Chapter 3

RATIONALE FOR STANDARDS OF CARE

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The primary goal of diabetes therapy is to prevent diabetes complications while minimizing the potential adverse effects of therapy. The complications of diabetes include:

- Cardiovascular disease ([CVD], coronary heart disease, cerebrovascular disease, and peripheral vascular disease), the leading cause of death in people with diabetes
- Retinopathy, the leading cause of adult blindness
- Nephropathy, the leading cause of end-stage renal disease requiring dialysis or transplantation
- Neuropathy, a potentially disabling and often symptomatic problem that is the leading contributor to lower extremity amputation

This chapter reviews the major standards of care for people with diabetes, which are aimed at minimizing the risk of complications of diabetes. It also presents some of the evidence on which these guidelines are based.

CADRE recommendations are based on evidence from a wide variety of studies. To whatever extent possible, CADRE tries to align its recommendations with the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) to avoid confusion and discord. It should be recognized that the evidence base for the management of diabetes is thin in many areas. Thus, it is possible for groups or individuals to disagree as to whether available evidence is adequate to support a particular recommendation:

- When evidence is referred to as "strong" or "substantial," data are from well-conducted randomized controlled clinical trials (RCTs).
- Lesser degrees of evidence largely consist of epidemiologic studies, which may be inadequate to some to drive treatment recommendations without additional support.
- CADRE recommendations for which there is limited evidence base are clearly labeled as "consensus only."

GLYCEMIC CONTROL

RCTs such as the Diabetes Control and Complications Trial (DCCT), the Kumamoto Study, and the United Kingdom Prospective Diabetes Study (UKPDS) provide strong support for the notion that more intensive treatment of diabetes is of benefit in reducing complications.

Hemoglobin A1c (A1C), an index of average glycemia over a period of approximately 3 months, has been well validated as a surrogate marker of risk of complications in diabetes in both RCTs and in epidemiologic studies. Prospective epidemiologic studies indicate that, well into the normal range of A1C (<6%), there is no lower limit (or threshold) of A1C below which further benefit in microvascular and cardiovascular outcomes is not observed. The adverse consequences of more intensive therapy of diabetes (eg, hypoglycemia and weight gain) are likewise related to A1C, with increased risk associated with lower levels of A1C; however, there is good clinical trial support that the benefits outweigh the risks at an A1C of 7%.

These evidence-based conclusions form the basis of the CADRE recommendation that patients and providers aim for the lowest A1C possible without unacceptable adverse consequences.

The following studies illustrate A1C decreases with intensive therapy and show the direct relationship between A1C levels and the microvascular and macrovascular complications of diabetes:

- The Diabetes Control and Complications Trial (DCCT) examined 1,441 patients with type 1 diabetes randomized into two groups and followed for an average of 6.5 years. One group received traditional care (one or two daily insulin injections with daily monitoring of blood or urine glucose, standard diabetes education and dietary counseling, and routine quarterly visits). The intensively treated group received training in diabetes self-management principles, frequent contact with a health care team, self-monitored blood glucose (SMBG) several times per day, and multiple daily insulin injections or insulin infusion. During the study period, intensively treated patients experienced a significant drop in mean A1C levels compared with traditionally treated patients (7.2% vs 9.1%).[1]

- The Kumamoto Study examined 110 patients with insulin-treated type 2 diabetes without obesity or cardiovascular risk factors. These patients were randomized and treated in a fashion analogous to the DCCT and achieved A1C measurement separation between groups nearly identical to the DCCT.[2]

- The UKPDS examined 5,102 patients with new-onset type 2 diabetes followed for an average of 10 years. In this study, subjects with a fasting plasma glucose (FPG) of >108 mg/dL after a 3-month dietary run-in were randomized to either continue on diet and exercise with the goal of remaining asymptomatic with an FPG of <270 mg/dL or a more intensive program involving initial drug therapy with insulin, sulfonylurea, or metformin with a goal of achieving FPG <108 mg/dL. In both arms, if FPG rose to >270 mg/dL or if patients developed symptoms, an additional antidiabetic agent could be administered. The vast majority of patients in the diet-treated group and more than half of those randomized to initial drug therapy were eventually unable to meet their glycemic targets and had additional agents added to their regimen to improve glycemic control.

