# Diabetes: An Update for Subspecialists

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# Dualities of Interest

**David M. Nathan, M.D. has no conflicts of interest.**

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# Prevalence of Diabetes in the U.S.

## CDC 2015

| | | |
|---|---|---|
| **Prevalence of all diabetes** | **29.1** | **million (9.3%)** |
| **Type 1** | **1+** | **million (0.4%)** |
| **Type 2** | **28** | |
| **Diagnosed** | **21** | |
| **Undiagnosed** | **6** | |

## 1,500,000 new cases per year

| | | |
|---|---|---|
| **GDM** | **>150,000** | **(~5-10% of all pregnancies)** |
| **Prediabetes** | **86** | **million (20%)** |

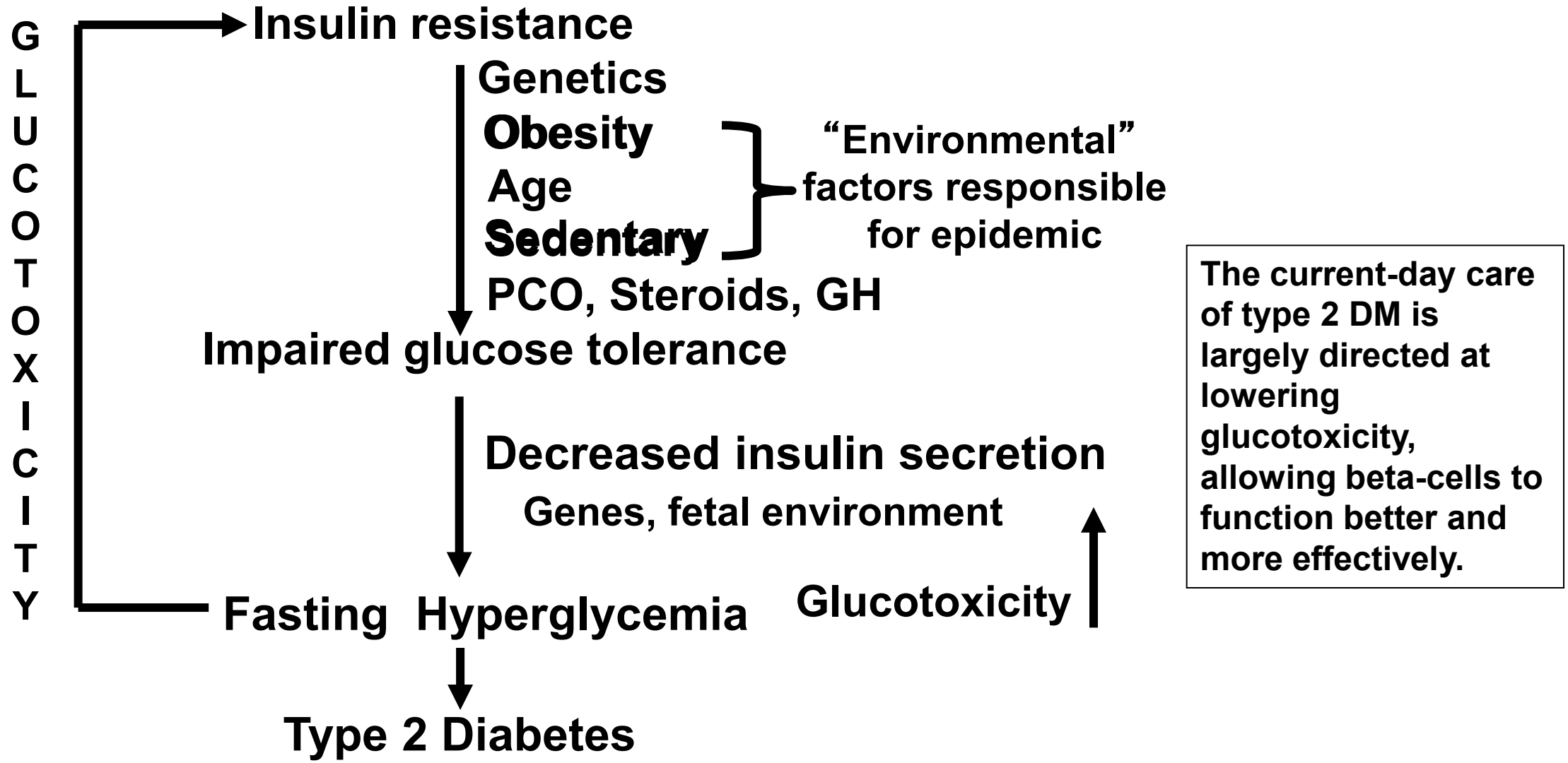
**>100,000,000 with diabetes and pre-diabetes**

# Consequences of Diabetes in the U.S.

## CDC 2015

- Most common cause of ESRD in adults
- Most common cause of blindness
- Most common cause of amputations
- 2-5 fold increased risk for CVD
- >$327 billon per year in US (ADA, 2017)

# Pathophysiology of Type 2 Diabetes




The current-day care of type 2 DM is largely directed at lowering glucotoxicity, allowing beta-cells to function better and more effectively.

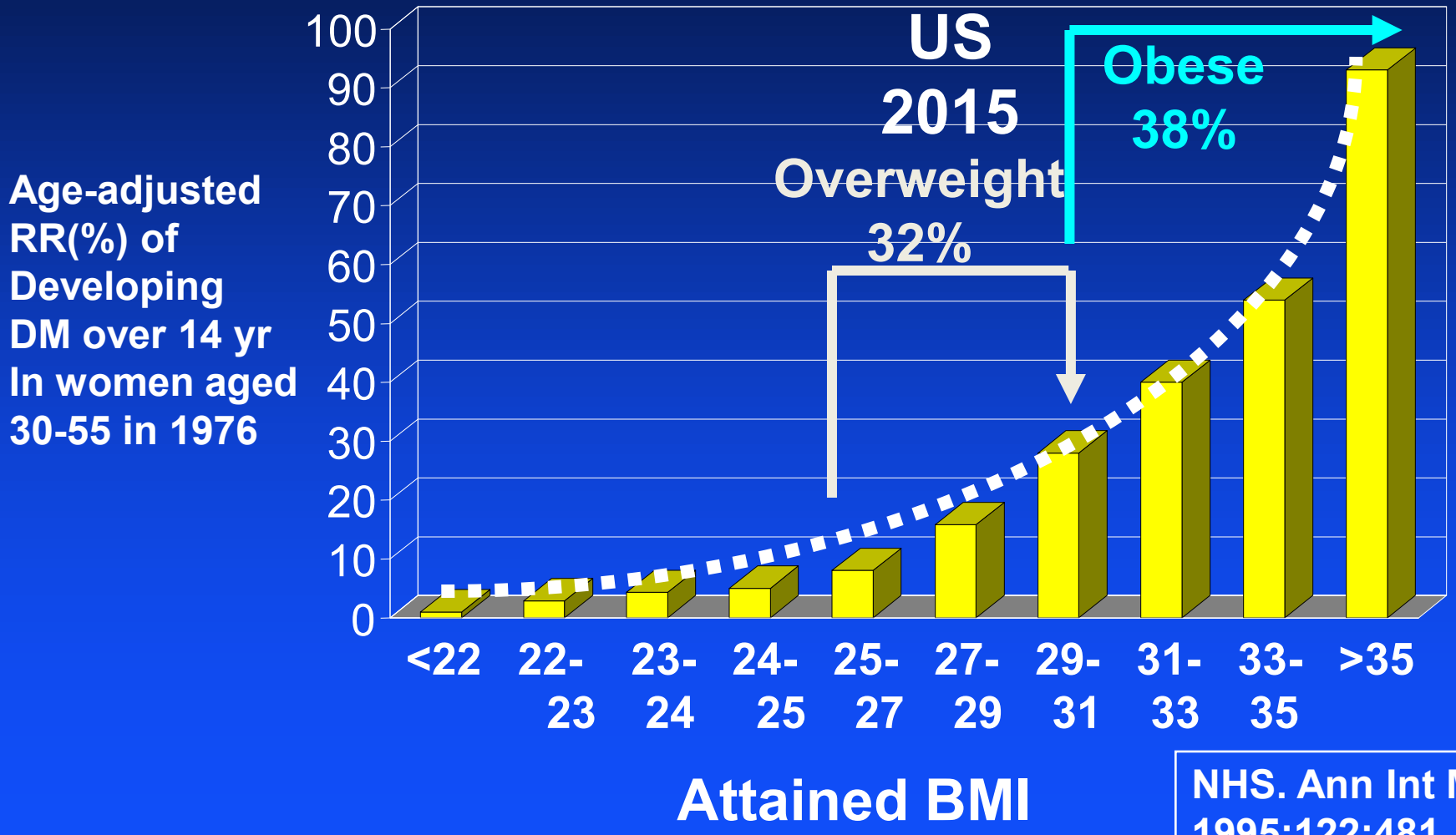
# Pathophysiology of Type 2 Diabetes

**Solving- treating more effectively- the obesity "problem" is the single greatest challenge and would be the most effective means of preventing and treating diabetes.**

**The best example of the potential beneficial effects of weight loss derive from bariatric surgery where loss of 35-50% of excess weight ameliorates the majority of diabetes, including remissions in 30-65%.**

# Risk for Development of Type 2 Diabetes

## Effect of BMI in Women

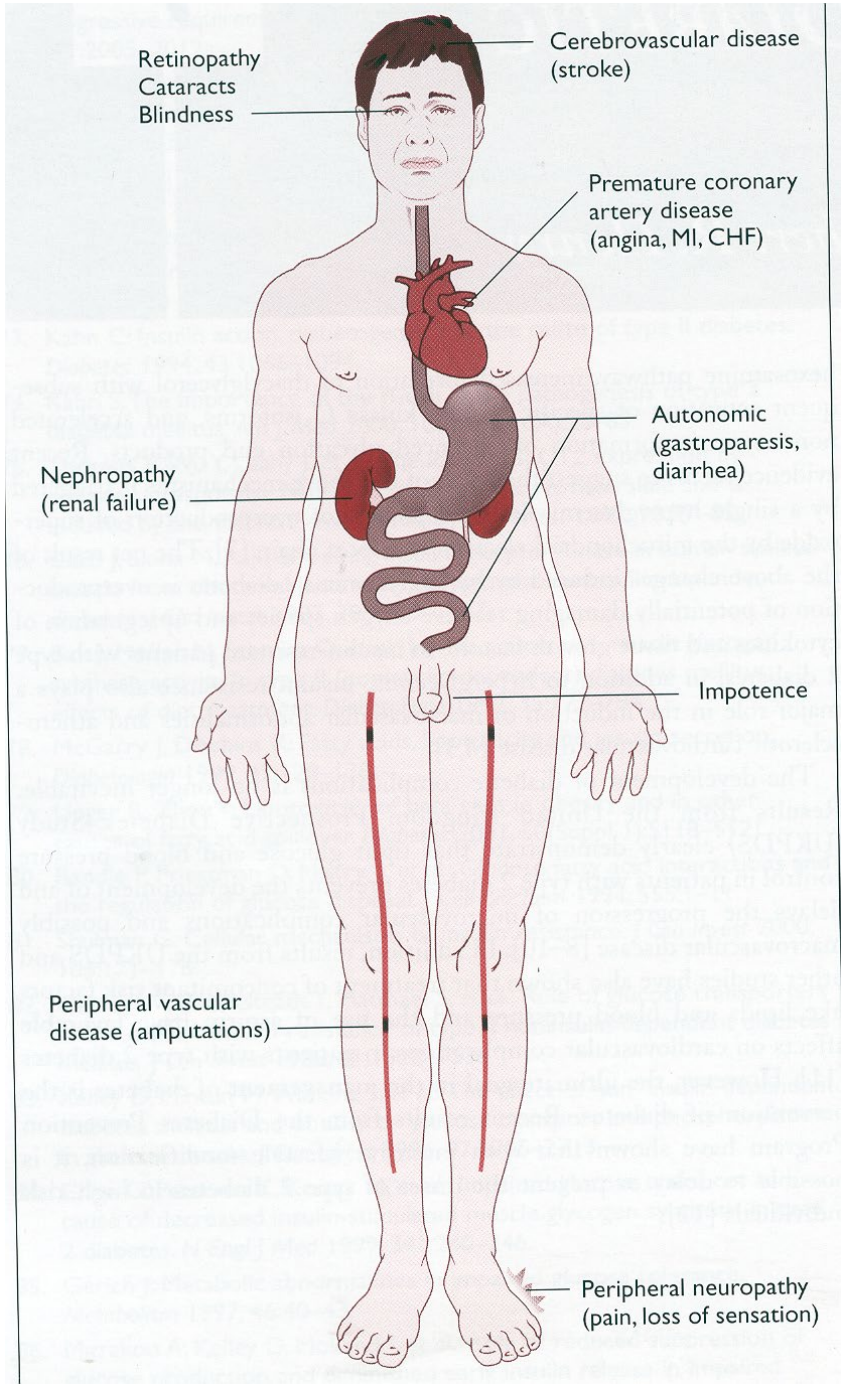



NHS. Ann Int Med 1995;122:481

# Complications of Diabetes

**Result of Level of**
**Glycemia x duration**
**Plus**
**other risk factors:**
**Hypertension**
**Lipids**
**Smoking**

**The outpatient and inpatient management of diabetes interfaces with virtually every area of medical care**



# Diabetes and Subspecialties

## Special issues

- Cardiovascular/peripheral vascular
  - MI- intensive management
  - Foot care, ulcers, wound healing
- Renal- CKD
- Neurology- peripheral, autonomic, stroke
- Anesthesiology- perioperative management
- Oncology- nutrition, chemotherapy, steroids
- Rheumatology- steroid management
- Psychiatry- atypical antipsychotics, depression, behavior/self-care

