Pharmacologic Management of Patients with Diabetes in 2022

Wendy L. Wright,
DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP
Adult / Family Nurse Practitioner
Owner – Wright & Associates Family Healthcare
Owner – Wright & Associates Family Healthcare, Concord, NH
Owner – Partners in Healthcare Education, LLC

1

Disclosures

- Speaker Bureau:
  - Sanofi-Pasteur, Merck, Pfizer, AbbVie, Biohaven
- Consultant:
  - Sanofi-Pasteur, Merck, Pfizer, GlaxoSmithKline, Moderna, Seqirus, Bayer, Idorsia

Wright, 2022

2

Objectives

- Upon completion of this lecture, the participant will be able to:
  - Discuss the impact of diabetes mellitus in the United States
  - Discuss the non-pharmacologic and pharmacologic treatments for the patient with Type 2 diabetes
  - Compare/contrast pharmacologic options

Wright, 2022

3

Diabetes

- Group of metabolic diseases characterized by hyperglycemia
- Results from eight defects

- Decreased insulin secretion
- Inefficient glucose uptake (skeletal muscle)
- Increased hepatic glucose production
- Decreased incretin effect
- Increased glucagon secretion
- Increased free fatty acids
- Neurotransmitter dysfunction
- Increased glucose resorption

DeFronzo RA. Diabetes. 2009;58:773-795

Wright, 2022

4

Physiologic Abnormalities

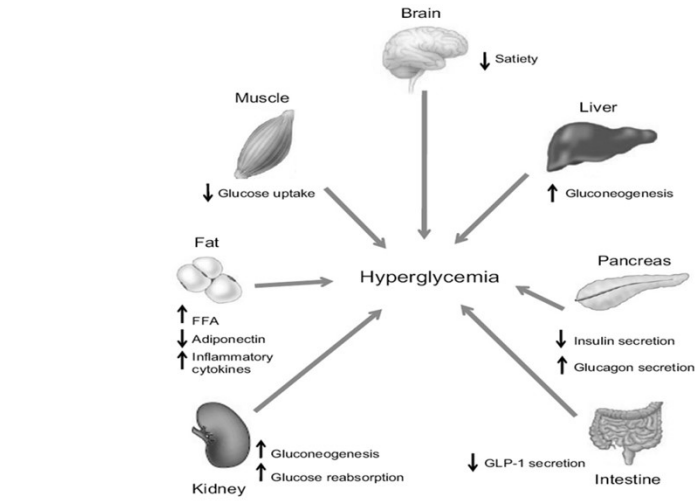


Figure 1 Multiorgan and tissue pathophysiology of type 2 diabetes.
Notes: Adapted with permission from DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773–795.[4]
Abbreviations: FFA, free fatty acids; GLP-1, glucagon-like peptide-1.

5

Statistics Regarding Prediabetes

- 88 million American adults—approximately 1 in 3—have prediabetes (2018)
- Approximately, 11% of individuals with prediabetes develop type 2 diabetes each year over a 3-year study
- Majority of individuals with prediabetes develop type 2 diabetes within 10 years

https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html
accessed 02-06-2021

6

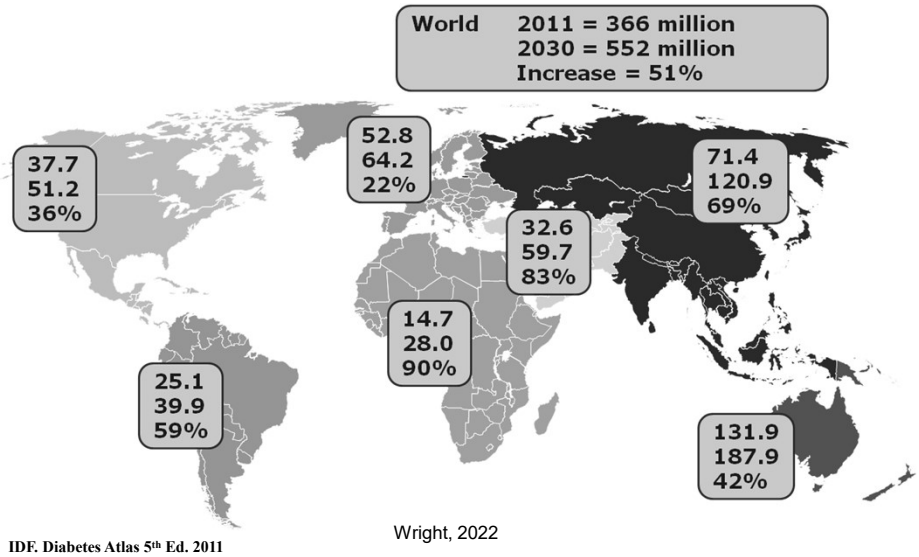
Statistics Regarding Diabetes

- In 2018, 34.2 million Americans, or 10.5% of the population, had diabetes (1 in 10 people)
- Increasing by 1 million people per year
- Cost: 1 in every 5 dollars spent in the United States is spent on diabetes care/costs
- In 2015, diabetes was the seventh leading cause of death in the U.S

https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html
accessed 02-06-2021

7

The Diabetes Epidemic: Global Projections, 2010–2030

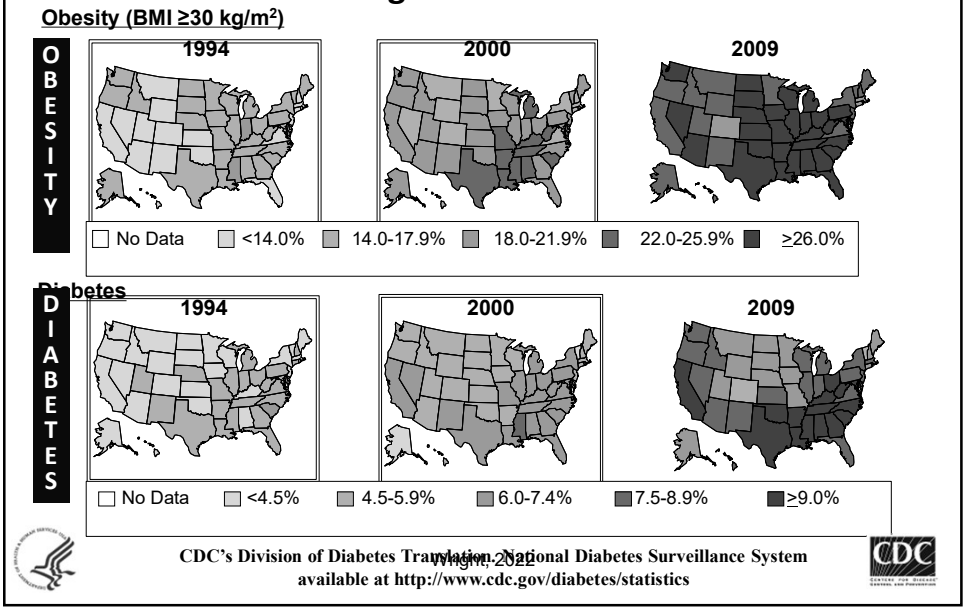


IDF. Diabetes Atlas 5th Ed. 2011

Wright, 2022

8

Age-adjusted Percentage of U.S. Adults with Obesity or Diagnosed Diabetes



CDC's Division of Diabetes Translation, National Diabetes Surveillance System
available at http://www.cdc.gov/diabetes/statistics

