The New ACE/AACE Treatment Algorithm for Diabetes Mellitus Type 2

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AACE/ACE Diabetes Algorithm

AACE: American Association of Clinical Endocrinologists

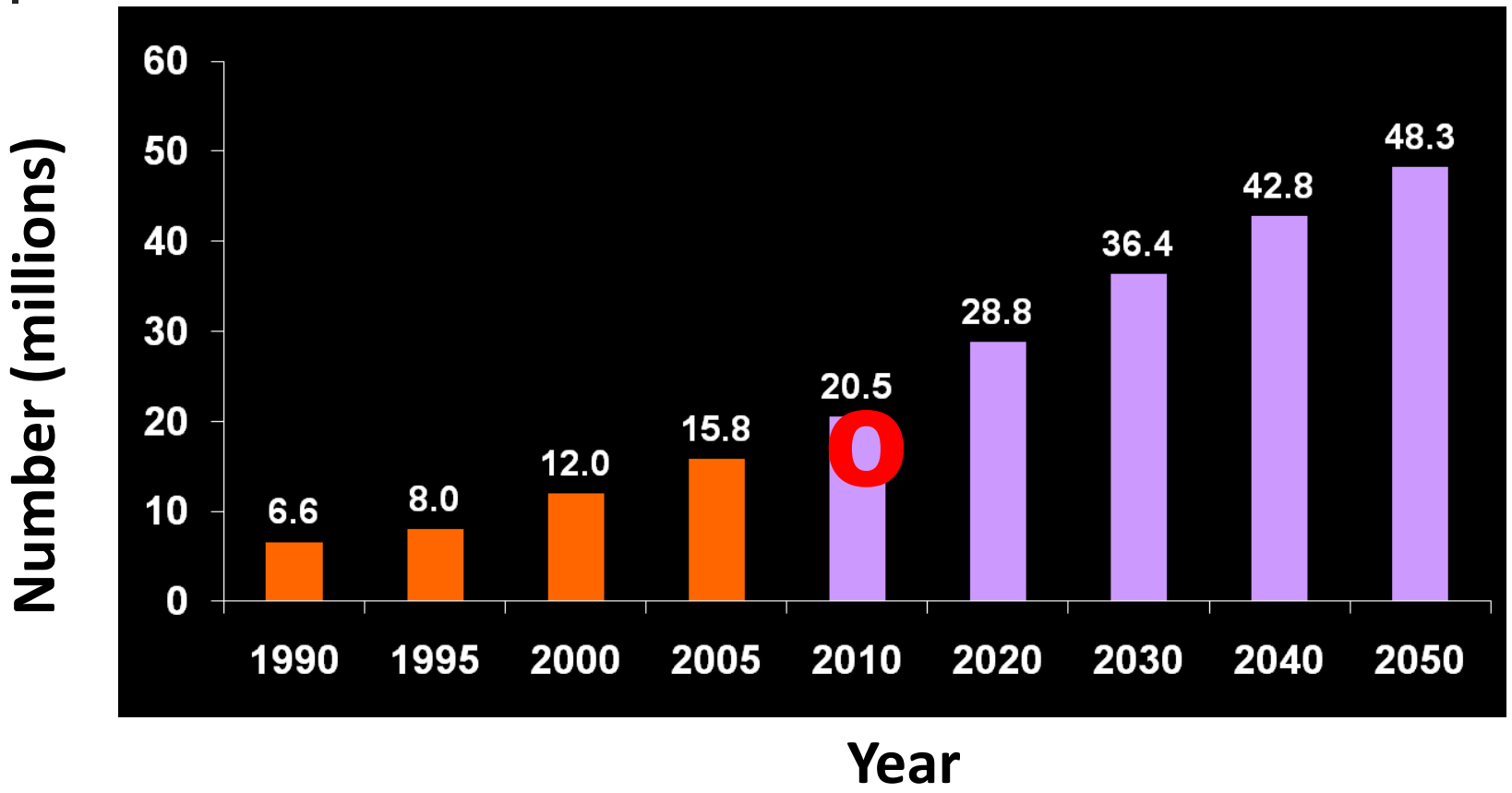
ACE: American College of Endocrinology

Diabetes Algorithm:

Translating Science Into Clinical Care

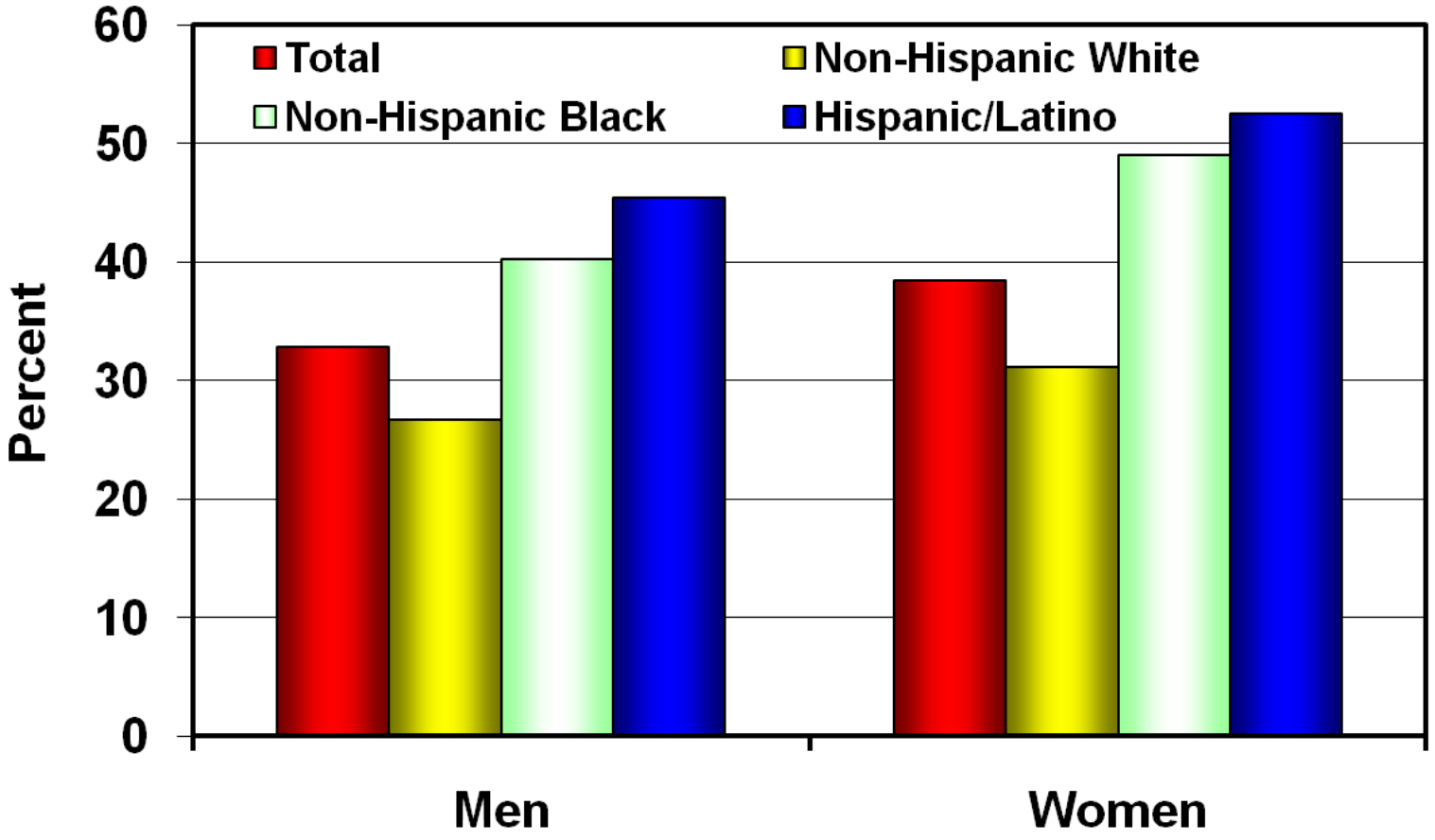
The USA Concerns!

USA Diabetes Projections. A Call for Action: Today's Numbers are well Above the Projections



National Diabetes Surveillance System. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm.
Narayan KMV, et al. *Diabetes Care*. 2006;29:2114-2116.

Estimated Lifetime Risk of Developing Diabetes for Individulas Born in the USA in 2000



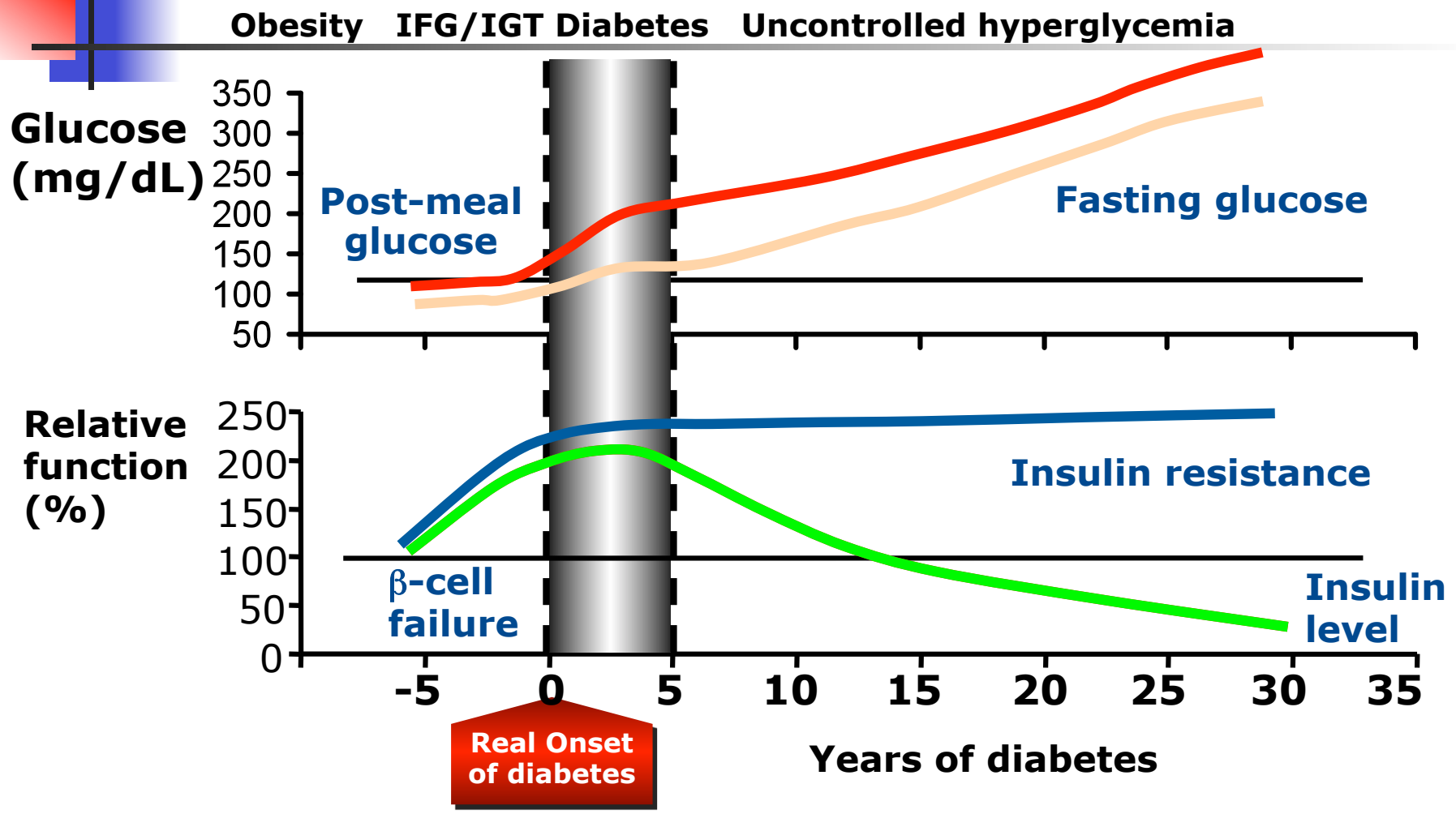
Narayan et al, JAMA, 2003

AACE's Conviction

….Type 2 diabetes is an underrecognized but very serious disease that must be treated as aggressively as type 1 diabetes…

AACE Diabetes Guidelines. *Endocrine Practice.* 2005

Type 2 diabetes is a progressive disease, so pharmacological interventions must address such issues



IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
Adapted from International Diabetes Center (Minneapolis, MN).

Diagnostic Criteria

Symptoms of diabetes plus random plasma glucose **≥200 mg/dL***

or

FPG ≥126 mg/dL*

or

2-h PG during a 75-g OGTT **≥200 mg/dL***

or

A1C 6.5% ? Why do I disagree.

First reason is lack of standardization in the world and…

***Requires confirmation by repeat testing**

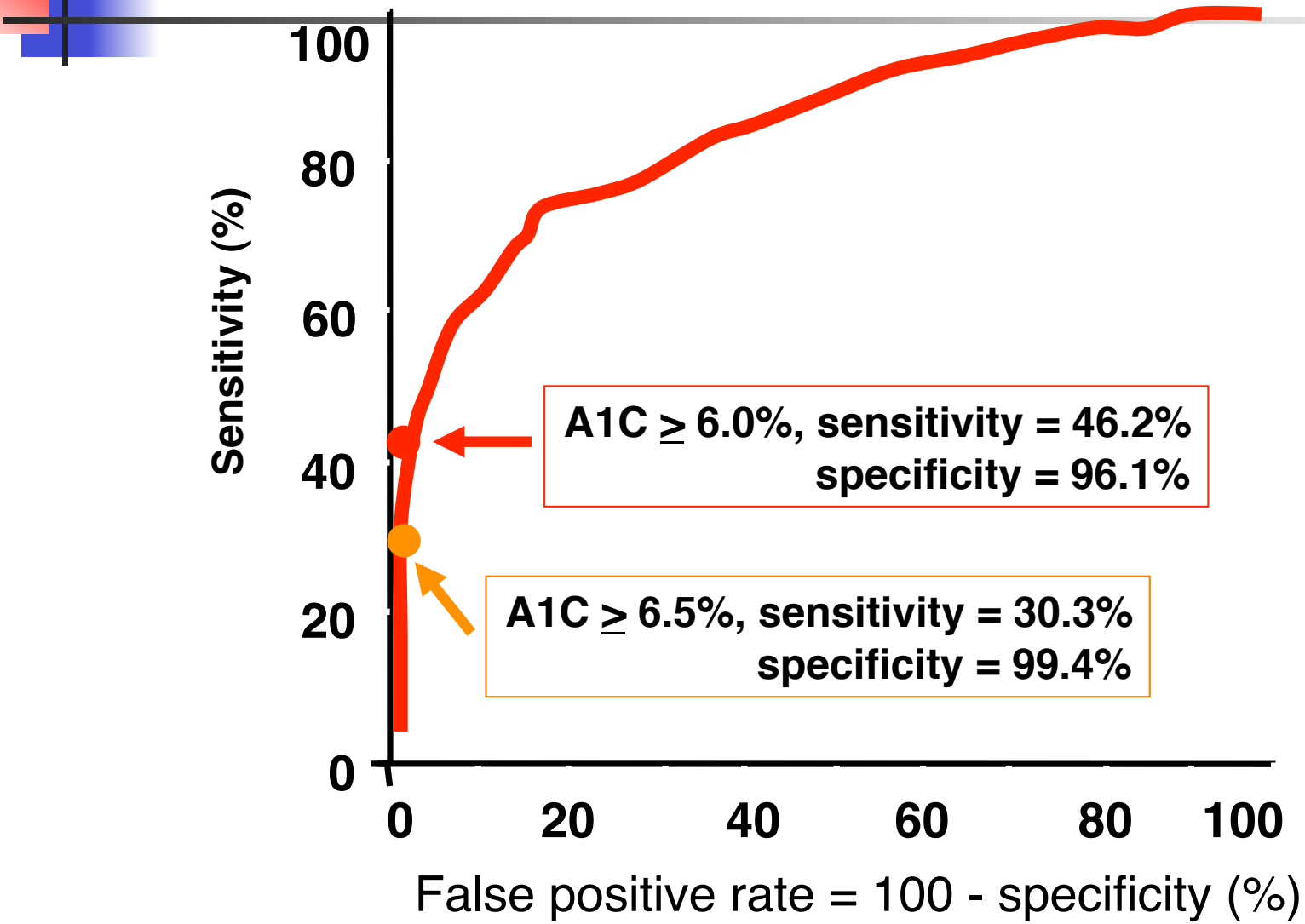
American Diabetes Association. *Diabetes Care.* 2003;26(suppl 1):S5-S20

