Midland Quality Alliance

MIDLAND QUALITY ALLIANCE

ALGORITHM FOR MANAGEMENT OF

ADULT TYPE II DIABETES PATHWAY

AND

PHARMACOLOGICAL MANAGEMENT

Revised May 2018

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Adult Type 2 Diabetes Pathway

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Prevention of Diabetes

- For people with pre-diabetes, lifestyle interventions (healthy eating, physical activity, and sustained weight loss of 5%-7%) has been shown to delay the onset of type 2 diabetes.
    - Midland Health's Lifestyle Medicine Center offers a variety of resources and services to assist with lifestyle modifications. Classes and workshops such as the Lifestyle Medicine Clinic assists with lifestyle interventions under the supervision of an experienced physician (Dr. Padmaja Patel).
    - The Diabetes and Nutrition Learning Center provides classes and appointments that covers topics such as whole food plant based nutrition, diabetes self-management training, dietician-assisted medical nutrition therapy, etc. Please visit the website for more details and contact information.
- Metformin can be considered in addition to lifestyle interventions in delaying the onset of type 2 diabetes, especially in those with prediabetes and with BMI ≥ 35kg/m^2, those aged <60 years, and women with prior Gestational Diabetes Mellitus (GDM)

Screening for Type 2 Diabetes

Table 1 – Criteria for testing for diabetes or prediabetes in asymptomatic adults
1. Testing should be considered in overweight or obese (BMI ≥ 25kg/m^2 or ≥ 23 kg/m^{2}in Asian Americans) adults 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 cardiovascular disease (CVD) - Hypertension (≥140/90 mmHg or on therapy for hypertension) - HDL cholesterol level <35 mg/dL (0.99 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 (AIC ≥5.7%, 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 45 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

Source: Standards of Medical Care in Diabetes – 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S13-S27

Diagnosis

Diagnosis for an **asymptomatic** patient requires two abnormal test results, which can be from the same test on different days, or from different test performed on either the same day or different days. If only one test comes back abnormal, repeat the abnormal test on a different day. An abnormal result on the repeated test is diagnostic for diabetes.

Diagnosis for a patient **with classic symptoms of hyperglycemia** (i.e., polyuria, polydipsia, weight loss) can be made with a single random plasma glucose result of 200 mg/dL or higher. A repeat measurement is not needed.

Table 2 – Diagnosing diabetes

Test	Results	Interpretation
HbA1c	6.5% or higher	Diabetes
	5.7-6.4%	Impaired glucose tolerance
	Lower than 5.7%	Normal
Random plasma glucose	200 mg/dL or higher	Diabetes
	140-199 mg/dL	Impaired glucose tolerance
	Lower than 140 mg/dL	Normal
Fasting plasma glucose	126 mg/dL or higher	Diabetes
	100-125 mg/dL	Impaired glucose tolerance
	Lower than 100 mg/dL	Normal

Lifestyle Modifications and Non-Pharmacological Options

1. Diet and physical activity
    a. There is some evidence that intensive programs of lifestyle interventions targeting patients with impaired fasting blood glucose reduce the incidence of type 2 diabetes. Lifestyle interventions include dietary and physical activity counseling. Please visit the Lifestyle Medicine Center [or call (432)221-LIFE (5433)] and the Diabetes and Nutrition Learning Center for more information.
    b. A low-carbohydrate Mediterranean diet rich in fruits, vegetables, nuts, whole grains, legumes, fish, and healthy fats from plant and fish sources is recommended.
    c. It is recommended to have at least 150 min/week of moderate-intensity physical activity, such as brisk walking. For patients who have been inactive, recommend to slowly work up to at least 30 minutes of moderate physical activity per day. If unable to be active for 30 minutes at one time, suggest accumulating activity in 10- to 15-minute sessions throughout the day.

