# Current Controversies in Diabetes Control

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## ADA, AACE/ACE, and ACP Guidelines: Treatment Goals for A1C, FPG, and PPG

| Parameter | Normal[1,2] Level | ADA[3] Goal | AACE/ACE[2] Goal | ACP[4] Goal |
|---|---|---|---|---|
| FPG, mg/dL | <100 | 70–130 | <110 | — |
| PPG, mg/dL | <140 | <180 | <140 | — |
| A1C, % | 4–6 | <7 | ≤6.5 | <7 |

**ADA: The goal for an individual patient is to achieve an A1C as close to normal (<6%) as possible without significant hypoglycemia. Less stringent A1C goals may be appropriate for certain patients with a history of severe hypoglycemia, patients with limited life expectancies, children, patients with comorbid conditions, and patients with long-standing diabetes and minimal or stable microvascular complications.**

**ACP: An A1C <7% based on individualized assessment is a reasonable goal for many, but not all, patients. This goal should be based on individualized assessment of risk of complications from diabetes, comorbidity, life expectancy, and patient preferences.**

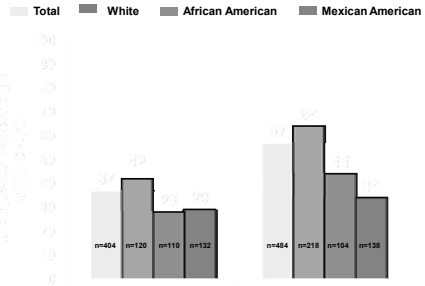
AACE=American Association of Clinical Endocrinologists; ACE=American College of Endocrinology; ACP=American College of Physicians; ADA=American Diabetes Association; FPG=fasting plasma glucose; PPG=postprandial glucose.

1. Adapted from Buse JB et al. In: *Williams Textbook of Endocrinology*. 11th ed. 2008. Copyright © 2008 Elsevier.
2. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. *Endocr Pract*. 2007;13(suppl 1):3–68.
3. ADA. *Diabetes Care*. 2008;30(suppl 1):S12–S54
4. Quaseem A et al. *Ann Int Med*. 2007;147(6):417–422.

# Objectives

- Review current controversies in tight diabetes control
- Discuss best practices for diabetes control of Outpatients
- Review of the studies to support the consensus statement

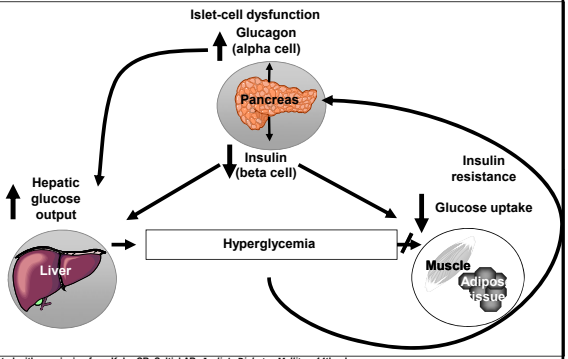
## Trends in A1C in Adults With Diagnosed Diabetes: Percentage of A1C <7%




NHANES=National Health and Nutrition Examination Survey.
Ford ES et al. *Diabetes Care*. 2008;31(1):102–104.

# Why is diabetes so difficult to manage?

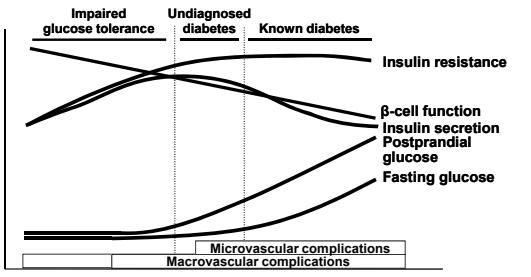
## Major Pathophysiologic Defects in T2DM




Adapted with permission from Kahn CR, Saltiel AR. *Joslin's Diabetes Mellitus*. 14th ed. Lippincott Williams & Wilkins; 2005:145–168.
1. Del Prato S, Marchetti P. *Horm Metab Res*. 2004;36:775–781. 2. Porte D Jr, Kahn SE. *Clin Invest Med*. 1995;18:247–254.