Elevated Mealtime Glucose Is a Concern at All Levels of A1C

A1C	Mean FPG	% of Pts With FPG >140 mg/dL	Mean 2-Hour PG	% of Pts With 2-Hour PG >200 mg/dL
<6	116	7	208	67
6–6.9	132	28	233	77
7–7.9	172	83	315	94
8–8.9	205	94	371	100
>9	278	100	432	100

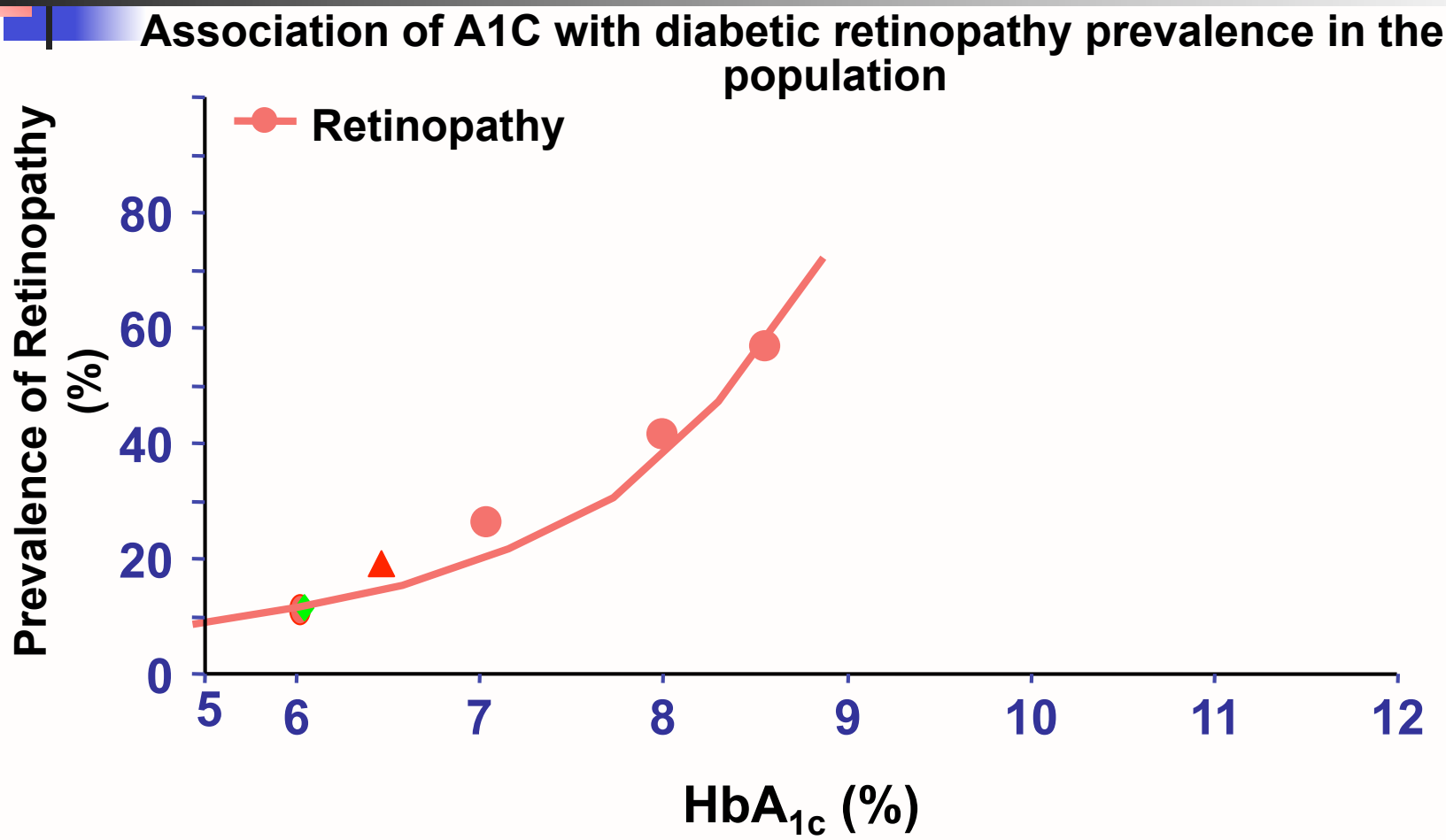
In diagnosed and undiagnosed diabetes only from NHANES III (1988–1994).

ROC Curves for Detecting Subjects with $DM_{1999WHO}$ for A1C



Lorenzo & Hoffner, Diabetes Care 33:335, 2010

Relationship between prevalence of retinopathy and HbA_{1c}



Cheng et al. Diabetes Care 2009, 32,11,2027-2032

HbA_{1c} and Mortality EPIC-NORFOLK Study; BMJ 322:1, 2001

Mortality at Follow-up	<5.0% (N=1204)	5.0-5.4% (N=1605)	5.5-6.9% (N=1611)	7.0%** (N=81)
All Cause				
Rate*	1.65	2.33	3.43	4.35
Relative Risk	1.00	1.41	2.07	2.64
CV-Disease				
Rate*	0.50	1.27	1.24	2.54
Relative Risk	1.00	2.53	2.46	5.04
IHD				
Rate*	0.31	0.86	0.87	1.63
Relative Risk	1.00	2.74	2.77	5.20

*Per 100 patient years adjusted for known risk factors; **known diabetes excluded.

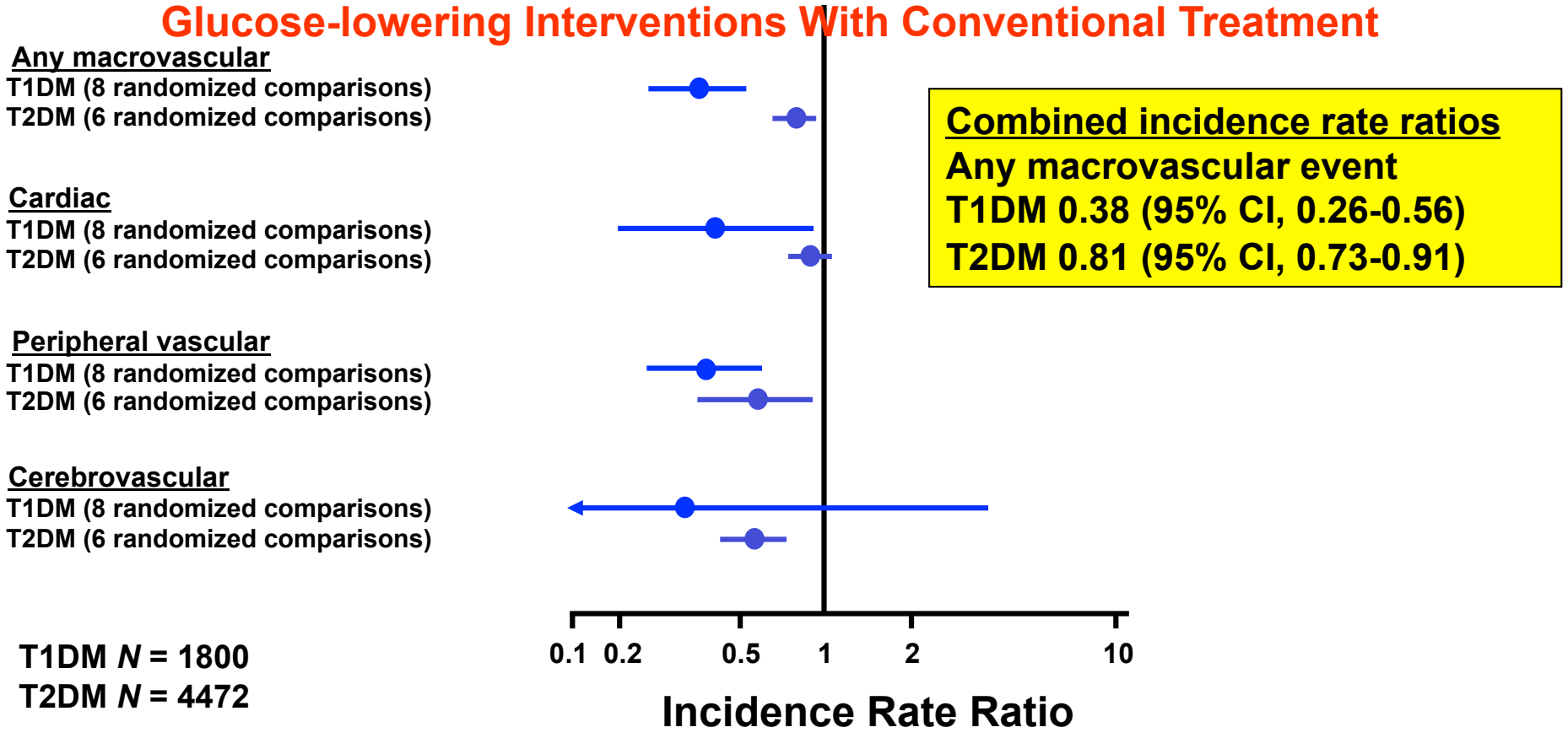
The Role of A1C

- Surrogate marker for risk of diabetic complications
- Useful assessment of glycemic control during clinical management
- Measure for confirming the diagnosis of diabetes

American Diabetes Association. *Diabetes Care.* 2003;26(suppl 1):S106-S108;
Rohlfing CL et al. *Diabetes Care.* 2000;23:187-191

Meta-analysis: Glucose-lowering Reduces Macrovascular Events

Meta-analysis of Randomized Trials Comparing Glucose-lowering Interventions With Conventional Treatment



Stettler C, et al, *Am Heart J.* 2006;152:27–38.

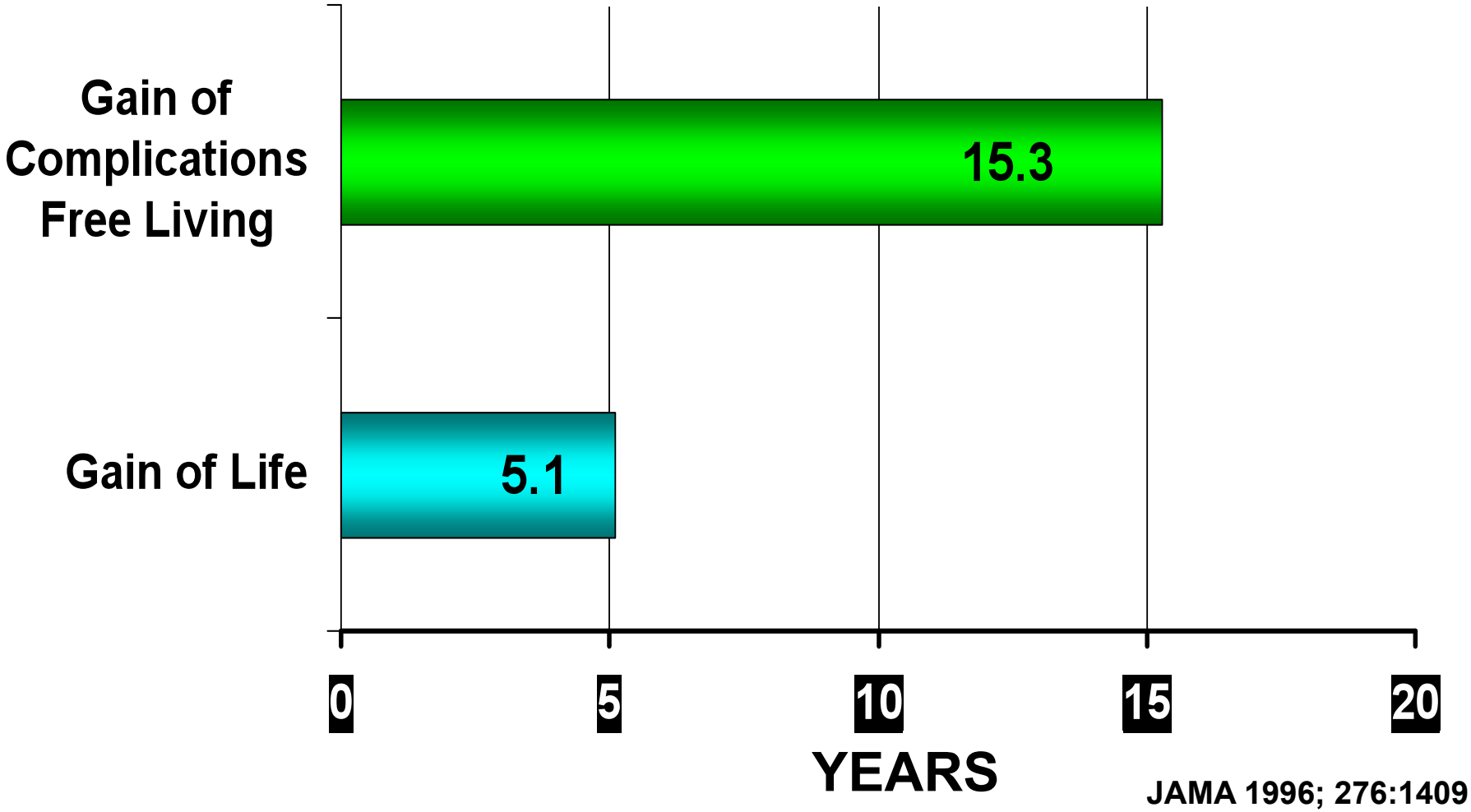
Good Glycemic Control Reduces Complications

	DCCT	Kumamoto	UKPDS
A1C	9% vs. 7%	9% vs. 7%	8% vs. 7%
Retinopathy	63%	69%	17%-21%
Nephropathy	54%	70%	24%-33%
Neuropathy	60%	–	–
Macrovascular disease	–	–	16%*

* *p = 0.052*

Diabetes Control and Complications Trial (DCCT) Research Group. *N Engl J Med*. 1993.
Ohkubo Y et al. *Diabetes Res Clin Pract*. 1995.
UK Prospective Diabetes Study Group (UKPDS) 33: *Lancet*. 1998.

Lifetime Benefits of Intensive Therapy (DCCT)



JAMA 1996; 276:1409

UKPDS: Original and late-follow-up relative risk reduction with metformin

End point	1997: Relative risk reduction (%)	1997: p	2007: Relative risk reduction (%)	2007: p
Any diabetes-related end point	32	0.0023	21	0.013
Microvascular disease	29	0.19	16	0.31
MI	39	0.010	33	0.005
All-cause mortality	36	0.011	27	0.002

Holman RR et al. *N Engl J Med* 2008;available at: http://www.nejm.org.

Road Maps to Achieve Glycemic Control In Type 2 Diabetes Mellitus

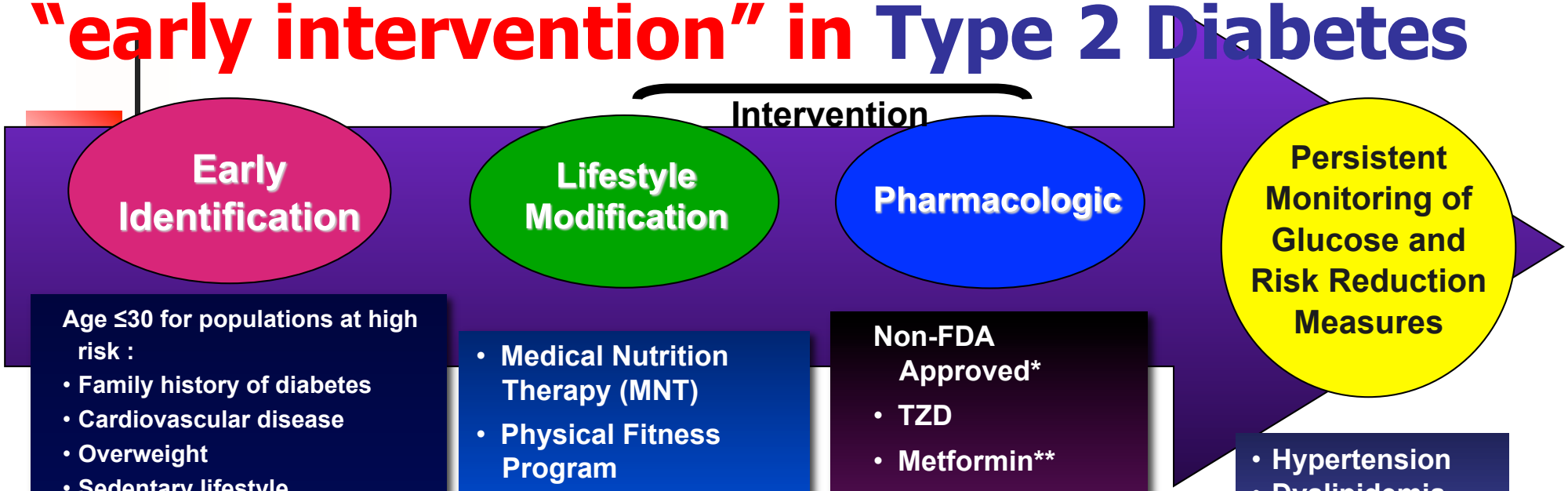
ACE/AACE Diabetes Recommendations

The algorithm is intended for newly diagnosed patients.

