

# Intensive Therapy of Type 2 Diabetes

Minimal hypoglycemia  
Weight gain  
No excess CVD  
Effort  
Expense

UKPDS  
Kumamoto  
ACCORD  
ADVANCE  
VADT

Reduced  
development and  
progression of  
microvascular  
complications.  
?? CVD ??

Individualize goals, assess proportionate age, projected drug life span and risk/burden of therapy DM

# Development of Medications Used in the Treatment of Type 2 Diabetes



# 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**

**A prescriptive approach: Old School**

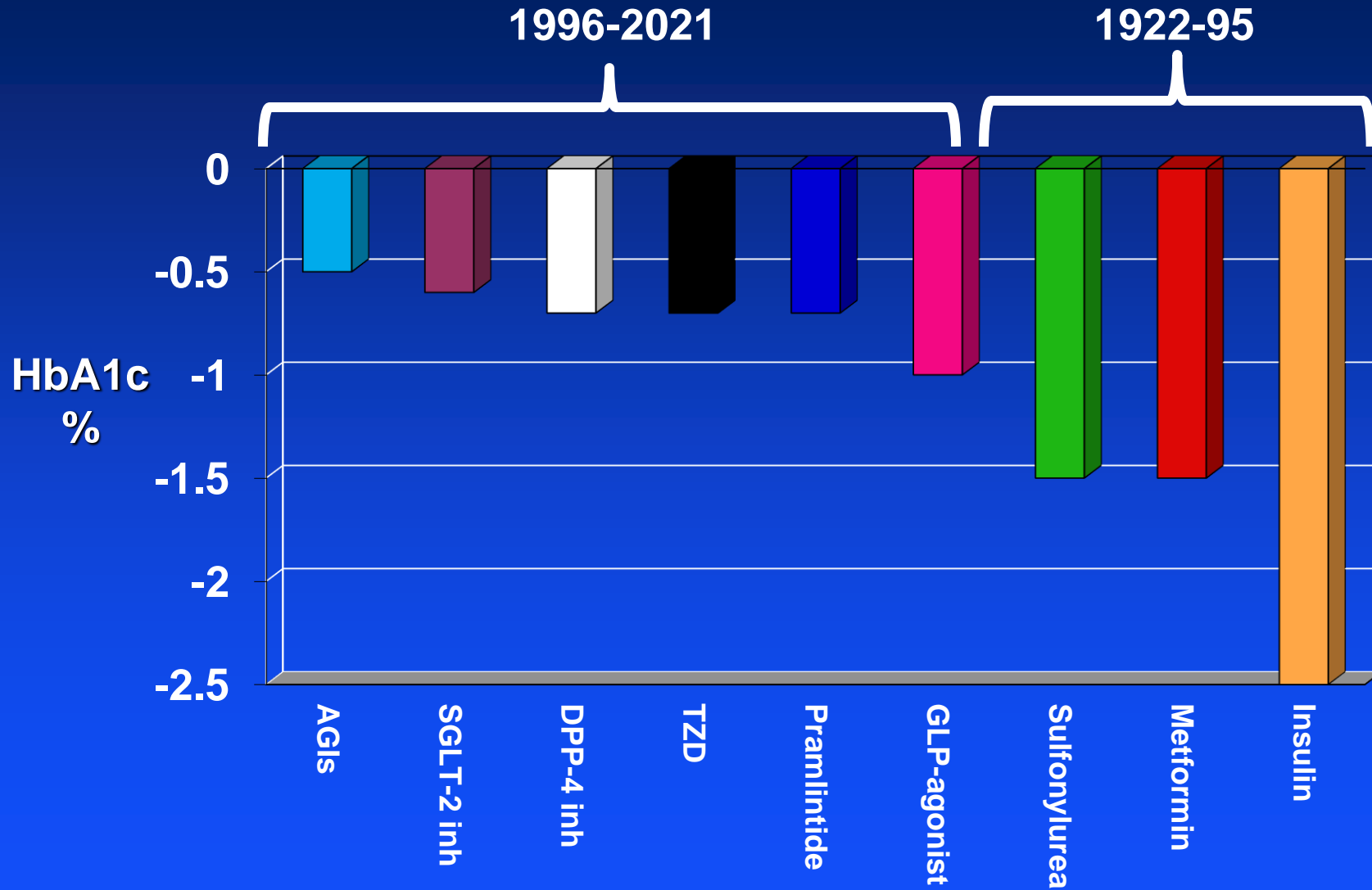
