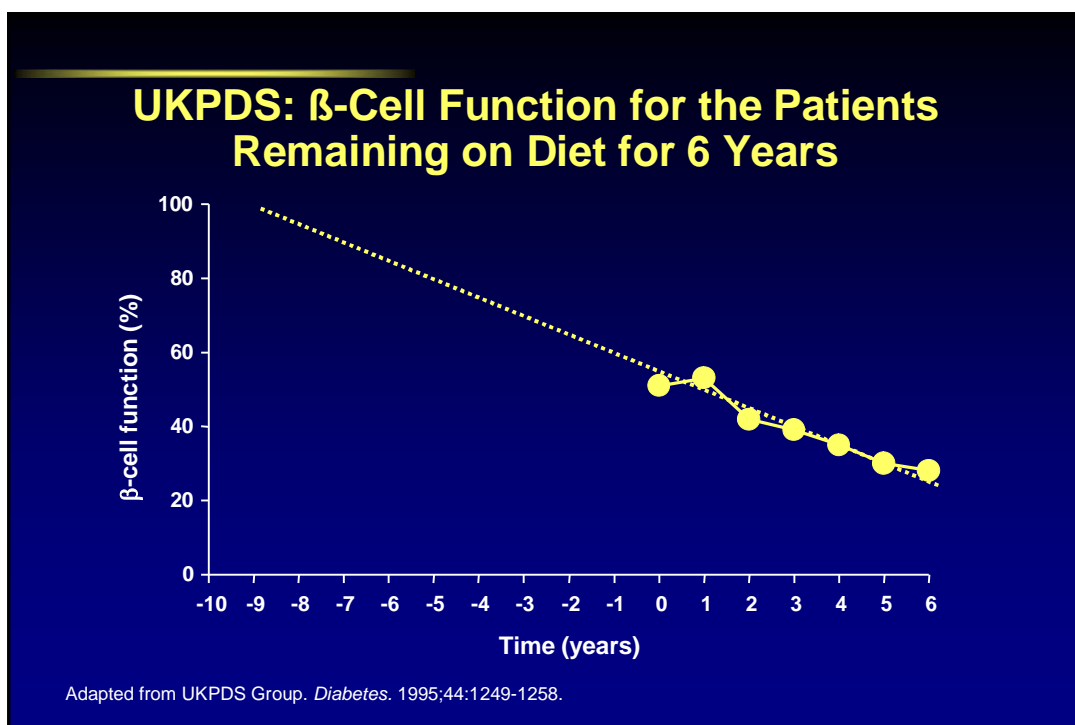
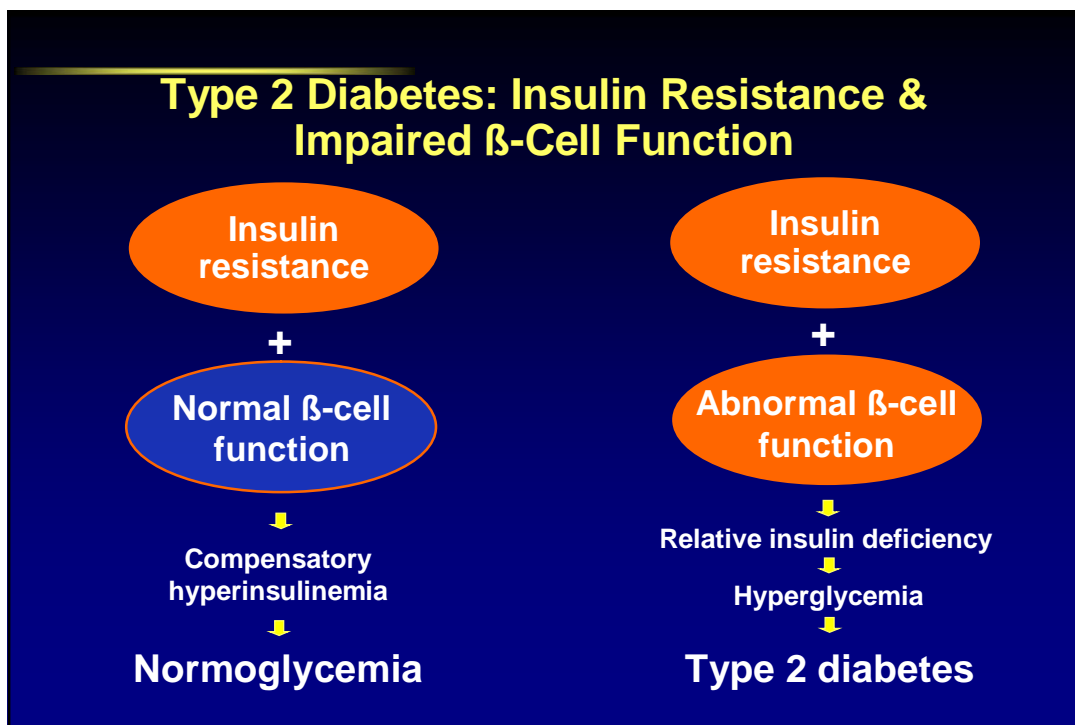


