

# Management of Type 2 Diabetes Mellitus

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**Patient population.** Adults with, or at risk for Type 2 Diabetes

**Objectives. To reduce morbidity and mortality by** improving adherence to important recommendations for preventing, detecting, and managing diabetic complications.

## Key points

**Prevention.** Type 2 diabetes may be delayed or prevented through diet, exercise, and pharmacologic interventions. [IA]

**Screening.** Consider screening every 3 years, beginning at age 45, or annually at any age if BMI  $\geq 25$  kg/m<sup>2</sup> [IID], history of hypertension [IB], gestational diabetes [IC], or other risk factors.

**Diagnosis.** Diagnosis is made by (1) an A1c  $\geq 6.5\%$ , (2) a fasting glucose  $\geq 126$  mg/dL, (3) a 2h post 75 gm glucose load glucose of  $\geq 200$  mg/dL, or (4) a random glucose  $\geq 200$  mg/dL with symptoms, confirmed by a repeat or second test. Diagnostic criteria are shown in Table 1. An abbreviated differential diagnosis of diabetes is shown in Table 2. It is important to recognize diabetes types due to insulin deficiency as the pathophysiology directs treatment recommendations. An A1c of  $\geq 6.5\%$ , confirmed by second test, is diagnostic of diabetes. Alternatively, diabetes is diagnosed by two separate fasting glucose tests  $\geq 126$  mg/dL; with symptoms, a glucose  $\geq 200$  mg/dL confirmed on a separate day by a fasting glucose  $\geq 126$  mg/dL; or 2-hour postload glucose  $\geq 200$  mg/dL during an oral glucose tolerance test (OGTT). [IC].

**Treatment.** Essential components for diabetes treatment include: diabetes self-management education and support, lifestyle interventions, and goal setting (Table 3); glycemic management (Tables 4-7); and pharmacologic management of hypertension (Table 8) and hyperlipidemia.

**Screening for comorbidities and complications.** Routine screening and prompt treatment for cardiovascular risk factors (hypertension, hyperlipidemia, tobacco use) and for microvascular disease (retinopathy, nephropathy, neuropathy) are recommended in the time frames below.

**Treatment of comorbidities and complications.** Table 9 summarizes Management of risk factors and complications. Diet, exercise, and pharmacologic interventions should be initiated for: Hypertension [IA], Hyperlipidemia [IA], Cardiovascular risk reduction [IA], Diabetes complications as indicated.

Each regular diabetes visit	Annually
<ul style="list-style-type: none"><li>• Measure blood pressure and ensure controlled. [IA]</li><li>• Optimize glycemic control. [IA]. Review CGM or glucose readings 2 weeks after initiation of insulin, or 6 weeks after non-insulin agent.<ul style="list-style-type: none"><li>– Monitor A1c every 3 months if at target and taking insulin.</li><li>– Monitor every 6 months if at target and not on insulin. [IC].</li></ul></li><li>• Review and reinforce diet and physical activity. [IID]</li><li>• Monitor weight, calculate BMI. [IID]</li><li>• Inspect feet at each visit if neuropathy present. Otherwise, perform visual foot exam and neuropathy evaluation annually. [IA]</li><li>• Provide smoking cessation counseling for those with tobacco dependence [IB].</li><li>• Review and reinforce key self-management goals (Table 3) [IA].</li></ul>	<ul style="list-style-type: none"><li>• Dilated retinal examination performed by eye care specialist.<ul style="list-style-type: none"><li>– Biennial exam is appropriate if both A1c and blood pressure are in target range and previous eye exam was within normal limits.</li><li>– Any history of retinopathy or macular edema requires annual exam, or more frequently per eye care provider. [IB]</li><li>– Treat retinopathy. [IA]</li></ul></li><li>• Screen for microalbuminuria. [IB] Prescribe an ACE inhibitor (or ARB, if ACE contraindicated) for microalbuminuria or proteinuria. [IA]</li><li>• Perform serum creatinine and estimated glomerular filtration rate (eGFR). [ID]</li><li>• Monofilament testing of feet (Table 10). [IA]</li><li>• Prescribe a moderate dose statin; measure lipids for adherence.</li><li>• Assess smoking status. [IB]</li><li>• Review and reinforce all self-management goals (Table 3).</li><li>• Vaccinate annually for influenza and confirm, or administer pneumococcal and hepatitis B vaccinations.</li></ul>

**Special considerations: Pregnancy.** Preconception counseling and glycemic control targeting a normal A1c in women with diabetes mellitus is essential to reduce the risk of congenital malformations and results in optimal maternal and fetal outcomes. [1B]

**\* Strength of recommendation:**

I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

**Level of evidence supporting a diagnostic method or an intervention:** A=Systematic review of randomized controlled trials; B=Randomized controlled trials; C=Systematic review of non-randomized controlled trials; group observational studies; D=Individual observation descriptive studies; E=Expert opinion

**Table 1. Diagnosis of Diabetes: Diagnostic Tests and Glucose Values**

Diagnostic Test	Normal	Pre-diabetes	Diabetes
Hemoglobin A1c (A1c) <sup>a</sup>	<5.7%	5.7-6.4%	≥6.5%
Fasting plasma glucose (FPG) <sup>a</sup>	<100 mg/dL	100-125 mg/dL	≥126 mg/dL
Random plasma glucose (RPG) <sup>a,b</sup>	<130 mg/dL	130-199 mg/dL	≥200 mg/dL
Oral glucose tolerance test (OGTT) 2 hours after a 75 gm oral glucose load	<140 mg/dL	140-199 mg/dL	≥200 mg/dL

<sup>a</sup> The diagnosis must be confirmed by a second test.

<sup>b</sup> A random glucose of 130-199 mg/dL is abnormal and further testing is indicated, eg, fasting glucose, OGTT, or hemoglobin A1c.

**Table 2. Abbreviated Differential Diagnosis of Diabetes**

<u>Type 1 diabetes</u>	<u>Diabetes due to other endocrinopathies</u>	<u>Drug induced diabetes</u>
<u>Type 2 diabetes</u>	<ul style="list-style-type: none"> <li>• Acromegaly</li> <li>• Cushing's syndrome</li> <li>• Pheochromocytoma</li> <li>• Glucagonoma</li> <li>• Others</li> </ul>	<ul style="list-style-type: none"> <li>• Transplant or steroid related diabetes</li> <li>• HIV/AIDS treatment related diabetes</li> <li>• Antipsychotic medication related diabetes<sup>1</sup></li> <li>• Others</li> </ul>
<ul style="list-style-type: none"> <li>• Ketosis Prone Type 2</li> <li>• Monoclonal Gammopathies</li> <li>• Liver disease</li> </ul>	<u>Monogenic forms of diabetes</u>	<u>Diabetes as part of congenital syndrome</u>
<u>Diabetes due to diseases of the exocrine pancreas (Type 3c)</u>	<ul style="list-style-type: none"> <li>• Maturity-onset diabetes of the young</li> <li>• Diabetes due to point mutations in mitochondrial DNA</li> <li>• Lipotrophic diabetes</li> <li>• Others</li> </ul>	<ul style="list-style-type: none"> <li>• Congenital rubella syndrome</li> <li>• Down syndrome</li> <li>• Turner syndrome</li> <li>• Wolfram syndrome</li> <li>• Myotonic dystrophy</li> <li>• Prader-Willi syndrome</li> <li>• Bardet-Biedl</li> <li>• Others</li> </ul>
<ul style="list-style-type: none"> <li>• Pancreatitis, pancreatectomy, or pancreatic adenocarcinoma</li> <li>• Cystic fibrosis</li> <li>• Hemochromatosis</li> <li>• Others</li> </ul>		

**Table 3. Self-Management Topics\***

**At each regular visit (eg, every 3-6 months) ask about:**

- 1) **Diet / Meal plan:** Review daily meal content, snacks, drinks. Encourage reduction in sugary drinks, decrease highly processed carbohydrates, 5 a day vegetables and fruits. Consider providing a meal plan or referral to a dietician.
- 2) **Physical Activity:** Ask about current level of physical activity including occupational, transportation related and leisure time physical activity. Encourage a minimum of 30 min / day at least 5 days a week, intensity equivalent to a brisk walk. Resistance exercise (body weight exercises and weight lifting) has been shown to improve glycemia both alone and in combination with aerobic exercise such as walking, running or cycling.
- 3) **Weight Gain / Loss:** Review weight trajectory over the past 3 to 6 months. If weight is stable or decreasing give positive feedback and encouragement. If weight gain, see the section on obesity for weight loss strategies.
- 4) **Medication adherence:** Review diabetes medication dose and schedule. For each medication: Over the last 7 days, how many days were you able to take your [specific medicine] exactly as prescribed? Do you sometimes have trouble affording medication? Are you worried about side effects? If hypertension, repeat for blood pressure medication.
- 5) **Home Blood Pressure Monitoring:** Do you have a home blood pressure monitor? Review log of blood pressure. If no log, ask: Over the last 7 days, about how many times a day did you check your blood pressure? What time of day do you typically check it? What was the range of blood pressure? Review blood pressure goals.
- 6) **Home Blood Glucose Monitoring:** Do you check your blood sugar at home? Review log of blood glucose. If no log, ask: Over the last 7 days, about how many times a day did you check your blood sugar? What time of day do you typically check it? What was the range of blood sugar? Review blood sugar goals.
- 7) **Symptoms of Hypoglycemia and Hyperglycemia:** How many times in the past 7 days have you had symptoms of low blood sugar such as sweating, shakiness, weakness, dizziness, difficulty with concentration or confusion. How many times in the past 7 days have you had symptoms of high blood sugar such as blurry vision, drinking a lot or urinating a lot.
- 8) **Distress, Stress, Coping, Depression:** Do you often feel overwhelmed by all you have to do to manage your diabetes? Are you feeling more stressed than usual? How do you cope with this stress? How is diabetes affecting you emotionally? Are your emotions interfering with your ability to manage your diabetes? How do you handle these feelings?
- 9) **If diabetic neuropathy:** Do you check your feet each day? Review home foot care basics. Consider ordering diabetic shoes if needed.

**Ask about ask about (at least annually):**

**Identification.** Do you wear or carry diabetes identification?

**If taking insulin: Injection sites for insulin.** Do you rotate your injection sites around your abdomen and inspect sites?

**For premenopausal women:** What are your plans for pregnancy? What are you using for birth control?

\* Based on expert opinion.

**Table 4. Targeting and Monitoring Glycemic Control in Patients with Diabetes Mellitus**

**Target A1c: assess individual's risks and benefits of treatment.**

Factors heightening risk of tight control (hypoglycemia)

History of severe hypoglycemia (inability to treat without assistance).  
Hypoglycemia unawareness.  
Advanced cardiovascular, cerebrovascular and especially renal disease.  
Autonomic neuropathy (especially cardiac).  
Functional or cognitive limitations that cause inability to safely carry out treatment regimen.

Factors limiting benefit of tight control

Severe comorbidities (eg, end-stage cancer, severe heart failure).  
Limited life expectancy (<10 years)  
Adverse effects of treatment

If neither factors heightening risk nor limiting benefit of tight control: prevent long-term complications and early mortality.

<6.5% Consider for:

- Patients with long life expectancy (eg, younger adults) IIC
- Reproductive age women (protect fetus) IC
- Patients with low risk of hypoglycemia IIC

≤7% General target.

If factors heightening risk of tight control (hypoglycemia)

<7% Consider if achievable with medications that do not incur risk of hypoglycemia (acarbose, metformin, TZDs, GLP-1s, or SGLT-2s). IA

<8% General target if using medications increasing risk of hypoglycemia. IA

If factors limiting benefit of tight control: minimize symptoms of hyperglycemia and controlling glucose as well as possible without incurring side effects or excessive treatment burden.

<8% General target. IA

<8.5% Consider if multiple coexisting chronic illnesses, cognitive impairment, or functional dependence. IIC

<9% Consider for very sick patients with limited life expectancy in order to avoid acute symptoms. IIE

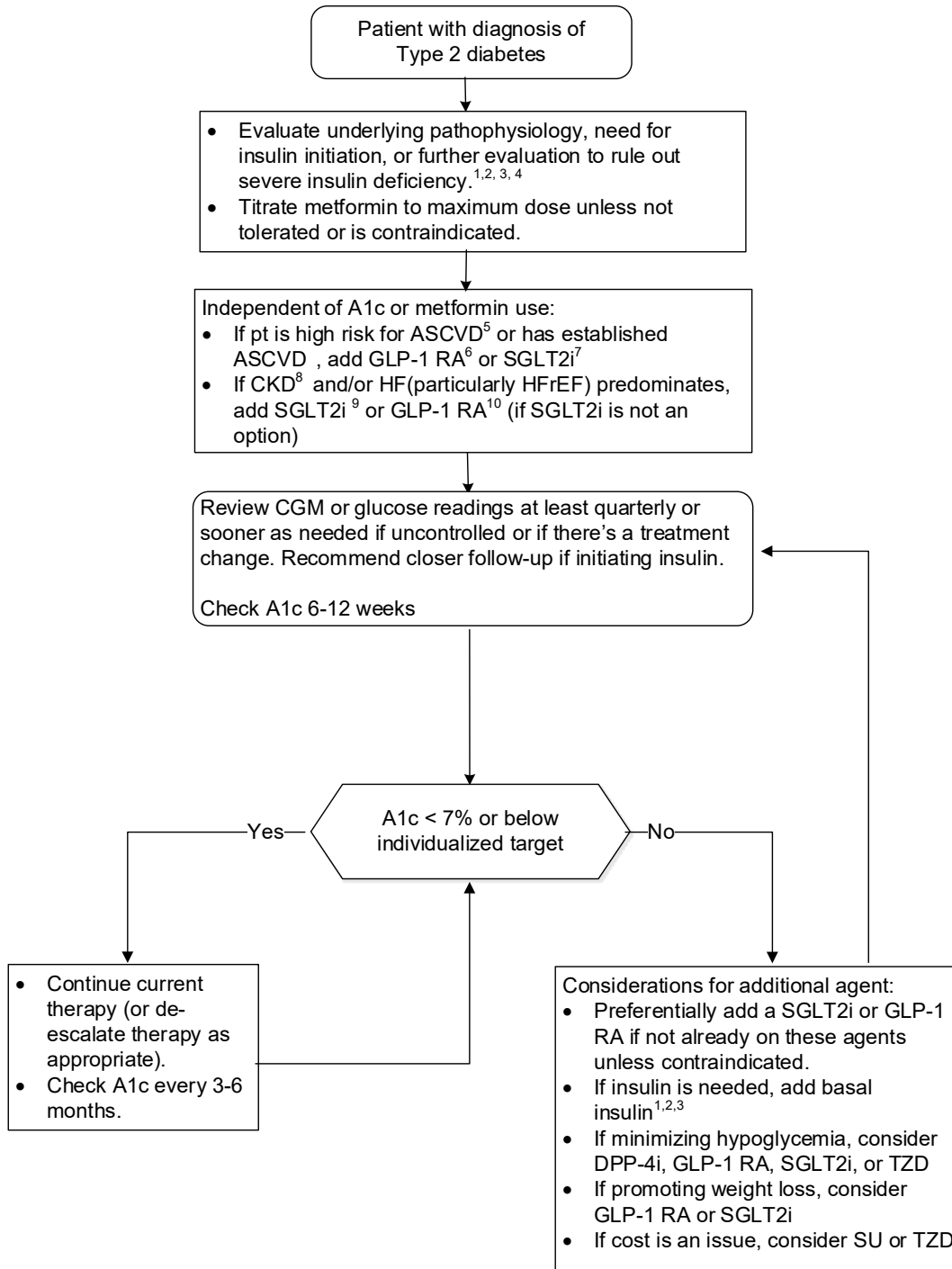
**If A1c is above goal:**

1. Assess treatment regimen.
2. Diabetes/dietary education or referral.
3. Start a new medication or increase medication.

**Reassess Glycemia:**

Review CGM or glucose readings 2 weeks after initiation of insulin or 6 weeks after non-insulin agent  
Recheck A1c in 3 months for patients not at target or with recent changes to medications/lifestyle or on insulin.  
Recheck A1c in 6 months for patients at target and who are not on insulin and have not had a recent change in medications.

**Figure 1. Medication Flowchart**



<sup>1</sup> Patients who are diagnosed at age <30 years old, require insulin < 6 months after diagnosis, have normal BMI or recent weight loss, history of pancreatitis, recent treatment with a check point inhibitor or personal/family history of autoimmune disease, consider screening for insulin deficiency with C-peptide/glucose and anti-GAD antibody.

<sup>2</sup> Insulin therapy is recommended to be initiated immediately in patients with one of the following conditions: A1c >10%, T2DM diagnosis and symptomatic hyperglycemia, blood glucose levels  $\geq 300$  mg/dL, evidence of catabolism (weight loss, severe hypertriglyceridemia, ketosis).

<sup>3</sup> Refer to Insulin Initiation and Insulin Adjustment protocols

<sup>4</sup> SGLT-2i increase risk of DKA in patients with severe insulin deficiency, so use in caution.

<sup>5</sup> Indicators of high ASCVD risk: patients  $\geq 55$  years of age with coronary, carotid, or lower-extremity artery stenosis >50% of left ventricular hypertrophy

<sup>6</sup> Proven GLP-1 RA with CVD benefit: Evidence for liraglutide, dulaglutide, semaglutide (injectable)

<sup>7</sup> Proven SGLT-2i with CVD benefit: Evidence for empagliflozin, canagliflozin,

<sup>8</sup> Proven SGLT-2i for CKD: Specifically, eGFR 30-60 mL/minute/1.73 m<sup>2</sup>, or Urine albumin-to-creatinine ratio (UACR) >30mg/g, particularly UACR>300mg/g

<sup>9</sup> Proven SGLT-2i for reduction in HF and to reduce CKD progression in cardiovascular outcome trials (CVOTs): Evidence for empagliflozin, canagliflozin, dapagliflozin.

<sup>10</sup> Proven GLP-1 RA on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide, dulaglutide

**Table 5. Comparisons of Oral Agents for Glycemic Control in Patients with Type 2 Diabetes**

Generic	Brand Name	A1c Reduction <sup>b</sup>	Δ Weight	Hypo-glycemia	Strength (mg)	Initial dose (mg)	Max Daily dose (mg)	Usual daily dose (mg)	Cost <sup>d</sup> 30 days(range) Generic (\$) Brand	Renal Dose Adjust	Other Side Effects/ Precautions	
<b>Biguanide</b>												
Metformin	Glucophage IR	⇓⇓	↔/⇓	None <sup>a</sup>	500, 850, 1000	500 daily or 850 with meal	2550	1500 – 2000 2x daily	\$22-43 \$3674	Contraindicated with eGFR <30 mL/min/1.73 m <sup>2</sup> . Starting metformin in patients with an eGFR between 30-45 mL/min/1.73 m <sup>2</sup> is not recommended.	GI side effects - GERD, nausea, diarrhea. Annual eGFR recommended, more often if at risk of developing renal impairment or have existing DKD.	
Metformin extended release	Glucophage XR				500, 750, 1000	500 to 1000 daily with evening meal	2000	1500-2000 daily or divided			B12 deficiency	
<b>Oral incretin mimetic Glucagon-like Peptide 1 Receptor Agonist (GLP1 RA)<sup>h</sup></b>												
Semaglutide	Rybelsus	⇓	⇓⇓	None <sup>a</sup>	3, 7, 14	3 daily	14	3-14 daily	NA \$834	None	Increased amylase and lipase, nausea, vomiting, diarrhea, abdominal pain, dyspepsia, flatulence, GERD, cholelithiasis  Pancreatitis  FDA black box warning: risk of thyroid C-cell tumor in rodents.	
<b>Dipeptidyl peptidase 4 (DPP4) Inhibitor<sup>g,h</sup></b>												
Sitagliptin	Januvia				25, 50, 100	5-100 daily	100	100	N/A \$412	Adjust for eGFR <45 mL/ min/1.73 m <sup>2</sup>	Class-wide: pancreatitis (rare), joint pain (rare) angioedema (rare)	
Saxagliptin <sup>i</sup>	Onglyza	⇓	↔	None <sup>a</sup>	2.5-5	2.5-5 daily	5	2.5-5 daily	N/A \$416	Adjust for eGFR <45 mL/ min/1.73 m <sup>2</sup>	Saxagliptin: increased risk of heart failure	
Linagliptin	Tradjenta				5	5 daily	5	5 DAILY	N/A \$412	None		
Alogliptin	Nesina				6.25, 12.5, 25	25 daily	25	25 QD	NA \$405	Adjust for CrCl <60 ml/min		

**Table 5. Comparisons of Oral Agents for Glycemic Control in Patients with Type 2 Diabetes, continued**

<b>Sodium-glucose cotransporter 2 (SGLT2 Inhibitor)<sup>j</sup></b>												
Canagliflozin	Invokana				100, 300	100 daily	300	100 daily before first meal	NA	\$476	Adjust for eGFR <60 mL/min/1.73 m <sup>2</sup>	Canagliflozin: lower limb amputations, bone fractures, hyperkalemia
Dapagliflozin	Farxiga				5, 10	5 daily	10	5 in AM	NA	\$465	Dapagliflozin, Empagliflozin, Ertugliflozin: Adjust for eGFR <45 mL/min/1.73 m <sup>2</sup> Not recommended for eGFR <30 mL/min/1.73 m <sup>2</sup>	Class-wide: hypotension, risk of volume depletion, diabetic ketoacidosis, urinary tract infection increases LDL, urosepsis, genital mycosis, polyuria, nausea, AKI, risk of Fournier's gangrene
Empagliflozin	Jardiance	↓	↓	None <sup>a</sup>	10, 25	10 daily	25	10-25 daily	NA	\$465		To avoid any potential DKA, discontinue before scheduled surgery.
Ertugliflozin	Steglatro				5, 15	5 daily	15	5-15 daily	NA	\$319		

**Table 5. Comparisons of Oral Agents for Glycemic Control in Patients with Type 2 Diabetes, continued**

Generic	Brand Name	A1c Reduction <sup>b</sup>	Δ Weight	Hypo-glycemia	Strength (mg)	Initial dose (mg)	Max Daily dose (mg)	Usual daily dose (mg)	Cost <sup>d</sup> 30 days (range) Generic (\$) Brand	Renal Dose Adjust	Other Side Effects/Precautions
<b>Sulfonylureas (2nd Generation)<sup>e</sup></b>											
Glimepiride	Amaryl				1, 2, 4	1-2 daily	8	4 daily	\$17-25 \$172-526		Glimepiride and glyburide: avoid in elderly patients due to risk of prolonged hypoglycemia.
Glipizide	Glucotrol				5, 10	2.5, 5 daily	40	10 - 20 divided (2x daily)	\$8-13 \$167-330		
Glipizide XL	Glucotrol XL	↓↓	↑	↑	2.5, 5, 10	5 daily	20	5 - 20 daily or divided (2x daily)	\$15-50 \$89-330		
Glyburide	Diabeta, Micronase				1.25, 2.5, 5	2.5-5 daily	20	5 - 20 daily or divided (2x daily)	\$15-50 N/A		
Glyburide, micronized	Glynase				1.5, 3, 4.5, 6	0.75-3 daily	12	3 - 12 daily or divided (2x daily)	\$11-45 \$150-500		
<b>Thiazolidinedione<sup>f</sup></b>											
Pioglitazone	Actos	↓↓	↑↑	None <sup>a</sup>	15, 30, 45	15-30 daily	45	15-45 daily	\$14-16 \$420-640	None	CHF, macular edema, LE edema, fractures, bladder cancer
<b>Alpha-glucosidase inhibitor</b>											
Acarbose	Precose	↓	↔	None <sup>a</sup>	25, 50, 100	25 daily with meal	300	50 - 100 TID before meals	\$46-55 \$98-120	Contraindicated for CrCl <25 ml/min or Scr ≥2	GI side effects - flatulence, nausea, diarrhea, elevated LFTs
<b>Non-sulfonylurea insulin secretagogues</b>											
Repaglinide	Prandin	↓	↑	↑	0.5, 1.2	0.5 with meals	16	0.5 - 4 AC daily to QID	\$55 \$600	Dose adjustment for CrCl <40 ml/min	Rare
Nateglinide	Starlix				60, 120	60-120 with meal	360	60 - 120 AC daily to QID	\$81-87 \$321-334	None	

\*Combination oral products are available.