# Major Premises

## Selection of Interventions

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

# Glycemic Potency of Hypoglycemic Agents

Decrease in HbA1c: Potency of Monotherapy



# Anti-Hyperglycemic Agents in Type 2 Diabetes

## Mechanisms

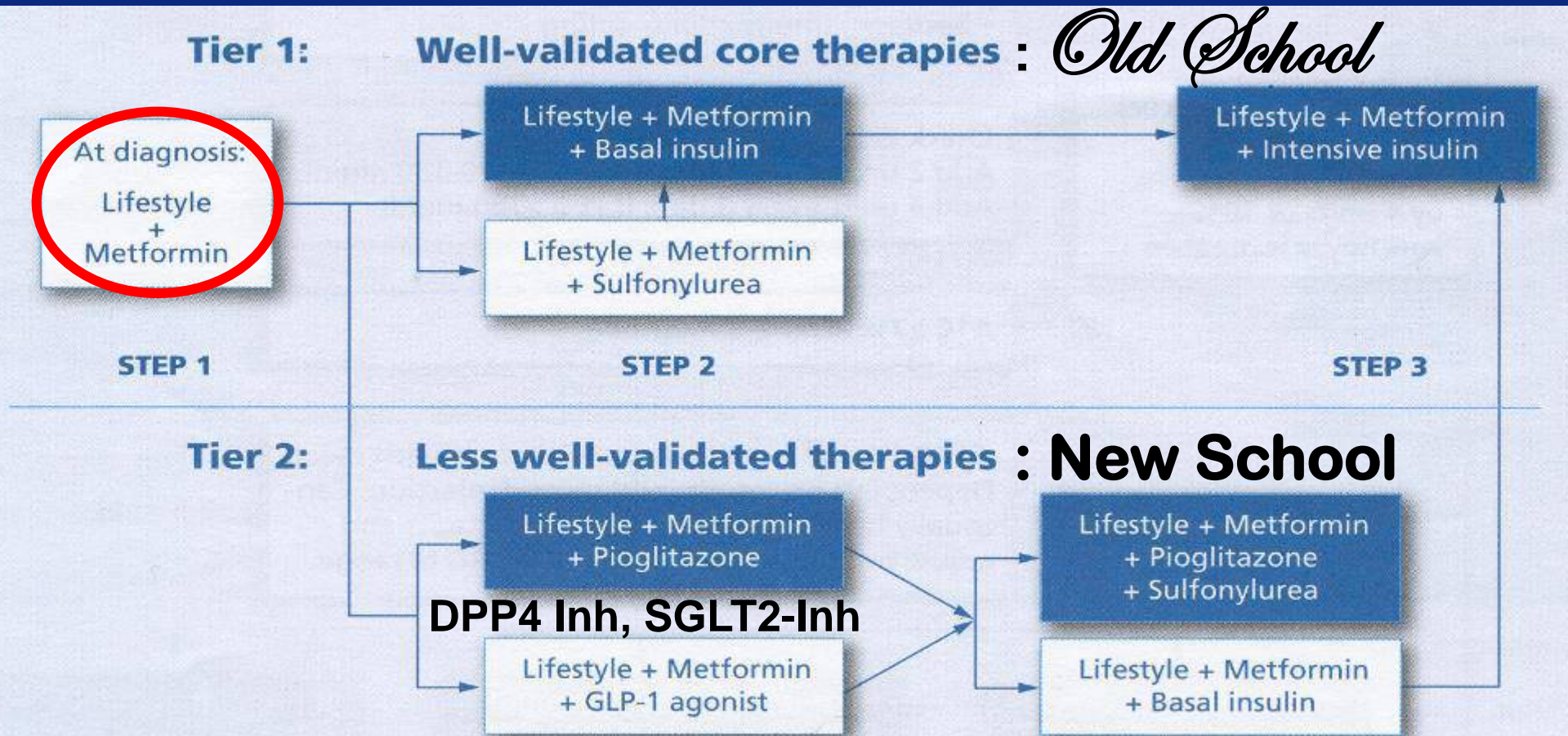
Class	Primary
Insulin	Supply
Sulfonylureas	Supply
“Glinides”	Supply
Biguanides (metformin)	Liver sensitivity (HGO)
Thiazolidinediones	Peripheral sensitivity
Alpha-glucosidase inhibitors	GI absorption rate
Amylin-mimetics (pramlintide)	GI motility
Incretin agonists	Supply
DPP-IV inhibitors	Supply
SGLT-2 inhibitors	Glycosuria

