Controversies in Type 2 Diabetes

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Educational Objectives

1. Discuss recent clinical data regarding diabetes treatment goals
2. Select appropriate therapies to help patients with type 2 diabetes meet current treatment goals
Question #1
What is your target A1c for the majority of your patients with type 2 diabetes?

A. < 6%
B. < 6.5%
C. < 7%
D. < 7.5%
E. < 8%

Question #2
What is your preferred 2nd line therapy for your patients with type 2 diabetes?

A. Sulfonylurea
B. Thiazolidinedione
C. DPP-IV inhibitor
D. Glucagon-like peptide 1 (GLP-1) agonist
E. Insulin
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Diabetes and Gestational Diabetes Trends Among Adults in the U.S.


Controversy #1: Target A1c

The New England Journal of Medicine

Original Article

Long-Term Effects of Intensive Glucose Lowering on Cardiovascular Outcomes

The ACCORD Study Group

(Action to Control Cardiovascular Risk in Diabetes)

ACCORD Study Hypothesis

In middle aged/older people with type 2 DM at high risk for a CVD event, does a therapeutic strategy that targets an A1C < 6.0% reduce CVD event rates more than a strategy that targets an A1C between 7.0% & 7.9% (with the expectation of achieving a median level of 7.5%)?


ACCORD Design

- Multi-center, randomized, controlled, double 2x2 factorial
  - Glycemia and BP Trials: Open Label with Blinded Endpoint Assessment
  - Lipid Trial: placebo controlled
    - Simvastatin ± Fenofibrate
- Primary outcome:
  - First occurrence of nonfatal MI or nonfatal stroke or CV death

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Double 2 X 2 Factorial Design

<table>
<thead>
<tr>
<th></th>
<th>BP (SBP&lt;120)</th>
<th>BP (SBP&lt;140)</th>
<th>Lipid (Masked)</th>
<th>Lipid (Study Drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive Glycemia (A1C&lt;6%)</td>
<td>1178</td>
<td>1193</td>
<td>1383</td>
<td>1374</td>
</tr>
<tr>
<td>Standard Glycemia (A1C 7-7.9%)</td>
<td>1184</td>
<td>1178</td>
<td>1370</td>
<td>1391</td>
</tr>
</tbody>
</table>

2362* 2371* 2753* 2765* 10,251

*Primary analyses compare the marginals for main effects


ACCORD Participant Eligibility

- Stable Type 2 Diabetes for 3+ months
- A1C ≥ 7.5%
- Age 40-79 with previous CVD events
- Age 55-79 with:
  - anatomical ASCVD, albuminuria, LVH OR
  - > 2 additional CVD risk factors (dyslipidemia, hypertension, smoking, obesity)
- BMI < 45; Cr ≤ 1.5 mg/dL
- No frequent/recent serious hypoglycemia
- Able/willing to take insulin, do glucose monitoring

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intensive (N = 5128)</th>
<th>Standard (N = 5123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.2</td>
<td>62.2</td>
</tr>
<tr>
<td>Women</td>
<td>38.7</td>
<td>38.4</td>
</tr>
<tr>
<td>Median DM Duration</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Previous CVD Event</td>
<td>35.6</td>
<td>34.8</td>
</tr>
<tr>
<td>White/Black</td>
<td>64.4/19.7</td>
<td>64.5/18.9</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>14.3</td>
<td>13.7</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>32.2</td>
<td>32.2</td>
</tr>
<tr>
<td>Mean SBP/DBP</td>
<td>136.2/74.8</td>
<td>136.5/75.0</td>
</tr>
<tr>
<td>Mean/Median A1C</td>
<td>8.3 / 8.1</td>
<td>8.3 / 8.1</td>
</tr>
<tr>
<td>Mean FG</td>
<td>175</td>
<td>176</td>
</tr>
<tr>
<td>Mean LDL / HDL</td>
<td>105 / 47</td>
<td>105 / 47</td>
</tr>
</tbody>
</table>


ACCORD Glycemia Formulary

- Metformin
- Rosiglitazone
- Glimepiride
- Repaglinide
- Acarbose
- Glargine Insulin
- Aspart Insulin
- 70/30, N, R Insulin
- Exenatide

