Glucose Goals and Complications Management for Type 2 Diabetes
Type 2 Diabetes Glucose Goals and Complications Management

INDIVIDUALIZED GOALS
### AACE Comprehensive Diabetes Care: Glucose Goals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Goal for Nonpregnant Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>Individualize targets:</td>
</tr>
<tr>
<td></td>
<td>• ≤6.5 if it can be achieved without substantial hypoglycemia or other unacceptable consequences</td>
</tr>
<tr>
<td></td>
<td>• &gt;6.5% to 8% for those at risk*</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>&lt;110</td>
</tr>
<tr>
<td>2-hour PPG (mg/dL)</td>
<td>&lt;140</td>
</tr>
</tbody>
</table>

*As long as patient remains free of polydipsia, polyuria, polyphagia, or other symptoms of hyperglycemia. Factors indicating a higher A1C target include:

- Risk for hypoglycemia
- History of severe hypoglycemia
- Limited life expectancy

- Long-standing T2D in which the A1C goal has been difficult to attain despite intensive efforts

# Algorithm for Individualizing Glycemic Targets

<table>
<thead>
<tr>
<th>Most intensive</th>
<th>Less intensive</th>
<th>Least intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0%</td>
<td>7.0%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

**Psychosocioeconomic considerations**
- Highly motivated, adherent, knowledgeable, excellent self-care capacities, and comprehensive support systems
- Less motivated, nonadherent, limited insight, poor self-care capacities, and weak support systems

**Hypoglycemia risk**
- Low
- Moderate
- High

**Patient age, years**
- 40
- 45
- 50
- 55
- 60
- 65
- 70
- 75

**Disease duration, years**
- 5
- 10
- 15
- 20

**Other comorbid conditions**
- None
- Few or mild
- Multiple or severe

**Established vascular complications**
- None
- Cardiovascular disease
- Early microvascular
- Advanced microvascular

---

## ADA-Recommended Glucose Goals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Goal for Nonpregnant Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>Individualize</td>
</tr>
<tr>
<td></td>
<td>• &lt;7.0% for most nonpregnant adults</td>
</tr>
<tr>
<td></td>
<td>• &lt;6.5 if it can be achieved without significant hypoglycemia or other adverse effects of treatment*</td>
</tr>
<tr>
<td></td>
<td>• &lt;8% for those at risk†</td>
</tr>
<tr>
<td>Preprandial glucose (mg/dL)</td>
<td>80-130</td>
</tr>
<tr>
<td>Peak postprandial glucose (mg/dL)</td>
<td>&lt;180</td>
</tr>
</tbody>
</table>

*Appropriate patients
- Short duration of diabetes
- T2D treated only with lifestyle or metformin
- Long life expectancy
- No significant cardiovascular disease

†At risk patients
- History of severe hypoglycemia
- Limited life expectancy
- Advanced micro- or macrovascular complications
- Extensive comorbid conditions
- Long-standing T2D in which A1C goal has been difficult to attain despite intensive efforts
# ADA-Recommended Approach to Management of Hyperglycemia

<table>
<thead>
<tr>
<th>More stringent</th>
<th>A1C 7%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks potentially associated with hypoglycemia, other drug adverse events</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Disease duration</strong></td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td><strong>Life expectancy</strong></td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td><strong>Important comorbidities</strong></td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td><strong>Established vascular complications</strong></td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td><strong>Patient attitude and expected treatment efforts</strong></td>
<td>Highly motivated, adherent, excellent self-care capacities</td>
<td>Less motivated, nonadherent, poor self-care capacities</td>
</tr>
<tr>
<td><strong>Resources, support system</strong></td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

* ADA. *Diabetes Care.* 2018;41:S55-S64.*
Risk Factors for Hypoglycemia

Well-Known Risks

- Use of insulin secretagogues or insulin therapy in any of the following settings:
  - Missed or irregular meals
  - Advanced age
  - Longer duration of diabetes
  - Impaired awareness of hypoglycemia
  - Exercise
  - Taking greater than the prescribed medication dose
  - Excessive alcohol intake
  - Preexisting impairment, or sudden worsening, of renal or hepatic function

