Management of Type 2 Diabetes Mellitus

Diabetes Mellitus Guideline Team

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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.

Patient population. Adults

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

Key points

Prevention. In individuals at risk for type 2 diabetes (see Table 1), type 2 diabetes can be delayed or prevented through diet, exercise, and pharmacologic interventions *[IA]*.

Screening. Although little evidence is available on screening for diabetes, screening should be considered every 3 years beginning at age 45 or annually at any age if BMI ≥ 25 kg/m^2 *[evidence: IID]*, history of hypertension *[IIB]*, gestational diabetes *[IC]*, or other risk factors.

Diagnosis. An A1c of 6.5% or greater, confirmed by second test, is diagnostic of diabetes. Alternatively, diabetes can be diagnosed by two separate fasting glucoses ≥ 126 mg/dL; with symptoms, a glucose ≥ 200 mg/dL confirmed on a separate day by a fasting glucose ≥ 126 mg/dL; or 2-hour postload glucose ≥ 200 mg/dl during an oral glucose tolerance test *[B]*. (See Table 1. See Table 2 for differential diagnosis.)

Treatment. Essential components of the treatment for diabetes include diabetes self-management education and support, lifestyle interventions, and goal setting (see Table 3); glycemic management (see Tables 4-10); and pharmacologic management of hypertension (see Table 11) 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. Management of risk factors and complications is summarized in Table 12. Diet, exercise, and pharmacologic interventions should be initiated for:

Hypertension *[IA]*	Cardiovascular risk reduction *[IA]*
Hyperlipidemia *[IA]*	Diabetes complications as indicated

Each regular diabetes visit	Annually
• Blood pressure measured and controlled *[IA]*.	• Dilated retinal examination by eye care specialist: if good blood sugar and blood pressure control and previous eye exam was normal, every 2 years; if diabetic changes, annually or more frequently per eye care provider *[IB]*. Treat retinopathy *[IA]*.
• Check HbA1c every 3 months if on insulin; every 6 months if on oral agents or diet only and well-controlled. *[II]*. Optimize glycemic control *[IA]*.	• Screen for microalbuminuria if not already on an ACE inhibitor or ARB *[IB]*. Prescribe an ACE inhibitor (or ARB, if ACE contraindicated) for microalbuminuria or proteinuria *[IA]*.
• Review and reinforce diet and physical activity *[IID]*.	• Serum creatinine and estimated glomerular filtration rate (eGFR) *[ID]*.
• Check weight, calculate BMI *[IID]*.	• Monofilament testing of feet (see Table 13) *[IA]*.
• Feet should be inspected at each visit if neuropathy present. Otherwise visual foot exam and neuropathy evaluation annually *[IA]*.	• Prescribe moderate dose statin; measure lipids for adherence.
• Smoking cessation counseling provided for patients with tobacco dependence *[IB]*.	• Smoking status assessed *[IB]*.
• Review and reinforce key self-management goals (See Table 3) *[IA]*.	• All self-management goals reviewed and reinforced. (See Table 3).
	• Influenza vaccination (annual) and confirm or give pneumococcal and hepatitis B vaccinations.

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

*** 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=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

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

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

[a] For A1c and fasting glucose, the diagnosis must be confirmed by a second test

[b] A random glucose ≥ 200 mg/dL must be confirmed with a fasting glucose ≥ 126 mg/dL or the OGTT. A random glucose of 130-199 mg/dL is abnormal and further testing is indicated, e.g., fasting glucose, OGTT, or hemoglobin A1c.

Table 2. Abbreviated Differential Diagnosis of Diabetes

Type 1 diabetes

Type 2 diabetes

Diabetes due to diseases of the exocrine pancreas
- pancreatitis, pancreatectomy, or pancreatic adenocarcinoma
- cystic fibrosis
- hemochromatosis
- others

Diabetes due to other endocrinopathies
- acromegaly
- Cushing's syndrome
- pheochromocytoma
- glucagonoma
- others

Monogenic forms of diabetes
- Maturity-onset diabetes of the young
- Diabetes due to point mutations in mitochondrial DNA
- Lipoatrophic diabetes
- others

Drug induced diabetes
- Transplant or steroid related diabetes
- HIV/AIDS related diabetes

Diabetes as part of congenital syndrome
- Congenital rubella syndrome
- Down syndrome
- Turner's syndrome
- Wolfram's syndrome
- Myotonic dystrophy
- Prader-Willi syndrome
- Bardet-Biedl
- others

Table 3. -Self-Management Topics *

At each regular visit (e.g. every 3-6 months) ask about:

Active responsibility for own care. What do you do each day to take care of your diabetes? What is hardest for you to do? (Demonstrate through words and actions that diabetes is a serious illness.)

Progress toward blood pressure, glucose, and cholesterol goals. Do you know your most recent blood pressure level, HbA1c level, and LDL cholesterol levels and your progress toward your goals for these levels?

Blood glucose monitoring if on insulin. Do you know (1) the rationale for monitoring your blood glucose (sick day management, insulin dose adjustments)? (2) Your monitoring schedule? (3) How to use the results? How do you use this information in your daily diabetes care?

Medications. What time of the day do you take your pills or insulin each day? Do you take them even if you are ill and unable to eat? What are your current doses? About what percent of the time have you missed your medicines in the past month?

Symptoms and treatment of hyperglycemia and hypoglycemia. What are the (1) symptoms and treatment for hypoglycemia? (2) symptoms and treatment for hyperglycemia? (3) when should you contact your health care provider?

Complementary therapies. What herbal supplements, over-the-counter medicines, or other treatments do you use?

Physical activity. What physical activity do you do and at what time relative to meals and snacks? Does your physical activity contribute to low or high blood glucose levels?

Meal plan. Do you have a meal plan? Are you able to use your meal plan? How many meals do you eat each day?

Weight reduction. (If overweight:) What strategies for weight loss are you following?

Distress, stress and coping. 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?

Psychological status. How is diabetes affecting you emotionally? Are your emotions interfering with your ability to manage your diabetes? How do you handle these feelings?

Family planning/birth control. Are you considering pregnancy? If so, are you at your glucose control goal? If not, are you using birth control?

At least annually ask about:

Identification. Do you wear or carry diabetes identification?

Complications screening. Do you know (1) your results on screening tests? (2) when you should be tested next?

Foot care. (1) What do you do to take care of your feet? (2) Do you check your feet each day?

Injection sites for insulin. Do you rotate your injection sites around your abdomen and inspect sites?

* Based on expert opinion.

Table 4. Meal Planning for Glycemic Management Based on Medication

Medication	Recommended Meal Planning
No medication or oral medication *	Portion control or healthful choices
Secretagogues *	Carbohydrate at each meal.
Fixed daily insulin *	Consistent injection time and carbohydrate intake (time and amount)
Premixed insulin *	Consistent injection times and meal times
Intensive flexible insulin program (basal/bolus) *	Carbohydrate counting and dosage adjustments including carb:insulin ratios and correction doses
* For weight loss (modest weight loss may provide benefit, especially early in the disease process)	Portion control and increased physical activity. Intensive lifestyle interventions (counseling, behavioral change, physical activity) with on-going support are needed for weight loss.

Table 5. Targeting and Monitoring Glycemic Control in Patients with Diabetes Mellitus

Target A1c should be defined based on personal assessment of risks and benefits of treatment. Listed below are factors that limit the benefit of tight control*, or heighten the risk of tight control,**. Patients who do not have any of these factors should generally have a target A1c of ≤ 7%. Patients who do have these factors should have a goal of minimizing symptoms of hyperglycemia and to control glucose as well as possible without incurring side effects or excessive treatment burden; while an appropriate A1c is difficult to define exactly, treatment should be aimed to keep the A1c under 9%.

HbA1c should be measured every 3–6 months

If HbA1c is above goal:

1. Assess treatment regimen.
2. Diabetes/dietary education or referral.
3. Start or increase medication.
4. Recheck HbA1c in 3 months.

* Factors limiting benefit of tight control

- Comorbidities (e.g., end-stage cancer, severe heart failure).
- Advanced diabetes complications (e.g., proliferative retinopathy, renal failure).
- Inability to safely carry out treatment regimen.
- Limited life expectancy

** Factors heightening risk of tight control

- History of severe hypoglycemia (inability to treat without assistance).
- Hypoglycemia unawareness.
- Advanced cardiovascular or cerebrovascular disease.
- Autonomic neuropathy (especially cardiac).
- Comorbidities that impair the detection of hypoglycemia (e.g., alteration in mental status, alcoholism, etc.).
- Poor social support

Table 6. Steps in Glycemic Control with Oral Agents in Patients with Type 2 Diabetes

Step 1. Essential treatment for all patients with type 2 diabetes

Comprehensive diabetes education
Healthy eating
Physical activity
Metformin at maximum dose tolerated, not to exceed 2000 mg/daily*, unless not tolerated or otherwise contraindicated

Re-measure A1c in 6-12 weeks after initiation or dose change of medication

Step 2. If A1c:

< 7% or below individualized target (Table 5), no additional agents.
≥ 9%, consider insulin
≥ 7% but < 9%, add a second agent or insulin customized to patient. (See Table 7 for agent comparisons.) Re-measure A1c in 6-12 weeks after initiation or dose change of medication

Step 3. With addition of second agent, if A1c:

< 7% or below individualized target (Table 5), no additional agents.
≥ 9%, consider insulin

≥ 7% but < 9%, consider adding a third agent or insulin customized to patient. (See Table 7 for comparison of agents.) If suboptimal control persists, despite maximal oral therapy, insulin therapy should be initiated.