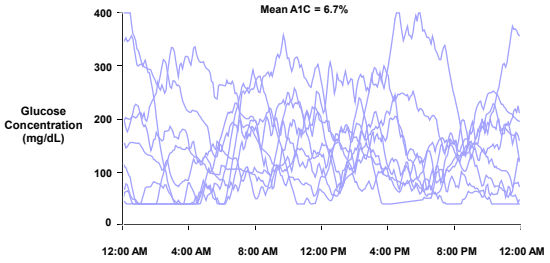
## The Natural History of T2DM

Decreasing Insulin Secretion in the Context of Insulin Resistance Leads to Increases in Blood Glucose and Diabetes Complications



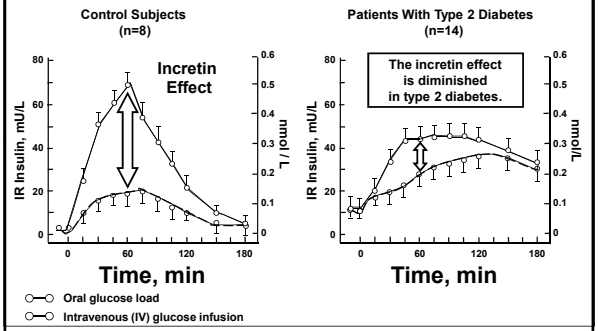

Adapted from Ramlo-Halsted BA, et al. *Prim Care*. 1999;26:771-789. Reproduced with permission from Elsevier and the Council for the Advancement of Diabetes Research and Education (CADRE).

## Excessive Glucose Fluctuations



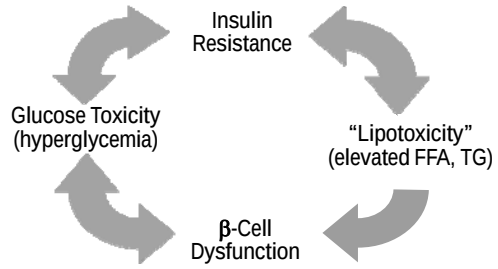

24-hour CGMS glucose sensor data
Type 1 diabetes (N=9)

## The Incretin Effect in Subjects Without & With Type 2 Diabetes




Adapted with permission from Nauck M et al. *Diabetologia*. 1986;29:46–52. Copyright © 1986 Springer-Verlag.

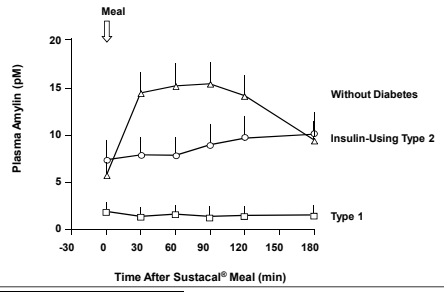
## Factors That Contribute to Progressive Nature of Type 2 Diabetes




FFA = free fatty acids; TG = triglycerides.

Kahn SE. *J Clin Endocrinol Metab*. 2001;86:4047-4058.
Ludwig DS. *JAMA*. 2002;287:2414-2423.

## Amylin is Deficient in Diabetes




Without diabetes (n=27)
Insulin-using type 2 (n=12)
Type 1 (n=190)

Data from Kruger D, et al. *Diabetes Educ* 1999; 25:389-398

## Conflicts for Inpatient Blood Glucose Management

- **What is the best range of glucose for the inpatient?**
- **What should be done for the nondiabetic hyperglycemic patient?**

# Diabetes in Hospitalized Patients

- At least 4 million patients with diagnosed diabetes are admitted to hospitals annually in the United States
- In 2000, 12.4% of hospital discharges in the United States listed diabetes as a diagnosis
- Prevalence of diabetes estimated at 12%–25% of hospitalized patients and may be significantly underestimated

Centers for Disease Control 2004.
American Diabetes Association. *Diabetes Care*. 2005;28(suppl 1):S4-S36.