# 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



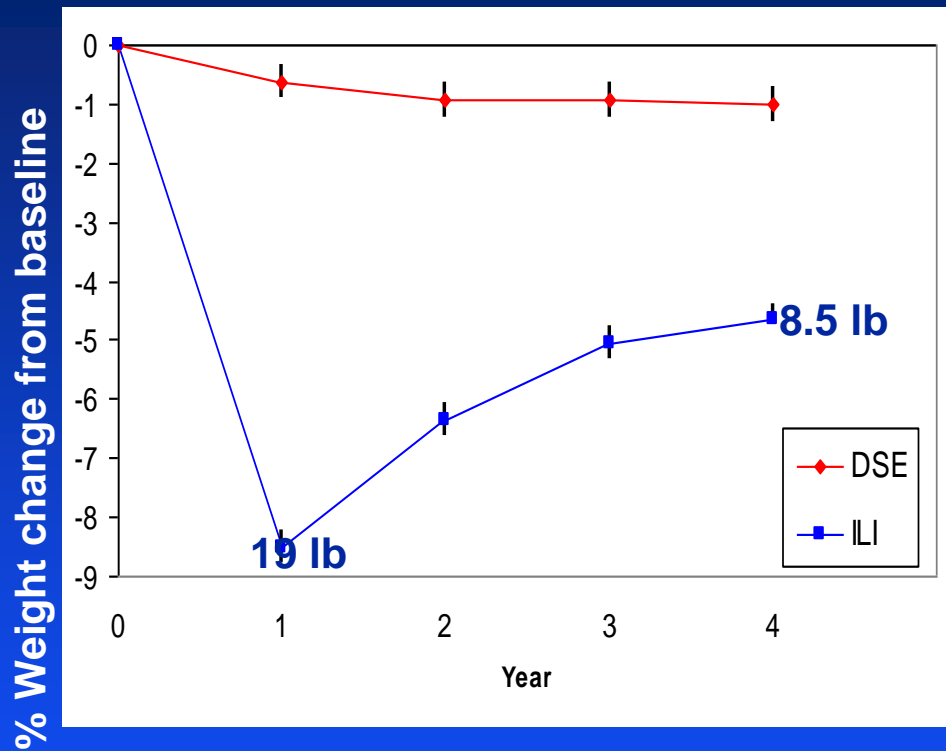
# Therapy of Type 2 Diabetes

## Lifestyle: Diet and Exercise

- **Highly effective in short term.**
- **5-10 lb weight loss usually sufficient to ameliorate hyperglycemia.**
- **Long-term benefit (unfortunately) parallels results of obesity therapy.**
- **More effective lifestyle interventions (such as those used in DPP or LookAHEAD) are available but require more effort than the usual “diet”.**



# Effects of Intensive Behavioral Intervention



## Weight

However, most patients on “diets” fail to maintain weight loss for  $\geq 1$  year.

# First Step- Lifestyle + Metformin

- Recognizes failure of life-style alone
- Inhibits hepatic glucose output- predominantly lowers fasting glycemia
- 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
- Can use safely down to eGFR of 30-45 ml/min

# Metformin

**Virtually every guideline and recommendation has metformin as the substrate medicine to treat type 2 diabetes, to be continued throughout its course, assuming no specific contraindication or intolerance.**

