Diabetes Update-2015

Ambulatory Management

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Type 2 Diabetes Mellitus

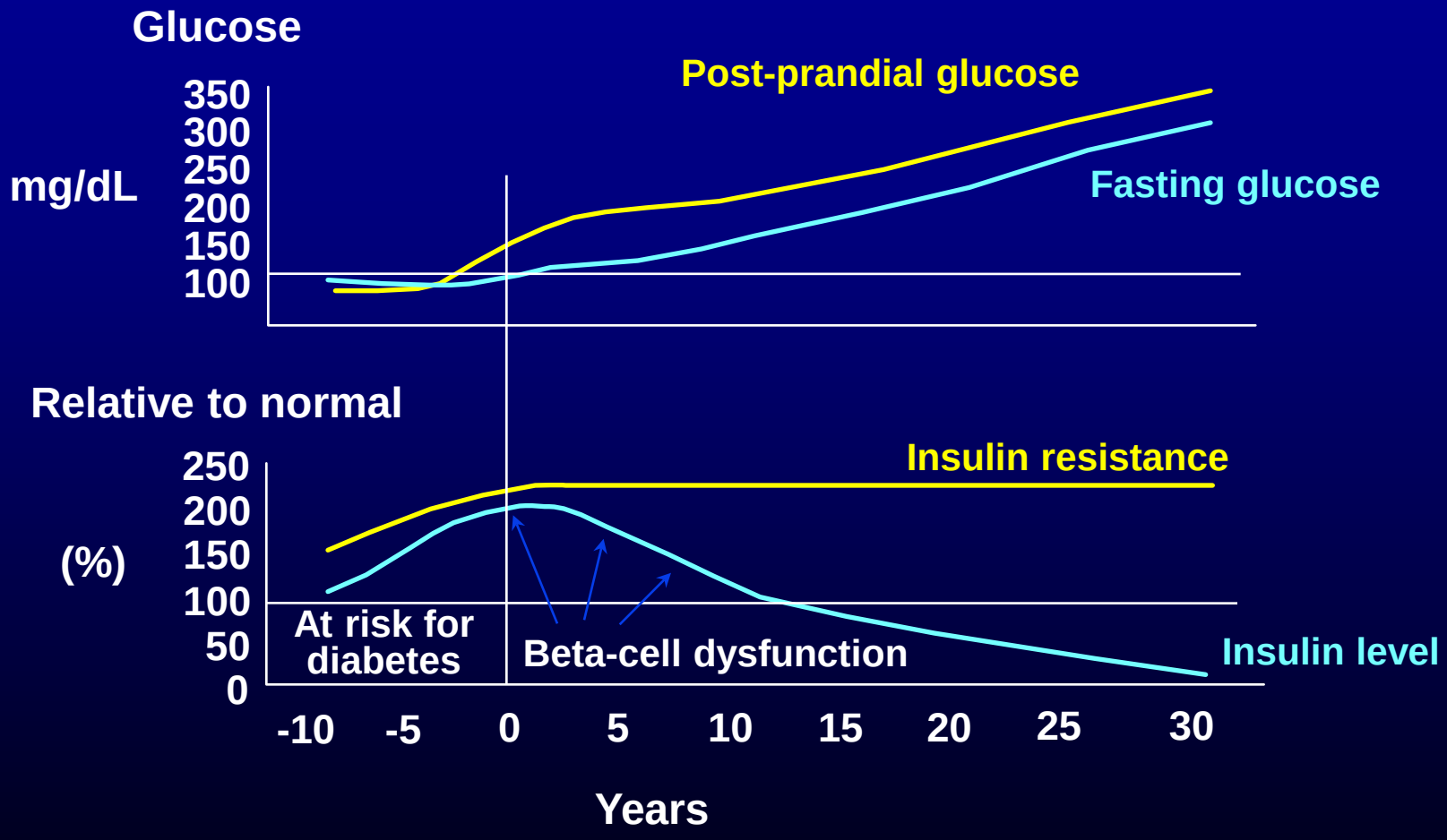
- What
- Why
- How

Type 2 Diabetes Mellitus

Diabetes is a generalized vascular disease that is associated with multiple abnormalities

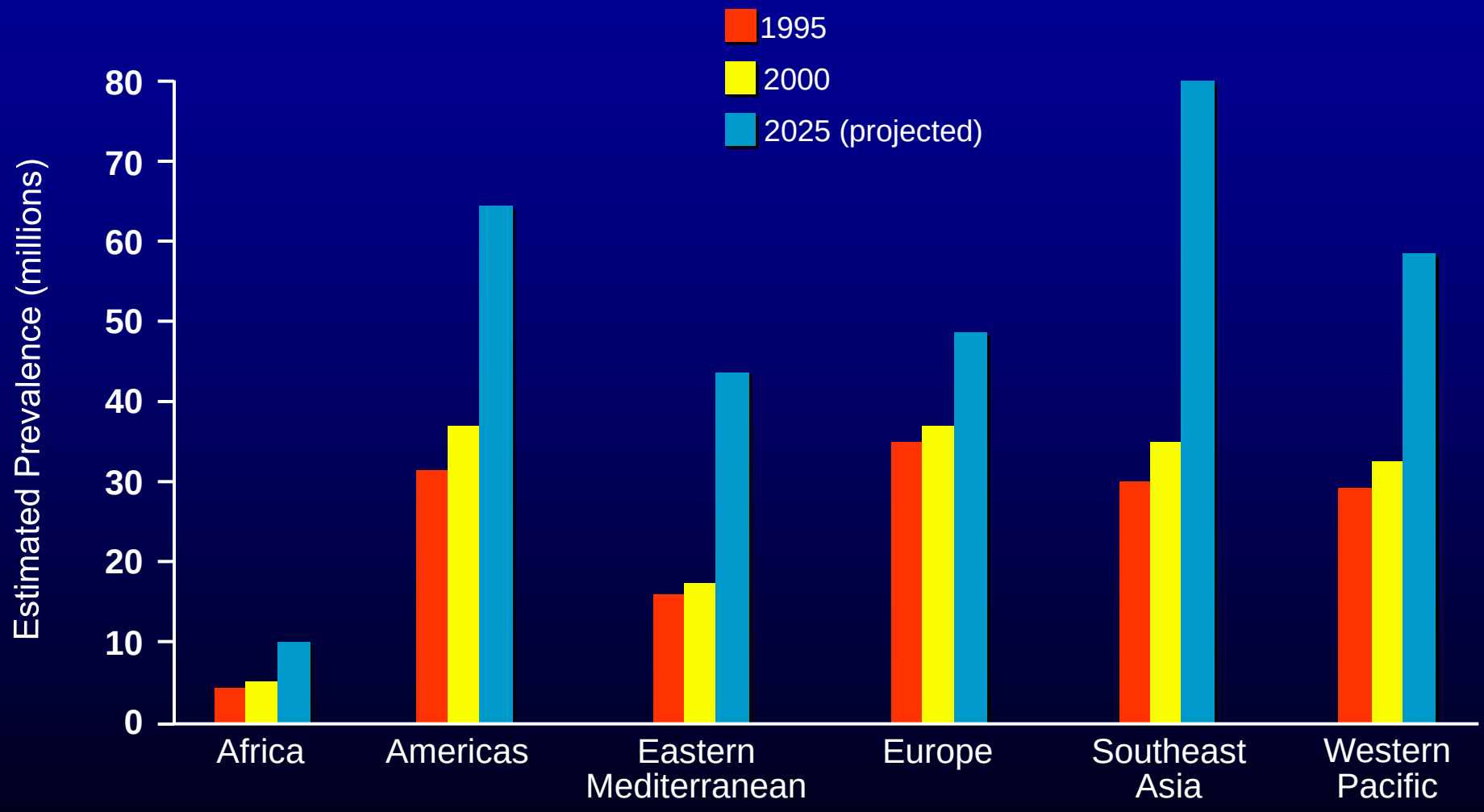
- Hyperglycemia
- Lipid abnormalities
- Hypertension
- Obesity
- Behavioural issues

Natural History of Type 2 Diabetes



R.M. Bergenstal, International Diabetes Center

Worldwide Diabetes Prevalence Rates



World Health Organization; 2001.

