

Translating Diabetes Medications into Protocol

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International Diabetes Center




WORLD HEALTH ORGANIZATION
Collaborating Center for Diabetes
Education, Translation, and Computer
Technology

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International Diabetes Center

 Park Nicollet

Priorities of Care for Adults with Diabetes

Diagnosis–Prevention
 Dx Fasting Glucose ≥ 126 Casual ≥ 200 + Symptoms
 Prevent Pre-diabetes (IFG-IGT) & Metabolic Syndrome

Self-Management Knowledge and Skill
 Monitoring Medication Problem solving Food plan & nutrition
 Risk reduction Living & coping Physical activity

Glucose

D 5

Hemoglobin A1C
 Target $< 7.0\%$
SMBG
 Pre 70-120 mg/dL
 2 hr. Post < 160 mg/dL
 (~ 50% of readings)
 Minimize Hypoglycemia

Lipids

CVD Risk
 ASA, tobacco, ACEI/ARB, statin

Annual Lipid Profile
 LDL < 100
 HDL > 40
 Trigs < 150
DM + CVD
 LDL < 70

Hypertension

Blood Pressure
 (every visit)
 Dx and Rx
 $< 130/80$

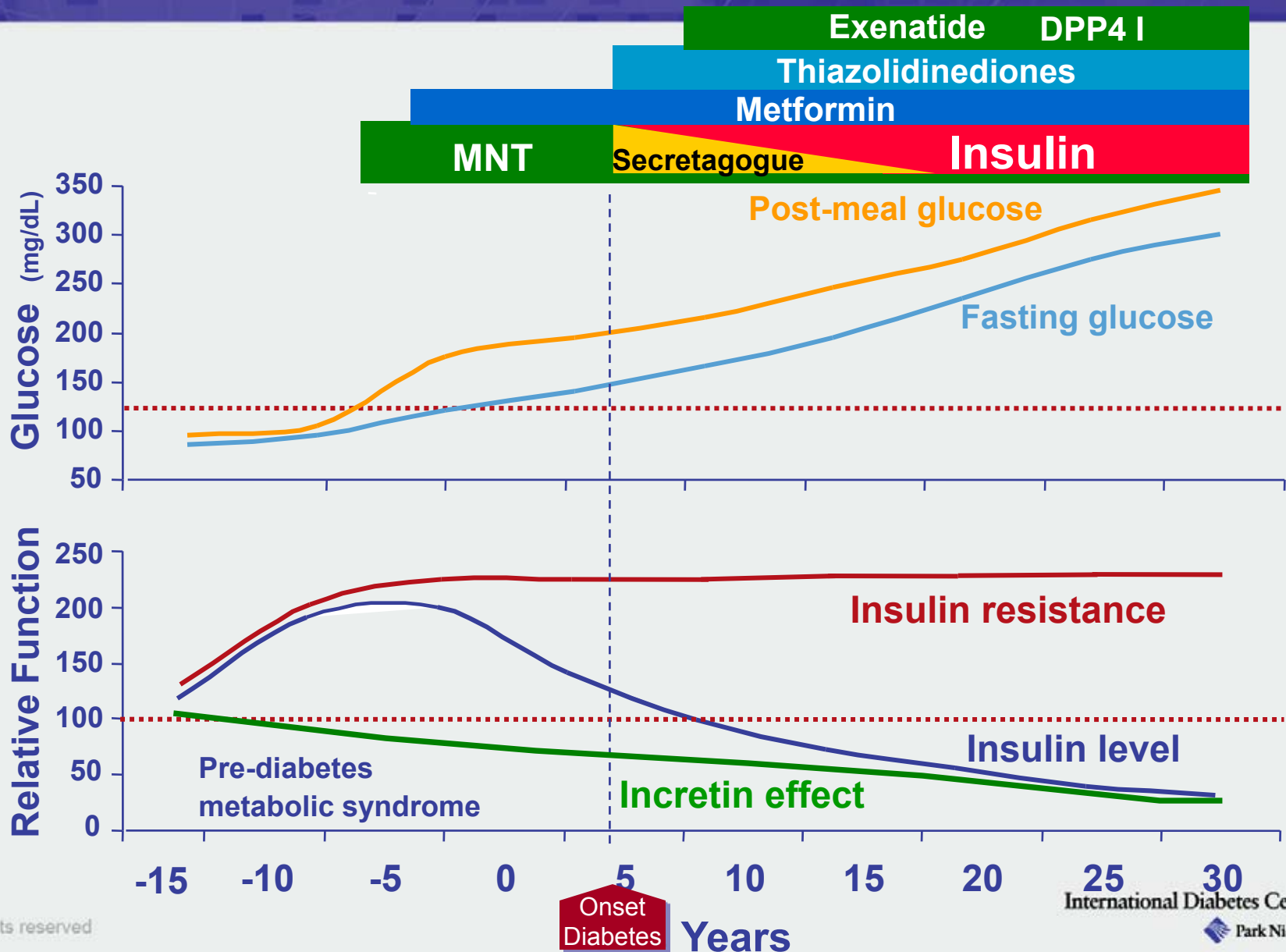
Microvascular complications

Annual Screening
Nephropathy
 Microalbumin Screening
 Estimated GFR
Retinopathy
 Dilated retinal exam
Neuropathy
 Neuro and Foot exam
 Sexual Health

Other essentials of care

Hospital Care
Foot Care
Dental Care
Immunizations

Natural History of Type 2 Diabetes

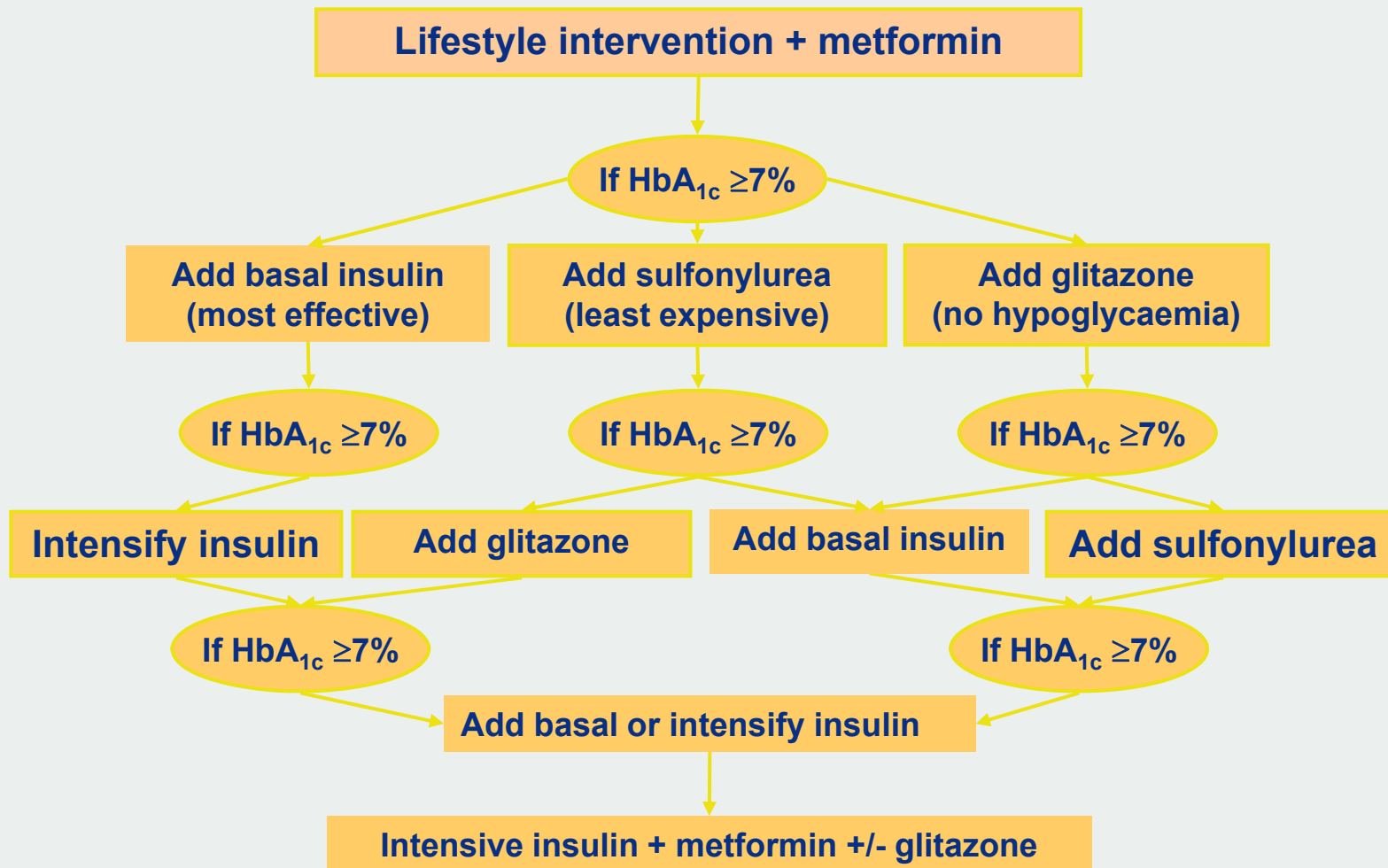


Diabetes Algorithms – A Brief History

- 1950-1990 Treatment approaches widely varied
- 1993 DCCT ends – “Metabolic Control Matters”
- **1994 Staged Diabetes Management (IDC)**
- 1995 ADA/EASD standards of diabetes care
- 2002 Royal College of General Practitioners
- 2000's Joslin, Texas Diabetes Council, Kaiser algorithms
- 2005 ADA Treatment algorithm
- 2006 AACE Roadmap
- **2007 Revised IDC algorithm (5th edition) SDM**
- 2008 (Sept) Canadian Diabetes Association algorithm
- 2008 (Oct) Revised ADA algorithm