Wright, 2022

9

Race/Ethnicity

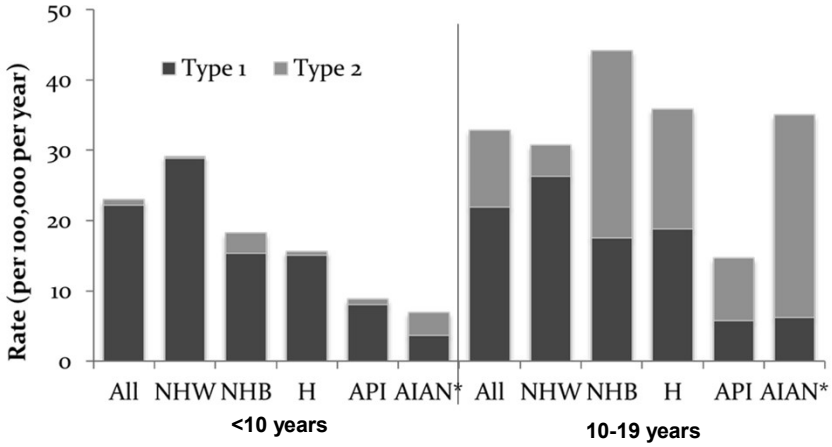
- **Race and ethnic differences in prevalence of diagnosed diabetes**
  - Non-Hispanic whites: 7.4 percent
  - Asian Americans: 8.0 percent
  - Hispanics: 12.1 percent
  - Non-Hispanic blacks: 12.7 percent
  - American Indians and Alaska Natives: 15.1 percent
-

https://www.medicalnewstoday.com/articles/318472#Diabetes-and-ethnicity accessed 01-02-2022

10

Q16. How is a comprehensive care plan established in children and adolescents?

Annual Incidence of DM in Youth



AI = American Indians; API = Asians/Pacific Islanders; DM = diabetes mellitus; H = Hispanics; NHB = non-Hispanic blacks; NHW = non-Hispanic whites.

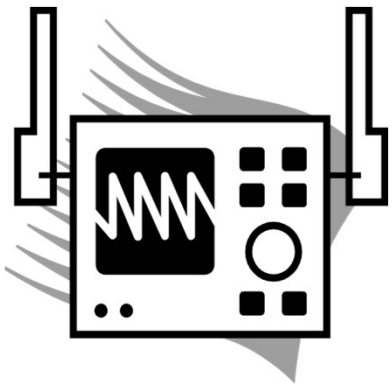
CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.

11

Diabetes and Cardiovascular Disease

7th leading cause of death in the United States

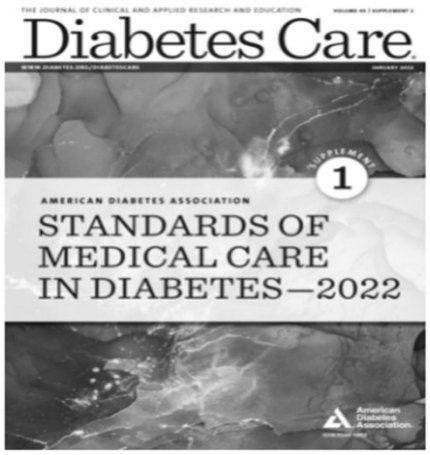
Majority of cardiovascular or cerebrovascular



https://www.cdc.gov/media/releases/2017/p0718-diabetes-report.html accessed 01-03-2019

12

Standards of Medical Care in Diabetes—2022



https://professional.diabetes.org/content-page/practice-guidelines-resources accessed 01-10-2022

13

Prediabetes:

(Impaired Fasting Glucose or Impaired Glucose Tolerance)

Wright, 2022

14

Testing for Prediabetes

TABLE 2.3 Criteria for Screening for Diabetes or Prediabetes in Asymptomatic Adults

1. Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], impaired glucose tolerance, or impaired fasting glucose]) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 35 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
6. People with HIV

American Diabetes Association; *Standards of Medical Care in Diabetes—2022* Abridged for Primary Care Providers. *Clin Diabetes* 1 January 2022; 40 (1): 10–38.

15

Recommendations: Prediabetes

- Screening for prediabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults
  - Testing should begin at age 35 years of age
  - Consider testing for prediabetes in asymptomatic adults of any age w/ BMI ≥25 kg/m2 or ≥23 kg/m2 (in Asian Americans) who have 1 or more additional risk factors for diabetes
- If tests are normal, repeat at a minimum of 3-year intervals
- A1C monitoring should be done at least once yearly

16

2015

- The BMI cut point for screening overweight or obese Asian Americans for prediabetes and type 2 diabetes was changed to 23 kg/m2 (vs. 25 kg/m2) to reflect the evidence that this population is at an increased risk for diabetes at lower BMI.

American Diabetes Association; *Standards of Medical Care in Diabetes—2022* Abridged for Primary Care Providers. *Clin Diabetes* 1 January 2022; 40 (1): 10–38.

17

CLASSIFICATION AND DIAGNOSIS OF DIABETES

Table 2.5—Criteria defining prediabetes*

FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; 2-h PG, 2-h plasma glucose. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

American Diabetes Association; *Standards of Medical Care in Diabetes—2022* Abridged for Primary Care Providers. *Clin Diabetes* 1 January 2022; 40 (1): 10–38.

18

Children and Screening

- Begin at 10 years of age in children at risk or at the onset of puberty, if earlier than 10 years
  - Repeat every 3 years, if normal

www.diabetes.org
www.aace.com

19

What Constitutes a Risk Factor in Children?

- Overweight (BMI>85th %tile for age and sex, weight for height >85th %tile, or weight >120% of ideal for height)
  - ***Plus => ONE risk factors***
    - Family history of type 2 diabetes in first- or second-degree relative
    - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
    - Signs of, or conditions associated with, insulin resistance including acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, small for gestational age at birth history in the child
    - Maternal history of DM or gestational DM

20

CLASSIFICATION AND DIAGNOSIS OF DIABETES

Table 2.2—Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S15-S33

21

Important to Remember

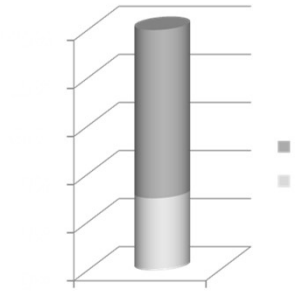
- Postprandial hyperglycemia is a significant contributor to A_1C levels, particularly at the lower end of A_1C's
  - For instance:
    - A_1C of 7.3% to 9.2%: postprandial glucose accounts for 50% of this number
    - $A_1C < 7.3\%$: postprandial glucose accounts for 70% of this number
    - Take away message – someone with an A_1C of 6.8% - look very closely at reducing postprandial glucose

Monnier L, Lapinski, H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26:881-885.

