

Critical View of the Current Management of Type 2 Diabetes

David M. Nathan, M.D.

January, 2009

III Reunion de Diabetes y Obesidad



MASSACHUSETTS
GENERAL HOSPITAL



HARVARD
MEDICAL SCHOOL

“All the News
That’s Fit to Print”

The New York Times

VOL. CLV . . . No. 53,455

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TUESDAY, JANUARY 10, 2006



Vincent Laforet/The New York Times

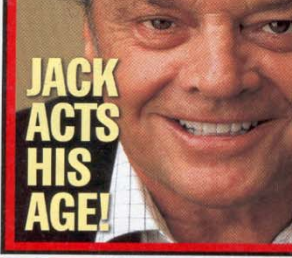
Santos Alicea and his daughter, Alicia Rodriguez, have Type 2 diabetes. The disease is ubiquitous in East Harlem, where they live.

Living at an Epicenter of Diabetes, Defiance and Despair



New York Times
Wednesday, January 11, 2006

TIM



**JACK
ACTS
HIS
AGE!**

Hillary Carroll, 11,
has "adult-onset"
diabetes

- **WHO'S GETTING IT**
- **WHY IT'S STRIKING SO MANY**
- **WHAT YOU CAN DO TO FIGHT IT**

DIABETES ARE YOU AT RISK?

#BXBDJLX *****CHR-RT-LOT**C-020
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Prevalence of Diabetes in the U.S.

Prevalence of all diabetes	28 million
Type 1	1+ million (0.4%)
Type 2	16 million (6%)
Diagnosed	13 million (4%)
Undiagnosed	5 million (2%)
1,200,000 cases per year	
GDM	75,000 (3% of pregnancies)
Prediabetes	42 million (~20%)

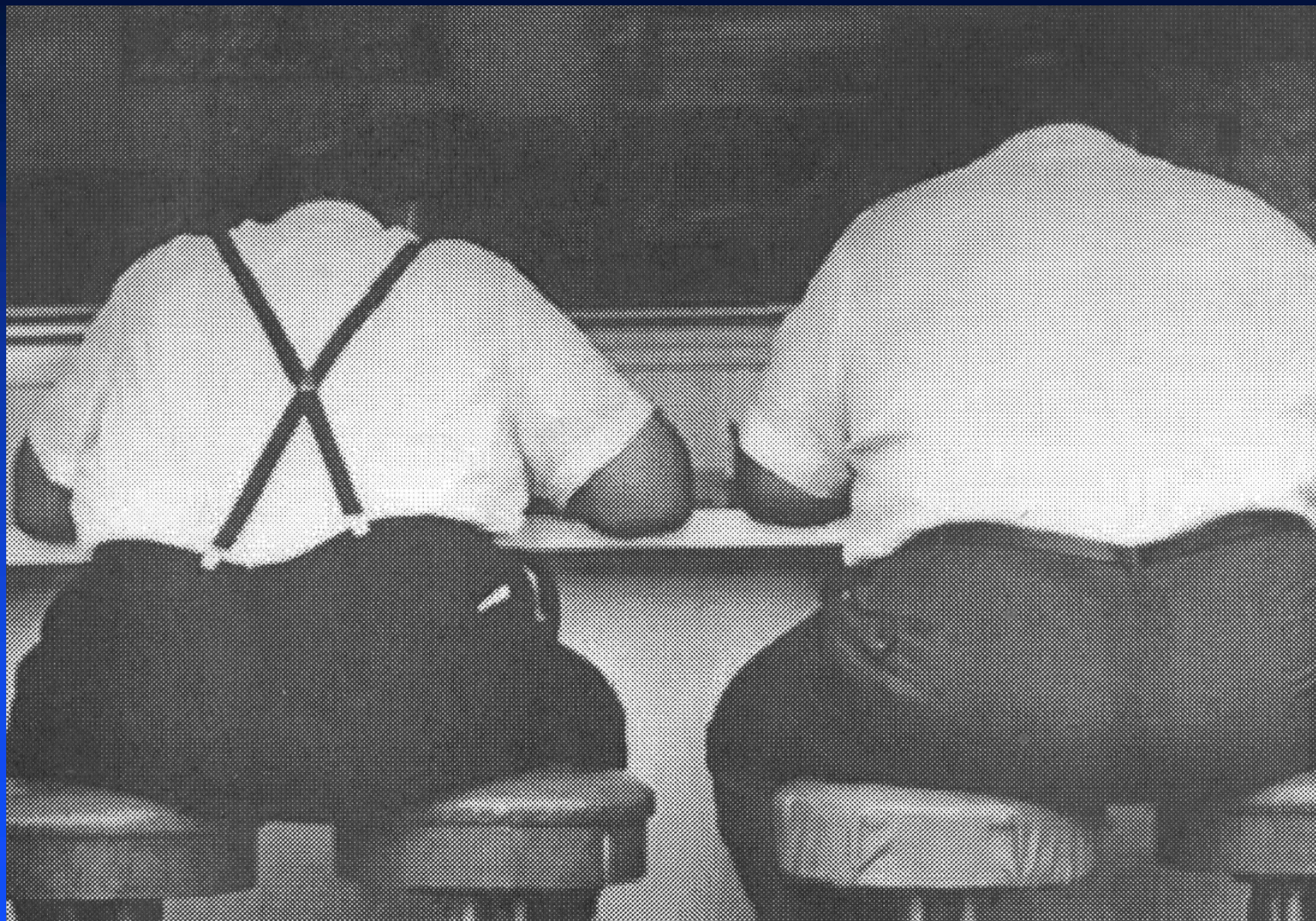
CDC ~~October~~ 2002 October 26, 2005

Prevalence of Diabetes in the U.S.

Prevalence of all diabetes	24 million
Type 1	1+ million (0.4%)
Type 2	22 million (8%)
Diagnosed	16 million (6%)
Undiagnosed	6 million (2%)
1,600,000 cases per year	
GDM	75,000 (3% of pregnancies)
Prediabetes	42 million (~20%)

CDC 2008

Pathophysiology of Type 2 Diabetes



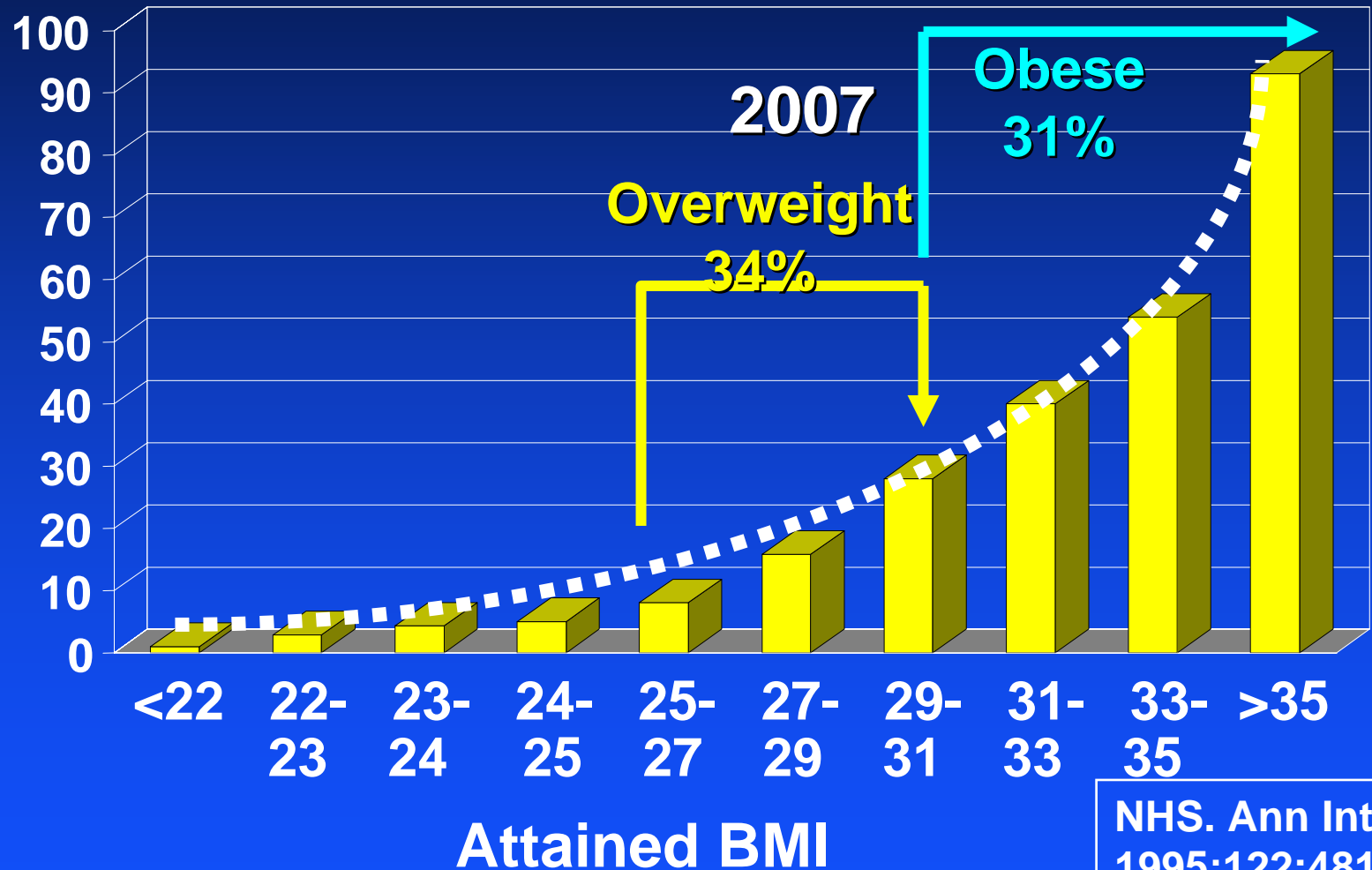
©2008 David M. Nathan

Type 2 Diabetes

Risk for Development of Type 2 Diabetes

Effect of BMI in Women

Age-adjusted
RR(%) of
Developing
DM over 14 yr
In women aged
30-55 in 1976

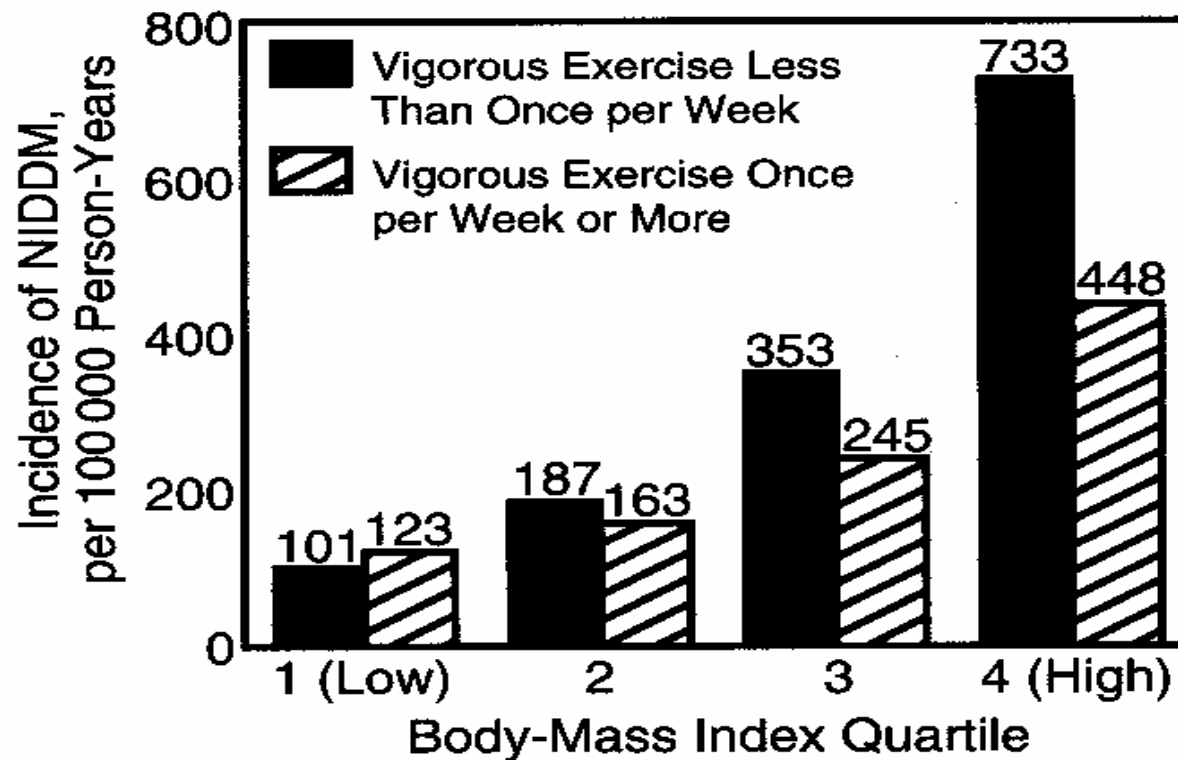


NHS. Ann Int Med
1995;122:481

Relationship between Exercise and Incidence of Diabetes

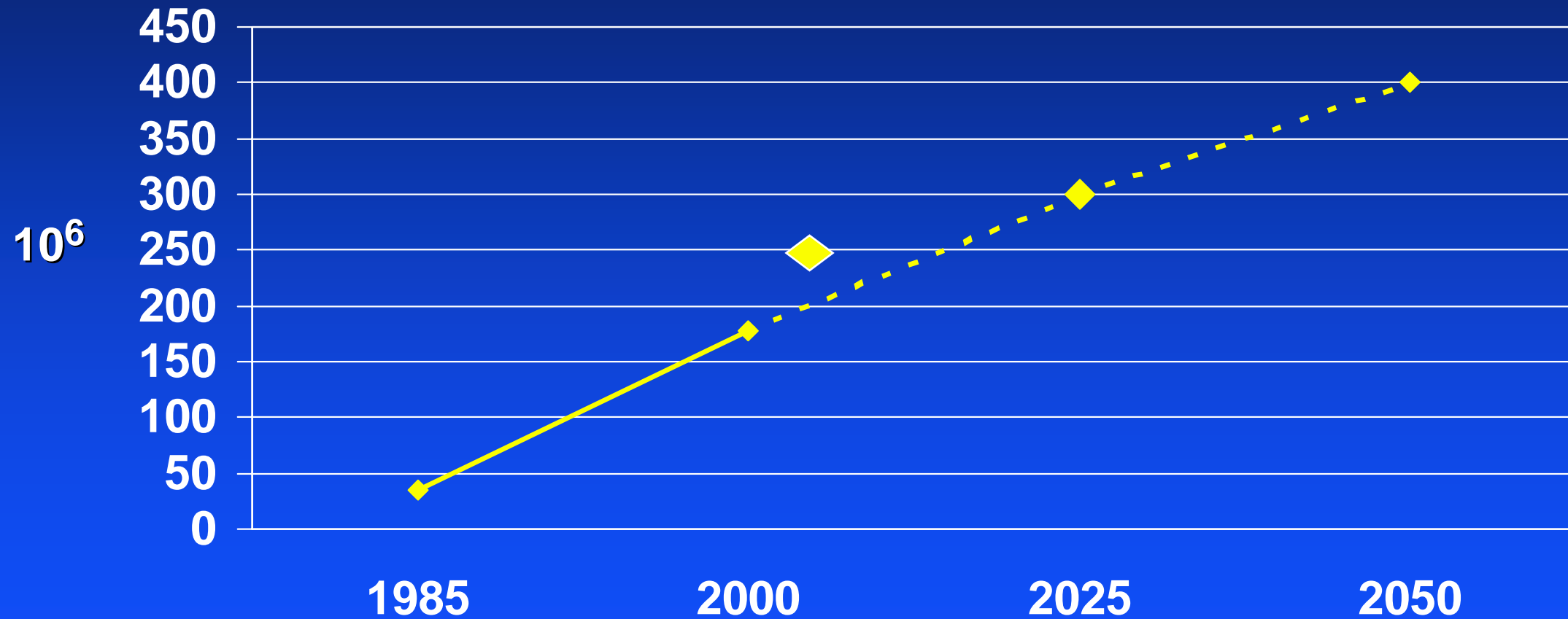
Physicians' Health Study

21,000
physicians
followed for
a mean of
5 years



Manson,
Nathan et al.
JAMA 1992;
268:63

Diabetes Pandemic



HEALTH CARE BURDEN ASSOCIATED WITH DIABETES IN U.S.

