Insulin Initiation in Type 2 Diabetes

Michelle Downie

Southern DHB

15 August 2013

Overview

- Size of the problem
- HbA1c as a diagnostic test
- Setting a target HbA1c
- Achieving your target
- Insulin Initiation & Titration

Islets of Humor

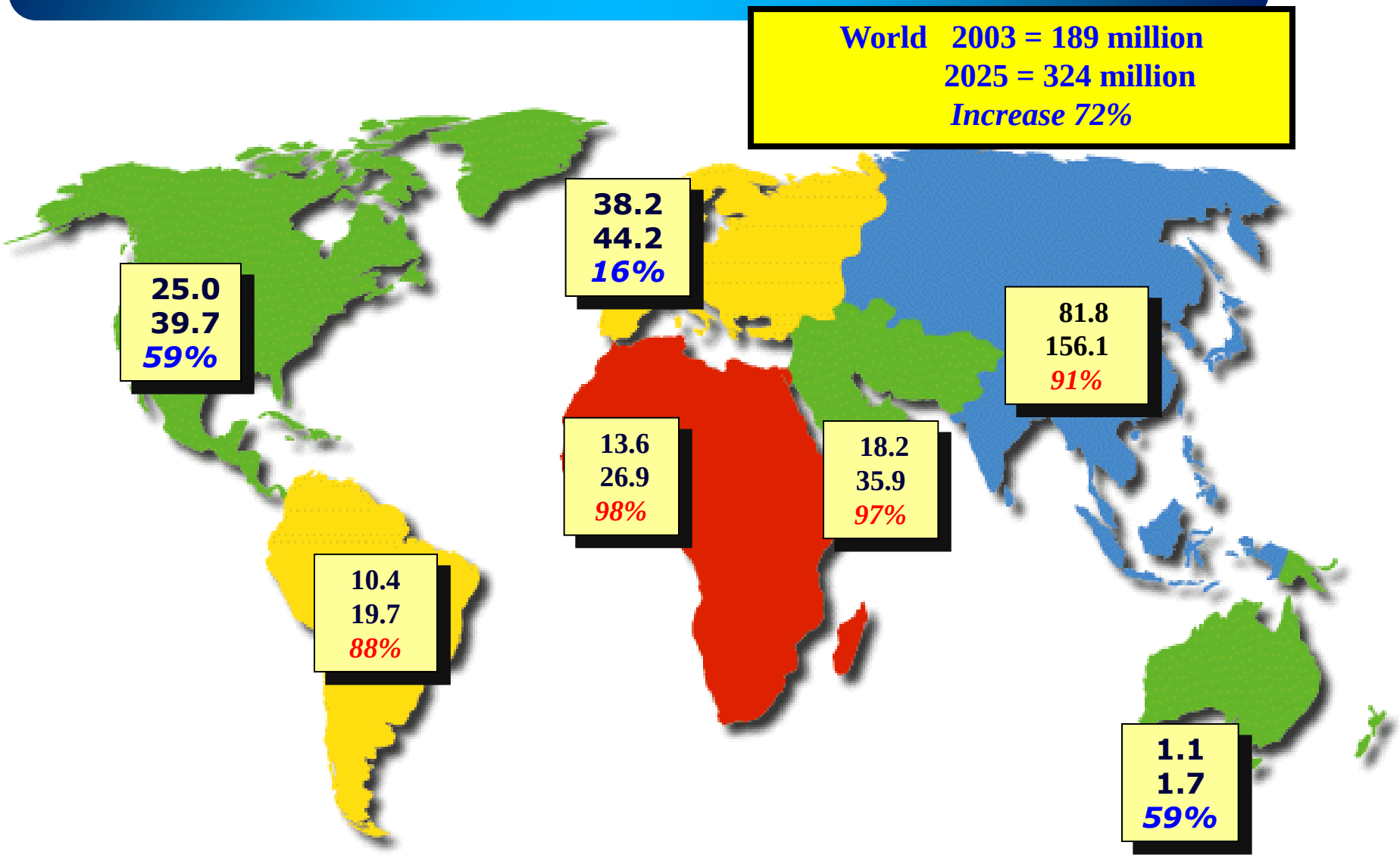
by Theresa Garnero

The global burden

- 366 million have diabetes in 2011; by 2030 will have risen to 552 million
- 80% of people with diabetes live in low-and middle-income countries
- The greatest number of people with diabetes are between 40 to 59 years
- 183 million people (50%) with diabetes are undiagnosed
- Diabetes caused 4.6 million deaths in 2011
- Diabetes caused at least USD 465 billion dollars in healthcare expenditures in 2011; 11% of total healthcare expenditures in adults (20-79 years)
- 78,000 children develop type 1 diabetes every year

IDF atlas – 5th Edition

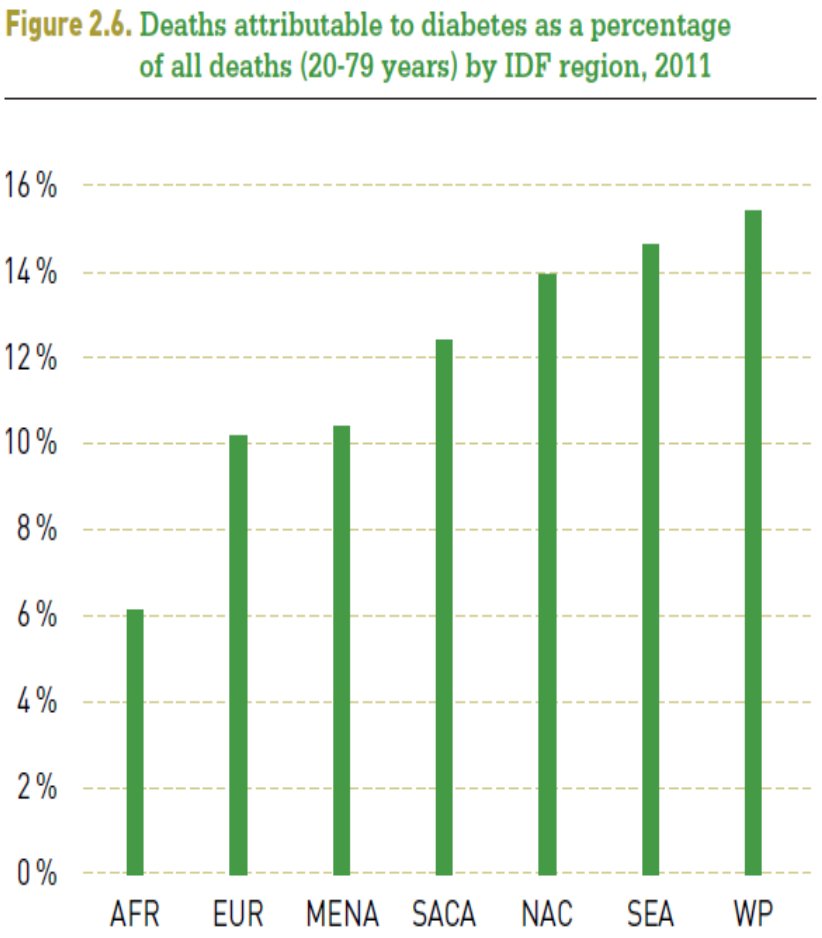
Global projections for the diabetes epidemic: 2003–2025 (millions)



Amos *et al. Diabet Med* 1997;14:S1–S85; Zimmet *et al. Nature* 2001;414:782–7

Deaths due to diabetes

- 4.6 million deaths due to diabetes in 2011
- 8.2% of all-cause mortality
- 48% in people under 60



Size of the problem in NZ

- Currently approx 208,000 people in NZ with diagnosed Diabetes
- Compared to 110,000 in 2001
- 50 new diagnoses per day in NZ
- Prevalence diagnosed diabetes between 4-8%
  - Average increase in prevalence is 8-9% per year (14% in Auckland)
- Projection is 500,000 by 2036
- OECD report – NZ is second worst for life years lost to Diabetes

DHB Figures June 2012

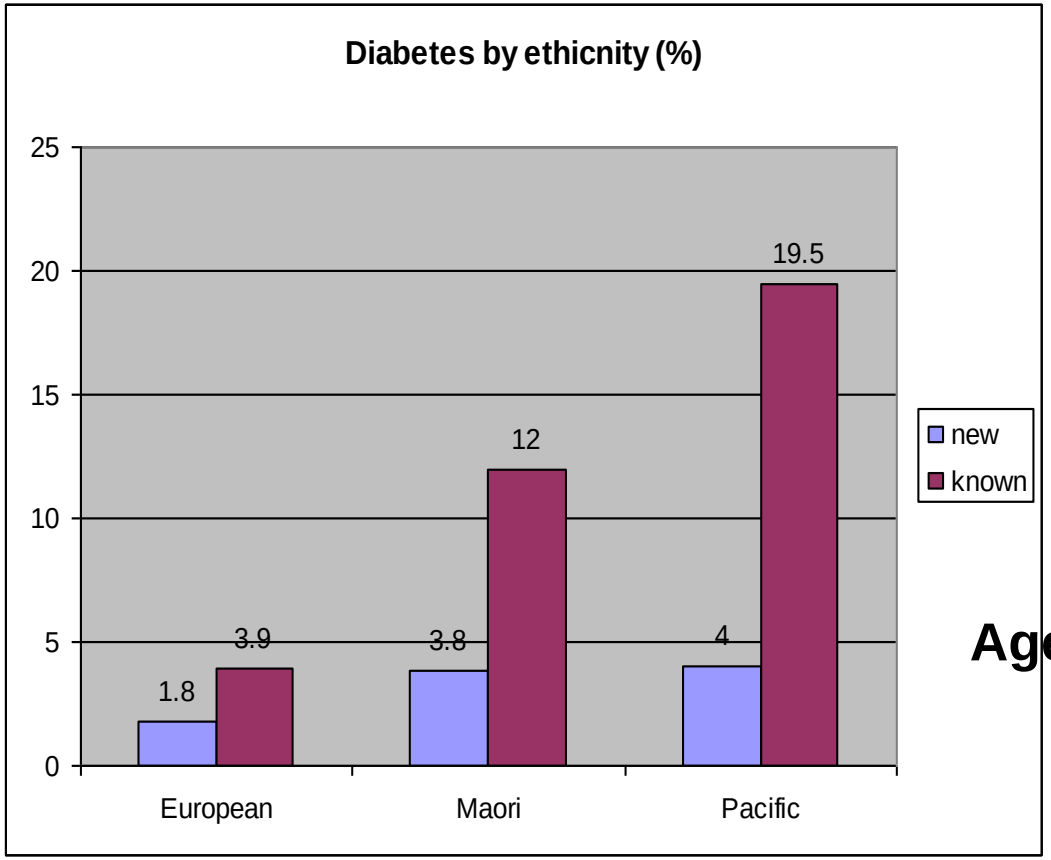
Region	Maori	Pacific	Indian	Europ	Total
Auckland	1,509	4,982	3,256	11,909	21,656
Bay of Plenty	2,547	176	303	7,255	10,281
Canterbury	1,084	709	276	17,370	19,439
Capital & Coast	956	1,594	679	7,232	10,461
Counties/Manu	4,066	9,939	3,524	13,494	31,023
Hawke's Bay	1,761	319	102	5,098	7,280
Hutt	894	862	297	4,390	6,443
Lakes	1,644	167	88	2,868	4,767
MidCentral	933	231	103	6,102	7,369
Nelson-Marlb	394	67	42	5,142	5,645

DHB Figures June 2012

Region	Maori	Pacific	Indian	Europ	Total
Northland	3,342	121	63	5,375	8,901
Sth Canterbury	130	20	15	2,855	3,020
Southern	712	321	107	12,218	13,358
Tairawhiti	1,401	70	18	1,655	3,144
Taranaki	922	79	57	5,785	6,843
Waikato	3,792	622	567	12,639	17,620
Wairarapa	308	50	11	1,711	2,080
Waitemata	1,734	3,081	1,748	17,435	23,998
West Coast	111	13	7	1,178	1,309
Whanganui	768	55	37	2,441	3,301
Grand Total	29,019	23,518	11,304	144,235	**208,076**

Undiagnosed rate ratios

Auckland Heart and health Survey (2007)



Age 35+

"Diabetes has increased dramatically over the past 10 years. That proves that diabetes is caused by global warming!"

HbA1c as the Diagnostic test

- Lack of need of fasting
- Cheaper than OGTT
- Less time consuming
- Concern over validity of 75g OGTT for all ages, genders and sizes
- Equally good relationship with risk of retinopathy and CVD

HbA1c as the Diagnostic test

- Risk of retinopathy continuous with significant risk > 50 mmol/mol, almost no risk below 40 mmol/mol
- Between 40-50 mmol/mol may show some background retinopathy at diagnosis, but minimal risk of significant retinopathy
- Above 40 mmol/mol increased risk for CVD however

HbA1c Old	HbA1c New
%	mmol/mol
4.0	20
4.5	26
5.0	31
5.5	37
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
8.5	69
9.0	75
9.5	80
10.0	86
10.5	91
11.0	97
11.5	102
12.0	108
12.5	113
13.0	119
13.5	124
14.0	130
14.5	135
15.0	140
15.5	146
16.0	151

HbA1c New	HbA1c Old
mmol/mol	%
20	4.0
25	4.4
30	4.9
35	5.4
40	5.8
45	6.3
50	6.7
55	7.2
60	7.6
65	8.1
70	8.6
75	9.0
80	9.5
85	9.9
90	10.4
95	10.8
100	11.3
105	11.8
110	12.2
115	12.7
120	13.1
125	13.6
130	14.0
135	14.5
140	15.0
145	15.4
150	15.9

Exact equations are:

New	=	10.93 x Old - 23.5	mmol/mol
Old	=	0.0915 x New + 2.15	%

New HbA1c values are reported to the nearest integer e.g. 103 mmol/mol

Type 2 Diabetes is a progressive condition

"I'm Diabetes, and these are my constant companions: Stereotype, Ignorance and Rudeness."