22

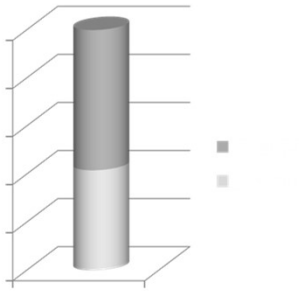
Treatment of Patient Based on A_IC

A1C is less than 7.3%



A1C <7.3%

A1C is 7.3% - 9.2%



A1C <7.3%

Monnier L, Lapinski, H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: Variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26:881-885.

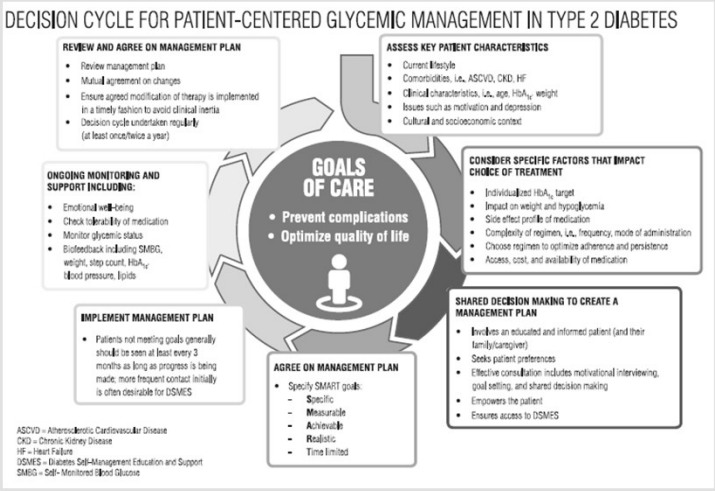
23

Multimodal Treatment

Wright, 2022

24

COMPREHENSIVE MEDICAL EVALUATION AND ASSESSMENT OF COMORBIDITIES

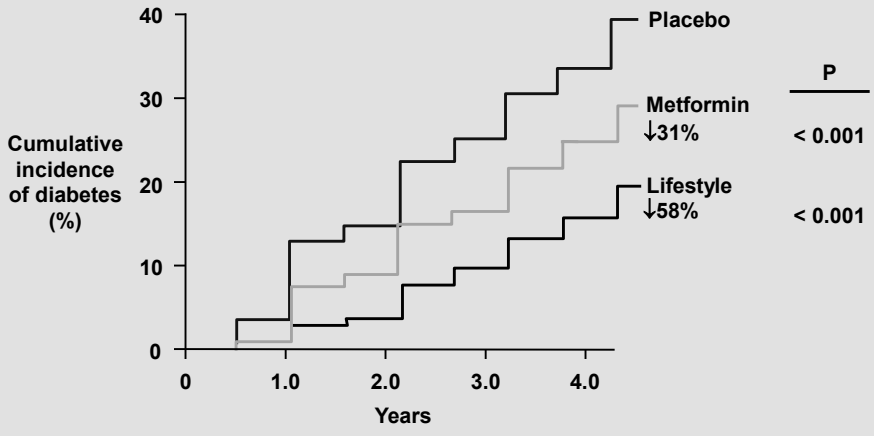


Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S40-S52

25

DPP: Benefit of diet/exercise or metformin on diabetes prevention in at-risk patients

N = 3234 with IFG/IGT without diabetes

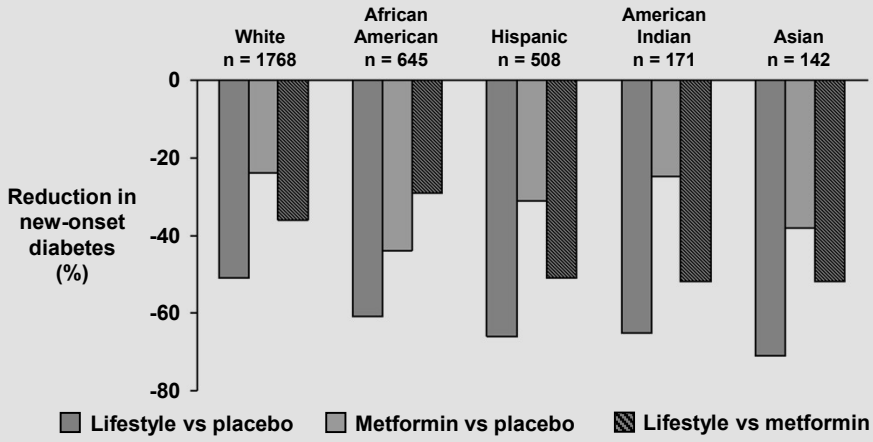


DPP Research Group. *N Engl J Med*. 2002;346:393-403.

26

DPP: Benefit of diet/exercise or metformin on diabetes by race/ethnicity

N = 3234 with IFG/IGT and without diabetes



DPP Research Group. *N Engl J Med*. 2002;346:393-403.

27

Recommendations: Prevention or Delay of T2DM

- Patients with prediabetes should be referred to an intensive diet and physical activity behavioral counseling program adhering to the tenets of the DPP targeting a loss of 7% of body weight, and should increase their moderate physical activity to at least 150 min/week. A

https://care.diabetesjournals.org/content/diacare/suppl/2020/12/09/44.Supplement_1.DC1/DC_44_S1_final_copyright_stamped.pdf accessed 02-06-2021

Wright, 2022

28

Recommendations: Prevention or Delay of T2DM

- Metformin therapy for prevention of type 2 diabetes should be considered in adults with prediabetes, especially those aged 25–59 years with BMI 35 kg/m2, higher fasting plasma glucose (e.g., 110 mg/dL), and higher A1C (e.g., 6.0%), and in women with prior GDM.

American Diabetes Association; *Standards of Medical Care in Diabetes—2022* Abridged for Primary Care Providers. *Clin Diabetes* 1 January 2022; 40 (1): 10–38.

Wright, 2022

29

Q2. How is prediabetes managed?

