When and How to Start and Adjust Insulin in Type 2 Diabetes (T2DM)

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- Minneapolis, MN
- President, Medicine and Science, American Diabetes Association

Disclosure Statement

Richard M. Bergenstal, MD

I have participated in clinical research and/or served as a consultant for:

- **Eli Lilly**
- **Novo Nordisk**
- **sanofi-aventis**
- **MannKind**
- Roche
- LifeScan/J&J
- Abbott
- Bayer
- Medtronic
- Intuity
- Amylin
- Merck
- Pfizer
- ResMed
- Takeda

I have received no personal compensation for any of these activities and all contracts are with the non-profit Park Nicollet Institute

I have inherited Merck stock

I am a volunteer officer of the American Diabetes Association

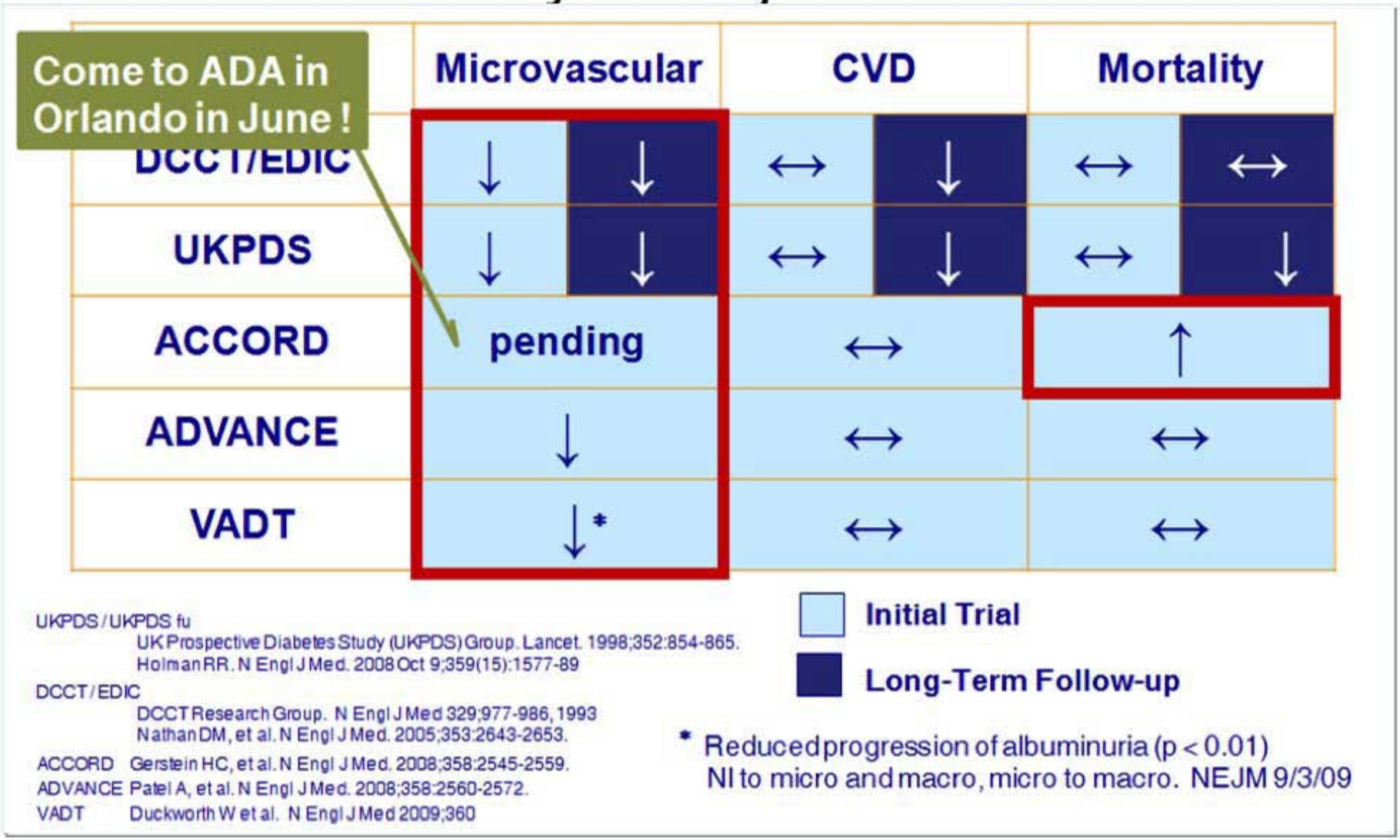
Glycemic Targets for Type 2 Diabetes

	IDC Target	ADA
A1C	<7%*	<7%*
Fasting and Premeal	70–120 mg/dL	70–130 mg/dL
2 hr. Postmeal	<160 mg/dL**	<180 mg/dL***

* Less stringent A1C goals are appropriate for some individuals.
** Note: 2 hour postmeal value should be no more than 40 mg/dL above premeal value
*** Postmeal 1–2 hours after start of meal

American Diabetes Association: Clinical Practice Recommendations 2010, Diabetes Care, Vol 33, Supplement 1

Impact of Intensive Therapy in Diabetes
Summary of Major Clinical Trials



UKPDS / UKPDS fu
UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-865.
Holman RR. N Engl J Med. 2008 Oct 9;359(15):1577-89

DCCT / EDIC
DCCT Research Group. N Engl J Med 329;977-986, 1993
Nathan DM, et al. N Engl J Med. 2005;353:2643-2653.

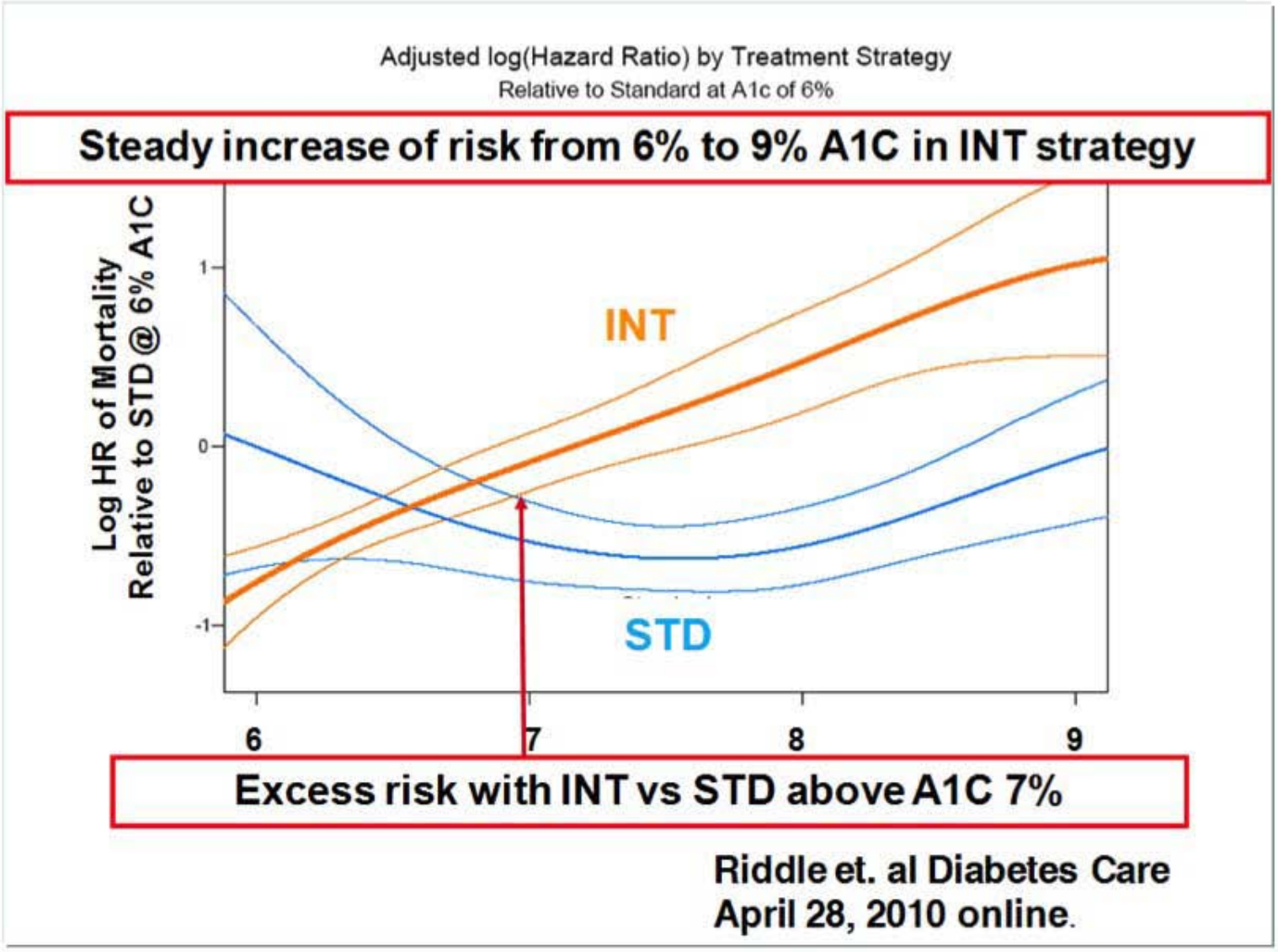
ACCORD Gerstein HC, et al. N Engl J Med. 2008;358:2545-2559.

ADVANCE Patel A, et al. N Engl J Med. 2008;358:2560-2572.

VADT Duckworth W et al. N Engl J Med 2009;360

* Reduced progression of albuminuria ($p < 0.01$)
NI to micro and macro, micro to macro. NEJM 9/3/09

Risk of Death over Range of Ave. A1C



Summary of Recommendations for Adults with DM

ADA 2010, ACCORD Findings

Measures	ADA Targets	Post ACCORD
A1C	**< 7%** (individualize)	**Do not target < 6%** individualize <7% if it can be achieved without excessive therapy - if not then <8%
• Premeal glucose	70 – 130 mg/dl	
• Peak postmeal glucose	< 180 mg/dl	
Blood Pressure	**< 130/80 mmHg** (individualize)	**Do not target <120 mmHg** individualize <130/80 mmHg if it can be achieved without excessive therapy - if not then <140/80
LDL-c	**< 100 mg/dL** (individualize)	**< 100 mg/dL** individualize - at least on statin to achieve a 30-40% drop in LDL
Triglycerides	**< 150 mg/dL**	**< 150 mg/dL** In most cases* do not add a **Fibrate** to statin to reduce CVD risk or LDL
HDL-c	**> 40 mg/dL**	**> 40 mg/dl**

ADA *Diabetes Care* 33 (Suppl 1), 2010

my benefit those with **both TG>200 & HDL<34*

Estimated Average Glucose (eAG)

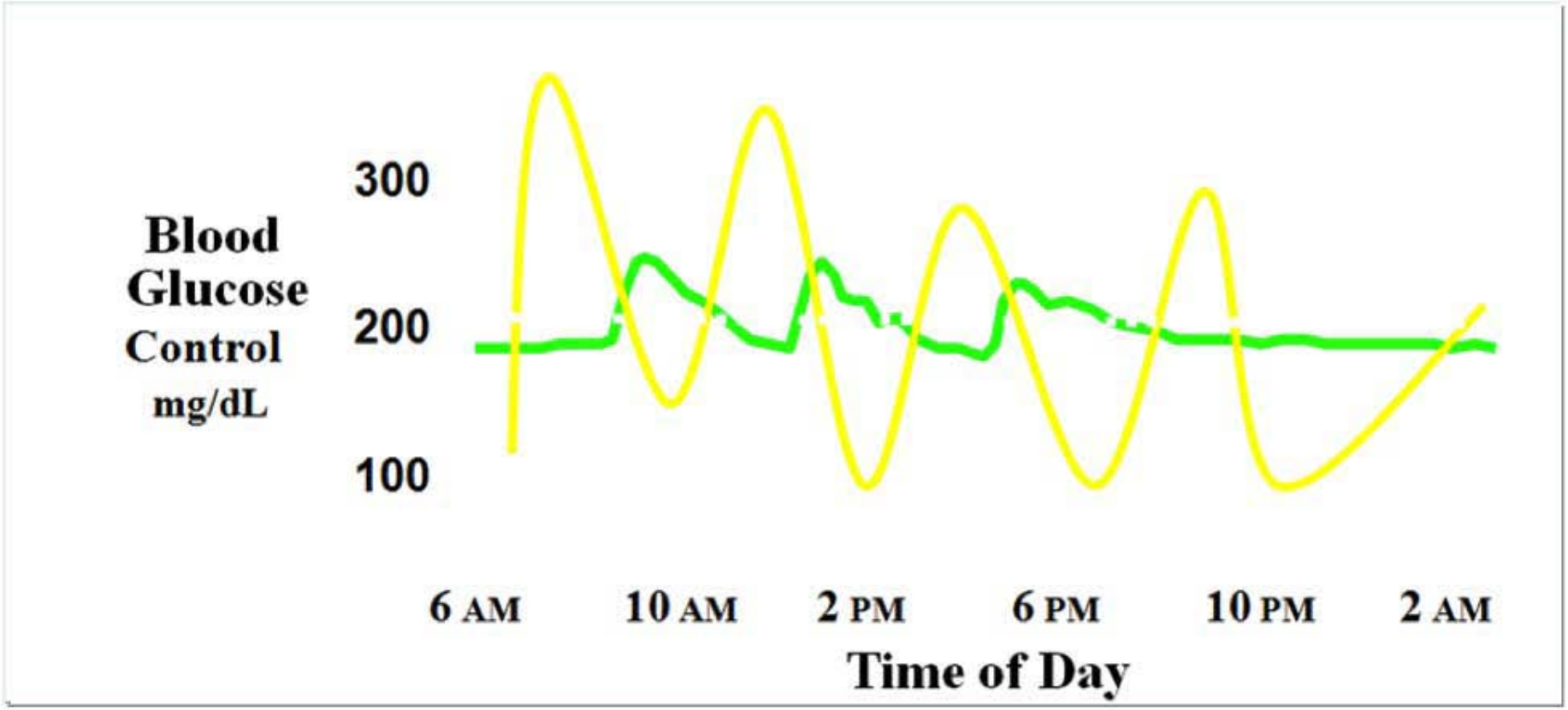
Estimated Average Glucose

Help your patients make the connection between daily and long-term glycemic control.

A1C	eAG	
%	mg/dl	
6	126	7.0
6.5	140	7.8
7	154	8.6
7.5	169	9.4
8	183	10.1
8.5	197	10.9
9	212	11.8
9.5	226	12.6
10	240	13.4
11	269	
12	298	

Formula: 28.7 X A1C – 46.7 = eAG

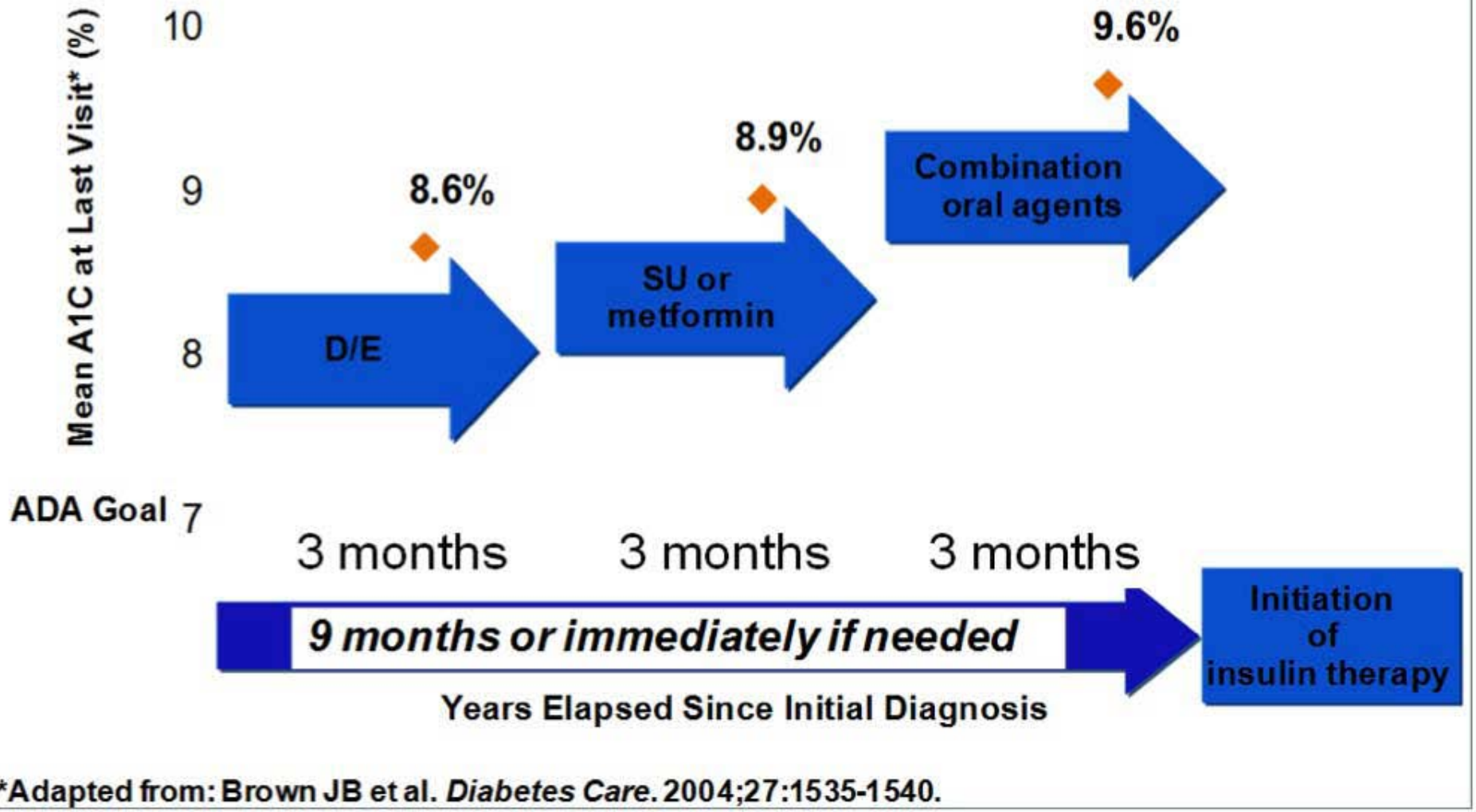
A1C and eAG Do Not Tell Whole Story



Do We Really Need Both A1C and SMBG to Control Blood Glucose?