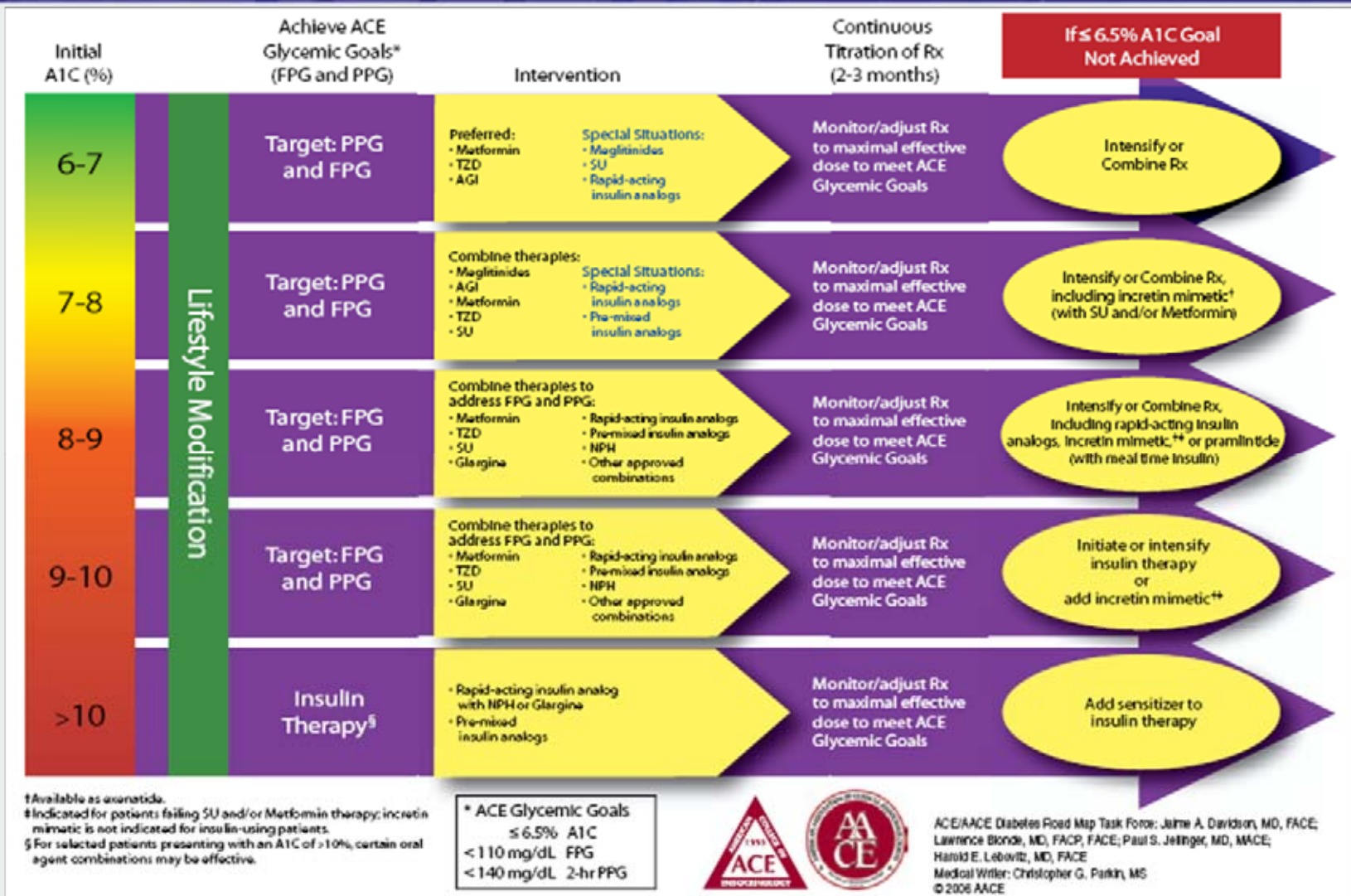
ADA /EASD Glycemic Algorithm 2006

Nathan DM, et al. *Diabetes Care & Diabetologia* 2006
Updated January 2008



*A1C checked every 3 mo until <7%, then every 6 mo. *Insulin treatment preferred over 3 oral agents.

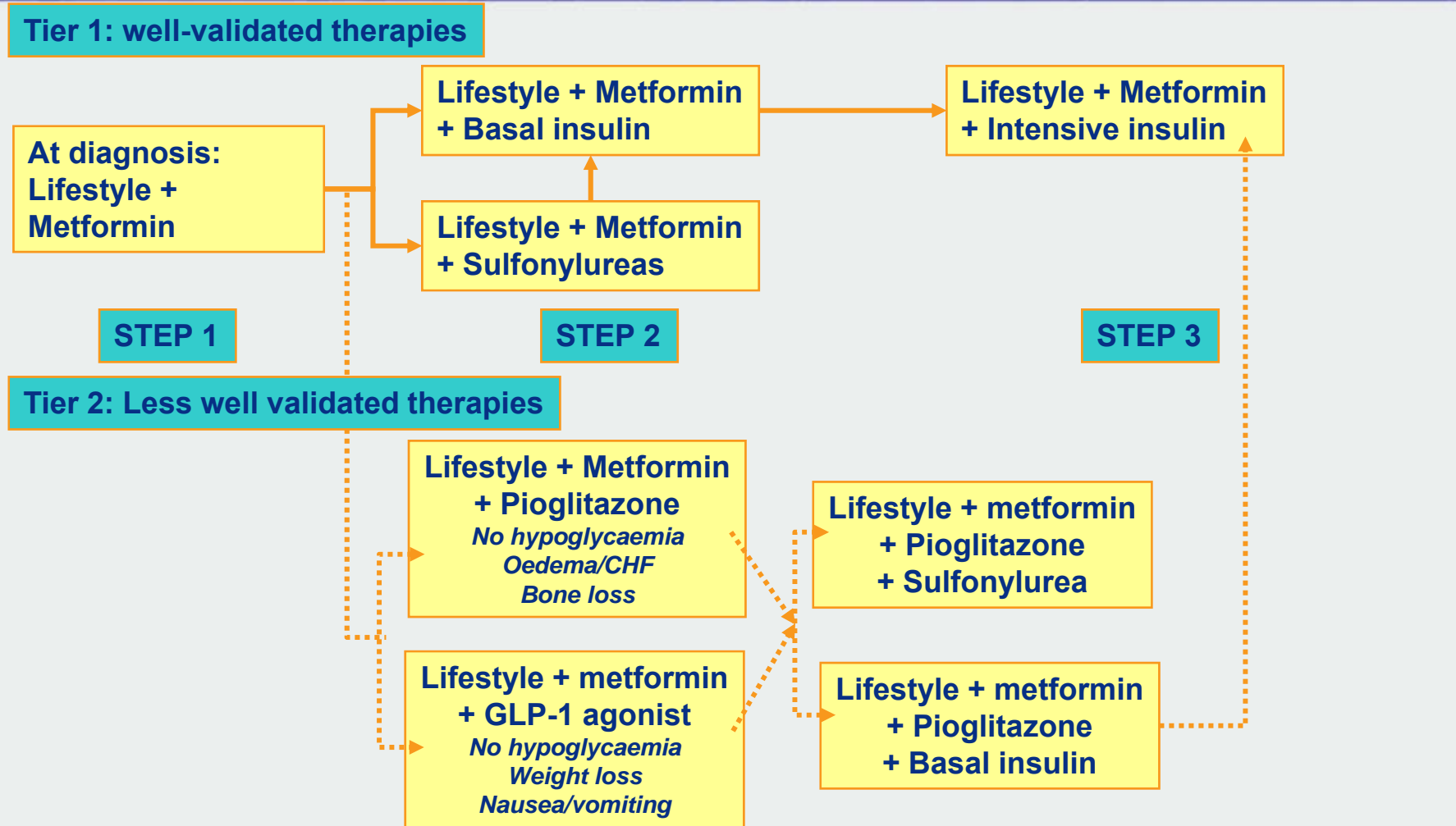
AACE Roadmap to Achieve Glycemic Goals – 2007



Modified from Jellinger PS et al. *Endocr Pract.* 2007;13:260-268.