Medical and Surgical Interventions Shown to Delay or Prevent T2D

Intervention	Follow-up Period	Reduction in Risk of T2D (*P* value vs placebo)
Antihyperglycemic agents		
Metformin[1]	2.8 years	31% (*P*<0.001)
Acarbose[2]	3.3 years	25% (*P*=0.0015)
Pioglitazone[3]	2.4 years	72% (*P*<0.001)
Rosiglitazone[4]	3.0 years	60% (*P*<0.0001)
Weight loss interventions		
Orlistat[5]	4 years	37% (*P*=0.0032)
Phentermine/topiramate[6]	2 years	79% (*P*<0.05)
Bariatric surgery[7]	10 years	75% (*P*<0.001)

Lifestyle modification should be used with all pharmacologic or surgical interventions.

T2D, type 2 diabetes.

1. DPP Research Group. *N Engl J Med*. 2002;346:393-403. 2. STOP-NIDDM Trial Research Group. *Lancet*. 2002;359:2072-2077.
3. Defronzo RA, et al. *N Engl J Med*. 2011;364:1104-15. 4. DREAM Trial Investigators. *Lancet*. 2006;368:1096-1105.
5. Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161. 6. Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.
7. Sjostrom L, et al. *N Engl J Med*. 2004;351:2683-2693.

30

ADA Guidelines 2022

31

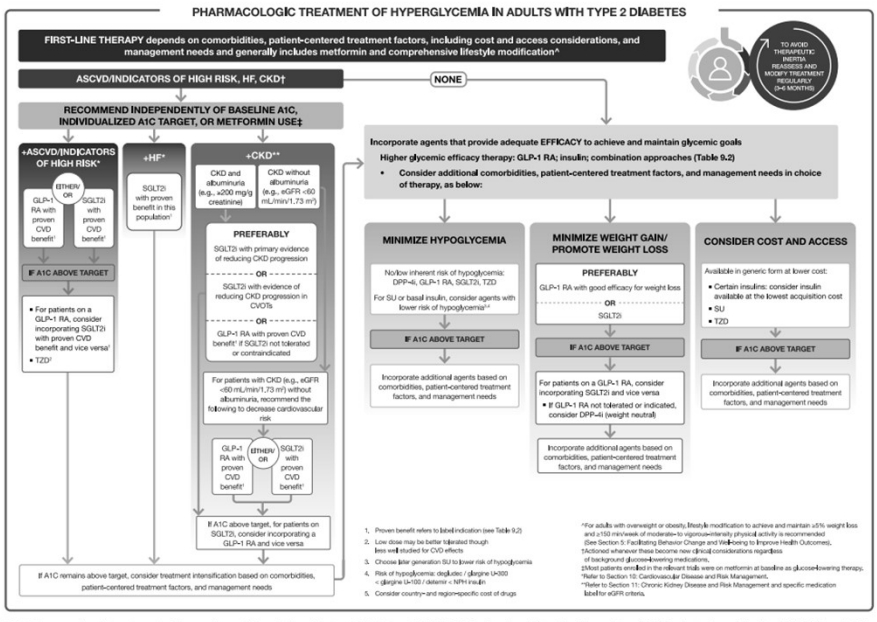


FIGURE 9.3 Pharmacologic treatment of hyperglycemia in adults with type 2 diabetes. 2022 ADA Professional Practice Committee (PPC) adaptation of Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701 and Buse JB, Wexler DJ, Tsapas A, et al. Diabetes Care 2020;43:487–493. For appropriate context, see Figure 4.1. The 2022 ADA PPC adaptation emphasizes incorporation of therapy rather than sequential add-on, which may require adjustment of current therapies. Therapeutic regimen should be tailored to comorbidities, patient-centered treatment factors, and management needs. Refer to sections 10 and 11 in the complete 2022 Standards of Care for detailed discussions of CVD and CKD risk management. CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

32

Table 9.1—Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of CKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m²	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin, dapagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• Should be discontinued before any scheduled surgery to avoid potential risk for DKA • DKA risk in all agents, rare in T2D • Risk of bone fractures (canagliflozin) • Genitourinary infections • Risk of volume depletion, hypotension • T1DS, rhabdomyolysis • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral, semaglutide once weekly, dulaglutide Benefit: dulaglutide, liraglutide†, semaglutide†	Neutral	High	SQ and semaglutide	Benefit on renal end points in CVOTs, driven by cardiovascular outcomes (liraglutide, semaglutide, dulaglutide	• Dulaglutide, liraglutide, and semaglutide avoid for eGFR <30 mL/min/1.73 m² • No dose adjustment for dulaglutide, liraglutide, semaglutide • Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function. Consider reporting severe adverse GI reactions when initiating or increasing dose of therapy.	• **FDA Black Box:** Risk of thyroid C-cell tumors (liraglutide, semaglutide); balance not determined (dulaglutide, **albiglutide, exenatide extended-release, semaglutide**) • GI side effects common (nausea, vomiting, diarrhea) • Injection site reactions • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	• Renal dose adjustment required (alogliptin, saxagliptin, sitagliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure (pioglitazone, rosiglitazone) • Thrombotic/edema, heart failure • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • T1DS, rhabdomyolysis (pioglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide not recommended • Glipizide and glimepiride initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin: Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ, inhaled	Neutral	• Lower insulin dose required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin: Analogs						High	SQ			

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HF, heart failure; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2D, type 2 diabetes. *For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA-approved for cardiovascular disease benefit. ‡FDA-approved for heart failure indication. §FDA-approved for chronic kidney disease indication.

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021. Diabetes Care* 2021;44(Suppl. 1):S111-S124

33

Table 9.2—Median monthly (30-day) AWP and NADAC of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Median NADAC (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	850 mg (IR) 1,000 mg (IR) 1,000 mg (ER)	$108 ($6, $109) $87 ($4, $88) $242 ($242, $7,214)	$3 $2 $188 ($188, $572)	2,550 mg 2,000 mg 2,000 mg
Sulfonylureas (2nd generation)	• Glimepiride • Glipizide • Glyburide	4 mg 10 mg (IR) 10 mg (XL) 6 mg (micronized) 5 mg	$74 ($71, $198) $75 ($67, $97) $48 $52 ($48, $71) $93 ($63, $103)	$4 $5 $11 $10 $11	8 mg 40 mg (IR) 20 mg (XL) 12 mg (micronized) 20 mg
Thiazolidinediones	• Pioglitazone • Rosiglitazone	45 mg 4 mg	$348 ($283, $349) $407	$5 $330	45 mg 8 mg
α-Glucosidase inhibitors	• Acarbose • Miglitol	100 mg 100 mg	$106 ($104, $106) $241	$28 $311	300 mg 300 mg
Meglitinides (glinides)	• Nateglinide • Repaglinide	120 mg 2 mg	$155 $878 ($162, $897)	$31 $38	360 mg 16 mg
DPP-4 inhibitors	• Alogliptin • Saxagliptin • Linagliptin • Sitagliptin	25 mg 5 mg 5 mg 100 mg	$234 $530 $555 $568	$175 $424 $444 $456	25 mg 5 mg 5 mg 100 mg
SGLT2 inhibitors	• Ertugliflozin • Dapagliflozin • Empagliflozin • Canagliflozin	15 mg 10 mg 25 mg 300 mg	$354 $621 $627 $622	$284 $496 $501 $499	15 mg 10 mg 25 mg 300 mg
GLP-1 RAs	• Exenatide (extended release) • Exenatide • Dulaglutide • Semaglutide • Liraglutide • Lixisenatide	2 mg powder for suspension or pen 10 µg pen 4.5/0.5 mL pen 1 mg pen 14 mg (tablet) 18 mg/3 mL pen 300 µg/3 mL pen	$882 $752 $957 $973 $927 $1,161 $774	$706 $720 $766 $779 $738 $930 N/A	2 mg** 20 µg 4.5 mg** 1 mg** 14 mg 1.8 mg 20 µg
Bile acid sequestrant	• Colesevelam	625 mg tabs 3.75 g suspension	$710 ($674, $712) $804	$105 $318	3.75 g 3.75 g
Dopamine-2 agonist	• Bromocriptine	0.8 mg	$960	$772	4.8 mg
Amylin mimetic	• Pramlintide	120 µg pen	$2702	$2,097	120 µg/injection††

