Management of Adult Diabetes Mellitus
Clinical Practice Guideline
MedStar Health

"These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient's primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication, but should be used with the clear understanding that continued research may result in new knowledge and recommendations".

This clinical practice guideline is based on Standards of Medical Care for Diabetes-2018 found in Diabetes Care Volume 41, Supplement 1, January 2018. MedStar Health Ambulatory Best Practices Committee endorses this guideline. http://diabetesed.net/wp-content/uploads/2017/12/2018-ADA-Standards-of-Care.pdf

Introduction

The prevalence of diabetes in adults is estimated to be 5.8 to 12.9 percent of the United States adult population. Some estimates report that more health care resources are spent on diabetes than any other health condition. In addition to the economic impact, medical complications from diabetes impact quality of life**.**

General Principles

Hyperglycemia is the pathognemonic feature of all forms of diabetes. Treatment aimed at lowering blood glucose levels is mandated by the following proven benefits:

1. The danger of acute decompensation due to diabetic ketoacidosis or hyperosmolar hyperglycemic non-ketotic syndrome with their accompanying morbidity and mortality is markedly reduced.
2. The risk of blurred vision, polyuria, polydipsia, fatigue, weight loss with polyphagia, vaginitis or balanitis, days missed from work, emergency room visits and hospital admissions may be reduced.
3. The risks of development or progression of diabetic retinopathy, nephropathy, and neuropathy are all greatly decreased. These complications may even be prevented by early normalization of metabolic status.
4. Targeted blood glucose control has been demonstrated to be associated with a less atherogenic lipid profile and fewer macrovascular events.

Strategies for Improving Care from the ADA Guideline

Recommendations

●A patient-centered communication style that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care should be used.

●Treatment decisions should be founded on evidence-based guidelines that are tailored to individual patient preferences, prognoses, and comorbidities.

●Care should be aligned with components of the Chronic Care Model (CCM) to ensure productive interactions between a prepared proactive practice team and an informed patient.

Initial Approval Date and Reviews:	**Most Recent Revision and Approval Date: May 2018**	**Next Scheduled Review Date:**
3/ 2011, 7/ 2013, 3/2014, 5/ 2015, 5/ 2016, 5/ 2017. 5/2018		May 2019 Ambulatory Best Practice Condition: Diabetes Mellitus

● Care systems should support team-based care, community involvement, patient registries and decision support tools to meet patient needs.
●Treatment programs include the following: self monitoring of blood glucose (SMBG), meal planning, physical activity, when and how to take their medication(s), information on the prevention and treatment of hypoglycemia as well as other acute and chronic complications, sick day protocol, when to call their doctor or go to the emergency department
●Address psychosocial issues in all aspects of care including self-management, mental health, language barriers, complications, comorbidities, food insecurity, housing stability, financial barriers and life-stage considerations

PREDIABETES- Patients with a predisposition to diabetes (prediabetes) are individuals with impaired fasting glucose (IFG of 100/mg/dL (5.6mmol/L) to 125 mg/dL (6.9 mmol/L)), impaired glucose tolerance (IGT: 2-h PG in the 75-g OGTT 140 mg/dL (7.8mmol/L) to 199 mg/dL (11.0 mmol/L)) or an A1C of 5.7-6.4%. Some of these patients already have the characteristic microvascular changes associated with diabetes. Early identification of individuals with pre-diabetes will provide opportunities for lifestyle management and potentially prevent complications related to diabetes.

I. Screening: Targeted screening for prediabetes is recommended for the populations at high risk for development of diabetes. (see "Screening for Diabetes" section)

II. Treatment:

- Lifestyle modification is the fundamental treatment and should be reinforced at every visit
- Physical activity equivalent to at least 150 minutes (30 minutes on most days of the week) of moderate physical activity per week such as walking.
- Weight loss equivalent to 7% of body weight, reducing caloric intake while maintaining a healthful eating pattern is recommended to promote and maintain weight loss.
- Limit or avoid intake of sugar-sweetened beverages (from any caloric sweetener including high-fructose corn syrup and sucrose) to reduce risk for weight gain and worsening of cardiometabolic risk profile. Individuals at high risk for type 2 diabetes should be encouraged to achieve the U.S. Department of Agriculture (USDA) recommendation for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake).
- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m2, age <60 years and women with prior gestational diabetes.
- Monitoring for the development of diabetes in those with prediabetes should be performed every year.
- Screening and treatment of modifiable risk factors for CVD is suggested

Medicare will cover diabetes prevention programs for prediabetics

III. Goals of Management- individuals with prediabetes should have the same lipid and BP goals as those with Diabetes.

- Thyroid palpation
- Skin examination (for acanthosis nigricans and insulin injection sites)
- Comprehensive foot examination
    - Inspection
    - Palpation of dorsalis pedis and posterior tibial pulses
    - Presence/absence of patellar and Achilles reflexes
    - Determination of proprioception, vibration, and monofilament sensation
    - All patients with insensate feet, foot deformities, or a history of foot ulcers should have their feet examined at every visit.

Laboratory evaluation

- A1C, if results not available within past 3 months
- If not performed/available within past year
    - Fasting lipid profile, including total, LDL, HDL cholesterol and triglycerides
    - Liver function tests
    - Test for urine albumin excretion with spot urine albumin-to-creatinine ratio
    - Serum creatinine and calculated GFR
    - TSH in type 1 diabetes, dyslipidemia, or women over age 50 years

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- Consider serum testosterone in diabetic men with signs/symptoms of hypogonadism
- Vitamin B12 if on metformin
- Serum potassium if on ACE, ARB, diuretic

** Most payors provide coverage for Medical Nutritional Therapy (MNT) and/or Diabetes Self-Management Education (DSME) for diabetes patients with a provider referral/ prescription to a certified diabetes educator. Specify: type of diabetes; MNT for nutrition/meal planning; DSME for other services.*

Below is a new table copied from the 2018 Standards of Medical Care in Diabetes (Section 3, page S30, table 3.1). This is a summary of the recommendations for the comprehensive diabetes medical evaluations.

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history** ▪ Characteristics at onset (e.g., age, symptoms) ▪ Review of previous treatment regimens and response ▪ Assess frequency/cause/severity of past hospitalizations	✓ ✓ ✓		
	Family history ▪ Family history of diabetes in a first-degree relative ▪ Family history of autoimmune disorder	✓ ✓		
	Personal history of complications and common comorbidities ▪ Macrovascular and microvascular ▪ Common comorbidities ▪ Presence of hemoglobinopathies or anemias ▪ High blood pressure or abnormal lipids ▪ Last dental visit ▪ Last dilated eye exam ▪ Visits to specialists	✓ ✓ ✓ ✓ ✓ ✓ ✓	✓	✓ ✓ ✓
	Interval history ▪ Changes in medical/family history since last visit		✓	✓
SOCIAL HISTORY	**Assess lifestyle and behavior patterns** ▪ Eating patterns and weight history ▪ Sleep behaviors and physical activity ▪ Familiarity with carbohydrate counting in type 1 diabetes ▪ Tobacco, alcohol, and substance use ▪ Identify existing social supports	✓ ✓ ✓ ✓ ✓	✓ ✓	✓ ✓
	Interval history ▪ Changes in social history since last visit		✓	✓
MEDICATIONS AND VACCINATIONS	▪ Medication-taking behavior ▪ Medication intolerance or side effects ▪ Complementary and alternative medicine use ▪ Vaccination history and needs	✓ ✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓ ✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc. ▪ Glucose monitoring (meter/CGM): results and data use ▪ Review insulin pump settings	✓ ✓ ✓	 ✓ ✓	✓ ✓ ✓
SCREENING	**Psychosocial conditions** ▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted ▪ Consider assessment for cognitive impairment*	✓ ✓		✓ ✓
	Diabetes self-management education and support ▪ History of dietitian/diabetes educator visits ▪ Screen for barriers to diabetes self-management ▪ Refer or offer local resources and support as needed	✓ ✓ ✓	✓ ✓	✓ ✓ ✓
	Hypoglycemia ▪ Timing of episodes, awareness, frequency and causes	✓	✓	✓
	Pregnancy planning ▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)	✓	✓	✓
	• Screen for PAD (pedal pulses; refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year			
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides[#]	✓		✓^
	• Liver function tests[#]	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate[†]	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes[#]	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics[†]	✓		✓
ASSESSMENT AND PLAN	**Goal setting**			
	▪ Set A1C/blood glucose target and monitoring frequency	✓	✓	✓
	▪ If hypertension diagnosed, establish blood pressure goal	✓		✓
	▪ Incorporate new members to the care team as needed	✓	✓	✓
	▪ Diabetes education and self-management support needs	✓	✓	✓
	Cardiovascular risk assessment and staging of CKD			
	▪ History of ASCVD	✓	✓	✓
	▪ Presence of ASCVD risk factors (see Table 9.2)	✓	✓	✓
	▪ Staging of CKD (see Table 10.1)[†]	✓	✓	✓
	Therapeutic treatment plan			
	▪ Lifestyle management	✓	✓	✓
	▪ Pharmacologic therapy	✓	✓	✓
	▪ Referrals to specialists (including dietitian and diabetes educator) as needed	✓	✓	✓
	▪ Use of glucose monitoring and insulin delivery devices	✓	✓	✓