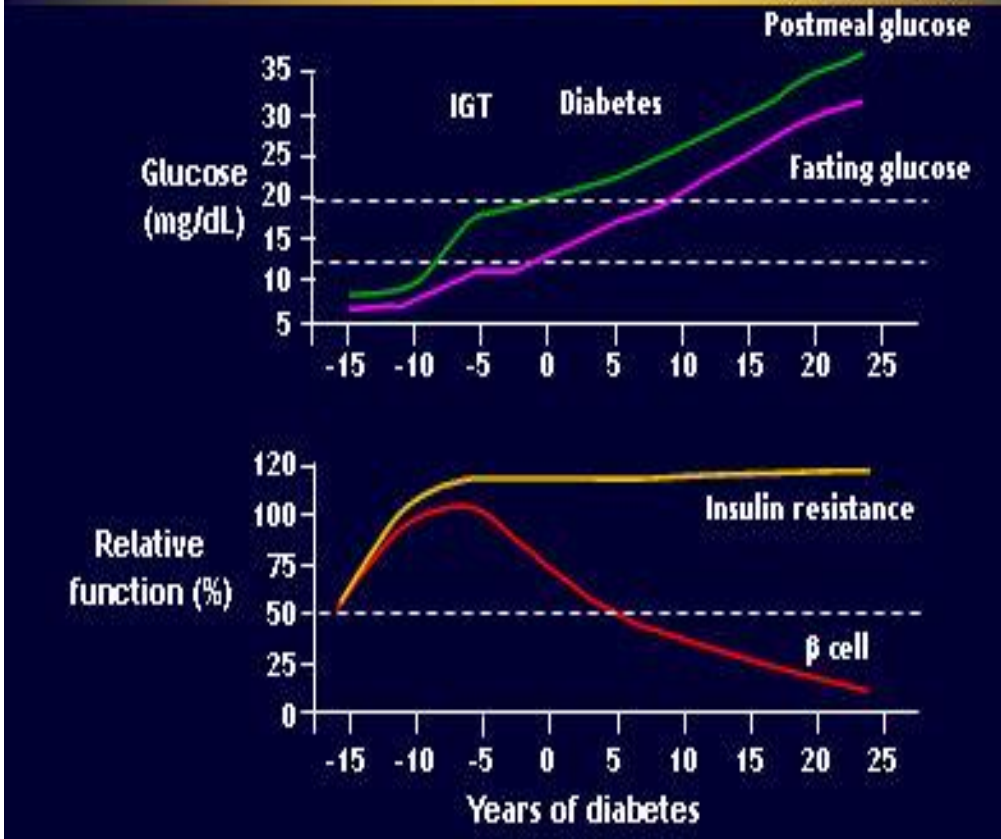
Type 2 Diabetes is a progressive condition...and changes with time.

The mechanisms of T2DM is multifactorial including:

- Pancreatic islet cell dysfunction
  - Deficient insulin response due to decline in functional β-cells
  - Excessive production of glucagon by α-cells
- Excessive hepatic output of endogenous glucose
  - A consequence of diminished insulin & insulin sensitivity, and excess glucagon
- Impaired uptake of glucose in the peripheral tissues
  - A consequence of insulin resistance

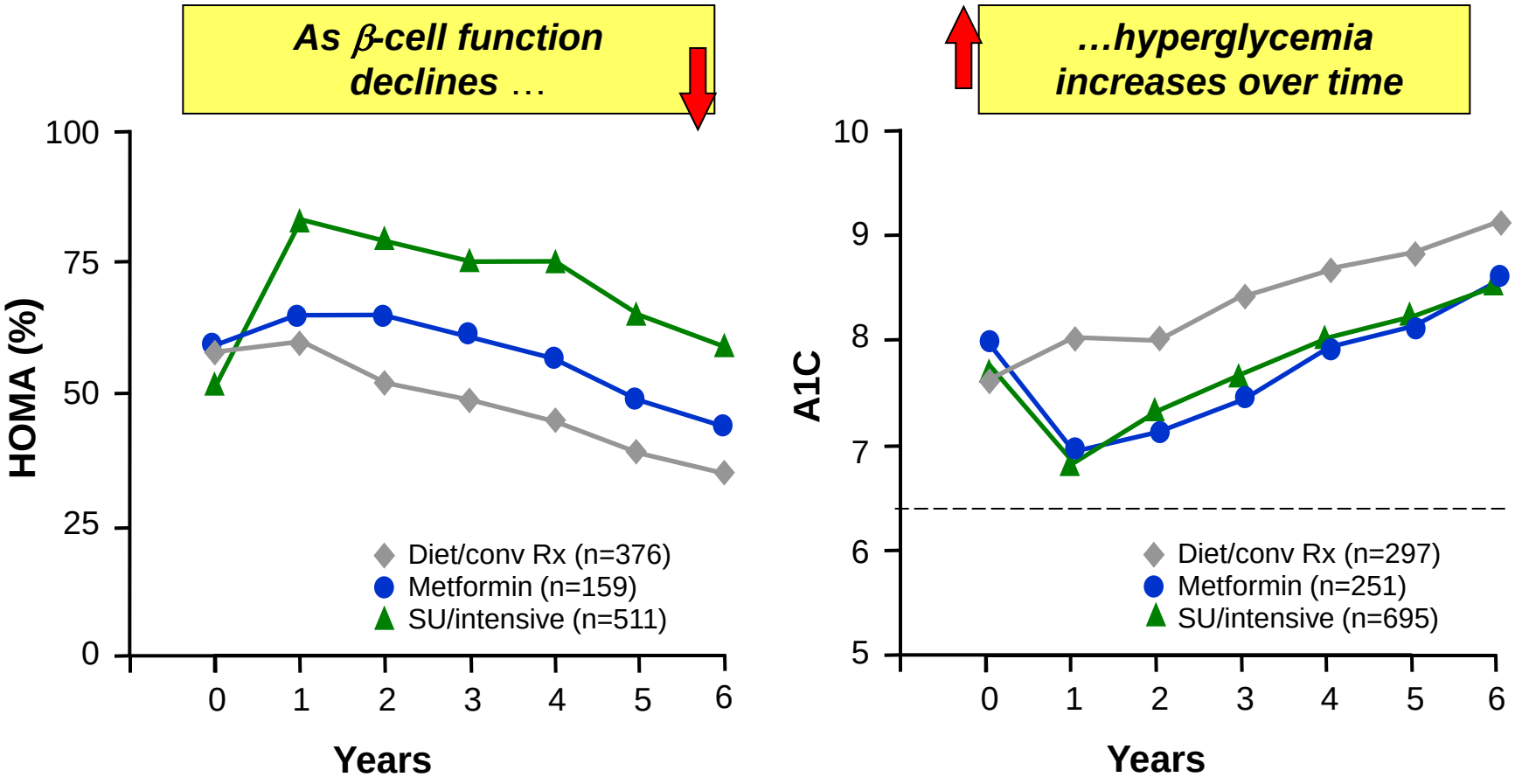
With progressive worsening over time

Natural History of Type 2 Diabetes



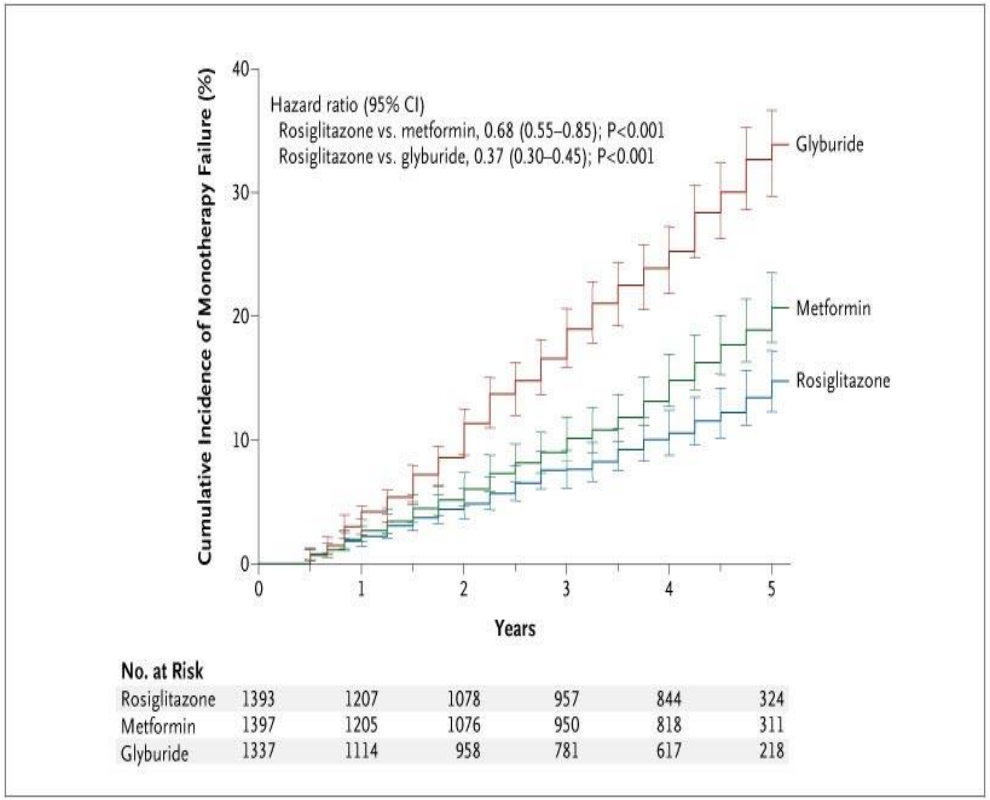
Adapted from: International Diabetes Center (Minneapolis, Minnesota).

β-Cell Function & Glycaemic Control in T2DM



UKPDS=United Kingdom Prospective Diabetes Study; SU=sulfonylurea.
Reprinted UK Prospective Diabetes Study Group 16. *Diabetes.* 1995;44:1249–1258.

ADOPT Study: Monotherapy Failure at 5 Years



No. at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

Kahn SE et al. N Engl J Med 2006;355:2427-2443

The NEW ENGLAND JOURNAL of MEDICINE

"God sent Adam and Eve out of the garden because of the apple. Apples have carbs and carbs are evil!"

Setting a target HbA1c

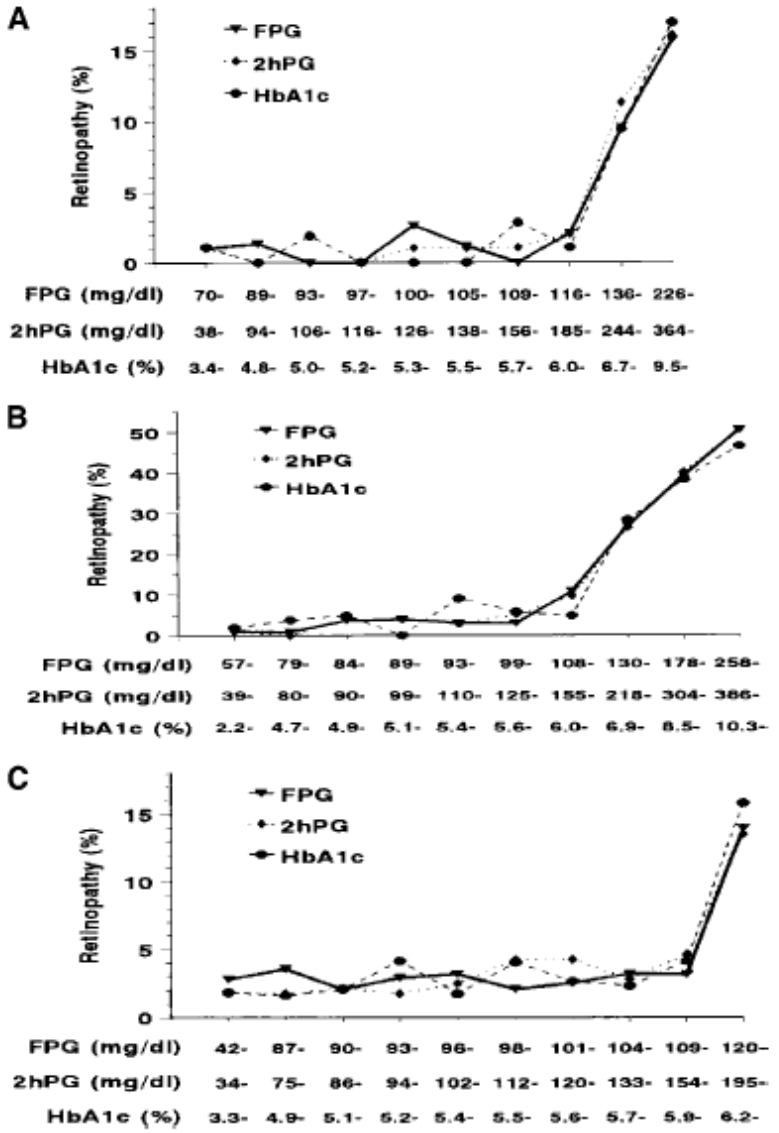
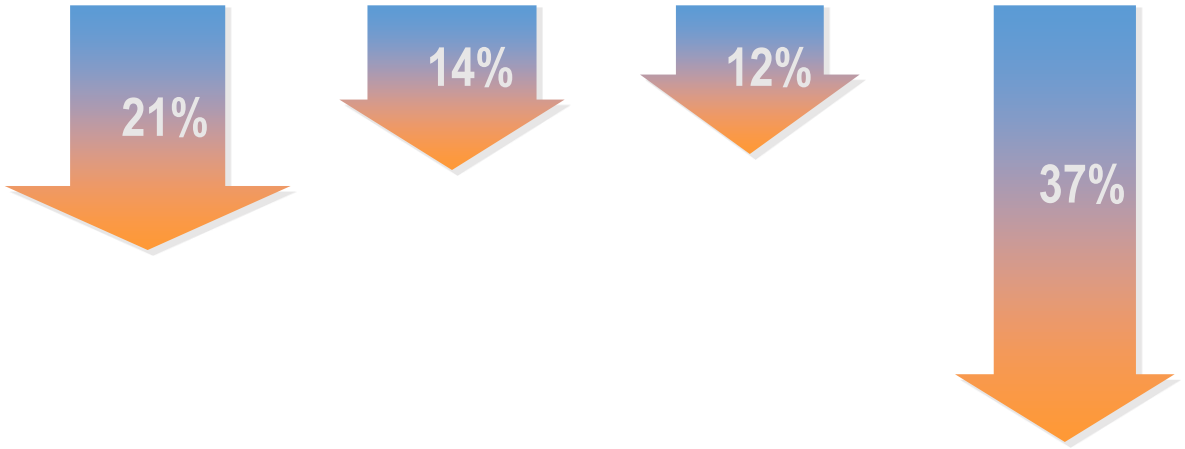