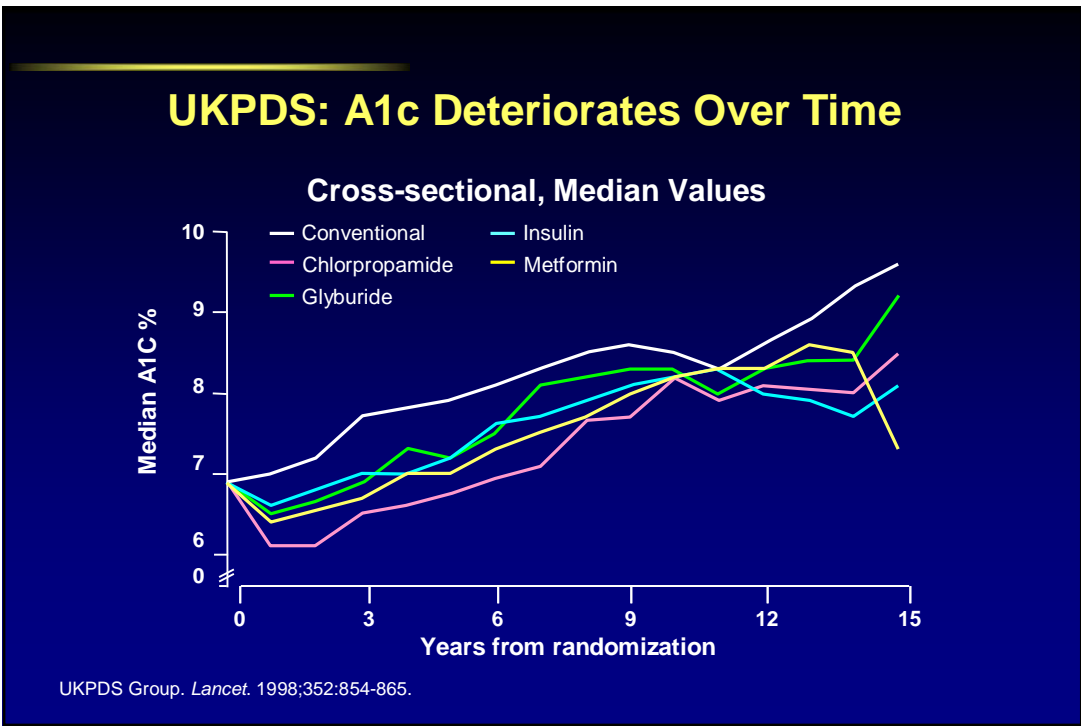
Type 2 Diabetes: Managing Secondary Failure to Oral Agents

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Type 2 Diabetes Arises From Dual Impairments

- **Insulin resistance**
 - Decreased peripheral glucose uptake
 - Increased hepatic glucose production
 - Abnormalities in FFA and triglyceride metabolism
- **Impaired β -cell function**
 - Inadequate insulin secretion (relative or absolute insulin deficiency)





ADA Treatment Goals and Diagnostic Targets

Biochemical Index	Normal	Diagnostic Criteria	Goal
A1C (%)*	< 6	—	< 7
Plasma fasting glucose (mg/dL)	< 100	≥ 126	90–130
OGTT (mg/dL) †	< 140	≥ 200	<180

* DCCT (HPLC) method (normal range: 4% to 6%).
 † 2 hours after a 75-g glucose load.

American Diabetes Association. *Diabetes Care* 2008;31(suppl 1):S12-S54.
 American Diabetes Association. *Diabetes Care* 2008;31(suppl 1):S55-S60.