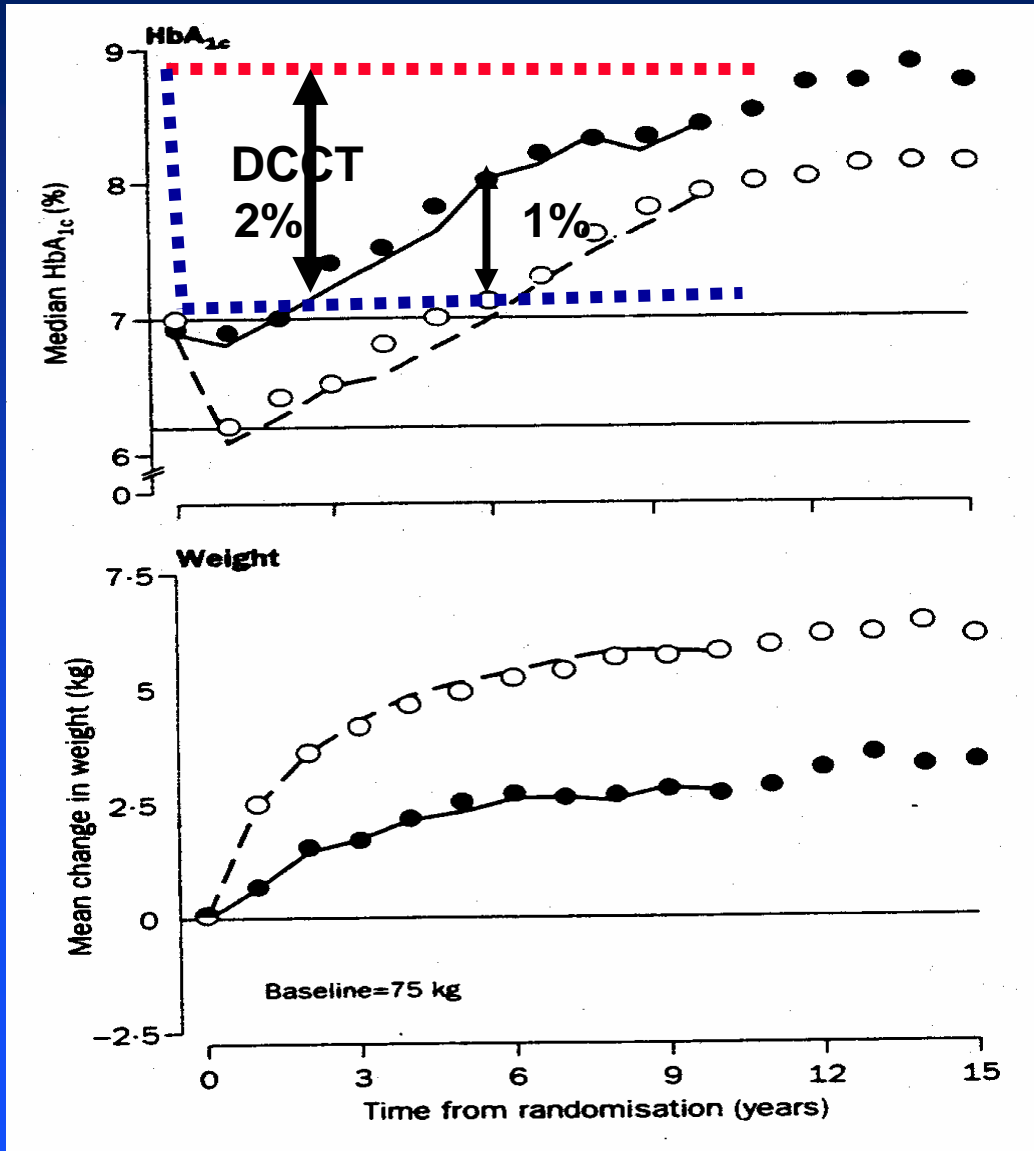
- Most common cause of ESRD in adults
- Most common cause of blindness
- Most common cause of amputations
- 2-5 fold increased risk for CVD

In the aggregate, costs attributed to diabetes total more than **\$176** billion dollars per year.*

*ADA, **2008**

UKPDS Results

Obese and non-obese treated with conventional vs insulin/sulphonylureas



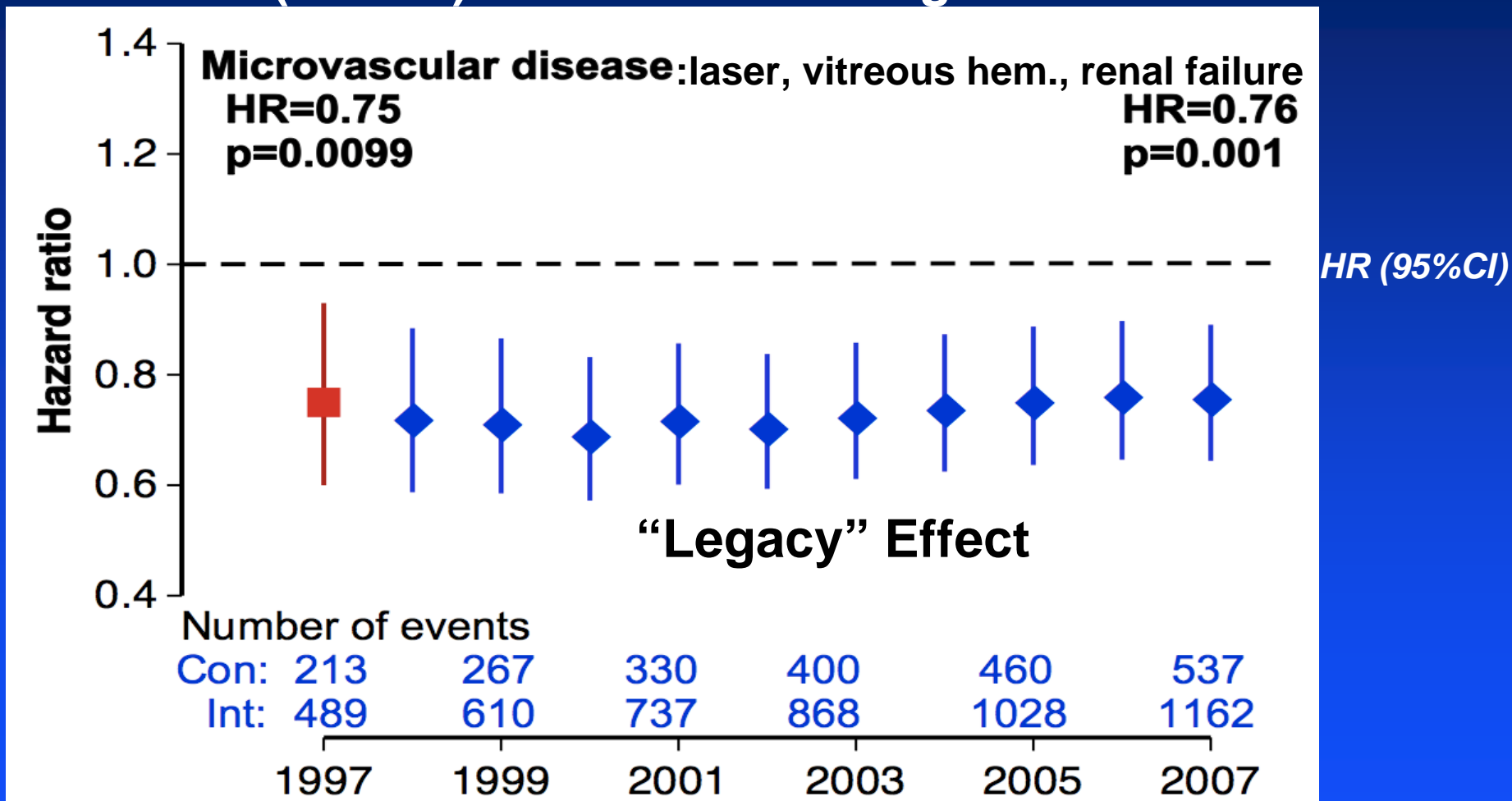
The worsening HbA_{1c} over time in type 2 diabetes, despite the addition of more medications, was due, in large part to progressive beta-cell failure

UKPDS
Lancet
1998;352; 837.

Microvascular Disease Hazard Ratio

UKPDS

Intensive (SU/Ins) vs. Conventional glucose control



Intensive Therapy of Type 2 Diabetes

Minimal hypoglycemia
Weight gain
No excess CVD
Effort
Expense

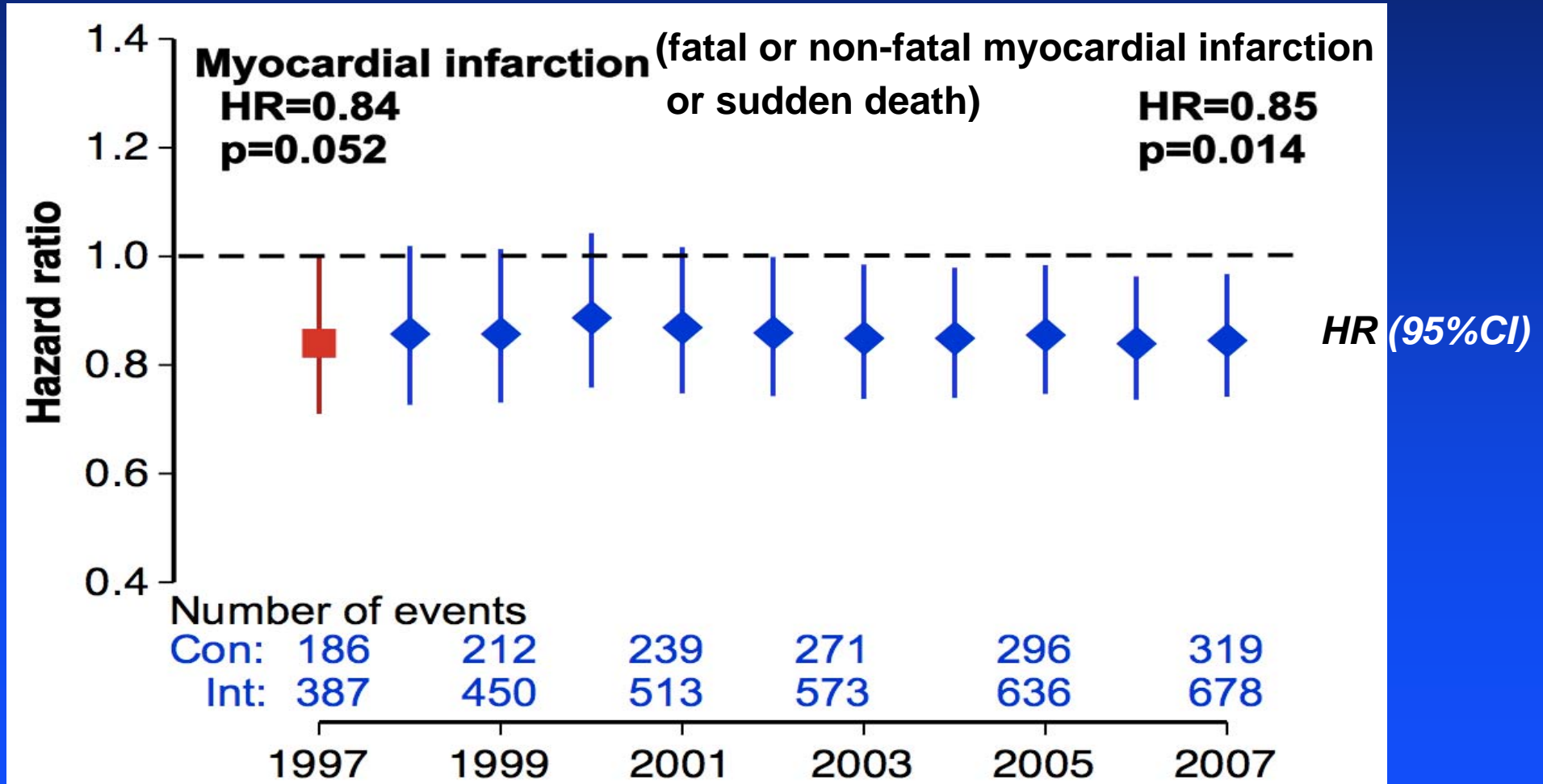
UKPDS
Kumamoto

Reduced
development and
progression of
microvascular
complications

Myocardial Infarction Hazard Ratio

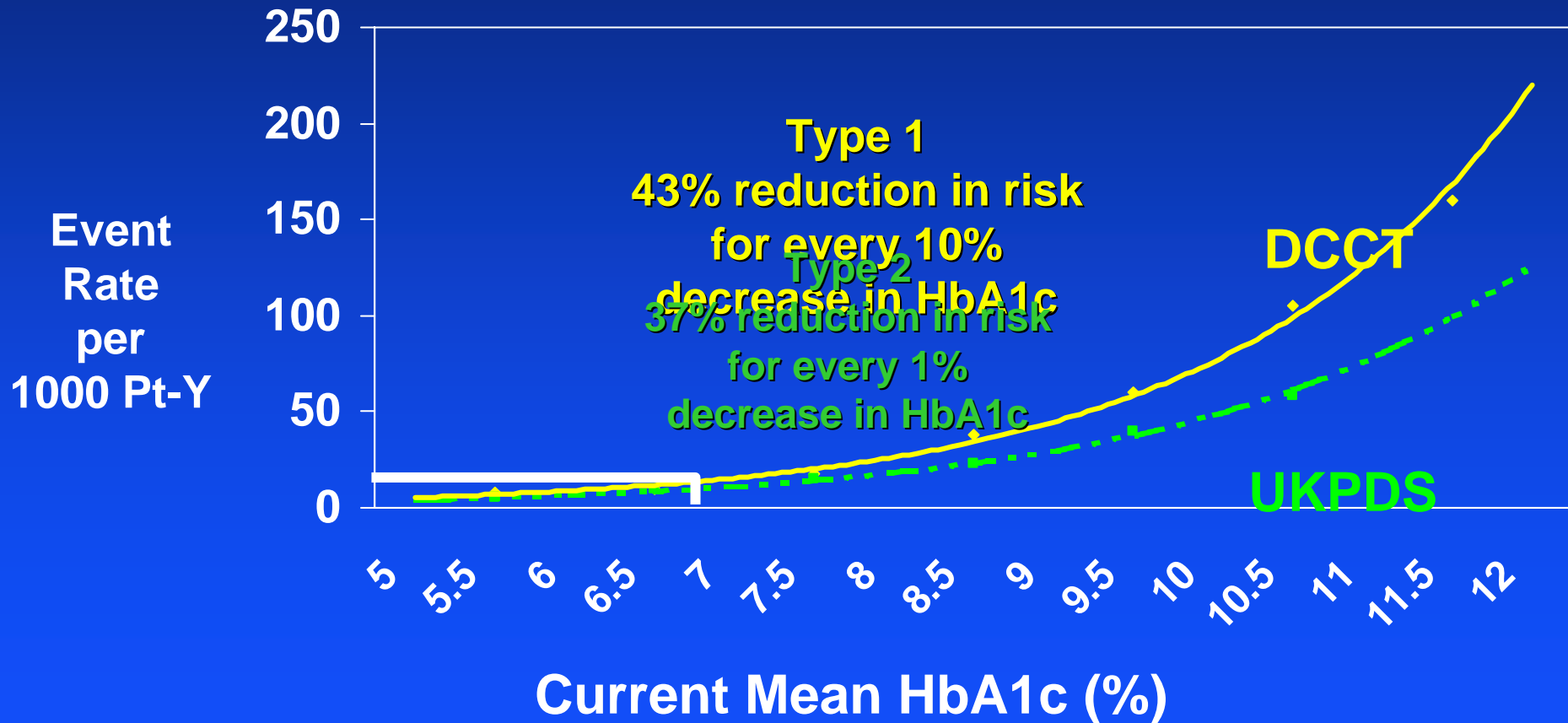
UKPDS

Intensive (SU/Ins) vs. Conventional glucose control



Relationship between Glycemia and Complications

DCCT and UKPDS



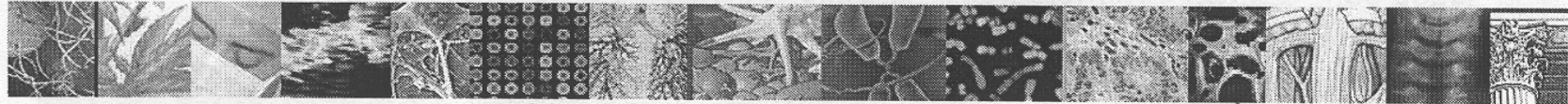
Current Treatment Goals

	Glucose-mg/dl (mmol/l)		
	<u>HbA1c</u>	<u>Pre-</u>	<u>Post-prandial</u>
• ADA	< 7.0	70-120 (3.9-6.7)	< 180 (10)
• AACE	< 6.5	≤ 110 (6.1)	< 140 (7.8)
• IDF -Europe	< 6.5	< 110 (6.1)	≤ 135 (7.5)

However

- Limited data in HbA1c range $< 7\%$, until recently
- Not clear if the increased expense, effort, and risk for hypoglycemia is merited by added benefit
- No data to support benefit of very tight control on CVD
 - ACCORD, ADVANCE, VADT
 - 30-year UKPDS follow-up shows benefit of 7.0 v 7.9%
- ACCORD suggests possible harm

How to Achieve Metabolic Goals of Therapy



The NEW ENGLAND JOURNAL *of* MEDICINE

Perspective
FEBRUARY 1, 2007

Finding New Treatments for Diabetes — How Many, How Fast . . . How Good?