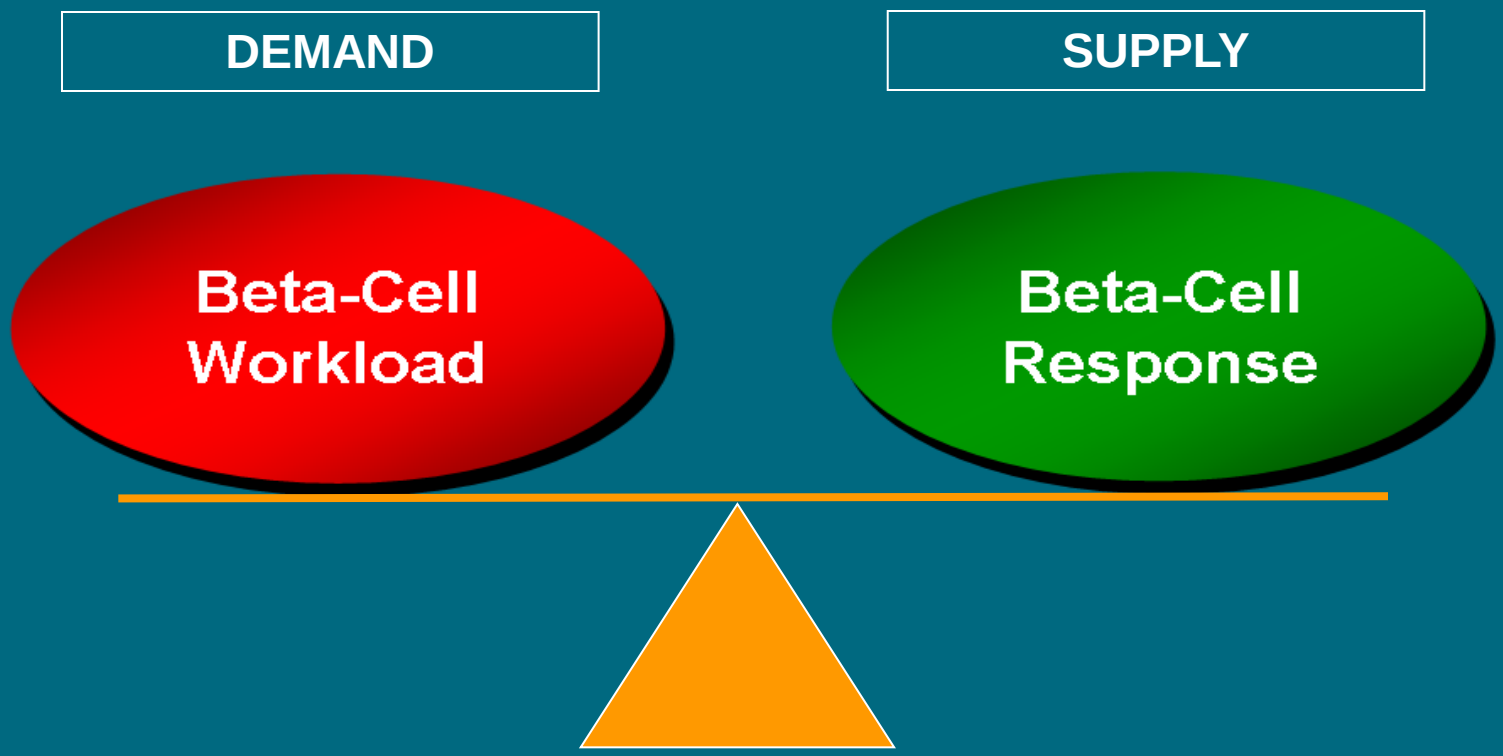
Type 2 Diabetes

Dual Impairment

- Impaired α & β-cell function
  - insulin secretion
  - glucagon secretion
- Impaired insulin action
  - insulin resistance
    - Liver
    - Muscle, Fat

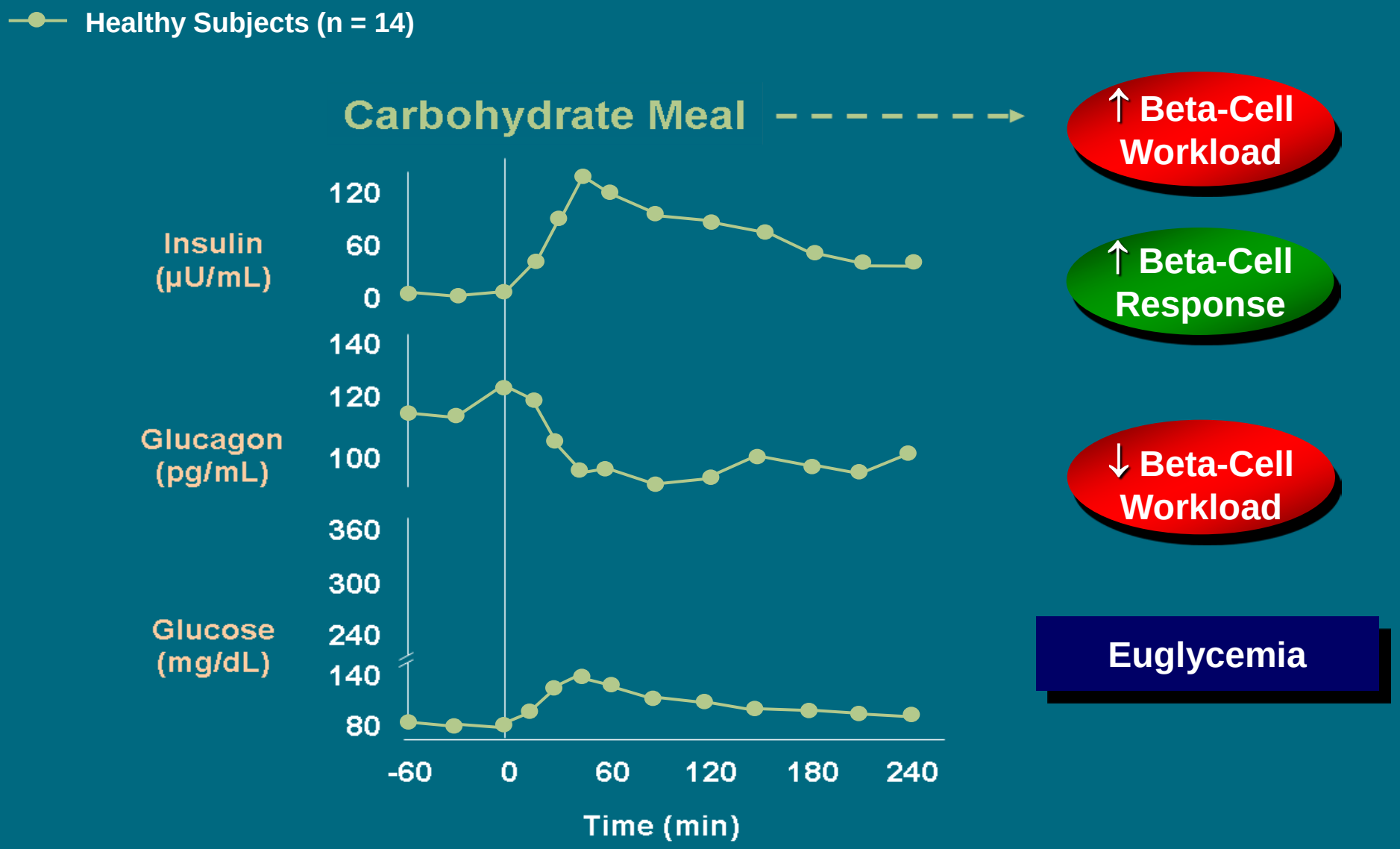
Beta-Cell Workload and Beta-Cell Response
Normally Balanced to Maintain Euglycemia