Initiating Pharmacological Therapy for Glucose Lowering in Type 2 Diabetes

1. Initiate metformin (first-line glucose-lowering agent).
2. In patients with type 2 diabetes not controlled on metformin monotherapy, initiate combination therapy using a second-line agent (sulfonylurea, thiazolidinediones [TZDs], DPP-4, basal insulin, SGLT-2 inhibitor, or GLP-1 receptor agonist).
    a. Consider factor such as comorbidities, patient preferences (e.g., oral vs injectable, side effect profile, cost to patient, etc.), adherence, and drug characteristics.
3. **Highlighted factors in differentiating the second-line agents:**
    a. Sulfonylureas and basal insulin are associated with higher incidence of hypoglycemia; with a rate of 1-3% of severe hypoglycemic episodes associated with sulfonylureas.
    b. TZDs are associated with higher rates of CHF (<0.2% in general studies and 2-5% in high-risk patients with CVD). It is contraindicated in Class III or IV heart failure patients.
    c. Weight gain of <5 kg is associated with TZDs, sulfonylureas, and insulin. DPP-4 inhibitors are associated with no weight change, and SGLT-2 inhibitors and GLP-1 agonists are associated with modest weight loss.
    d. GLP-1 agonists are associated with increased risk of gastrointestinal side effects.
    e. Some patients may prefer oral over an injectable agent. Also, cost differences between older and newer therapies are significant and may determine patient decisions.
    f. No recommendations are made for or against meglitinides and alpha-glucosidase inhibitors.
4. May consider a third-line oral agent if HbA1c is within 1% of goal while on metformin plus second-line agent. Consider adding basal insulin as third-line agent if HbA1c is ≥1% above goal.

Glycemic Control Target

1. HbA1c goal of <7% is reasonable for many non-pregnant adults.
2. Less stringent HbA1c goal of <8% may be appropriate for patients with history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes despite appropriate management.
3. More stringent HbA1c goal of <6.5% can be considered in certain patients if it can be achieved without significant hypoglycemia or other adverse effects of treatment.

