Initiating Insulin in Primary Care for Type 2 Diabetes Mellitus

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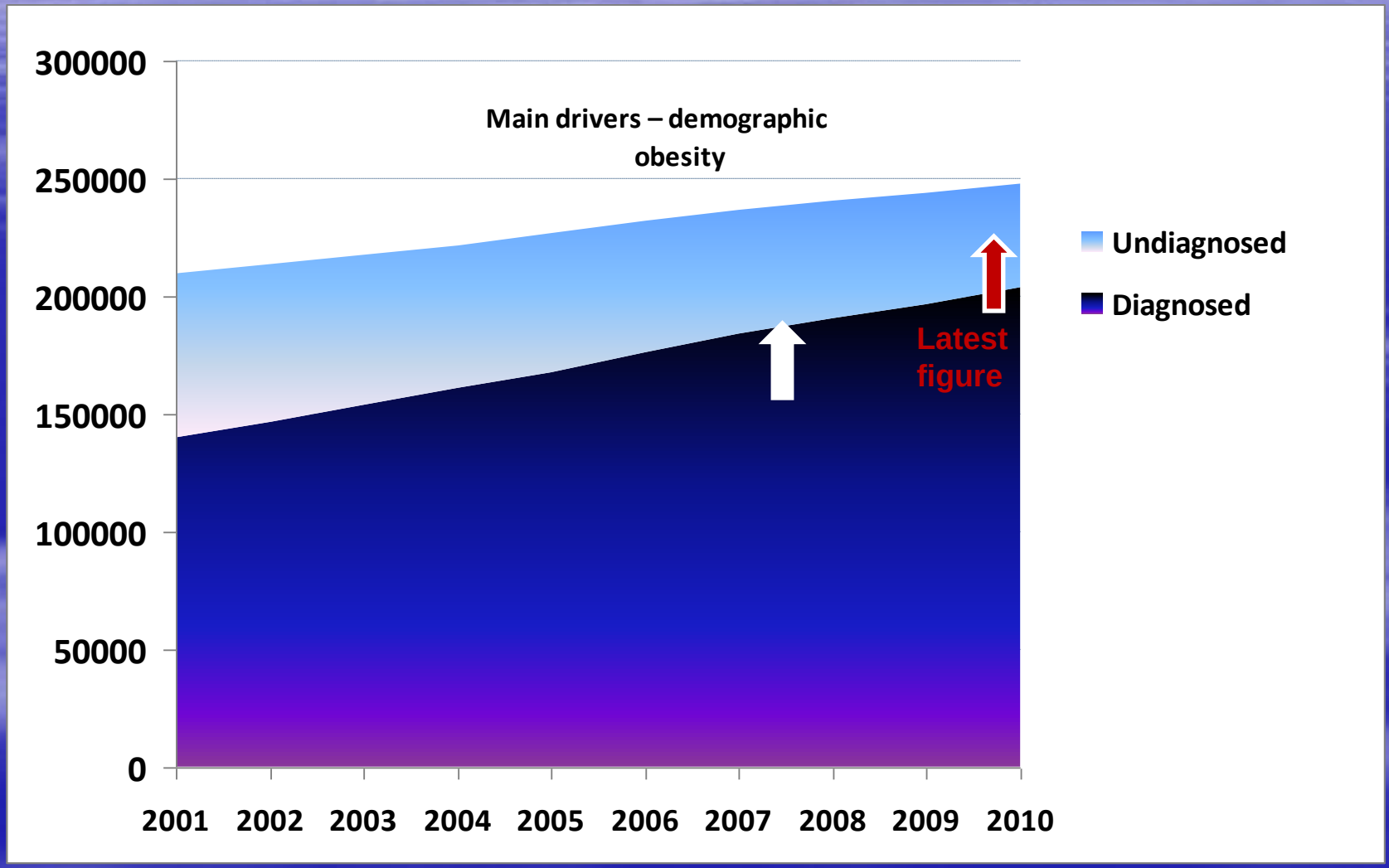
Outline

- *How big is the problem?*
- Natural progression of type 2 diabetes
- What to tell (and what not to) patients
- After all does better control matter….
- Legacy effect
- Why early insulin?
- Can we keep things safe and simple?

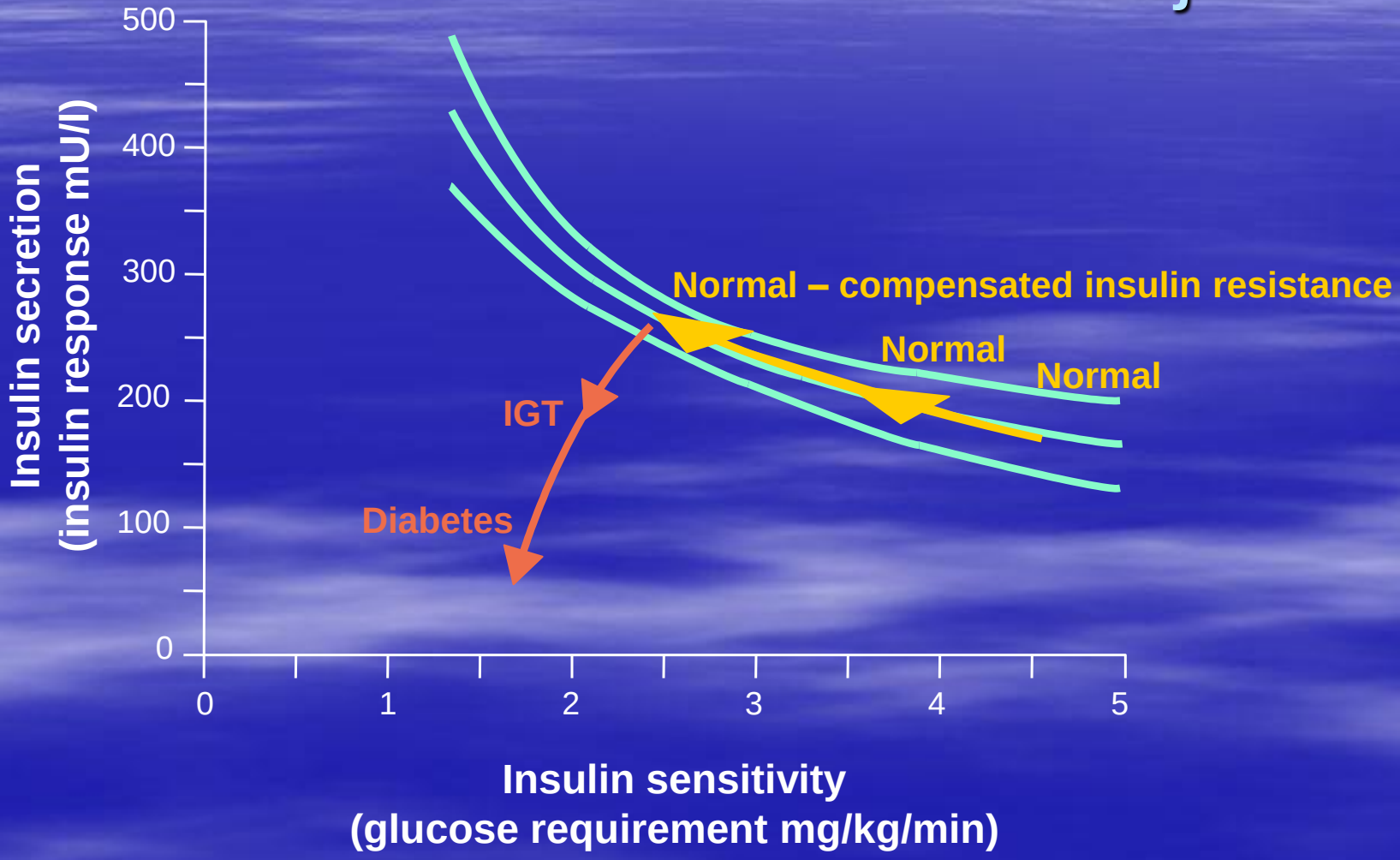
How big is the problem?



Global Epidemic of Type 2 Diabetes

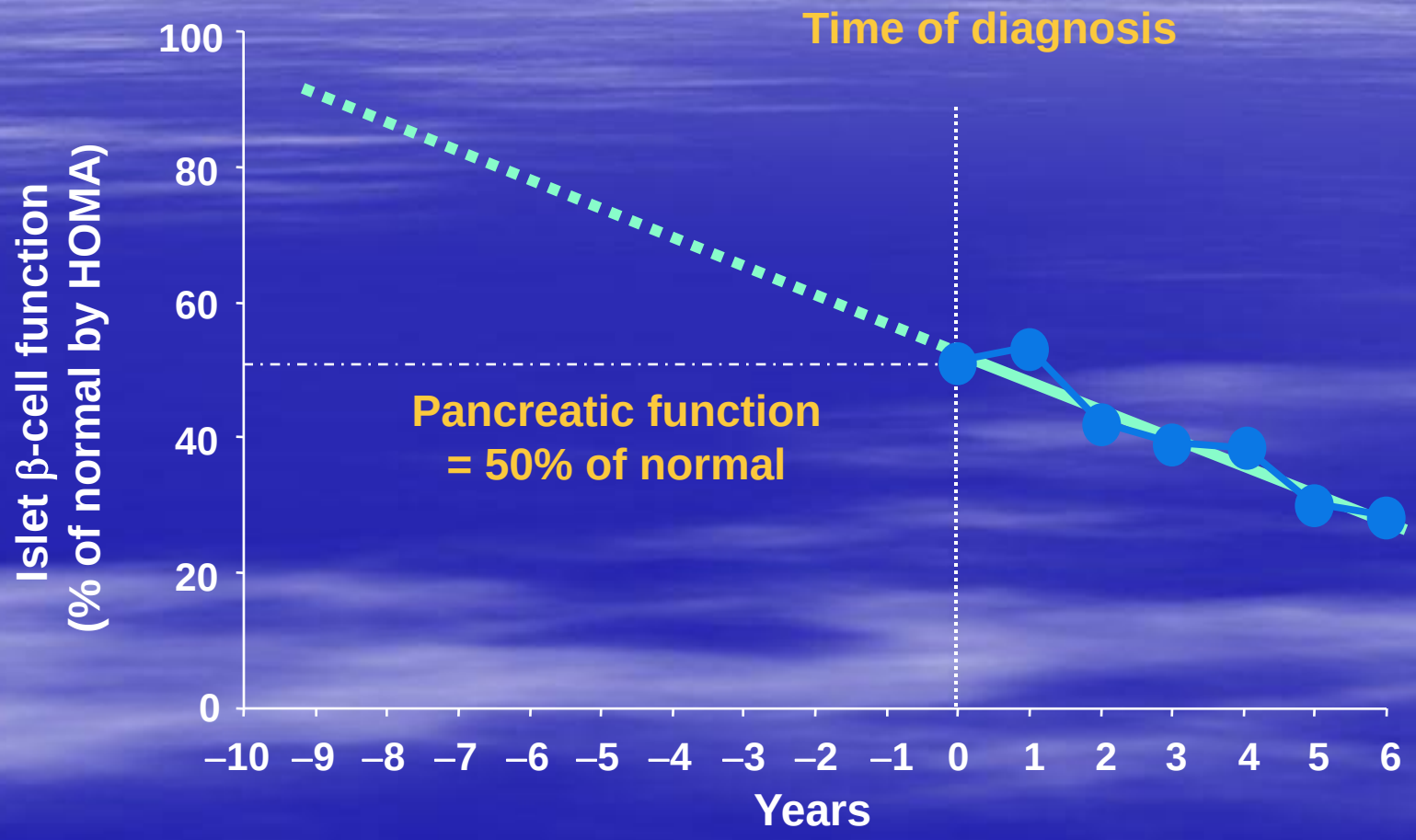
- **Ageing Population**
- **Global Lifestyle "Westernization"**
- **Surging Obesity**

