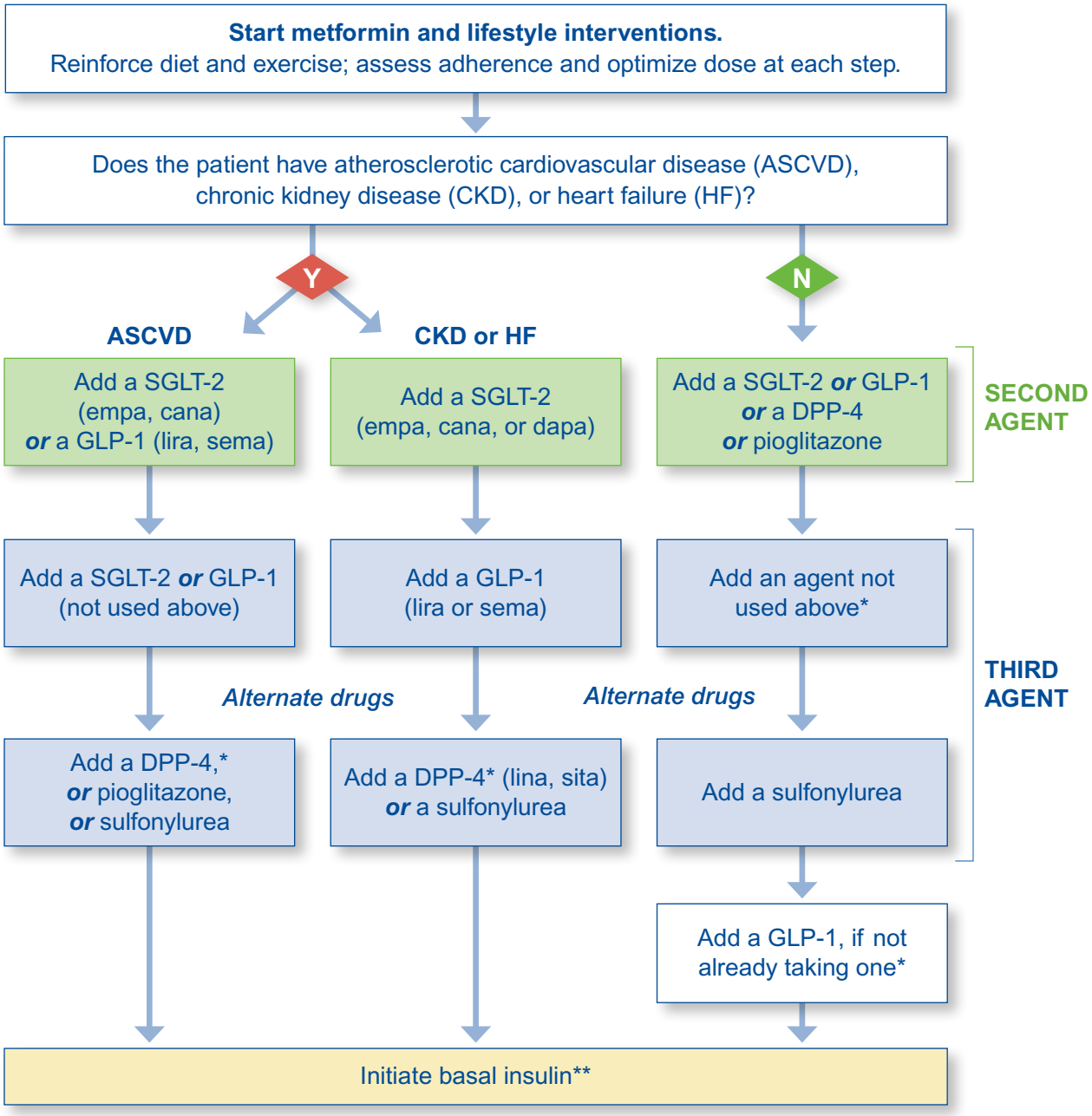
Decline in renal function was defined as a 40% reduction in eGFR, new renal replacement (e.g., dialysis), or death due to renal disease.

The cardiovascular and renal benefits of these drugs are independent of their glucose lowering effects.

Moving further toward the HbA1c goal

What to do when lifestyle and metformin are not enough

FIGURE 7. Treatment paths for patients who are not at HbA1c goal. Use patient characteristics, preferences, and insurance coverage to select the best regimen.[4]



* Avoid prescribing a DPP-4 and GLP-1 together.