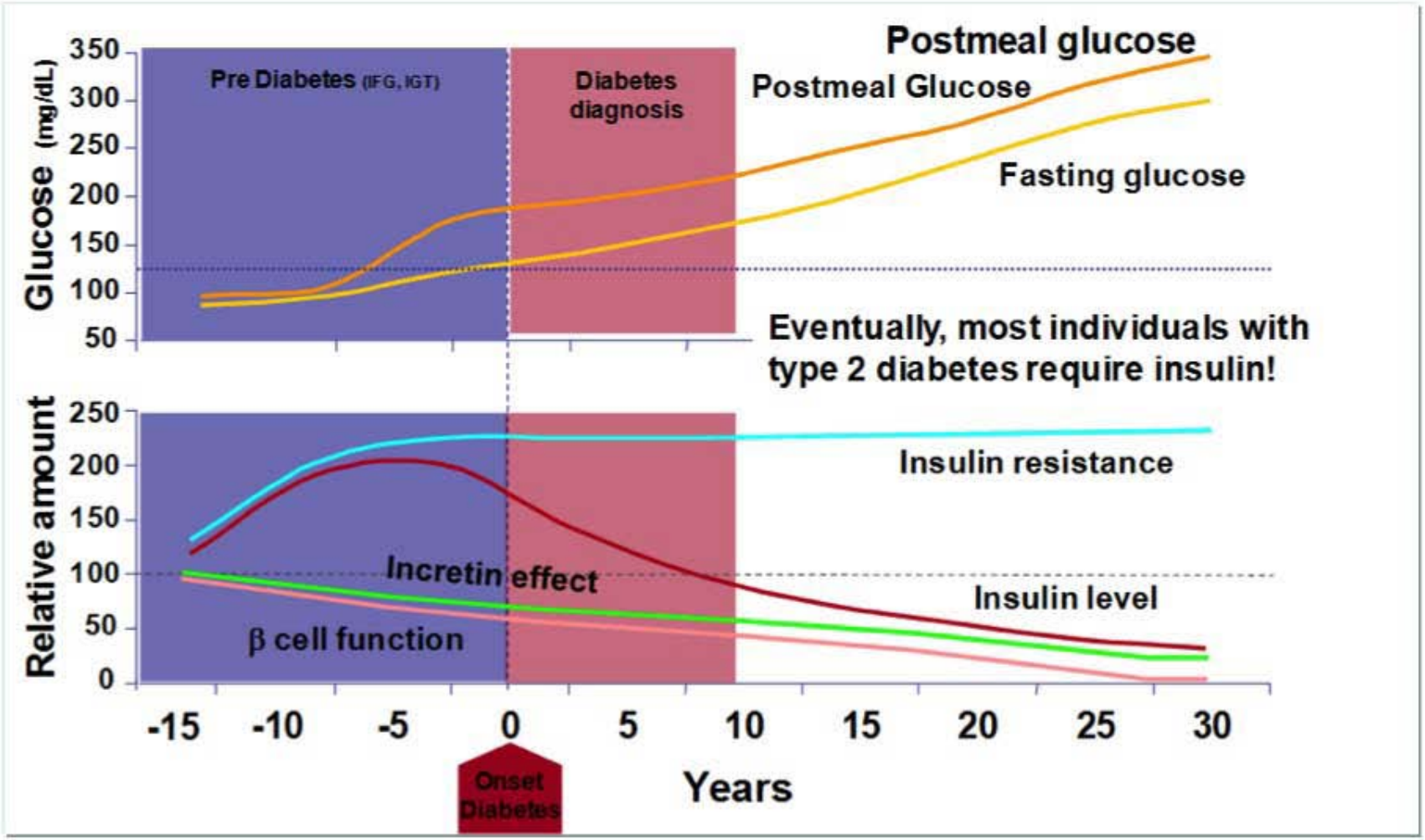
- **HbA_{1c}/eAG above target**
  - **Indicates an increased risk for complications**
  - **Indicates a change in therapy is needed**
- **Abnormal SMBG readings/patterns**
  - **Indicate what changes to make**
    - **First: Correct patterns of low glucose**
    - **Next: Correct patterns of high glucose**

Clinical Inertia: "Failure to Advance Therapy When Recommended"



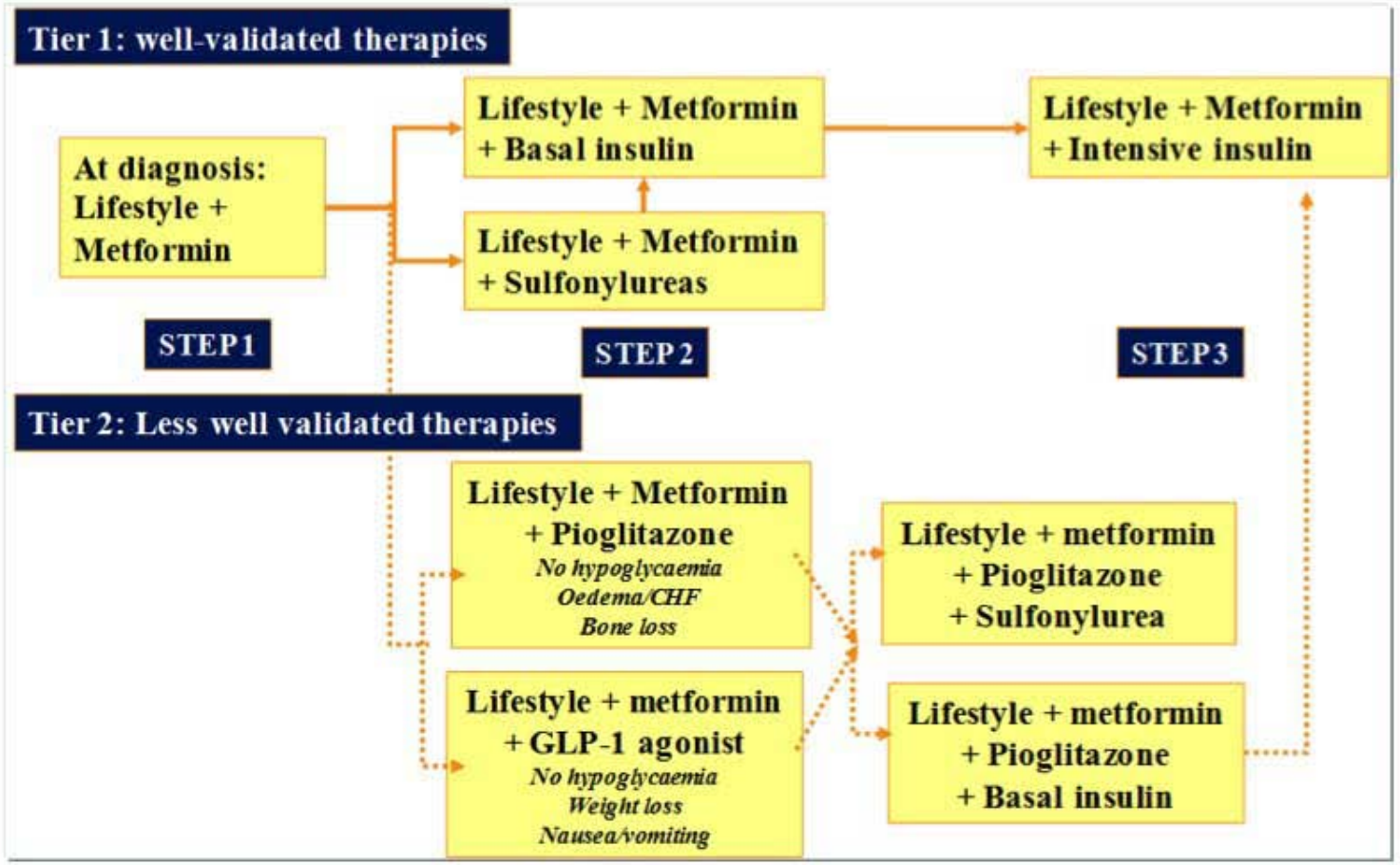
*Adapted from: Brown JB et al. *Diabetes Care*. 2004;27:1535-1540.

Natural History of Type 2 Diabetes



ADA/EASD Consensus Group Algorithm for T2DM

Nathan DM, *et al.* *Diabetes Care & Diabetologia* *January 2009*.



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

American Diabetes Association.

Cure • Care • Commitment®

26-JUN-2009

ADA Statement on Insulin Glargine and Cancer

Statement from the American Diabetes Association Related to Studies Published in *Diabetelogia* Suggesting Possible Link Between Insulin Glargine and Cancer

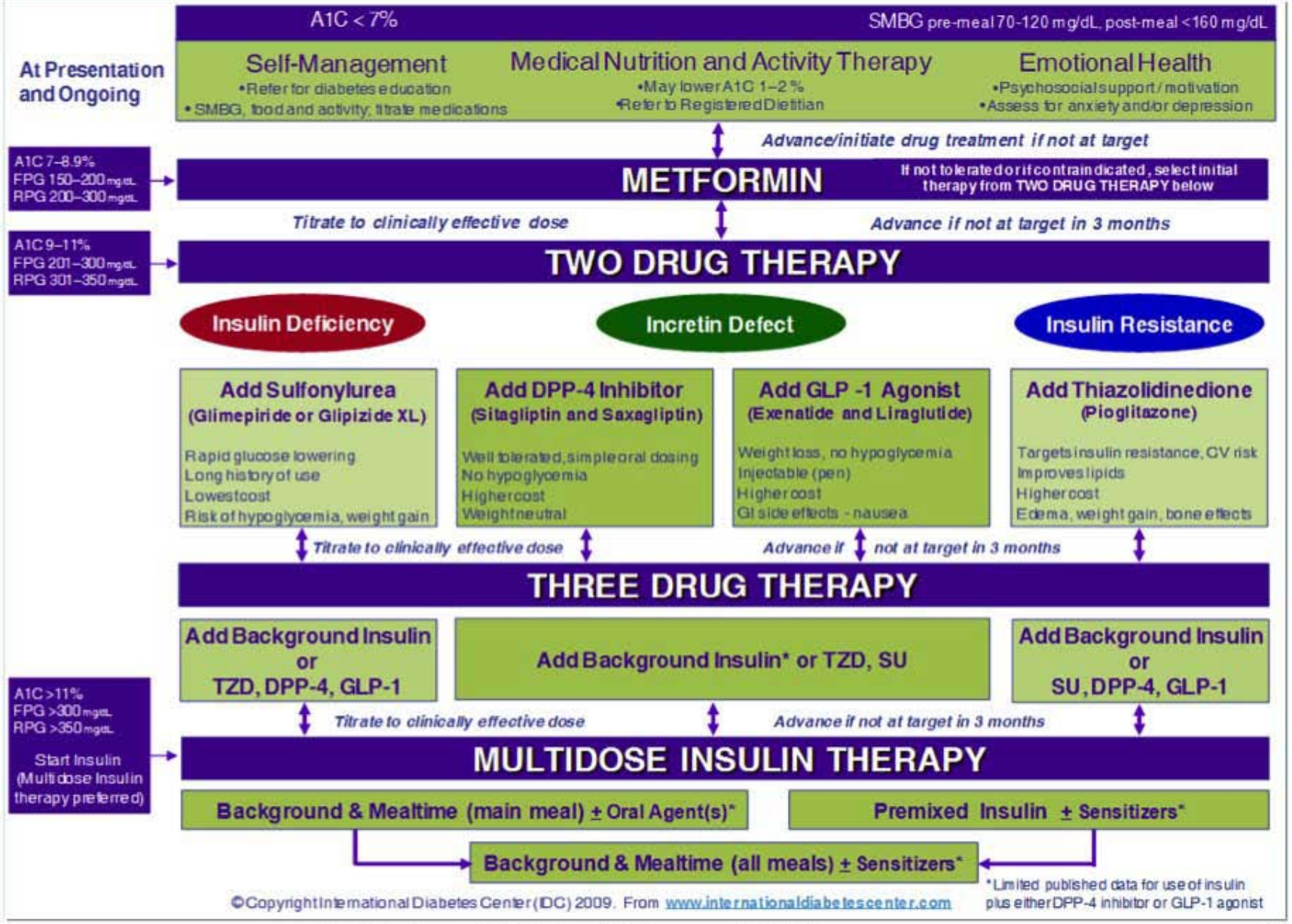
-- Research conflicting and inconclusive; Patients should not stop using insulin and should talk to their doctor

Cancer Risk in Diabetes

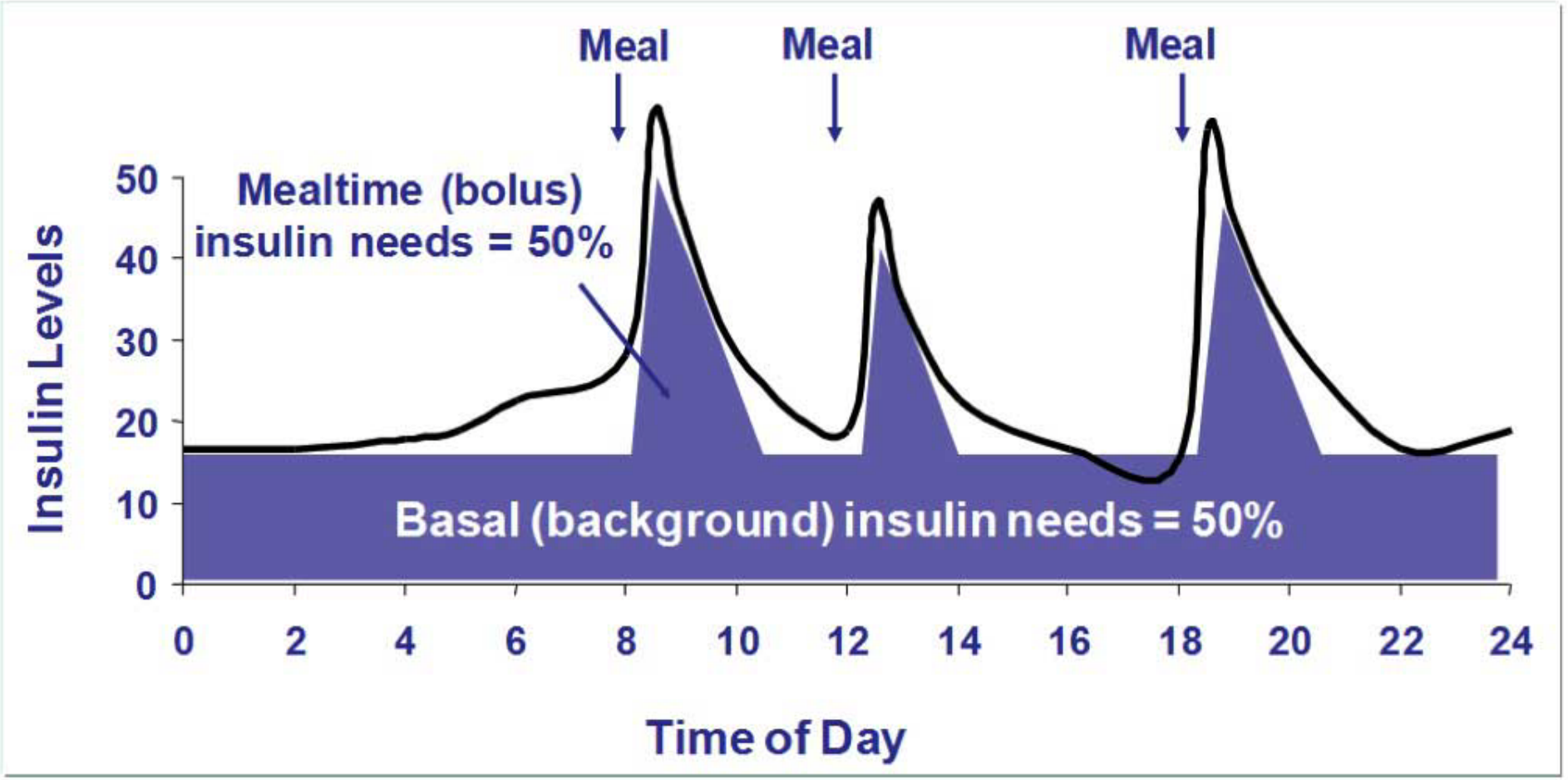
Cancer Type	RR vs Nondiabetes	95% C.I.
Breast[1]	1.20	1.12–1.28
Bladder[2]	1.24	1.08–1.42
Colorectal[3]	1.30	1.20–1.40
Pancreatic[4]	1.82	1.66–1.99
Hepatocellular[5]	2.54	1.84–3.50

1. Larsson et al. *Int J Cancer.* 2007;121:856-862.
2. Larsson et al. *Diabetologia.* 2006;49:2819-2832.
3. Larsson et al. *j Natl Cancer Inst.* 2005;97:1679-1687
4.Huxlet et al. *Br J Cancer* 2005; 92:2076-2083.
5. El-Serag et al. *Clin Gastroenterol Hepatol* 2006; 4:369-380.

Treatment of Type 2 Diabetes: Glycemic Control

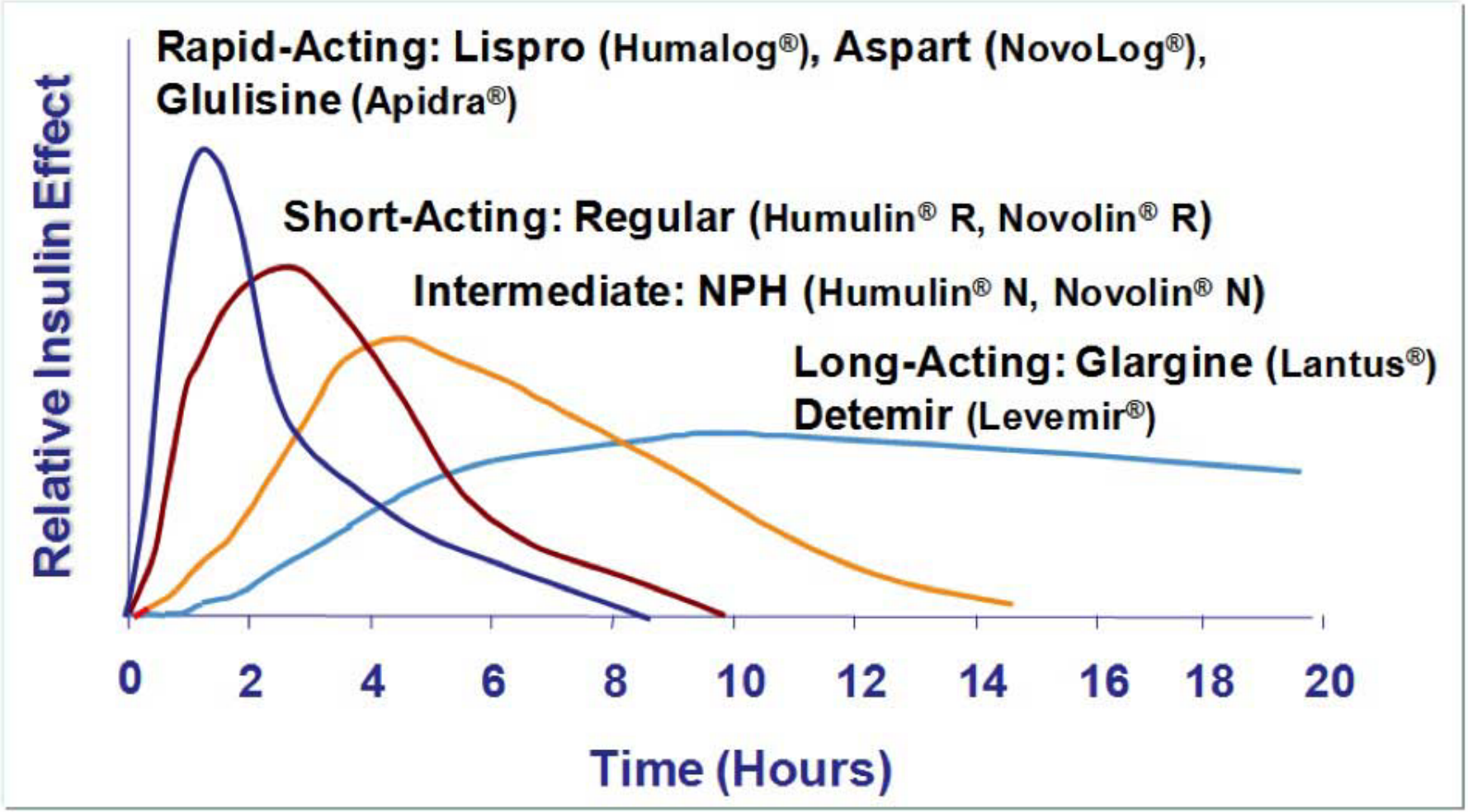


Using Insulin Effectively
Physiologic Insulin Replacement



Adapted from Polonsky. *N Engl J Med*. 1996;334:777-783.
Kendall DM. *N Engl J Med* 322: 898-903, 1990.

Insulin Time Action Curves



Bergenstal, "Effective insulin therapy," *International Textbook of Diabetes Mellitus* vol 1. 3rd ed, Chichester NY, John Wiley and Sons, Inc., 2004:995-1015.