Progression to Type 2 diabetes is usually from failure of insulin secretion in insulin resistant subjects



Weyer C et al. *J Clin Invest.* 1999;104:787-794

UKPDS: Islet β-cell function and the progressive nature of diabetes



HOMA = homeostasis model assessment

Holman RR. *Diab Res Clin Pract*. 1998;40(suppl):S21-S25;
UKPDS. *Diabetes*. 1995;44:1249-1258

What should be told to Type 2 diabetes patients about insulin?

'Most people with Type 2 diabetes eventually will need insulin'

- There is a progressive failure of insulin production in people with type 2 diabetes
- Compliance with healthy lifestyle and oral medications is important but is likely that eventually additional help from insulin may be required

And what should never be told!

- Better comply with your medications and lifestyle and bring your act together

OR ELSE

Never Ever use Insulin as a weapon

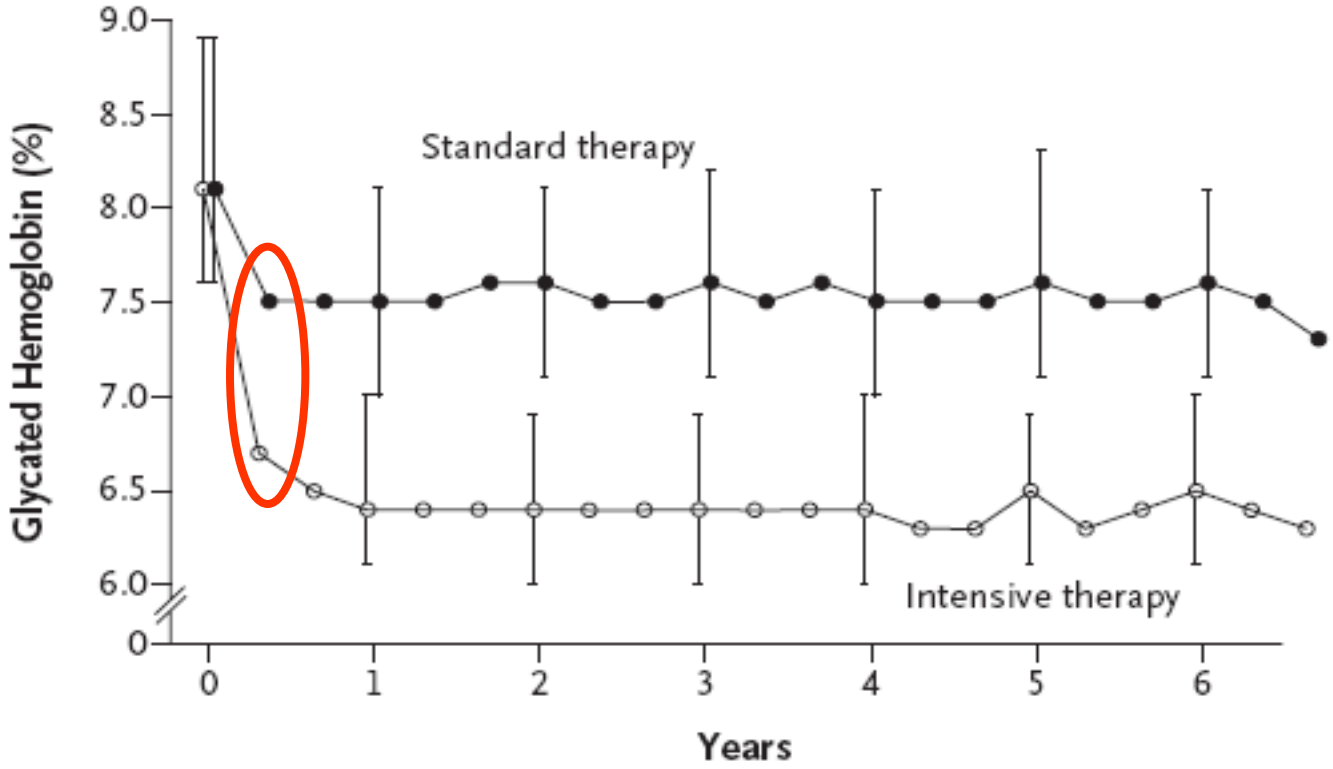
Does good control matter?

ACCORD

- 10251 high risk T2DM patients
- Intensive arm target HbA1c < 6%
- Primary: nonfatal MI or stroke or death from CV causes. Secondary: Death from any cause
- **STOPPED 17 months early as increased CV deaths with intensive tx**

The Action to Control Cardiovascular Risk in Diabetes Study Group. NEJM. 2008; 358:2545-2559

Glycaemic control in ACCORD



No. at Risk							
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

The Action to Control Cardiovascular Risk in Diabetes Study Group. NEJM. 2008; 358:2545-2559

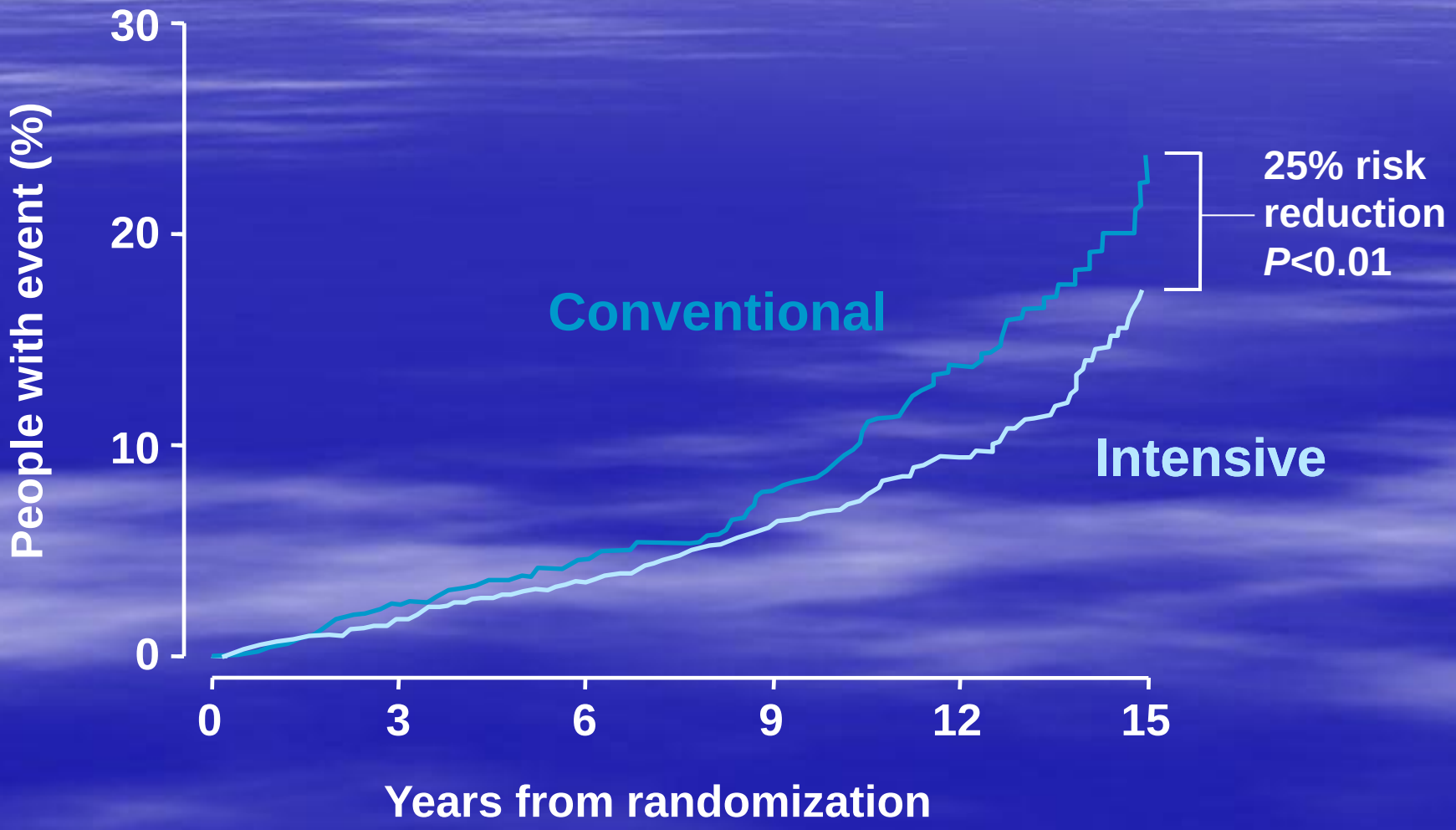
Adverse events

Table 3. Adverse Events, Clinical Measures, Tobacco Use, and Use of Nonglycemic Medication after Randomization.*

Variable	Intensive Therapy (N=5128)	Standard Therapy (N=5123)	P Value†
Adverse events			
Hypoglycemia — no. (%)			
Requiring medical assistance	538 (10.5)	179 (3.5)	<0.001
Requiring any assistance	830 (16.2)	261 (5.1)	<0.001
Fatal or nonfatal heart failure — no. (%)	152 (3.0)	124(2.4)	0.10
Motor vehicle accident in which patient was driver — no./total no. (%)	9/5033 (0.2)	14/5036 (0.3)	0.40
Any nonhypoglycemic serious adverse event — no. (%)	113 (2.2)	82 (1.6)	0.03
Fluid retention — no./total no. (%)‡	3541/5053 (70.1)	3378/5054 (66.8)	<0.001
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.001