David M. Nathan, M.D.

Two modern-day epidemics, HIV–AIDS and type 2 diabetes mellitus, have inspired impassioned calls for more effective interventions. In the 1980s, the rapid spread of HIV, with its associated severe,

er been faster. Nine classes of medications are now available for the treatment of type 2 diabetes, as compared with four barely a decade ago (see table).

Intensive Therapy of Type 2 Diabetes

Goal: Normoglycemia

Diet

Diet and exercise

Diet and sulfonylurea

Diet and **glinides**

9 classes of drugs

Diet and metformin

Diet and **α glycosidase inhibitor**

Diet and **thiazolidinedione**

Diet and insulin

Combinations

Insulin analogues

GLP analogues- exenatide (Byetta™)

Amylin analogues- pramlintide (Symilin™)

DPP IV inhibitors-sitagliptin (Januvia™)

Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

Update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

Diabetologia, Diabetes Care Jan. 2008

Diabetologia

2009; 52:17-30

Diabetes Care

2009;32:193-203

D. M. Nathan • J. B. Buse • M. B. Davidson •

E. Ferrannini • R. R. Holman • R. Sherwin • B. Zinman

Major Premises

Selection of Interventions

- **Effectiveness in lowering A1c- goal $<7\%$**
 - Use more effective drugs if initial A1c higher
 - Can use less effective medications if A1c < 8.5
- **Safety**
- **Side-effects, tolerability/acceptance**
- **Other characteristics, effect (s) on**
 - Weight
 - CVD risk factors
 - Beta-cell preservation
- **Cost**

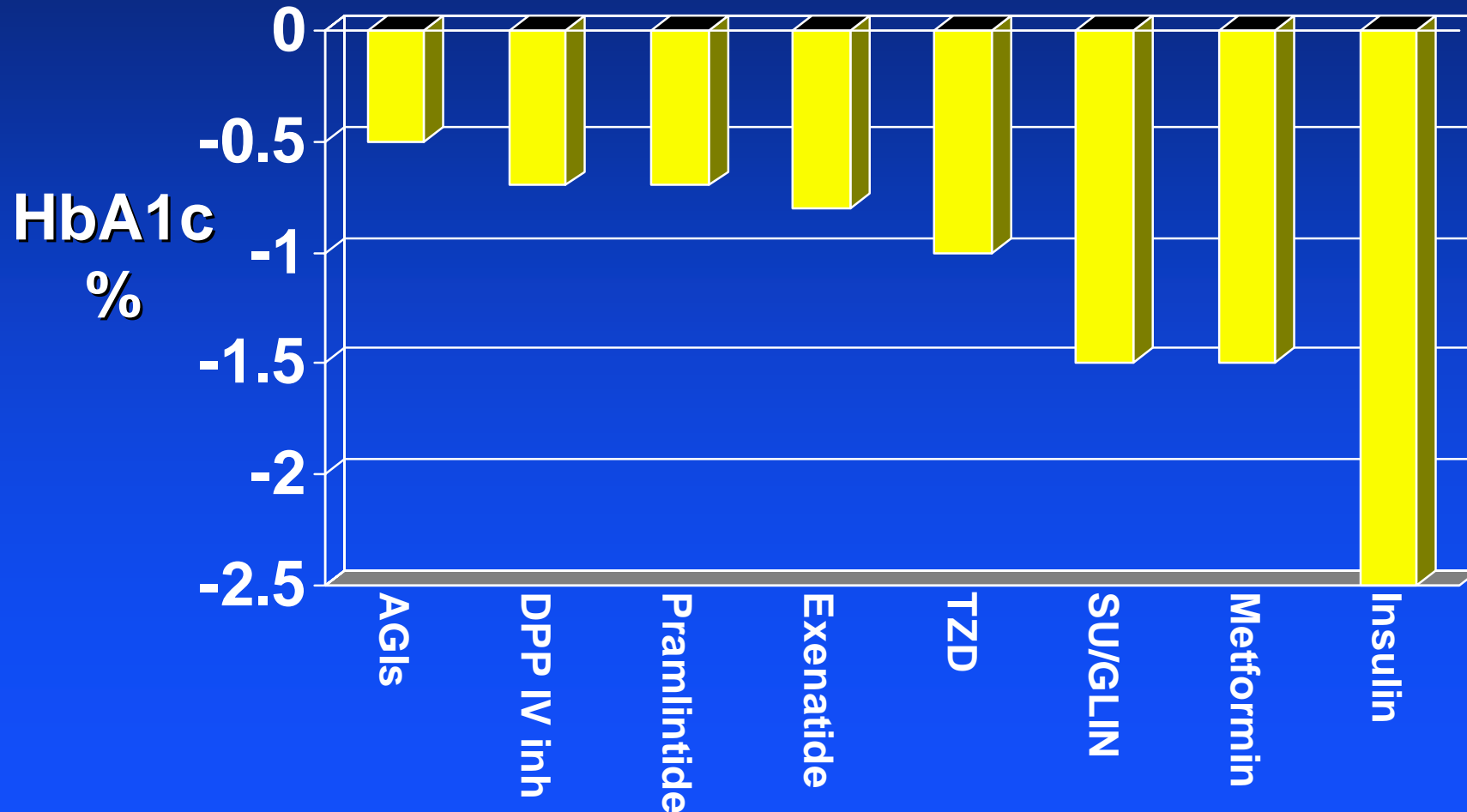
Treatment of Type 2 Diabetes

Choice of Agents

- No convincing data that any class of agents is superior to another in reducing microvascular complications beyond their efficacy in lowering HbA1c
- Check HbA1c every 3 months and if $\text{HbA1c} \geq 7\%$, go to next step

Relative Merits of Hypoglycemic Agents

Decrease in HbA1c: Potency of Monotherapy



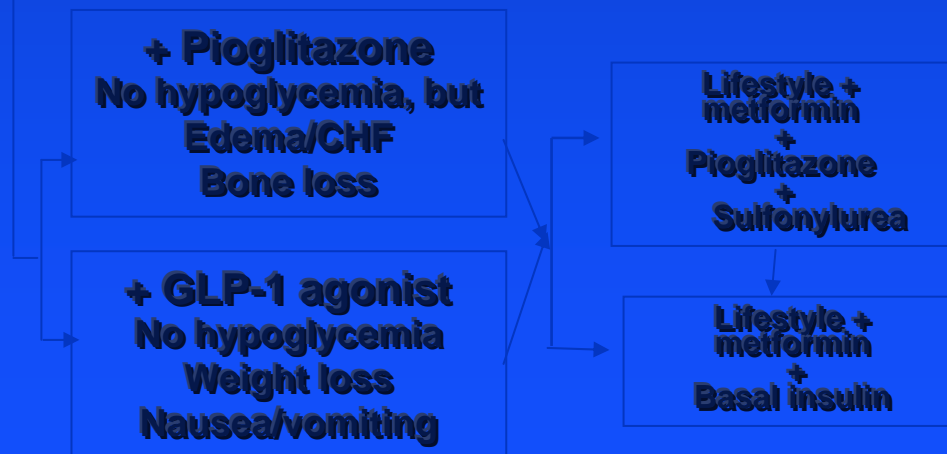
Consensus algorithm-2009

Tier 1: Well-validated core therapies



Tier 2:

Less well-validated therapies



Step One- Metformin + Lifestyle

- **Recognizes failure of life-style alone**
- **Inhibits hepatic glucose output- predominantly lowers fasting glycemia**
- **Cellular mechanism unknown (AMP kinase)**
- **Lowers HbA1c by ~1.5%**
- **Effective in obese and non-obese patients and in preventing diabetes in pre-diabetics (DPP)**
- **Glucophage off-patent, very inexpensive**

Intensive Therapy of Type 2 Diabetes

Lifestyle: Diet and Exercise

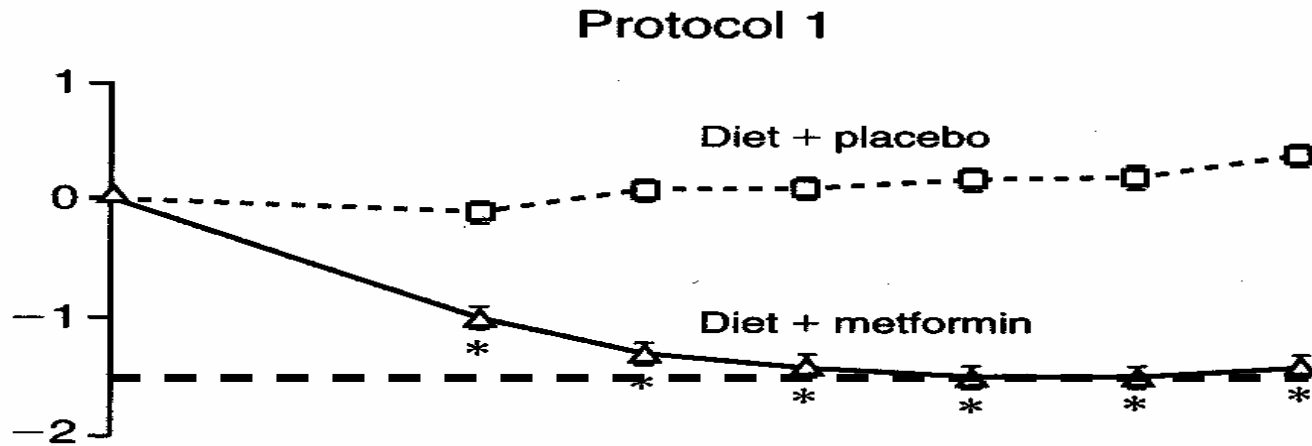
- **Highly effective in short term**
- **5-10 lb weight loss usually sufficient to ameliorate hyperglycemia**
- **Long-term benefit parallels results of obesity therapy**

First Step- Metformin + Lifestyle

- Recognizes failure of life-style alone
- Inhibits hepatic glucose output- predominantly lowers fasting glycemia
- Cellular mechanism unknown (AMP kinase)
- Lowers HbA1c by ~1.5%
- Effective in obese and non-obese patients and in preventing diabetes in pre-diabetics (DPP)
- Extremely safe, generally well-tolerated
- Glucophage off-patent, very inexpensive

Metformin

Change in Glycosylated Hemoglobin Values (percentage points)



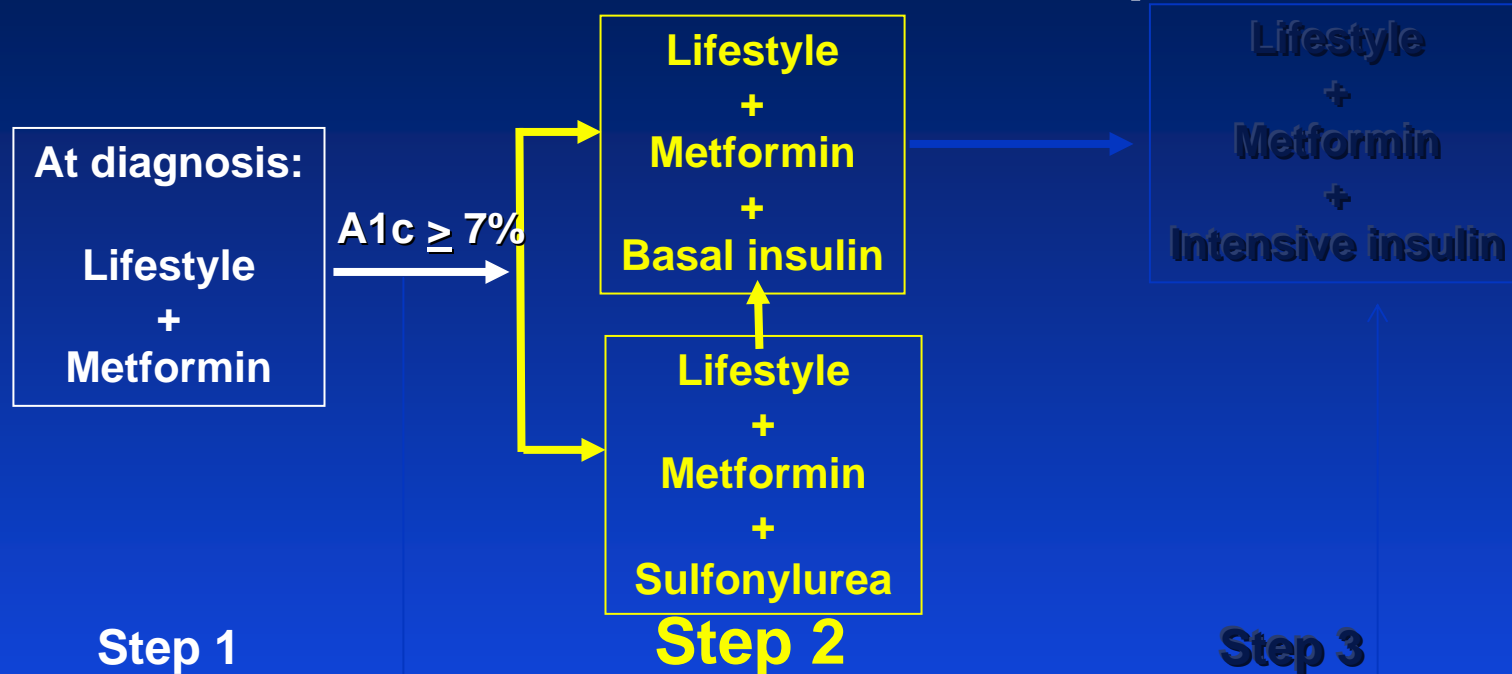
DeFronzo
NEJM
1995;333:541

Step Two

Adding to Lifestyle and Metformin

Consensus algorithm-2009

Tier 1: Well-validated core therapies



Tier 2:

