Type 2 Diabetes:
Role of Insulin-Based Therapy

Educational Partner:
Asante Communications, LLC

April 11, 2012
Anaheim Convention Center—Anaheim, California
Session 6: Type 2 Diabetes:  
Role of Insulin-Based Therapy

Learning Objectives
1. Describe the pathophysiology of T2DM and its practical implications for multi-organ disease mandating early recognition and treatment.
2. Conduct an initial and ongoing assessment of A1C, fasting blood glucose, and postprandial blood glucose to achieve tight glycemic control, with appropriate referral when necessary.
3. Evaluate the mechanisms and clinical profiles of insulin formulations, addressing dosing regimen, patient age, ethnicity, and other determinants of individualized care.
4. Collaborate with endocrinologists, cardiologists, nurse practitioners, dietitians, diabetes educators, and other care providers to formulate and implement a comprehensive treatment that includes pharmacologic as well as lifestyle interventions.
5. Educate patients on the causes, symptoms, and risks associated with hypoglycemia and implement new models of care to overcome patient and system barriers to therapeutic regimen adherence.

Faculty
Jeff Unger, MD  
Director, Metabolic Studies  
Catalina Research Institute  
Chino, California

Dr Unger is an assistant professor of family medicine at Loma Linda University School of Medicine. He is the founder of the Unger Primary Care Medical Center and the associate director for metabolic studies at the Catalina Research Institute in Chino, California. The center uniquely incorporates primary care with clinical research in areas related to metabolism, pain, obesity, mental illness, and GI disorders. Dr Unger is the recipient of the National Headache Foundation Speaker of the Year Award and has published over 130 peer-reviewed articles and book chapters on diabetes, mental illness, and pain management. Over the past six years, Dr Unger has spoken internationally on topics linking mental illness with metabolic dysfunction, chronic pain disorders, diabetic neuropathy, and ways by which primary care physicians might assist their diabetic patients to successfully achieve their metabolic targets. His medical textbook, Diabetes Management in Primary Care (Lippincott, Williams & Wilkins), was published in April 2007. The 2nd edition of the textbook, edited by Zac Schwartz, will be released September 2012. Dr Unger is also publishing a consumer book entitled Diabetes for the Disinterested with Dr Bill Polonsky.

Daniel Einhorn, MD, FACP, FACE  
Medical Director  
Scripps Whittier Diabetes Institute  
Clinical Professor of Medicine  
University of California, San Diego  
President  
Diabetes and Endocrine Associates  
La Jolla, California

Daniel Einhorn is clinical professor of medicine at University of California, San Diego and the medical director of the Scripps Whittier Institute for Diabetes. He received his BA from Yale University (summa cum laude, Phi Beta Kappa, varsity letter) and his MD from Tufts Medical School (Alpha Omega Alpha). He did his internship, residency, and fellowship, and later served as an instructor in medicine, at Beth Israel Hospital, Harvard Medical School. Since 1984, he has been a clinical endocrinologist with Diabetes and Endocrine Associates, associate clinical professor of medicine at UC San Diego, director of the Diabetes Treatment and Research Center at Sharp HealthCare, and director of clinical research for the Scripps Whittier Institute of Diabetes. He is a fellow of the American College of Physicians and the American College of Endocrinology.
**Faculty Financial Disclosure Statements**
The presenting faculty report the following:

Jeff Unger, MD, is a principal investigator for Abbott Laboratories; Dexcom, Inc.; Eli Lilly and Company; Novo Nordisk; Johnson & Johnson; LifeScan, Inc.; Pfizer Inc.; and sanofi-aventis U.S. LLC.

Daniel Einhorn, MD, FACP, FACE, receives consulting honorarium from Novo Nordisk and Amylin, and is a stockholder with Haloyme Therapeutics and MannKind Corporation.

**Education Partner Financial Disclosure Statement**
The content collaborators at Asante Communications, LLC, report the following:
Alan Morrice, PhD, Group Scientific Writer, has no financial relationships to disclose.