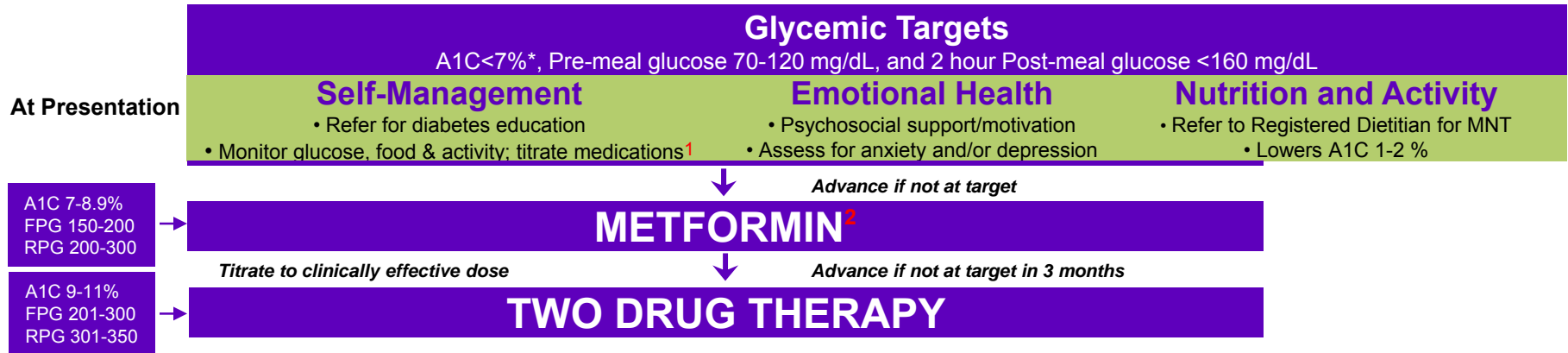
ADA/EASD Revised Algorithm for T2DM

Nathan DM, et al. *Diabetes Care & Diabetologia* October 22, 2008.



A1C every 3 months until A1C is $<7\%$ and then at least every 6
The interventions should be changed if A1C is $\geq 7\%$.

IDC Treatment of Type 2 Diabetes: Glycemic Control



Intensive Diabetes Therapy: Reduces Microvascular Complications

	DCCT	Kumamoto	UKPDS
HbA1c	9 → 7%	9 → 7%	8 → 7%
Retinopathy	63%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	Improved	-
Cardiovascular disease	NS (reduced in follow-up study)	-	NS (16%) (Reduced in follow-up study)

DCCT Research Group. *N Engl J Med.* 1993;329:977-986.
 Ohkubo Y, et al. *Diabetes Res Clin Pract.* 1995;28:103-117.
 UKPDS 33: *Lancet* 1998; 352, 837-853.

ACCORD, ADVANCE, VADT

Study	Number of subjects	Follow-up (years)	A1C Targets (%) Int. vs. Std	Intensive A1C Achieved	Standard A1C Achieved	Results
ACCORD	10,251	3.5	< 6.0 vs. 7.0-7.9	6.4 %	7.5 %	Intensive Inc. risk mortality (micro pending)
ADVANCE	11,140	~ 4.5	≤ 6.5 vs. local guidelines	6.4%	7.0%	Intensive control no reduction in CVD, reduces microvasc
VADT	1791	5	Action >6.5 vs. delta of 1.5	6.9%	8.4%	Intensive control no reduction in CVD

Glycemic Control in Type 2 Diabetes

Recommended Treatment Targets

Measure	How about A1C for diagnosis of DM?	IDC	ADA/ EASD/ Canadian	AACE/ IDF
A1C (%)		<7% *	<7% *	≤6.5% *
Fasting and premeal glucose (mg/dL)		70-120	70-130	<110
2 hr postmeal (mg/dL)		<160	<180	<140

Consider A1C <8% in this population

****Less stringent A1C goals are appropriate for some individuals:***

- Children (maybe most with type 1 diabetes)*
- Reduced life expectancy (over age 75 or other criteria)*
- History of CVD*
- History of severe complications – blindness, amputation, ESRD*
- History of severe hypoglycemia (hypoglycemia unawareness)*

Using A1C to Screen for and Dx Diabetes

SPECIAL FEATURE

Consensus Statements

A New Look at Screening and Diagnosing Diabetes Mellitus

. (*J Clin Endocrinol Metab* 93: 2447–2453, 2008)

Christopher D. Saudek, William H. Herman, David B. Sacks, Richard M. Bergenstal, David Edelman, and Mayer B. Davidson

Incorporate the long-established and universally accepted measure of chronic glycemia, HbA1c, into criteria for screening and diagnosing diabetes. HbA1c of 6.5% or greater would be diagnostic if confirmed by another test as described above. This cut point provides acceptable specificity and sensitivity.

IDC Treatment of Type 2 Diabetes: Glycemic Control (*SDM*)

Self-Management

- Refer for diabetes education
- SMBG, food & activity; titrate medications¹

Glucose Targets

- A1C < 7%
- Pre-meal <120 Post-meal <160

Nutrition and Activity

- Refer to Dietitian for MNT
- Lowers A1C 1-2 %



Advance/initiate drug treatment if not at target

METFORMIN

Titrate to clinically effective dose



Advance if not at target in 3 months

TWO DRUG THERAPY

Insulin secretion

Add Sulfonylurea

Insulin secretagogue

Risk of hypoglycemia,
Non-glucose dependent action
Weight gain, reduces A1C rapidly
Low Cost

Weight neutral

Add DPP4-inhibitor

Incretin enhancer

Stimulates glucose-dependent
insulin secretion
Suppresses glucagon
Expensive

Weight loss

Add Exenatide

Incretin mimetic

Stimulates glucose-dependent
insulin secretion, suppresses
glucagon, weight loss
Most expensive

Insulin sensitizer

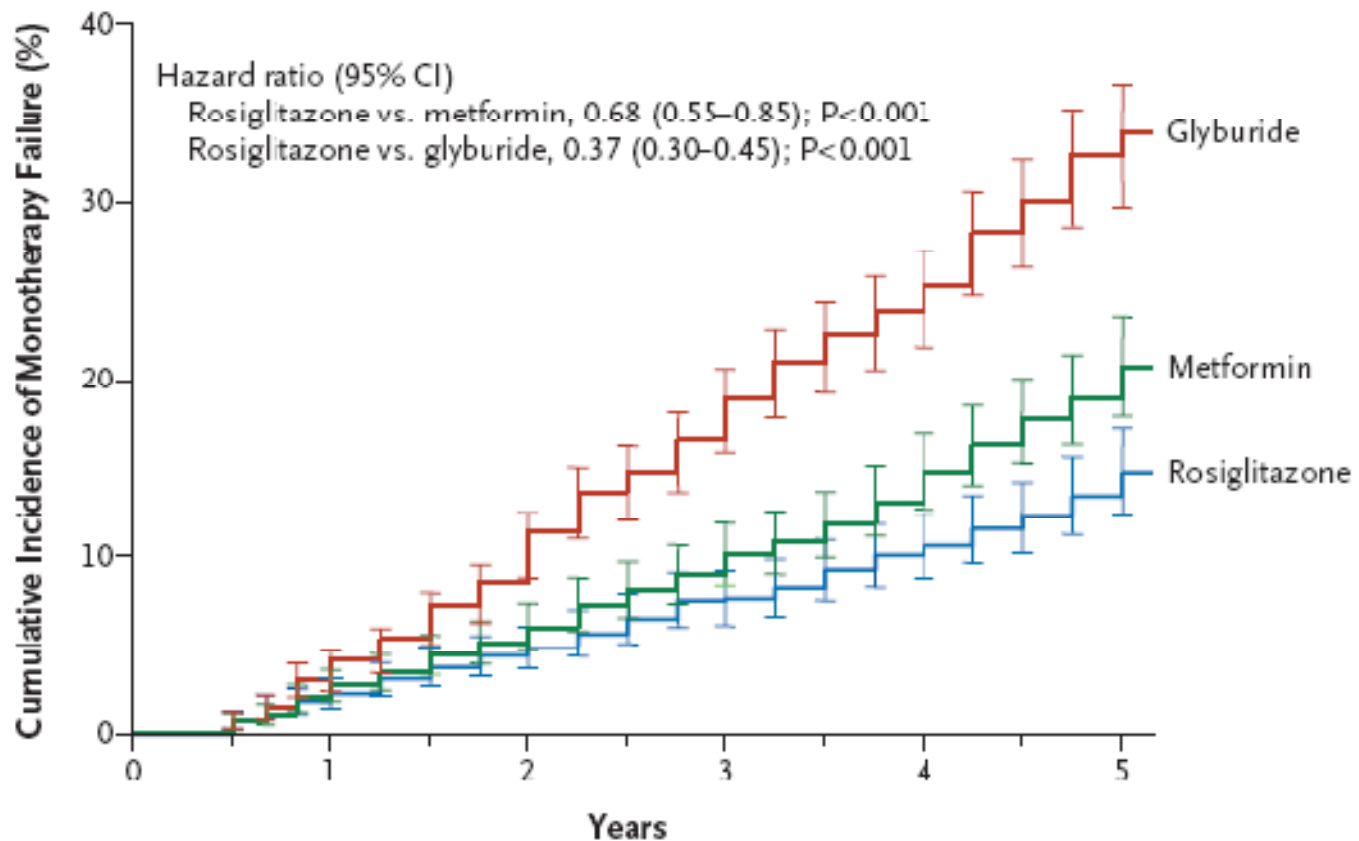
Add Pioglitazone

Insulin sensitizer

Improves insulin action
improve lipid profile, CVD risk
Weight gain, fluid retention, bone fx
Expensive

Monotherapy Failure at 5 Years

ADOPT Study; FPG >180 mg/dL



No. at Risk

Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

IDC Treatment of Type 2 Diabetes: Glycemic Control (*SDM*)

