



Interventions in Type 2 Diabetes: Revisiting the Evidence

DIABETES MELLITUS currently affects more than 20 million Americans, or approximately 7 percent of the U.S. population.¹ For individuals born in the year 2000, the estimated lifetime risk of developing diabetes is approximately one in three.² And for some minority populations (African Americans and Hispanics), the estimated lifetime risk of diabetes is now one in two. This burgeoning epidemic has led to increased attention regarding the management and treatment of type 2 diabetes.

Several organizations have published guidelines regarding the routine management of type 2 diabetes. Commonly recommended interventions include: tight glucose control, tight blood pressure control, aspirin therapy, statin therapy, ACE inhibitor use, eye examinations, foot care, and pneumococcal and influenza vaccinations.³ In this article, I will review the evidence, and when available, the cost effectiveness of each of these commonly recommended diabetes-related interventions.* Please refer to the summary table on page 14 for a side-by-side comparison.

Tight Glucose Control

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive blood glucose control reduced the relative risk of any diabetes-related endpoint by 12% and any microvascular endpoint by 25%.⁴ Intensive blood glucose control was also associated with a nonsignificant reduction in all-cause mortality and myocardial infarction. Applied to a population of newly diagnosed patients with diabetes,

intensive blood glucose control offers a cost-effectiveness ratio of \$41,384 per quality-adjusted life-year (QALY).

Tight Blood Pressure Control

UKPDS also showed that tighter blood pressure control led to a 24% reduction in diabetes-related endpoints, 32% reduction in diabetes-related deaths, 44% reduction in strokes, and a 37% reduction in microvascular endpoints. Like tight glucose control, tight blood pressure control was associated with a nonsignificant decrease in all-cause mortality and myocardial infarction. Applied to a population of newly diagnosed patients with diabetes and hypertension, tight blood pressure control offers a cost-effectiveness ratio of -\$1959 per QALY, which means that the intervention leads to a net cost savings.⁵

Aspirin Therapy

Although well-established in the secondary prevention of cardiovascular disease, aspirin therapy as a primary prevention strategy in patients with diabetes is less clear. In the Early Treatment and Diabetes Retinopathy Study of the 1980s, aspirin was incidentally found to have a nonsignificant reduction in all-cause mortality and a significant reduction in myocardial infarction rates in patients with diabetes.⁷ Subsequently, the American Diabetes Association (ADA) recommended aspirin therapy as a primary prevention strategy in those with diabetes who are over age 40 or who have additional risk factors (family history, hypertension, hyperlipidemia, smoking, and albuminuria).³

Learning Objectives

After reading this article, learners should be able to:

1. Outline evidence for at least three clinical recommendations for patients with diabetes.
2. Select diabetes treatment options for your patients based on evidence, as well as on patient profile and needs.
3. Differentiate among clinical options by cost-effective measures.



Covered in CFP
Post-test, page 14.

* "Diabetes" refers to type 2 mellitus diabetes unless otherwise specified.

More recently, the above ADA recommendation was tested by the Primary Prevention Project (PPP) trial. It found that in patients with diabetes without prior cardiovascular disease, low-dose aspirin resulted in a nonsignificant reduction in cardiovascular events, but a non-significant increase in all-cause mortality.⁸ Interestingly, the PPP trial suggested that nondiabetic controls benefited from aspirin to a greater degree than patients with diabetes with regard to both cardiovascular events and cardiovascular deaths.

Statin Therapy

Similar to aspirin, indications for statin therapy have expanded beyond the secondary prevention of cardiovascular disease. Currently, the ADA recommends statin therapy for the primary prevention of cardiovascular disease in all diabetic patients who are over age 40.³ This recommendation stems from a series of trials, including the Heart Protection Study (HPS) and the Collaborative Atorvastatin Diabetes Study (CARDS).