* Maximum effective dose

Table 7. Comparisons of Agents for Glycemic Control in Patients with Type 2 Diabetes

Generic	Brand Name	A1c Reduction	Δ Weight	Hypo-glycemia	Renal Dose Adjust	Other Side Effects/ Precautions
Biguanide						
Metformin	Glucophage	⇩⇩	⇩	None[1]	Contraindicated in patients with an eGFR below 30 mL / minute/1.73 m2. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended.	GI side effects- GERD, nausea, diarrhea. Annual monitoring of eGFR recommended for all patients on Metformin
Metformin extended release	Glucophage XR	⇩⇩	⇩	None[1]	Contraindicated in patients with an eGFR below 30 mL / minute/1.73 m2. Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m^2 is not recommended.	GI side effects- GERD, nausea, less diarrhea. Annual monitoring of eGFR recommended for all patients on Metformin
Sulfonylureas (2nd Generation)						
Glimepiride	Amaryl	⇩⇩	⇧	⇧	Dose adjust for renal patients	Rare
Glipizide	Glucotrol	⇩⇩	⇧	⇧	Preferred in class for renal patients given greater hepatic metabolism	Rare
Glipizide XL	Glucotrol XL	⇩⇩	⇧	⇧	Preferred in class for renal patients given greater hepatic metabolism	Rare
Glyburide	Diabeta, Micronase	⇩⇩	⇧	⇧	Dose adjust for renal patients	Rare
Glyburide, micronized	Glynase	⇩⇩	⇧	⇧	Dose adjust for renal patients	Rare
Thiazolidinedione						
Pioglitazone	Actos	⇩⇩	⇧⇧	None[1]	None	CHF, macular edema, LE edema, fractures, bladder cancer
Alpha-glucosidase inhibitor						
Acarbose	Precose	⇩	⇔	None[1]	Contraindicated for CrCl <25 ml/min	GI side effects- flatulence, nausea, diarrhea
Miglitol	Glyset	⇩	⇔	None[1]	Contraindicated for CrCl <25 ml/min	GI side effects- flatulence, nausea, diarrhea
Non-sulfonylurea insulin secretogogues						
Repaglinide	Prandin	⇩	⇧	⇧	Dose adjustment for CrCl <40 ml/min	Rare
Nateglinide	Starlix	⇩	⇧	⇧	None	Rare

(continued on next page)

Table 7. Comparisons of Agents for Glycemic Control in Patients with Type 2 Diabetes, continued

Generic	Brand Name	A1c Reduction	Δ Weight	Hypo-glycemia	Renal Dose Adjust	Other Side Effects/ Precautions
DPP4 Inhibitor						
Sitagliptin	Januvia	⇩	⇔	Rare[1]	Dose adjustment for CrCl <50 ml/min	Rare
Saxaglipton	Onglyza	⇩	⇔	Rare[1]	Dose adjustment for CrCl <50 ml/min	Consider discontinuing saxagliptin in patients who develop heart failure
Linagliptin	Tradjenta	⇩	⇔	Rare[1]	None	Rare
Alogliptin	Nesina	⇩	⇔	Rare[1]	Dose adjustment for CrCl <60 ml/min	Consider discontinuing saxagliptin in patients who develop heart failure
Sodium-glucose cotransporter 2 (SGLT2) Inhibitor						
Canagliflozin	Invokana	⇩	⇩	Rare[1]	Dose adjustment for CrCl <60 ml/min	Hypotension, hyperkalemia, urinary tract infection, urosepsis, ketoacidosis, genital mycosis, polyuria, bone fracture, & decreased bone mineral density
Dapagliflozin	Farxiga	⇩	⇩	Rare[1]	Not Recommended for CrCl <60 ml/min	Hypotension urinary tract infections, urosepsis, ketoacidosis, genital mycosis, possible bladder cancer
Empagliflozin	Jardiance	⇩	⇩	Rare[1]	Not recommended for eGFR <45 mL / minute/1.73 m2.	Hypotension, urinary tract infection, urosepsis, ketoacidosis, dyslipidemia, genital mycosis, polyuria, polydipsia, increased hematocrit, nausea, hypovolemia, decreased eGFR
Incretin mimetic						
Exenatide	Byetta	⇩	⇩⇩	Rare[1]	Contraindicated for CrCl <30ml/min	Headache, nausea/vomiting, pancreatitis, injection site reaction
Exenatide extended-release	Bydureon	⇩	⇩⇩	Rare[1]	Contraindicated for CrCl <30ml/min	Headache, nausea/vomiting, pancreatitis, injection site nodule, medullary thyroid cancer [3]
Liraglutide	Victoza	⇩	⇩⇩	Rare[1]	Limited data; use with caution	Headache, nausea/vomiting, diarrhea, constipation, increased heart rate, pancreatitis, medullary thyroid cancer [3]
Dulaglutide	Trulicity	⇩	⇩⇩	Rare[1]	None. Use caution when initiating or escalating doses	Nausea/vomiting, diarrhea, abdominal pain, medullary thyroid cancer [3]
Albiglutide	Tanzeum	⇩	⇩⇩	Rare[1]	None. Use caution when initiating or escalating doses	Diarrhea, nausea, injection site reaction, upper respiratory infection, medullary thyroid cancer [3]

Table 7. Comparisons of Agents for Glycemic Control in Patients with Type 2 Diabetes, continued

Generic	Brand Name	A1c Reduction	Δ Weight	Hypo-glycemia	Renal Dose Adjust	Other Side Effects/ Precautions
Amylinomimetic						
Pramlintide	Symlin	⇩	⇩⇩	Rare[1]	None	Nausea/vomiting
Rapid-acting insulin						
Lispro	Humalog	⇩⇩⇩	⇧	⇧⇧	None	Rare
Aspart	NovoLog	⇩⇩⇩	⇧	⇧⇧	None	Rare
Glulisine	Apidra	⇩⇩⇩	⇧	⇧⇧	None	Rare
Short-acting insulin						
Regular		⇩⇩⇩	⇧	⇧⇧	None	Rare
NPH		⇩⇩⇩	⇧	⇧⇧	None	Rare
Intermediate-acting insulin						
Determir	Levemir	⇩⇩⇩	⇧	⇧⇧	None	Rare
Long-acting insulin						
Glargine	Lantus	⇩⇩⇩	⇧	⇧⇧	None	Rare

[1] When used as monotherapy [2] A1c reduction is dose dependent [3] in animal models

Table 8. Prescribing Essentials for Oral Agents for Glycemic Control in Patients with Type 2 Diabetes

Generic (Brand Name)	Strength (mg)	Initial Dose (mg)	Max Daily Dose (mg)	Usual Daily Dose (mg)	Cost[a] 30 days(range) Generic	Brand
Biguanide						
Metformin (Glucophage)	500, 850, 1000	500 once or 850 daily	2550	1500-2000 mg divided (BID)	$9	$92-154
Metformin extended release (Glucophage XR, Fortamet, Glutmetza)	500, 750	500 daily with evening meal	2000, 2500 mg for Fortamet	1500-2000 daily or divided	$11	$93-123
Sulfonylureas (Second Generation)[b]						
Glimepiride (Amaryl)	1, 2, 4	1-2 daily	8	4 daily	$9-19	$82-163
Glipizide (Glucotrol)	5, 10	2.5, 5 daily	40	10 - 20 divided (BID)	$8-16	$51-204
Glipizide ER (Glucotrol XL)	2.5, 5, 10	5 daily	20	5 - 20 daily or divided (BID)	$9-24	$27-105
Glyburide (Diabeta, Micronase)	1.25, 2.5, 5	2.5-5 daily	20	5 - 20 daily or divided (BID)	$15-27	$54-214
Glyburide, micronized (Glynase)	1.5, 3, 4.5, 6	0.75-3 daily	12	3 - 12 daily or divided (BID)	$8-11	$50-200
Thiazolidinedione [c]						
Pioglitazone (Actos)	15, 30, 45	15-30 daily	45	15 - 45 daily	$10-14	$279-463
Alpha-glucosidase inhibitor						
Acarbose (Precose)	25, 50, 100	25 daily with meal	300	50 - 100 TID before meals	$47-56	$103-205
Miglitol (Glyset)	25, 50, 100	25 daily with meal	300	25 - 100 TID	NA	$136-177
Non-sulfonylurea insulin secretagogues						
Repaglinide (Prandin)	0.5, 1.2	0.5 with meals	16	0.5 - 4 AC to QID	$22-43	$76-277
Nateglinide (Starlix)	60, 120	60–120 with meal	360	60 - 120 AC	$30-32	$77-239
DPP 4 Inhibitors						
Sitagliptin (Januvia)	25, 50, 100	50-100 daily [d]	100	100 daily	NA	$306
Saxagliptin[h] (Onglyza)	2.5, 5	2.5-5 daily [d]	5	2.5-5 daily	NA	$301
Linagliptin (Tradjenta)	5	5 mg daily	5	5 mg daily	NA	$307
Alogliptin[h] (Nesina)	6.25, 12.5, 25	25 mg daily	25	25 mg daily	NA	$393
Sodium-glucose cotransporter 2 (SGLT2) Inhibitor						
Canagliflozin (Invokana)	100, 300	100 mg daily[g]	300	100 daily before first meal	NA	$312
Dapagliflozin (Farxiga)	5, 10	5 mg daily[g]	10	5 mg in AM	NA	$312
Empagliflozin (Jardiance)	10, 25	10 mg daily[g]	25	10-25 mg daily	NA	$424

(Continues with combination formulations on next page)

Table 9. Prescribing Essentials for Oral Agents for Glycemic Control in Patients with Type 2 Diabetes (Continued)

Generic (Brand Name)	Strength (mg)	Initial Dose (mg)	Max Daily Dose (mg)	Usual Daily Dose (mg)	Cost[a] 30 days (range) Generic	Brand
Combination formulations	*[Less dosing flexibility]*					
Glipizide/metformin (Metaglip)	2.5/250, 2.5/500, 5/500	2.5/250 daily-2.5/500 BID [e] or 2.5/500-5/500 BID[f]	10/2000 or 20/2000	Titrate to effective dose (not over max)	$28-30	NA
Glyburide/metformin (Glucovance)	1.25/250, 2.5/500, 5/500	1.25/250 daily-BID [e] or 2.5/500-5/500 BID [f]	10/2000 or 20/2000	2.5/500 – 10/1000 daily-BID	$11-14	$79 all
Repaglinide/metformin (PrandiMet)	1/500, 2/500	1/500 BID within 15 min prior to meal	10/2500	Titrate to effective dose (not over max)	NA	$253
Pioglitazone/metformin [c] (Actoplus Met)	15/500, 15/850	15/500-15/850 daily-BID	45/2550	Titrate to effective dose (not over max)	NA	$424
Pioglitazone/metformin ER [c] (Actoplus Met XR)	15/1000, 30/1000	15/1000-30/1000 daily	45/2000	Titrate to effective dose (not over max)	NA	$230-455
Sitagliptin/metformin (Janumet)	50/500, 50/1000	50/500 BID [e] or 50/1000 BID [f]	100/2000	Titrate to effective dose (not over max)	NA	$306
Sitagliptin/metformin ER (Janumet XR)	50/500, 50/1000, 100/1000	50/500 BID [e] or 50/1000 BID [f] or 100/1000 daily	100/2000	Titrate to effective dose (not over max)	NA	$393
Linagliptin/metformin ER (Jentadueto)	2.5/500, 2.5/850, 2.5/1000	2.5/500 BID[e] or 2.5/850 BID[f] or 2.5/1000 BID[f]	5/2000	2.5-5/2000 mg per day	NA	$388
Saxagliptin/metformin ER (Kombiglyze XR)	2.5/1000, 5/500, 5/1000	2.5/1000 BID[f] 5/500 BID[e] or 5/1000 BID[f]	5/2000	2.5-5/2000 mg per day	NA	$393
Alogliptin/metformin (Kazano)	12.5/500, 12.5/1000	12.5/500 BID[e] or 12.5/1000[f]	25/2000	25/2000 mg per day	NA	$392
Canagliflozin/metformin (Invokamet)	50/500, 150/500, 50/1000, 150/1000	50/500 BID[e] or 150/500[f] or 50/1000[f] or 150/1000[f]	300/2000	100-300/2000 mg per day	NA	$212-423
Dapigliflozin/metformin ER (Xigduo XR)	5/500, 10/500, 5/1000, 10/1000	5/500 daily-BID[e] or 5/1000 daily-BID[f] or 10/500 daily[f] or 10/1000mg daily[f]	10/2000	5-10/2000 mg per day	NA	$423
Empagliflozin/metformin (Synjardy)	5/500, 5/1000, 12.5/500, 12.5/1000	5/500 BID[e] or 5/1000 BID[f] or 12.5/500 BID[e] or 12.5/1000 BID[f]	25/2000	10-25/2000 mg per day	NA	$423

