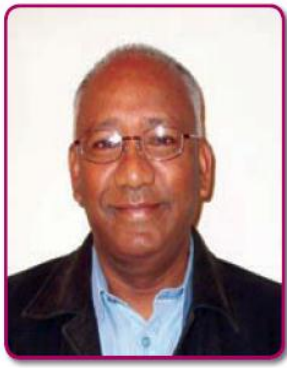
Dr Kingsley Nirmalaraj

Endocrinologist, Tauranga Hospital



RN Rab Burtun

Diabetes Nurses Specialist, Waitemata DHB

Starting Insulin in General Practice Workshop - Pre-Conference Workshop

Thursday, 09 June 2011 Start 2:00pm Duration: 4 hours Works

Starting Insulin Sooner Rather Than Later

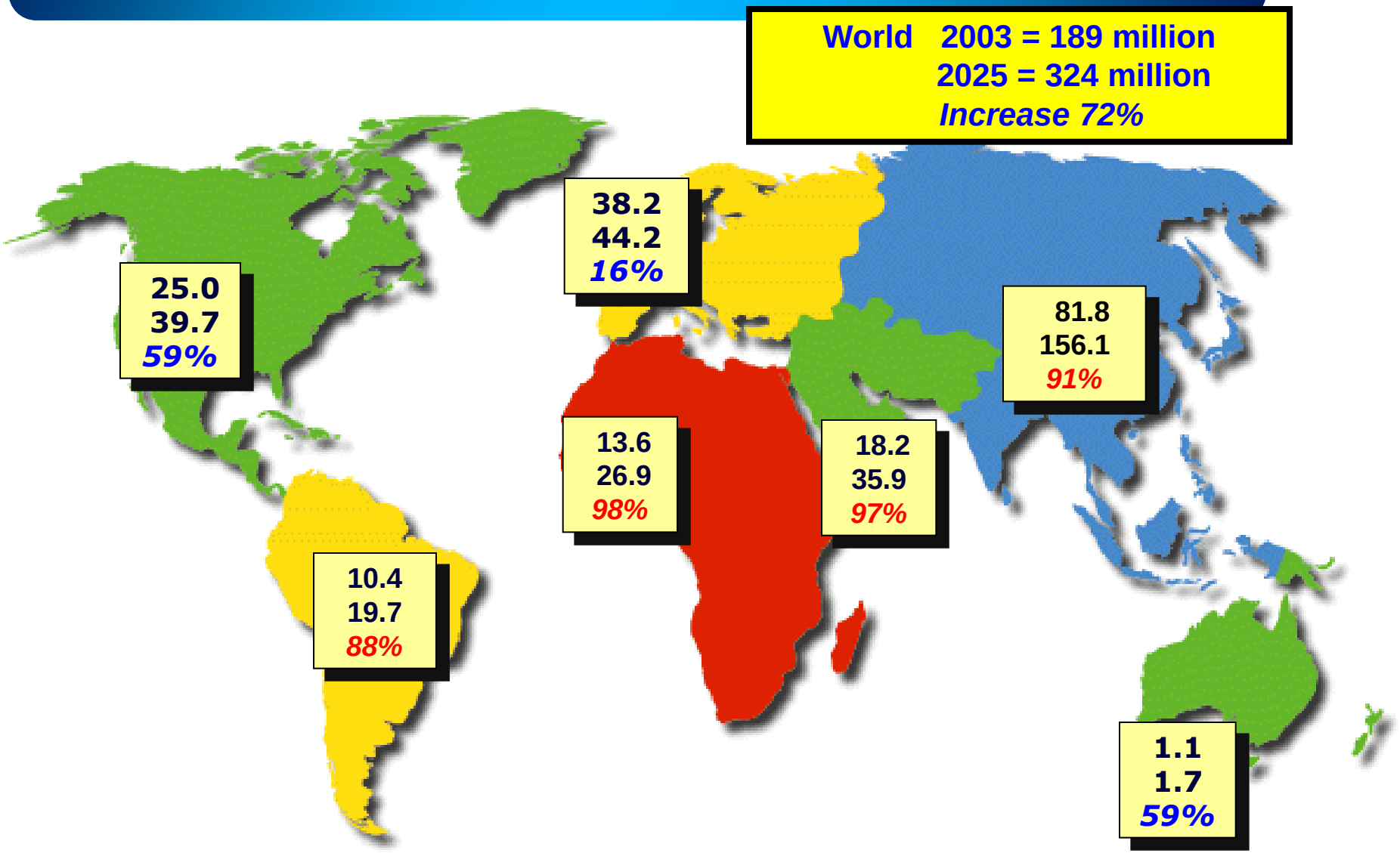
Rotorua GP CME June 2011

Kingsley Nirmalaraj FRACP
Endocrinologist and Physician
BOPDHB

Agenda

- Size of the problem
- What is T2DM anyway?
- Natural History of Type 2 diabetes
- Does management of glycaemia matter?
- Self-monitoring of blood glucose (SMBG)
- ADA/EASD Guidelines for the treatment of hyperglycaemia in type 2 diabetes (DM2)
- Treatment targets

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

Update: NZHS Findings

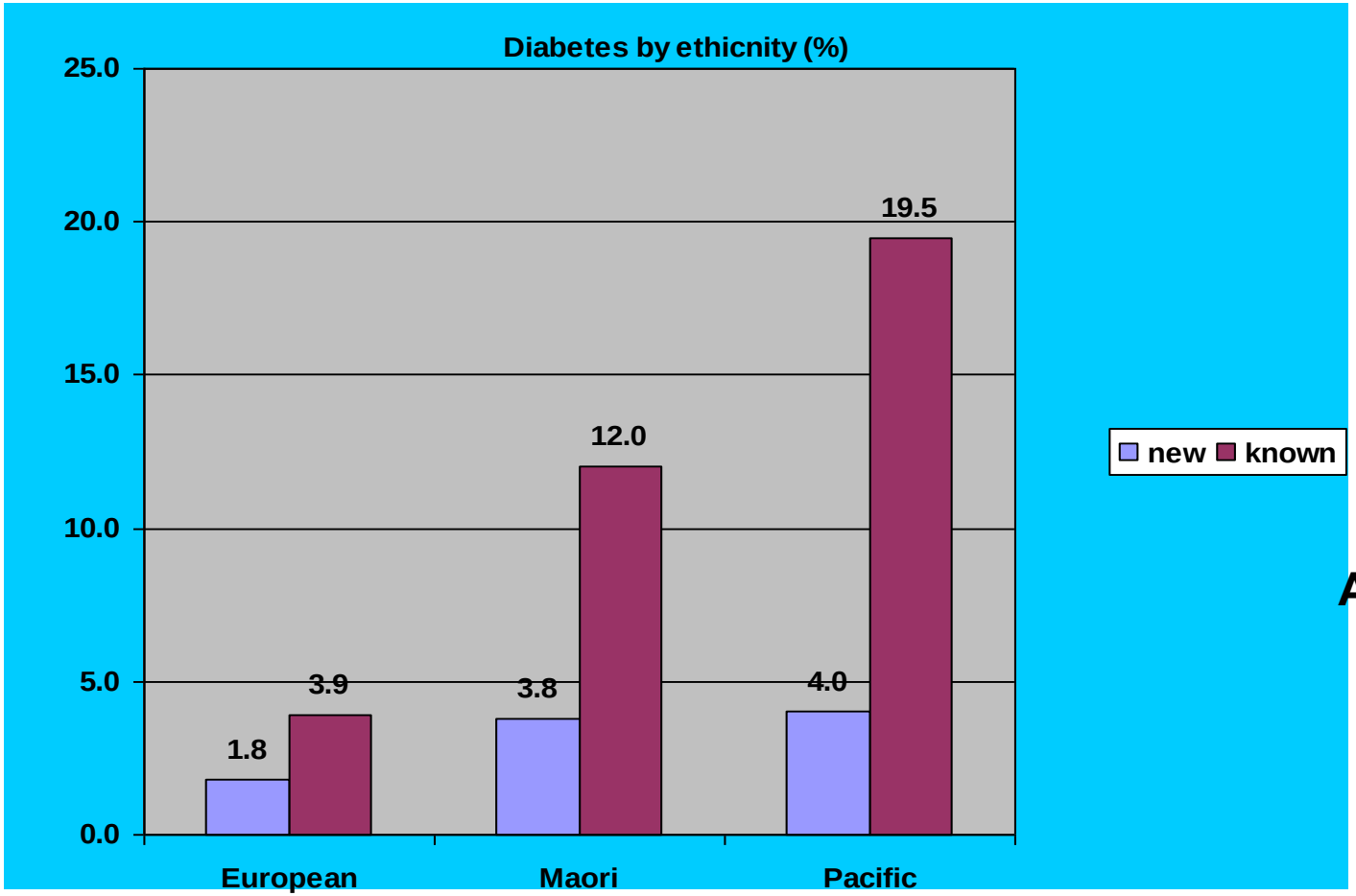
Diagnosed diabetes for adults, by DHB area (unadjusted)