# Diabetes and Subspecialties

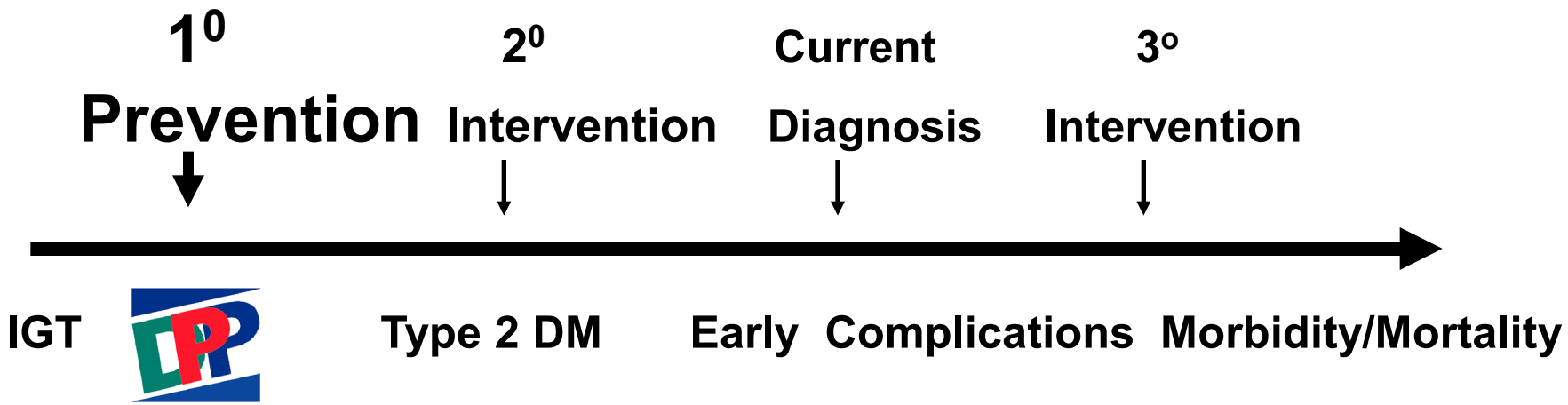
## Special issues

- GI- maldigestion, autonomic neuropathy, sprue
- Infectious diseases- increased risk + specific infections
- Surgery- management
  - Vascular-Peripheral, cardiac, neuro
  - Transplantation- kidney, pancreas, heart, liver
  - Orthopedic- cheiropathy (adhesive capsulitis, trigger fingers, carpal tunnel), amputations, corrective foot
  - Urology- bladder dysfunction, ED
- Ophthalmology- retina, cataract, glaucoma

# Topics

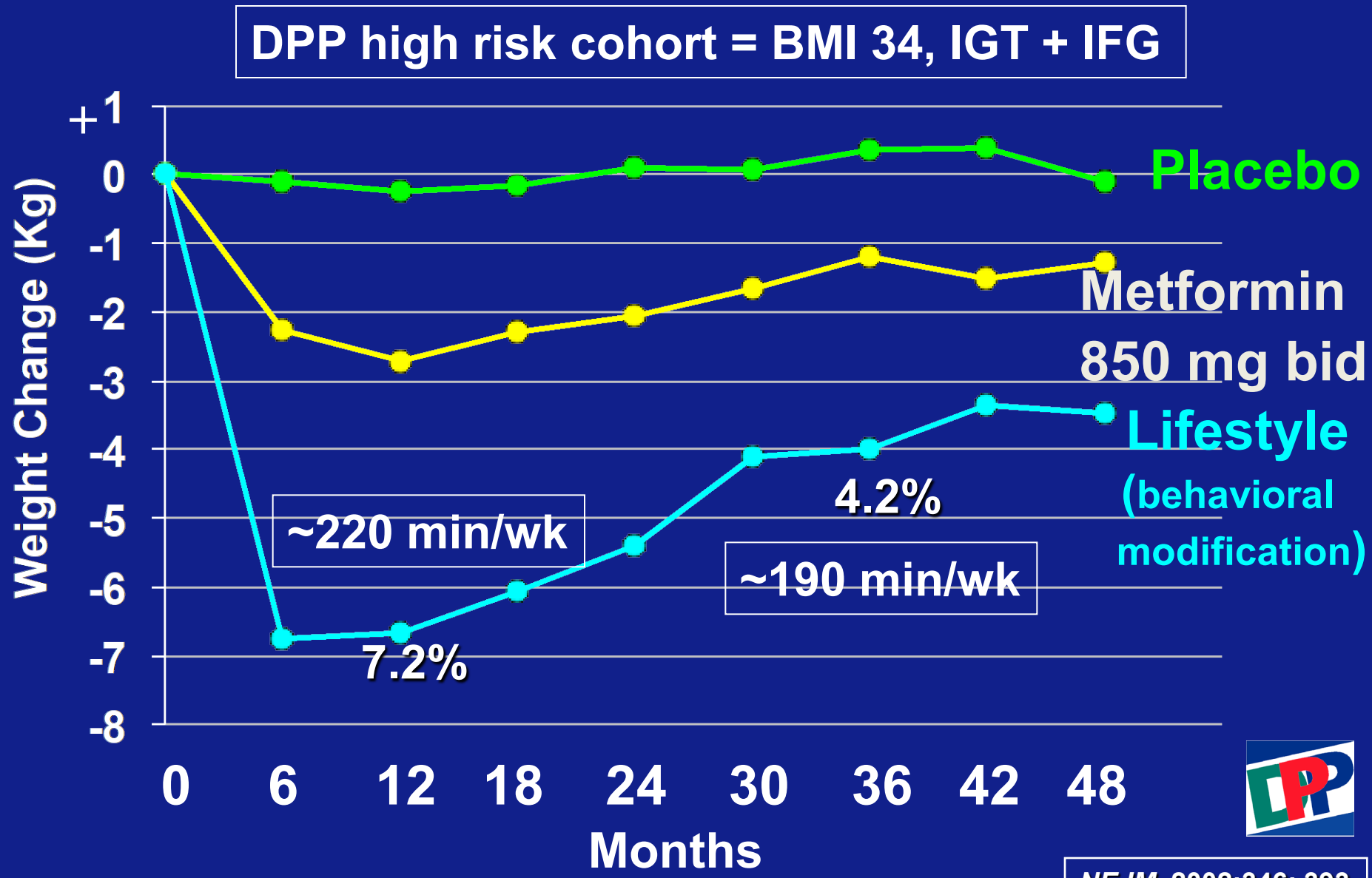
- Prevention
- Management
  - Outpatient
    - Metabolic treatment goals
    - Algorithm
  - Inpatient
  - Other “special cases”

# Response to an Epidemic: Prevention



# Mean Weight Change from Baseline

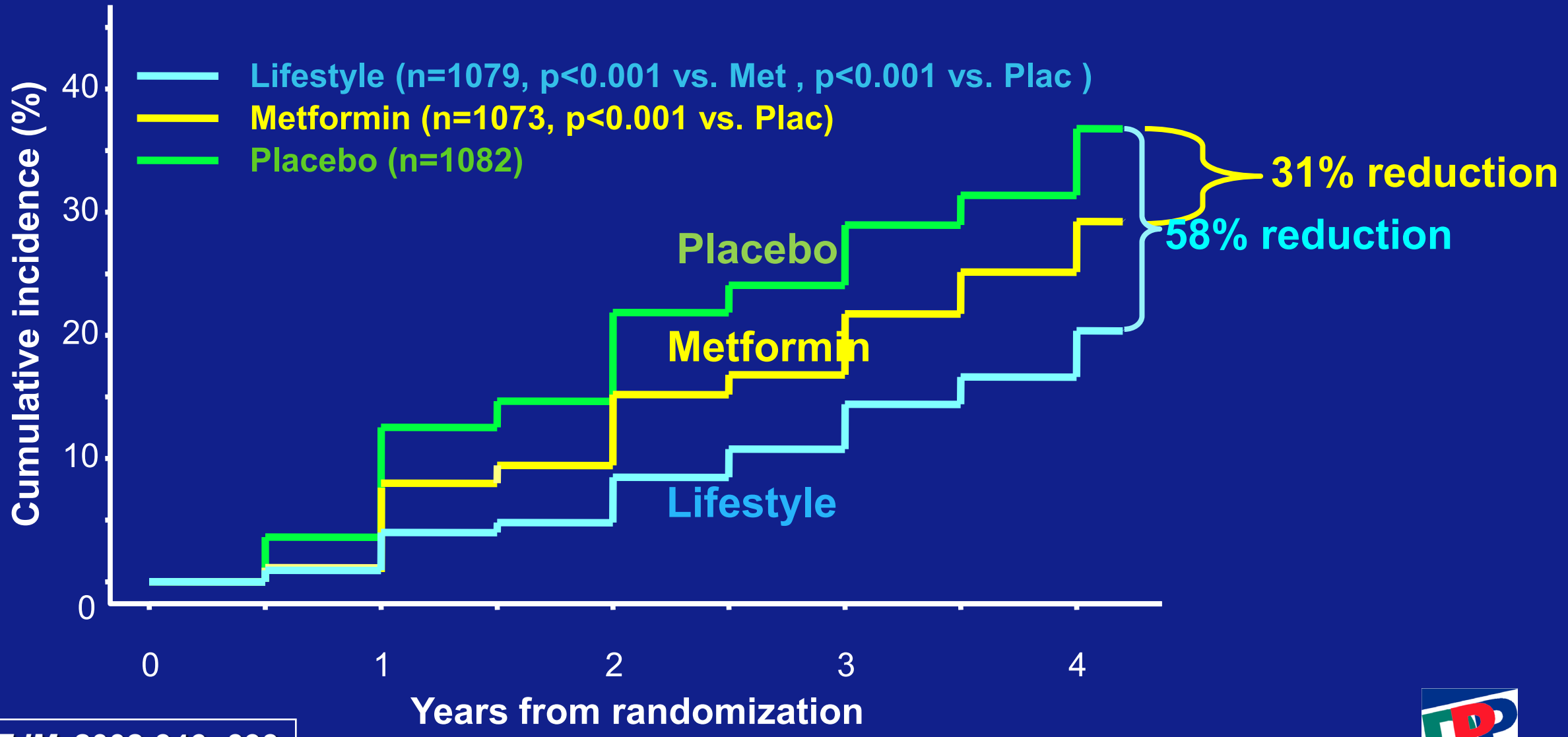
Tested a behavioral lifestyle intervention that achieved a 7% weight loss (~15 lb) or metformin to prevent diabetes in a high risk population with pre-diabetes




*NEJM* 2002;346: 393

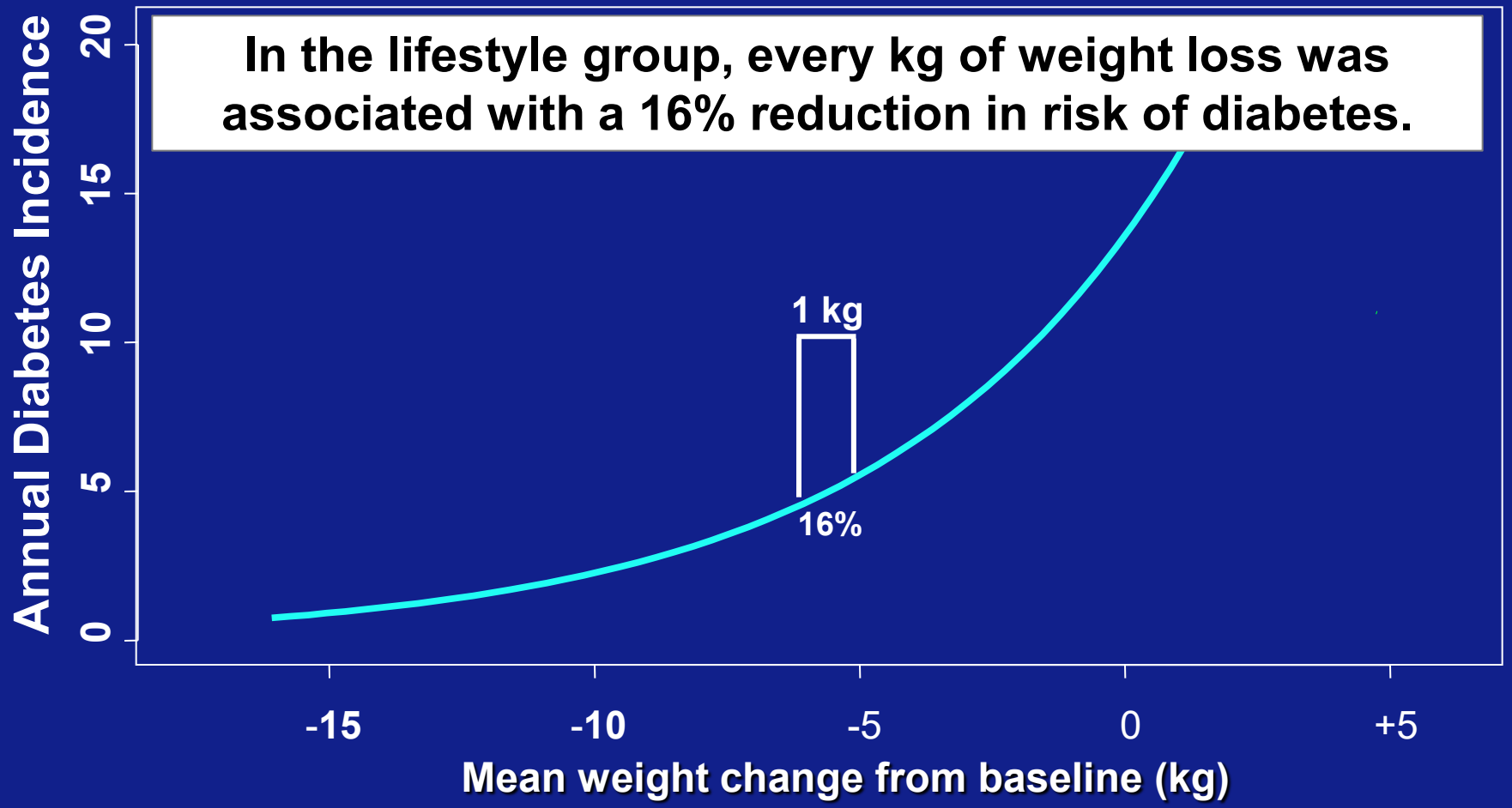
# Percent developing diabetes

**All participants-2.8 years**




*NEJM* 2002;346: 393

# Effect of Weight Loss on Diabetes Prevention




*Diabetes Care* 2006;29:2102-2017

# Long-term Diabetes Prevention

## Risk Reduction

| | After 2.8 y of DPP | After 10 y DPP/DPPOS | After 15 y DPP/DPPOS |
|---|---|---|---|
| ILS v PLBO | 58% | 34% | 27% |
| MET v PLBO | 31% | 18% | 18% |
| | *NEJM* 2002;346:393 | *Lancet* 2009;374:1677 | *Lancet* D&E 2015; 3: 866 |