Figure 1—*Prevalence of retinopathy by deciles of the distribution of FPG, 2HPG, and A1C in Pima Indians (A), Egyptians (B), and 40- to 74-year-old participants in NHANES III (C). Adapted with permission from ref. 17.*

Improved Glycemic Control Has Been Shown to Reduce 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)

microvascular complications (*P*<.0001)

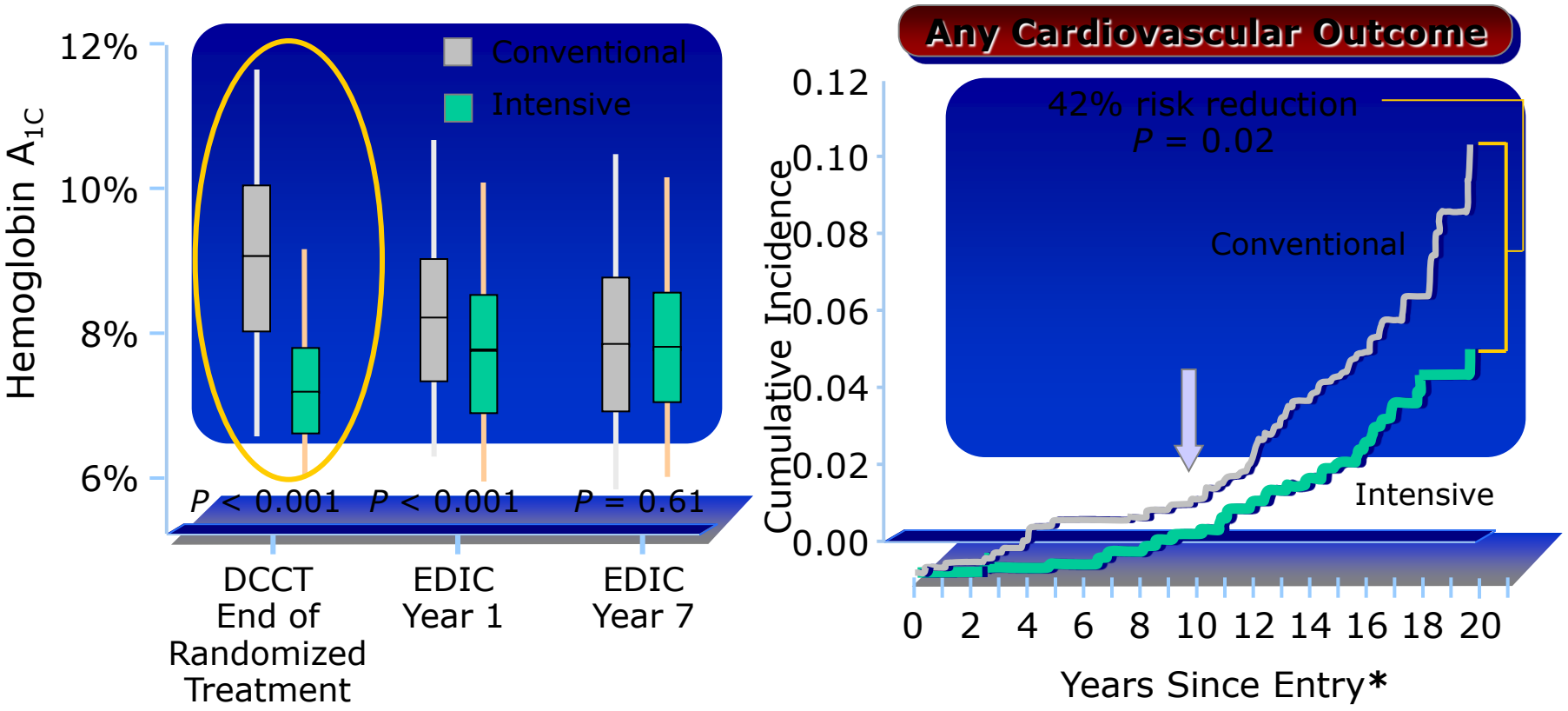
Stratton IM et al. *BMJ.* 2000;321:405-412.

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



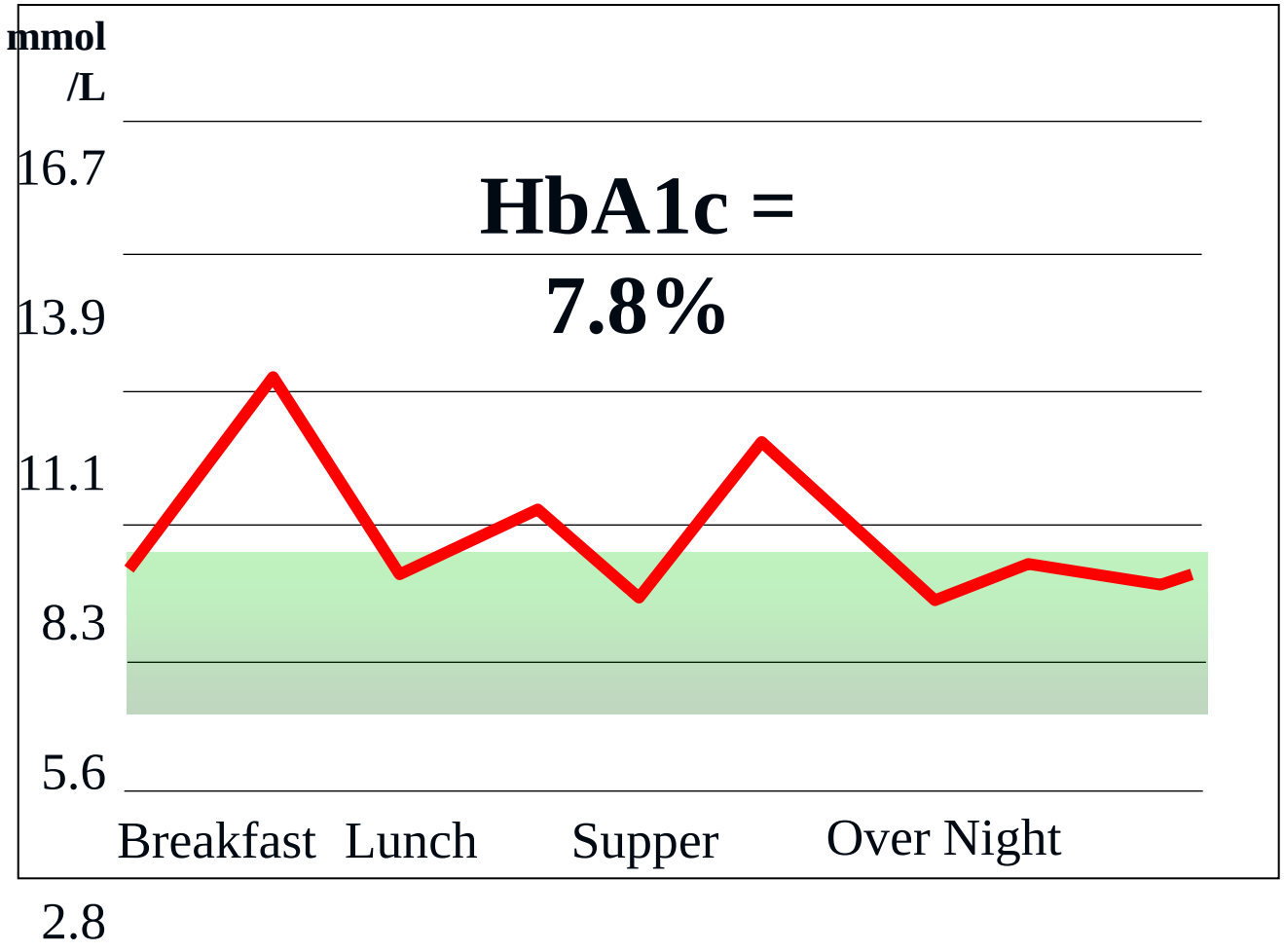
*Diabetes Control and Complications Trial (DCCT) ended and Epidemiology of Diabetes Interventions and Complications (EDIC) began in year 10 (1993). Mean follow-up: 17 years.

Trade Off

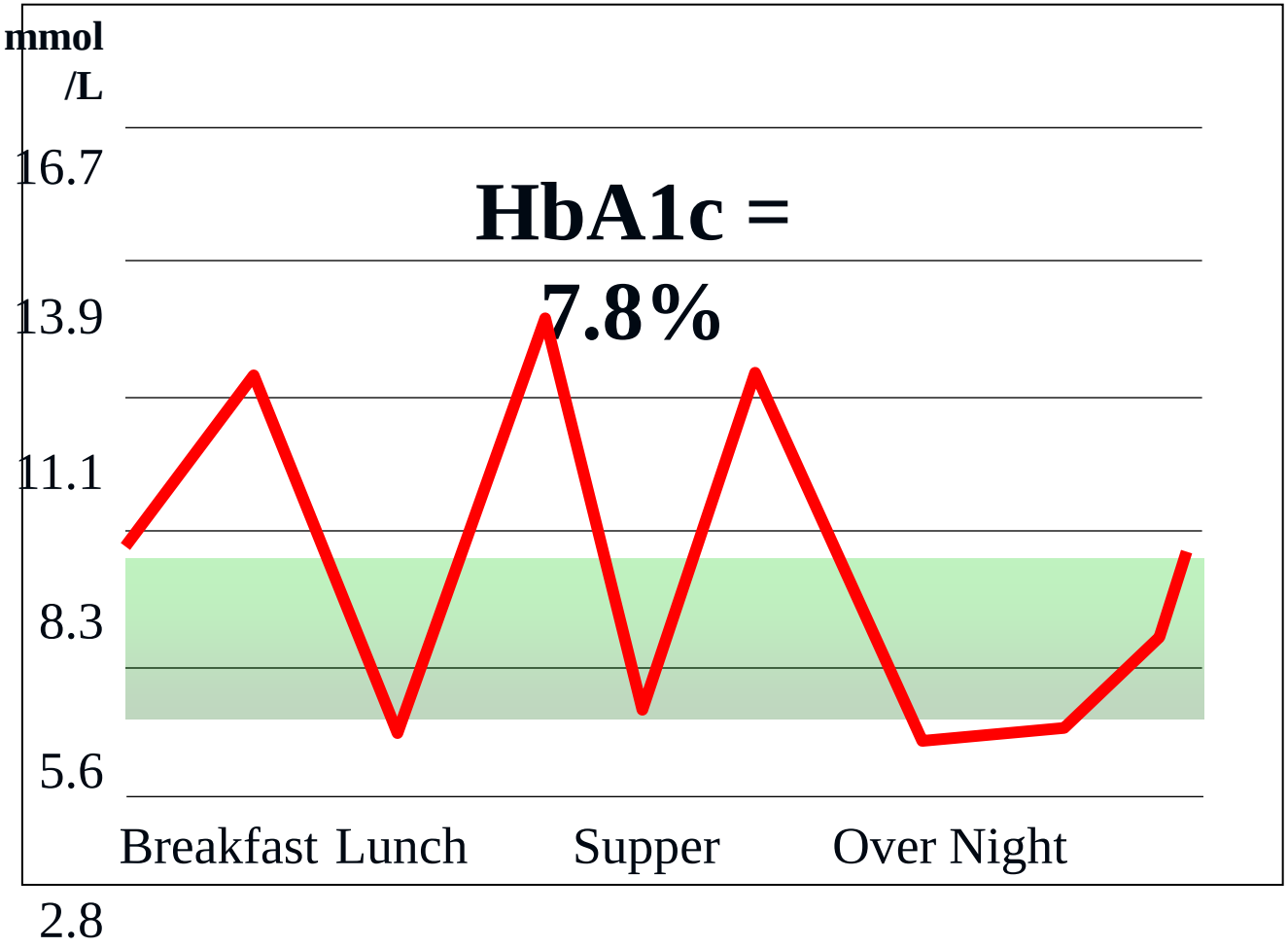
- **11mmol/mol drop or 1% fall in A1C reduces microvascular complications by 37%,[1] but risk of:[2]**
  - **Hypoglycaemia**
  - **Weight gain (approx 2kg)**

1. Stratton IM et al. *BMJ* 2000; 321: 405–12; 2. Phillips PJ. *Medicine Today* 2007; 8(4): 43-52.

HbA1c's are not created equal



HbA1c's are not created equal



Target HbA1c

- Used to be 7.0 % (53 mmol/mol)
- ACCORD, ADVANCE, VADT
  - All large studies that looked at more intensive glucose control

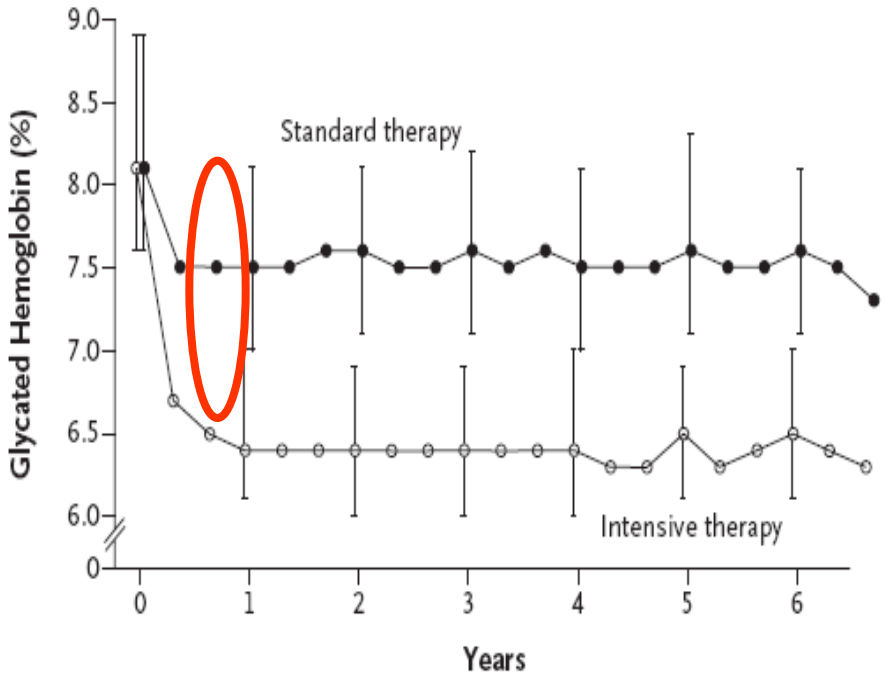
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