**Suggested Reading List**


Type 2 Diabetes

Role of Insulin-Based Therapy

Demographics

- What is your degree?
  1. MD
  2. DO
  3. PharmD
  4. DNP

Demographics

- What is your specialty?
  1. Internal Medicine
  2. Endocrinology
  3. Diabetes Education

Demographics

- How many patients do you see during a typical week?
  1. None
  2. 1-40
  3. 41-80
  4. 81-120
  5. >120

Pre-Activity Questions

- A 39-year-old overweight patient is being treated with metformin and has an A1C of 7.5%. What is your add-on therapy?
  1. Glucagon-like peptide (GLP)-1 agonist or dipeptidyl-peptidase (DPP)-4 inhibitor
  2. Thiazolidinedione
  3. Sulfonylurea
  4. Insulin

Pre-Activity Questions

- An intensive A1C goal would generally not be selected for T2DM patients with macrovascular or microvascular disease.
  1. Strongly disagree
  2. Disagree
  3. Neutral
  4. Agree
  5. Strongly agree
Pre-Activity Questions

• Insulin-based therapy could be considered in a symptomatic patient with an A1C of 8.5%.
  1. Strongly disagree
  2. Disagree
  3. Neutral
  4. Agree
  5. Strongly agree

Pre-Activity Questions

• A 75-year-old patient with T2DM and renal impairment has an A1C of 7.8% on dual oral therapy. Intensifying the regimen could be considered.
  1. Strongly disagree
  2. Disagree
  3. Neutral
  4. Agree
  5. Strongly agree

Pre-Activity Questions

• When determining an A1C target for a patient, how often do you CURRENTLY evaluate T2DM duration?
  1. Never
  2. Sometimes
  3. Most of the time
  4. Always
  5. Only in select patients

Educational Objectives

1. Describe the pathophysiology of type 2 diabetes mellitus (T2DM) and its practical implications for multi-organ disease mandating early recognition and treatment
2. Conduct an initial and ongoing assessment of A1C, fasting blood glucose, and postprandial blood glucose to achieve tight glycemic control, with appropriate referral when necessary
3. Evaluate the mechanisms and clinical profiles of insulin formulations, addressing dosing regimen, patient age, ethnicity, and other determinants of individualized care
4. Collaborate with endocrinologists, cardiologists, nurse practitioners, dietitians, diabetes educators, and other care providers to formulate and implement a comprehensive treatment that includes pharmacologic as well as lifestyle interventions
5. Educate patients on the causes, symptoms, and risks associated with hypoglycemia and implement new models of care to overcome patient- and system-related barriers to therapeutic regimen adherence

Clinical and Scientific Advances in Assessment
Natural History of Type 2 Diabetes
T2DM Is a Multifactorial Disease

- Multiple abnormalities contribute to complications as T2DM progresses
- Fasting hyperglycemia is a late manifestation of T2DM
- Treatment should address these multiple components, not just hyperglycemia

T2DM = type 2 diabetes mellitus.


Complications of T2DM May Be Present Prior to Diagnosis
Argument for Early Diagnosis and Treatment of Prediabetes

Urine Albumin (>0.25 g/L)
Cardiovascular Disease
Absent Foot Pulses (≥2)
Absent Reflexes (≥2)
Retinopathy

Prevalence (%) 0 5 10 15 20

Relative Risk of Progression of Diabetic Complications

Relative Risk* Retinopathy Nephropathy Neuropathy Microalbuminuria

Mean A1C (%) 6 7 8 9 10 11 12

Relative Risk

*Relative risk.

Loss of β-Cell Function Begins Before T2DM Diagnosis
San Antonio Metabolism Study

2-h Plasma Glucose (mmol/L)

T2DM Non-OB OB

0 5 10 15 20

Relative Risk of Progression of Diabetic Complications

CHD Events (Events/100 Persons)

A1C (%)*

*P < 0.001 for linear trend across A1C categories.

A1C Predicts Coronary Heart Disease

CHD Events (Events/100 Persons)

A1C (%)*

*P = 0.80 for linear trend across A1C categories.

Epidemiology
1. Hyperglycemia is a continuous risk factor
2. No A1C threshold is apparent
3. Worse A1C implies longer duration T2DM

Mechanisms
I. Metabolic Disorder
II. Individual Susceptibility
III. Acquired Delayed Complications
IV. Modulating Factors
V. Early Late

V. Early Path of metabolic "no return" eg, macroalbuminuria, proliferative retinopathy

O2 = oxygen; PKC = protein kinase C.