## Other Benefits over Time with ILS

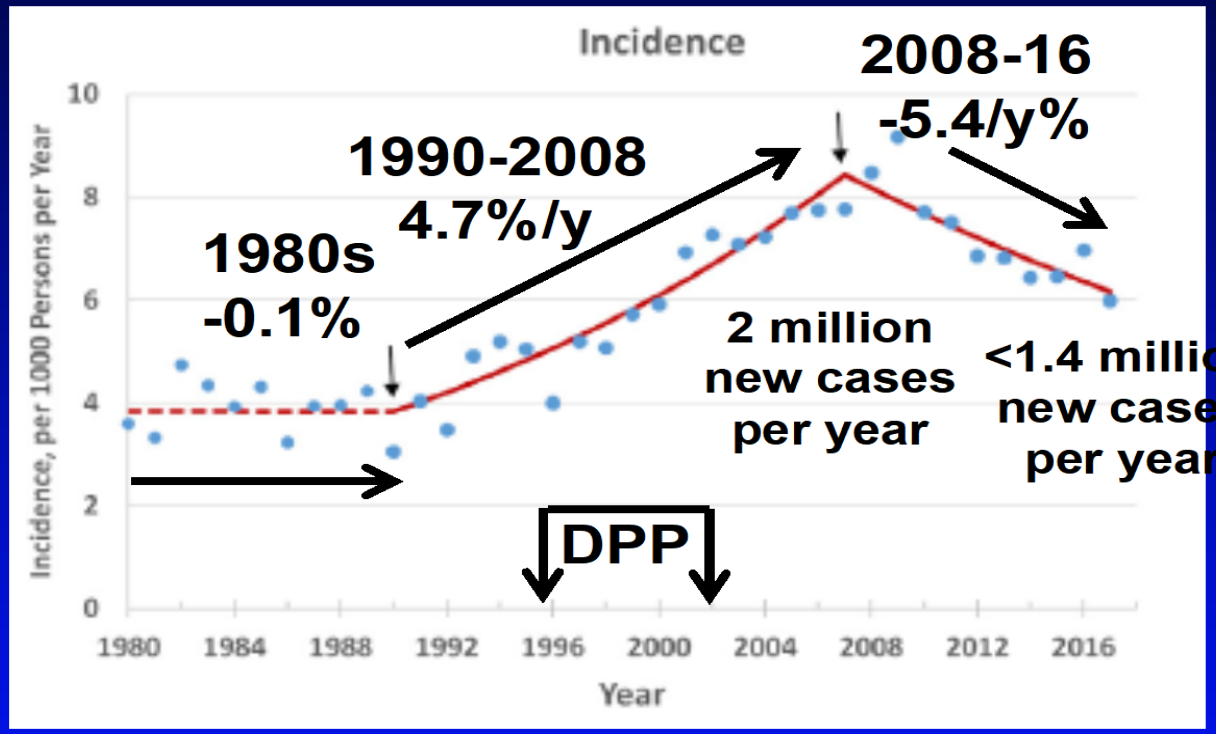
## (compared with placebo)

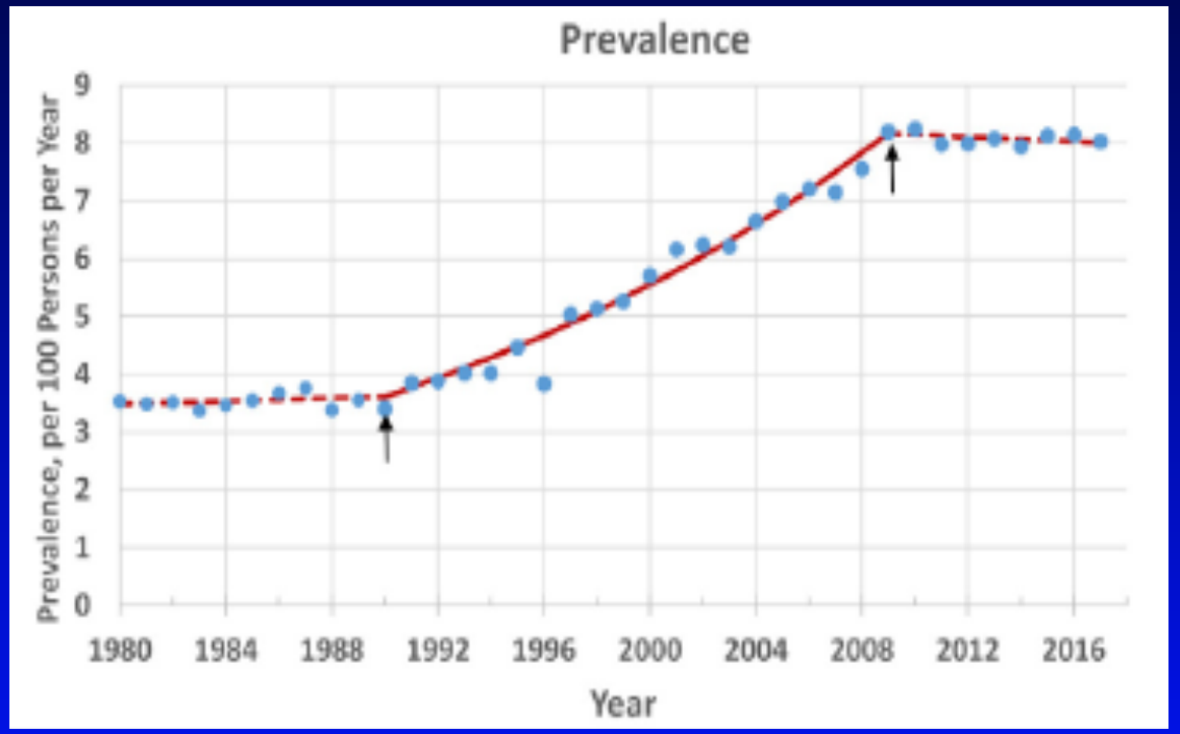
- Lower HbA1c with fewer meds
- Lower BP and lipid levels with fewer meds

DPPOS OUTCOMES STUDY

# Have We Turned the Corner?

## Trends for Diagnosed Diabetes Among Adults Aged 20 to 79 Years, United States, 1980-2016




**For the first time in 20 years, the annual rate of diabetes development in the U.S. has decreased**

*BMJ Open Diab Res & Care* 2019

CMS.gov
Centers for Medicare & Medicaid Services

**CMS support for DPP programs effective 1/18**

Home > Newsroom > Media Release Database > Press releases > 2016 Press releases items > Medicare finalizes substantial impro diabetes prevention

# Medicare finalizes substantial improvements that focus on primary care, mental health, and diabetes prevention

| | |
|---|---|
| **Date** | 2016-11-02 |
| **Title** | Medicare finalizes substantial improvements that focus on primary care, mental health, and diabetes prevention |
| **Contact** | press@cms.hhs.gov |

*Medicare finalizes policies to expand the Diabetes Prevention Program Model*

# Treatment: Standards of Care

| | A1c | BP+ | LDL* | HDL | TRI |
|---|---|---|---|---|---|
| ADA 2019 | <7.0 | <140/90^ | Like ACC-moved away from numbers | | |
| AACE 2007 | ≤6.5 | <130/80 | <100 | >50/40 | <150 |
| CDA 2008 | ≤7.0 | <130/80 | < 80 | TC/HDL <4.0 | |
| NICE 2009 | <6.5 | <140/80 | < 80 | | <400 |
| ACP 2018 | 7.0-8.0 "for most patients" | | | | |

+SPRINT study (no diabetics) suggests that BP 120/80 may be new goal

*AHA/ACC recommendations- statin use based on >7% 10-yr CVD risk

^ <130/80 for high CVD risk patients

# Treatment with Statins

## No longer primarily LDL level driven (ADA and ACC)

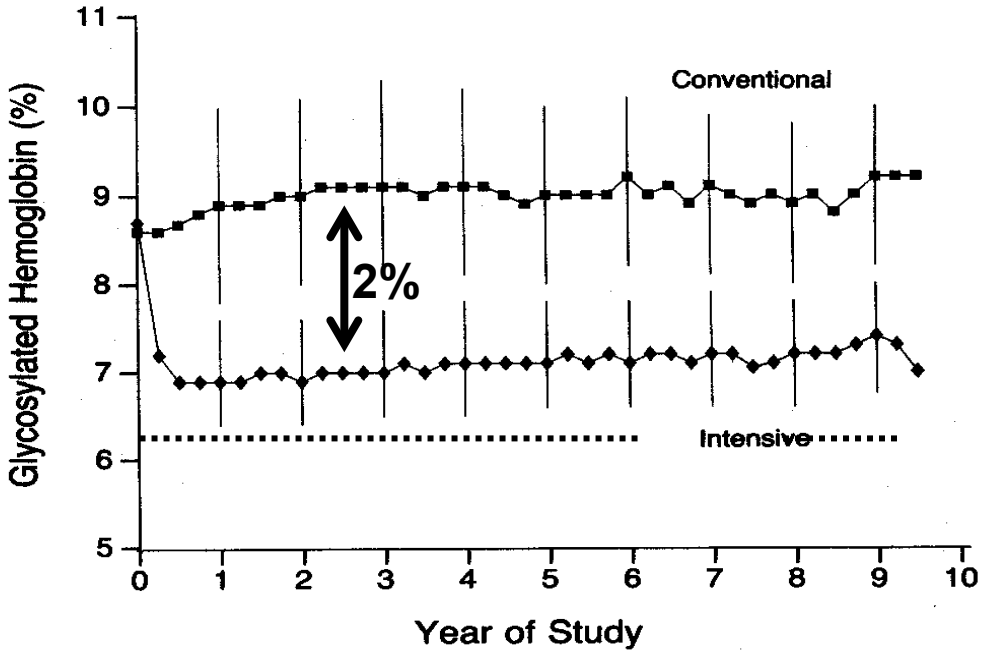
| Age | No CVD | CVD |
|---|---|---|
| <40 | None | High |
| ≥40 | Moderate | High |

Moderate intensity statin can also be considered for patients w/o CVD but with risk factors (LDL ≥100, hypertension, smoking, CKD, albuminuria, family history or premature CVD)

Moderate = atorva 10-20, rosuva 5-10, simva 20-40
High intensity = atorva 40-80, rosuva 20-40, add PCSK-9 or ezetemibe if LDL ≥ 70 mg/dl

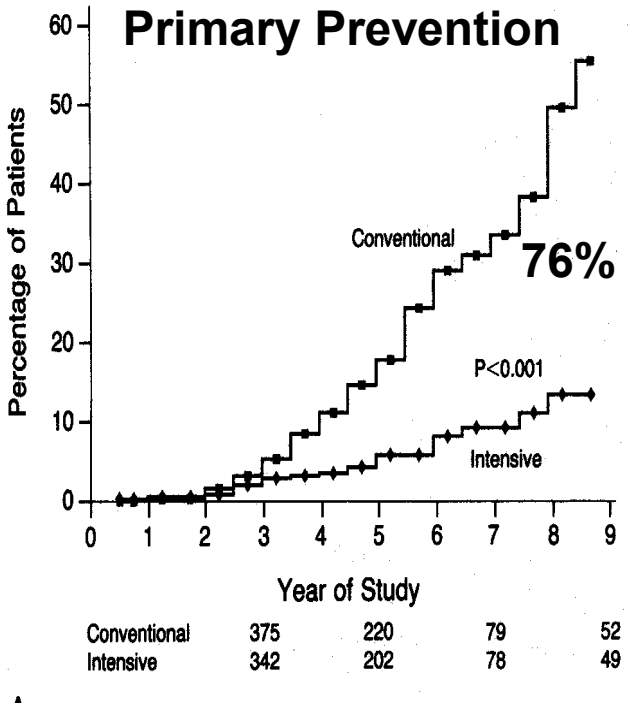
# Metabolic Therapy and Type 1 Diabetes

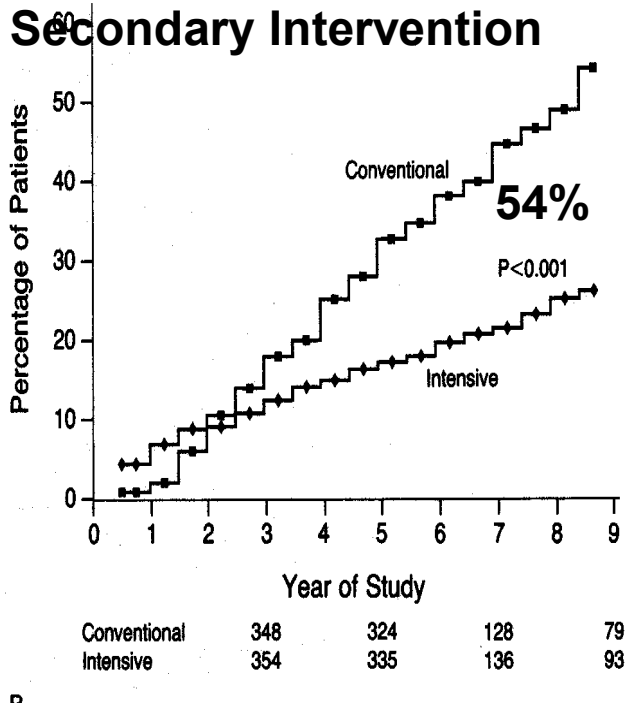
## DCCT Retinopathy Results




**"Intensive" therapy was aimed at achieving glucose and HbA1c levels as close to the non-diabetic range as safely possible.**

**Long-term follow-up of DCCT showed:**
**~ 50% reduction of <u>late-stage, severe complications</u> (e.g. need for eye surgery, CKD-3 or worse, CVD events).**
**Mortality reduced by 33%.**