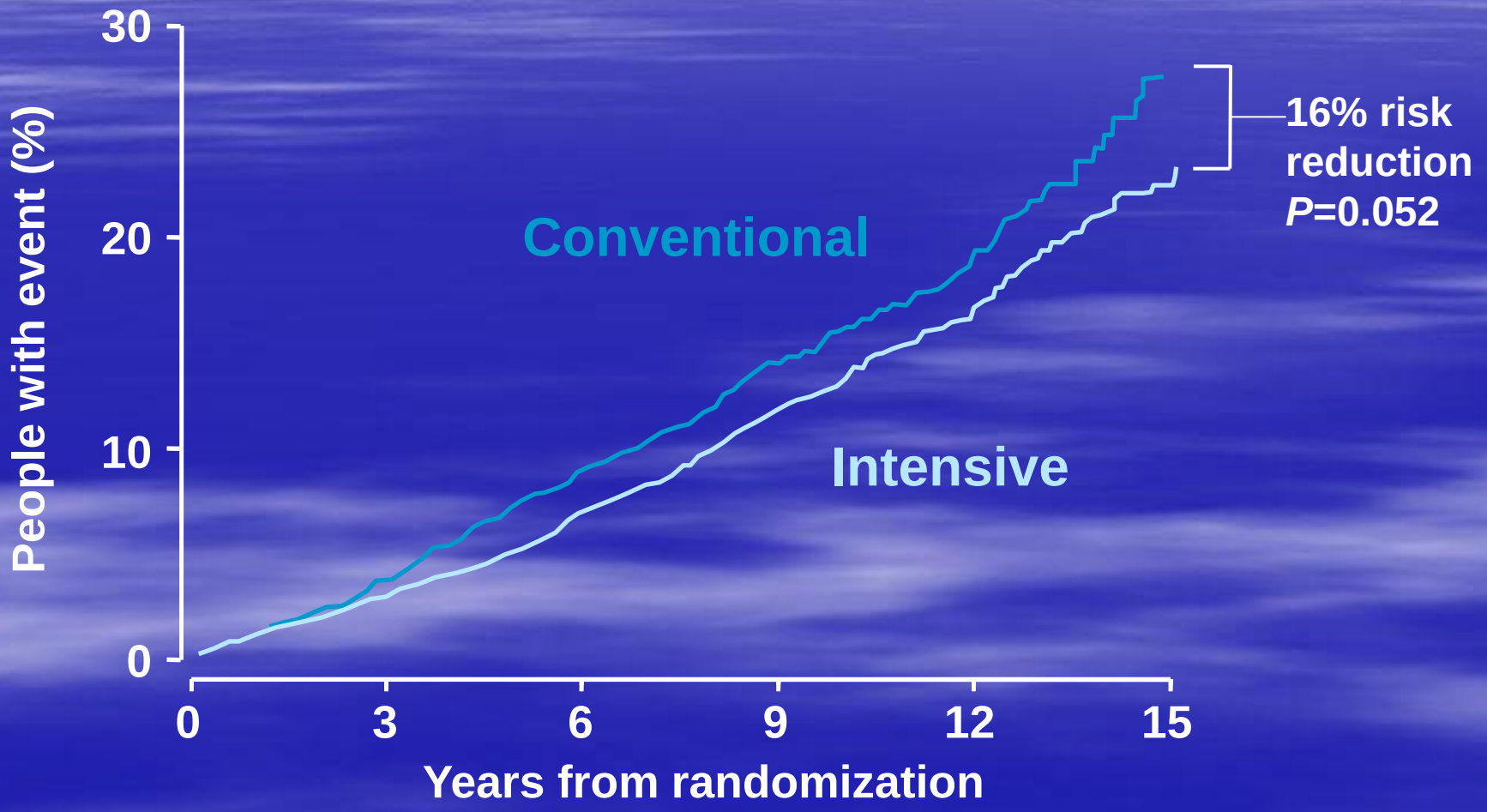
The Action to Control Cardiovascular Risk in Diabetes Study Group. NEJM. 2008; 358:2545-2559

UKPDS: effects of management on microvascular endpoints



UKPDS Group. *Lancet.* 1998;352:837-853

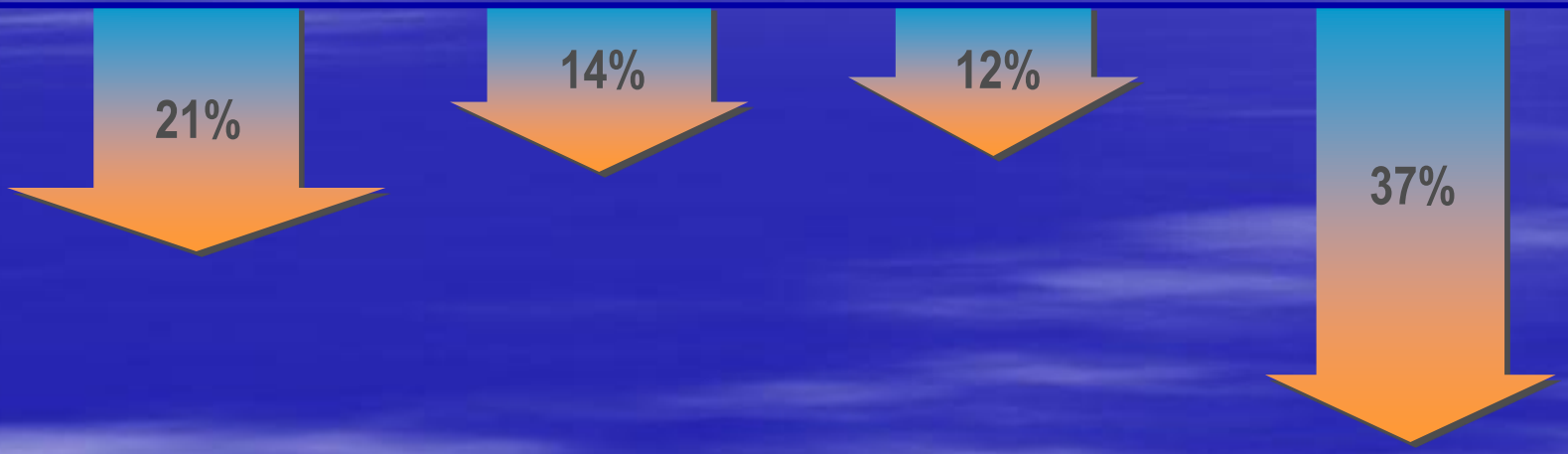
UKPDS: effects of treatment on myocardial infarction in Type 2 diabetes



UKPDS Group. *Lancet.* 1998;352:837-853

Improved Glycemic Control Has Been Shown to Reduce the Risk of Complications

According to the United Kingdom Prospective Diabetes Study (UKPDS) 35, Every 1% Decrease in A1C Resulted in:



Decrease in risk of any diabetes-related end point (*P*<.0001)

Decrease in risk of MI (*P*<.0001)

Decrease in risk of stroke (*P*=.04)

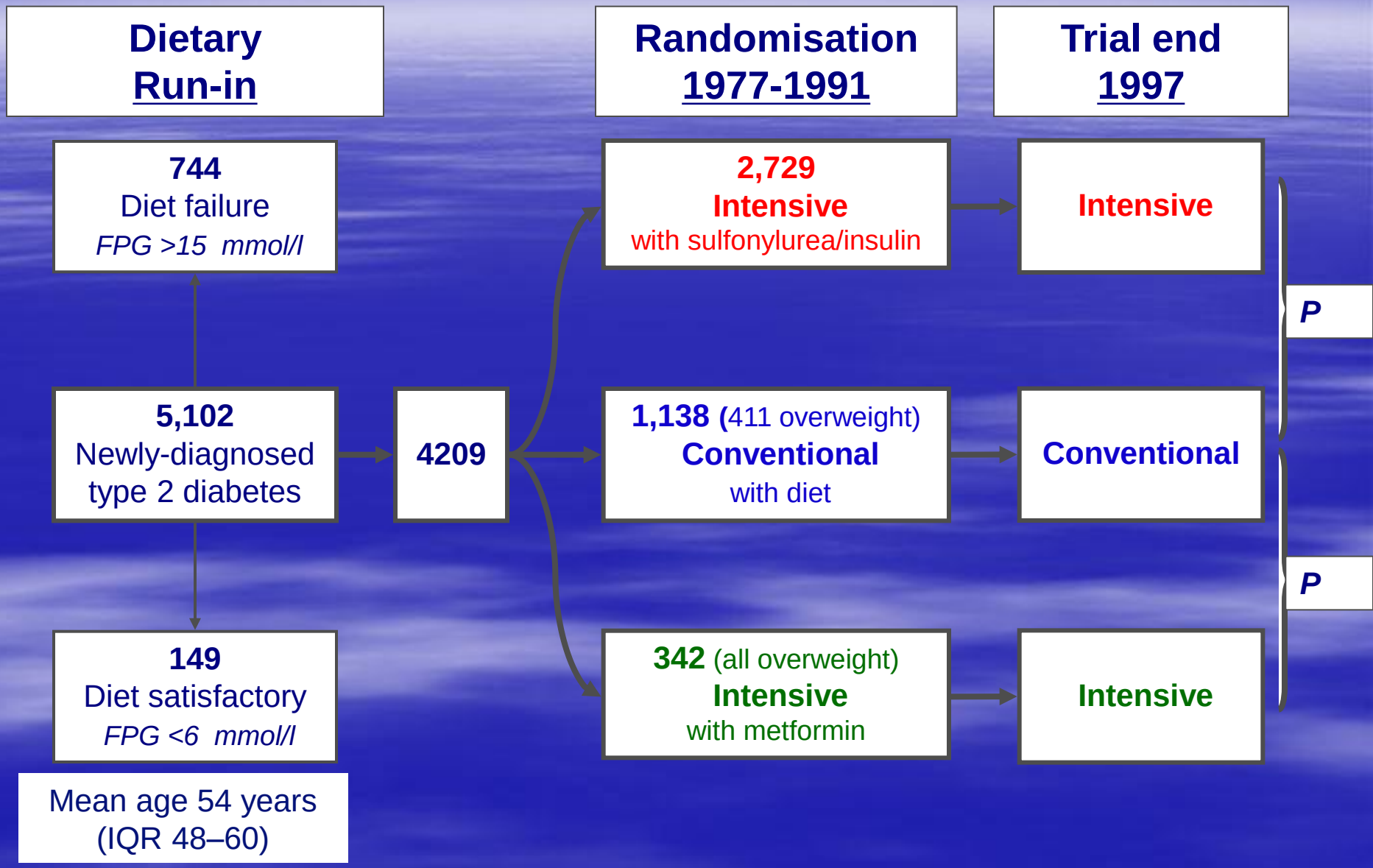
Decrease in risk of microvascular complications (*P*<.0001)