DHB area	Prevalence (95% CI)	Number of adults
Northland / Tairawhiti / Hawke's Bay / Lakes / Whanganui	4.5 (3.4–5.7)	17000
Waitemata	4.0 (2.8–5.2)	15200
Auckland	4.9 (3.4–6.3)	15600
Counties Manukau	8.2 (6.4–9.9) +	26400
Waikato	5.6 (4.2–7.0)	14400
Bay of Plenty / Taranaki / MidCentral	4.8 (3.5–6.1)	16900
Wairarapa / Hutt Valley / Capital and Coast	5.1 (3.6–6.7)	17700
Canterbury	4.4 (2.7–6.1)	16500
Nelson Marlborough / West Coast / South Canterbury / Otago / Southland	4.4 (3.0–5.8)	17400
New Zealand total	5.0 (4.6–5.5)	157100

Undiagnosed rate ratios

Auckland Heart and Health Survey (2007)

1:2 **1:3** **1:5**

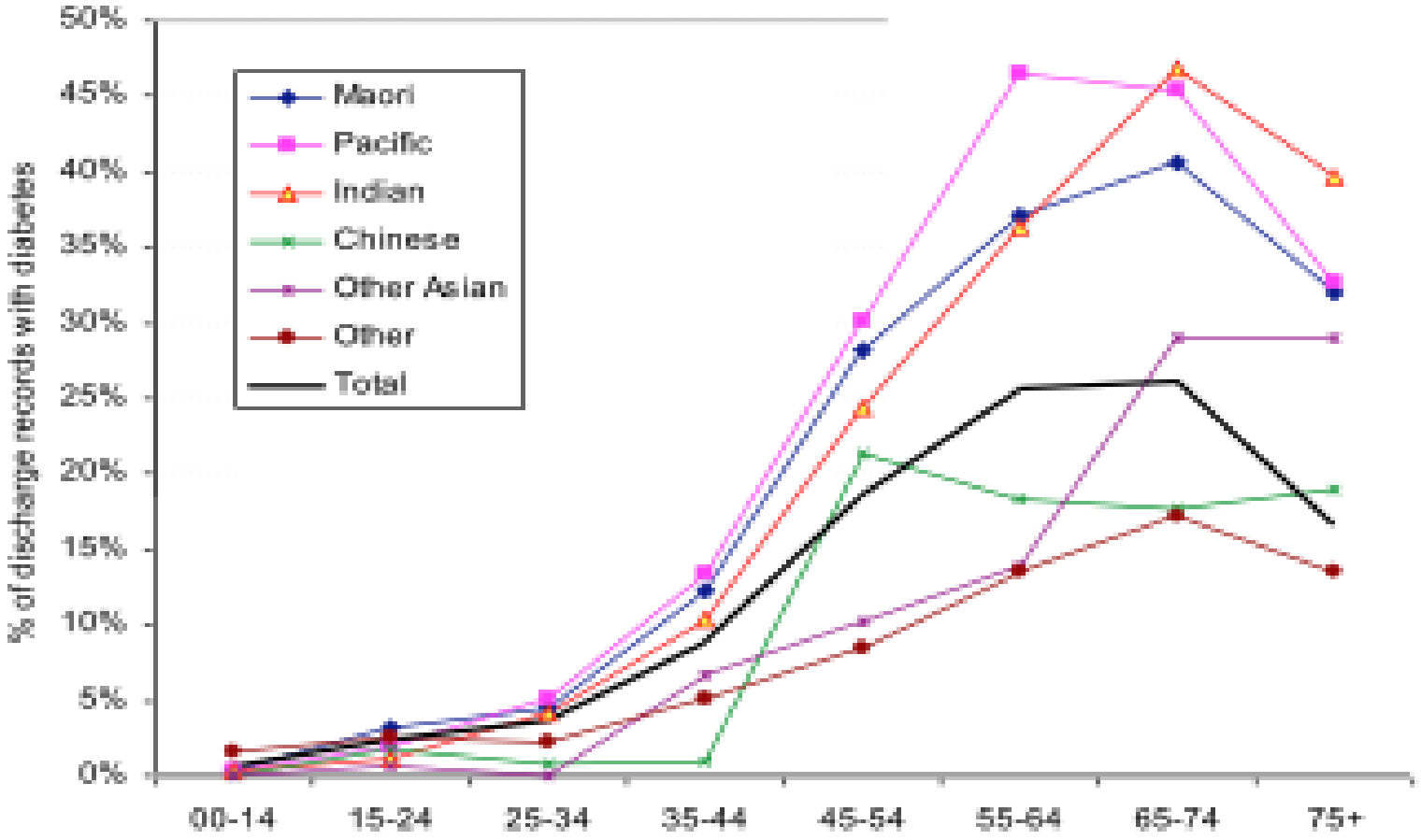


Age 35+

Numbers

- People in NZ with known diabetes 190,000
- Number with undiagnosed diabetes
- Practices ~1100 (173/Practice)
- GPs ~3500 (54/GP)
- Your practice?

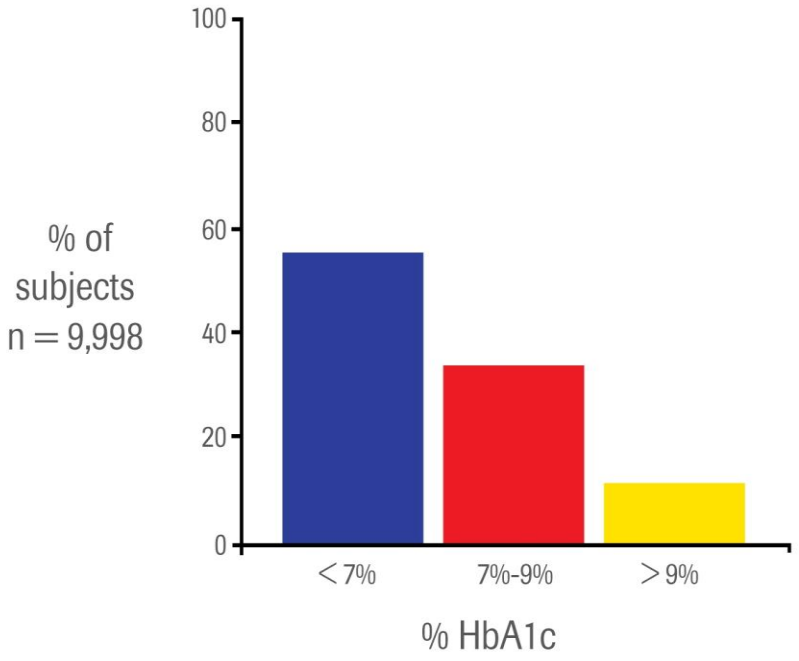
People with diabetes are over represented as hospital inpatients