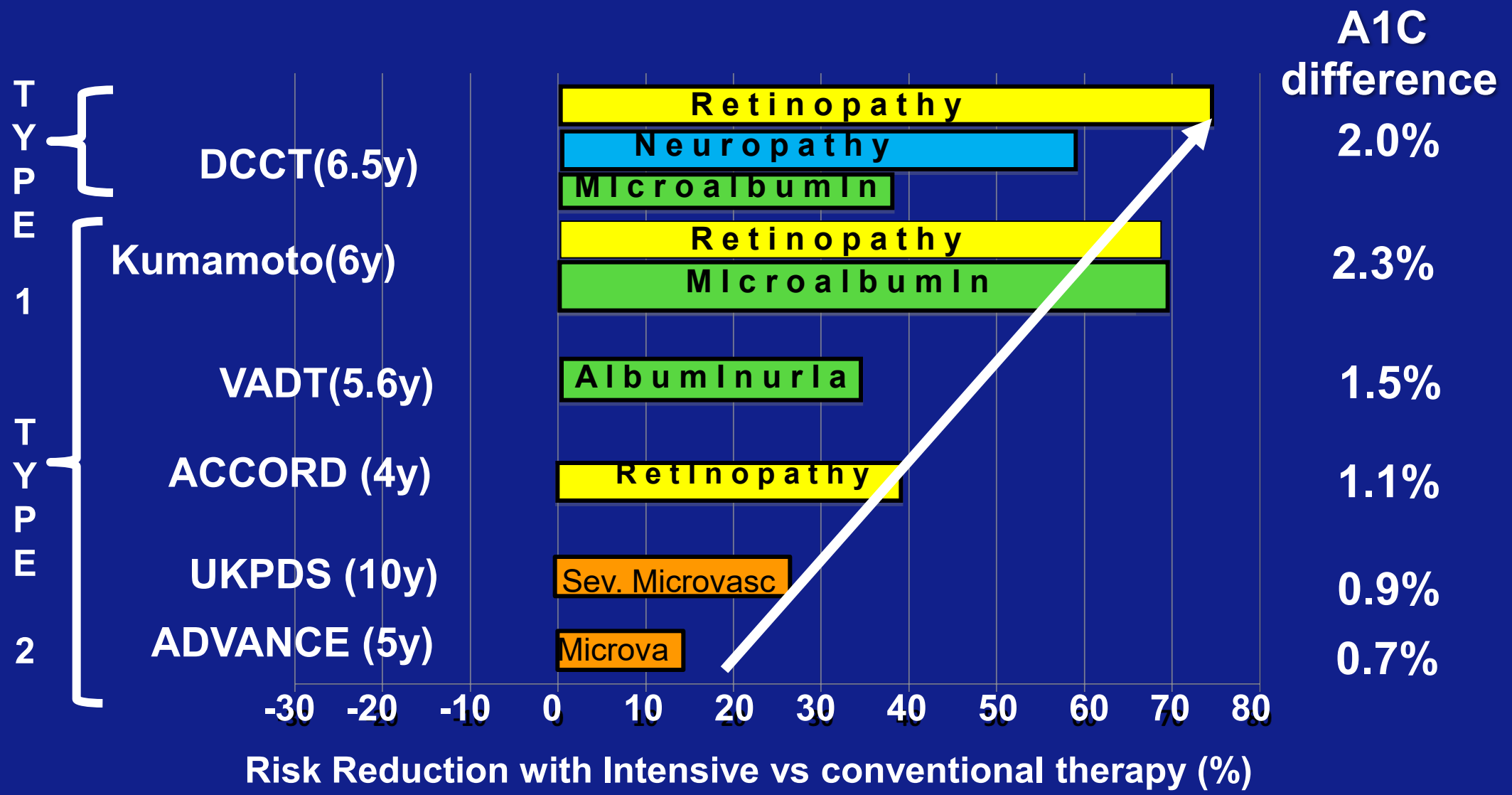



DCCT Research Group
*NEJM* 1993;342:381

# Setting Treatment Goals: Glycemia & Microvascular

## Reduction in microvascular complications roughly proportional to A1c reduction.



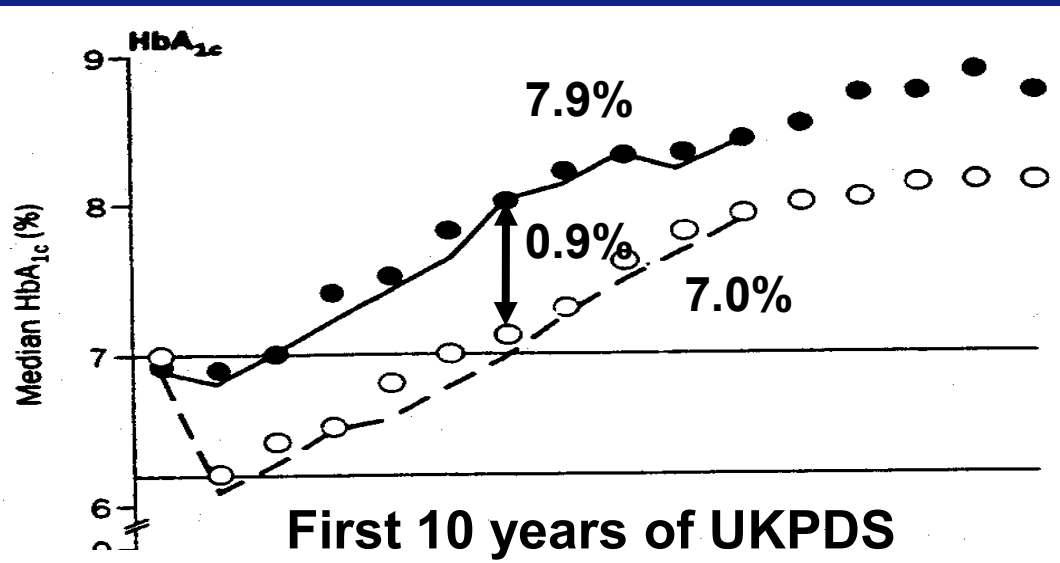
# Intensive Therapy and Type 2 Diabetes

**UKPDS**

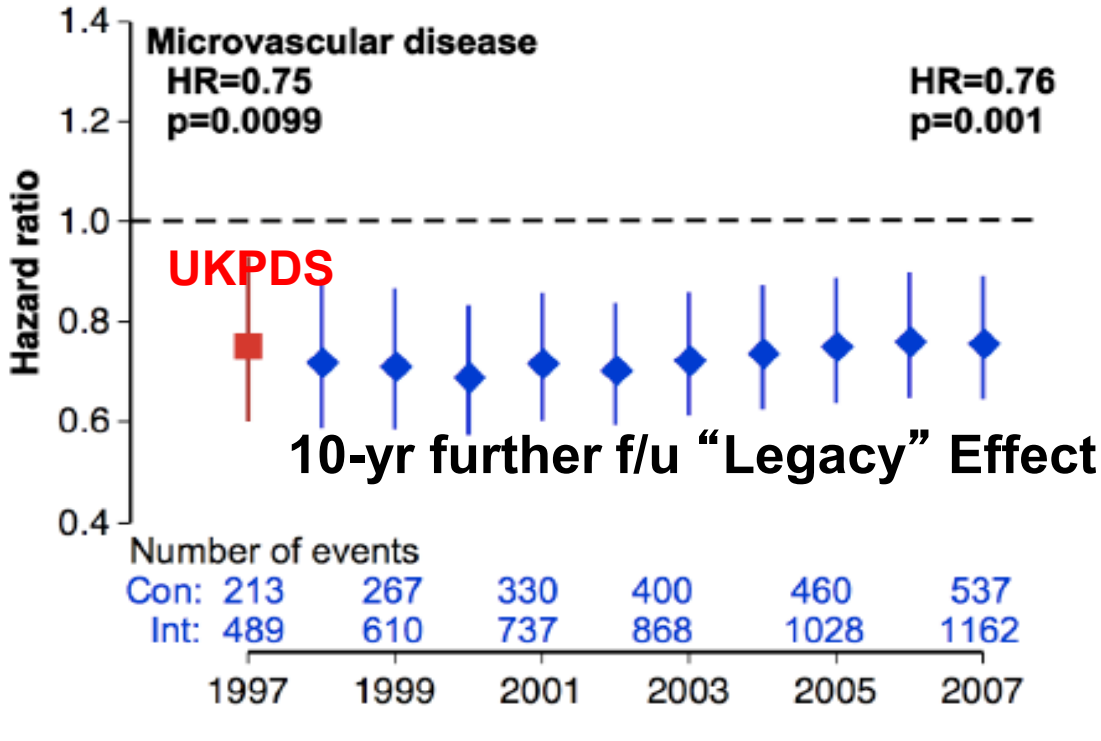
5102
Age 53
"New-onset"
No prior CVD
10-yr median f/u

25% reduction in advanced complications during UKPDS.
Continued benefit with 10 more years follow-up.

*Lancet* 1998; 352: 837

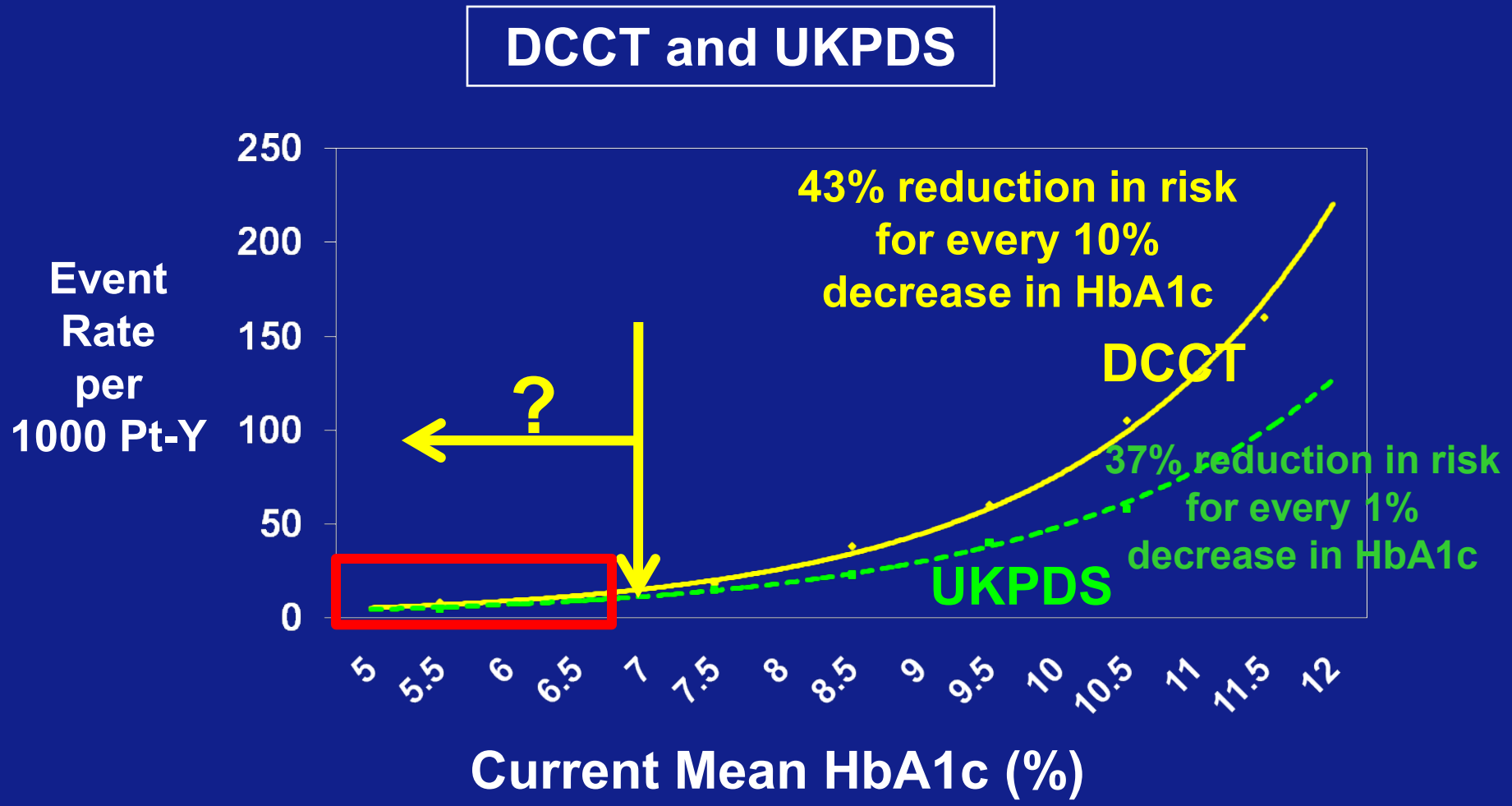



First 10 years of UKPDS




10-yr further f/u "Legacy" Effect

# Relationship between Glycemia and Complications



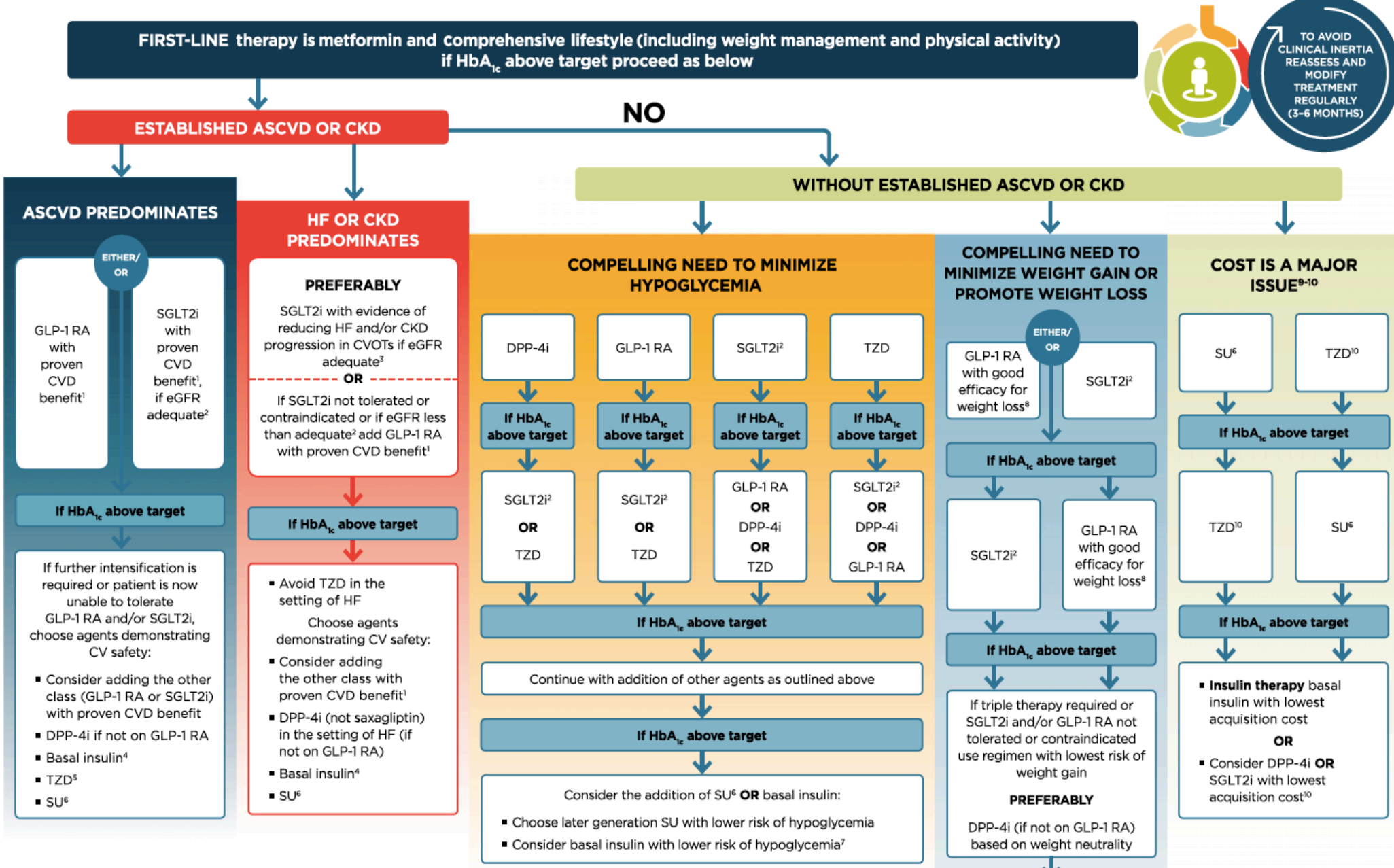
# Selecting Metabolic Goals

- HbA1c ~7% substantially reduces microvascular complications; limited data in HbA1c range <6.5%
- Not clear if the increased expense, effort, and risk for hypoglycemia is merited by added benefit
- No data to support benefit for CVD for A1C<6.5%
  - ACCORD, ADVANCE, VADIT
- ACCORD suggests possible harm

**A1c Goal < 7% is justifiable for many/most patients at this time**

However, A1c goals must be individualized based on age, expected survival, co-morbidities, and risks.