Causes of Severe Insulin Resistance

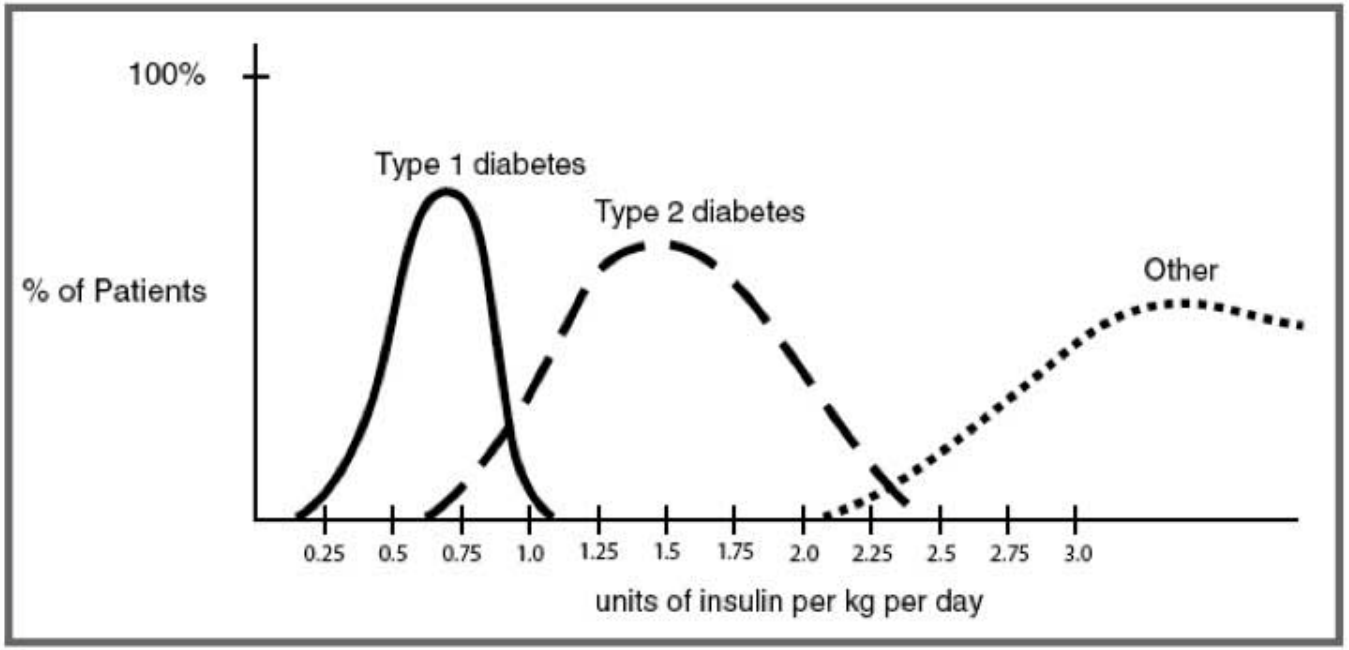
Syndromic Forms of Resistance ("other" class of diabetes)

- Type A and Type B insulin resistance
- Lipodystrophy
- Hyperandrogenism, insulin resistance, acanthosis nigricans
- Rabson-Mendenhall syndrome

Increased insulin needs due to obesity

- Dose exceeds 200 units/day

Typical Insulin Dose Requirements



Units/kg

- Type 1 0.25–1.0
- Type 2 0.6–2.5
- Other > 2.0

Diabetes Spectrum 22(2), 116-122, 2009

Problems with Large Doses of U 100

Decreased compliance

- Frequently need more than 1 injection per dose
- Pens only dose 60 units

Volume of insulin per dose

- Decreased/delayed absorption

Cost

Fear of hypoglycemia

Fear of weight gain

Concern more insulin means worse diabetes

Sample U-500 Cost Comparison

Based on: Total Daily Dose of 250 units
Total Monthly Dose = 7500 units

Insulin	Strength	Units Per Vial	Vials Per Month	Cost Calculation**	Monthly Cost
Rapid-Acting*	U-100	1000 (10 ml x 100 units/ ml)	7.5	7.5 vials x $109	$817
Regular	U-100	1000 (10 ml x 100 units/ml)	7.5	7.5 vials x $ 49	$367
Regular	U-500	10,000 (20 ml x 500 units/ml)	0.75	0.75 vial x $310	$232

Dosage Conversion

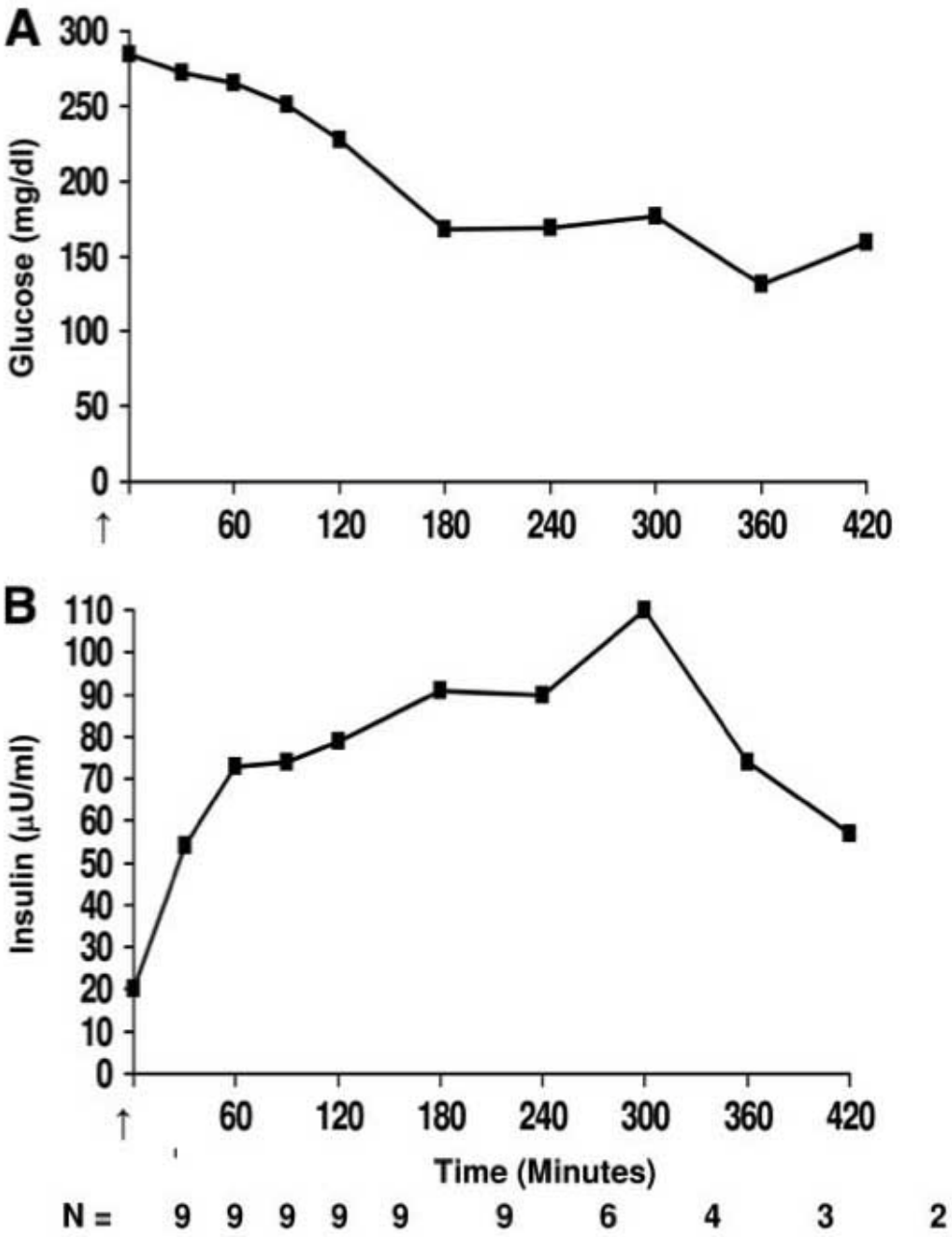
Based on Type of Syringe

U-500 Regular (actual units)	U-100 Insulin Syringe (unit marking)	Tuberculin Syringe (volume [mL])
25	5	0.05
50	10	0.10
75	15	0.15
100	20	0.20
125	25	0.25
150	30	0.30
175	35	0.35
200	40	0.40
225	45	0.45
250	50	0.50
300	60	0.60

Dose(actual units) x 0.2 = unit marking with u-100 syringe
x 0.002 = volume (mL) in a tuberculin syringe

U-500 Insulin Action in Severely Resistant, Obese, Type 2 Patients

Injected 100 units of U-500 regular



The glucose concentrations in the two subjects remaining at 420 min were above 100 mg/dl, but the clinical research center was closing for the day.

Davidson et al: Diabetes Care 33(2), 282, 2010

Comparing U-500 to U-100 Regular

- Human form available since 1997
- Used with or without basal insulin therapy

Benefits

- Fewer Injections
- Lower Cost
- Smaller volume

Barriers

- Confusion with dosing
- Errors during transition home to hospital
- Syringe selection
- Inexperience of providers/ educators
- Risk of hypoglycemia

The Use of U-500 in Patients With Extreme Insulin Resistance

Less than 200U of insulin prescribed per day

↓

U100 insulin therapy
(NPH, regular, lente, lispro, glargine, aspart, mixtures)

200U or greater of insulin/day*

↓

U-500 exclusively

↓

200U-300U/day

↓

Twice daily
(Pre-breakfast & pre-dinner)

↓

300U-750U/day

↓

Three times a day
(Pre-breakfast, pre-lunch, pre-dinner)

↓

750U-2000U/day

↓

Four times a day
(Pre-breakfast, pre-lunch, pre-dinner. Bedtime dose slightly less than pre-meal

↓

>2000U

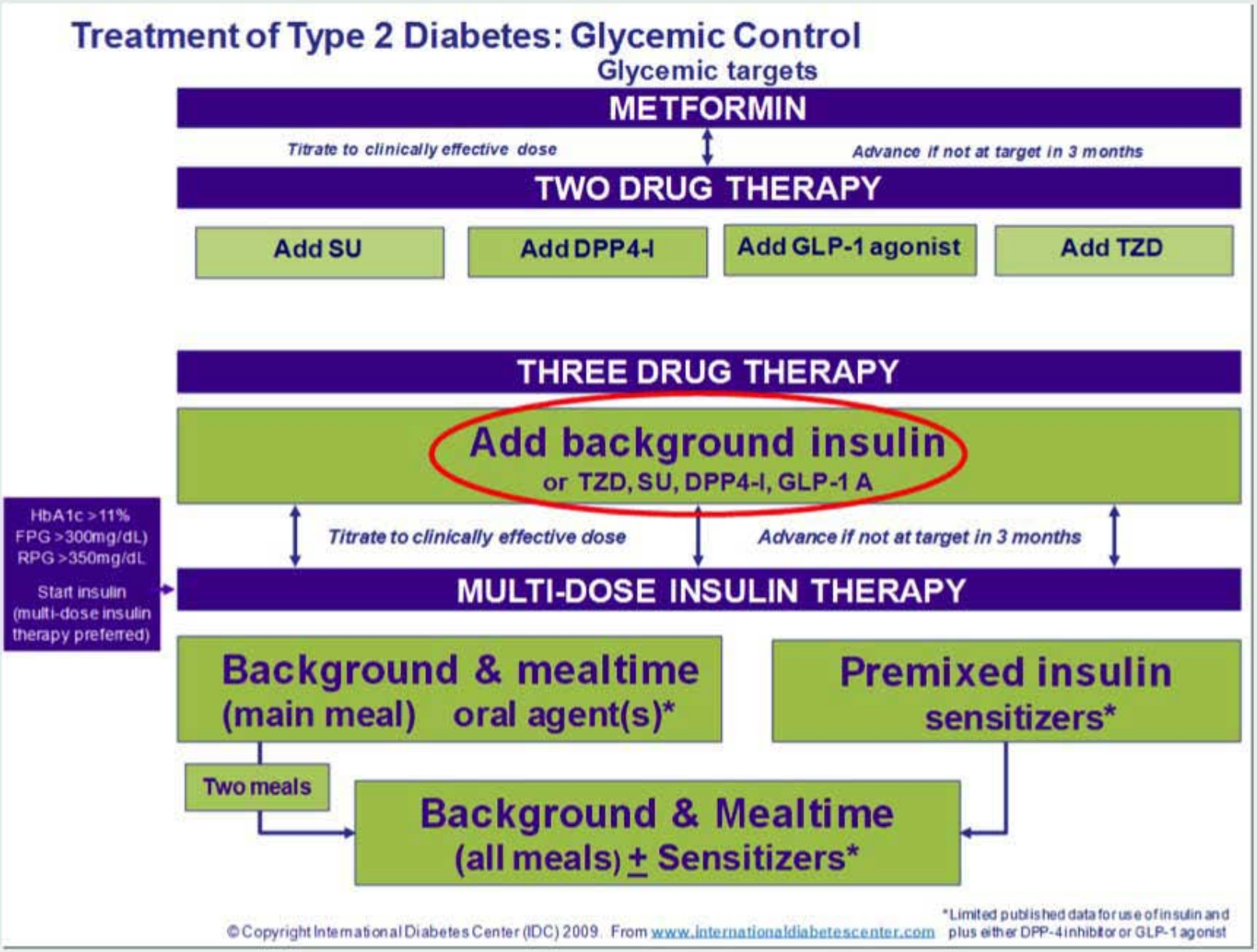
↓

Consider delivery of U-500
Via infusion pump

*Pediatric patients doses >3 units $\cdot kg^{-1} \cdot day^{-1}$.

ELAINE COCHRAN, MSN, CRNP
CARLA MUSSO, MD
PHILLIP GORDEN, MD

DIABETES CARE, VOLUME 28, NUMBER 5, MAY 2005


Treatment of Type 2 Diabetes: Glycemic Control
Glycemic targets
METFORMIN
Titrate to clinically effective dose
Advance if not at target in 3 months
TWO DRUG THERAPY
Add SU
Add DPP4-I
Add GLP-1 agonist
Add TZD
THREE DRUG THERAPY
Add background insulin
or TZD, SU, DPP4-I, GLP-1 A
HbA1c >11%
FPG >300mg/dL)
RPG >350mg/dL
Start insulin
(multi-dose insulin therapy preferred)
Titrate to clinically effective dose
Advance if not at target in 3 months
MULTI-DOSE INSULIN THERAPY
Background & mealtime
(main meal) oral agent(s)*
Premixed insulin
sensitizers*
Two meals
Background & Mealtime
(all meals) ± Sensitizers*
*Limited published data for use of insulin and plus either DPP-4 inhibitor or GLP-1 agonist
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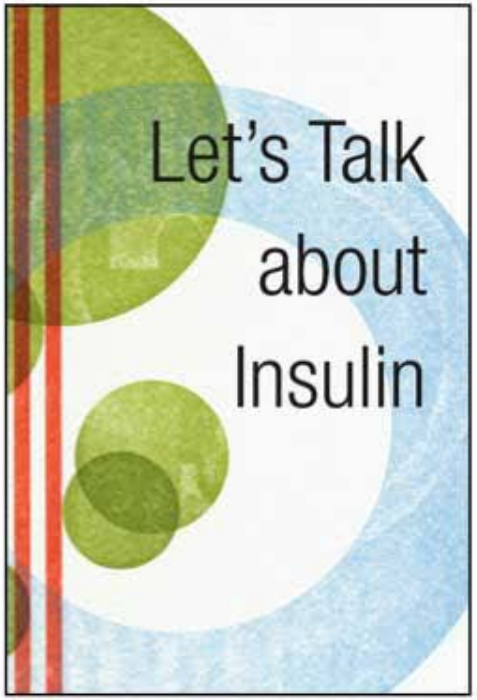
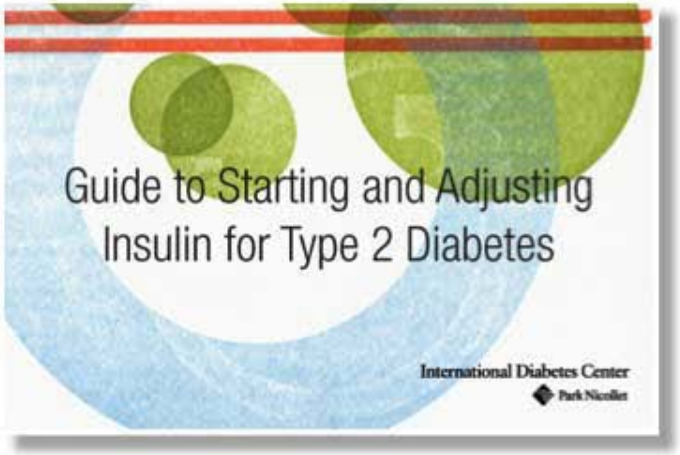
Guide to Insulin Therapy





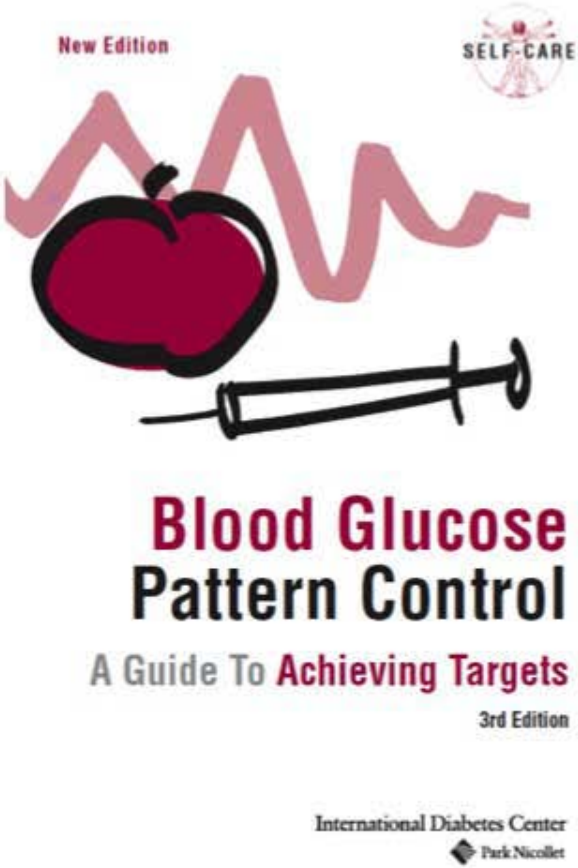


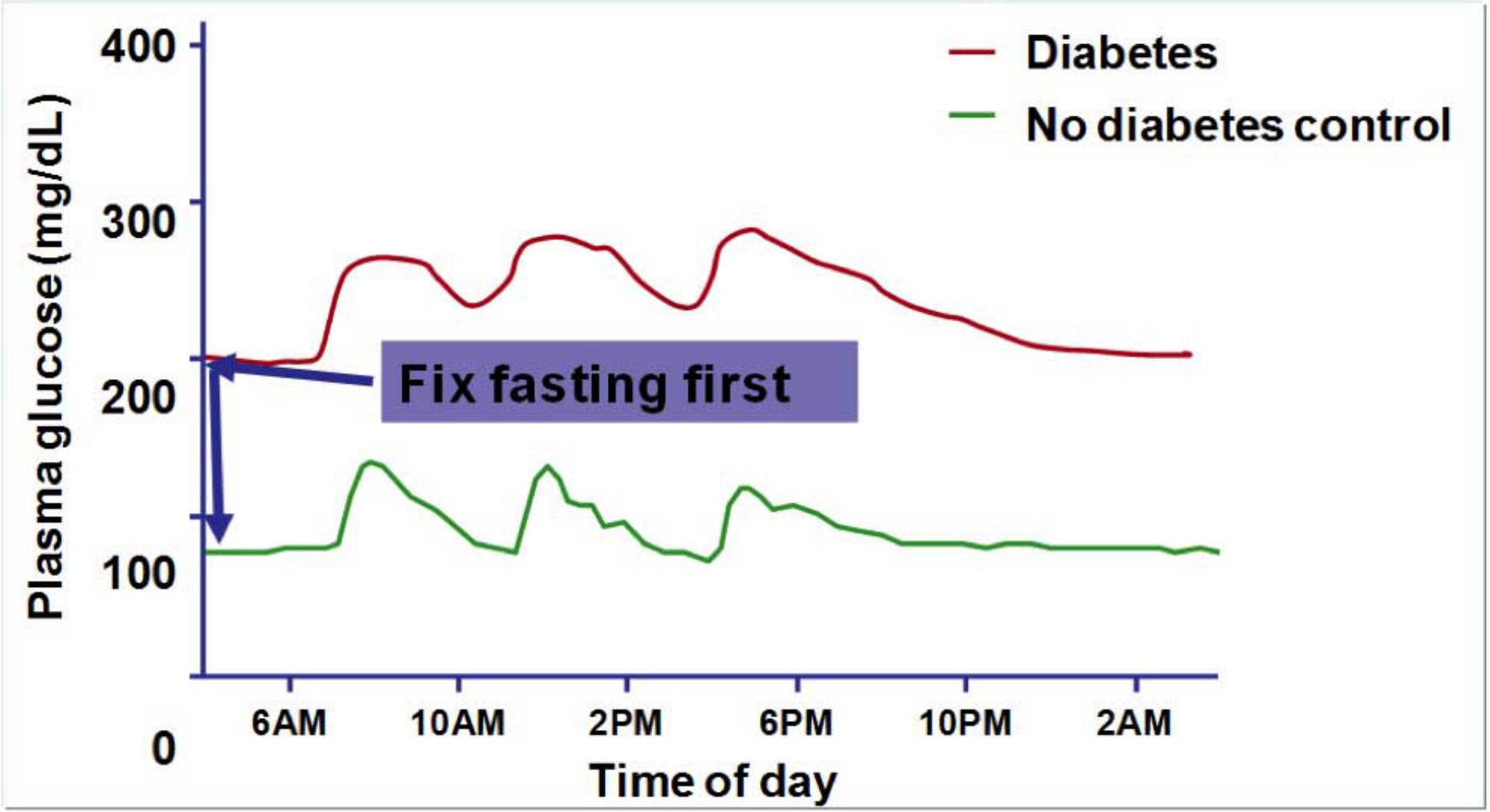
Table 1: Select initial regimen

Three primary insulin regimens	Consider as initial regimen if patient:
Background (basal) insulin (added to oral agents)	Is feeling overwhelmed; is fearful of injections Has mostly elevated fasting BG and postmeal targets are achieved with current oral agent therapy
Premixed insulin*	Is opposed to more than 2 injections a day; has consistent meal times and food intake Has elevated fasting and/or postmeal BG
Background (basal) & mealtime (bolus) insulin*	Desires tight control and a flexible schedule Has elevated fasting and/or postmeal BG

Note: Initial regimen may not be the most beneficial physiologically, yet may be the best behavioral choice initially.