FIGURE 1: Type 2 Diabetes Medication Treatment Algorithm

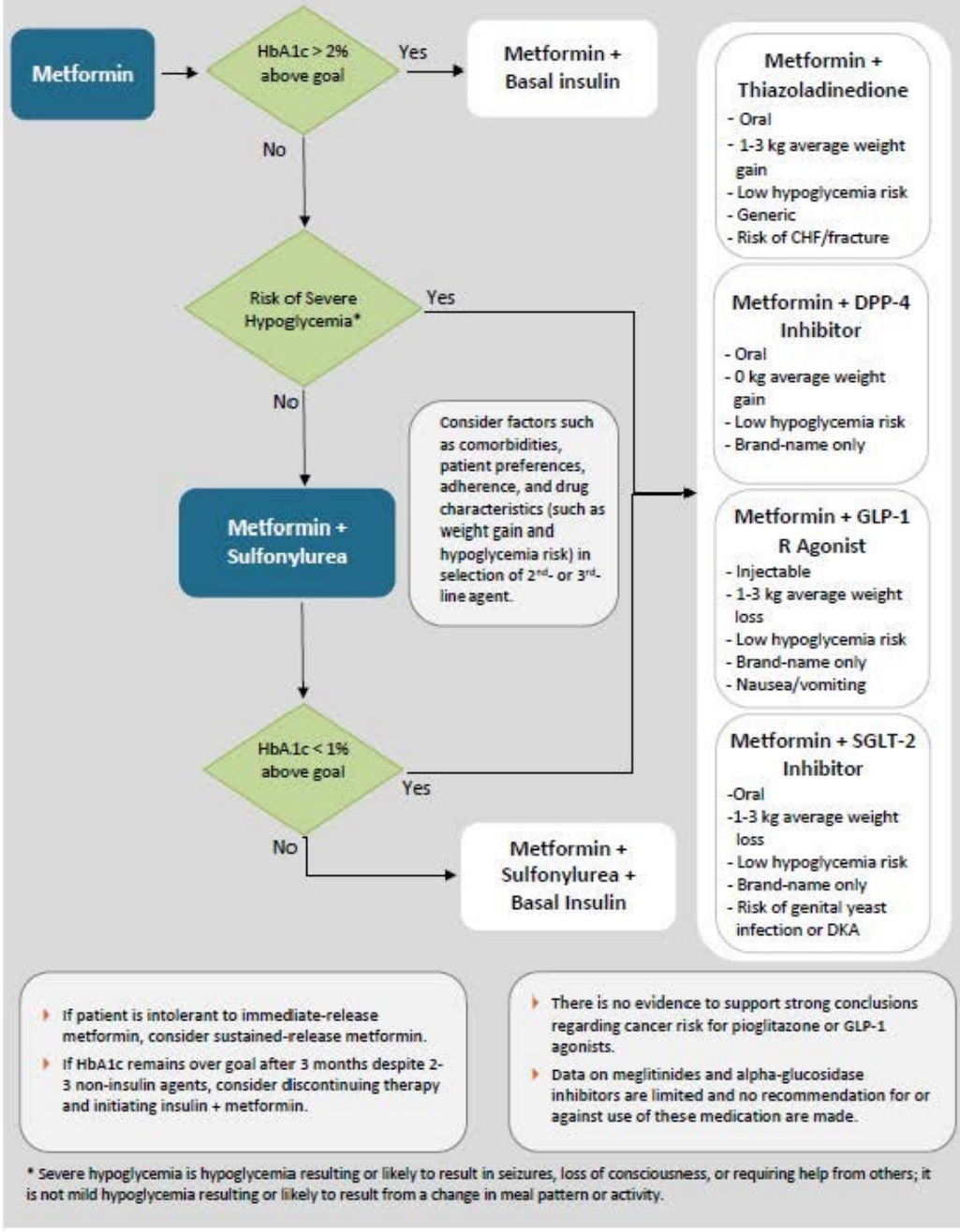

Figure 1 – Type 2 Diabetes Medication Treatment Algorithm. Source: Kaiser Permanente National Adult Diabetes Clinical Guidelines 2016

Pharmacological options flowchart

Metformin

Metformin should be titrated as tolerated. A reasonable initial titration schedule is:

- 500 mg ½ tab once daily x 7 days;
- 500mg 1 tab once daily x 7 days;
- 500mg 1 tab twice daily.
- Therapeutic goal: 1000mg twice a day or 850mg three times a day.

If patient does not experience any GI side effects after 2-3 days, the dose may be titrated to goal more quickly.

If a patient develops GI side effects, reduce the dose and reassess. Consider a more conservative titration schedule starting with 500mg ¼ tab (125 mg) orally once daily; alternatively, consider prescribing the XL formulation for patients who cannot tolerate the dose with regular release formulation.

Precaution with prescribing metformin:

- **Reduce metformin** to a maximum of 500mg twice daily in patients with eGFR 30-45
- **Discontinue metformin** in patients with eGFR < 30.
- **Avoid use of metformin** in patients with known binge or excessive alcohol use. Instruct patients to avoid excessive acute or chronic alcohol use.
- **Suspend use of metformin** if a patient is to undergo a surgical procedure or be given iodinated contrast media for a radiological procedure. Restart metformin when normal renal function is verified. Metformin should be withheld in patients with dehydration and/or prerenal azotemia.

Basal Insulin (NPH insulin is preferred)

Check fasting blood glucose (FBG) every day and get weekly average. The target is mean FBG of 80-130 mg/dL. For adults over age 65, a higher (140 mg/dL) may be considered.

- Less than 200 lb, FBG lower than 200 – 12 U and up by 4 U/week.
- Less than 200 lb, FBG higher than 200 – 16 U and up by 8 U/week.
- More than 200 lb, FBG lower than 200 – 20 U and up by 4 U/week.
- More than 200 lb, FB higher than 200 – 30 U and up by 10 U/week.