Mrs. Chan: Uncontrolled on Metformin Monotherapy

Background

- 68-year-old Chinese woman
BMI 29 kg/m² (18.5-24.9)
- Medical history:
 - Hypertension (lisinopril 20 mg/d)
 - Dyslipidemia (pravastatin 40 mg/d)



Diabetes History

- Diagnosed 6 years ago; used diet & exercise for 2 years
 - A1C 9.5% → 8.6%
- Started metformin 4 years ago; dose increased to 2000 mg/d over 3 months
 - A1C 8.6% → 7% at 1 yr
 - After 4 years, A1C = 8.3%

Mrs. Chan: Uncontrolled on Metformin Monotherapy

Current Labs

- FPG 165 mg/dL
- A1C 8.3%
- BP 138/86 mmHg
- T. Chol 189 mg/dL
 - HDL 37 mg/dL
 - TG 148 mg/dL
 - LDL 118 mg/dL
- Alb:Cr 56 mg/g

Current Meds

- Metformin 1000 mg BID
- Lisinopril 20 mg/d
- Pravastatin 40 mg/d
- ASA 325 mg/d

Summary

- Type 2 DM known duration 6 years
- Responded to metformin initially; A1C gradually increased
- Now needs further therapy

Goals of Therapy for Mrs. Chan

- Preprandial Glucose < 70-130 mg/dL (3.9-7.2 mmol/L)
- A1C $\leq 7\%$ ($\Delta 1.3\%$)
- BP < 130/80 mmHg
- LDL < 100 mg/dL (2.6 mmol/L)
- Weight loss
- Symptom Free
 - Hypoglycemia
 - Fatigue
 - Polyuria
 - Infections
 - Microvascular complications
 - Cardiovascular complications

Selecting Therapy – Consider...

- Drug Factors
 - Mechanism
 - Efficacy: Δ A1C
 - Side Effects: Weight gain, hypoglycemia, GI, CVD
 - Dosing methods and frequency
- Patient Factors
 - Level of control
 - Organ function
 - Concurrent diseases and medications
 - Ability to adhere to complex regimens

Relative Efficacy of Oral Agents as Monotherapy

Decrease in	Sulfonylureas/ Repaglinide (varies with agent)	Metformin (immediate or extended release)	Rosiglitazone/ Pioglitazone	Acarbose	Exanatide/ Sitagliptin	Pramlintide
FPG (mg/dL)*	60–70 PPG 50-90	59–78 PPG 25-50	45–46	20-30 PPG 25-50	10-17 PPG 50-70	?
A1c (%)*	1.5–2.0	0.9–2.0	0.8-1.5	0.5–1.0	0.7–0.9	0.4