Relative Risk

0 5 10 15 20

Relative Risk

3.8 6.4 8.7 10.2 16.7 21.9

3.6 6.4 7.3 10.2 9.6 21.9

28.4 27.0 T2DM

Women

Men

Ox = oxygen; PKC = protein kinase C.


San Antonio Metabolism Study*

P < 0.05 obese vs non-obese.

ΔG = incremental glucose response; ΔI = incremental insulin response; OB = obese.
Impact of Intensive Therapy in Type 2 Diabetes
Summary of Major Clinical Trials
Subset Evaluations Show Reduced CV Outcomes if Shorter Duration of T2DM, Without Significant Pre-existing Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>Macrovascular</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGDP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS</td>
<td></td>
<td></td>
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<tr>
<td>DCCT/EDIC</td>
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<tr>
<td>ACCORD</td>
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<tr>
<td>VADT</td>
<td></td>
<td></td>
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</tbody>
</table>

*Adjusted/unadjusted for baseline A1C;
*Action to Control Cardiovascular Risk in Diabetes; and "adjusted, ADVANCE + Action in Diabetes and Vascular Disease: Preventing macrovascular and microvascular complications with an intensive percutaneous coronary intervention programme" (ADVANCE) + Action in Diabetes and Vascular Disease: PREvention of macrovascular and microvascular endpoints in type 2 diabetes patients studied with an intensive percutaneous coronary intervention programme and treatment of hypertriglyceridaemia (DISCOVER HEART). Keys to successful diabetes treatment: Diabetic nephropathy group (Diagnostic Categorization and Individual Treatment Selection for Hyperglycaemia - Diabetic Nephropathy); Diabetic nephropathy group (Diagnostic Categorization and Individual Treatment Selection for Hyperglycaemia - Diabetic Nephropathy); Diabetic nephropathy group (Diagnostic Categorization and Individual Treatment Selection for Hyperglycaemia - Diabetic Nephropathy); Diabetic nephropathy group (Diagnostic Categorization and Individual Treatment Selection for Hyperglycaemia - Diabetic Nephropathy); Diabetic nephropathy group (Diagnostic Categorization and Individual Treatment Selection for Hyperglycaemia - Diabetic Nephropathy).}

Intensive Glucose Lowering Caused Weight Gain and Hypoglycemia

<table>
<thead>
<tr>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive Glucose Lowering</td>
<td>Weight Gain</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>8 lbs</td>
<td>~30% of patients gained &gt;20 lbs!</td>
<td>RR = risk reduction.</td>
</tr>
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<td>RR = risk reduction.</td>
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</tbody>
</table>

Severe Hypoglycemia and Vascular Events by Treatment Regimen

<table>
<thead>
<tr>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Treatment</td>
</tr>
<tr>
<td>0-12</td>
</tr>
<tr>
<td>13-24</td>
</tr>
<tr>
<td>25-36</td>
</tr>
<tr>
<td>37-48</td>
</tr>
<tr>
<td>48-60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Months From Hypoglycemia to Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Sulfonylureas and Ischemic Preconditioning

AF receptor antagonists, P2Y12 receptor antagonists, and bradykinin receptor antagonists.
Impact of Intensive Glucose Control on Coronary Heart Disease Events

**Meta-analysis**

<table>
<thead>
<tr>
<th>Intensive Treatment/Standard Treatment</th>
<th>Participants Events</th>
<th>Odds Ratio (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>3071/1549 426/259</td>
<td>0.75 (0.54-1.04)</td>
<td></td>
</tr>
<tr>
<td>PROactive*</td>
<td>2605/2633 164/202</td>
<td>0.81 (0.65-1.00)</td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5571/5569 310/337</td>
<td>0.92 (0.78-1.07)</td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>892/899 7799</td>
<td>0.85 (0.62-1.17)</td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>5128/5123 205/244</td>
<td>0.82 (0.68-0.99)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>17,267/15,773 1182/1136</td>
<td>0.85 (0.77-0.93)</td>
<td></td>
</tr>
</tbody>
</table>

*Included nonfatal myocardial infarction and death from all-cause mortality.