Two major premises:
1) Lower glycemia to reduce risk of microvascular disease and
2) In setting of CVD or renal disease, use specific drugs demonstrated in recent CVOTs (SGLT-inhib, GLP-agonists).




**ADA Standards of Care**
**Diabetes Care 2019;42 (Suppl 1)**

# How to Achieve Metabolic Goals

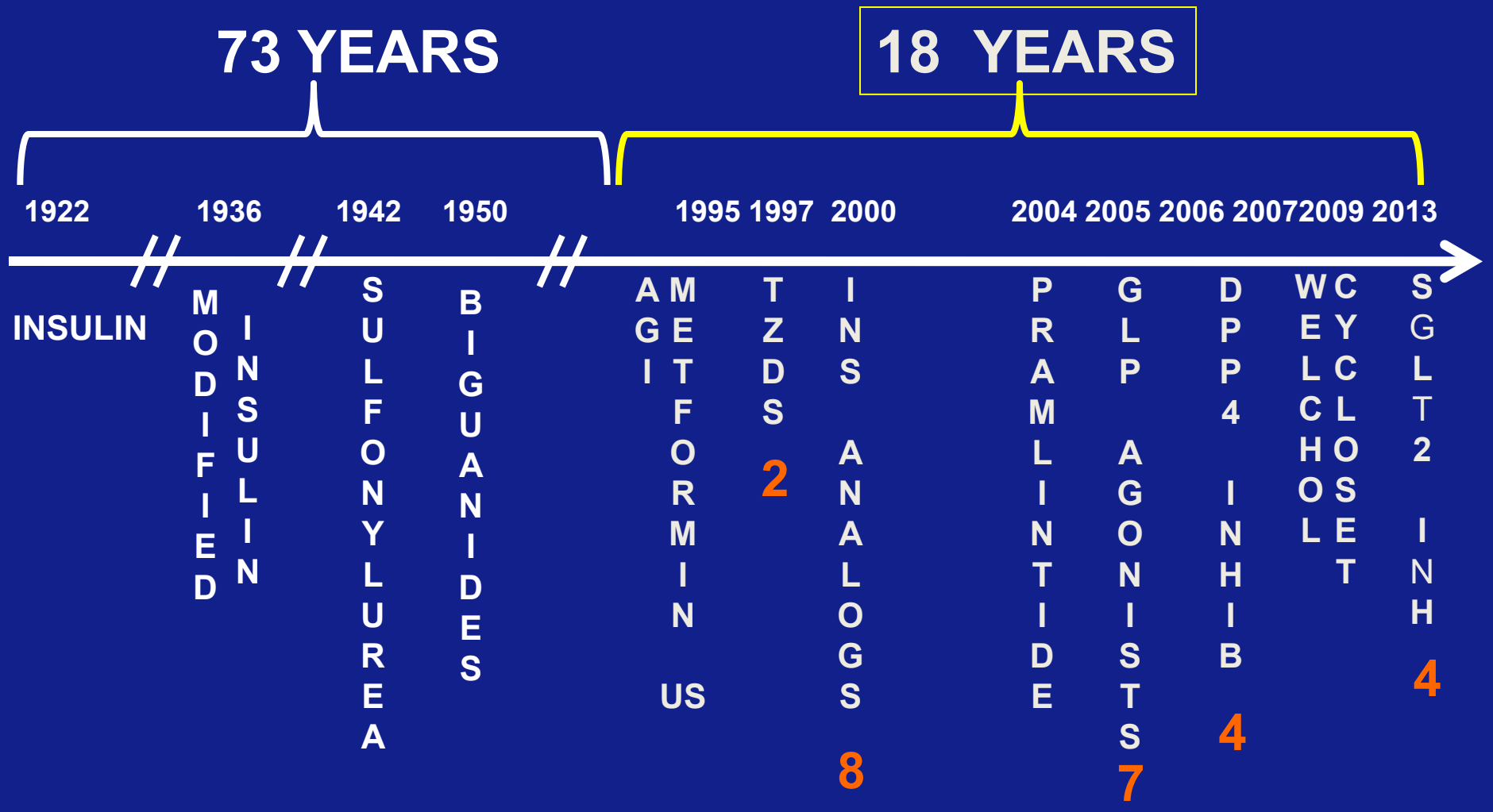
## Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy

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

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

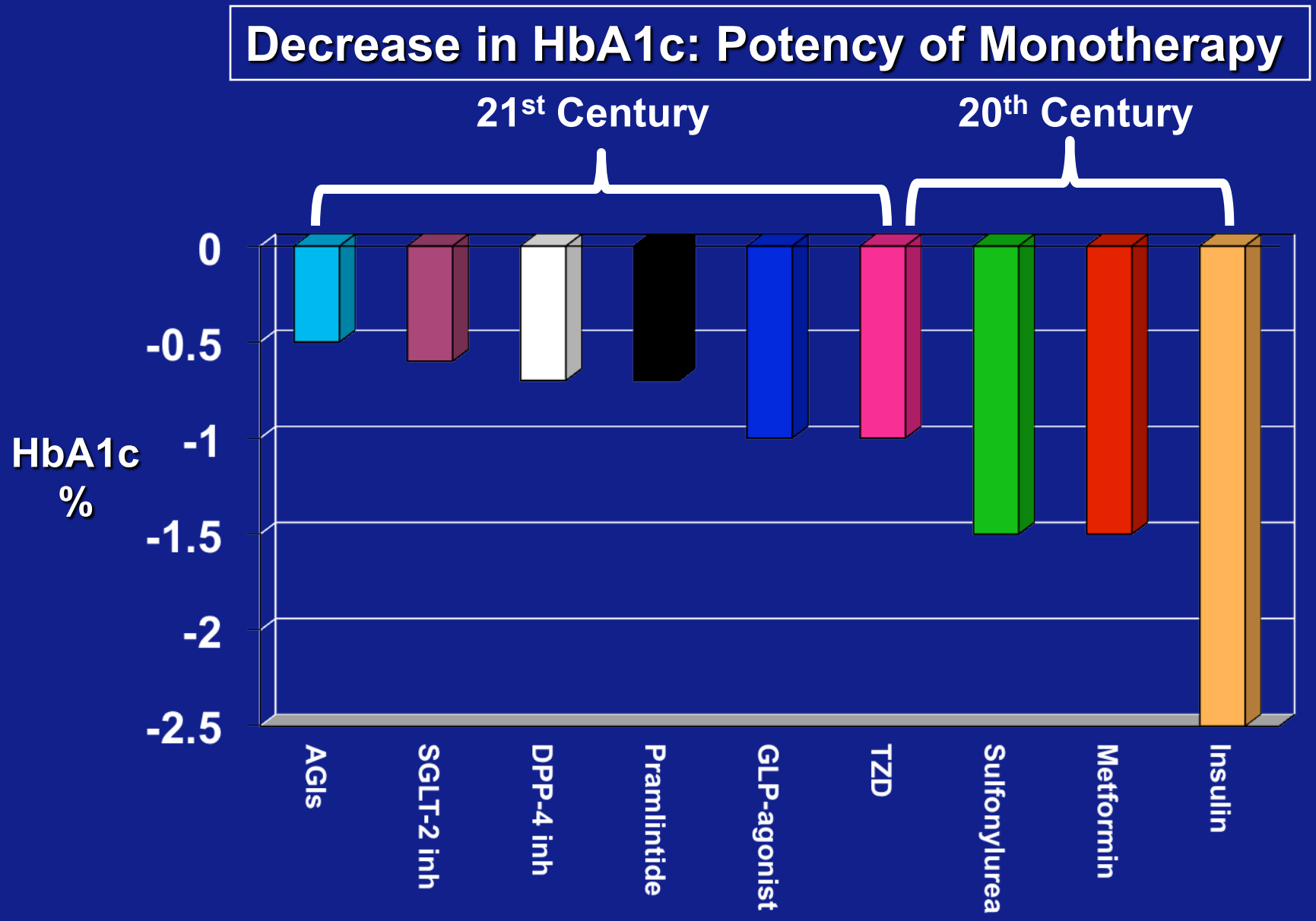


# Major Premises

## Selection of Interventions

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

# Glycemic Potency of Hypoglycemic Agents



# Anti-Hyperglycemic Agents in Type 2 Diabetes

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

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

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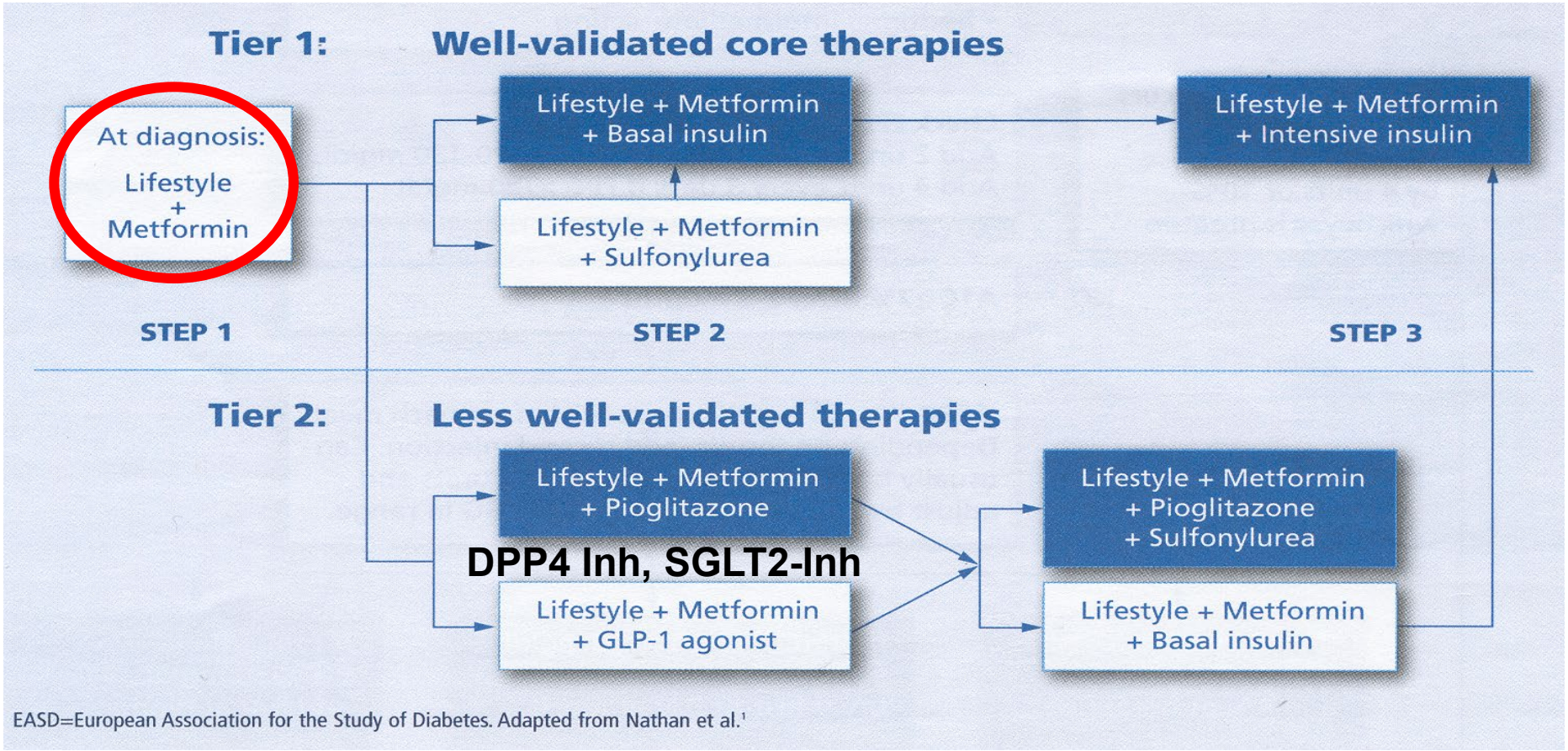


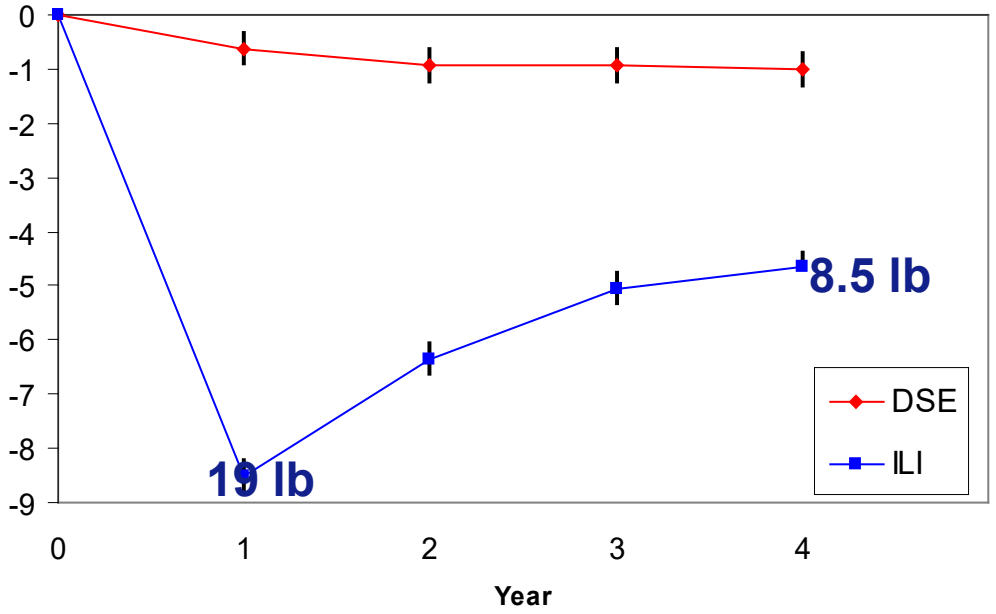

EASD=European Association for the Study of Diabetes. Adapted from Nathan et al.[1]