ABI, ankle-brachial pressure index; ARBs, angiotensin receptor blockers; ASCVD, atherosclerotic cardiovascular disease; CGM, continuous glucose monitoring; CKD, chronic kidney disease; PAD, peripheral arterial disease.

*≥65 years;

[†]may be needed more frequently in patients with known chronic kidney disease or with changes in medications that affect kidney function and serum potassium (see Table 10.2);

[#]may also need to be checked after initiation or dose changes of medications that affect these laboratory values (i.e., diabetes medications, blood pressure medications, cholesterol medications, or thyroid medications);

^in people without dyslipidemia and not on cholesterol-lowering therapy, testing may be less frequent.

V. Goals of Treatment for Diabetes

A. Glycemic Goals in Adults

- Lowering A1C to below or around 7% has been shown to reduce microvascular complications of diabetes and if implemented soon after the diagnosis of diabetes is associated with long-term reduction in macrovascular disease. Therefore, a reasonable A1C goal for many nonpregnant adults is <7%.
- Providers might reasonably suggest more stringent A1C goals (such as 6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy and no significant CVD.
- Less stringent A1C goals (such as 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and in those with longstanding diabetes in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin.
- Postprandial glucose should be targeted if A1C goals are not met despite reaching pre-prandial glucose goals.

Glycemic control	
Hemoglobin A1C*	• The A1C goal *for patients in general* is <7%. • The A1C goal *for the individual patient* is an A1C as close to normal as possible without significant hypoglycemia • Less stringent A1C goals (such as 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple lowering agents including insulin.
Preprandial plasma glucose	80–130 mg/dl (4.4–7.2 mmol/l)
Postprandial plasma glucose	<180 mg/dl (<10.0 mmol/l) postprandial glucose measurements should be made 1-2hrs after beginning of meal
Blood pressure	< 140/90 mmHg, but <130/80 mmHg maybe be appropriate for certain patients if it can be achieved without undue treatment burden; all diabetic patients with HTN should monitor their blood pressure at home
Lipids[***]	Screening lipid profile at diabetes diagnosis, at an initial medical evaluation and/or at age 40 years; periodically thereafter. Treatment should be based on risk status. (See Table Below for additional information.)

LDL	Goals – see below table "Recommendations for statin treatment in people with diabetes"
Triglycerides	<150 mg/dl (<1.7 mmol/l)
HDL	>40 mg/dl (1.1 mmol/l) for males, and HDL goal > 50mg/dl (1.3mmol/l) in women

*****Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay; ADA Standards of Medical Care in Diabetes 2018

******Postprandial glucose measurements should be made 1 ½ to 2 hrs after the beginning of the meal, generally peak levels in patients with diabetes.

***** Lipid treatment:** Goals include diet and lifestyle modification with intense lifestyle therapy and optimizing glycemic control for patients with elevated triglyceride levels (≥150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (<40 mg/dL [1.0 mmol/L] for men, <50 mg/dL [1.3 mmol/L] for women).
For patients with fasting triglyceride levels ≥500 mg/dL (5.7 mmol/L), evaluate for secondary causes and consider medical therapy to reduce risk of pancreatitis.

Recommendations for statin treatment in people with Diabetes

Age	Risk factors	Recommended statin intensity*	Monitoring with lipid panel
<40 years	None CVD risk factor(s)** Overt CVD*** ACS and LDL≥70mg/dL on maximum tolerated statin dose	None Moderate High Consider adding additional LDL lowering agents (e.g. ezetimibe or PCSK9 inhibitor	Annually or as needed to monitor for adherence
≥40	None CVD risk factors Overt CVD ACS and LDL cholesterol ≥70mg/dL (1.3mmol/L) on maximum tolerated statin dose or in patients with a history of ASCVD who cannot tolerate high-intensity statins	Moderate High High Consider adding additional LDL lowering agents (e.g. ezetimibe or PCSK9 inhibitor)	As needed to monitor adherence

*In addition to lifestyle therapy.
**CVD risk factors include LDL cholesterol >100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria family history of premature ASCVD and overweight and obesity.
***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Lowers LDL-C ≥50%	*Lowers LDL-C 30-50%*
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvstatin 20-40 mg (FDA does not recommend use of simvastatin 80 mg due to increased risk of myopathy) Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Pitavastatin 2-4 mg

Stain + ezetimibe: Adding ezetimibe to moderate-intensity statin therapy has been shown to provide CV benefit compared with moderate statin therapy alone. This combination is a consideration for individuals with recent ACS and LDL-C ≥50mg/dL or those who cannot tolerate a high-intensity statin.

Statin + fibrate: This combination has not been shown to improve ASCVD outcomes and as such, it is NOT recommended

Statin + niacin: This combination has not been shown to provide additional CV benefit above statin therapy alone and may increase the risk for stroke. Therefore, this combination is NOT recommended.

VI. Referrals

- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for Medical Nutrition Therapy (MNT)
- Diabetes Self-Management Education (DSME)
- Dentist for comprehensive periodontal examination
- Mental health professional, if needed

Referral to Podiatry is recommended in the following instances:

- High risk patient (neuropathy, vascular disease, structural deformities, abnormal gait)
- Hx. of previous ulcers or infections
- Sensorimotor deficiencies for foot wear modifications
- Skin/nail deformities

Referral to Endocrinology is recommended when:

- The initial clinical and/or biochemical state is markedly abnormal
- The response to standard therapy is unsatisfactory (i.e. A1C goal not attained in 6-12 months)
- Metabolic complications.

Referral to Cardiac or Vascular Specialist should be considered when:

- EKG with left bundle branch block, myocardial infarction, or change from baseline at any time.
- Decline in exercise capacity

- Angina, atypical chest pain or claudication
- Absent or diminished pedal pulses
- Abdominal aortic aneurysm
- Embarking on new exercise program if previously sedentary and/or over 40 years old, or longstanding DM

VII. Continuing Care

Recommended intervals for continuing care:

Service	Recommended Interval
Frequency of return visits	At least quarterly * for Type 1 patients. At least semi-annually * for Type 2 patients if A1C at goal; quarterly if not at goal. **More frequently when indicated for follow up of DKA, hyperglycemia, hypoglycemia, hypertension, retinopathy, nephropathy, cardiovascular disease, neuropathy, or foot conditions.*
Review of Management Plan	During every regular follow up visit
Focused physical, including reflexes and monofilament exam	Annually
Hemoglobin A1C	Quarterly for Type 1 diabetes or insulin using patients and poorly controlled patients; Every 6 months for Type 2 diabetes with A1C≤ 7.0%.
Fasting lipid profile	At least annually. More frequent testing may be considered on an individual basis (e.g. to monitor for adherence and efficacy)
Hepatitis B vaccine	All adults 19 to 59 years of age and consider vaccination in adults 60 years and older
Influenza	Annually
Pneumococcal vaccine	Administer pneumococcal polysaccharide vaccine 23 (PPSV23) to all patients with diabetes ages 2 through 64. -Adults ≥65 years of age, who have NOT received any pneumoccal vaccines should receive pneumococcal conjugate vaccine 13 (PCV13), followed by PPSV23 at least 12 months after initial vaccination. -Adults ≥65 years of age, previously vaccinated with PPSV23 prior to age 65 , should receive PCV13 at least 12 months after receipt of the most recent PPSV23. A final dose of PPSV23 should be given at least 1 year after PCV13 and at least 5 years after any PPSV23 that was given before age 65 -Adults ≥65 who previously received PPSV23 at age ≥65, should receive PCV13 at least 1 year after the PPSV23
Random urine microalbumin/creatinine	At least once a year, quantitatively assess urinary albumin (e.g., urine albumin-to-creatinine ratio [UACR]) and estimated glomerular filtration rate (eGFR) in patients with type 1 diabetes duration of ≥5 years and in all patients with type 2 diabetes.
Dilated eye exam	• Patients with Type 1 diabetes should have an initial dilated and