Treat-to-target strategy:

1. Initial dose of 10 units basal insulin at bedtime.
2. If FBG is higher than 130, increase bedtime insulin dose by 1 unit.
3. Continue increasing bedtime insulin dose by 1 unit at a time until FBG is in the target range.
4. If FBG is lower than 80 mg/dL, decrease bedtime insulin dose by 1 unit.
5. Continue decreasing bedtime insulin dose by 1 unit at a time until FBG is in the target range.

If HbA1c is higher than 7.0% and blood glucose checks before lunch, dinner, and bedtime are indicating a steady rise in BG throughout the day, the patient very likely needs daytime insulin therapy.

Sulfonylureas (glimepiride is preferred, glipizide is alternative)

For preferred sulfonylurea (**glimepiride**), a reasonable titration schedule is:

- Increase to 2 mg once daily for 1-2 weeks;
- Increase by 2 mg once daily at 1- to 2-week intervals to maximum of 8 mg once daily.

For alternative sulfonylurea (**glipizide**), a reasonable titration schedule is:

- 5 mg ½ tab twice daily x 7 days;
- 5 mg 1 tab twice daily x 7 days;
- 5 mg 2 tabs twice daily x7 days.

Consider prescribing the XL formulation for patients who cannot tolerate regular release formulation.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (Empagliflozin is preferred)

Empagliflozin is recommended for a subset of patients who are currently on metformin or have a contraindication or intolerance to metformin **and** have a history of clinical atherosclerotic cardiovascular disease (ASCVD) and eGFR > 45.

- Initiate with 12.5mg once daily.

Dapagliflozin and canagliflozin are not recommended.

Glucagon-like peptide-1 (GLP-1) receptor agonists (Bydureon is preferred)

Exenatide XR (Bydureon) may be appropriate for a subset of patients who are on the maximum tolerated dose of metformin and have HbA1c < 9.0% and weight gain with insulin. Please consult endocrinology.

- Initiate with 2 mg subcutaneously once every seven days.

Table 3 – Drug-specific and patient factors to consider when selecting antihyperglycemics in adults with type 2 diabetes

	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			

†FDA approved for CVD benefit. CVD, cardiovascular disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; NASH, nonalcoholic steatohepatitis; RAs, receptor agonists; SQ, subcutaneous; T2DM, type 2 diabetes. Source: Standards of Medical Care in Diabetes – 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S77

Hypertension and Diabetes – Pharmacological Management

1. Systolic and diastolic blood pressure goals are <140 mmHg and <90 mmHg respectively.
2. Lower systolic and diastolic blood pressure targets of <130/80 mmHg may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden.