Intensive Glycemic Control Associated With Positive Effects on Microvascular Outcomes

**Annual Event Rates Per 1000 Patients**

<table>
<thead>
<tr>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive</td>
<td>Standard</td>
<td>Intensive</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1.83*</td>
<td>2.00</td>
</tr>
<tr>
<td>Visual Deterioration</td>
<td>4.84</td>
<td>5.05</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>2.91*</td>
<td>2.94</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>3.38*</td>
<td>4.14</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>0.73*</td>
<td>1.05</td>
</tr>
</tbody>
</table>

*P < 0.05 vs standard glycemic therapy.

Margot

- 47-year-old African American teacher
- Initial visit to your office for fatigue and "unintentional" weight loss
- Nonsmoker
- Does not drink alcohol
- Too tired to exercise!
- Family history
  - Mom has T2DM, chronic kidney disease stage 4
  - Dad is unknown
  - 1 brother has stage 2 hypertension and lives in Mississippi. He’s “a bit overweight.”

Margot Clinical Profile

- Height, 69”
- Weight, 175 lbs
- BMI, 25.8 kg/m²
- A1C, 9.6%
- FPG, 231 mg/dL
- eGFR, 68 mL/min/1.73 m²
- Albumin:creatinine 12 mcg/mg creatinine
- Peripheral pulses normal

- Blood pressure, 130/90 mm Hg
- Lipids
  - TC: 205 mg/dL
  - LDL-C: 110 mg/dL
  - VLDL-C: 57 mg/dL
  - HDL-C: 35 mg/dL
  - TG: 300 mg/dL
  - Non-HDL-C: 170 mg/dL
  - Apo B: 118 mg/dL

Margot Psychosocial Considerations

- Single and lives alone, but indicates she has several friends she sees regularly
- Volunteers at local dog rescue
- College degree in mathematics and ongoing graduate work
- Steady, secure job with reasonably good health insurance
- Admits she does not eat a healthy diet due to time pressures—job, graduate work, volunteering

ARS Question

**What Is Margot’s A1C Target?**

1. 6.0
2. 6.5
3. 7.0
4. 7.5
5. 8.0
Changes in A1C and Glycemic Burden (in months)

<table>
<thead>
<tr>
<th></th>
<th>Pre-Tx A1C</th>
<th>Best Rx A1C</th>
<th>Last Rx A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet + Exercise n = 2319</td>
<td>9.6%</td>
<td>8.0%</td>
<td>6.5%</td>
</tr>
<tr>
<td>SU n = 3394</td>
<td>9.5%</td>
<td>8.5%</td>
<td>7.0%</td>
</tr>
<tr>
<td>MET n = 513</td>
<td>9.0%</td>
<td>8.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>SU + MET n = 982</td>
<td>8.5%</td>
<td>7.5%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

A1C >8% (mo) 4 17 12 26
A1C >7% (mo) 16 37 26 51

MET = metformin; Rx = response; SU = sulfonylurea; Tx = treatment.


The ABCD of Patient-Specific A1C Targets

A1C >8% (mo) 4 17 12 26
A1C >7% (mo) 16 37 26 51

Age

- ACCORD
  - Trend toward lower all-cause mortality among participants aged <65 years at baseline who were assigned to standard treatment (P = NS)
- ADVANCE
  - Lower rates of combined major macro- and microvascular events in younger patients in the intensive therapy group (P = NS)
- VAIDT
  - Patients with lower coronary calcium scores had fewer CVD events with intensive control

Body Weight

- Intensive goals require polypharmacy, which can lead to weight gain
- Increasing emphasis on weight-neutral or weight-reducing regimens
- Comorbid conditions such as obesity may limit life expectancy
  - Reduce period in which diabetic complications can develop

Complications

- Macrovascular disease
  - Patients with more advanced CVD show no reduction in CVD events with intensive glycemic treatment
- Microvascular disease
  - More aggressive glycemic control may be considered in patients with microalbuminuria without elevated serum creatinine levels or in patients with early retinopathy
  - Strict glucose control does not alter progression of renal disease once serum creatinine level is elevated