Normal Physiology



Balancing Beta-Cell Response and Beta-Cell Workload

Insulin Is Enhanced and Glucagon Is Suppressed

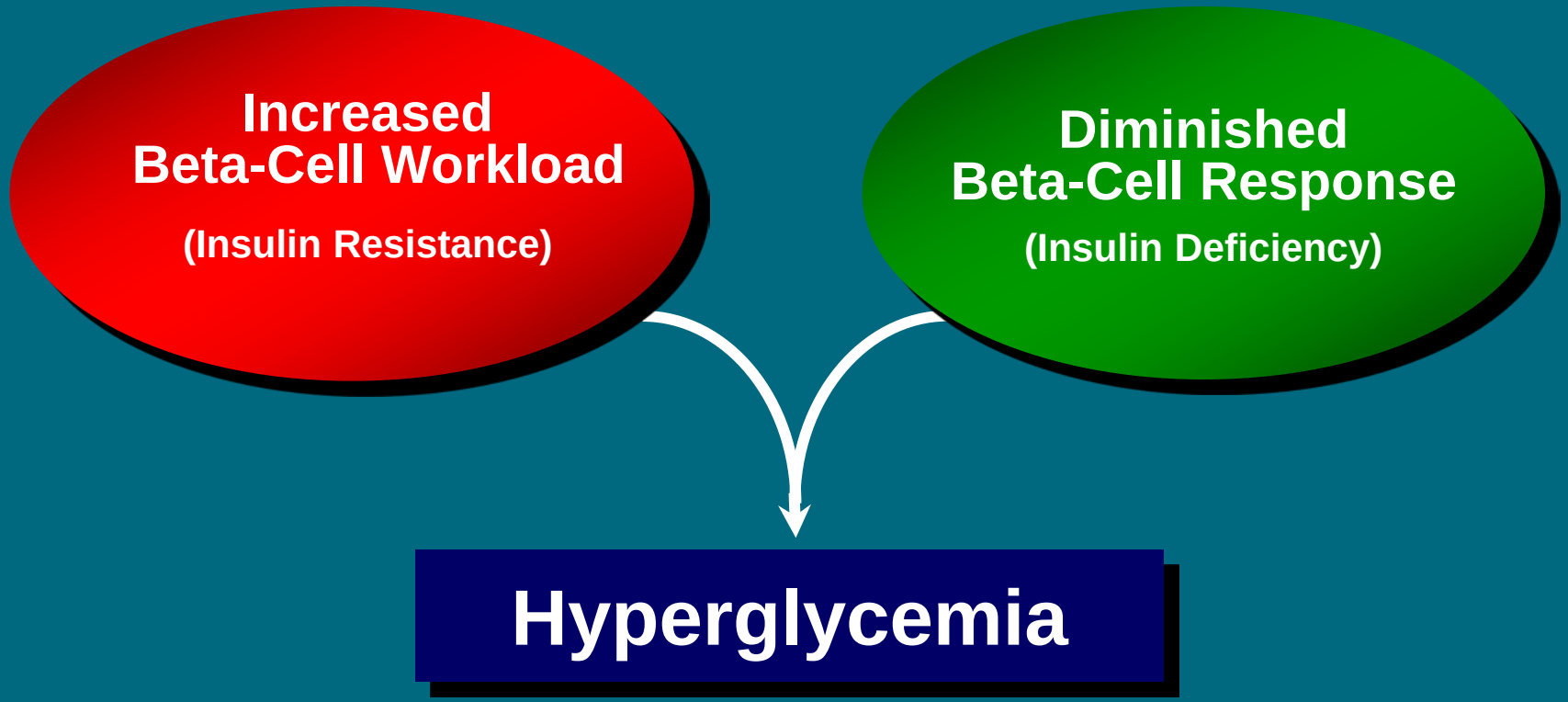


Mean (SE)

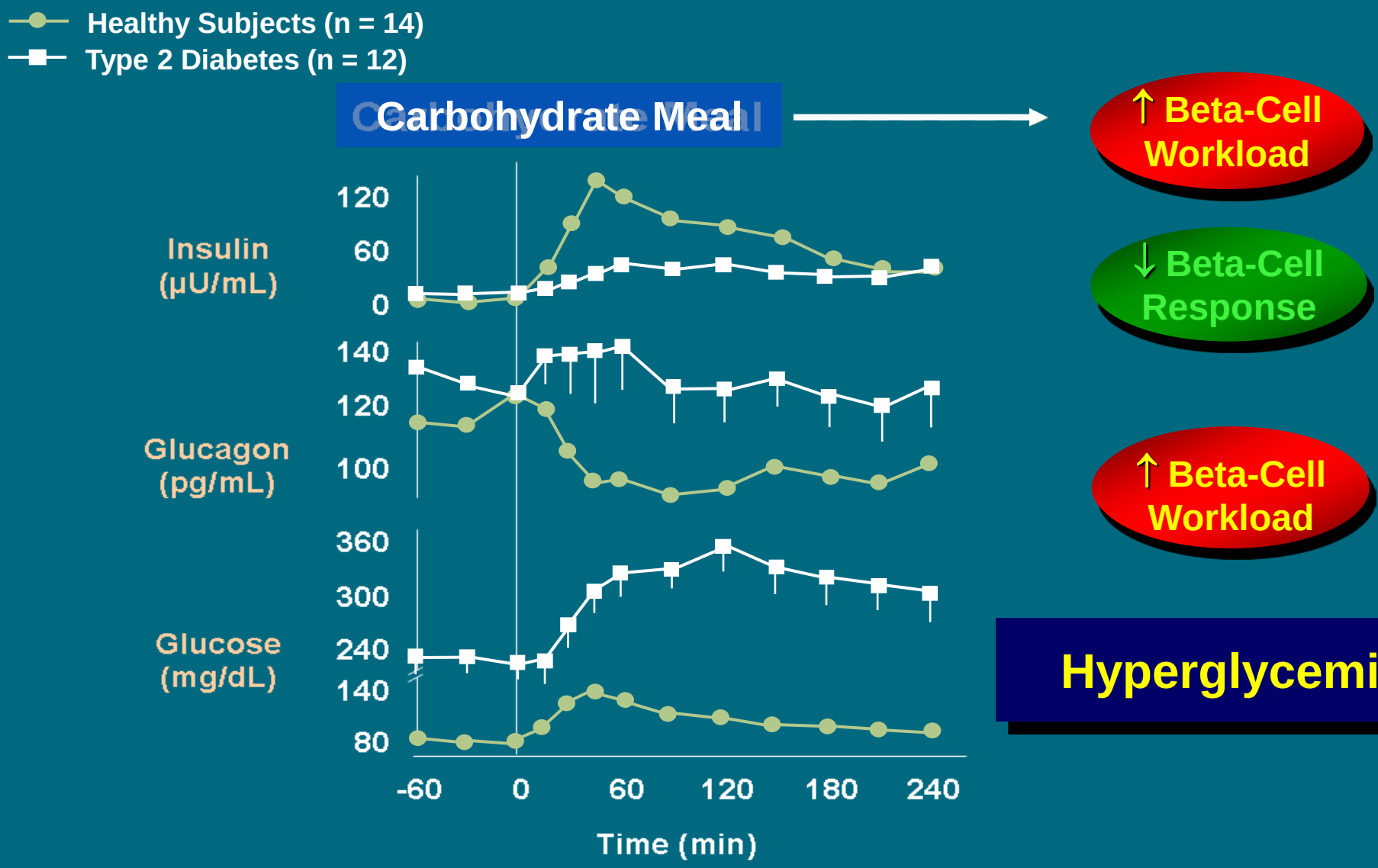
Data from Müller WA, et al. *N Engl J Med*. 1970;283:109-115