[a] Cost = Average Wholesale Price minus 10%. AWP from Red Book Online 05/2014. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 05/2014.
[b] Second generation sulfonylureas have a better safety profile compared to first generation sulfonylureas.
[c] 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.
[d] When administered with a sulfonylurea, a lower dose of the sulfonylurea may be required.
[e] Dose for initial therapy, i.e., starting both agents for the first time.
[f] Dose for second line therapy, i.e., previously treated with one or both of the agents.
[g] Assess volume status and renal function before initiation and correct volume depletion before initiation.
[h] Consider discontinuing saxagliptin in patients who develop heart failure

Table 10. Prescribing Essentials for Injectable Agents for Glycemic Control in Patients with Type 2 Diabetes

Type of Injectable	Examples	Onset of Action	Peak of Action	Duration of Action	Cost[1] – 30 days
Incretin mimetic	Exenatide (Byetta)[2]	1 hour	2.1 hours	10 hours	$178
	Exenatide Extended Release (Bydureon)[2]	2 weeks	6-7 weeks	10 weeks	$110
	Liraglutide (Victoza)[3]	< 8 hours	8-12 hours	24 hours	$64
	Dulaglutide (Trulicity)[4]		24-72 hours		$610
	Albluglitide (Tanzeum)[5]		3-5 days		$475
Amylinomimetic	Pramlintide (Symlin)	<20 minutes	20 minutes	3 hours	$119
Rapid-acting insulin	Lispro U100, U200 (Humalog)	15 min	0.5-2.5 hrs	3-5 hrs	$181
	Aspart (Novolog)	15 min	1-3 hrs	3-5 hrs	$182
	Glulisine (Apidra)	20 min	1-2 hrs	5-6 hrs	$170
Short-acting	Regular (Humulin R, Novolin R)	30-60 min	2-3 hrs	3-6 hrs	$98
Intermediate-acting	NPH (Humulin N, Novolin N)	2-4 hrs	4-10 hrs	10-16 hrs	$98
	Detemir (Levemir)	3-4 hrs	6-8 hrs	6-23 hrs	$327
Long-acting	Glargine (Lantus)	2-4 hrs	None	20-24 hrs	$207
	Glargine U300 (Toujeo)	6 hrs	None		$363
	Degludec U100, U200 (Tresiba)	1 hr	9 hrs		$480
Intermediate- and short/rapid-acting mixtures	75/25 NPL/lispro (Humalog Mix 75/25) 50/50 NPL/lispro (Humalog Mix 50/50)	Varies according to types and Percentages of insulin			$188
	70/30 NPH/aspart (Novolog Mix 70/30)				$189
	70/30 NPH/regular (Humulin 70/30, Novolin 70/30)				$98
Long-acting and rapid-acting mixture	70/30 Degludec/aspart (Ryzodeg)	See individual agent profiles			$478
Concentrated, intermediate acting	U500 regular	30 minutes	1.5-3.5 hrs	Up to 24 hrs	$980

[1] Cost = Average Wholesale Price minus 10%. AWP from Red Book Online 05/2014. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 05/2014. Byetta, Victoza, Symlin, and Levemir come as pen syringes. Other injectable price quotes are for 10 ml vial.

[2] The FDA warns that exenatide (Byetta, Bydureon) may be associated with an increased risk for pancreatitis and for acute renal failure. If pancreatitis is suspected, exenatide should be discontinued. If pancreatitis is confirmed, exenatide should not be restarted unless an alternative etiology is identified. Exenatide should not be used in those with GFR <30 ml/min. It should be used cautiously in those with GFR between 30 and 50 ml/min, with careful monitoring of renal function and GI side effects. The FDA warns of an increased incidence of thyroid C-cell tumors has been reported in rats. It has not been determined whether exenatide causes thyroid C-cell tumors in humans, and routine monitoring is of unknown value. Use is contraindicated in patients with multiple endocrine neoplasia syndrome type 2 or with a personal or family history of medullary thyroid

carcinoma, and education on the risk and symptoms of thyroid tumors should be provided to all patients treated with extended-release exenatide

[3] The FDA warns that liraglutide (Victoza) may be associated with an increased risk of pancreatitis and thyroid C-cell hyperplasia. If pancreatitis is suspected, liraglutide should be discontinued. Do not restart if pancreatitis is confirmed. Increased risk of thyroid C-cell tumors in animals and unknown risk in humans.

[4] The FDA warns that dulaglutide caused thyroid C-cell tumors in rats, that was related to dose and duration of treatment. However, it is unknown if dulaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Dulaglutide is contraindicated in patients who have a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2. The value of monitoring calcitonin levels or thyroid ultrasound routinely is uncertain

[5] Albiglutide is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia type 2 (MEN2). Counsel patients regarding the potential risk of MTC with the use of albiglutide and inform them of the symptoms of thyroid tumors (eg, mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value for early detection of MTC in patients treated with albiglutide.

Table 11. Steps in Pharmacologic Treatment of Hypertension in Patients with Diabetes Mellitus

Step 1. Elevated BP (systolic BP ≥ 140 [1] and/or diastolic BP ≥ 90) uncontrolled by prior lifestyle modifications

***Without* microalbuminuria- initiate therapy with either:**

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)

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

If ACE inhibitor contraindicated: **Angiotensin II Receptor Blocker (ARB)**
Losartan 25-50 mg daily.[2] Titrate by doubling dose in 2-4 weeks if BP goal NOT met (max dose: 100 mg)

***With* microalbuminuria**

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

If ACE inhibitor contraindicated: **Angiotensin II Receptor Blocker (ARB)**
Losartan 25-50 mg daily.[2] Titrate by doubling dose in 2-4 weeks if BP goal NOT met (max dose: 100 mg)

Step 2. If dose is optimized on agent from Step 1 and patient BP remains ≥ 140/90 [1]

Add a **Thiazide diuretic** or **ACE/ARB** to the first agent.
Consider combination therapy to reduce cost (e.g., lisinopril/HCTZ, losartan/HCTZ, atenolol/chlorthalidone)
Do not use ACE inhibitor in combination with ARB as combination may increase risk of renal failure.

Step 3. If above agents are contraindicated or dose is optimized and patient BP remains ≥ 140/90 [1]

Add a **Dihydropyridine Calcium Channel Blocker** – initiate therapy
Amlodipine (Norvasc ®) 2.5 - 5 mg daily. Titrate by doubling dose in 2-4 weeks if BP goal is NOT met (max dose: 10 mg)

Step 4. If above agents are contraindicated or dose is optimized and patient BP remains ≥ 140/90 [1]

Add a **Beta-Blocker** to the first two agents. Initiate therapy with either metoprolol (preferred) or atenolol:
Metoprolol tartrate 25 to 50 mg BID.[3] Titrate by doubling dose every 2-4 weeks until BP goal met (max dose: 200 mg)
Atenolol 25 mg daily.[3] Titrate by doubling dose every 2-4 weeks until BP goal met (max dose: 100 mg)

[1] 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.
[2] Check serum creatinine and potassium levels 1-2 weeks after starting medication or increasing its dose.
[3] Check heart rate 1-2 weeks after starting the medication or increasing dose.

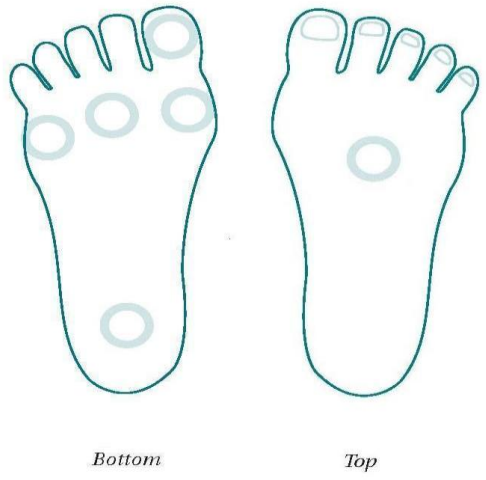
Table 12. Prevention, Screening, and Treatment of Complications in Patients with Diabetes Mellitus