** **Basal insulin can be initiated if needed at any point.**

Select drug based on patient factors

TABLE 2. Medication effects and considerations for prescribing

Class / medication	CV outcome: ASCVD	CV outcome: HF	Worsening nephropathy	Weight change	Hypoglycemia	Precautions
biguanide metformin (Glucophage)	benefit	*	*	loss	no	GI intolerance (start with low dose to minimize)
SGLT-2 inhibitors (flozins) canagliflozin (Invokana) empagliflozin (Jardiance)	benefit	benefit	benefit	loss	no	UTI, ketoacidosis, genital infections, hypotension, fractures (cana), amputation (cana)
dapagliflozin (Farxiga)	neutral					
ertagliflozin (Steglatro)	*	*	*			
GLP-1 receptor agonists liraglutide (Victoza) semaglutide† (Ozempic)	benefit	neutral	benefit	loss	no	GI side effects common pancreatitis
exenatide† (Bydureon) lixisenatide (Adlyxin)	neutral	neutral	*			
dulaglutide† (Trulicity) exenatide (Byetta)	*	*	*			
DPP-4 inhibitors (gliptins) linagliptin (Tradjenta) sitagliptin (Januvia)	neutral	neutral	*	*	no	joint pain, pancreatitis
alogliptin (Nesina) saxagliptin (Onglyza)	*	potential risk	*	*		
Thiazolidinediones (TZD) pioglitazone (Actos)	benefit	increased risk	*	gain	no	bone fractures, bladder cancer
sulfonylureas glyburide (DiaBeta, Glynase)	neutral	*	*	gain	yes	
glipizide (Glucotrol) glimepiride (Amyarl)	*	*	*			
insulin lispro, aspart, glulisine, regular, NPH	*	*	*	gain	yes	
glargine, degludec, detemir	neutral	*	*			

*no data available; †given weekly

Renal dose adjustment is required for metformin, GLP-1s, and SGLT-2 inhibitors.

The other 'resistance': starting insulin

Many patients can successfully achieve their HbA1c target with basal insulin (e.g., NPH, glargine) combined with other non-insulin agents.

FIGURE 8. If insulin is required to reach the HbA1c goal, initiate basal insulin first, adding mealtime doses as needed to achieve goal.[4]

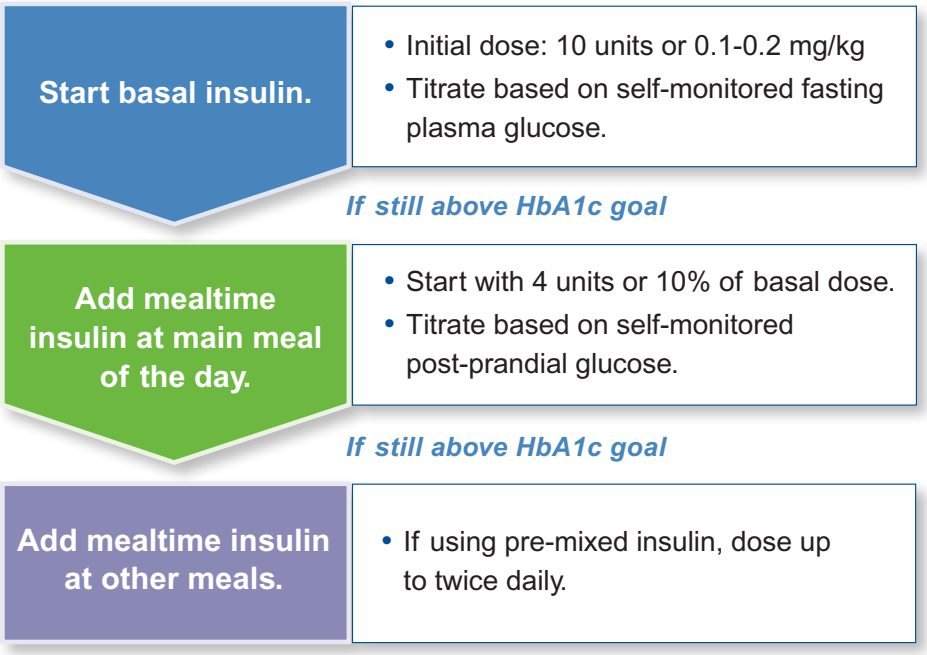


TABLE 3. The "Treat to Target" criteria provide an evidence-based approach to increase insulin doses in patients without frailty or cognitive impairment.[12]