Less Well-Known Risks

- Female sex
- African-American race
- Lower education level

Potential Consequences of Hypoglycemia

• Neurogenic symptoms
  – Tremor, palpitations, anxiety, sweating, hunger (weight gain), paresthesias
• Neuroglycopenia morbidity
  – Cognitive impairment, psychomotor abnormalities, abnormal behavior, seizure, coma, mortality (brain death)
• Rebound hyperglycemia, brittle diabetes
• Barrier to glycemic control and adherence to treatment secondary to fear of hypoglycemia
• Greater risk of dementia
• Prolonged QT interval with increased risk of dysrhythmias, sudden death
• Harm to property or to others (eg, if driving)
Hypoglycemia and Mortality

ACCORD Posthoc Analysis

Risk of Hypoglycemia with Each 1% Change in Updated A1C

Risk of Mortality in Patients with Severe Hypoglycemia

1% Decrease  1% Increase

14%  28%  76%  15%

2.9X

Standard
Intensive

28%
Glucose Control and Mortality

ACCORD Posthoc Analysis

Adjusted Log (Hazard Ratio) by Treatment Strategy Relative to Standard at A1C of 6%

Risk increase with each 1% increase in A1C

*P* Value

66% <0.0001

14% 0.17

A1C and Mortality in Clinical Practice

Retrospective Cohort Study
(N=27,965)
Macrovascular Benefits of Glycemic Control Depend on Duration of Diabetes

Veterans Affairs Diabetes Trial

Effect of intensive glycemic control

Hazard ratio
Years with diabetes

Neutral
Reduced risk
Neutral
Elevated risk

VADT, Veterans Affairs Diabetes Trial.
Type 2 Diabetes Glucose Goals and Complications Management

MICROVASCULAR COMPLICATIONS
Hyperglycemia-Induced Tissue Damage: General Features

- Genetic determinants of individual susceptibility
- Repeated acute changes in cellular metabolism
- Cumulative long-term changes in stable macromolecules
- Independent accelerating factors (e.g., hypertension, dyslipidemia)
- Diabetic tissue damage

Microvascular Complications of Diabetes

Nephropathy

Retinopathy

Neuropathy
Microvascular Complications Increase With Increasing A1C

Diabetes Control and Complications Trial

Reducing A1C Reduces Microvascular Risk

United Kingdom Prospective Diabetes Study

37% Decrease per 1% reduction in A1C

Prevalence of CKD in Diagnosed Diabetes

Diabetic Kidney Disease Is the Leading Cause of Kidney Failure in the United States

NKF Stage | Description | GFR
---|---|---
1 | Kidney damage* with normal or ↑ GFR | ≥90
2 | Kidney damage* with mild ↓ GFR | 60-89
3 | Moderate ↓ GFR | 30-59
4 | Severe ↓ GFR | 15-29
5 | Kidney failure or ESRD | <15 or dialysis

*Pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

ESRD, end-stage renal disease; GFR, glomerular filtration rate (mL/min/1.73 m²); NKF, National Kidney Foundation.


Development of Diabetic Nephropathy

- Genetically susceptible individuals
  - Hyperglycemia
  - Hypertension
  - Angiotensin II

- Hyperfiltration
  - Enlarged kidneys

- Breakdown of glomerular filtration barrier
  - Micro-albuminuria

- Decreasing GFR
  - Macro-albuminuria

- Protein reabsorption and accumulation in renal epithelial cells
- Capillary occlusion
- Tubule and podocyte damage
- Tubular atrophy and fibrosis, podocyte destruction
- Renal failure

References:
CV Risk Increases With Comorbid Diabetes and CKD

AMI, acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; PVD, peripheral vascular disease.

*ASVD was defined as the first occurrence of AMI, CVA/TIA, or PVD.