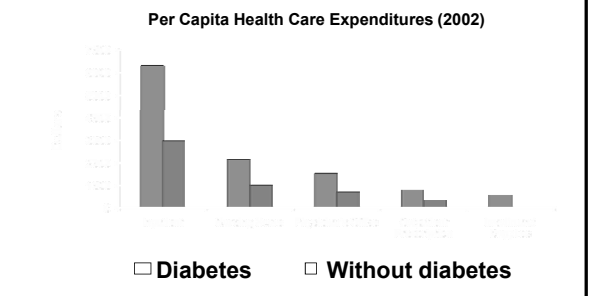
# Consequences of Poor Glycemic Control in Hospital Patients

Hyperglycemia, with or without a diagnosis of diabetes, can result in:

- Mortality
- ICU Admission
- Need for extended care
- Overall poor outcomes

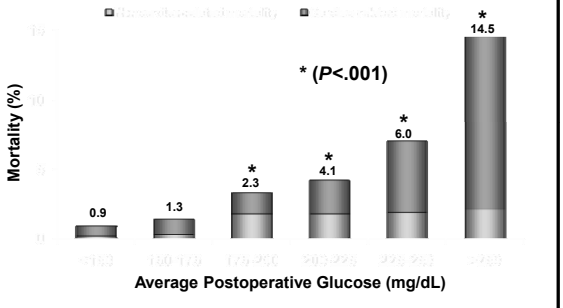
Umpierrez GE et al. *J Clin Endocrinol Metab*. 2002;87:978-982. Bolk J et al. *Int J Cardiol*. 2001;79:207-214. Williams LS et al. *Neurology*. 2002;59:67-71. Malmberg K, et al. *BMJ*. 1997;314:1512. Van den Berghe G et al. *N Engl J Med*. 2001;345:1359-1367. Capes SE et al. *Stroke*. 2001;32:2426-2432.

# Hospital Costs Account for Majority of Total Costs of Diabetes




ADA. *Diabetes Care*. 2003;26:917–932.

# Postoperative Glycemic Control Correlates With Reduced Cardiac-Related Mortality




Furnary AP et al. *J Thorac Cardiovasc Surg*. 2003;125:1007-1021.

## Recent Reports in the Surgical Literature

- **Bone joint surg am. 2008 90(1):62. Preop and 5d postop glucose higher in patients with surg site infection. Hba1c linked to complication with joint replacement**
- **Ann surg 2008 247(2):380. Opportunities for improvement for better clinical outcomes. Joint replace, chole, hyster, vascular**
- **Thorac cardiovasc surg 2008. 136(3):631. Preop Hba1c assoc with mortality, renal failure, CVA, MI, DSWI. Hba1c>8.6 4 fold increase in mortality.**
- **Am J Infect Control 2008 36(3):192. Mastectomy operations – higher glucose independent risk for SSI**

The NEW ENGLAND JOURNAL of MEDICINE

MARCH 26, 2009

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

ABSTRACT

BACKGROUND

The optimal target range for blood glucose in critically ill patients remains unclear.

METHODS

Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). We defined the primary end point as death from any cause within 90 days after randomization.

RESULTS

Of the 6104 patients who underwent randomization, 1054 were assigned to undergo intensive control and 1050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 1031 and 1012 patients, respectively. The two groups had similar characteristics at baseline. A total of 829 patients

## Previous Goals for Upper Limits of Glucose Levels for Optimal Glycemic Control

| Patients | Preprandial | Postprandial | Labor and Delivery |
|---|---|---|---|
| Critical (ICU) | 110 mg/dL | 110 mg/dL | |
| Noncritical | 110 mg/dL | 180 mg/dL | |
| Pregnancy | 100 mg/dL | 120 mg/dL* | 100 mg/dL |

American College of Endocrinology. *Endocr Pract*. 2004;10(suppl 2):4-9.

Preiser et.al. *Crit Care Med 2007, 35(9)suppl 503*. Improvement in outcomes consistently assoc 140-150mg/dl. Variability of glucose issue

## *The AACE/ADA recommendations 2009 for Hospitalized Patients*

- **A target of 140-180 mg/dl is preferable for MOST patients.**
- **A target of 110-140 mg/dl may be appropriate in SELECTED patients (patients treated in sites with extensive experience and appropriate support: perhaps CABG surgical patients, sites with low rates of hypoglycemia, patients on TPN etc).**
- **A target > 180 mg/d/ or < 110 mg/dl is NOT recommended.**