The Pathogenesis of Type 2 Diabetes

A New Perspective of the Core Defects Paradigm



The Pathogenesis of Type 2 Diabetes
Beta-Cell Workload Outpaces Beta-Cell Response

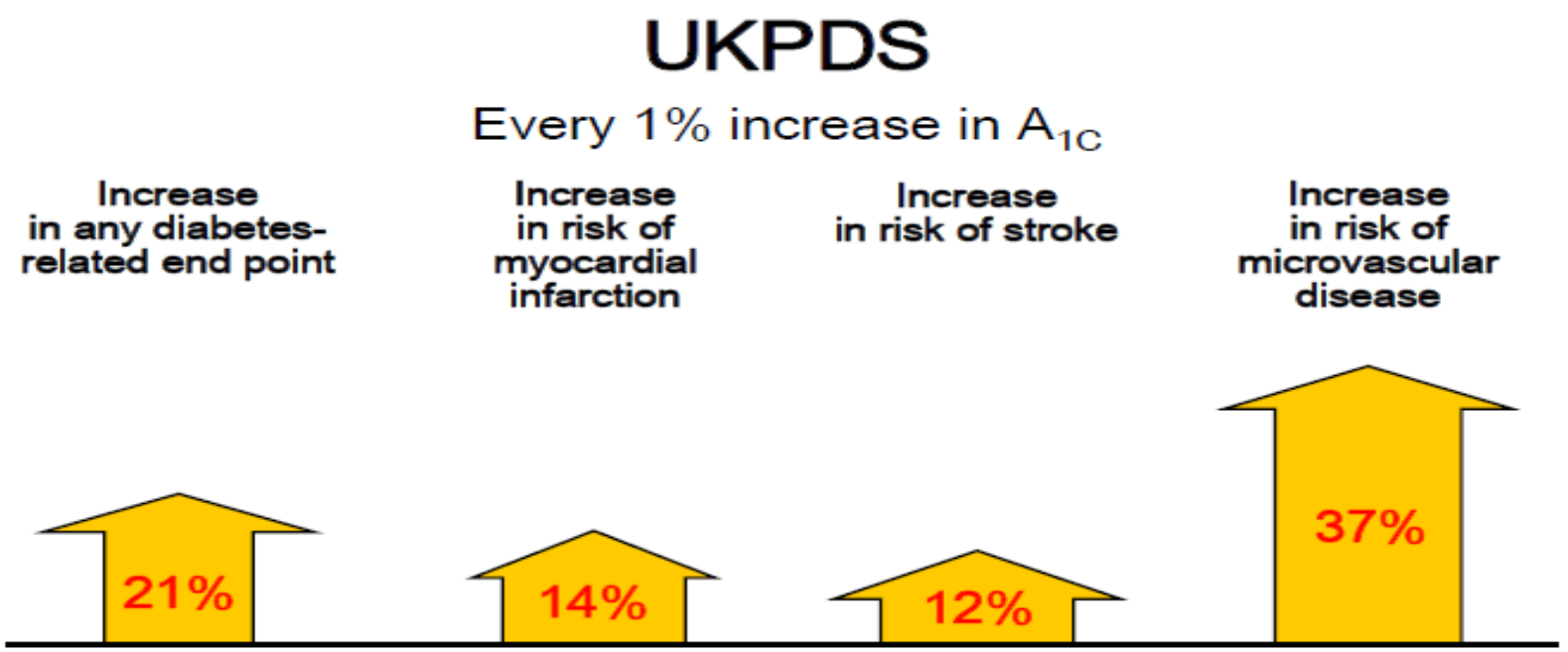


Mean (SE)

Data from Müller WA, et al. *N Engl J Med*. 1970;283:109-115

Why?

Lack of Glycemic Control Results in Diabetic Complications



Stratton IM, et al. *BMJ*. 2000;321:405-412.

Table 4. Primary and Secondary Outcomes.*

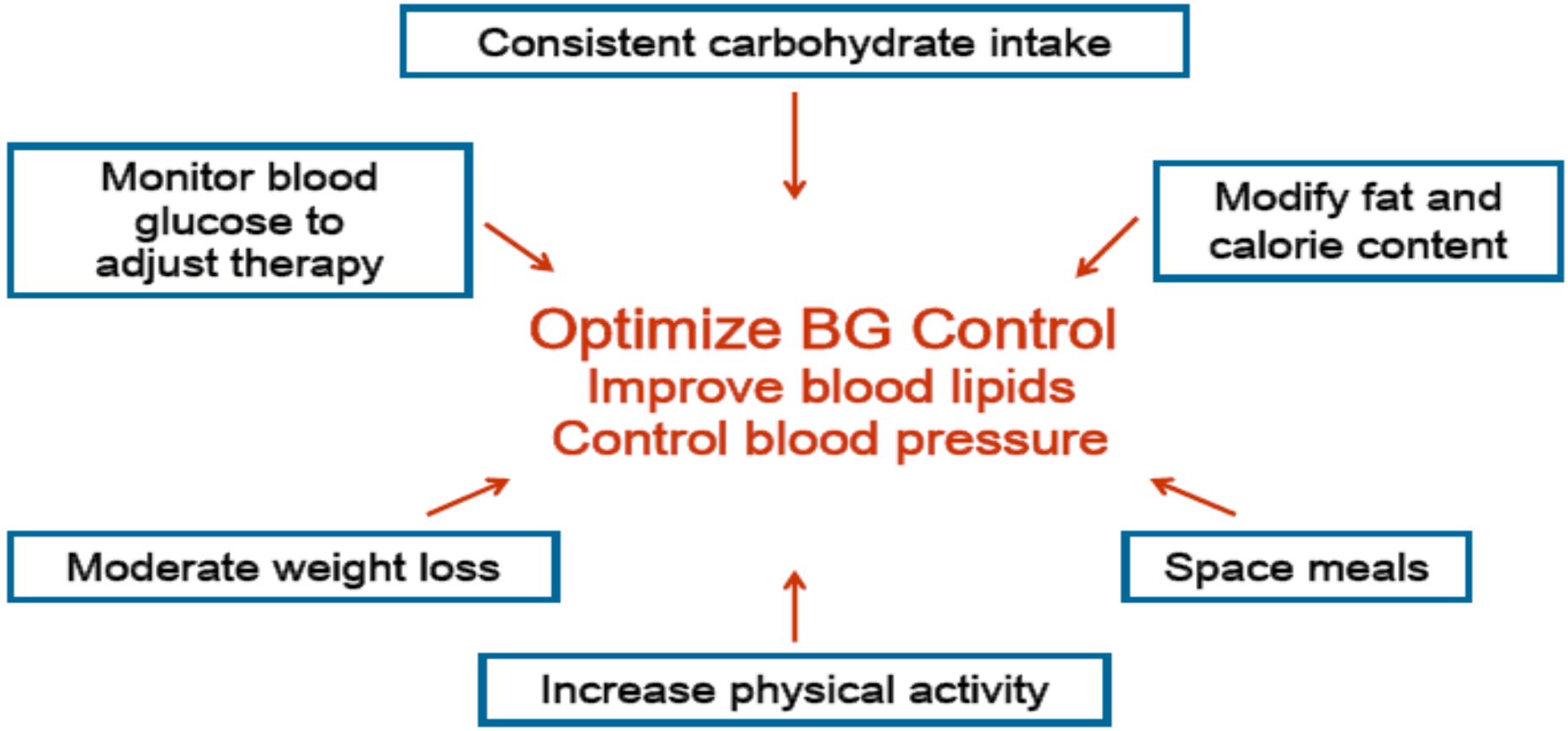
Outcome	Intensive Therapy (N=5128)		Standard Therapy (N=5123)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per yr*	*no. of patients (%)*	*% per yr*		
Primary outcome	352 (6.9)	2.11	371 (7.2)	2.29	0.90 (0.78–1.04)	0.16
Secondary outcome						
Death						
Any cause	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Cardiovascular causes	135 (2.6)	0.79	94 (1.8)	0.56	1.35 (1.04–1.76)	0.02
Nonfatal myocardial infarction	186 (3.6)	1.11	255 (4.6)	1.45	0.76 (0.62–0.92)	0.004
Nonfatal stroke	67 (1.3)	0.39	61 (1.2)	0.37	1.06 (0.75–1.50)	0.74
Fatal or nonfatal congestive heart failure	152 (3.0)	0.90	124 (2.4)	0.75	1.18 (0.93–1.49)	0.17
Causes of death						
Any	257 (5.0)	1.41	203 (4.0)	1.14	1.22 (1.01–1.46)	0.04
Unexpected or presumed cardiovascular disease†	86 (1.7)		67 (1.3)			
Fatal myocardial infarction†	19 (0.4)		13 (0.3)			
Fatal congestive heart failure†	23 (0.4)		16 (0.3)			
Fatal procedure†						
For cardiovascular disease	10 (0.2)		3 (0.1)			
For noncardiovascular disease	1 (<0.1)		3 (0.1)			
Fatal arrhythmia†	4 (0.1)		10 (0.2)			
Fatal stroke†	9 (0.2)		11 (0.2)			
Other cardiovascular disease†	8 (0.2)		10 (0.2)			
Cancer	65 (1.3)		63 (1.2)			
Condition other than cancer or cardiovascular disease‡	50 (1.0)		35 (0.7)			
Undetermined	7 (0.1)		11 (0.2)			