Cardiovascular Risk Factors	Microvascular Complications
Hypertension Check blood pressure (BP) (each visit). • If not on therapy and BP ≥ 140/90 *[IA[g]†]*(see text & Table 3). 1. Check electrolytes and serum creatinine. 2. Check for microalbuminuria. 3. Recommend lifestyle interventions, including weight loss, exercise and dietary referral. 4. Consider therapy if repeated BP measurements are elevated. Either a thiazide diuretic or an ACE inhibitor (or an ARB, if ACE inhibitor not tolerated) is recommended for patients without microalbuminuria. An ACE inhibitor or ARB (if ACE inhibitor not tolerated) is recommended for patients with microalbuminuria. Other agents can be added as needed. Second line agents are thiazide diuretics and long-acting dihydropyridine calcium channel blockers. Other agents may also be necessary but have less supporting data. • If on therapy and BP ≥ 140/90 *[IA[g]†]*, adjust medication. **Hyperlipidemia** Check lipid profile – fasting or non-fasting (annually) • Prescribe at least a moderate potency statin in all non-pregnant patients with diabetes starting at age 40 and older.*[IA[d]]*. • The AHA recommends annual screening of LDL to assess adherence with a goal of a 30-50% reduction in LDL from baseline. While evidence for specific LDL target levels is lacking, , the American Diabetes Association recommendations are for LDL < 100 mg/dL and for < 70 mg/dl in patients with known CVD. **Smoking** Check smoking status (at least annually). If non-smoker, reinforce nonsmoking. • If a smoker 1. Educate about increased CV risk (diabetes + tobacco). 2. Encourage smoking cessation *[IB[d]]*. **Cardiac Risk Reduction** • Many patients with diabetes will benefit from low dose aspirin therapy; however recent data are less clear on the benefit of aspirin for primary prevention in patients with diabetes *[IIA[d]]*. - [g] = studies in general population [d] = diabetes patient studies	**Retinopathy** Perform dilated retinal exam by eye care specialist *[IB[d]]* 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. • If retinopathy 1. Treatment per ophthalmology *[AI[d]]* 2. Consider improving glycemic and BP control *[IA[d]]*. **Nephropathy** Check spot urinary albumin/creatinine ratio (annually) if not on an ACE/ARB and without diagnosis of diabetic nephropathy. If > 30 mg/gm, check UA to rule out asymptomatic UTI. • Repeat spot urine ratio twice within 6 months. If 2 of 3 spot urine albumin/creatinine ratios > 30 mg/gm 1. Check creatinine, electrolytes and estimated glomerular filtration rate (eGFR) *[ID[g]]*. 2. Begin ACE inhibitor or ARB *[IA[d]]* (if electrolytes allow use of ACE inhibitor). Recheck creatinine and electrolytes within 1–2 weeks of initiating therapy. **Neuropathy** Perform foot exam: (1) inspect and check pulse (each visit if patient has a history of neuropathy; otherwise annually), and (2) monofilament (annually), see Table 13 *[IB[d]]*. • If structural abnormality 1. Prescription for customized shoe and/or orthotics. 2. Consider podiatry referral. • If neuropathy 1. Optimize glycemic control *[IA[d]]*. 2. Treatment of painful neuropathy if indicated. • If not sensitive to monofilament 1. Education regarding proper foot care and increased risk of ulceration. 2. Consider podiatry referral. • If foot ulcer: 1. Prescription for customized shoe and/or orthotics. 2. Aggressive wound care with close follow up. 3. Refer to a multidisciplinary team specializing in the care of diabetic foot ulcers *[IA[d]]*.

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=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel

† **BP ≥ 140/90** is recommended for treatment by the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC 8) while ≥140/80 is recommended by the American Diabetes Association, although there is no level A evidence for the systolic BP goal.

Table 13. How to Use a Monofilament

	• 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. • Ask the patient to turn his/her head and close his/her eyes or look at the ceiling. • Hold the monofilament perpendicular to the skin. • 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. DO NOT ASK THE PATIENT 'did you feel that'? • 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, RETEST the area(s) where the patient did not feel the monofilament. • Push the monofilament until it bends, then hold for 1-3 seconds. • Lift the monofilament from the skin (Do not brush or slide along the skin). • Repeat the sequence randomly at each of the testing sites on each foot. • Avoid areas of callus

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 autoimmune destruction of the pancreatic beta cell. 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 8% of the adult U.S population has diabetes, with 95% of these people having type 2 diabetes. The prevalence of diabetes increases with age, with over 25% of the elderly 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 3.7% of those aged 20 to 39 years.

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 ≥ 120% of ideal body weight, while type 1 diabetes occurred in patients under 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 year) pre-symptomatic phase, and national studies suggest that approximately 1/3 of subjects with type 2 diabetes are unaware that they have the disease. 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. Diabetes has significant associated morbidity and mortality. Patients with diabetes have a 2 to 4 fold increase in the risk of both cardiovascular and cerebrovascular disease, resulting in an increased mortality rate among patients with diabetes compared to the general population. Microvascular complications also occur, including retinopathy, nephropathy and neuropathy, and these can progress to the end-stage outcomes of blindness, renal failure, and amputation. Diabetes is the leading cause of new cases of blindness in adults ages 20-74 and the leading cause of end stage kidney disease in the U.S. Seventy percent of non-traumatic lower extremity amputations occur in patients with diabetes. The morbidity and mortality of diabetes are higher for minorities than for Caucasians.

Rationale for Recommendations

Diabetes prevention. Multiple large randomized controlled trials have demonstrated that lifestyle modification programs delay or prevent type 2 diabetes in patients who have impaired glucose tolerance. Studies 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 week) can reduce the risk of progression from impaired glucose tolerance (IGT) to diabetes by 42-58%. The intensive lifestyle intervention tested in the Diabetes Prevention Program was expensive, but cost-effective. A large number of translational studies are ongoing.

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. A trial of acarbose 100 mg TID demonstrated a 25% risk reduction in progression from IGT to diabetes. These studies suggest that a pharmacologic approach to diabetes prevention may also be feasible, but lifestyle interventions remain the most effective and safe preventive strategy studied to date. The few studies combining lifestyle interventions with medication for diabetes prevention have not shown any benefit over lifestyle intervention alone but a number of these studies are ongoing.

Screening for diabetes. Studies of screening 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.

Based on expert opinion, the American Diabetes Association (ADA) recommends that screening be considered at least at 3-year intervals beginning at age 45. Screening individuals with risk factors for diabetes should be considered at earlier ages.

Individuals with hypertension (>135/80) should be screened for diabetes (USPSTF level B recommendation). In adults who have hypertension and diabetes, lowering blood pressure below conventional target values reduces the incidence of cardiovascular events and cardiovascular mortality and justifies screening.

Screening may be reasonable for other at-risk subjects (e.g., those with obesity, history of gestational diabetes mellitus, family history, and high-risk ethnic minorities).

Based on expert opinion the ADA recommends considering earlier or more frequent screening for those with other risk factors, including family history, physical inactivity, minority ethnicity, previously identified impaired fasting glucose or impaired glucose tolerance, a history of HDL cholesterol ≤ 35 mg/dL, and/or a triglyceride level of ≥ 250 mg/dL, polycystic ovarian disease, or a history of vascular disease.

Women who have had gestational diabetes mellitus (GDM) should be screened for diabetes, as about 50% will have type 2 diabetes within 10 years. While the long-term benefits of earlier diagnosis in this population are uncertain, both expert opinion and the epidemiology of diabetes post-GDM support screening. The optimal test for screening in this group is not clear. The ADA currently recommends screening with a 2 hour, 75 gram oral glucose tolerance test (OGTT) at 6-12 weeks postpartum. The frequency and method of screening after this point is debated. Our current recommendation for these patients is that A1c be used as the screening test of choice and that screening be conducted every 3 years.

Another group for whom to consider screening is women who are planning pregnancy and have risk factors for type 2 diabetes. 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 (see Table 1).

One possible additional benefit of screening for diabetes is the identification of people with impaired glucose tolerance. These people carry substantially increased risks of developing atherosclerotic disease, and have a high risk of developing diabetes (about 11% per year). Those with a fasting glucose of 100-125 mg/dL, A1c 5.7-6.4, or a 2-hour OGTT of 140-199 mg/d are considered at risk for diabetes. (A random glucose of 130-199 mg/dL is abnormal and further testing is indicated, e.g., fasting glucose, OGTT, or hemoglobin A1c.) Intervention is recommended for those with pre-diabetes, as lifestyle modification (including diet, exercise, and weight loss), acarbose, and metformin have all been shown to reduce the progression of pre-diabetes to diabetes.

Diagnosis. The American Diabetes Association (ADA) has added HbA1c as a screening as well as diagnostic test for diabetes. While some disagreement exists concerning the specific level that defines type 2 diabetes, the current ADA definition is that diabetes is diagnosed if A1c is 6.5% or higher. This cut point is specific but not sensitive and thus individuals with A1c between 6.0 and 6.4 will meet criteria for diabetes using fasting glucose or OGTT tests. The cases missed are most likely to be very early stage disease. The choice of A1c was made in large part based on the convenience of the test; unlike other methods, it does not require fasting, and international efforts have led to a highly standardized assay. However, A1c may not be accurate for patients with hemoglobinopathies, thallasemia, hemolysis, blood loss, or iron deficiency.

Alternatively, a fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) may also be used to diagnose diabetes. The diagnosis can be made if a *fasting* glucose level is greater than or equal to 126 mg/dL (7.0

mmol/l), but should be confirmed on a separate day. Diabetes may also be diagnosed on the basis of symptoms (polydipsia, polyuria, unintentional weight loss) and elevated glucose level (≥ 200 mg/dL), but should also be confirmed on a separate day by a fasting glucose ≥ 126 mg/dL. The oral glucose tolerance test (OGTT) is a reasonable diagnostic alternative, and in the view of many experts remains the diagnostic test of choice; however, it is somewhat limited by concerns about inconvenience for patients. A 2-hour glucose level of 200 mg/dL or greater is diagnostic for diabetes. All tests should be repeated or confirmed with alternative tests on a separate day.

Treatment

Diabetes Self-Management

As diabetes is a largely self-managed disease, psychosocial and educational factors affect outcomes. Therefore, these issues need to be addressed in detail to allow optimization of treatment and reduce the likelihood of adverse outcomes. Diabetes education should provide consistent, evidence-based teaching that conforms with treatment guidelines, standards for self-management education and patient goals.

Diabetes self-management refers to all of the activities in which patients engage to care for their diabetes, promote health, augment physical, social and emotional resources and prevent long and short-term effects from diabetes. Diabetes self-management education (DSME) is the essential first step in becoming an effective self-manager. DSME is designed to help patients make informed decisions and evaluate the costs and benefits of those choices. In addition to DSME, patients with diabetes also need on-going self-management support (DSMS) in order to sustain improvements gained during DSME. Table 3 summarizes self-management topics that clinicians should address at each visit and annually.

DSME has evolved from didactic programs based on information-transfer and compliance or adherence as outcomes, to more patient-centered, empowerment based approaches. Recent findings related to DSME include:

- Diabetes self-management education is effective for improving psychosocial and health outcomes (including HbA1c) 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.

While patients need DSME, it is unreasonable to believe that a one-time educational program will be adequate for a lifetime. Self-management support is defined as the on-going assistance and resources patients need in order to make self-management decisions and sustain behavioral changes. Office-based practices providing multiple interventions in which patient education was included or where the role of the nurse was enhanced reported favorable outcomes. Organizational interventions that improve diabetes self-management include computerized tracking systems, regular recall and review of patients by nurses, the addition of patient-centered educational and counseling approaches, and behavioral goal-setting. Effective strategies to incorporate on-going self-management support include the use of case or care managers, use of information technologies, peer support, and group or cluster visits.