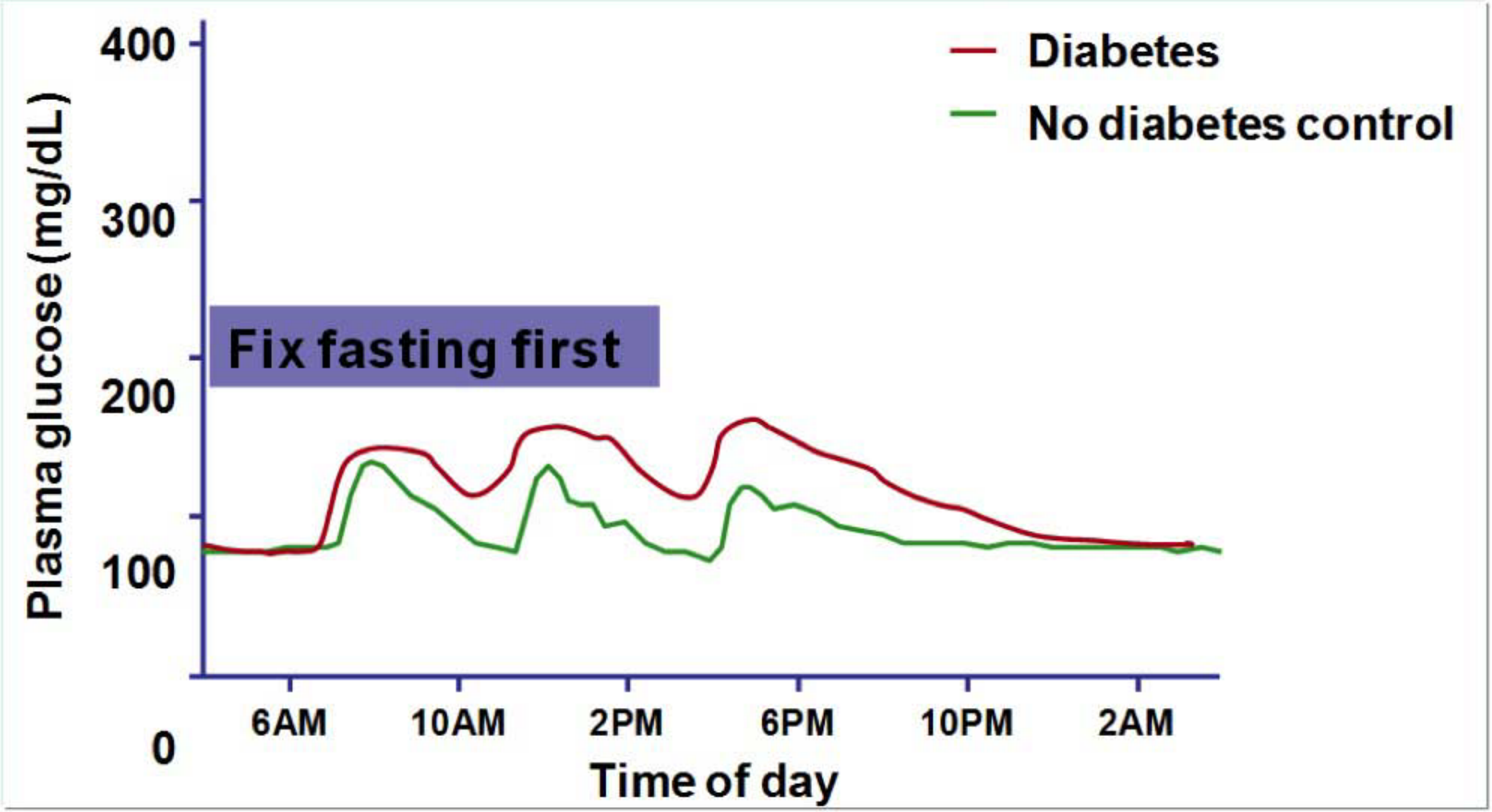
*** Discontinue sulfonylureas; consider adding or maintaining Metformin and/or TZD**

Plasma Glucose Normally Maintained in Narrow Range



Adapted from Polonsky KS, et al. N Engl J Med. 1988;318:1231–39

Plasma Glucose Normally Maintained in Narrow Range



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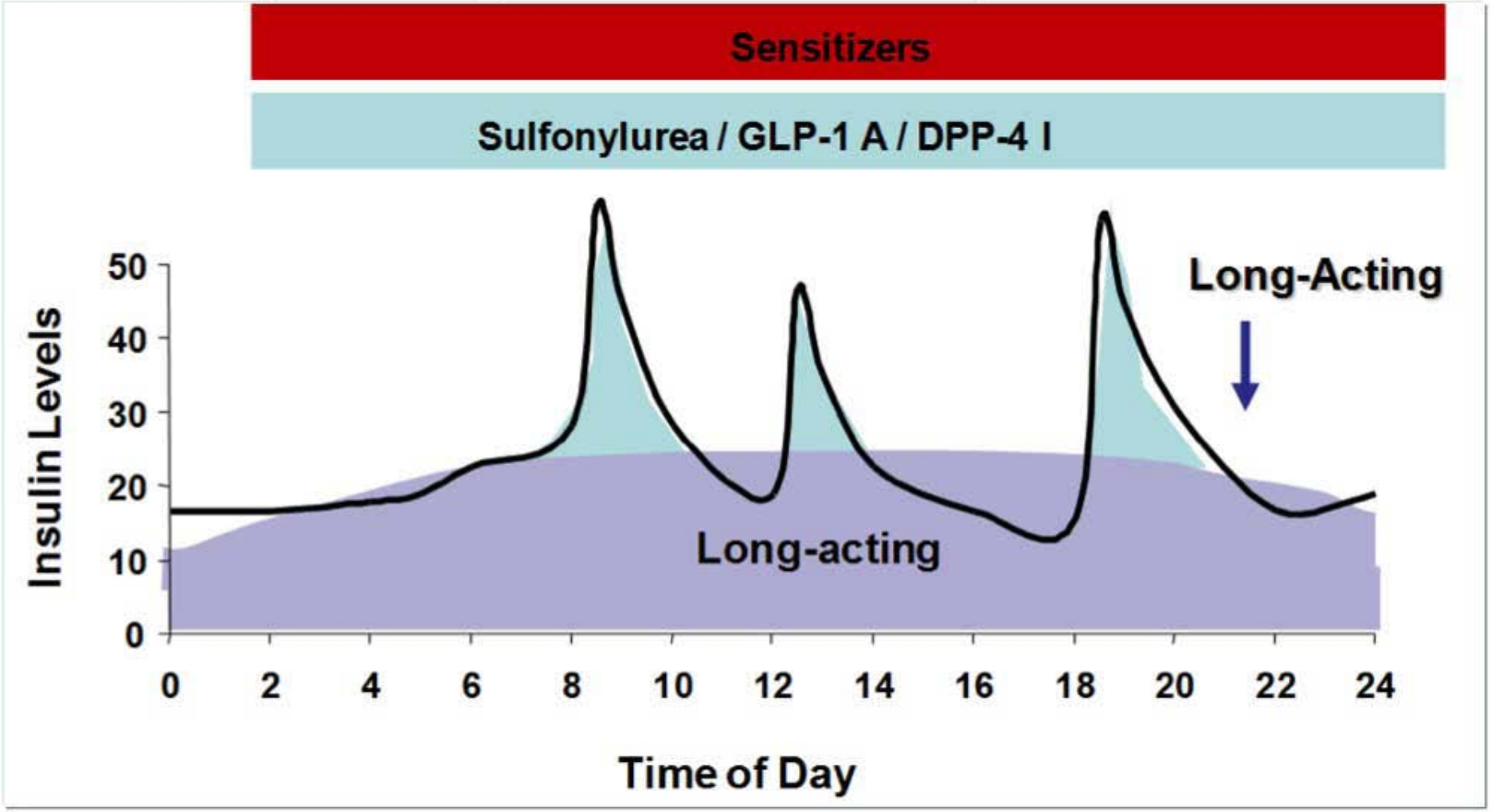
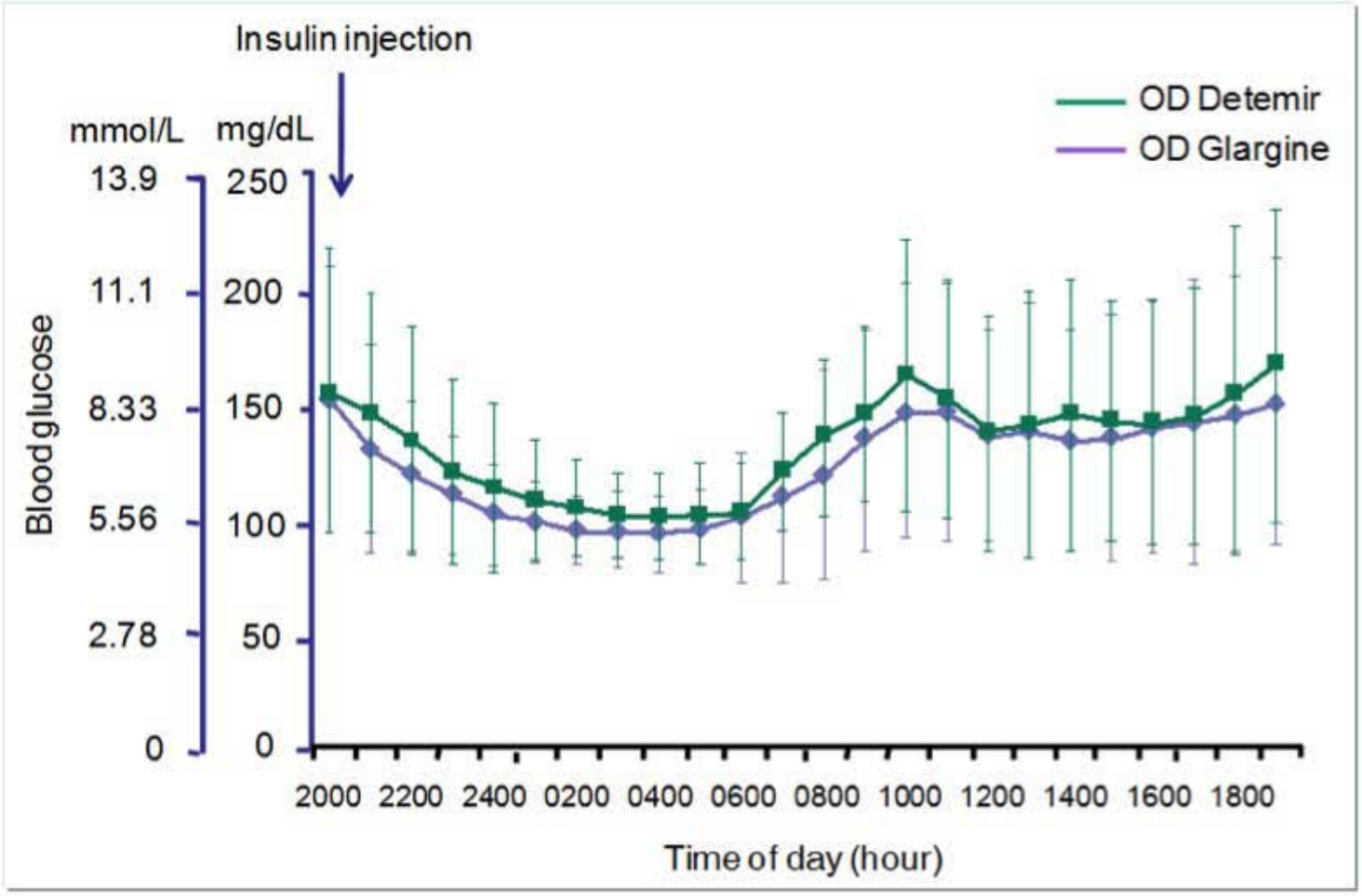
Using Insulin Effectively
Physiologic Insulin Replacement



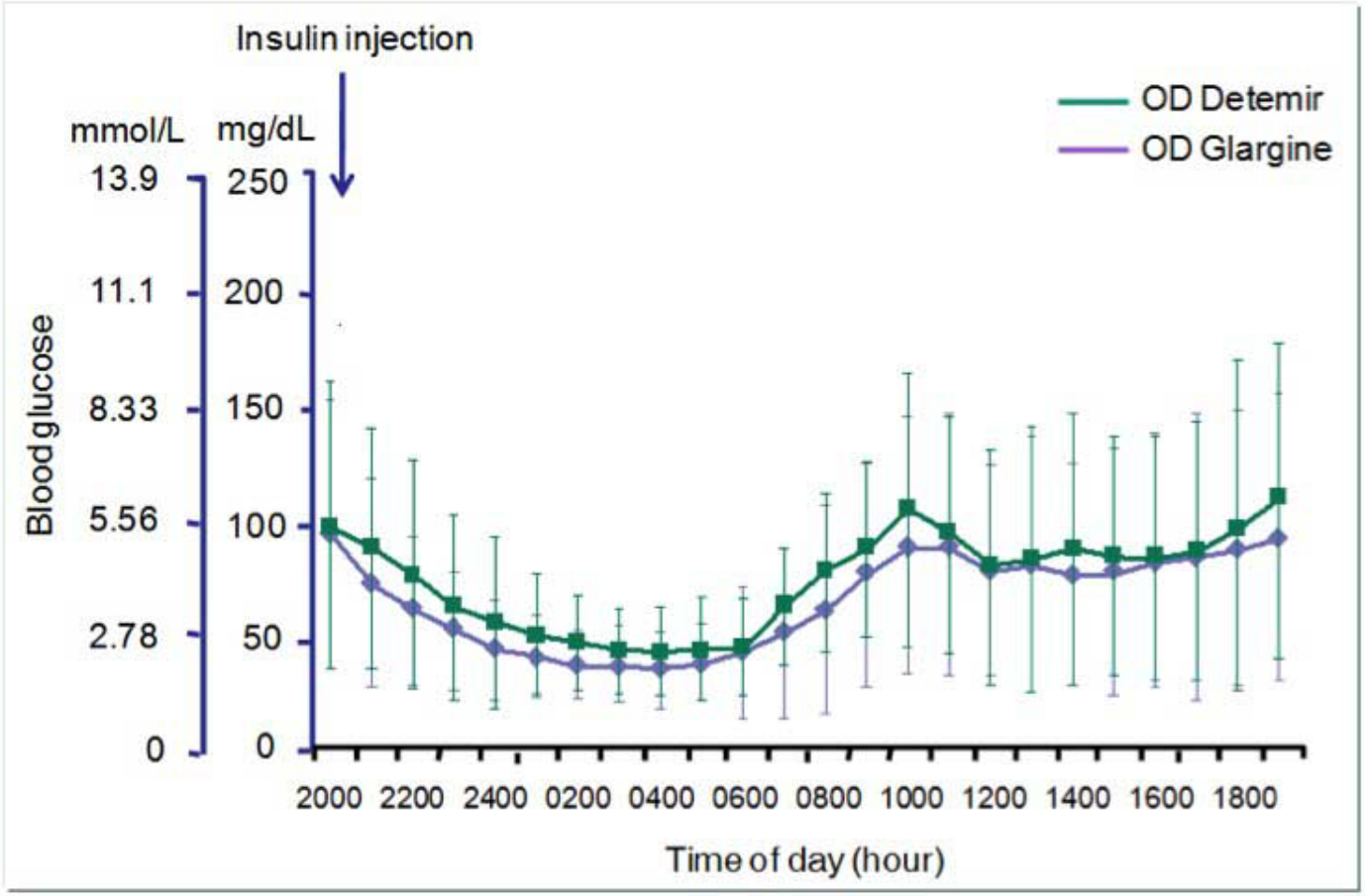
Adapted from Polonsky. *N Engl J Med*. 1996;334:777-783.
Kendall DM. *N Engl J Med* 322: 898-903, 1990.

Basal Insulin Analogues in Type 2 Diabetes: Similar CGMS Profiles



King. *Diabetologia* 2008;51(Suppl. 1):S401

Basal Insulin Analogues in Type 2 Diabetes: Similar CGMS Profiles



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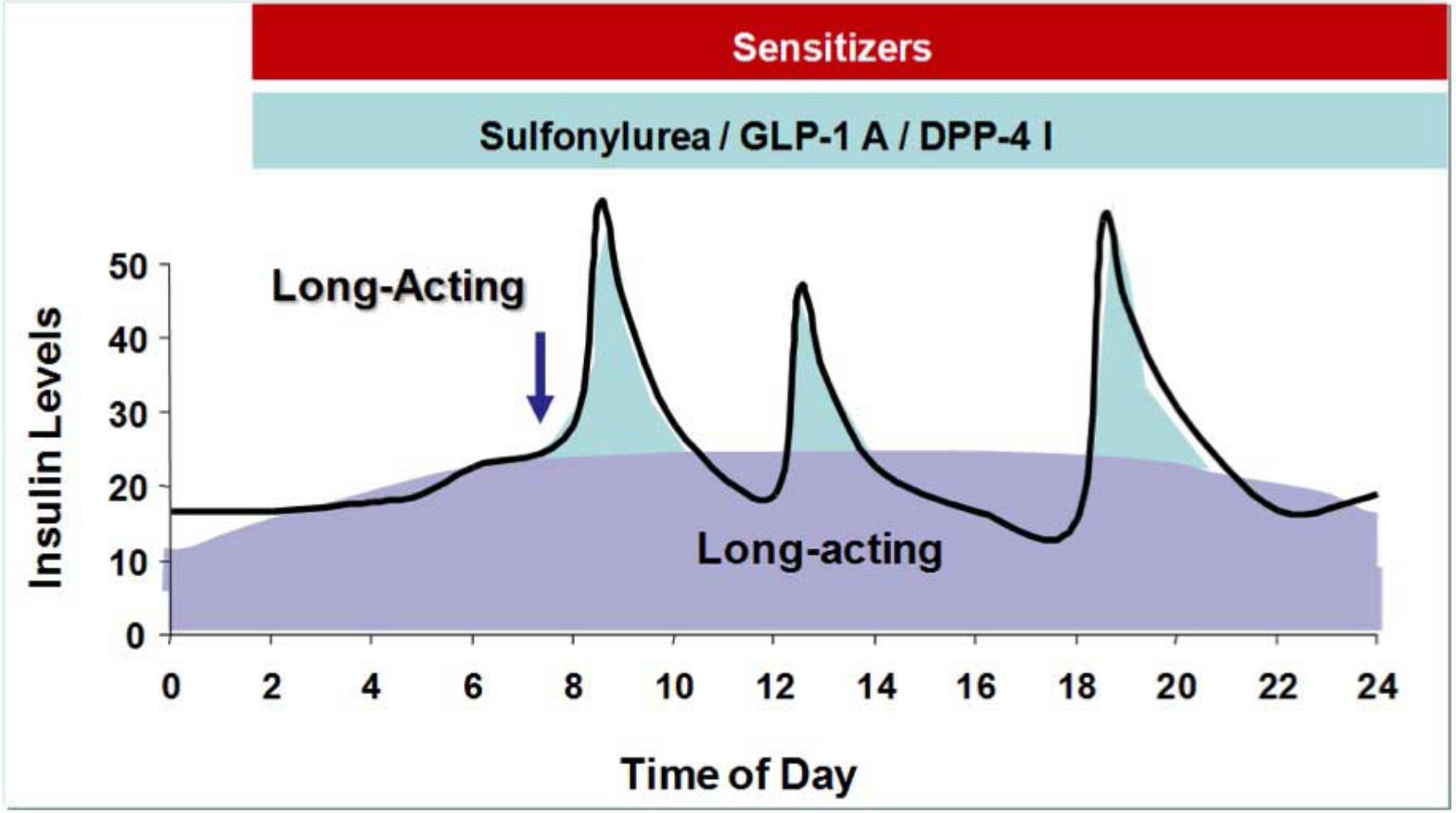
Using Insulin Effectively
Physiologic Insulin Replacement