(by Ophthalmology or Optometry)	comprehensive eye examination within 5 years after the onset of diabetes. • Patients with Type 2 diabetes should have an initial dilated and comprehensive eye examination shortly after the diagnosis of diabetes. • Subsequent examinations should be repeated annually. Less frequent exams (i.e. every 2 years) may be considered with the advice of an eye care professional in the setting of a normal eye exam. Examinations will be required more frequently if retinopathy is progressing or patient planning to or becomes pregnant.
Foot Exam	Visual exam at every regular visit Annual comprehensive exam (tuning fork, monofilament, palpation of pulses, and visual exam); educate regarding risk and prevention.
Diabetes education	Evaluate annually
Medical Nutrition Therapy	Evaluation at time of diagnosis and annually
Physical Activity Prescription	Adults with diabetes should be advised to perform at least 150 min/ week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise. Evidence supports that all individuals, including those with diabetes, should be encouraged to reduce sedentary time, particularly by breaking up extended amounts of time (>90 min) spent sitting. In the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week.
Smoking Cessation Counseling	Advise all patients not to smoke. Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care. eCigarettes are not recommended as an alternative.
ABI	Screening of ABI recommended for patients • with symptoms of PAD • >50 years of age • and should be considered in patients <50 who have PAD risk factors
Other Treatment Modalities	
ASA	▪ Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes with a history of CVD ▪ Consider aspirin therapy (75–162 mg/ day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men or women with diabetes aged ≥50yr with ≥1 additional major risk factor: fm hx of premature ASCVD, hypertension, smoking, dyslipidemia or albuminuria. ▪ Do not use aspirin in pts. < 21 yr. of age because of the increase risk of Reyes syndrome ▪ Aspirin is not recommended for those at low CVD risk (women and men under age 50 years with no major CVD risk factors; 10-year

	CVD risk under 5%) Clinical judgment should be used for those in these age ranges with multiple risk factors. ▪ In patients with aspirin allergy and CVD clopidogrel 75mg/day should be used
FDA Approved Weight Loss Medications	▪ Consider in select type 2 diabetics with BMI≥27kg/m^2 as an adjunct to diet, physical activity and behavioral counseling ▪ If after 3 months response to weight loss medications is <5%, medication should be stopped
Bariatric Surgery	▪ Should be considered in certain type 2 diabetics
Service - Other Treatment Modalities	**Recommended Interval**
ACE inhibitors or ARB (Initial agent of choice for hypertensive diabetics and for non hypertensive type I diabetes pts. with microalbuminuria)	Monitor serum potassium levels and renal function. Titrate dose to minimize urine protein level.
ACE or ARB (Initial agent of choice for hypertensive type 2 diabetic pts. with microalbuminuria; ARB if patient does not tolerate ACE therapy).	Monitor serum potassium levels and creatinine. Titrate dose to minimize urine protein level.
Target BP <130/80 or 140/80 mmHg	Every visit (Patients found to have systolic blood pressure ≥130 or ≥140 (depending on target) or diastolic blood pressure ≥ 80 mmHg should have blood pressure confirmed on a separate day, and therapy initiated. Home bp monitors are encouraged. ACE inhibitors and ARBs considered first line agents for tx in patients with microalbuminuria; nutritionist consult for review of dietary sodium intake and 'hidden salt'.)

Note: This guideline is for reference only and is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by providers. This guideline is recommended for adults with either insulin dependent or non-insulin dependent diabetes mellitus. Patients younger than 18 years and pregnant females with diabetes are not included.

III. Resources Available

www.betterdiabetescare.nih.gov - an online resource maintained by The National Diabetes Education Program to aide health care providers with designing and implementing health care delivery systems for diabetics.

Sources Provided by ADA:

Diabetes.org

http:www.diabetes.org/ -This is in English
http:www.diabetes.org/es/ -This is in Spanish
Call 1-800-DIABETES

Facebook: American Diabetes Association
Twitter: @AmDiabetesAssn
Instagram: @AmDiabetesAssn

Beginning in 2018 ADA will continuously update their online Standards of Medical Care in Diabetes.
This information will also be available as an interactive app (web and mobile devices) beginning 2018 Spring.

VIII. References

1. Standards of Medical Care in Diabetes- 2018, American Diabetes Association. Diabetes Care volume 41, supplement 1, January 2018.
2. ACE/ACCE consensus Statement: Diagnosis and Management of Prediabetes in the Continuum of Hyperglycemia; 2008. Endocrine Practice (14) 7. October 2008.
3. Prediabetes Diagnosis and Treatment: A Review, World Journal Diabetes March 2015
4. Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. *Diabetes Care* January 2009 vol. 32 no. 1 193-203
5. Individualizing Glycemic Targets in Type 2 Diabetes Mellitus: Implications of Recent Clinical Trials. American College of Physicians, Annals of Internal Medicine. Volume 154 • Number 8. April 2011
6. AACE Guidelines (American Association of Clinical Endocrinology) Medical Guideline for Clinical Practice For Developing A Diabetes Mellitus Comprehensive Care Plan. Endocrine Practice (Vol 17) March/April 2011.
7. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl. 1)
8. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-1197

IX. Attachments

- Oral Diabetes Agents
- Insulins and other injectables
- Treatment Algorithms: tables from the ADA Standards of Medical Care in Diabetes 2018 taken from the following sections:
    - Section 8, page S76, Figure 8.1 Antihyperglycemic Therapy in Adults with Type 2 Diabetes
    - Section 8, page S77, Table 8.1 Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes
    - Section 8, page S78, Figure 8.2 Initiate Basal Insulin (Combination injectable therapy for type 2 diabetes
    - Section 9, S90, Figure 9.1 Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

Attachment 1

ORAL DIABETES AGENTS

Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Sulfonylureas				
glyburide (Glynase® [micronized], and generics) ($20) glipizide (Glucotrol®, Glucotrol XL® and generics) ($18) glimepiride (Amaryl® or generics) ($20)	Stimulates the release of insulin from the pancreas Glipizide is preferred in patients with moderate to severe renal function impairment	FPG: ⇩ 50-60mg/dl HbA1c: ⇩ 1.5-2%	Glynase (micronized)®: 0.75-12mg/day; max 12mg/day (divide doses >6mg) glyburide: 1.25-20mg/day; max 20mg/day (divide doses >10mg) glipizide (immediate release): 5-40mg/day 30 min. prior to meals; max 40mg/day (divide doses >15mg) Glucotrol XL®: 5-10mg/day with breakfast; max 20mg/day glimepiride: 1-4mg/day with breakfast; max 8mg/day	Hypoglycemia, weight gain, GI upset **Precautions** hepatic/renal impairment increased risk of hypoglycemia with Glucotrol® XL if the patient misses a meal glyburide implicated in negative outcomes post-MI empty Glucotrol® XL tablet shell may appear in stool Glyburide – increased risk of prolonged hypoglycemia in the elderly; micronized and conventional tablets are not bioequivalent Glimepiride – contraindicated severe renal function

Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Biguanides				
metformin (Glucophage®, , Glumetza®, Fortamet®, Glucophage XR® and generics)($42) Available in Liquid form, Riomet® , at a concentration of 500mg/5mL. ($253)	Decreases hepatic glucose production and improves insulin sensitivity	FPG: ⇩ 50-60mg/dl HbA1c: ⇩ 1.5-2% ⇩ TG, LDL, Chol ⇧ HDL	500-2000mg/day with a meal increasing slowly by 500mg q 2 weeks; max 2550mg/day (2-3 times a day dosing is more effective and better tolerated; divided doses >2000mg into 3x/day dosing) Extended release tablets: 500mg/day with evening meal increasing by 500mg weekly; max 2500mg/day for Fortamet, 2000mg/day for other brands and generic (if 2000mg/day ineffective, may try 1000mg twice a day or switch to regular release metformin on a mg-per-mg basis) **Adjusting for reduced GFR:** **If eGFR ≥30 to <45 mL/minute/1.73 m^2: Do not initiate therapy. In patients currently receiving metformin, assess benefits and risks of continuing therapy; ADA guidelines recommend considering dosage reduction (eg, 50% reduction or 50% of maximal dose) , and advising patients to stop the drug for nausea, vomiting, or dehydration.** **If eGFR <30 mL/minute/1.73 m^2: Do not initiate therapy . If on metformin, discontinue use.** **(FDA revised labeling April 2016 and ADA Standards of Care 2016)**	Nausea, diarrhea; often resolve after 2-3 weeks of use and minimized by taking with a meal or using XL formulation . Vitamin B12 deficiency with chronic use; periodic monitoring is recommended **Precautions** For patients who will receive intra-arterial contrast or patients with eGFR between 30 and 60 or a history of liver disease or heart failute who will receive intravascular iodinated contrast media do not administer metformin at the time of or for 48 hours after procedures and resume therapy only when normal renal function returns. Avoid in patients with frequent alcohol use, or liver or kidney disease due to increased risk of lactic acidosis. Obtain eGFR at least annually in all patients taking metformin. Assess more frequently in patients atincreased risk of renal impairment such as the elderly.

Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Alpha-Glucosidase Inhibitors				
acarbose (Precose® and generics)($105) miglitol (Glyset® and generics) ($241)	Delays dietary absorption of complex carbohydrates thereby lowering postprandial glucose	FPG: little effect HbA1c: ⇩ 0.5-1% PPG: ⇩ 50mg/dl	acarbose: 25mg three times a day with the first bite of each main meal increasing to 50mg three times a day and then 100mg three times a day after 4-8 weeks; max 100mg three times a day if patient is >60kg and 50mg three times a day if ≤60kg miglitol: 25mg three times a day with the first bite of each main meal increasing to 50mg three times a day after 4-8 weeks and 100mg three times a day after 3 months; max 100mg three times a day	Abdominal pain, diarrhea, bloating, flatulence, ↑ LFTs (with acarbose only) **Precautions** Not recommended for patients with SCr>2mg/dl. Asymptomatic / reversible increases in AST and/or ALT has occurred in up to 14% of acarbose-treated patients. Fulminant hepatitis –rare. **Contraindicated in patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction.** **Use glucose to treat hypoglycemia – sucrose products are ineffective due to the medication's mechanism of action**
Sulfonylurea + Biguanide				
metformin + glyburide (Glucovance®)($93) metformin + glipizide (generics only) ($59)	Stimulates the release of insulin from the pancreas; increases the sensitivity of peripheral tissues to insulin; and decreases hepatic glucose production	FPG: ⇩ 50mg/dl HbA1c: ⇩ 2%	**Glucovance** initial treatment: 1.25mg/250mg once daily with meals (twice daily if a1c>9% or FPG >200mg/dL) and increase by 1.25mg/250mg every 2 weeks; max 10mg/2000mg/day previously treated patients: 2.5mg/500-5mg/500mg twice a day with meals and increase by 5mg/500mg; max 20mg/2000mg/day **Metformin+Glipizide** initial treatment: 2.5mg/250mg daily or 2.5mg/500mg twice a day with meals if FPG 280-320mg/dL and increase by 1 tablet daily every 2 weeks; max 10mg/2000mg daily in divided doses previously treated patients: 2.5mg/500mg – 5mg/500mg twice a day with meals and increase in increments not to exceed 5mg/500mg; max 20mg/2000mg daily in divided doses	Hypoglycemia, weight gain, diarrhea, GI upset **Precautions** **See individual agents** Bioequivalence has not been established for metformin and glyburide in comparison with Glucovance® therefore, metformin and glyburide should not be substituted for Glucovance® The starting dose of metformin +glipizide should not exceed the current dose of metformin or glipizide already being taken

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Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Thiazolidinediones				
pioglitazone (Actos® and generics) ($321) rosiglitazone (Avandia®) ($203)	Improves insulin sensitivity and increases peripheral glucose disposal	FPG: ⇩ 50-100mg/dl HbA1c: ⇩ 1-2% ⇧ LDL, Chol, HDL	pioglitazone: 15-30mg once daily (increase in15mg increments ; max 45mg/day) rosiglitazone: 4mg/day in single or divided doses, may increase to 8mg/day in single or divided doses after 8-12 weeks; max 8mg/day	Edema, weight gain, hypoglycemia, diarrhea, ↑ LFTs **Precautions** Not recommended for patients with NYHA class III or IV heart failure, CYP450 drug interactions, or with history of CAD. If patient is stable on medication continue at lower dosage and continue to monitor.
Thiazolidinedione + Sulfonylurea				
Pioglitazone + Glimepiride (Duetact(R)and generics) ($468)	Improves insulin sensitivity and increases peripheral glucose disposal; Stimulates the release of insulin from the pancreas		Initial dose should be based on current dose of pioglitazone and/or sulfonylurea. Patients inadequately controlled on **glimepiride** alone: Initial dose: 30 mg/2 mg or 30 mg/4 mg once daily Patients inadequately controlled on **pioglitazone** alone: Initial dose: 30 mg/2 mg once daily Maximum dose: Pioglitazone 45 mg/glimepiride 8 mg daily	Edema, weight gain, hypoglycemia, diarrhea, ↑ LFTs. May cause or exacerbate heart failure. Not recommended in any patient with symptomatic heart failure; initiation contraindicated with NYHA class III or IV heart failure

Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Thiazolidinedione + Biguanide				
Pioglitazone + metformin (Actoplus Met® and generics) ($320) Pioglitazone + metformin (varied release) (Actoplus Met XR®) ($340)	Improves insulin sensitivity and decreases hepatic glucose production	FPG: 33-48mg/dl HbA1c: ⇩0.6-0.8%	Initial dose should be based on current dose of pioglitazone and/or metformin; daily dose should be divided and given with meals. If not switching from individual components, initial dose is 15mg/500mg twice daily or 15mg/850mg once daily Patients inadequately controlled on **metformin alone**: Initial dose: 15mg/500mg or 15mg/850mg twice daily depending on current dose of metformin. Patients inadequately controlled on **pioglitazone alone**: Initial dose: 15mg/500mg twice daily or 15mg/850mg once daily **Dosing adjustment:** Doses may be increased as increments of pioglitazone 15 mg and/or metformin 500-850 mg, up to the maximum dose; doses should be titrated gradually. Guidelines for frequency of adjustment (adapted from rosiglitazone/metformin combination labeling): ▪ After a change in the **metformin** dosage, titration can be done after 1-2 weeks ▪ After a change in the **pioglitazone** dosage, titration can be done after 8-12 weeks ▪ Maximum dose: Pioglitazone 45 mg/metformin 2550 mg daily. Metformin daily dose >2000mg better tolerated as 3x/day dosing. • Usual initial dose of Actoplus Met XR: metformin 1000 mg and 15 or 30 mg pioglitazone given once daily with evening meal	Edema, weight gain, hypoglycemia, diarrhea, ↑ LFTs, nausea, diarrhea **Precautions** CYP450 drug interactions Temporarily discontinue 48 hours prior to procedures involving intravascular iodinated contrast media or surgery and resume therapy only when normal renal function returns. Avoid in patients with frequent alcohol use, or liver or kidney disease due to increased risk of lactic acidosis. **Check LFTs at baseline and periodically thereafter. D/C if LFTs>3x upper limit of normal.** **Contraindicated in severe renal impairmet (eGFT < 30 ml/min.**

Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Meglitinides				
repaglinide (Prandin® and generics) ($330) nateglinide (Starlix® and generics) ($150)	Stimulates glucose-dependent insulin secretion Short half-life (1 hr) – quick onset (15-30 min)	FPG: 10-40mg/dl HbA1c: ⇩ 0.5-2% PPG: ⇩ 50mg/dl	repaglinide: 0.5-2mg 15-30 minutes before each meal, depending on a1c; max 4mg/dose and 16mg/day At least 1 week should elapse between dose adjustments nateglinide: 60-120mg three times a day 30 minutes prior to each meal; max 120mg/dose and 360mg/day	hypoglycemia, weight gain **Precaution** hepatic and renal impairment, CYP450 drug interactions
Meglitinide + Biguanide				
Repaglinde and metformin (generics only) ($614)	See individual agents	FPG: 10-40mg/dl HbA1c: ⇩ 1.4%	Initial doses should be based on patient's current dose of each component *Patients not controlled on metfomrin alone:* initial dose 1mg/500mg twice daily with meals *Patients not controlled on repaglinide alone:* initial dose 500mg metformin twice daily with meals plus similar repaglinide dose as patient's current dose Maximum daily dose 10mg/2500mg	Need to adjust dose if patient is also using clopidogrel or cyclosporine

Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Dipeptidyl Peptidase IV (DPP-IV) inhibitor				
Sitagliptin (Januvia®)($516)	inhibits dipeptidyl peptidase IV (DPP-IV) enzymes resulting in prolonged active incretin levels.	HbA1c: ⇩ 0.5-0.6%	100 mg once daily	▪ Adjust dose in renal dysfunction for sitagliptin, saxagliptin, and alogliptin No dosage adjustment required for mild-moderate hepatic impairment (sitagliptin, saxagliptin). Use 2.5mg saxagliptin daily for patients with CrCl ≤45 ml/min or if on a CYP3A4/5 inhibitor (azole antifungal, protease inhibitor, clarithromycin). 2.5mg postdialysis for patients with ESRD requiring hemodialysis. Effectiveness of linagliptin is decreased when used in combination with CYP3A4 inducers (rifampin) – use alternative therapy No dosage adjustment for linagliptin needed for renal or hepatic impairment. Acute and chronic pancreatitis have been reported with DPP-IV inhibitor use; monitor for signs/ symptoms of pancreatitis Cases of fatal and nonfatal hepatic failure have been reported. Monitoring and appropriate therapy interruption are necessary
Saxagliptin (Onglyza®) ($490)			2.5-5mg once daily	
Linagliptin (Tradjenta®)($497)			5mg once daily	
Alogliptin (Nesina® and generics) ($234)			25mg once daily	

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Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Dipeptidyl Peptidase IV (DPP-IV) Inhibitor + Biguanide				
Sitagliptin + metformin (Janumet®, Janumet XR®) ($258)	inhibits dipeptidyl pepase IV (DPP-IV) enzymes resulting in prolonged active incretin levels and decreases hepatic glucose production and improves insulin sensitivity	FPG: ⇩ 50-60mg/dl HbA1c: ⇩ 1.5-2% ⇩ TG, LDL, Chol ⇧ HDL	Janumet®: Initial doses should be based on current dose of sitagliptin and metformin; daily doses should be divided and given twice daily with meals (immediate release) or once daily (extended release). Maximum: Sitagliptin 100 mg/metformin 2000 mg daily *Patients inadequately controlled on metformin alone:* Initial dose: Sitagliptin 100 mg/day plus current daily dose of metformin. **Note:** Per manufacturer labeling, patients currently receiving metformin 850 mg twice daily should receive an initial dose of sitagliptin 50 mg and metformin 1000 mg twice daily *Patients inadequately controlled on sitagliptin alone:* Initial dose: Metformin 1000 mg/day plus sitagliptin 100 mg/day. **Note:** Patients currently receiving a renally adjusted dose of sitagliptin should not be switched to combination product. **Dosing adjustment:** Metformin component may be gradually increased up to the maximum dose. Maximum dose: Sitagliptin 100 mg/metformin 2000 mg daily	Avoid metformin in severe renal impairment, an eGFR <30 ml/min Avoid with hepatic insufficiency or clinical or laboratory evidence of hepatic disease

Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Linagliptin plus metformin (Jentadueto®, Jentadueto XR®) ($494)		HbA1C ↓1.7%; FBG↓ 33-40 mg/dl	Jentadueto®: Initial doses should be based on current doses of the components. Should be given in 2 divided doses (immediate release) or once daily (extended release). *Patients inadequately controlled on metformin alone:* Initial dose: linagliptin 5mg/day plus current daily dose of metformin *Patients inadequately controlled on linagliptin alone:* initial dose: linagliptin 5mg and metformin 1000mg daily When converting from immediate to extended release dose is 5mg linagliptin and current daily dose of metformin once daily. Dosing Adjustment: Metformin component may be lly increased to the maximum dose. Maximum dose: Linagliptin 5 mg / metformin 2000 mg daily.	

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Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
Dipeptidyl Peptidase IV (DPP-IV) Inhibitor + Biguanide				
Saxaglipin plus metformin (Kombiglyze ER ®) ($490)			Kombiglyze ER: Initial doses should be based on current daily dose of the components. Should be administered once daily. **Note:** Patients requiring saxagliptin 2.5mg and metformin >1000mg/day should not be switched to combination product. *Patients inadequately controlled on metformin alone:* initial: saxagliptin 2.5-5mg once daily plus current daily dose of metformin. *Patients inadequately controlled on saxagliptin alone:* initial: 5mg/500mg once daily. Maximum dose: saxagliptin 5mg/metformin 2000mg once daily	See individual agents
Alogliptin plus metformin (Kazano® and generics) ($234)			Kazano: Initial doses should be based on current daily dose of the components. Usual dosing: 12.5mg/500-1000mg twice daily Maximum dose: 12.5mg/1000mg twice dialy	
Alogliptin plus pioglitazone (Oseni®) ($449)			Oseni: initial doses should be based on current daily dose of the components *Patients indadequately controlled on pioglitazone alone:* 25mg alogliptin plus current daily dose of pioglitazone once dialy *Patients inadequately controlled on alogliptin* 25mg/15mg or 25mg/30mg once daily Maximum dose: 25mg/45mg daily	

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Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
SGLT2 (Sodium-glucose-cotransporter 2) Inhibitors				
Canagliflozin (Invokana®) ($558)	Reduces reabsoption of filtered glucose from the tubular lumen and lowers renal threshold for glucose	HbA1C ↓0.77-1.03% FBG↓36-43 mg/dl	Invokana:: Initial 100 mg once daily prior to first meal of day; may increase to 300 mg once daily (only in patients with Clcr ≥60). Max dose 300 mg once daily. Clcr 45 to <60: Max dose 100 mg daily Clcr 30-45: Use not recommended Clcr <30, ESRD, and hemodialysis: Use is contraindicated	SGLT2 inhibitor use may lead to ketoacidosis. Patients should seek medical attention if they experience any signs or symptoms they may be related to ketoacidosis. Side Effects: May increase risk of genital mycotic infections; may cause hypotension due to intravascular depletion in patients with renal impairment; may cause hyperkalemia, may cause dose-related LDL elevation Boxed warning (Invokana): patients with cardiovascular disease or at risk for cardiovascular disease are at a higher risk for possible limb amputation
Dapagliflozin (Farxiga®) ($557)		HbA1C ↓0.8-0.9% FBG↓ 24-29 mg/dl	Farxiga: Initial 5 mg once daily in the morning with or without food; may increase to 10 mg once daily Clcr <60: use not recommended Clcr <30, ESRD, and hemodialysis: Use contraindicated	
Empagliflozin (Jardiance®) ($558)		HbA1C ↓0.8% FBG↓ 19 -25 mg/dl	Jardiance: Initial: 10 mg once daily; may increase to 25 mg once daily Clcr <45: use not recommended Clcr < 30, ESRD, and hemodialysis: Use contraindicated	
Ertugliflozin (Steglatro®) ($322)			Steglatro: initial 5mg once daily; may increase to 15mg once daily ClCr <60 use not recommended CrCl<30, ESRD, and hemodialysis: use contraindicated	