<sup>a</sup> When used as monotherapy

<sup>b</sup> A1c reduction is dose dependent

<sup>c</sup> In animal models

<sup>d</sup> Cost = Average Wholesale Price minus 10%. AWP from Red Book Online 5/17. For generic drugs, Maximum Allowable Cost plus \$3 from BCBS of Michigan MAC List, 5/17.

<sup>e</sup> Second generation sulfonylureas have a better safety profile compared to first generation sulfonylureas.

<sup>f</sup> Pioglitazone is preferred over rosiglitazone because of its cardiovascular risks. However, the FDA recently cautioned that pioglitazone has been associated with increased risk of bladder cancer after 12 months of use. Physicians should avoid pioglitazone in patients with active bladder cancer and with caution in patients with a prior history of bladder cancer.

<sup>g</sup> When administered with a sulfonylurea, a lower dose of the sulfonylurea may be required.

<sup>h</sup> DPP-4 and GLP-1 RA are considered therapeutic duplicates. Do not use DPP4 and GLP-1 RA together.

<sup>i</sup> Consider discontinuing saxagliptin in patients who develop heart failure.

<sup>j</sup> Assess volume status and renal function before initiation. Correct volume depletion before initiation.



**Table 6. Comparisons of Injectable Agents for Glycemic Control in Patients with Type 2 Diabetes**

Generic	Brand Name	A1c Reduction <sup>b</sup>	Δ Weigh	Hypo-glycemia	Strength	Initial dose	Max dose	Cost <sup>d</sup> 30 days (\$)	Renal Dose Adjust	Other Side Effects/Precautions
<i>Glucagon-like Peptide 1 Receptor Agonist (GLP1 RA): incretin mimetics<sup>h</sup></i>										
Exenatide	Byetta				5, 10 mcg	5 mcg BID	10 mcg BID	\$721	Exenatide: contraindicated for CrCl <30mL/min	Class-wide: nausea, vomiting, diarrhea, constipation, abdominal pain, pancreatitis,
Exenatide extended-release	Bydureon, Bydureon BCise				2 mg	2mg once weekly	2mg once daily	\$675	Exenatide XR: contraindicated for CrCl <45mL/min	Exenatide, exenatide extended release: injection site reaction/nodule
Liraglutide	Victoza	⇓⇓	⇓⇓	None <sup>a</sup>	0.6, 1.2, 1.8 mg	0.6 mg daily	1.8 mg daily	\$538	Liraglutide, dulaglutide, semaglutide: No specific guideline. Use caution when initiating or escalating doses	Exenatide, exenatide extended release, liraglutide: headache
Dulaglutide	Trulicity				0.75, 1.5, 3, 4.5 mg	0.75 mg once weekly	4.5 mg once weekly	\$730		
Lixisenatide	Adlyxin				10, 20 mcg	10 mcg daily	20 mcg daily	\$334	Lixisenatide: contraindicated for CrCl <15mL/min	Liraglutide, dulaglutide, exenatide extended release: risk of thyroid C-cell tumors <sup>c</sup>
Semaglutide	Ozempic				0.25, 0.5, 1 mg	0.25 mg weekly	1 mg daily	\$943		
Generic	Brand Name	A1c Reduction <sup>b</sup>	Δ Weight	Hypo-glycemia	Onset of action	Peak of Action	Duration of Action	Cost <sup>d</sup> 30 days (\$)	Renal Dose Adjust	Other Side Effects/Precautions
<i>Ultra Rapid-acting insulin</i>										
Aspart	Fiasp	⇓⇓⇓	↑	↑↑	5-15 min	1.5-2hours	5-7 hours		None	Rare
Lispro-aabc	Lyumjev									
<i>Rapid-acting insulin</i>										
Lispro	Humalog, Admelog				15 min	0.5-2.5 hours	3-5 hours	\$574		
Aspart	NovoLog	⇓⇓⇓	↑	↑↑	15 min	1-3 hours	3-5 hours	\$575	None	Rare
Glulisine	Apidra				20 min	1-2 hours	5-6 hours	\$532		Insulin human: pulmonary toxicity; requires normal PFTs prior to prescription.
Insulin human										
<i>Short-acting insulin</i>										
Regular	Humulin R, Novolin R	⇓⇓⇓	↑	↑↑	30-60 min	2-3 hours	3-6 hours	\$150	None	Rare
<i>Intermediate insulin</i>										
NPH	Humulin N, Novolin N				2-4 hours	4-10 hours	10-16 hours	\$150		
Detemir	Levemir	⇓⇓⇓	↑	↑↑	3-4 hours	6-8 hours	6-23 hours	\$435	None	Rare

Long acting insulin											
Glargine	Lantus, Basaglar	↓↓↓↓	↑	↑↑	2-4 hours	None	20-24 hours	\$405		None	Rare
Glargine U300	Semglee, Toujeo, Toujeo Max				6 hours	None	Up to 24 hrs				
Degludec	Tresiba				1 hour	9 hours	Up to 42 hours	\$480			

\*Combination injectable products are available.

**Table 6. Comparisons of Injectable Agents for Glycemic Control in Patients with Type 2 Diabetes, continued**

Combination Insulin											
Intermediate- and short/rapid-acting mixtures	75/25 Insulin lispro protamine/insulin lispro (Humalog Mix 75/25)							\$570			
	50/50 Insulin lispro protamine/insulin lispro (Humalog Mix 50/50)							\$310			
	70/30 Insulin aspart protamine/ insulin aspart (Novolog Mix 70/30)				Varies according to types and percentages of insulin			\$310		None	Rare
Long-acting and rapid-acting mixture	70/30 NPH/regular (Humulin 70/30, Novolin 70/30)				See individual agent profiles						
	70/30 Degludec/aspart (Ryzodeg)										
Concentrated, intermediate acting	U500 regular (Humulin R)				30 minutes	1.5-3.5 hours	Up to 24 hours	\$290			

<sup>a</sup> When used as monotherapy

<sup>b</sup> A1c reduction is dose dependent

<sup>c</sup> In animal models

<sup>d</sup> Cost = Average Wholesale Price minus 10%. AWP from Red Book Online 5/17. For generic drugs, Maximum Allowable Cost plus \$3 from BCBS of Michigan MAC List, 5/17.

<sup>e</sup> Second generation sulfonylureas have a better safety profile compared to first generation sulfonylureas.

<sup>f</sup> Pioglitazone is preferred over rosiglitazone because of its cardiovascular risks. However, the FDA recently cautioned that pioglitazone has been associated with increased risk of bladder cancer after 12 months of use. Physicians should avoid pioglitazone in patients with active bladder cancer and with caution in patients with a prior history of bladder cancer.

<sup>g</sup> When administered with a sulfonylurea, a lower dose of the sulfonylurea may be required.

<sup>h</sup> Assess volume status and renal function before initiation. Correct volume depletion before initiation.

<sup>i</sup> Consider discontinuing saxagliptin in patients who develop heart failure

**Table 7. Comparisons of Agents for Glycemic Control on ASCVD, CHF and DKD in Patients with Type 2 Diabetes**

<b>Cardiovascular and Renal Benefits</b>				
<b>Drug Class</b>	<b>Medication</b>	<b>ASCVD</b>	<b>CHF</b>	<b>DKD progression</b>
Biguanides	Metformin	Potential Benefit	Neutral	Neutral
SGLT-2 inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin	Benefit (Empagliflozin <sup>a</sup> , Canagliflozin)	Benefit (Canagliflozin, Dapagliflozin <sup>b</sup> , Empagliflozin <sup>a</sup> )	Benefit (Canagliflozin <sup>c</sup> , Dapagliflozin, Empagliflozin)
GLP-1 agonists	Exenatide, Liraglutide, Exenatide extended release, Dulaglutide, Lixisenatide, Semaglutide	Benefit: Liraglutide <sup>a</sup> , Dulaglutide <sup>a</sup> , Semaglutide <sup>a</sup>  Neutral: Lixisenatide, Exenatide extended release	Neutral	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: Liraglutide, Semaglutide, Dulaglutide
DPP-4 inhibitors	Sitagliptin, Saxagliptin, Linagliptin, Alogliptin	Neutral	Potential risk: saxagliptin	Neutral
Thiazolidinediones	Pioglitazone	Potential benefit	Increased risk	Neutral
Sulfonylureas	Glimepiride, Glipizide, Glyburide	Neutral	Neutral	Neutral
Insulin	All	Neutral	Neutral	Neutral

<sup>a</sup> FDA approved for CVD benefit

<sup>b</sup> FDA approved for heart failure indication

<sup>c</sup> FDA approved for DKD indication

**Table 8. Steps in Pharmacologic Treatment of Hypertension in Patients with Diabetes Mellitus**

**Step 1. Evaluate Cardiovascular Disease Risk (CVD) and DKD risk** - Many but not all people with Type 2 diabetes already have known CVD or are at high risk for CVD. Use a CVD risk calculator: [ACC / AHA Risk Calculator](#). Assess for DKD with serum creatinine and urine microalbumin / creatinine ratio.

**Step 2. Establish Blood Pressure targets.**

**Low CVD risk:** No known CVD or DKD and 10-year CVD risk <10%: Blood Pressure Target <140/90 mmHg

**High CVD risk:** Known CVD or DKD or 10-year risk >10%, no hypotension: Blood Pressure Target <130/ 80 mmHg

**Step 3: Assess blood pressure accurately:** Average over several measures and use proper assessment technique ([see seven steps](#)). Home blood pressure monitors should be calibrated at least once a year. Consider ambulatory blood pressure monitoring if high variability in measures or discrepancy between home and office blood pressure.

**Step 4: Encourage lifestyle change:** diet, exercise, and weight loss, decrease ETOH, limit salt intake, smoking cessation.

**Step 3. If blood pressure is above goal and patient has CAD or albuminuria, consider starting first line anti-hypertensive medication:**

**ACE inhibitor** – initiate therapy unless contraindication (hypersensitivity reaction, angioedema) or documented persistent cough. [Lisinopril](#) 10 mg daily.<sup>2</sup> Titrate by doubling dose every 2-4 weeks until the BP goal is met (max dose: 40 mg)

**Alternatives if no microalbuminuria, CAD, or if contraindication to ACE Inhibitor/ARB**

**Thiazide diuretic** – initiate therapy.

[Chlorthalidone](#) 25 mg daily. Titrate by doubling dose in 2-4 weeks if BP goal NOT met. (max dose: 50 mg daily)

[Hydrochlorothiazide](#) 12.5 mg daily. Titrate by doubling dose in 2-4 weeks if BP goal NOT met. (max dose: 25 mg daily)

**Dihydropyridine Calcium Channel Blocker** – initiate therapy

[Amlodipine](#) 2.5 - 5 mg daily. Titrate by doubling dose in 2-4 weeks if BP goal is NOT met (max dose: 10 mg)

**Angiotensin II Receptor Blocker (ARB)**

[Losartan](#) 25-50 mg daily.<sup>2</sup> Titrate by doubling dose in 2-4 weeks if BP goal NOT met (max dose: 100 mg)

Consider adding and **SGLT-2 inhibitor** for glucose management, cardio-protection, and blood pressure control<sup>2</sup> if not following a very low carbohydrate / keto diet (increased risk of normo-glycemic diabetic ketoacidosis).

[Empagliflozin](#) 10 mg daily. (max dose: 25 mg daily)

**Step 4. If dose is optimized on agent from Step 3 and patient BP remains above goal<sup>1</sup>**

Add a second agent from the list above. Do not use ACE inhibitor with ARB as combination may increase risk of renal failure.

**Step 5. If above agents are contraindicated or dose is optimized, and patient BP remains goal.<sup>1</sup>**

Assess for secondary causes of Hypertension including hyperaldosteronism – see Hypertension guidelines.

Consider trial of [Spironolactone](#) orally at a dose of 25 mg daily if appropriate creatinine and potassium levels.

Or consider adding a **Beta-Blocker**. Initiate therapy with either metoprolol (preferred) or atenolol:

[Metoprolol tartrate](#) 25 to 50 mg BID.<sup>3</sup> Titrate by doubling dose every 2-4 weeks until BP goal met (max dose: 200 mg)

[Atenolol](#) 25 mg daily.<sup>3</sup> Titrate by doubling dose every 2-4 weeks until BP goal met (max dose: 100 mg)

<sup>1</sup> Systolic BP ≥ 130 recommended for treatment by JNC 7 and 140 is recommended by ADA, although there is no level A evidence for this upper limit.

<sup>2</sup> Check serum creatinine and potassium levels 1-2 weeks after starting medication or increasing its dose.


<sup>3</sup> Check heart rate 1-2 weeks after starting the medication or increasing dose.

**Table 9. Prevention, Screening, and Treatment of Complications in Patients with Diabetes Mellitus**

Cardiovascular Risk Factors	Microvascular Complications
<p><b>Hypertension</b></p> <ul style="list-style-type: none"> <li>At each visit: Check <u>blood pressure</u> (BP) and review home BP log. Document and reinforce <u>BP goal</u>.</li> <li><u>Labs</u>: Check electrolytes, serum creatinine, microalbuminuria annually and with change medication.</li> <li>Recommend <u>lifestyle interventions</u>, including weight loss, exercise and healthy diet. Consider dietician referral. Limit alcohol and salt.</li> <li>Medications: review adherence, side effects and barriers to access. Consider increase dose or additional medication therapy if repeated BP measurements are elevated (Table 8 for BP medication options)</li> </ul> <p><b>Hyperlipidemia</b><sup>3,4</sup></p> <p><b>Testing:</b></p> <ul style="list-style-type: none"> <li>Screen all diabetes patients for hyperlipidemia every 5 years.</li> <li>In patients with known hyperlipidemia, test lipid profile annually to assess for adherence and efficacy of treatment.</li> </ul> <p><b>Treatment:</b></p> <ul style="list-style-type: none"> <li>For patients with diabetes and known ASCVD, or-ASCVD risk greater than 20%: <ul style="list-style-type: none"> <li>Treat with high dose statin.</li> <li>If LDL not &lt;70 mg/dL on statin therapy, consider adding a second agent, like ezetimibe or a PCSK9</li> </ul> </li> <li>For patients with diabetes who are &lt;40yo: <ul style="list-style-type: none"> <li>Initiate statin if LDL ≥190 mg/dL with goal of achieving a 50% reduction.</li> <li>If LDL&lt;190 mg/dL, consider moderate dose statin if multiple ASCVD risk factors</li> </ul> </li> <li>For patients with diabetes 40-75 yo without known ASCVD and an ASCVD risk &lt;20%<sup>d</sup>: <ul style="list-style-type: none"> <li>Prescribe at least a moderate potency statin in all non-pregnant patients.</li> </ul> </li> <li>For patients with diabetes &gt;75yo without known ASCVD and an ASCVD risk &lt;20% <ul style="list-style-type: none"> <li>Previously prescribed statin should be continued.</li> <li>A moderate dose statin is recommended</li> </ul> </li> </ul> <p><b>Smoking</b></p> <p>Check <u>smoking status</u> (use of cigarettes, tobacco products and e-cigarettes) at least annually. If non-smoker, reinforce nonsmoking including e-cigarettes.</p> <ul style="list-style-type: none"> <li>If a smoker <ol style="list-style-type: none"> <li>Educate about increased CV risk microvascular complications, worsen glycemic control (diabetes + tobacco).</li> <li>Encourage <u>smoking cessation</u> including pharmacological agents plus counseling.</li> <li>Discourage use of e-cigarettes as a form of tobacco cessation method.</li> </ol> </li> </ul> <p><b>Cardiac Risk Reduction</b></p> <ul style="list-style-type: none"> <li>Prescribe aspirin for secondary prevention to patients with a history of atherosclerotic cardiovascular disease.</li> <li>Most patients with Type 2 diabetes and no ASCVD history do not benefit from aspirin for primary CVD prevention.</li> <li>Consider starting an GLP1-RA or SGLT-2i in patients with a history of or high risk for ASCVD.</li> </ul> <p>-----</p> <p><sup>g</sup> = studies in general population  <sup>d</sup> = diabetes patient studies</p>	<p><b>Retinopathy</b></p> <ul style="list-style-type: none"> <li>Perform <u>dilated retinal exam</u> by eye care specialist every 2 years if previous eye exam was normal and good glucose and BP control. Otherwise, annually or more frequently as recommended by the eye care provider.</li> <li>Consider more frequent eye exams in patients who are pregnant or are being initiated on insulin, GLP1-RAs, TZDs, or sulfonylureas.</li> <li>If retinopathy: <ul style="list-style-type: none"> <li>Treatment per ophthalmology.</li> <li>Consider improving glycemic and BP control.</li> </ul> </li> </ul> <p><b>Nephropathy</b></p> <ul style="list-style-type: none"> <li>Check <u>spot urinary albumin/creatinine ratio</u> annually.</li> <li>If albumin/creatinine ratio &gt;30 mg/gm, check UA to rule out asymptomatic UTI and repeat spot urine ratio twice within 6 months.</li> <li>Check creatinine, electrolytes, and estimated glomerular filtration rate annually (eGFR)<sup>g</sup>.</li> <li>If 2 of 3 spot urine albumin/creatinine ratios &gt;30 mg/gm: <ul style="list-style-type: none"> <li>Begin ACE inhibitor or ARB (if electrolytes allow use of ACE inhibitor). Recheck creatinine and electrolytes within 1–2 weeks of initiating therapy.</li> <li>Consider initiating an SGLT2i if eGFR is &gt;30 and albumin / creatinine ratio remains elevated or if A1c is above the patient’s individualized goal.</li> </ul> </li> </ul> <p><b>Neuropathy</b></p> <p>Perform <u>foot exam</u>: (1) visually inspect, (2) check pulses (each visit if patient has a history of neuropathy; otherwise annually), and (3) monofilament (annually) (Table 1).</p> <ul style="list-style-type: none"> <li>If structural abnormality: <ol style="list-style-type: none"> <li>Prescription for customized shoe and/or orthotics.</li> <li>Consider podiatry referral.</li> </ol> </li> <li>If neuropathy: <ol style="list-style-type: none"> <li>Optimize glycemic control.</li> <li>Treatment of painful neuropathy if indicated. See text.</li> </ol> </li> <li>If not sensitive to monofilament: <ol style="list-style-type: none"> <li>Education regarding proper foot care and increased risk of ulceration.</li> <li>Consider podiatry referral.</li> </ol> </li> <li>If foot ulcer, pre-ulcerative callous or history of ulcer/amputation: <ol style="list-style-type: none"> <li>Prescription for customized shoe and/or orthotics.</li> <li>Aggressive wound care with close follow up.</li> <li>Refer to podiatry.</li> </ol> </li> </ul> <p><b>Non-alcoholic Fatty Liver Disease (NAFLD)</b></p> <ol style="list-style-type: none"> <li>NAFLD is common in Type 2 Diabetes. Patients with elevated transaminases should undergo liver ultrasound<sup>5</sup> as an initial non-invasive test.</li> <li>Vaccinate for Hep B, test and treat for Hep C, limit alcohol consumption.</li> <li>Evidence supports diet and exercise for weight loss<sup>6</sup>, a Mediterranean Diet<sup>7</sup> or low calorie ketogenic diet<sup>8</sup> in NAFLD. Preliminary data supports the use of SGLT-2 inhibitors and GLP-1 and larger trials of these medications are ongoing.<sup>9,10</sup></li> <li>Consider referral to hepatology to evaluate for cirrhosis.</li> </ol>
<p><b>Strength of recommendation:</b> I=generally should be performed; II=may be reasonable to perform; III=generally should not be performed.</p> <p><b>Level of evidence supporting a diagnostic method or an intervention:</b> A = Systematic review of randomized controlled trials; B = randomized controlled trials; C = systematic review on non-randomized controlled trials, non-randomized controlled trials, group observation studies; D = Individual observation descriptive study, E = expert opinion.</p> <p>* <b>BP &lt; 130/80</b> is target for patients with ASCVD, ASCVD risk &gt;10%, or DKD, but consider &lt;140/90 if also risk for hypotension. Target is 140/90 if without risk, ie no ASCVC, ASCVD risk ≤ 10%, and no DKD. (Most patients with diabetes have risk). These targets are recommended in current guidelines of the American College of</p>	



**Table 10. How to Use a Monofilament to Test for Foot Neuropathy**

<p>The solid circles indicate four required testing sites. Testing other sites (outlined circles) is at provider discretion.</p>  <p style="text-align: center;">Left                      Right</p>	<p style="text-align: center;"><u>Testing Process</u></p> <p>Show the monofilament to the patient. Place the end of the monofilament on his/her hand or arm to show that the testing procedure will not hurt.</p> <p>Ask the patient to turn his/her head and close his/her eyes or look at the ceiling.</p> <p>Hold the monofilament perpendicular to the skin.</p> <p>Place the tip of the monofilament on the sole of the foot. Ask the patient to say 'yes' when s/he feels you touching his/her foot with the monofilament. <b>DO NOT ASK THE PATIENT 'did you feel that?'</b></p> <p>If the patient does not say 'yes' when you touch a given testing site, continue on to another site. When you have completed the sequence, <b>RETEST</b> the area(s) where the patient did not feel the monofilament.</p> <p>Gently push the monofilament until it bends, then hold for 1-3 seconds.</p> <p>Lift the monofilament from the skin (Do not brush or slide along the skin).</p> <p>Repeat the sequence randomly at each of the testing sites on each foot.</p> <p>Avoid areas of callus.</p>
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**Table 11. Obesogenic medications and alternatives for common conditions <sup>11,12</sup>**

Condition	Avoid	Choose
Depression	Paroxetine, amitriptyline, nortriptyline, mirtazapine	Bupropion, escitalopram, citalopram, fluoxetine, sertraline, imipramine, trazodone, duloxetine, venlafaxine
Anti-epileptic drugs	Valproic acid; gabapentin; divalproex; carbamazepine	Weight loss: felbamate, topiramate, zonisamide Weight neutral: lamotrigine, levetiracetam, phenytoin
Anti-psychotics	Olanzapine; quetiapine; risperidone; perphenazine; clozapine	Aripiprazole; ziprasidone
Inflammatory	Prednisone	NSAIDs, etanercept
Anti-histamines	Cyproheptadine, diphenhydramine	Loratadine, fexofenadine, certirizine
Diabetes	Insulin, pioglitazone, rosiglitazone, sulfonylureas	Metformin, GLP-1, DPP-4, SGLT-2 inhibitors, acarbose, pramlintide, miglitol
Hypertension	Beta-blockers	ACE inhibitors, ARB, CCB
Contraception	Depomedroxyprogesterone acetate	OCPs, if not contraindicated

**Table 12. Medications for Weight Loss <sup>11,13,14</sup>**

Medication	Weight loss above lifestyle change alone	Contraindications*	Common Side effects
Phentermine	7.9 lbs	Heart disease, uncontrolled HTN, MAO inhibitor use, hyperthyroidism, glaucoma, h/o drug abuse	Headache; increased BP/HR; dry mouth; constipation; anxiety; MI; palpitation; dizziness; tremor; impotence; decreased libido
Diethylpropion	6.6 lbs		
Phendimetrazine			
Orlistat (Xenical, Alli)	22.9-3.4%	Chronic malabsorption; cholestasis; use of levothyroxine, warfarin, or anti-	Decreased absorption of fat-soluble vitamins (A,D,E,K); steatorrhea; fecal incontinence

Phentermine/topiramate (Qsymia)	6.6% to 8.6%	seizure medications See phentermine	Insomnia, nausea, fatigue See phentermine
Naltrexone / bupropion (Contrave)	4.8%	Uncontrolled HTN; seizure d/o; anorexia; bulimia; drug/alcohol withdrawal, MAO-I or narcotic use	Nausea, constipation, NA, vomiting, dizziness, neuropsych reactions
Liraglutide (Saxenda)	4.5%	Caution: h/o pancreatitis, gastroparesis Avoid: Medullary Thyroid Carcinoma; MEN-2	Nausea, vomiting, pancreatitis

\*All contraindicated in pregnancy and breastfeeding.  
Note: review drug-specific stoppage rules (i.e., when to discontinue medication if weight loss target is not achieved).