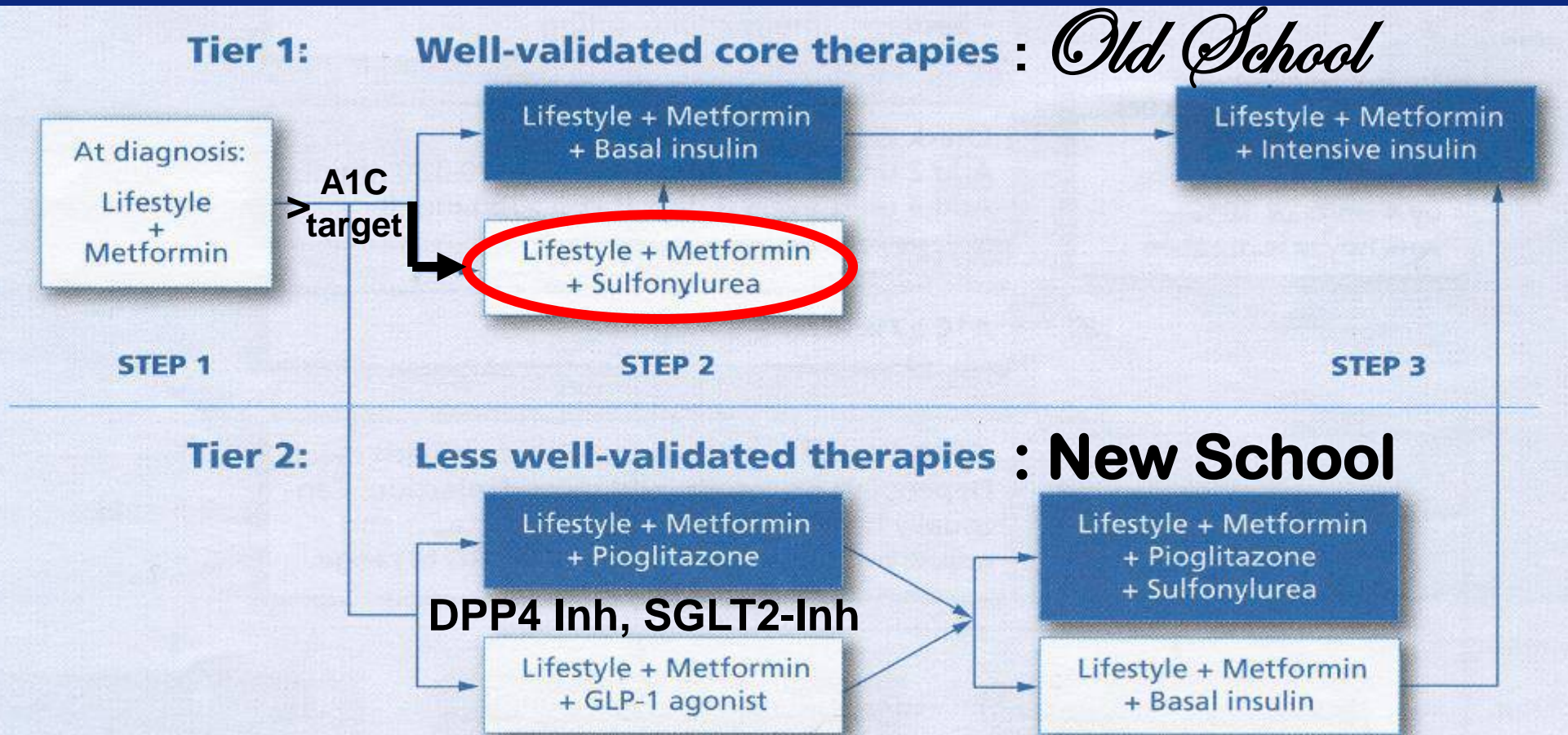
- **Start with 500 mg with meal to decrease GI intolerance**
- **Increase dose by 500 mg every 4-7 days**
- **Aim for 850-1000 mg BID**
- **If GI intolerance develops, try XR**
- **“New” FDA guidelines- safe to start at eGFR > 45 and use down to ~30 ml/min**

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

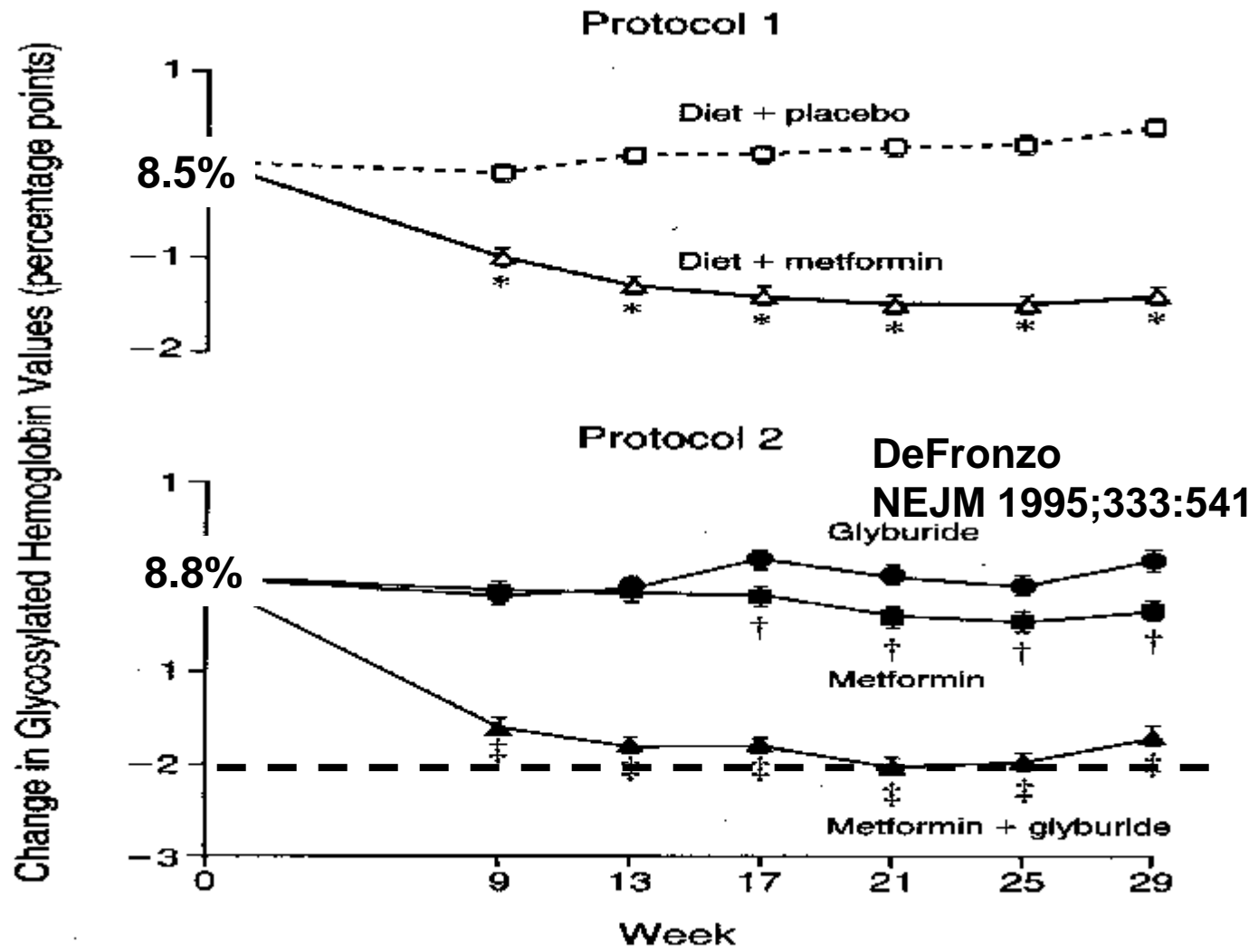
A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