Concerns

Risk of Hypoglycemia

- 2.7% of intensively managed patients with T2DM experience an annual severe hypoglycemic event vs 1.5% of conventionally managed patients
- The cost of a single episode of severe hypoglycemia is ~$600
- Recurrent hypoglycemic events may result in hypoglycemia-associated autonomic failure (HAAF)
- A single nonsevere hypoglycemic episode occurring at work typically results in lost productivity of up to 10 hours
- A nonsevere hypoglycemic episode outside of work results in people arriving late for work up to 24% of the time
Concerns
Psychosocial Considerations

- Patient-specific psychological, social, and economic considerations—as well as underlying capacity for self-management—play a critical role in setting A1C targets
- When setting A1C target, consider:
  - Availability of support system
  - Psychological and cognitive status
  - Patient attitude toward self care
  - Economic status
  - Adverse effects of medications

Most Intensive vs Less Intensive Glycemic Control

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>Number of Patients/Events</th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>4910/334</td>
<td>0.84 (0.71-0.98)</td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td>2218/249</td>
<td>1.00 (0.84-1.20)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>2053/257</td>
<td>0.93 (0.78-1.10)</td>
<td></td>
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</table>

Conclusions

- Diabetes is a multifactorial disease
  - Supports an approach to treatment that addresses the underlying pathophysiology of the individual patient
- Epidemiologic studies indicate that A1C correlates with macrovascular and microvascular risk
  - Studies of intensive vs conventional treatment have not proved or disproved the benefit of intensive treatment
  - Younger patients with no apparent CVD and shorter disease duration may benefit most from intensive treatment
- A1C targets can and should be adapted based on individual patient clinical and psychosocial characteristics

Matching Therapy to the Patient

Margot

Treatment Course

- Margot is started on lifestyle therapy, metformin, and DPP-4 inhibitor
- At a return visit at 3 months, her A1C has decreased to 8.9%, but she is symptomatic
  - Fatigue 2 hours after eating lunch
  - Blurry vision
  - Paresthesias in feet
  - Increased thirst
  - Metformin dose increased but associated with diarrhea
ADA/EASD Consensus Statement Recommendations

Diagnosis of T2DM
Lifestyle Intervention + Metformin
Continuous Current Management

Renal function
Relative contraindication in very elderly

A1C ≥ 7%

Contraindicated in patients with heart failure or heart disease
Hypoglycemia if not dosed near meal

Add Sulfonylurea
Add Basal Insulin
Add Glitazone (TZD)
Add GLP-1 Agonist

ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes; GLP-1 = glucagon-like peptide-1; TZD = thiazolidinedione.


Timing of Insulin Initiation
AACE/ACE Recommendations Based on A1C Diagnosis

A1C 6.5% - 7.5%
A1C 7.6% - 9.0%

Lifestyle Modifications

If under treatment
If drug naïve

Monotherapy
Dual Therapy
Insulin Plus Other Agent(s)*

Triple Therapy
Insulin Plus Other Agent(s)*

Therapeutic choice, based on safety/efficacy, should match the drug characteristics with patient characteristics.

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology.

*Pramlintide can be used with prandial insulin, but insulin secretagogues should be discontinued with multidose insulin. Adapted from Rodbard HW, et al. Endocrine Pract. 2009;15;540-559.

Typical A1C Reduction by Treatment Regimen
Approved Antidiabetes Medications in the United States

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of Administration</th>
<th>Year of Introduction or FDA Approval</th>
<th>Efficacy as Monotherapy, (reduction in A1C, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Parenteral</td>
<td>1921</td>
<td>≥2.5</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>1946</td>
<td>1.5</td>
</tr>
<tr>
<td>Metformin*</td>
<td>Oral</td>
<td>1995</td>
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<tr>
<td>GLP-1 analogs</td>
<td>Oral</td>
<td>2005</td>
<td>0.6</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Oral</td>
<td>2006</td>
<td>0.5-0.9</td>
</tr>
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</table>

*Metformin has been available in other countries since 1957, but was approved in the United States in 1995.