Self-Management <ul style="list-style-type: none"> Refer for diabetes education SMBG, food & activity; titrate medications¹ 	Glucose Targets <ul style="list-style-type: none"> A1C < 7% Pre-meal <120 Post-meal <160 	Nutrition and Activity <ul style="list-style-type: none"> Refer to Dietitian for MNT Lowers A1C 1-2 %
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↓ Advance/initiate drug treatment if not at target

METFORMIN

Titrate to clinically effective dose



Advance if not at target in 3 months

TWO DRUG THERAPY

Insulin secretion

Weight neutral

Weight loss

Insulin sensitizer

Add Sulfonylurea
Insulin secretagogue

Risk of hypoglycemia,
Non-glucose dependent action
Weight gain, reduces A1C rapidly
Low Cost

Add DPP4-inhibitor
Incretin enhancer

Stimulates glucose-dependent
insulin secretion
Suppresses glucagon
Expensive

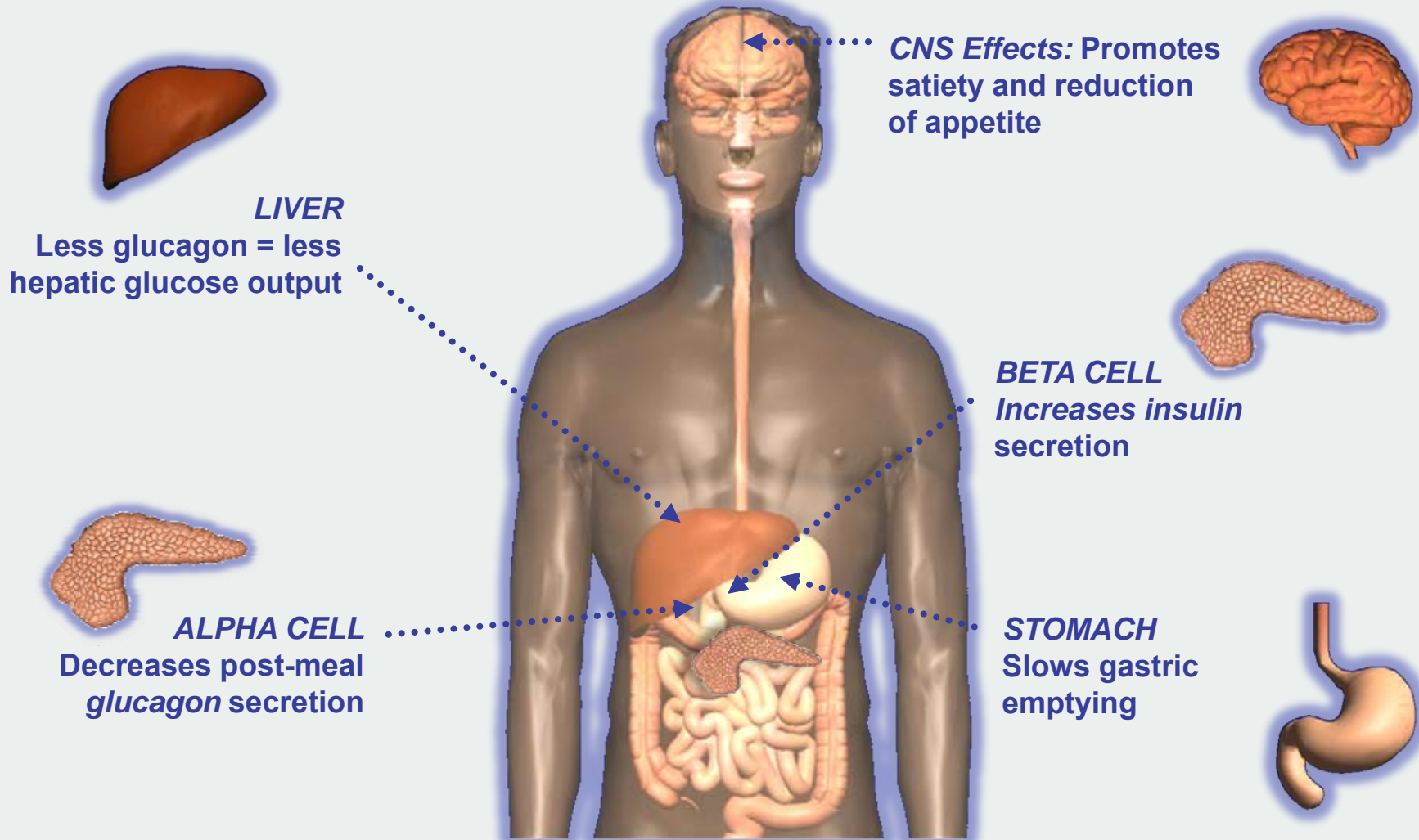
Add Exenatide
Incretin mimetic

Stimulates glucose-dependent
insulin secretion, suppresses
glucagon, weight loss
Most expensive

Add Pioglitazone
Insulin sensitizer

Improves insulin action
improve lipid profile, CVD risk
Weight gain, fluid retention, bone fx
Expensive

Glucagon Like Peptide -1 (GLP-1) Action



Ahren B Curr Diab Rep 2003; 3:365-372.

Baggio LL and Drucker DJ. Gastroenterology 2007; 132:2131-2157.

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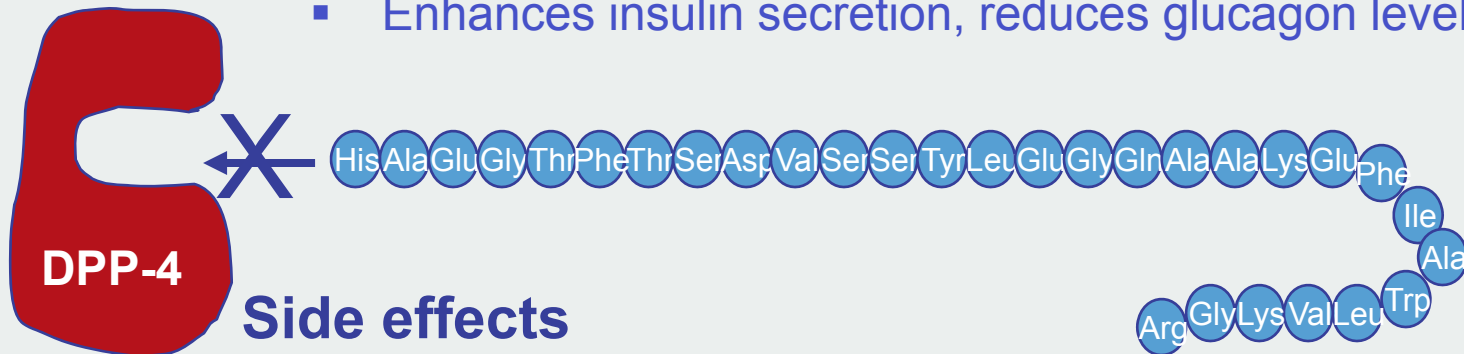
Overview of Dipeptidyl Peptidase-4 Inhibitor

Sitagliptin

Action

Sitagliptin

- Selective inhibitor of dipeptidyl peptidase-4 (DPP-4)
- Increases GLP-1 levels 2-3 fold
- Enhances insulin secretion, reduces glucagon levels



Side effects

- Very well tolerated; very low risk of hypoglycemia
- Weight neutral

Precautions and contraindications

- Kidney disease: adjust dosage
- Pregnancy (Category B)

Sitagliptin Indications and Dosing

Clinical Indicators

- Monotherapy and in combination with metformin, or thiazolidinedione
- Elevated post-meal BG; modest lowering of fasting BG