- 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

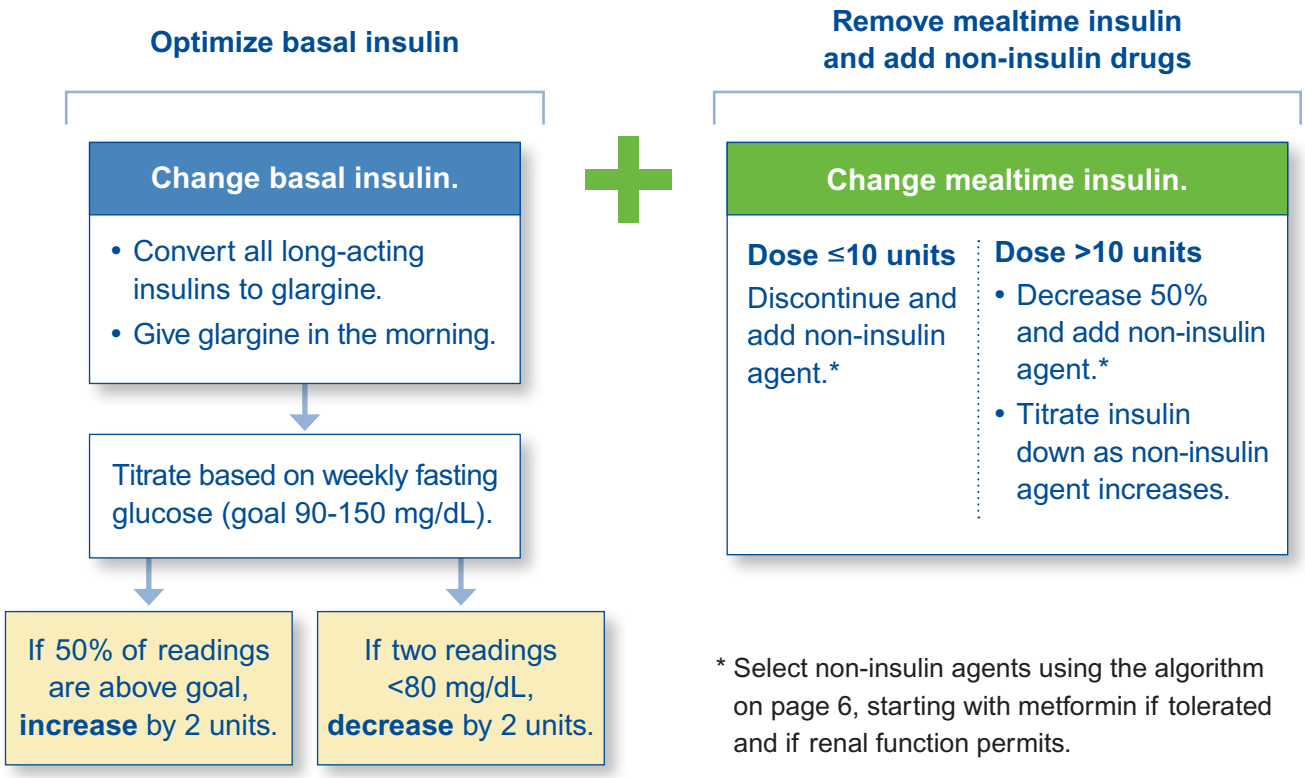
A slower, more gradual titration may be required for older adults to avoid hypoglycemia.

Preventing hypoglycemia in frail older adults

Reassessing insulin regimens can:

- avoid hypoglycemia, which can cause poorer outcomes in older adults.
- reduce treatment burden and the number of injections required each day.

FIGURE 9. A small pragmatic implementation study in older people with diabetes used an algorithm to simplify the insulin regimen.[4,13]