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Participant Follow-up

Randomized
N=10,251

Intensive Group (N=5128)
Refused Intensive Approach (N=11)

Standard Group (N=5123)
Refused Standard Approach (N=26)

Lost to Follow-up (N=26)
Discontinued Intervention (N=336)

Lost to Follow-up (N=24)
Discontinued Intervention (N=322)

Analyzed (N=5128)
Excluded from analysis (N=0)

Analyzed (N=5123)
Excluded from analysis (N=0)


Median A1C and Interquartile Ranges

The mean difference during the trial was 1.1%

### Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intensive N (%)</th>
<th>Standard N (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>352 (6.86)</td>
<td>371 (7.23)</td>
<td>0.90 (0.78-1.04)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>257 (5.01)</td>
<td>203 (3.96)</td>
<td>1.22 (1.01-1.46)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>186 (3.63)</td>
<td>235 (4.59)</td>
<td>0.76 (0.62-0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>67 (1.31)</td>
<td>61 (1.19)</td>
<td>1.06 (0.75-1.50)</td>
<td>0.74</td>
</tr>
<tr>
<td>CVD Death</td>
<td>135 (2.63)</td>
<td>94 (1.83)</td>
<td>1.35 (1.04-1.76)</td>
<td>0.02</td>
</tr>
<tr>
<td>CHF</td>
<td>152 (2.96)</td>
<td>124 (2.42)</td>
<td>1.18 (0.93-1.49)</td>
<td>0.17</td>
</tr>
</tbody>
</table>


### Primary Outcome

- Intensive: 2.29%/yr
- Standard: 2.11%/yr

HR = 0.90 (0.78-1.04)

P = 0.16

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All Cause Mortality

- **1.41%/yr** vs **1.14%/yr**
- **HR = 1.22 (1.01-1.46)**
- **P = 0.04**


Lower A1C Targets (achieved median)
- <6% (6.4%) vs 7-7.9% (7.5%)

Greater use of medications:
- More multiple oral meds: 70% vs 45% on 3-5 oral classes
- More insulin: 77% vs 55% on insulin
- More combination orals + insulin: 62% vs 18% on 3-5 orals + insulin

More consequences of therapy:
- Severe hypoglycemia: 10.5% vs 3.5% w/ hypoglycemia event requiring medical assistance
- W eight gain: 28% vs 14% >10 kg gain
- More SAEs: 2.2% vs 1.6% w/ non-hypo SAE

Conclusions

- In people with type 2 diabetes at high risk for CVD and an A1C of 7.5% or more, a therapeutic strategy that targeted an A1C <6% vs. 7.0-7.9% increased mortality over 3.5 years.

- There was no significant effect of the glycemic intervention on reducing major cardiovascular events.


ACCORD BP Results

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.

ACCORD Lipid Results

- Compared with simvastatin alone, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke.


The Need for Tight Glycemic Control

According to the United Kingdom Prospective Diabetes Study (UKPDS) 35, every 1% drop in HbA1c resulted in:

- Decrease in any diabetes-related end point: 21%
- Decrease in risk of myocardial infarction: 14%
- Decrease in risk of stroke: 12%
- Decrease in risk of microvascular disease: 37%

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UKPDS: Blood Pressure Control in Type 2 DM

Effect of BP Lowering on Risk of Micro & Macrovascular Complications

Benefits of 144/82 vs 154/87


Benefits of Aggressive LDL-C Lowering in Diabetes


*Atorvastatin 10 vs 80 mg/day
†Statin vs placebo
Summary of Treatment Goals in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80 mmHg</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt;100 mg/dl (without overt CVD)</td>
</tr>
<tr>
<td></td>
<td>&lt;70 mg/dl (with overt CVD)</td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>≤6.5% (AACE)</td>
</tr>
<tr>
<td></td>
<td>&lt;7.0% (ADA)</td>
</tr>
</tbody>
</table>

Diabetes Care, Vol. 34, Suppl. 1, Jan. 2011

Summary of Treatment Goals in Type 2 Diabetes

- More stringent A1C goals?
  - Short duration of diabetes
  - Long life expectancy
  - No significant cardiovascular disease