In the USA more than 4000 new patients with type 2 diabetes are diagnosed every single day.

AACE/ACE will like to offer a practical approach to physicians treating diabetes.

Road Map to PREVENT? or should it be "early intervention" in Type 2 Diabetes



Age ≤30 for populations at high risk :

- Family history of diabetes
- Cardiovascular disease
- Overweight
- Sedentary lifestyle
- Latino/Hispanic, African American, Asian American, Native American, or Pacific Islander
- Previously identified IGT or IFG
- Hypertension
- Elevated triglycerides, low HDL or both
- History of gestational diabetes
- Delivery of a baby weighing more than 9 lbs
- Polycystic ovary syndrome
- Psych Illness

- Medical Nutrition Therapy (MNT)
- Physical Fitness Program
- Weight Loss

- **5%-7% reduction in body weight (if overweight)**
- **30 minutes of exercise, 5 times per week at the equivalent of brisk walking**

Non-FDA Approved*

- TZD
- Metformin**
- Orlistat
- AGI

- Hypertension
- Dyslipidemia
- Physical Fitness
- Weight Control

* Shown to be effective in delaying the onset of type 2 diabetes in clinical studies.

**A recent report (NEJM; 6/14/07) suggests a possible link of rosiglitazone to cardiovascular events that requires further evaluation.

FPG or 2-h OGTT the recommended screening procedure.

Jellinger, Davidson, et al. 2007.

AACE/ACE Diabetes Algorithm *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET	TZD [2]	DPP4 [1] GLP-1	AGI [3]

2 - 3 Mos.***

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

2 - 3 Mos.***

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

2 - 3 Mos.***

INSULIN ± Other Agent(s) [6]

A1C 7.6 – 9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1,10] or TZD [2]
		SU or Glinide [4,5]

2 - 3 Mos.***

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1] + TZD [2]
		GLP-1 or DPP4 [1] + SU [7]
		TZD [2]

INSULIN ± Other Agent(s) [6]

A1C > 9.0%

Drug Naive | **Under Treatment**

Symptoms | **No Symptoms**

INSULIN ± Other Agent(s) [6]

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

INSULIN ± Other Agent(s) [6]

* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 AGI if ↑ PPG

4 Glinide if ↑ PPG or SU if ↑ FPG

5 Low-dose secretagogue recommended

6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin

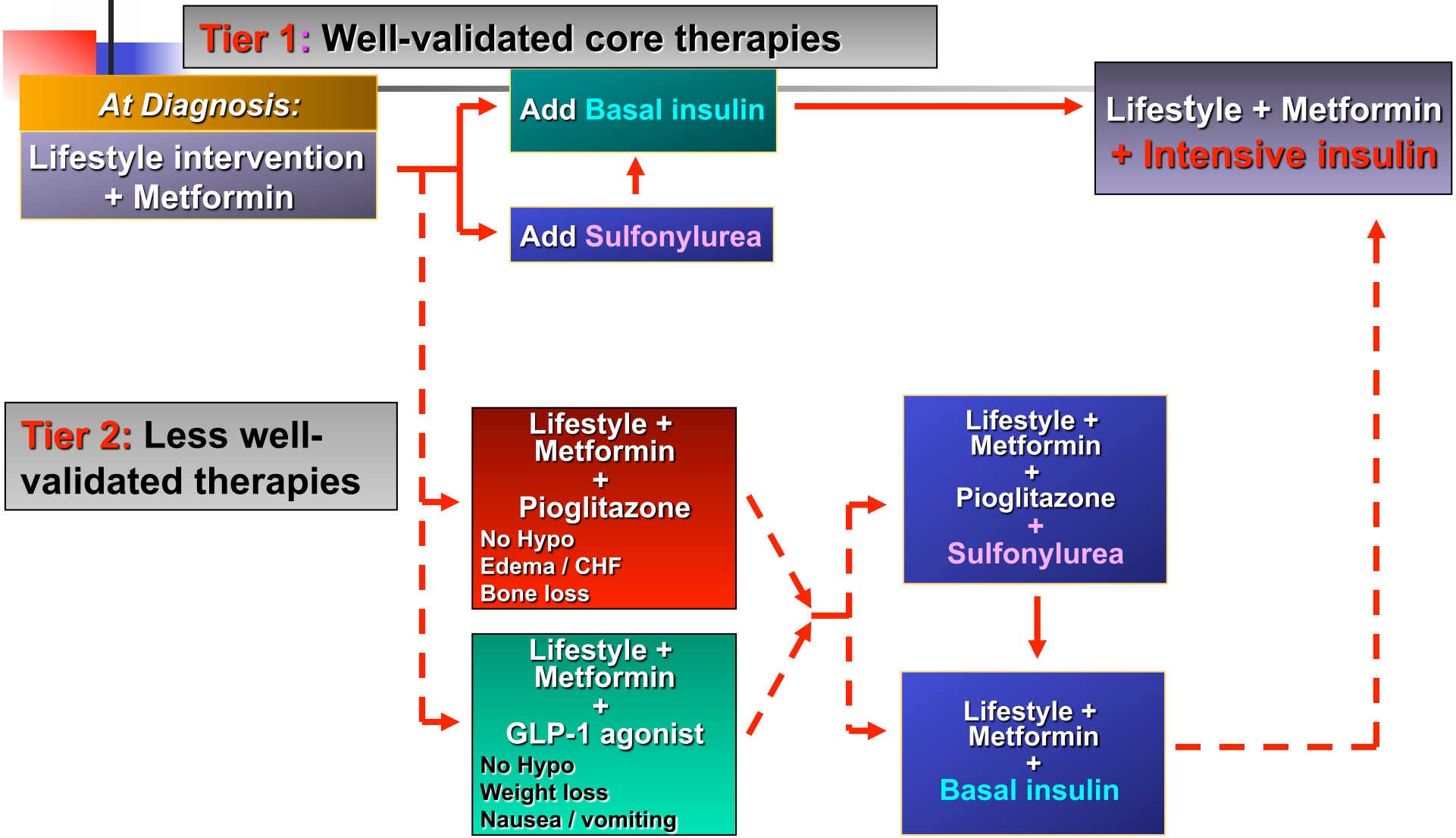
7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

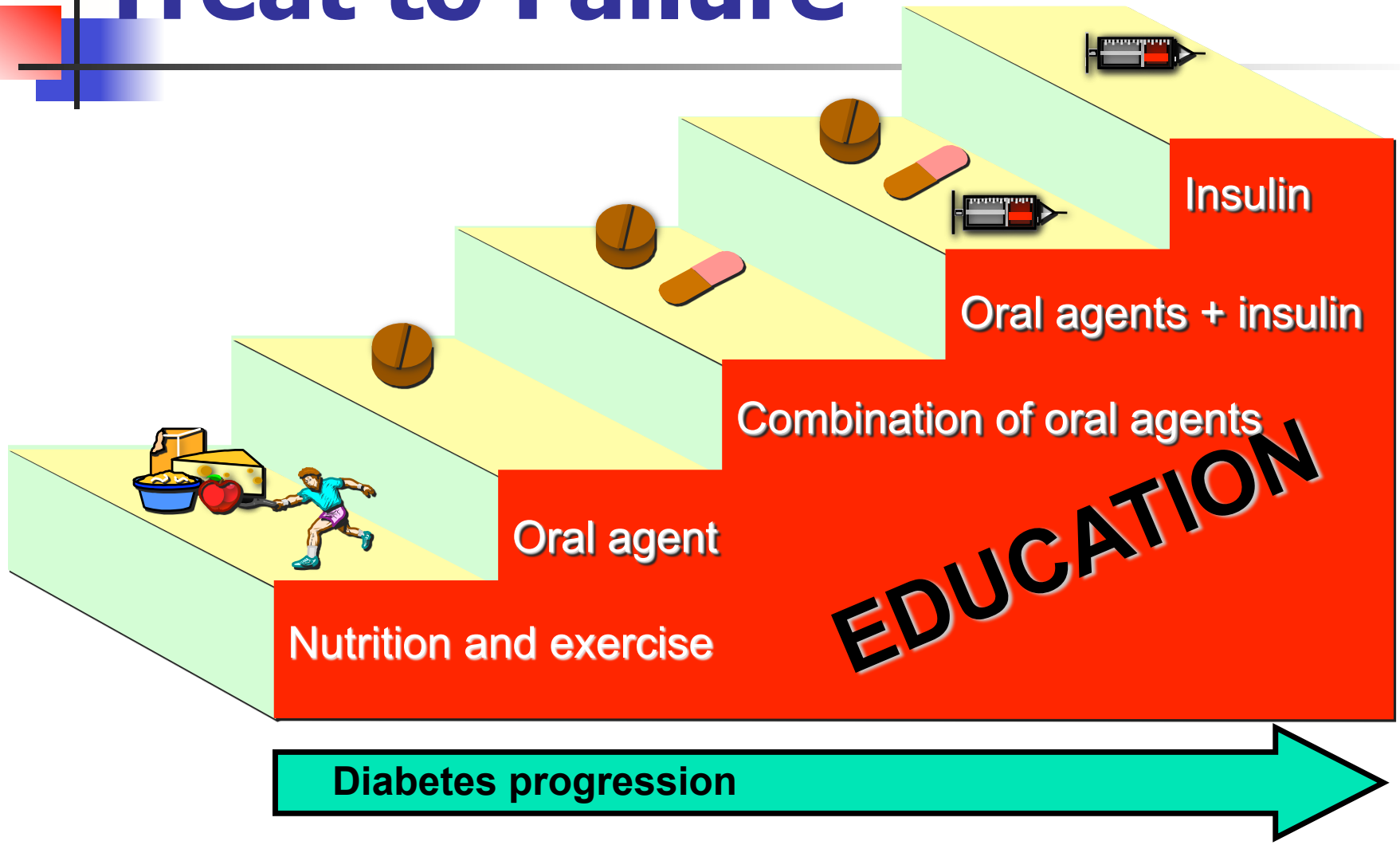
Available at www.aace.com/pub

Non Official Consensus Algorithm for Type 2 Diabetes Management: ADA & EASD

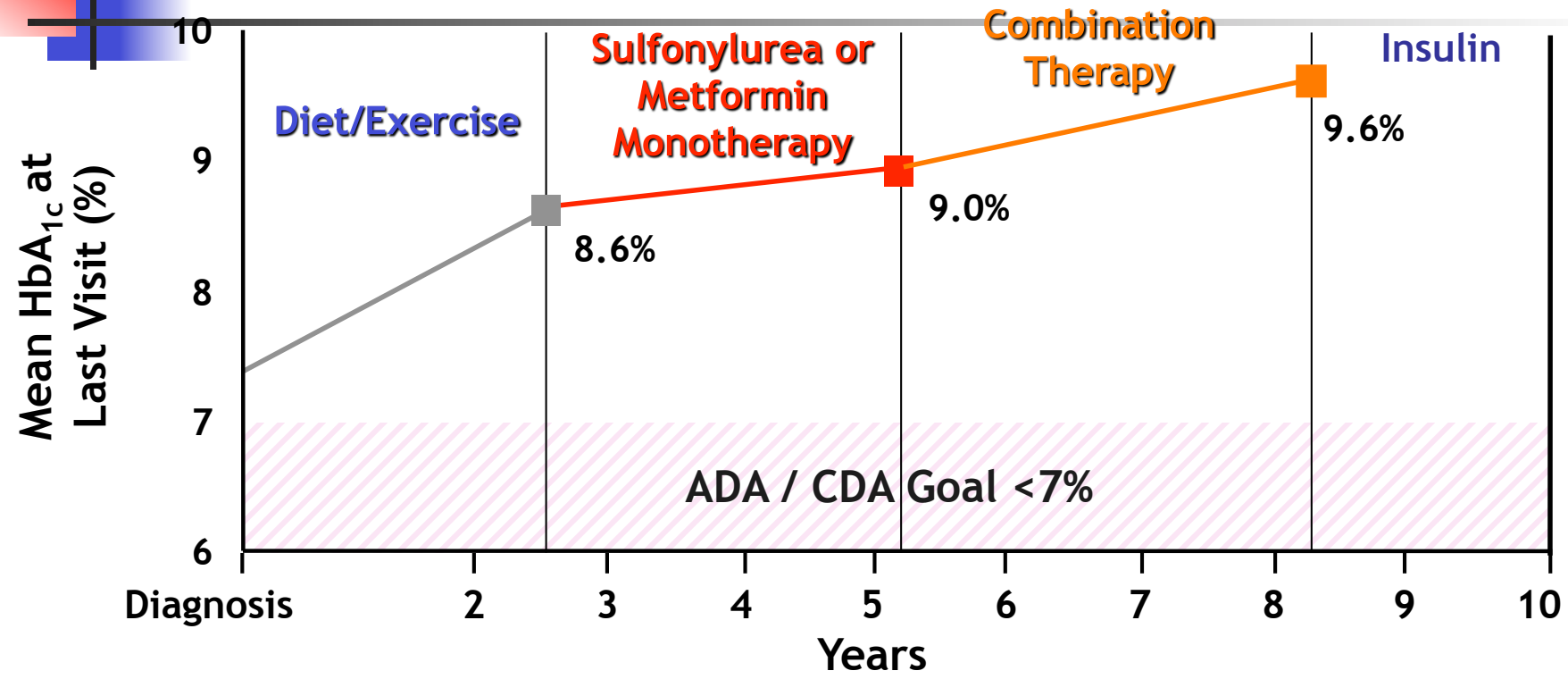


ADA, American Diabetes Association; EASD: European Association for the Study of Diabetes.

The Paradigm of Treatment: Treat to Failure



Traditional Approaches to Therapy Result in Prolonged Exposure to Elevated Glucose



At insulin initiation, the average patient had:

- 5 years with HbA_{1c} >8%
- 10 years with HbA_{1c} >7%

The Bad Memory

Brown JB, et al. *Diabetes Care*. 2004;27(7):1535-1540.

Why an A1C Goal of <6.5%? Plus if no hypoglycemia and a newly diagnosed patient 6% is achievable and should be considered as the target

Recent Clinical Trials Achieve that Level Without Increasing the Risk of our Patients plus ACE recommends intervention in early diabetes, are we going to let people unattended with A1c levels between 6 and 7%?

Is it ethical?