Add = sulfonylurea; basal = DPP-4 + basal insulin; TZD + metformin should be discontinued with multidose insulin.


ARS Question

How Would You Intensify Margot’s Pharmacologic Regimen?
1. Add sulfonylurea to maximum dose of metformin
2. Add TZD to maximum dose of metformin
3. Continue metformin. Add on either basal or mixed insulin analog
4. Use a GLP-1 analog plus basal insulin (off-label)
5. Use an approved DPP-4 + metformin with a mixed or basal insulin analog

Insulin Delivery Devices (2011)

Insulin Pens and Cartridges
Adopted Worldwide

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GLP-1 Agonists in Patients Receiving Insulin
Emerging Option

Patients with A1C 7.1% to 10.5% receiving insulin glargine alone or with metformin and/or pioglitazone randomized to exenatide 10 µg bid or placebo.


Early Insulin-Based Therapy
Reduction in Vascular Events

Any Diabetes-Related Endpoint
Myocardial Infarction
Microvascular Disease
Death From Any Cause


Initiating Insulin
ADA Algorithm

- Check fasting glucose daily and increase dose until fasting levels are consistently in target range (70-130 mg/dL).
- Typical dose increase is 2 units every 3 days.
- Larger increments may be warranted if fasting glucose is >180 mg/dL.
- If hypoglycemia or fasting glucose <70 mg/dL occurs, reduce bedtime dose by 4 units or 10%, whichever is greater.

Early Intensive Insulin Therapy
Durable Glycemic Control

P = 0.0012


Selecting Insulin Therapies
Starting Strategy

- Earlier stages of T2DM
- Elevated FPG
- Stable daytime BG
- Single daily injection

Long-acting (basal)
- Detemir
- Glargine
- NPH if cost is an issue

Basal Insulin + Oral Agent(s)
- Gold standard but more complicated
- More flexible

Basal-Bolus Insulin ± Sensitizer(s)
- Elevated PPG
- May be used 1, 2, or 3 times a day

Premixed Insulin ± Sensitizer(s)
- More flexible

Premixed
- Human premix 70/30
- Analogs
- Insulin glargine 70/30, 30/70
- Biphasic insulin aspart 70/30
- Self-mix
- Rapid-acting analog or regular + NPH

**Natural History of Insulin Therapy**

*Rational Approach to Achieve and Sustain Glycemic Goals*

- Adding 1 injection of long-acting insulin to OADs is the easiest way to start insulin
- Premixed insulin twice a day or the split-mixed regimen can be effective if the above combo fails
  - Pharmacokinetics of insulin in obese T2DM patients are flatter (ie, experience slower peaks)
- Basal/bolus regimens and pumps are appropriate if glycemic goals are not met with other regimens

OADs = oral antidiabetic drugs.

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**Insulin-Based Therapy in T2DM**

- If elevated fasting glucose, use basal insulin
- If elevated postprandial glucose, use prandial insulin
- If both basal and prandial insulin are needed, role of oral agents is unclear
- Morning vs evening regimens similar
  - Easier for patient to not have to watch the clock or meal time

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**Morning vs Bedtime Insulin Glargine**

![Graph showing A1C at Baseline and Study Endpoint](chart.png)

- Morning Glargine Group: 8.8% A1C at Baseline, 7.2% A1C at Endpoint
- Bedtime Glargine Group: 8.8% A1C at Baseline, 7.2% A1C at Endpoint

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**Canadian INSIGHT Trial**

- PCPs vs endocrinologists
- N = 405 randomized to either
  - Insulin glargine via self-titration algorithm (10 U at bedtime; ↑ 1 U/day until FPG <100 mg/dL), OR
  - Initiate or maintain oral therapy with physician-directed dose adjustments over 24 weeks
- Inclusion criteria: A1C 7.5%-11% (median 8.6%)
- Goal was to achieve 2 consecutive A1C ≤ 6.5%

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**Margot**

*Treatment Course*

- Insulin glargine was added at night (10 units) and titrated up to 46 units over the next few weeks
- A1C 7.8%
- Post-dinner hyperglycemia