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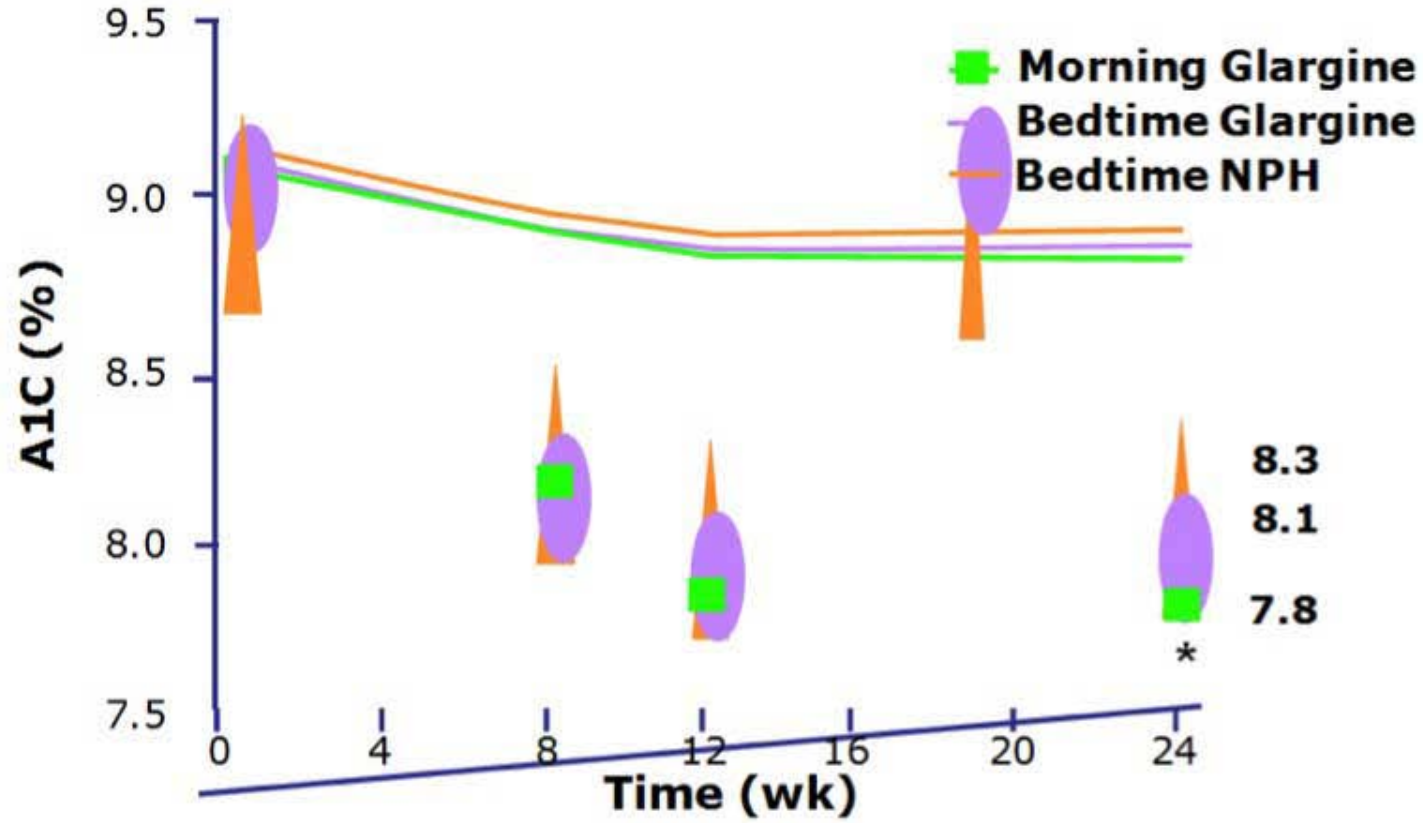
Kendall DM. *N Engl J Med* 322: 898-903, 1990.

Mean A1C Levels During Study



*Decrease in A1C from baseline for morning glargine: $P<0.001$ vs bedtime NPH and $P=0.008$ vs bedtime glargine

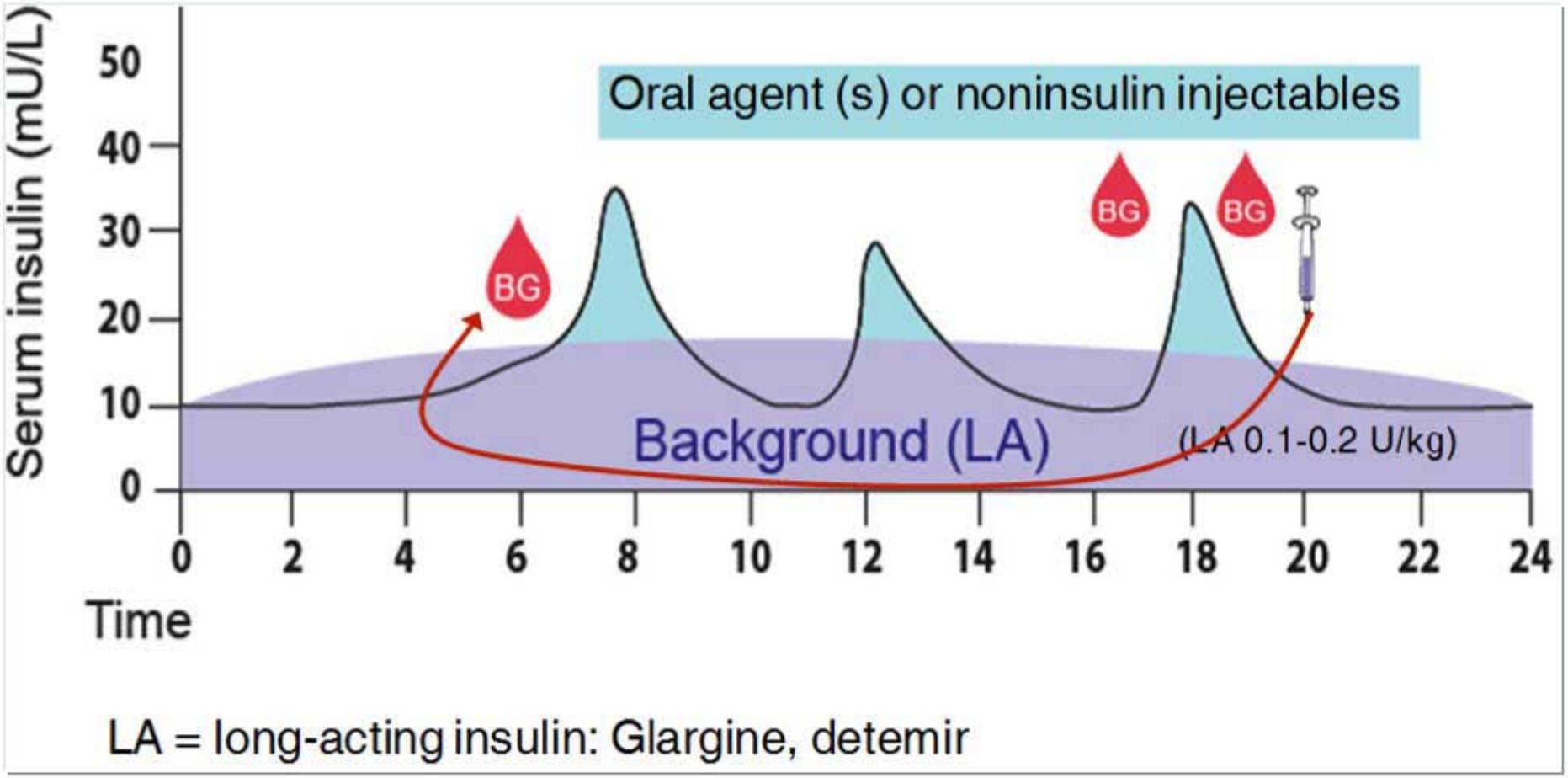
Adapted with permission from Fritsche A et al, and the 4001 Study Group. *Ann Intern Med.* 2003:138:952

Starting Background Insulin

	A1C <9%	A1C ≥9%
Background Insulin Dose	0.1 units/kg	0.2 units/kg

- Maintain oral agents (SU – often half dose) , Metformin, maybe TZD, DPP-4 Inhibitors and/or GLP-1 mimetic

Basal Insulin in Type 2 Diabetes



LA = long-acting insulin: Glargine, detemir

Titrating Insulin for Background Regimen

If most AM fasting BG >120 mg/dL	Titrate until fasting glucose at target BG If dose reaches 0.5–0.7 units/ kg body weight, consider adding mealtime insulin
If most AM fasting BG <120 mg/dL and A1C remains above target	Test presupper and bedtime (or 2-hour postsupper) and consider need for mealtime insulin

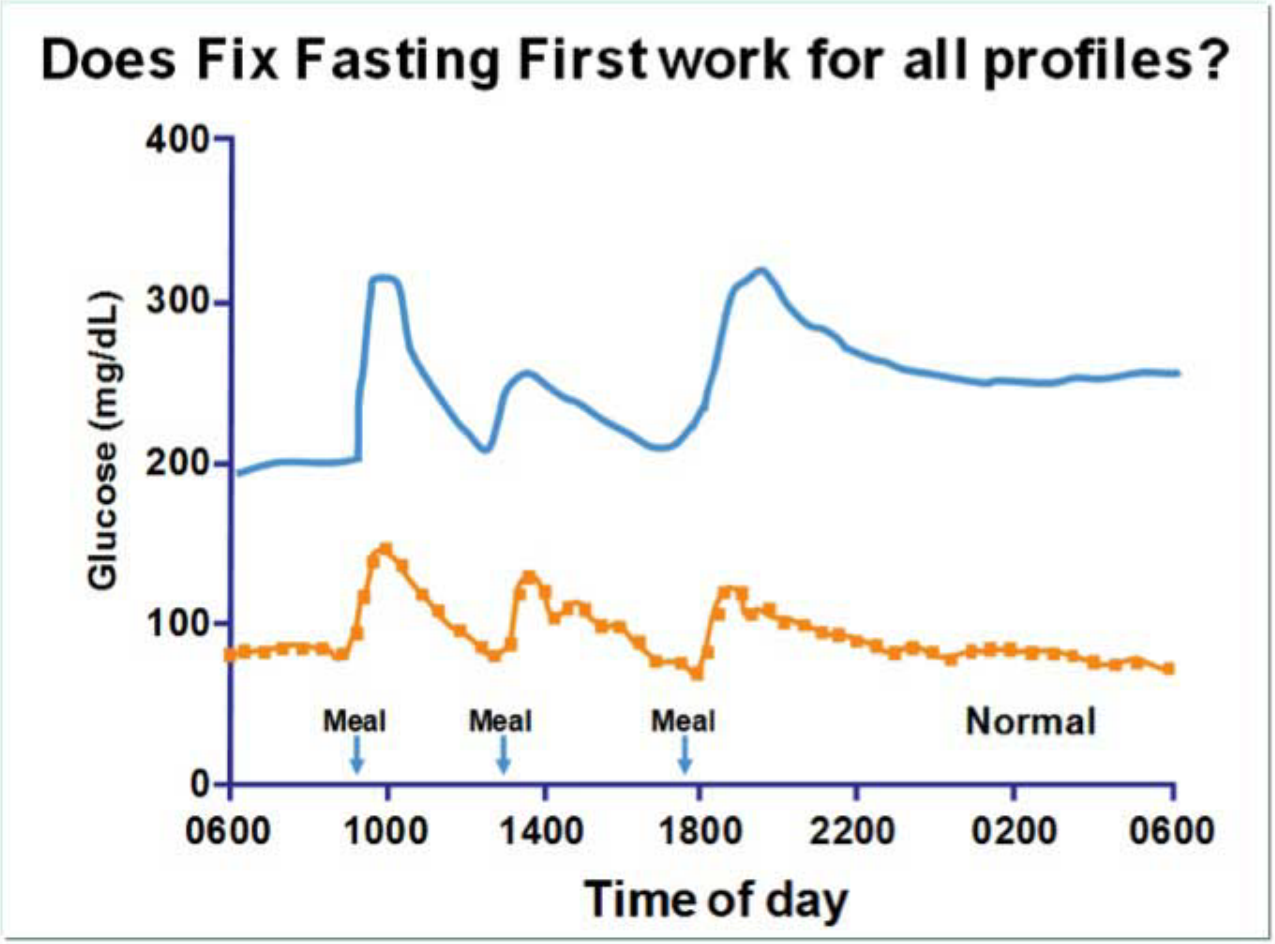
Guide to Starting and Adjusting Insulin for Types 2 Diabetes

Titrating Insulin
(I Prefer Weekly Dose Adjustments)

If most BG <200 mg/dL	
<70 mg/dL	Decrease by 1–3 units
70–120 mg/dL	No change
121–200 mg/dL	Increase by 1–3 units
>200 mg/dL	Increase by 3–5 units or 10%

Guide to Starting and Adjusting Insulin for Types 2 Diabetes

24-Hour Plasma Glucose Curve
Normal and People with Type 2 Diabetes



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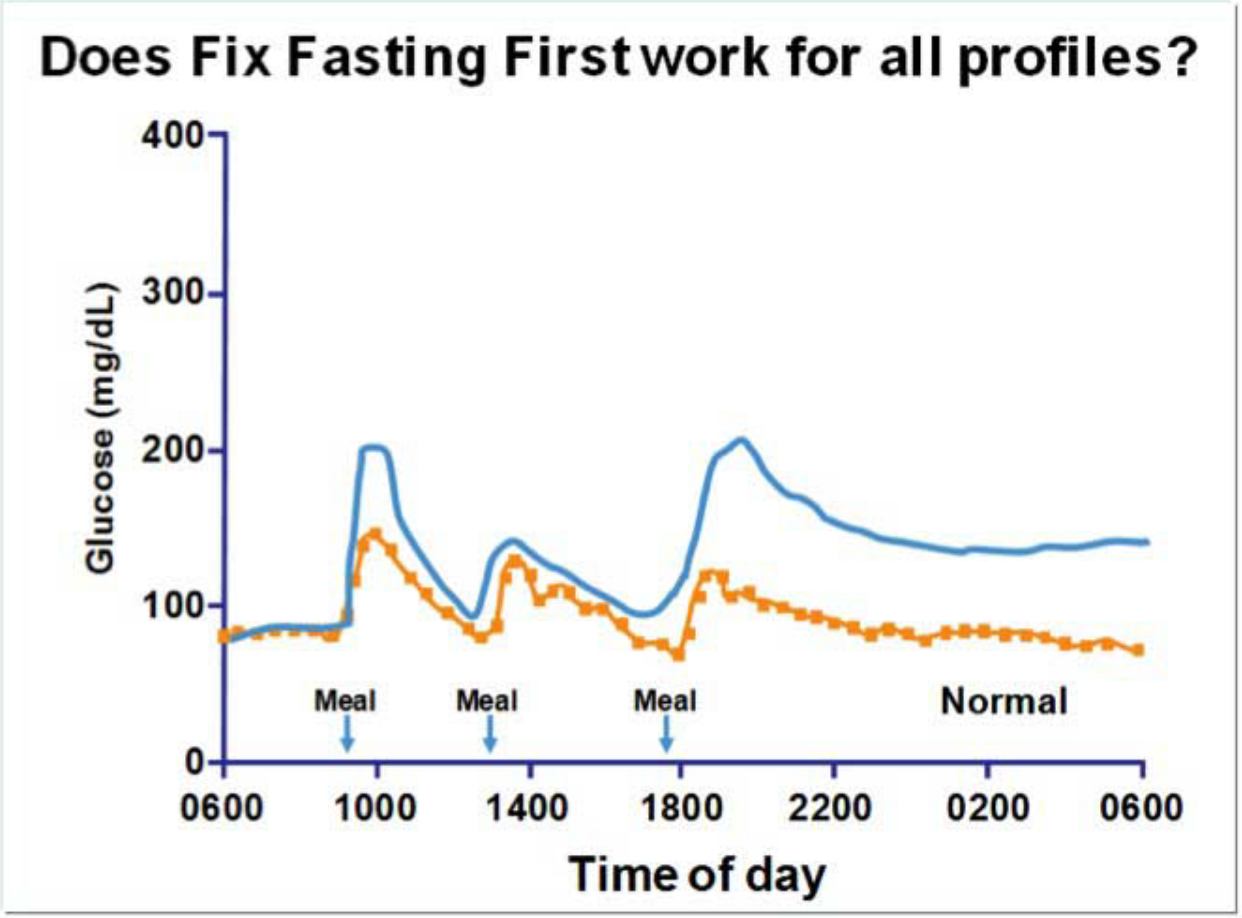
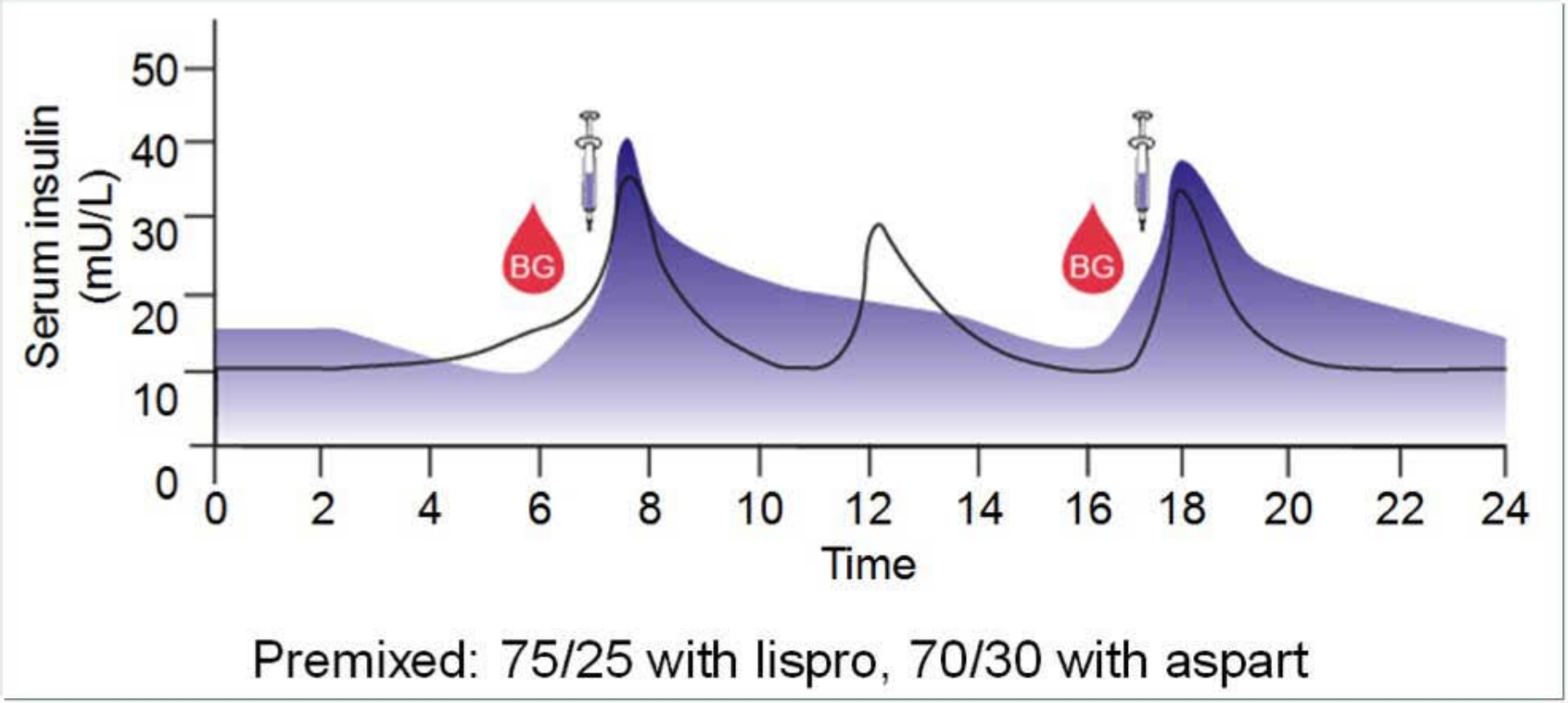
24-Hour Plasma Glucose Curve
Normal and People with Type 2 Diabetes