100 mg once daily pill with or without food

- Half-life 12 hours, time to max conc. 1 - 4 hours

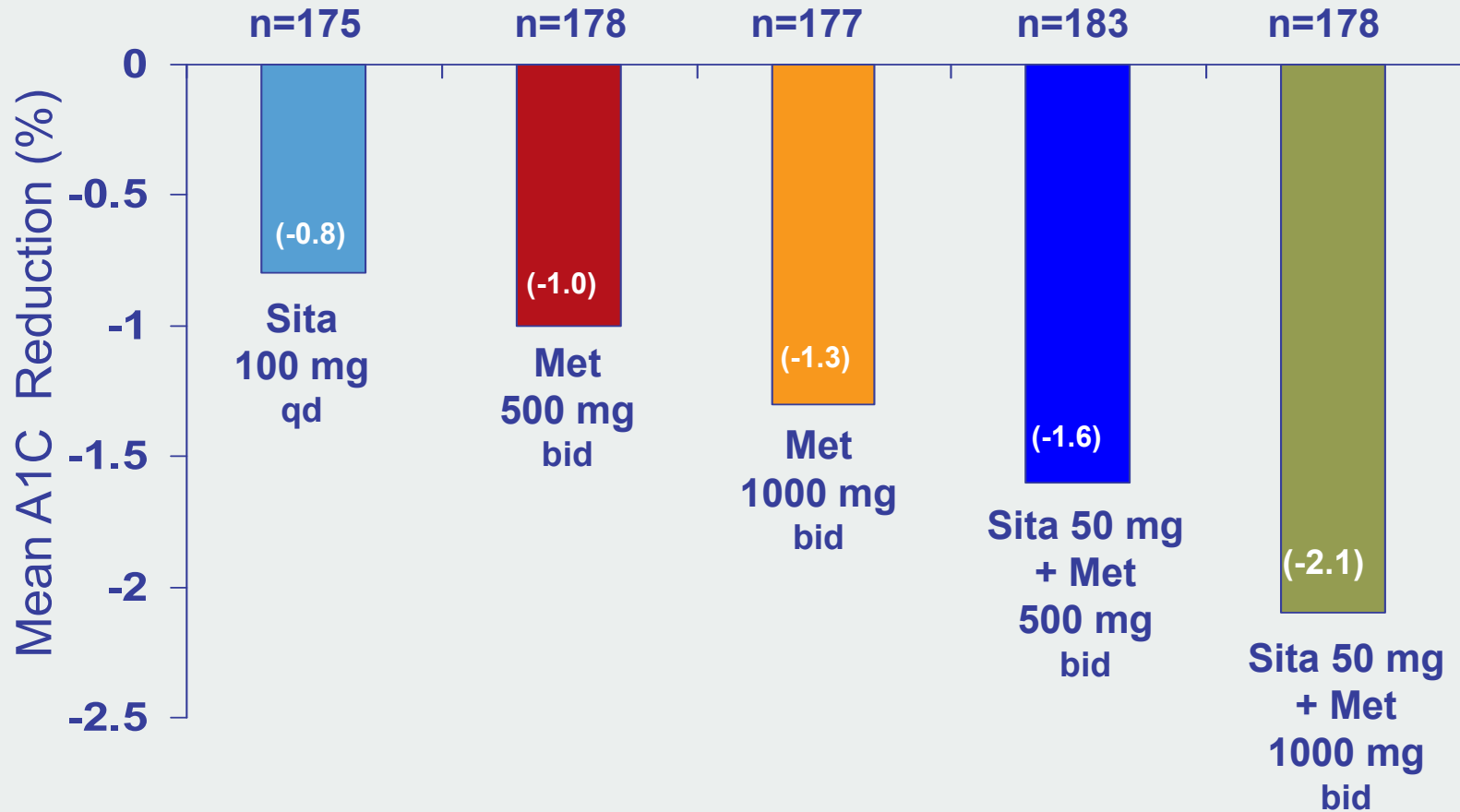
Dosing for chronic kidney disease

- CrCl \geq 50 mL/min 100 mg
- CrCl \geq 30 – 49 mL/min 50 mg
- CrCl <30 mL/min 25 mg

Sitagliptin and Metformin

Monotherapy and Combination

Duration 24 weeks; Baseline A1C = 8.8%



Incretin Mimetic (GLP-1 Mimetic)

Exenatide

Action

- Enhances glucose-dependent insulin secretion
- Reduces post-meal glucagon secretion
- Slows gastric emptying and reduces food intake

Clinical indicators

- Elevated post-meal BG
- In combination with metformin, sulfonylurea, or thiazolidinedione
- Triple therapy with metformin/sulfonylurea or metformin/thiazolidinedione

Side effects

- **Nausea (~40% patients), vomiting (13%), and diarrhea (13%)**
- Rare Hypoglycemia except with sulfonylurea

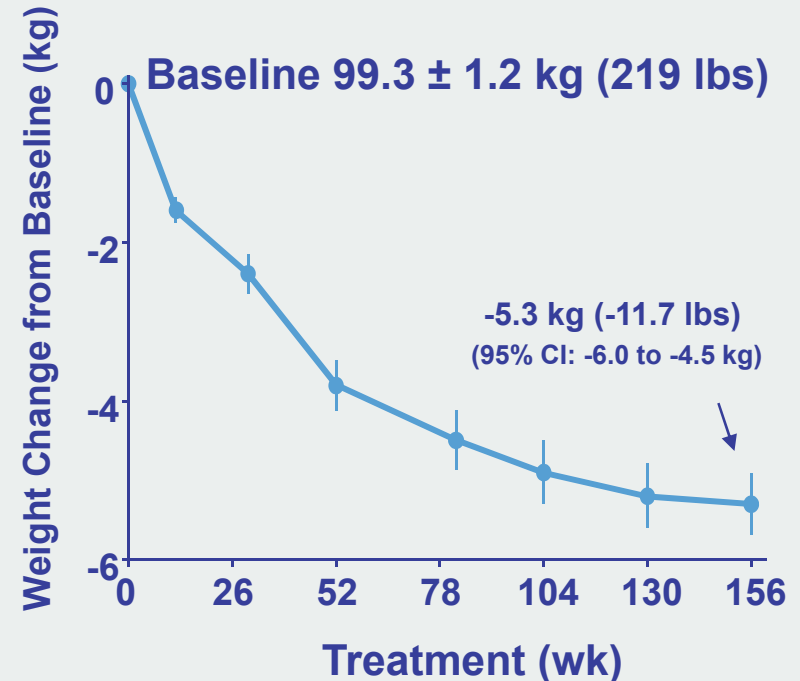
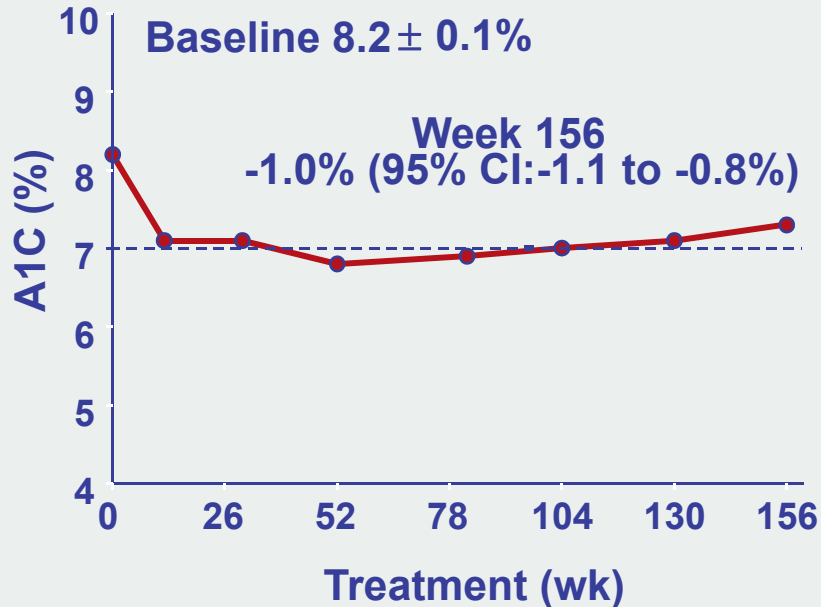
Precautions and contraindications

- Gastrointestinal disease – may be increase risk of **pancreatitis** (increased in T2DM)
- Kidney disease: Creatinine clearance <30 ml/min
- Pregnancy (Category C)

Dosing

- 5micogram injected bid – then after one month 10 micrograms bid
- 30 day supply in disposable pen – no need to refrigerate for the month of use.
- Take before meal 0-60 minutes not after meal

Change in Weight and A1C with 3-Years of Exenatide Therapy



Note: N = 527 eligible, N = 217 completers [primary loss due to patient/provider decision (41%) followed by adverse event (11%)]

Comparison of Clinical Utility & Concerns

	EXENATIDE	SITAGLIPTIN
A1C Reduction	~1.0%	~ 0.8%
Side Effects	GI side effects common	Well-tolerated
Weight	>85% patients lose weight	Weight neutral
Administration	BID injection (Fixed dose pen)	Oral, 1 tablet/day
Cost*	~\$245/month (10 µg BID retail)	\$195/month (100 mg retail cost)
Other Cardiac Risk Factors	↓ Triglycerides ↑ HDL-c ↓ BP	???

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 14, 2007

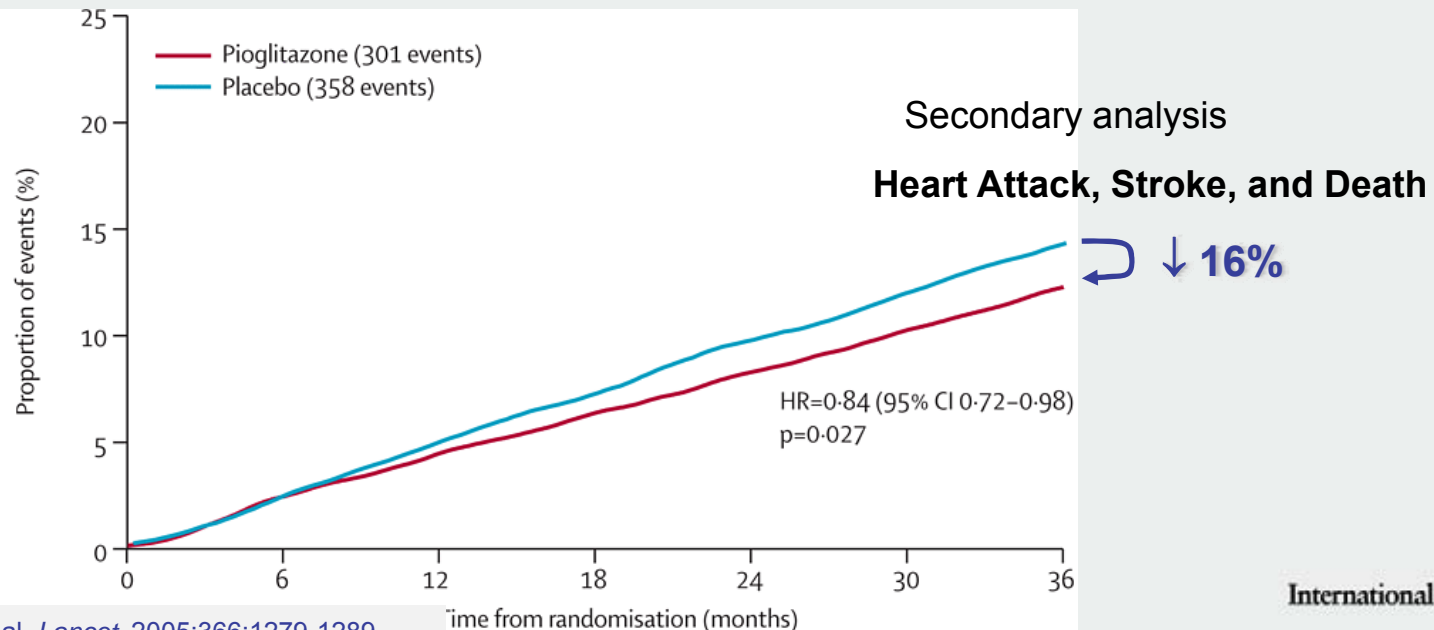
VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