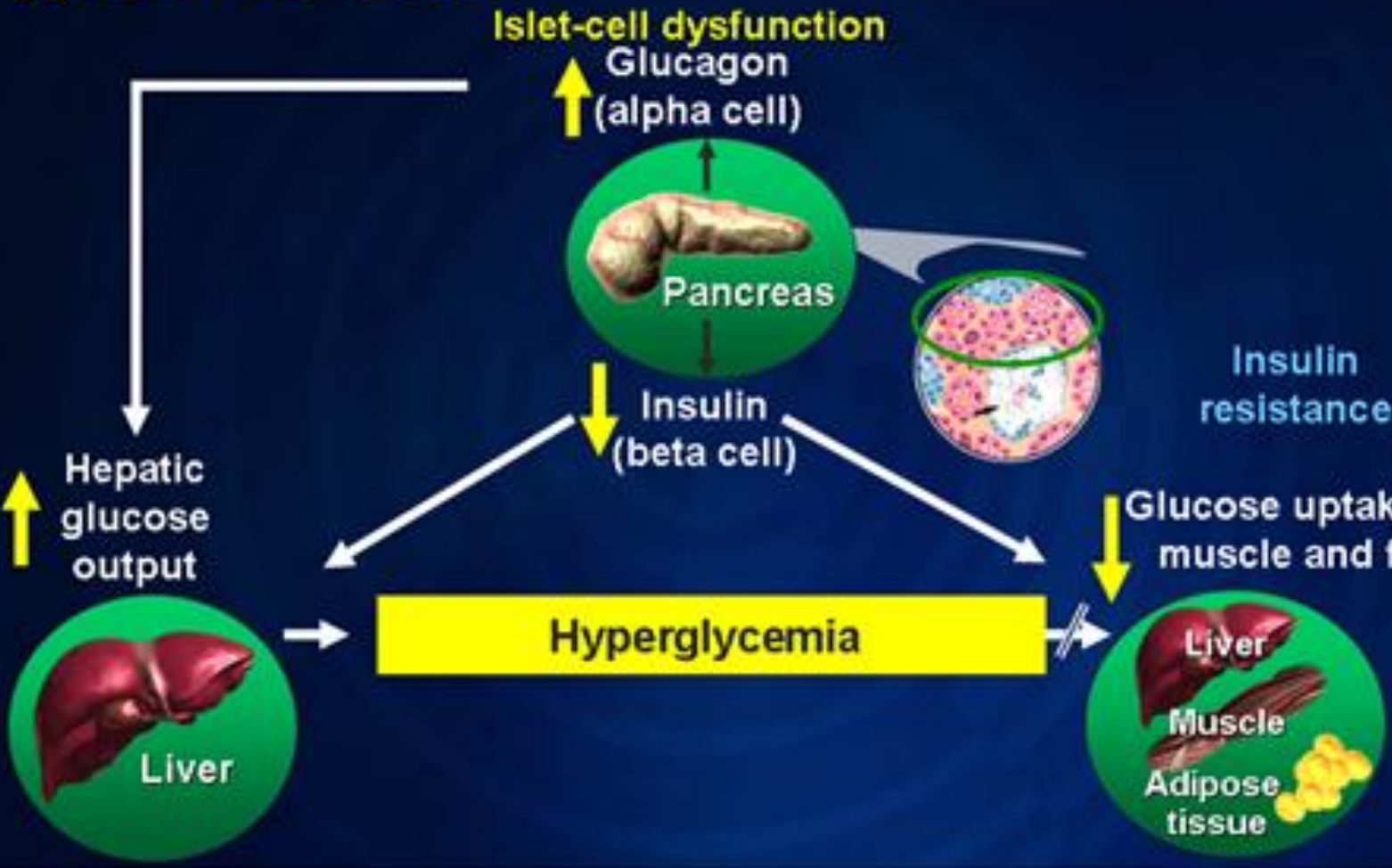
Diabetes Management Remains Suboptimal

- Over 40% of individuals with Type 2 had an HbA1c over 7%
- Over 90% of individuals with Type 1 had an HbA1c over 7%

NZ Get Checked data

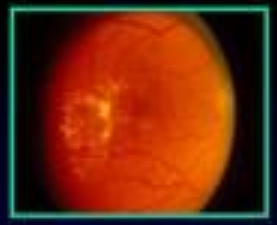


Pathophysiologic Defects in Type 2 Diabetes

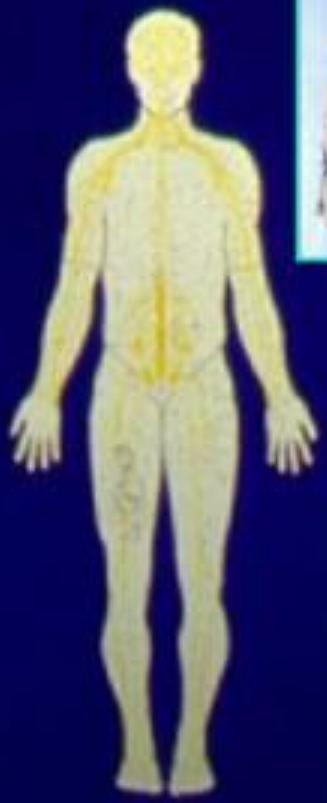


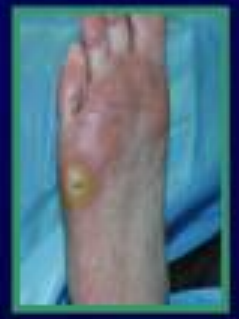
Adapted with permission from Kahn CR, Saltiel AR. *Joslin's Diabetes Mellitus*. 14th ed. Lippincott Williams & Wilkins; 2005:145-168. Del Prato S, Marchetti P. *Horm Metab Res*. 2004;36:775-781 Porte D Jr, Kahn SE. *Clin Invest Med*. 1995;18:247-254.






Diabetes End-Organ Complications

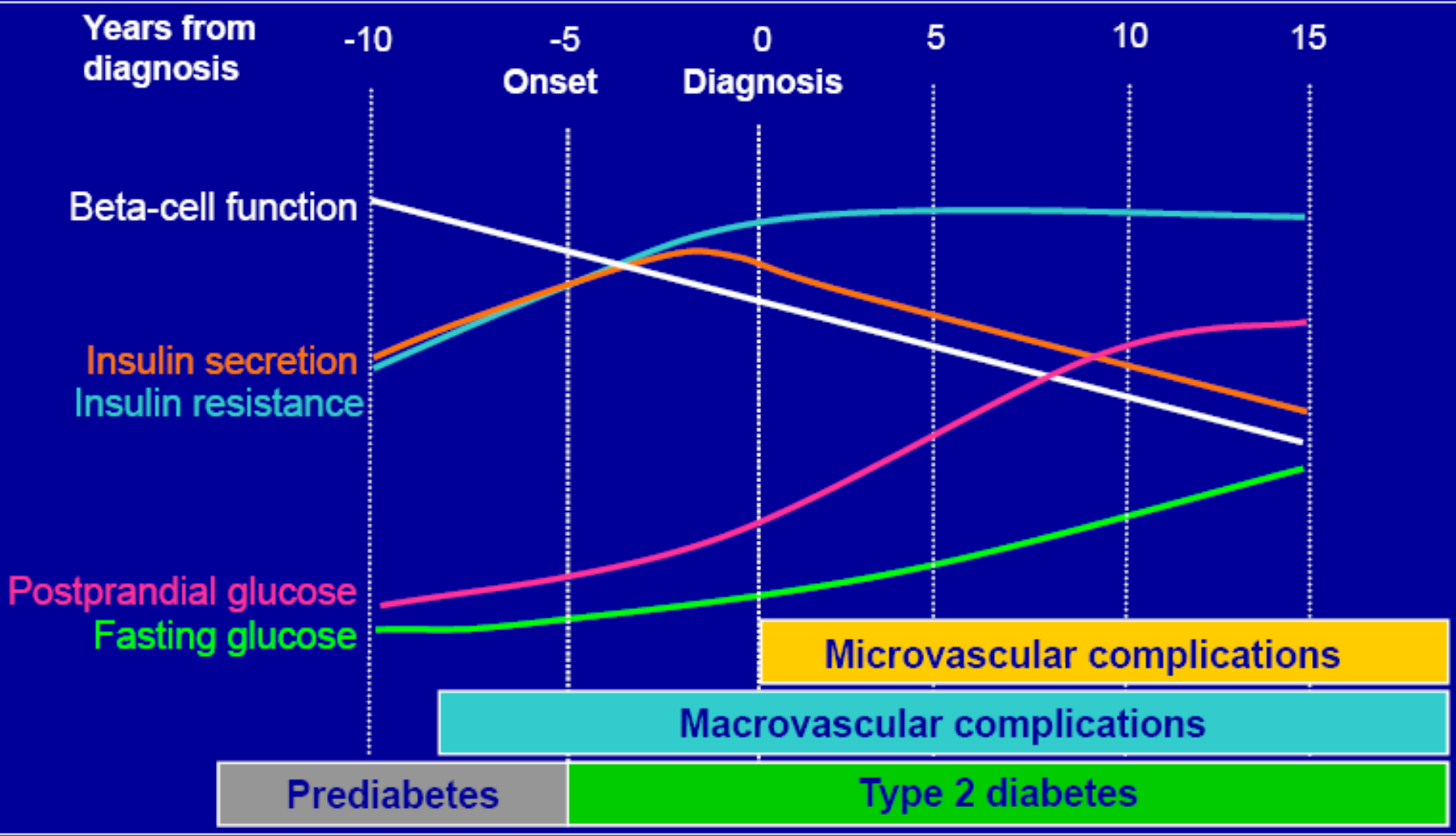



What is Type 2 Diabetes (DM2)?