Adapted from Polonsky KS, et al. N Engl J Med 1988;318:1231–9

Premixed Regimen with Rapid-Acting Insulin



BG = blood glucose

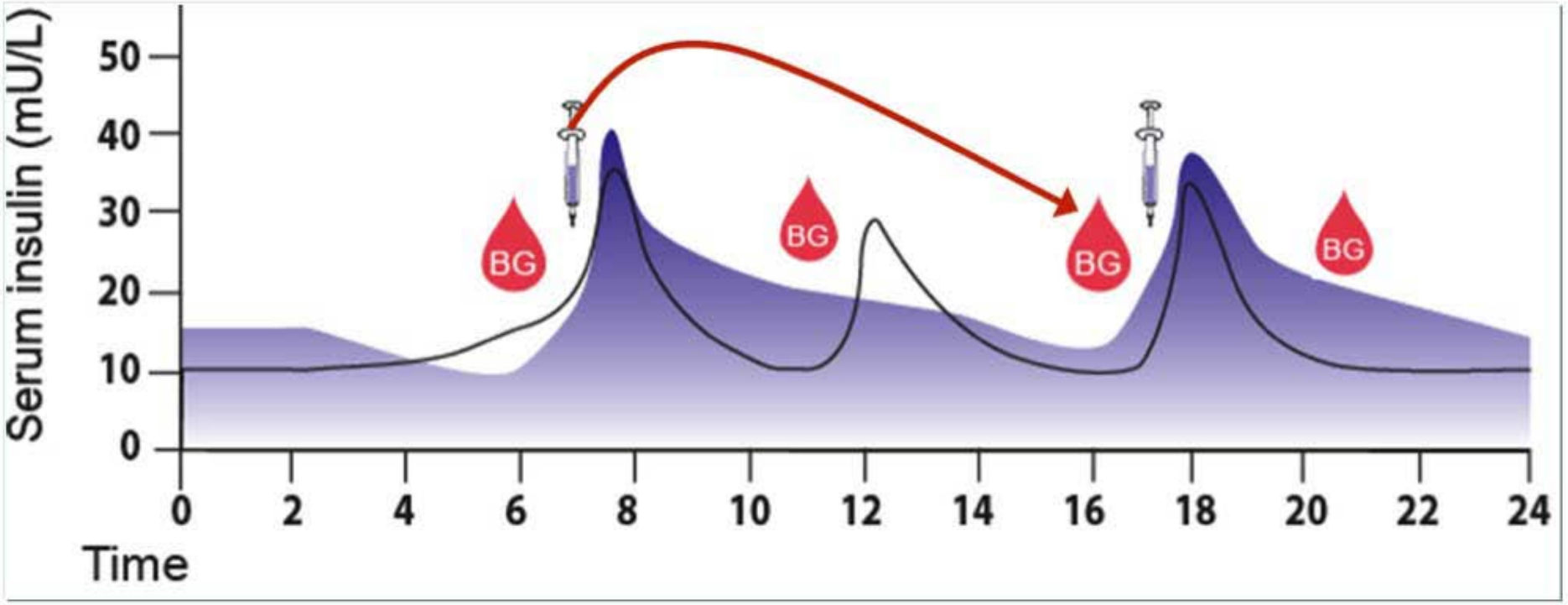
Starting Premixed Insulin

	A1C < 9%	A1C ≥ 9%
Premixed Insulin Dose	0.1 units/kg (2 times/day) **0.2 units/kg total**	0.2 units/kg (2 times/day) **0.4 units/kg total**

- Start with two doses; before breakfast and dinner
- Continue or consider adding Metformin

Guide to Starting and Adjusting Insulin for Types 2 Diabetes

Premixed Regimen with Rapid-Acting Insulin



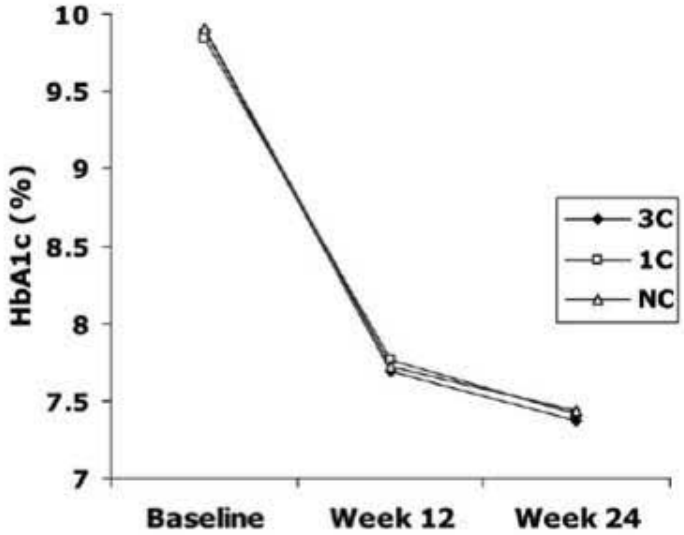
Premixed: 75/25 with lispro, 70/30 with aspart,

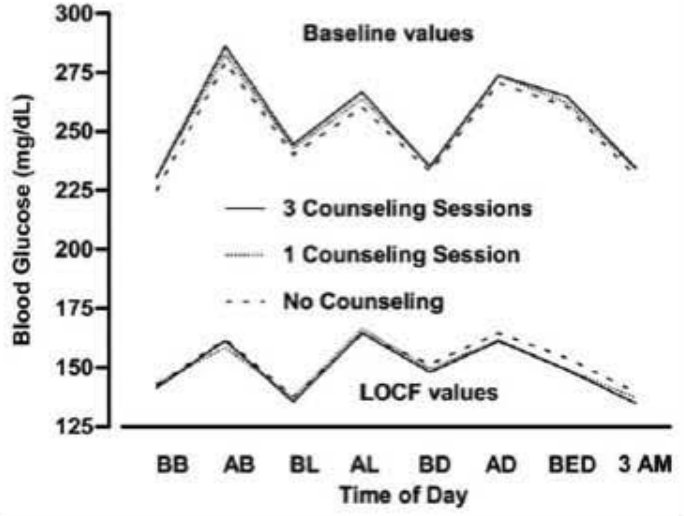
50/50 with lispro

A_{1c} Control in a Primary Care Setting: Self-titrating an Insulin Analog Pre-mix (INITIATE*plus* Trial)

David S. Oyer, MD,[a] Mark D. Shepherd, MD,[b] Franklin C. Coulter, MD,[c] Anuj Bhargava, MD,[d] Jason Brett, MD,[e] Pei-Ling Chu, PhD,[e] and Bruce S. Trippe, MD,[f] on behalf of The INITIATE*plus* Study Group*

[a]*Feinberg School of Medicine, Northwestern University, Chicago, Ill;* [b]*Endocrinology Consultants, Tupelo, Miss;* [c]*Coulter Clinic, Orangeburg, SC,* [d]*Iowa Diabetes and Endocrinology Center, Des Moines;* [e]*Novo Nordisk Inc., Princeton, NJ;* [f]*Endocrinology Associates, Montgomery, Ala.*





CLINICAL SIGNIFICANCE

- A simple dosing algorithm allowed patients with high HbA_{1c} values (study mean = 9.9%) to regain glycemic control (endpoint mean HbA_{1c} = 7.4%).
- Daily blood glucose self-monitoring is an important component for effective self-adjusted insulin dose titration.
- Biphasic insulin aspart 70/30, twice a day, is an effective treatment option for patients with type 2 diabetes in a primary care setting.

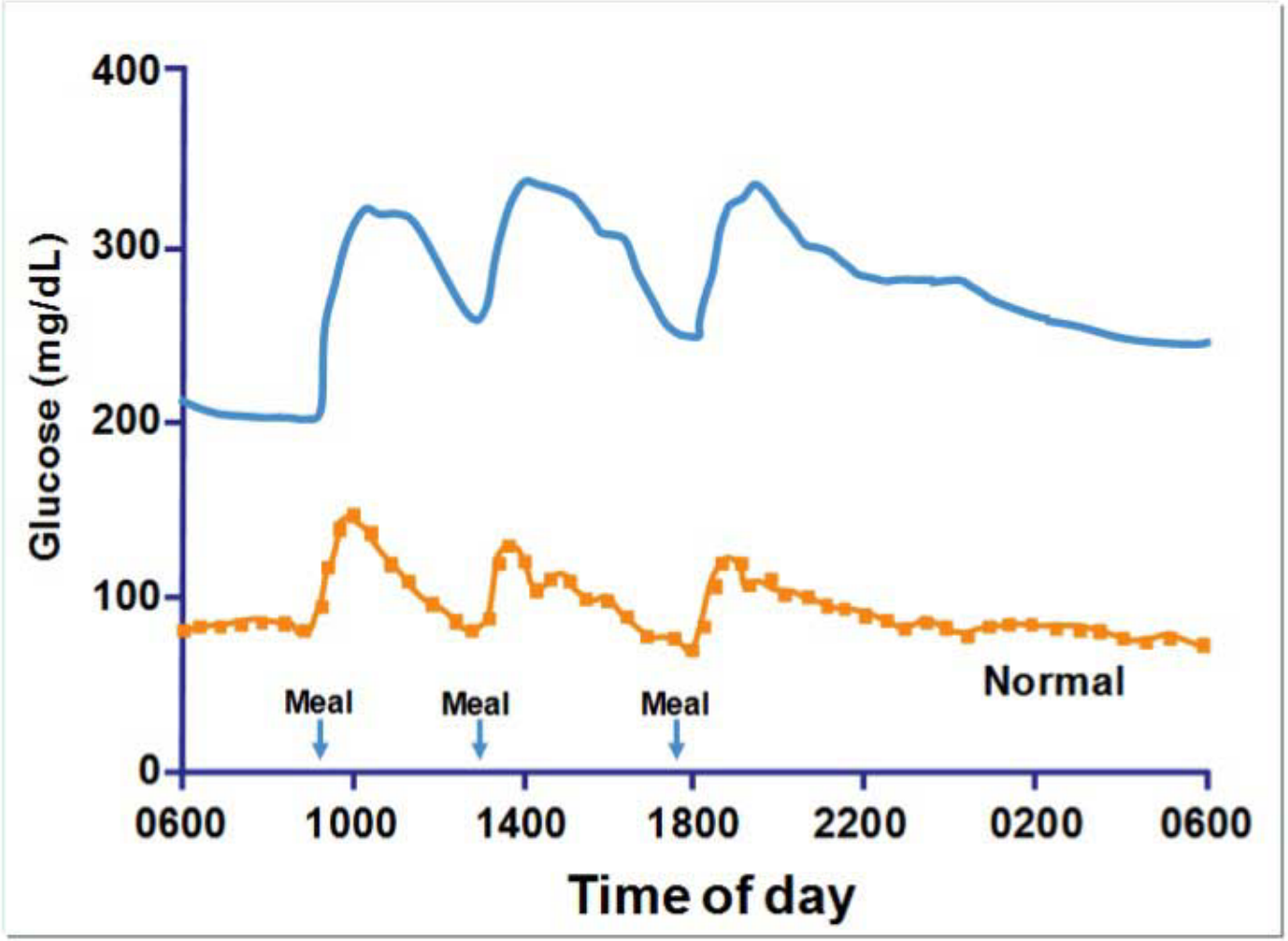
The American Journal of Medicine, Vol 122, No 11, November 2009

Advancing from Premixed to Background and Mealtime Regimen

- Total Daily Dose of bid Premix
  - A1C < 9% subtract 10% for modified TDD
  - A1C ≥ 9% take original TDD
- Original or Modified TDD
  - ½ as Long Acting Background (once daily)
  - ½ split over 3 meals (per CHO content or 30, 30, 40%.
  - Adjust background and meals insulins per weekly assessment of patterns

24-Hour Plasma Glucose Curve
Normal and People with Type 2 Diabetes

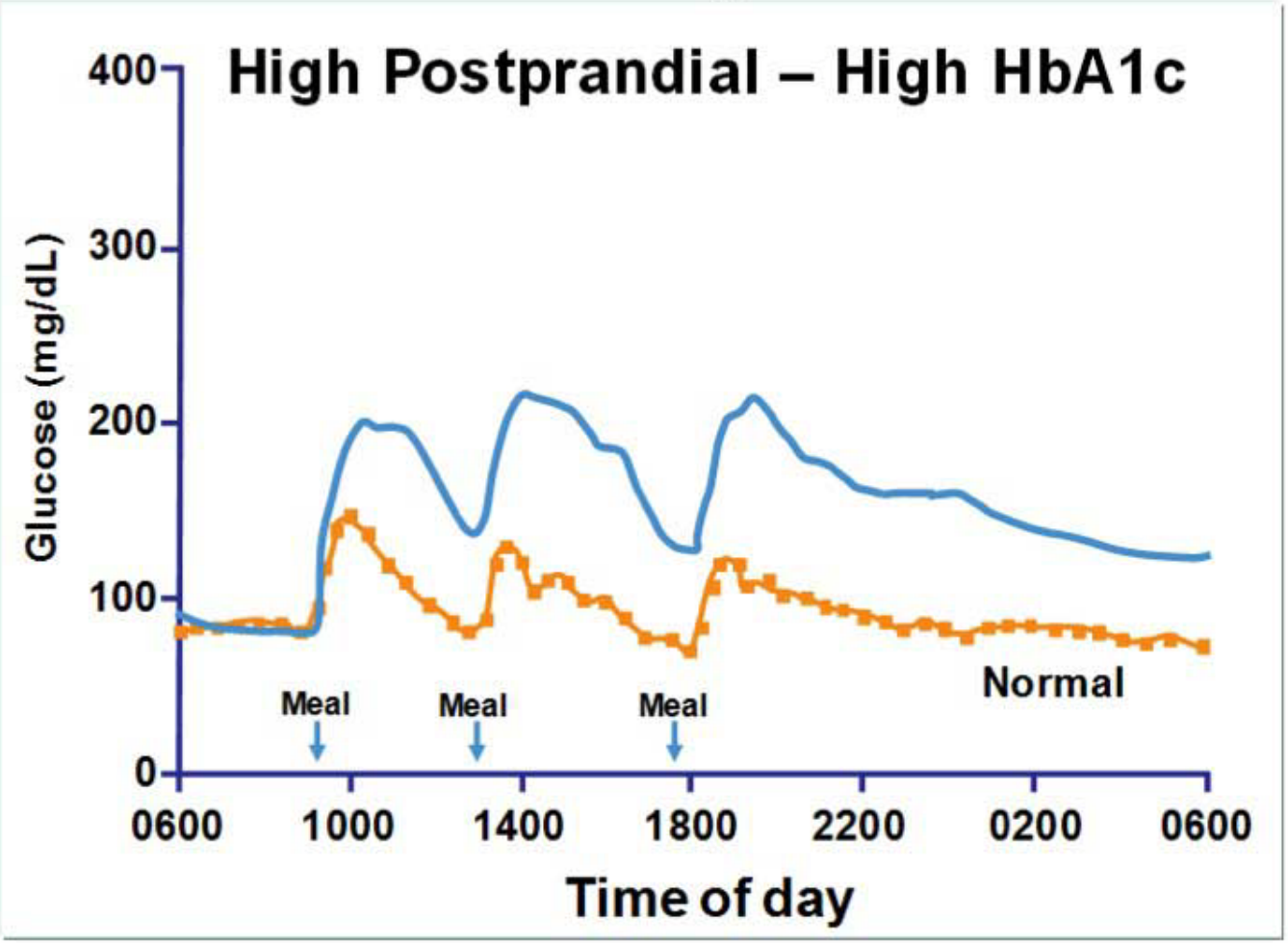
Fix Fasting First



Adapted from Polonsky, et al. N Engl J Med 1988;318:1231–9

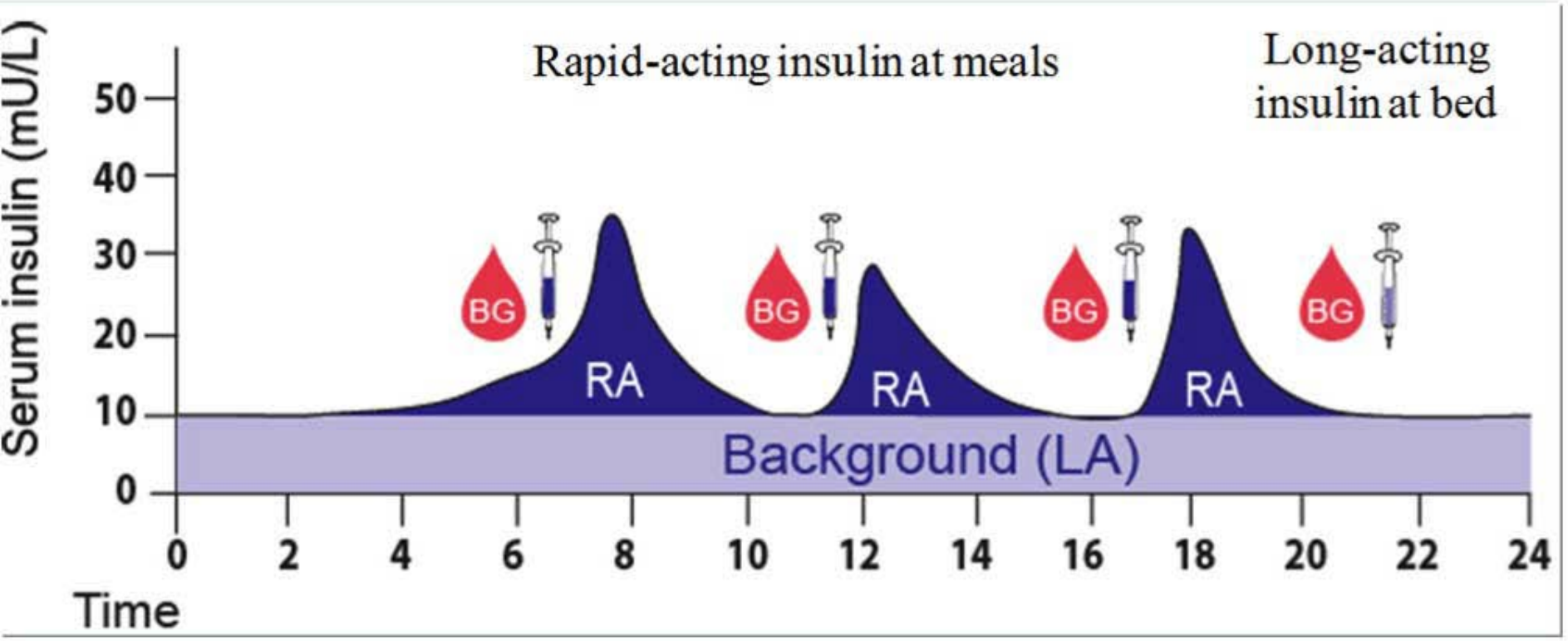
24-Hour Plasma Glucose Curve
Normal and People with Type 2 Diabetes

Fix Fasting First



Adapted from Polonsky, et al. N Engl J Med 1988;318:1231–9

Background/Mealtime Insulin Regimen



RA = rapid-acting insulin: lispro, aspart, glulisine

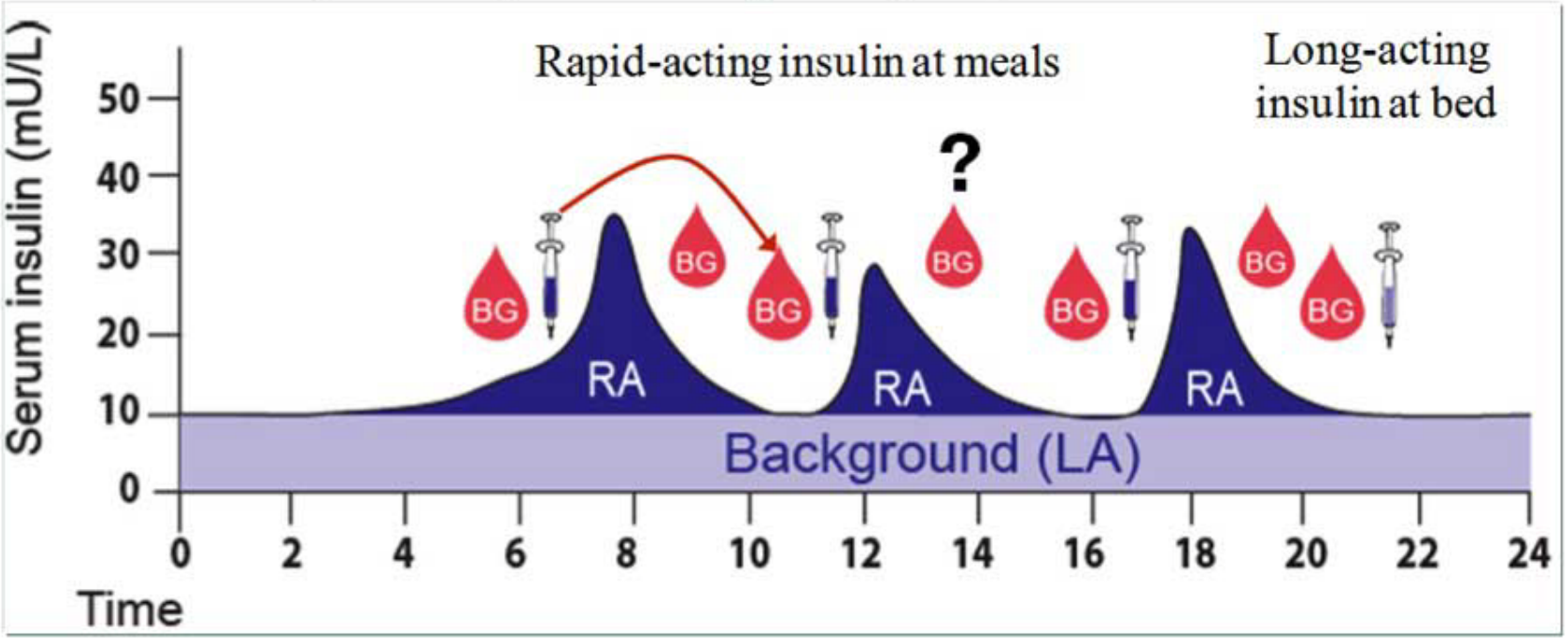
Starting Background and Mealtime Insulin