Risk of Cardiovascular Mortality with Decreasing eGFR and Increasing Albuminuria

ACR = albumin-creatinine ratio; eGFR = estimated glomerular filtration rate.
# KDIGO CKD Classification by Relative Risk

<table>
<thead>
<tr>
<th>Albuminuria stages (mg/g)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal and high normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-299</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300-1999</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≥2000</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high and nephrotic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR stages (mL/min per 1.73 m² body surface area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 High and optimal</td>
</tr>
<tr>
<td>&gt;105</td>
</tr>
<tr>
<td>90-104</td>
</tr>
<tr>
<td>Very low</td>
</tr>
<tr>
<td>Very low</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>G2 Mild</td>
</tr>
<tr>
<td>75-89</td>
</tr>
<tr>
<td>60-74</td>
</tr>
<tr>
<td>Very low</td>
</tr>
<tr>
<td>Very low</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>G3a Mild to moderate</td>
</tr>
<tr>
<td>45-59</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>G3b Moderate to severe</td>
</tr>
<tr>
<td>30-44</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>G4 Severe</td>
</tr>
<tr>
<td>15-29</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>G5 Kidney failure</td>
</tr>
<tr>
<td>&lt;15</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>Very high</td>
</tr>
<tr>
<td>Very high</td>
</tr>
</tbody>
</table>

Staging and Monitoring of CKD in Diabetes

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Normal to mildly increased</td>
</tr>
<tr>
<td>A2</td>
<td>Moderately increased</td>
</tr>
<tr>
<td>A3</td>
<td>Severely increased</td>
</tr>
<tr>
<td>30 mg/g &lt;3 mg/mmol</td>
<td>30-300 mg/g 3-30 mg/mmol</td>
</tr>
<tr>
<td>&gt;300 mg/g &gt;30 mg/mmol</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous NKF CKD stage</th>
<th>Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G1 Normal or high ≥90 1 if CKD 1 2</td>
</tr>
<tr>
<td>2</td>
<td>G2 Mildly decreased 60-89 1 if CKD 1 2</td>
</tr>
<tr>
<td>3</td>
<td>G3a Mild to moderately decreased 45-59 1 2 3</td>
</tr>
<tr>
<td></td>
<td>G3b Moderately to severely decreased 30-44 2 3 3</td>
</tr>
<tr>
<td>4</td>
<td>G4 Severely decreased 15-29 3 3 4+</td>
</tr>
<tr>
<td>5</td>
<td>G5 Kidney failure &lt;15 4+ 4+ 4+</td>
</tr>
</tbody>
</table>

CKD = chronic kidney disease; GFR = glomerular filtration rate; NKF = National Kidney Foundation.
Reducing A1C Reduces Nephropathy Risk in T2D

A1C reduction (%)*
- UKPDS: 0.9
- ADVANCE: 0.8
- ACCORD: 1.3

Nephropathy risk reduction (%)*
- UKPDS: 30
- ADVANCE: 21
- ACCORD: 21

- New onset microalbuminuria ($P=0.033$)
- New or worsening nephropathy ($P=0.006$)
- New microalbuminuria ($P=0.0005$)

*Intensive vs standard glucose control.

Management of Diabetic Nephropathy

• Optimal control of blood pressure, glucose, and lipids
• Smoking cessation
• RAAS blockade
  – ACE inhibitor, ARB, or renin inhibitor
  – Do not combine RAAS blocking agents
  – Monitor serum potassium
• Nephrologist referral
  – Atypical presentation
  – Rapid decline in eGFR or albuminuria progression
  – Stage 4 CKD

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAAS = renin angiotensin aldosterone system.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal</th>
<th>Management Recommendation</th>
</tr>
</thead>
</table>
| Hyperglycemia | Individualized A1C goals ≤6.5% for most (AACE) ~7.0% (NKF)           | Avoid metformin in moderate to severe CKD  
Consider need for dose reductions and/or risk of hypoglycemia and other renal-related AEs with other antidiabetic agents  
Do not target A1C <7% in patients at risk of hypoglycemia |
| Hypertension | BP ~130/80 mmHg                                                       | Use ACE inhibitor or ARB in combination with other antihypertensive agents as needed         |
| Proteinuria  |                                                                      | Use ACE inhibitor or ARB as directed                                                        |
| Dyslipidemia | LDL-C <100 mg/dL, <70 mg/dL an option for high risk                   | Statin +/- ezetimibe therapy recommended for all patients except those on dialysis (NKF)   
Fibrate dose reduction may be required                  |
# Use of Antihyperglycemic Agents in Kidney Disease