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## Clinical Problem: Prevalence and Outcomes

**Definitions.** Type 2 Diabetes is defined as chronic hyperglycemia resulting from either decreased insulin secretion, impaired insulin action, or both in the absence of Type 1 diabetes (autoimmune destruction of the pancreatic beta cell), Type 3c diabetes (pancreaticogenic diabetes) or other specific type (Table 2). Classically, type 2 diabetes occurs in the older, obese patients in the setting of strong family histories of diabetes and in association with other components of the metabolic syndrome.

**Prevalence.** About 10.5% of the U.S population has diabetes, with 85% of these people having type 2 diabetes. In addition, 34.5% of the adult US population has prediabetes. The prevalence of diabetes increases with age, with over 26.8% of those  $\geq 65$  years old having type 2 diabetes. Non-Caucasians have a prevalence of type 2 diabetes mellitus that is 2 to 6 times greater than that of Caucasians.

Increasing obesity in the general population is driving a world-wide epidemic of type 2 diabetes. Obesity is also increasing the prevalence of type 2 diabetes at younger ages. Type 2 diabetes is now present in 4.2% of those aged 20 to 39 years.<sup>15</sup>

Obesity is also affecting characteristics that previously distinguished populations likely to have type 2 or type 1 diabetes. Type 2 diabetes typically occurred in patients over 30 years old and weighing  $\geq 120\%$  of ideal body weight, while type 1 diabetes occurred in patients under age 30 and weighing  $<120\%$  of ideal body weight. In addition to obesity lowering the age at which type 2 diabetes is commonly seen, population weight increases are resulting in a greater proportion of patients with type 1 diabetes being overweight.

**Inadequate screening and treatment.** Type 2 diabetes often has a long (up to 10 years) pre-symptomatic phase, and national studies suggest that approximately a third of subjects with type 2 diabetes are unaware that they have the disease.<sup>16-19</sup> Studies suggest that early treatment can reduce long term complications. Furthermore, screening for and treatment of co-morbidities and early diabetic complications is effective in reducing the incidence of end-stage complications. However, implementation rates of recommended screening procedures are low, leading to ineffective and/or delayed treatment of diabetes, and its comorbidities and complications. This, in turn, increases the costs of medical care and adversely affects quality of life.

**Outcomes.** Despite significant improvements in care, diabetes continues to have high morbidity and mortality. Based on data from 2016 reported by the CDC, diabetes remained the leading cause of blindness in working age adults, with 11.7% of patients with diabetes affected by visual impairment.<sup>15</sup> Diabetic kidney disease (DKD) occurs in 37% of diabetic patients. In the United States, 38.6% of ESRD cases were attributed to diabetes,<sup>15</sup> making diabetes the leading cause of ESRD in the US. In 2016 alone, 5.6 of every 1000 patients with diabetes were admitted for a lower extremity amputation.<sup>15</sup> This culminates in diabetes being the 7<sup>th</sup> most common cause of death in the US.

## Rationale for Recommendations

### Diabetes Prevention

#### Recommendations:

Refer patient to a Diabetes Prevention program if screening test results are in the pre-diabetes range.

Provide resources for weight loss (goal of 5-7% reduction in baseline weight) if the patient is not able to, or is unwilling to participate in a Diabetes Prevention Program.

Prescribe Metformin 850 mg a day and increase to BID (as tolerated) if unable to lose weight.

Several large randomized controlled trials have demonstrated that lifestyle modification programs delay or prevent type 2 diabetes in patients who have impaired glucose tolerance.<sup>20</sup> One possible additional benefit of screening for diabetes is the identification of people with impaired glucose tolerance. Those with a fasting glucose of 100-125 mg/dL, A1c 5.7-6.4, or a 2-hour OGTT of 140-199 mg/dL are considered at risk for diabetes.<sup>21</sup> (A random glucose of 130-199 mg/dL is abnormal and further testing is indicated, eg, fasting glucose, OGTT, or hemoglobin A1c). Large randomized controlled trials from China, Finland, India, and the United States have shown that programs targeting modest improvements in diet and physical activity (7% reduction in body weight and 150 minutes of brisk walking per

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week) can reduce the risk of progression from impaired glucose tolerance (IGT) to diabetes by 42-58%.<sup>19</sup> The intensive lifestyle intervention tested in the [Diabetes Prevention Program \(DPP\)](#) was expensive, but cost-effective. A large number of translational studies have shown that both group-based DPP<sup>22</sup> and online DPP<sup>23</sup> are effective and less expensive.

A number of medications have also been shown to decrease progression to diabetes in pre-diabetic patients. In the Diabetes Prevention Program, metformin 850 mg twice daily demonstrated a 31% risk reduction in progression from IGT to diabetes, about half as effective as lifestyle. Other medications that have shown efficacy in diabetes prevention include pioglitazone, acarbose, liraglutide, and orlistat, either alone or in combination with lifestyle interventions.<sup>24</sup> These studies suggest that a pharmacologic approach to diabetes prevention may also be feasible, but lifestyle interventions remain the standard of care. For those who cannot or will not engage in a lifestyle change program, metformin is a reasonable alternative to prevent diabetes.

### Screening for diabetes

#### Recommendations:

Consider screening for diabetes every 3 years beginning at age 45, or annually at any age if BMI  $\geq 25$  kg/m<sup>2</sup>, history of hypertension, gestational diabetes or other risk factors.

Studies of screening for diabetes do not clearly suggest that screening will lead to significant improvements in diabetes outcomes; therefore, the effectiveness (or cost-effectiveness) of screening on a population-wide basis is not clear. The value of screening for diabetes increases when adding in the benefits of detecting prediabetes and intervening with effective diabetes prevention strategies. The American Diabetes Association (ADA) recommends screening be considered at least at 3-year intervals, beginning at age 45 in people with a BMI  $>25$  (Asians  $>23$ ) and with one other risk factor for diabetes. Individuals with multiple risk factors for diabetes may be considered for screening at earlier ages. Individuals with hypertension ( $>135/80$ ) should be screened for diabetes (USPSTF level B recommendation). In adults who have hypertension and diabetes who are at higher risk for cardiovascular disease, achieving lower blood pressure targets reduces the incidence of cardiovascular events and cardiovascular mortality and justifies screening. Individuals who have been diagnosed with pre-diabetes benefit from diabetes prevention interventions and should be tested annual for progression to diabetes.

Screening every 3 years may be reasonable for other at-risk people, including those with obesity, a history of gestational diabetes mellitus, polycystic ovarian disease, or a strong family history of diabetes. Women planning pregnancy may also benefit from screening as Type 2 diabetes is increasingly common in this population and identifying and treating undiagnosed diabetes preconception can prevent congenital malformations. If a provider elects to screen for diabetes, the tests outlined in the “diagnosis” section should be used (Table 1).

### Depression

Elevated depressive symptoms and depressive disorders affect 25% of patients with type 2 diabetes,<sup>25</sup> and increase the risks of hyperglycemia, insulin resistance, and micro- and macrovascular complications.<sup>26</sup>

Providers should consider screening diabetes patients for depressive symptoms annually, and whenever there are major changes in medical status (eg, new complications, treatment intensification, etc).<sup>27</sup>

Depression screening can be done with the PHQ-2. For example: “Over the last 2 weeks, how often have you been bothered by any of the following problems?”

- (a) “Little interest or pleasure in doing usual things?”
- (b) “Feeling down, depressed or hopeless?”

Patients who respond “yes” to either question should be further evaluated using the full PHQ-9 to determine whether they meet criteria for a depressive disorder. See [UMHS clinical guideline on depression](#) for more information on the PHQ-9.

Both psychotherapy and antidepressant medication are moderately effective for depression, and cognitive behavior therapy (CBT) has additional benefits for glycemic control.<sup>28</sup>

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If PHQ-9 total  $\geq 10$ : Patients should be treated for depression with pharmacotherapy and/or referral to a behavioral health specialist for cognitive behavioral therapy (CBT), or antidepressant management. See [UMHS clinical guideline on depression](#) for full details on depression treatment.

PHQ-9 totals of 5-9: Consider depression treatment, counseling/psychotherapy, or watchful waiting, and repeat PHQ-9 at follow-up.

### **Disordered eating behaviors**

Consider screening for disordered/disrupted eating or omission of insulin doses when hyperglycemia is unexplained. Patients with diagnosable eating disorder can be referred to a specialty behavioral health provider.

### **Diabetes-related distress**

Diabetes distress refers to significant negative psychological reactions to having diabetes. This is distinct from depressive and anxiety disorders, affects up to 45% of patients, and is linked with poor glycemic control, medication non-adherence, and poor dietary and exercise behaviors.

Routinely monitor for diabetes distress, especially when treatment targets are not met and/or at the onset of diabetes complications.<sup>27</sup>

Screening can be accomplished with the Diabetes Distress Scale – 2 (DDS-2).<sup>29</sup> Patients rate how much each problem has distressed or bothered them over the past month using the following 6-point scale: 1-Not a problem, 2-Slight problem, 3-Moderate problem, 4-Somewhat serious problem, 5-Serious problem, 6-Very serious problem.

- 1) Feeling overwhelmed by the demands of living with diabetes.
- 2) Feeling that I am often failing with the prescribed diabetes regimen.

A total score of 6 or more indicates significant diabetes distress and is an indication for intervention.

Patients who screen positive for diabetes distress should first be offered diabetes education to address the areas of self-management that are most relevant to their personal concerns and health outcomes. Those who do not respond to education should be referred to a specialty behavioral health provider familiar with diabetes self-management.

## **Diagnosis**

### **Recommendations:**

An A1c of 6.5% or greater confirmed by another test on a second day is diagnostic of diabetes.

Various methods can be used to diagnose diabetes according to the American Diabetes Association (ADA). One common test for diagnosis is the A1c. Diabetes is diagnosed if A1c is 6.5% or higher. This cut point is specific, but not sensitive, and thus individuals with A1c 6.0% - 6.4% may meet criteria for diabetes using fasting glucose or OGTT tests. Advantages of the A1c as a diagnostic test include convenience (as it does not require fasting) and a highly standardized assay. A1c may not be accurate for patients with hemoglobinopathies, thalassemia, hemolysis, blood loss, or iron deficiency.

Alternatively, a FPG or OGTT may also be used to diagnose diabetes. The diagnosis can be made if a FPG level is  $\geq 126$  mg/dL (7.0 mmol/L), a repeat verification is necessary. Diabetes may also be diagnosed on the basis of symptoms (polydipsia, polyuria, unintentional weight loss) and elevated glucose level ( $\geq 200$  mg/dL). The OGTT is a reasonable diagnostic alternative, and in the view of many experts remains the diagnostic test of choice, however, may be inconvenient for patients. A 2-hour glucose level of  $\geq 200$  mg/dL is diagnostic for diabetes. All tests (except for the OGTT) should be repeated or confirmed with alternative tests on a separate day.

While most patients diagnosed with diabetes are classified as having Type 2 diabetes, it is important to consider other forms of diabetes, as this can affect prognosis and treatment. Type 1 diabetes occurs at relatively similar rates across the lifespan, and ultimately accounts for between 5-10% of diabetes cases. Patients aged 30 to 60 years account for 4% to 14% of newly diagnosed Type 1 diabetes.<sup>30,31</sup>

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The dramatically increasing incidence of Type 2 diabetes in the 30 to 60 year age group confounds the diagnosis and contributes to the delay of insulin initiation in 38% of those with Type 1. Furthermore, nearly half of those with Type 1 in this age group self-report that they have Type 2 diabetes.<sup>32</sup>

Consider Type 1 diabetes in patients with personal / family history of autoimmune disease including thyroid, celiac, and B12 deficiency, normal or low BMI, weight loss preceding diagnosis, exposure to checkpoint inhibitor medications (ipilimumab, nivolumab, etc.), or severe hyperglycemia requiring early initiation of insulin.

Pancreaticogenic diabetes (Type 3c) accounts for roughly 8% of diabetes cases.<sup>33</sup> Consider pancreaticogenic diabetes in patients with personal / family history of chronic pancreatitis, pancreatic cancer, cystic fibrosis or hemochromatosis, personal history of alcoholism, chronic GI complaints, elevated AST/ALT, normal or low BMI, weight loss preceding diagnosis, or severe hyperglycemia requiring early initiation of insulin.

There are many rare forms of diabetes, which combined, account for up to 3% of diabetes cases. These include MODY 1-11, PNDM, Wolfram's syndrome, lipodystrophic diabetes, mitochondrial forms of diabetes, myotonic dystrophy, etc. Consider unusual forms of diabetes in patients with evidence of congenital syndromes, early hearing or visual loss, normal or low BMI, unusual body fat distribution, severe obesity, severe hypertriglyceridemia, and early age of diagnosis.

Recognizing Type 1 diabetes, pancreaticogenic diabetes and other less common forms at the time of diagnosis will ensure that patients who require insulin receive it promptly, avoid admissions for diabetic ketoacidosis (DKA), and reduce morbidity.

In patients with Type 2 diabetes consider contributing factors, such as chronic liver disease, medications, endocrinopathies and monoclonal gammopathy, which may be driving insulin resistance. Hepatitis C is present in over 5% of patients with Type 2 Diabetes. Treatment for Hepatitis C has been shown to improve glycemic status.<sup>34</sup> Numerous medications have been shown to increase insulin resistance and contribute to Type 2 diabetes. Careful review of the medication list is essential. Endocrinopathies, most commonly Cushing's syndrome and Hyperaldosteronism, contributes to over 2% of cases of Type 2 diabetes.<sup>35</sup> Monoclonal gammopathies are present in roughly 20% of patients with Type 2 diabetes and neuropathy.<sup>36</sup>

## Treatment

### Recommendations:

Treatment goals include reducing glycemia, controlling blood pressure, reducing cardiovascular disease risk, and preventing complications.

Glycemia targets should be individualized. Weight loss, exercise and diet changes can dramatically improve glycemia.

Medications that improve long-term outcomes (metformin, SGLT2i, and GLP1RA) are preferred.

Cardiovascular disease prevention is critical including adequate blood pressure control, smoking cessation, and statins.

Screening, self-management and treatment for diabetic complications including: retinopathy, lower extremity ulcers, and diabetic kidney disease also improves long term outcomes.

## Diabetes Self-Management

Most of the diabetes management takes place outside of the doctor's office. Diabetic patients require daily self-management. Individuals may be instructed to dramatically change their diet, engage in a regular exercise program, take multiple medications, monitor their blood glucose and blood pressure, and check their feet daily. The burden of self-managing diabetes can be overwhelming, particularly for those with limited psychosocial supports or pre-existing mental health problems. Consider a referral to an intensive diabetes self-management education class (DSME) for those who may be struggling with self-management (newly diagnosed or persistent poor control). In addition to DSME, patients also need on-going self-management support in order to sustain improvements gained during DSME. Table 3 summarizes self-management topics that clinicians should address at each visit and annually.

- Diabetes self-management education is effective for improving psychosocial and health outcomes (including A1c) and for reducing costs.

- Traditional knowledge based DSME is essential but not sufficient for sustained behavior change. People with diabetes need on-going clinical, psychosocial and behavioral diabetes self-management support (DSMS).
- No single strategy or programmatic focus shows any clear advantage, but interventions that incorporate behavioral and affective components are more effective.
- DSME is more effective when tailored to the patient's preferences, social and cultural situation.
- DSME is most effective when coupled with appropriate care and reinforcement by all health care professionals and on-going DSMS.
- Organizational interventions that improve diabetes self-management include computerized tracking systems, regular recall and review of patients, the addition of patient-centered educational and counseling approaches, and behavioral goal-setting.
- On-going self-management support can be effectively delivered by appropriately trained panel managers, or care managers, dietitians, nurses, Pharm. Ds, remotely delivered eHealth programs, peer support, and group or cluster visits.

Meal planning. Meal planning is recommended for all stages of diabetes.

Medication adherence. Medication adherence is associated with better glycemic control, lower rates of hospitalization and mortality, and lower healthcare costs.<sup>37</sup> However, only about 68% and 59% of patients adhere adequately to oral agents and insulin, respectively. Non-adherence is more likely among patients who are younger, female,<sup>38</sup> socioeconomically disadvantaged,<sup>39,40</sup> of low health literacy, and depressed.<sup>41</sup>

Providers should screen patients who have persistently poor glycemic control, recent regimen intensification, or other risk factors. Note that patients seldom report non-adherence spontaneously. Clinicians should inquire non-judgmentally by acknowledging the widespread difficulty of taking medication as prescribed,<sup>42</sup> eg, "Most people have trouble taking medication exactly as prescribed, every dose and every day. Do you ever have any difficulty taking your [diabetes medication] exactly as prescribed?"

Because such direct queries are more specific than sensitive, clinicians should maintain a low threshold for suspecting non-adherence, and further inquire about reasons for nonadherence.<sup>42</sup> Eg,

"Do you ever forget to take your [diabetes medication]?"

"Do you believe that your [diabetes medication] is effective enough?"

"Do you ever worry that your [diabetes medication] may be harmful?"

"Are you burdened by your medication costs?"<sup>43</sup>

Educational interventions with behavioral support can be effective in addressing non-adherence, although they often need to be extended for months. For persistent non-adherence, referral to a diabetes educator or behavioral health clinician is usually indicated.<sup>44</sup>

### **Practical/logistical issues**

One of the most common barriers to adherence is the ability to obtain testing supplies and medications by both patients and physicians. There are several practical considerations.

Diabetes medications are frequently the target of the insurance companies' ever-changing formularies, resulting in unexpected changes to patients' out-of-pocket expenses. Physicians often experience requests for a medication change (within and outside of drug class) and prior authorization requests. Increased medication expenses often lead to patient non-adherence and/or financial hardship. Delays may occur in obtaining crucial medications while prescriptions are changed and/or prior authorizations are acquired. In order to minimize disruptions, ACUs should have processes and procedures in place to facilitate physicians, nurses, pharmacists, and other team members to identify financial barriers to medication adherence, update nursing protocols regularly regarding pre-approved medication substitutions, and employ an efficient and effective medication prior authorization procedure. (Nursing protocols can be found at [http://www.med.umich.edu/i/acs/nursing/standingorders/standingorders\\_protocols.html](http://www.med.umich.edu/i/acs/nursing/standingorders/standingorders_protocols.html))

Ordering diabetes testing supplies often represents an even greater challenge. Physicians are often not familiar with the pros and cons of various devices, and insurers often limit the available options, making writing specific prescriptions challenging. If a specific meter known for its accuracy is prescribed it may not be covered by insurance, unintentionally delaying care. If the meter choice is made by the DME, or pharmacy, the result may be a meter that is

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only within an acceptable margin of error 75% of the time. For a recent study of glucometers, please see: <https://www.diabetestechology.org/surveillance.shtml> .