	A1C <9%	A1C ≥9%
Background Insulin Dose	0.1 units/kg (once daily)	0.2 units/kg (once daily)
Mealtime Insulin Dose	0.1 units/kg (divided evenly between meals)	0.2 units/kg (divided evenly between meals)
Total Insulin Dose	0.2 units/kg	0.4 units/kg

- Stop Sus–continue or consider adding Metformin

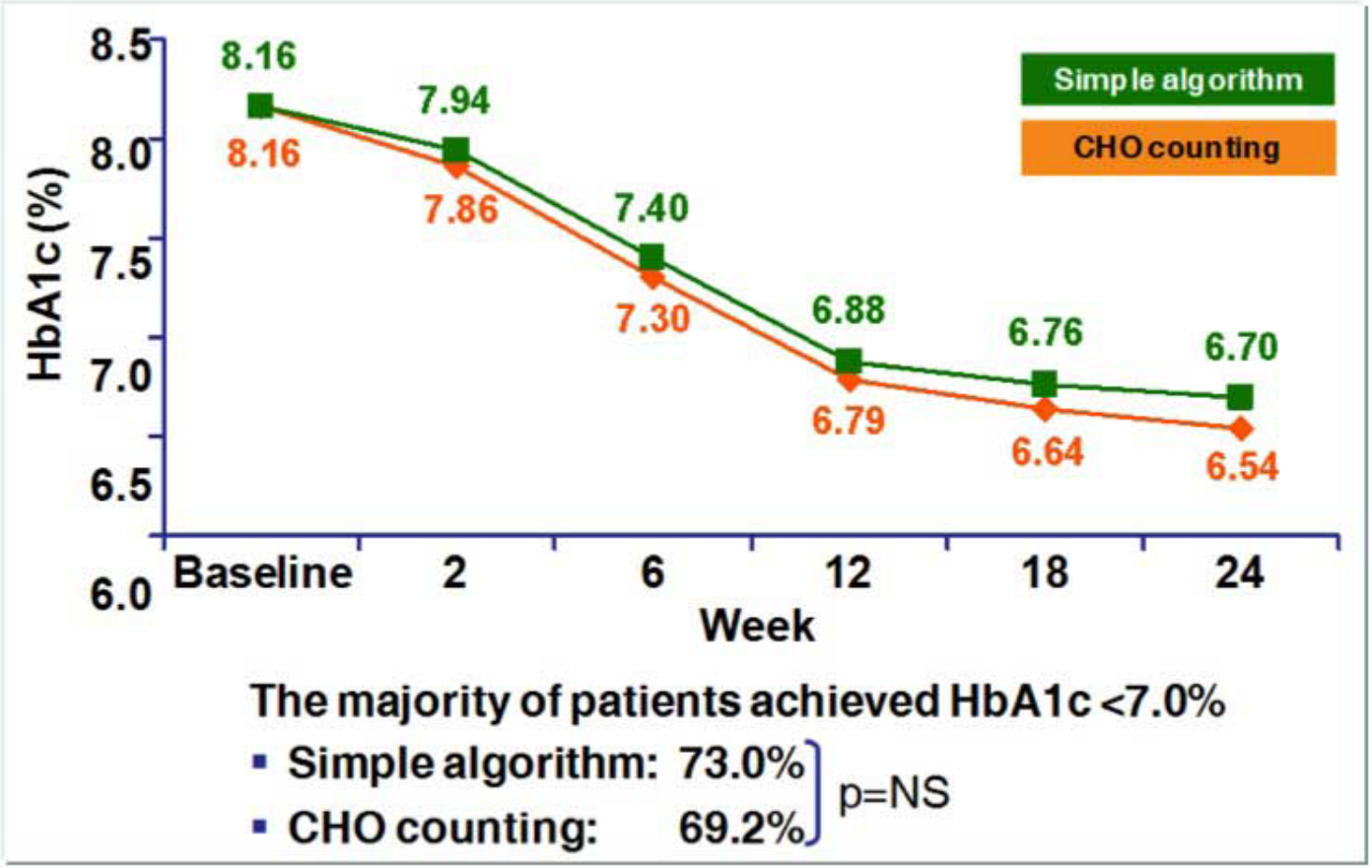
Background/Mealtime Insulin Regimen

RA = rapid-acting insulin: Lispro, aspart, glulisine



1. Do you need to test postprandial glucose?
2. Should you use I:CHO ratio to dose premeal RA insulin or just give same dose that is adjusted weekly based on glucose patterns?

Improvement in HbA1c with Basal:Bolus Insulin *Regimen in T2DM*

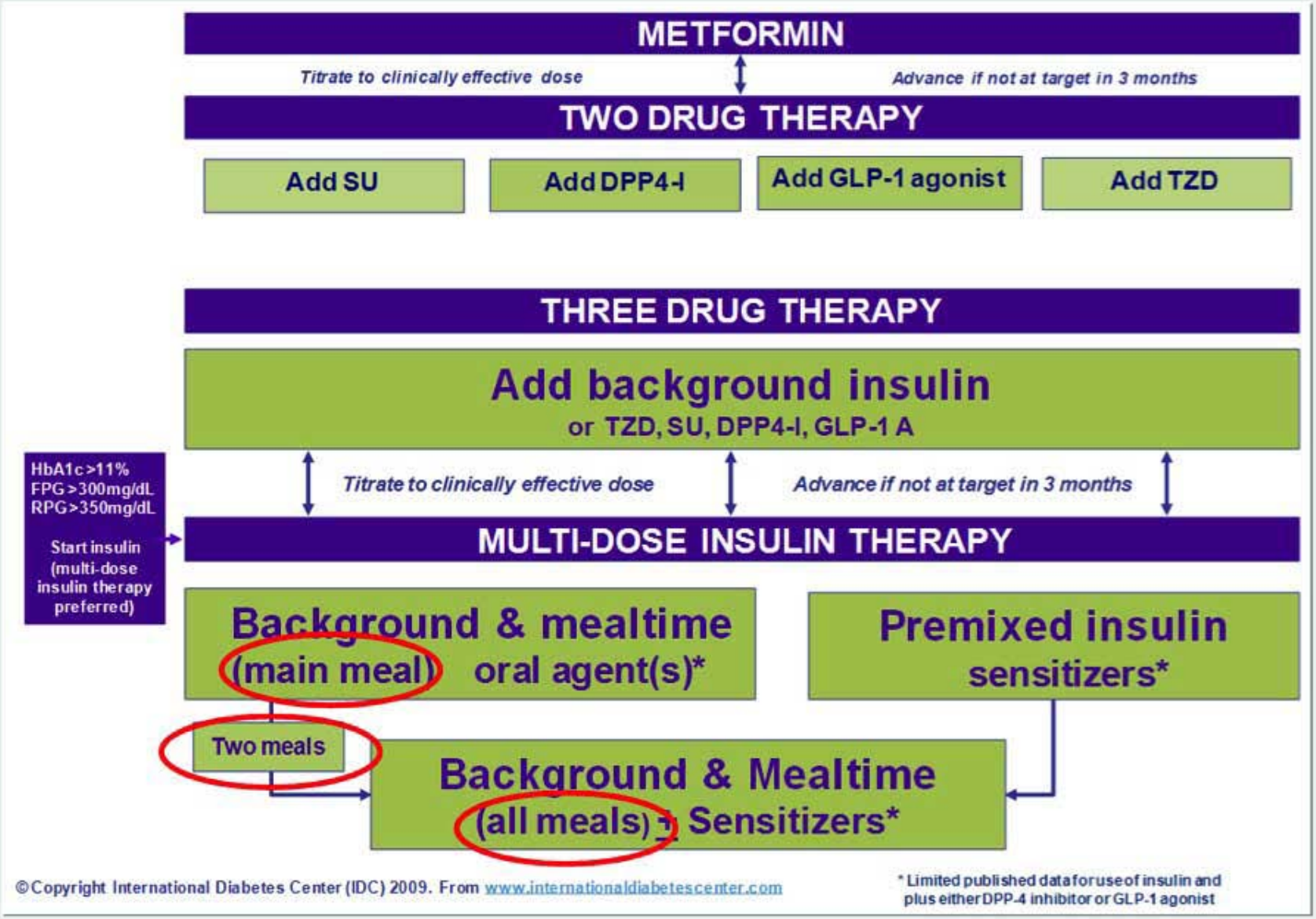


CHO = carbohydrate; NS = not significant

Bergenstal RM, et al. Diabetes Care 2008;31:1305–10

Treatment of Type 2 Diabetes: Glycemic Control

Glycemic targets



The NEW ENGLAND JOURNAL of MEDICINE

Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P., Jonathan C. Levy, M.D., F.R.C.P., Julie L. Darbyshire, M.A., M.Sc., Joanne F. Keenan, B.A., and Sanjoy K. Paul, Ph.D., for the 4-T Study Group*

CONCLUSIONS

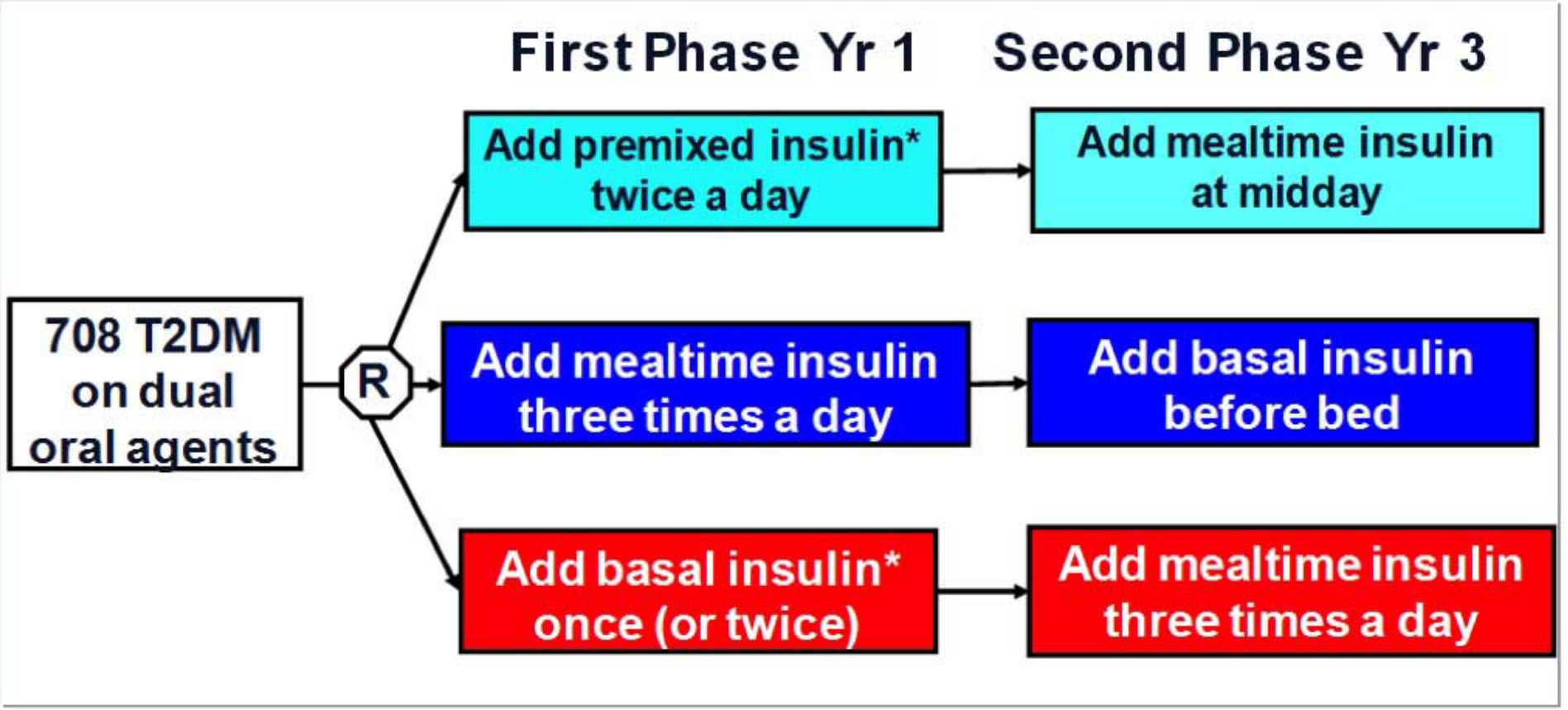
Patients who added a basal or prandial insulin-based regimen to oral therapy had better glycated hemoglobin control than patients who added a biphasic insulin-based regimen. Fewer hypoglycemic episodes and less weight gain occurred in patients adding basal insulin. (Current Controlled Trials number, ISRCTN51125379.)

N ENGL J MED 361;18 NEJM.ORG OCTOBER 29, 2009

TREATING TO TARGET IN TYPE 2 DIABETES

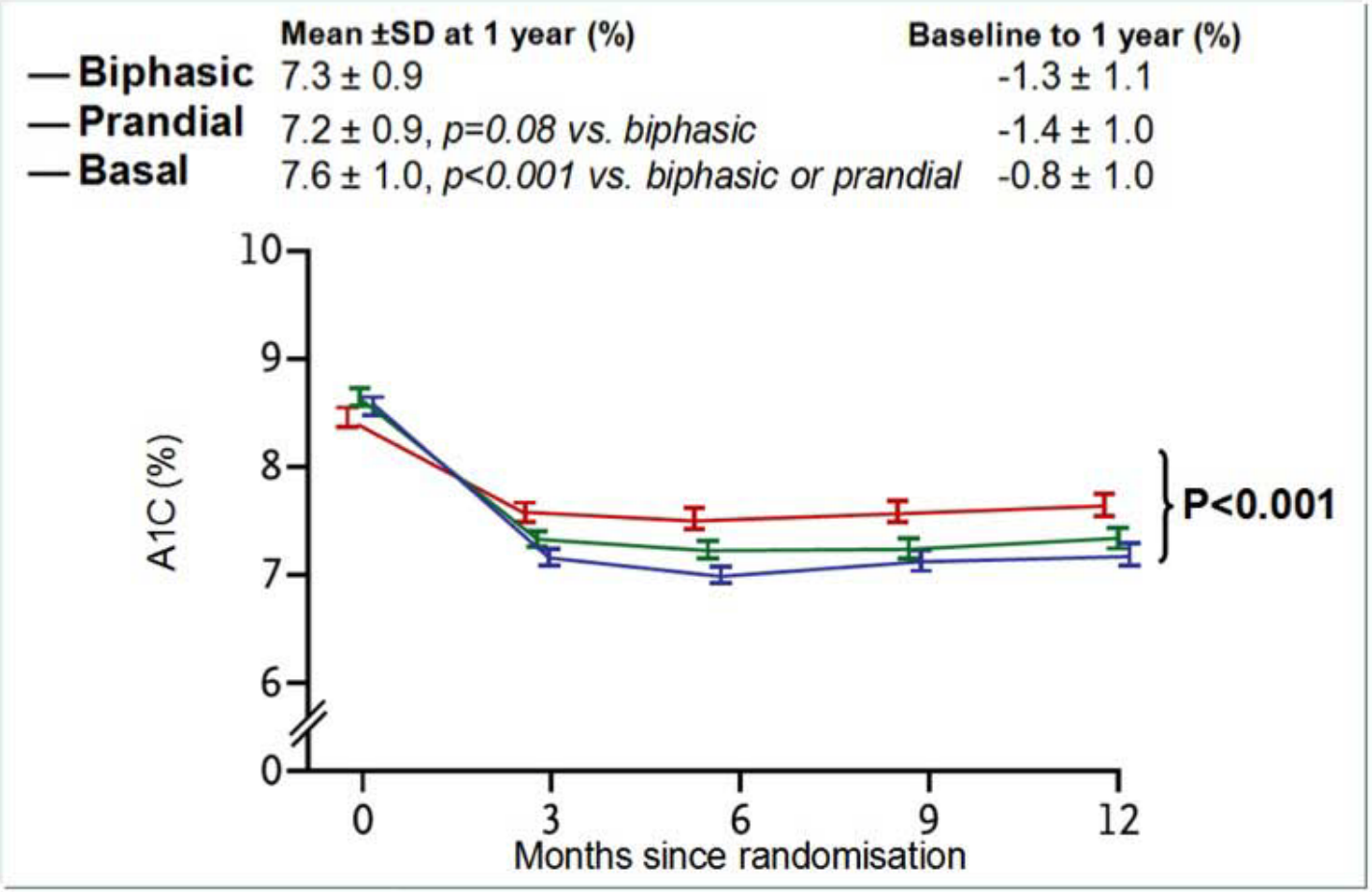
The Oxford Centre
for Diabetes, Endocrinology and Metabolism

Starting and Adjusting Insulin–What Works the Best?



* ***Intensify to a complex insulin regimen in year one if unacceptable hyperglycaemia***

Primary Outcome: A1C at One Year



Holman et al. NEJM 2007; 357:1716-1730.

Overview of Main Results at **3 years**

	Premixed	**Mealtime**	**Basal**
HbA_{1c} targets achieved	+	++	++
Mean SMBG level achieved	+	++	++
Fewer hypoglycaemic episodes	++	+	+++
Less weight gain	+	+	++
Less increase in waist circumference	+	+	++

Table 2: Select a Starting Dose

	A1C <9%	A1C ≥ 9%
Background insulin (added to oral agents) Start with one dose; take at same time each day	**0.1 units/kg**	**0.2 units/kg**
Premixed insulin* Start with 2 doses: before breakfast and before evening meal	0.1 units/kg (two times/day) (Total = 0.2 units/kg)	0.2 units/kg (two times/day) (Total = 0.4 units/kg)
Background and mealtime insulin* Calculate background and mealtime doses Initially, mealtime insulin dose is divided evenly between meals	**Background** 0.1 units/kg (once daily) + **Mealtime** 0.1 units/kg (divide evenly between meals) (Total = 0.2 units/kg)	**Background** 0.2 units/kg (once daily) + **Mealtime** 0.2 units/kg (divide evenly between meals) (Total = 0.4 units/kg)

Table 4: Provide Nutrition Guidelines

1 carbohydrate choice = 15 grams carbohydrate

Background insulin (added to oral agents)	Aim for 3 meals per day: Women 2–4 carb choices per meal Men 3–5 carb choices per meal	Not needed If desired, should be small; 1–2 carb choices per snack
Premixed insulin	Eat 3 meals at consistent times with consistent carb intake Do not skip meals No more than 10–12 hours between breakfast and dinner	Rapid-acting: snack not usually needed; if desired should be small; 1–2 carb choices per snack Regular: may need small snacks
Background & mealtime insulin	Initially, a consistent carb intake When patient is ready, advance from carb counting to insulin-to-carb ratio to maximize therapy	Rapid-acting: not needed; if greater than 1 carb choice may require additional insulin injection Regular: may need small snacks

Note: A registered dietitian can help assess usual food intake, provide guidance in selecting foods in a variety of situations, and evaluate BG records based on food intake and activity.

Hypoglycemia: All who take insulin should be taught to recognize hypoglycemia and carry a carbohydrate food or beverage to treat it. Usual treatment is 15 grams of carbohydrate.