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Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
SGLT2 Combinations				
canagliflozin plus metformin (Invokamet®, Invokamet XR®) ($557)	(see individual agents)	HbA1C ↓1% FBG↓ 30 mg/dl	**Invokamet XR®:** daily dose is 2 tabs/day Initial dose: 50mg/500mg, 2 tablets, once daily Max daily dose: 300mg/2000mg *Patients on metformin:* Initial dose: canagliflozin 100 mg plus similar total dose of metformin daily. **Note:** patients taking metformin ER in the evening should skip the last dose before starting combination product the following morning. *Patients on canagliflozin:* Initial dose: Metformin 1000 mg daily plus similar total dose of canagliflozin daily. *Patients switching from immediate to extended release:* use current total daily dose once daily **Invokamet®:** daily dose is 1 tab twice daily *Patients on metformin:* Initial dose: canagliflozin 50 mg plus similar total dose of metformin daily. *Patients on canagliflozin:* Initial dose: Metformin 500 mg daily plus similar total dose of canagliflozin daily. *Patients switching from combination therapy of canagliflozin and metformin as separate tablets:* Use current total dose.	
dapagliflozin plus metformin (Xigduo XR®) ($557)		HbA1C ↓0.9% FBG↓ 61 mg/dl	**Xigduo XR®:** Initial daily dose: 5mg/500mg once daily **Note:** patients taking metformin ER in the evening should skip the last dose before starting the combination product the next morning Max daily dose: 10mg/2000mg once daily.	
empagliflozin plus linagliptin (Glyxambi®) ($628)		HbA1C ↓1.2% FBG↓ 35 mg/dl	**Glyxambi®:** Initial: Empagliflozin 10 mg/linagliptin 5 mg once daily; may increase to empagliflozin 25 mg/linagliptin 5 mg once daily	

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Class/Agent	Primary Action	Efficacy	Typical Dose	Side Effects and Monitoring
SGLT2 Combinations				
Empagliflozin plus metformin (Synjardy®, Synjardy XR®) ($558)			Immediate release: administered in 2 divided doses Extended release: administered once daily *Patients on metformin*: empagliflozin 10mg/day plus similar total daily dose of metformin *Patients on empagliflozin*: metformin 1000mg/day plus similar total daily dose of empagliflozin Max daily dose: 25mg/2000mg	
Dapagliflozin plus saxagliptin (Qtern®) ($557) Ertugliflozin plus sitagliptin (Steglujan®) ($628) Ertugliflozin plus metformin (Segluromet®) ($322)			10mg dapagliflozin/ 5mg saxagliptin 5mg ertugliflozin/100mg sitagliptin once daily Max daily dose: 15mg ertugliflozin/100mg sitagliptin *Patients on metfomrin*: ertugliflozin 5mg/day plus similar total daily dose of metformin in 2 divided doses *Patients on ertugliflozin*: metformin 1000mg/day plus similar total daily dose of ertugliflozin in 2 divided doses Max daily dose: 15mg/2000mg	

(Attachment II INSULINS)

Type	Onset	Peak	Duration	Rx or OTC	Cost
Rapid					
lispro (Humalog®)*	15-30 minutes	30-90 minutes	3-5 hours	Rx	Vial $99/300units (=$330/1000 units) Pen $127/300 units (=$423/1000 units)
Insulin aspart (NovoLog®, Flasp®)†	10-20 minutes	40-50 minutes	5-8 hours	Rx	Vial $331/1000 units; Pen $125/300 units
Insulin glulisine (Apidra®)	12-30 minutes	30-90 minutes	3-4 hours	Rx	Vial $323/1000 units; Pen $125/300 units
Insulin Oral Inhalation - Rapid					
Afrezza® (contraindicated in patients with COPD or asthma)	15-30 minutes	53 minutes	2-3 hours	RX	$357360 units (=$992/1000 units)
Short					
Regular (Humulin R , Novolin R)	30-60 minutes	2-4 hours	6-8 hours	OTC	$165/1000 units
Intermediate					
NPH (Humulin N, Novolin N, Novolin N Relion)	1-2 hours	4-12 hours	10-24 hours	OTC	$165/1000 units
Long					
Insulin glargine (Lantus®)‡	1-2 hours	(no pronounced peak)	>24 hours	Rx	Vial $323/1000 units Pen $97/300 units
Insulin glargine (Basaglar®)	1-2 hours	(no pronounced peak)	>24 hours	Rx	Pen $78/300 units
Insulin detemir (Levemir®)	3-4 hours	6-8 hours	6-23 hours	Rx	Vial $336/1000 units Pen $101/300 units
Insulin glargine 300u/ml (Toujeo®, Toujeo Max®)	Up to 6 hours	12-20 hours	Up to 36 hours	RX	Pen $149/450 units
Insulin degludec 100 or 200 units/mL (Tresiba®)	1 hour	(no pronounced peak)	>42 hours	Rx	Pen $111/300 units Pen $222/600 units
Combination					
70/30 (Humulin 70/30, Novolin 70/30) (70% NPH/30% regular)	30-60 minutes	3-12 hours	12-20 hours	OTC	Vial $166/1000 units Pen $113/300 units
Humalog® Mix 75/25 (75% lispro protamine/25% lispro)*	15-30 minutes	1-3 hours	10-20 hours	RX	Vial $342/1000 units Pen $127/300 units
Humalog 50/50 (50% lispro protamine/50% lispro)*	15-30 minutes	1-3 hours	10-20 hours	RX	Vial $342/1000 units Pen $127/300 units
NovoLog® Mix 70/30 (70% insulin aspart protamine/30% insulin aspart)†	10-20 minutes	1-4 hours	12-24 hours	RX	Vial $343/1000 units Pen $128/300 units

* Lispro insulin (Humalog®), Humalog® Mix 75/25, and Humalog® 50/50 should be given 0-15 minutes before a meal or immediately after a meal

† Insulin aspart (NovoLog®) and NovoLog® Mix 70/30 should be given 0-10 minutes before a meal

‡ Dosing recommendations for insulin glargine (Lantus®). **Note that Insulin glargine should not be mixed with other types of insulin.**

Switching from once daily NPH to insulin glargine: no change in dosage.

Switching from twice a day NPH to insulin glargine: decrease insulin glargine dose by 20% and titrate to patient's response to reduce incidence of hypoglycemia.

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OTHER INJECTABLE AGENTS

Agent	Primary Action	Efficacy	Dose	Side Effects	
Pramlintide (Symlin®)($1274)	Slows the rate of postprandial glucose increase by slowing gastric emptying, suppressing glucagons secretion, and decreasing food intake through increase in satiety.	HbA1c: ⇩0.5-1% Weight: ⇩1-2kg	Type 1 diabetes: initiate with 15 mcg SC immediately prior to each main meal and increase by 15 mcg increments to 30-60 mcg Type 2 diabetes: initiate with 60 mcg SC immediately prior to each main meal and increase to 120 mcg when tolerated Increase dose only when no significant nausea has occurred for 3-7 days. If significant nausea, reduce to prior dose.	Hypoglycemia Nausea, diarrhea, vomiting (usually mild) Contraindications: gastroparesis, hypoglycemia unawareness Do not mix with insulin Reduce preprandial insulin doses (rapid and short acting insulin and 70/30, 50/50, 75/25) by 50% Administer into abdomen or thigh only due to variable absorption through the arm	
GLP-1 receptor agonists					

Exenatide (Byetta®) ($850)	Glucose dependent insulin release, lowers glucagon during hyperglycemia, slows gastric emptying, reduces food intake through increase in satiety. Secondary effect of medication is weight loss or prevention of weight gain as glucose control improves	FPG: 15-25mg/dl HbA1c: ⇩ 1% Weight: ⇩2.5-4kg	5mcg SC up to 60 minutes prior to the morning and evening meals. After 1 month, can increase to 10mcg per dose	Class Warning: Risk of thyroid tumors Contraindicated in patients with a personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia Syndrome type 2.Cases of acute pancreatitis have been reported Class side effects: Hypoglycemia Nausea, diarrhea, vomiting (usually mild) Exenatide, Dulaglutide, Albiglutide Not recommended to be used in patients with gastroparesis or severe gastrointestinal disease. Liraglutide – Most common side effects are GI and may be dose related. Exenatide: Can be used in combination with metformin, a sulfonylurea, or both. May need to reduce sulfonylurea dose. *For use only in type 2 diabetes* Anti-exenatide antibodies: Use may be associated with the development of anti-exenatide antibodies. Use not recommended in severe renal impairment (CrCl<30 mL/minute).	
Exenatide extended release (Bydureon®) ($792)			2 mg once weekly without regard to meals (may administer missed dose as soon as noticed as long as the next scheduled dose is at least 3 days away, then resume schedule of every 7 days) Converting from immediate release: start ER day after stopping IR. This may cause high blood glucose for ~2 weeks.		
Liraglutide (Victoza®) ($774)		HbA1c: ⇩ 0.7-0.9% FPG ⇩: 16-25 mg/dl	0.6mg SC daily x 1 week, then 1.2mg SC daily. May increase to 1.8mg SC daily. Allow at least 1 week in between dose increases. Given independent of meals.		