1-2-3 study: cumulative percent of patients achieving HbA_{1C} goals

Completer analysis

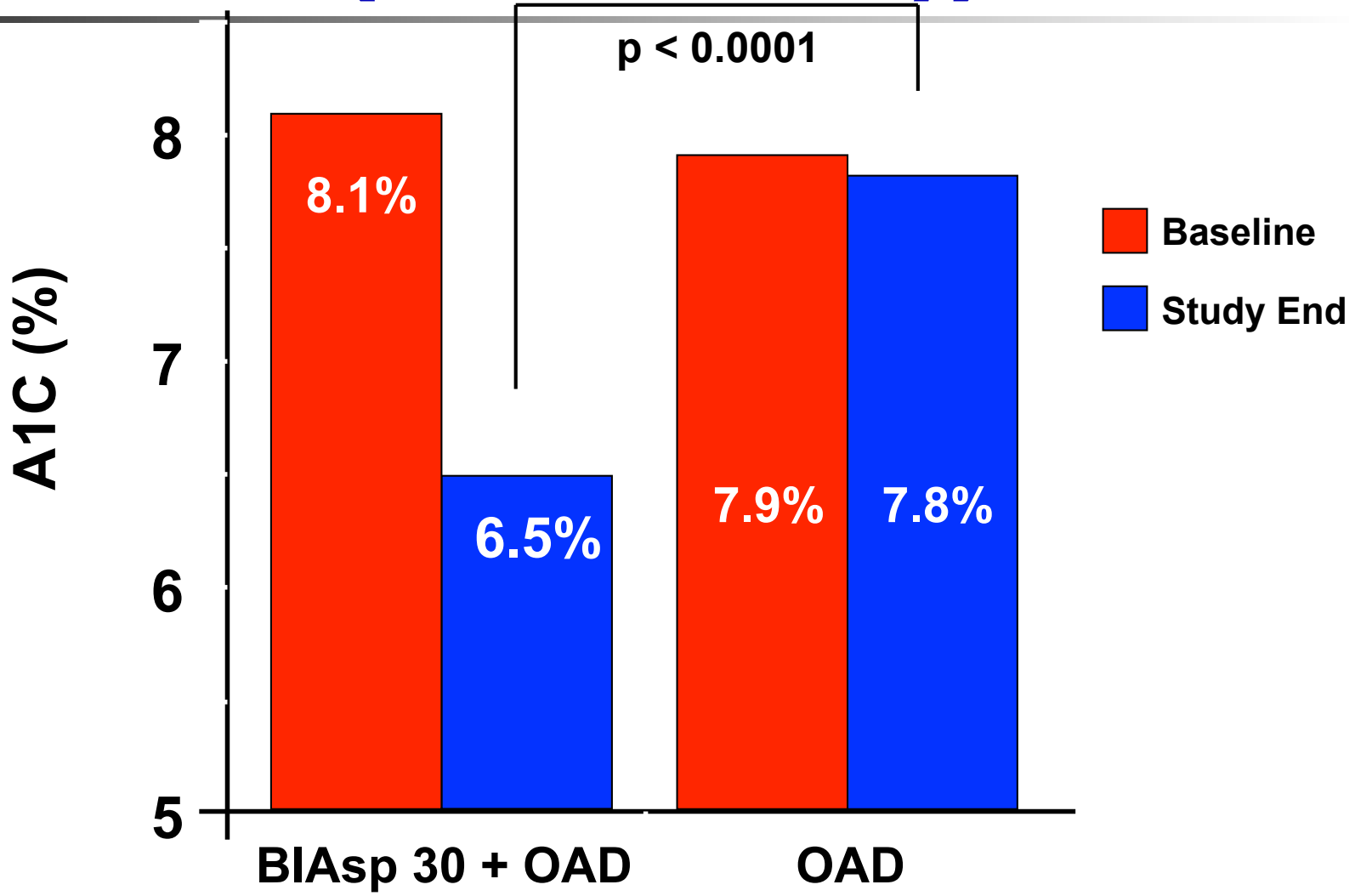
	$HbA_{1C} \leq 6.5\%$ (AACE, IDF goal)		$HbA_{1C} < 7\%$ (ADA goal)	
OD	28%	ITT 21%	46%	**ITT 41%**
BID	**66%**	52%	78%	**70%**
TID	**77%**	60%	89%	**77%**

Mean baseline HbA_{1C} was 8.7%

Garber et al. Diab Obes Metab. in press 2005

Addition of Biphasic Insulin Aspart 30 to Optimized Metformin and Pioglitazone Treatment in Type 2 Diabetes

The (ACTION Study)

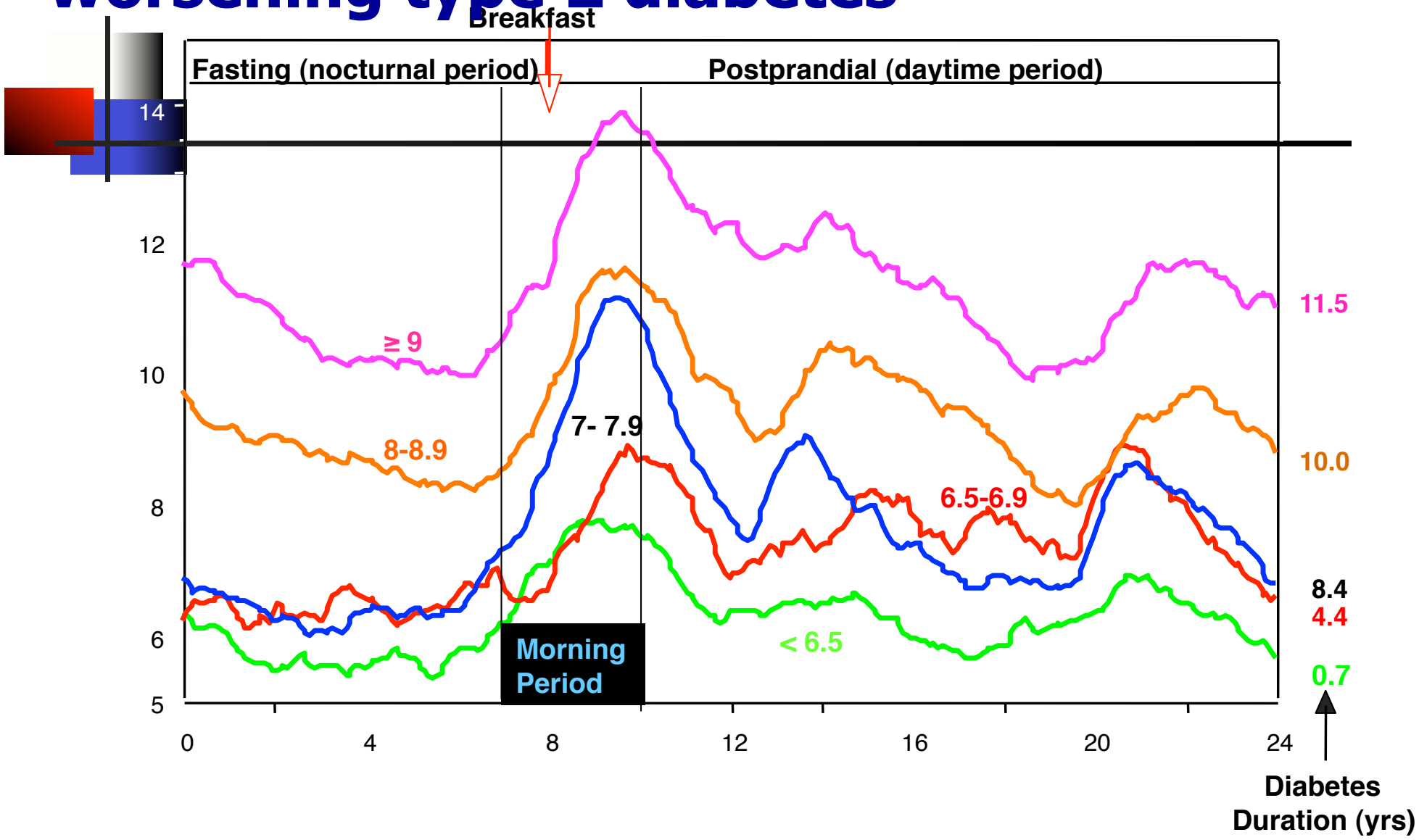


Raskin, et al Diabetes, Obesity and Metabolism 11:27, 2009

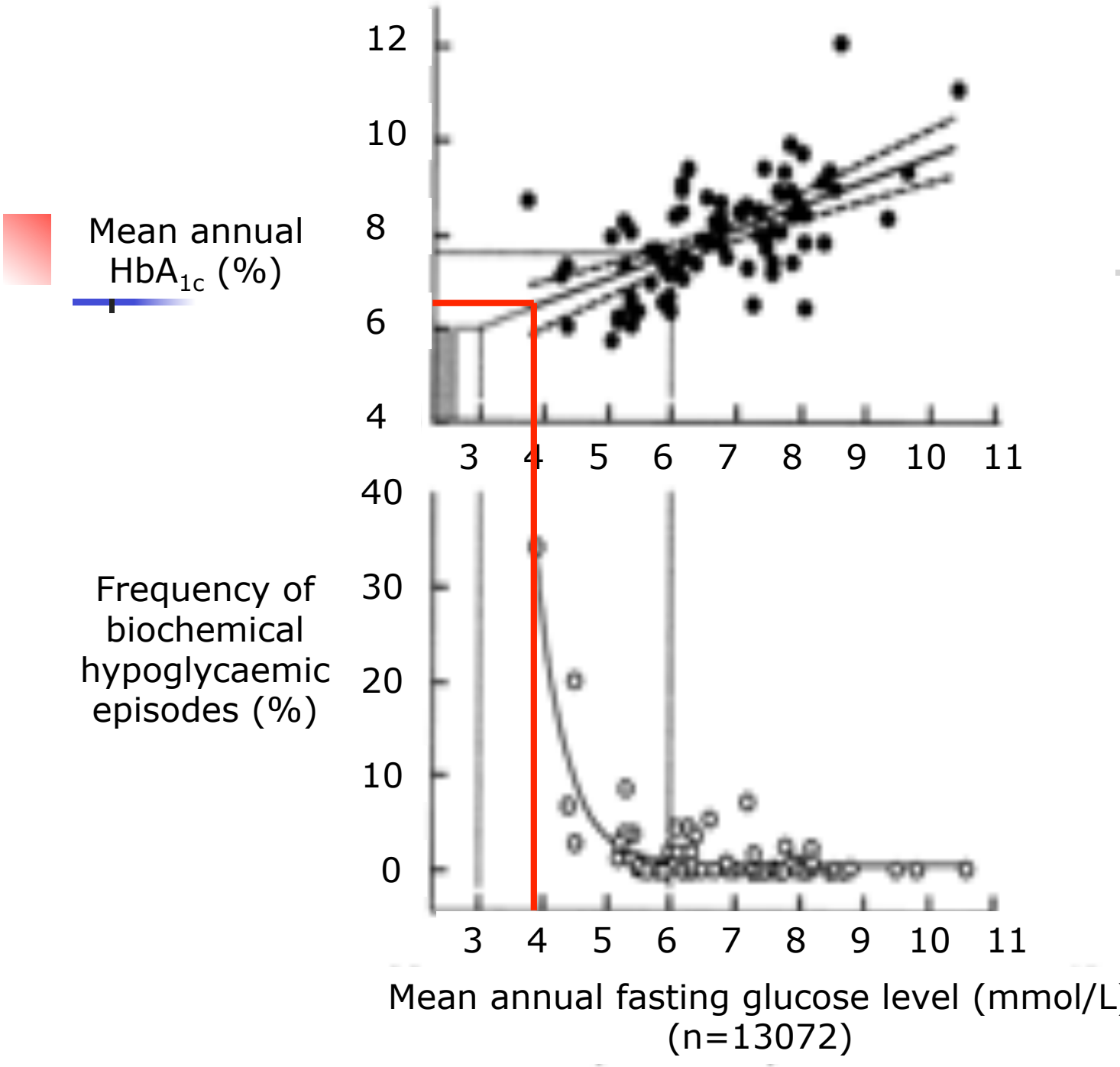
ADA/EASD Guidelines: Ad Basal Insulin at an A1C of 7%

?

Daily glycemic variation (mmol/L) with worsening type 2 diabetes

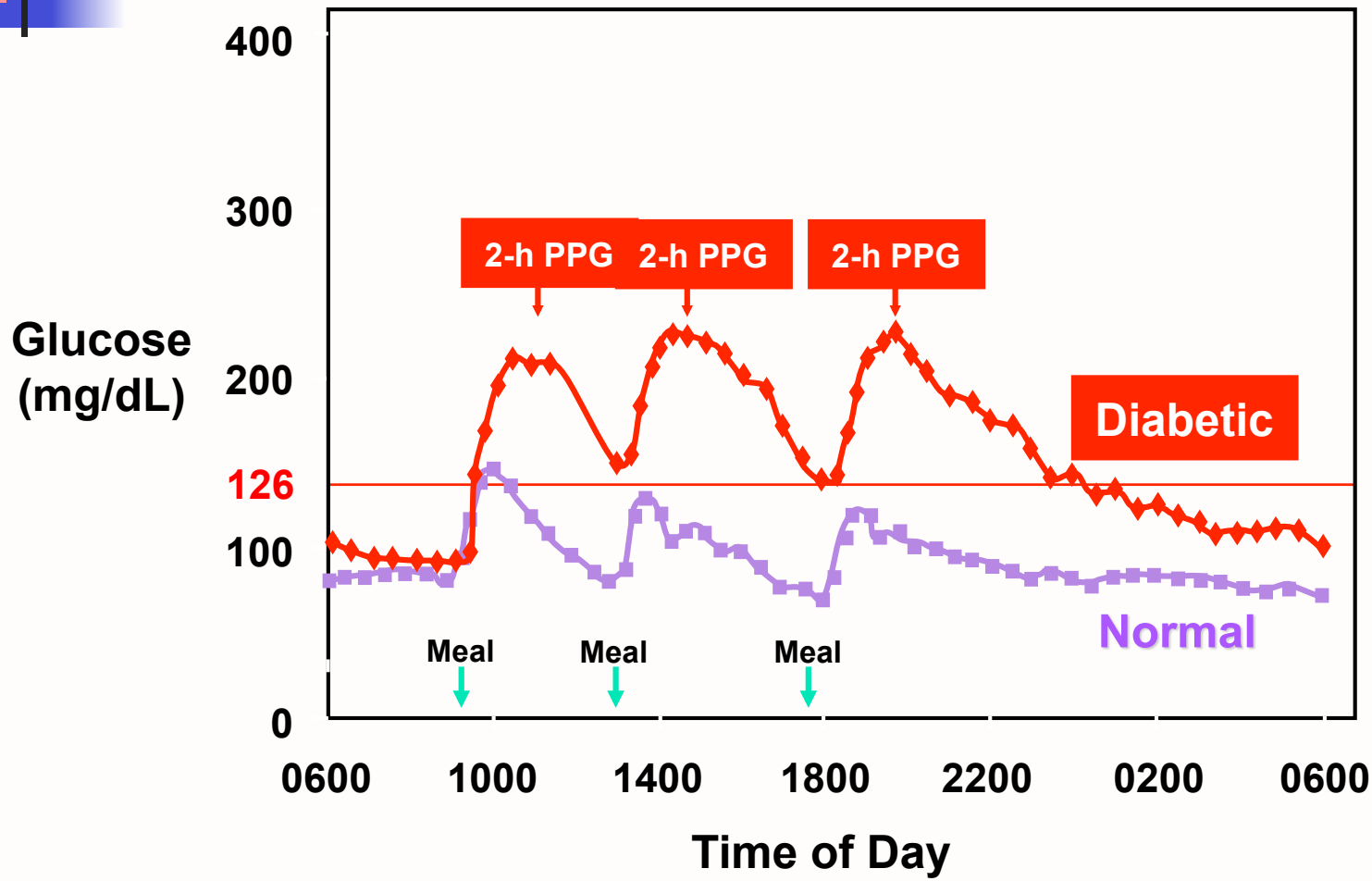


L Monnier ,C Colette, G Dunseath and D Owens . Diabetes Care. 2007;30:263-269



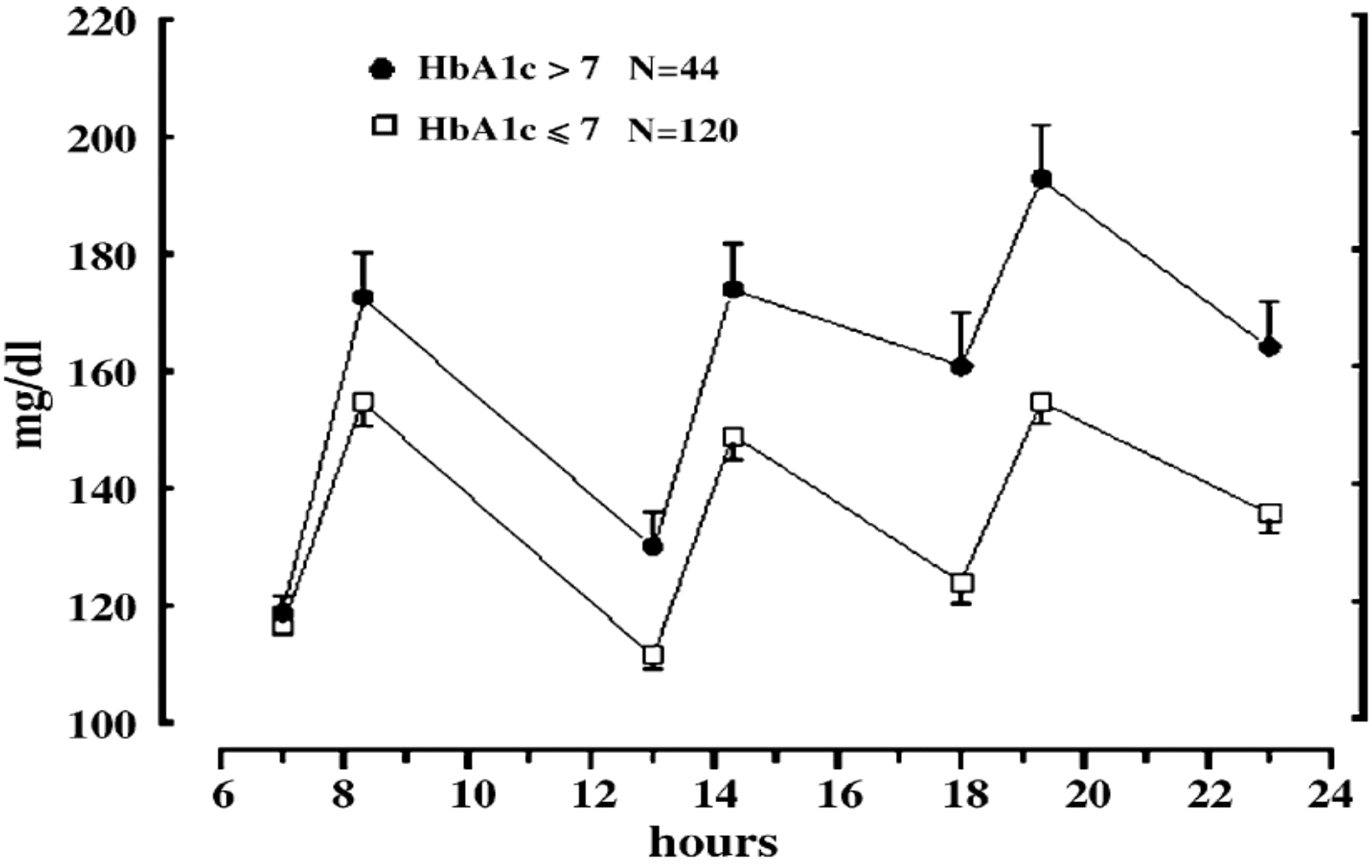
Yki-Jarvinen, Ann. Int. Med. 1999,

24-Hour Plasma Glucose Curve Normal and Type 2 Diabetes



Adapted from Polonsky et al, *N Engl J Med* 1988.