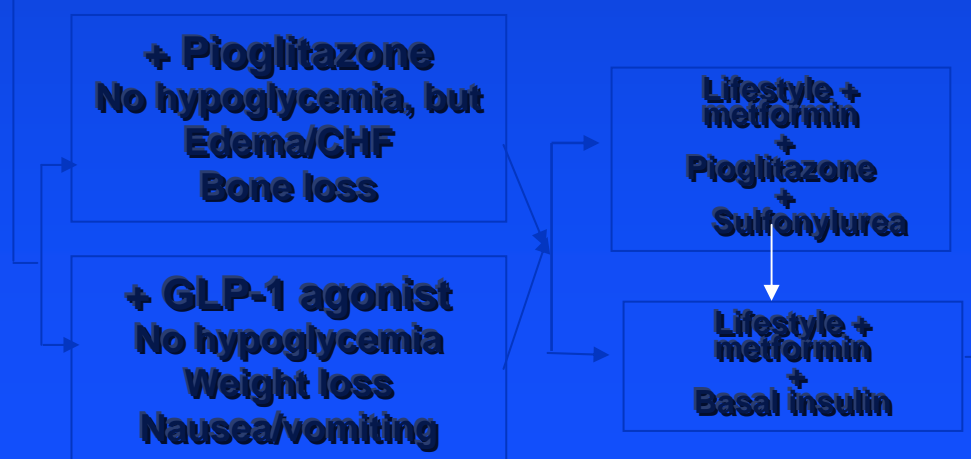
Less well-validated therapies

+ Pioglitazone
No hypoglycemia, but
Edema/CHF
Bone loss

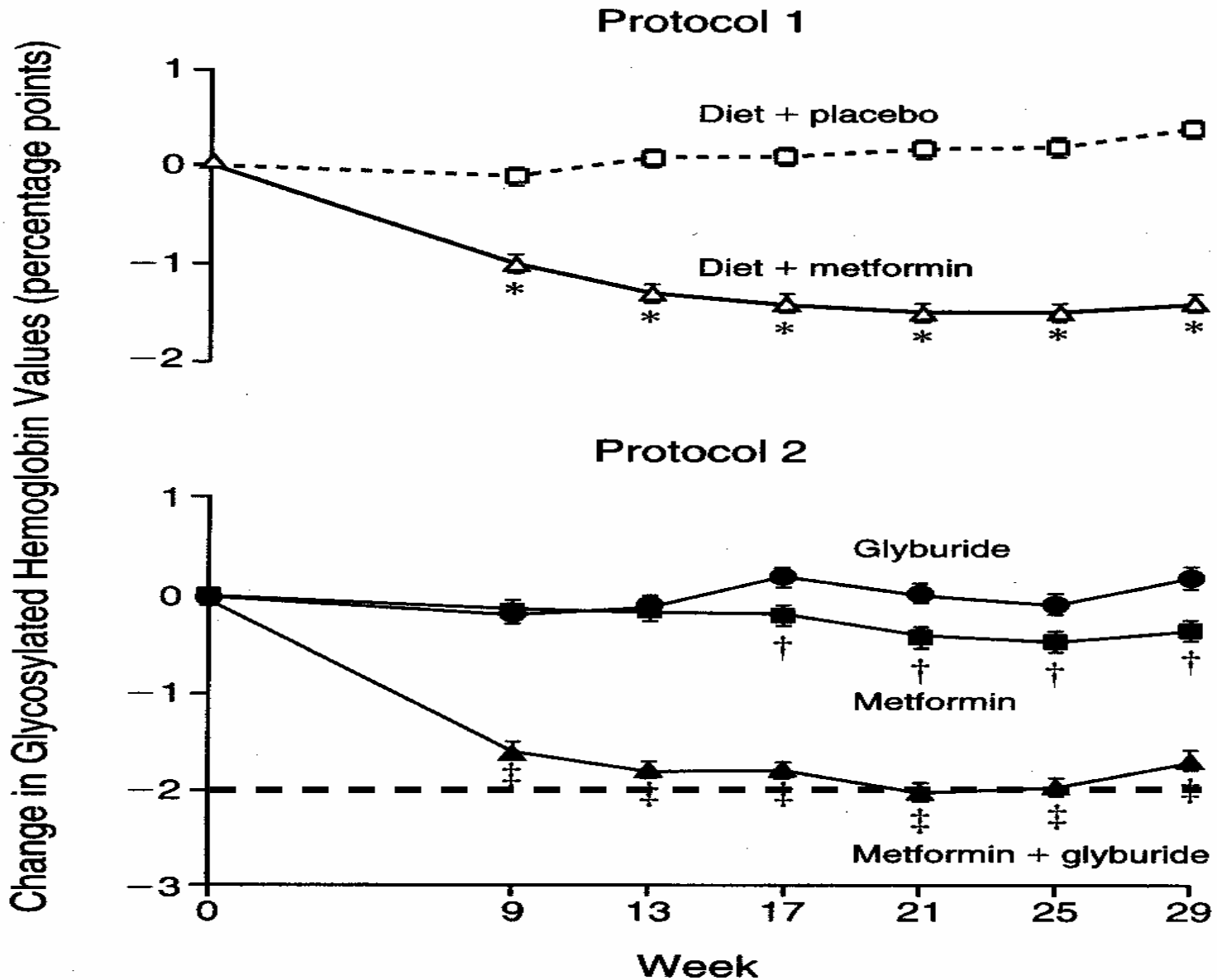
+ GLP-1 agonist
No hypoglycemia
Weight loss
Nausea/vomiting

Lifestyle +
metformin
+
Pioglitazone
+
Sulfonylurea

Lifestyle +
metformin
+
Basal insulin



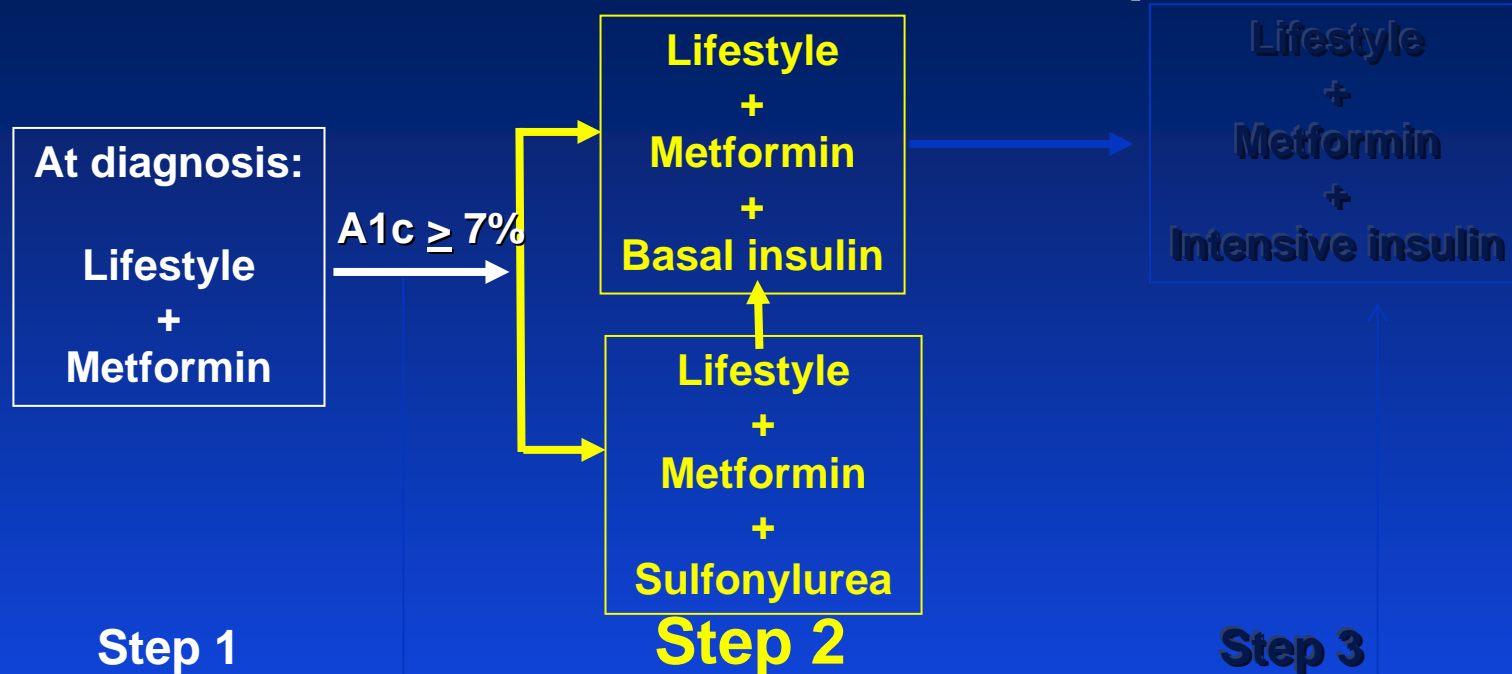
Metformin



DeFronzo
NEJM
1995;333:541

Consensus algorithm-2009

Tier 1: Well-validated core therapies



Tier 2:

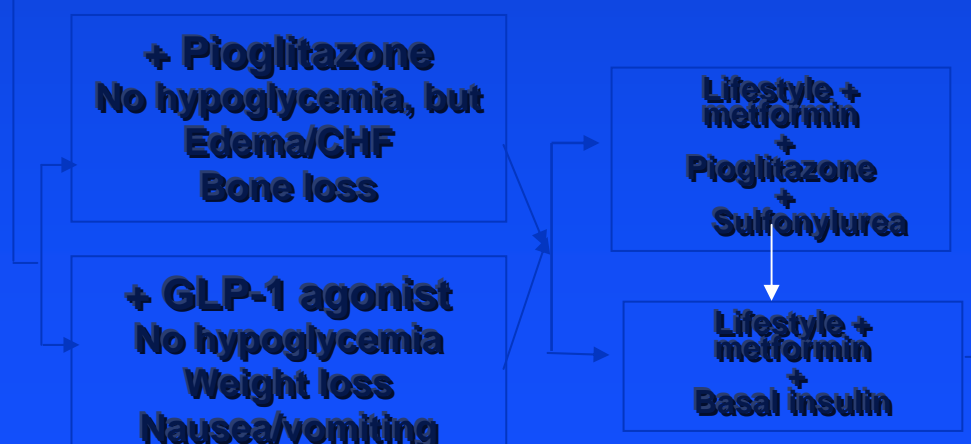
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Lifestyle +
metformin
+
Pioglitazone
+
Sulfonylurea

Lifestyle +
metformin
+
Basal insulin



Insulin Therapy

Morning

- Intermediate-acting
- Long-acting
- Intermediate or long-acting plus rapid or very rapid acting or pre-mixed