* The primary outcome was the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. Data within categories are not mutually exclusive, and patients who were classified as having more than one possible cause of death are listed in the relevant categories. Hazard ratios are for the intensive-therapy group as compared with the standard-therapy group.

† This condition was a component of the outcome of fatal cardiovascular disease.

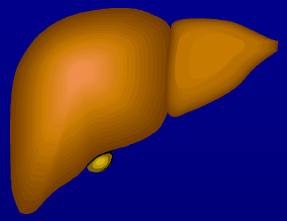
‡ Additional details are provided in the Supplementary Appendix.

Medical Nutrition Therapy for Type 2 Diabetes



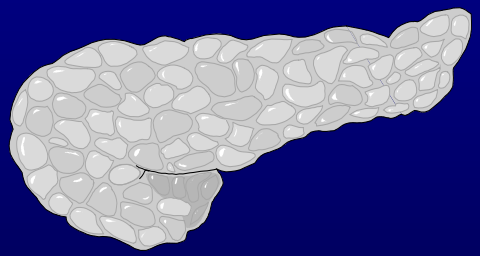
Sites of Action by Therapeutic Options Presently Available to Treat Type 2 Diabetes

LIVER



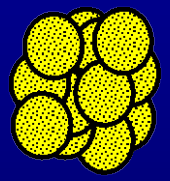
GLUCOSE PRODUCTION
Biguanides
Thiazolidinediones

PANCREAS

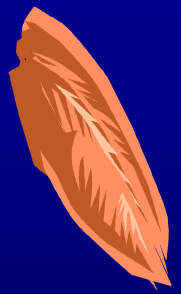


INSULIN Secretion
Sulfonylureas
Meglitinides
Insulin
GLP-1 analogues
DPP-IV Inhibitors

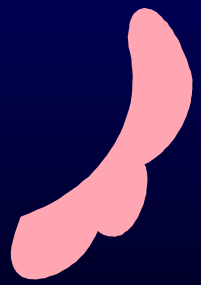
ADIPOSE TISSUE



MUSCLE

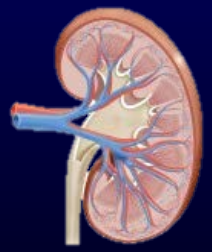


PERIPHERAL
GLUCOSE UPTAKE
Thiazolidinediones
(Biguanides)



INTESTINE

GLUCOSE ABSORPTION
alpha-glucosidase inhibitors



Renal effects:
SGLT2

Choice of Therapy (1):

- Obese
- Non-obese
- Fasting Hyperglycemia
- Post-prandial hyperglycemia

Choice of Therapy (2):

- Obese
- Non-obese
- Fasting Hyperglycemia
- P. P hyperglycemia

Insulin resistance

Beta Cell Dysfunction

Hepatic Gluconeogenesis

Muscle/Adipose Tissue uptake

Rapid Gut absorption

Increased Renal threshold

Choice of Therapy (3):

• Insulin resistance	Insulin sensitizers
• Beta Cell Dysfunction	GLP-1/DDP-IV Inhibitors/ Glinides/SU
• Hepatic Gluconeogenesis	Biguanides, GLP-1/DPP-IV inhibitors, Dopamine agonists
• Muscle/Adipose Tissue uptake	Thiazolidinediones
• GI Absorption	Alpha Glucosidase Inhibitors
• Renal Reabsorption	SGLT-2 Inhibitors

Metformin (Glucophage)

Advantages

- Correction of a primary pathophysiologic impairment: insulin resistance via AMP kinase
- High initial response rate
- Long record of relative safety
- No weight gain or modest weight loss
- Advantageous lipid profile
- Decreased myocardial infarctions in the UKPDS

Metformin (Glucophage)

Disadvantages

- Gastrointestinal (GI) side-effects on initiation
- Must be held after radiologic studies using intravascular iodinated contrast media.

- Risk of lactic acidosis—caution in
  - impaired renal function
  - impaired hepatic function
  - cardiovascular compromise

Insulin Secretagogues

- Sulfonylureas
- Glinides
- GLP-1 analogues
- DDP-IV inhibitors

Sulfonylureas

- Tolbutamide (Orinase)
- Chlorpropamide (Diabinese)
- Acetohexamide (Dymelor)
- Tolazamide (Tolinase)
- Glyburide (Micronase, Diabeta, Glynase)
- Glipizide (Glucotrol, Glucotrol XL)
- Glimiperide (Amaryl)

Sulfonylureas

Advantages

- Improvement of a primary pathophysiologic impairment: insulin secretion
- “Physiologic” route of insulin delivery
- High initial response rate
- No lag period before response