# Therapy of Type 2 Diabetes

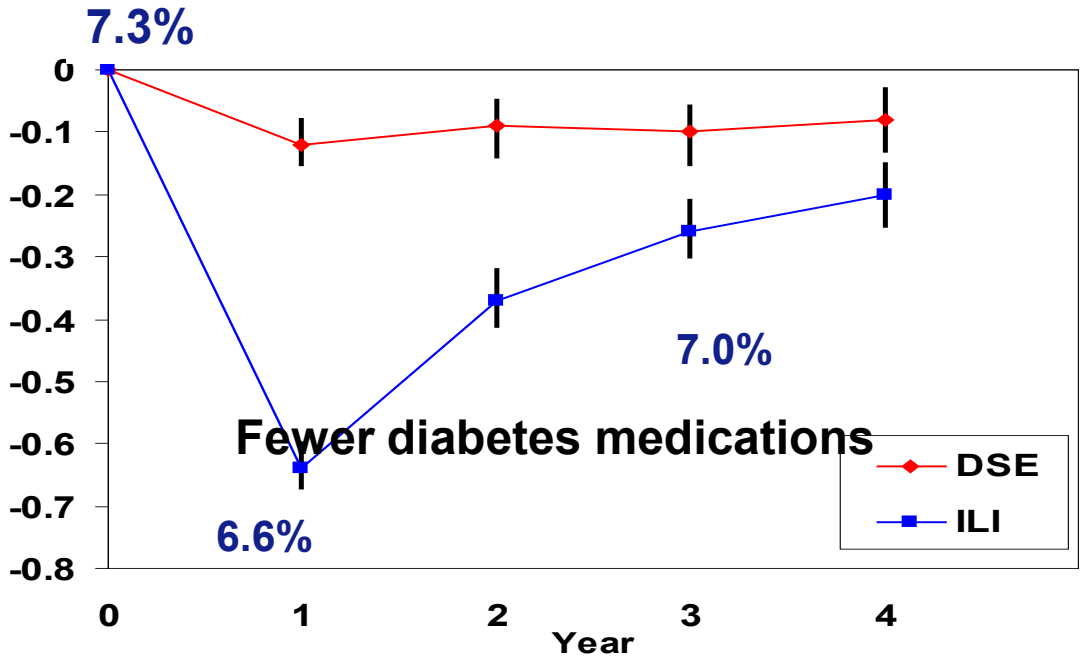
## Lifestyle: Diet and Exercise

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

# Effects of Behavioral Intervention




**Weight**




**HbA1c**

Look AHEAD
Action for Health in Diabetes

# First Step- Metformin + Lifestyle

- **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)
- Extremely safe, generally well-tolerated including down to eGFR as low as 45 ml/min
- Glucophage off-patent, very inexpensive

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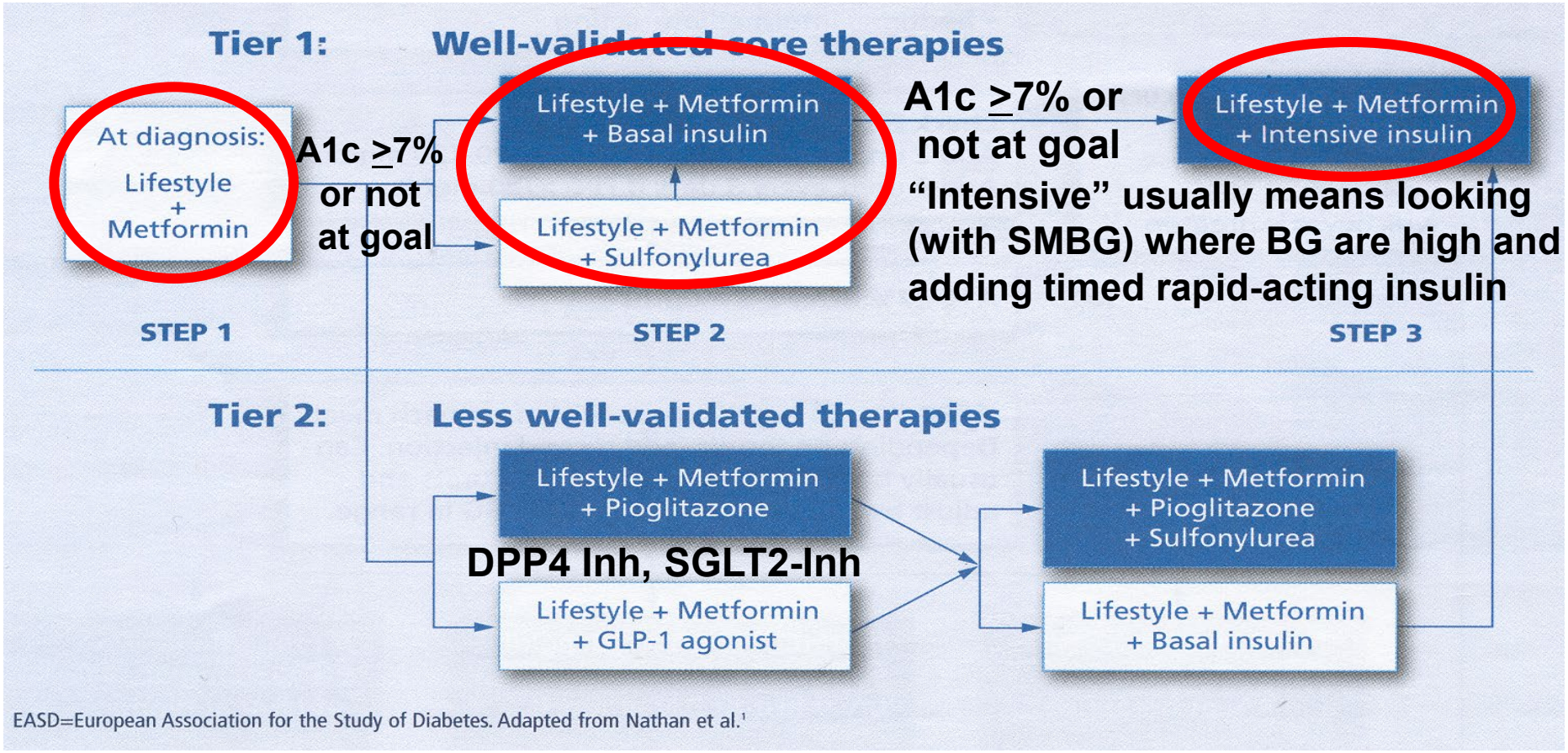

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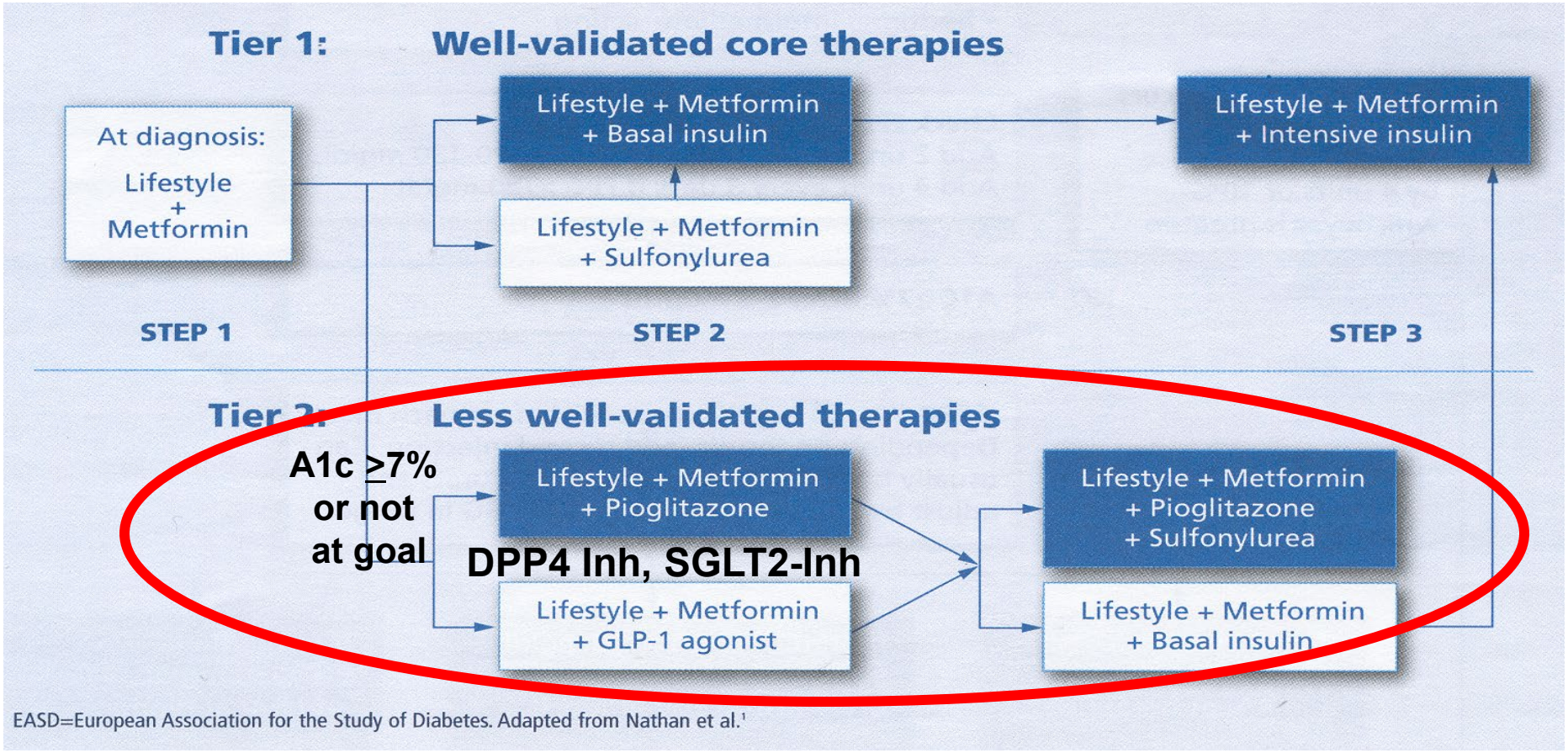



EASD=European Association for the Study of Diabetes. Adapted from Nathan et al.[1]

# GLP and DPP4 Inhibitors

## GLP and its Analogues

- Stimulate insulin secretion
- Suppress glucagon
- Slow motility
- Lower A1c by ~1.0%
- Injections twice per day
- Weight loss of ~ 6 lb
- Associated with nausea, vomiting, diarrhea- ~40%
- CVD benefit with lira- and semaglutide
- Expensive

## DPP 4 Inhibitors

- Inhibit breakdown of endogenous GLP, raising levels by ~2-fold
- Decrease A1c by ~0.6%
- Oral medication
- No weight loss
- No GI side-effects
- Neutral for CVD
- Expensive

# GLP and DPP4 Inhibitors

## Results of CVOTs

### DPP-4 inhibitors

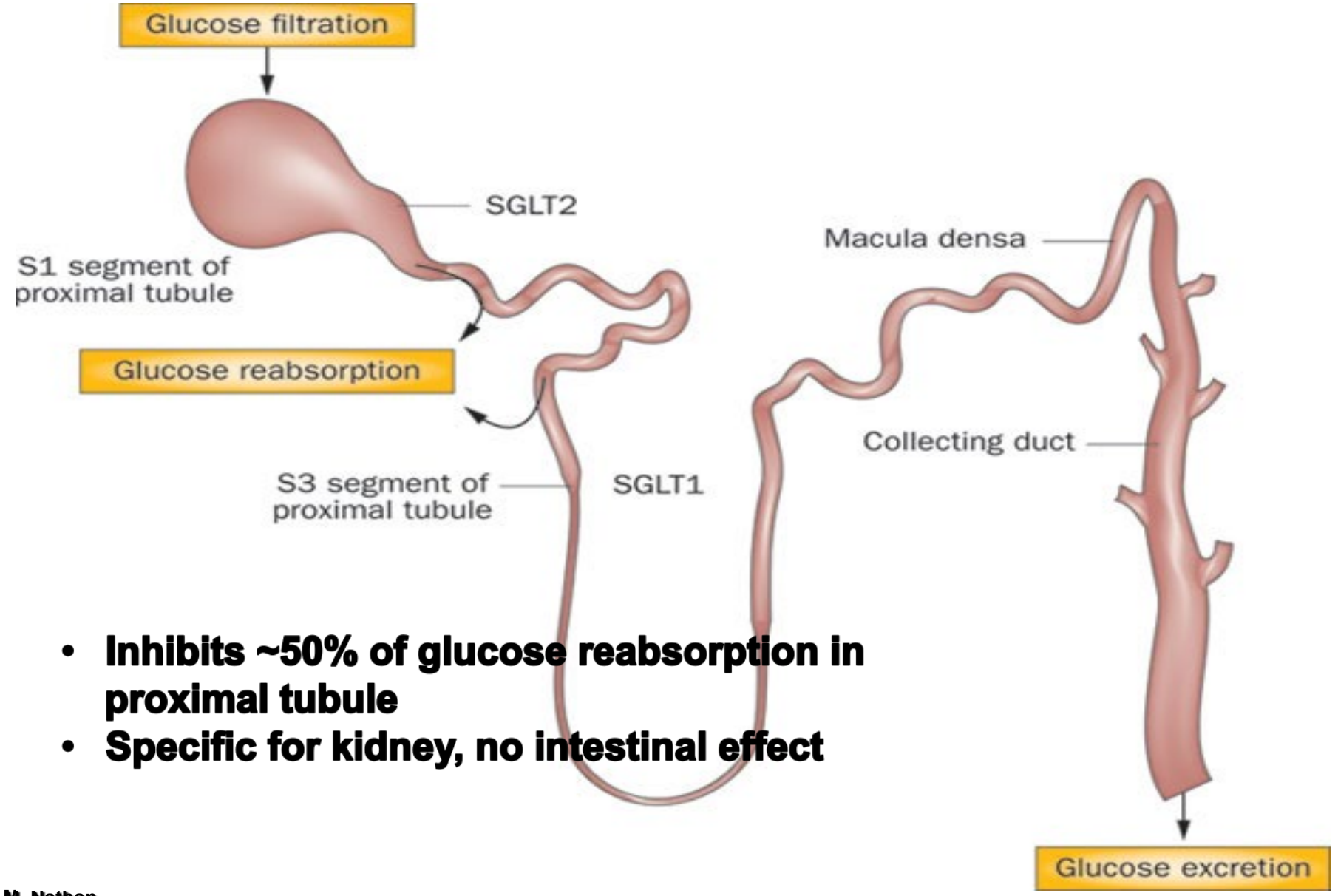
- SAVOR (saxagliptin): increased CHF hospitalizations
- EXAMINE (alogliptin): no risk
- TECOS (sitagliptin): no risk

NO BENEFIT with any of the DPP4 inhibitors

### GLP-1 agonists

- LEADER: CVD Benefit with liraglutide
- SUSTAIN: CVD Benefit with semaglutide
- ELIXA: NO Benefit with lixisenatide
- EXCSEL: NO Benefit with Exenatide-LAR.