Diurnal plasma glucose profiles after intensified therapy intervention in subjects who achieved HbA1c targets of ≤ 7% (□) and those who did not (●)



Barriers to Diabetes Management

Clinical Inertia

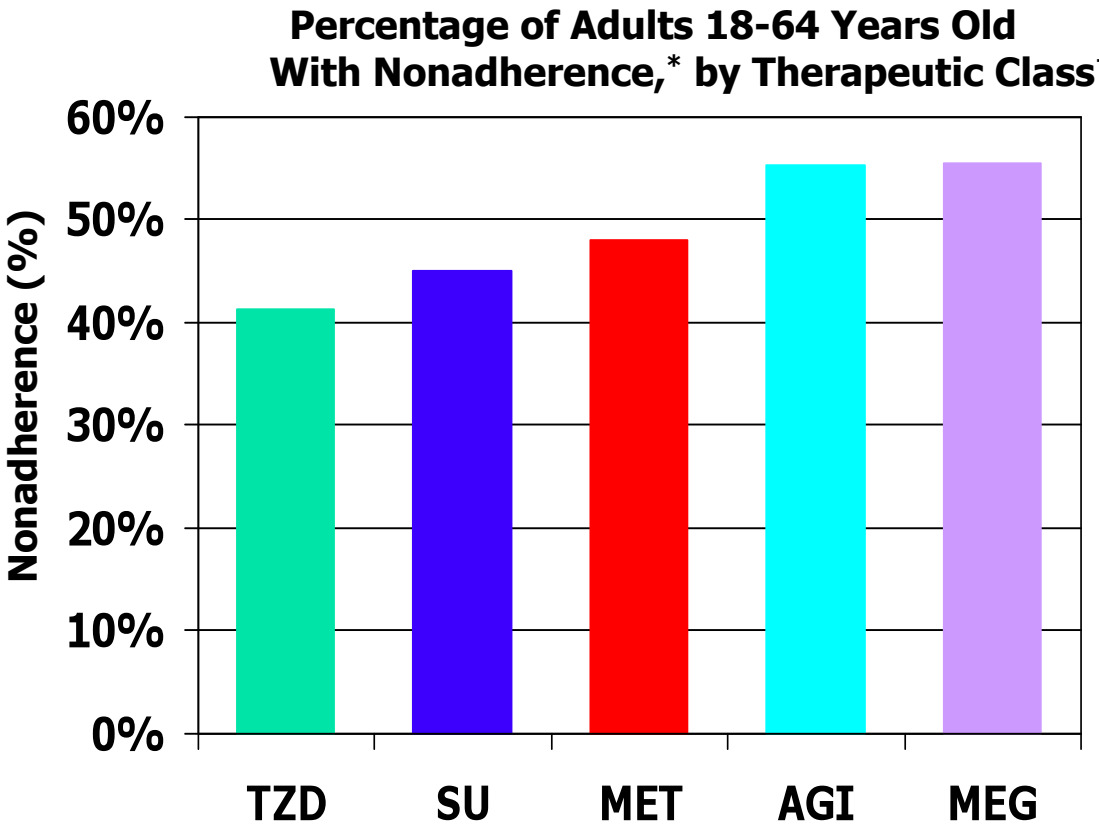
Failure of health care providers to intensify medical management

Patient non-adherence

Failure of patients to initiate or continue physician-recommended changes in medical management

Barriers to Clinical Management Poor Adherence and Persistence Rates in Oral Antidiabetic Therapy

- Over 12 months:
  - 37% of patients discontinued therapy
  - 10.5% of patients failed to fill a second Rx for any hypoglycemic agent
- About 46% of patients were nonadherent.*

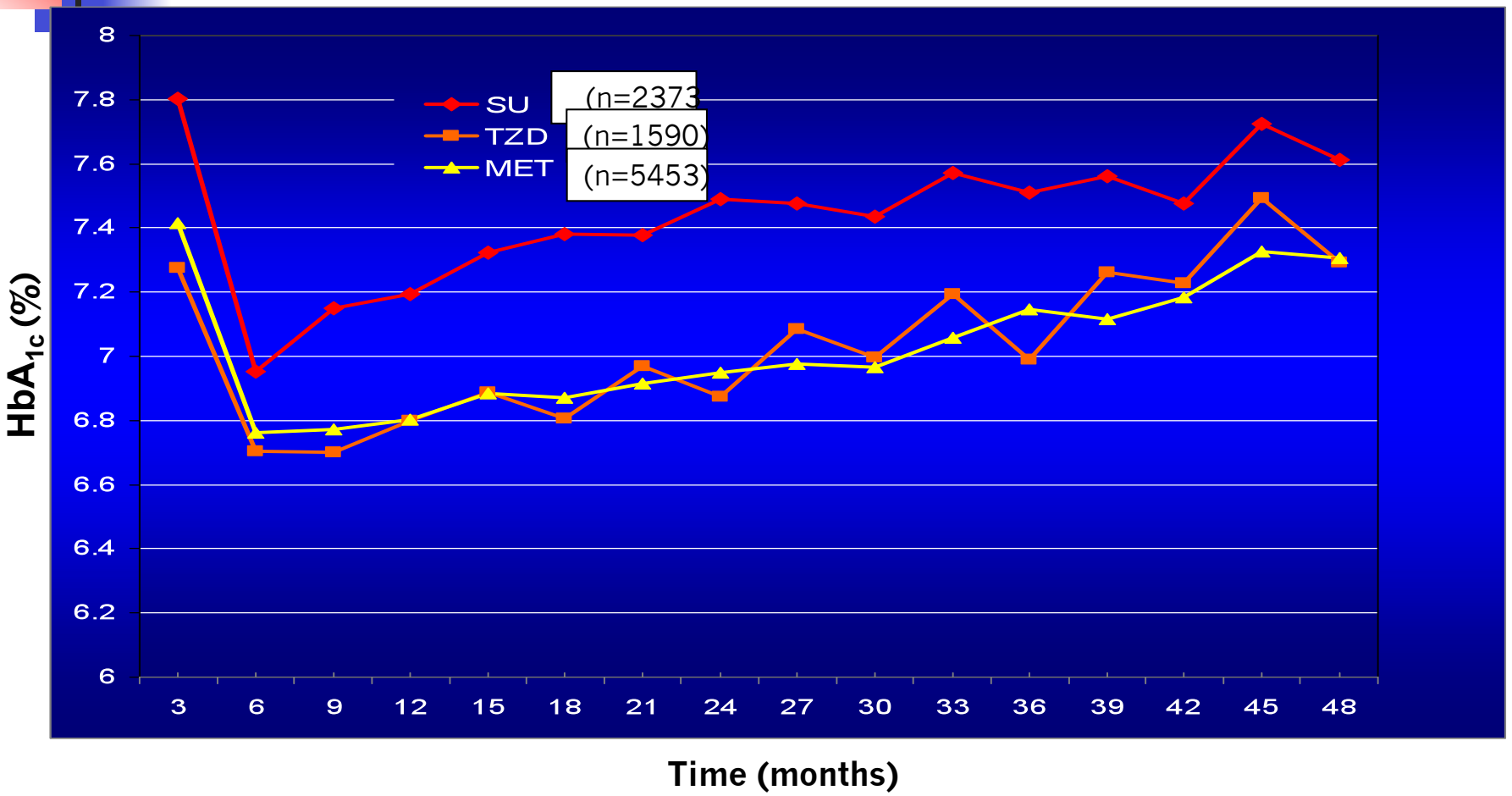


*Nonadherence = Medication Possession Ratio <80%

†TZD=thiazolidinediones; SU=sulfonylureas; MET=metformin; AGI=α-glucosidase inhibitors; MEG=meglitinides.

Hertz RP, et al. *Clin Ther.* 2005;27:1064-1073.

Similar Loss of Glucose Control Seen in Managed Care–Treated Patients Over 4 Years (n=9616)



SU=sulfonylurea; TZD=thiazolidinedione; MET=metformin.
Riedel et al. *Diabetes*. 2006.

ACCORD: Who contributed to the increased deaths in the intensive arm?

- **Higher A1C upon randomization**
- **No improvement during the trial**
  - **More severe disease**
  - **Difficult-to-manage disease**
  - **Patient issues with adherence or understanding**
  -
- **Lessons from ACCORD**
  - **If your patient is not improving her/his glucose control during intensification of any regimen, be aware of increase risk of death.**

Calles-Escandón J, et al. *Diabetes Care*. 2010 Jan 26. [Epub ahead of print].

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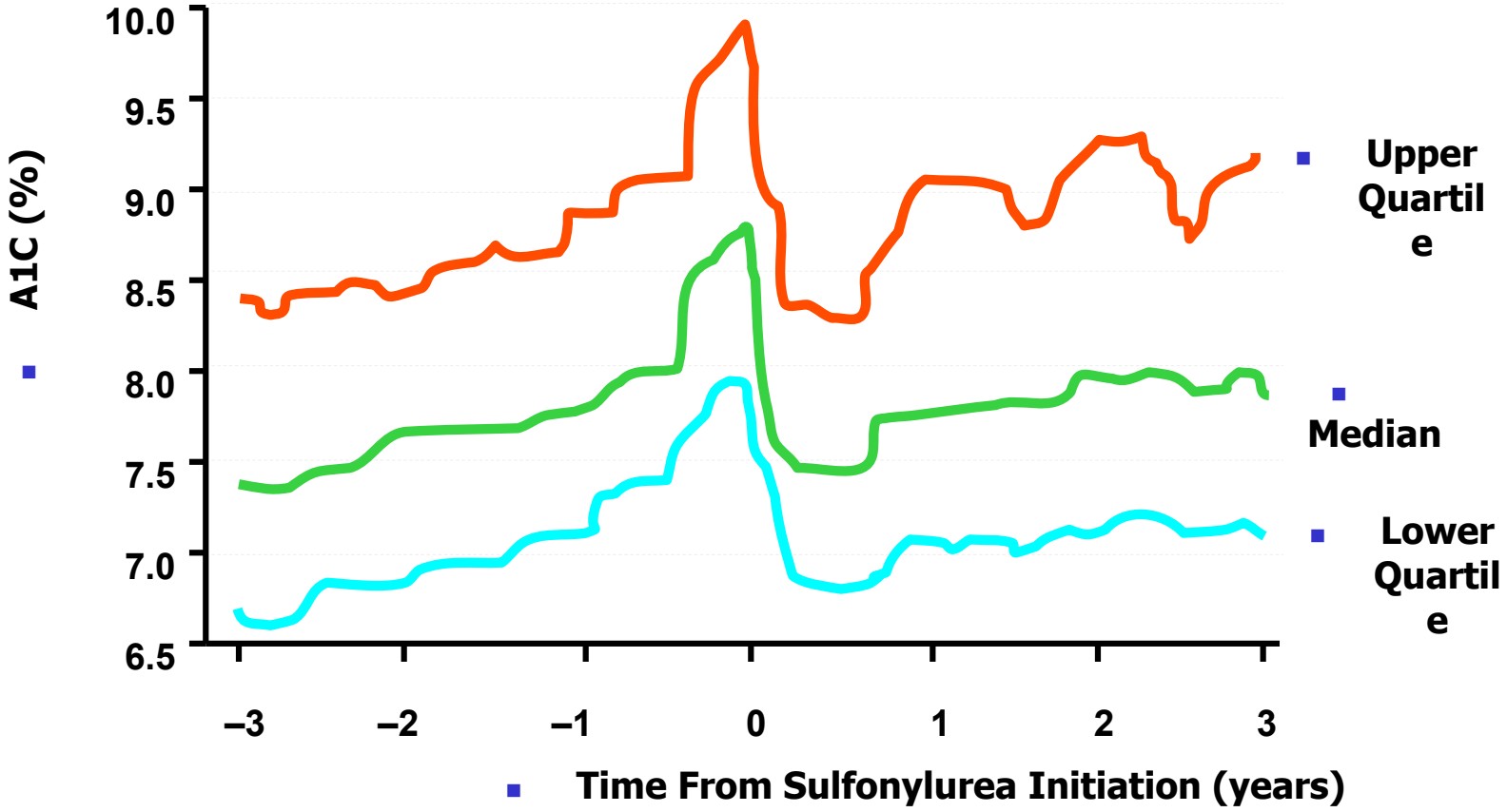
INSULIN
± Other Agent(s) [6]

Available at **www.aace.com/pub**

Within 6 Months of Adding SU's to Metformin, A1C Continues to Deteriorate



Cook MN, et al. *Diabetes Care.* 2005;28:995-1000.

AACE Guidelines 2009

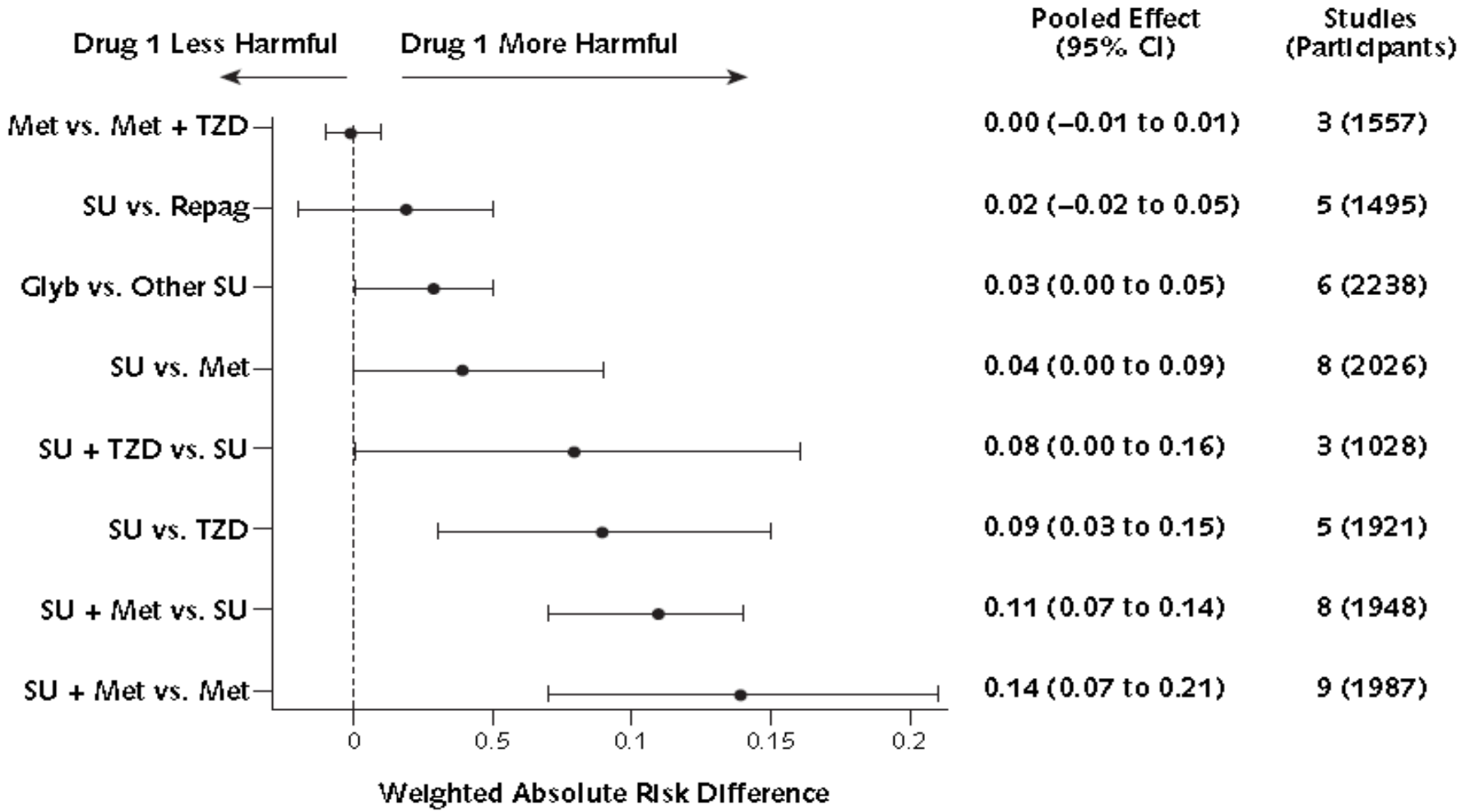
1. Most Important Principle : recognition
   of the importance of avoiding hypoglycemia (24-28)

.