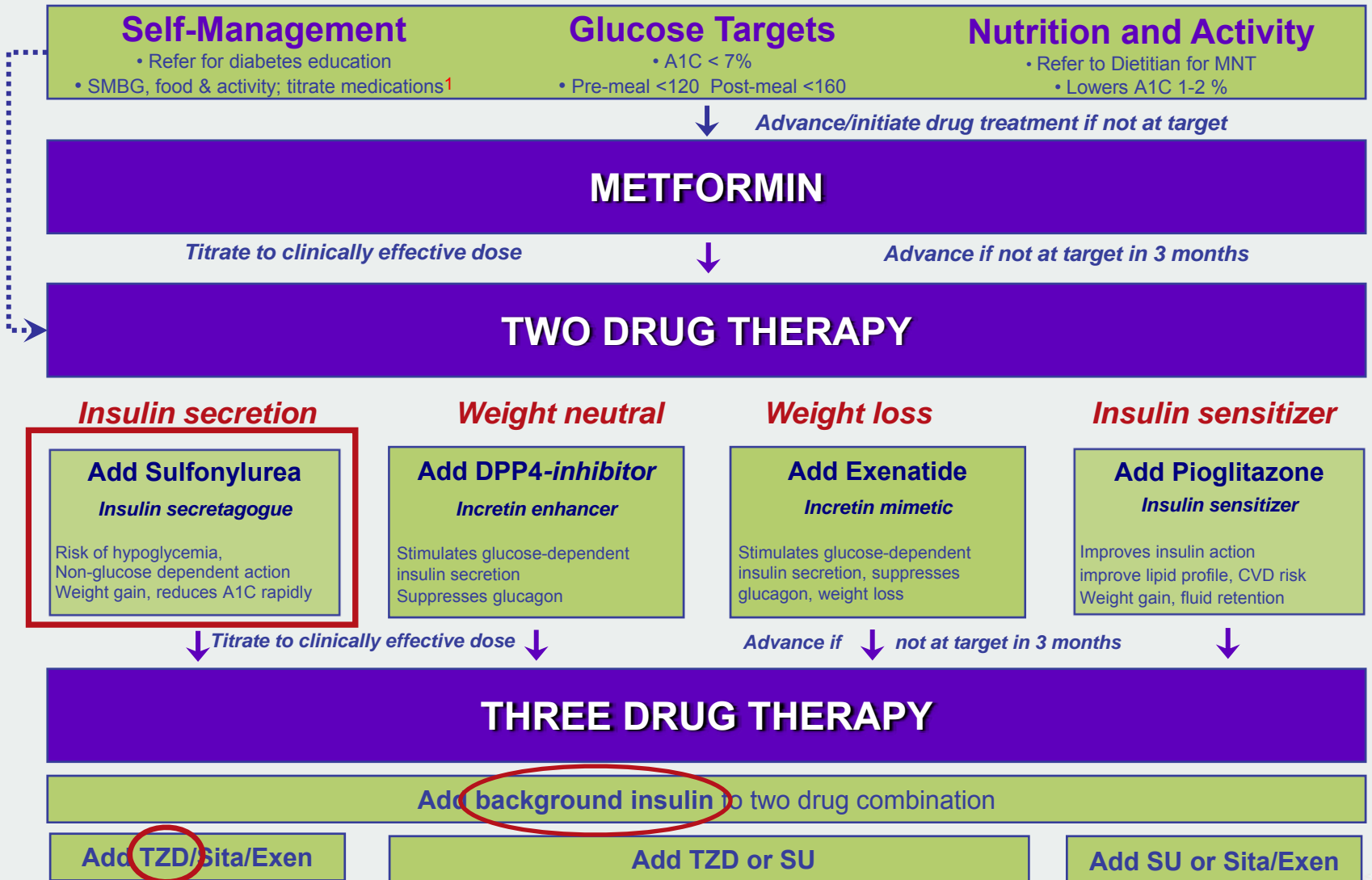
Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

N Engl J Med 2007;356:2457-71.