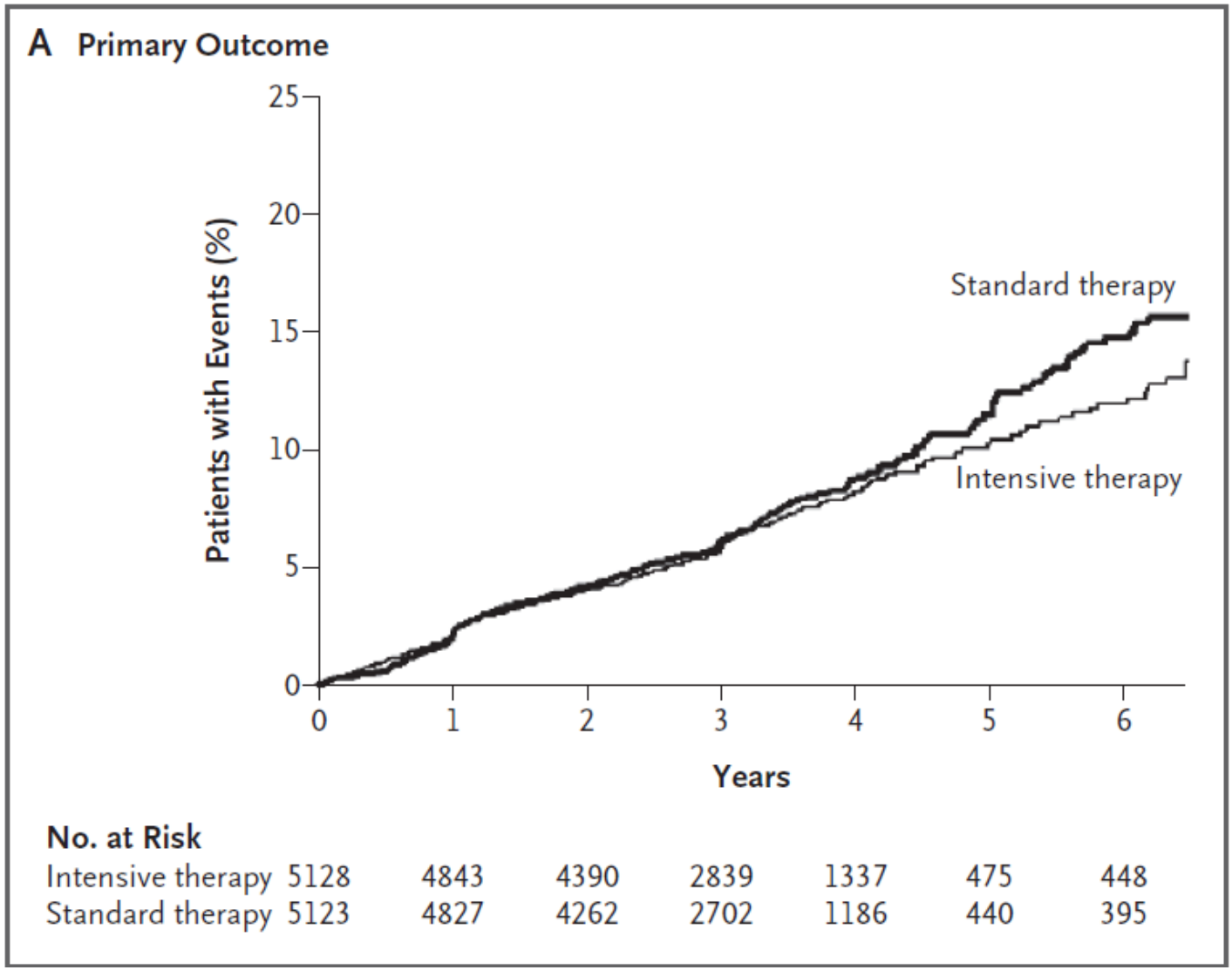
The Action to Control Cardiovascular Risk in Diabetes Study Group*

Glycaemic control

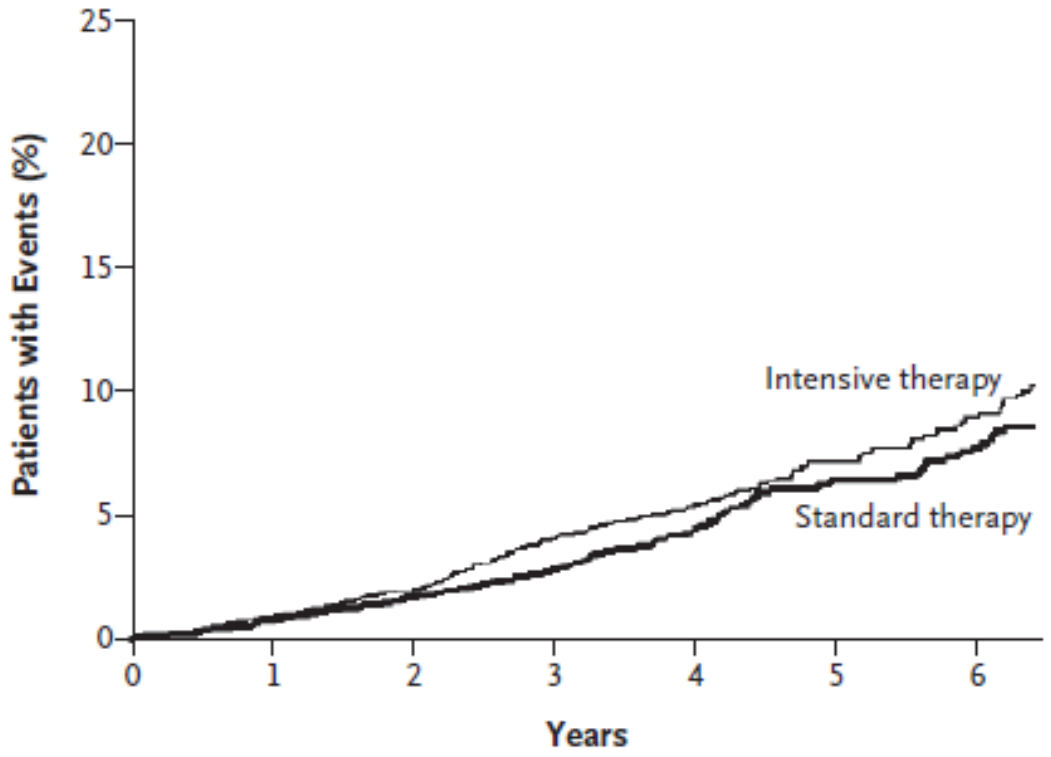


No. at Risk							
Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

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


A Primary Outcome
Patients with Events (%)
25
20
15
10
5
0
0
1
2
3
4
5
6
Years
Standard therapy
Intensive therapy
No. at Risk
Intensive therapy 5128 4843 4390 2839 1337 475 448
Standard therapy 5123 4827 4262 2702 1186 440 395

B **Death from Any Cause**



No. at Risk

Intensive therapy	5128	4972	4803	3250	1748	523	506
Standard therapy	5123	4971	4700	3180	1642	499	480

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)	<0.00
Requiring any assistance	830 (16.2)	261 (5.1)	<0.00
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)	<0.00
Clinical measures			
Weight gain >10 kg since baseline — no./total no. (%)	1399/5036 (27.8)	713/5042 (14.1)	<0.00

Target HbA1c

- Current target in NZ – 50-55mmol/mol
  - BUT trend to “individualized” targets
  - Concern over increaased mortality in ACCORD
  - Higher for some
  - Terminal disease – avoidance of osmotic symptoms

  - What would you want your HbA1c to be?

"I think diabetes is affecting my eyesight. I have trouble seeing the consequences of poor food choices."

Achieving a target HbA1c

Islets of Humor

by Theresa Garnero

When to introduce insulin

A1C persistently above target

↓

Lifestyle
Patient compliant with agreed modifications?
Any further modifications that can be considered?

Oral hypoglycaemic medication
Is patient taking as prescribed?
Can these be maximised further?

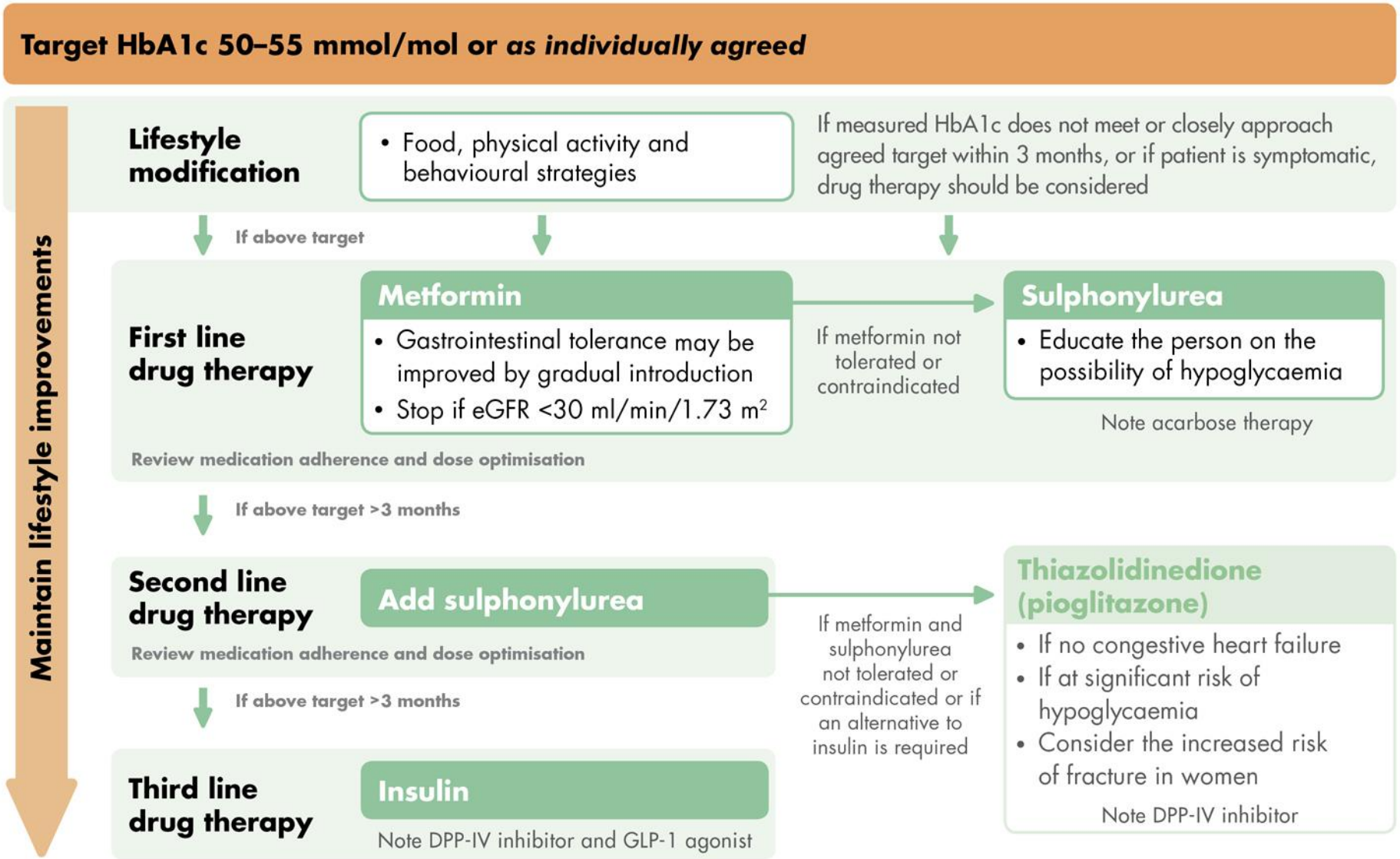
Secondary causes for hyperglycaemia?
Medications (e.g. contraceptive pill, thiazides,beta-blockers, oral corticosteroids) Medical conditions (e.g. hyperthyroidisim, urinary or dental infections, occult malignancy)

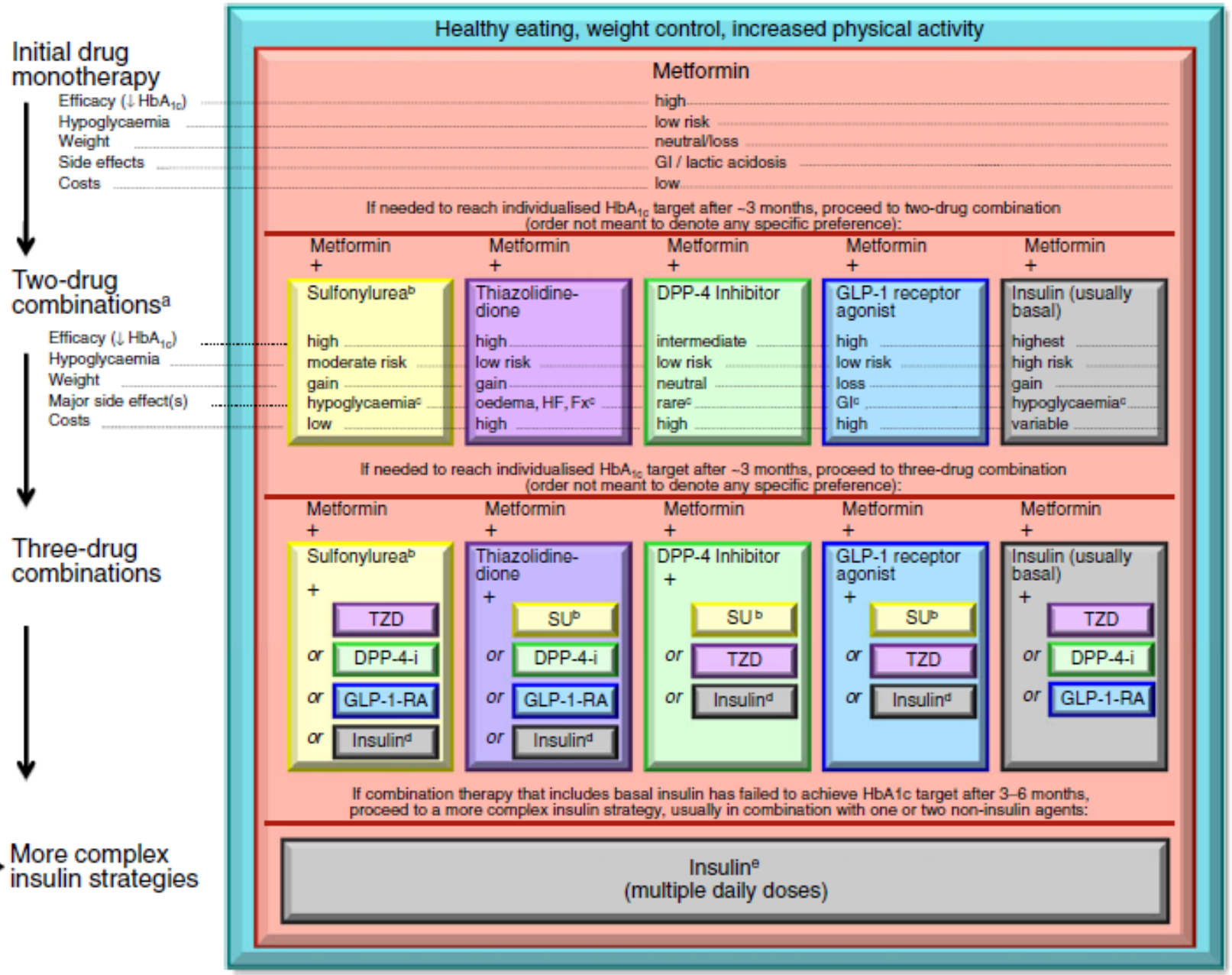
↓

A1C still above target — Initiate insulin

Philips P. *Medicine Today* 2007; 8: 23-34.