Diabetes Care, Vol. 34, Suppl. 1, Jan. 2011
Summary of Treatment Goals in Type 2 Diabetes

- Less stringent A1C goals?
  - History of severe hypoglycemia
  - Limited life expectancy
  - Advanced microvascular or macrovascular complications
  - Extensive comorbid conditions

Diabetes Care, Vol. 34, Suppl. 1, Jan. 2011

Controversy #2: Intensive Inpatient Glucose Control

Hyperglycemia and Mortality in the Medical Intensive Care Unit

N=1826 ICU patients. Mean Glucose Value (mg/dL)

**Intensive Insulin Therapy in Critically Ill Patients: The Leuven SICU Study**

- Randomized controlled trial: 1548 patients admitted to a surgical ICU, receiving mechanical ventilation. Patients were assigned to receive either:
  - **Conventional therapy**: IV insulin only if BG >215 mg/dL
    - Target BG levels: 180-200 mg/dL
    - Mean daily BG: 153 mg/dL
  - **Intensive therapy**: IV insulin if BG >110 mg/dL
    - Target BG levels: 80-110 mg/dL
    - Mean daily BG: 103 mg/dL


**Intensive Insulin Therapy in Critically Ill Patients: SICU**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk Reduction (%)</th>
<th>*P &lt; 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged (&gt;10 d) antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged (&gt;14 d) ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged (&gt;14 d) ICU stay</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NICE-SUGAR Study

- Multicenter-multinational RCT (Australia, New Zealand, and Canada) in 6104 ICU patients, randomized to:
  - **Intensive, BG target**: 4.5 and 6.0 mmol/L (81 - 108 mg/dL)
  - **Conventional, BG target**: < 10.0 mmol/L (180 mg/dL)
- **Primary Outcome**:
- **Death from any cause within 90 days after randomization**


NICE-SUGAR: Baseline Characteristics

- **Age**: ~ 60 years
- **Gender**: ~ 36% female
- **Diabetes**: ~ 20% (BMI ~ 28 kg/m²)
- **Interval, ICU admission to randomization**: 13.4 hrs
- **Reason for ICU admission**:
  - Surgical* ~ 37%
  - Non-surgical† ~ 63%
- **Sepsis**: ~ 22%
- **Trauma**: ~ 15%

* Did not include significant numbers of CT surgery patients
† Did not include significant numbers of CCU patients

NICE-SUGAR: Intensive vs Conventional Glucose Control in Critically Ill Patients

Bars are 95% confidence intervals. The dashed line indicates 108 mg/dL, the upper limit of target range for intensive glucose control.


### NICE-SUGAR Study Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Intensive Group</th>
<th>Conventional Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning BG (mg/dL)</td>
<td>118 ± 25</td>
<td>145 ± 26</td>
</tr>
<tr>
<td>Hypoglycemia (≤ 40mg/dL)</td>
<td>206/3016 (6.8%)</td>
<td>15/3014 (0.5%)</td>
</tr>
<tr>
<td>28 Day Mortality (p=0.17)</td>
<td>22.3%</td>
<td>20.8%</td>
</tr>
<tr>
<td>90 Day Mortality (p=0.02)</td>
<td>27.5%</td>
<td>24.9%</td>
</tr>
</tbody>
</table>

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NICE-SUGAR: Intensive vs Conventional Glucose Control in Critically Ill Patients

Kaplan–Meier Estimates For The Probability Of Survival

HR = 1.11 (95% confidence interval, 1.01-1.23)


NICE-SUGAR: Probability of Survival and Odds Ratios for Death, According to Treatment Group

NICE SUGAR: Conclusions

- Intensive glucose control did not offer any benefit in critically ill patients.
- Blood glucose target of less than 180 mg/dL resulted in lower mortality than a target of 81-108 mg/dL.
- There was increased hypoglycemia with lower glucose targets.