Most medications are covered by a patient's pharmacy benefit, however 80% of insurance plans categorize diabetes testing supplies, including continuous glucose meters, and some insulin delivery devices (insulin pumps) as Durable Medical Equipment (DME). Like medications, the brand and type of diabetes testing supplies available under a plan changes from year-to-year, but there is the additional provision of where to obtain them (specific DMEs or Pharmacies). This frequently leads to patients presenting at a pharmacy with a prescription for test strips, only to be told that test strips are not covered under their pharmacy benefit plan; and failing to be told that they are covered under their DME coverage. It is a Michigan law that insurers cover testing supplies. ([https://www.michigan.gov/difs/0,5269,7-303-12902\\_35510\\_92612\\_92613\\_92614\\_92867-497018--,00.html](https://www.michigan.gov/difs/0,5269,7-303-12902_35510_92612_92613_92614_92867-497018--,00.html))

Most insurers, including Medicare, require more than a testing supply prescription for reimbursement. Most DME companies and some pharmacies fax or email staff questionnaires, or Certificates of Medical Necessity (CMNs) for completion. In an effort to eliminate unnecessary, duplicative paper work, Michigan Medicine's Adult Diabetes Education program designed order sets in the Meds and Orders tab in MiChart. When signed, these are automatically sent to the selected DME company. Pharmacies require separate prescriptions for each item and a follow up fax for CMNs. The Adult Diabetes Education program continues to work with the remaining local and national DMEs and local pharmacies, in conjunction with the Endocrine Society and other academic institutions, to achieve greater acceptance of our electronic ordering of diabetes supplies.

There are two order sets in Michart. Diabetes DME- Testing supplies, (available for any provider to use to order glucometers, test strips, and lancets from a DME) and Diabetes DME – insulin pump and CGM supplies, (which is restricted to adult and pediatric diabetes education.) This restriction is due to the need to understand the various insurers requirements to obtain these devices and supplies. Please place a referral to diabetes education if you are wish to order an insulin pump or CGM for your patient.

### **Smoking cessation: Tobacco and E-Cigarettes**

#### Recommendations:

Assess routinely and advise to not use tobacco products, cigarettes or e-cigarettes.

Provide tobacco cessation education/counseling along with pharmacological treatment.

Discourage use of e-cigarettes as a way to stop smoking tobacco products.

Smoking and diabetes are synergistic risk factors for the development of atherosclerotic cardiovascular disease, microvascular disease, premature death and worsen glycemic control. Smoking is a risk factor for type 2 diabetes. Centers for Disease Control and Prevention recommends against the use of e-cigarettes either as a tobacco cessation product or as a recreational drug in light of deaths related to e-cigarettes. People with diabetes should be counseled regarding these risks, and all possible measures should be used to encourage patients to stop smoking. This includes enrollment in formal tobacco cessation programs and use of alternative nicotine delivery systems or pharmacologic therapies. Pharmacological therapy in addition to counseling is more effective than either treatment alone.

### **Glycemic Control**

Hemoglobin A1c is the most commonly accepted measurement of long-term glycemic control, although factors such as hemolytic anemia and hemoglobinopathies can cause A1c measurement to be inaccurate.

#### **Targets for glycemic control**

#### Recommendations:

A1c goals should be individualized.

Selection of an A1c goal should be based on:

- Factors that increase the risks associated with tight control; and
- Factors that limit the benefit of tight control. See Table 4 for more specific recommendations.

For CGM users, a reasonable goal is more than 70% time in range, with no more than 4% time below range.

- Both the range and the goal for TIR should be individualized, similarly to the A1c.

Targets for therapy of Type 2 diabetes have been evaluated in four large clinical trials: UK Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk in Diabetes study (ACCORD), Action in Diabetes and Vascular Disease Controlled Evaluation (ADVANCE) and The VA Diabetes Trial (VADT). An overview of each of these four trials is included in Appendix A. The intensive control group in each of the four trials achieved A1c levels  $\leq 7.0$ . All four trials demonstrated reduction in microvascular outcomes with intensive glycemic control. All except ACCORD demonstrated reduction in macrovascular outcomes with intensive glycemic control. Therefore, many patients will benefit from a hemoglobin A1c goal less than 7%.

Conversely, a strict A1c goal of  $<7\%$  may not be appropriate for many patients. ACCORD demonstrated an increase in macrovascular outcomes with intensive glycemic control. A 2019 metanalysis demonstrated that patients with pre-existing cardiovascular disease do not derive macrovascular benefit from strict control.<sup>45</sup> Additionally, much of the microvascular benefit demonstrated by the four key trials derives from reduction in surrogate endpoints that may not be clinically important to patients such as microalbuminuria and fundoscopic appearance of early asymptomatic retinopathy.

Therefore, A1c targets should be individualized based on patient-specific factors. A1c targets should be discussed with patients. Providers should weigh patient-specific factors when considering glycemic goals (Table 4). Two important concepts that need consideration when selecting an A1c goal are 1. it takes years for symptomatic benefits to become apparent and 2. hypoglycemia is a potent predictor of mortality. Therefore, a number of factors may modify target levels. Factors that increase risk of hypoglycemia and its consequences include history of cardiovascular disease, previous history of hypoglycemia, hypoglycemia unawareness, and functional and/or cognitive limitations. Factors that limit life expectancy such as severe advanced comorbidities (advanced cancers, advanced heart failure) will limit the benefit of strict control. Furthermore, the burden, cost, and risk of the regimen needed to achieve a goal should also be considered.

## Home Glucose Monitoring

Historically, evidence to support home blood glucose monitoring using finger stick glucose testing in type 2 diabetes treated with oral agents has been unconvincing. In addition to the fact that testing alone does not change glycemia, many patients find that finger sticks are painful, and thus is a common barrier to glucose self-monitoring.

More recently trials of continuous glucose monitoring (CGM), paired with behavioral coaching to help patients identify effective strategies for improving glycemia, have shown positive results.<sup>46</sup> CGM provides patients with real time feedback about the carbohydrate load in their diet and about episodes of hypoglycemia. Newer technologies including low cost and user friendly CGM such as the Abbott Freestyle Libre<sup>®</sup> and the Dexcom G6<sup>®</sup> do not require finger sticks and provide more detailed glucose feedback, including glucose levels during sleep. CGM is increasingly being used in patients struggling to control their type 2 diabetes. Medicare insures CGM for people with Type 2 Diabetes who test 4 times a day. Monitoring with these devices is less expensive than covering lancets and test strips. As the cost of CGM continues to decrease, finger stick glucose testing will be replaced by CGM for most patients with type 2 diabetes.

CGM also provides summary measures including percent time in range, percent time above range and percent time below range. Typically, the recommended range is 70 to 180 mg/dL but this can be adjusted for patient specific factors in most CGM devices. A target of 70% time in range and no more than 4 % time below range, allowing some time for post-prandial glucose over 140 mg/dL has been recommended, but the evidence base for this recommendation is limited.

## Glycemic management

### Recommendations:

Initiate Metformin, along with lifestyle modifications, as first line pharmacologic agent for type 2 diabetes.

- Continue metformin as long as it is tolerated and not contraindicated. Agents should be added to metformin.

Independent of A1c or metformin use:

- If patient is at high risk for ASCVD or has established ASCVD start a GLP1-RA
- If CKD or heart failure predominates, start a SGLT2i (or GLP-1RA if SGLT2i not available or safe)

Early combination therapy at treatment initiation can extend time to treatment failure in some patients.

- If there is evidence of catabolism (weight loss, hypertriglyceridemia, ketosis), symptoms of hyperglycemia, or A1c level is high (>10%) or blood glucose levels are high ( $\geq 300$  mg/dL), initiate insulin.
- GLP-1 RA is preferred over insulin (unless noted above) if injectables are needed.

If additional pharmacological agents are needed, treat based on patient specific factors (Figure 1):

- To minimize hypoglycemia, consider SGLT2i, GLP-1 RA, DPP-4i, or TZD.
- If compelling need to minimize weight gain, consider GLP-1 RA or SGLT2i
- If cost is an issue, consider sulfonylurea or TZD

Evaluate for over-basalization with insulin therapy which includes basal dose more than  $\sim 0.5$  IU/kg, high bedtime-morning or post-preprandial glucose differential, hypoglycemia, and high variability. Further individualize therapy and re-design regimen.

Do not delay intensification of treatment to meet target A1c goal.

Evaluate regimen every 6 weeks until target is achieved and then every 3 to 6 months thereafter.

In patients with type 2 diabetes, diet and physical activity are essential first line therapies, and many groups now recommend initiating metformin at diagnosis. A patient-centered approach should aid in the choice of subsequent agents (Figure 1). Patient factors to consider are co-morbidities (ASCVD and indicators of high ASCVD risk, DKD, and HF), risk of hypoglycemia, impact on weight, side effect profile, costs, and patient preference.

In general, if the patient has not achieved glycemic goal after 6 weeks of therapy at a maximal dose, the therapy should be considered inadequate. Numerous randomized controlled studies have shown SGLT2i and GLP-1 RA to have positive clinical outcomes on ASCVD, DKD and HF; therefore, SGLT-2i and GLP-1 RA should be considered if there is presence of ASCVD, DKD and/or HF. Choice of agents should have proven evidence for CVD, DKD, or HF benefits (Table 7).

For patients without established ASCVD, indicators of high ASCVD risk, HF, or DKD, there is little empiric evidence to guide next choice of agent. There are numerous trials comparing dual therapy with metformin alone but little comparative studies to support the use of one combination over the other. The GRADE study is the first large multicenter randomized control trial that compares the effects of sulfonylureas, DPP4 inhibitors, GLP-1 RA and insulin with metformin; however, until the trial is completed (estimated to be completed in 2022), the next agent should be chosen based on patient factors, cost, side effects, and patient preference.

Insulin therapy has the advantage of being effective and should be considered when hyperglycemia is severe or presence of catabolism. Once glucose toxicity has resolved, simplifying or changing therapy to other agents is possible. Otherwise, GLP-1 RA and SGLT2i's are preferred over insulin when more glucose lowering is needed than can be achieved with metformin alone.

Figure 1 provides a stepwise summary of treatment recommendations. Table 5 summarizes cost, dosing and the medical advantages and disadvantages of the available oral agents to be considered for the management of type 2 diabetes. Table 6 summarizes the injectable agents to be considered for management of type 2 diabetes. Table 7 summarizes the impact pharmacological agents for type 2 diabetes has on ASCVD, DKD, and HF.

**Metformin.** The first recommended pharmacologic agent for type 2 diabetes is generally metformin. Metformin decreases hepatic glucose production, decreases intestinal absorption and increases peripheral glucose uptake and utilization by improving insulin sensitivity. It typically reduces A1c by 1-1.5%. Metformin has several characteristics that may provide secondary benefit:

- When used as a single agent, it rarely causes hypoglycemia and it does not cause weight gain.
- It appears to have favorable effects on lipid profiles and have cardiovascular protection. It has been associated with significant relative risk reduction in major adverse cardiovascular events (MACE) compared to sulfonylureas.

However, metformin has negative side effects and may not be tolerated by some patients.

- Nausea and diarrhea are the most common side effects; GI side effects are dose related. Metformin XR formulation may decrease diarrhea compared to the immediate release. The incidence of diarrhea for IR tablet is 12% to 53%; while ER tablet is 10%-17%.



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- Metformin is associated with vitamin B12 deficiency which can lead to neuropathy. Recommend periodic testing for vitamin B12.
  - Metformin is contraindicated in patients with eGFR <30 mL/min and should not be initiated in patients with eGFR between 30 and <45 mL/min. (ADA 2019) However, others recommend that in the absence of active kidney disease and/or conditions that predispose to hypoperfusion and hypoxemia (i.e. acute heart failure, dehydration), therapy may be initiated at half the usual initial dose with close monitoring.<sup>47</sup> In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m<sup>2</sup>, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m<sup>2</sup>. Metformin is renally eliminated, so continuing metformin in acute renal failure has been associated with lactic acidosis, however, this complication is very rare.

Note that Metformin should be discontinued at the time of, or before an iodinated contrast imaging in patients with an eGFR between 30 and 60 mL/minute/1.73 m<sup>2</sup>; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

When initiating metformin, start with 500 mg daily with food. Then increase the dose by 500 mg per week to 2000 mg per day as 2 or 3 divided doses as tolerated. Metformin therapy should be considered inadequate if the patient has not achieved his or her glycemic goal after four weeks of therapy at a maximum dose. Even after instituting pharmacologic therapy, careful attention should still be given to diet and physical activity.

In patients who are either not candidates for metformin therapy or have failed to achieve glycemic goals on maximal tolerated metformin dose, a second agent should be added. Options include SGLT2i, GLP-1 RA, sulfonylureas, DPP4 inhibitors, alpha-glucosidase inhibitors, thiazolidinediones and insulin. The choice of a second agent should be tailored to the individual patient.

Sodium-glucose cotransporter 2 (SGLT2) Inhibitors. This class works on the proximal renal tubules lowering the threshold for glucose excretion and increasing the urinary glucose clearance. This effect causes a light osmotic diuresis effect and net excretion of calories through the glucose urination.

A SGLT2 inhibitor is second tier in those with established atherosclerotic cardiovascular disease, those at high risk of heart failure or those with pre-existing heart failure or those with chronic kidney disease. Multiple large randomized controlled trials namely CANVAS, CREDENCE, EMPA-REG OUTCOME and DECLARE-TIMI-58 have all shown that canagliflozin, empagliflozin and dapagliflozin resulted in reduction in heart failure and in DKD progression in patients with type 2 diabetes and established ASCVD or DKD. Empagliflozin statistically significantly decreased composite three-point major cardiovascular event: MI, stroke and cardiovascular death (MACE) outcome by 14% and cardiovascular deaths by 38% (EMPA-REG OUTCOME). Similarly, canagliflozin reduced occurrence of MACE in those at high risk for ASCVD vs placebo (CANVAS and CANVAS-Renal Trial). Dapagliflozin did not reach statistical significance for lower rates of MACE but significantly lowered cardiovascular deaths or hospitalization for heart failure (DECLARE-TIMI 58 and DAPA-HF trial).

In addition, these trials examined kidney effects. They indicated that they reduced the risk of incidence or worsening nephropathy. CREDENCE trial evaluated the primary outcome for composite of end-stage kidney disease, doubling of serum creatinine or death from renal or cardiovascular causes with canagliflozin 100mg vs placebo. Primary composite outcome was 30% lower with canagliflozin vs placebo. Overall, the endpoint of end-stage renal disease was reduced by 32% in the canagliflozin group. It is therefore, useful in patients at high risk of DKD progression (ie, with albuminuria or a history of eGFR loss). Prior to these studies, FDA strengthened the existing warning about the risk of acute kidney injury with canagliflozin and dapagliflozin. Providers should consider factors that may increase the risk of acute kidney injury prior to initiation. These factors include decreased blood volume, chronic kidney insufficiency, congestive heart failure, and taking other medications such as diuretics, blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Check electrolytes and kidney function before and again 8 weeks after initiation of SGLT2 inhibitors.

Hypoglycemia is rare when used as monotherapy. There are recommendations to dose reduce insulin or other concomitant insulin secretagogues. Although not indicated for hypertension or obesity, this class can cause hypotension and slight weight loss (~400 kcal/day, but only 2.5% weight loss in one trial at 52 weeks suggesting a compensatory mechanism). Monitor for hypotension and adjust blood pressure medications as needed.

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Although there are renal and cardiac benefits, there are adverse side effects and warnings that should be taken into consideration before prescribing.

- Studies show an increased risk for urinary tract infections as well as genital mycosis infections in users as the most common side effects. FDA released a warning of rare but serious cases of Fournier's gangrene.
- In patients taking canagliflozin, risk of bone fracture increased along with decreased bone mineral density at the hip and lower spine, suggesting avoiding use in patients with history of osteoporosis.
- Two large trials concluded that canagliflozin increased risk of leg and foot amputations vs placebo (6.3 vs 3.4 participants per 1,000 patients-years; HR 1.97 [95% CI 1.41-2.75]).<sup>48,49</sup> Consider factors that may put patients at risk for amputations including history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers.
- Among users of dapagliflozin risk of bladder cancer increased in clinical trials suggesting avoiding use in patients with a history of bladder cancer.
- Trials have shown a mean transient acute reduction in GFR of about 4 points during the first 2 weeks followed by a progressive recovery and stabilization of renal function. After 12 months average decline in GFR becomes more favorable in the SGLT2i group than in the placebo group. No SGLT2i is currently approved for GFR <30.<sup>50</sup>

The FDA has issued a warning that SGLT2 inhibitors can cause ketoacidosis in euglycemic patients. Patients on SGLT2i who become ill with dehydration, nausea, vomiting, or malaise are at risk especially after a decrease in insulin dose or with alcohol consumption. If glucosuria is significantly elevated this should prompt a work-up for ketoacidosis even in the absence of significantly elevated serum glucose levels. Discontinuation of the SGLT2i, hydration and increased carbohydrate intake along with an increase in insulin dose will allow the ketoacidosis to resolve in most patients with Type 2 Diabetes.<sup>51</sup> While euglycemic ketoacidosis can occur in patients with Type 2 diabetes on SGLT2i, it is more common and more severe in patients with Type 1 diabetes on SGLT2i. Consider screening for insulin deficiency with C-peptide, glucose and anti-GAD antibody after the acute DKA episode has resolved.

GLP-1 RA (incretin mimetic agents). Exenatide (Byetta), Liraglutide (Victoza), Extended-Release Exenatide (Bydureon), Dulaglutide (Trulicity), Semaglutide injectable (Ozempic), Lixisenatide (Adlyxin) (see Table 6, injectable agents), Semaglutide oral (Rybelsus) are approved for type 2 diabetes. They are typically used with metformin or other oral agents. They enhance insulin release in presence of hyperglycemia, slow gastric emptying and suppress appetite, which can lead to weight loss in overweight individuals.

GLP-1 receptor agonists reduce risk of DKD progression and CVD events and therefore should be considered for patients with type 2 diabetes and DKD or ASCVD as second tier agents who require an additional agent to metformin to attain target or cannot use or tolerate metformin. Data, specifically LEADER trial, suggests that liraglutide demonstrate favorable renal effects and greater benefit for reduction of ASCVD. In people with type 2 diabetes with ASCVD or increased risk for ASCVD, the addition of liraglutide decreased MACE and mortality. Dulaglutide also demonstrated cardiac and renal benefits in the REWIND trial. There was a reduction in risk for nonfatal myocardial infarction, nonfatal stroke and CV deaths by 12% compared with placebo in the REWIND study. In SUSTAIN-6 trial, Semaglutide also demonstrated favorable effects on cardiovascular endpoints and composite indices for DKD. In PIONEER-6, oral semaglutide demonstrated non-inferiority versus placebo for major cardiovascular events indicating cardiovascular safety. For secondary outcome, it was strongly associated with reduction in CV and all-cause mortality. In the EXSCEL trial, MACE events were lower with extended-release exenatide vs placebo but it was not statistically significant. All-cause mortality was statically significantly lower in the extended-release exenatide group.

Oral semaglutide is the first GLP-1 RA administered orally and has similar efficacy compared to the injectable GLP-1 RAs. In studies, it was superior to empagliflozin and sitagliptin for A1c and weight reduction. Rybelsus has specific administration instructions. It should be taken at least 30 minutes before the first food, oral medication or beverages of the day, with no more than 4 ounces of plain water. It does not have any known drug-drug interactions but food may decrease the absorption of the drug.

Hypoglycemia is rare when these agents are used as a single agent or in combination therapy with metformin. The most common side effects are nausea and vomiting. The FDA warns that exenatide may be associated with an increased risk for pancreatitis and subsequent acute renal failure. If pancreatitis is suspected, incretin mimetic agents should be discontinued. If pancreatitis is confirmed, exenatide should not be restarted unless an alternative etiology for the pancreatitis is identified. Exenatide should not be used in those with GFR<30. It should be used cautiously in those with GFR between 30 and 50, with careful monitoring of renal function and GI side effects. Liraglutide, Dulaglutide and Semaglutide may be used with care in renal insufficiency. In large randomized control safety and

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efficacy trials for each individual medication, weight loss was seen in order of most to least in semaglutide, liraglutide, dulaglutide, exenatide and lastly lixisenatide.

Sulfonylureas. Sulfonylureas lower serum glucose by increasing insulin secretion. While sulfonylureas are no longer considered 1<sup>st</sup> line agents, in type 2 diabetes, they should be considered when cost is an issue or all other options are not tolerated or the patient does not have specific comorbidities. Compared to metformin, DPP4 inhibitors, SGLT-2i, GLP-1 RAs, sulfonylureas have less favorable effects on weight and increased risk of hypoglycemia. There has been debate of sulfonylurea and cardiovascular risk with weak evidence indicating that patients treated with sulfonylureas (mainly first generation) have higher cardiovascular mortality compared to patients treated with metformin. More recent large randomized controlled trials have suggested the lack of excess cardiovascular risk with glimepiride versus linagliptin and therefore suggests a neutral effect for glimepiride.

Glyburide, glipizide and glimepiride all have comparable efficacy at A1c reduction. For patients with any renal impairment, glipizide is preferred. Severe hypoglycemia can occur in patients with significant renal impairment. Avoid use of glyburide and glimepiride in elderly patients (>65 years) due to risk of prolonged hypoglycemia.

Patients are typically treated with a second-generation sulfonylurea starting at a low dose. Dose increments may be made every two weeks. If the patient has not achieved glycemic goal after four weeks of therapy at a maximal sulfonylurea dose, sulfonylurea therapy should be considered inadequate.

Non-sulfonylurea insulin secretagogues. These medications also lower serum glucose by increasing insulin secretion. They are often used in the place of sulfonylureas in sulfonylurea -allergic patients or when their shorter half-life and frequent dosing might reduce the risk of hypoglycemia in the event of skipped or delayed meals. Effects on weight and hypoglycemia risk are comparable to sulfonylureas.

Dipeptidyl peptidase-4 (DPP-4) inhibitors. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones that stimulate insulin secretion and suppress glucagon. These incretin hormones are rapidly degraded by DPP-4. DPP-4 inhibitors enhance the effect of these incretin hormones by inhibiting DPP-4. A DPP-4 inhibitor may be used as monotherapy in the event of intolerance to metformin and is a useful second tier agent for use in combination therapy. DPP-4 inhibitors are not associated with weight gain. When used as monotherapy, hypoglycemia is rare with these agents. Data on the effects of these drugs on lipid profiles or cardiovascular outcomes is limited. Recent large randomized control trial indicated neutral effect on cardiovascular risk with linagliptin vs placebo.<sup>52</sup> Dosage adjustments are required for renal insufficiency with sitagliptin, saxagliptin, and alogliptin but not with linagliptin. FDA safety review has found that saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. However, the EXAMINE trial showed no increase of cardiovascular events including heart failure with alogliptin compared to placebo, so the ADA recommends to avoid only saxagliptin in patients with heart failure.