Diabetes self-management behaviors are affected by the psychological status of the patient. In both the DAWN1 AND DAWN2 studies, a large majority of the patients reported a high level of distress at the time of diagnosis, including feelings of shock, guilt, anger, anxiety, depression and helplessness. Many years after diagnosis, problems of living with diabetes remained common, including fear of complications and immediate social and psychological burdens of caring for diabetes. Forty-one percent of patients reported poor well-being, however only 10% reported receiving psychological treatment.

DSME is increasingly available through group programs and reimbursement structures are more available. DSME/S programs that achieve Certification from the Michigan Department of Community Health are reimbursable by Medicaid and state regulated health plans, including many Managed Care Organizations. The University of Michigan's DSME?S program is housed in the MEND clinic at Domino's Farms (734-647-5871), but holds classes in the Canton, Brighton and Chelsea locations as well. A list of non U of M programs is available at www.Michigan.gov. In addition, DSME programs that are recognized by the American Diabetes Association are reimbursable by Medicare. A list of these programs by state is available at www.diabetes.org.

Obesity is increasing at an alarming rate worldwide and contributes to the rise in not only type 2 diabetes, but also hypertension, hyperlipidemia, macrovascular disease, osteoarthritis, etc. 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.

Meal planning. Meal planning is recommended for all stages of diabetes. New guidelines are presented in Table 4

for specific meal planning strategies based on whether or not the patient is on a medication for glucose control, the type of medication, and whether weight loss is to be a part of meal planning.

Glycemic Control

HbA1c is the most commonly accepted measurement of long-term glycemic control. Current recommendations are that HbA1c be checked at least every 6 months if the patient is well controlled (HbA1c ≤ 7%) and on a stable oral anti-hypoglycemic regimen, otherwise every 3 months.

Targets for therapy have been evaluated in clinical trials. Two trials have achieved A1c levels slightly greater than 7%. Neither showed reduction in end-stage complications in the time frame of the trials (e.g., visual loss, renal failure amputation). However, early and intermediate microvascular complications were reduced, and longer-term follow-up of one study showed that benefits did begin to accrue by 15-20 years. This suggests that a target A1c of 7% to 7.5% is reasonable in those with life expectancies in this range or longer.

Lower A1c targets are generally not recommended; one trial with a target A1c of 6% (achieved 6.4%) showed increased mortality relative to an A1c target between 7 and 7.9% (achieved 7.5%), and another showed no benefit, suggesting that there may be a narrow therapeutic window for intensive glucose control.

An A1c target of ≤ 7% is generally recommended in patients without factors that limit potential benefit (see Table 5). However, recent trials assessed the impact of intensive glycemic control, raising concerns about potentially increasing adverse events in patents with ischemic artery disease, congestive heart failure (CHF), chronic renal failure, dementia, and blindness. Given these results, patients in these groups should have a target A1c of ~7.5%. Nearly all patients, regardless of life expectancy or comorbidity status, should target levels of < 9%.

A1c targets should be discussed with patients, and providers should weigh patient-specific factors when considering glycemic goals (see Table 5). Given that it takes years for symptomatic benefits to become apparent, a number of factors may modify target levels. These include limited life expectancy (based on significant comorbidity), advanced diabetes complications, a history of hypoglycemic unawareness, or limitations in the ability to carry out a treatment regimen.

Since type 2 diabetes is typically a progressive disease, glycemic control often deteriorates over time. Providers should expect that medication requirements will increase with duration of disease. Combining different classes of oral agents is often effective in improving blood glucose control, but there is no clear consensus on optimal sequence or combinations. Combinations of oral agents and basal insulin preparations (e.g., NPH, glargine) may also be effective. These approaches are discussed later.

Glycemic management. In patients with type 2 diabetes, diet and physical activity are essential first line therapies, and many groups now recommend initiating metformin at diagnosis.

Pharmacologic intervention should be considered at diagnosis for patients with type 2 diabetes. Metformin should be prescribed as the first line agent unless there are contradictions to its use. Note that Metformin should discontinued at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m^2; 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. The choice of subsequent agents remains controversial. Sulfonylureas should be considered as a second-line agent. Weight-neutral medications have clinical appeal, but no outcomes data to support their use over any other medication. In general, if the patient has not achieved glycemic goal after four weeks of therapy at a maximal dose of an oral agent, the therapy should be considered inadequate. Insulin is the only anti-diabetic medication (besides metformin) with well documented clinical outcome data.

Table 6 provides a stepwise summary of treatment recommendations. Table 7 summarizes the medical advantages and disadvantages of the available oral and injectable agents to be considered for the management of type 2 diabetes. Tables 8, 9, and 10 summarize their dosing and cost considerations. Meal planning recommendations based on type of medication were presented in Table 4.

<u>Metformin.</u> 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 is associated with slightly lower cardiovascular mortality compared to sulfonylureas or insulin.

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

- Nausea and diarrhea are seen in up to 30% of patients; GI side effects are dose related. Metformin XR formulation may decrease diarrhea compared to the immediate release.

- Metformin is contraindicated in patients with eGFR <30 mL/min. It should not be initiated in patients with eGFR between 30 and <45 mL/min. In patients taking metformin

whose eGFR later falls below 45 mL/minute/1.73 m^2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m^2. Discontinue metformin in the clinical setting of dehydration, surgery, and at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m^2; 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 sulfonylureas, non-sulfonylurea secretagogues, DPP4 inhibitors, alpha-glucosidase inhibitors, SGLT2 inhibitors, and injectable medications. The choice of a second agent should be tailored to the individual patient, taking into consideration a variety of factors including BMI, renal function, medical problem list and patient preferences.

Sulfonylureas. Sulfonylureas lower serum glucose by increasing insulin secretion. While sulfonylureas were traditionally used as first line agents in type 2 diabetes, they should now be considered a second tier choice. Compared to metformin, sulfonylureas have equivalent but less favorable effects on weight and increased risk of hypoglycemia. Additionally, weak evidence indicates that patients treated with sulfonylureas have higher cardiovascular mortality compared to patients treated with metformin.

Glyburide, glipizide and glimeperide 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.

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 secretogogues. 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. Dosage adjustments are required for renal insufficiency with Sitagliptin and Saxagliptin but not with Linagliptin.

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 small. 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, however due to their side effect profile, they should be considered third tier agents. TZDs are associated with significant weight gain.

The FDA has issued a box warning for both available 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 post-menopausal women. TZDs may worsen diabetic macular edema. Renal dosage adjustment is not necessary. Pioglitazone has been associated with an increased risk of bladder cancer. SGT2 inhibitors have shown no apparent cardiovascular benefit or risk in short-term studies.

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. 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). Dosage adjustments are required for renal insufficiency with both available agents and contraindicated below eGFR of 30 ml/min. Hepatic dosage adjustment is only required for canagliflozin in Child-Pugh class C. Studies show an increased risk for urinary tract infections as well as genital mycosis infections in users as the most common side effects. 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. Among users of dapagliflozin risk of bladder cancer increased in clinical trials suggesting avoiding use in patients with a history of bladder cancer. Long term renal safety data is currently unavailable. Trials have shown a slight increase in serum creatinine, decreases in eGFR and elevations in LDL-C.

Combination oral therapy. Each class of oral agents works by a different mechanism and they may be combined to achieve optimal glucose control. The obvious exceptions are sulfonylureas and non-sulfonylurea insulin secretagogues, which should not be combined. Typically, patients with type 2 diabetes are started on metformin, with a second agent or third agent added as needed. In general, the addition of an oral agent will reduce HbA1c by an additional 1.0%. Tablets combining two classes of oral agents are now available. See the bottom of Table 9 for examples. Combinations offer less dosing flexibility but cost is not necessarily greater compared to single-agent tablets.

Incretin mimetic agents. Exenatide (Byetta), Exenatide Liraglutide (Victoza), and Extended-Release Exenatide (Bydureon) (see Table 10, injectable agents) 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. Hypoglycemia is rare when these agents are used as a single agent or in combination therapy with metformin. Data are limited regarding cardiovascular outcomes in relation to these drugs, though favorable effects on lipid profiles have been suggested. 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. Lira glutidemay be used with care in renal insufficienty.

Combination of oral/injectable therapy. Patients with type 2 diabetes who do not have adequate glucose control on oral agents will need to start an injectable agent or insulin therapy. DPP-4 inhibitors should not be combined with incretin mimetics such as exenatide or liraglutide. If insulin is initiated, most experts would agree that metformin should be continued. However, other hypoglycemic agents are usually discontinued. Arguments can be made for continuing other hypoglycemic agents in combination with insulin; however, no consensus exists as to what combinations should be used.

The addition of bedtime NPH remains a traditional approach. However, therapy with once daily Lantus has become increasingly popular due to its lack of an insulin peak and its 24-hour duration of action. Therapy may be intensified as needed with twice daily split/mixed insulin, or a basal/bolus insulin approach as needed to achieve glycemic goals.

Insulin. Insulins are categorized by their duration of action (see Table 10). The initiation and adjustment of insulin is addressed in Appendix B.

Rapid acting insulins (Lispro [Humalog], Aspart [NovoLog], Glulisine [Apidra]) or short-acting insulin (Regular) are used in conjunction with meals or to treat anticipated post-prandial increased 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) has a duration of action of approximately 24 hours. It can be used as a 'basal' insulin in both type 1 and type 2 diabetes. It is frequently prescribed at a starting dose of 20 units at bedtime and titrated by 2 to 4 units every 2-3 days for fasting blood sugar > 130 mg/dl.

Mixtures of NPH and short acting insulins are available in many forms. The two mixtures most frequently used are 75/25 NPH/lispro (Humalog mix) and 70/30 NPH/aspart (Novolog mix). Twice daily injections (before breakfast and supper) of these mixtures may provide good control for patients with type 2 diabetes. However, their use is rarely successful in patients with type 1 diabetes.

Symlin. Symlin is not a type of insulin but an amylinomimetic agent approved as adjunct therapy in patients with type 1 and type 2 diabetes who use mealtime insulin but who are not achieving optimal control. Symlin is used at mealtimes to augment the effects of insulin on glycemic control. This can cause hypoglycemia which can occur within 3 hours after a symlin injection. Symlin and insulin should never be mixed in the same syringe. Symlin can also suppress appetite and lead to weight loss. Nausea is the most common side effect but improves with time in most patients.

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, 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 usage in patients who remain refractory to therapy or who have clinical syndromes suggestive of these conditions.