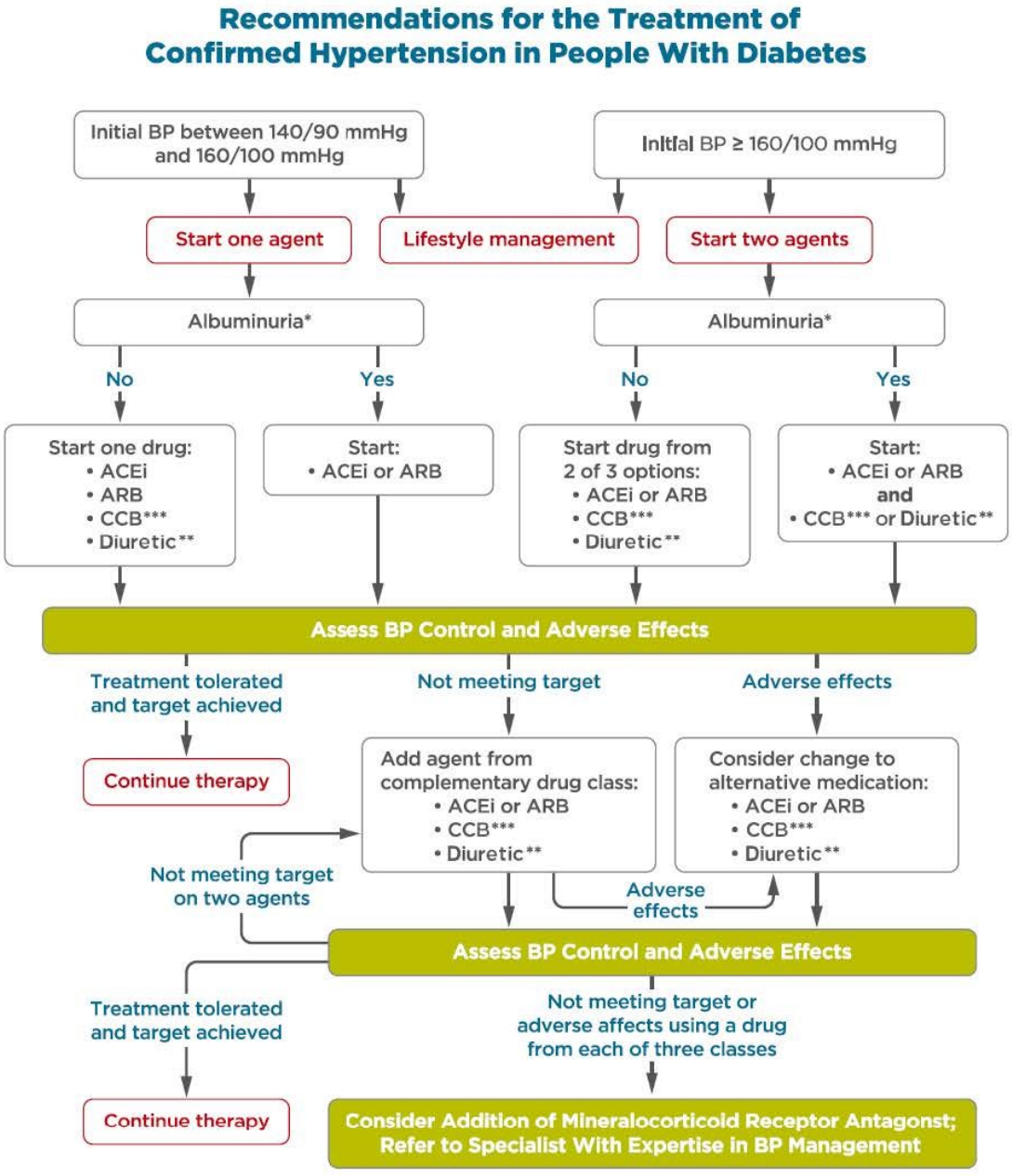

Figure 2 – Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or ARB is suggested to treat hypertension for patients with urinary albumin-to-creatine ratio (UACR) 30-299 mg/g creatinine and strongly recommended for patients with UACR ≥300 mg/g 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. Source: Standards of Medical Care in Diabetes – 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S90

Lipid Management

1. There is no recommendation for or against specific low-density lipoprotein cholesterol (LDL-C) or non-HDL-C targets for the primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD).

Table 4 – Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD	Recommended statin intensity^ and combination treatment*
<40 years	No	None †
	Yes	High - If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe)#
≥40 years	No	Moderate‡
	Yes	High - If LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe)

*In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL, high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin-based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences. Source: Standards of Medical Care in Diabetes – 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S92

Table 5 – High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30% to 50%)
Atorvastatin 40-80mg	Atorvastatin 10-20mg
Rosuvastatin 20-40mg	Rosuvastatin 5-10mg
	Simvastatin 20-40mg
	Pravastatin 40-80mg
	Lovastatin 40mg
	Fluvastatin XL 80mg
	Pitavastatin 2-4mg
*Once-daily dosing. XL, extended release.	

Source: Standards of Medical Care in Diabetes – 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S92

2. Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is not recommended.
3. Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effect, and is not recommended.