Alpha-glucosidase inhibitors. Alpha-glucosidase inhibitors slow the digestion of ingested carbohydrates, delay glucose absorption into the bloodstream, and decrease postprandial blood glucose levels. Their effect on lowering A1c is minimal and there is no significant cardiovascular benefit with regards to mortality and morbidity, but they are safe in patients with heart disease.<sup>53</sup> They are not associated with weight gain, nor do they cause hypoglycemia when used as monotherapy or in combination with metformin. Gastrointestinal side effects including abdominal pain, flatulence, and diarrhea are common. These effects usually diminish over time (4-8 weeks), but frequently lead to discontinuation of the drug.

Thiazolidinediones. Thiazolidinediones (TZD) reduce insulin resistance and lower blood glucose levels by improving sensitivity to insulin in muscle and adipose tissue. They reduce both glucose and insulin levels and do not cause hypoglycemia when used as single agents (or in combination with metformin). These medications are very effective at lowering A1c and have been shown to improve fibrosis in NASH, however due to their side effect profile, they should be considered only if cost or hypoglycemia is an issue. TZDs are associated with significant weight gain.

The FDA has issued a box warning for TZDs due to an increased risk of congestive heart failure (CHF). Therefore, these drugs should be avoided in patients with CHF. Both TZDs are associated with fluid retention and peripheral edema, which occur in at least 15% of patients. TZDs are strongly associated with increased fracture risk in postmenopausal women. TZDs may worsen diabetic macular edema. Renal dosage adjustment is not necessary. Pioglitazone has been associated with an increased risk of bladder cancer. FDA safety review recommends not to use in patients with active bladder cancer or history of bladder cancer.

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Combination therapy. Since Type 2 diabetes is a progressive disease state, monotherapy treatment is often possible for only a few years in which combination therapy is often necessary thereafter. Patients with type 2 diabetes who do not have adequate glucose control on metformin will need to start an additional medication. (Figure 1) Studies like the VERIFY trial demonstrate that initial combination therapy had some benefits in extending therapeutic failure and slowing decline of glycemic control compared to initiating metformin alone. ADA recommends consideration of initial combination therapy in patients with A1c levels 1.5%-2.0% above target A1c goal. Therefore, treatment intensification for patients not meeting goal should not be delayed. The choice of medications in combination with metformin should be based on patient characteristics. In trials comparing addition of GLP-1 RA and insulin, the efficacy was similar with less hypoglycemia and more weight loss with GLP-1 RA. More gastrointestinal side effects were noted in patients taking GLP-1. It is preferable to add GLP-1 RA (with demonstrated CVD benefits), or a SGLT2i before starting insulin (if available and not contraindicated). This is especially true, for patients with established ASCVD or indicators of high ASCVD risk, heart failure, or DKD. When considering medication combinations, DPP-4 inhibitors should not be combined with GLP-1RA as it is considered a duplicative therapeutic. Most experts agree metformin should be continued if insulin is initiated. While it is common to discontinue hypoglycemic agents other than metformin when initiating insulin, it is not required. The weight loss and renal and cardio-protective benefits of SGLT2i and GLP-1A, as well as the benefits of reduced exogenous insulin dose, (lower cost, less weight gain) should be considered before discontinuing these agents.<sup>54,55</sup>

The addition of basal insulin including NPH, or one of the long-acting insulins, to oral medications is a common approach especially for those who have had diabetes for a longer duration of time. Once daily glargine therapy has become increasingly popular due to its convenience, lack of an insulin peak, and 24-hour duration of action. However, because long-acting insulin effects on glycemia are relatively constant throughout the day, this approach may make it difficult to address both nocturnal hypoglycemia and inadequately controlled post-prandial hyperglycemia simultaneously. Therapy may be intensified as needed with twice daily split/mixed insulin, or a basal/bolus insulin approach as needed to achieve glycemic goals.

If A1c is still above target and basal insulin has been titrated to a dose that is >0.5 units/kg/day or acceptable fasting blood glucose level, then consider addition of a GLP-1 RA or oral agents such as SGLT-2 inhibitors to minimize weight gain and potentially reduce the amount of insulin needed. Further intensification with prandial insulin can be done if more post prandial glucose lowering is needed for a patient with irregular eating and there is more needed for flexibility.

Insulin. Insulins are categorized by their duration of action (see Table 6). The initiation and adjustment of insulin is addressed in Appendix B.

Rapid acting insulins (Lispro [Humalog, Admelog], Aspart [NovoLog], Glulisine [Apidra]) or short-acting insulin (Regular) are used in conjunction with meals to treat anticipated post-prandial increases in blood glucose. Since the onset and duration of rapid-acting insulins are more physiologic than regular insulin, some practitioners prefer their use. However, in type 2 patients, regular insulin is an appropriate choice and is less expensive.

Intermediate insulins (NPH and Detemir [Levemir]) are typically given twice daily. A morning dose provides for daytime basal insulin requirements, and the post-lunchtime peak of action may reduce the need for short-acting insulin at lunchtime. An evening dose, often given at bedtime, is titrated to fasting blood glucoses, to avoid nocturnal hypoglycemia.

Long acting insulin, Glargine (Lantus, Basaglar, Toujeo) has a duration of action of approximately 24 hours. It is frequently prescribed at a starting dose of 20 units at bedtime in patients with normal renal function and titrated by 2 to 4 units every 2-3 days for fasting blood sugar <130 mg/dL. Ultra-long acting insulin, (Degludec [Tresiba]), may result in a lower hypoglycemia risk compared with U-100 glargine.

Mixtures of intermediate and short acting insulins are available in many forms. The three mixtures most frequently used are 75/25 insulin lispro protamine and insulin lispro (Humalog mix) and 70/30 insulin aspart protamine and insulin aspart (Novolog mix) and 70/30 NPH/insulin regular (HumuLIN 70/30, NovoLIN 70/30). Twice daily injections (before breakfast and supper) of these mixtures may provide good control for patients with type 2 diabetes. However, there is higher risk of hypoglycemia; therefore, education of not skipping meals is recommended to avoid hypoglycemia.

NPH and insulin regular are available as cheaper alternatives at pharmacies through discount programs.

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All types of insulin are renally cleared and thus individuals with worsening chronic kidney disease or acute kidney injury will need to reduce their insulin dose to avoid hypoglycemia.

### **Medications that increase blood sugar**

Hyperglycemia is clinically defined as glucose greater than 180 mg/dL for more than two hours. Medications commonly contributing to elevated blood glucose or hyperglycemia include atypical antipsychotics, corticosteroids, calcineurin inhibitors (cyclosporine, sirolimus, tacrolimus), and protease inhibitors. Corticosteroids are a very common cause of hyperglycemia in patients with or without diabetes because they blunt the action of insulin and promote hepatic gluconeogenesis. Clore and Thurby-Hay recommend using NPH insulin for treating glucocorticoid-induced hyperglycemia or basal/prandial insulin can be used as well.

For atypical antipsychotics, second generation antipsychotics may increase risk of hyperglycemia or type 2 diabetes – particularly olanzapine and clozapine whereas ziprasidone (Geodon) and aripiprazole (Abilify) have the lowest risk. Newer atypical antipsychotics such as asenapine, iloperidone, paliperidone and lurasidone also have lower metabolic risk similar to aripiprazole and ziprasidone.

Calcineurin inhibitors are often used to avoid allograft rejection in transplant which can result in post-transplant diabetes. The incidence of post-transplants diabetes is ~24% within 3 years post-transplant. These medications inhibit pancreatic islet beta cell expansion promoted by calcineurin.

Protease inhibitors are essential in the treatment of HIV and AIDS. They are thought to cause decrease in insulin sensitivity thereby resulting in insulin-resistance associated hyperglycemia. This occurs in 3-17% of patients.

Other agents that increase blood glucose include antibiotics specifically fluoroquinolones (Gatifloxacin and Levofloxacin), beta blockers, statins, and thiazide diuretics. Beta blockers like atenolol, metoprolol and propranolol elevate blood glucose level by impairing release of insulin from pancreatic beta-cells. Carvedilol and nebivolol have not been associated with development of hyperglycemia or new-onset diabetes. For thiazides, like hydrochlorothiazide patients may not experience elevated levels for weeks (or not at all) if doses are kept low (12.5-25mg). Lastly, for statins, FDA drug safety announcement reported an increase in blood glucose and risk of diabetes with statins (JUPITER and PROVE-IT TIMI 22 trial) but that cardiovascular benefits outweighed risk of not using statins in patients with diabetes.

Vigilant monitoring of blood glucose should be done for patients on these medications irrespective of previous diabetes diagnosis. Use of these drugs are not contraindicated and clinical judgement while evaluating benefits versus risk of the use of these medications is recommended.

### **Hypoglycemia**

#### **Recommendations:**

Assess for hypoglycemia at every encounter in patients taking medication that increase the risk of hypoglycemia (especially insulin and sulfonylureas).

Assess patient for hypoglycemia unawareness.

- Modify medication, diet, and/or glycemic targets if patient has hypoglycemia unawareness, frequent or severe events requiring assistance for treatment.
- Consider using a continuous glucose monitor to detect and alarm for dangerously low glucose.
- Educate that beta-blockers can alter or inhibit symptoms of hypoglycemia thus masking symptoms of hypoglycemia except sweating.

Fast-acting glucose is preferred for conscious patients with level 1 hypoglycemia or blood glucose <70 mg/dL (3.9 mmol/L) who are taking medication that can cause hypoglycemia.

- After treatment of hypoglycemia, recommend snack or meal to prevent recurrence of hypoglycemia.

Prescribe glucagon for patients at risk of level 2 hypoglycemia or glucose <54 mg/dL (3.0 mmol/L) or level 3 hypoglycemia defined as an event altering physical or mental status requiring assistance for treatment of hypoglycemia.

Educate patients on situations that increase risk for hypoglycemia, symptoms, and treatment of hypoglycemia.

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Hypoglycemia is linked with increased risk of mortality thus outweighing the potential benefits on microvascular complications in some patients. It is also a marker of high absolute risk of cardiovascular events. Findings from ACCORD, ADVANCE and VADT trials caution aggressive approach in achieving glycemic targets in high-risk patients and recommends individualization of glycemic targets based on patient factors, comorbidity and life expectancy. Of note, these studies pre-date the GLP1-RA and SGLT2i drug classes where cardiovascular and renal benefits are seen.

Risk factors that increase treatment-associated hypoglycemia include: use of insulin or secretagogues, impaired kidney or hepatic function, longer duration of diabetes, frailty and elderly patients, declined cognitive function, hypoglycemia unawareness, alcohol use, polypharmacy (ie, beta blocker).

While healthy, non-diabetic individuals can be asymptomatic with fasting serum glucose as low as 45 mg/dL without concerns, in patients with Type 2 diabetes who are taking medications that increases the risk for hypoglycemia (especially insulin and sulfonylureas), the definition of hypoglycemia is glucose <70 mg/dL (3.9 mmol/L). Some patients with diabetes who desire very tight control (ie, pregnant women) may tolerate and possibly benefit from lower glucose levels without adverse effects, but the risk of serious hypoglycemia increases with tighter control. There are three levels of hypoglycemia. Level 1 is glucose <70 mg/dL (3.9 mmol/L) and  $\geq 54$  mg/dL (3.0 mmol/L). Level 2 is glucose <54 mg/dL (3.0 mmol/L) and level 3 is defined as a severe event marked by altered physical and/or mental status requiring assistance in the treatment of hypoglycemia. There are patients who have hypoglycemia unawareness which is defined as level 2 hypoglycemia without any symptoms.

Symptoms of hypoglycemia include but are not limited to: irritability, sweating, shakiness, confusion, lightheadedness, hunger, and dizziness. Level 3 hypoglycemia can result in seizures, loss of consciousness, coma, or death. A large trial suggested that a history of level 3 hypoglycemia was associated with greater risk of dementia. Symptoms may vary between patients; therefore, education and assessment of symptoms of hypoglycemia is important.

The best approach for treatment is fast-acting glucose or carbohydrate (15-20 grams) in patients who are conscious with blood glucose <70 mg/dL (3.9 mmol/L). Pure glucose is preferred versus the total carbohydrate content of the food as it results in quicker response. Any form of glucose is acceptable. Added fat and protein may blunt glucose and increase insulin response thus prolonging acute glucose response. Avoid carbohydrate sources high in protein or fat to treat hypoglycemia. Fifteen minutes after the glucose consumption, check glucose. If blood glucose is still <70 mg/dL (3.9 mmol/L), repeat with 15-20 grams of glucose. Once glucose returns to normal, then patient should have a meal or snack to prevent the recurrence of hypoglycemia.

Glucagon should be prescribed to patients who are at risk of level 2 and 3 hypoglycemia. Glucagon is indicated when patients are unable or unwilling to consume carbohydrates by mouth. Glucagon administration teaching should be given to caregivers, school staff, or family members.

Hypoglycemia unawareness, severe (one or more level 3 hypoglycemia) or frequent hypoglycemia is an indication for modification of treatment regimen and glycemic targets. In addition, consider prescribing a continuous glucose monitor to detect and alarm for dangerously low glucose. Beta blockers can inhibit symptoms of hypoglycemia such as tachycardia and flight or fight symptoms except sweating.

Assessment of cause of hypoglycemia and education on how to prevent and treat hypoglycemia is recommended. Patient education on situations (ie, lifestyle including diet and exercise) and medications that can increase risk of hypoglycemia should be provided.

Use of CGM technology can be a useful tool in reducing time in hypoglycemic range in people with hypoglycemia unawareness.

## **Co-Morbid Conditions**

### **Hypertension**

Hypertension (HTN) is the predominant predictor of adverse events in patients with type 2 diabetes. Treatment of blood pressure reduces risks of major cardiovascular events such as myocardial infarction, stroke, or cardiovascular death, and also reduces the risk of microvascular outcomes such as visual loss, photo-coagulation for retinopathy,

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and the development of end-stage renal disease. Treatment of HTN in patients with type 2 diabetes should be a high priority for clinicians.

The majority of patients with diabetes and HTN have essential hypertension. However, it is important to identify secondary causes of HTN such as renal artery stenosis, primary hyperaldosteronism, pheochromocytoma, Cushing's disease, and oral contraceptive use in patients who remain refractory to therapy, or who have clinical syndromes suggestive of these conditions.

Blood pressure target. The target BP depends on the presence of other risk factors.

Without risk: 140/90 mmHg with no ASCVD, ASCVD 10-year risk < 10%, and no DKD. (ASCVD risk is based on the ACC/AHA pooled cohort ASCVD risk calculator. Diabetes is already considered in calculating ASCVD risk.)

With ASCVD, ASCVD 10-year risk  $\geq$  10%, or DKD:

- <130/80 mmHg if without risk for hypotension (eg, without: orthostatic hypotension, heart failure, older age).
- Consider <140/90 mmHg if risk for hypotension.

Both age and diabetes are important factors in the ACC/AHA ASCVD risk calculator, resulting in a BP target of <130/80 mmHg for most patients with diabetes. Having diabetes essentially doubles an individual's risk that results from other factors. Even with normal values for blood pressure, cholesterol, and a history of no smoking, with diabetes men age  $\geq$  55 years and women age  $\geq$  65 years will have a 10 -year ASCVD risk >10%. Many middle-age adults and some younger adults with diabetes and with other risk factors for ASCVD will have a calculated 10-year ASCVD risk >10%.

For patients at risk for hypotension (eg, orthostatic hypotension, heart failure, older age), consider a treatment target of <140 mmHg systolic and <90 mmHg diastolic blood pressure. The BP target is higher to avoid hypotension, which may result in insufficient blood flow to organs (eg, kidneys in patients with DKD), dizziness, and fainting.

Clinical trial data reviewed by the Seventh Report of the Joint National Committee (JNC 7) support reducing SBP to <140 mmHg and DBP to <90 mmHg. This was confirmed by the panel members of the Eighth Joint National Committee for ages 60 years and younger. For ages 60 years and over, the latter recommended reducing SBP to <150 mmHg and DBP to <90 mmHg. The 2017 ACC/AHA guidelines recommended reducing to <130 mmHg systolic and to <80 mmHg diastolic, based on new data from SPRINT. Systolic blood pressure had not been evaluated as rigorously as diastolic until SPRINT looked at SBP control and clinical outcomes. For patients with elevated blood pressure and elevated ASCVD risk, aggressive treatment of HTN provides significant improvements in clinical outcomes. Recent data suggest that a SBP target of <130 mmHg is reasonable.

In all guidelines, accurate BP measurement using automated office BP measurements or home BP measurement was recommended. A sustained decrease in SBP of 10 mmHg or DBP of 5-6 mmHg for patients with hypertension decreases the risk of stroke by 35-40% and decreases the chance of coronary heart disease by 20-25%.

For patients with diabetes, goals for blood pressure treatment have been evaluated in several randomized trials, particularly ACCORD. SPRINT did not include patients with diabetes. For DBP, a target of  $\leq$ 90 and likely  $\leq$ 80 mmHg provides marked benefits. Caution is suggested when DBP falls below 70 mmHg. Mortality increased when patients with diabetes had DBP below 70.

The American Diabetes Association's 2019 Standards for Medical Care in Diabetes synthesize results from ACCORD and SPRINT by focusing on diabetes as a risk factor for ASCVD. The ADA recommends that BP targets for patients with diabetes be based on the patient's ASCVD status and 10-year risk for ASCVD, consistent with the ACC/AHA approach to setting BP targets based on ASCVD and ASCVD risk. The one difference is that for a BP target of <130/80 mmHg, ACC/AHA set 10-year ASCVD risk level at  $\geq$ 10% and the ADA set the level at  $\geq$ 15%. This difference is of little practical consequence. The effect of increasing age on the calculation of ASCVD risk is sufficiently strong that anyone with an estimated 10-year risk that is >10% and <15% will have an estimated risk  $\geq$ 15% within a couple of years. Using 10-year ASCVD risk level of  $\geq$ 10% initiates lowering the goal to <130/80 mmHg slightly earlier.

Blood pressure assessment and treatment. Blood pressure should be measured at all clinic visits for patients with diabetes, and treatment is more aggressive than for patients without diabetes. If diastolic blood pressure is  $\geq$  90 mmHg or systolic blood pressure is  $\geq$  140 mmHg on two visits, antihypertensive therapy should be instituted (Tables 6 and 9). Lifestyle modification with dietary alteration, physical activity, and weight loss (if indicated) should be

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advocated. However, expert opinion from The Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) recommends that in patients with diabetes, lifestyle measures should nearly always be augmented by pharmacologic therapy.

**Recommendations:**

Initiate pharmacologic agent addition to lifestyle modifications, if blood pressure in clinic is  $\geq 140/90$  mmHg.

Initiate two drugs or single-pill combination of drugs in addition to lifestyle modifications, if blood pressure in clinic is  $\geq 160/100$  mmHg to reduce cardiovascular events.

Treat hypertension with ACE inhibitors, angiotensin receptor blockers (ARB), thiazide-like diuretics or dihydropyridine calcium channel blockers as these drug classes have demonstrated reduction in cardiovascular events in patients with diabetes.

Use ACE inhibitors or ARBs as first line treatment for hypertension in patients with diabetes and CAD, or urinary albumin-to-creatinine ratio  $\geq 300$  mg/g creatinine or 30-299 mg/g creatinine

Monitor EGFR serum creatinine, and electrolytes (potassium) if using ACE inhibitor, ARBs or thiazides after initiation and then at least annually.

Do not use ACEI inhibitors in combination with ARBs.

Initial treatment is based on severity of hypertension. Patients with blood pressure  $\geq 140/90$  mmHg, a single agent can be initiated. Patients with blood pressure  $\geq 160/90$  mmHg, initial treatment should include a two drug therapy.

The choice of first-line antihypertensive drugs for patients with diabetes is controversial and not entirely based on the available literature. In the ALLHAT trial, the largest and most representative direct drug-vs.-drug comparison to date, a strategy beginning with a thiazide diuretic (chlorthalidone) reduced myocardial infarction as much as strategies beginning with other agents and reduced stroke and congestive heart failure more than beginning with other agents. That result held across all subgroups, including patients with diabetes. The ADA guidelines recommends Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) as first-line therapy for hypertension in patients with established coronary artery disease and diabetes (HOPE trial).

ACE inhibitors and ARBs reduce progression of established diabetic renal disease and reduce cardiovascular mortality (HOPE trial). Thus, ACE inhibitors or ARBs are recommended as first-line therapy in patient with albuminuria (urine albumin-to-creatinine ratio [UACR]  $\geq 30$  mg/g). An important note is that the combination of ACE inhibitors and ARBs should be avoided. Although together they reduce blood pressure and proteinuria, they also clearly increase the rate of end-stage renal disease and mortality. In patients without albuminuria or kidney disease, ACE inhibitors and ARBs have not been found to be superior for cardioprotection when compared to thiazide-like diuretics and dihydropyridine calcium channel blockers.

Dihydropyridine calcium-channel blockers was superior in reducing cardiovascular events when in combination with a renin-angiotensin system blocker (benazepril) compared to hydrochlorothiazide in patients with diabetes (ACCOMPLISH trial).

Beta-blockers are also effective agents in controlling blood pressure, but should probably be added after thiazides and ACE inhibitors, ARB or dihydropyridine calcium channel blockers (see Table 8). Beta blockers are beneficial for treatment of prior MI, active angina, or heart failure but have not been shown to reduce mortality in absence of these disease states. In patients taking insulin for Type 2 diabetes, beta blockers can worsen hypoglycemia episodes particularly during acute illness or hospitalization.<sup>56</sup> Other classes of agents have not been as rigorously evaluated in patients with diabetes. Alpha-blockers are not recommended, as they appear to deliver less improvement in outcome than other agents.

Low-dose thiazide diuretics (eg, 12.5 to 25 mg of hydrochlorothiazide or 25-50 mg chlorthalidone) do not appear to have clinically important adverse effects, and have been proven to reduce mortality in patients with diabetes. High-dose thiazide diuretics have been reported to have a variety of adverse effects including worsening of hyperlipidemia, hyperuricemia and gout flares, deterioration of glycemic control, impotence, and increased mortality, therefore thiazides should be used at low doses.

Patients with coronary disease or congestive heart failure (CHF) should receive beta-blockers unless a clear contraindication exists. Beta-blockers may decrease high density lipoprotein (HDL) and increase triglyceride levels. In one major trial, beta-blockers led to more weight gain and higher requirements for glucose-lowering agents than ACE inhibitors. If a beta-blocker is used, it should be cardioselective to minimize side-effects.



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Patients with CHF or coronary disease with diminished left ventricular function should receive an ACE inhibitor, or an ARB (if ACE inhibitors are not tolerated). ACE inhibitors can lead to cough in up to 20% of patients. Both ACE inhibitors and ARBs can precipitate renal insufficiency and hyperkalemia. Careful monitoring of renal function and serum electrolytes is warranted with these agents.