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Combination Products					
Insulin degludec plus liraglutide (Xultophy®)	See individual components	See individual components	Initial dose: 16 units/0.58mg once daily Dose may be titrated up or down every 3-4 days in increments of 2 units/0.072mg Maximum daily dose: 50units/1.8mg	See individual components	$1190/month (at 50 unit/1.8mg dose)

Cost = AWP for one month therapy, lowest price for generic offering is listed if generic available, based on mid-range maintenance where applicable

Weight loss medications may be considered in for type 2 diabetics with a BMI ≥27. They can be used in conjunction with diet, exercise and behavioral counseling.

Medications Approved by the FDA for Treatment of Obesity			
Medication Name	**Usual Dosing**	**Side Effects and Comments**	**Price***
Short-Term Treatment (a few weeks) *Sympathomimetic central nervous system stimulant*			
Phentermine (Lomaira®)	37.5mg daily before breakfast or 1-2 horus after breakfast or 8mg three times daily 30 minutes before meals	Common side effects: headache, elevated blood pressure, elevated heart rate, insomnia, dry mouth, anxiety, constipation No longer available OTC Controlled substance (C-IV) Need to adjust dose for renal dysfunction	37.5mg: $46 8mg (brand only): $52
Long-Term Treatment (more than a few weeks)			
Lipase inhibitor			
Orlistat (Alli®, Xenical®)	Xenical: 120mg three times daily with each meal containing fat Alli: 60mg three times daily with each meal containing fat (max dose 180mg/day)	Common side effects: abdominal pain or discomfort, flatulence, malabsorption of fat-soluble vitamins and medications Serious side effects: may cause liver failure – monitor liver function if symptoms appear Xenical may be taken up to 1 hour after the meal if dose is missed Skip dose if meal is missed or contains no fat Patients on cyclosporine should take it 3 hours after orlistat Patients on levothyroxine should space medications by at least 4 hours Alli is available OTC	Alli (brand only): $53 Xenical (brand only): $703

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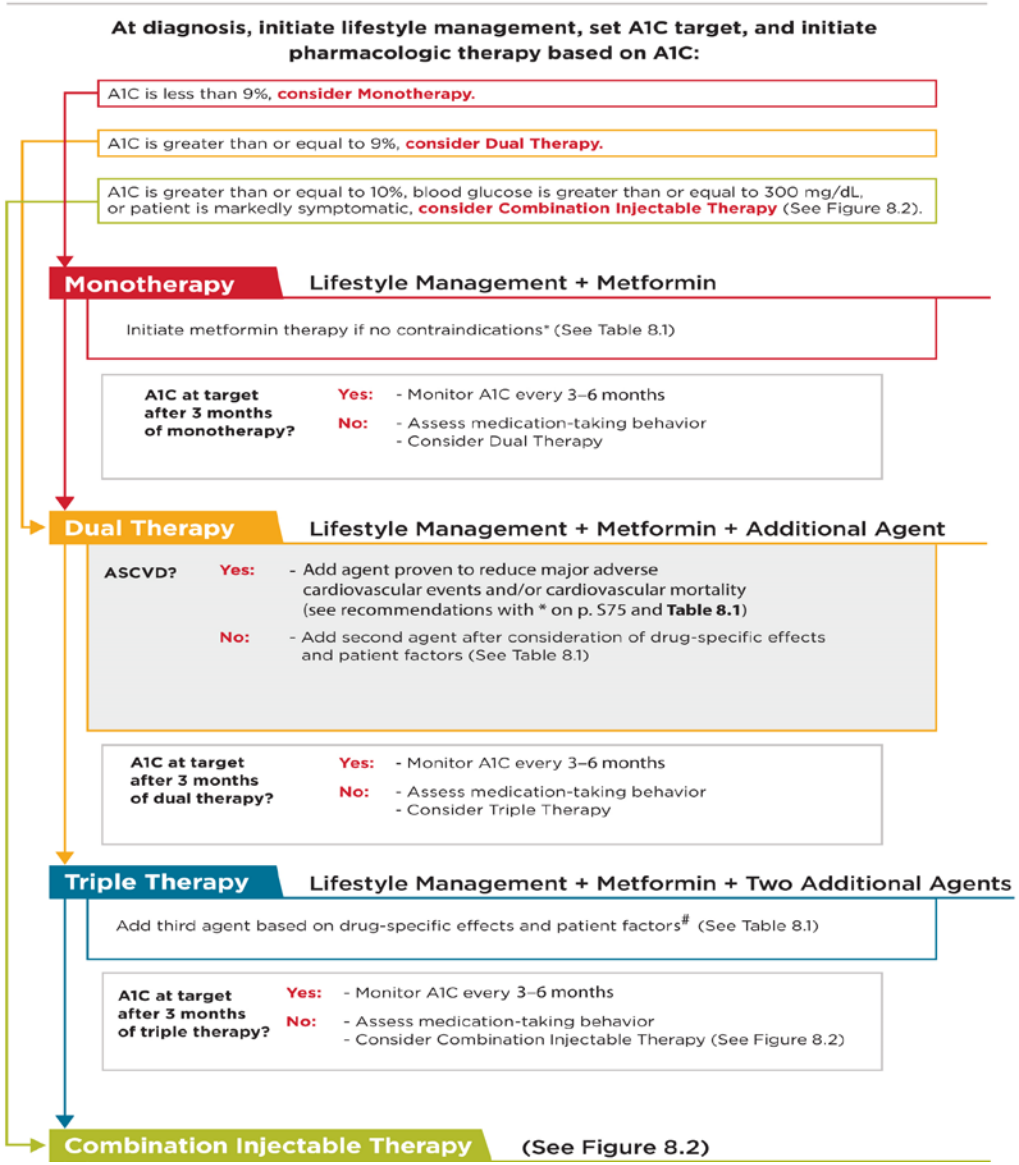
Selective Serotonin Receptor Agonists			
Lorcaserin (Belviq®)	10mg twice daily without regard to meals	Common side effects: hypoglycemia, headache, fatigue Serious side effects: serotonin syndrome, suicidal ideation, heart valve disorder, bradycardia Use with caution in patients with CrCl 30-50mL/min Controlled substance (C-IV)	Belviq (brand only): $318
Lorcaserin extended release (Belviq XR®)	20mg daily without regard to meals		Belviq XR (brand only: $318
Glucagon-like peptide 1 (GLP-1) Receptor Agonist			
Liraglutide (Saxenda®)	3mg SubQ daily Initial dose: 0.6mg once daily, increased by 0.6mg increments weekly to target dose (3mg daily).	Common side effects: hypoglycemia, nausea, vomiting, diarrhea, constipation, headache Serious side effects: risk of thyroid tumors. Contraindicated in patients with a personal or family history of medullary thyroid cancer or Multiple Endocrine Neoplasia Syndrome type 2.Cases of acute pancreatitis have been reported If patient does not tolerate dose increase, may need to delay escalation for additional week. Discontinue if patient does not tolerate 3mg dose – no documented efficacy at lower doses.	Saxenda (brand only): $1440
Combination Products			

Sympathomimetic + antiepileptic Phentermine/Topiratmate ER (Qsymia®)	Titration: 3.75mg/23mg every morning for 14 days then 7.5mg/46mg every morning Max dose: 15mg/92mg daily in the morning	Common side effects: paresthesia, xerostomia, constipation, headache Topiramate is proven to be teratogenic – avoid in pregnancy Dose adjustment needed in renal dysfunction and moderate-severe hepatic impairment Controlled substrance (C-IV) Taper needed if discontinuing therapy	Qsymia (brand only): $216--$239
Opioid antagonist + aminokenone antidepressant Naltrexone/bupropion (Contrave®)	Titration: 8mg/90mg once daily in the morning for 1 week, then increase in 8mg/90mg increments weekly until maintenance dose of 16mg/180mg twice daily is reached Max dose: 32mg/360mg daily in two divided doses	Common side effects: nausea, constipation, headache, vomiting Serious side effects: depression, mania Contraindicated in patients with seizure disorder Dose adjustment needed in renal dysfunction Do not administer with high fat meals	Contrave (brand only): $334