Blood pressure target. The goals for blood pressure treatment in diabetes have been evaluated in several randomized trials.

Systolic blood pressure levels < 140 mm Hg have not been evaluated rigorously. Until recently, expert opinion had been that systolic blood pressure < 140 mm Hg reduced cardiovascular morbidity and mortality. However, recent trials have demonstrated that strict systolic blood pressure control provides little benefit over usual blood pressure control.

For diastolic blood pressure, a post-hoc analysis of the diabetic population enrolled in the HOT trial demonstrated that a target of 80 mmHg provided marked benefits. However, that was not found in the ACCORD trial with a combined BP goal of 120/80. It is not clear how to reconcile these data. Data show that mortality is increased when hypertensive patients with diabetes had treated diastolic blood pressure below 70.

Based on the above evidence, JNC8 recommends starting treatment when blood pressure exceeds 140/90 mm HG.
The American Diabetes Association recommends a blood pressure target of < 140/80. Both agree that diastolic blood pressure should be ≥ 70 mmHg.

The National Committee for Quality Assurance (NCQA), which establishes the Health Plan Employer Data and Information Set (HEDIS), reports blood pressure <140/90 mmHg to measure quality of care regarding blood pressure control in patients with diabetes. (The NCQA no longer uses blood pressure < 140/80 as a performance measure.

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 ≥ 90 mmHg or systolic blood pressure is ≥ 140 mmHg on two visits, antihypertensive therapy should be instituted (Tables 11 and 10). Lifestyle modification with dietary alteration, physical activity, and weight loss (if indicated) should be 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.

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.

Angiotensin-converting enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARBs) reduce progression of established diabetic renal disease and reduce cardiovascular mortality (HOPE trial). Thus, ACE inhibitors are recommended as first-line therapy, with ARBs as a second-line agent given their higher cost. 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.

Calcium-channel blockers and beta-blockers are also effective agents in controlling blood pressure, but should probably be added after thiazides and ACE or ARB (see Table 11). 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 (e.g., 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.

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. Therefore careful monitoring of renal function and serum electrolytes is therefore 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.

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.

Check baseline liver function tests (LFTs) and if normal, no further monitoring of LFTs is required. If baseline LFTs are mildly abnormal (over upper limit of normal but < 5 times the upper limit of normal): reassess LFTs after 6-12 weeks of statin treatment for stability. Consider monitoring annually for stability if baseline LFTs are abnormal. Abnormal baseline liver biochemistries can frequently improve with statin therapy. The UMHS Clinical Care Guideline "Screening and Management of Lipids" provides additional information beyond the summary below.

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.

Optimal screening and follow-up intervals for cholesterol testing have not been evaluated in patients with type 2 diabetes. Expert opinion suggests that annual testing is reasonable. An annual lipid profile provides a check on statin adherence and an opportunity to reinforce lifestyle modifications – the cornerstone of ASCVD risk reduction.

Obtain a baseline screening lipid profile (TC, LDL-C, HDL-C, and TG). Ideally this should be obtained when the patient is fasting for a more accurate evaluation of potential dyslipidemias, including hypertriglyceridemia. However, if patient convenience or compliance is an issue, a non-fasting lipid profile is adequate to assess cardiovascular risk and to monitor statin compliance. Only total cholesterol and HDL-C are needed for cardiovascular risk calculators. While non-fasting LDL-C is less accurate than fasting LDL-C, non-fasting values are sufficient for monitoring general statin compliance. If lipids are obtained non-fasting and are abnormal (i.e. TC > 200 mg/lL, HDL-C < 40 mg/dL, or triglycerides > 500 mg/dL, consider obtaining a follow up fasting lipid panel to better evaluate for dyslipidemias.

Treatment goals for various types of cholesterol abnormalities have been evaluated with differing levels of rigor. Most of the literature is focused on LDL cholesterol. In meta-analyses of randomized trials, HMGCo-A reductase inhibitors ("statins") have consistent effects in reducing the risk of cardiovascular events.

While the efficacy of statins is not in question, 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, (e.g., lovastatin [generic] 40 mg/d) 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 (e.g., rosuvastatin 40 mg/d or atorvastatin 40-80 mg/d), 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. See the UMHS guideline Screening and Management of Lipids for information regarding drug interactions with statins.

For primary prevention, younger patients who are otherwise at lower risk may receive less benefit. Trials have not firmly established an age threshold for initiating therapy, but delaying use until age 40 or later may be reasonable if patients do not have other cardiovascular risk factors.

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.

Low HDL levels are also a known cardiovascular risk factor. One well-conducted randomized controlled trial has shown that gemfibrozil is effective in reducing cardiovascular events in patients with diabetes, an HDL of 40 mg/dL or less, and an untreated LDL of 140 mg/dL or less. At this point, statins are preferred over fibrates as first-line agents in patients with diabetes.

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 (e.g., over 1000 mg/dL), then treatment may be warranted to avoid pancreatitis. If triglyceride levels are between 500 mg/dL and 1000 mg/dL, treatment may be considered

The effectiveness of combination therapy with statins and fibrates has been recently tested in the ACCORD trial. Combination therapy with statins and fenofibrate did not reduce the rate of cardiovascular events in this study. Post-hoc subgroup analysis suggested – but did not definitively show – that patients with both higher baseline triglycerides (~284 mg/dl) and lower HDL (~30 mg/dl) may have benefitted from therapy. At this point, the evidence is not strong enough to suggest that combination therapy is warranted, particularly in light of higher rates of side effects with two lipid lowering agents.

Macrovascular Disease

Diabetes increases an individual's risk of coronary artery disease, stroke and peripheral vascular disease. Reducing other cardiovascular risk factors (see Table 12) 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 positive family history of premature coronary disease, and the presence of micro- or macroalbuminuria.

Smoking. Smoking and diabetes are synergistic risk factors for the development of atherosclerotic disease. 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 smoking cessation programs and use of alternative nicotine delivery systems or pharmacologic therapies.

Aspirin. The ADA and most other organizations recommend use of aspirin in all patients with diabetes who have known coronary artery disease. Recent data suggest that aspirin may not be as effective as previously believed in people without coronary artery disease, even in those with diabetes. Current recommendations suggest that aspirin use for primary prevention be reserved for those with a greater than 10% 10 year risk of cardiovascular events. This roughly translates to 50-year old men or 60-year old women with at least one major additional risk factor (hypertension, smoking, family history, albuminuria, or dyslipidemia) besides diabetes.

Screening

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

Specifically, candidates for screening exercise stress (electrocardiogram [ECG]) testing include those with:

- typical or atypical cardiac symptoms
- an abnormal resting ECG
- a history of peripheral or carotid occlusive disease
- sedentary lifestyle, age >35 years, and plans to begin a vigorous exercise program or
- those with two or more risk factors noted above.

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.

Depression. Screening should also address depression. Recent meta-analyses and reviews of randomized controlled trials indicate that depression is twice as common among people with diabetes. Depression is associated with hyperglycemia and decreased self-care behaviors, such as medication-taking and meal planning. All patients with diabetes should therefore be evaluated for depression. Successful treatment of depression is associated with improved glycemic control. Better glycemic control is associated with improved quality of life, vitality and fewer days missed from work.

Screening questions for depression from the PHQ-2 are:

Over the past month, have you been bothered by:
(a) little interest or pleasure in doing usual things?
(b) feeling down, depressed or hopeless?"

If the patient indicates yes to either question, further assessment is needed with standardized tools such as the full PHQ-9 (see UMHS clinical guideline on depression for PHQ-9 questionnaire and references), Zung Depression Scale or the Center for Epidemiologic Studies Depression Scale.

Diabetes-related distress. Due to the prevalence and impact on clinical outcomes, patients should be routinely screened for diabetes-related distress. Screening questions from the PAID and Diabetes Distress Scale are:

- Too what extent do you often feel overwhelmed by the demands of living with diabetes?
- To what extent do you often feel that you are failing with your diabetes regimen?
- To what extent do you feel that you will end up with serious long-term complications from diabetes no matter what you do?

Microvascular Complications

Screening and treatment should also address microvascular disease (see Table 12).

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 (e.g., 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 (a) have no retinopathy on a baseline retinal exam by an expert and (b) have 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 biannually 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.

Nephropathy. Diabetic nephropathy affects 20%-40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD) in the US. 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 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, if the first test is positive, the test should be repeated on at least two more occasions over a 3- to 6 month period. Two of three tests should be positive (greater than 30 mg albumin per gm of creatinine) before microalbuminuria is considered present. Albuminuria is defined as albumin excretion greater than 300mg/day. Patients who are taking an ACE inhibitor or ARB or who have a diagnosis of diabetic nephropathy may not require yearly screening for microalbuminuria.

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 (e.g., lowering of LDL cholesterol, antihypertensive therapy, cessation of smoking, institution of regular physical activity, etc.).

Patients with diabetes with a glomerular filtration rate (GFR) < 30-45 ml/min 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.

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.

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 studies to date have demonstrated a reduction in the rate of fall of GFR. Some members of the dihydropyridine class of calcium channel blockers (e.g., 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:

Urine Albumin Excretion	Blood Pressure Goal
< 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.

In certain CKD populations, including the elderly and those with renovascular disease, aggressive BP control could lead to negative outcomes such as acute deterioration in kidney function, increased risk for cardiovascular events and orthostatic hypotension. In general, systolic blood pressure should remain > 110 and even higher if orthostatic symptoms occur. For diastolic blood pressure, caution is suggested when diastolic BP falls below 70 mmHg or less. Mortality increased when patients with diabetes had diastolic BP below 70.

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

Neuropathy. 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. Attention should be paid to the etiology of pain in diabetic feet. Occasionally, mechanical factors rather than neuropathy are the mechanism underlying pain.

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

Examination. Patients with diabetes need visual foot inspection, checking of pulses and sensation annually, and with every routine visit if they have abnormalities. Inspection should also include identifying 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.

Sensory testing with a 5.07 (10g) nylon monofilament should be done yearly to identify insensate feet without protective sensation. Instructions on "How to Use a Monofilament" are in Table 13. Individuals with insensitive feet are at high risk of developing foot ulcers and other related complications.

Education. Education regarding appropriate foot care should be provided. All patients need 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, as foot ulcers are among the most common reasons for hospitalization among people with diabetes. Foot ulcers are the leading cause of lower extremity amputations and up to 85% of amputations can be avoided with patient education on foot care, medical professional monitoring and early intervention. Should a foot ulcer be found, infection and vascular status should be carefully evaluated and early treatment should be undertaken with aggressive wound care, orthotic prescriptions or casting to offload the ulcer, antibiotics, and revascularization when necessary. Studies have shown that patients with diabetic foot ulcers have the best outcomes if managed by a multidisciplinary team that specializes in diabetic foot care.