# Newest Medication: SGLT-2 inhibitors



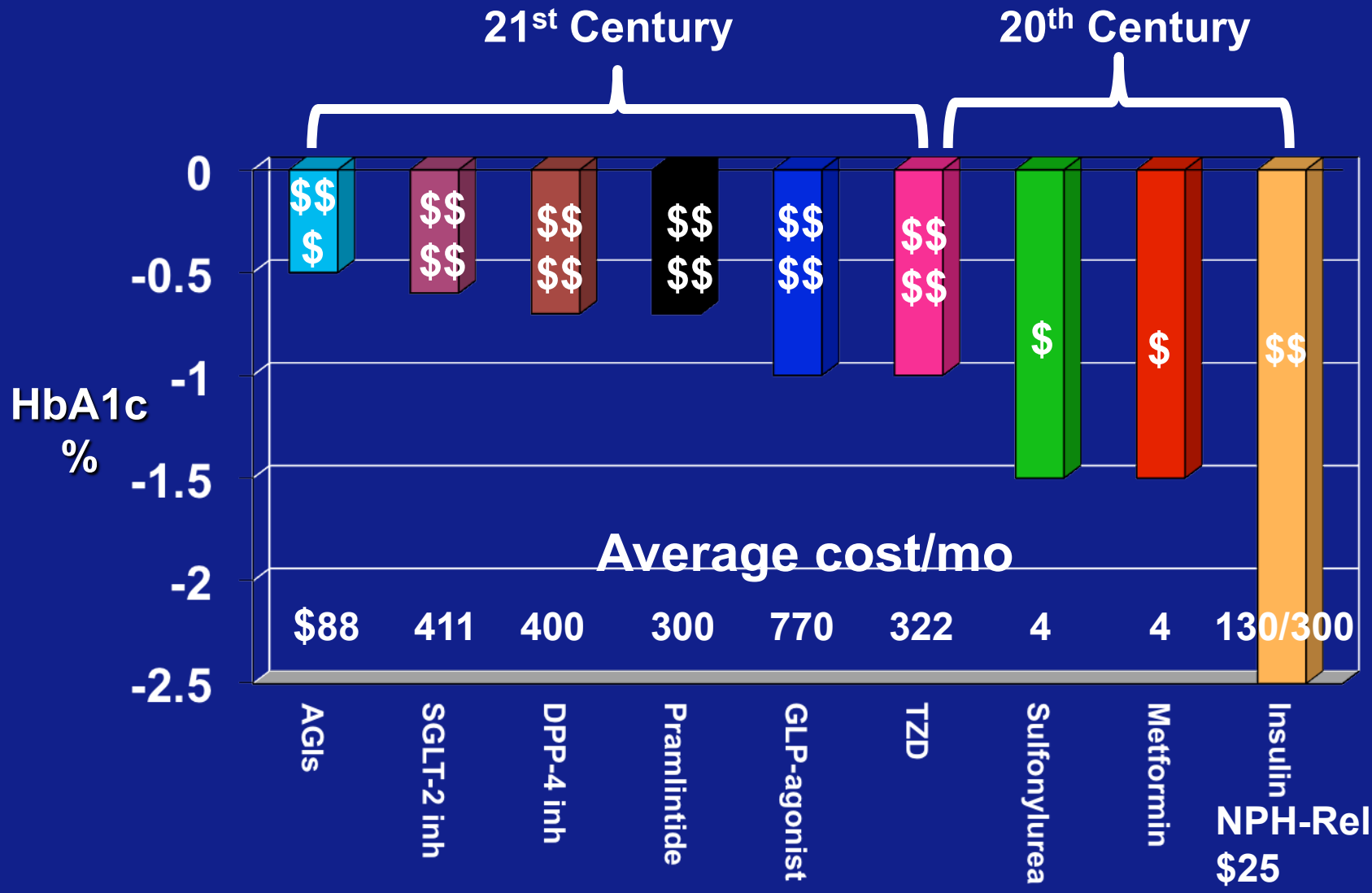

- **Inhibits ~50% of glucose reabsorption in proximal tubule**
- **Specific for kidney, no intestinal effect**

# Newest Medication: SGLT-2 inhibitors

- Inhibits re-absorption of glucose in proximal tubule
- Limited lowering of BG on basis of glycosuria
- Lowers A1c by ~0.6
- ? Added benefit- +/- lower BP, minor weight loss
- Added risk- vaginitis, UTIs
- Dapagliflozin, canagliflozin, empagliflozin
- CVD benefit with empagliflozin and canagliflozin
- Increased risk of amputations with canagliflozin

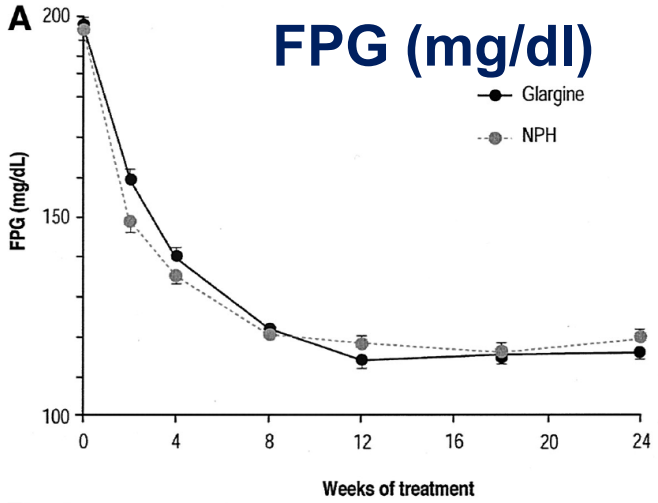
# Glycemic Potency vs Costs

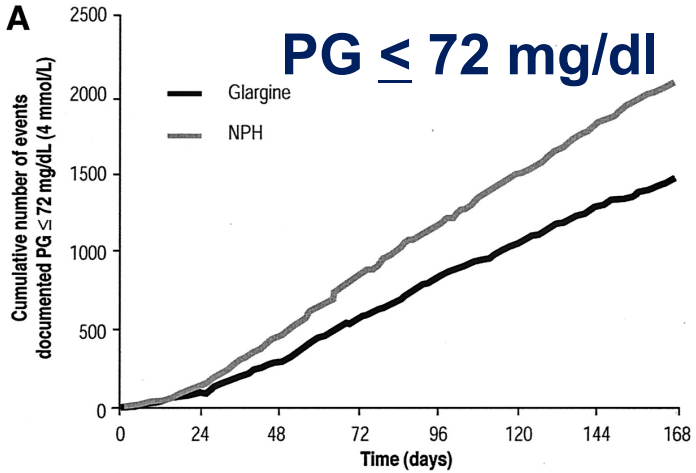
## Decrease in HbA1c: Potency of Monotherapy vs Cost

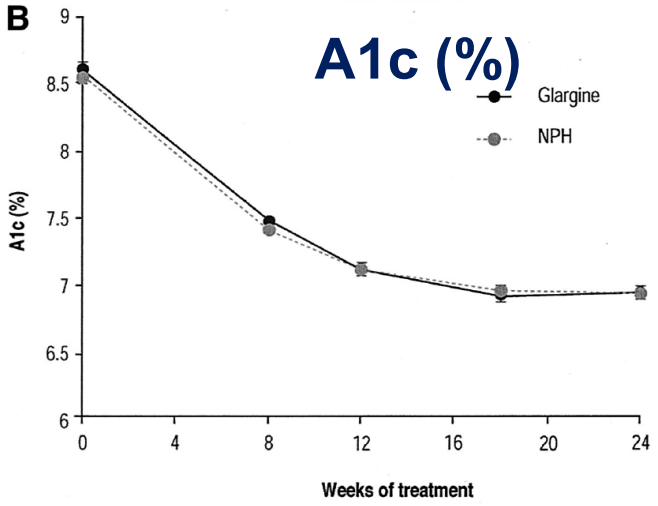


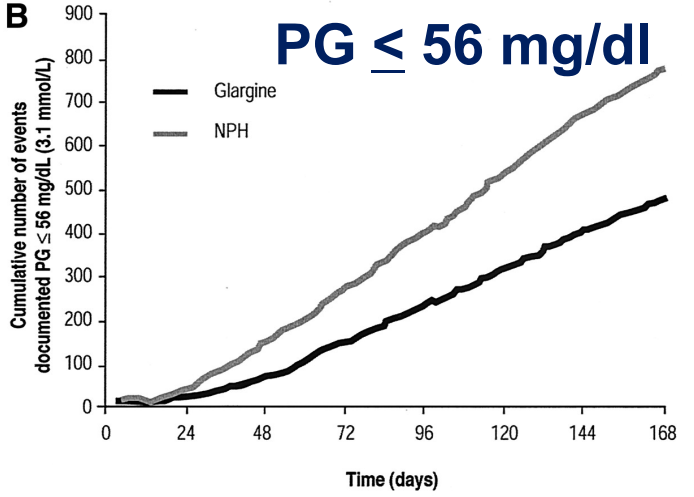

**Are the new drugs "worth it"?**

# Is Glargine better than NPH?




**756 T2DM with A1c >7.5%**
**(baseline A1c 8.6%) on OA**

Treat to Target Trial, Riddle et al.
Diabetes Care 2003; 26:30380

# Hypoglycemia with Glargine vs NPH

## Events per patient-year

| | Symptomatic | BG ≤72 mg/dl | BG ≤ 56 mg/dl | Severe* |
|---|---|---|---|---|
| NPH | 17.7 | 12.9 | 5.1 | 0.049 (9) |
| Glargine | 13.9 | 9.2 | 3.0 | 0.08 (14) |
| % reduction Glargine v NPH | -21 | -29 | -41 | +28 |
| Absolute diff. Events/pt-yr | -3.8 | -3.7 | -2.1 | +0.03 |

*None involved loss of consciousness or seizure.

Treat to Target Trial, Riddle et al. Diabetes Care 2003; 26:30380

# Updated Meta-analysis
## Long-acting Analogues vs Non-analogues: 49 RCTs

**The consensus for T2DM is that compared with NPH, long-acting analogues:**

- **Don’t reduce HbA1c (nominally higher)**
- **Reduce the frequency of nocturnal hypoglycemia modestly**
- **The frequency of total hypoglycemia is about the same**
- **Severe hypoglycemia is very rare and generally no different**

**Singh, SR**
**CMAJ 2009;180:385**

# If you Use a New Drug

| Class | Advantage | Disadvantage | When to Use |
|---|---|---|---|
| DPP-4 | Well-tolerated<br>Probably safe<br>One dose | Weak<br>Expensive | Mild DM |
| GLP-1 | Weight loss<br>No hypos | GI side effects<br>Limited efficacy<br>Injections<br>Expensive | Moderate DM<br>Weight gain or risk of hypos major issue.<br>Advanced CVD. |
| TZDs | No hypos | Edema, CHF, CVD risk,<br>Expensive | Never? NASH |
| SGLT-Inhib. | No hypos.<br>Dec. BP | Weak, DKA<br>UTIs, yeast<br>Expensive | Mild DM<br>Advanced CVD, CHF, CKD |

# Inpatients with Diabetes

## Background

- Almost 20% of MGH inpatients have diagnosis of diabetes
- An additional 9% have undiagnosed diabetes
- Average stay is 20% longer than non-diabetics

Wexler, Nathan, Cagliero
JCEM 2008;93: 4238

# Barriers to Good Care for Inpatients with Diabetes

## Impact of Hospitalization

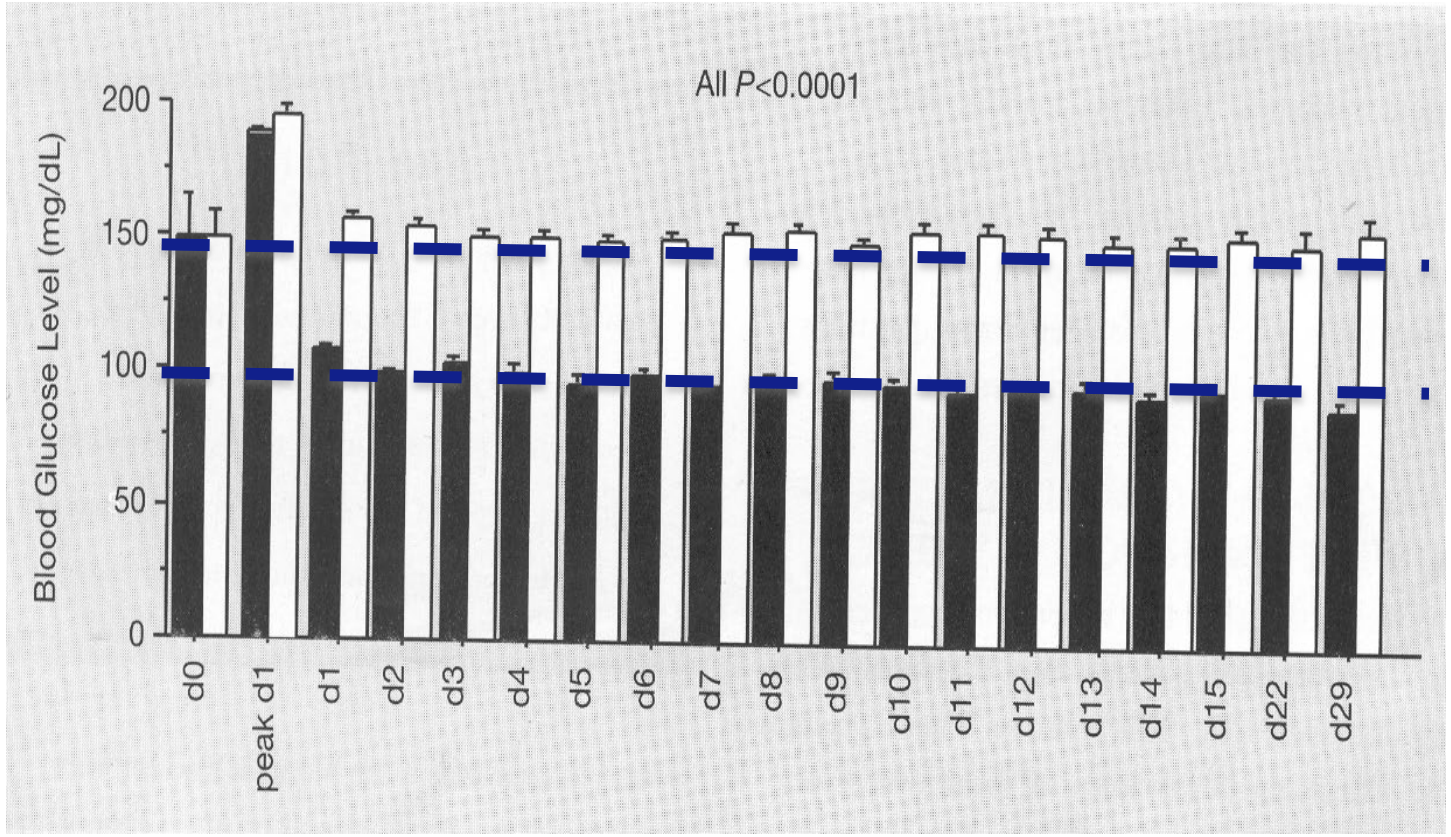
**Adversely affects:**

- **Schedule- late, missed meals**
- **Diet- different**
- **Medications- changed, delayed, held**
- **Activity- less**
- **Monitoring- different**
- **Stress- more**
- **Self-care- gone**