- DM2
  - FPG $\geq$ 7.0 mmol/L or
  - 2 hr GTT $\geq$ 11.1 mmol/L
  - HBA1c $\geq$ 6.5% (new)
  - Symptomatic + random glucose $\geq$ 11.1
- Impaired fasting glucose or impaired glucose tolerance
  - FPG of 6.1 (5.6 in ADA guidelines) to 6.9
  - 2 hr GTT of 7.8 to 11.0
  - HBA1c of 5.7-6.4% (66% sensitivity & 88% specificity for 6Y incidence of DM - Diabetes Care. 2011. 34:S62.)
  - HBA1c of 6-6.4% imparts a > 10 X greater risk DM.

Natural History of T2DM

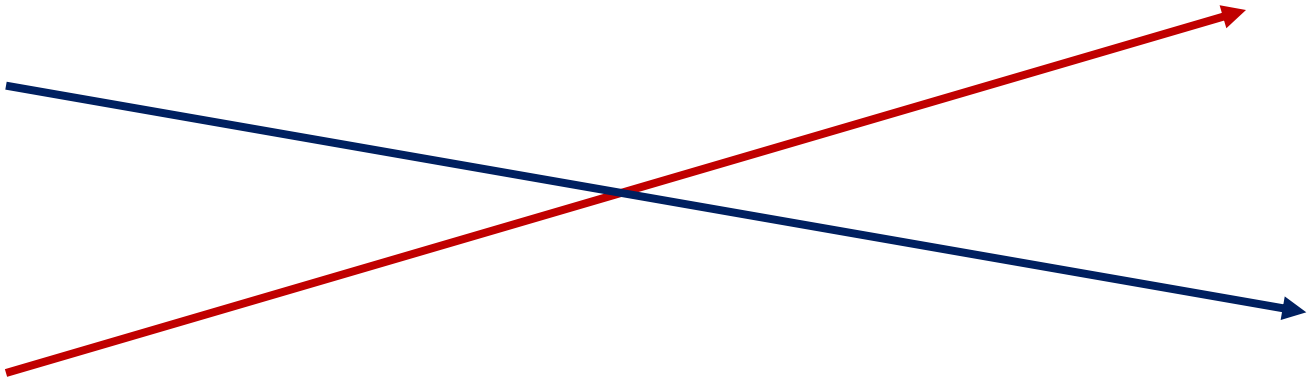


Data extrapolated.

Adapted from Holman RR. *Diabetes Res Clin Pract.* 1998;40(Suppl):S21–S25; Ramlo-Halsted BA, et al. *Prim Care.* 1999;26:771–789; Nathan DM. *N Engl J Med.* 2002;347:1342–1349.