<table>
<thead>
<tr>
<th>Class: Agent(s)</th>
<th>Kidney Disease Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylin analog: pramlintide</td>
<td>Not recommended for CKD stage ≥4</td>
</tr>
<tr>
<td>Biguanide: metformin</td>
<td>Contraindicated if SCr &gt;1.5 (men) or 1.4 (women) mg/dL</td>
</tr>
<tr>
<td>Bile acid sequestrant: colesvelam</td>
<td>No dosage adjustment</td>
</tr>
<tr>
<td>Dopamine-2 agonist: bromocriptine</td>
<td>Use with caution</td>
</tr>
<tr>
<td>DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin</td>
<td>Reduce dosage for alogliptin, saxagliptin and sitagliptin if CrCl &lt;50 mg/dL</td>
</tr>
<tr>
<td>Glinides: nateglinide, repaglinide</td>
<td>Start at lowest effective dose if GFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>GLP-1 receptor agonists: albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide</td>
<td>Exenatide and liraglutide not recommended with GFR &lt;30 mL/min/</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors: acarbose, miglitol</td>
<td>Avoid if GFR &lt;25 (miglitol) or &lt;30 (acarbose) mL/min/1.73 m²</td>
</tr>
<tr>
<td>Insulin: aspart, detemir, glargine, glulisine, inhaled, lispro, NPH, regular</td>
<td>Adjust dose based on patient response</td>
</tr>
<tr>
<td>SGLT inhibitors: canagliflozin, dapagliflozin, empagliflozin</td>
<td>Ineffective if GFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Sulfonylureas: glimepiride, glipizide, glyburide</td>
<td>No dose adjustment for glipizide; start glimepiride conservatively; avoid glyburide and all other SUs</td>
</tr>
<tr>
<td>Thiazolidinediones: pioglitazone, rosiglitazone</td>
<td>No dosage adjustment</td>
</tr>
</tbody>
</table>

## Dietary Guidelines for DKD

<table>
<thead>
<tr>
<th>Macronutrient</th>
<th>CKD Stage</th>
<th>CKD Stage</th>
<th>CKD Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>1-2</td>
<td>1-4</td>
<td>3-4</td>
</tr>
<tr>
<td>Total fat, % calories*</td>
<td>&lt;2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated fat, % calories</td>
<td>&lt;30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/day</td>
<td>&lt;200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate, % calories</td>
<td>50-60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein, g/kg/day (% calories)</td>
<td>0.8 (~10)</td>
<td>0.6-0.8 (~8-10)</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.7</td>
<td></td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Potassium</td>
<td>&gt;4</td>
<td>2.4</td>
<td></td>
</tr>
</tbody>
</table>

*Adjust so total calories from protein, fat, and carbohydrate are 100%.

Emphasize such whole-food sources as fresh vegetables, whole grains, nuts, legumes, low-fat or nonfat dairy products, canola oil, olive oil, cold-water fish, and poultry.

Tailor dietary counseling to cultural food preferences.

Diabetic Retinopathy

NHANES 2005-2008
Adults Age ≥40 Years (N=1006)

- None, 71.5%
- NPDR, 24.1%
- Vision-threatening*, 4.4%

- All T2D patients should have a dilated eye examination by experienced ophthalmologist annually, starting at diagnosis to detect clinically significant retinopathy before vision is threatened

- Lesion types
  - Background or nonproliferative retinopathy
  - Macular edema
  - Preproliferative retinopathy
  - Proliferative retinopathy

*Severe NPDR, PDR, or clinically significant macular edema.

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T2D, type 2 diabetes.

Reducing A1C Reduces Retinopathy Progression in T2D

A1C reduction (%)

UKPDS

ACCORD

Retinopathy risk reduction (%)*

0.9

1.3

29

17

33

Retinopathy onset (P=0.003)

Retinopathy progression (P=0.017)

Retinopathy progression (P=0.003)

*Intensive vs standard glucose control.