Treatment of painful diabetic peripheral neuropathy (PDN). Optimizing glycemic control is of paramount importance in slowing the progression of established diabetic neuropathy.

NSAIDS should be used cautiously for chronic neuropathic pain due to increased cardiovascular risk as well as GI and renal side effects that are of concern in this population. 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.

First line therapies for the treatment of PDN supported by the literature include tricyclic antidepressants (TCAs), gabapentin, pregabalin, and duloxetine.

- TCAs may be used to treat painful neuropathy and their use is supported by research. They should be used with caution in the elderly, started at low doses

and titrated to maximize pain relief while minimizing side effects of dry mouth, sedation, orthostatic hypotension and constipation. Nortriptyline is the preferred tricyclic as it has fewer anticholinergic properties. It can be started at dinner at a dose of 10-25 mg and titrate up as tolerated to maximum of 150 mg/day.

- Gabapentin up to 1600 mg/day as divided doses or more may be required. Use lowest effective dose. Sedation is a side effect that limits its use.
- Pregabalin (150-300 mg/day as divided doses) is FDA-approved and is less sedating.
- Duloxetine (60 mg to 120 mg/day) and venlafaxine (75-450 mg/day), serotonin and norepinephrine reuptake inhibitors (SNRIs) are useful in treating patients with co-morbid depression. Selective Serotonin Reuptake Inhibitors (SSRIs) and trazodone are not as effective in treating painful PDN.

Lidocaine 5% patches have been proven to relieve PDN pain and improve quality of life ratings. No side effects were found with the regimen of up to 3 patches worn 12 hours overnight and removed.

Other agents. Among other agents, including carbamazepine (200 – 600 mg/day) and valproate (500 mg/day) have been shown to decrease PDN. Their use is limited by their side effect profiles.

Opioids. As a last option, opioids may be considered, though general use is discouraged. Tramadol is a weak opioid and dose of 37.5 mg tramadol 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.

Special Considerations

Pre-Conception Counseling

All women with diabetes who are of child-bearing age should be counseled regarding the increased risks of pregnancy in the setting of diabetes to both mother and fetus. Family planning and contraception should be emphasized, as unplanned pregnancy has a high risk of poor outcome. A significantly higher incidence of miscarriage and congenital anomalies occur when maternal HbA1c is elevated above the normal range at the time of conception. Specific preconception care for women with diabetes who are currently planning pregnancy is of critical importance to achieve optimal outcomes for both mother and baby.

Women not currently planning pregnancy. Women not currently planning pregnancy require general information regarding the risks of pregnancy and the need for pre-pregnancy planning. Effective birth control should be discussed and provided. Maintaining good glycemic control as a way of life can avoid periconception hyperglycemia in the event of an unplanned pregnancy.

Women who are planning to become pregnant. Women with diabetes who are planning to become pregnant should be counseled regarding the increased risks of pregnancy. They should be referred to specialists in caring for pregnancy in women with diabetes mellitus. One of the most important components of preconception care is an effective birth control plan that remains in place until glycemic goals are met. Comprehensive preconception care includes counseling regarding the risks of diabetes to the mother, the risks of diabetes to the infant, the effect of pregnancy on glycemic control, the genetics of diabetes, lifestyle, diet and physical activity before and during pregnancy, the critical importance of optimal glucose control before and after conception, and appropriate therapy for comorbid conditions, such as hypertension, hyperlipidemia and thyroid disease, smoking cessation, rubella immunization.

Women who are pregnant. Women with diabetes who are pregnant should be seen immediately by specialists in caring for pregnant women with diabetes mellitus.

Immunizations. Patients with diabetes should be given vaccines to prevent influenza (annual), pneumococcal disease, and hepatitis B.

Annually provide an influenza vaccine to all patients with diabetes 6 months of age or older.

Provide at least one lifetime pneumococcal vaccine for adults with diabetes. A one-time revaccination is recommended for individuals 65 years of age or older who were previously immunized when they were younger than 65 years of age if the vaccine was administered more than 5 years ago. Other indications for repeat vaccination include nephrotic syndrome, chronic renal disease, and other immunocompromised states, such as post-organ transplantation.

Hepatitis B vaccine (usually 3 doses over 6 months) should be routinely provided to unvaccinated adults with diabetes mellitus ages 19-59 years. The risk of hepatitis B increases twofold for patients with diabetes due primarily to sharing inadequately cleaned blood glucose monitors (including healthcare settings, households, worksite health clinics, schools and camps). Hepatitis B vaccine may be administered to unvaccinated adults with diabetes aged ≥ 60 years who are increased risk, including those who live in

nursing homes and assisted living facilities and receive blood glucose monitoring. Hepatitis B vaccine is also appropriate pre-dialysis for those with incipient renal failure.

Complementary and Alternative Therapies

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. This information can then lead to a dialogue regarding safety and efficacy issues. A number of traditionally used supplements have shown promise in the treatment of diabetes and are in the process of undergoing large randomized trials. Research studies should continue investigating novel agents for diabetes management.

Supplementation with multivitamins and aspirin is generally considered safe; however, megavitamin therapy should be discouraged. Relaxation therapy, yoga, 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.

When to Consider Endocrine Consultation or Referral

Consider consultation or referral for patients with:

- Uncertain classification of diabetes, e.g., 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).
- Type 1 diabetes and frequent hypoglycemia or hyperglycemia or HbA1c level greater than glycemic goal. Patients with type 1 diabetes should be managed by a multidisciplinary team using a regimen of 3-4 insulin injections a day in conjunction with 3-4 times/day self-monitoring of blood glucose.
- Plans for pregnancy
- Multiple severe complications of diabetes
- Chronic lack of adherence to their treatment regimen
- Family problems or significant psychiatric problems interfering with treatment
- Substantial disability despite adequate therapy
- Frequent emergency room or hospital admission

Literature Search

The literature search for this update began with the results of the literature searches performed in 1995 to develop the guideline and in 2003 for a major update that included literature through February 2003. The literature search conducted in April 2010 for this update used keywords that were similar to those used in previous searches, with the addition of a few new topics for searches. An exception was made for topics related to the diagnosis of diabetes mellitus. For these topics we accepted the recommendations of the American Diabetes Association's guidelines for Diagnosis and Classification of Diabetes Mellitus (see Related National Guidelines, below).

The searches for treatment were performed prospectively on Medline using the major key words of diabetes mellitus; clinical guidelines, controlled trials, cohort studies; adults; and English language; and published from 1/1/2003 to present. Terms for specific topic searches within the major key words included: pre-diabetes or impaired fasting glucose tolerance; glycemic goal; lifestyle modifications: diet, exercise; treatment for type 1 diabetes: insulin; treatment for type 2 diabetes: sulfonylureas, metformin, alpha-glucosidase inhibitors, thiazolidinediones, nonsulfonyluric secretogones (repaglinide, nateglanide), new insulins (glargine, aspart, lispro), exenetide, amylin, liraglutide; sitaglipitin, saxagliptin; screening and treatment for hypertension, lipids, retinopathy, nephropathy, neuropathy, macrovascular disease; and preconception planning in pregnancy. Specific search terms and strategy available upon request.

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.

Team members identified recent major evidence searches and major clinical trials. The evidence summary and clinical practice recommendations of the American Diabetes Association (ADA; 2011) was the basis for screening and diagnosis recommendations. Glycemic control was based on the UKPDS for control value *[A]* and the ADA recommendations for goal *[C]*. Life style modifications (diet, exercise) were based on the UKPDS *[A]* and DPP *[A]* studies. The evidence summary and recommendations of the National Standards for Diabetes Self-Management Education and Support (AADE & ADA, 2013) were the basis the basis for self-management recommendations. Comments about treatment for type 1

diabetes and insulin use are based on the Diabetes Control and Complications Trial (DCCT) *[A]*. Treatment for type 2 diabetes with sulfonylureas and metformin is based on the UKPDS *[A]*. Screening and treatment of hypertension and lipid levels in type 2 diabetes is based on an evidence review and recommendations performed by the American College of Physicians, which included a member of our team. Screening and treatment for retinopathy were based on a literature review performed by the U. S. Veterans Administration. Recent evidence reviews were not available for the remaining topics.

Related 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 Athersclerotic Cardiovascular Risk in Adults (2013)

American Diabetes Association:
- Diagnosis and Classification of Diabetes Mellitus (2011)
- Nutrition Therapy Recommendations for the Management of Adults with Diabetes (2014)
- Standards of Medical Care in Diabetes (2014)

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)

Measures of Clinical Performance

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 (e.g., method of data collection, population inclusions and exclusions), the general measures are summarized below.

<u>HbA1c testing.</u> The percentage of patients 18–75 years of age who had an HbA1c test within 12 months (measurement period). (GPRO, ACO, PGIP)

<u>HbA1c control.</u> The percentage of patients 18–75 years of age with diabetes mellitus who had HbA1c < 8.0% within 12 months (measurement period). (MU,ACO, BCN)

<u>HbA1c poor control.</u> The percentage of patients 18–75 years of age with diabetes mellitus who had HbA1c >9.0% within 12 months (measurement period). (GPRO, MU, ACO)

<u>Blood pressure control.</u> 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 mmHb within 12 months (measurement period). (MU, ACO).

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

<u>LDL control.</u> 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)

<u>Statin.</u> 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)

<u>Eye exam.</u> 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)

<u>Foot exam.</u> 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)

<u>Neuropathy screening.</u> 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)

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and 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. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

Team Member / Consultant	Relationship	Company
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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 Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

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1996: Deryth Stevens, MD, Family Medicine, Sandeep Vijan, MD, General Internal Medicine, Martha Funnell, MS, RN, Diabetes Research and Training Center, Douglas Greene, MD, Endocrinology and Metabolism, R. Van Harrison, PhD, Postgraduate Medicine, William Herman, MD, Endocrinology and Metabolism, Roland Hiss, MD, Postgraduate Medicine, Catherine Martin, MS, RN, Endocrinology and Metabolism, Evelyn Piehl, MS, RN, Obstetrics and Gynecology, B.J. Ratliff, RN, Primary Care Nursing, Connie Standiford, MD, General Internal Medicine.