2. It favors the use of GLP-1 agonists and
   DPP-4 inhibitors with higher priority-
   effectiveness and overall safety profiles.

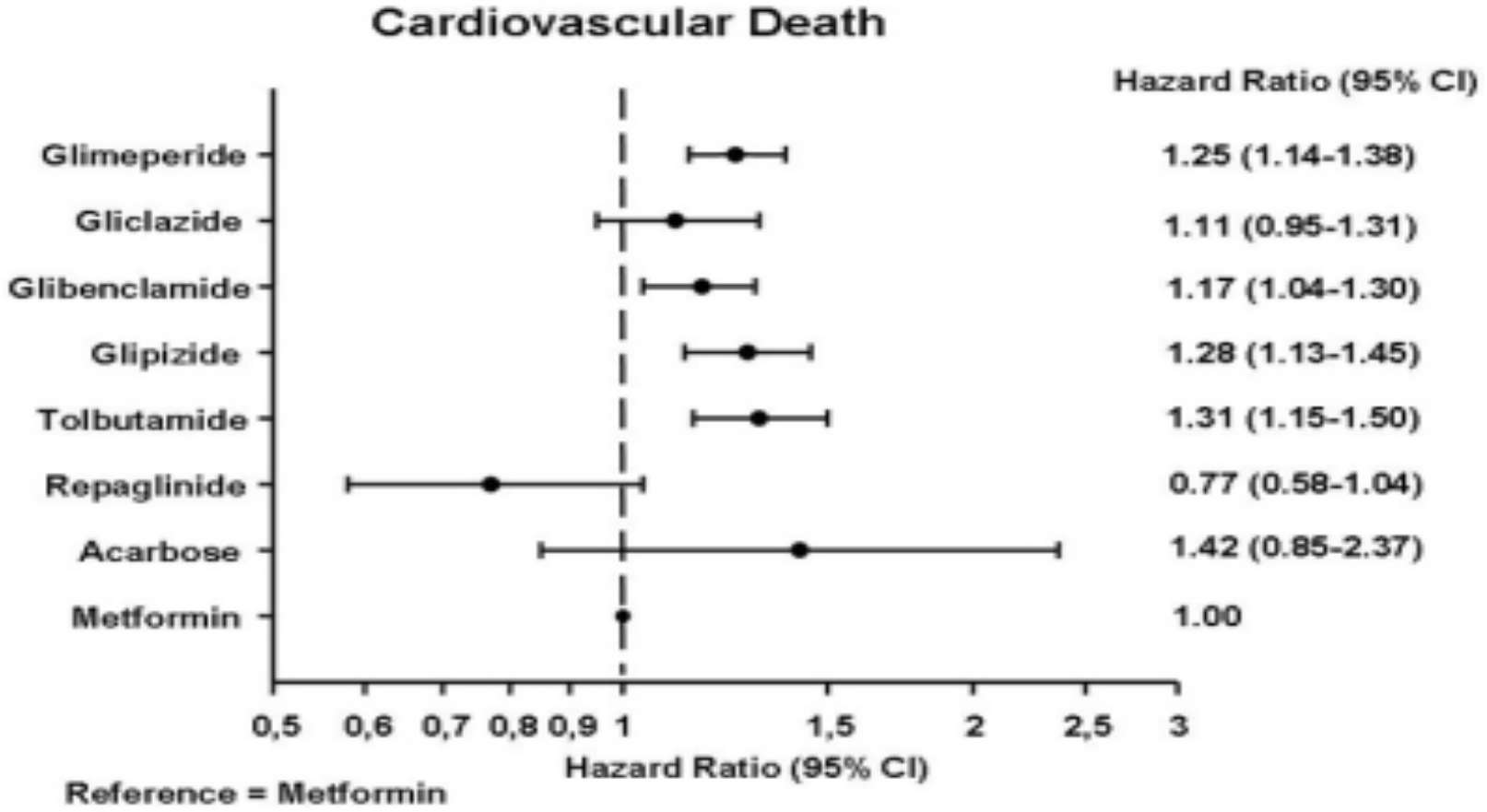
3. It moves sulfonylureas to a lower priority because of the
   associated risks
   a. hypoglycemia
   b. weight gain
   c. glycemic control only for relatively short
      period (<1 to 2 years in typical patients).

Pooled Hypoglycemia Risk



Differences in Risk of Cardiovascular Death According to Type of Oral Glucose-lowering Therapy in Patients With Diabetes:

A Danish Nationwide Study



ADA. The Danish Diabetes Registry, June 6, 2009, 1:45–3:45 PM

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AACE 2009 Guidelines

5. TZDs as “well-validated”, effective durable and good in the presence of fatty liver disease

6. It considers 3 other classes of agents (AGIs, colesevelam, and glinides) only for relatively narrow, well-defined clinical situations in view of their limited efficacy.

7. Rapid-acting insulin analogues are superior to “regular human insulin” - safer alternative.

8. NPH insulin - superseded by synthetic analogues insulin glargine and insulin detemir, which provide a relative peakless profile , yield better reproducibility and consistency, corresponding reduction in the risk of hypoglycemia.

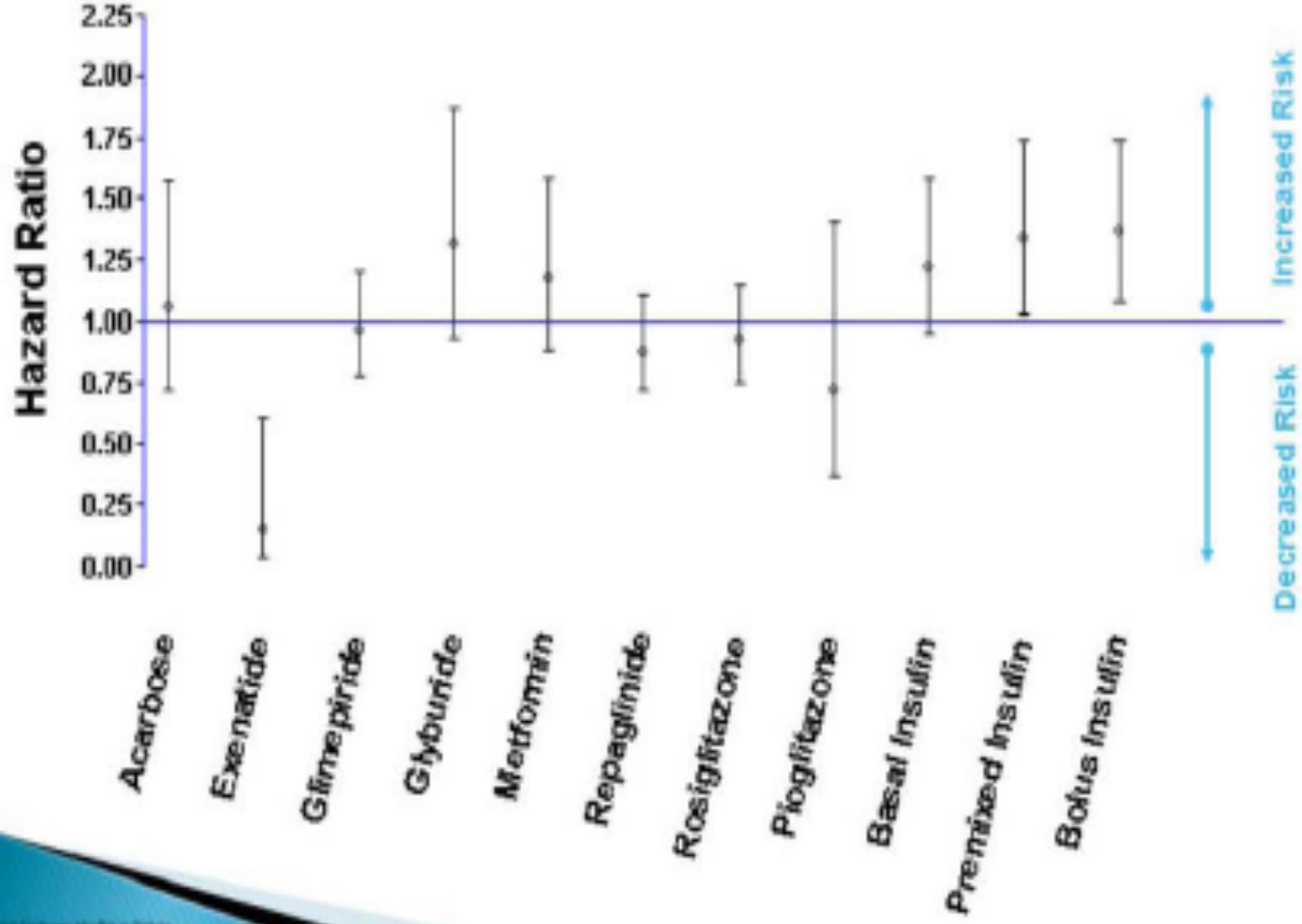
General Safety and Tolerability of DPP-4 Inhibitors

- **Based on meta-analysis of several studies,[1] DPP-4 inhibitors were**
  - **Well tolerated overall, with low absolute rates of adverse events, no weight gain and no or very low rates of hypoglycemia compared with SU's**
  - **Associated with small increased rates of**
    - Nasopharyngitis
    - Urinary tract infection
    - Headache
  - **Associated with low risk of hypoglycemia**
  - **Weight neutral**
- **There have been postmarketing reports of hypersensitivity reactions with sitagliptin[2]**

1. Amori RE, et al. *JAMA*. 2007;298:194-206.

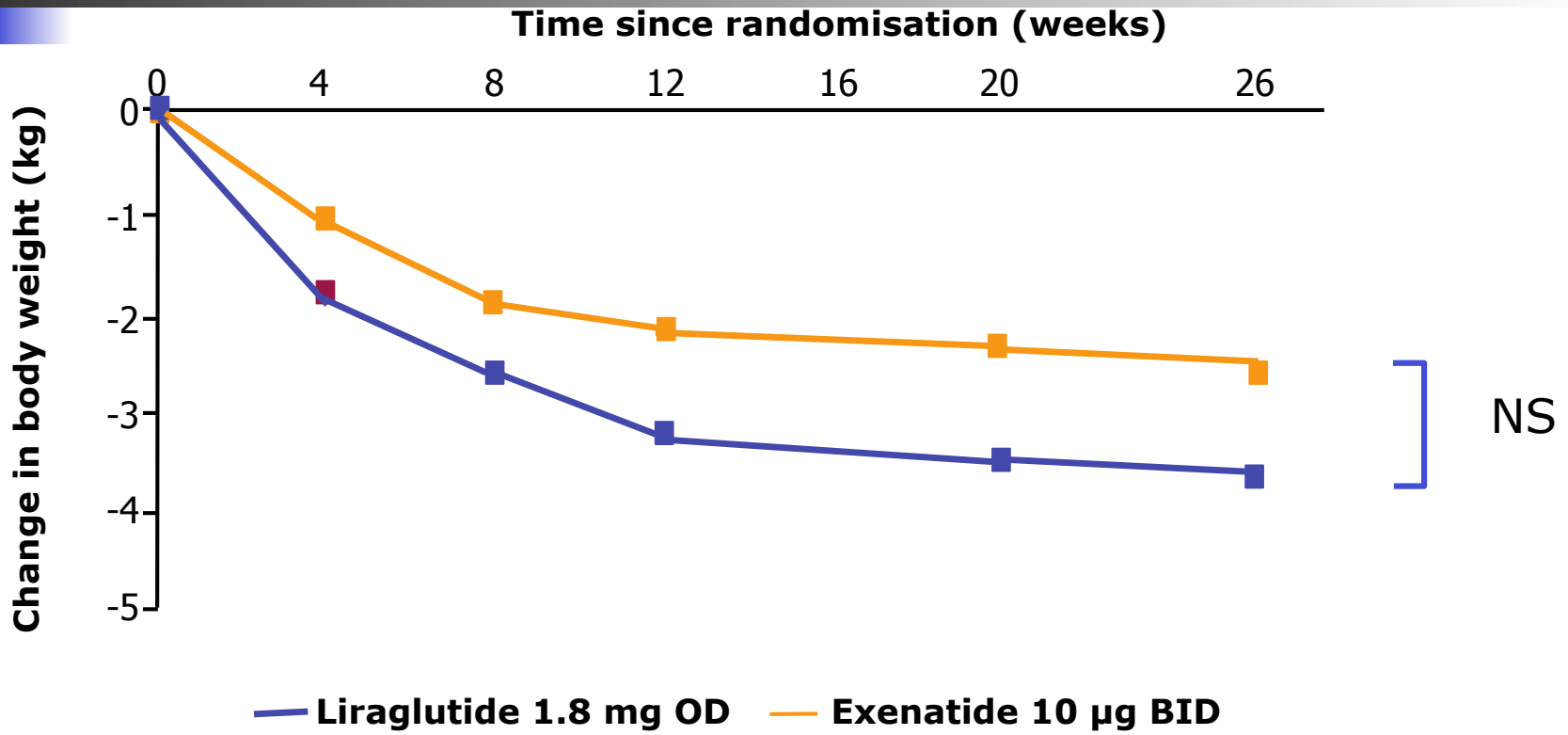
Mortality Hazard Ratios for Post-Randomization Prescription of Glycemia Medications

(Adjusted for Baseline Participant Characteristics)



ACCORD

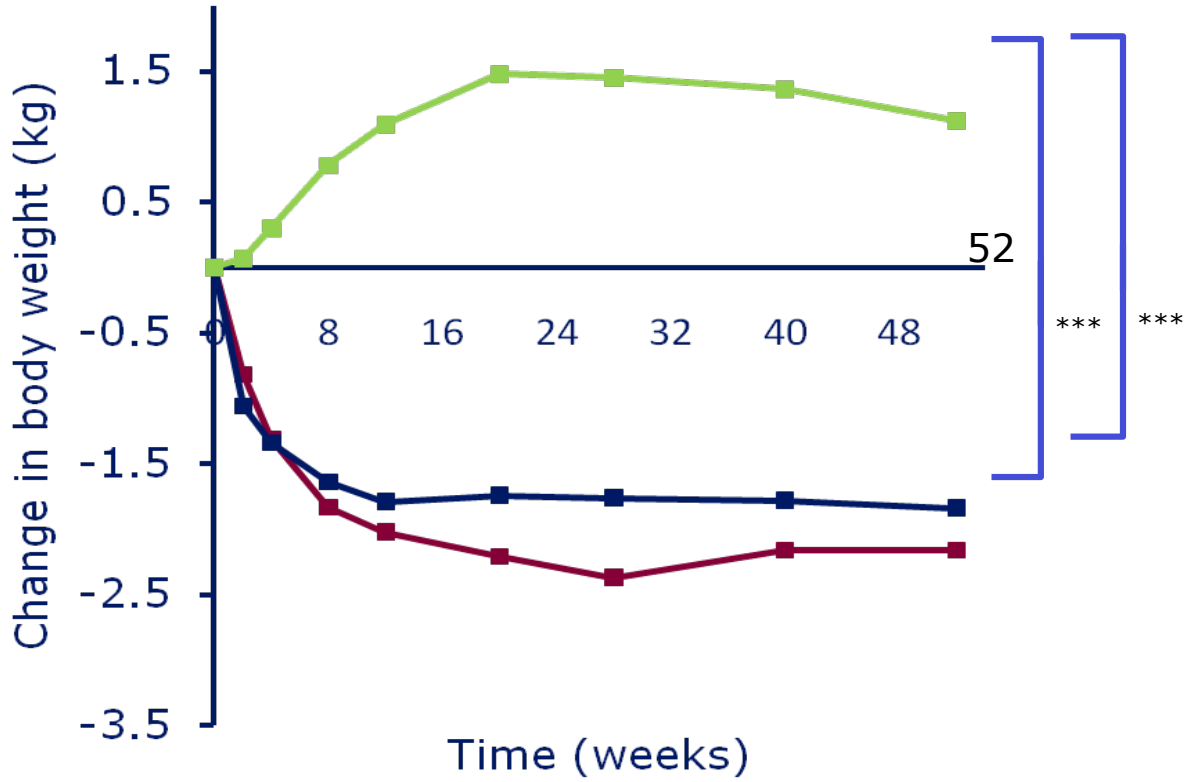
Liraglutide and exenatide both reduce body weight (subjects receiving metformin only)



Blonde *et al. Can J Diabetes* 2008;32(Suppl): A107 (LEAD 6).