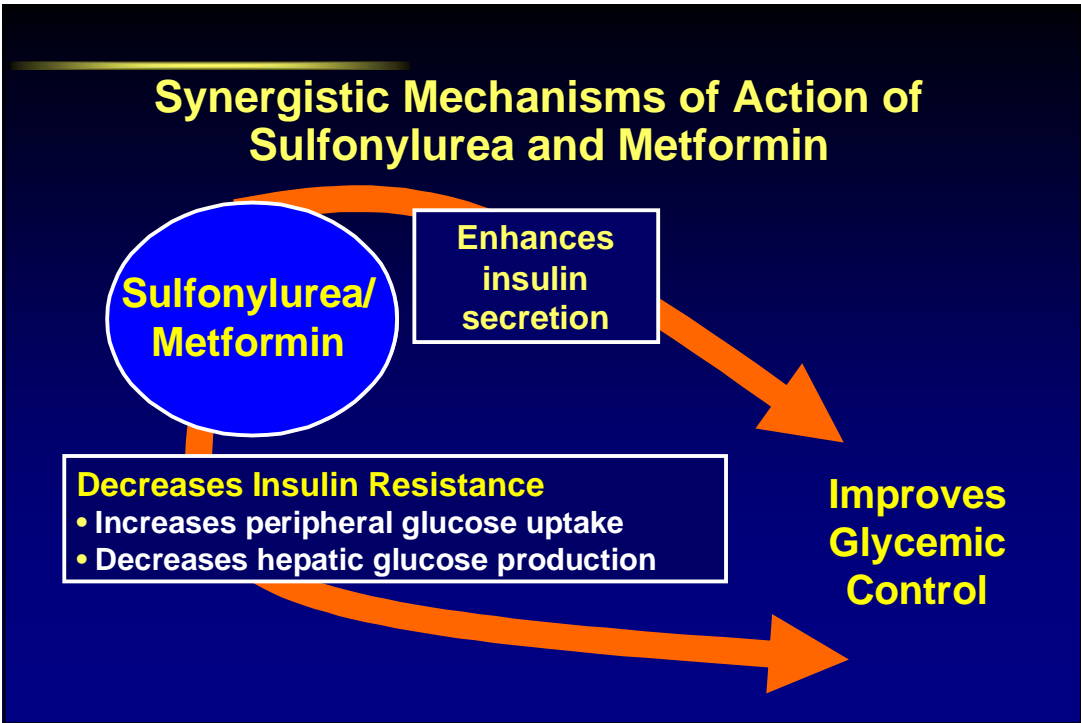
*Change from placebo

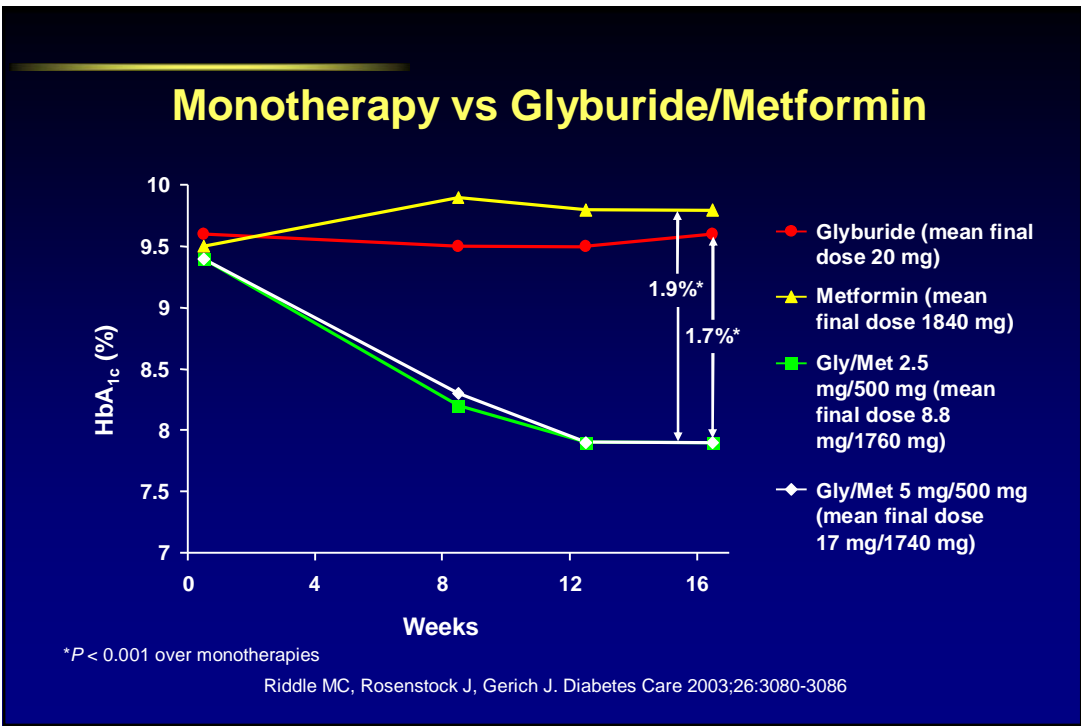
Pharmacologic Differences Among Oral Antidiabetic Agents

Mechanism of action	Metformin (immediate or extended release)	Sulfonylureas/ meglitinides/ nateglinide	α -Glucosidase inhibitors	TZDs
	↓ Insulin resistance	↑ Insulin secretion	↓ Digestion of complex carbohydrates	↓ Insulin resistance
	↓ Hepatic glucose output			↓ Hepatic glucose output
	↑ Peripheral glucose utilization			↑ Peripheral glucose utilization

Pharmacologic Differences Among Oral Antidiabetic Agents

	Exanotide GLP-1	Sitagliptin DPP-4 Inhibitor	Pramlintide
Mechanism of action	↑ Insulin secretion ↓ PP glucagon secretion Slow gastric emptying	↑ Insulin secretion ↓ PP glucagon secretion Slow gastric emptying	↑ Insulin secretion ↓ hepatic glucose production Slows gastric emptying





- ### Add Sulfonylurea to Patient's Therapy
- Efficacy: ↓ A1C 1.5-2.0%
 - Relative safety
 - Low cost
 - Use Glipizide
 - Shorter acting than glyburide
 - Less hypoglycemia in elderly
 - Low dose in elderly: 2.5 mg daily
 - Once daily OK