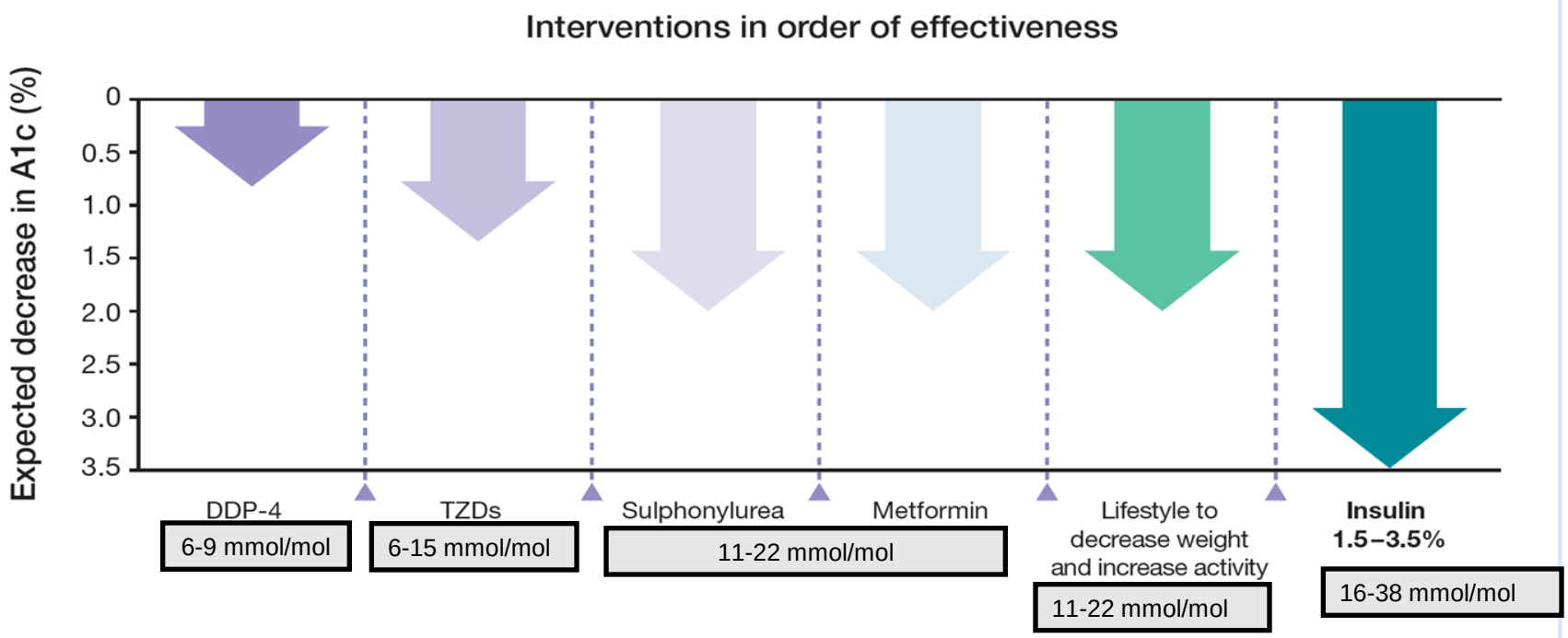
Management of glycaemic control




Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Efficacy (↓ HbA1c)
Hypoglycaemia
Weight
Side effects
Costs
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
If needed to reach individualised HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):
Two-drug combinations[a]
Efficacy (↓ HbA1c)
Hypoglycaemia
Weight
Major side effect(s)
Costs
Metformin + Sulfonylurea[b]
high
moderate risk
gain
hypoglycaemia[c]
low
Metformin + Thiazolidine-dione
high
low risk
gain
oedema, HF, Fx[c]
high
Metformin + DPP-4 Inhibitor
intermediate
low risk
neutral
rare[c]
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI[c]
high
Metformin + Insulin (usually basal)
highest
high risk
gain
hypoglycaemia[c]
variable
If needed to reach individualised HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):
Three-drug combinations
Metformin + Sulfonylurea[b] + TZD or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + Thiazolidine-dione + SU[b] or DPP-4-i or GLP-1-RA or Insulin[d]
Metformin + DPP-4 Inhibitor + SU[b] or TZD or Insulin[d]
Metformin + GLP-1 receptor agonist + SU[b] or TZD or Insulin[d]
Metformin + Insulin (usually basal) + TZD or DPP-4-i or GLP-1-RA
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3–6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:
More complex insulin strategies
Insulin[e] (multiple daily doses)

HbA1c decrease by agent

A1c lowering potential of individual therapeutic options[2]

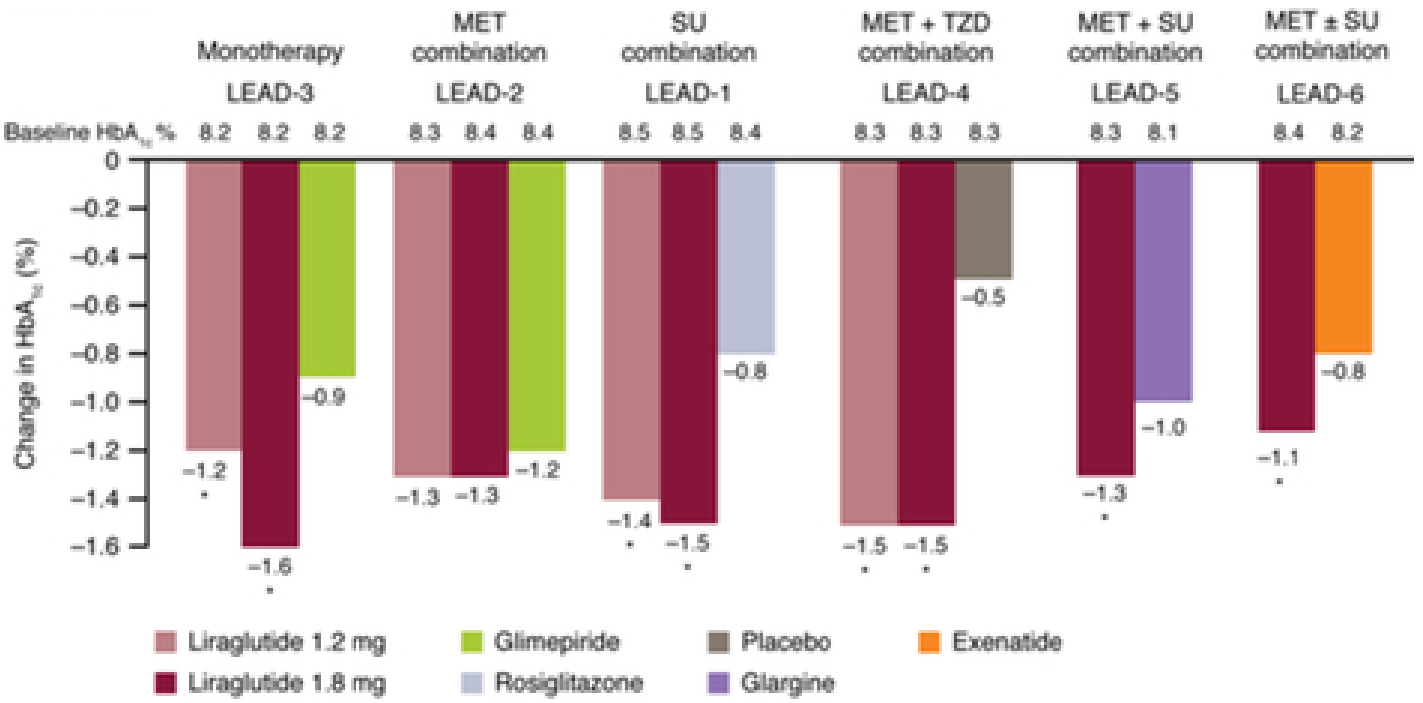


Adapted from Nathan *et al.*, 2009. DDP-4 = Dipeptidyl peptidase-4 inhibitor. TZDs = Thiazolidinedione.

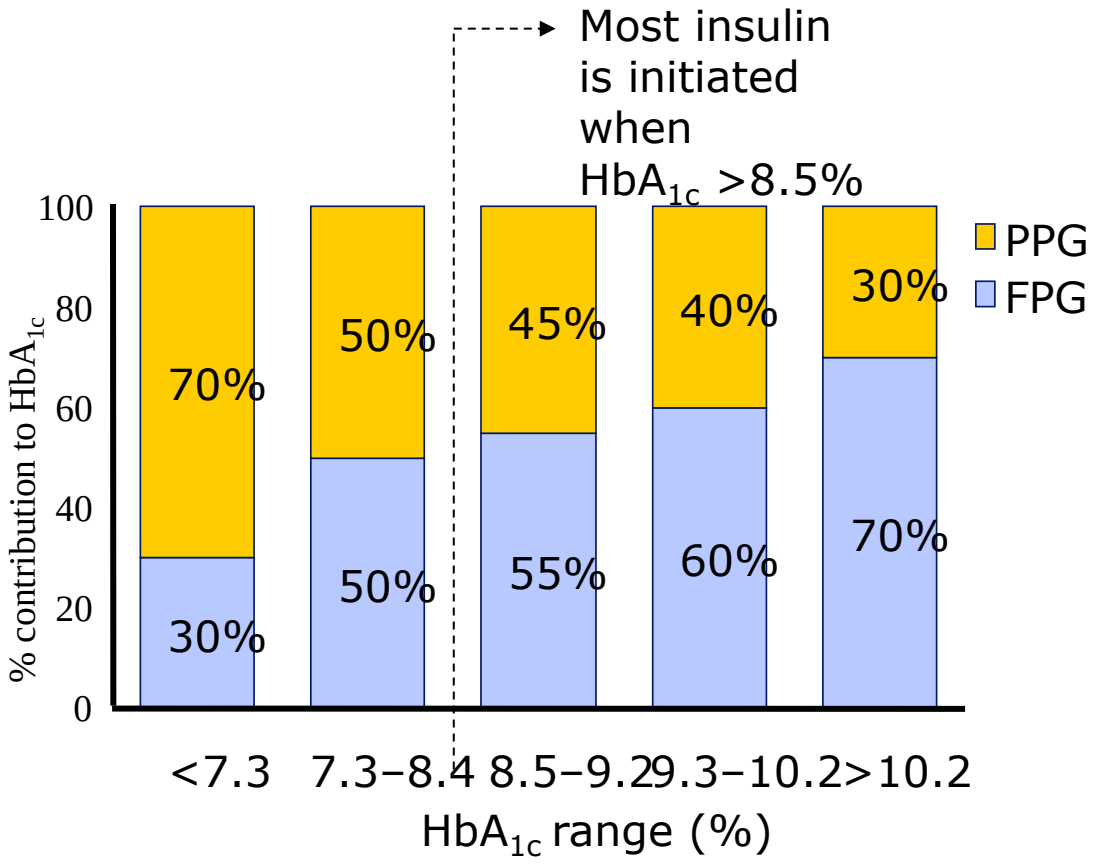
Insulin Even more

Insulin Leadership Summit
THE FUTURE OF TYPE 2 DIABETES IN PRIMARY CARE FROM SANOFI-AVENTIS

LEAD Trials


Monotherapy
LEAD-3
MET combination
LEAD-2
SU combination
LEAD-1
MET + TZD combination
LEAD-4
MET + SU combination
LEAD-5
MET ± SU combination
LEAD-6
Baseline HbA1c %
8.2 8.2 8.2
8.3 8.4 8.4
8.5 8.5 8.4
8.3 8.3 8.3
8.3 8.1
8.4 8.2
Change in HbA1c (%)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
−1.2
−1.6
−0.9
−1.3
−1.3
−1.2
−1.4
−1.5
−0.8
−1.5
−1.5
−0.5
−1.3
−1.0
−1.1
−0.8
Liraglutide 1.2 mg
Liraglutide 1.8 mg
Glimepiride
Rosiglitazone
Placebo
Glargine
Exenatide