AACE/ADA Consensus Statement on Inpatient Glycemic Control

AMEERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN DIABETES ASSOCIATION

CONSENSUS STATEMENT ON INPATIENT GLYCEMIC CONTROL

**ICU setting:**
- Starting threshold of no higher than 180 mg/dL
- Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL
- Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients
- Targets <110 mg/dL or >180 mg/dL are not recommended

**Non–ICU setting:**
- Premeal glucose targets <140 mg/dL
- Random BG <180 mg/dL
- To avoid hypoglycemia, reassess insulin regimen if BG levels fall below 100 mg/dL
- Occasional patients may be maintained with a glucose range below and/or above these cut-points

**Hypoglycemia** = BG <70 mg/dL
**Severe hypoglycemia** = BG <40 mg/dL
Inpatient Glycemic Control: Conclusions

- Hyperglycemia is associated with poor clinical outcomes across many disease states in the hospital setting
- Good glucose control, as opposed to near-normal control, is likely sufficient to improve clinical outcomes in the ICU setting

Controversy #3
Treatment Options in Type 2 Diabetes

- Metformin
- DPP-4 inhibitor/GLP-1 agonist
- Sulfonylurea
- TZD
- Insulin
- Bariatric Surgery
- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide
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A1C 6.5 – 7.5%

Monotherapy
MET + GLP-1 or DPP4 1
TZD 2
Glinide or SU 5

Dual Therapy
MET + GLP-1 or DPP4 + TZD
Glinide or SU

Triple Therapy
MET + GLP-1 or DPP4 + TZD + SU

A1C > 9.0%

No Symptoms
Drug Naive
Under Treatment

INSULIN ± Other Agent(s) 6

Symptoms

INSULIN ± Other Agent(s) 6

AACE/ACE Diabetes Algorithm for Glycemic Control
A1C Goal ≤ 6.5%

Lifestyle Modification

A1C 6.5 – 7.5%

Monotherapy
MET + GLP-1 or DPP4

Dual Therapy
MET + GLP-1 or DPP4 + TZD
Glinide or SU

Triple Therapy
MET + GLP-1 or DPP4 + TZD + SU

A1C 7.6 – 9.0%

Dual Therapy
MET + GLP-1 or DPP4 + TZD
Glinide or SU

Triple Therapy
MET + GLP-1 or DPP4 + TZD + SU

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**The abbreviations used here correspond to those used on the algorithm (Fig. 1).**

**The term 'glinide' includes both repaglinide and nateglinide.**

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease (NAFLD). Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects relative importance of the benefit or risk.*

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### Treatment Considerations in Type 2 Diabetes

- Hemoglobin A1c
- Body mass index
- Age/Kidney disease
- Congestive heart failure
- Liver failure
- Cost of medications
Treatment Options in Type 2 Diabetes: A1c > 9%

- Metformin plus:
- DPP-4 inhibitor/GLP-1 agonist, or
- Sulfonylurea, or
- TZD, or
- Insulin
- Bariatric Surgery

- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide

Treatment Options in Type 2 Diabetes: BMI > 35

- Metformin
- DPP-4 inhibitor/GLP-1 agonist
- Sulfonylurea
- TZD
- Insulin
- Bariatric Surgery

- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide
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Treatment Options in Type 2 Diabetes:
Age < 35
- Metformin
- DPP-4 inhibitor/GLP-1 agonist
- Sulfonylurea
- TZD
- Insulin
- Bariatric Surgery
- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide

Treatment Options in Type 2 Diabetes:
Age > 75 and/or Renal Insufficiency
- Metformin
- DPP-4 inhibitor/GLP-1 agonist
- Sulfonylurea
- TZD
- Insulin
- Bariatric Surgery
- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide
Treatment Options in Type 2 Diabetes: Congestive Heart Failure

- Metformin
- DPP-4 inhibitor/GLP-1 agonist
- Sulfonylurea
- TZD
- Insulin
- Bariatric Surgery
- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide

Treatment Options in Type 2 Diabetes: Liver Failure

- Metformin
- DPP-4 inhibitor/GLP-1 agonist
- Sulfonylurea
- TZD
- Insulin
- Bariatric Surgery
- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide
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Treatment Options in Type 2 Diabetes: Cost of Medications

- Metformin
- DPP-4 inhibitor/GLP-1 agonist
- Sulfonylurea
- TZD
- Insulin (Regular, NPH)
- Bariatric Surgery

- Meglitinide
- Glucosidase inhibitor
- Colesevelam
- Pramlintide