Achieving Optimal Control
In Type 2 Diabetes

Screening For Diabetes....

ADA’s Recommendations:

FBS ≥ 126 mg/dl
Random Glucose ≥ 200 mg/dl
A1C ≥ 6.5%
What's The Optimal A1C Goal??

Intensive Therapy for Diabetes Reduction in Incidence of Complications

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Type 1 DCCT</th>
<th>Type 2 Kumamoto</th>
<th>Type 2 UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 → 7%</td>
<td>9 → 7%</td>
<td>8 → 7%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>76%</td>
<td>69%</td>
<td>17-21%</td>
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<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24-33%</td>
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<tr>
<td>Neuropathy</td>
<td>60%</td>
<td>-</td>
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</table>
What About Glycemic Control And Macrovascular Disease?

Recent Trials Modify The Paradigm

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

The New England Journal of Medicine
NEJM 360: 2560-2572, 2009

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group

The New England Journal of Medicine
NEJM 358: 129-139, 2008

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The ADVANCE Collaborative Group

The New England Journal of Medicine
NEJM 358: 2545-2559, 2008
Diabetic Control and Macrovascular Disease

<table>
<thead>
<tr>
<th></th>
<th>VADT</th>
<th>ACCORD</th>
<th>ADVANCE</th>
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<tr>
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<tr>
<td>Age (Yrs)</td>
<td>60</td>
<td>62</td>
<td>66</td>
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<tr>
<td>Gender (% M/F)</td>
<td>97/3</td>
<td>62/38</td>
<td>58/42</td>
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<tr>
<td>DM Duration (Yrs)</td>
<td>11.5</td>
<td>10</td>
<td>8</td>
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<tr>
<td>HbA1c</td>
<td>9.4</td>
<td>8.1</td>
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<tr>
<td>CV Events (%)</td>
<td>~40</td>
<td>~35</td>
<td>~32</td>
</tr>
<tr>
<td>Insulin Use (%)</td>
<td>~50</td>
<td>~35</td>
<td>~1.5</td>
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<tr>
<td>Follow-Up (Yrs)</td>
<td>5.6</td>
<td>3.4</td>
<td>5</td>
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</table>

VADT, ACCORD, ADVANCE: Primary Outcome CV Events

CV Death, MI Stroke

Cumulative incidence (%) vs. Follow-up (months)

- Standard Control
- Intensive Control

HR 0.94 (0.84-1.06)
P = 0.32
**Hypoglycemia In Recent Major Clinical Trials**

- After the results became available, hypoglycemia was identified as an area of concern in 3 recent major clinical trials in which intensive glucose control was compared with standard glucose control:
  - ACCORD\(^1\)
  - VADT\(^2\)
  - ADVANCE\(^3\)


---

**Hypoglycemia and CV Disease**

**Hemodynamic Responses To Hypoglycemia**

- Heart Rate Increases
- Systolic BP Increases
- Diastolic BP Decreases
- Cardiac Output Increases
- Myocardial Contractility Increases
  - EKG Changes
    - T wave flattening or inversion
    - ST depression
    - QT prolongation

Wright R et al *Diabetes/ Metabolism Research and Reviews* 2008
Hypoglycemia and CV Disease

Hematologic Responses To Hypoglycemia

- Increased RBCs Leading To Increased Blood Viscosity
- Enhanced Platelet Aggregation
- Increased Platelet Factor 4
- Increased Thromboglobulin
- Increased Coagulation Factor VIII
- Increased Von Willebrand Factor
- Increased Thrombin Generation

Wright R et al Diabetes/ Metabolism Research and Reviews, 2008

Is intensive glucose control ever beneficial to the vasculature?
### UKPDS
United Kingdom Prospective Diabetes Study

<table>
<thead>
<tr>
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<td>~10</td>
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### UKPDS
United Kingdom Prospective Diabetes Study Follow-Up

#### Myocardial Infarction

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<th>Sulfonylurea–insulin</th>
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<tr>
<td>1999</td>
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<td>296</td>
<td>636</td>
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<td>2007</td>
<td>339</td>
<td>678</td>
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</table>

Summary: Trials and Metabolic Memory

- Get In There Early With Tight Glycemic Control BUT Relax Glycemic Control Later!