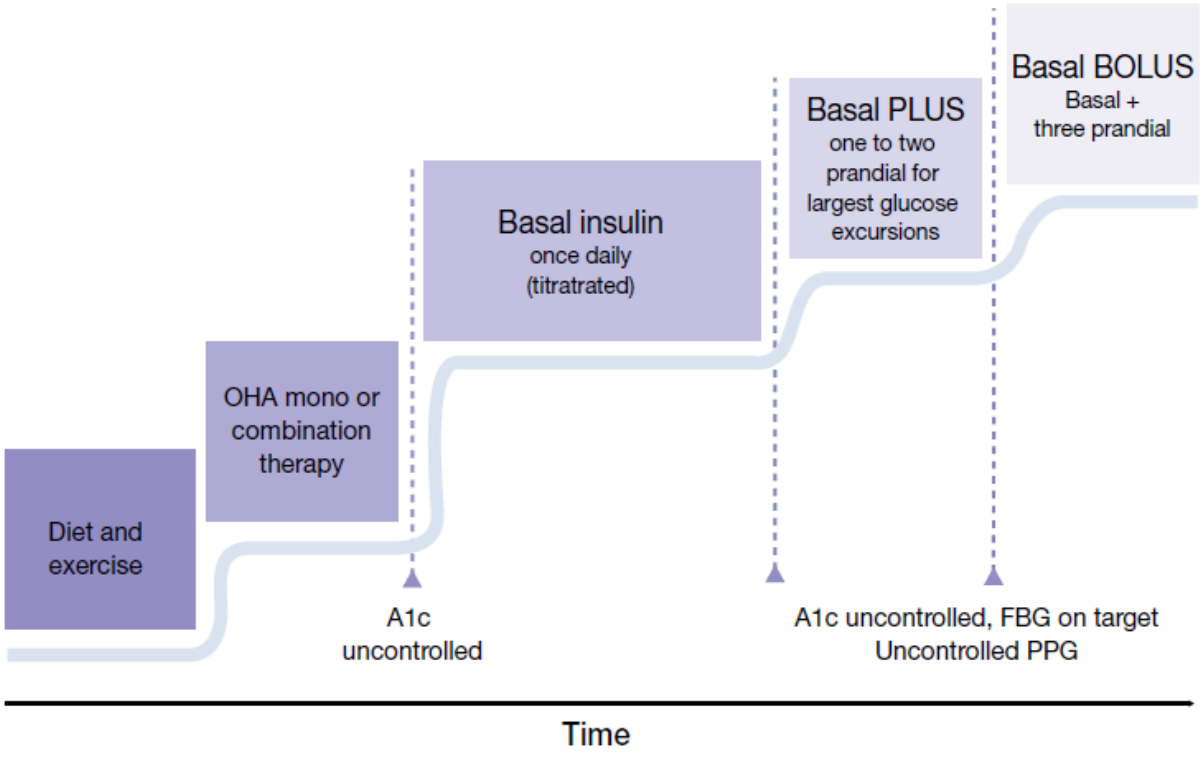
Fix the Fasting First



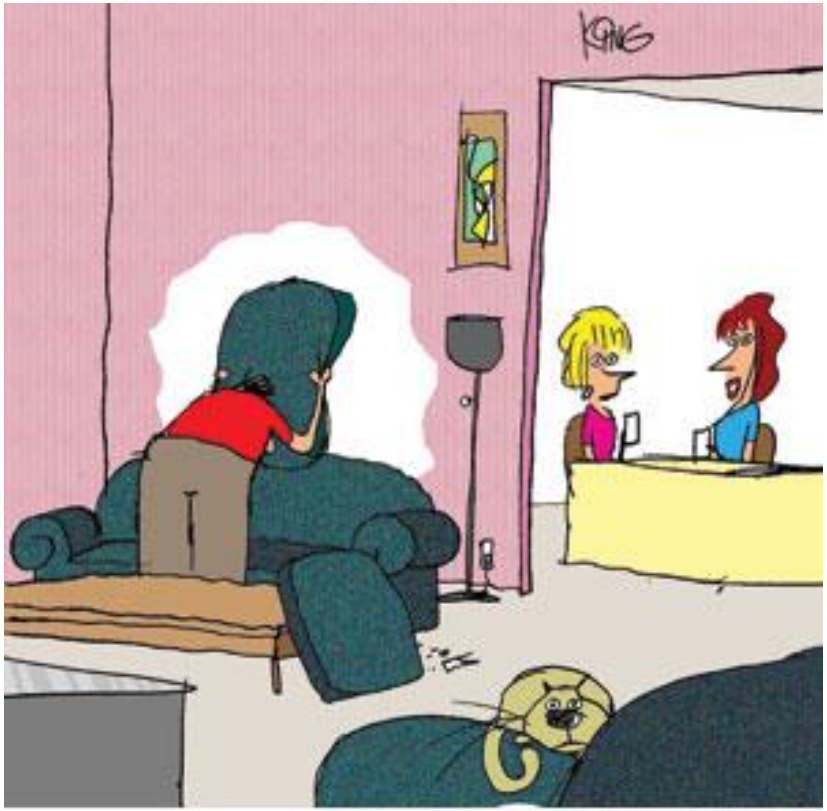
Monnier L *et al. Diabetes Care* 2003;26:881–5

Stepwise approach for T2D

with progressive deterioration of beta cell function



Adapted from Raccah 2008'. OHA = Oral hypoglycaemic agent, FBG = Fasting blood glucose, PPG = Post-prandial blood glucose.



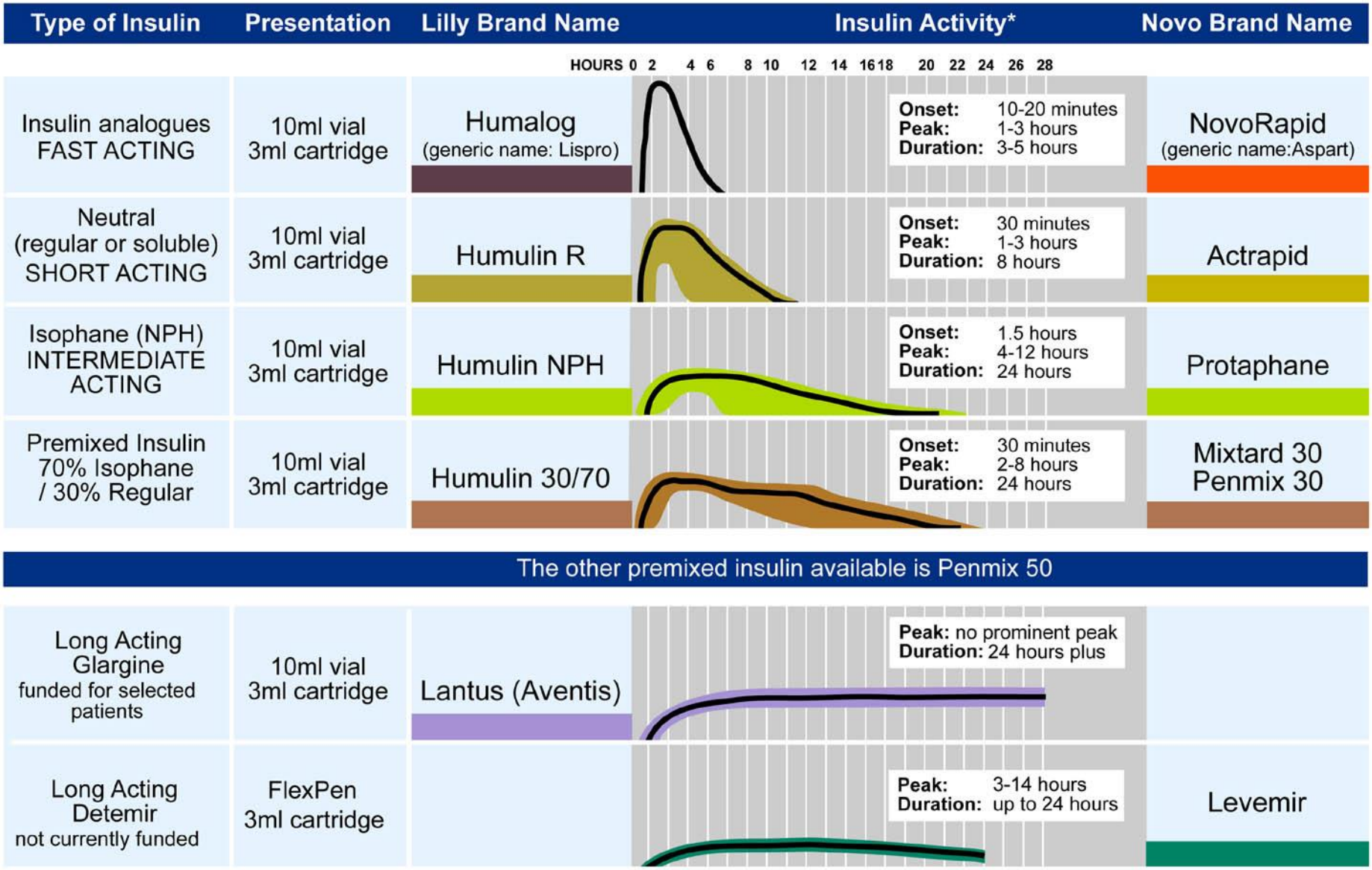
"Jim was diagnosed with diabetes, and his doctor says he needs to keep active, so I hide his TV remote three times a week."

"Insulin is a remedy primarily for the wise and not for the foolish,
whether they be patients or doctors.
Everyone knows it requires brains to live long with diabetes, but to use insulin successfully requires more than brains."

Elliot Joslin (1923).

Starting Insulin

- **Which insulin would you recommend as first line and why?**
  - **Rapid-acting insulin to the meal with the highest preprandial BGL**
  - **Intermediate-acting insulin in the morning or night**
  - **Insulin premixed for ease of use**
  - **Basal insulin to reduce both postprandial and fasting BGLs**



* **Insulin activity may vary from patient to patient**

Diabetes Centre February 2007 Christchurch District Health Board

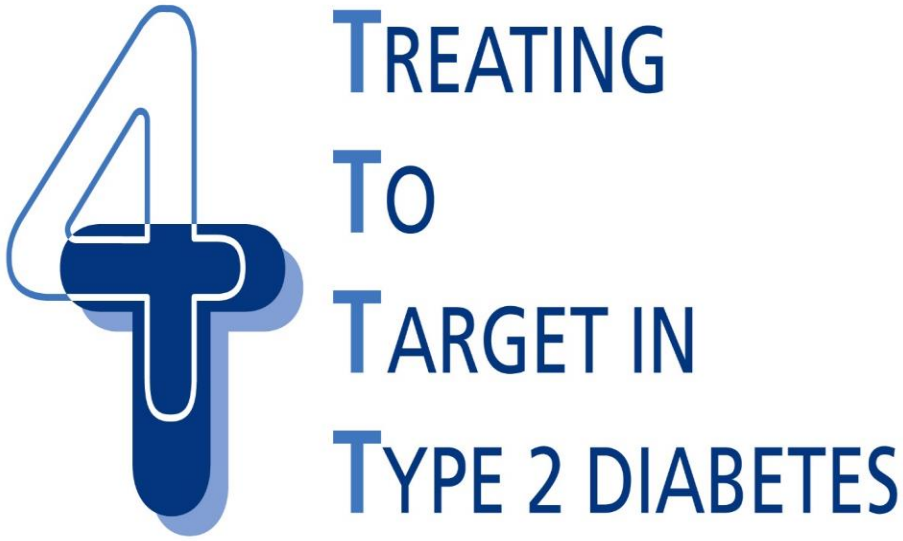
Medical IllustrationCD misc/00116

Insulin Treatment

- Glucose control can be achieved in the vast majority with the addition of insulin in those on maximal (dual therapy) oral medication
- Weight gain is modest
- Hypoglycaemia rates are modest compared with similar management goals in Type 1 DM patients
  - Approx 4 episodes per year vs 0.5 on OHA's

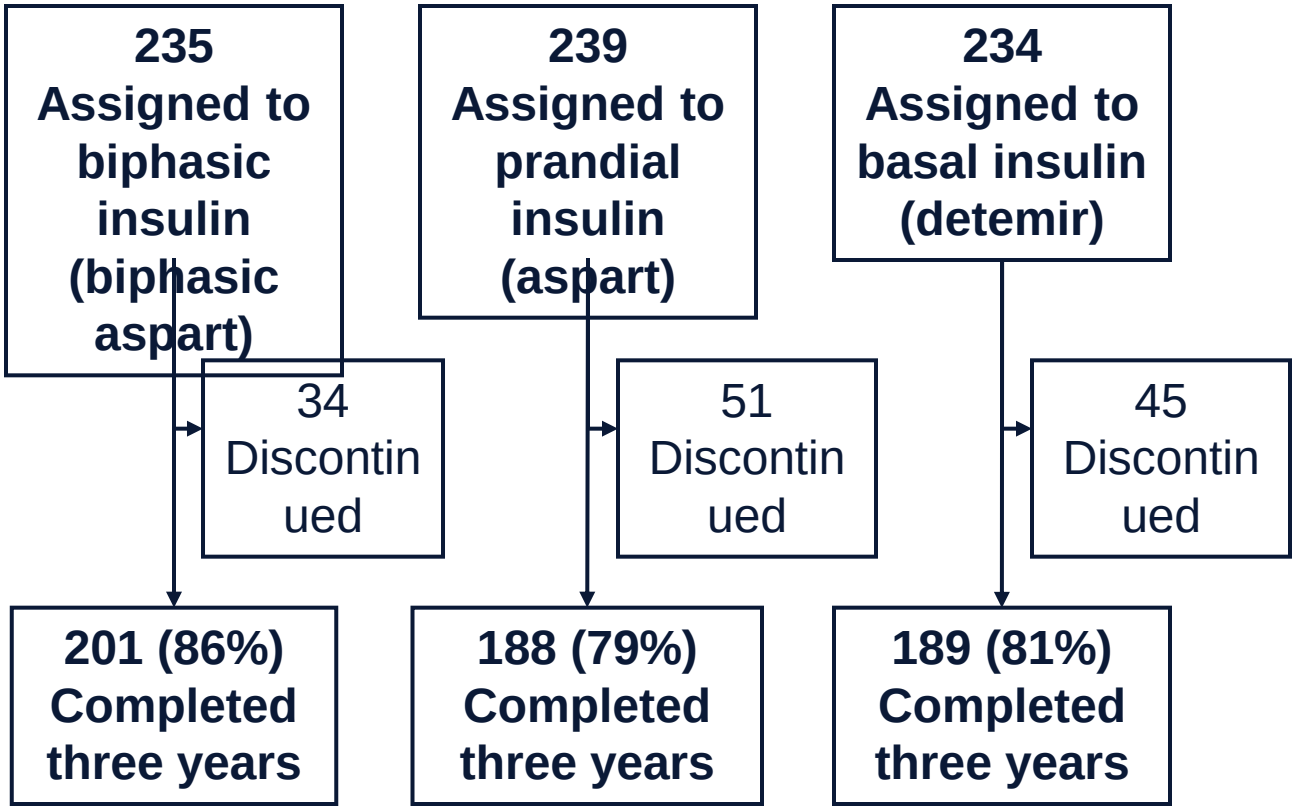
Insulin Treatment

- Several insulin initiation strategies have been tested against each other, and are broadly equivalent at 3 years with basal insulin addition having modestly less hypos and weight gain than premixed or prandial strategies BUT
  - *By 3 years a large proportion of patients are on more than one "mode" of insulin to keep control*