- MOA: via K-ATP channels

Sulfonylureas

Disadvantages

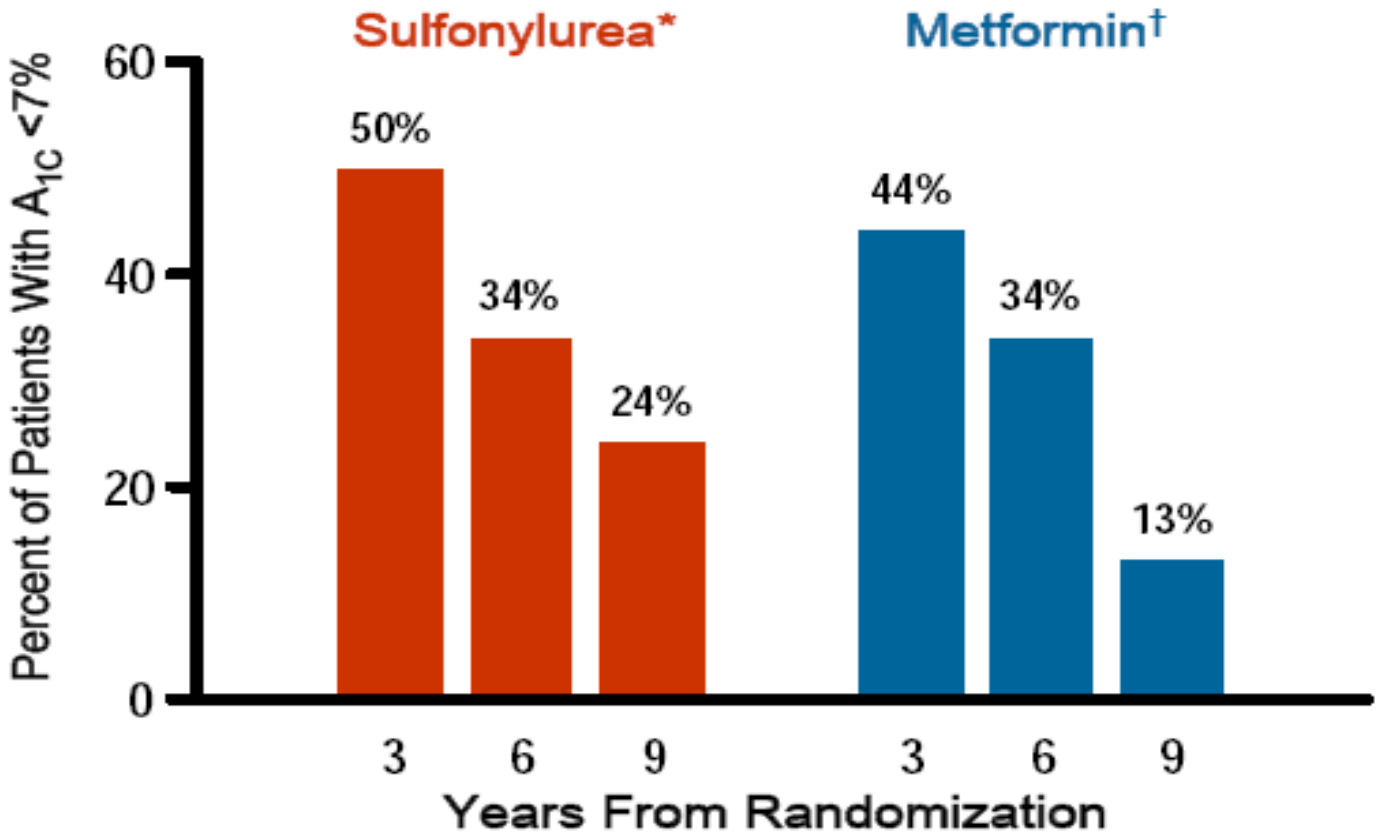
- No restoration of first phase insulin secretion
- Hypoglycemia
  - may be prolonged or severe
- Weight gain
- Drug interactions (especially first generation)
- Hyponatremia (with chlorpropamide)
- Cannot use if allergic to sulfa compounds

Glinides

- Repaglinide (Prandin)
- Nateglinide (Starlix)

MOA: via non-SU K-ATP channels

UKPDS Demonstrated That Traditional Agents Do Not Maintain Patients at A_{1C} Goal



*Normal weight and overweight drug-naïve patients.
†Overweight drug-naïve patients.

Turner RC, et al. *JAMA*. 1999;281:2005-2012.

Glitazones

- Rosiglitazone (Avandia)

- Pioglitazone (Actos)

MOA: via PPAR – γ receptors
increased insulin sensitivity

Glitazones

Advantages

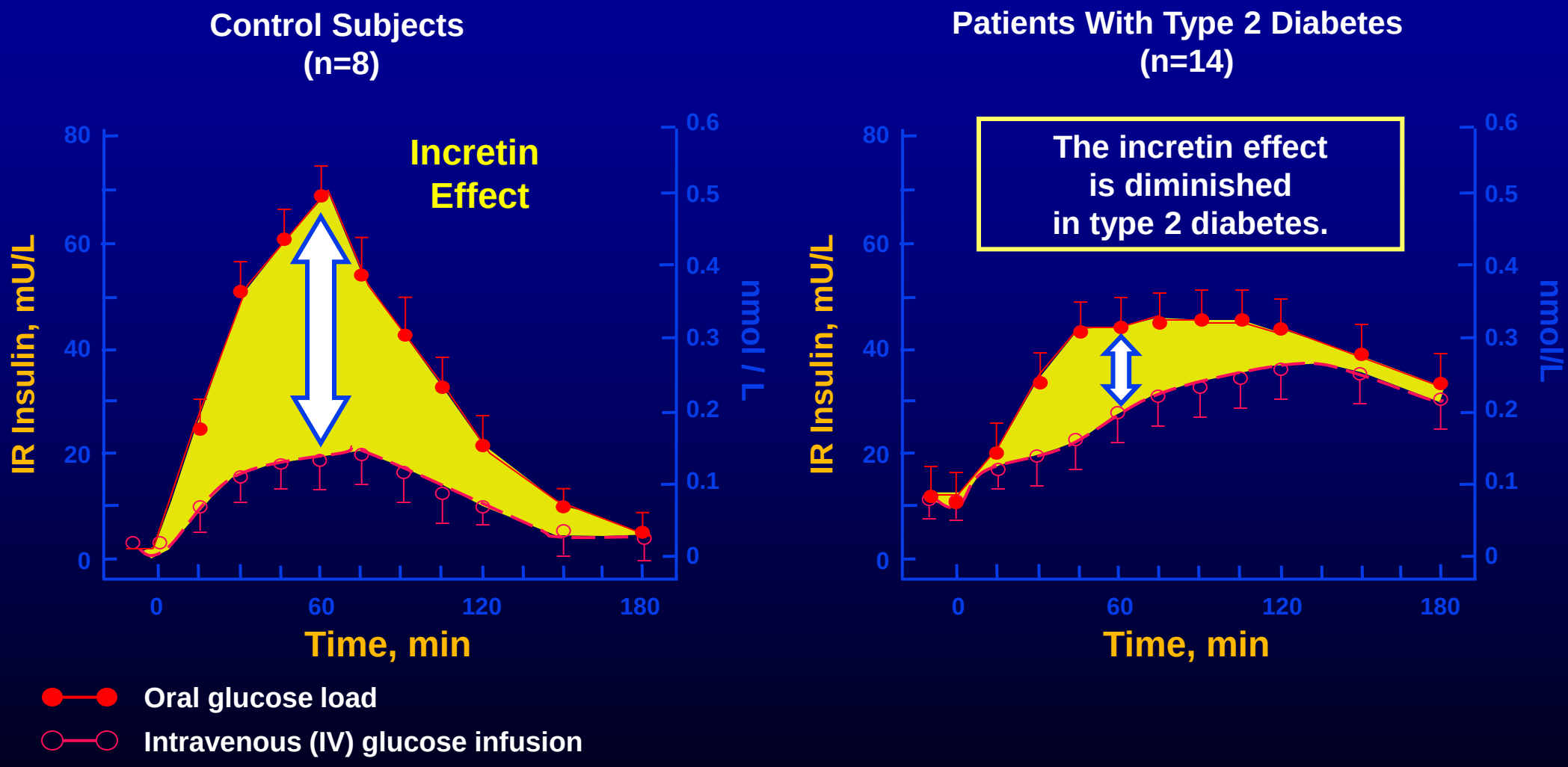
- Correction of a primary pathophysiologic impairment: insulin resistance
- Once-daily dosing for most
- Lower serum triglycerides
- Some may be used in renal insufficiency
- Improves components of insulin-resistance syndrome