- If CV Risk Factors Are Controlled, There Is No Benefit And Potential Harm To Intensive Glycemic Control In High Risk Patients With A Long Duration Of DM

Natural History of Type 2 Diabetes

*IFG=impaired fasting glucose.
Multi-factorial Pathogenesis of Type 2 Diabetes

- Decreased insulin secretion
- Inefficient glucose uptake (skeletal muscle)
- Increased hepatic glucose production
- Decreased incretin effect
- Increased glucagon secretion
- Increased free fatty acids
- Neurotransmitter dysfunction
- Increased glucose reabsorption

Multiple Factors Drive Progressive Decline Of β-Cell Function

- Hyperglycemia (Glucose Toxicity)
- Insulin Resistance
- "Lipotoxicity" Elevated FFA, TG
- Amyloid Deposition
- Protein Glycation
- Interleukin 1 α and β
The Sulfonylureas

The Good
- Efficacious (↓A1C 1.2%)
- Increase Insulin Secretion
- Long Track Record
- Inexpensive

Not So Good
- Hypoglycemia
- Weight Gain
- Failure In 3-5 Years

Multi-factorial Pathogenesis of Type 2 Diabetes

- Decreased Insulin secretion
- Inefficient glucose uptake (skeletal muscle)
- Increased hepatic glucose production
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- Increased glucose reabsorption
Fat Topography in Insulin Resistance

Adiponectin: Increases Insulin Sensitivity

Hi TG  
Hi FFA

Intramuscular  
Intrahepatic  
Subcutaneous

Intra-Abdominal

FFA  
TNF α  
Resistin  
Leptin  
IL-6  
CRP  
Tissue Factor  
PAI-1  
Angiotensinogen
**Medications To Break Insulin Resistance: Metformin**

**The Good:**
- Efficacious (↓A1C 1.2%)
- Long Track Record
- ↓ Hepatic Glucose Production (90%)
- Helps Muscle Glucose Uptake (10%)
- Colon Cancer Protection

**Not So Good:**
- GI Upset
- Hold For Procedures and CT Dye Load
- Watch Creatinine Stop If > 1.5mg

**Medications To Break Insulin Resistance: Thiazolidinediones**

**The Good:**
- Efficacious (↓A1C 1.2%)
- Reasonably Long Experience
- No Hypoglycemia
- β Cell Preservation
Thiazolidinediones (TZD’s)

The Good:
- Efficacious
- Reasonably Long Experience
- No Hypoglycemia
- β Cell Preservation

Not So Good
- Increased CV Risk?
- Edema
- Weight Gain
- Fractures
- Bladder Cancer?

Multi-factorial Pathogenesis of Type 2 Diabetes

Decreased Insulin secretion
- Inefficient glucose uptake (skeletal muscle)
- Increased hepatic glucose production
- Decreased incretin effect
- Increased glucagon secretion
- Increased free fatty acids
- Neurotransmitter dysfunction
- Increased glucose reabsorption

DeFronzo RA. Diabetes 2009;58:732-768.
GLP-1 Modes of Action in Humans

Upon Ingestion of Food...

- Stimulates Insulin Secretion
- Suppresses Glucagon
- Slows Gastric Emptying
- Reduces Food Intake

GLP-1 Is Secreted From the L-cells In the Intestine

This in Turn...

Drucker DJ. Curr Pharm Des 2001; 7:1399-1412
Drucker DJ. Mol Endocrinol 2003; 17:161-171

One More Point
Going Back to Those \( \beta \) Cells.....
Natural History of Type 2 Diabetes

Insulin Resistance

β-Cell Failure

Insulin Level

Fasting Glucose

Post-meal Glucose

Glucose (mg/dL)

Relative Function (%)

Years of Diabetes

Obesity IFG* Diabetes Uncontrolled Hyperglycemia

*IFG=impaired fasting glucose.