Bedtime

- Intermediate
- Long-acting

Twice per day

- Morning mixed and bedtime intermediate
- Morning and pre-dinner mixed

Multiple daily injection

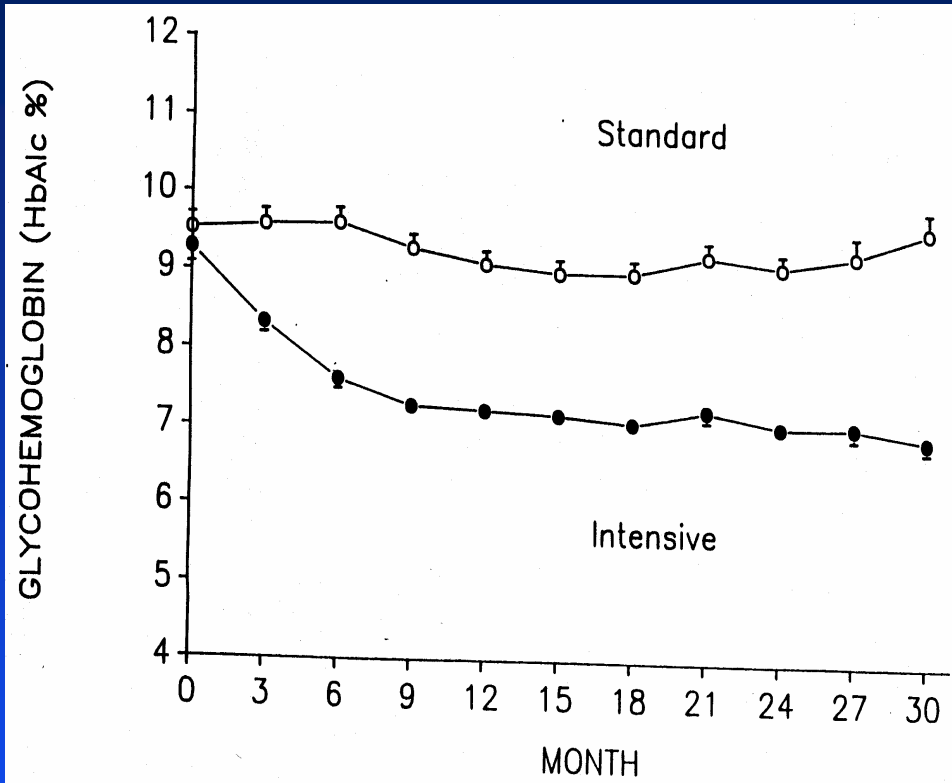
Pumps- external, implantable

Rectal

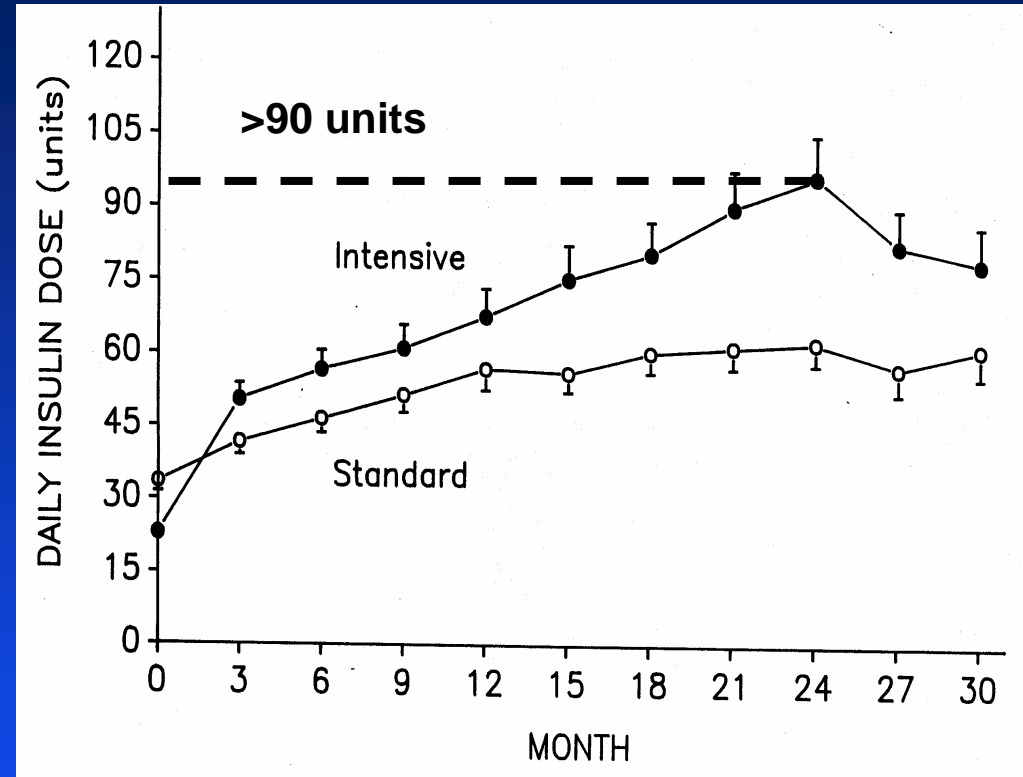
Nasal

Inhaled

Insulin Therapy



HbA1c



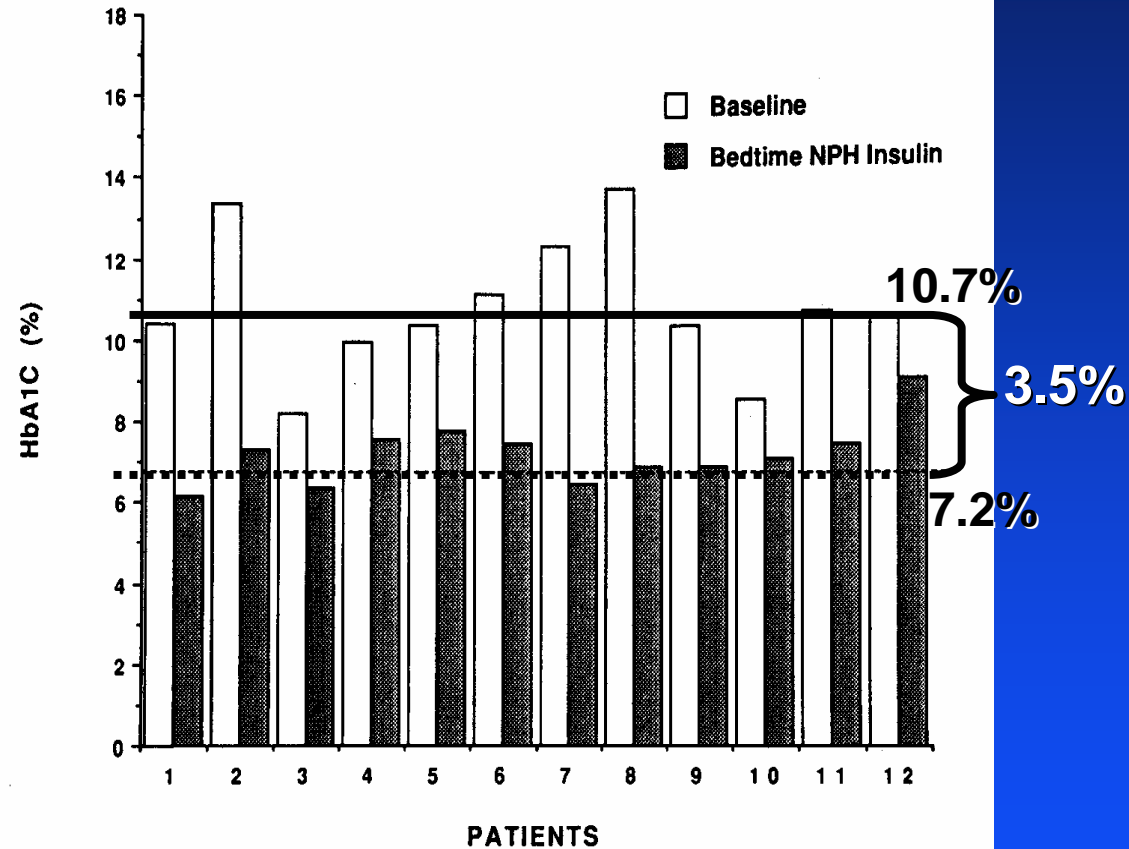
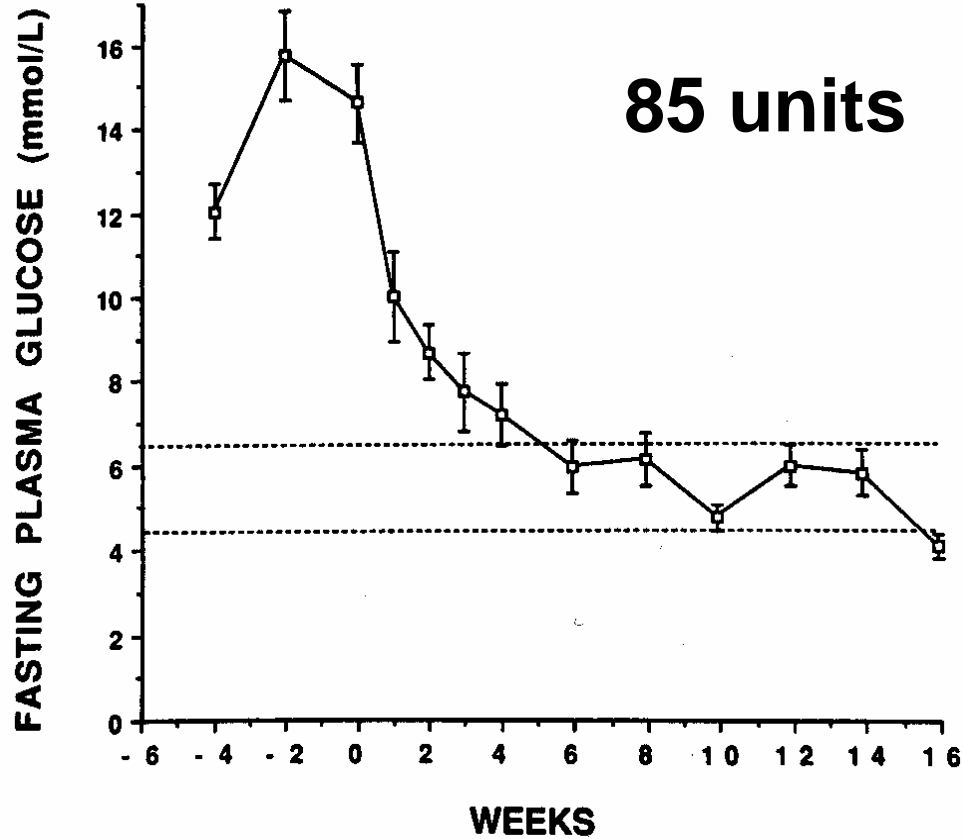
Insulin dose

153 Type 2 diabetic men
Mean age 60

VA Cooperative Study
Diabetes Care 1995;18:1113

Insulin Therapy of Type 2 DM

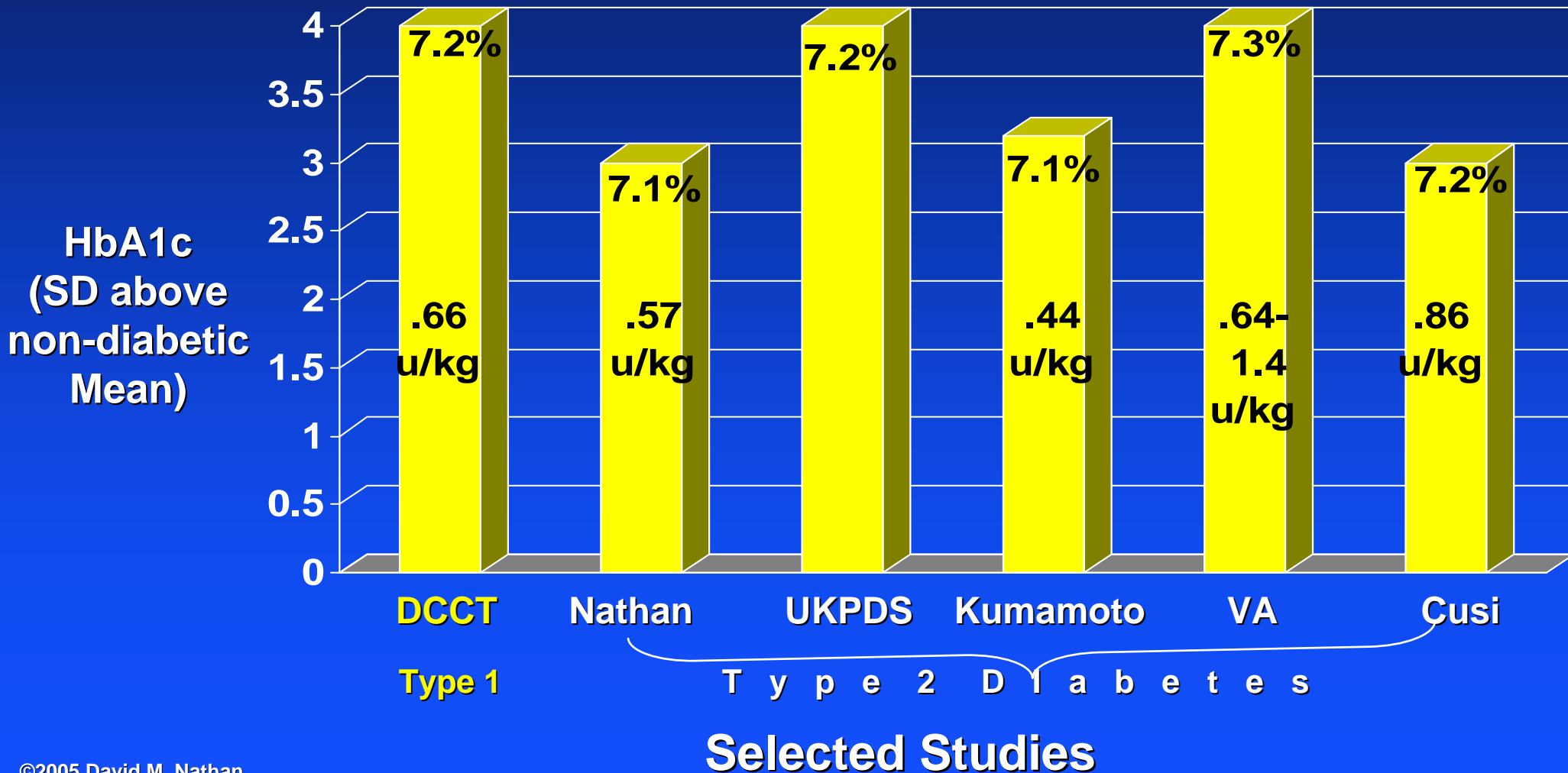
Bedtime NPH



Cusi et al. Diabetes Care
1995;18: 843

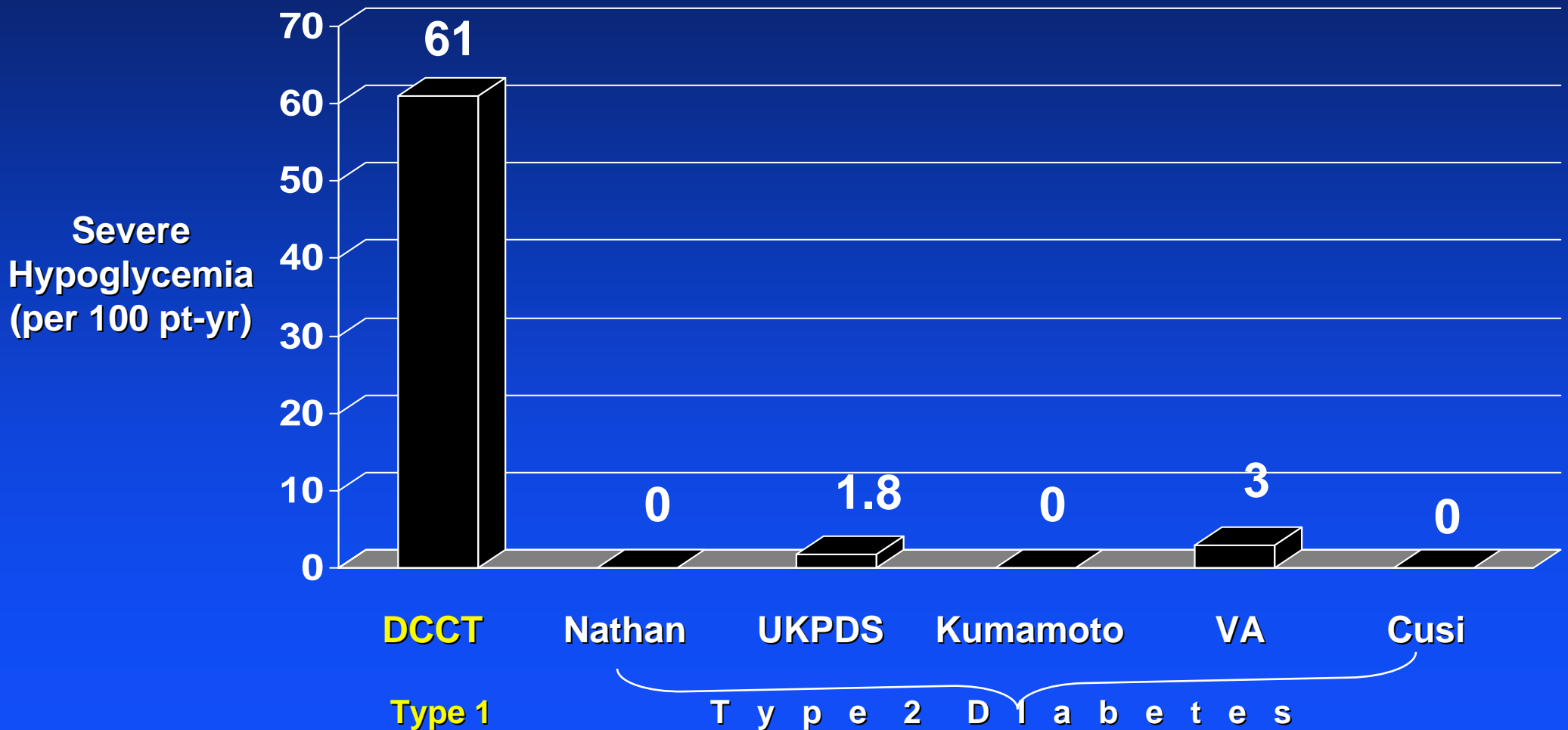
Results of Insulin Therapy with Insulin Monotherapy

Glycemia



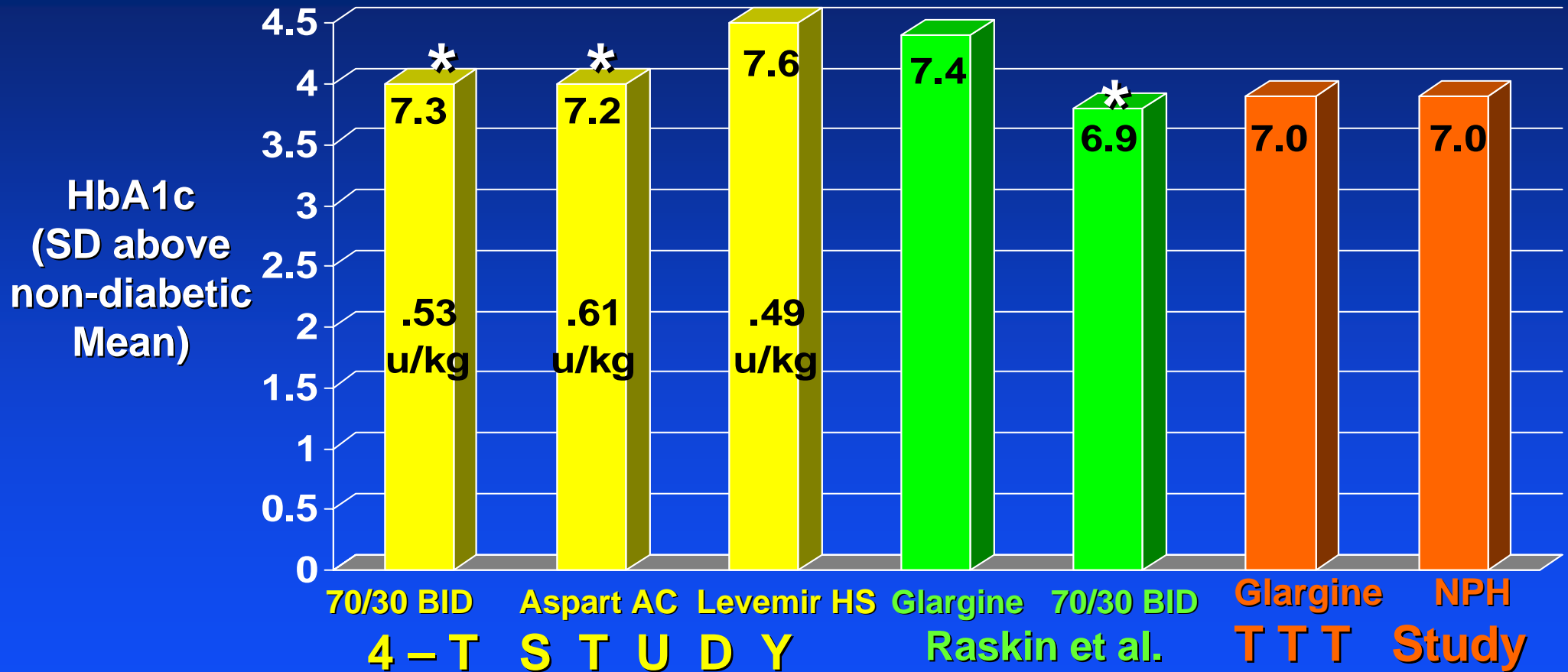
Results of Intensive Insulin Therapy with Insulin Monotherapy