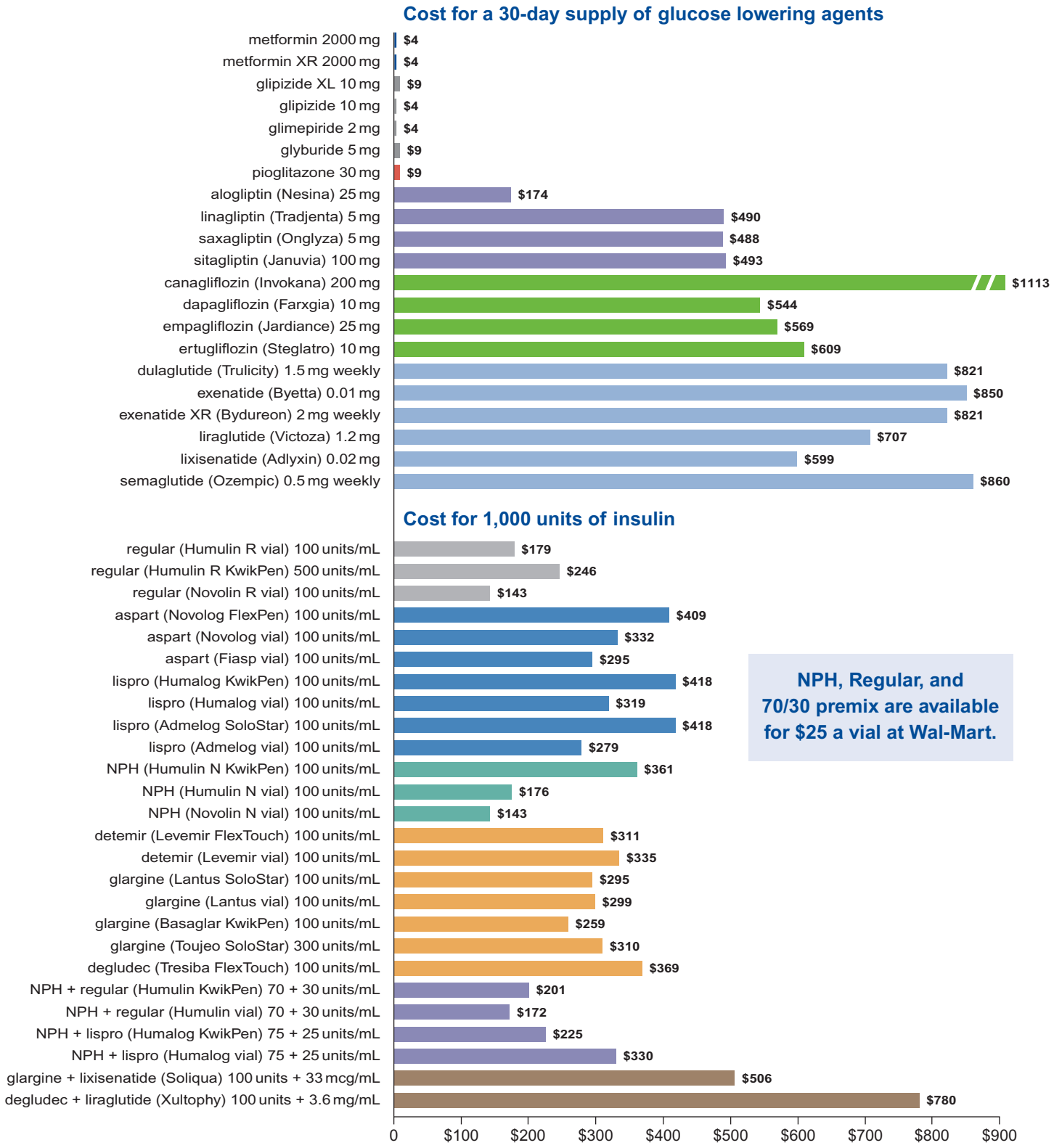
* Select non-insulin agents using the algorithm on page 6, starting with metformin if tolerated and if renal function permits.

Insulin simplification:[13]

- ✓ lowered time in hypoglycemia nearly 3-fold,
- ✓ reduced insulin injections from almost 4 injections to 1 a day, and
- ✓ did not change HbA1c control.

Costs

FIGURE 10. Price of agents used to treat diabetes



Prices from goodrx.com, January 2019. Listed doses are based on Defined Daily Doses by the World Health Organization and should not be used for dosing in all patients. All prices shown are for generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

Key messages

- **Diet and exercise** can slow the progression of prediabetes to type 2 diabetes, and can improve glucose control in patients with established diabetes.
- **Aim for a target HbA1c of 7% for most patients**, but modify the goal (to <8.5%) for many frail older patients in whom overtreatment can pose its own risks.
- **Use metformin as the initial treatment** for the vast majority of patients who require drug treatment.
- **Focus on adherence** before increasing doses or adding a new drug.
- **Intensify treatment with a second agent for patients who are not controlled on metformin.**
  - Choose a second-line treatment based on patient characteristics.
  - Prescribe a GLP-1 or SGLT-2 inhibitor for patients with ASCVD, heart failure, or CKD, based on trial data.
- **Add insulin promptly when other agents are not sufficient** to achieve HbA1c goal.
- In all patients with diabetes, **manage hypertension and hyperlipidemia** aggressively, and focus on smoking cessation when necessary.
- Continuously **promote weight control, exercise, and adherence to medications.**

More information is available at AlosaHealth.org/Diabetes.

References:

(1) Centers for Disease Control and Prevention. National diabetes statistic report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services;2017. **(2)** 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. **(3)** Diagnosed Diabetes. https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html. Accessed 26 Jan 2019. **(4)** American Diabetes Association. Standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S1-S193. **(5)** 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. **(6)** Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-657. **(7)** Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347-357. **(8)** Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311-322. **(9)** Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844. **(10)** Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(13):1228-1239. **(11)** Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):323-334. **(12)** 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. **(13)** Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of Insulin Regimen in Older Adults and Risk of Hypoglycemia. *JAMA Intern Med*. 2016;176(7):1023-1025.

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.

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