# Hyperglycemia in Patients With Undiagnosed Diabetes

- **Hyperglycemia occurred in 38% of patients admitted to the hospital**
  - ✓ **26% had known history of DM**
  - ✓ **12% had no history of DM**
- **Newly discovered hyperglycemia associated with:**
  - ✓ **Higher in-hospital mortality rate (16%) compared with patients with a history of DM (3%) and patients with normoglycemia (1.7%; both *P*<.01)**
  - ✓ **Longer hospital stays; higher admission rates to ICUs**
  - ✓ **Less chance to be discharged to home (required more transitional or nursing home care)**

**Umpierrez GE et al. *J Clin Endocrinol Metab*. 2002;87:978–982.**


Managing Hyperglycemia
INTRAVENOUS INSULIN INFUSION GUIDELINE


Inpatient Management of Diabetes Mellitus
in Non-Pregnant Adult

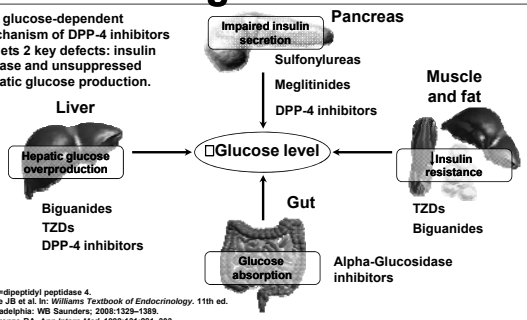

Inpatient Management of Diabetes Mellitus
in Non-Pregnant Adult

## Challenges/Controversies for Outpatient Blood Glucose Management

- **Available therapies and how best to use them**
- **The ADA algorithm**
- **What are the best long-term goals**

# Major Targeted Sites of Oral Drug Classes

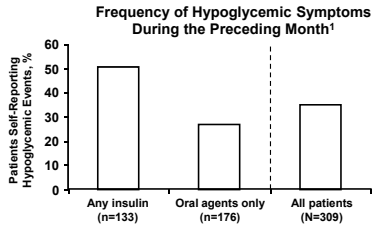
The glucose-dependent mechanism of DPP-4 inhibitors targets 2 key defects: insulin release and unsuppressed hepatic glucose production.




DPP-4=dipeptidyl peptidase 4.


1. Buse JB et al. In: *Williams Textbook of Endocrinology*. 11th ed. Philadelphia: WB Saunders; 2008:1329–1389.
2. DeFronzo RA. *Ann Intern Med*. 1999;131:281–303.
3. Inzucchi SE. *JAMA*. 2002;287:360-372.
4. Porte D et al. *Clin Invest Med*. 1995;18:247–254.


# Frequency of Hypoglycemic Symptoms Among Patients With Type 2 Diabetes




Other studies in Asia and Europe have shown similar prevalence of self-reported hypoglycemia in patients with type 2 diabetes treated with oral agents.[2,3]

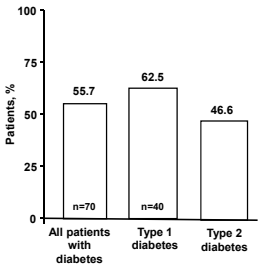

1. Lundkvist J et al. *Eur J Health Econom*. 2005;6(3):197–202. Permission pending.
2. Asia RECAP-DM Study Group. 7th IDF Western Pacific Region Congress, Wellington, New Zealand. Poster No. P45.
3. Álvarez Guisasola F et al. *Diabetes Obes Metab*. 2008;10(suppl 1):25–32.


# Selected Potential Barriers to Glycemic Control

- Patient-related barriers
  - ✓ Diet, weight control, exercise[1,2]
  - ✓ Literacy level[3]
  - ✓ Ethnicity[4]
  - ✓ Socioeconomic status[5]
- Provider-related and health care system barriers
  - ✓ Treatment-related adverse events, such as hypoglycemia[1,2]
  - ✓ Cost of disease management[6]


1. Davies M. *Int J Obes*. 2004;28(suppl 2):S14–S22.
2. Hermansen K et al. *Vasc Health Risk Manag*. 2008;4(3):561–574.
3. Williams MV et al. *Arch Intern Med*. 1998;158(2):166–172.
4. Harris M et al. *Diabetes Care*. 1999;22(3):403–408.
5. Bihan H et al. *Diabetes Care*. 2005;28(11):2680–2685.
6. ADA. *Diabetes Care*. 2003;26(3):917–932.