Sustained weight reduction over 52 weeks with liraglutide

***p<0.0001 for change from baseline



- **Waist circumference was reduced from baseline by 3.0 cm with liraglutide 1.8 mg**
- **Waist circumference increased by 0.4 cm with glimepiride (p<0.0001)**

Glimepiride 8 mg/day
Liraglutide 1.2 mg/day
Liraglutide 1.8 mg/day

Garber et al, *The Lancet*, early online publication, 25 Sept 2008 (LEAD 3).

TABLE 1

SUMMARY OF KEY BENEFITS AND RISKS OF MEDICATIONS

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease (NAFLD). Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects relative importance of the benefit or risk.*

MEDICATIONS*	Metformin (MET)	DPP4 Inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylurea (SU)	Glinide**	Thiazolidinedione (TZD)	Colesevelam	Alpha-glucosidase inhibitor (AGI)	Insulin	Pramlintide
BENEFITS										
Postprandial Glucose (PPG) - lowering	Mild	Moderate	Moderate to Marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to Marked	Moderate to Marked
Fasting glucose (FPG) - lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to Marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
RISKS										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
Gastrointestinal Symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Unknown
Contraindicated in Liver Failure or Predisposition to Lactic Acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure / Edema	Contra-indicated in CHF	Neutral	Neutral	Neutral	Neutral	Mild / Moderate Contraindicated in class 3,4 CHF	Neutral	Neutral	Neutral unless with TZD	Neutral
Weight Gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to Moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-Drug interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

* *The abbreviations used here correspond to those used on the algorithm (Fig. 1).*

** *The term 'glinide' includes both repaglinide and nateglinide.*

AACE/ACE Diabetes Algorithm *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 7.6 – 9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1,10] or TZD [2]
		SU or Glinide [4,5]

2 - 3 Mos.***

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

2 - 3 Mos.***

INSULIN ± Other Agent(s) [6]

A1C > 9.0%

Drug Naive | **Under Treatment**

Symptoms | **No Symptoms**

INSULIN ± Other Agent (s) [6]

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

INSULIN ± Other Agent(s) [6]

AACE/ACE Algorithm for Glycemic Control Subcommittee

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* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 AGI if ↑ PPG

4 Glinide if ↑ PPG or SU if ↑ FPG

5 Low-dose secretagogue recommended

6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

10 GLP-1 not approved for initial combination Rx

Available at **www.aace.com/pub**

AACE 2009 Guidelines

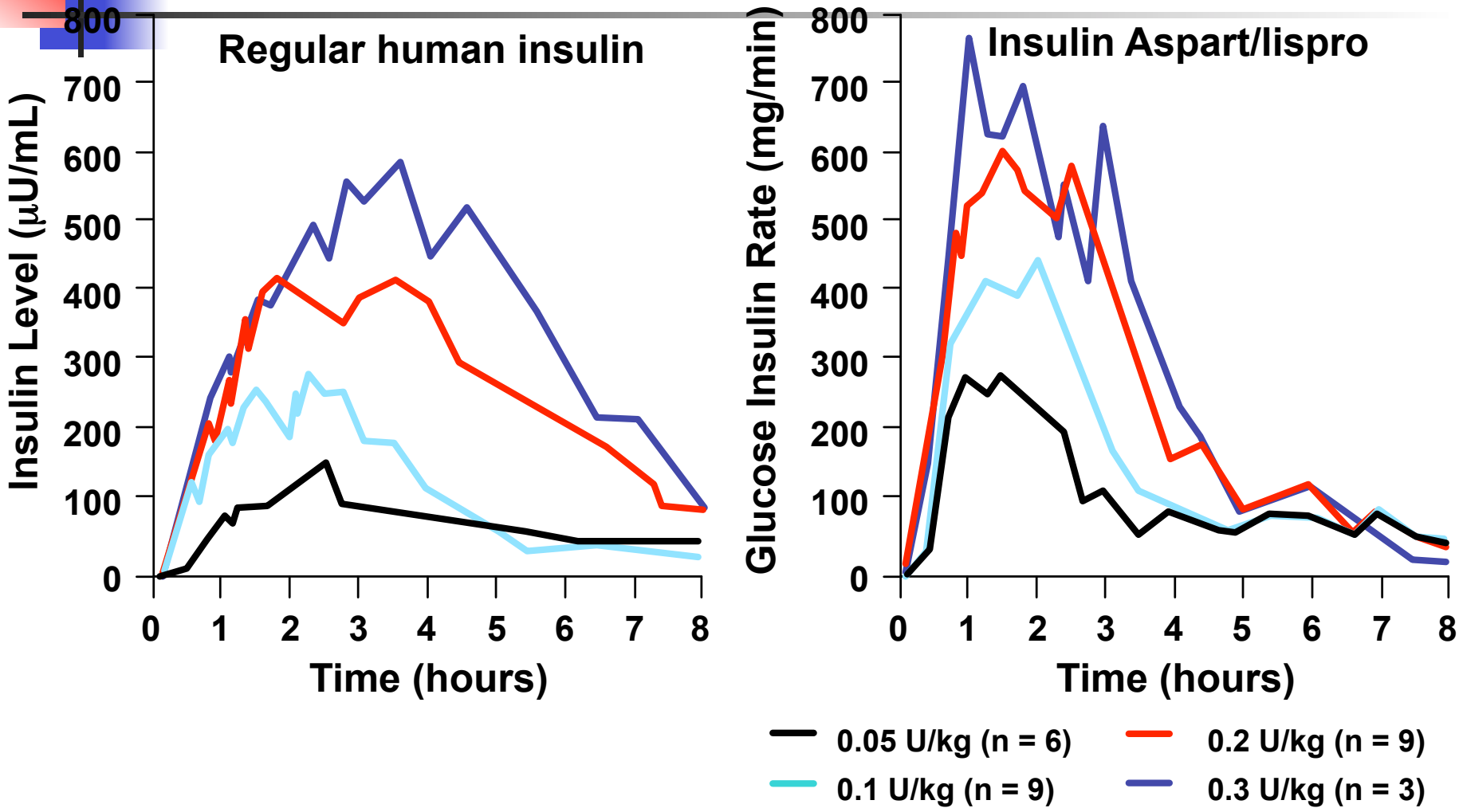
5. TZDs as “well-validated”, effective durable and good in the presence of fatty liver disease

6. It considers 3 other classes of agents (AGIs, colesevelam, and glinides) only for relatively narrow, well-defined clinical situations in view of their limited efficacy.

7. Rapid-acting insulin analogues are superior to “regular human insulin” - safer alternative.

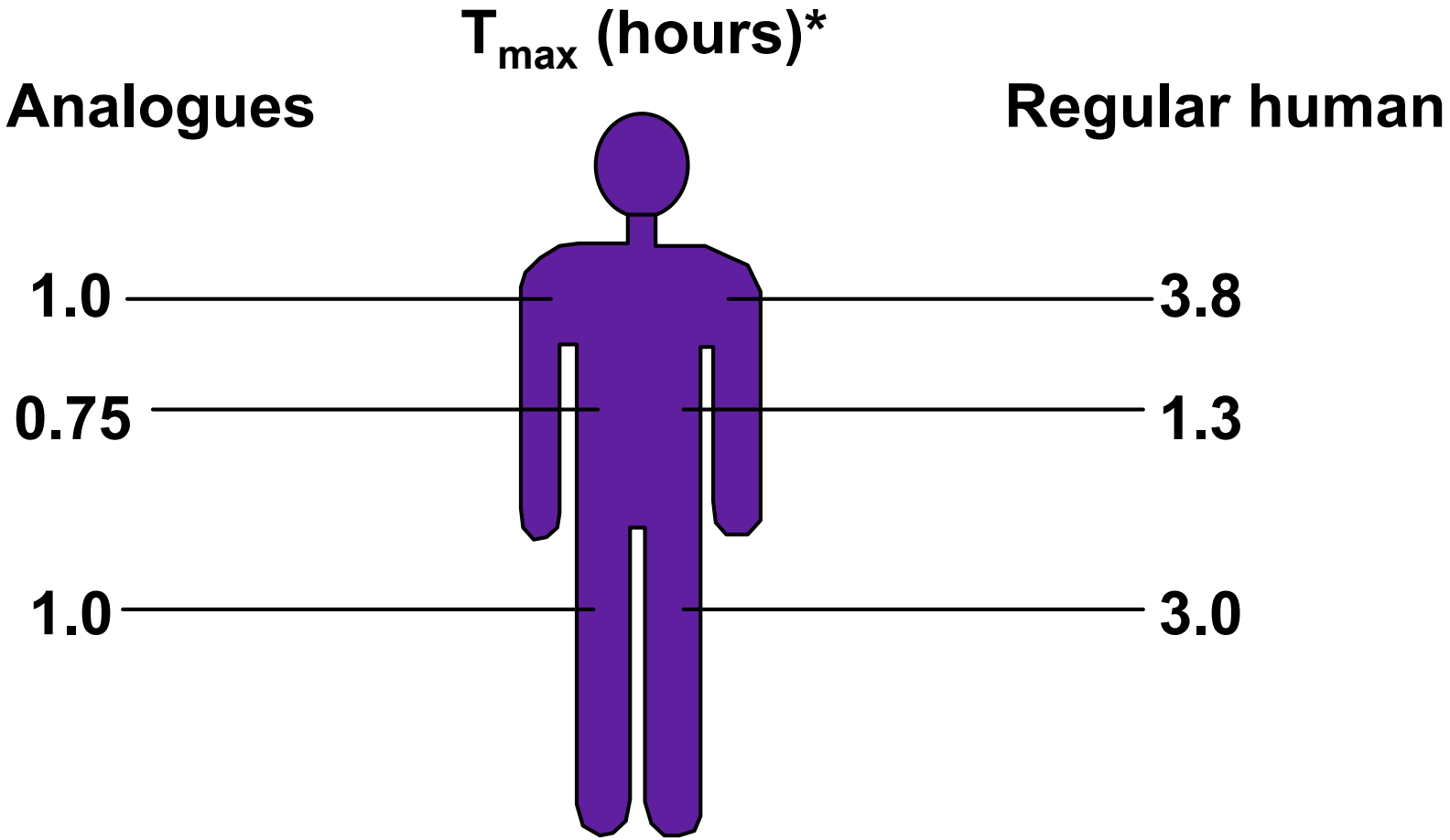
8. NPH insulin - superseded by synthetic analogues insulin glargine and insulin detemir, which provide a relative peakless profile , yield better reproducibility and consistency, corresponding reduction in the risk of hypoglycemia.

Rapid Acting Analogues vs Regular Human Insulin



Woodworth, et al. *Diabetes*. 1993;42(suppl 1):54A.

Rapid Analogues vs Regular Human Insulin= Convenience+



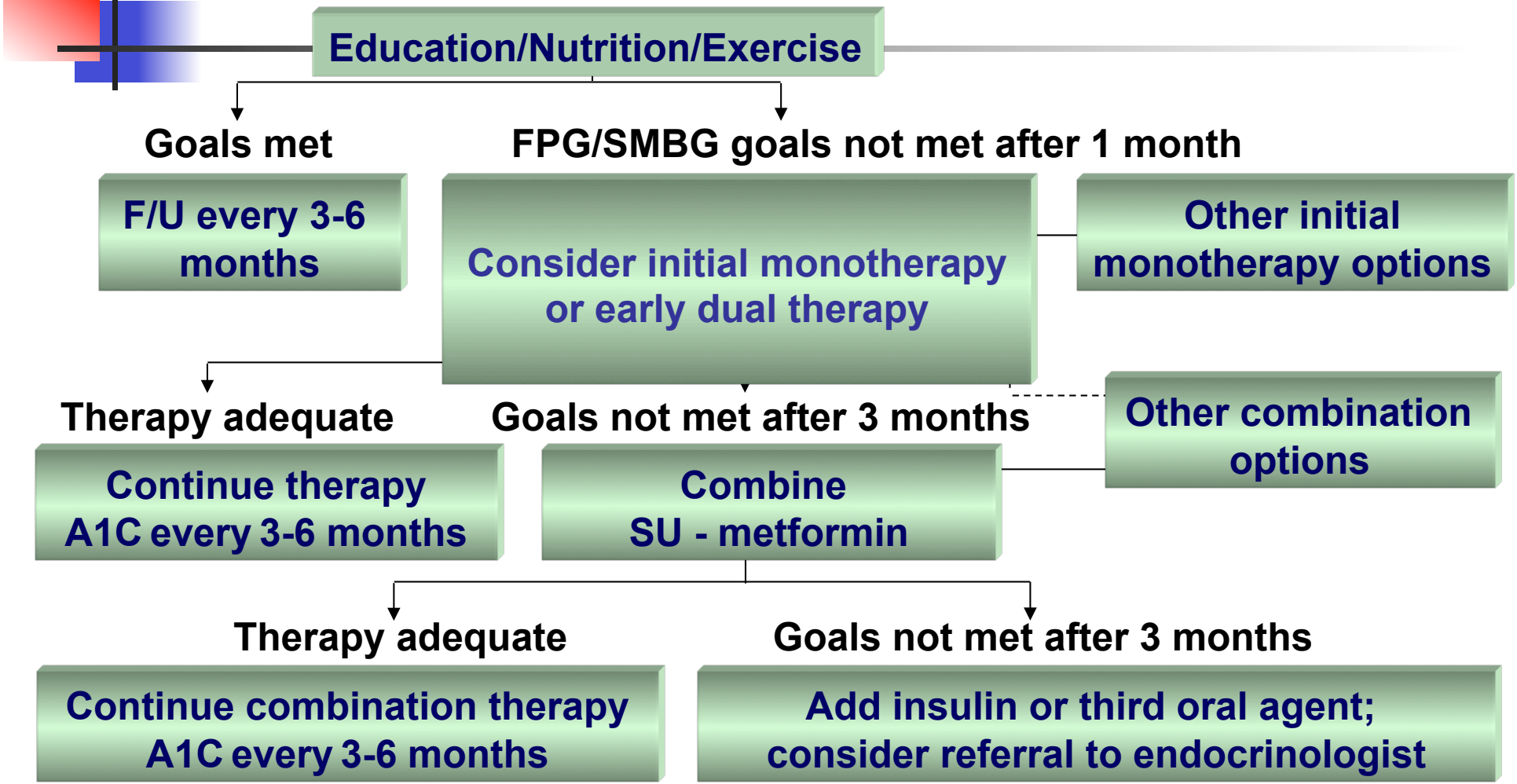
* 0.2 U/kg SC.

Diabetes Care. 1996;19:1437.

Why Guidelines, Road Maps or Algorithms?

Do They Work?

Texas Diabetes Council Algorithm



Goal: FPG <110 mg/dL; SMBG <120 mg/dL; A1C <6.5%.