Proactive Study --- Pioglitazone effect on CVD & Mortality



Treatment of Type 2 Diabetes: Glycemic Control



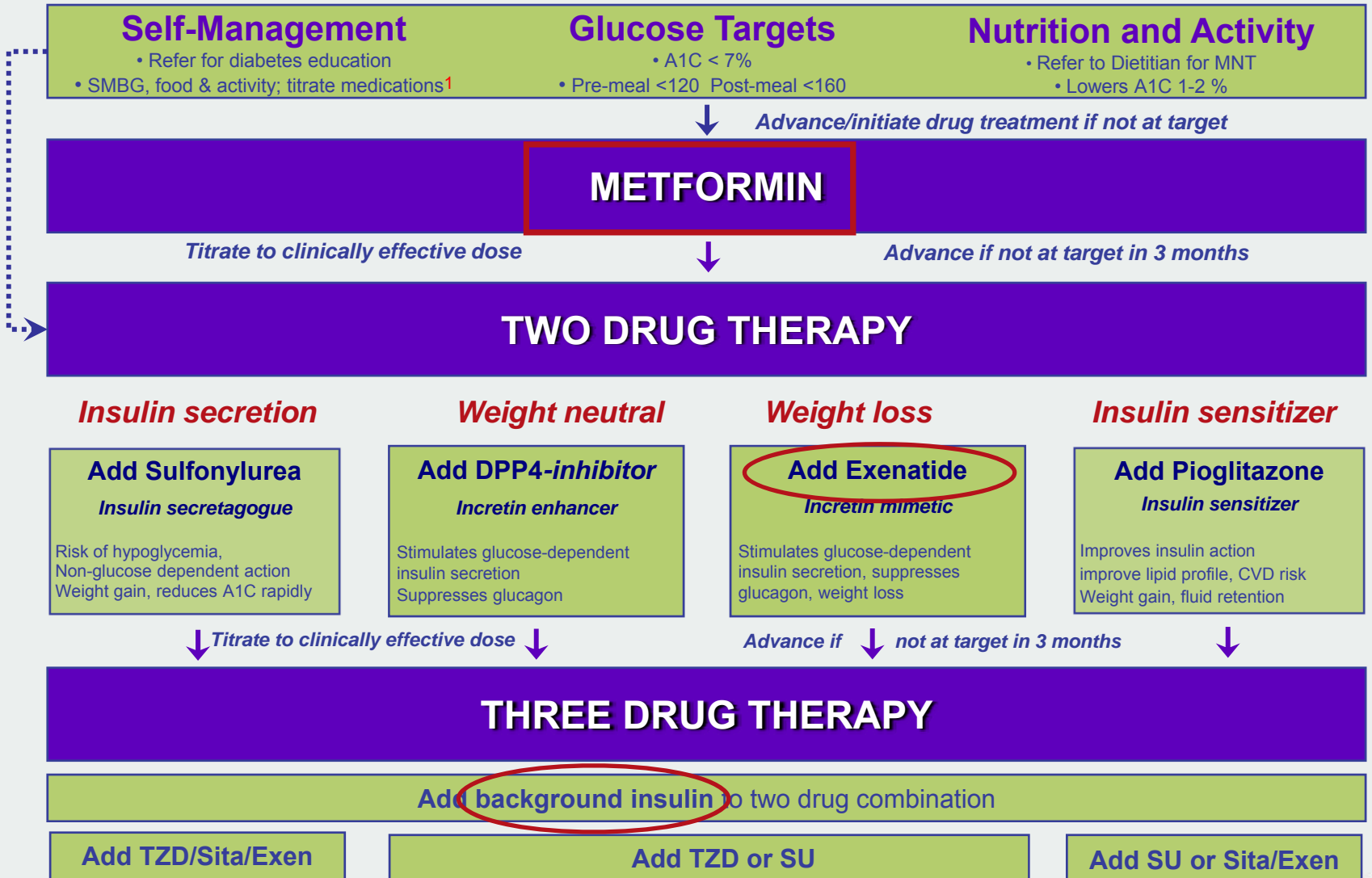
Triple Therapy in Type 2 Diabetes

Insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin naïve patients

n= 217 pts on SU + metformin

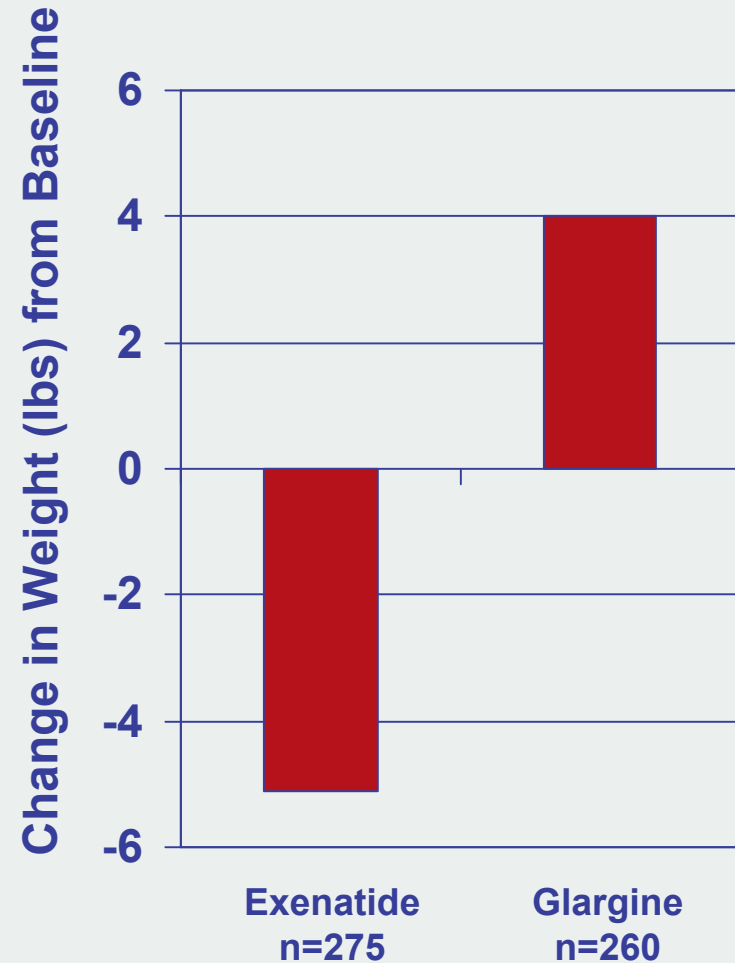
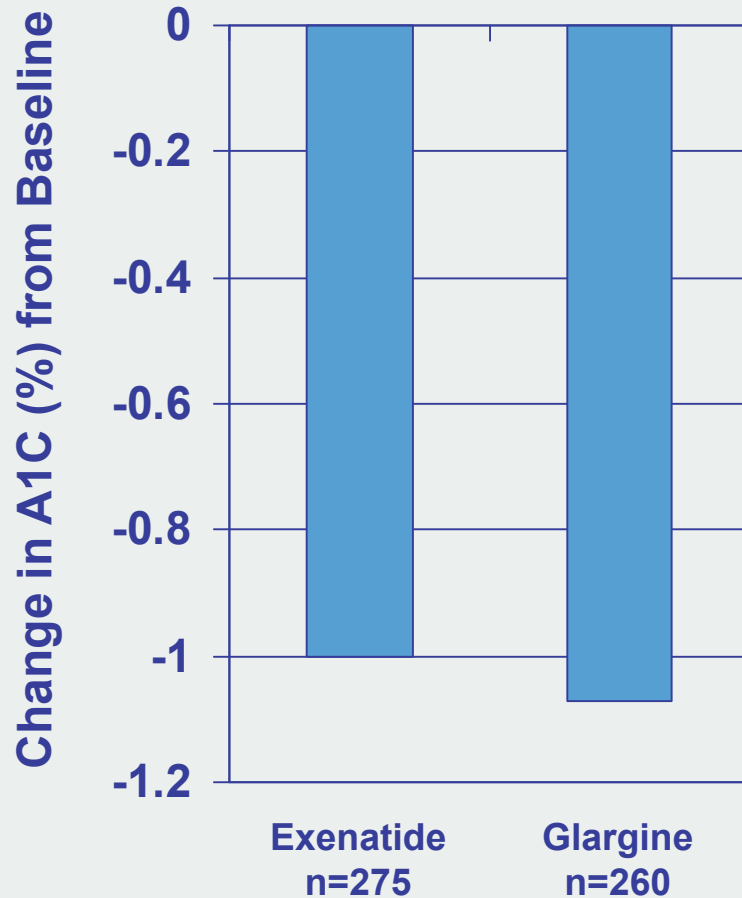
	+ rosiglitazone (24 weeks)	+ glargine (24 weeks)	p value
A1C	1.5	1.7	p= N.S.
FPG	46 mg/dL	65 mg/dL	p= 0.001
Weight	↑ 3.0 kg	↑ 1.6 kg	p= 0.02
Hypoglycemia	3.4/pt-year	7.7/pt-year	p= 0.007
Total Cost	\$1,603	\$1,368	

Treatment of Type 2 Diabetes: Glycemic Control



Exenatide vs. Glargine added to oral agents

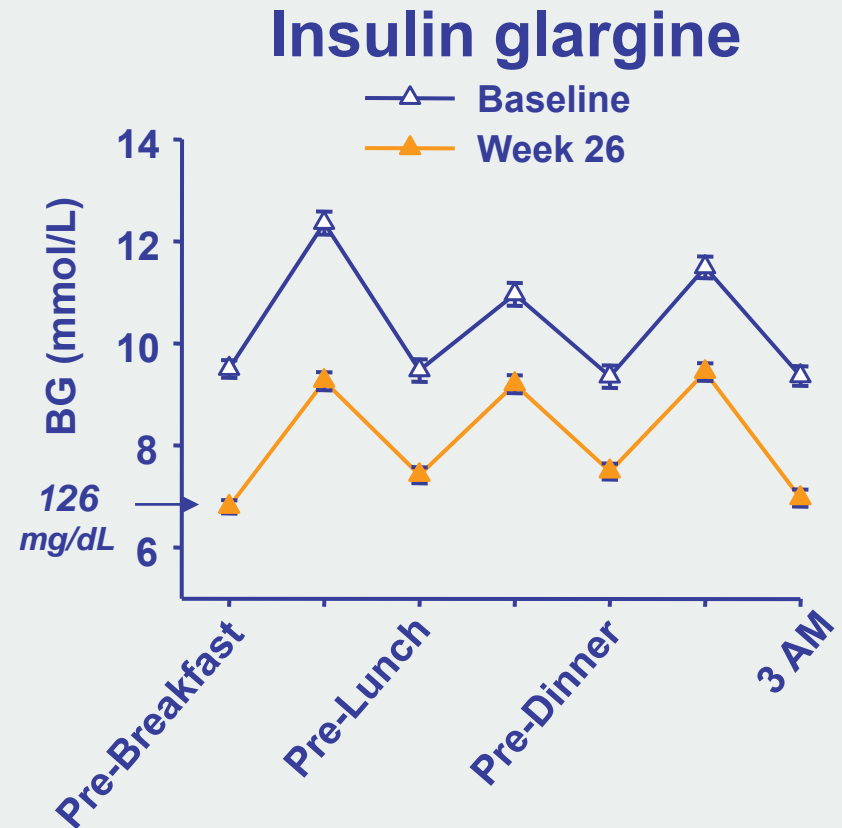
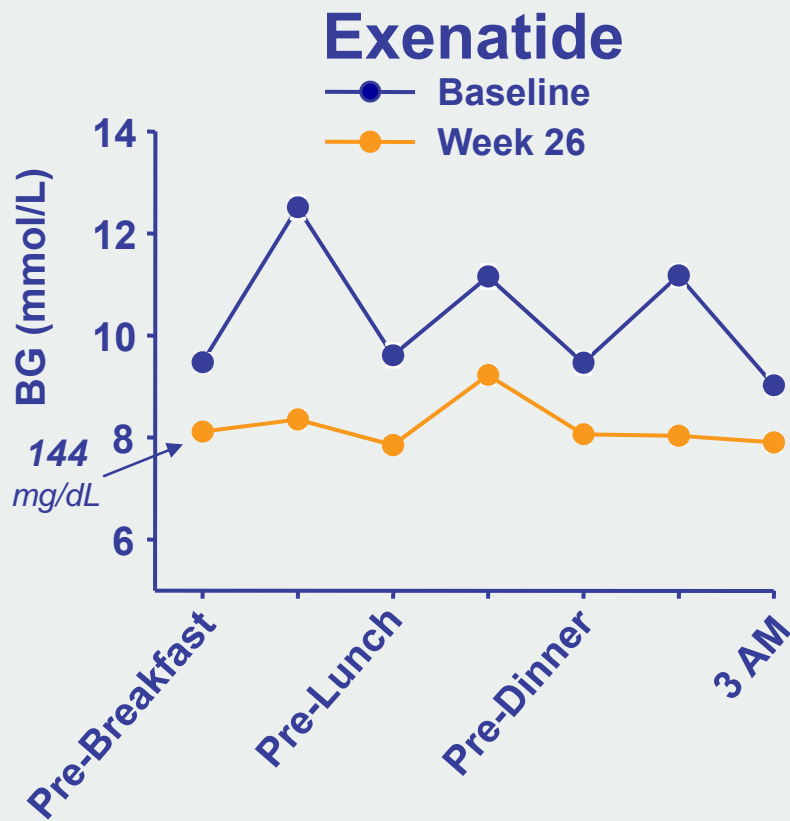
Effects on A1C and Weight at 26 Weeks



Heine RJ et al. *Ann Intern Med.* 2005;143:559–569.