AWP, average wholesale price; DPP-4, dipeptidyl peptidase 4; ER and XL, extended release; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IR, immediate release; max, maximum; min, minimum; N/A, data not available; NADAC, National Average Drug Acquisition Cost; SGLT2, sodium–glucose cotransporter 2. *Calculated for 30-day supply [AWP [62] or NADAC [63] unit price × number of doses required to provide maximum approved daily dose × 30 days]; median AWP or NADAC listed alone when only one product and/or price. †Utilized to calculate median AWP and NADAC (min, max); generic prices used, if available commercially. **Administered once weekly. ††AWP and NADAC calculated based on 120 mg three times daily.

Median monthly cost of maximum approved daily dose of noninsulin glucose-lowering agents in the U.S.

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021. Diabetes Care* 2021;44(Suppl. 1):S111-S124

34

Table 9.3—Median cost of insulin products in the U.S. calculated as AWP (62) and NADAC (63) per 1,000 units of specified dosage form/product

Insulins	Compounds	Dosage form/product	Median AWP (min, max)*	Median NADAC*
Rapid-acting	• Lispro follow-on product	U-100 vial	$157	$125
		U-100 prefilled pen	$202	$161
	• Lispro	U-100 vial	$165†	$132†
		U-100 cartridges	$408	$326
		U-100 prefilled pen	$212†	$170†
		U-200 prefilled pen	$424	$339
	• Lispro-aabc	U-100 vial	$330	N/A
		U-100 prefilled pen	$424	N/A
		U-200 prefilled pen	$424	N/A
	• Glulisine	U-100 vial	$341	$272
		U-100 prefilled pen	$439	$350
	• Aspart	U-100 vial	$174†	$139†
		U-100 cartridges	$215	$344
		U-100 prefilled pen	$223†	$179†
	• Aspart ("faster acting product")	U-100 vial	$347	$278
		U-100 cartridge	$430	N/A
		U-100 prefilled pen	$447	$356
	• Inhaled insulin	Inhalation cartridges	$924	$606
Short-acting	• human regular	U-100 vial	$165††	$133††
Intermediate-acting	• human NPH	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
Concentrated human regular insulin	• U-500 human regular insulin	U-500 vial	$178	$143
		U-500 prefilled pen	$229	$183
Long-acting	• Glargine follow-on product	U-100 prefilled pen	$190 (118, 261)	$210
		U-100 vial	$190 (118, 261)	N/A
	• Glargine	U-100 vial; U-100 prefilled pen	$340	$272
		U-300 prefilled pen	$340	$272
	• Detemir	U-100 vial; U-100 prefilled pen	$370	$296
	• Degludec	U-100 vial; U-100 prefilled pen; U-200 prefilled pen	$407	$325
Premixed insulin products	• NPH/regular 70/30	U-100 vial	$165††	$133††
		U-100 prefilled pen	$208	$167
	• Lispro 50/50	U-100 vial	$342	$273
		U-100 prefilled pen	$424	$338
	• Lispro 75/25	U-100 vial	$342	$274
		U-100 prefilled pen	$212	$340
	• Aspart 70/30	U-100 vial	$180	$144
		U-100 prefilled pen	$224	$179
Premixed insulin/GLP-1 RA products	• Glargine/Lixisenatide	100/33 prefilled pen	$589	$471
	• Degludec/Liraglutide	100/3.6 prefilled pen	$874	$701

AWP, average wholesale price; GLP-1 RA, glucagon-like peptide 1 receptor agonist; N/A, not available; NADAC, National Average Drug Acquisition Cost. *AWP or NADAC calculated as in **Table 9.2**. †Generic prices used when available. ††AWP and NADAC data presented do not include vials of regular human insulin and NPH available at Walmart for approximately $25/vial; median listed alone when only one product and/or price.

Median cost of insulin products in the U.S. calculated as AWP and NADAC per 1,000 units of specified dosage

Pharmacologic Approaches to Glycemic Management: *Standards of Medical Care in Diabetes - 2021. Diabetes Care* 2021;44(Suppl. 1):S111-S124

35

Biguanides

- **Biguanides decrease hepatic glucose production and increase insulin-mediated peripheral glucose uptake.**
- **Efficacy**
  - **Decrease fasting plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)**
- **Other Effects**
  - **Diarrhea and abdominal discomfort**
  - **Lactic acidosis**
  - **Cause small decrease in LDL cholesterol level and triglycerides**
  - **No specific effect on blood pressure**
  - **No weight gain, with possible modest weight loss**
  - **B12 deficiency**
- **Medications in this Class: metformin, metformin hydrochloride extended release**

36

Metformin Updates

- **Metformin is contraindicated in patients with an eGFR below 30 mL/minute**
- **Starting metformin in patients with an eGFR between 30 to 45 mL/minute is not recommended**
- **In patients taking metformin whose eGFR later falls below 45 mL/minute, assess the benefits and risks of continuing treatment**
- **Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30-60 mL/minute; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast.**
- **GFR: 30 – 35 mL/min: maximum dosage 1000 mg daily**

Citation: US Food and Drug Administration. Metformin-containing drugs: Drug safety communication – revised warnings for certain patients with reduced kidney function. *FDA Web site*. April 8, 2016.**www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm494829.htm**. Accessed April 11, 2016.