Regardless of initial agent, most patients with type 2 diabetes will require multiple agents in order to achieve their blood pressure goal. Indeed, many patients will not achieve their goal even with the use of 3 or 4 agents. Further evaluation for secondary causes of hypertension should be considered in these patients.

Lastly, there has been small evidence suggesting reductions in ASCVD events when dosing at least one antihypertensive medication in the evening vs morning.<sup>57</sup>

### **Lipid screening and treatment**

Prescribe at least a moderate potency statin for patients with Type 2 diabetes who are  $\geq 40$  years old. Avoid statins in women who are contemplating pregnancy or may become pregnant.

Hyperlipidemia is common in patients with type 2 diabetes. Characteristically, they have elevated triglyceride levels, while HDL levels are low, and LDL levels are typically normal or elevated. Given the high prevalence (up to an 80% lifetime risk) of vascular disease in patients with diabetes, the National Cholesterol Education Program (NCEP) suggests that lipid-lowering treatment is an essential component of diabetes care.

Expert opinion suggests that annual lipid profile provides a check on statin adherence and an opportunity to reinforce lifestyle modifications – the cornerstone of ASCVD risk reduction.

A non-fasting lipid profile is adequate to assess cardiovascular risk and to monitor statin compliance. If lipids are obtained non-fasting and are abnormal (ie, TC  $>200$  mg/dL, HDL-C  $<40$  mg/dL, or triglycerides  $>500$  mg/dL,) consider obtaining a follow up fasting lipid panel to better evaluate for dyslipidemias.

Current ADA and AHA guidelines recommend that for patients with diabetes and known ASCVD or ASCVD risk greater than 20%, treatment should be initiated with high dose statin. If LDL  $<70$  mg/dL or non-HDL cholesterol  $\geq 100$  mg/dL is not achieved on maximally tolerated statin therapy, addition of a second agent, like ezetimibe or a PCSK9, should be considered. For patients with diabetes who are  $<40$ yo, a statin should be started if LDL  $\geq 190$  mg/dL with goal of achieving a 50% reduction.

For patients with diabetes under the age of 40, and without extreme elevations of LDL, a moderate dose statin could be considered if there are multiple ASCVD risk factors.

For patients with diabetes 40-75 years old without known ASCVD and an ASCVD risk  $<20\%$ , at least a moderate potency statin should be started. For patients with diabetes  $>75$  years without known ASCVD and an ASCVD risk  $<20\%$ , any previously prescribed statin should be continued. Consider a moderate dose statin for patients with diabetes age  $>75$  years without known ASCVD after a risk / benefit discussion.

The issue of LDL targets is controversial. Experts have suggested LDL targets of less than 100 or even 70 mg/dL for patients with diabetes. However, few studies have established a specific LDL target level; instead nearly all trials compared the efficacy of a fixed dose of a statin with placebo. The best evidence suggests that patients receive about the same level of benefit across all baseline LDL levels and with any degree of LDL reduction. This suggests that the benefits of statins are not fully captured by LDL and argues for their empiric use. A reasonable approach is to start most patients with diabetes on moderate potency statins, (eg, lovastatin [generic] 40 mg/dL) without specific LDL targets. For secondary prevention, essentially all patients with diabetes should be on statins; some evidence supports the use of higher dose statins in these populations (eg, rosuvastatin 40 mg/dL or atorvastatin 40-80 mg/dL), particularly in those who are admitted for acute coronary syndrome. Avoid prescribing simvastatin 80 mg because of the increased risk of myalgias. Careful monitoring of potential drug interactions with statins is critical; many drugs can increase the risk of myalgias and rhabdomyolysis when combined with statins.

Non-HDL is a measurement of all atherogenic lipoproteins (lipoprotein(a), very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and low-density lipoproteins (LDL)). Unlike LDL, non-HDL is not dependent on fasting and is more accurate when triglycerides are elevated. Non-HDL thresholds for adults should be 30 mg/dL higher than the equivalent LDL threshold.

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Statins may not be appropriate in some patients with diabetes, especially those with severe, chronic malnutrition from pancreatic insufficiency, or women planning pregnancy. When deciding to start a statin, consider the patient's 10 year ASCVD risk, nutritional status and life expectancy.

In patients with diabetes, observational data suggest that triglycerides are also an independent risk factor for the development of atherosclerotic disease. However, only very limited trial data evaluate the effectiveness of lowering triglycerides on cardiovascular outcomes. The first-line of treatment for hypertriglyceridemia is optimization of glucose and thyroid (if hypothyroid) control. Use of fibrates is generally discouraged as there is no evidence of benefit in trials using fibrates alone or in combination with statins. If triglycerides are markedly elevated (eg, >500 mg/dL), then treatment may be warranted to avoid pancreatitis.

### **Non-alcoholic fatty liver disease (NAFLD)**

It is estimated that approximately 25-30% of adults in the United States have underlying NAFLD.<sup>58</sup> NAFLD has been reported in one- to two-thirds of adult patients with type 2 diabetes.<sup>59,60</sup> Despite this high prevalence, there is some debate about routine screening in high-risk patient groups "because of uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to long-term benefits and cost-effectiveness of screening".<sup>61</sup> It is recommended that clinicians maintain a high index of suspicion for NAFLD and Non Alcoholic Steatohepatitis (NASH) in patients with type 2 diabetes.<sup>61</sup> In the 2021 ADA guidelines, patients with type 2 diabetes who have elevated transaminases or evidence of fatty liver on ultrasound should be evaluated for NASH and fibrosis.<sup>62</sup> Non-invasive risk-stratification tools may be helpful to identify individuals at low or high risk of advanced fibrosis. These include serologic biomarker calculators like the NAFLD fibrosis score (NFS), the fibrosis-4 index (FIB-4) or vibration controlled transient elastography (VCTE).<sup>61</sup> Non-alcoholic steatohepatitis (NASH) is a subgroup of people with NAFLD who have inflammation in addition to fatty infiltration and are thus at high risk of progression to cirrhosis. NASH is currently one of the leading indications for liver transplant in the US. The only way to definitively diagnose NASH is by liver biopsy. The primary treatment that slows the progression of NAFLD/NASH is diet, exercise, and weight loss with strong evidence for benefit from adopting a Mediterranean diet or a low carbohydrate diet.<sup>7,8</sup> Additional benefits may come from decreasing or eliminating alcohol consumption, vaccinating against hepatitis A and B, screening for hepatitis C, and treating if appropriate, avoiding liver toxic medications, supplements, and alcohol. Preliminary data supports the use of SGLT-2 inhibitors and GLP-1 agonists and larger trials of these medications are ongoing.<sup>10,63</sup> Individuals identified as being high risk for advanced fibrosis, or individuals with indeterminate risk assessment scores and multiple metabolic comorbidities, may benefit from referral to GI/Hepatology.

### **Obesity**

Obesity is increasing worldwide and contributes to the rise of not only type 2 diabetes, but also hypertension, hyperlipidemia, macrovascular disease, osteoarthritis, and other conditions. The treatment of obesity is central to the comprehensive treatment of type 2 diabetes in many cases. Lifestyle interventions for obesity, medications to promote weight loss, and bariatric surgery should all be considered in the approach to the obese patient with type 2 diabetes.

The majority of patients with type 2 diabetes have overweight or obesity. Weight loss of 5-10% can help patients with type 2 diabetes reduce or eliminate the need for anti-hyperglycemic medications.<sup>13,64</sup> A comprehensive weight management approach that considers individual patients' barriers to weight loss as well as their needs, preferences, and goals is recommended.

Addressing barriers:

1. Replace obesogenic medications with weight-neutral alternatives, if appropriate.
2. Screen for medical conditions (eg, obstructive sleep apnea, insomnia, Cushing syndrome, hypogonadism, hypothyroidism, polycystic ovarian syndrome, depression, or eating disorders) or life events (eg, marriage, divorce, retirement) that may promote weight gain and/or hinder weight loss.
3. Ask about access to food and refer to Social Work for food insecurity resources, if appropriate

Developing a personalized weight loss plan:

Primary care-based resources: Although Medicare reimburses PCPs for intensive lifestyle counseling (ILC), most PCPs do not have the time or knowledge to engage patients in ILC.<sup>65</sup> Accordingly, PCPs should consider referring patients with obesity to dietitians, clinical pharmacists and/or evidence-based lifestyle change programs.

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**Lifestyle change programs:** Lifestyle programs aim to help patients lose weight through diet and physical activity changes. Patients should be educated that dietary changes are key to weight loss (see Nutrition section). Exercise promotes cardiovascular and mental health benefits, but is not required for weight loss. Exercise does, however, play a key role in weight loss maintenance.<sup>66</sup> Commercial lifestyle change and meal replacement programs supported by the literature include: Weight Watchers, Jenny Craig, Nutrisystem, Medifast, Optifast, Atkins, Slim-fast, TOPS and Health Management Resources.<sup>66–68</sup> Vitra Health’s online keto diet program for people with type 2 diabetes has been shown to induce diabetes remission in some type 2 diabetes patients.<sup>69</sup>

**Pharmacotherapy:** May be considered in patients who have failed to reach weight loss goals through lifestyle modification alone, have obesity-related health issues, and have BMI >30 kg/m<sup>2</sup>; or BMI >27 and at least one obesity-related health condition. A list of potentially obesogenic medications and non-obesogenic alternatives is listed in Table 11. Table 12 lists medications for weight loss.

**Supervised medical weight loss:** Often includes very low energy meal replacement (<800 kcal per day).

**Weight loss surgery:** Gastric bypass, laposcopic gastric banding, sleeve gastrectomy, or biliopancreatic diversion with duodenal switch may be considered in patients with BMI ≥40; or BMI ≥35 and suffer from an obesity-related condition.<sup>70,71</sup> Consider a patient who is prepared and willing to commit to lifestyle changes that will be necessary after surgery eg, non-smoker; failed to lose weight with other approaches. These are associated with improvement or resolution of obesity-related chronic conditions and reduced mortality.<sup>72,73</sup>

Regardless of the treatment use, weight regain can occur. Strategies to promote weight loss maintenance (ie, maintain body fat mass within +5%) include regular physical activity, continued dietary adherence, self-weighing, and maintaining food log.<sup>74</sup>

### **Psychological comorbidities**

- Psychosocial care should be integrated into a collaborative patient-centered approach and provided to all people with diabetes.
- Consider assessing depression, diabetes distress, anxiety, eating disorders, and cognitive capacities using validated tools at the initial visit, at periodic intervals, and when there is a significant change in health, treatment, or major life circumstances. Caregivers and family members should be included when this is appropriate.

### **Pain**

**Recommendation:**

Recommend low impact exercise such as to yoga, tai chi, and warm pool-based activities to help improve quality of life for patients with chronic musculoskeletal pain.

In addition to causing diabetic peripheral neuropathy, diabetes predisposes to chronic musculoskeletal pain. Observational studies have shown an increased risk for chronic back, shoulder, and neck pain. Diabetes appears to increase disability and emergency room visits due to chronic pain. Chronic pain may be a barrier to achieving diabetes-related benchmarks. Chronic pain presents a major barrier to frequent exercise, which is a key part of diabetes management. Low impact activities such as yoga, tai chi, and warm pool-based exercise have all been shown to improve quality of life and some diabetes-related outcomes.

### **Macrovascular Disease**

Diabetes increases an individual’s risk of coronary artery disease, stroke, and peripheral vascular disease. Reducing other cardiovascular risk factors (Table 9) in patients with diabetes reduces their overall risk. Cardiovascular risk factors should be assessed annually in patients with type 2 diabetes. These risk factors include hyperlipidemia, hypertension, smoking, a family history of premature coronary disease, obesity, and the presence of micro- or macroalbuminuria.

### **Aspirin**

**Recommendations:**

Prescribe aspirin for secondary prevention to patients with a history of atherosclerotic cardiovascular disease. Most patients with Type 2 diabetes and no ASCVD history do not benefit from aspirin for primary CVD prevention.

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The ADA and most other organizations recommend use of aspirin for secondary prevention in all patients with diabetes who have known atherosclerotic cardiovascular disease. However, the use of aspirin for primary prevention of atherosclerotic disease events is not recommended for most people with diabetes as a routine practice. Recent data do not consistently show that aspirin used for primary prevention leads to a decrease in major cardiovascular events. Aspirin used for primary prevention increases the occurrence of major bleeding events such as GI bleeding and intracranial hemorrhage due to falls.<sup>75-78</sup> This is an area of ongoing debate and research. The USPSTF states that there is some evidence to support using aspirin for primary prevention for patients between the ages of 50 and 69 who are at high risk for adverse CVD events and at low risk for GI bleeding.<sup>79</sup>

### **SGLT2 inhibitors and GLP-1 RAs**

#### Recommendation:

Consider initiating an SGLT-2 inhibitor or GLP1-RA for patients with a history of ASCVD or those at high risk for ASCVD.

Multiple randomized controlled trials have demonstrated the cardiovascular benefit of these drug classes in people with type 2 diabetes.<sup>80-85</sup> A reduction in major adverse cardiovascular events (MACE) and in some instances a reduction in mortality have been demonstrated for members of both these drug classes. These findings have led the ADA to recommend initiation of these drugs for diabetic patients with history of ASCVD or those at high risk for ASCVD. The term “high risk” has been variably defined, but generally includes individuals without history of ASCVD but presence of classical CVD risk factors such as hypertension, LDL >140, LVH, and tobacco smoking. Review the Glycemic Management section for a more information on the efficacy of the SGLT-2 inhibitors and GLP1-RAs.

### **Screening for Coronary Artery Disease**

#### Recommendations:

Do not screen for coronary artery disease in asymptomatic patients.

Consider screening for coronary artery disease in sedentary patients who plan to begin a vigorous exercise program.

Clinicians should maintain a high index of suspicion for macrovascular disease in patients with type 2 diabetes. Symptoms suggestive of coronary artery disease, transient ischemic attack, stroke, or peripheral vascular disease should prompt consideration of further testing.

Screening for coronary artery disease in asymptomatic individuals is not recommended as a routine practice. A large randomized control trial demonstrated that screening for CAD in asymptomatic type 2 diabetes did not reduce the rate of cardiac death or myocardial infarction.<sup>86</sup>

However, screening for coronary artery disease may be considered for individuals over age 30 with type 2 diabetes and additional risk factors for CVD who wish to start an exercise program more rigorous than a brisk walk. The prospective Look AHEAD study showed 22% of people with diabetes who were asymptomatic of coronary artery disease displayed objective abnormalities on exercise ECG stress testing.<sup>87</sup>

### **Cardiovascular Autonomic Neuropathy**

Cardiovascular autonomic neuropathy (CAN) is defined as the impairment of autonomic control of the cardiovascular system. CAN is particularly concerning because it may lead to silent ischemia and/or silent myocardial infarction. CAN may manifest clinically as resting tachycardia, orthostatic hypotension, syncope, impaired blood pressure/heart rate response to exercise, and exaggerated drop in blood pressure/heart rate during induction of general anesthesia.

### **Autonomic neuropathy and cardiovascular disease**

Although less common in Type 2 than Type 1 diabetes, autonomic neuropathy can occur. This is primarily of concern in the detection of cardiovascular disease, as angina may be silent in adults with diabetes. Care should be taken to elicit a history of possible atypical anginal symptoms or equivalents and consideration should be given to risk assessment and stress testing.<sup>88</sup>

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## Microvascular Complications

Include microvascular disease in screening and treatment (Table 7).

### Retinopathy

#### Recommendations:

Refer for a dilated retinal exam by an eye care specialist every 2 years if previous eye exam was normal and good glucose and BP control. Otherwise, annually or more frequently as recommended by the eye care provider.

Ophthalmologists should treat diabetic retinopathy.

Consider intensifying glycemic control and blood pressure control for patients diagnosed with diabetic retinopathy.

Consider more frequent dilated eye exams in patients being initiated on insulin, sulfonylureas, GLP1-RAs, and TZDs as they may increase risk for development of diabetic retinopathy.

Retinopathy and macular edema affect a substantial proportion of patients with Type 2 diabetes. Between 10 and 30% of subjects have retinopathy at the time of diabetes diagnosis, and most will eventually develop some level of retinopathy. Severe retinopathy requiring treatment is somewhat less common, but still makes diabetes the leading causes of visual loss in US adults and the leading cause of blindness in working age adults. Prevention of retinopathy is best achieved by optimizing blood pressure and glucose control.

Dilated retinal examination reduces the incidence of severe visual loss by allowing timely treatment (eg, laser photocoagulation, anti-VEGF intraocular injections) of proliferative retinopathy and macular edema. Optimal screening intervals for retinopathy depend on the risk in the individual patient. Patients who have been diagnosed with retinopathy should be screened at least annually, and many will require much more frequent examination depending on the degree of retinal abnormality. Patients have a low risk of developing retinopathy that will require treatment over the short term if they have no retinopathy on a baseline retinal exam by an expert and have both reasonable glucose and blood pressure control. These patients can be screened less frequently, at 2 year intervals. For measuring quality of care for diabetes, the HEDIS interval for retinal examinations is biennially for patients with previous normal eye exam and at least annually for patients with abnormal eye exam.

Unless the primary caregiver has been specifically trained to perform dilated retinal examinations, the accuracy of fundoscopic examination is poor. Thus, all screening should be performed by a trained eye-care professional.

Glucose-lowering drugs capable of producing rapid drops in A1c have been associated with increased rates of diabetic retinopathy. Insulin, sulfonylureas, TZDs, and GLP1-RAs have all been associated with increased rate of retinopathy presumable due to rapid reduction in glucose levels. If these medicines are being initiated, more frequent A1c checks and fundoscopic exams should be considered.

### Nephropathy

#### Recommendations:

Check spot urinary albumin/creatinine ratio and creatinine, electrolytes and eGFR annually.

If albumin/creatinine ratio >30 mg/gm, check UA to rule out asymptomatic UTI and repeat spot urine ratio twice within 6 months.

If 2 of 3 spot urine albumin/creatinine ratios >30 mg/gm:

- Begin ACE inhibitor or ARB and recheck creatinine and electrolytes within 1–2 weeks of initiating therapy.
- Consider initiating an SGLT2 inhibitor if A1c is above the patient's individualized goal and the GFR is >30 mL/min.

Patients with diabetes with a glomerular filtration rate (GFR) <30-45 mL/min/1.73m<sup>2</sup> with or without nephrotic range proteinuria should be referred to a nephrologist for evaluation for other causes of nephropathy and for discussion of potential treatment options.

Diabetic nephropathy affects 20%-40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD) in the United States. A CDC analysis showed the age-adjusted incidence of ESRD caused by diabetes declined by one-third from 1996 to 2007, which may be related to more screening and aggressive use of

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ACE/ARB in treatment of blood pressure. Yearly screening and treatment for microalbuminuria can reduce the incidence of renal failure. The spot urinary albumin-creatinine ratio is a simple method for testing for microalbuminuria. Because of day-to-day variation in urinary albumin excretion, the test should be repeated on at least two more occasions over a 3- to 6-month period, if the first test result is positive. Two of three tests should be positive (>30 mg albumin per gm of creatinine) before microalbuminuria is considered present. Albuminuria is defined as albumin excretion >300mg/day.

Causes of elevated urinary albumin excretion in the absence of diabetic nephropathy include urinary tract infection, recent exercise, acute febrile illness, hematuria related to urinary tract infection (UTI) or menses, and congestive heart failure. If screening microalbumin is >30 mg/dL, check urinalysis to assess for other causes.

Microalbuminuria is a marker for greatly increased cardiovascular morbidity and mortality for patients with diabetes. Therefore, aggressive intervention is recommended to reduce all cardiovascular risk factors (eg, lowering of LDL cholesterol, antihypertensive therapy, cessation of smoking, institution of regular physical activity, etc.).

For people with diabetes and diabetic kidney disease (either micro- or macroalbuminuria), reducing the amount of dietary protein below usual intake is not recommended because it does not alter glycemic measures, cardiovascular risk measures or the course of GFR decline. Consider dietary referral to evaluate dietary protein in patients with proteinuria.

Multiple glucose lowering drugs have been shown to improve renal outcomes. A 2019 meta-analysis of RCTs that included patients with DKD and GFR>30 mL/min/1.73m<sup>2</sup> showed SGLT2 inhibitors reduced the incidence of decline in GFR, need for renal replacement therapy, doubling of serum creatinine, and development of albuminuria.<sup>89</sup> DPP4 inhibitors have been shown to decrease albuminuria. GLP1-RAs have been shown to reduce development of albuminuria. The evidence favors SGLT2 inhibitors, compared to other drug classes and therefore, should be considered for glycemic management in patients with DKD with a GFR of >30 mL/min, whose A1c is above goal. However, SGLT2 inhibitors have been associated with genitourinary tract infection, acute renal failure, and increased risk of diabetic foot amputation, therefore consider the risk factors carefully.

ACE inhibitors reduce the rate of progression from microalbuminuria to overt proteinuria and diabetic nephropathy, independent of their effect on blood pressure. ARBs show similar benefits to ACE inhibitors in patients with type 2 diabetes and microalbuminuria and diabetic nephropathy. Direct comparisons between ACE inhibitors and ARBs have not been performed in patients with type 2 diabetes. ACE inhibitors and ARBs are regarded as functionally equivalent in protecting against progressive diabetic nephropathy, although more evidence exists in the literature for therapy with an ARB to continue to show benefit even up to the development of end stage renal disease. An ACE inhibitor or an ARB should be used in all patients with microalbuminuria. Combination ACE/ARB therapy for patients with persistent albuminuria is NOT recommended. While the combination reduces proteinuria, it also increases renal failure and adverse events in patients with diabetes, without any benefits on cardiovascular or renal outcomes.

Other antihypertensives (including beta-blockers and non-dihydropyridine classes of calcium-channel blockers (NDCCB) can reduce the level of albuminuria, but no antihypertensive studies to date have demonstrated a reduction in the rate of fall of GFR. Some members of the dihydropyridine class of calcium channel blockers (eg, nifedipine, felodipine) may increase urinary albumin excretion, and should be avoided in patients with microalbuminuria.

Control of blood pressure is important. Recommended blood pressure goals in patients with diabetes and chronic kidney disease are:

<u>Urine</u>	<u>Albumin</u>	<u>Blood Pressure Goal</u>
<u>Excretion</u>		
<30mg/24 hours		<140/90 (recommended)
>30mg/24 hours		<130/80 (suggested)

In normotensive patients with microalbuminuria, target dosages of ACE inhibitors are difficult to define. Some experts recommend titrating medications upward until a normal albuminuria is seen or side effects occur.