Exenatide vs Glargine Added to Oral Agents

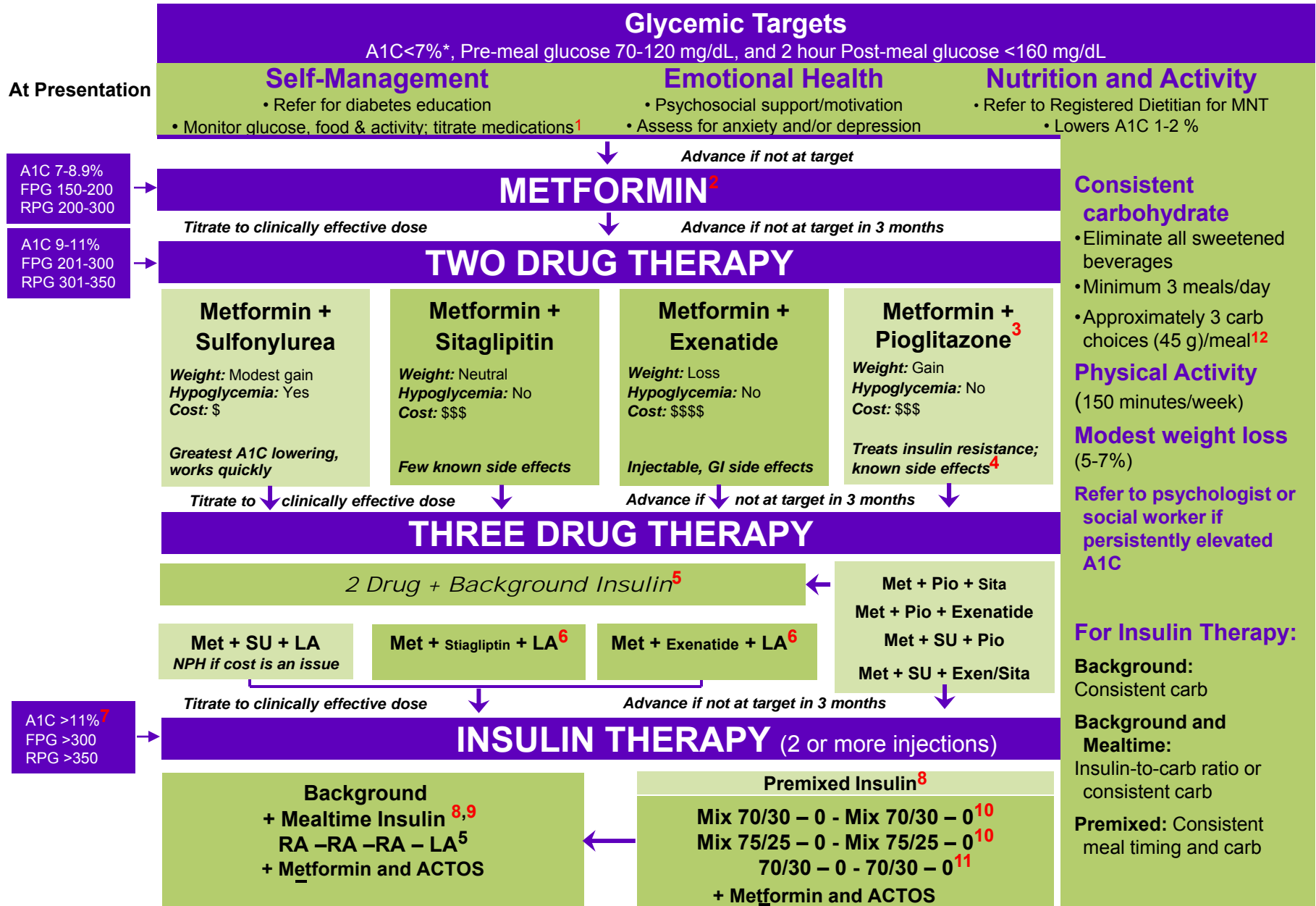
Change in Glucose Control



ITT population; Mean \pm SE shown

Heine RJ et al. *Ann Intern Med.* 2005;143:559–569.

IDC Treatment of Type 2 Diabetes: Glycemic Control



Consistent carbohydrate

- Eliminate all sweetened beverages
- Minimum 3 meals/day
- Approximately 3 carb choices (45 g)/meal¹²

Physical Activity
(150 minutes/week)

Modest weight loss
(5-7%)

Refer to psychologist or social worker if persistently elevated A1C

For Insulin Therapy:

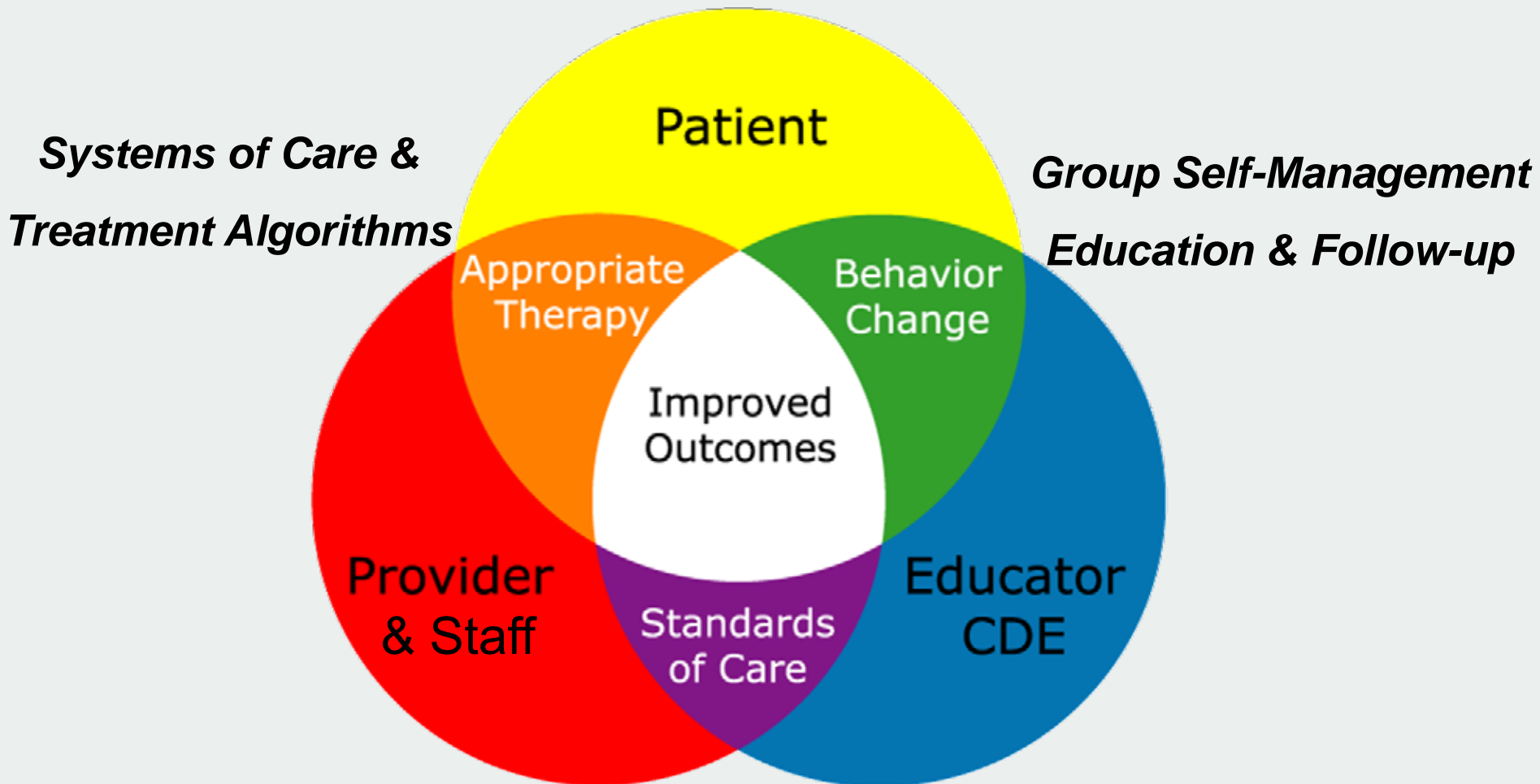
Background:
Consistent carb

Background and Mealtime:
Insulin-to-carb ratio or consistent carb

Premixed: Consistent meal timing and carb

*Less stringent A1C goals are appropriate for some individuals (those with repeated severe hypoglycemia or hypoglycemia unawareness, frail elderly, children, and, based on preliminary ACCORD trial findings, those at high risk for CVD).

Diabetes Patient Centered Team Care



Richard M. Bergenstal, MD

Potential Conflict of Interest

- Conducts clinical research or participates on a scientific advisory board for:
 - Eli Lilly, Novo Nordisk, sanofi-aventis, Merck, Roche, Johnson & Johnson, Bayer, Abbott.
 - Dr Bergenstal does not receive any personal compensation for any of these activities. Any compensation goes to the non-profit Park Nicollet Institute for Research and Education.
- Member of American Diabetes Association – executive committee 2008-2011 – no compensation
- Principal investigator on two NIH trials – DCCT and ACCORD – no direct compensation.