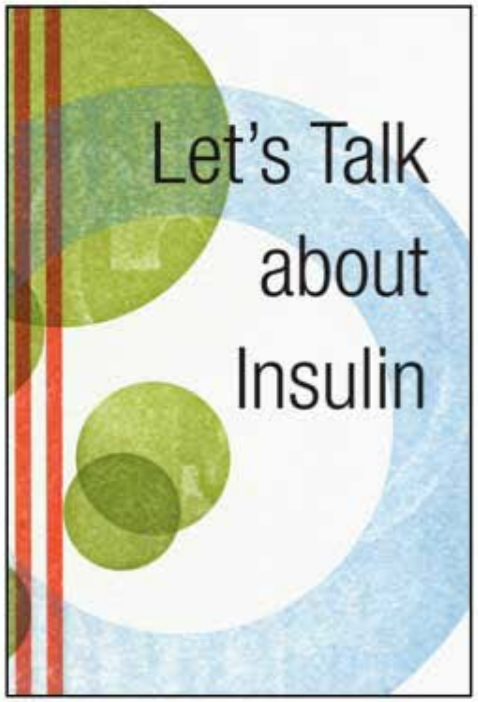
Self-Reported Antecedents to Hypoglycemia Events in ACCORD

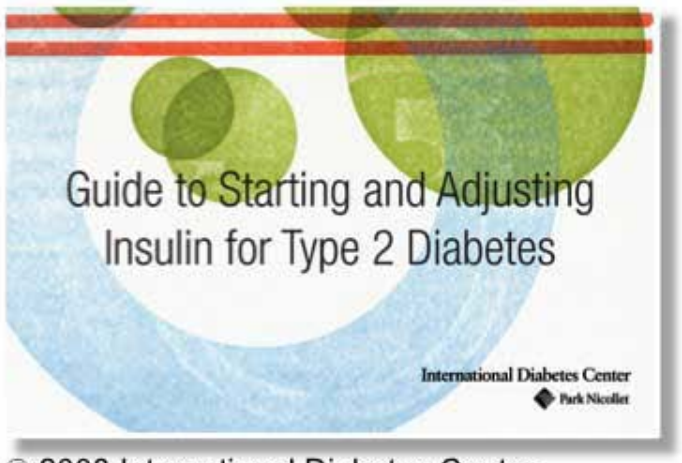
Reason	% (n=875 events)
Delayed/missed meal *or* ate fewer carbohydrates	**58% (510)**
None	17% (148)
Took incorrect dose of glucose lowering medication	9% (82)
Cognitive decline	8% (70)
Intercurrent illness	5% (44)
Ingested alcohol	3% (26)
Recent weight loss	3% (29)
Started or increase of other medication	3% (28)

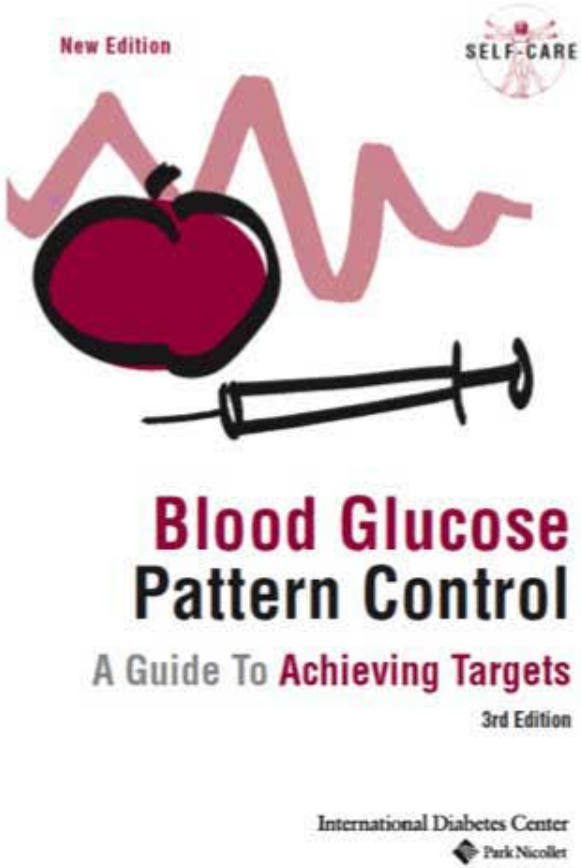
Simons-Morton D. Endocrine Society Annual Meeting. ACCORD Update, June 10, 2009


Accu-Chek Softclix
Accu-Chek

Guide to Insulin Therapy







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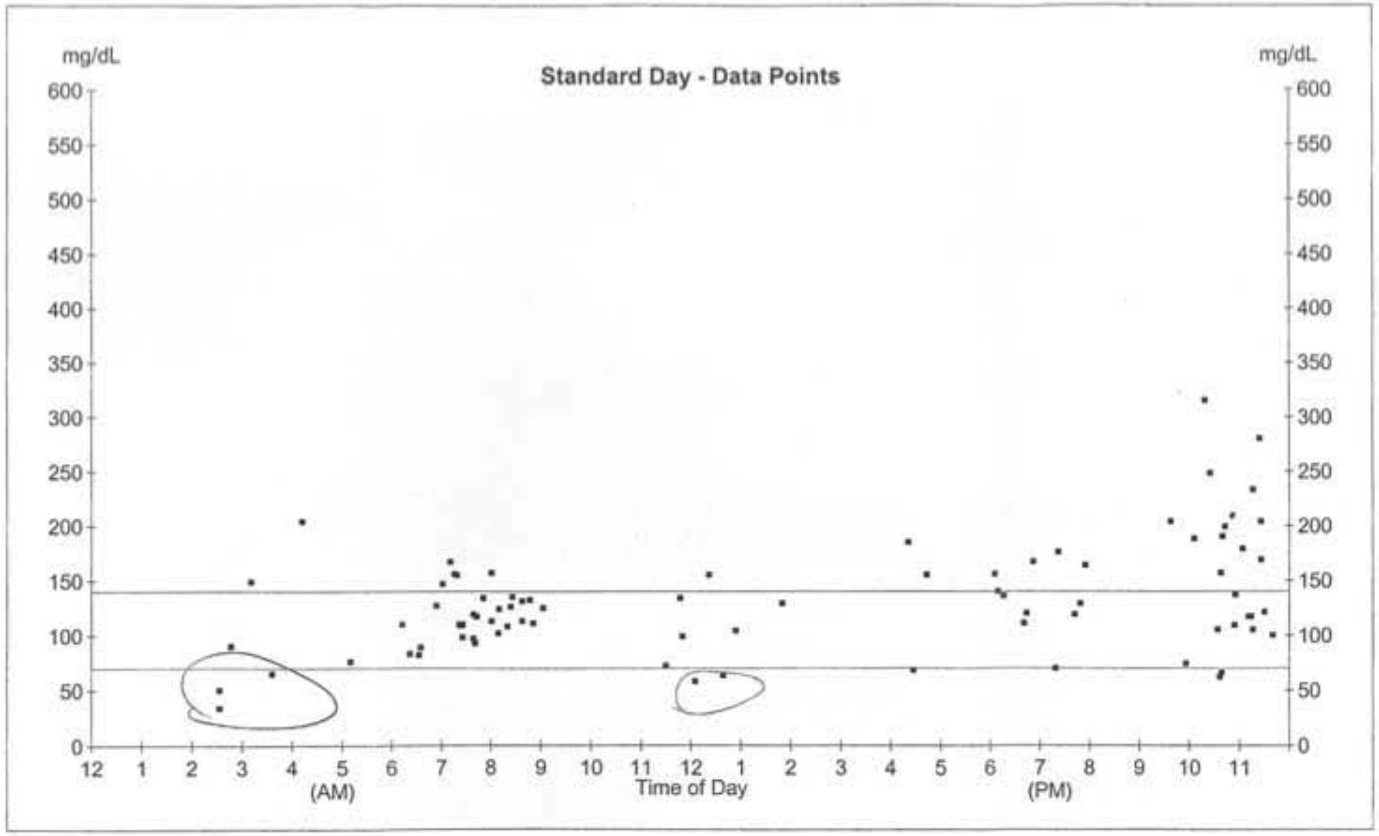


Target Range:

High: 140

Low: 70

Date: Weekdays and Weekends

From: 06/22/2008

to : 07/21/2008

Latest Pump Technology

Disposable Patch Pumps

Evolving from today's insulin pumps into

The next generation of intensive insulin therapy

Introducing

OmniPod™

Insulin Management System

Ground-breaking innovation designed to make diabetes a smaller part of life and CSII* therapy easy to prescribe

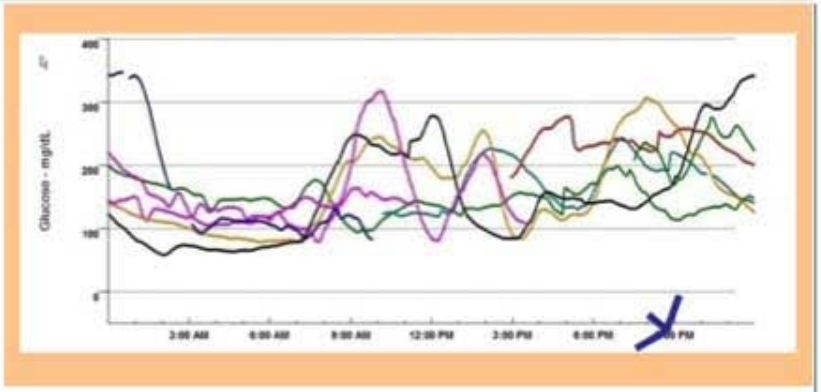
* Continuous Subcutaneous Insulin Infusion

More patch pumps coming for Type 2 Diabetes

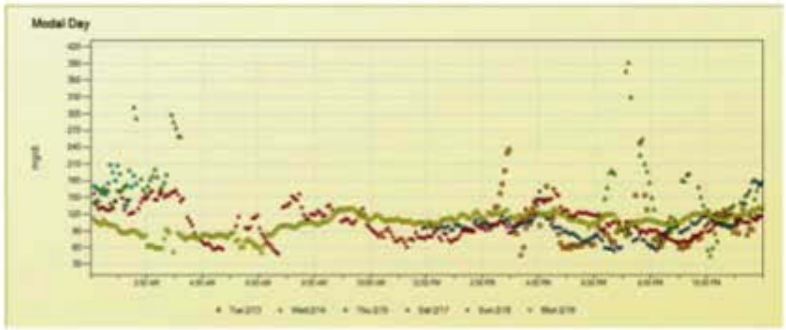

MiniLink Transmitter

DIFFERENT DEVICES—DIFFERENT OUTPUTS

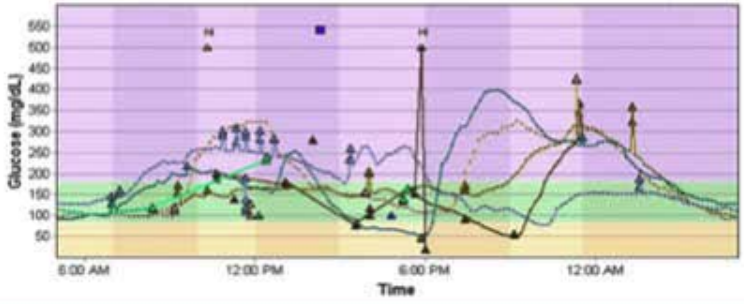
Guardian RT



DexCom Seven

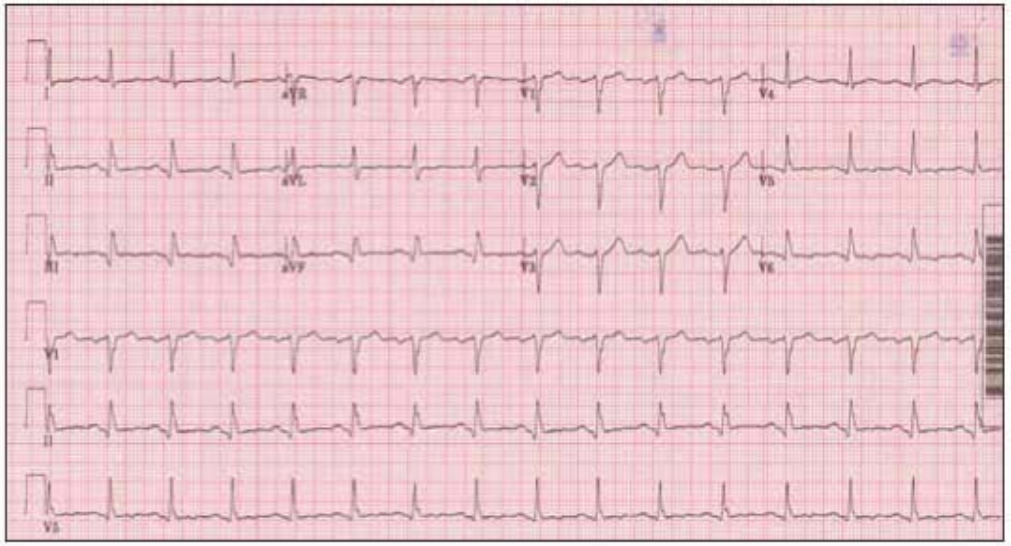


FreeStyle Navigator



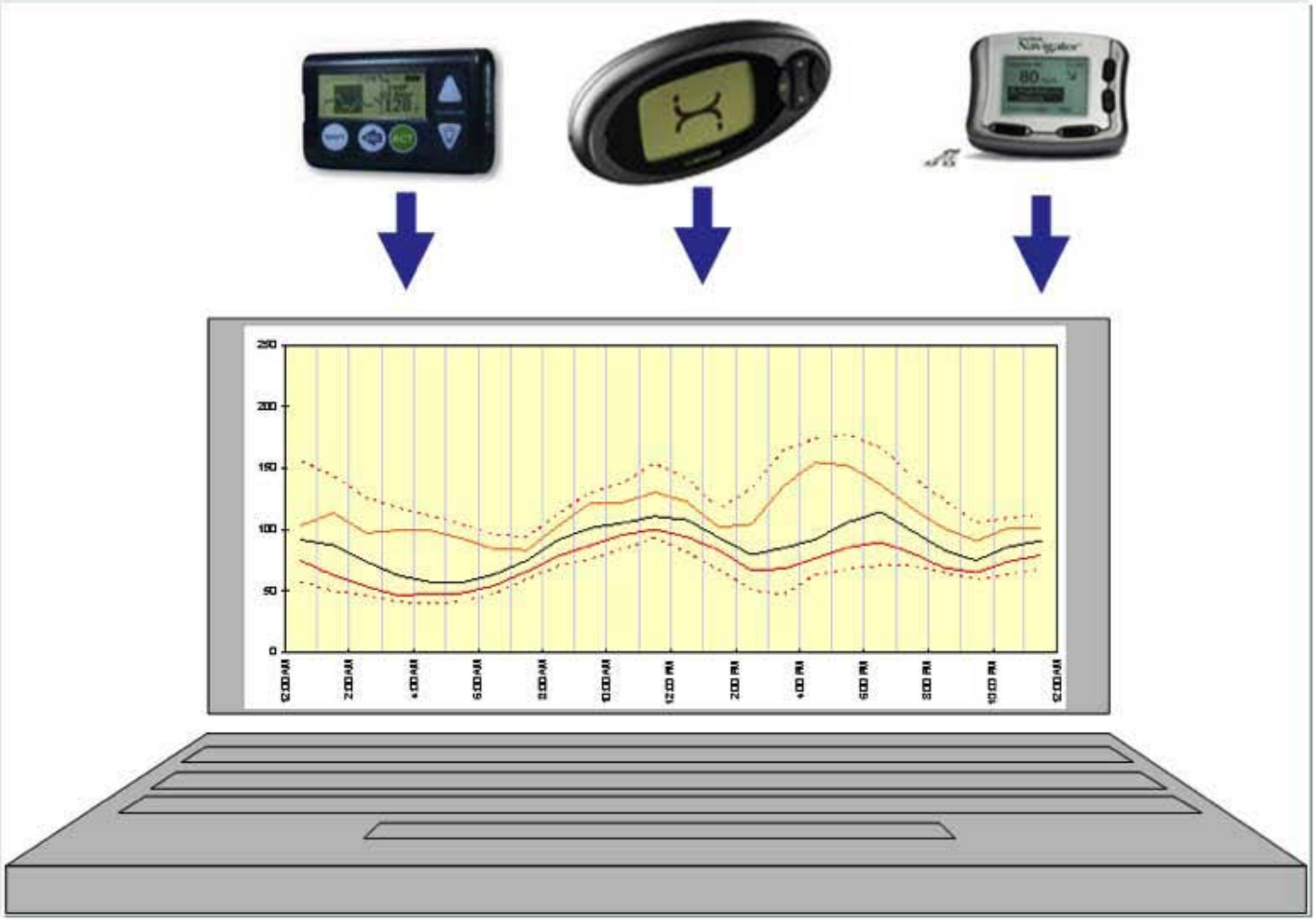
Different Devices–Same Output

Biologic
General Electric
Philips
Welch-Alyn
+ 8 other companies

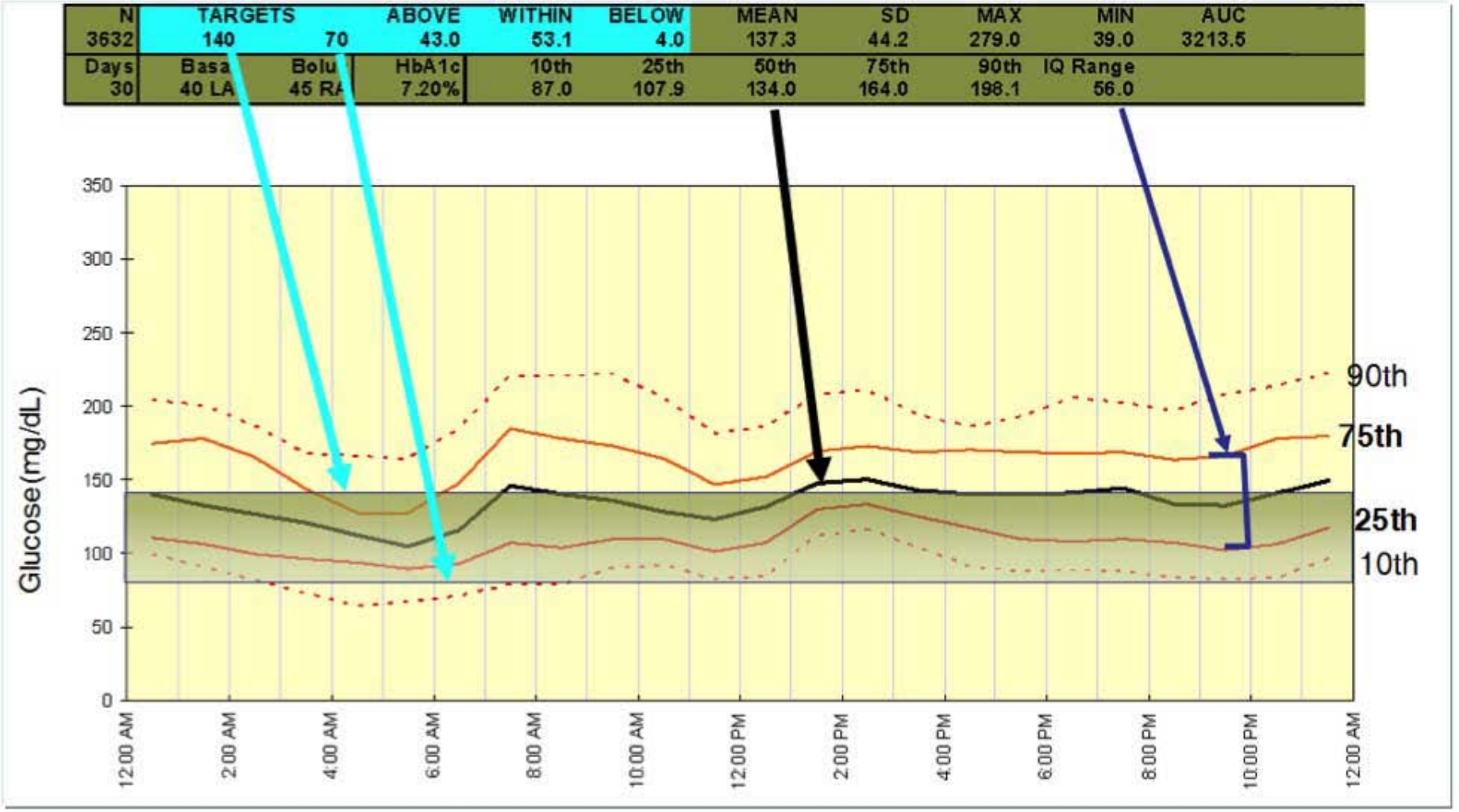


EKG

Ambulatory Glucose Profile™ Using CGM



Searching for an Underlying Pattern
Ambulatory Glucose Profile (AGP) Analysis




Thank You–Questions?