# Asymptomatic Episodes of Hypoglycemia May Go Unreported



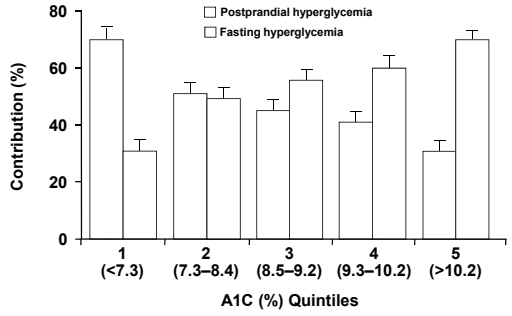

Patients With ≥1 Unrecognized Hypoglycemic Event, %

- In a cohort of patients with diabetes, more than 50% had asymptomatic (unrecognized) hypoglycemia, as identified by continuous glucose monitoring[1]
- Other researchers have reported similar findings[2,3]



2. Weber KK et al. *Exp Clin Endocrinol Diabetes*. 2007;115(8):491–494.
3. Zick R et al. *Diab Technol Ther*. 2007;9(6):483–492.

## Relative Contributions of Fasting and Postprandial Plasma Glucose to Total Glycemic Excursions as a Function of A1C




Monnier L et al. *Diabetes Care.* 2003;26:881-885.

## Summary of Available Non-oral Agents

| Agent | Administration | Glucose-lowering Effect | | Mimic Normal Physiology? |
|---|---|---|---|---|
| | | Fasting | Postprandial | |
| **Insulins** | | | | |
| NPH | Once or twice daily | ✓ | | ? |
| Detemir | Once or twice daily | ✓ | | Yes |
| Glargine | Once daily | ✓ | | Yes |
| Premixed | Twice daily | ✓ | ✓ | No? |
| Regular | With meals | | ✓ | ? |
| Aspart, glulisine, lispro | With meals | | ✓ | Yes |
| Inhaled insulin | With meals | ? | ✓ | Yes |
| **Injectable Noninsulin Agents** | | | | |
| Exenatide<br>Liraglutide | Twice daily<br>Once daily | | ✓ | Yes |
| Pramlintide | With meals | | ✓ | Yes |

NPH = neutral protamine hagedorn

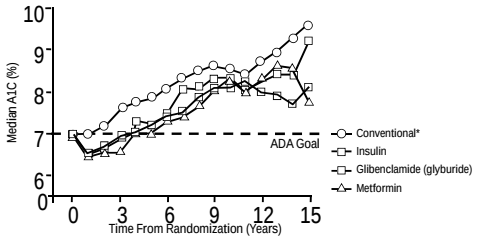
## Factors Affecting PPG Levels

- PPG levels affected by
  - ✓ Overall glycemic control
  - ✓ Meal size and nutrient composition
  - ✓ Time of day
  - ✓ Insulin sensitivity
  - ✓ Insulin secretion
  - ✓ Pharmacodynamics of drug therapies

PPG = postprandial glucose.

## Traditional Monotherapies Do Not Maintain A1C Control Over Time

United Kingdom Prospective Diabetes Study (UKPDS)



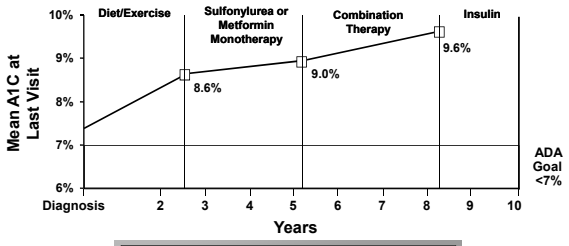

Conventional therapy defined as dietary advice given at 3-month intervals where FPG was targeted at best levels feasible in clinical practice. If FPG exceeded 270 mg/dL, then patients were re-randomized to receive non-intensive metformin, chlorpropamide, glibenclamide, or insulin. If FPG exceeded 270 mg/dL again, then those on SU would have metformin added. If FPG exceeded 270 mg/dL after this, then insulin was substituted.
Adapted with permission from UK Prospective Diabetes Study (UKPDS 34) Group. *Lancet.* 1998;352:854-865.