37

Sulfonylureas

- Sulfonylureas increase endogenous insulin secretion
- Efficacy
  - Decrease fasting plasma glucose 60-70 mg/dl (3.3-3.9 mmol/L)
  - Reduce A1C by 1.0-2.0%
- Other Effects
  - Hypoglycemia
  - Weight gain
  - No specific effect on plasma lipids or blood pressure
  - Cost is minimal; one of the least expensive classes of medication
- Medications in this Class:
  - Second generation sulfonylureas: glyburide, glimepiride, glipizide

38

Thiazolidinediones

- Thiazolidinediones decrease insulin resistance by making muscle and adipose cells more sensitive to insulin. They also suppress hepatic glucose production.
- Efficacy
  - Decrease fasting plasma glucose ~35-40 mg/dl (1.9-2.2 mmol/L)
  - Reduce A1C ~0.5-1.0%
  - 6 – 12 weeks for maximum effect

39

Thiazolidinediones

- Other Effects
  - Weight gain, edema
  - Hypoglycemia (if taken with insulin or agents that stimulate insulin release)
  - Contraindicated in patients with abnormal liver function or CHF
  - Improves HDL cholesterol and plasma triglycerides; usually LDL neutral
- Medications in this Class: pioglitazone, rosiglitazone, troglitazone - taken off market due to liver toxicity

40

GLP-1R Agonists

- GLP-1R Agonists
- Mechanism of action:
  - lowers blood glucose by increasing insulin secretion, suppresses glucagon secretion and slows gastric emptying
  - Because it only has this effect in the presence of elevated blood glucose levels, it does not tend to increase the risk of hypoglycemia on its own

41

GLP-1R Agonists

- Average Efficacy:
  - 0.8% - 1.1% decrease in A1C from baseline
  - Weight loss (1-3 kg)
- Precautions:
  - Pancreatitis
  - Thyroid C-cell carcinomas (medullary thyroid carcinoma)
  - Hypoglycemia
  - Category C
  - Gastroparesis

42

Options

- 6 options
  - Dulaglutide (once weekly)*CVD;
  - Exenatide (twice daily)
  - Exenatide ER (once weekly)
  - Liraglutide (once daily)*CVD
  - Lixisenatide (once daily)
  - Semaglutide (once weekly)*CVD;
  - Semaglutide (oral daily)

43

Recent Studies

- No increased risks of retinopathy when using the GLP-1 receptor agonists

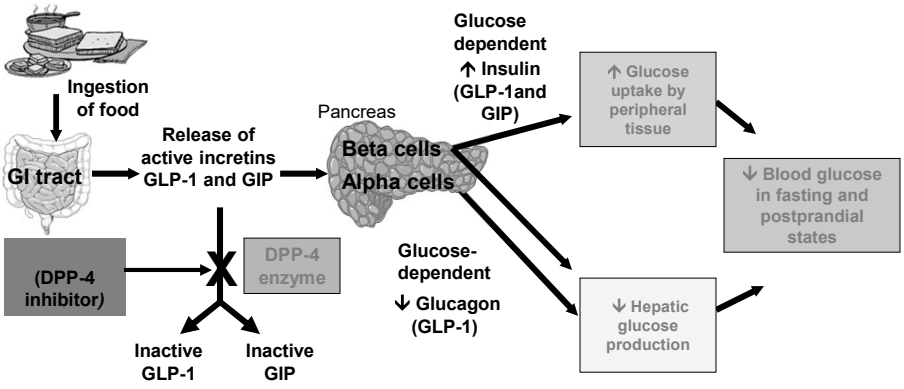
44

DPP-4 Inhibitors

- DPP-4 Inhibitors
- Mechanism of action:
  - Blocks enzyme which breaks down GLP-1 and GIP, allowing these two incretins to:
    - Increase insulin production in response to increased glucose
    - Reduce glucagon production
    - Reduce hepatic glucose production
- Four options:
  - Sitagliptin
  - Saxagliptin*
  - Linagliptin
  - Alogliptin*

45

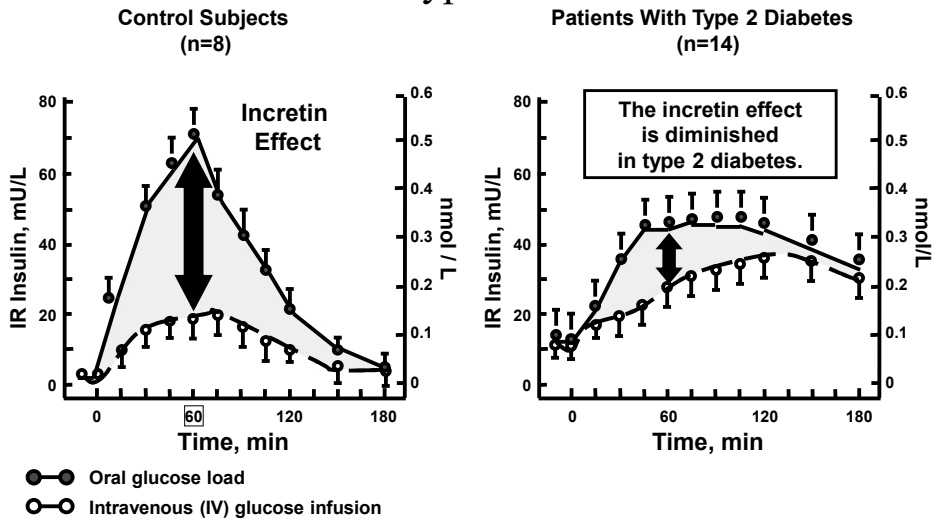
Mechanism of Action of DPP-4



- Incretin hormones GLP-1 and GIP are released by the intestine throughout the day, and their levels ↑ in response to a meal.

46

The Incretin Effect in Subjects Without and With Type 2 Diabetes



Adapted from Nauck M et al. *Diabetologia*. 1986;29:46–52. Copyright © 1986 Springer-Verlag. Permission pending.

47

DPP-4 Inhibitors

- A1C reduction:
  - 0.5% - 0.8%
  - Best with postprandial blood sugar reduction
- Precautions:
  - Reduce dosage in setting of CKD (except linagliptin)
  - Drug/drug interactions (saxagliptin)

Wright, 2022

48

Sodium Glucose Co-Transporter 2 Inhibitors

- Mechanism of action
  - Sodium glucose co-transporter 2 (SGLT2) inhibitor for the treatment of patients with type 2 diabetes.
  - The kidneys of people with type 2 diabetes reabsorb greater amounts of glucose back into the body compared to non-diabetic people, which may contribute to elevated glucose levels.
  - Blocks the reabsorption of glucose by the kidney, increasing glucose excretion and lowering blood glucose levels.

http://www.prnewswire.com/news-releases/phase-3-results-show-canagliflozin-as-add-on-therapy-to-metformin-and-pioglitazone-significantly-lowers-blood-sugar-levels-in-adult-patients-with-type-2-diabetes-178048581.html accessed 12-28-2012