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

The Legacy Effect (Metabolic memory)

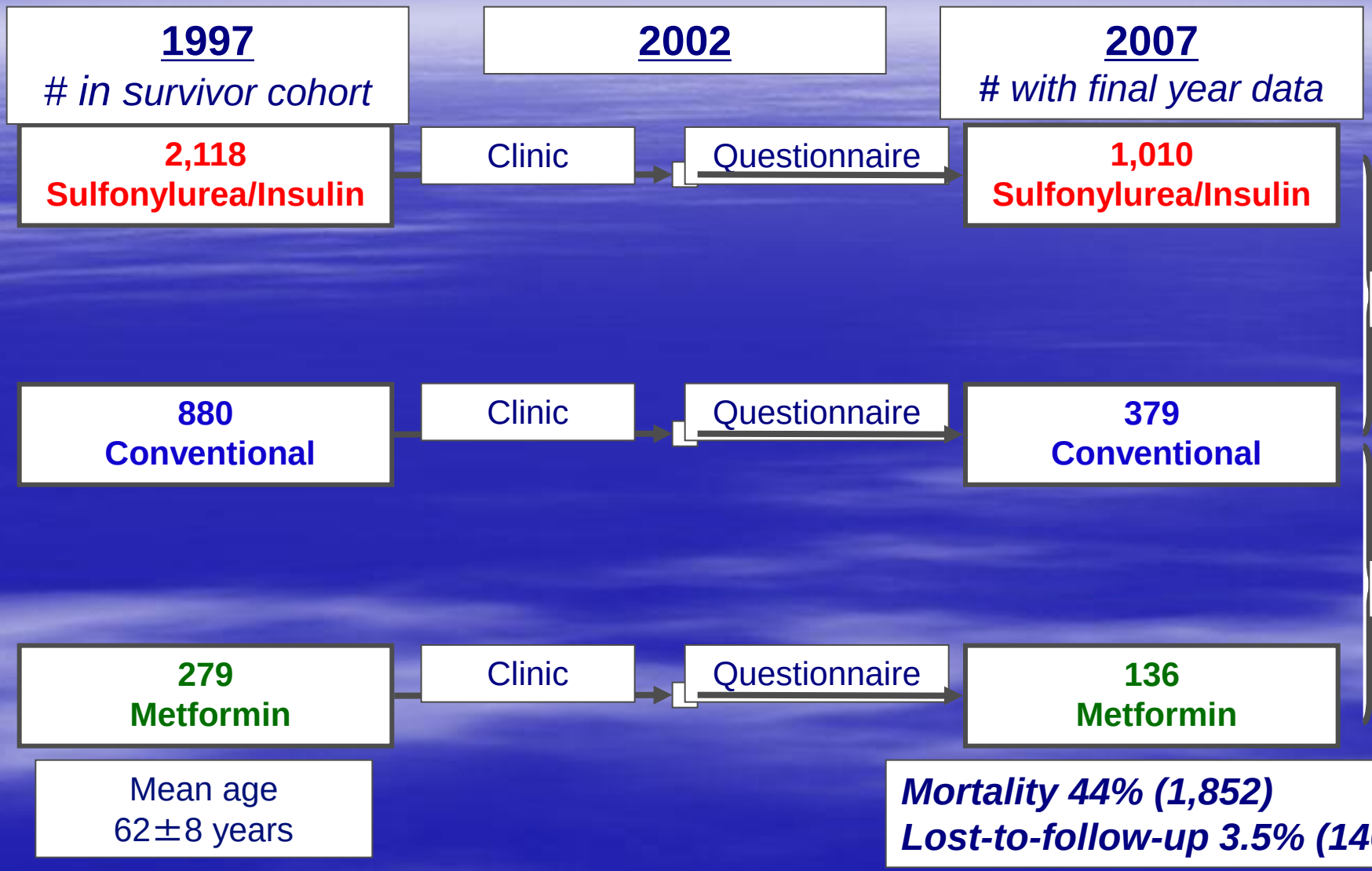
- What is Legacy? Something received from an ancestor or from the past

UKPDS Legacy study; NEJM 2008



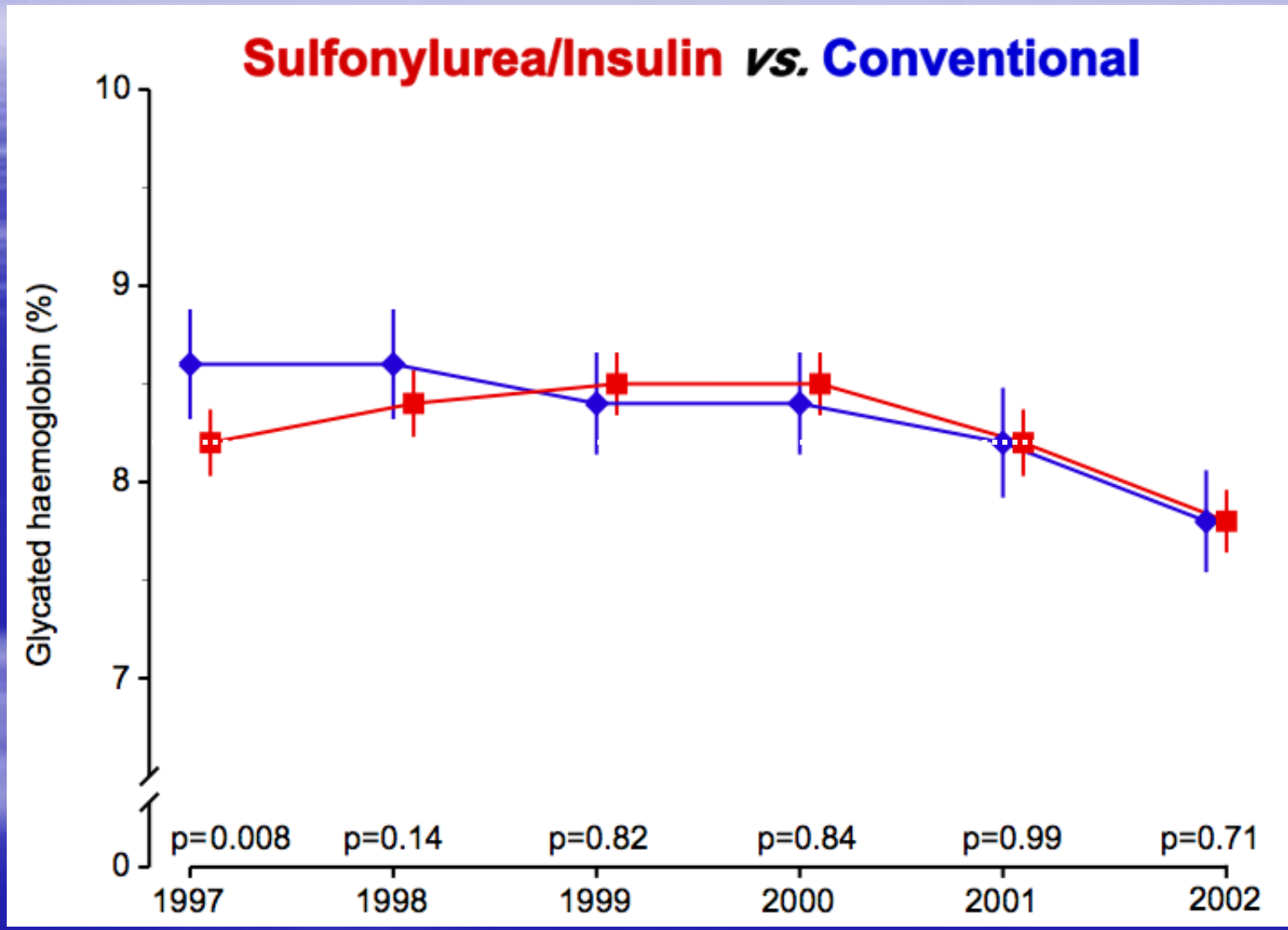
Holman RR et al. NEJM. 2008; 359(15):1577-89

Post-Trial Monitoring: Patients



Holman RR et al. NEJM. 2008; 359(15):1577-89

Post-Trial Changes in HbA_{1c}



Holman RR et al. NEJM. 2008; 359(15):1577-89

Legacy Effect of Earlier Glucose Control

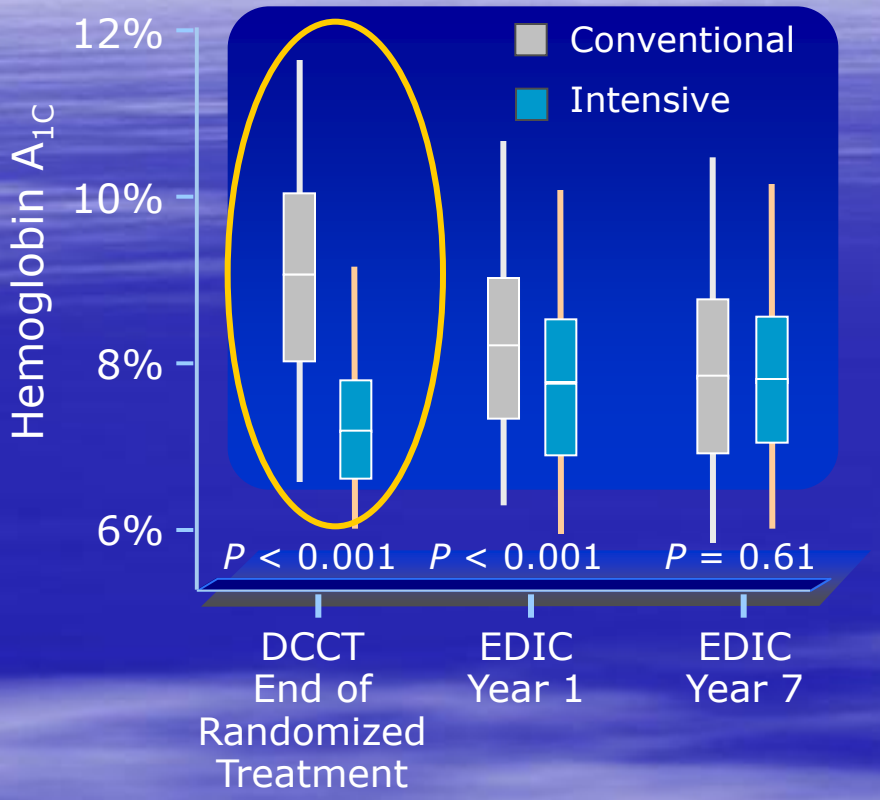
After median 8.5 years post-trial follow-up