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



# Metformin + Sulfonylurea



## Guide

- Use short-duration agents
- Titrate pre-meals

## Adverse effects

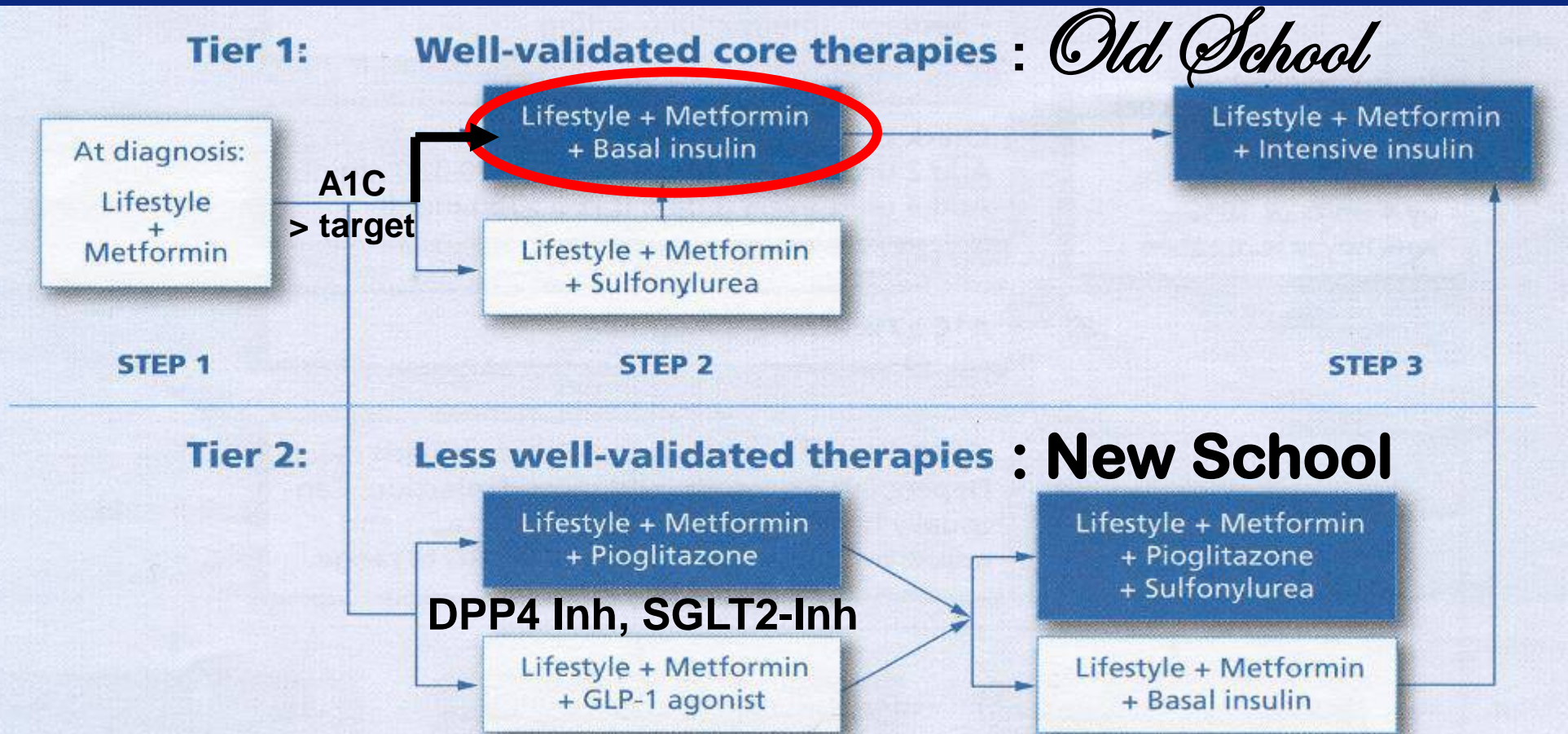
- Hypoglycemia
- Weight gain
- “Strains”  $\beta$ -cells
- Modern SUs are CVD “neutral”