Patients randomized to the more intensive interventions achieved A1C levels of about 7%, versus 7.9% for those treated initially with lifestyle interventions.[3]

Table 3-1 and Figure 3-1 outline the relative risk reduction per 1% reduction for each study. Figure 3-2 outlines the risk of macrovascular complications versus A1C.

Techniques of Glycemic Control

Diet and exercise

The efficacy of lifestyle interventions—primarily diet (medical nutrition therapy [MNT]) and exercise—for improving glycemic control and preventing and reducing the severity of diabetes complications is well established, as shown by selected studies listed in Tables 3-2 and 3-3. However, because of the progressive nature of type 2 diabetes and poor compliance, pharmacologic treatment is almost inevitably needed.

Table 3-1 Reduction in A1C Levels and Relative Risk for Intensively Treated Patients in Diabetes RCTs

Study	DCCT[1]	Kumamoto[2]	UKPDS[3]
Difference in mean A1C between groups	1.9% (7.2% vs. 9.1%)	2.3% (7.1% vs. 9.4%)	0.9% (7.0% vs. 7.9%)
Reduction in retinopathy risk	63%	65%	21%
Reduction in nephropathy risk	50%	70%	34%
Reduction in neuropathy risk	60%	NA	NA

RCT, randomized controlled clinical trial; DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study; A1C, hemoglobin A1C; NA = not available.

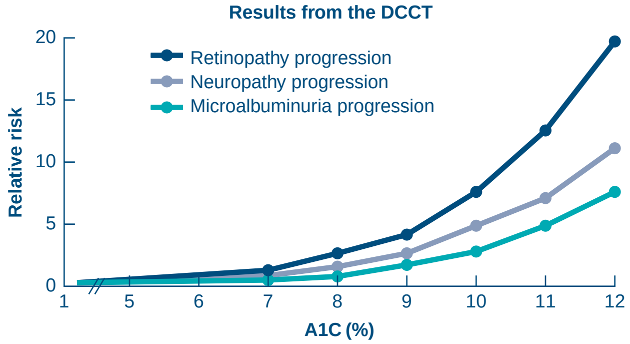

FIGURE 3-1. *Risk of microvascular complications of diabetes vs. A1C in the DCCT.* Skyler JS. *Endocrinol Metab Clin North Am.* 1996;25:243-254.

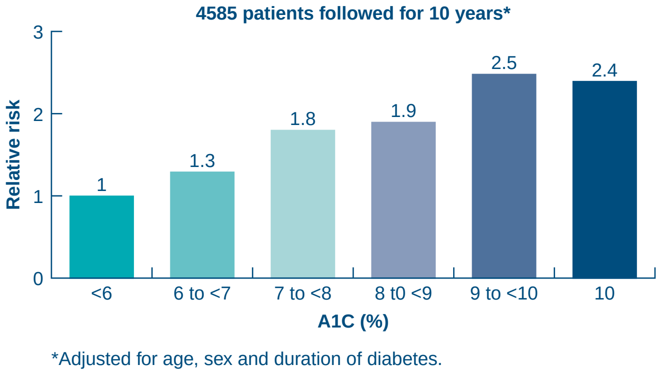

FIGURE 3-2. *Risk of macrovascular complications of diabetes vs. A1C in the UKPDS*. Stratton IM, et al. *BMJ*. 2000;321:405-412.

Table 3-2 Selected Studies on the Effect of MNT on A1C Levels

Clinical Trial	Design/Goal	Results
Kulkarni et al. (1998)[23]	To assess the effect of nutrition practice guidelines on dietitians' practices, and to measure their effect on patients' A1C levels	MNT resulted in a 1.0% decline in A1C in newly diagnosed patients with type 1 diabetes
UKPDS (1990)[24]	To evaluate the effect of dietary interventions on newly diagnosed patients with type 2 diabetes	MNT led to a 2.0% decline in A1C in newly diagnosed patients with type 2 diabetes
Franz et al. (1995)[25]	To determine the effects of MNT administered by dietitians on outcomes in patients with type 2 diabetes	MNT led to 1.0% decline in A1C in patients with type 2 diabetes with an average 4-year diabetes duration

MNT, medical nutrition therapy; A1C, hemoglobin A1C.