*Price based on average wholesale price (AWP) for 30 days of generic unless otherwise stated

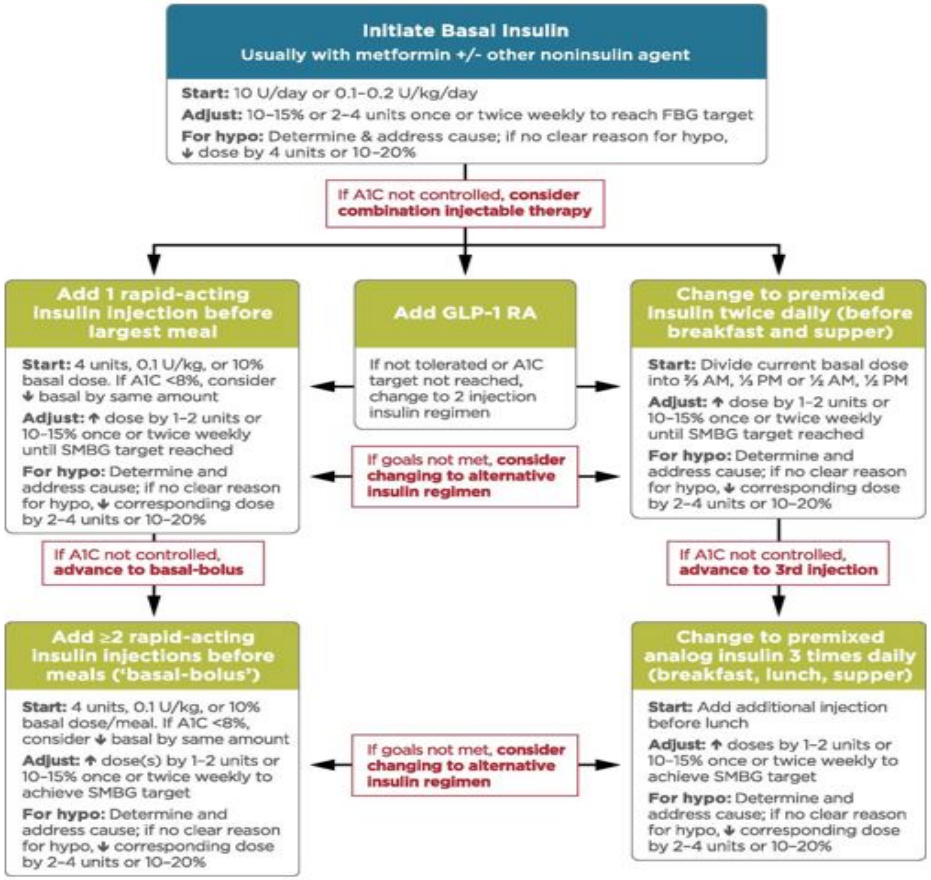
Efficacy should be assessed at least monthly for the first 3 months of treatment. If weight loss is <5% or if there are any safety issues, a new agent or treatment approach should be considered.

Antihyperglycemic Therapy in Adults with Type 2 Diabetes



Initial Approval Date and Reviews:	**Most Recent Revision and Approval Date: May 2018**	**Next Scheduled Review Date:**
3/ 2011, 7/2013, 3/2014, 3/ 2015, 5/2016, 5/2017, 5/2018		May 2019 Ambulatory Best Practice Condition: Diabetes Mellitus

Combination injectable therapy for type 2 diabetes.



American Diabetes Association Dia Care 2017;40:S64-S74

American Diabetes Association.

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	Efficacy*	Hypoglycemia	Weight Change	CV Effects		Cost	Oral/SQ	Renal Effects		Additional Considerations
				ASCVD	CHF			Progression of DKD	Dosing/Use considerations	
Metformin	High	No	Neutral (Potential for Modest Loss)	Potential Benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 Inhibitors	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin†	Benefit: canagliflozin, empagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Canagliflozin: not recommended with eGFR <45 • Dapagliflozin: not recommended with eGFR <60; contraindicated with eGFR <30 • Empagliflozin: contraindicated with eGFR <30	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide, exenatide extended release Benefit: liraglutide†	Neutral	High	SQ	Benefit: liraglutide	• Exenatide: not indicated with eGFR <30 • Lixisenatide: caution with eGFR <30 • Increased risk of side effects in patients with renal impairment	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Potential Risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required; can be used in renal impairment	• Potential risk of acute pancreatitis • 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**] • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide & 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	Neutral	• Lower insulin doses 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			

Initial Approval Date and Reviews:	**Most Recent Revision and Approval Date: May 2018**	**Next Scheduled Review Date:**
3/ 2011, 7/2013, 3/2014, 3/ 2015, 5/2016, 5/2017, 5/2018		May 2019 Ambulatory Best Practice Condition: Diabetes Mellitus

Recommendations for the Treatment of Confirmed Hypertension in People With Diabetes

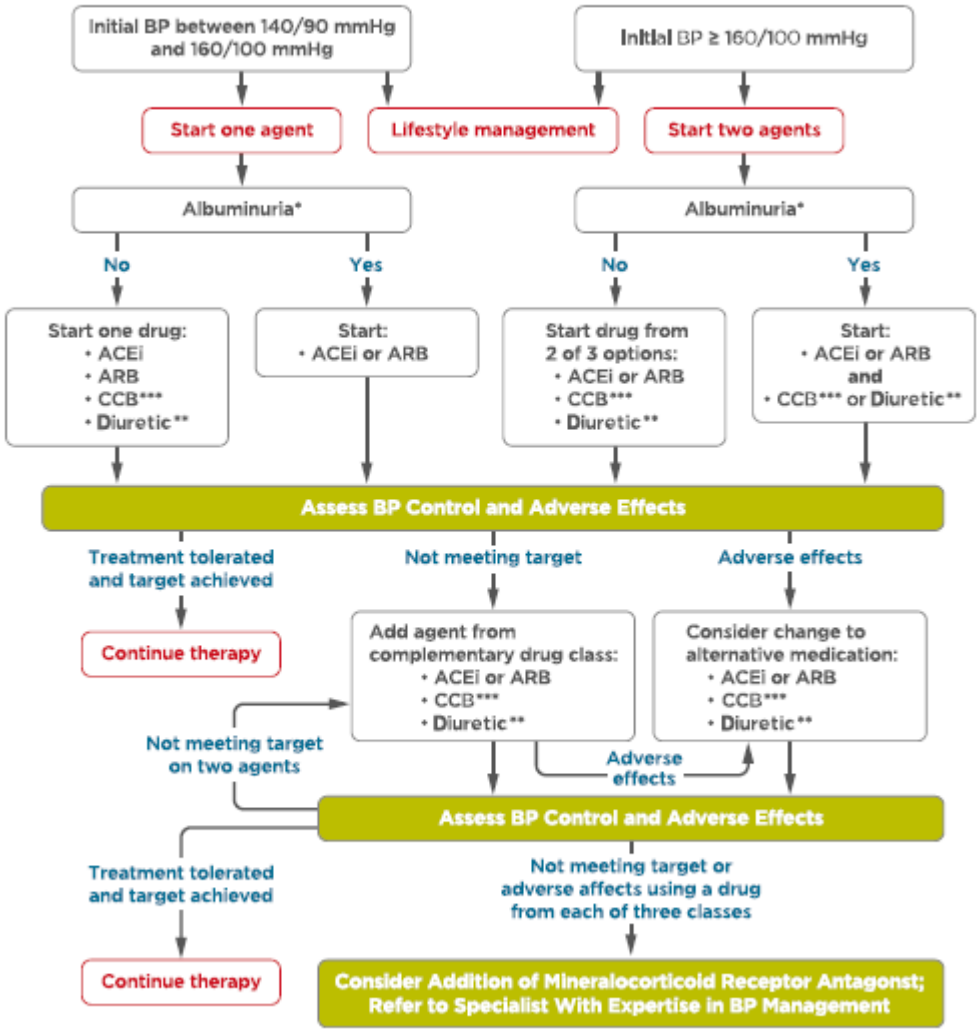

Figure 9.1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with UACR 30–299 mg/g creatinine and strongly recommended for patients with UACR ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker. BP, blood pressure. This figure can also be found in the ADA position statement "Diabetes and Hypertension" (5).