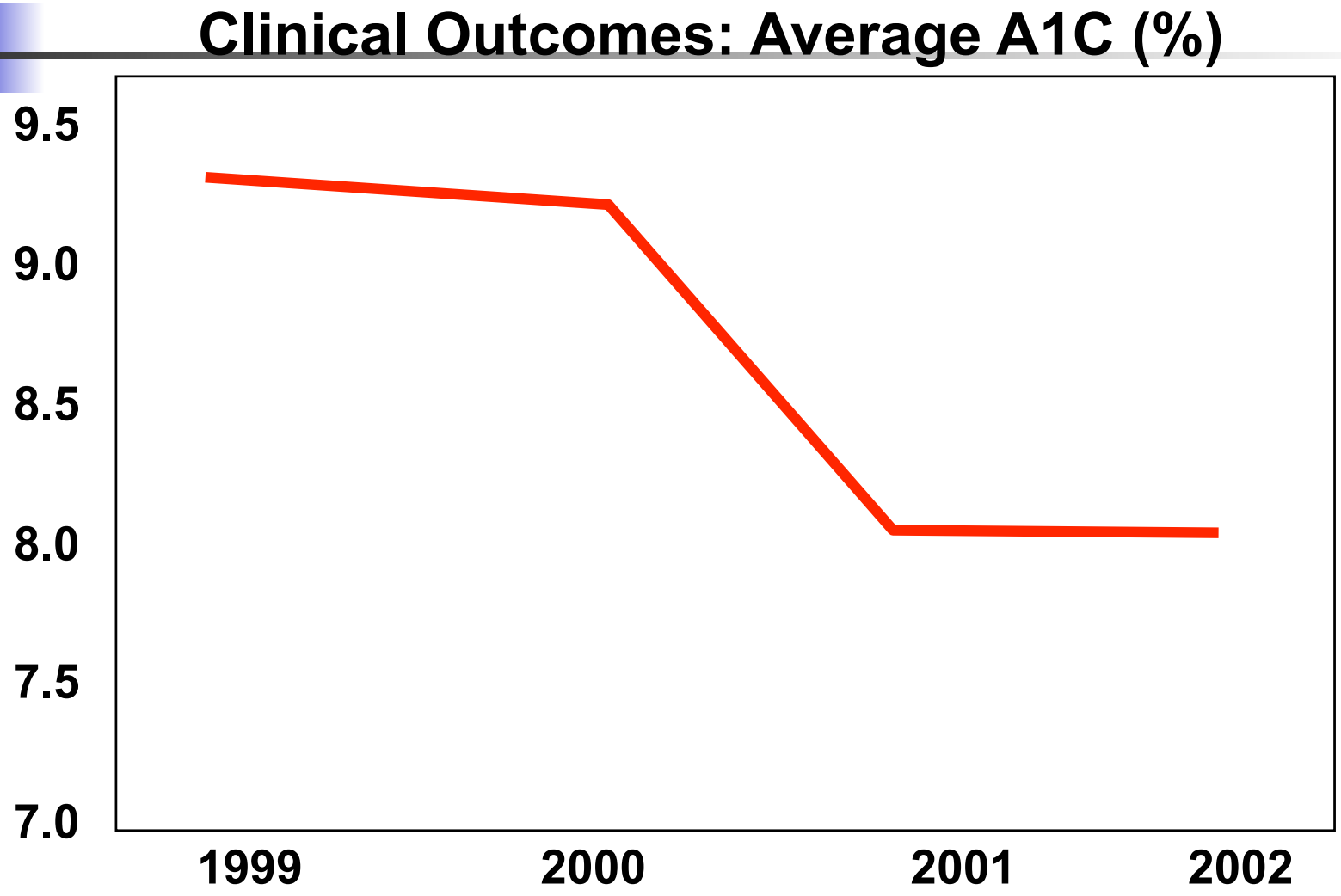
Heart of Texas Community Health Center

- A1C goal, 8% (then the ADA goal)
- Number of A1C per year, 2

- Initial data
- A1C, 9.29%
- # of A1C tests per year, 0.93

- Accomplishments
- A1C, 8.02
- # of A1C per year, 1.52

DQI (DM quality improv.): MRSA Health Collaborative



Barker T et al. HRSA Health Disparities Collaborative. Heart of Texas Community Health Center, Waco, TX (2003).

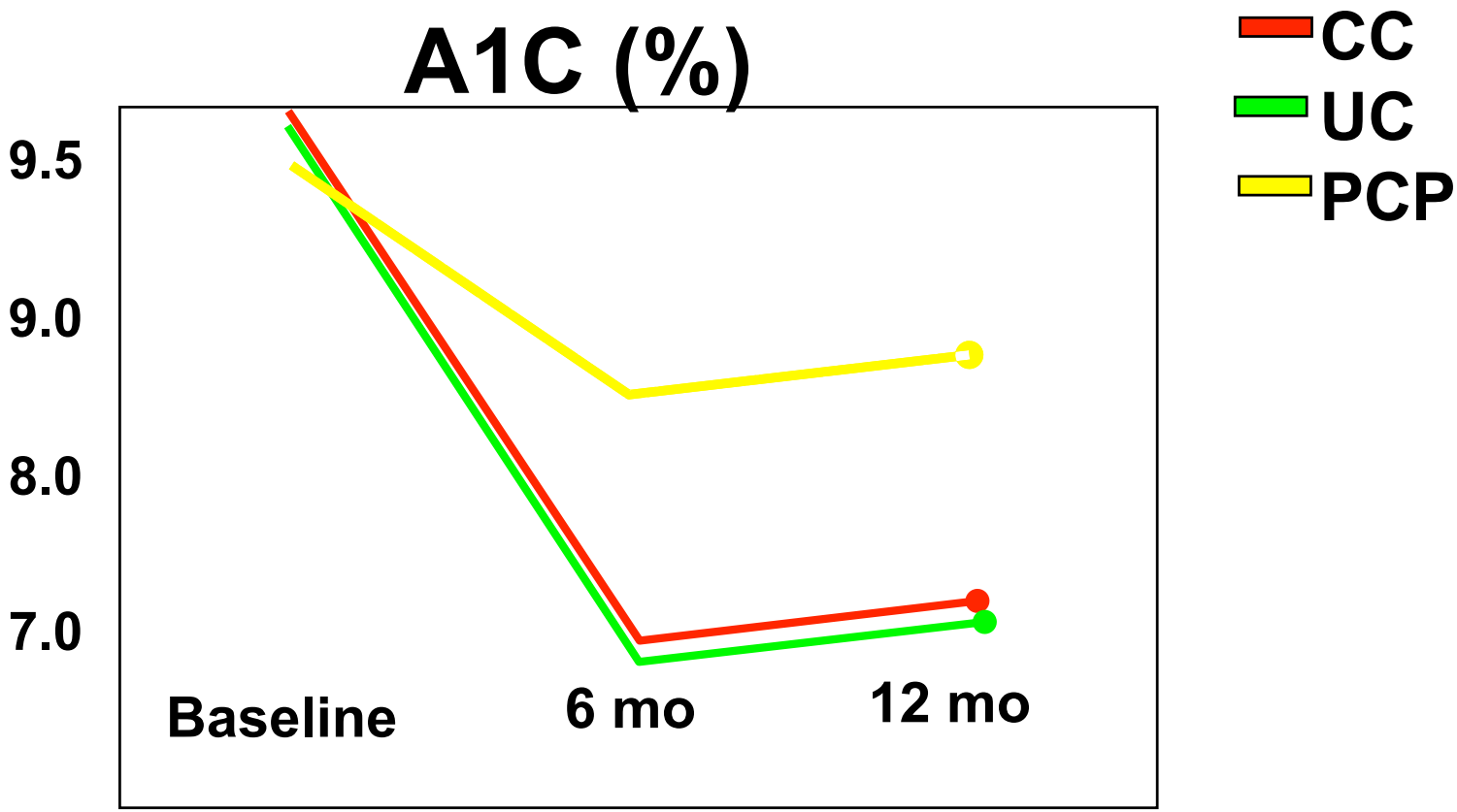
Outcomes Of Nurse Treatment Algorithms in Mexican American Patients with Type 2 Diabetes

- **Texas Algorithm given to Nurses in a Community Clinic (CC-TA), University Clinic (UC-TA), and Conventional Care in Community Clinic (PCP)**

ET Fanning, MD, RA Defronzo, MD, The Texas Diabetes Institute, University Center for Community Health

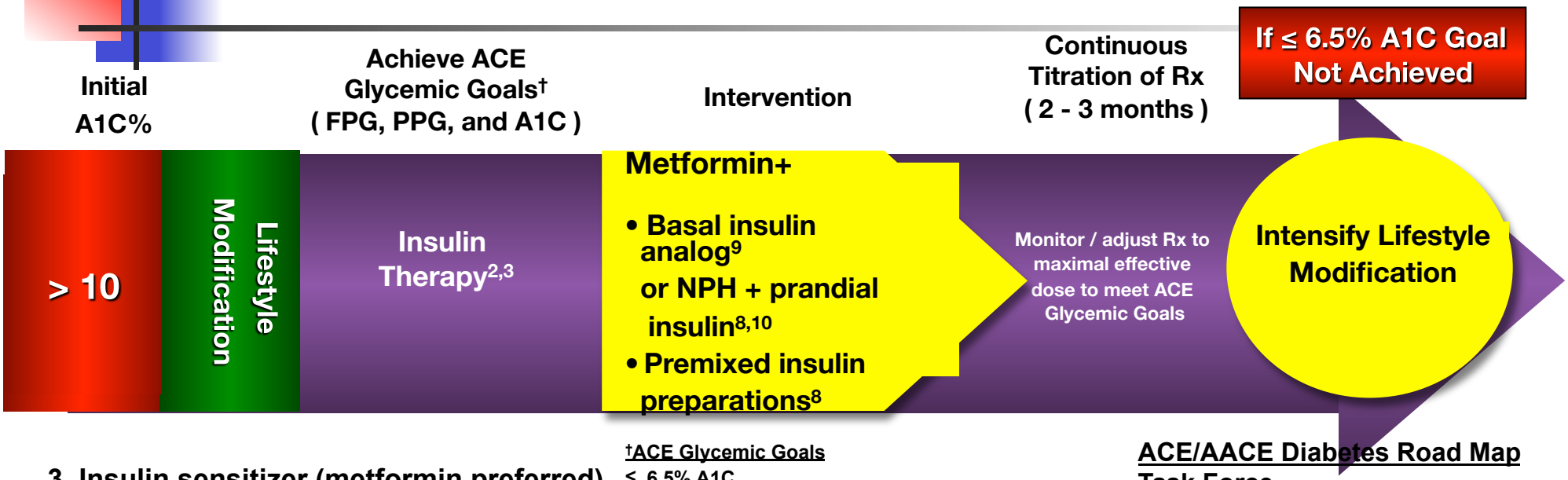
A1C Goal 7%

Glycemic Control in Mex-Am's with DM2 in a Community Setting, Texas Algorithm



Fanning EL et al. Department of Medicine, Division of Diabetes, University of Texas (2003)
Texas Department of Health, Texas Diabetes Council

Road Map to Achieve Glycemic Goals: Naïve to Therapy (Type 2)



3. Insulin sensitizer (metformin preferred) may be combined with initial insulin therapy

8. Analog preparations preferred

9. Available as glargine and detemir

10. Available as lispro, aspart and glulisine

†ACE Glycemic Goals
≤ 6.5% A1C
< 110 mg/dL FPG
< 110 mg/dL Preprandial
< 140 mg/dL 2-hr PPG

ACE/AACE Diabetes Road Map Task Force

Paul S. Jellinger, MD, MACE, Co-Chair
Jaime A. Davidson, MD, MACE, Co-Chair

Endocr Pract. 2007;13:260-268

Access Roadmap at:
www.aace.com/pub

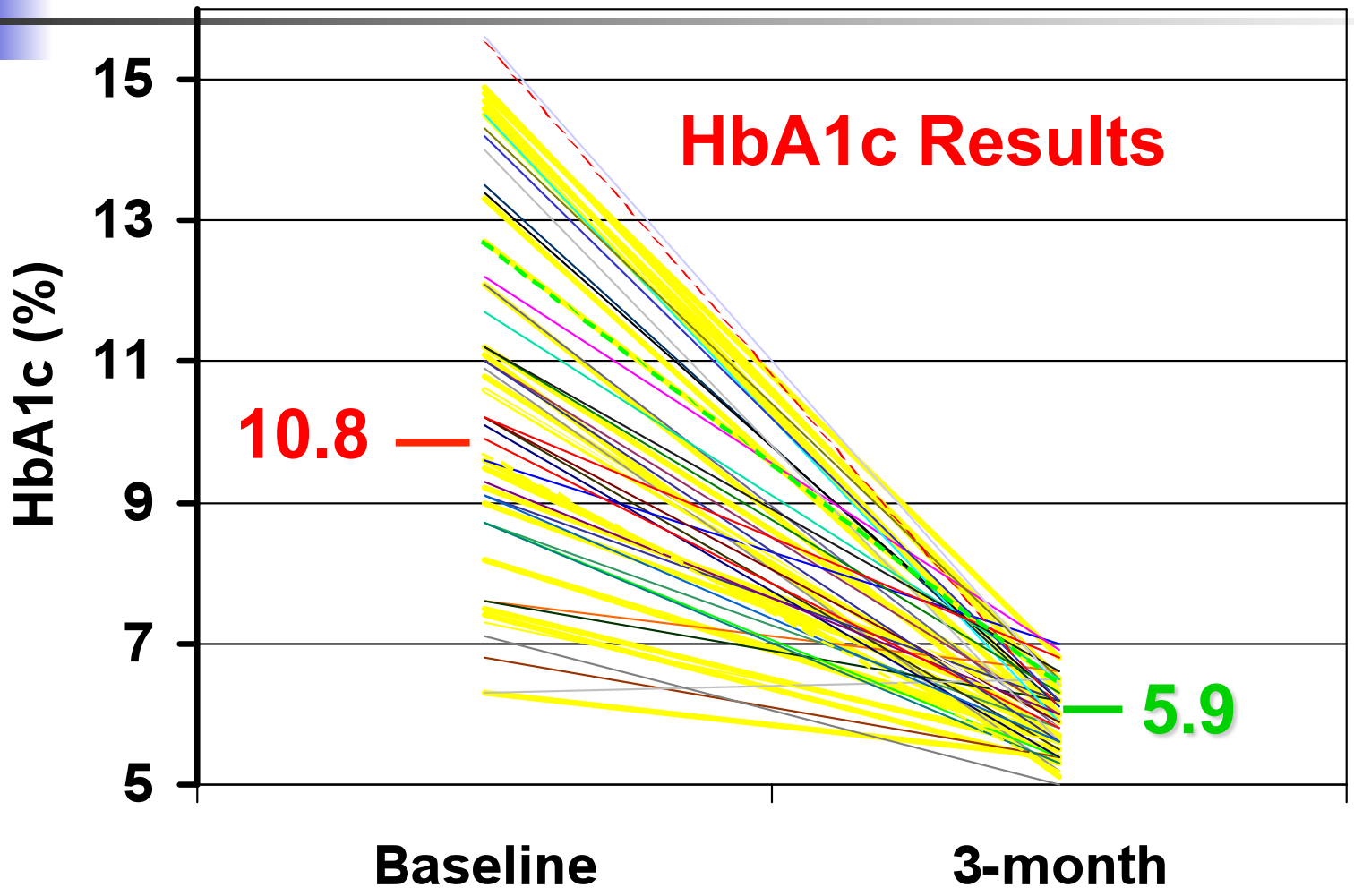
Insulin/Metformin As Initial Therapy in Type 2 Diabetes

Study Design

- 63 treatment naive individuals with Type 2 diabetes for less than 2 months
- Ages 21 to 70 Years old
- Initiation of treatment with Novolog Mix 70/30 Flexpen twice daily (0.2U/kg) plus metformin 500 mg per daily
- Insulin dose titrated upward base on targets (FPG 70 -110mg/dl, PPG <140 mg/dl)
- Weekly dose escalations of metformin of 500mg to target of 1000 mg BID
- Study duration was 3 months

Lingvay et al, J. Investigative Medicine 55: 62, 2007

Initial Treatment : Insulin plus Metformin in Type 2 Diabetes



Lingvay et al, J. Investigative Medicine 55: 62, 2007

Need to Constantly Re-evaluate Goals and Therapy

- Type 2 diabetes is a progressive disease
- Therefore, glucose and A1C levels need to be continually evaluated and therapeutic strategies updated in line with the disease process
- Symptoms in a diagnosed patient is a signal that A1C levels should be re-evaluated before the recommended time
- Algorithms helps the health care team achieve targets, it offers and action plan and it can be done

Thanks!