# Combination Therapy

- Only 25% of time does monotherapy establish adequate control
- Switching classes is not effective
- Often not necessary to "max out" dose before adding next agent

**Combinations of oral agents generally allow for lower doses of each component, thereby reducing the side effects associated with the individual components.**

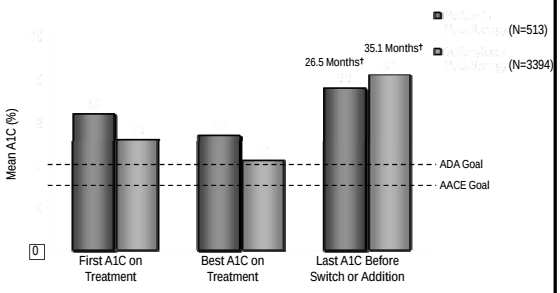
## Standard Approaches to Therapy Result in Prolonged Exposure to Elevated Glucose




At insulin initiation, the average patient had:
- 5 years with A1C >8%
- 10 years with A1C >7%

Brown JB, et al. *Diabetes Care*. 2004;27:1535-1540.

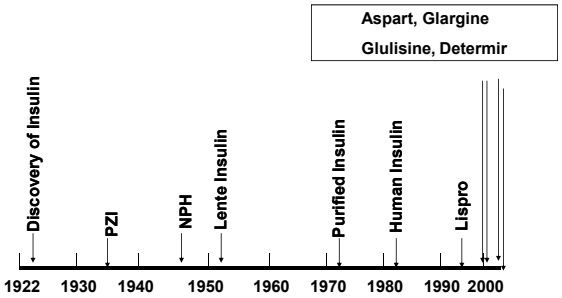
## Therapy is Not Modified* Until A1C is Well Above ADA and AACE Goals




*Monotherapy switched to another agent or additional agent added.
†Mean number of months that elapsed until a new or additional treatment was started.
Brown JB et al. *Diabetes Care*. 2004;27:1535-1540.

# When to Add Insulin

- HbA1c not at goal
- Preprandial or postprandial glucose ranges are not at goal
- Oral medication side effects
- Acute illness




Insulin Development

# Potential Benefits of Anti-diabetic Medication

- Improvement in lipid profile
- Reduction in density of LDL particles
- Change in body fat distribution
- Improvement in vascular reactivity
- Reduction in atherosclerotic burden
- Reduction in vascular markers of inflammation
- Reduction in microalbuminuria
- Improvement in beta cell integrity

# Hyperglycemia and Co-morbidities in T2DM

- Glucose control is only one of the goals of treatment for type 2 diabetes mellitus
- Aggressive therapy is necessary for
  - ✓ HTN
  - ✓ Hyperlipidemia
- Early assessment for potential end-organ complications (micro and macrovascular) may help direct therapy
- Anticipate the need to adjust the medications frequently

# Controversies in Outpatient Glucose Control

# ACCORD, ADVANCE, VADT

### Comparison of Participant Characteristics

| | ACCORD | ADVANCE | VADT |
|---|---|---|---|
| *n* | 10,251 | 11,140 | 1,791 |
| Mean age (years) | 62 | 66 | 60 |
| Duration of diabetes (yrs) | 10 | 8 | 11.5 |
| Sex (% male/female) | 39/61 | 42/58 | 97/3 |
| History of CVD (%) | 35 | 32 | 40 |
| BMI (kg/m$^2$) | 32 | 28 | 31 |
| ☆Median baseline A1C (%) | 8.1 | 7.2 | 9.4 |
| ☆On insulin at baseline (%) | 35 | 1.5 | 52 |

Diabetes Care 32:187-192, 2009

# On-Study Characteristics

| | ACCORD | ADVANCE | VADT |
|---|---|---|---|
| Median follow-up (yrs) | 3.5 | 5 | 5.6 |
| Achieved median A1C (%) | 6.4 vs. 7.5 | 6.3 vs. 7.0 | 6.9 vs. 8.5 |
| On insulin at study end (%) | 77 vs. 55* | 40 vs. 24 | 89 vs. 74 |
| On TZD at study end (%) | 91 vs. 58* | 17 vs. 11 | 53 vs. 42 |
| On statin at study end (%) | 88 vs. 88* | 46 vs. 48 | 85 vs. 83 |
| On aspirin at study end (%) | 76 vs. 76* | 57 vs. 55 | 88 vs. 86 |
| Mean BP study end (mmHg) | | | |
| Intensive arm | 126/67 | 136/74 | 127/68 |
| Standard arm | 127/68 | 138/74 | 125/69 |
| Weight changes (kg) | | | |
| Intensive arm | +3.5 | –0.1 | +7.8 |
| Standard arm | +0.4 | –1.0 | +3.4 |
| Severe hypoglycemia (%) | | | |
| Intensive arm | 16.2 | 2.7 | 21.2 |
| Standard arm | 5.1 | 1.5 | 9.9 |