For further information regarding care of patients with chronic kidney disease, see the [UMHS clinical guideline on Chronic Kidney Disease](#).

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## Neuropathy

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Diabetic neuropathy is reported in up to half of patients with diabetes. Most have loss of sensation, only a minority experience pain. Patients often describe pain as burning, shock sensation, or stabbing. Evidence indicates early detection of diabetic neuropathy and aggressive foot care results in fewer foot ulcers and amputations. Pay careful attention to the etiology of pain. Occasionally, mechanical factors rather than neuropathy are the mechanism underlying pain.

Glucose lowering medications may have an effect on neuropathy-related complications. GLP-1-RAs have been shown to decrease the risk of diabetic foot ulcer complications. Though SGLT-2 inhibitors on the whole have not been shown to increase the risk of diabetic foot ulcer complications, the CANVAS study results suggest that canagliflozin increases the risk of lower extremity amputations.<sup>48</sup> Risk factors for lower limb amputation should always be considered prior to initiation of this drug class. Risk factors for lower limb amputations include significant peripheral neuropathy, peripheral arterial disease, diabetic foot ulcer, and prior amputation.

Diabetic foot care. Foot care includes examination, preventive care, consideration of orthotic footwear, and treatment of foot ulcers.

Examination. Perform a visual foot inspection, pulse and sensation check annually, and with every routine visit if abnormalities are present. Identify areas of callus formation, claw toe deformity, prominent metatarsal heads (or other bony prominences), and other structural changes. Three simple tests detect peripheral neuropathy: pressure sensation, vibration sensation and temperature/pain perception.

Perform sensory testing with a 5.07 (10g) nylon monofilament annually, to identify insensate feet without protective sensation. Instructions on "How to Use a Monofilament" are in Table 10. Individuals with insensitive feet are at high risk of developing foot ulcers and other related complications.

Education. All patients require education regarding optimal foot and nail care, which includes daily inspection and appropriately fitting shoes. To minimize the risk of trauma, patients should be counseled to avoid walking barefoot and those with neuropathy should avoid high-impact exercise and the use of hot water.

Footwear. Orthotic footwear should be prescribed to accommodate major foot deformities and off-load pressure areas. Most insurance plans, including Medicare, cover therapeutic footwear for patients with diabetic neuropathy or deformity. For others with less deformity, athletic shoes with sufficient room for the toes and forefoot and cushioned socks are appropriate.

Foot ulcers. Detection and early treatment of foot ulcers is of paramount importance. Foot ulcers are among the most common reason for hospitalization in people with diabetes and are the leading cause of lower extremity amputations. However, evidence suggests that up to 85% of amputations are avoidable with patient education, medical monitoring, and early intervention.<sup>90</sup> Careful evaluation of vascular status and infection are required upon discovery of an ulcer. Initiate early treatment with aggressive wound care, antibiotics, revascularization, orthotic prescriptions, and casting to offload the ulcer when appropriate. Studies have shown patients with diabetic foot ulcers have the best outcomes if managed by a multidisciplinary team that specializes in diabetic foot care. Hyperbaric oxygen therapy may be recommended in managing diabetic foot ulcers, although trials have shown mixed results.

### **Treatment of painful diabetic peripheral neuropathy (PDN).**

#### Recommendations:

Optimize glycemic control to reduce progression of PDN.

Check for vitamin B12 deficiency in patients with chronic metformin use.

Treat painful diabetic peripheral neuropathy with pregabalin, duloxetine or gabapentin which are first line therapies and FDA approved for treatment of PDN.

Less preferred medications with some evidence of benefit but significant potential for side effects:

- Tricyclic antidepressants but use with caution in elderly patients due to anticholinergic side effects. Nortriptyline is preferred.
- Carbamazepine, valproate, topical capsaicin cream or lidocaine patch. Use is limited due to side effects.
- Use of opioids is last resort, but discouraged as evidence is inconclusive, with potential harms likely outweighing benefits.

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| <ul style="list-style-type: none"><li>• Non-pharmacological approach such as acupuncture, TENS.</li></ul> |
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Optimizing glycemic control is of paramount importance in slowing the progression of established diabetic neuropathy. Consider checking and treating vitamin B12 level in patients who use chronic metformin as vitamin B12 deficiency can contribute to worsening of neuropathy.

NSAIDs should not be used for chronic neuropathic pain as they are ineffective and increase cardiovascular risk, GI, and renal side effects. Long term NSAID treatment increases the risk of GI bleeding and renal insufficiency. NSAID use in patients with heart disease or its risk factors increases overall risk of heart attack or stroke.<sup>91</sup>

First line therapies for the treatment of PDN supported by the literature include pregabalin, duloxetine, and gabapentin. Pregabalin and duloxetine have FDA approval for treatment of neuropathic pain in diabetes. Tricyclic antidepressants (TCAs) are also options. Comparative effectiveness studies and trials that include quality of life outcomes are rare – so treatment decisions must consider patient's comorbidities, presentation, symptom improvement, medication adherence, and side effects.

- Pregabalin (up to 300-450 mg/day as divided doses) is FDA-approved and is less sedating. Most extensively studied and have favorable effects with at least 30-50% improvement in pain. Starting at 25-75 mg once daily or in divided doses then titrating up to lowest effective tolerable dose will minimize side effects especially in elderly patients.
- Duloxetine (60-120 mg/day) and venlafaxine (75-450 mg/day), serotonin and norepinephrine reuptake inhibitors (SNRIs) are useful in treating patients with co-morbid depression. Duloxetine is FDA-approved. It has been shown to improve neuropathy-related quality of life. Selective Serotonin Reuptake Inhibitors (SSRIs) and trazodone are not as effective in treating painful PDN.
- Gabapentin up to 900-3600 mg/day as divided doses, or more may be required. Use lowest effective dose. Sedation is a side effect that limits its use. May be a less expensive option.
- TCAs may be used to treat painful neuropathy. Use with caution in the elderly and start with low doses and titrate to maximize pain relief while minimizing side effects. Most common side effects include: dry mouth, sedation, orthostatic hypotension and constipation. Nortriptyline is the preferred tricyclic as it has fewer anticholinergic properties. Recommend initiating with dinner, a dose of 10-25 mg and titrate up as tolerated, to maximum of 150 mg/day.

Other agents. Carbamazepine (200 – 600 mg/day) and valproate (500 mg/day), topical capsaicin cream, and lidocaine patch have been shown to decrease PDN. Their use is limited by their side effect profiles.

Opioids. Tapentadol Extended Release is FDA approved for the treatment of neuropathic pain associated with diabetes based on data from two multicenter clinical trials but the design included patients who responded to tapentadol and therefore is not generalizable. As a last resort, opioids may be considered, though general use is discouraged given high risk for addiction and safety concerns compared to the relatively modest pain reduction. Tramadol is a weak opioid and dose of 37.5 mg with 325 mg acetaminophen showed an improvement in PDN compared to placebo. Refer to the UMHS Clinical Care Guideline "[Managing Chronic Non-Terminal Pain in Adults Including Prescribing Controlled Substances](#)".

Acupuncture and TENS. Several studies have shown the efficacy of using traditional acupuncture for the treatment of painful diabetic neuropathy. Transcutaneous Electrical Nerve Stimulation (TENS) has also been evaluated and has been shown to reduce lower extremity pain associated with PDN. Hyperbaric oxygen therapy as an adjunct therapy to standard treatment has been shown to reduce cell death, pain symptoms and rates of major amputations in patients with diabetic foot ulcers and peripheral arterial occlusive disease.

## Immunizations

Patients with diabetes should get the usual vaccinations recommended for the general population. Particular attention should be paid to influenza vaccination (annually) and Hepatitis B due to the increased risks for these diseases in patients with diabetes. In addition, patients with diabetes, regardless of their age, should be given Pneumovax 23 for pneumococcal pneumonia. If vaccination occurred prior to the patient turning age 65, a second dose is required at least 5 years after receiving the first dose. Patients over age 65, who were not previously vaccinated should receive one dose of Pneumovax 23.



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## Complementary and Alternative Therapies

### Recommendations:

Yoga, tai chi, and acupuncture should be encouraged.

Individuals with diabetes are using complementary and alternative (CAM) therapies in ever-increasing numbers. Often, the health care provider is unaware of such use, and such interventions may interact with conventional therapy, for example the addition of a glucose-lowering herbal supplement to a sulfonylurea leading to hypoglycemia. The importance of asking individuals which supplements or complementary therapies they use cannot be overemphasized.

Pharmacologic CAM therapies have been studied. A number of traditionally used supplements have shown promise for the treatment of diabetes. However, limitations for these studies are their short duration, small sample size, poor methodology, and lack of reporting of clinically important outcomes.

Supplementation with multivitamins is generally considered safe; however, megavitamin therapy should be discouraged. Relaxation therapy, yoga, tai chi, acupuncture and spiritual healing are helpful to individuals and can be encouraged. Interventions that are potentially harmful or have no real evidence of efficacy clearly should be discouraged. Patients should be commended, however, on their self-determination and encouraged to direct their efforts in areas that have proven benefits.

## Special Populations

### Diabetes in Women

#### Recommendations:

##### ***Preconception:***

- Screen women that are planning to get pregnant and are at high risk for type 2 diabetes prior to conception.
- Women with type 2 diabetes should be aware of the need for preconception counseling prior to planning pregnancy.
- Discuss and review contraceptive usage and pregnancy plans at each visit for women with type 2 diabetes.
  - Explain the rationale of continuing contraception until goal A1c is achieved.

##### ***Pregnant women without diagnosis of type 2 diabetes:***

- Refer women with a fasting glucose  $\geq 95$  mg/dl to the GDM program run by the Adult Diabetes Education Program and MEND.

##### ***Pregnancy with type 2 diabetes:***

- Insulin is the preferred medication for pregnancies complicated by diabetes.
- Check A1c urgently in women with T2DM and newly diagnosed pregnancy.
- Those with an A1c 5.7-6.4% and a fasting glucose  $< 95$  should be screened early for gestational diabetes.
- Refer those with an A1c  $\geq 6.5\%$  or a fasting glucose  $\geq 126$  mg/dL to high risk obstetrics urgently and to a gestational diabetes education program.
- Review glucose records and adjust insulin at least every 1-2 weeks during pregnancy, due to the physiologic changes in insulin requirements during pregnancy

##### ***Glycemic Targets in pregnancy:***

- Fasting  $< 95$  mg/dL (5.3 mmol/L)
- Two-hour postprandial  $< 120$  mg/dL (6.7 mmol/L)<sup>92</sup>
- A1c  $< 6.0\%$ , if it can be achieved safely

**Blood Pressure Targets in pregnancy:**

On exam, any pregnant patient without a history of hypertension and a BP >140/90, or with a known history of hypertension and a BP >150/100 is at risk. This necessitates an interventional plan and an urgent discussion with the obstetrical provider.

**Post-partum women:**

- Insulin requirements drop dramatically (~1/2 of pre-pregnancy) at delivery for women with pre-existing diabetes.<sup>93</sup>
- Screen for type 2 diabetes in patients where gestational diabetes resolved after delivery, annually by a fasting glucose, A1c, or OGTT (every 3 years).

An increasing number of premenopausal women have T2DM (~1%) which complicates decisions about contraception, preconception counseling, and management of pregnancy. Many are unaware of their diagnosis and its implications on pregnancy. In addition, another ~10% of women will manifest gestational diabetes (GDM) during pregnancy, indicating an inability of the pancreas to expand insulin production, which significantly increases the patient's risk of developing T2DM within 10 years.

**Contraception**

Approximately half of all pregnancies are unplanned, therefore, it is imperative that women with diabetes plan for their pregnancies and achieve an A1c < 6.5% prior to conception. The A1c at the time of conception is predictive of congenital malformations and other complications. Effective contraception is the first step in planning a successful pregnancy in women with diabetes. All women of child-bearing age with diabetes should have contraceptive usage and pregnancy plans reviewed at each visit, including at all their primary care, OB/GYN, and endocrinology appointments. No specific contraceptive choice is recommended, or contraindicated in women with diabetes, however reliability is important. Long-acting Reversible Contraception (LARC), such as an intrauterine device or subdermal implant, are the most effective reversible contraceptive methods available, should be considered for all patients

**Preconception Counseling and Care**

Women with diabetes should be educated on the risks of diabetes and pregnancy. Those who are considering pregnancy should receive preconception counseling and care (see checklist below).

## Check list for Preconception Care/ Counseling

## Education and counselling:

Relationship between A1c at the time of conception and through pregnancy and pregnancy outcomes, including congenital malformations, still birth and autism.

Relationship between A1c at the time of conception and throughout pregnancy with maternal complications, including vision loss, preeclampsia and kidney failure.

Preconception goal of an A1c of < 6.5%.<sup>94-97</sup>

Comprehensive diabetes education, if not previously performed, and targeted updates on nutrition and pregnancy.

Counseling on obesity and pregnancy, if indicated.

## Specific care recommendations for:

Referral for a Maternal Fetal Medicine consult (UMHS).

Referral to the MEND Endocrine Disorders in Pregnancy program for preconception care to optimize A1c is recommended.

Initiation of Prenatal vitamins.

Screening for diabetes complications and comorbidities, including thyroid disease.

Optimization of medications for diabetes and diabetes comorbidities for pregnancy.

– ACE inhibitors, ARBs and spironolactone should be discontinued and if antihypertensives are needed,

labetalol or nifedipine are preferred. Atenolol should be avoided.

- Statins and other lipid lowering medications should be discontinued.

Referral for a comprehensive eye exam.

Initiation of baby aspirin (162 mg daily) to reduce the risk of preeclampsia.

The importance of preconception counselling and care, especially the optimization of the A1c cannot be overstated. In an analysis of the TRUVEN database, pregnancies in women with type 2 diabetes were complicated by miscarriage (25.2% of pregnancies), stillbirth (0.8%), major congenital malformation (10.9%), and congenital heart defect (6.9%).<sup>98</sup> Often these complication rates were higher than in pregnancies complicated by type 1 diabetes, in part due to a higher level of exposure to diabetes education in women with type 1 diabetes. Preconception counselling and optimal A1c in the first trimester have been shown to reduce the risk of congenital malformations and other pregnancy complications dramatically in multiple studies.

### Screening and Diagnosis for GDM

Recent studies have shown an increased prevalence of type 1, type 2, and GDM during pregnancy in both the US and worldwide. Given the risks associated with diabetes and pregnancy, it is reasonable to screen for diabetes in women at high risk prior to conception. Most congenital malformations from hyperglycemia occur before women are even aware they are pregnant.

Michigan Medicine now recommends screening for undiagnosed diabetes and prediabetes at the first prenatal visit, using a fasting glucose and A1c. A fasting glucose  $\geq 95$  mg/dL is considered diagnostic of GDM. Patients with A1c in the prediabetes range (5.7-6.4) are at high risk for GDM and should be screened promptly for gestational diabetes with a 50 gm oral glucose challenge test, although it may be reasonable in some patients to establish a diagnosis of GDM based on this criterion alone.

### Treatment of DM in pregnancy

Treatment of GDM and pre-existing diabetes has been shown to reduce the risk of macrosomia, preeclampsia, and other known complications of diabetes in pregnancy. Optimization of medical nutrition therapy, exercise, sleep, and emotional wellbeing are essential components in the management of all types of diabetes.

Glycemic targets in pregnancy are:

- Fasting  $< 95$  mg/dL (5.3 mmol/L)
- Two-hour postprandial  $< 120$  mg/dL (6.7 mmol/L)<sup>92</sup>

Many women with GDM can achieve glycemic targets in pregnancy with the comprehensive lifestyle coaching. Michigan Medicine recommends all women diagnosed with GDM be referred to the GDM program.

Insulin is the preferred medication for treating diabetes during pregnancy, given it does not typically cross the placenta. Most women with preexisting diabetes require basal bolus therapy to achieve targets, however, some with GDM can achieve goals with once daily bedtime insulin, or mixed insulins dosed before both breakfast and dinner. Most oral medications for diabetes are not recommended in pregnancy. However, do not stop oral medication for diabetes in the first trimester, until insulin has been initiated. Urgently refer those patients to their endocrinologist.

All forms of diabetes are considered risk factors for the development of preeclampsia. A high degree of suspicion is imperative. Page the obstetric care provider (or if unavailable, the MFM on call) for any pregnant patient with no history of hypertension and a BP  $> 140/90$ ; or those with a known history of hypertension and a BP  $> 150/100$ .

### Monitoring

Self-monitored blood glucose is the mainstay of glycemic monitoring in pregnancy. Patients should check their glucose level 4-7 times a day. Both fasting and postprandial sugars should be followed on all patients. Some patients may require glucose monitoring before lunch, dinner, and at bedtime. Postprandial monitoring is recommended because it is associated with better glycemic control and lower risk of macrosomia and preeclampsia.<sup>99-101</sup>

A1c may not fully capture hyperglycemia and hypoglycemia, therefore should not be used as a primary measure of glycemic control in pregnancy. A1c values  $< 6\%$  during pregnancy are associated with the lowest risk of complications. Frequent hypoglycemia may increase the risk of small for gestational age infants.

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CGM technology has been shown to help achieve glycemic targets in type 1 diabetes and pregnancy in CONCEPTT.<sup>102</sup> Data in type 2 diabetes and GDM is lacking. CONCEPTT was a RCT of CGM which demonstrated a reduction in LGA and neonatal hypoglycemia, as well as improvement in A1c without an increase in hypoglycemia with CGM use. It is important to note that in both arms of CONCEPTT, patients used SBGM pre and post meals and used that information to achieve pre- and postprandial targets. CGM metrics were not used as outcomes, or substitutes for traditional postprandial targets. Therefore, CGM metrics should not be used as a substitute for fasting and postprandial targets.

Glucose records should be reviewed and insulin adjustments made at least every 1-2 weeks during pregnancy given the physiologic changes in insulin requirements during pregnancy.

### **Postpartum care**

Post-partum is a time of great change in a woman's life and offering psychosocial support during this time is important. Discussing and implementing a new contraceptive plan is a critical element of postpartum care. Also emphasizing preconception counselling for future pregnancies is essential.

For women with pre-existing diabetes, it is important to realize that insulin requirements drop dramatically at delivery, often to roughly ½ the pre-pregnancy requirements.<sup>93</sup> The first few weeks post-partum are a time to be especially cautious of severe hypoglycemia. Supporting breast feeding is sometimes challenging in women with diabetes as insulin often has to be adjusted to compensate for increased overnight hypoglycemia.

For patients with GDM, there is a 50% risk of progression to type 2 diabetes within 5-10 years after delivery, as well as increased risk for cardiovascular disease. For women with GDM, life-long screening for type 2 diabetes is recommended, starting with an OGTT at 4-12 weeks post-partum and continuing with either OGTT, fasting glucose, or A1c at least every 3 years. Referral to a National Diabetes Prevention Program is recommended with a goal of achieving weight loss of at least 7% of the pre-pregnancy weight and achieving at least 150 minutes of exercise weekly.

## **Older Individuals with Diabetes**

### Recommendations:

Decisions regarding A1c goal, blood pressure goal, use of screening for complications, and use of lipid lowering drugs should be individualized.

Use glucose lowering drugs that are not commonly associated with hypoglycemia.

De-intensify glucose-lowering drug regimens within the individualized A1c goal, when possible.

Avoid symptomatic hyperglycemia, especially when a more relaxed A1c goal set.

Screen for cognitive impairment beginning at age 65.

Patients receiving palliative care do not require strict blood pressure and glucose control; and lipid lowering therapy may be withdrawn.

Evidence is lacking for high quality studies to help guide management of diabetes in older adults, yet this is a population that presents unique challenges that require special attention. This population highlights the need for individualized care due to the heterogeneity in comorbidities, life expectancy, vitality, and patient preferences. Diabetes substantially increases the risk of developing dementia, fragility fractures, depression, falls, and urinary incontinence. Carefully screen for these conditions in older populations.

Older patients with diabetes are at increased risk for hypoglycemia and its complications. Hypoglycemia increases the risk for cognitive impairment and other adverse outcomes. Prioritize the avoidance of hypoglycemia and prescribe glucose lowering drugs which are not associated with inducing hypoglycemia.

Individualize A1c goals for older patients. Those who are otherwise healthy, with few coexisting chronic illnesses, have intact cognitive function, and functional status should have lower glycemic goals (eg, A1c <7.5%). Those with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less-stringent

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glycemic goals (eg, A1c <8.0 – 8.5%). Table 4 discusses A1c targets. De-intensification of glucose lowering regimens is recommended provided it can be accomplished within the individualized A1c goal. Symptomatic hyperglycemia should be avoided especially when a more relaxed A1c goal has been selected.

Controlling other cardiovascular risk factors beyond hyperglycemia may help to reduce cardiovascular events in older individuals. A 2008 RCT demonstrated that using antihypertensives to achieve a goal BP of less than 150/90 reduces risk of MI and stroke. There are no trials to date that have specifically examined older individuals' use of lipid-lowering therapy, but such therapy may be warranted for primary prevention of atherosclerotic disease events when the individual's life expectancy is comparable to the study duration, which is about five years.

When palliative care has been implemented, strict glucose and blood pressure control are usually not warranted. Discontinuation of lipid-lowering medications may be warranted in this situation as well.

### **Coordination with Other Care Providers**

How to adjust diabetes medication for procedures and surgeries is a common question for patients with diabetes and their health care providers. Table 13 summarizes these recommendations.

Table 14 list reasons to consider referral to Endocrinology.