Specific antidiabetic agents

The only study that has examined different techniques of glucose lowering and compared them with respect to event reduction was the UKPDS. In an epidemiologic analysis of the overall study, patients treated more intensively had a 16% reduction in myocardial infarction (MI) per 1% reduction in A1C. In the overweight subgroup, patients treated with metformin demonstrated a statistically significant 39% risk reduction in MI. Again in the overweight subgroup, patients treated with insulin or sulfonylurea demonstrated a trend toward reduction of MI, which did not quite reach

Table 3-3 Selected Studies on the Effect of Exercise on Glycemic Control and Diabetes Complications

Clinical Trial	Design/Goal	Results
Wei et al. (2000)[26]	To determine the mortality risk associated with physical inactivity and low cardiorespiratory fitness in men with type 2 diabetes	Poor fitness in middle-aged type 2 men led to a roughly twofold increased mortality risk
Dunstan et al. (2002)[27]	To study the effects of progressive resistance training plus moderate weight loss (vs weight loss alone) on glycemic control in sedentary, overweight patients with type 2 diabetes aged 60–80 years	A1C levels fell significantly in older patients on a program of high-intensity progressive resistance training
Yamanouchi et al. (1995)[28]	To evaluate the effects of walking and diet therapy (vs diet therapy alone) on insulin sensitivity in obese patients with type 2 diabetes	Daily walking helped patients with type 2 diabetes to shed pounds and improve insulin sensitivity

statistical significance (ie, $P = 0.052$). Since the insulin and sulfonylurea-treated group achieved lower A1C values than the metformin-treated patients in the UKPDS, metformin may exhibit some cardiovascular risk reduction mechanism beyond glucose lowering.[4]

Although it has been suggested that insulin treatment may have an adverse effect on CVD, there is no supporting evidence from human studies. In fact, the preponderance of evidence suggests the opposite, including the DCCT and UKPDS data in Table 3-3, as well as data from the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, which demonstrated that patients treated with intensive insulin therapy in the immediate post-MI period had an approximately 30% relative risk reduction in mortality over 1-, 3-, and 5-year follow-up.[5]

BLOOD PRESSURE CONTROL

- Hypertension is associated with increased risk of CVD, retinopathy, macular edema, and nephropathy.
- RCTs of hypertension management in diabetes provide strong support for the notion that more intensive treatment of hypertension is of benefit in reducing CVD, eye, and kidney disease.

Table 3-4 outlines important studies that contribute to current understanding of the importance of hypertension control in diabetes treatment. Notably, higher systolic blood pressure (BP) predicts cardiovascular risk in patients with type 2 diabetes, and no threshold exists for that risk.[6]

Several clinical trials have compared the relative effectiveness of antihypertensive agents, including the HOPE, LIFE, and ALLHAT studies. In the Heart Outcomes Prevention Evaluation (HOPE), researchers found that for 3,577 subjects with diabetes, the ACE inhibitor ramipril significantly reduced several of the risk factors associated with hypertension. Results (versus placebo) included a 25% reduction in risk for the combined overall outcome of MI, stroke, or cardiovascular (CV) death. Ramipril lowered the risk of MI by 22%, of stroke by 33%, of CV death by 37%, of total mortality by 24%, of revascularization by 17%, and of overt nephropathy by 24%.[7]

In the Losartan Intervention For Endpoint reduction (LIFE) study, the angiotensin-II receptor blocker losartan reduced (by approximately 14%) the primary composite endpoint of CV death, stroke, and MI versus atenolol in 9,193 hypertensive subjects. With losartan the relative risks for individual endpoints were as follows: CV disease, 0.89; stroke, 0.75. MI risk was slightly higher at 1.07, however. New-onset diabetes occurred less often in subjects taking losartan than those on atenolol, as well.[8]

In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, researchers followed, for an average of 4.9 years, more than 42,000 hypertensive patients over age 55 who had at least one additional cardiovascular risk factor (about a third of the patients had diabetes). To determine the effect on mortality and CV events, they compared treatment with various drug regimens (eg, a calcium channel blocker [amlodipine], an ACE inhibitor [lisinopril], or an α-adrenergic blocker [doxazosin]) with a more traditional approach using the diuretic chlorthalidone.