N Engl J Med 2007; 357: 1716-30

Patient Disposition

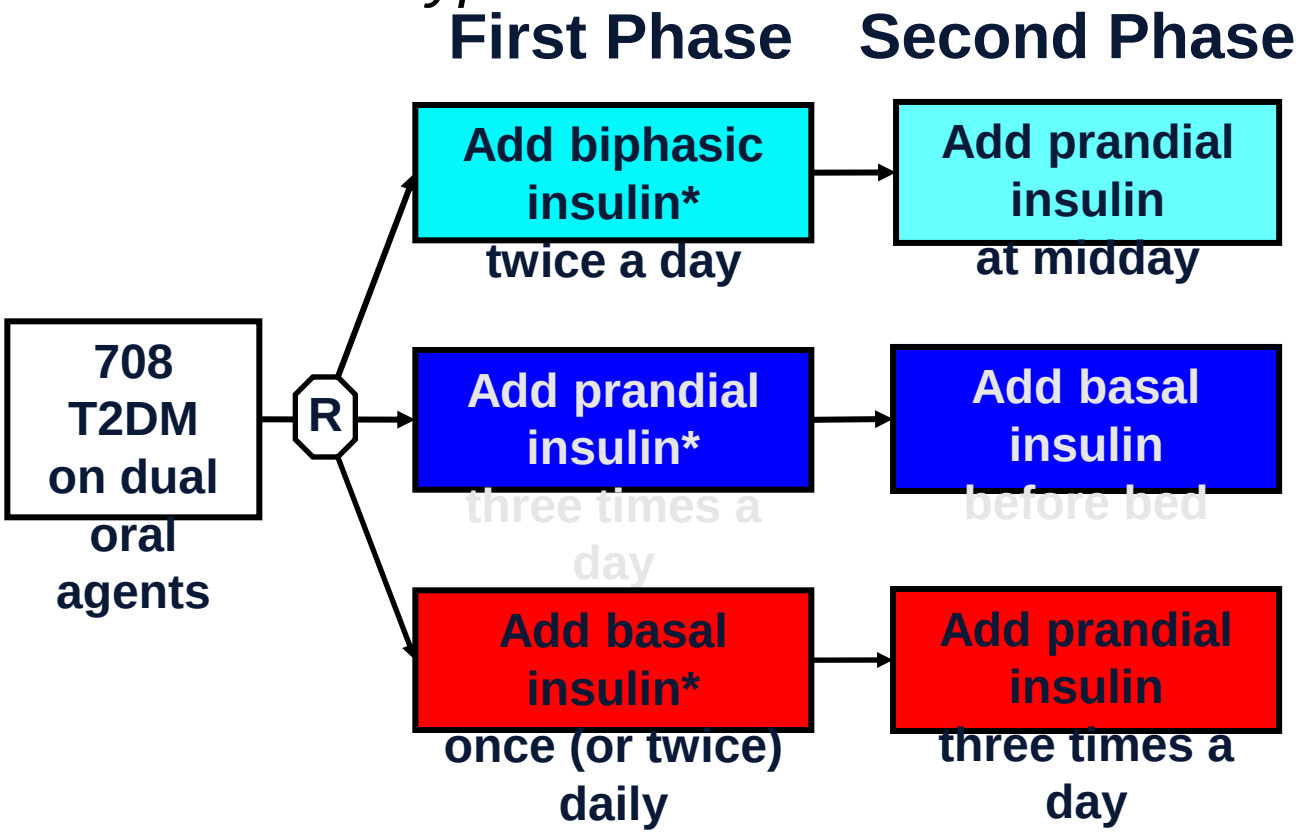


- Overall, 18.4% of patients did not complete three years
- No difference in proportions between groups (p=0.15)

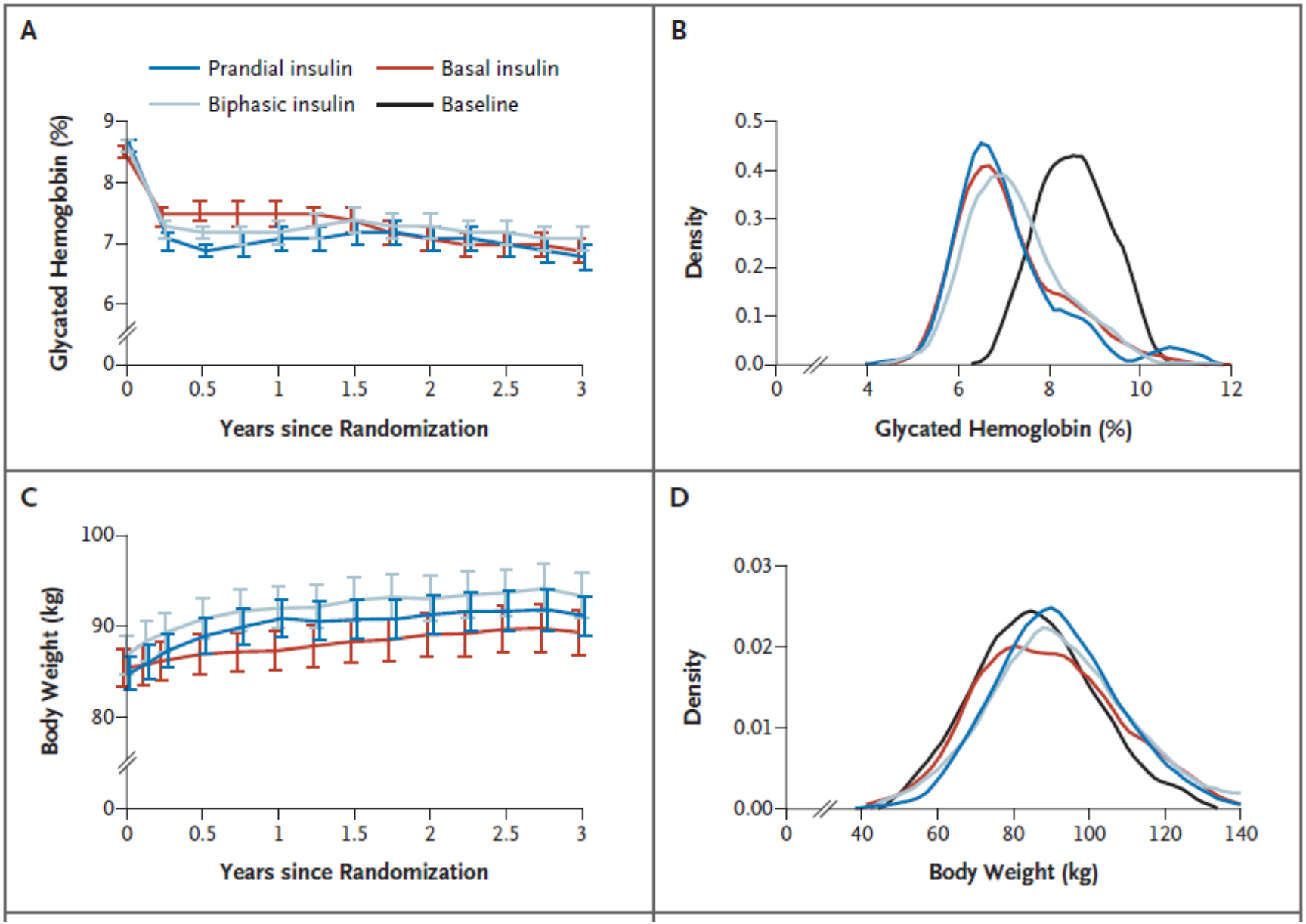
N Engl J Med 2007; 357: 1716-30

Transition to a Complex Insulin Regime

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



4T study 3 year results



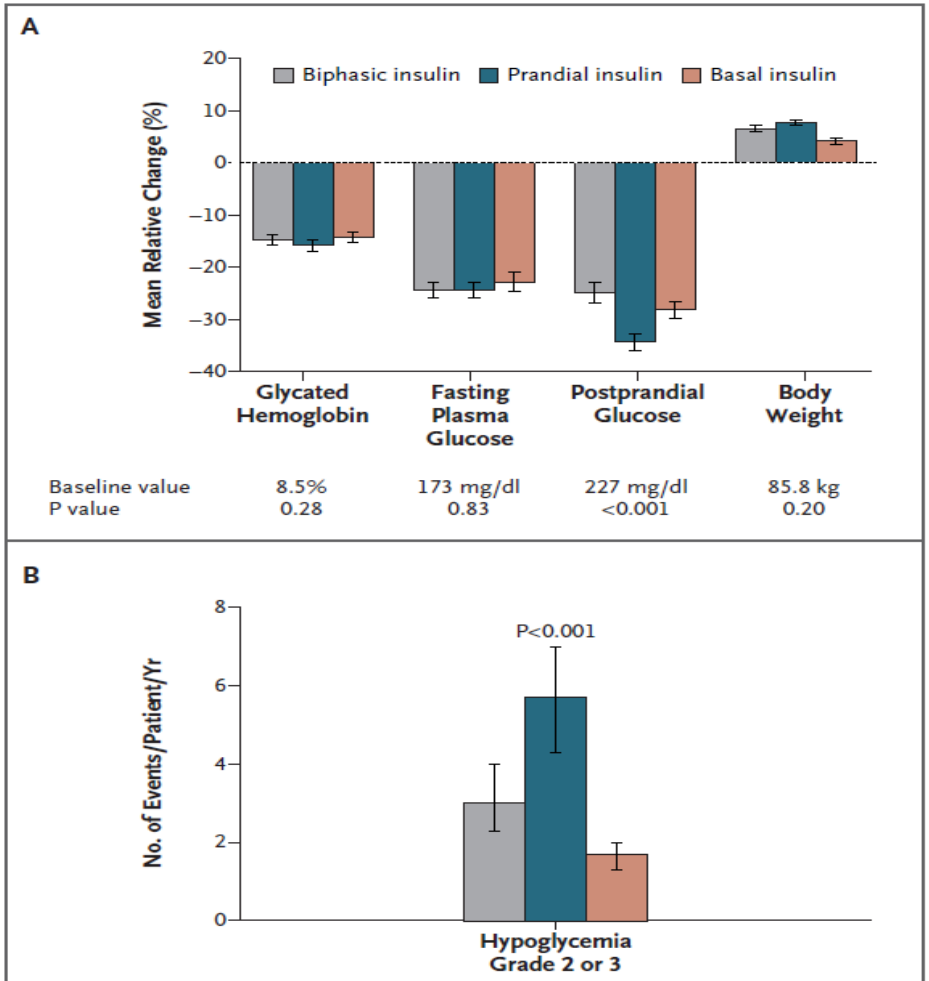
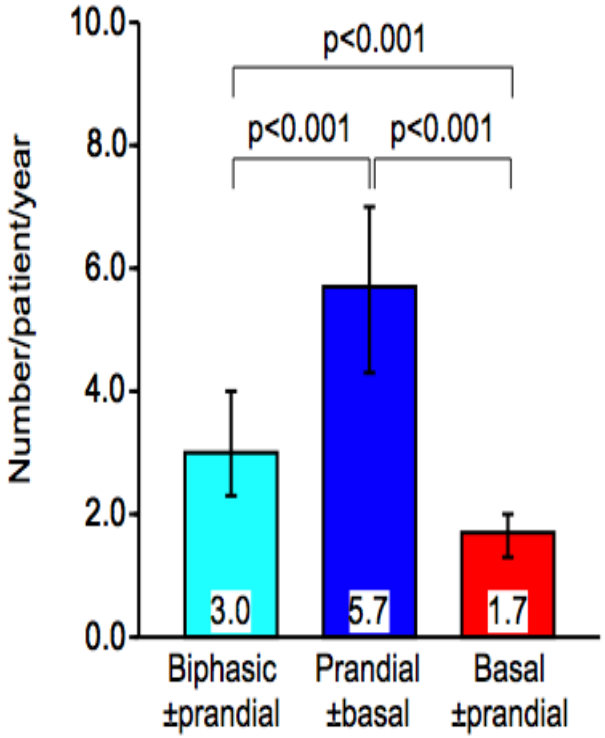


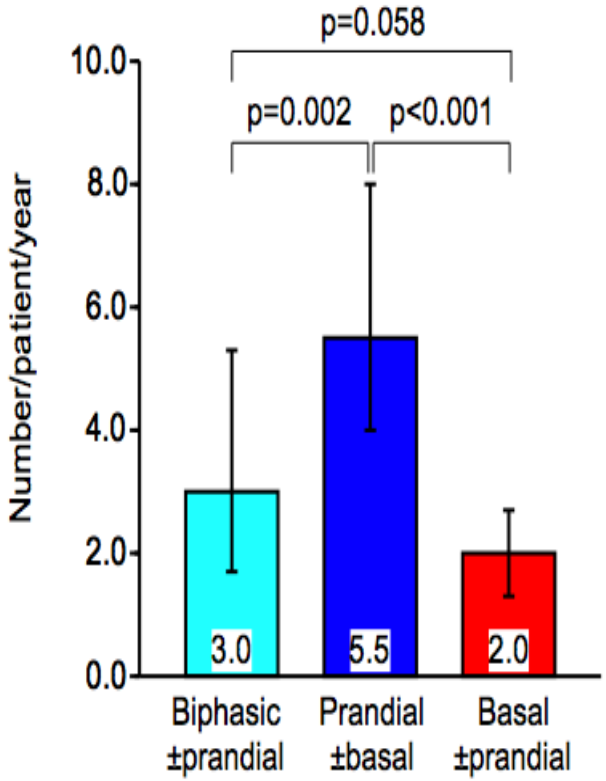
Figure 3. Changes from Baseline to 3 Years in Glycated Hemoglobin, Fasting Plasma Glucose, Postprandial Glucose, and Body Weight and the Rate of Hypoglycemia.