In HPS, patients with diabetes and no prior cardiovascular disease randomized to simvastatin were found to have a 31% reduction in first major vascular events when compared to placebo.⁹ CARDS reinforced the role of statin therapy in the primary prevention of cardiovascular disease in diabetic patients, while also suggesting a reduction in all-cause mortality with atorvastatin.¹⁰ A recent Markovian model estimates that statin therapy offers a cost-effectiveness ratio of \$51,889 per QALY.⁵

ACE Inhibitors

The evidence for angiotensin-converting-enzyme (ACE) inhibitor use in patients with diabetes who are 55 years and older derives primarily from the Heart Outcomes Prevention Evaluation (HOPE) study. More specifically, in the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO) HOPE substudy, patients with diabetes aged 55 years or older with either a previous cardiovascular event or at least one

additional cardiovascular risk factor were randomized to ramipril or placebo. At 4.5 years, ramipril lowered the risk of myocardial infarction by 22%, stroke by 33%, overt nephropathy by 24%, and all-cause mortality by 24%.¹¹ When applied to all patients with diabetes over age 50, ACE inhibitors have a cost-effectiveness ratio of \$15,240 per QALY.¹²

Eye Examinations

Although no randomized controlled trials exist to support the annual screening for retinopathy in patients with diabetes, the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that properly treated diabetic retinopathy could reduce the five-year risk of blindness by 87%-90%.^{13,14} Screening and treating diabetic eye disease has been estimated to have a cost-effectiveness ratio of \$3,190 per QALY.¹⁵ And screening every year as opposed to every other year has a marginal cost-effectiveness ratio ranging from \$40,530 per QALY in high-risk individuals to \$211,570 per QALY in low-risk individuals.¹⁶

Foot Care

There are no randomized controlled trials to support the annual foot examination for the primary prevention of foot ulcers or amputation.^{3,17} However, one small trial of 91 persons with diabetes with prior foot ulceration found that recommended monthly foot care (versus no recommended foot care) resulted in a 52% reduction in foot ulceration recurrence at one year.¹⁸ In another randomized trial of 203 persons with diabetes with foot infection, ulceration, or prior amputation, a single one-hour class (with slides depicting infected diabetic feet and amputated diabetic limbs) was found to decrease the incidence of foot ulceration and amputation three-fold.¹⁹ Overall, comprehensive foot care has an estimated cost-effectiveness ratio ranging from \$12,169 to \$220,100 per QALY depending on the presumed level of foot ulcer reduction attained.²⁰

Pneumococcal and Influenza Vaccinations



The Advisory Committee on Immunization Practices and the American Diabetes Association recommend that persons with diabetes receive annual influenza vaccines and at least one lifetime pneumococcal vaccine during adulthood.²¹ However, no well-controlled studies support this recommendation.³ The notion that persons with diabetes are at higher risk of contracting pneumococcal and influenza illnesses rests upon case series and observational studies.²² Interestingly, a recent analysis of hospitalization and mortality data collected on 15,556 persons with diabetes aged 65 years and older suggests that while influenza vaccination benefits the elderly, it does not appear to benefit diabetic persons more than nondiabetic persons.²³ And with regard to the pneumococcal vaccination, higher-risk (elderly) individuals may actually benefit less from the direct effects of targeted vaccination than the indirect effects of vaccinating the general pediatric population.²⁴

Conclusion

Numerous recommendations exist regarding the management of type 2 diabetes. However, some recommendations either lack adequate evidence (pneumococcal and influenza vaccinations) or are entirely consensus-based (semi-annual hemoglobin A1c, annual microalbuminuria screening). Diabetic-related interventions with the strongest supporting evidence include: tight blood pressure control, ACE inhibitor use, tight glucose control, and statin therapy. ■

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For the list of sources used in this article, go to page 28.