Hypoglycemia



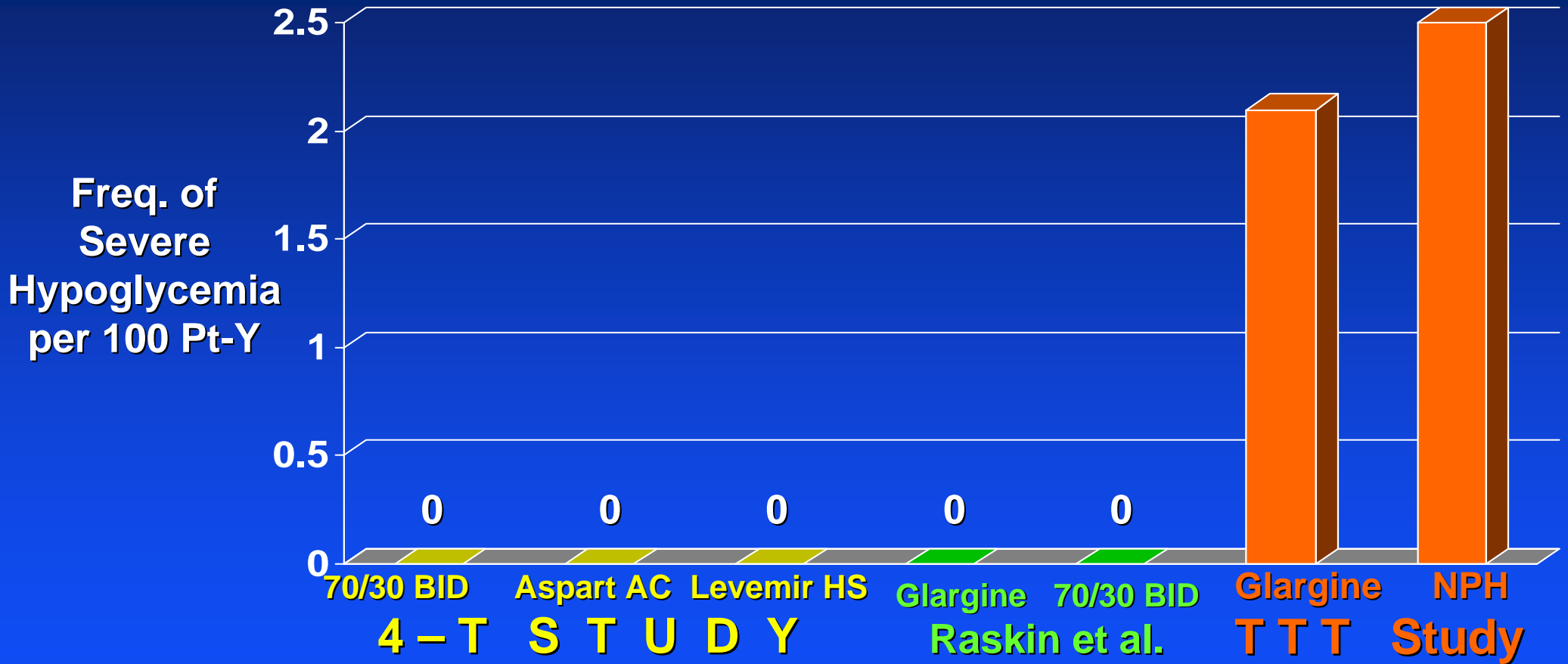
Results of Intensive Insulin Therapy with Metformin

Combination Therapy: Glycemia



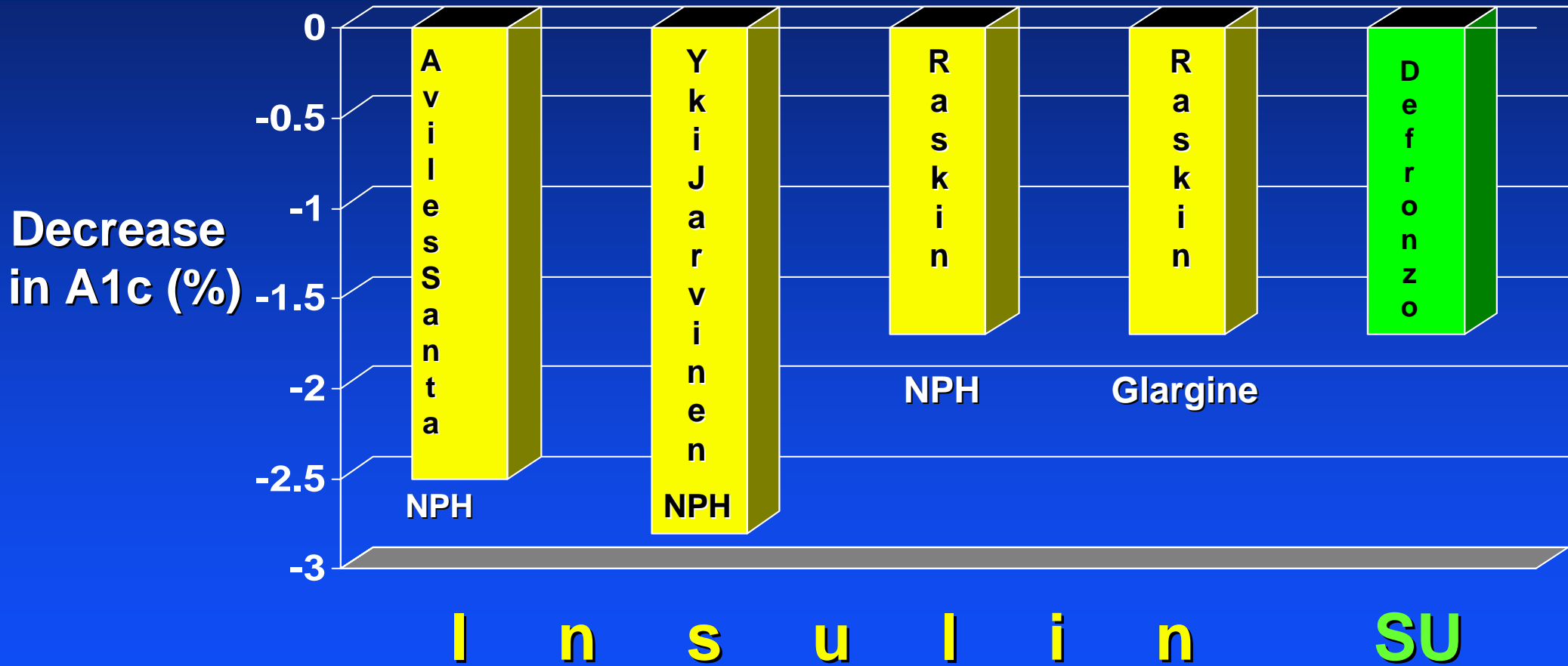
Results of Insulin Therapy with Metformin

Severe Hypoglycemia



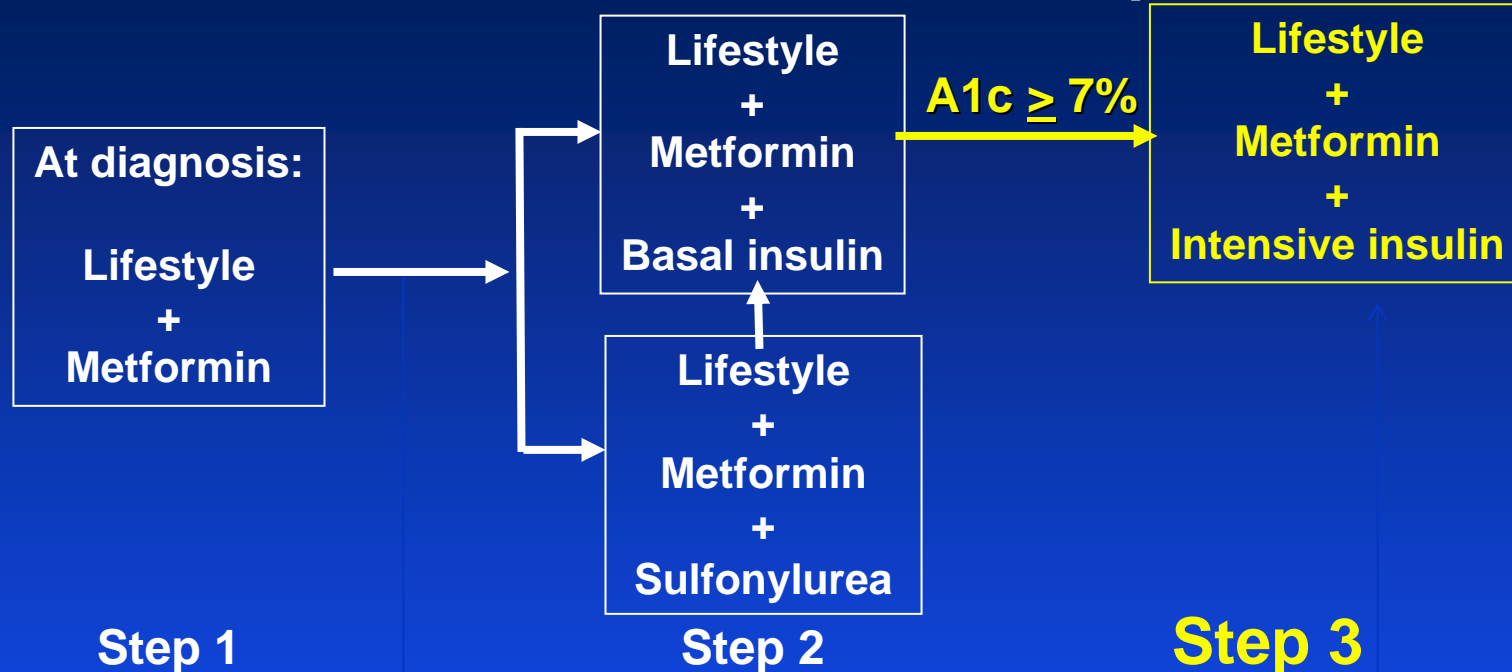
Results of Metformin Plus Other Therapy

Second Step



Consensus algorithm-2009

Tier 1: Well-validated core therapies



Tier 2:

Less well-validated therapies

+ Pioglitazone
No hypoglycemia, but
Edema/CHF
Bone loss

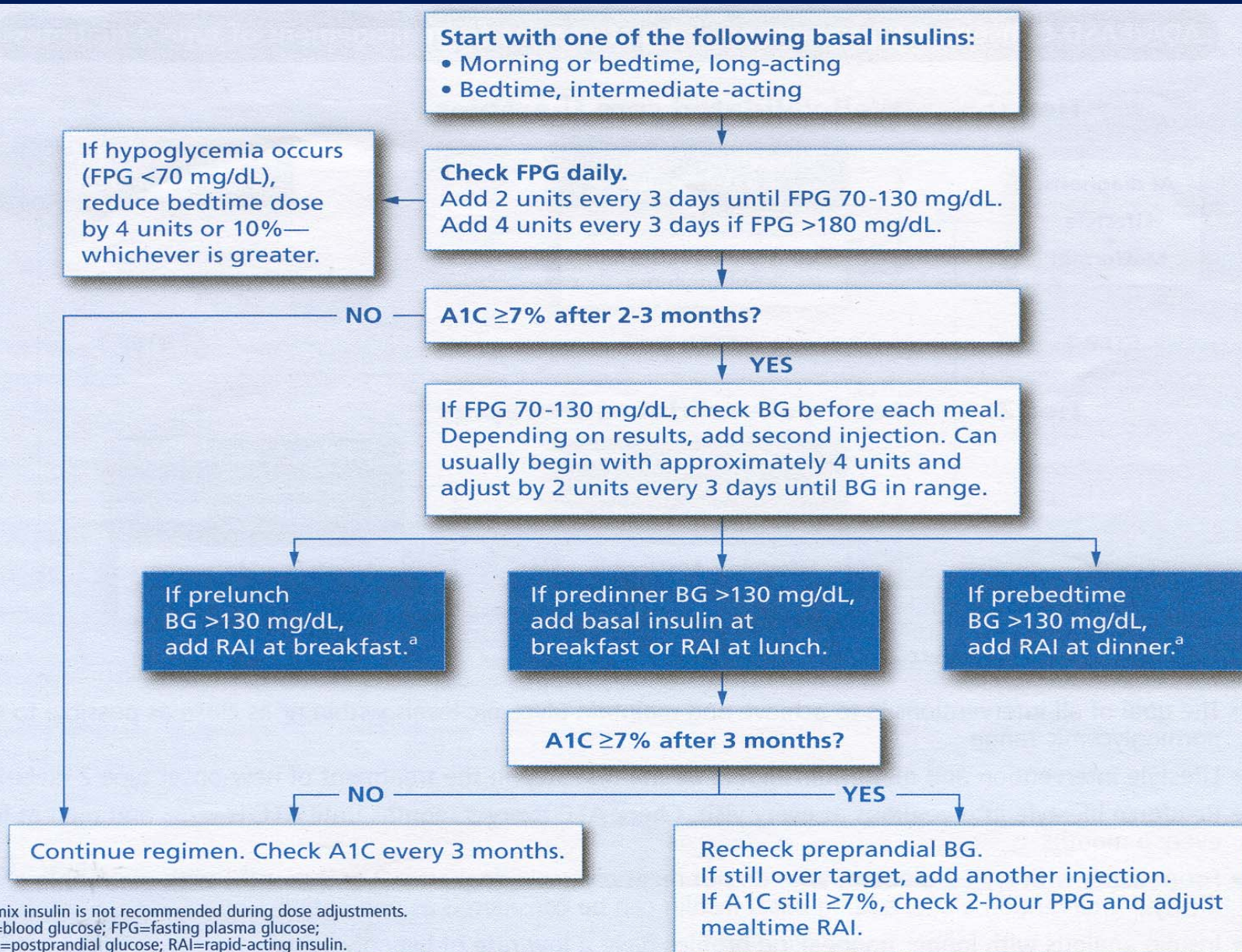
+ GLP-1 agonist
No hypoglycemia
Weight loss
Nausea/vomiting

Lifestyle +
metformin
+
Pioglitazone
+
Sulfonylurea

Lifestyle +
metformin
+
Basal insulin

Consensus algorithm: Initiation and adjustment of insulin

Diabetologia
2009; 52:17-30
Diabetes Care
2009;32:193-203



^aPremix insulin is not recommended during dose adjustments.
BG=blood glucose; FPG=fasting plasma glucose;
PPG=postprandial glucose; RAI=rapid-acting insulin.
Consider each patient's lifestyle and meal schedule when developing an insulin regimen.
Adapted from Nathan et al.¹

Consensus algorithm-2009

Tier 1: Well-validated core therapies



Step 1

Step 2

Step 3

Tier 2:

Less well-validated therapies

+ Pioglitazone
No hypoglycemia, but
Edema/CHF
Bone loss

+ GLP-1 agonist
No hypoglycemia
Weight loss
Nausea/vomiting

Lifestyle, +
metformin
+
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Lifestyle +
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Basal insulin

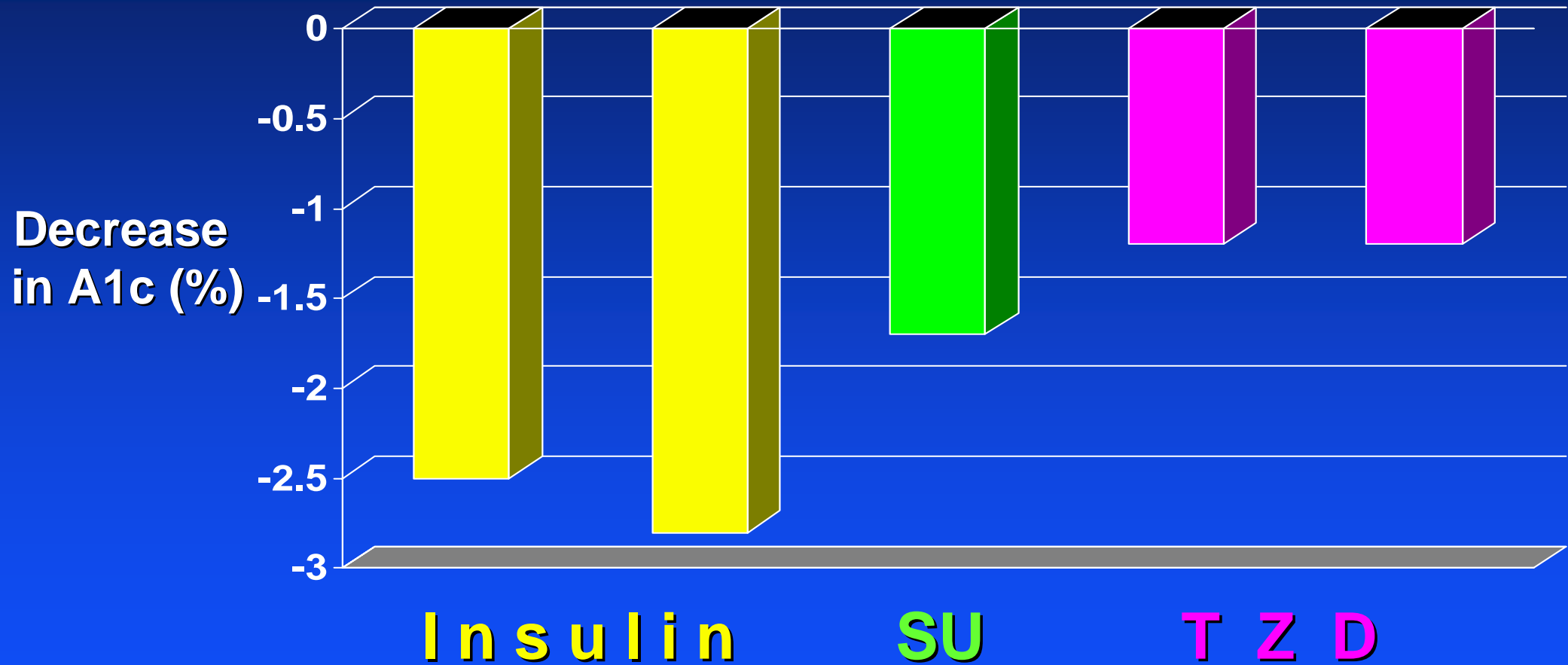
Intensive Therapy of Type 2 diabetes

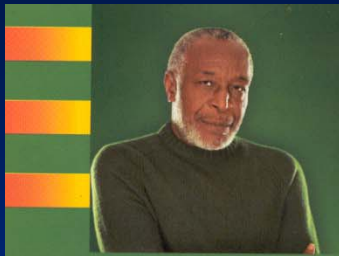
Thiazolidinediones

- Relatively weak as monotherapy
- More potent in combination with insulin, metformin, or sulfonylurea/glitinide
- Generally well tolerated- edema, CHF, bone loss
- Liver function monitoring no longer obligatory
- Rosiglitazone and pioglitazone available
- Pioglitazone has better lipid effects
- Concern regarding CVD with rosi. - meta-analysis
- No long-term, reliable data