49

SGLT2

- Four options
  - Canagliflozin *CVD; **CKD
  - Dapagliflozin*CHF, **CKD
  - Empaglifozin*CVD, **CHF
  - Ertugliflozin

50

Warnings SGLT2

- Hundreds of cases of DKA reported to FDA
  - Per FDA: "Ketoacidosis is not typically observed in patients with type 2 diabetes, the FDA notes, and the DKA case presentations were "atypical in that glucose levels were only mildly elevated at less than 200 mg/dL in some reports"
- Urosepsis and pyelonephritis
- Lower extremity amputations
- Fournier's gangrene

http://www.medscape.com/viewarticle/844754 accessed 05-27-2015

51

Combination Medications

- DPP4 Inhibitors with Biguanide
- DPP4 Inhibitor with TZD
- Glinide with Biguanide
- SGLT2 with Biguanide
- SGLT2 with DPP4 Inhibitor
- Sulfonylurea with Biguanide
- TZD with Biguanide
- TZD with Sulfonylurea

52

Insulins

53

Case Study 2 - John

- Age: 55 years
- A1C: 8.5%
- Weight: 220 pounds
- Medications:
  - Glimepiride 4 mg once daily
  - Sitagliptin/metformin 50/1000 mg 1 pill two times daily
  - Atorvastatin 40 mg 1 tablet daily
  - Aspirin 81 mg once daily
  - Lisinopril/HCTZ 20/25 mg 1 pill once daily

54

Rough Calculation

- How much insulin does someone need?
- Weight in kg/2 = total dose of insulin
  - Of total dose, 50%-60% basal
  - 40% – 50% rapid acting

55

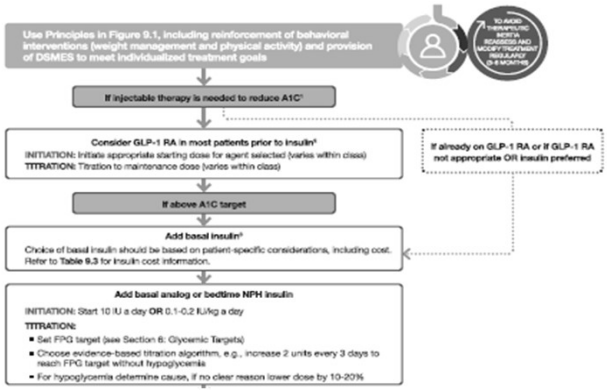
Introduction of Insulin

Insulin Type	Onset	Peak	Duration
Rapid Acting (Humalog, NovoLog, Apidra, Fiasp, Admelog)	10 – 15 minutes	1 – 2 hours	3 – 5 hours
Short Acting (Regular; Humulin R and Humulin N)	½ - 1 hour	2 – 4 hours	4 – 8 hours
Intermediate Acting (Humulin N or Novolin N)	1-3 hours	4 – 12 hours	10 – 18 hours
Long-Acting Analogues Glargine (Lantus, Basaglar, Toujeo) Detemir (Levemir) Degludec (Tresiba)	 2-3 hours 1 hour	 None None	 24 hours+ Up to 24 hours

56

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Intensifying to injectable therapies (1 of 2)

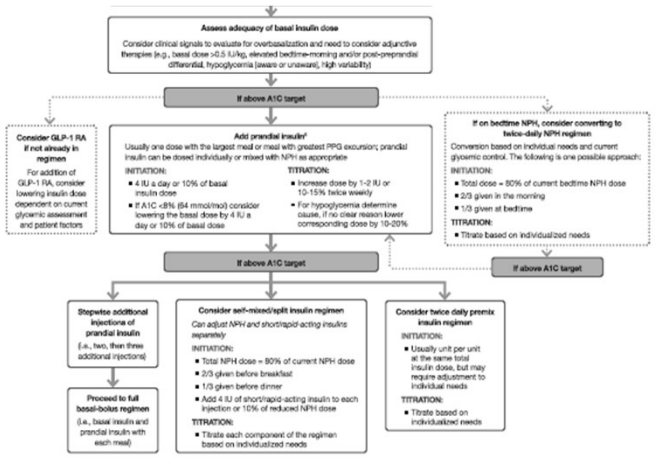


Pharmacologic Approaches to Glycemic Management:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S111-S124

57

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Intensifying to injectable therapies (2 of 2)



Pharmacologic Approaches to Glycemic Management:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S111-S124

58

How to Initiate Insulin on John

- Start with Long-acting at hs
  - 0.2 Units/kg at bedtime
  - 100 kg patient = 220 pounds
  - 0.2 units = 20 units at hs
- Once above 50 units per day, may find two times daily dosing works best
- Rapid acting – can be added immediately or later

59

How to Use NPH/Regular

- Calculate total dosage
- If you must use NPH and Regular insulin due to cost (60/40 am to pm ratio)
  - Morning dosage
    - TDD x 0.4 = am NPH dosage
    - TDD x 0.2 = am Regular dosage
  - PM dosage
    - TDD x 0.2 = pm NPH dosage
    - TDD x 0.2 = pm Regular dosage

60

Insulin/Carb Ratio

- 1 unit of rapid acting insulin covers 10 – 20 units of carbohydrates
- 1 unit of insulin lowers glucose about 50 mg/dL
- How do you figure what ratio to use?
- One method:

Weight (lbs)	Approx. I:C Ratio
<60	1:30
60-80	1:25
81-100	1:20
101-120	1:18
121-140	1:15
141-170	1:12
171-200	1:10
201-230	1:8
231-270	1:6
>270	1:5

http://integrateddiabetes.com/Articles/insu/carb%20ratio%20article%20for%20mendosa.pdf accessed 01-03-2019

61

Self-Monitoring Advice

- 2013 guidelines have modified these recommendations
  - Individualize recommendations
  - Those on intensive insulin therapy should:
    - Test at least before meals, occasionally after eating, at bedtime, before exercise or critical tasks such as driving, when low blood glucose is suspected, and after treating low blood glucose to ensure normoglycemia has been reached

Diabetes Care. 2013;36:S1-S110, e1-e4

62

Glucose Monitoring: Recommendations

- Most patients using intensive insulin regimens (multiple-dose insulin or insulin pump therapy) should perform SMBG: B
  - Prior to meals and snacks
  - At bedtime
  - Occasionally postprandially
  - Prior to exercise
  - When they suspect low blood glucose
  - After treating low blood glucose until they are normoglycemic
  - Prior to critical tasks such as driving

Glycemic Targets:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S55-S64

Wright, 2022

63

A1C Testing: Recommendations

- Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). E
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. E
- Point-of-care testing for A1C provides the opportunity for more timely treatment changes. E

https://care.diabetesjournals.org/content/diacare/suppl/2020/12/09/44.Supplement_1.DC1/DC_44_S1_final_copyright_stamped.pdf accessed 02-06-2021