2004: Deryth L Stevens, MD, Family Medicine, Sandeep Vijan, MD, General Internal Medicine, Martha M Funnell, MS, RN, Diabetes Research and Training Center, R Van Harrison, PhD, Medical Education, William H Herman, MD, Endocrinology and Metabolism, Robert W Lash, MD, Endocrinology and Metabolism

Annotated References

Guidelines

American Diabetes Association. Standards of medical care for diabetes – 2014. Diabetes Care, 2014; 37 Supplement 1: S14-S80..

The American Diabetes Association (ADA) has developed position statements on screening for diabetes, diagnosis and classification of diabetes, medical care for patients with diabetes, nutritional recommendations and principles for individuals with diabetes, diabetes and

exercise, screening for diabetic retinopathy, diabetic neuropathy, foot care in patients with diabetes mellitus, detection and management of lipid disorders in diabetes, and hospital admission guidelines for diabetes mellitus, among others.

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes care, 2011; 34:S62-S69

This article reviews the scientific basis for the ADA's recommendations for the diagnosis and classification of diabetes mellitus.

Haas L, Maryniuk M, Beck J, Cox CE, Duker P, Edwards L, Fisher E, Hanson L, Kent D, Kolb L, McLaughlin S, Orzeck E, Piette JD, Rhinehart AS, Rothman R, Sklaroff S, Tomky D, Youssef G. National Standards for Diabetes Self-management Education and Support. Diabetes Care 2012; 35:2393-2401.

This report, first published in 2008, defines national standards for quality education and on-going support in diabetes self-management. Aspects of structure, process, and outcome are addressed.

Evert AB, Boucher JL, Cypress M, Dunbar SA, et al: Position statement: Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2013; 36:3821-3842.

Current nutrition guidelines based on a review of the evidence and therapy.

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Recommendations for assessing cardiovascular risk.

James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the eight Joint National Committee (JNC 8). JAMA, doi: 10.1001/jama.2013.284427. Published online Dec. 18, 2013.

Recommendations for blood pressure goals and treatment for patients with high blood pressure.

Snow V, Weiss KB, Mottur-Pilson C. The evidence base for tight blood pressure control in the management of type 2 diabetes mellitus. Annals of Internal Medicine 2003; 138(7): 587-592.

The Clinical Efficacy Assessment Subcommittee of the American College of Physicians oversaw this summary of evidence and recommendations regarding the benefits of tight blood pressure control, target levels for blood pressure, and effectiveness of agents.

Snow V, Aronson MB, Hornbake ER, Mottur-Pilson C, Weiss KB. The evidence base for pharmacologic lipid lowering therapy in the management of type 2 diabetes mellitus. Annals of Internal Medicine 2004; 140(8): 644-649.

The Clinical Efficacy Assessment Subcommittee of the American College of Physicians oversaw this summary of evidence and recommendations regarding the benefits of pharmacologic lipid-lowering therapy in type 2 diabetes.

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Journal of the American College of Cardiology, 2013, doi: 10.1016/j.jacc.2013.11.002. Available at http://content.onlinejacc.org/article.aspx?articleid=1770217 Also printed in Circulation. 2013 Nov 12. Available at https://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.full.pdf+html

Recommends intensity of statin treatment for specific groups rather than treating to LDL-C goals.

Some Major Clinical Trials

UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837-53.

UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65.

These two reports from the UKPDS study are the only long-term trials showing the benefits of glucose control in type 2 diabetes. The findings show that intensive glucose control reduces the risk of early microvascular disease (retinopathy, nephropathy, neuropathy) but does not affect cardiovascular outcomes. The results also suggest that metformin monotherapy is superior to either sulfonylureas or insulin for overweight individuals with type 2 diabetes.

The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358: 2545-2559.

This study examined the efficacy of targeting an A1c of <6.0% on cardiovascular and microvascular diabetes outcomes. The achieved A1c in the intensive arm was 6.4%, vs. 7.5 % in the control arm. This study was stopped early due to significantly higher mortality in the intensive control arm, mostly due to cardiovascular mortality. It suggests that for typical patients with type 2 diabetes, aggressive glucose lowering may be harmful.

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317 (7160) 703-12.

Hansson L., Zanchetti A., Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principle results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group, Lancet 1998; 351: 1755-62.

These two studies demonstrated the importance of blood pressure control. UKPDS 38 (and 33, listed earlier) showed that control of hypertension was more important in prevention of macrovascular complications of type 2 diabetes than tight glycemic control.

The ACCORD study group. Effects of intensive blood pressure control in type 2 diabetes mellitus. N Engl J Med 2010; 362: 7575-85.

This study targeted a systolic BP goal of <120 mmHg, vs. < 140 mmHg (achieved 119 vs 133 mmHG). It found no benefit on cardiovascular events or mortality. It suggests that a BP target of 135-140 systolic is a reasonable goal for patients with type 2 diabetes.

The ACCORD study group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010; 362: 1563-74.

This study examine the efficacy of combination statin/fibrate vs. statin alone in patients with type 2 diabetes. It found no overall difference in risk of cardiovascular events between the two regimens, suggesting that statin therapy alone is adequate for many patients with diabetes. There was possible evidence of benefit of combination therapy in patients with both low HDL and high triglycerides; however, this is a subgroup analysis and needs verification.

The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–986.

This is the first key report from the Diabetes Control and Complications Trial, a prospective randomized controlled trial of intensive therapy for insulin-dependent diabetes mellitus. It conclusively demonstrated that intensive therapy, compared to conventional insulin therapy, reduced the development and progression of all of the microvascular and neuropathic complications of IDDM. The chief adverse event associated with intensive therapy was a two to three-fold increase in severe hypoglycemia. This study proved the glucose hypothesis: that hyperglycemia causes diabetic microvascular and neuropathic complications, and treatment of hyperglycemia delays or prevents those complications.

Early Treatment of Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology. 1991;98:766–785.

This report summarizes the results of the Early Treatment Diabetic Retinopathy Study, a controlled trial of early photocoagulation in the treatment of mild to severe non-proliferative or early proliferative diabetic retinopathy. The ETDRS results demonstrated that for eyes with macular edema, focal photocoagulation is effective in reducing the incidence of moderate visual loss. Focal treatment also increased the chance of visual improvement, decreased the frequency of persistent macular edema, and caused only minor visual field losses.

The Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle modification or metformin. N Engl J Med 2002; 346:393-403.

This report summarizes the proactive prevention of diabetes by treating individuals with borderline high levels of glucose, i.e. those most at risk for continuing on to develop diabetes.

Skovlund SE, Peyrot M on behalf of the DAWN International Advisory Panel: The Diabetes Attitudes, Wishes and Needs (DAWN) program: A new approach to improving outcomes of diabetes care. Diabetes Spectrum 2005; 18:136-142.
Peyrot M, Rubin RR, Lauritzen T, Snoek FJ, Matthews DR, Skovlund SE: Psychosocial problems and barriers to improved diabetes management: Results of the cross-national Diabetes Attitudes, Wishes and Needs study. Diabetic Medicine 2005; 22:1379-1385.

These two papers summarize the results of the Diabetes Attitudes, Wishes and Needs (DAWN) survey, a cross-sectional international study initiated in 2001 by Novo Nordisk in collaboration with the International Diabetes Federation. The purpose of the survey was to identify a broad set of attitudes, wishes and needs among persons with diabetes and care providers in order to lay a foundation for efforts to improve diabetes care nationally and internationally. Structured interviews were conducted in person or by telephone in 11 regions (representing 13 countries), including the United States. Survey participants consisted of 250 randomly selected generalist and specialist physicians per region (n=2,705), 100 randomly selected generalist and specialist nurses per region (n=1,122) and 250 randomly selected patients with self-reported type 1 diabetes per country and 250 patients with self-reported type 2 diabetes (n=5,104). In general, patients and providers identify a great deal of distress associated with diabetes and its management, but also identify that our current health care systems and care guidelines do little to address these issues.

Other References

Vijan S, Hofer TP, Hayward RA. Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. JAMA. 2000;283:8889-896.

This article evaluates the relative costs and benefits of more versus less frequent screening for retinopathy in patients with type 2 diabetes. For lower-risk patients who

do not have retinopathy at baseline, there is little benefit from screening every year versus every 2-3 years.

Appendix A. Insulin Initiation and Adjustment Protocol

1) Start with NPH, detemir, glargine
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 glucose meter and be educated on recognition and treatment of hypoglycemia.

NPH, Levemir, or Lantus insulin (bedtime)

a. Continue metformin +/- sulfonylurea depending on preprandial glucose.
b. Add 10-20 units of NPH, detemir, or Lantus insulin at bedtime.
c. Then increase insulin by 10% or 2-4 units every 3 days until attaining the goal of a fasting blood glucose < 130 mg/dL without hypoglycemia.
d. Once fasting glucose is at goal, check post-prandial glucoses; if > 180 mg/dL consider adding either rapid or regular insulin before meals.

NPH or Levemir insulin (BID)

a. Continue metformin, discontinue sulfonylurea.
b. Add 5-10 units of NPH or detemir insulin at breakfast and dinner (or bedtime).
c. Then increase insulin by 10% or at least 2 units every 3 days until the goal of a fasting blood glucose and pre-dinner glucose < 130 mg/dL without hypoglycemia.
d. Once fasting glucose is at goal, check post-prandial glucoses; if > 180 mg/dL consider adding either rapid or regular insulin before meals.

Premixed insulin (intermediate & 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% or at least 2 units every 3 days until the goal of a fasting and pre-meal glucose level < 130 mg/dL without hypoglycemia.

Insulin adjustment for RNs/PharmDs

If overnight or before breakfast glucoses are above/below target,	adjust the supper* or bedtime dose of NPH **or** Lantus
If before lunch glucoses are above/below target ,	adjust the breakfast dose of Regular or Rapid Acting Insulin
If before supper glucoses are above/below target,	adjust the breakfast dose of NPH **or** adjust the lunch dose of Regular or Rapid Acting Insulin
If before bedtime glucoses are above/below target,	adjust the supper dose of Regular or 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 3:00am for 2 days during the week. If the glucose levels are:	
- normal in the middle of the night,	increase the NPH supper dose
- low in the middle of the night,	decrease the NPH supper dose.

Basic principles:

- Adjust one insulin at a time.
- Adjust no more than 10% of the total insulin units per day. Wait at least 3 days before adjusting further doses.
- Decrease insulin based on unexplained hypoglycemia.

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

For NPH twice a day:

3 consecutive morning readings > 130	increase evening NPH by 2 units
3 consecutive morning readings > 150	increase evening NPH by 4 units
3 consecutive evening readings > 130	increase morning NPH by 2 units
3 consecutive evening readings > 150	increase morning NPH by 4 units