SUMMARY OF COMMONLY RECOMMENDED INTERVENTIONS IN TYPE 2 DIABETES

Intervention	Evidence	Comments	Cost-Effectiveness (\$/QALY)
Tight Glucose Control	UKPDS ⁴	<ul style="list-style-type: none"> • 25% reduction all diabetes-related endpoints (NNT = 19.6 over 10 yrs) • 25% reduction in microvascular endpoints (NNT = 35.7 over 10 yrs) 	\$41,384
Tight Blood Pressure Control	UKPDS ⁶	<p>144/82 mm Hg versus 154/87 mm Hg:</p> <ul style="list-style-type: none"> • 24% reduction diabetes-related endpoints (NNT = 5.7 over 8.4 yrs; p = 0.0035) • 32% reduction in diabetes-related deaths (NNT = 17.9 over 8.4 yrs; p = 0.019) • 37% reduction in microvascular endpoints (NNT = 13.9 over 8.4 yrs; p = 0.0092) • 44% reduction in strokes (NNT = 19.6 over 8.4 yrs; p = 0.013) 	-\$1,959 (cost savings)
Aspirin Therapy (primary prevention)	ETDRS ⁷ PPP ⁸	<ul style="list-style-type: none"> • Possible reduction cardiovascular events; in myocardial infarction rates in patients with diabetes (9.1%, down from 12.3%; NNT = 31.3 over 7 years; p = 0.04) • No clear mortality benefit • May be more effective in nondiabetics than diabetics (for cardiovascular events: nondiabetic RR = 0.69, diabetic RR = 0.89; cardiovascular deaths: nondiabetic RR = 0.32, diabetic RR = 1.23) 	N/A
Statin Therapy	HPS ⁹ CARDS ¹⁰	<ul style="list-style-type: none"> • 31% reduction in vascular events (9.3% versus 13.5%; NNT = 24 over 5 yrs; p < 0.0003) • Possible mortality benefit (4.3% versus 5.8%; NNT = 67 over 4 yrs; p = 0.059) 	\$51,889
ACE Inhibitor Use	MICRO-HOPE ¹¹	<ul style="list-style-type: none"> • 22% reduction myocardial infarction (10.2% versus 12.9%; NNT = 37 over 4.5 yrs; p = 0.0004) • 33% reduction stroke (4.2% versus 6.1%; NNT = 53 over 4.5 yrs; p = 0.0074) • 24% reduction nephropathy (6.5% versus 8.4%; NNT = 53 over 4.5 yrs; p = 0.027) • 24% reduction mortality (10.8% versus 14.0%; NNT = 33 over 4.5 yrs; p = 0.004) 	\$15,240
Eye Exam	ETDRS ^{13,14}	<ul style="list-style-type: none"> • Screening and treating retinopathy decreases 5-yr rate of blindness from 50% to 5% 	\$3,190 (\$40,530–\$211,570 for annual versus every other yr)
Foot Care	No RCTs	<ul style="list-style-type: none"> • 52% reduction in foot ulceration recurrence at one year (intervention = 22%, control = 38%; NNT = 6.25; p = 0.03) • Successful in secondary prevention of foot ulceration¹⁷ (foot ulceration rate down from 15% to 5%, NNT = 10, p = 0.005; amputation rate down from 12% to 4%, NNT = 12.5, p = 0.025) • Education may be more effective¹⁸ 	\$12,169–\$220,100 (based on level of foot ulcer reduction achieved)
Influenza and Pneumococcal Vaccines	No RCTs	<ul style="list-style-type: none"> • Questionable benefit • Influenza vaccine may be less beneficial in patients with diabetes than patients without diabetes²³ 	N/A
Semi-annual HgbA1c	Consensus only		
Microalbuminuria Screening	Consensus only		

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CME Post-Test

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1. Which of the following interventions is/are proven to have a significant mortality benefit in patients with diabetes? (You may choose more than one answer.)

a. tight glucose control	d. ACE inhibitors in those 55 years and older with additional cardiovascular risk factors
b. tight blood pressure control	e. lifetime pneumococcal vaccine
c. aspirin therapy for primary prevention	
2. Of the following diabetic interventions, which is the most cost-effective?

a. tight glucose control	d. statin therapy for primary prevention
b. tight blood pressure control	e. ACE inhibitors in those 55 years and older
c. aspirin therapy for primary prevention	
3. Which trial demonstrated the value of simvastatin in patients with diabetes with no prior cardiovascular disease?