## Pre-procedure and Pre-Operative Diabetes Medication Adjustment Guidelines

Pre-procedure and Pre-operative Diabetes Medication Adjustment Guidelines are in the table below

<b>PERIOPERATIVE and PERIPROCEDURE DIABETES MANAGEMENT</b>	
<b>For Adult Inpatients and Outpatients <span style="color: red;">NOT ON INSULIN PUMP</span></b>	
<b>PROVIDER DOCUMENT</b>	
<b>DAY(s) BEFORE PROCEDURE</b>	
1) Patient takes oral diabetes medications EXCEPT	Take usual dose
SGLT-2 inhibitors (listed below)	Hold for 2 days before procedure
2) Patient takes evening or bedtime insulin	
- NPH	Take usual dose
- Mixed insulins	Take usual dose
- Glargine/Glargine U-300/Detemir /Reg U-500 ( with no other insulin)	Take 50% of usual dose
- Degludec (with no scheduled meal insulin)	Take 50% of usual dose for 2 day before procedure
- Glargine /Glargine U-300/Detemir (as part of a regimen which includes scheduled meal insulin)	Take 70% of usual dose
- Degludec (as part of a regimen which includes scheduled meal insulin)	Take 70% of usual dose for 2 days before procedure
- Regular or aspart or lispro or glulisine or fiasp	Take usual dinner dose for regular meal Take 50% of usual dose for sugary beverage diet for bowel prep
3) Patient takes non-insulin injectables	Take usual dose
4) Patient uses insulin pump* - See Periprocedure and Perioperative Insulin Pump Guidelines.	Continue basal rate- unless frequent hypoglycemia Then reduce to temporary basal rate of 70%
<b>MORNING OF PROCEDURE</b>	
1) Patient takes oral diabetes medications	HOLD dose
2) Patient takes am insulin	
- NPH	Take 50% of usual dose
- Mixed insulins	Take 50% of usual dose
- Glargine/Glargine U-300/ Detemir /Reg U-500/Degludec (with no scheduled meal insulin)	Take 50% of usual dose
- Glargine/Glargine U-300/Detemir/Degludec (as part of a regimen which includes scheduled meal insulin)	Take 70% of usual dose
- Regular or aspart or lispro or glulisine or fiasp	HOLD doses
3) Patient takes non-insulin injectables	HOLD dose
4) Patient uses insulin pump* - See Periprocedure and Perioperative Insulin Pump Guidelines.	Reduce to temporary basal rate of 70%
<i>*Intraoperative and postoperative use of pump should be addressed on an individual basis in consultation with patient's endocrinologist</i> <b>MIXED INSULIN INCLUDE</b> (75/25,70/30 or 50/50) <b>ORAL SGLT2 INHIBITORS</b> - Canagliflozin; Dapagliflozin; Empagliflozin; Ertuglifloxin, Sotagliflozin; alone or in combination pills <b>NONINSULIN INJECTABLES</b> - Bydureon®, Byetta®, Victoza®, Symlin®, Ozempic®, Xultophy®, Soliqua®, or Trulicity®. <span style="background-color: yellow;">On days of bowel prep, use adjusted doses of Glargine/Glargine U-300/ Detemir /Reg U-500/Degludec as above</span>	

Last revised by Glycemic Management P&T Subcommittee 09/2019

<https://pharmwebsp.med.umich.edu/ layouts/15/WopiFrame.aspx?sourcedoc={1B2899A2-710D-4FCC-8F2A-FDAA84BAEC6B}&file=PeriprocedureNotOnInsulinPumps Provider.docx&action=default&DefaultItemOpen=1>

**Table 14: When to Consider Endocrine Consultation or Referral**

<ul style="list-style-type: none"><li>• <b>Uncertain classification of diabetes, eg, diabetes associated with endocrinopathies such as acromegaly, Cushing’s syndrome, or pheochromocytoma; genetic defects of beta-cell function (MODY); genetic defects in insulin action (Type A syndrome of insulin resistance).</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Type 1 diabetes</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Plans for pregnancy</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Multiple severe complications of diabetes</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Chronic lack of adherence to their treatment regimen</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Family problems or significant psychiatric problems interfering with treatment</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Frequent emergency room or hospital admission</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Difficulty achieving target A1c</b></li></ul>
<ul style="list-style-type: none"><li>• <b>Young adults</b></li></ul>

## **Related National Guidelines and Performance Measures**

### **National Guidelines**

This guideline generally conforms to:

American Association of Diabetes Educators and American Diabetes Association: National standards for diabetes self-management and support (2013)

American College of Cardiology/American Heart Association:  
Guideline on the Assessment of Cardiovascular Risk (2013)

Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)

American Diabetes Association:

Diagnosis and Classification of Diabetes Mellitus (2012)

Nutrition Therapy Recommendations for the Management of Adults with Diabetes (2014)

Standards of Medical Care in Diabetes (2021)

American College of Physicians, Clinical

Efficacy Assessment Subcommittee: The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus (2003)

American College of Physicians, Clinical Efficacy Assessment Subcommittee: Lipid control in the management of type 2 diabetes mellitus: (2004)

Panel Members appointed to the Eight Joint National Committee (JNC 8) (2013)

### **Clinical Performance Measures**

National programs that have clinical performance measures of diabetes include the following.

Centers for Medicare & Medicaid Services:

- Physician Quality Reporting Measures for Group Practice Reporting Option (GPRO)
- Clinical Quality Measures for financial incentives for Meaningful Use of certified Electronic Health Record technology (MU)
- Quality measures for Accountable Care Organizations (ACO)

National Committee for Quality Assurance: Healthcare Effectiveness Data and Information Set (HEDIS)

Regional programs that have clinical performance measures of cancer screening include the following.

Blue Cross Blue Shield of Michigan: Physician Group Incentive Program clinical performance measures (PGIP)

Blue Care Network [HMO]: clinical performance measures (BCN)

These programs have clinical performance measures for diabetes addressed in this guideline. While specific measurement details vary (eg, method of data collection, population inclusions and exclusions), the general

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measures are summarized below.

A1c testing. The percentage of patients 18–75 years of age who had an A1c test within 12 months (measurement period). (GPRO, ACO, PGIP)

A1c control. The percentage of patients 18–75 years of age with diabetes mellitus who had A1c < 8.0% within 12 months (measurement period). (MU, ACO, BCN)

A1c poor control. The percentage of patients 18–75 years of age with diabetes mellitus who had A1c >9.0% within 12 months (measurement period). (GPRO, MU, ACO)

Blood pressure control. Percentage of patients aged 18 through 75 years with diabetes mellitus who had most recent blood pressure in control: less than 140/80 mmHg (GPRO), less than 140/90 mmHg within 12 months (measurement period). (MU, ACO).

LDL testing. The percentage of patients 18-75 years of age with LDL tested within 12 months (measurement period). (GPRO, MU, ACO, PGIP, BCN)

LDL control. The percentage of patients 18-75 years of age with diabetes who had (a) LDL tested and (b) LDL <100 mg/dL within 12 months (measurement period). (GPRO, MU, ACO, BCN)

Statin. The percentage of patients between 40 and 75 years of age with one or more filled prescriptions for a statin drug within 12 months (measurement period). (PGIP)

Eye exam. The percentage of patient 18-75 years of age with diabetes (Type 1 or Type 2) who had a retinal or dilated eye exam or a negative retinal exam (no evidence of retinopathy) by an eye care professional within 12 months (measurement period). (GPRO, MU, ACO, BCN)

Foot exam. The percentage of patient aged 18-75 years with diabetes who had a foot exam (visual inspection, sensory exam with monofilament, or pulse exam within 12 months (measurement period). (GPRO, MU, ACO)

Neuropathy screening. The percentage of patient 18-75 years of age with diabetes who had a nephropathy (urine protein) screening test or evidence of nephropathy within 12 months (measurement period). (GPRO, MU, ACO, PGIP, BCN)

ACE/ARB with comorbid CHF, hypertension, or nephropathy. The percentage of patients between 18 and 75 years of age with a diagnosis of diabetes with comorbid congestive heart failure (CHF), hypertension, or nephropathy who received ACE/ARB therapy within 12 months (measurement period). (PGIP)

Tobacco use assessment. Percentage of patients aged 18 years or older who were queried about tobacco use one or more times within 24 months of the measurement end date. (MU, ACO – diabetes composite & diabetes tobacco use)

Advising tobacco users to how quit. The percentage of patients 18 years of age and older who were current smokers or tobacco users, who have had tobacco use cessation counseling one or more times within 24 months of the measurement end date. (MU, ACO – diabetes composite & diabetes tobacco use)

## **Guideline Development Methodology**

### **Funding**

The development of this guideline was funded by UMHS.

### **Guideline Development Team and Disclosures**

The multidisciplinary guideline development team consisted of:

- Caroline R Richardson, MD, Family Medicine; Jeffrey R Borgeson, MD, General Internal Medicine; Jennifer A Wyckoff, MD, Metabolism, Endocrinology & Diabetes; Anne S Yoo, PharmD, Pharmacy Innovations and



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Partnerships. Consultants: James E Aikens, PhD, Family Medicine; Dina H Griauzde, MD, General Internal Medicine; Monica A Tincopa, MD, MSc, Gastroenterology.

- Guideline development methodologists: R. Van Harrison, PhD, Learning Health Sciences, April Proudlock, RN Clinical Quality.
- Literature search services were provided by informationists at the Taubman Health Sciences Library, University of Michigan Medical School.

UMHS endorses the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Contributions of team members with relevant financial relationships are reviewed by team members without relevant financial relationships to assure the information is presented without bias.

Individuals with no relevant personal financial relationships:

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Individuals with relevant personal financial relationships:

Caroline R Richardson, MD:

- 1) Grant funding from industry – completed in last year - Apple, Dexcom, Twine
- 2) Grant funding from industry – ongoing –Blue Cross Blue Shield
- 3) Grant funding from industry being negotiated, potential – Renalytics

Dina Griauzde, MD

- 1) Consultant – National Kidney Foundation of Michigan

## **Systematic Review of Literature**

The team began the search of literature by accepting the results of a systematic literature review performed in 1995 to develop the guideline and again in 2003 and 2010 for major updates.:

VA/DoD Clinical Practice Guideline for the Management of Type 2 Diabetes Mellitus in Primary Care. Washington, DC: U.S. Departments of Veterans Affairs and of Defense, 2017. Search results performed through 3/25/16. (Topic specific search terms, pages 141-147.)

To update those results, we performed a systematic search of literature on Medline and in the Cochrane Database of Systematic Reviews for the time period 3/1/16 – 3/1/19.

The major search term was diabetes mellitus. The searches were for guidelines, controlled trials (including meta-analyses), and cohort studies, for literature on humans in the English language. Within these parameters individual searches were performed for the following topics:

- A. Prevention: Include drug-induced diabetes
- B. Screening: Diabetes, prediabetes
- C. Diagnosis: History (risk factors, symptoms), physical exam
- D. Diabetes self-management: Exercise, meal planning and nutrition, medication adherence, smoking cessation, insurance, cost
- E. Glycemic Control: Treatment, glucose monitoring, glycemic management, pharmacologic glucose management, insulin, medications that increase blood sugar
- F. Co-morbid medical conditions: Hypertension, treatment, non-alcoholic fatty liver disease (NAFLD), obesity, obstructive sleep apnea
- G. Other comorbid conditions not included in F above
- H. Psychological comorbidities and complications: Screening and treatment
- I. Macrovascular complications: Screening and treatment, stroke risk, CAD risk, autonomic neuropathy and cardiovascular disease
- J. Microvascular complications: Screening and treatment, retinopathy, nephropathy, neuropathy, diabetic foot care, first line therapies, other agents

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- K. Immunizations: Influenza, pneumococcal, hepatitis b
  - L. Complementary and alternative therapies
  - M. Special populations: Adolescents, preconception, pregnant women, gestational diabetes, older individuals
  - N. Other not in A-M above

The search was conducted in components each keyed to a specific causal link in a formal problem structure. The search was supplemented with very recent controlled trials known to expert members of the panel. Negative trials were specifically sought. The search was single cycle. Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data. If randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The “strength of recommendation” for key aspects of care was determined by expert opinion.

**Literature review and assessment:** Members of the guideline team reviewed the publications identified to be relevant to specific topics in order to select those with best evidence. Criteria to identify overall best evidence included relevance of the study setting and population, study design, sample size, measurement methods (variables, measures, data collection), intervention methods (appropriateness, execution), appropriateness of analyses, and clarity of description.

In considering level of evidence based on study design, the classification was:

- A = systematic reviews of randomized controlled trials with or without meta-analysis
- B = randomized controlled trials
- C = systematic reviews of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control)
- D = individual observation studies (case study or case series)
- E = expert opinion regarding benefits and harm

**Recommendations.** The guideline team reviewed the evidence and determined the importance of performing or not performing key aspects of care (listed on the first page of this guideline). In the absence of empirical evidence, the guideline team based recommendations on their expert opinion.

The strength of recommendations regarding care were categorized as:

- I = Generally should be performed
- II = May be reasonable to perform
- III = Generally should not be performed

## Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine; General Medicine; Geriatric Medicine; and Metabolism, Endocrinology, and Diabetes. The draft was revised based on comments from these groups.

The final version of this guideline was endorsed by the Clinical Practice Committee of the University of Michigan Medical Group and by the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.

## Acknowledgments

The following individuals are acknowledged for their contributions to previous versions of this guideline.

2019: Connie J Standiford, MD, General Internal Medicine, Sandeep Vijan, MD, General Internal Medicine, Hae Mi Choe, PharmD, College of Pharmacy, R Van Harrison, PhD, Medical Education, Caroline R Richardson, MD, Family Medicine, Jennifer A Wyckoff, MD, Metabolism, Endocrinology & Diabetes. Consultants: Martha M Funnell, MS, RN, CDE, Diabetes Research and Training Center, William H Herman, MD, Metabolism, Endocrine & Diabetes.

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**Initial Release**

May, 1996

**Most Recent Major Update**

October, 2021

**Substantive Revisions**

May, 2014

**Interim/Minor Revisions**

September, 2015,

June, 2017,

November, 2018

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These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

<b>APPROVALS</b>	
P&T	Date: 6/16/2021
ACOC	Date: 7/22/2021
CPC	Date: 9/28/2021
ECCA	Date: 10/26/2021



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## Appendix A. Four Large Clinical Trials Evaluating Targets for Therapy of Type 2 Diabetes

Targets for therapy of Type 2 diabetes have been evaluated in four large clinical trials: UK Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk in Diabetes study (ACCORD), Action in Diabetes and Vascular Disease Controlled Evaluation (ADVANCE) and The VA Diabetes Trial (VADT).

### UKPDS

The UKPDS randomized 3687 subjects newly diagnosed with Type 2 diabetes (mean age 54 years) without significant macrovascular or renal disease to intense control (FPG<108 mg/dL) with either sulfonylurea or insulin compared to conventional control (FPG<270mg/dl) over 10 years. Mean A1c achieved was 7% in the intervention arm and 7.9% in the conventional arm. Those in the sulfonylurea/insulin intervention arm had a 12% lower diabetes complication composite endpoint ( $p=0.029$ ) (driven largely by the reduction in the need for retinal photocoagulation).<sup>103</sup> The UKPDS also included a metformin intervention arm, where the achieved A1c in the intensive arm was 7.4 % compared to 8% in the conventional arm. Compared with the conventional treatment, those in the intensive metformin arm had a reduction of 32% (95% CI 13–47,  $p=0.002$ ) for any diabetes-related endpoint, 42% for diabetes-related death (9–63,  $p=0.017$ ), and 36% for all-cause mortality (9–55,  $p=0.011$ ), all significantly greater reductions than in the sulfonylurea/insulin arm.<sup>104</sup> One year after the conclusion of the UKPDS trial, there was no difference in glycemic control found between the groups. However, ten years after the end of the UKPDS trial, between group differences persisted. In the sulfonylurea–insulin group, relative reductions in risk for any diabetes-related end point (9%,  $P = 0.04$ ) and microvascular disease (24%,  $P = 0.001$ ) persisted, and risk reductions emerged for myocardial infarction (15%,  $P = 0.01$ ) and death from any cause (13%,  $P = 0.007$ ). In the metformin arm, risk reductions persisted for any diabetes-related end point (21%,  $P = 0.01$ ), myocardial infarction (33%,  $P = 0.005$ ), and death from any cause (27%,  $P = 0.002$ ).<sup>105</sup>

### ACCORD

ACCORD recruited 10,109 subjects between the ages of 40 and 79 with Type 2 diabetes and either known cardiovascular disease or known risk factors for cardiovascular disease and randomized them to A1c targets <6% (achieved 6.4%) or 7-7.9% (achieved 7.5%). No standard treatment regimen was applied. The study was terminated at 3.7 years due to increased all-cause mortality (hazard ratio, 1.21; 95% confidence interval [CI], 1.02 to 1.44y) in the intense arm.<sup>106</sup> This finding was surprising and multiple post hoc analyses have tried to understand it. As no defined medication treatment protocol was used in ACCORD, one avenue of investigation was that perhaps a specific medication or class of medications used more frequently in the intense arm increased mortality. However, that did not appear to be the case when studied. There was no relationship between insulin use/dose for example.<sup>107</sup> Another assumption that hypoglycemia was the cause of increased mortality did not appear to be correct. Increased mortality in the intensive arm was observed in subjects with an average A1c of >7 and either no change or an increase in A1c in the 1<sup>st</sup> year of the trial.<sup>108</sup> Analysis did show that DKD,<sup>109</sup> increased BMI, and increased age<sup>110</sup> were associated with increased mortality in the intensive control group. Despite increased all-cause mortality in the intense arm, ACCORD did demonstrate a benefit of acute control through a reduction in the progression of retinopathy -5.8% in the intense arm versus 12.7% in the standard arm (adjusted odds ratio [aOR] 0.42, 95% CI 0.28–0.63,  $P < 0.0001$ ).<sup>111</sup>

### ADVANCE

ADVANCE recruited 11,140 patients with Type 2 diabetes who were 55 years of age or older with at least one CV risk factor or a known macro or microvascular complication of diabetes. Subjects were randomized to intense control (target HbA1c of <6.5% and achieved A1c of 6.53%\_versus standard (no set target HbA1c and achieved HbA1c of 7.3 %). Subjects received gliclazide plus other medications (metformin, thiazolidinedione, acarbose, insulin) as needed in a sequential manner to achieve goal, and followed for 5 years. ADVANCE found a 10% relative risk reduction for the combined outcome of major macrovascular and microvascular outcomes. (18.1% vs 20.0% HR 0.90; 85% CI 0.82-0.98,  $P=0.01$ ) This finding was driven primarily by a reduction in renal events.<sup>112</sup> One particularly intriguing analysis of ADVANCE data suggested that there were A1c thresholds. At HbA1c levels below 7.0% for macrovascular events and death, and below 6.5% for microvascular events, there was no significant change in risks, but that above these thresholds, the risks increased. For every 1% higher HbA1c level, there was a 38% higher risk of a macrovascular event, a 40% higher risk of a microvascular event and a 38% higher risk of death (all  $p<0.0001$ ).<sup>113</sup> Another interesting analysis from ADVANCE demonstrated an increase in both macrovascular and microvascular risk with visit to visit variability in A1c and fasting glucose.<sup>114</sup>

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## VATD

The VATD study recruited veterans (mean age 60.4 years, mean duration of diabetes 11.4 years, mean A1c 9.4%), and randomized to tight control (achieved A1c of 6.9% versus 8.4%). A reduction in cardiovascular events was seen 5 years after the end of the VATD in the intense group. (Hazard ratio, 0.83; 95% confidence interval [CI], 0.70 to 0.99; P = 0.04)<sup>115</sup> as were persistent renal benefits as more of those in the intensive arm had an eGFR >60 mL min<sup>-1</sup> 1.73 m<sup>-2</sup> (OR 1.34 [95% CI 1.05, 1.71], p = 0.02).<sup>116</sup>

A meta-analysis of these studies, which included 27,049 participants, found that compared with less intensive glucose control, more intensive glucose control resulted in a reduction of relative risk by 20% for kidney end points (hazard ratio 0.80, 95% CI 0.72 to 0.88; p<0.0001) and by 13% for eye points (0.87, 0.76 to 1.00; p=0.04).<sup>116</sup>

## Appendix B. Insulin Initiation and Adjustment Protocol

- 1) Start with NPH, detemir, glargine, or degludec
- 2) The choice may vary depending on concerns regarding endogenous insulin secretion, need for meal- time insulin coverage, cost and convenience.
- 3) All patients started on insulin should demonstrate use of a glucometer and be educated on recognition and treatment of hypoglycemia.

Glargine, degludec, detemir, or NPH once **daily**

*Of note: NPH and detemir do not last for 24 hours and usually require twice daily dosing*

- a. Continue metformin +/- other antihyperglycemic agents depending on preprandial glucose.
- b. Add 10-20 units of glargine, degludec, detemir or NPH insulin daily
- c. Then increase insulin by 10-20% or 2-4 units every 3 days until attaining fasting blood glucose goal without hypoglycemia.
- d. Consider adding either rapid or regular insulin before meals if post-prandial glucose >180 mg/dL.

NPH or detemir insulin **twice daily**

- a. Continue metformin +/- other antihyperglycemic agents as appropriate
- b. Add 5-10 units of NPH or detemir insulin at breakfast and dinner (or bedtime).
- c. Then increase insulin by 10-20% or at least 2 units every 3 days until attaining a fasting blood glucose and pre-dinner glucose goal without hypoglycemia.
- d. Consider adding either rapid or regular insulin before meals if post-prandial glucose >180 mg/dL.

Premixed insulin (intermediate or long & short-acting or rapid-acting mixtures)

- a. Continue metformin, discontinue sulfonylurea.
- b. Add 10 units of pre-mixed insulin at breakfast and dinner.
- c. Then increase pre-breakfast and/or pre-dinner insulin by 10-20% or at least 2 units every 3 days until attaining a fasting and pre-meal glucose goal without hypoglycemia.

### Insulin Adjustment Protocol

If overnight or before breakfast glucoses are above/below target	Adjust the supper or bedtime dose of NPH, detemir, glargine or degludec
If before lunch glucoses are above/below target	Adjust the breakfast dose of regular, rapid acting or ultra-rapid acting insulin
If before supper glucoses are above/below target	Adjust the breakfast dose of NPH OR the lunch dose of regular, rapid acting or ultra-rapid acting insulin
If before bedtime glucoses are above/below target	Adjust the supper dose of regular, rapid acting or ultra-rapid acting insulin
If fasting glucose levels are significantly higher than bedtime levels (i.e. twice as high), consider nocturnal hypoglycemia. Have the patient check glucose level around 3 AM for 2 days during the week. If glucose levels are: - Normal or high in the middle of the night - Low in the middle of the night	Increase the NPH supper dose Decrease the NPH supper dose

#### Insulin adjustment for patients:

For NPH bedtime or Lantus dosing:

- |                                     |   |
|-------------------------------------|---|
| 3 consecutive morning readings >130 | increase bedtime NPH or Lantus by 2 units |
| 3 consecutive morning readings >150 | increase bedtime NPH or Lantus by 4 units |

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For NPH twice a day:

- |  |                                 |
|--|---------------------------------|
| 3 consecutive morning readings<br>>130 | increase evening NPH by 2 units |
| 3 consecutive morning readings<br>>150 | increase evening NPH by 4 units |
| 3 consecutive evening readings<br>>130 | increase morning NPH by 2 units |
| 3 consecutive evening readings >150    | increase morning NPH by 4 units |