# 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

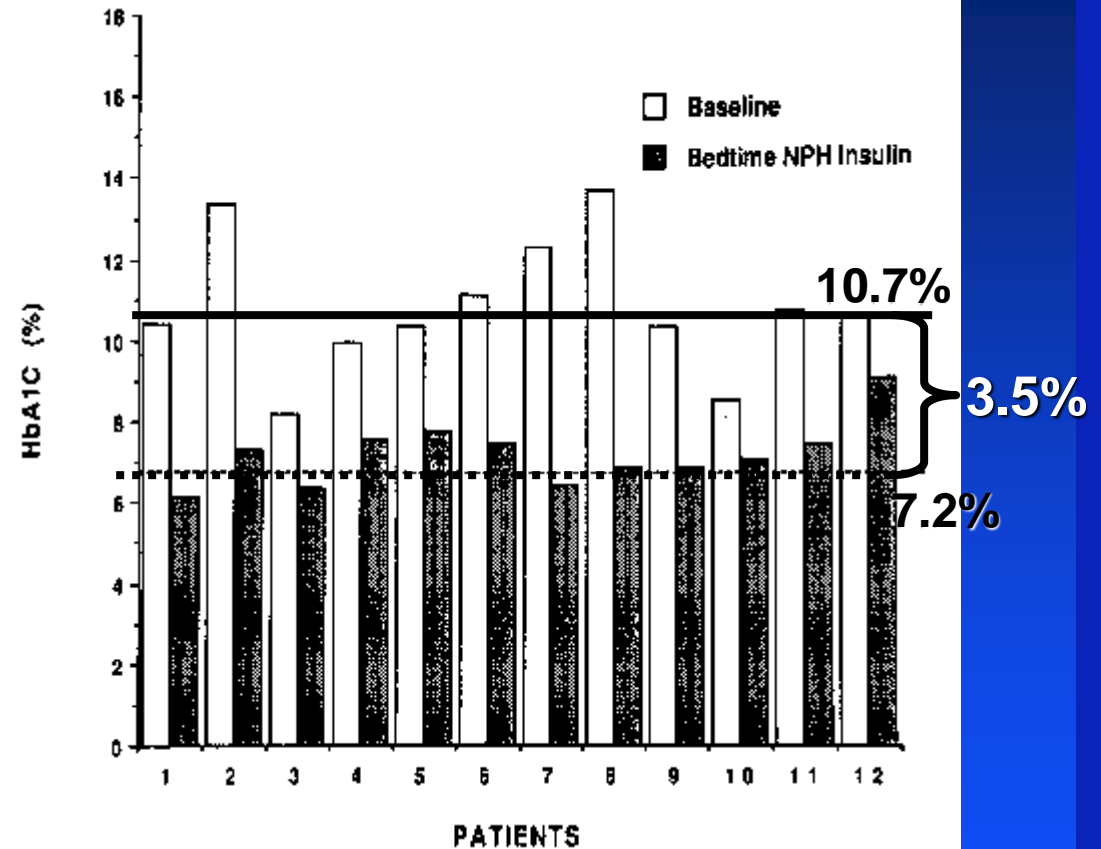
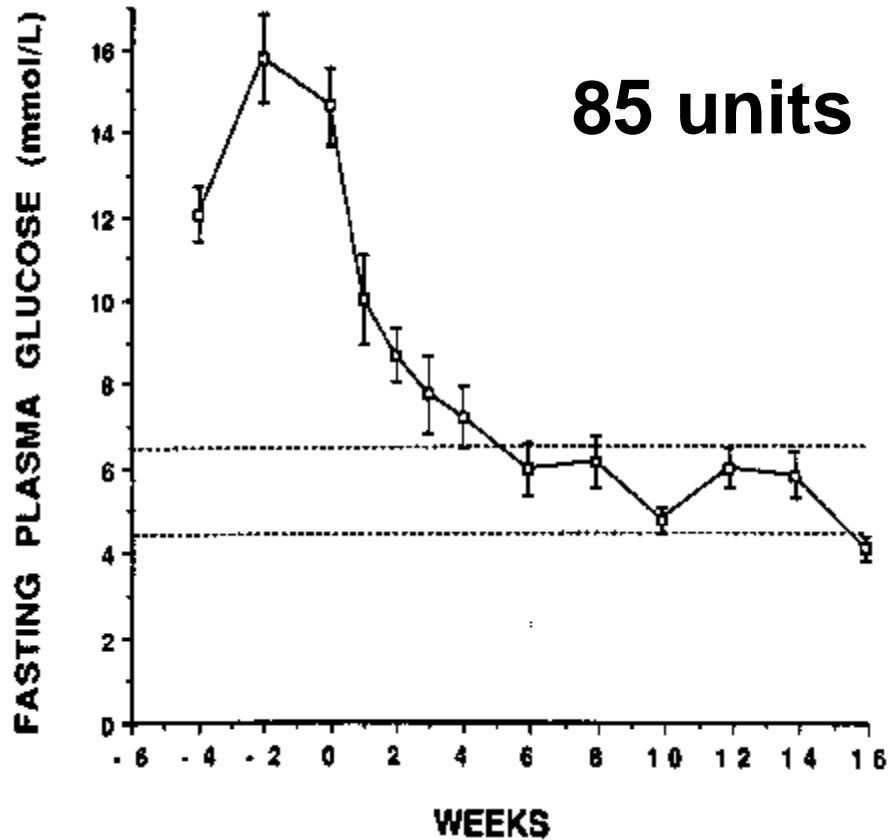
D. M. Nathan · J. B. Buse · M. B. Davidson ·  
E. Ferrannini · R. R. Holman · R. Sherwin · B. Zinman