Assessment of Diabetic Retinopathy

- Annual dilated eye examination by experienced ophthalmologist or optometrist
- Begin assessment
  - 5 years after diagnosis of T1D
  - At diagnosis of T2D
- More frequent examinations for:
  - Pregnant women with DM during pregnancy and 1 year postpartum
  - Patients with diagnosed retinopathy
  - Patients with macular edema receiving active therapy
## Diabetic Retinopathy Management

- **Goal:** detect clinically significant retinopathy before vision is threatened
- **Annual dilated eye examination by experienced ophthalmologist, starting at diagnosis for all T2D patients**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Management Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background or nonproliferative retinopathy</td>
<td>• Optimal glucose and blood pressure control</td>
</tr>
<tr>
<td>Macular edema</td>
<td>• Optimal glucose and blood pressure control</td>
</tr>
<tr>
<td></td>
<td>• Ranibizumab injection therapy</td>
</tr>
<tr>
<td></td>
<td>• Focused laser photocoagulation guided by fluorescein angiography</td>
</tr>
<tr>
<td>Preproliferative retinopathy</td>
<td>• Optimal glucose and blood pressure control</td>
</tr>
<tr>
<td></td>
<td>• Panretinal scatter laser photocoagulation</td>
</tr>
<tr>
<td>Proliferative retinopathy</td>
<td>• Optimal glucose and blood pressure control</td>
</tr>
<tr>
<td></td>
<td>• Panretinal scatter laser photocoagulation</td>
</tr>
<tr>
<td></td>
<td>• Vitrectomy for patients with persistent vitreous hemorrhage or significant vitreous scarring and debris</td>
</tr>
</tbody>
</table>
Prevalence of Diabetic Neuropathy

NHANES 1999-2004
Adults With Diabetes, Age ≥40 Years (N=559)

- Neuropathy is a heterogeneous disorder
- 70% to 100% of T2D patients may have at least mild damage to
  - Proximal nerves
  - Distal nerves
  - Somatic nerves
  - Autonomic nerves
- Neuropathy may be
  - Acute and self-limiting
  - Chronic and indolent

T2D, type 2 diabetes.
Causes of Death in Diabetic Autonomic Neuropathy

- Sudden unexplained
- Cardiac arrhythmia
- Silent myocardial infarction
  - More likely to die of heart attack
  - Greater incidence of cardiac failure
- Aspiration pneumonia
- Ulcers, amputations, gangrene
- Chronic renal failure
Relative Risk of Mortality from Cardiac Autonomic Neuropathy

Prevalence Rate Ratios and 95% CI from 15 Studies

(P<0.0001; N=2900)

Study 1
Study 2
Study 3
Study 4
Study 5
Study 6
Study 7
Study 8
Study 9
Study 10
Study 11
Study 12
Study 13
Study 14
Study 15

Pooled Data

Log Relative Risk

2.14 (1.83-2.51); 3.45 if >2 abnormalities

Reducing A1C Reduces Neuropathy Risk in T2D

**ACCORD**

A1C reduction (%)

1.3

Neuropathy risk reduction (%)*

12

Loss of sensation to light touch

(P=0.045)

*Intensive vs standard glucose control.

Assessment of Diabetic Neuropathy

- Complete neurologic examination annually
- Begin assessment
  - 5 years after diagnosis of T1D
  - At diagnosis of T2D

# Diabetic Neuropathy Evaluations and Tests

| Foot inspection            | Foot structure and deformities  
|                           | Skin temperature and integrity  
|                           | Ulcers                           
|                           | Vascular status                  
|                           | Pedal pulses                     
|                           | Amputations                      |
| Neurologic testing        | Loss of sensation, using 1 and 10-g monofilament  
|                           | Vibration perception using 128-Hz tuning fork  
|                           | Ankle reflexes                   
|                           | Touch, pinprick, and warm and cold sensation |
| Painful neuropathy        | May have no physical signs       
|                           | Diagnosis may require skin biopsy or other surrogate measure |
| Cardiovascular autonomic neuropathy | Heart rate variability with:  
|                           | • Deep inspiration               
|                           | • Valsalva maneuver              
|                           | • Change in position from prone to standing |
## Diabetic Neuropathy Management

### All neuropathies
- Prevent by controlling blood glucose to individual targets
- No therapies proven to reverse neuropathy once it is established
- May slow progression by maintaining optimal glucose, blood pressure, and lipid control and using other interventions that reduce oxidative stress