Antiplatelet therapy

1. Use aspirin therapy as a secondary prevention strategy in those with diabetes and history of ASCVD. If allergic to aspirin, should use clopidogrel.
2. Dual antiplatelet therapy (with low dose aspirin and a P2Y12 inhibitor) is recommended for 1 year after an acute coronary syndrome and may have benefits beyond this period.
3. In diabetes patients aged ≥50 years with at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or albuminuria) may consider aspirin therapy (75-162 mg/day) if not at increased risk of bleeding.

Coronary Heart Disease

1. In patients with known ASCVD, consider ACE inhibitor or ARB therapy to reduce risk of cardiovascular events
2. In patients with prior myocardial infarction, Beta-blockers should be continued for at least 2 years after event.
3. In patients with type 2 diabetes and stable congestive heart failure (CHF), metformin may be used if glomerular filtration rate remains >30 mL/min but should be avoided in unstable or hospitalized patients with CHF.
4. In patients with type 2 diabetes and established ASCVD, consider adding empagliflozin or liraglutide after beginning lifestyle changes and metformin, to reduce major adverse cardiovascular morbidity and mortality.

Diabetic Kidney Disease

1. In nonpregnant patients with diabetes and hypertension, ACEi or ARB is recommended for those with elevated urinary albumin-to-creatinine ratio (≥30 mg/g creatinine) and/or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

Follow-up and Monitoring

Table 6 – Periodic monitoring of conditions and complications

Condition/complication	Tests	Frequency
Hypertension	BP taken with appropriate size cuff using optimal technique	Every visit
Blood glucose control	HbA1c	Every 3 months until target level is reached; thereafter, at least every 12 months
Foot ulcers	Physical exam focused on ankle reflexes, dorsalis pedis pulse, vibratory sensation, and 5.07 monofilament touch sensation performed by a provider qualified to determine the level of risk for foot ulcers	Patients at **very high risk**[1] should be seen every 3 months by a wound care nurse. Patients at **high risk**[1] and **average risk**[1] should be screened annually
Microalbuminuria	Microalbumin/creatinine ratio	Annually
Retinopathy	Dilated eye exam by a trained eye services professional **or** Nondilated digital photography followed by a comprehensive exam for those who test positive	Patients **with** evidence of retinopathy should be screened annually Patients **without** evidence of retinopathy should be screened every 2 years
Electrolyte and chemistry abnormalities	Serum creatinine **and** Serum potassium	At least annually

[1] Foot-ulcer risk definitions:

- **Very high risk:** these are patients with a previous foot ulcer, amputation, or major foot deformity (claw/hammer toes, bony prominence, or Charcot deformity).
- **Increased risk:** these patients are insensate to 5.07 monofilament at any site on either foot or who have bunions, excessive corns, or callus.
- **Average risk**: these patients have none of the aforementioned complications.

Source: Kaiser Permanente Washington Type 2 Diabetes Screening and Treatment Guidelines 2017

Recommended immunizations

Table 7 – Recommended immunizations for patients with diabetes [1]	
Immunization	**Frequency**
Influenza	Annually, as early as possible when vaccine becomes available
Pneumococcal polysaccharide	- Once between ages 19 and 64 - Booster after age 65 years (at least 5 years after previous dose)
Hepatitis B [2]	- Three-dose series for ages 19-59 years - Ages 60 years and older, depending on risk
[1] See the CDC Recommended Adult Immunization Schedule for more detailed information [2] Results from observational studies suggest that patients with diabetes are at higher risk for hepatitis B compared with patients without diabetes (CDC 2011)	

Source: Kaiser Permanente Washington Type 2 Diabetes Screening and Treatment Guidelines 2017

References

Centers for Disease Control and Prevention (CDC). Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2011;60(50):1709-1711.

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Standards of Medical Care in Diabetes – 2018. *Diabetes Care* 2018; 41 (Suppl. 1)