Age, weight, sedentary

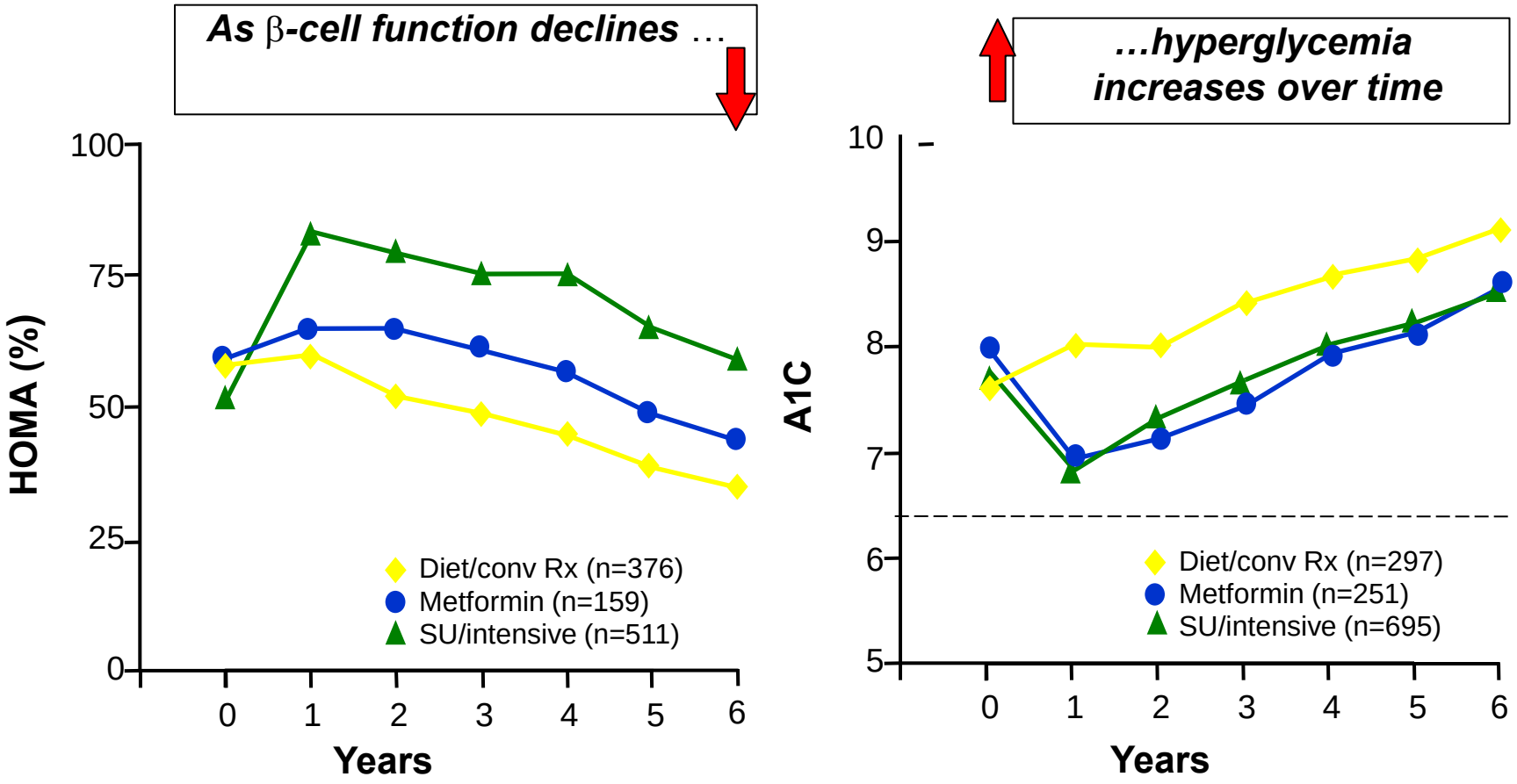
Insulin secretion



Insulin resistance

Age, genes, glucose

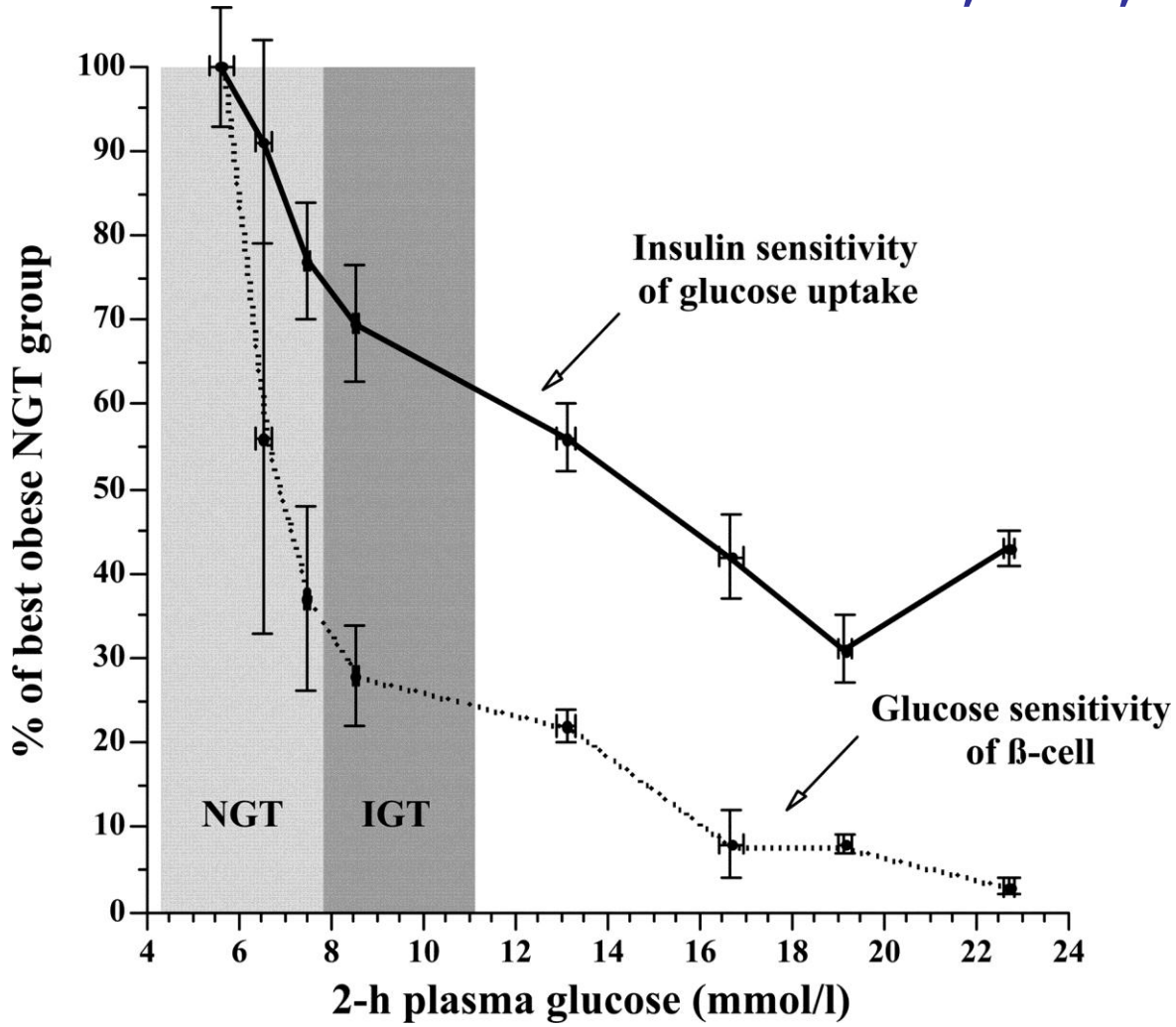
β-Cell Function & Glycaemic Control in DM2



UKPDS=United Kingdom Prospective Diabetes Study; SU=sulfonylurea.

Reprinted UK Prospective Diabetes Study Group 16. *Diabetes.* 1995;44:1249–1258.

β-cell glucose & insulin sensitivity vs. 2-h plasma glucose concentration in obese NGT, IGT, **&** DM2



Ferrannini, E. et al. J Clin Endocrinol Metab 2005;90:493-500

Type 1 Diabetes reflects an absolute lack of insulin and requires insulin replacement.

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

The mechanisms of T2DM is multifactorial including:

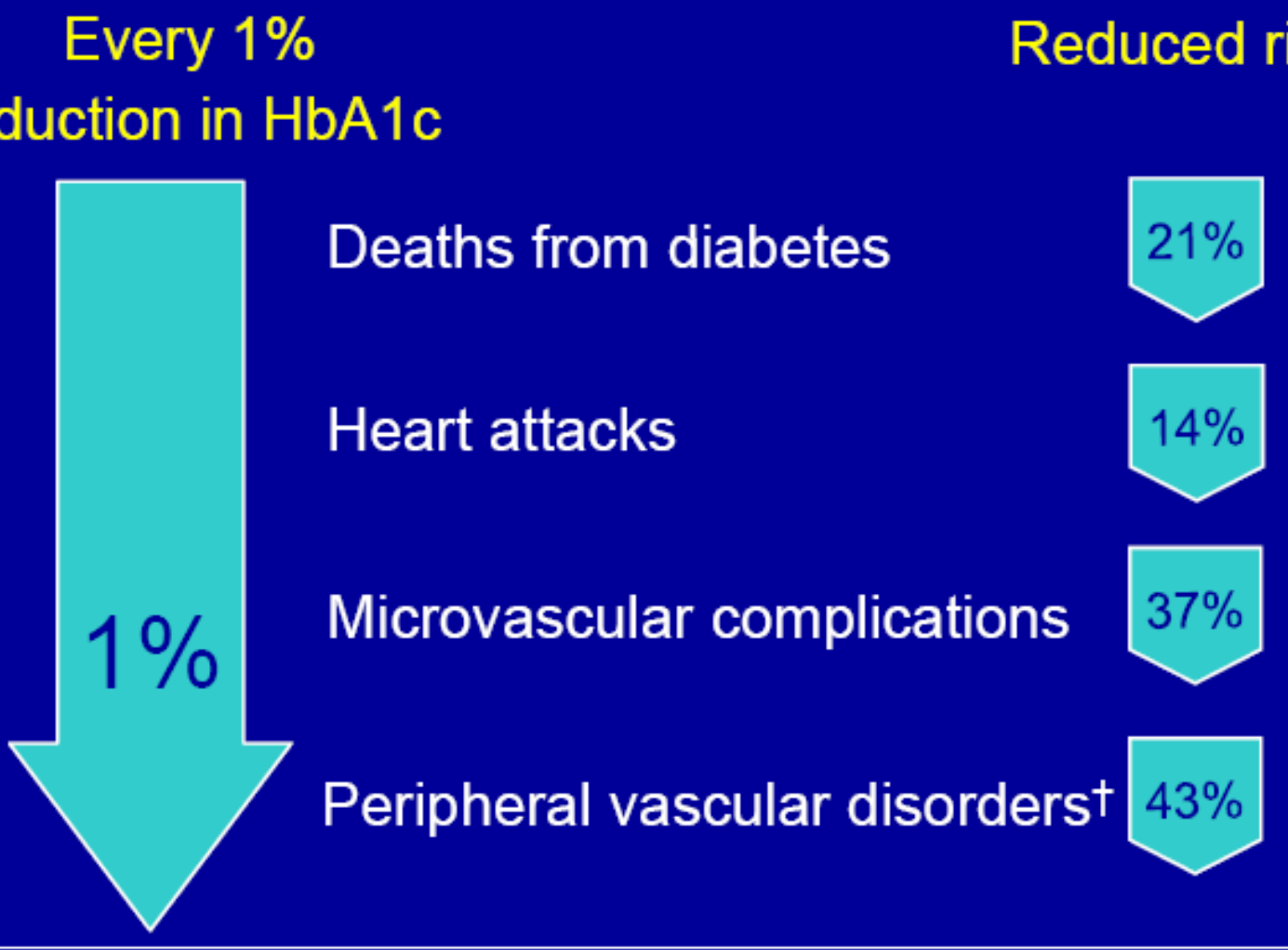
- Pancreatic islet cell dysfunction
  - Deficient insulin response by b-cells
  - Excessive production of glucagon by α-cells
- Excessive hepatic output of endogenous glucose
  - From diminished insulin & insulin sensitivity and excess glucagon
- Impaired uptake of glucose in the peripheral tissues
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

With progressive worsening over time

But, does glucose control prevent CVD?