β-cell Neogenesis, Proliferation and Apoptosis

Ductal Progenitor Cells

Neogenesis

Proliferation

Islet

Apoptosis

GLP-1 Stimulates

GLP-1 Inhibits
GLP-1: Effects On The Gastrointestinal, Cardiac And Central Nervous Systems

GLP-1: Modes of Action in Humans

GLP-1: Effects On The Gastrointestinal, Cardiac And Central Nervous Systems

GLP-1 Modes of Action in Humans

Upon Ingestion of Food…

- Stimulates Insulin Secetion
- Suppresses Glucagon
- Slows Gastric Emptying
- Reduces Food Intake

Long Term Effects Demonstrated in Animals…

→ Increases β Cell Mass & Efficiency

Drucker DJ. Curr Pharm Des 2001; 7:1399-1412
Drucker DJ. Mol Endocrinol 2003; 17:161-171

**Glucose Dependent Effects of GLP-1**

*Type 2 Diabetics (n=10)*

Mean (se) <p.05  Nautack MA Diabetologia 1983

**GLP-1 Effect : Blocked By DPP-4**

**Mixed Meal**
- Intestinal GLP-1 Secretion
  - GLP-1(7-36) Active
  - DPP-IV Rapid Inactivation

**Plasma**
- GLP-1 Actions
- Renal Clearance

GLP-1(9-36) Inactive

Deacon *et al.* Diabetes 1995; 44:1126
GLP-1: Rapidly Degraded by DPP-4

Secreted GLP-1 Rapidly Degraded

- GLP-1 (green) released into intestinal capillaries is immediately exposed to DPP-4 (red)\textsuperscript{1}
- >50% of secreted GLP-1 is already degraded before it reaches the general circulation\textsuperscript{2}
- >40% of circulating GLP-1 is already degraded before it reaches β-cells\textsuperscript{2}

\textsuperscript{1}Hansen L. et al. Endocrinology. 1999;140:5356-5363;

Mentlein, R Regulatory Peptides 85:9-24, 1999
Enhance GLP-1 Effect By...

GLP-1 RECEPTOR AGONISTS

❖ Exenatide (Byetta/Bydureon) sc
❖ Liraglutide (Victoza) sc
❖ Dulaglutide (Trulicity) sc
❖ Albiglutide (Tanzeum) sc
❖ Lixisenatide sc

GLP-1 Mimetics

The Good:
✓ Efficacious (ΔA1C 1.2-1.5%)
✓ Decrease Post-Prandial Glucose
✓ No Hypoglycemia
✓ Potential For Weight Loss
✓ Perhaps β Cell Preservation

The Not So Good:
✓ Daily/Twice Daily/Weekly Injection
✓ GI Upset
✓ Rare Reports Of Pancreatitis
✓ Cost
GLP-1 Effect: Blocked By DPP-4

Mixed Meal

Intestinal GLP-1 Secretion

GLP-1(7-36) Active

DPP-4

Rapid Inactivation

GLP-1(9-36) Inactive

Renal Clearance

Deacon et al. Diabetes 1995; 44:1126

Enhance GLP-1 Effect By…

GLP-1 RECEPTOR AGONISTS

- Exenatide (Byetta/Bydureon)
- Liraglutide sc (Victoza)
- Dulaglutide (Trulicity) sc
- Albiglutide (Tanzeum) sc
- Lixisenatide sc

DPP-4 INHIBITORS

- Sitagliptin po (Januvia)
- Saxagliptin po (Onglyza)
- Linagliptin po (Tradjenta)
- Alogliptin po (Nesina)
DPP-4 Inhibitors

The Good:
- Efficacious (↓A1C 0.7%)
- Decrease Post-Prandial Glucose
- No Hypoglycemia
- Weight Neutral
- Safe In Renal Disease
- No GI Upset
- Perhaps β Cell Preservation

The Not So Good:
- Cost
- Rare Reports Of Pancreatitis

Multi-factorial Pathogenesis of Type 2 Diabetes

- Increased hepatic glucose production
- Increased glucagon secretion
- Increased free fatty acids
- Neurotransmitter dysfunction
- Increased glucose reabsorption
- Carbohydrate absorption
- Decreased insulin secretion
- Inefficient glucose uptake (skeletal muscle)

*Image credit: Joslin Diabetes Center. Joslin does not endorse products or services.*
**α Glucosidase Inhibitors**

**Good**
- Efficacious (↓ A1C 0.5%)
- Long Experience
- No Hypoglycemia
- No Weight Gain

**Not So Good**
- Dosing With Meals
- GI Intolerance

---

**Multi-factorial Pathogenesis of Type 2 Diabetes**

- Decreased insulin secretion
- Inefficient glucose uptake (skeletal muscle)
- Increased hepatic glucose production
- Decreased incretin effect
- Increased glucagon secretion
- Increased free fatty acids
- Neurotransmitter dysfunction
- Increased glucose reabsorption
**Dopamine Receptor Agonists**