Glitazones

Disadvantages

- Delayed action (onset: 3 weeks; full effect: 10 to 12 weeks)
- Variable response in monotherapy
- Weight gain
- Edema
- Increased LDL cholesterol
- Unknown long-term adverse effects

The Incretin Effect in Subjects Without and With Type 2 Diabetes



GLP-1 Analogues

Exenatide (Byetta), Liraglutide (Victoza)

Exenatide LAR (Bydureon), Albiglutide (Tanzeum), Dulaglutide (Trulicity)

- Stimulates Beta cell secretion of Insulin
- Suppresses Alpha cell secretion of Glucagon
- Stimulates satiety center in the hypothalamus
- Delays gastric emptying
- In animal studies, shown beta-cell regeneration
- Weight loss

DPP-IV Inhibitors

- Sitagliptin (Januvia)/ Saxagliptin (Onglyza) / Linagliptin (Trajendta)
  - Stimulates beta-cell insulin response to meals
  - Suppresses alpha-cell glucagon response
  - Stimulates satiety center
  - Delays gastric emptying
  - Weight neutral

α-glucosidase inhibitors

- Miglitol (Precose)
- Acarbose (Glyset)

MOA- inhibits the disaccharides in the gut wall to prevent absorption of monosaccharides

AE- Flatus

Efficacy, ease of use, hypoglycemia Mx

Sodium Glucose Co-transporter-2 inhibitors (SGLT2)

- Canagliflozin (Invokana)
- Dapagliflozin (Farixga)
- Empaglofozin (Jardiance)

MOA- reversibly binds the SGLT-2 to prevent glucose reabsorption in the proximal renal tubule

AE- genital infections

Long term safety

Insulin & Insulin Analogues

Advantages

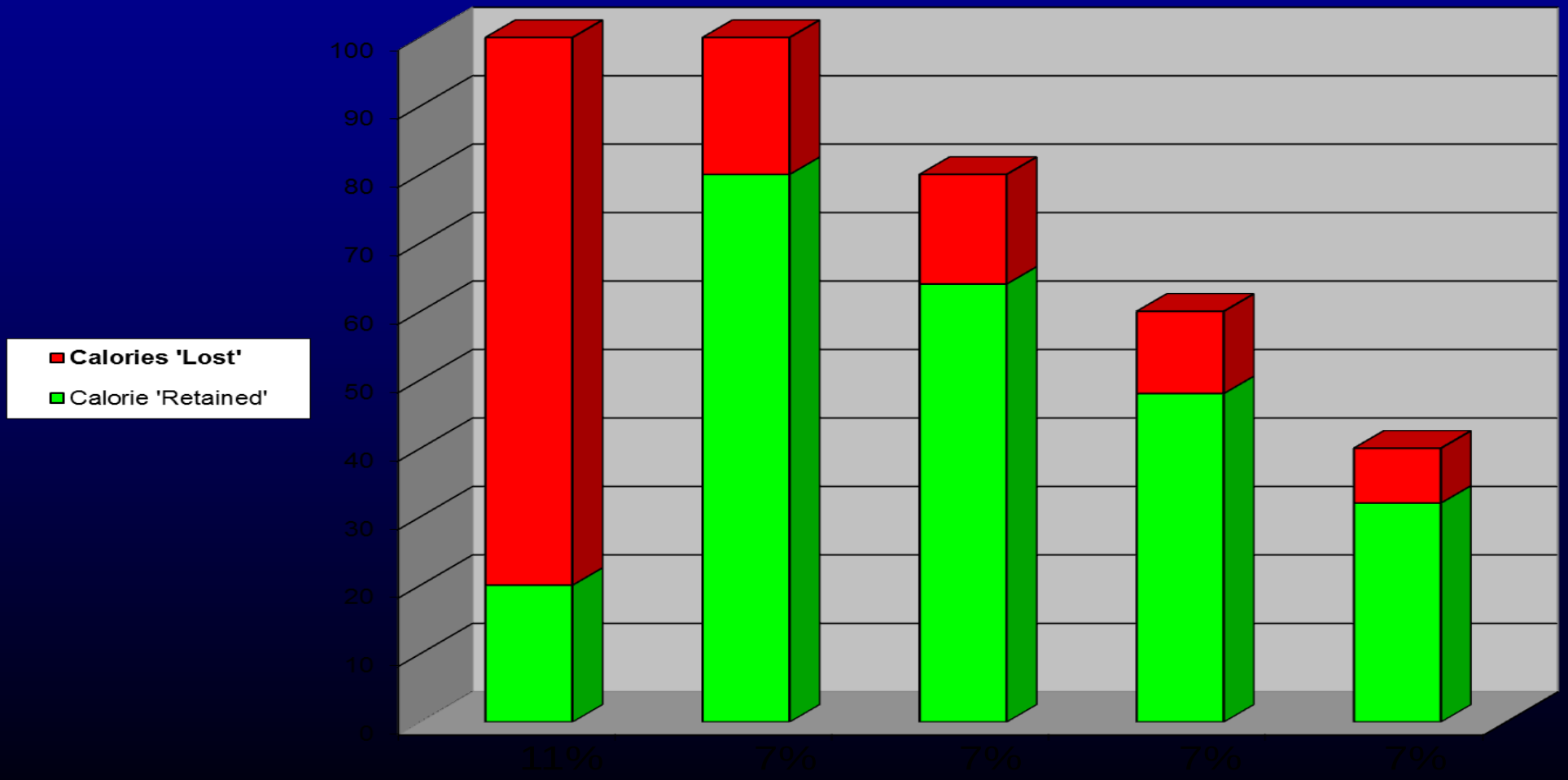
- Will control all patients
- Can be used to overcome glucose toxicity
- Provides flexibility in dosing and lifestyle
- Supplied in multiple preparations with different action profiles