Chlorthalidone proved superior at preventing CVD events versus the other drugs. Amlodipine patients had a 38% higher risk of heart failure versus those taking chlorthalidone, for example, and the lisinopril group had a greater risk of stroke (15%), heart failure (19%), and angina (11%). Some effects were particularly pronounced in African Americans, who had a 40% higher risk of stroke in the lisinopril group (no additional risk was observed for other ethnic groups). The study suggested that thiazide-type diuretics should be the drugs of choice for initial antihypertensive therapy. ACE inhibitors, calcium channel blockers, or β-blockers should be used in those who do not tolerate diuretics. In any case, however, most patients will require more than one drug for optimal BP control.[9]

Aspirin Therapy

The Hypertension Optimal Treatment (HOT) study, the first to examine low-dose aspirin therapy in hypertension, was a multicenter clinical trial designed to assess the optimal target diastolic BP and the benefit of adding low-dose aspirin to a five-step baseline therapy in 18,790 hypertensive patients.[2] The five-step approach began with felodipine (5 mg/day); other agents were added as indicated to reach target BP goals. These included ACE inhibitors or β-blockers at step 2; dosage titrations of these and felodipine at steps 3 and 5, and the addition of a diuretic at step 5. Roughly one-half of the

Table 3-4 Importance of Blood Pressure Control on Macrovascular and Microvascular Outcomes

Clinical Trial	Design/Goal
Appropriate Blood pressure Control in Diabetes (ABCD) Trial (Estacio et al. 1998, 2000)[29,30]	To compare the effects of intensive BP control (target dBP 75 mm Hg) to moderate BP control (target dBP 80–89 mm Hg) on complication rates in hypertensive patients; in secondary study, to compare an ACE inhibitor with a calcium-channel blocker in CV outcomes
United Kingdom Prospective Diabetes Study (UKPDS) Hypertension in Diabetes Study (UKPDS 1998)[31]	To determine whether tight BP control lowers complication risks, and to see whether there is any advantage in using ACE inhibitors vs. β-blockers
Systolic Hypertension in the Elderly Population (SHEP 1991)[32]	To assess the ability of antihypertensive drug treatment to reduce stroke risk in patients with isolated systolic hypertension

sBP, systolic blood pressure; dBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; MI, myocardial infarction; CV, cerebrovascular.

Results

- Both intensive and moderate approaches were associated with similar outcomes in terms of renal function, retinopathy, and neuropathy
- The ACE inhibitor enalapril was associated with a significantly lower risk of fatal and nonfatal MI versus the calcium-channel blocker nisoldipine

Tight control led to a mean BP of 144/82 vs 154/87 mm Hg in the control group; it also reduced complication risks as follows:

- Any diabetes-related endpoint by 24%
- MI by 21%
- Stroke by 44%
- Heart failure by 56%
- All macrovascular disease by 34%
- All microvascular endpoints by 37%

No significant advantage was seen using ACE inhibitors vs β-blockers

Treatment led to a 5-year average systolic BP of 143, vs. 155 in the placebo group. It was associated with:

- A stroke incidence of 5.2 (vs. 8.2 respectively) per 100 participants (relative risk [RR] 0.64).
- A reduction in RR for coronary heart disease of 25%
- An RR reduction of 54% for congestive heart failure
- An RR reduction of 32% for cardiovascular disease

study's patients (n = 9,399) also received aspirin (75 mg/day of acetylsalicylic acid). Aspirin treatment reduced major CV events by 15% and reduced all MI by 36% with no effect on stroke. The study also concluded that ≤ 80mm Hg diastolic BP was optimal for diabetes patients with hypertension.