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



# Insulin Therapy of Type 2 DM

## Bedtime NPH

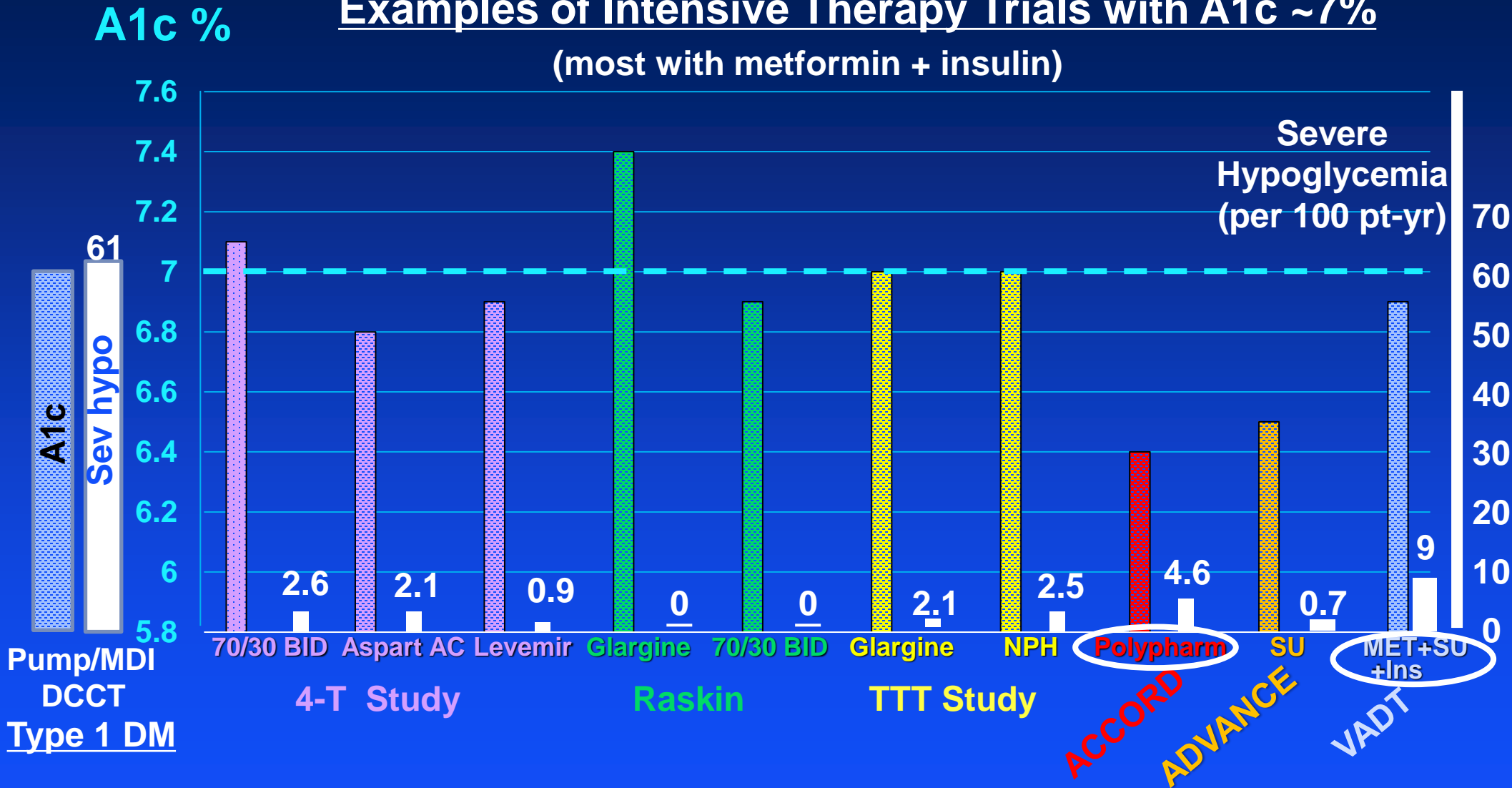


Cusi et al. *Diabetes Care*  
1995;18: 843

# Intensive Therapy of T2DM with Insulin

Examples of Intensive Therapy Trials with A1c ~7%

(most with metformin + insulin)



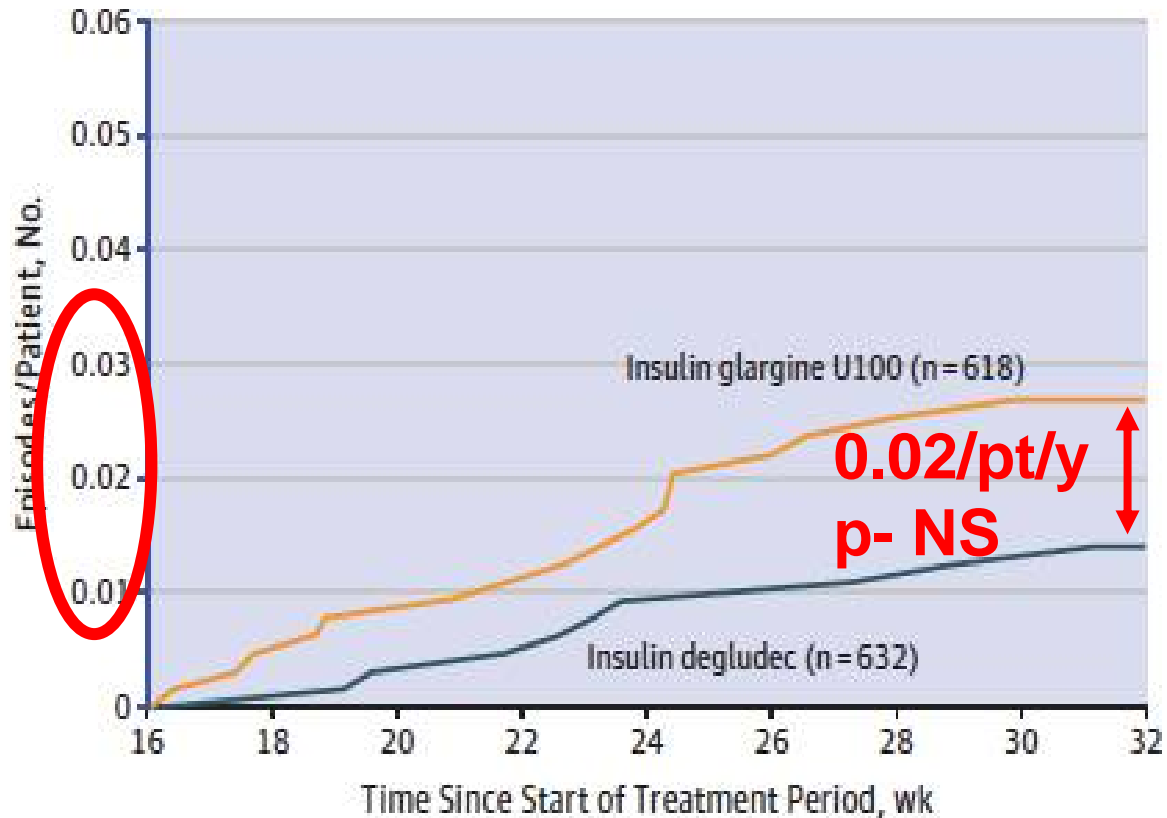
Risk of severe hypoglycemia with insulin in T2DM is quite low



# Most Recent Insulin Analog

## DeGludec vs Glargine

### Severe hypoglycemia



- Identical potency to glargine.
- All symptomatic hypo 30% lower.
- However, absolute rate difference 0.2 episodes/pt-y.
- Severe hypo, very rare (0.02/pt-y) and no sig. difference.

# 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



Usually add rapid or very-rapid acting before largest meal but may include MDI or NPH or mixed-insulins, depending on individual lifestyle factors, acceptability.



EASD=European Association for the Study of Diabetes. Adapted from Nathan et al.<sup>1</sup>