Results of Metformin Plus Other Therapy

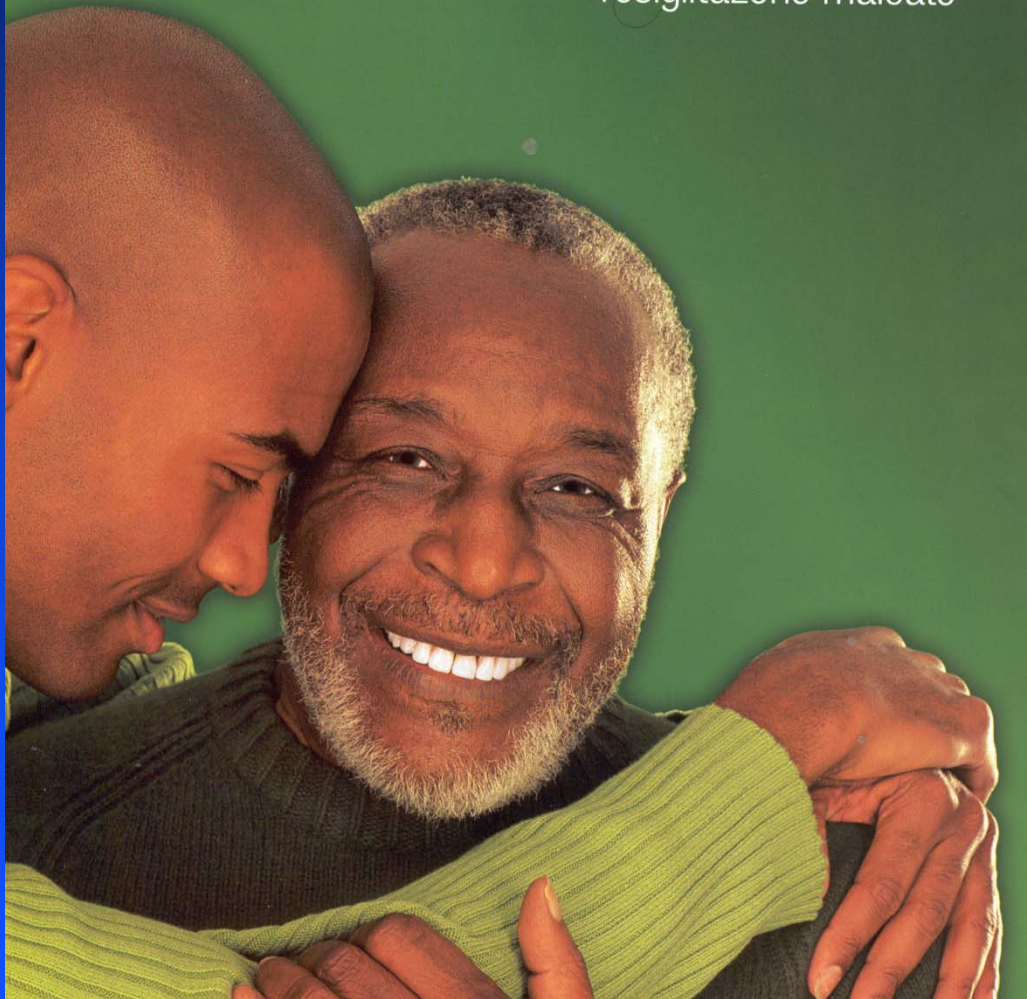
Second Step





The 20th century brought him type 2 diabetes...
...The 21st century gave him

Insulin-sensitizing
Avandia[®]
rosiglitazone maleate



VOLUME 271
NUMBER 142

50 cents
75 cents beyond
30 miles from Boston

The Boston Globe

TUESDAY, MAY 22, 2007

2007
The Boston Globe
GLOBE
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The best of
Massachusetts
business

SPECIAL MAGAZINE

Yankees
cool off
Red Sox,
6-2

SPORTS

Diabetes drug said to raise risk of heart attack

Maker defends safety,
calls findings flawed

REACHING THE HEIGHTS



T JOURNAL.

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MEDICAL DETECTIVE

Sequel for Vioxx Critic: Attack on Diabetes Pill

*Glaxo Shares Plunge
As Dr. Nissen Sees Risk
To Heart From Avandia*

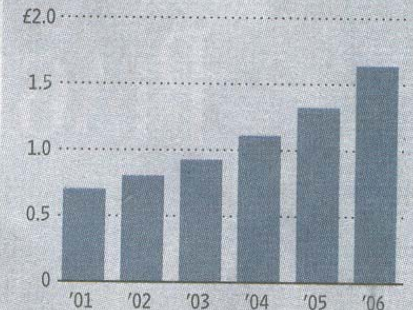
By ANNA WILDE MATHEWS

An analysis linking the widely used diabetes drug Avandia to higher risk of heart attacks represents a serious blow to GlaxoSmithKline PLC and underscores how outside critics have been empowered to challenge big-selling drugs after the outcry over the withdrawn painkiller Vioxx.

Glaxo rang up
more than \$3 billion in world-wide
sales of Avandia

Drug in Demand

Sales of GlaxoSmithKline's Avandia,
in billions of pounds:



Note: £1 = \$1.97 at the current rate; includes sales of Avandamet and Avandaryl

Source: the company

EDITORIAL



Rosiglitazone and Cardiotoxicity — Weighing the Evidence

David M. Nathan, M.D.

“The jury may still be out with regard to the cardiotoxicity of rosiglitazone, but when it comes to patient safety, ‘first, do no harm’ outweighs any presumption of innocence”.

NEJM
E-published
June 5, 2007

New Drugs

Byetta

- Exenatide
- GLP-1 receptor agonist
- Similar to exenatide
 - Similar to exenatide
 - Similar to exenatide
 - Different
 - More
 - Greater

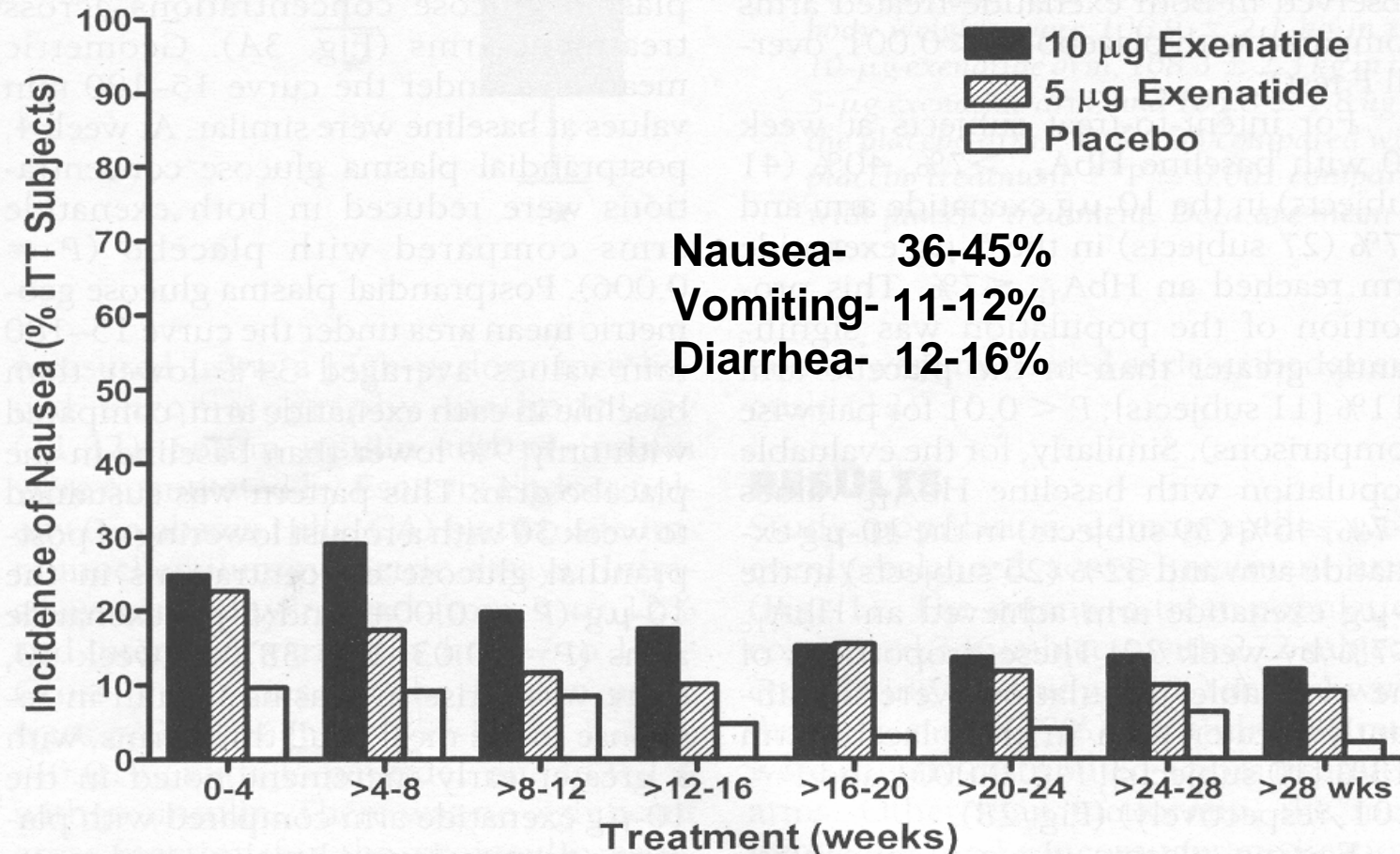


Gila

New Drugs

Byetta

30 week CCT
in metformin
failures (n=336)
19% loss to f/u.
BMI- 34 kg/m²
HbA1c- 8.2%
Inactive placebo
Injected BID



DeFronzo et al.
Diabetes Care
2005;28:1092



BYETTA secondary

- Across there w 1.2% a
- Patient experie A1C at

BYETTA is inc control in patie metformin, a su metformin and thiazolidinedio

Important Saf

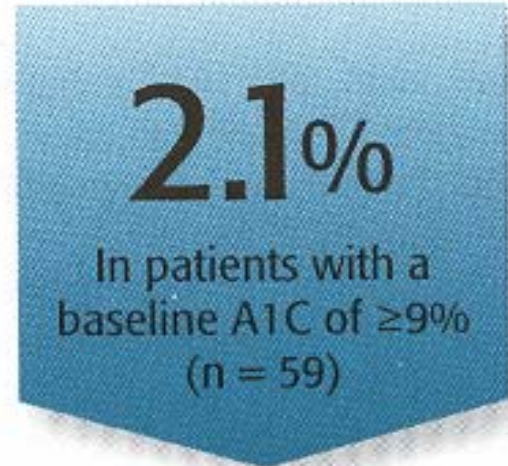
BYETTA is no patients, and s or for the treat

Patients should hypersensitivity

BYETTA is no renal disease, s disease. The de treated with B¹ warning sign of

Patients receiving BYETTA concomitantly with a sulfonylurea had an increased risk of hypoglycemia.

Reference: 1. Data on file, Amylin Pharmaceuticals, Inc. and Eli Lilly and Company. 02-07-4432-A The BYETTA mark and BYETTA design mark are trademarks of Amylin Pharmaceuticals, Inc.



A1C reduction*¹
(Change from baseline)

n*¹
(endpoint)

r 10 mcg,
5 mcg or
IA 10 mcg BID
Note: all values

EA
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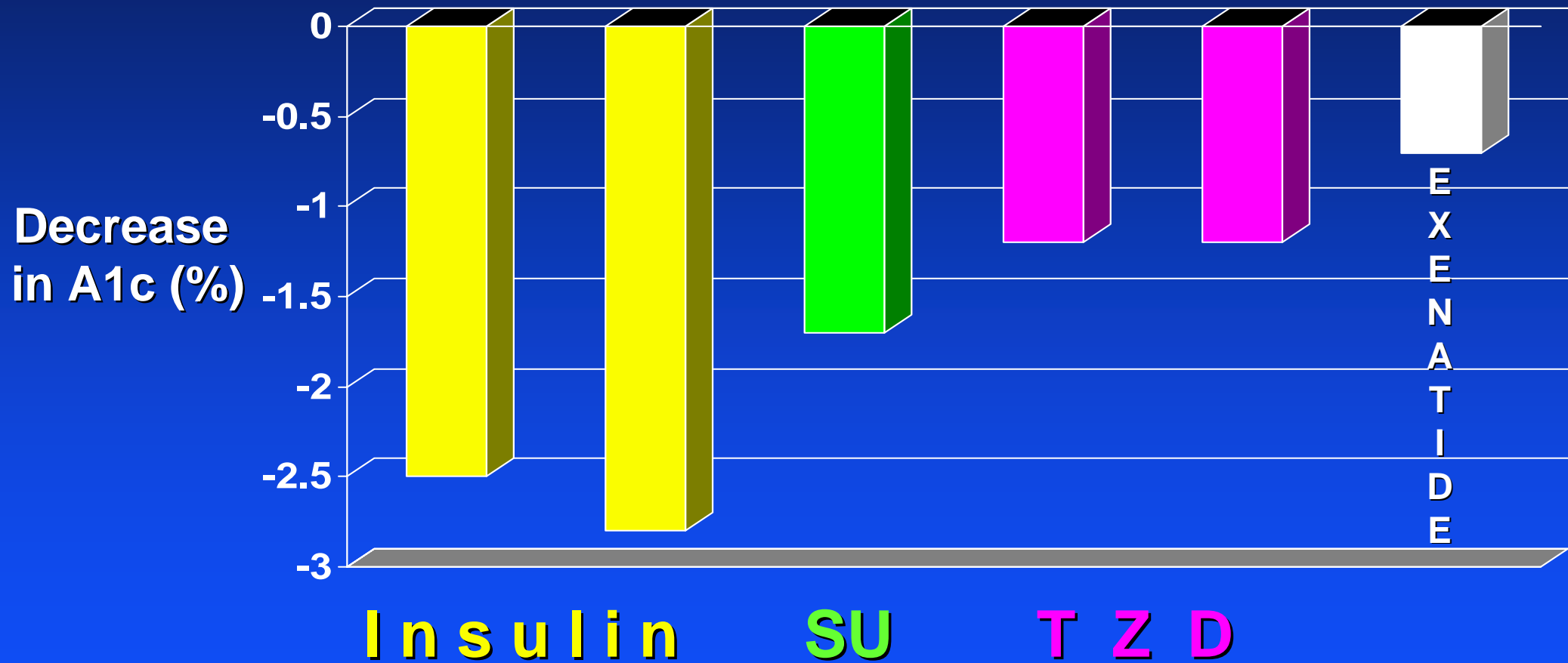
ng oral
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Results of Metformin Plus Other Therapy

Second Step



Why didn't we include the other newer approved medications in the Type 2 diabetes algorithm?