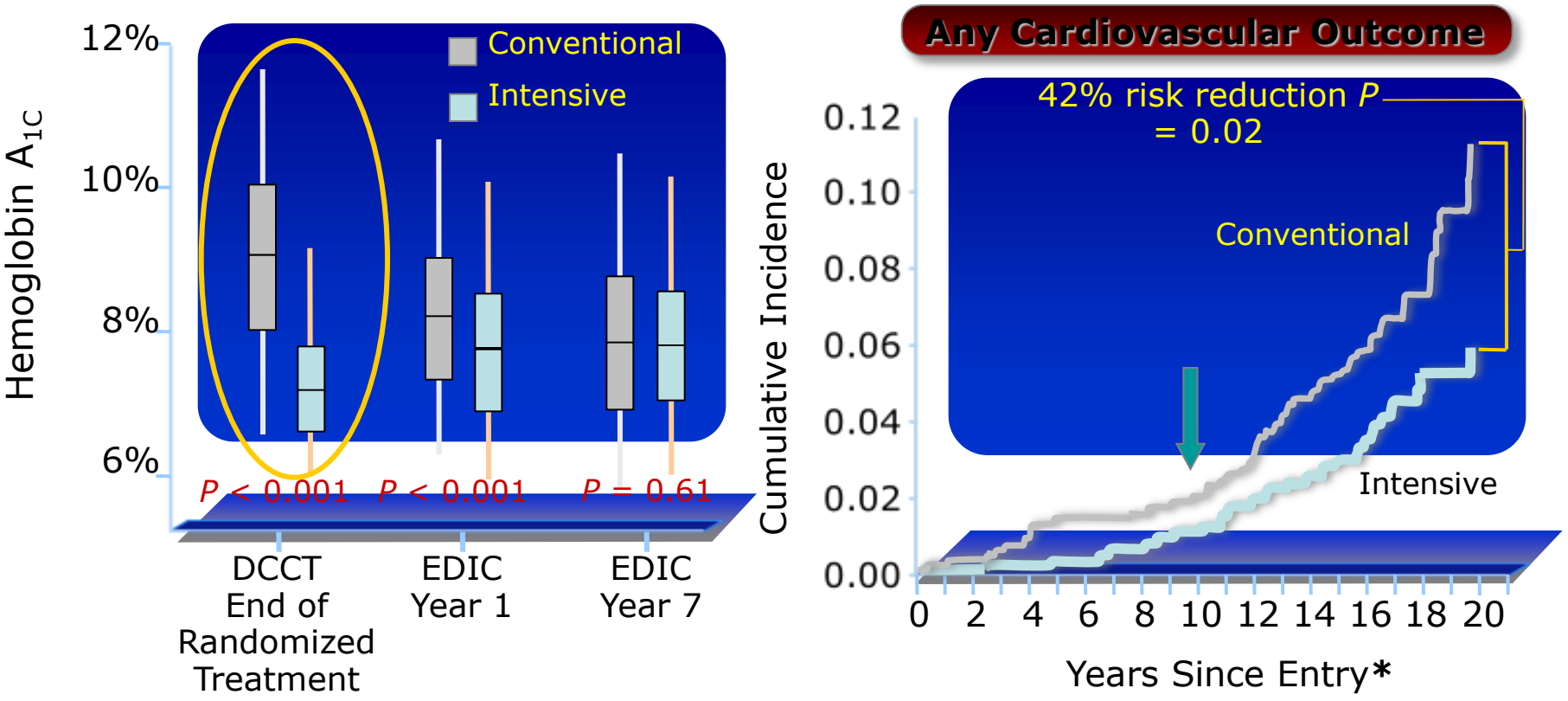
How long does the investment take to pay the dividend?

Lessons from UKPDS: Better Control Means Fewer Complications



HbA1c: Glycosylated haemoglobin; UKPDS: UK Prospective Diabetes Study.
*p<0.0001; †Lower extremity amputation or fatal peripheral vascular disease.
Stratton IM, et al. *BMJ.* 2000;321:405–412.

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.

**There is a metabolic "memory" of good glucose control.

Recent Trials of Glycaemic Control

- Both DCCT and UKPDS intensive treated arm were able to reach an average HBA1c average of 7.0%.
- UKPDS took newly diagnosed patients with DM2.
- Rates of DM complications were log linear and extended down to HBA1c of 6.0% begging the question of whether lower HBA1c target would lead to better outcomes.

- ADVANCE (3.5Y) & ACCORD (5Y) tested this hypothesis
  - Patients:
    - Established DM2 (average duration 8-10 years of disease)
    - CV disease or CV risk factors already present

ACCORD & ADVANCE

- Decreased microvascular complications in intensive Rx.

- Lower rates of CV event than predicted studies. (Secondary to high levels of statins use, BP control, ASA usage, smoking cessation?

- No statistical difference in composite CV outcome
  - Trend towards decreased CV events in intensive arm
  - But, increased mortality in intensive arm of ACCORD only-Why?
  - ACCORD vs. ADVANCE patients
    - Longer duration of diabetes (by 2 yrs) in ACCORD
    - Worse DM (more patients already on insulin & with higher HBA1c @ baseline)
    - More obese with greater weight gain through the study
    - Higher usage of TZDs and insulin
    - HBA1c was lowered more rapidly in ACCORD vs. ADVANCE ($\leq$1yr vs >1 yr)
    - Much higher rate of severe hypoglycaemia**

Primary & Secondary Outcomes

	Intensive N (%)	Standard N (%)	HR (95% CI)	P
Primary	352 (6.86)	371 (7.23)	0.90 (0.78-1.04)	0.16
Secondary				
Mortality	257 (5.01)	203 (3.96)	1.22 (1.01-1.46)	0.04
Nonfatal MI	186 (3.63)	235 (4.59)	0.76 (0.62-0.92)	0.004
Nonfatal Stroke	67 (1.31)	61 (1.19)	1.06 (0.75-1.50)	0.74
CVD Death	135 (2.63)	94 (1.83)	1.35 (1.04-1.76)	0.02
CHF	152 (2.96)	124 (2.42)	1.18 (0.93-1.49)	0.17

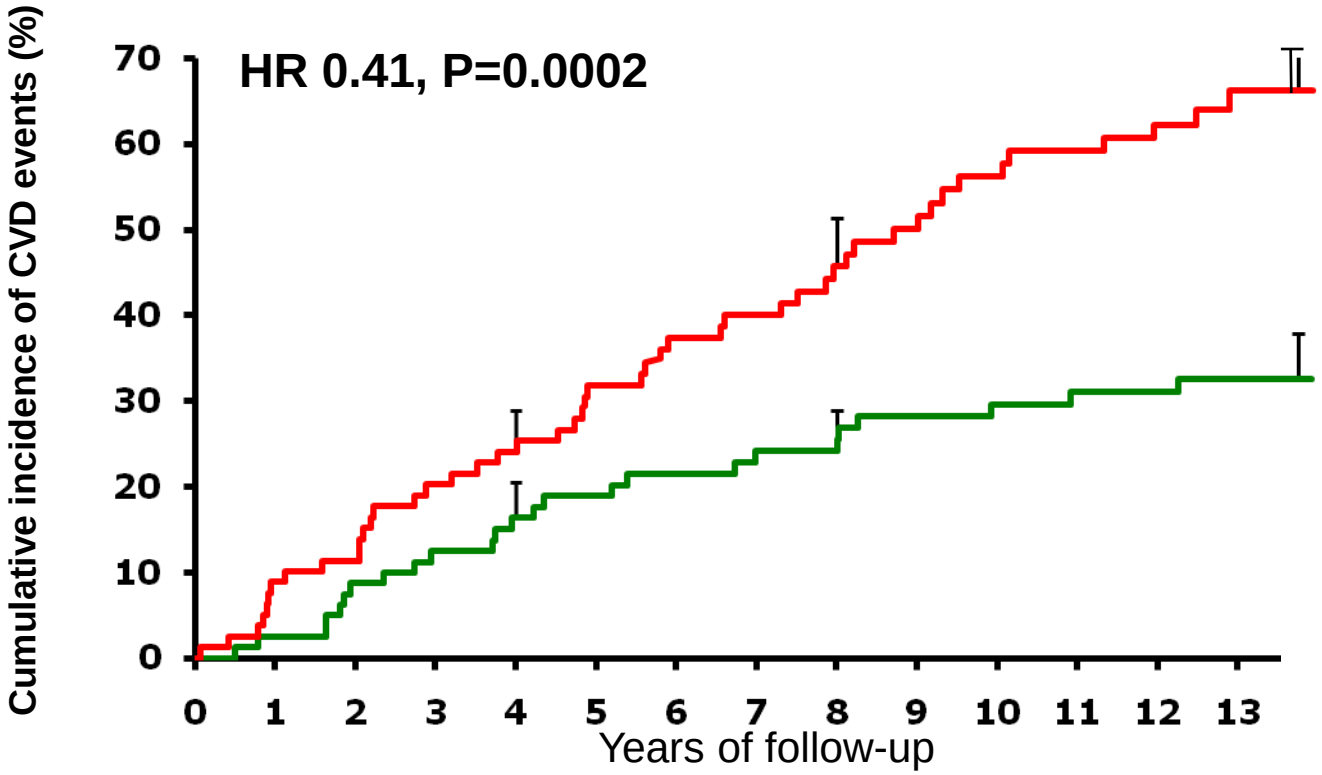
Subset Analysis

- Significant decrease in CV events in those with:
  - Shorter duration of DM
  - Absence of known CV disease