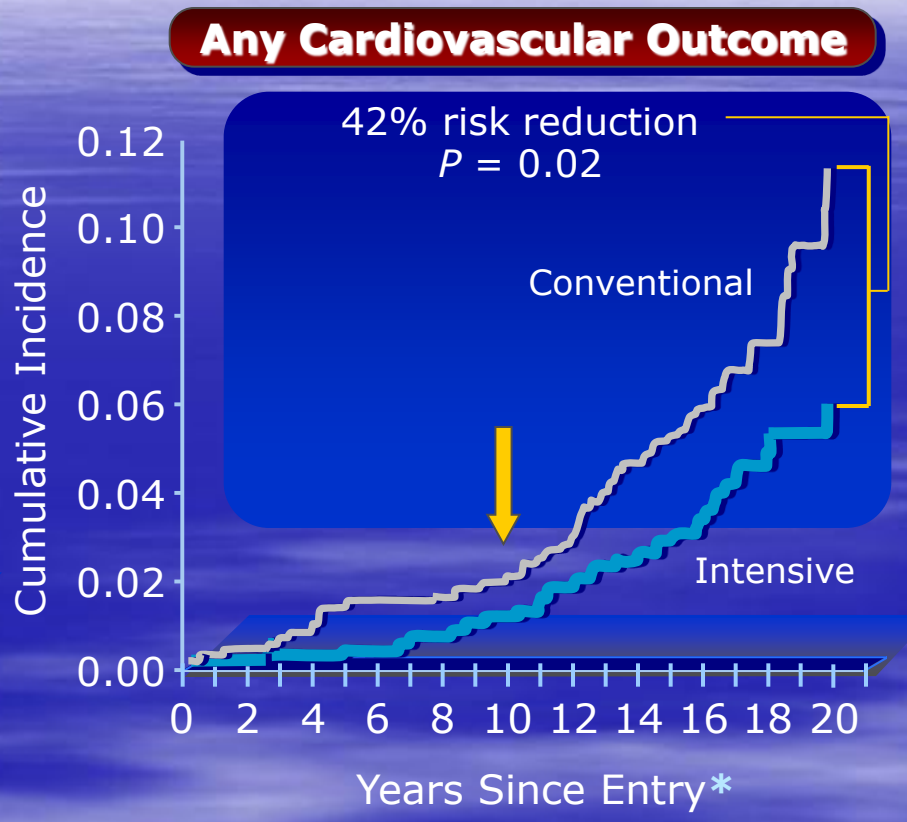
Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	**9%**
	P:	0.029	**0.040**
Microvascular disease	*RRR:*	25%	**24%**
	P:	0.0099	**0.001**
Myocardial infarction	*RRR:*	16%	**15%**
	P:	0.052	**0.014**
All-cause mortality	*RRR:*	6%	**13%**
	P:	0.44	**0.007**

RRR = Relative Risk Reduction, P = Log Rank

Holman RR et al. NEJM. 2008; 359(15):1577-89

DCCT-EDIC: Long-term Risk of Macrovascular Complications

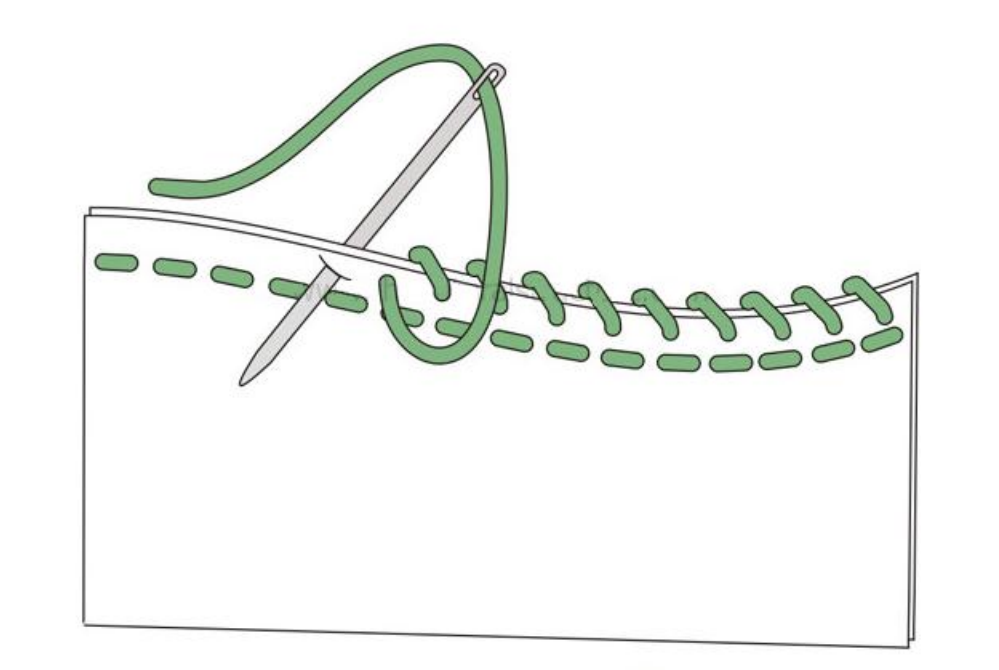




*Diabetes Control and Complications Trial (DCCT) ended and Epidemiology of Diabetes Interventions and Complications (EDIC) began in year 10 (1993). Mean follow-up: 17 years.

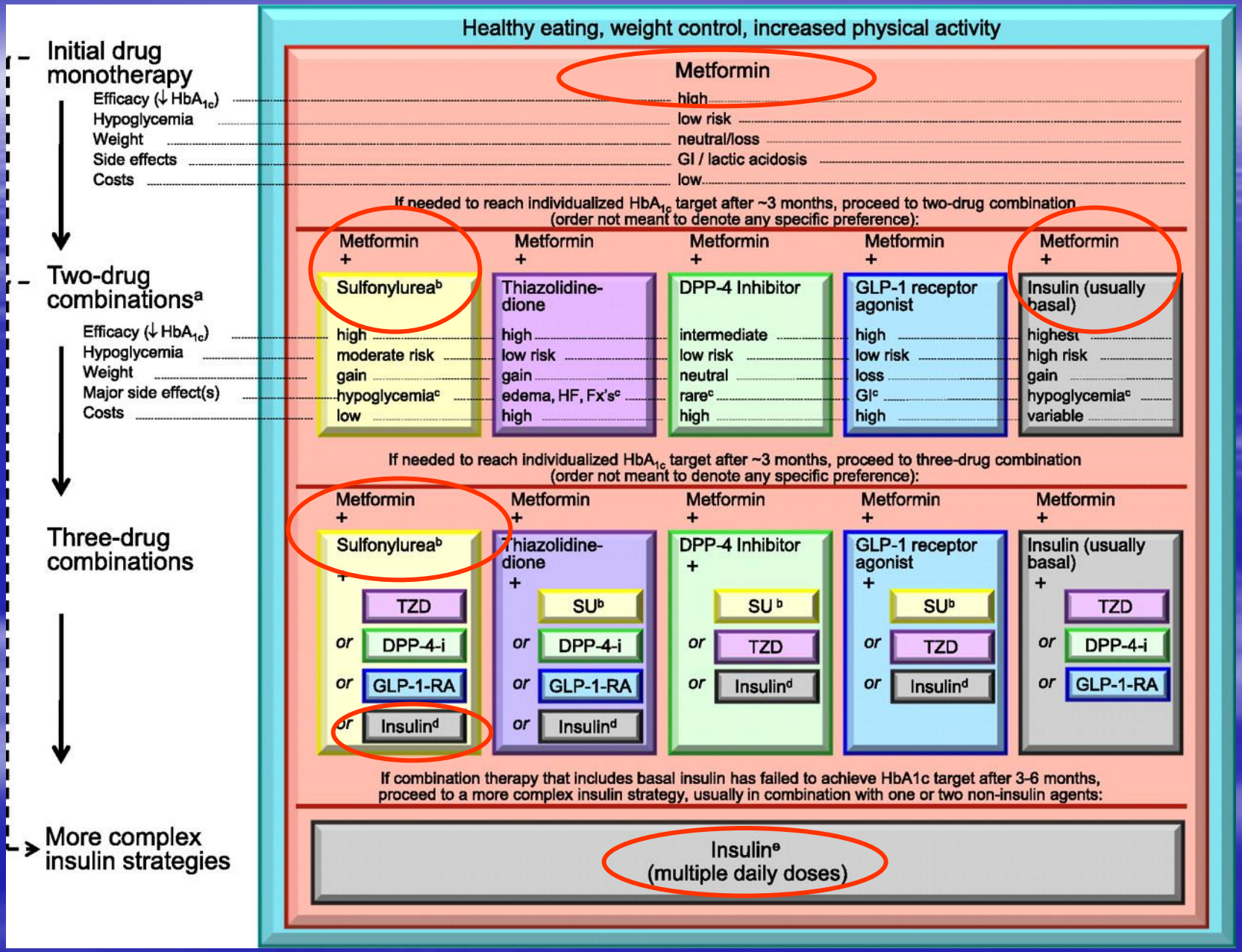
DCCT/EDIC Research Group. *JAMA*. 2002;287:2563-2569.