Wright, 2022

64

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

3. ANTI-HYPERGLYCEMIC THERAPY

- **Glycemic targets**
  - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)
  - **Individualization** is key:
  - ➢ Tighter targets (6.0 - 6.5%) - younger, healthier
  - ➢ Looser targets (7.5 - 8.0%$^{+}$) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of pri

65

Goals for A1C

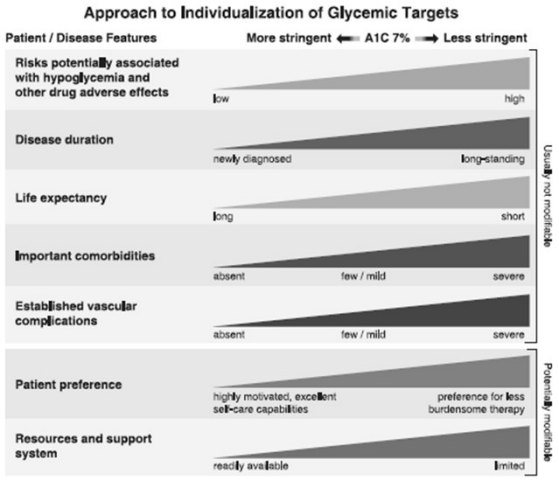
- More stringent HbA1c targets (e.g., 6.0– 6.5%) might be considered in select patients
  - Short disease duration, long life expectancy, no significant CVD if this can be achieved without significant hypoglycemia
- Conversely, less stringent HbA1c goals e.g., 7.5–8.0% or even slightly higher are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain

http://professional.diabetes.org/admin/UserFiles/Position%20Statement%20ADA_EASD_2012.full.pdf accessed 12-30-2012

Wright, 2022

66

GLYCEMIC TARGETS



Glycemic Targets:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S73-S84

67

Glycemic Recommendations for Nonpregnant Adults with Diabetes

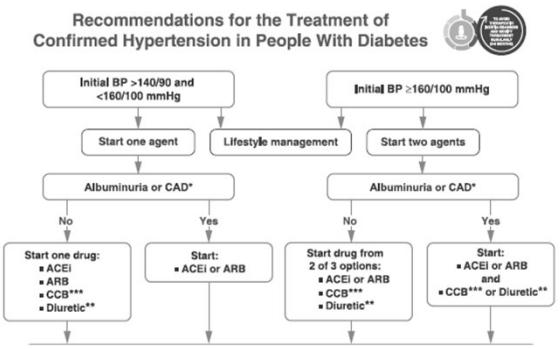
A1C	<7.0%* (<53 mmol/mol)
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)

* Goals should be individualized.
† Postprandial glucose measurements should be made 1–2 hours after the beginning of the meal.

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

68

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

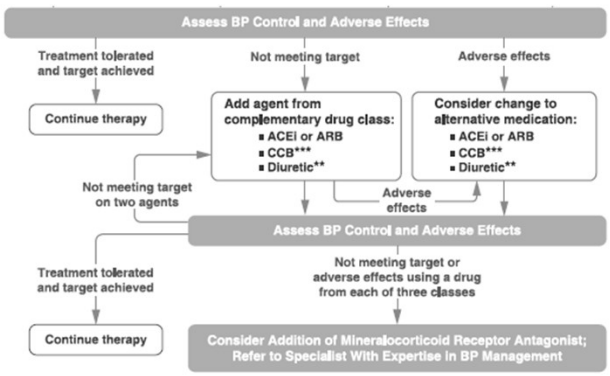


Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes (1 of 2)

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S111-S150

69

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT



Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes (2 of 2)

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S111-S150

70

BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

71

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

Statin Treatment—Primary Prevention

10.19 For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease, use moderate-intensity statin therapy in addition to lifestyle therapy. A

10.20 For patients with diabetes aged 20–39 years with additional atherosclerotic cardiovascular disease risk factors, it maybe reasonable to initiate statin therapy in addition to lifestyle therapy. C

10.21 In patients with diabetes at higher risk, especially those with multiple atherosclerotic cardiovascular disease risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy. B

10.22 In adults with diabetes and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more. C

72

Recommendations: Antiplatelet Agents

- Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2021. Diabetes Care 2021;44(Suppl. 1):S111-S150

Wright, 2022

73

Immunization: Recommendations

- Provide routinely recommended vaccinations for children and adults with diabetes by age. C
- Annual vaccination against influenza is recommended for all people ≥6 months of age, including those with diabetes. C
- Administer 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes aged 19-59 years. C
- Consider administering 3-dose hepatitis B vaccine to unvaccinated adults with diabetes ages ≥ 60 years. C

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S28-S37

Wright, 2022

74

Immunization: Recommendations (2)

- Vaccination against pneumococcal disease, including pneumococcal pneumonia, with 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for children before age 2 years.
- People with diabetes ages 2-64 years should also receive 23-valent pneumococcal polysaccharide vaccine (PPSV23).
- At age ≥65 years, regardless of vaccination history, additional PPSV23 vaccination is necessary. C

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S28-S37

Wright, 2022

75

Covid Vaccine

- Two dose series plus booster shot are important to those with diabetes

Wright, 2022

76

Let's Summarize

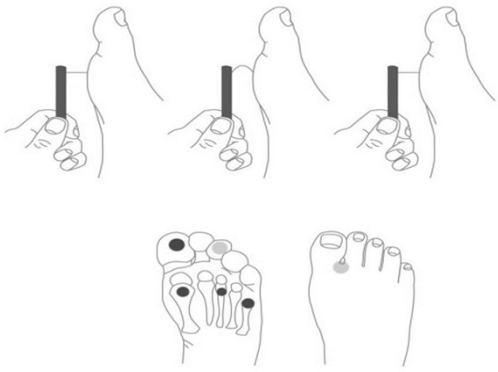
- A: A1C, aspirin (if appropriate)
- B: blood pressure control
- C: cholesterol management, Lipid annually, creatinine, GFR, urine microalbumin
- D: diet
- E: dilated eye examination yearly
- F: monofilament and vibratory/position sense, ankle reflex (or similar) annually
- G: goals reviewed at every visit
- I: immunizations

Wright, 2022

77

Foot Care: Recommendations (5)

- To perform the 10-g monofilament test, place the device perpendicular to the skin; Apply pressure until monofilament buckles.
- Hold in place for 1 second & release.
- The monofilament test should be performed at the highlighted sites while the patient's eyes are closed.



Boulton A, Armstrong D, Albert, S et. al. Comprehensive Foot Examination and Risk Assessment. Diabetes Care. 2008; 31: 1679-1685

Wright, 2022

78

Thank you for your time and attention.

Wendy L. Wright,
DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP
WendyARNP@aol.com

79