### Painful neuropathy
- Tricyclic antidepressants, anticonvulsants, serotonin reuptake inhibitors, or norepinephrine reuptake inhibitors

### Large-fiber neuropathies
- Strength, gait, and balance training
- Orthotics to prevent/treat foot deformities
- Tendon lengthening for pes equinus
- Surgical reconstruction
- Casting

### Small-fiber neuropathies
- Foot protection (eg, padded socks)
- Supportive shoes with orthotics if needed
- Regular foot inspection
- Prevention of heat injury
- Emollient creams

Type 2 Diabetes Glucose Goals and Complications Management

MACROVASCULAR COMPLICATIONS
Macrovascular Complications

- Cardiovascular disease
  - Coronary artery disease
  - Myocardial infarction
- Cerebrovascular disease (stroke)
- Peripheral vascular disease
Diabetes and Cardiovascular Risk

<table>
<thead>
<tr>
<th></th>
<th>No prior MI</th>
<th>Prior MI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without diabetes</td>
<td>3.5</td>
<td>18.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=1373)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>20.2</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n=1059)</td>
<td></td>
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</tr>
</tbody>
</table>

MI, myocardial infarction.
Lower A1C Is Associated With Lower Risk of Myocardial Infarction

United Kingdom Prospective Diabetes Study

14% Decrease per 1% reduction in A1C

Hazard Ratio

Updated Mean A1C

P<0.0001

### Effect of Intensive Glycemic Control on Macrovascular Risk in Older Patients With Longer Duration of Disease

<table>
<thead>
<tr>
<th>T2DM duration (years)</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.9</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A1C reduction (%)*</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.8</td>
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<td></td>
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<tr>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Macrovascular risk (%)*</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td></td>
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</tr>
<tr>
<td>6</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
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<td></td>
</tr>
</tbody>
</table>

*Intensive vs standard glucose control.

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction; PVD, peripheral vascular disease; VADT, Veterans Affairs Diabetes Trial.

Intensive Glycemic Control May Have Macrovascular Benefit in Healthier People

**Action to Control Cardiovascular Risk in Diabetes**

<table>
<thead>
<tr>
<th>Secondary endpoint (nonfatal MI; entire cohort)</th>
<th>Primary endpoint (CV death, nonfatal MI, nonfatal stroke) subgroup analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk reduction (%)*</td>
<td>Baseline A1C ≤8%</td>
</tr>
<tr>
<td></td>
<td>No prior CV events</td>
</tr>
<tr>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>*Intensive vs standard glucose control.</td>
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</tr>
</tbody>
</table>

CV, cardiovascular; MI, myocardial infarction.

Intensive Glycemic Control Reduces Long-term Macrovascular Risk

DCCT
T1D, 5-6 years duration
(N=1441)

42% risk reduction
P=0.02

UKPDS
T2D, newly diagnosed
(N=4209)

15% risk reduction
P=0.01

CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction;
T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

Long-Term Effect of Intensive Glycemic Control on Macrovascular Risk

VADT Follow-up Study

VADT, Veterans Affairs Diabetes Trial.
Effects of Intensive Glucose Control on Macrovascular Risk in T2D

Meta-analysis of 5 Prospective RCTs Assessing Effect of Intensive Glucose Lowering on CV Outcomes
(ACCORD, ADVANCE, PROactive, UKPDS, VADT)

<table>
<thead>
<tr>
<th>Event</th>
<th>Odds ratio</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI</td>
<td>0.83 (0.75-0.93)</td>
<td>-17%</td>
</tr>
<tr>
<td>Any CHD event</td>
<td>0.85 (0.77-0.93)</td>
<td>-15%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.93 (0.81-1.06)</td>
<td>-7% (NS)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.02 (0.87-1.19)</td>
<td>+2% (NS)</td>
</tr>
</tbody>
</table>

Intensive treatment better Standard treatment better

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; NS, not significant; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Macrovascular Risk Reduction in Type 2 Diabetes

- Individualized glucose control
- Hypertension control
- Dyslipidemia control
- Smoking cessation
- Aspirin therapy
- Diagnosis and management of:
  - Autonomic cardiac neuropathy
  - Kidney disease