Reasons Newer Medications Not Chosen

- **Comparable or lower effectiveness in lowering glycemia than older drugs**
 - alpha-glucosidase inhibitors, amylin analogues, DPP 4 inhibitors
- **Side-effects**
 - α GI- GI
 - GLP analogues- GI
 - Amylin- GI
- **Experience- limited for all**
- **Cost- higher than for generics**

First in a new class for type 2 diabetes: The breakthrough of DPP-4* inhibition



Enhancing physiology

Enhancing control

- Powerful A1C reductions as monotherapy

- One tablet, once daily, proven to deliver 24-hour glycemic control

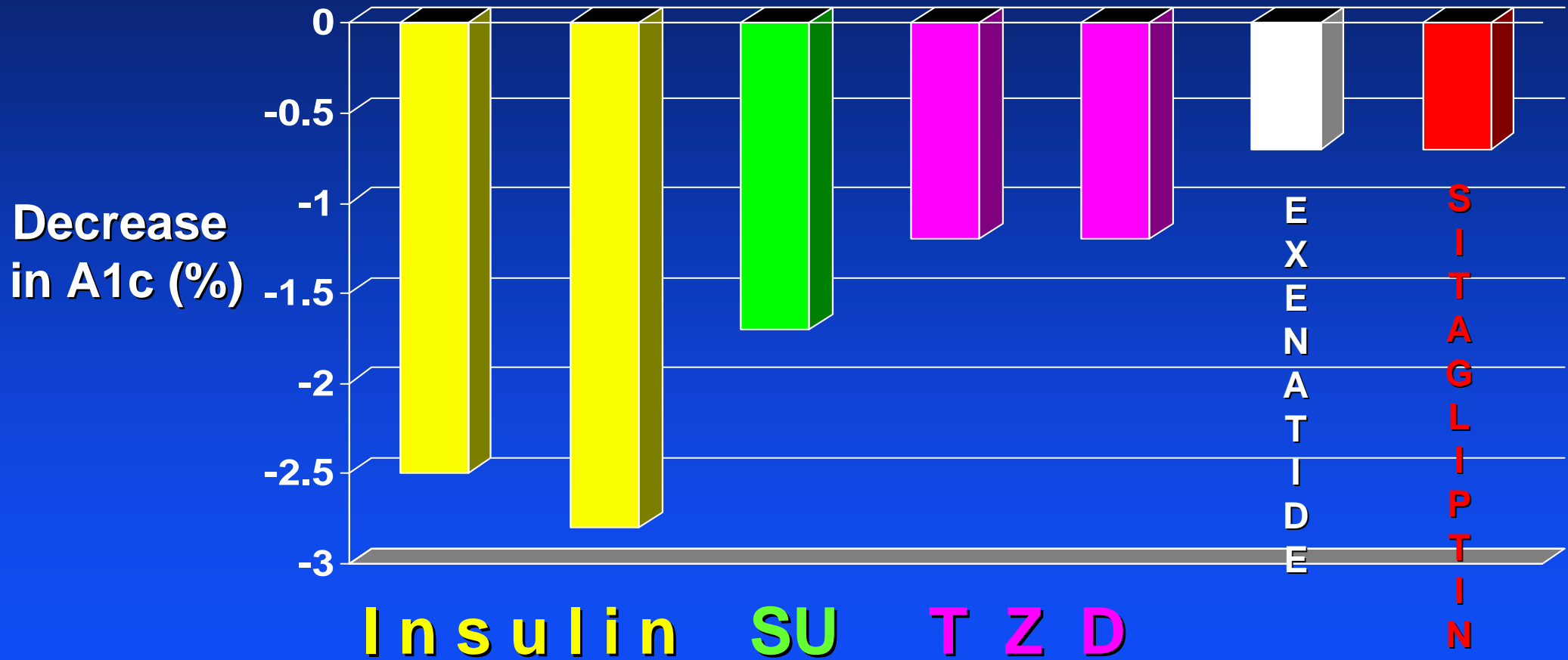
Introducing

NEW ONCE-DAILY
Januvia[™]
(sitagliptin) tablets

* Dipeptidyl peptidase-4.

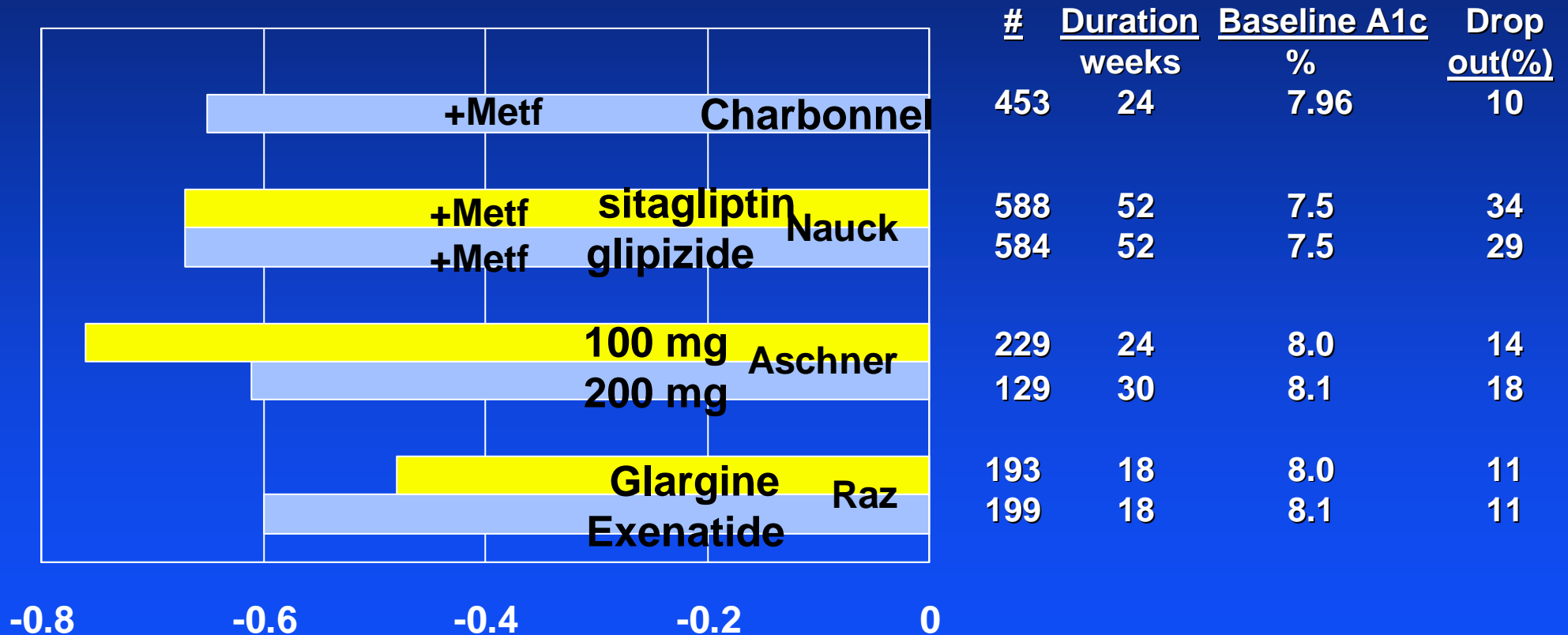
Results of Metformin Plus Other Therapy

Second Step



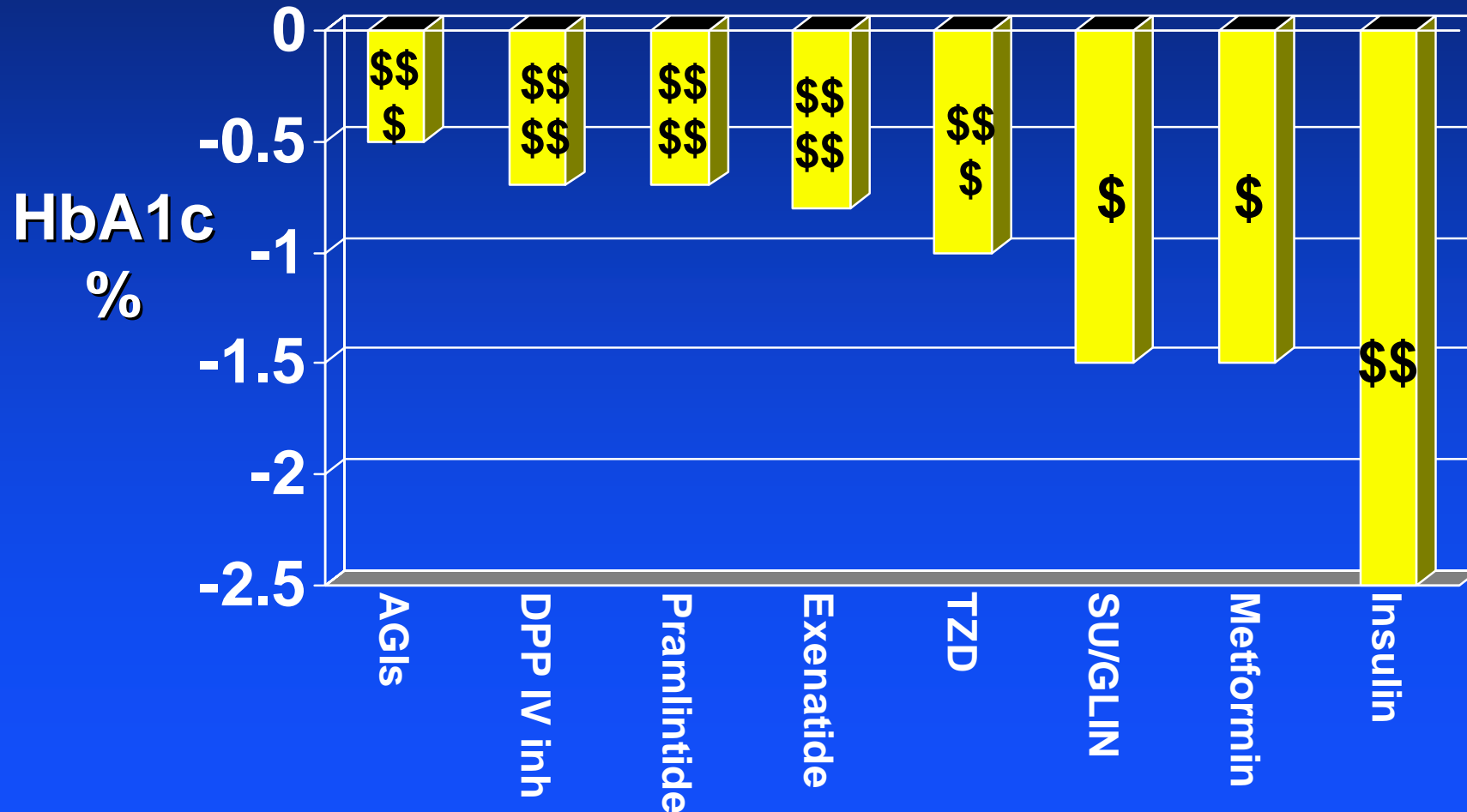
Efficacy of New Drugs

Decrease A1c from Baseline: Sitagliptin



Relative Merits of Hypoglycemic Agents

Decrease in HbA1c: Potency of Monotherapy



Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

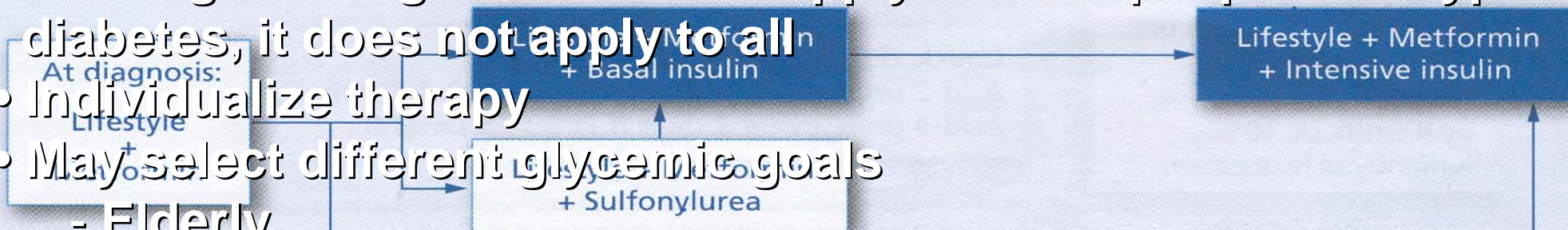
D. M. Nathan · J. B. Buse · M. B. Davidson ·
E. Ferrannini · R. R. Holman · R. Sherwin · B. Zinman

Diabetologia
2009; 52:17-30
Diabetes Care
2009;32:193-203

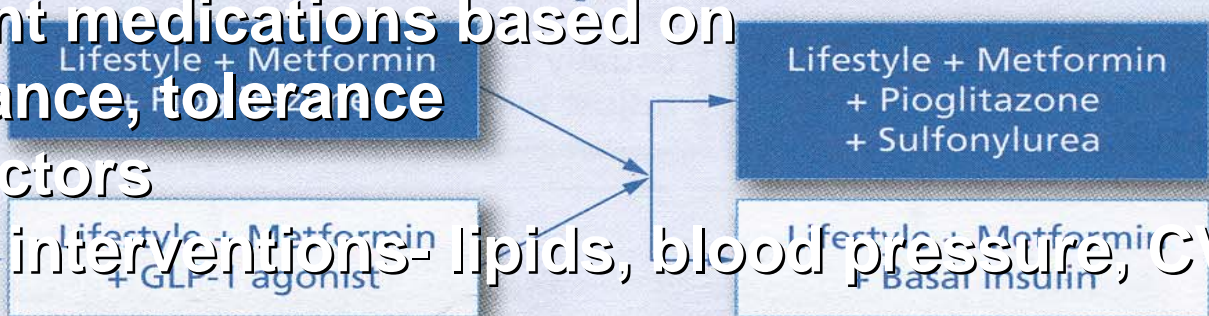
Caveats

- Although the algorithm should apply to most people with type 2 diabetes, it does **not apply to all**
- Individualize therapy
- May select different glycaemic goals
 - Elderly
 - Persons whose life projected span is too short to benefit
 - Persons in whom risk for side-effects outweighs benefits
- May select different medications based on
 - Patient acceptance, tolerance
 - Specific risk factors
- Don't forget other interventions- lipids, blood pressure, CVD prevention

Tier 1: Well-validated therapies



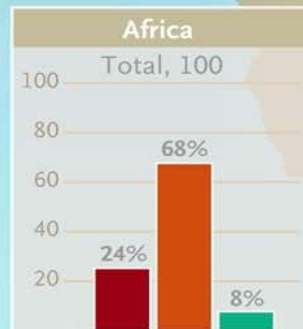
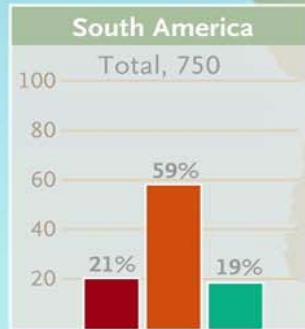
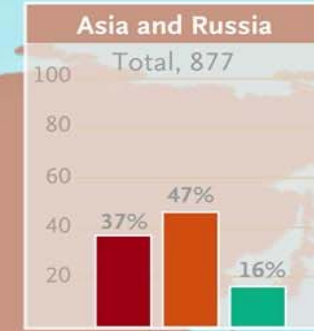
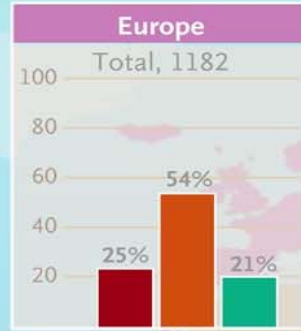
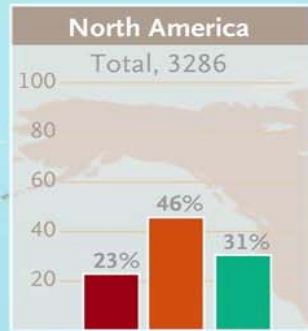
Tier 2: Less well-validated therapies



Management of Type 2 Diabetes

New England Journal of Medicine Case and Poll

Obese type 2 diabetes with HbA1c of 8.1 on metformin and glipizide



■ Add Pioglitazone

■ Add NPH Insulin before Bedtime

■ Add Exenatide Twice Daily

Management of Type 2 Diabetes

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What to use next?