Basal Insulin Glargine + Oral Agents Forced Titration Schedule

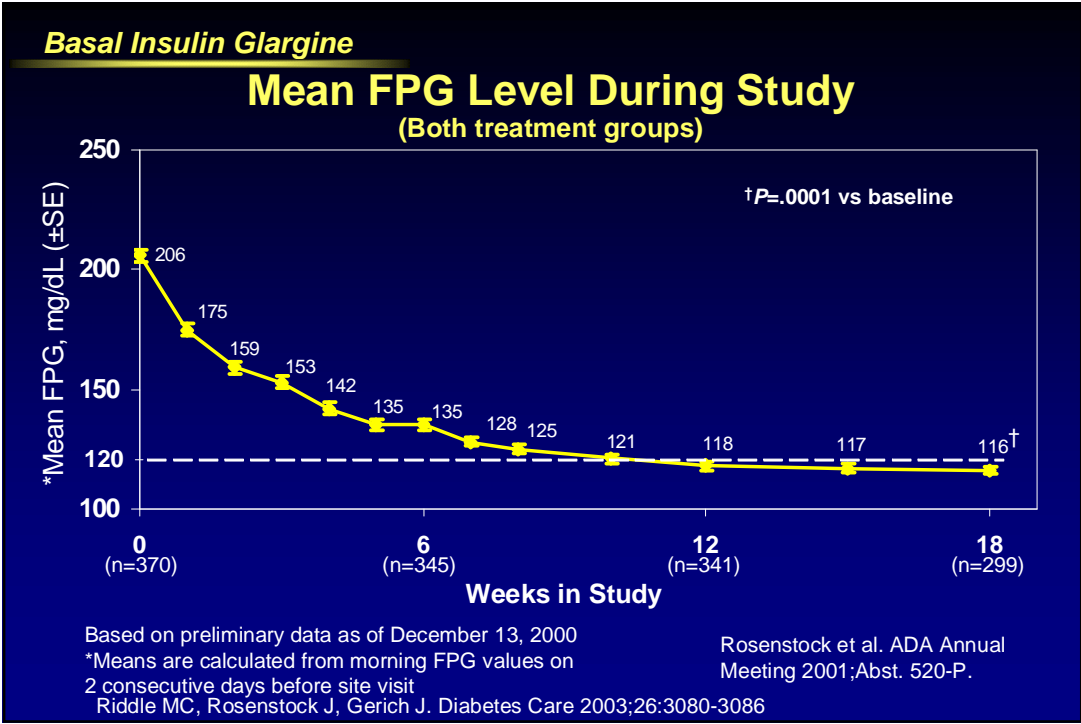
Start with 10 IU/day bedtime basal insulin dose and adjust weekly