Grade 2 or 3 Hypoglycaemia Over 3 Years

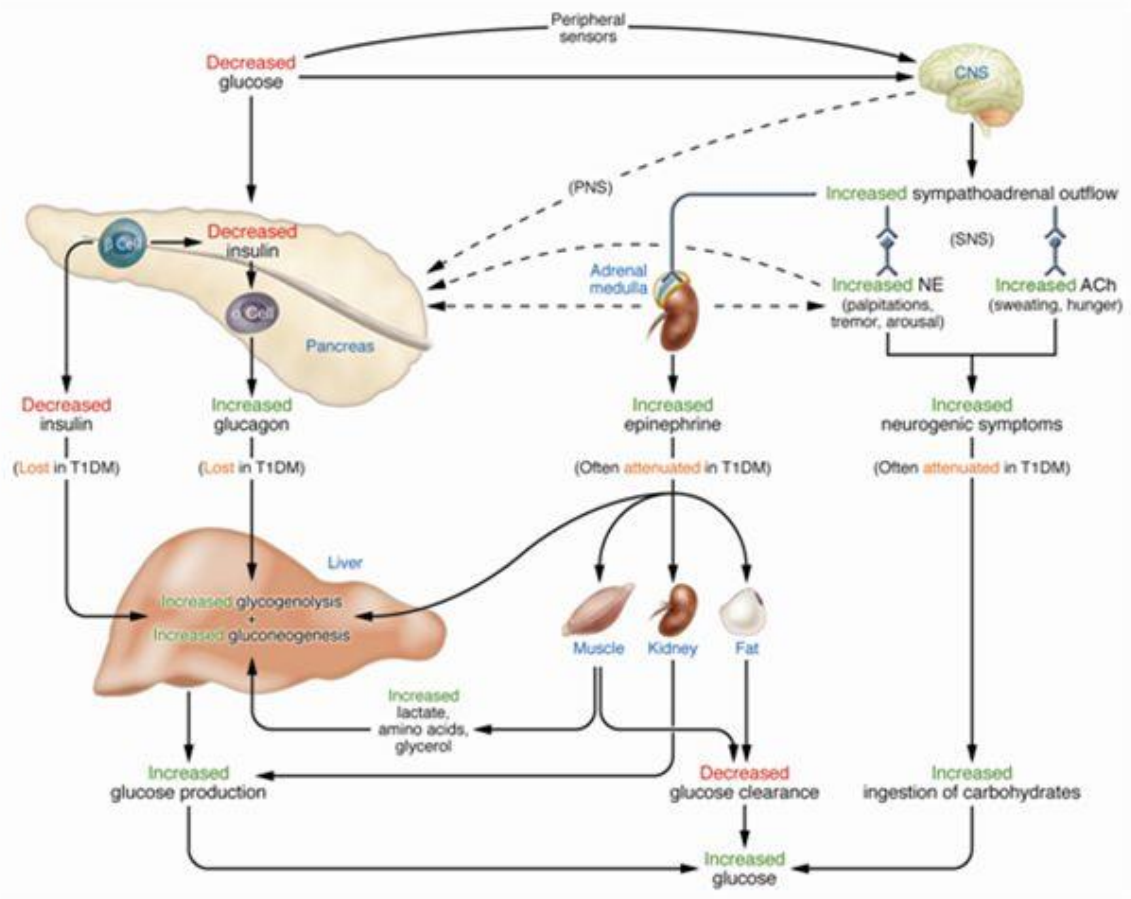
All patients



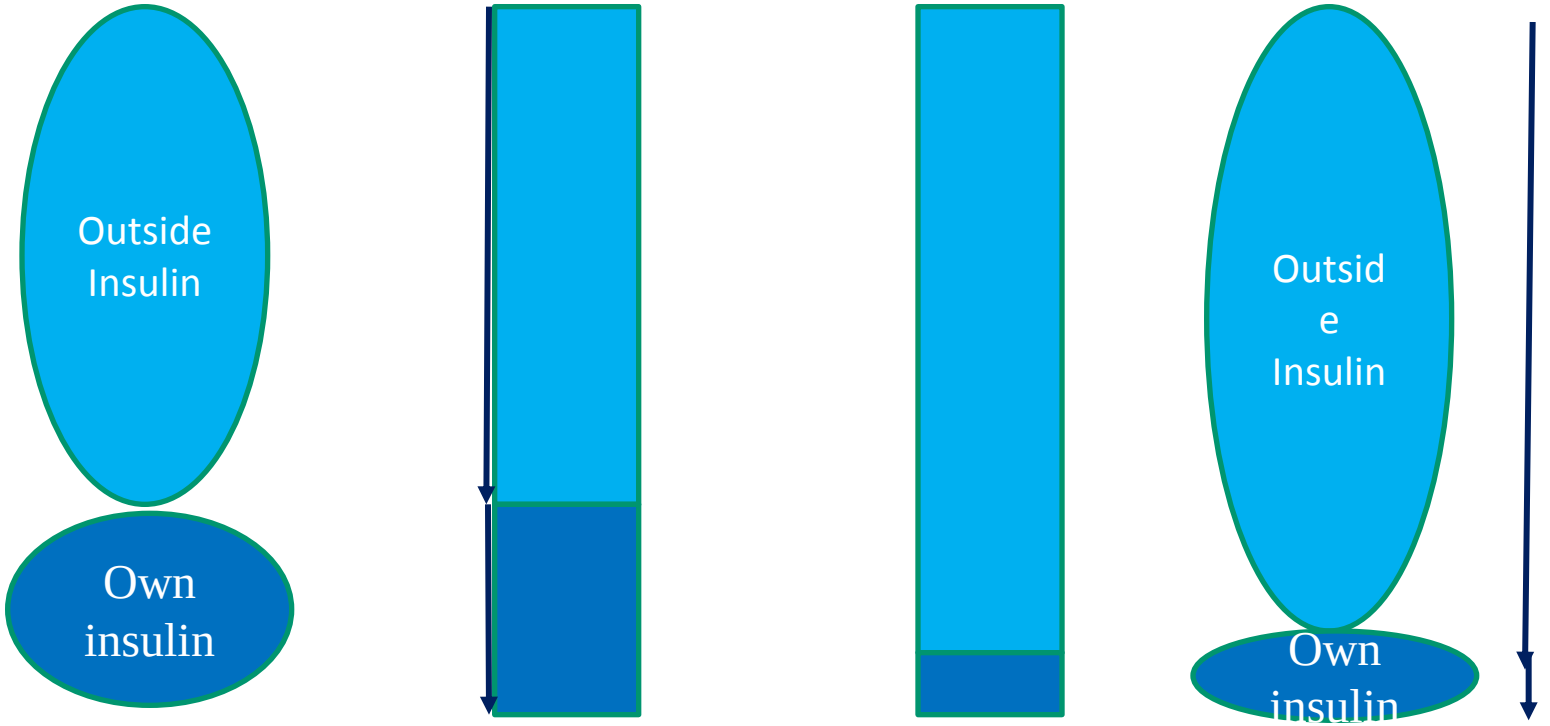
Patients with HbA_{1c} ≤6.5%



Hypoglycaemia



Hypoglycaemia risk increases with time in T2D



Early T2D

Late T2D

Does Adjustment of Basal Insulin

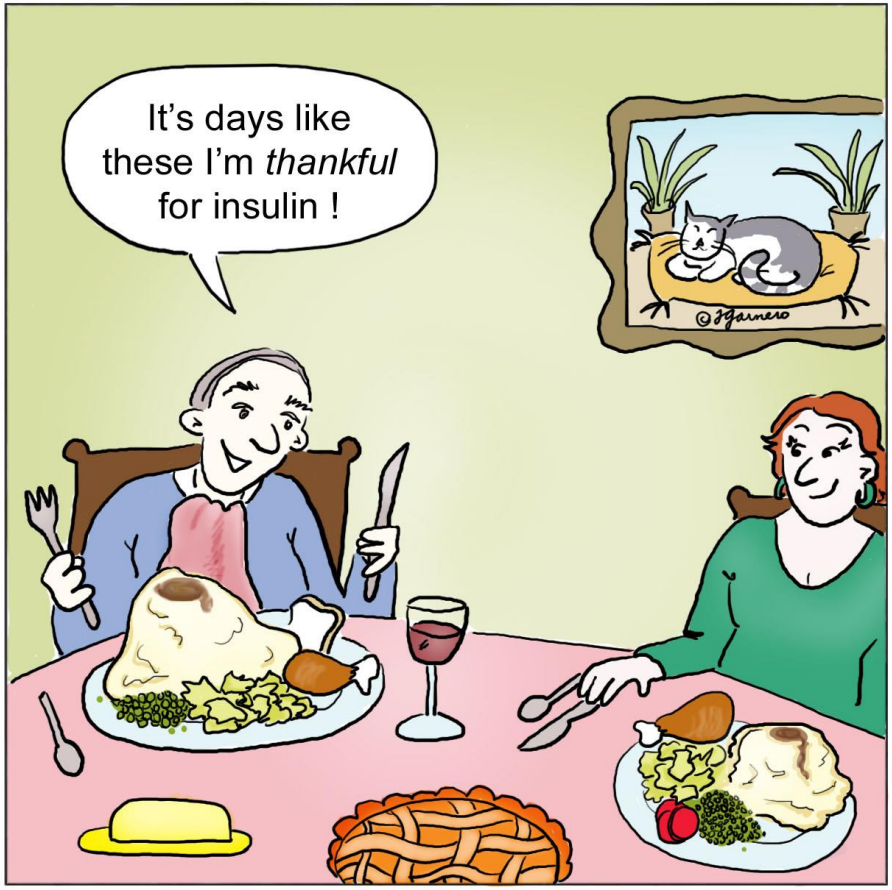
- Slow, patient led titration
  - Increase by 2 units per day every 3 days until FBG < 6.0mmol/l

Adding Prandial insulin

- Either Humalog, Novorapid or Apidra
- Start 4 units per meal, increase by 2 units every 3 days until achieve target
  - (post prandial < ?8mmol/l, single figures at least)
  - Get one meal at a time right

Islets of Humor

by Theresa Garnero



Mixes

- Humalog Mix 25, Novomix 30
- Most useful in patients who want to limit number of injections
- Again start 10 units once or twice a day and titrate by 2 units every 3 days
- If transitioning from an intermediate only regime, start with equivalent number of units then titrate up

Transitioning to Lantus

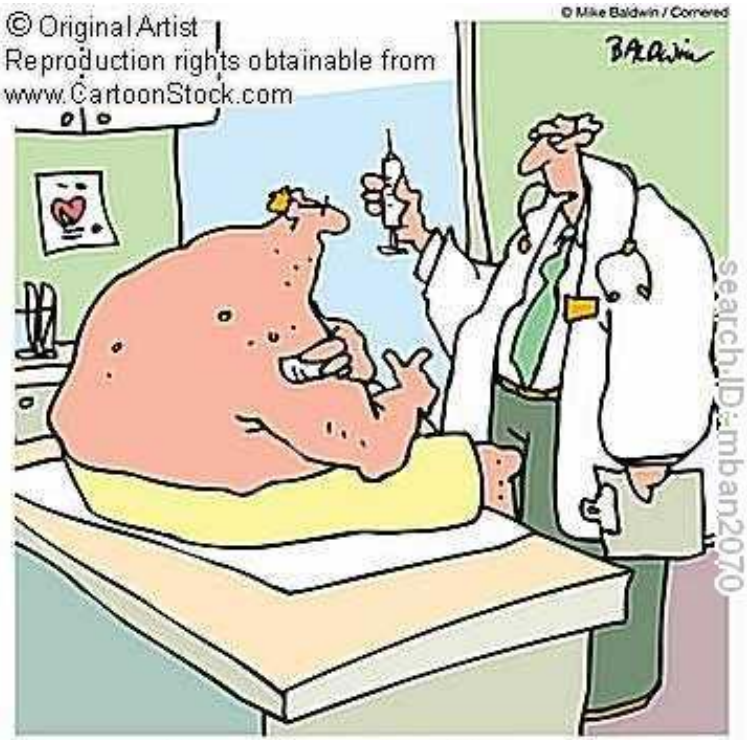
- If on a OD dose of intermediate
  - Start with same number of units
- If on BD intermediate dosing
  - 80% of Total Daily dose

SMBG

- Lifestyle or OHA's alone
  - Helpful intermittently to see effect of food, exercise
- In Basal insulin
  - Useful in mornings to titrate dose
  - Useful if HbA1c climbs
- In Mixes
  - Four point testing one day a week
- In Basal/Bolus regimes
  - Useful to adjust prandial doses

Summary

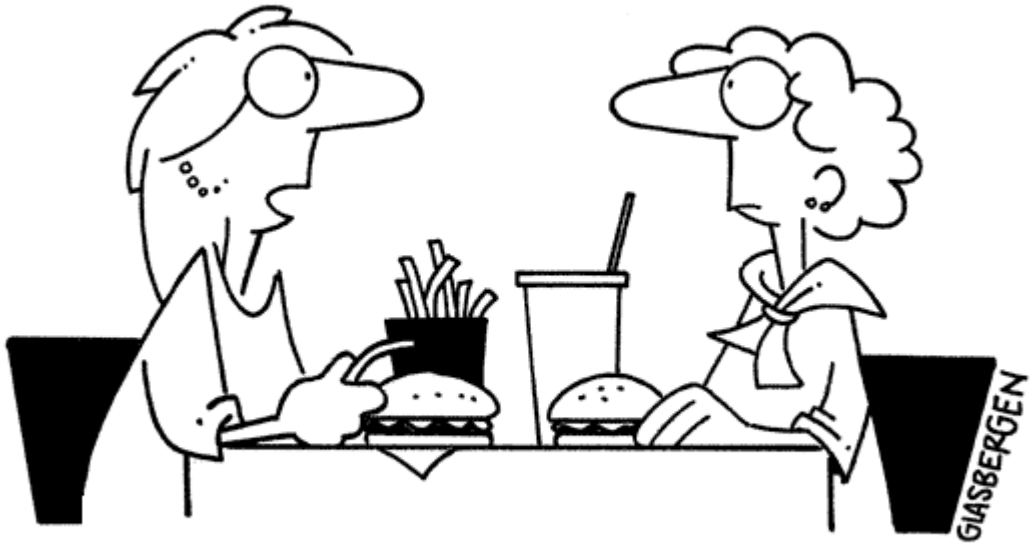
- Diabetes is an ever increasing epidemic
- Diet & Exercise remain crucial to management at all stages
- HbA1c targets are there for a reason
- Benefits of good glycaemic control are long lasting
- Good glycaemic control is achievable in most patients with escalation of therapy, including Insulin
- Many fears of insulin therapy are unwarranted



"It wasn't really insulin. You don't have diabetes yet. It was just a warning shot."

Summary

- It doesn’t really matter what Insulin you start, anything will be better than nothing!!
- Important to escalate dose when required



"Every time I go on a diet, I lose my mind. Unfortunately, it doesn't weigh very much."