In the Early Treatment Diabetic Retinopathy Study (ETDRS), researchers evaluated the effectiveness of laser photocoagulation and aspirin therapy for delaying or preventing progression of early diabetic retinopathy in 3,711 diabetes patients. Aspirin did not affect the progression of retinopathy, but neither did it increase the risk of vitreous hemorrhage. Moreover, it was associated with a relative all-cause mortality risk of 0.91 versus placebo and 0.83 for MI during follow-up.[10]

Finally, the Antithrombotic Trialists' (ATT) Collaboration conducted a meta-analysis of 287 studies involving 135,000 subjects to assess the value of aspirin and other antiplatelet therapy versus placebo in preventing serious vascular events, including MI and stroke, in patients at increased risk of such events (eg, those with acute or previous MI, ischemic stroke, angina, peripheral artery disease, or atrial fibrillation). Researchers concluded that antiplatelet therapy (typically with aspirin) reduced the combined risk of serious vascular events by about 25%. Risk of nonfatal MI dropped by about a third, nonfatal stroke by a quarter, and overall vascular mortality by roughly a sixth. In each of the high-risk categories, the benefits of therapy significantly outweighed the risks of major extracranial bleeding.[11]

DYSLIPIDEMIA

Dyslipidemia in patients with diabetes contributes to higher rates of cardiovascular disease, and subgroup analyses of numerous studies show that bringing lipids into more normal ranges reduces the risk of CV events and stroke—particularly in patients who have already suffered an MI or related problems.[12-14] The results of important studies—notably the CARE Trial[15] and the 4S Trial[16]—demonstrate the significant benefits of lipid management in reducing CV risk, as described in Table 3-5.

Table 3-5 Important Clinical Trials on Lipid Control in Macrovascular Outcomes

Clinical Trial	Design/Goal	Results
Scandinavian Simvastatin Survival Study (4S Group, 1994)[16]	To evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with CHD (subgroup analysis)	Simvastatin lowered total cholesterol by 25%; lowered LDL by 35%; raised HDL by 8% Simvastatin reduced risks as follows: ◢ Any death: 30% ◢ Coronary death: 42% ◢ Major coronary event: 34% Other benefits: ◢ 37% reduction in the risk of cardiac revascularization
Cholesterol And Recurrent Events (CARE) Trial (Goldberg, 1998)[15]	To determine whether lipid-lowering treatment with pravastatin prevents recurrent CV events in patients with diabetes (subgroup analysis)	Pravastatin lowered total cholesterol by 19%; lowered LDL by 26%; lowered triglycerides by 13%; raised HDL by 4%. Pravastatin reduced risks as follows: ◢ Fatal MI: 46% ◢ Nonfatal MI: 18% ◢ Total MI: 23% ◢ Overall CHD death: 3% ◢ CABG: 30% ◢ Stroke: 14%

(table continues)

Table 3-5 (continued)

Clinical Trial	Design/Goal	Results
Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT)[33]	To assess the effect of gemfibrozil on coronary outcomes (nonfatal MI or death from coronary causes) in subjects with coronary heart disease whose primary lipid abnormality is low HDL cholesterol	At one year, gemfibrozil resulted in a mean HDL that was higher by 6%, a mean triglyceride level 31% lower, and a mean total cholesterol 4% lower versus placebo. Gemfibrozil treatment was also associated with: ▲ A 4.4% overall reduction in risk of a primary event (events in 17.3% of gemfibrozil patients vs. 21.7% of those treated with placebo), which constituted a 22% reduction in relative risk ▲ A 24% reduction in combined outcome of death from coronary heart disease, nonfatal MI, and stroke. Subsequent analysis confirmed that only the reduction in HDL-C significantly predicted a lower risk of CHD events.

(table continues)

Table 3-5 (continued)

Clinical Trial	Design/Goal	Results
Air Force/ Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS)[34]	To compare lovastatin to placebo for preventing a first acute major coronary event in men and women without atherosclerotic CV disease who have average total and LDL cholesterol but below-average HDL-C.	After an average 5.2-year follow-up, lovastatin reduced LDL-C by 25% and increased HDL-C by 6%. Its effect on risks, versus placebo, was as follows: ◢ For a first major coronary event, 116 vs. 183 (relative risk [RR] 0.63) ◢ MI, 57 vs. 95, RR 0.60 ◢ Unstable angina, 60 vs. 87, RR 0.68 ◢ Coronary revascularization, 106 vs. 157, RR 0.67 ◢ Cardiovascular events, 194 vs. 255, RR 0.75

CV, cerebrovascular; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MI, myocardial infarction; CHD, coronary heart disease; CABG, coronary artery bypass graft.