# Comparison of Protocol Characteristics

| | ACCORD | ADVANCE | VADT |
|---|---|---|---|
| A1C goals (%) | <6.0 vs. 7.0–7.9 | 6.5 vs. "based on local guidelines" | <6.0 vs. separation of 1.5 |
| Protocol for glycemic control | Multiple drugs in both arms | Multiple drugs added to gliclizide vs. multiple drugs with no gliclizide | Multiple drugs in both arms |
| Management of other risk factors | Embedded BP and lipid trials | Embedded BP trial | Protocol for intensive treatment in both arms |

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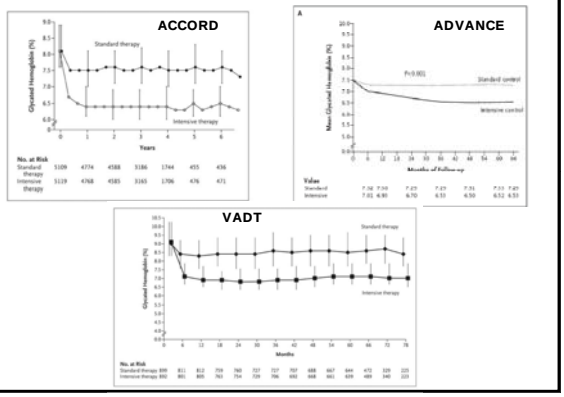
# Comparison of A1C Reduction



## Comparison of Outcomes

| | ACCORD | ADVANCE | VADT |
|---|---|---|---|
| Definition of primary outcome | Nonfatal MI, nonfatal stroke, CVD death | Microvascular plus macrovascular (nonfatal MI, nonfatal stroke, CVD death) outcomes | Nonfatal MI, nonfatal stroke, CVD death, hospitalization for heart failure, revascularization |
| Primary outcome HR (95% CI) | 0.90 (0.78–1.04) | 0.9 (0.82–0.98); macrovascular 0.94 (0.84–1.06) | 0.88 (0.74–1.05) |
| Mortality HR (95% CI) | 1.22 (1.01–1.46) | 0.93 (0.83–1.06) | 1.07 (0.81–1.42) |

Diabetes Care 32:187-192, 2009

## Post-Trial F/u of UKPDS and DCCT: *Metabolic Memory*

- Despite early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and all-cause mortality were observed during 10 years post-trial follow-up.

## Why no CVD Benefit?

- Patients likely had CVD at baseline
  - ✓ Glycemic control may play a greater role before CVD is well developed
- All 3 studies had lower rates of CVD than originally predicted
  - ✓ Benefit may require longer/larger studies
- Compared intensive to modest (not poor) control (A1c >9% may still be harmful)

Diabetes Care 32:187-192, 2009

## Steno-2 Supports Aggressive Multifactorial Intervention in Type 2 Diabetes

- Target-driven, long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria
  - ✓ Blood pressure < 130/80 mm Hg
  - ✓ A1C < 6.5%
  - ✓ Total cholesterol < 175 mg/dL
  - ✓ Triglycerides < 150 mg/dL
- Produced risk reductions in CV and microvascular outcomes
  - ✓ Primary outcome (combined CV disease) 53% decrease
  - ✓ Nephropathy 61% decrease
  - ✓ Retinopathy 58% decrease
  - ✓ Autonomic neuropathy 63% decrease

N Engl J Med. 2008;358(6):580-91.

# Take Home Message

- **HbA1c <7% in *most patients with diabetes* (reduce microvascular disease)**
- **HbA1c closer to 6% in *select individuals* - the young, shorter duration of DM, no CVD, longer life expectancy**
- **Optimal prevention of CVD requires multiple risk factor management**

**Diabetes Care 32:187-192, 2009**