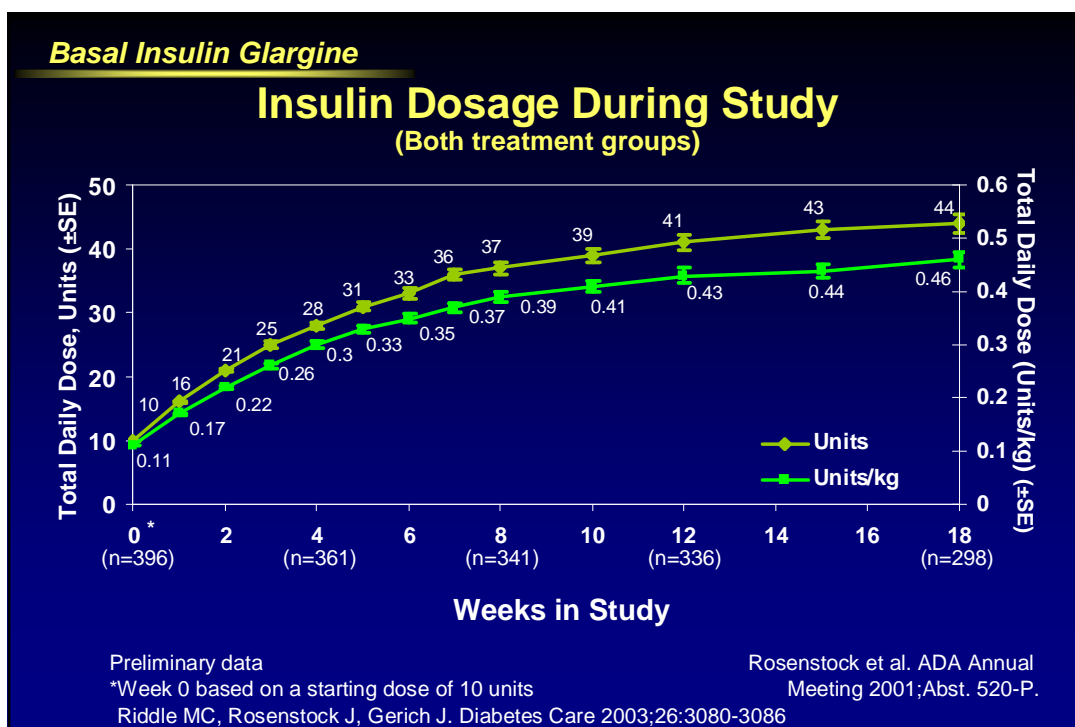
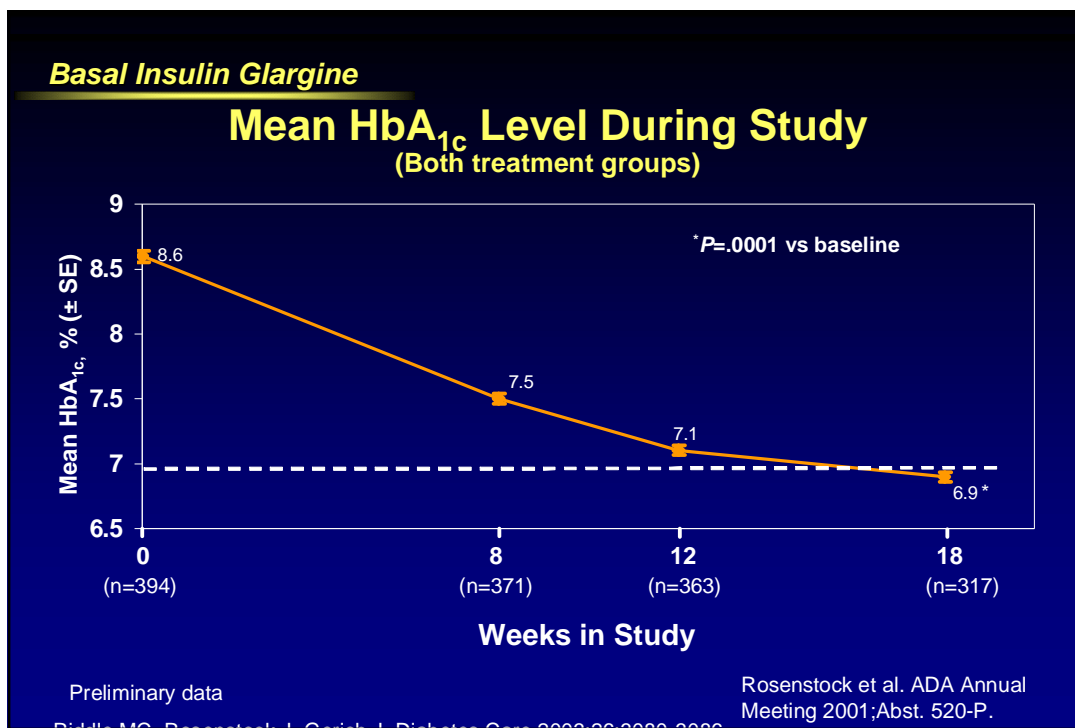
Self-monitored FPG (mg/dL) for two consecutive days with no episodes of severe hypoglycemia or PG ≤ 72 mg/dL	Increase in insulin dose (IU/day)
100-120 mg/dL	2
120-140 mg/dL	4
140-180 mg/dL	6
≥ 180 mg/dL	8

Treat to Target FPG ≤ 100 mg/dL

Small decreases (2-4 IU/day per adjustment) in dose are allowed in instances of self-monitored plasma glucose < 56 mg/dL or the occurrence of a severe hypoglycemic episode

Riddle MC, Rosenstock J, Gerich J. Diabetes Care 2003;26:3080-3086





Conclusions

- The tactic of basal insulin combined with prior oral therapy restores excellent glycemic control when a structured titration is used
- Using this strategy, serious hypoglycemia is uncommon

Riddle MC, Rosenstock J, Gerich J. Diabetes Care 2003;26:3080-3086

Stepped Care Approach For Type 2 Diabetes



Kroon L, Assemi M, Carlisle B. Chapter 50 Diabetes Mellitus. Applied Therapeutics Ed 9, 2008