Type 2 Diabetics Have Low Levels Of Brain Dopamine

Quick Release Bromocriptine Increases Brain Dopamine Levels

**Bromocriptine Mesylate: Proposed Mechanism Of Action**

- Morning administration (within 2 hours of waking) of Cycloset
- Low dopaminergic tone in hypothalamus in early morning in diabetes
- Restoration of morning peak in dopaminergic activity (via D2 receptor-mediated activity)
- Sympathetic tone
- HPA axis tone
- Hepatic gluconeogenesis
- FFA and TG
- Insulin resistance
- Inflammation/hypercoagulation

- Decreased postprandial glucose levels
- Reduction in insulin resistance
- Day-long reduction in plasma glucose, TGs and FFAs

Fonseca. Use of Dopamine agonists in Type-2-Diabetes. Oxford American Pocket Cards. OUP, 2010
Quick Release Bromocriptine

The Good
- Efficacious (↓A1C 0.5%)
- Resets Hypothalamic Circadian Clock
- Surprisingly Good CV Profile

Not So Good
- Hypotension
- Short Track Record
- Cost

Multi-factorial Pathogenesis of Type 2 Diabetes

- Decreased insulin secretion
- Inefficient glucose uptake (skeletal muscle)
- Increased hepatic glucose production
- Decreased incretin effect
- Increased glucagon secretion
- Increased free fatty acids
- Neurotransmitter dysfunction
- Increased glucose reabsorption
Glucose is filtered in the glomerulus. SGLT1 transports the remaining 10% of filtered glucose, SGLT2 transports 90% of filtered glucose out of the tubular lumen. SGLT1 is the primary SGLT in the small intestine.


SGLT = sodium-glucose co-transporter.

Normal Kidney: Glucose Reabsorption (Plasma Glucose ≤180 mg/dL)
Decreased glucose reabsorption into systemic circulation

SGLT = sodium-glucose co-transporter.


Renal Threshold for Glucose Excretion ($RT_G$) in Healthy Adult Subjects

Abdul-Ghani MA, DeFronzo RA.
Renal Threshold for Glucose Excretion \((RT_g)\) Is Increased in T2DM

Renal glucose reabsorption is increased in T2DM.

Abdul-Ghani MA, DeFronzo RA.

SGT1-2’s Lower Renal Threshold for Glucose Excretion \((RT_g)\)

Abdul-Ghani MA, DeFronzo RA.
T2DM = type 2 diabetes mellitus.
**The Gliflozin’s**

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ipragliflozin

**The SGLT-2 Inhibitors**

**The Good**
- Efficacious (↓A1C 1.0%)
- Inhibits Glucose Reabsorption At Renal Level
- Weight Reduction
- No Drug Interactions

**Not So Good**
- Increased UTI’s/Vaginitis
- Short Track Record
- Cost
**Combination Pills for Type 2 Diabetes**

- Glyburide/Metformin (Glucovance)
- Sitagliptin/Metformin (Janumet)
- Saxaglitin/Metformin (Kombiglyze)
- Linagliptin/Metformin (Jentadueto)
- Canaglifozin/Metformin (Invokamet)
- Dapaglifozin/Metformin (Xigduo)
- Empaglifozin/Metformin (Jardamet)
- Empaglifozin/Linagliptin (Glyxambi)

---

**Anti-Hyperglycemic Monotherapy: Maximum Therapeutic Effect on A1C**

- Acrabose
- Sita/Saxa/Saxagliptin
- QR Bromocriptine
- SGLT’s
- Exena/Linagliudide
- Pioglitazone
- Glimepiride
- Metformin
- Insulin

Reduction in A1C Level (%)

-0.5  -1.0  -1.5  -2.0

**References:**
A Basic Principle:

Fix The Fasting First

Physiologic Insulin Secretion:
Basal/Bolus Concept

- Suppresses Glucose Production Between Meals & Overnight
- Basal = 50% of Daily Needs
**Basal Insulins**

- Neutral Protamine Hagedorn (1946)
- Glargine (Lantus-2001 & Trujedo-2015)
- Detemir (2006)
- Degludec (2015)