# Principles of Inpatient Care for Persons with Diabetes

- Maintain metabolic control in a safe, acceptable range- probably 80-200 mg/dl
  - Avoid large fluctuations in blood glucose that would lead to dehydration, hypoglycemia; prevent DKA
  - Never stop insulin in type 1
  - Usually stop oral agents in type 2, cover with insulin
  - Basal insulin recommended
- Protect feet
- Decrease risk of macrovascular and microvascular "events"- heart, kidney

# Effect of Intensive Insulin Therapy in Critically Ill SICU Patients



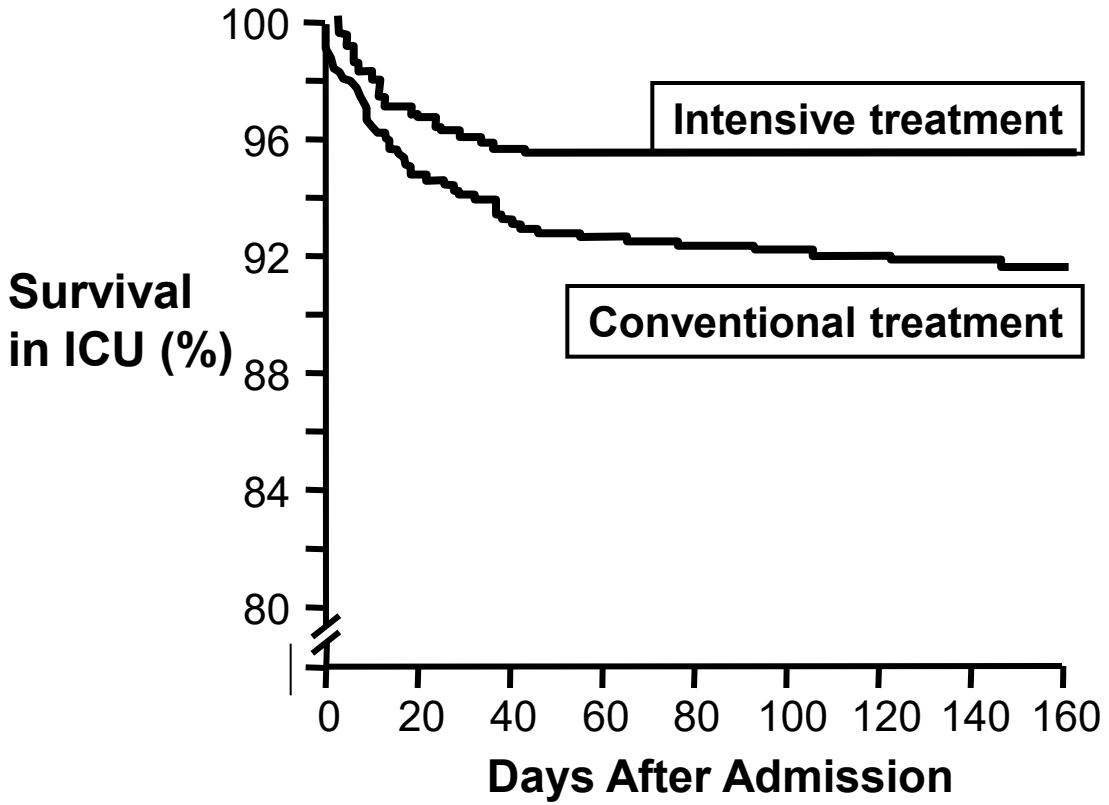

- 1548 ventilated surgical ICU patients
- 63% s/p cardiac surgery
- Randomized to:
  - -Conventional therapy goal 180-200 mg/dL
  - - Intensive therapy with insulin infusions if BG > 110 mg/dL to keep bg 80-110

  All patients received ~9 g IV glucose/hr followed by enteral or parenteral feeding.
- After discharge from ICU, target 180-200 mg/dL for all.

van den Berghe G
*N Engl J Med.* 2001;345:1359–1367.

Van den Berghe
Crit Care Med 2003;31:359

# Intensive Insulin Therapy in Critically Ill Surgical Patients Improves Survival

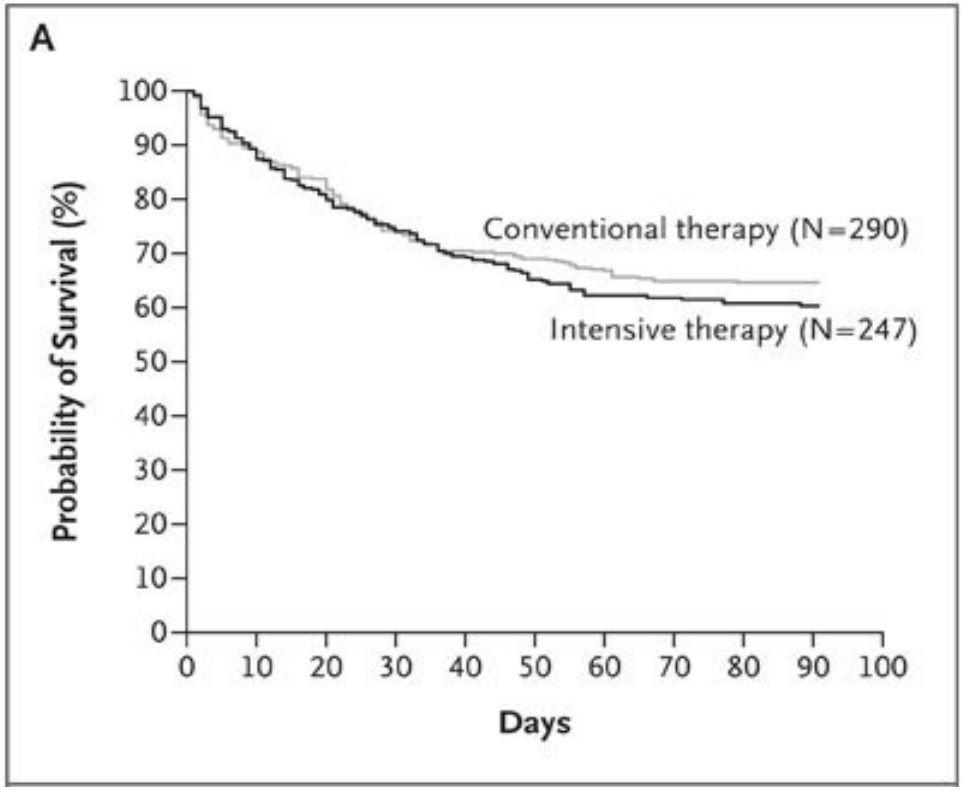



- Intensive therapy reduced mortality by 43% (4.6 vs 8%)
- Bacteremia, antibiotic use, polyneuropathy, duration of ventilation, and multi-organ failure reduced .

van den Berghe G
*N Engl J Med.* 2001;345:1359–1367.

# Subsequent Studies: No benefit of intensive insulin in sepsis

- Mean am glucose 112 vs 151 mg/dl
- No difference in death or organ failure at 28 days
- Stopped early for increased hypoglycemia (17% vs 4%) in intensive group

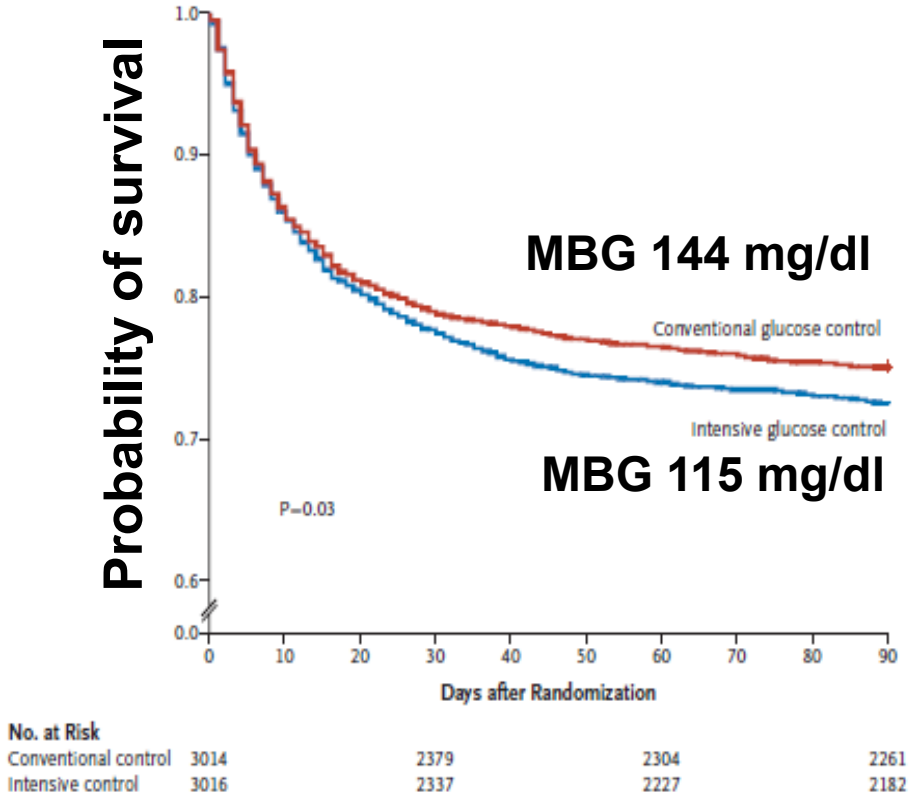



Brunkhorst, *NEJM* 2008.

# Subsequent Studies: NICE-SUGAR Study

## Medical and Surgical ICU Patients

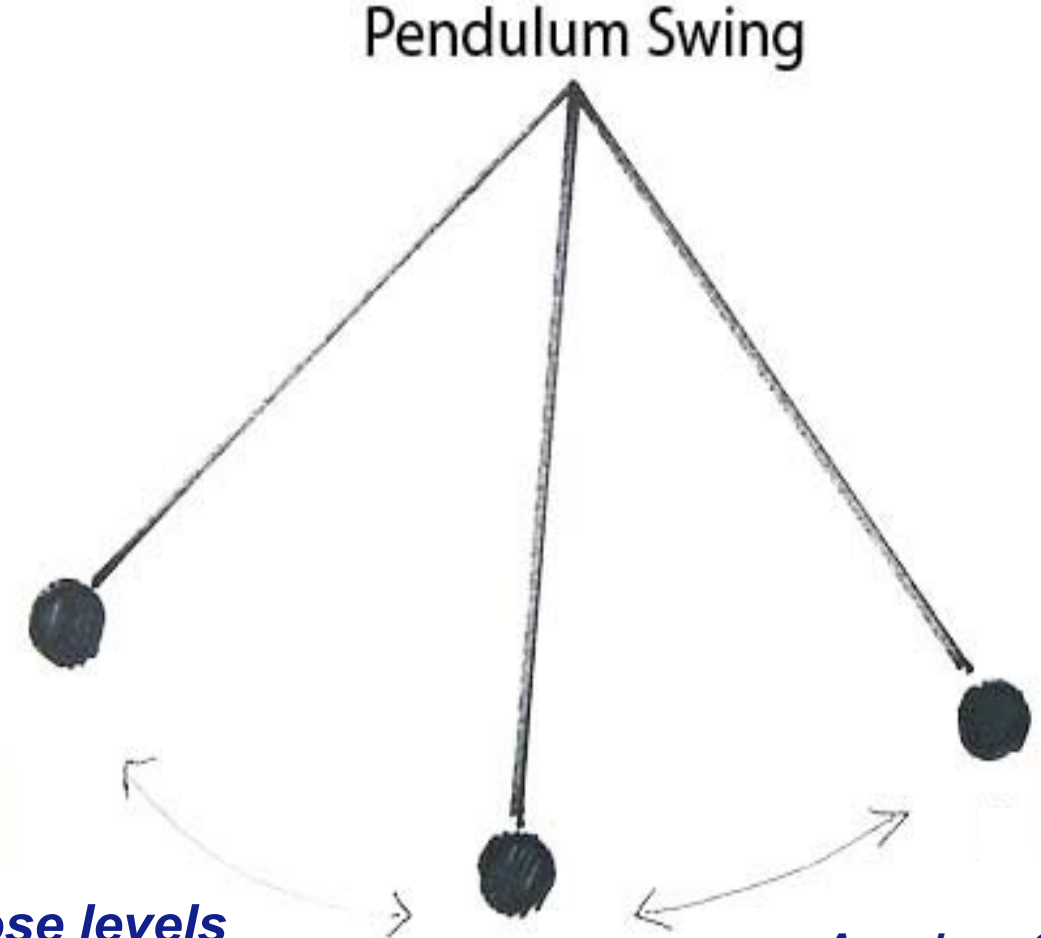
- Multicenter trial in Canada and Australia
- 6104 patients
- Mean glucose of 115 versus 144 mg/dl
- Increased mortality (2.6%) in intensive control group
- Severe hypoglycemia in 6.8% versus 0.5%




*N Engl J Med* 2009; 360:1283-97

# Inpatient Management of Glycemia
## Summary of Current Evidence

- Substantial observational data link hyperglycemia in hospitalized pts to poor outcomes- ?causal, ?marker of disease severity
- Normalizing glycemia in intensive care units with inconsistent results; several meta-analyses have shown no mortality benefit, a decrease in post-op infections but with more hypoglycemia
- Almost no data to demonstrate role of tight glucose control in non-critically ill patients




Extreme

***Target glucose levels of 80-110 mg/dl***

**140-180 mg/dl**
**ICU & Non-ICU**

Middle

***ADA 2019***

Extreme

***American College of Physician 2011: "not using intensive insulin therapy to strictly control blood glucose"***

# Special “Cases”

## Glucocorticoids

- Glucocorticoids used in pharmacologic doses (e.g. prednisone > 10 mg/day, dexamethasone > 1mg/day) can precipitate diabetes or raise BG

- The hyperglycemic effect of prednisone has the same time course as NPH insulin

- NPH insulin can be given (or dose adjusted) in AM to help control BG during steroid therapy

# Special “Cases”

## Atypical Antipsychotics: olanzapine, clozapine, quetiapine and others

- Mechanisms unclear, but associated with weight gain, insulin resistance and β-cell failure
- May precipitate, worsen DM, cause DKA
- Advisable to check a HbA1c prior to initiation and follow BG carefully
- Insulin may be necessary if psych medications can’t be changed

# Conclusions

- Diabetes, and especially type 2, affects a substantial minority of the inpatient and outpatient population
- Owing to its frequency and effects on virtually every aspect of clinical medicine, practitioners should be familiar with its prevention, diagnosis, and treatment
- Endocrinologists can’t do it all on our own