Maintain good glycaemic control from start



- Timely initiation of insulin is hence crucial

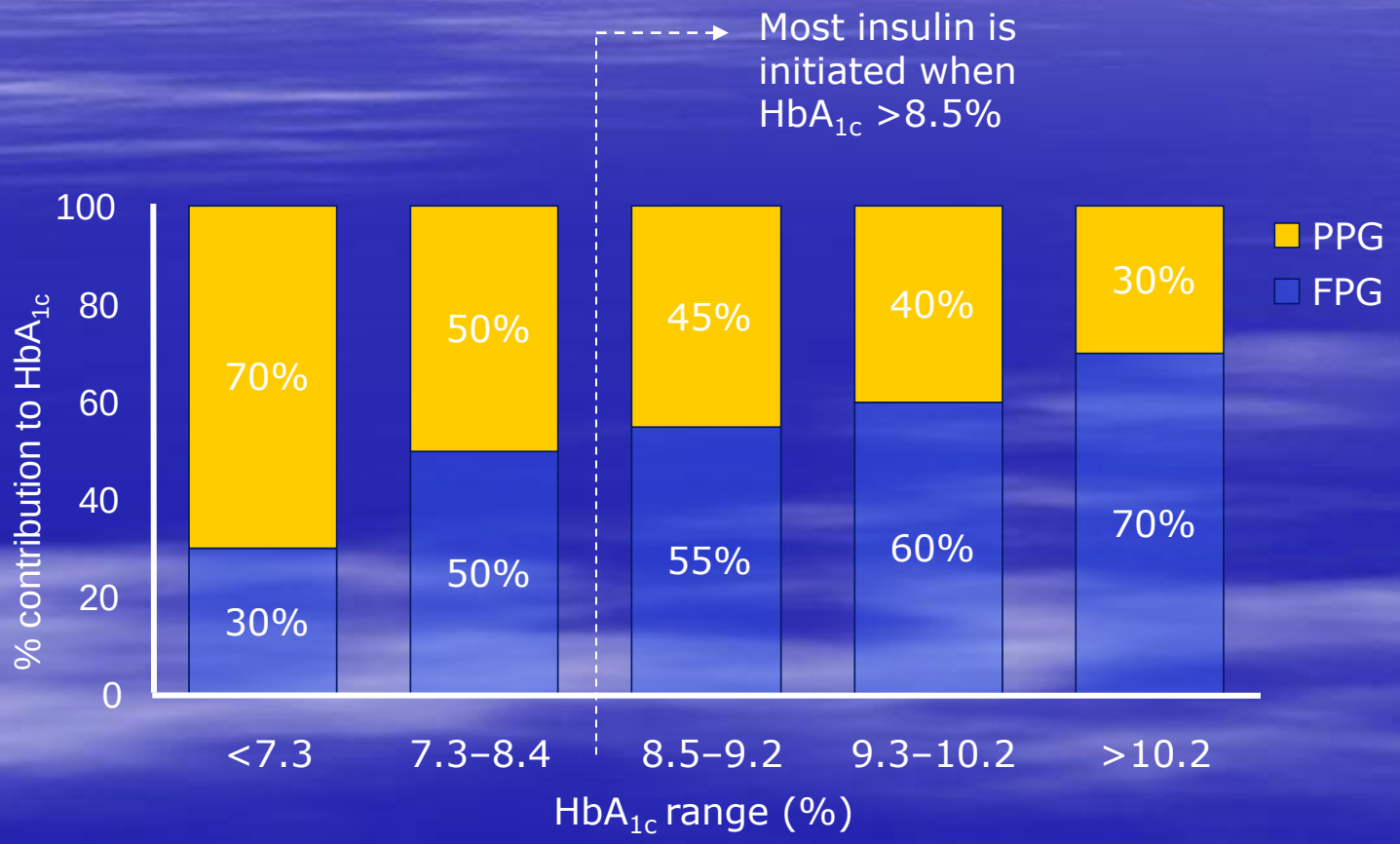
Position Statement ADA/EASD 2012



Inzucchi S E et al. Dia Care 2012;35:1364-1379

But how do we keep things safe and simple?

Fix the Fasting First



Monnier L *et al. Diabetes Care* 2003;26:881–5

TREATING TO TARGET IN TYPE 2 DIABETES

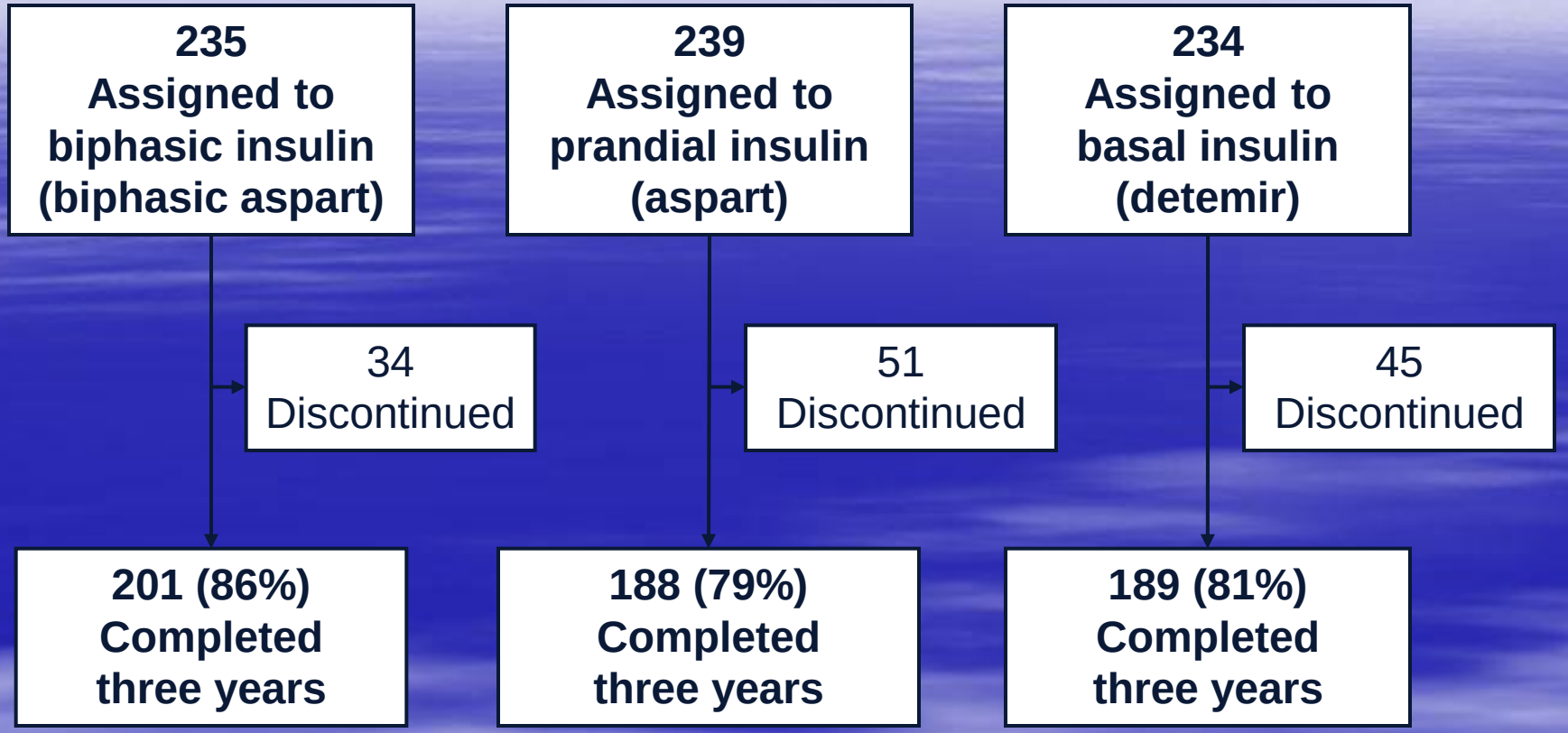
N Engl J Med 2007; 357: 1716-30

Major Inclusion Criteria

- Adults with Type 2 diabetes for one year or more
- On maximal tolerated metformin and sulfonylurea
- HbA_{1c} 7.0% to 10.0% inclusive
- Body mass index not more than 40 kg/m^2

N Engl J Med 2007; 357: 1716-30

Patient Disposition

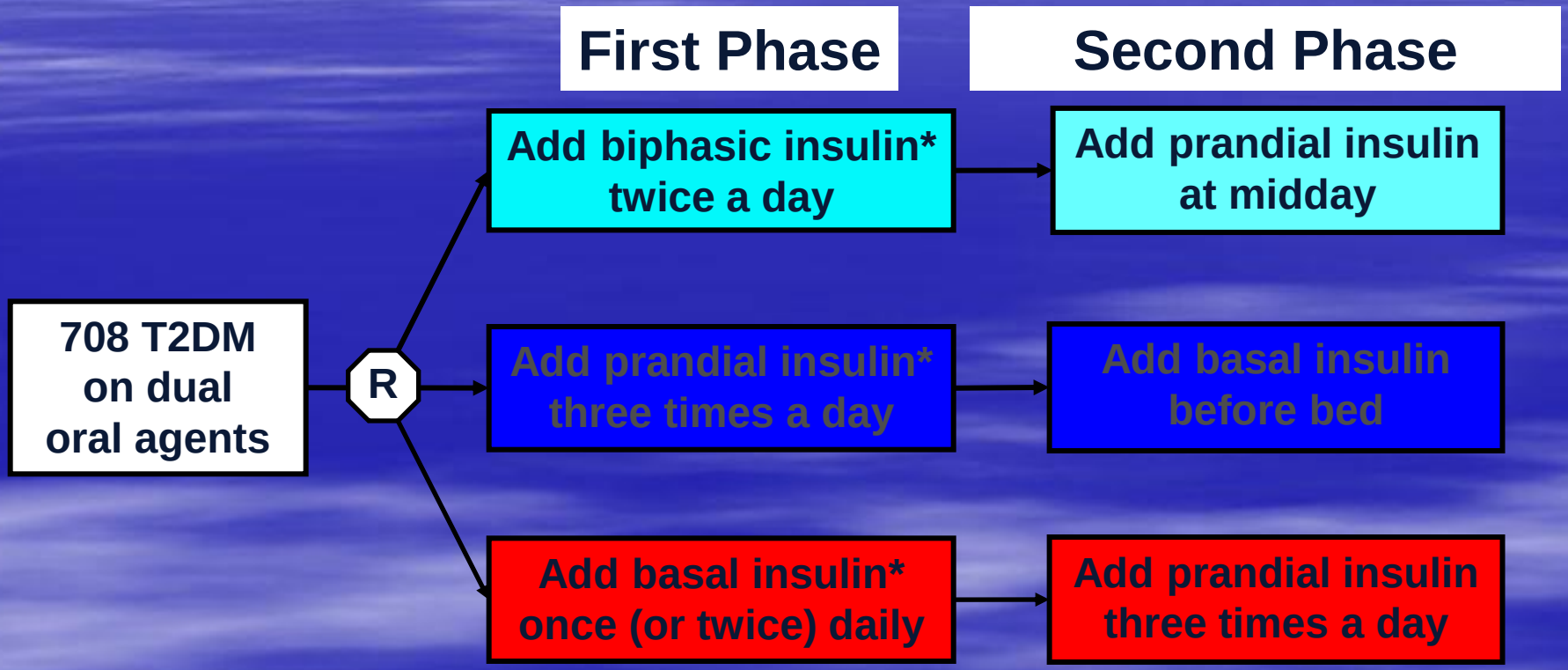


- Overall, 18.4% of patients did not complete three years
- No difference in proportions between groups (p=0.15)
- No difference in baseline characteristics between those who completed or did not complete three years follow up