a. United Kingdom Prospective Diabetes Study (UKPDS)	d. Microalbuminuria, Cardiovascular, and Renal Outcomes substudy of the Heart Outcomes Prevention Evaluation (MICRO-HOPE)
b. Primary Prevention Project (PPP) trial	e. Early Treatment Diabetic Retinopathy Study (ETDRS)
c. Heart Protection Study (HPS)	
4. ___ True, or ___ False: Comprehensive annual diabetic foot examinations have been shown to be effective in the primary prevention of foot ulcers and amputation.
5. According to the American Diabetes Association, which of the following interventions is/are recommended for a hypothetical 42 year-old patient with type 2 diabetes, no additional cardiovascular risk factors, and no microalbuminuria or nephropathy? (You may choose more than one answer.)

a. tight glucose control	d. ACE inhibitors
b. aspirin therapy	e. yearly influenza vaccine
c. statin therapy	



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Interventions in Type 2 Diabetes Sources *From page 13*

- 1 American Diabetes Association. Total Prevalence of Diabetes and Pre-diabetes. www.diabetes.org/diabetes-statistics/prevalence.jsp. Accessed January 26, 2006.
- 2 Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime Risk for Diabetes Mellitus in the United States. *JAMA* 2003; 294: 1884-1890.
- 3 American Diabetes Association. Standards of Medical Care in Diabetes - 2006. *Diabetes Care*, 29(1):S4-S42.
- 4 United Kingdom Prospective Diabetes Study 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). *The Lancet* 1998; 352: 837-53.
- 5 CDC Diabetes Cost-Effectiveness Group. Cost-Effectiveness of Intensive Glycemic Control, Intensified Hypertension Control, and Serum Cholesterol Level Reduction for Type 2 Diabetes. *JAMA* 2002; 287: 2542-2551.
- 6 United Kingdom Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *British Medical Journal* 1998; 317: 703-713.
- 7 Early Treatment Diabetic Retinopathy Study Investigators (ETDRS). Aspirin Effects on Mortality and Morbidity in Patients with Diabetes Mellitus: Early Treatment Diabetic Retinopathy Study Report 14. *JAMA* Sept 9 1992; 268: 1292-1300.
- 8 Sacco M, Tognoni G, Pellegrini F, Roncaglioni MC, Avanzini F. Primary Prevention of Cardiovascular Events with Low-Dose Aspirin and Vitamin E in Type 2 Diabetic Patients: Results of the Primary Prevention Project (PPP) Trial. *Diabetes Care* 2003; 26:3264-3272.
- 9 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet* 2003; 361: 2005-16.
- 10 Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* 2004; 364: 685-696.
- 11 Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355: 253-359.
- 12 Golan L, Birkmeyer JD, Welch HG. The Cost-Effectiveness of Treating All Patients with Type 2 Diabetes with Angiotensin-Converting Enzyme Inhibitors. *Annals of Internal Medicine* 1999; 131: 660-667.
- 13 Ferris, Frederick. How Effective Are Treatments for Diabetic Retinopathy? *JAMA* 1993; 269: 1290-1291.
- 14 Ferris FL, Davis MD, Aiello LM. Treatment of Diabetic Retinopathy. *NEJM* 1999; 341: 667-678.
- 15 Javitt JC, Aiello LP. Cost-Effectiveness of Detecting and Treating Diabetic Retinopathy. *Annals of Internal Medicine* 1996; 124: 164-169.
- 16 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: 889-896.
- 17 Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005; 293: 217-228.
- 18 Plank J, Haas W, Raovac I, et al. Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects. *Diabetes Care* 2003; 26: 1691-1695.
- 19 Malone JM, Snyder M, Anderson G, et al. Prevention of Amputation by Diabetic Education. *American Journal of Surgery* 1989; 158: 520-524.
- 20 Ortegon MM, Redekop WK, Niessen LW. Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. *Diabetes Care* 2004; 27: 901-907.
- 21 Advisory Committee on Immunization Practices. ACIP Recommendations. www.cdc.gov/nip/publications. Accessed January 26, 2006.
- 22 Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care* 2000; 23: 95-108.
- 23 Heymann AD, Shapiro Y, Chodick G, et al. Reduced hospitalizations and death associated with influenza vaccination among patients with and without diabetes. *Diabetes Care* 2004; 27: 2581-2584.
- 24 Lexau CA, Lynfield R, Danila R, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal vaccine. *JAMA* 2005; 294: 2043-2051.

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