**Starting Basal Insulin**

Continue Oral Agent(s) at Same Dosage (Eventually Reduce)
Add Single Insulin Dose (~ 15 units)
- Glargine (Anytime)
- Increase Insulin Dose 1 unit Daily Until FBS < 100 mg &/or HbA1C < 7%
Suggested Titration Options
For Glargine

Start with 10-15 units basal insulin and adjust weekly²*

<table>
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<tr>
<th>Mean of self-monitored FPG values from preceding 2 days</th>
<th>Increase in insulin dose (IU/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥180 mg/dL</td>
<td>+8</td>
</tr>
<tr>
<td>140-179 mg/dL</td>
<td>+6</td>
</tr>
<tr>
<td>120-139 mg/dL</td>
<td>+4</td>
</tr>
<tr>
<td>100-119 mg/dL</td>
<td>+2</td>
</tr>
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</table>

Or

Increase by 1 unit daily until FBS ≤ 100mg/dl

REPEAT


Insulin Pens

✓ More Convenient Than Vial And Syringe
✓ Repeatedly More Accurate Dosages
✓ Easier To Use For Those With Visual Or Fine Motor Skills Impairments
✓ Less Injection Pain
  Coated Needles Not Dulled By Insertion Into A Vial Before Insertion Into The Skin
Natural History of Type 2 Diabetes

Glucose Patterns in Type 2 Diabetes Mellitus

*IFG=impaired fasting glucose.
**Currently Available Bolus Insulins**

- Regular (1921)
- Insulin Lispro (1996)
- Insulin Aspart (2000)
- Insulin Glulisine (2006)
- Inhaled Insulin (2015)

**Fine Tuning The Bolus**

*The Bolus Has 2 Components:*

- **Prandial** → Fine Tune By Carbohydrate Counting
- **Correction Factor** → Adjustment For Pre-Meal Hyperglycemia
**Dosing Prandial Insulin**

✓ Considerations For Initial Dosing\(^1\)\(^-\)\(^3\)
  ✓ 5-10 u/meal OR 0.1 - 0.15 u/kg/meal
  ✓ Prandial Insulin Should Cover 50% Of Total Daily Dose ➔ 30% At Breakfast, 30% Lunch, 40% Dinner

✓ Considerations For Dosing Adjustments\(^1\)\(^-\)\(^3\)
  ✓ Titration To Adjust For Patterns In BG Levels
  ✓ Variable Meal Dosing To Adjust For Carbohydrate Intake
  ✓ Supplemental Dosing To Correct For BG Before Meals


---

**Glucose Patterns in Type 2 Diabetes Mellitus**

Discontinue SU/Tide/DPP-4 Inhibitor; Continue Metformin, TZD
Finally, For Your Larger Patients….

Extreme Insulin Resistance
> 200 units/day → Consider Using U500

✓ 5 Times As Concentrated---» 500 units/ml
✓ Dosed BID or TID
✓ Huge Cost Savings
Don’t Forget The ABCs

✓ A = Aspirin (if over age 50)
✓ B = Blood Pressure
✓ C = Cholesterol

BP Goals:

- SBP < 140
- SBP < 130 If Can Achieve Without Undue Treatment Burden, Such As Younger Pts.
- DBP < 90
- At Least One Anti-hypertensive At Bedtime
**Lipid Goals:**

- Goal LDL < 100 If No Overt CVD
- Goal LDL < 70 If CVD Or > 40 With One Or More CVD Risk Factor (Fam Hx, HTN, Smoking, Albuminuria)
- HDL > 40 and TG < 150 Desirable However LDL Targeted Statin Therapy Is Preferred Strategy

**Lipids: Statins Trump Other Meds**

- Combination Therapy Provides No Additional CVD Benefit Over Statin And Is Not Recommended
- If Goal LDL Not Reached On Max Tolerated Statin, Treat To Goal Of 30-40% Reduction In LDL From Baseline
Coronary Disease

- Screening Asymptomatic Patients Not Recommended
- Beta-blocker For At Least 2 Years After MI
- Metformin May Be Used In Patients With Stable Compensated CHF If Renal Function Normal; Avoid If Unstable CHF Or Hospitalized

Thanks For Listening