N Engl J Med 2007; 357: 1716-30

Transition to a Complex Insulin Regimen

From one year onwards, if HbA_{1c} levels were >6.5%, sulfonylurea therapy was stopped and a second type of insulin was added

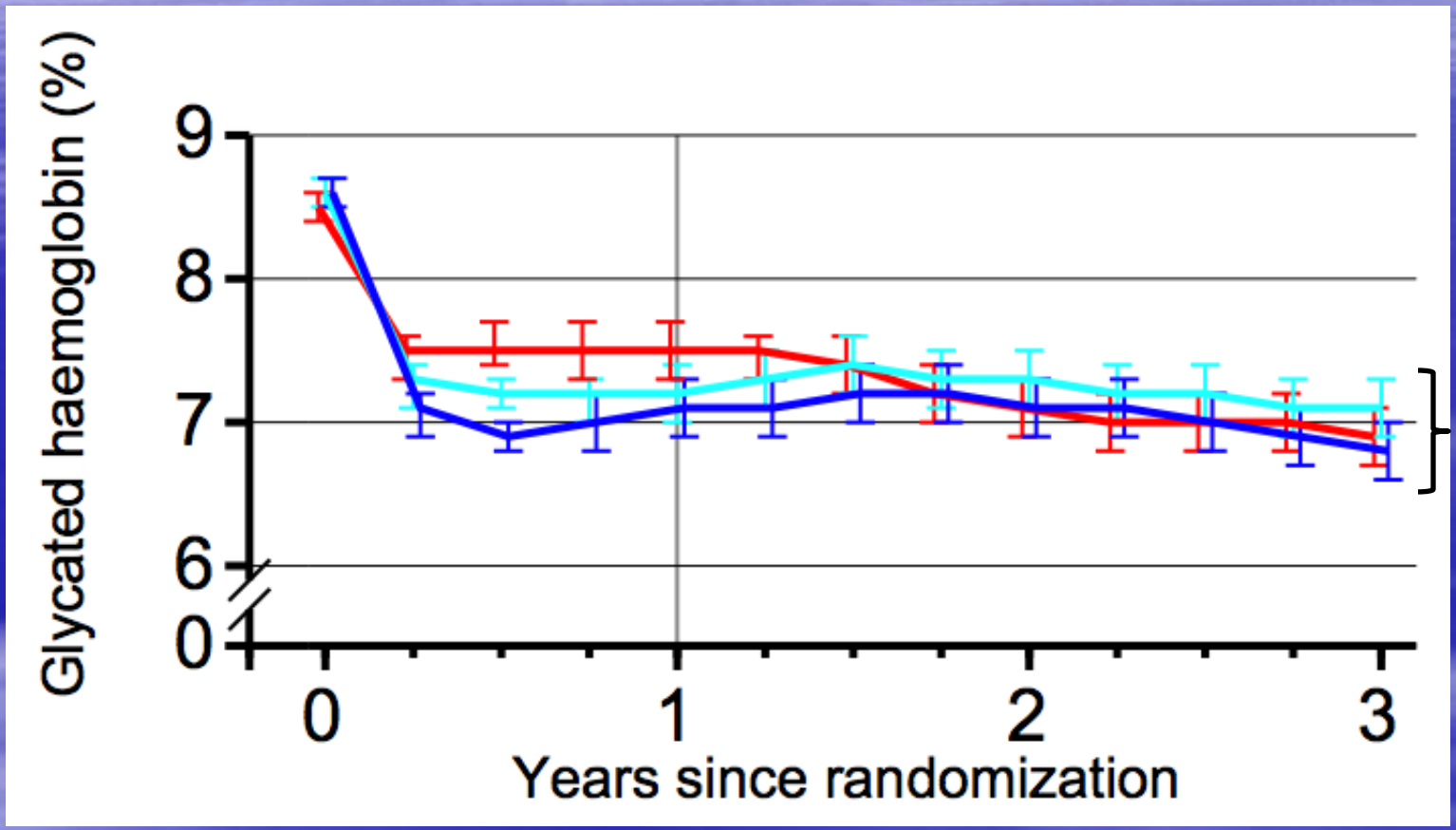


* *Intensify to a complex insulin regimen in year one if unacceptable hyperglycaemia*