- Higher risk of mortality in those with:
  - Severe hypoglycaemia (& higher HBA1c?)
  - (Hypoglycaemia unawareness is associated with cardiovascular autonomic neuropahty which is a strong risk factor for sudden death)

Steno-2 Post Trial: Any CVD events

Cumulative incidence of patients with a major CVD event during follow-up



Numbers at risk								
Conventional	80	70	60	46	38	29	25	14
Intensive	80	72	65	61	56	50	47	31

Gaede et al. NEJM 2008

Diabetes Treatment = "PLAGUE-F"

Pressure

Lipids

Aspirin

Glucose

Urine albumin/creatinine ratio

Eye exam yearly

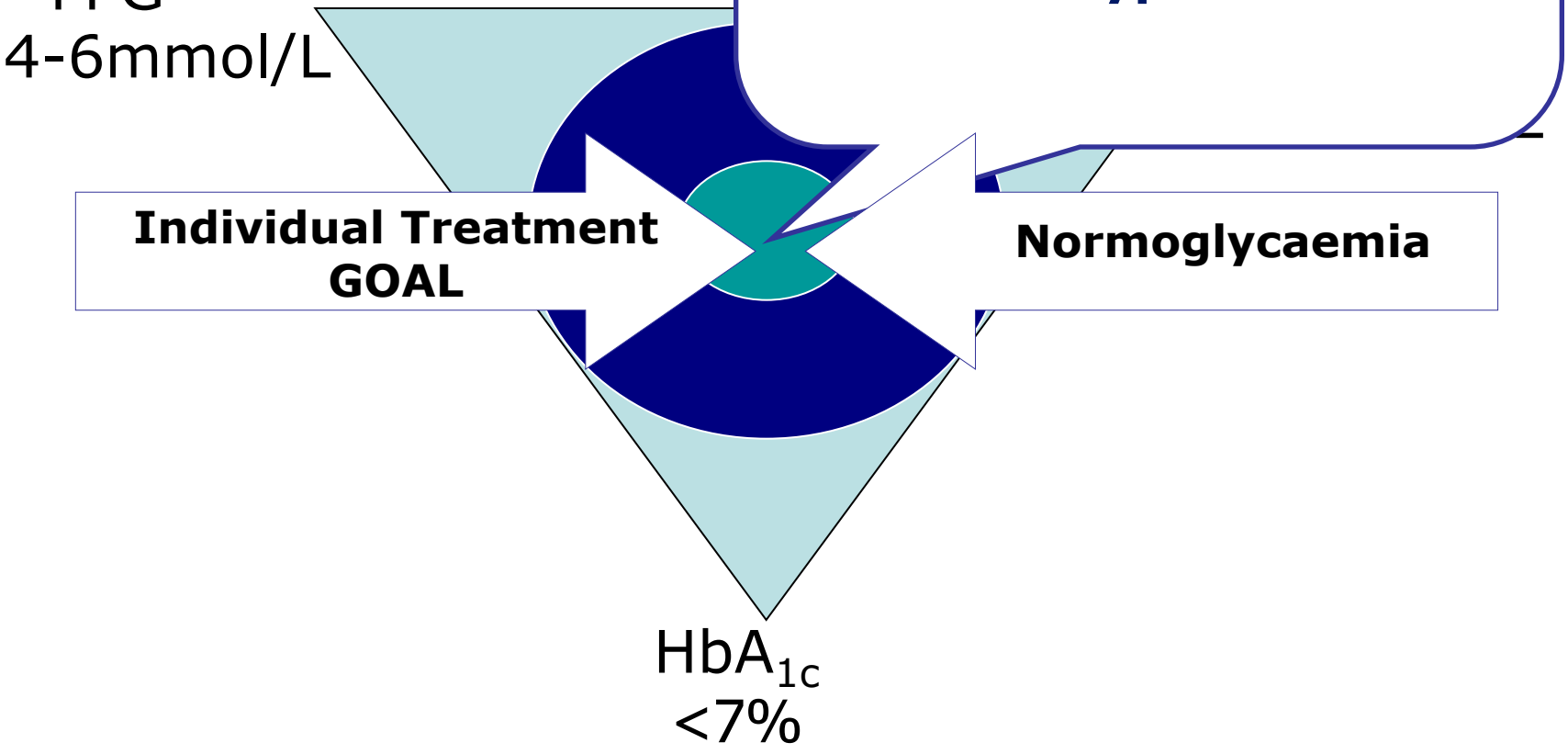
Foot exam each visit

Barnes, *The Diab Educ* 2004; 30: 126

Glycaemic con

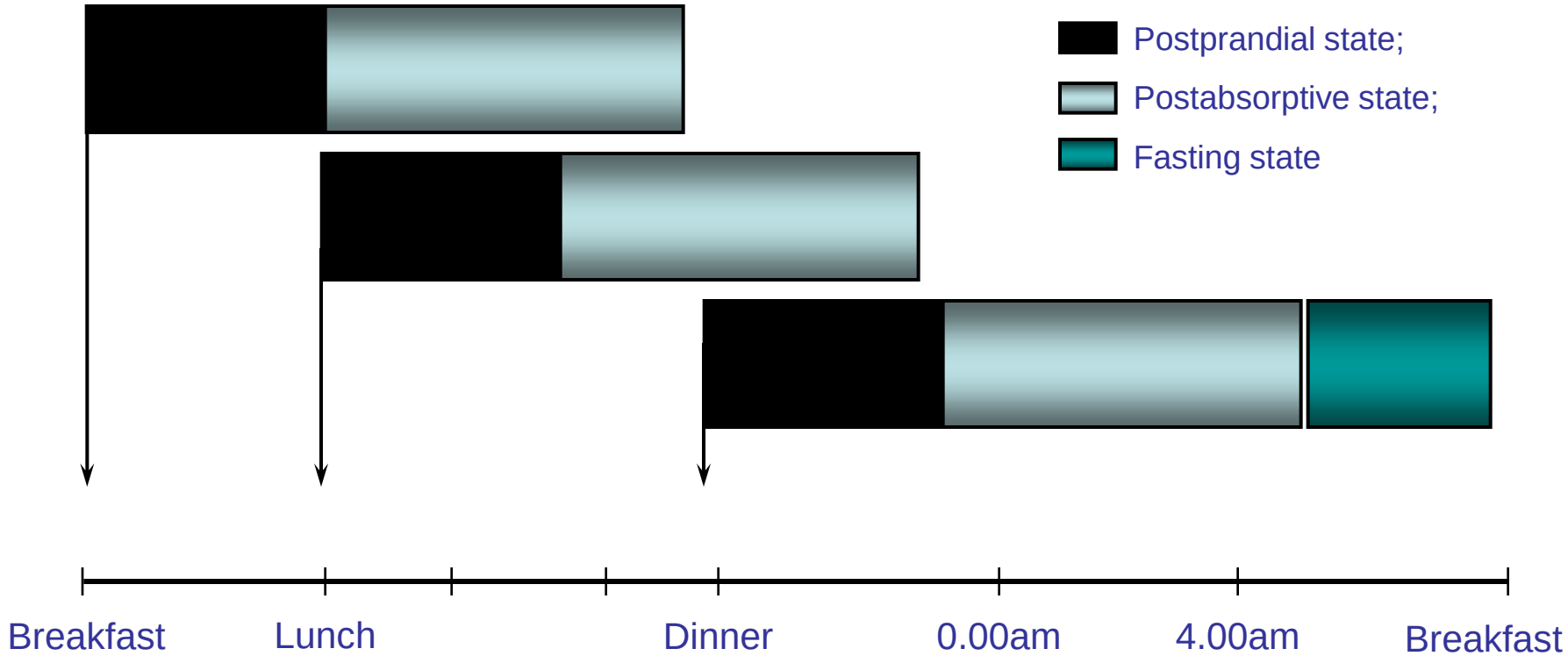
Reach "individual" HbA1c target WITH SAFETY