Insulin & Insulin Analogues

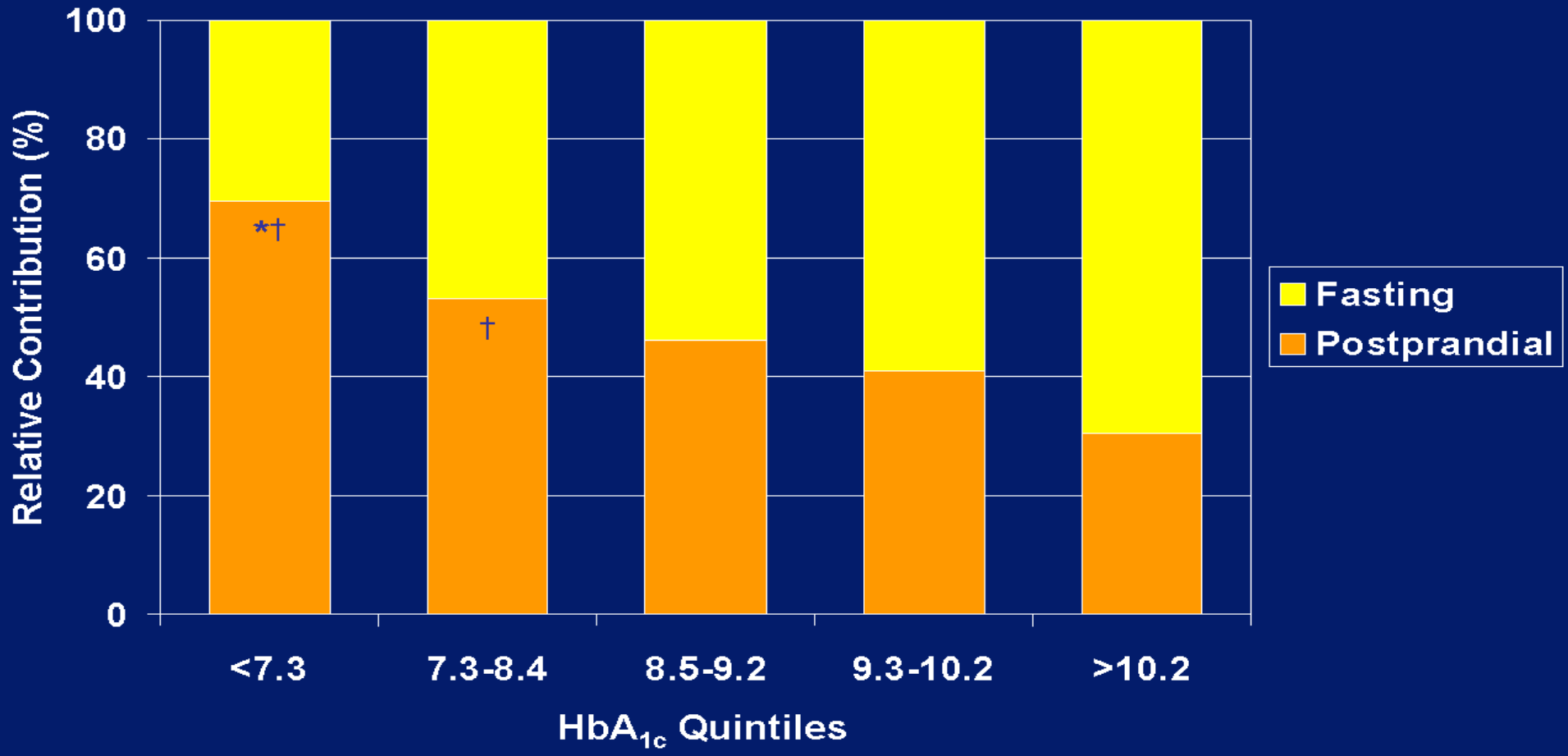
Disadvantages

- Hypoglycemia
- Weight gain
- Need for injections
- Non-physiologic route of administration (peripheral)
- Patient and physician non-acceptance

Weight gain in Diabetics on Insulin



Postprandial Glucose Is an Important Contributor to Overall Hyperglycemia



*P<0.001 vs fasting glucose, first quintile.
†P<0.001 vs postprandial glucose, fifth quintile.

Adapted from Monnier L et al. *Diabetes Care.* 2003;26:881-885.

The Importance of Elevated Mealtime Glucose in Treatment Decisions

- Clinically significant reductions in HbA1c can be seen by lowering postmeal glucose[1]
- Approximately 50% of the day is spent in the postmeal state[2]
- Elevated mealtime glucose is present in most patients[3]

Bastyr EJ, et al. *Diabetes Care*. 2000;23:1236-1241.
Riddle MC. *Diabetes Care*. 1990;13:676-686.
Erlinger TP, Brancati, FL. *Diabetes Care*. 2001;24:1734-1738.

Basal-Bolus Insulin Therapy Defined

A therapeutic regimen which aims to mimic physiologic insulin secretion.

- Basal insulin—long-acting insulin controls basal glucose (FPG)
- Bolus insulin—short-acting insulin controls mealtime glucose

Targeted Glucose Control

Treatment Steps

- Set glycemic goals
  - target both fasting and postprandial glucose
- Institute medical nutrition therapy and an exercise plan for all
- Conduct diabetes education for all
- If needed, administer temporary insulin to overcome glucose toxicity
- Initiate pharmacologic therapy

Targeted Glucose Control

- Base therapy on glycemic goals
- Target both fasting and postprandial glucose levels
- Monotherapy is not usually effective long-term
- Implement step-wise approach
- Use whatever therapy necessary to achieve glycemic goals

Glycemic Targets*

Table 6.2—Summary of glycemic recommendations for nonpregnant adults with diabetes

A1C	<7.0%*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (<10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

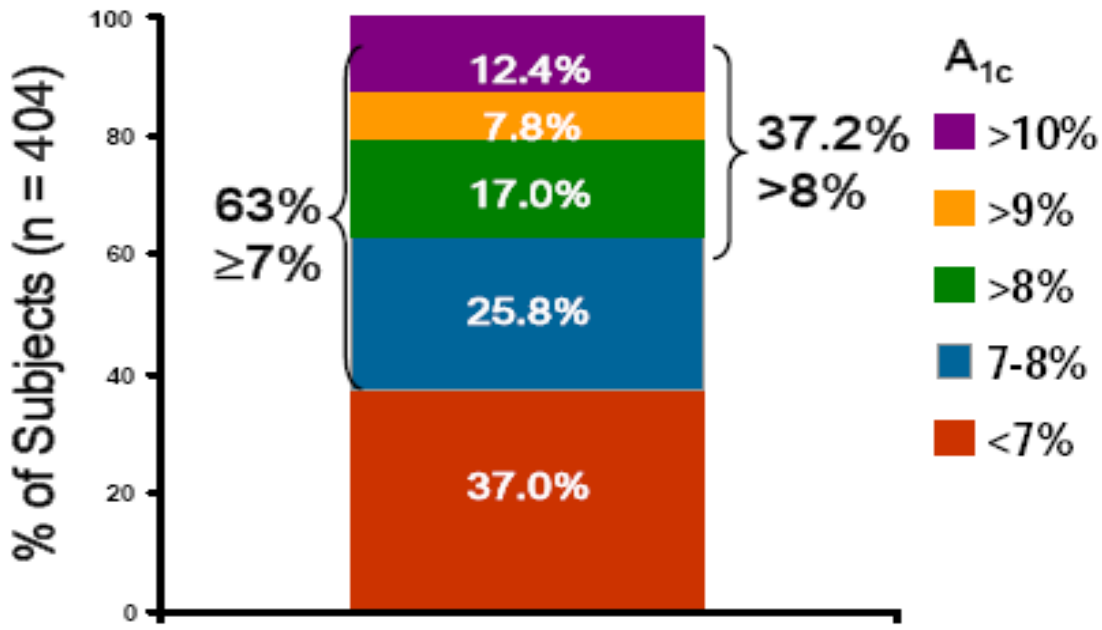
†Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Conclusions:

Management of glycemia in T2DM needs a target driven, multi-risk factor modifying, team based approach.

- Behavioral intervention
  - Weight loss
  - Dietary modifications
  - Exercise
- Glucose intervention
- Lipid intervention
- Blood pressure intervention

63% of Patients With Diabetes Are Not at A_1 Goal of <7%



Only 7% of adults with diabetes in NHANES 1999-2000 attained:

- A_{1C} <7%
- BP <130/80 mm Hg
- Total cholesterol <200 mg/dL

National Health and Nutrition Examination Survey (NHANES), 1999-2000.
Saydah SH et al. *JAMA*. 2004;291:335-342.

Take Home points:

- 85% of diabetics are obese
- 92% of diabetics have insulin resistance
- “Insulin sensitizers should be first line therapy in a majority of Type 2 diabetics”
- “Sulphonylurea should NOT be used as the first line monotherapy in a majority of Type 2 diabetics”
- Combination therapy should be the norm in the pharmcotherapy of Type 2 diabetes

KEEP CALM AND GO CRAZIE

#dukebasketball