N Engl J Med 2007; 357: 1716-30

HbA_{1c} Values Over 3 Years

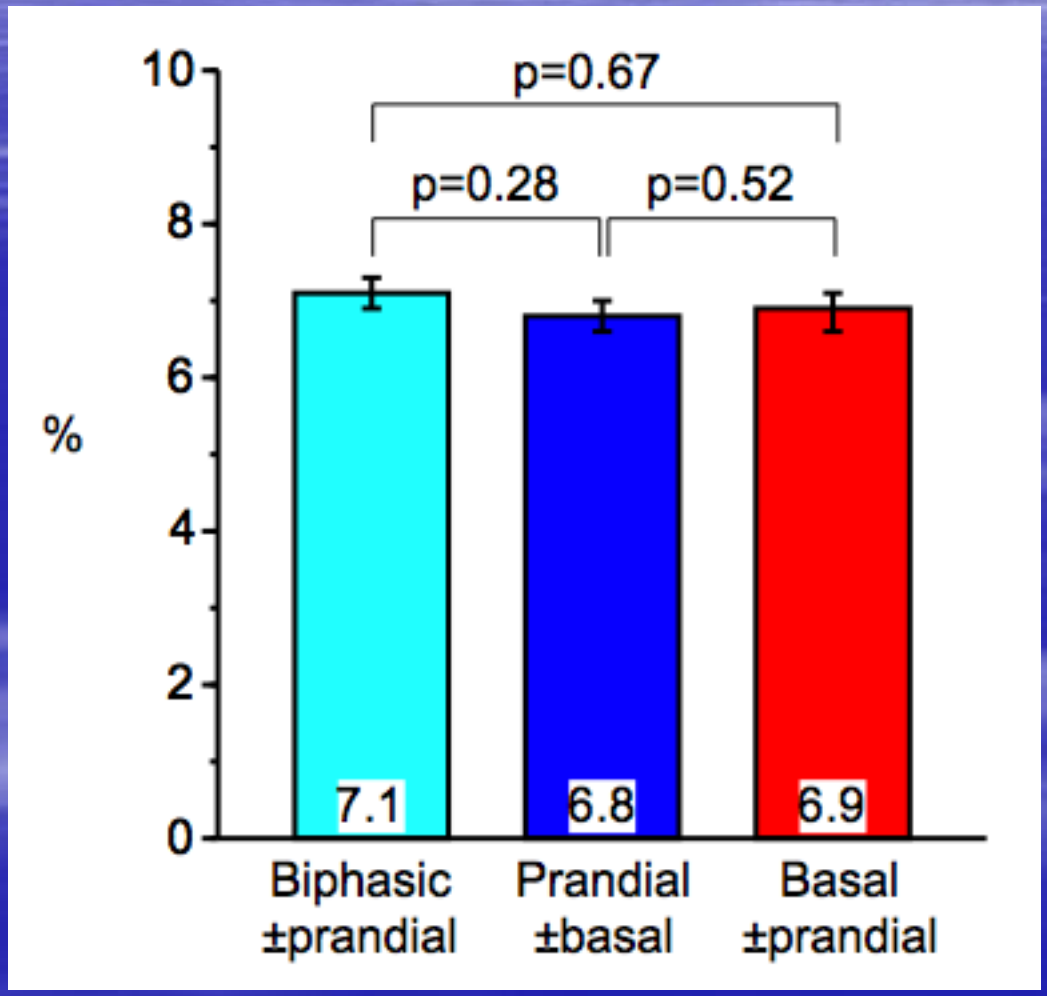
Median ±95% confidence interval



N Engl J Med 2007; 357: 1716-30

Primary Outcome: HbA_{1c} at 3 Years

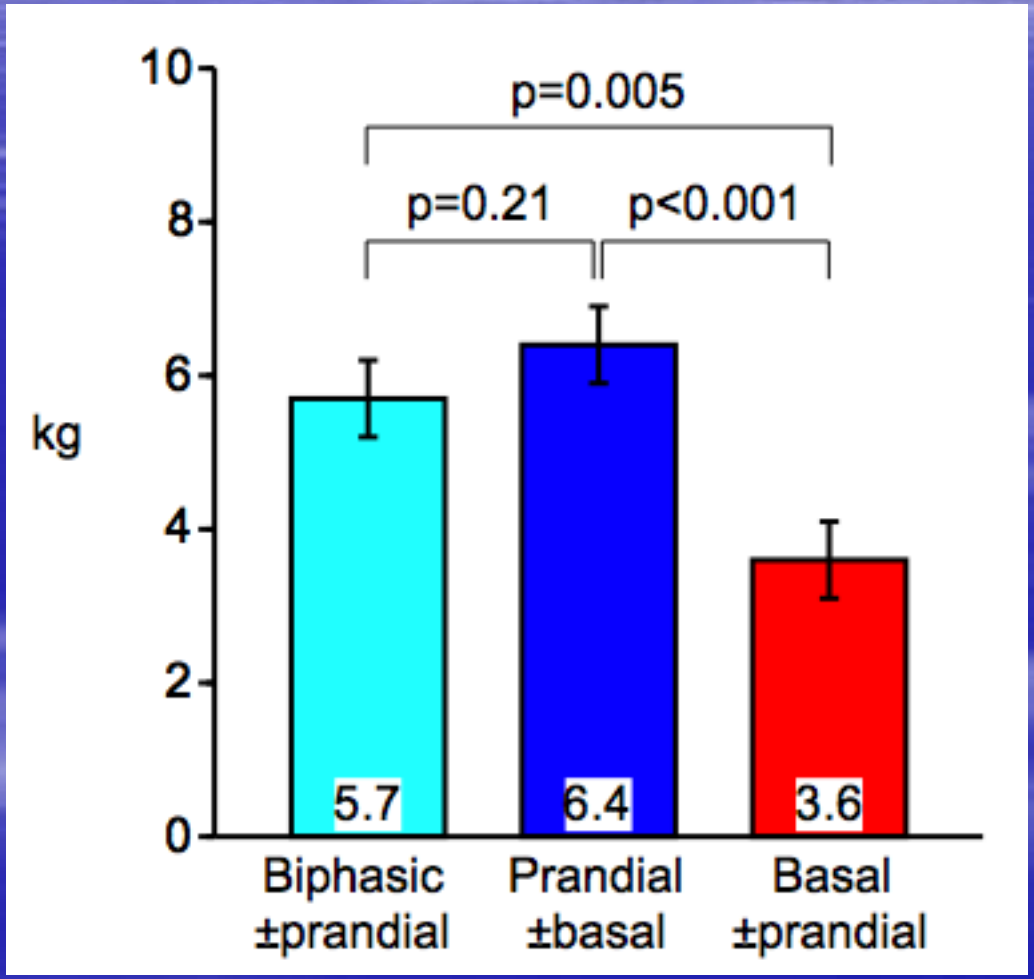
Median ±95% confidence interval



N Engl J Med 2007; 357: 1716-30

Increase in Body Weight Over 3 Years

Mean ±1SD

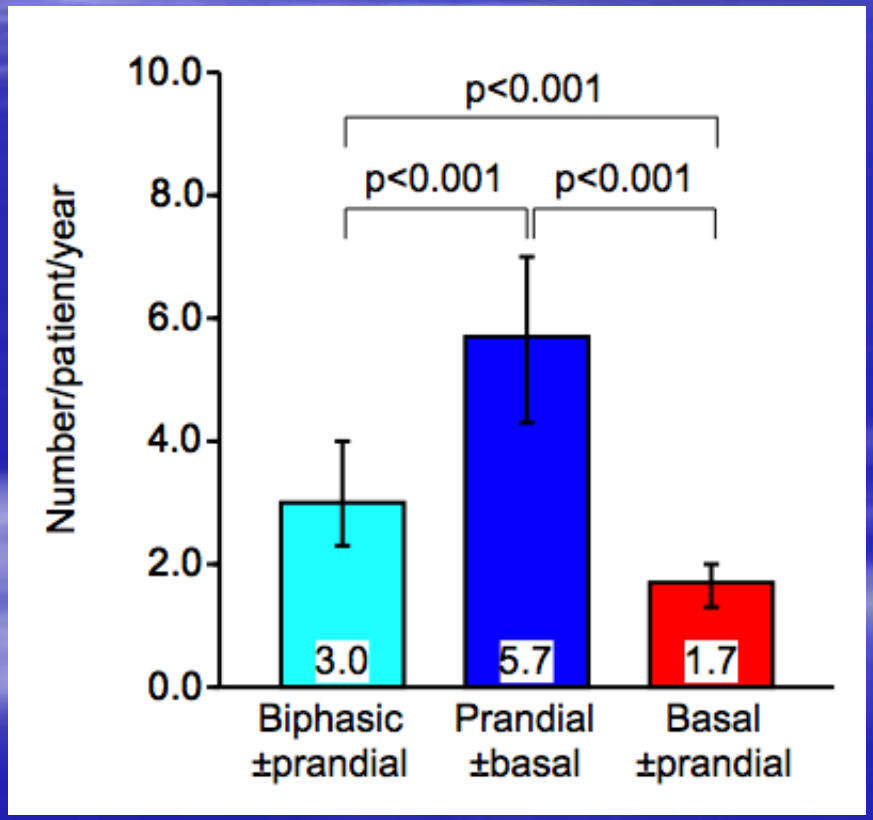


N Engl J Med 2007; 357: 1716-30

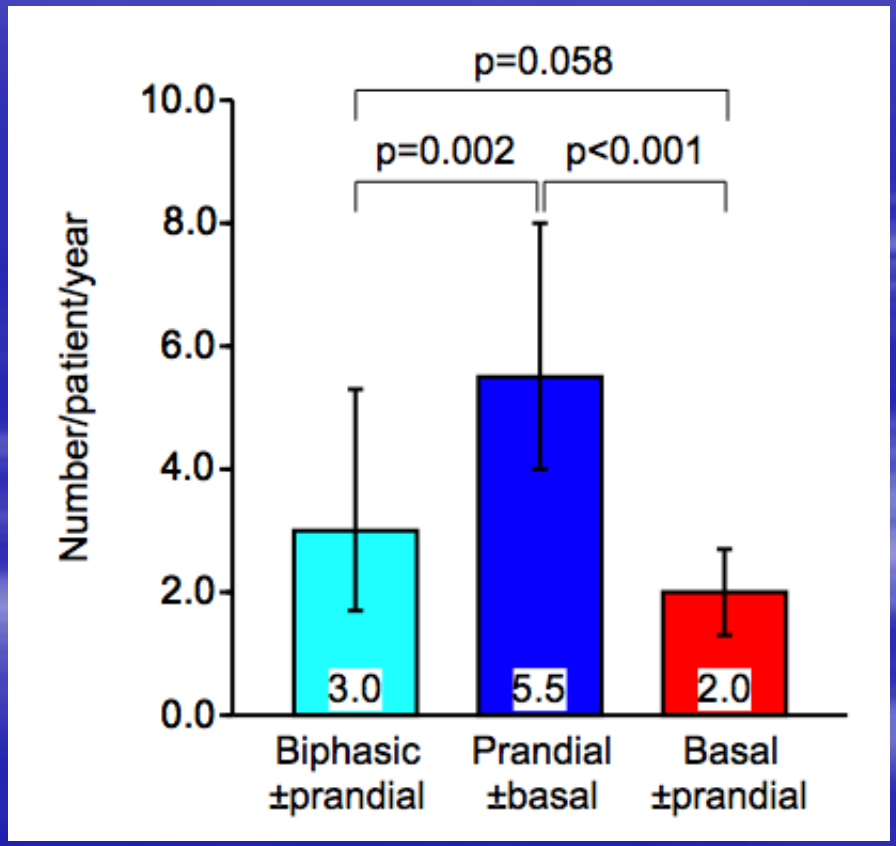
Grade 2 or 3 Hypoglycaemia Over 3 Years

Median ±95% confidence interval

All patients



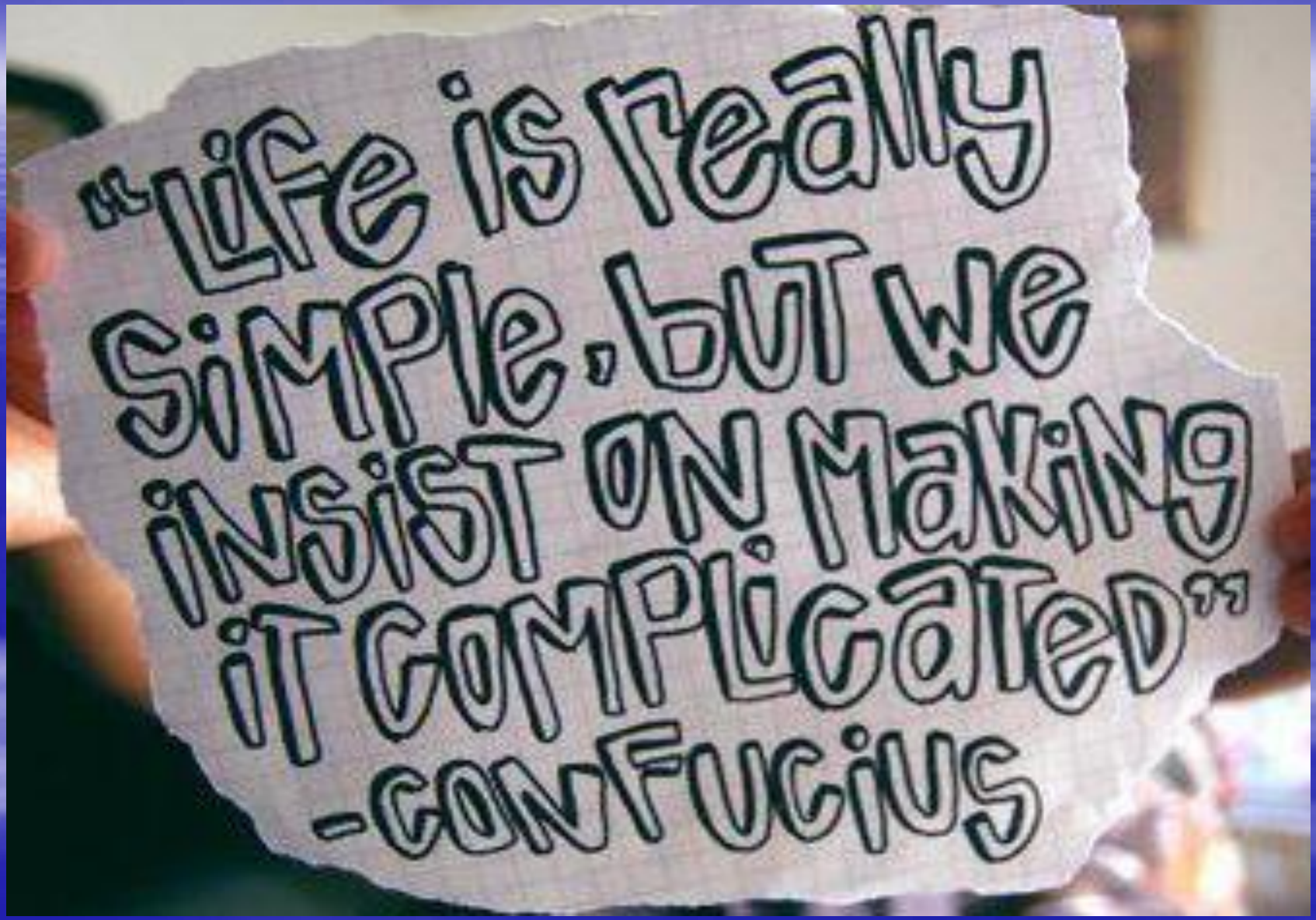
Patients with HbA_{1c} ≤6.5%



N Engl J Med 2007; 357: 1716-30

Summary

- *Most patients with type 2 diabetes will eventually need insulin.*
- *Timely initiation of insulin is important.*
- *Fix the fasting first to keep things safe and simple.*
- *Once OHAs fail, good evidence supporting insulin initiation with a basal insulin as less weight gain and hypoglycaemic episodes.*


"Life is really
simple, but we
insist on making
it complicated"
-Confucius