SPECIAL CONSIDERATIONS

A variety of accessible approaches can decrease diabetes-related complications. Among these are smoking cessation and immunization. The following sections outline the evidence for these approaches.[17]

Smoking Cessation

Smoking increases morbidity and premature death due to cardiovascular and pulmonary disease.[18] Although the link between smoking and health risks is well documented in all populations, patients with diabetes, and who smoke, are particularly vulnerable to the development and exacerbation of both macrovascular and microvascular complications,[17] as shown in Tables 3-6 and 3-7.

Smoking increases the risk for diabetes[19,20] and appears to aggravate insulin resistance.[21,22] As such, substantial evidence exists for strong encouragement of smoking cessation in patients with diabetes.

Table 3-6 Smoking and Other Risk Factors in Macrovascular Complications in Diabetes

Clinical Trial	Design/Goal	Results
Moy et al. (1990)[35]; Uusitupa et al. (1993)[36]; Manson et al. (1991)[37]; Stamler et al. (1993)[38]	To examine the relationship of diabetes-related risk factors and smoking to CV complications	Patients with diabetes who smoke are at increased risk of CV-related morbidity and mortality versus the general population, particularly in the presence of other risk factors such as hypertension and dyslipidemia
Tuomilehto et al. (1996)[39]	To assess diabetes as a primary risk factor for stroke and determine the relative importance of other risk factors	Although diabetes itself was the strongest risk factor for stroke, smoking, and sBP were also independent risk factors

sBP, systolic blood pressure; CV, cerebrovascular.

Table 3-7 Smoking and Other Risk Factors in Microvascular Complications in Diabetes

Clinical Trial	Design/Goal	Results
Muhlhauser et al. (1996)[40]; Klein et al. (1989)[41]; Ritz et al. (1996)[42]; Chase et al. (1991)[43]	To determine the relationship of smoking to other risk factors for microvascular complications	Smoking—particularly in the presence of other risk factors—increases the risk of both retinal and renal complications, including albuminuria and nephropathy. Chase et al found that albuminuria improves significantly when patients discontinue smoking.
Tesfaye et al. (1996)[44]; Maser et al. (1989)[45]; Mitchell et al. (1990)[46]; Sands et al. (1997)[47]	To evaluate the most important risk factors for the development and progression of neuropathy in patients with diabetes	Smoking increases the risk of neuropathy development and progression, as do other risk factors, including metabolic control, age, diabetes duration, CV disease, dyslipidemia, and history of MI. Mitchell et al found that in patients with type 1 diabetes, heavy smokers were three times more likely to have neuropathy than those who smoked less or not at all.

CV, cerebrovascular; MI, myocardial infarction.

Immunization

Influenza and pneumonia take an especially high toll on those with chronic diseases such as diabetes, particularly among the elderly. Based on clinical studies, outlined in Table 3-8, and on professional consensus, the importance of immunization for patients with diabetes should be emphasized.[16]

Table 3-8 Immunization and Diabetes

Clinical Trial	Design/Goal	Results
Housworth and Langmuir (1974)[48]; Cameron et al. (1985)[49]; Bouter et al. (1991)[50]	To examine trends in hospitalization and mortality related to influenza	Patients with diabetes face up to twice the relative risk of death from influenza or its complications
Bouter et al. (1991)[50]	To examine trends in hospitalization and mortality related to influenza, particularly in epidemic years	During epidemic years, patients with diabetes were six times more likely to be admitted than age- and sex-matched nondiabetic controls; they were also much more likely to develop ketoacidosis
Colquhoun et al. (1997)[51]	To assess the effectiveness of flu vaccination for reducing hospitalization of patients with diabetes during flu epidemics	During epidemics, vaccination reduced diabetes-related hospital admission by 79%

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