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**Adjusting Insulin**

*ADA Algorithm*

- A1C <7% after 2 to 3 months
  - Continue regimen; check A1C every 3 months
- If fasting bg in target range, check bg before lunch, dinner, bedtime
- Add second injection as below (begin with ~4 units and adjust by 2 units every 3 days until bg is in range)
  - Pre-lunch out of range: Add rapid-acting insulin at breakfast
  - Pre-dinner out of range: Add NPH insulin at noon or rapid-acting at lunch
  - Pre-bed out of range: Add rapid-acting insulin at dinner
- A1C ≥ 7% after 3 months
  - Recheck pre-meal bg levels; if out of range, additional injections may be needed
  - If A1C continues to be out of range, check 2 postprandial levels and adjust preprandial rapid-acting insulin

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*References*

Intensifying Insulin Therapy
Basal-Bolus

• If A1C >7% or basal insulin dose >60 U, add rapid-acting insulin 0.1 U/kg/meal at largest meal
• If A1C not at target after 3 months, add second rapid-acting injection at next largest meal
• If still not at target after 3 more months, add third mealtime rapid-acting insulin

Basal-Bolus and Premixed Regimens
General Considerations

• Basal-bolus insulin therapy is flexible and recommended for intensive insulin therapy
  – Provides flexibility for meal timing
  – Doses can be adjusted depending on meal carbohydrate content
  – Require multiple daily injections
• Premixed insulin analogs may be considered in any patient in whom adherence is an issue
  – However, these preparations
    • Lack component dosage flexibility
    • May increase risk for hypoglycemia

Premixed vs Basal-Bolus

Premixed Insulin Therapy

Good Adherence Is Critical But Hard to Achieve

• In a twice-daily regimen, missing as little as 1 insulin dose per week increases risk for hyperglycemia
• Up to 73% of physicians reported that their patients with diabetes are nonadherent to treatment
• Common reasons for nonadherence
  – Too busy
  – Traveling
  – Skipped meals
  – Stress/emotional problems
  – Public embarrassment

Margot
Initiating Insulin

• Margot is started on premixed insulin in addition to her current oral antidiabetic medications
  – Premixed considered best option given her busy schedule
• Returns at 3 months and reports one mild, manageable episode of hypoglycemia
• Minimal weight increase
• A1C: 6.8%
  – A repeat appointment with diabetes educator is made to reinforce critical concepts
Conclusions

- Current treatment algorithms have only limited flexibility in glycemic goals, do not include many current agents, and only account for individual patient characteristics to a limited extent
- Insulin is a valuable treatment option in many patients with diabetes
  - Most effective at lowering glycemia
  - Most patients with diabetes will eventually require insulin
  - Selection of appropriate insulin regimen and titration to goal requires individualized attention

Post-Activity Questions

- A 39-year-old overweight patient is being treated with metformin and has an A1C of 7.5%. What is your add-on therapy?
  1. Glucagon-like peptide (GLP)-1 agonist or dipeptidyl-peptidase (DPP)-4 inhibitor
  2. Thiazolidinedione
  3. Sulfonylurea
  4. Insulin

Post-Activity Questions

- An intensive A1C goal would generally not be selected for T2DM patients with macrovascular or microvascular disease.
  1. Strongly disagree
  2. Disagree
  3. Neutral
  4. Agree
  5. Strongly agree

Post-Activity Questions

- Insulin-based therapy could be considered in a symptomatic patient with an A1C of 8.5%.
  1. Strongly disagree
  2. Disagree
  3. Neutral
  4. Agree
  5. Strongly agree

Post-Activity Questions

- A 75-year-old patient with T2DM and renal impairment has an A1C of 7.8% on dual oral therapy. Intensifying the regimen could be considered.
  1. Strongly disagree
  2. Disagree
  3. Neutral
  4. Agree
  5. Strongly agree

Post-Activity Questions

- When determining an A1C target for a patient, how often do you NOW PLAN evaluate T2DM duration?
  1. Never
  2. Sometimes
  3. Most of the time
  4. Always
  5. Only in select patients
Post-Activity Questions

• When determining an A1C target for a patient, how often do you NOW PLAN evaluate the patient’s psychosocial profile?
  1. Never
  2. Sometimes
  3. Most of the time
  4. Always
  5. Only in select patients