i.e. with reduced risk of hypos



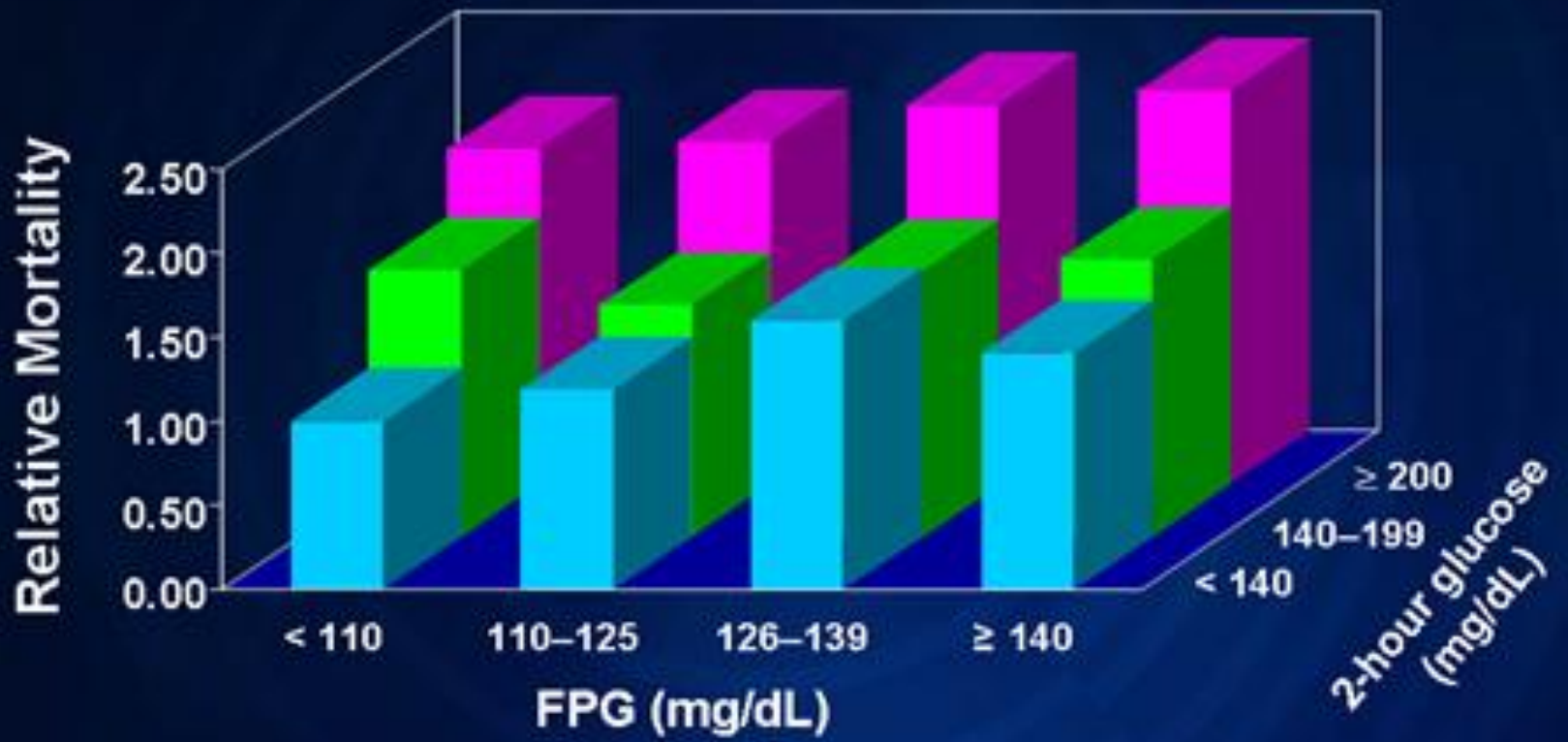
New Zealand Guidelines Group December 2003. European Diabetes Policy Group 1999. International Diabetes Federation (Europe). A desktop guide to Type 2 diabetes mellitus. Diabetic Medicine 16 (716-730). RACGP. Diabetes Management in General Practice 2005/6.

Most of Our Lives are Spent in the Postprandial State



Reference: Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in type 2 diabetes? *Eur J Clin Invest* 2000;30(Suppl 2): 3-11.

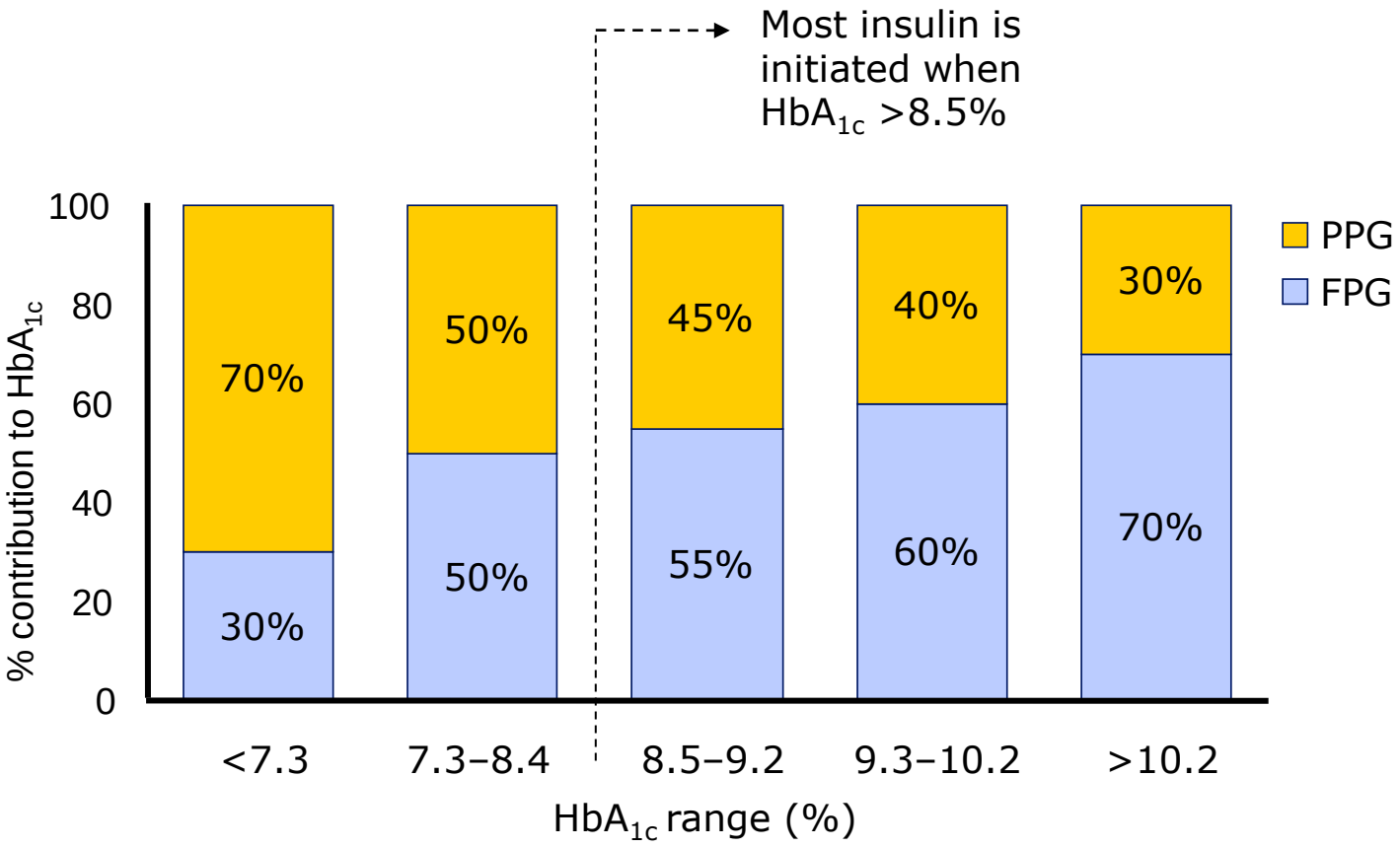
FPG, 2-Hour Postchallenge Glucose, and Mortality in Individuals Not Known as Diabetic: DECODE Study



* Adjusted for age, gender, and study center.

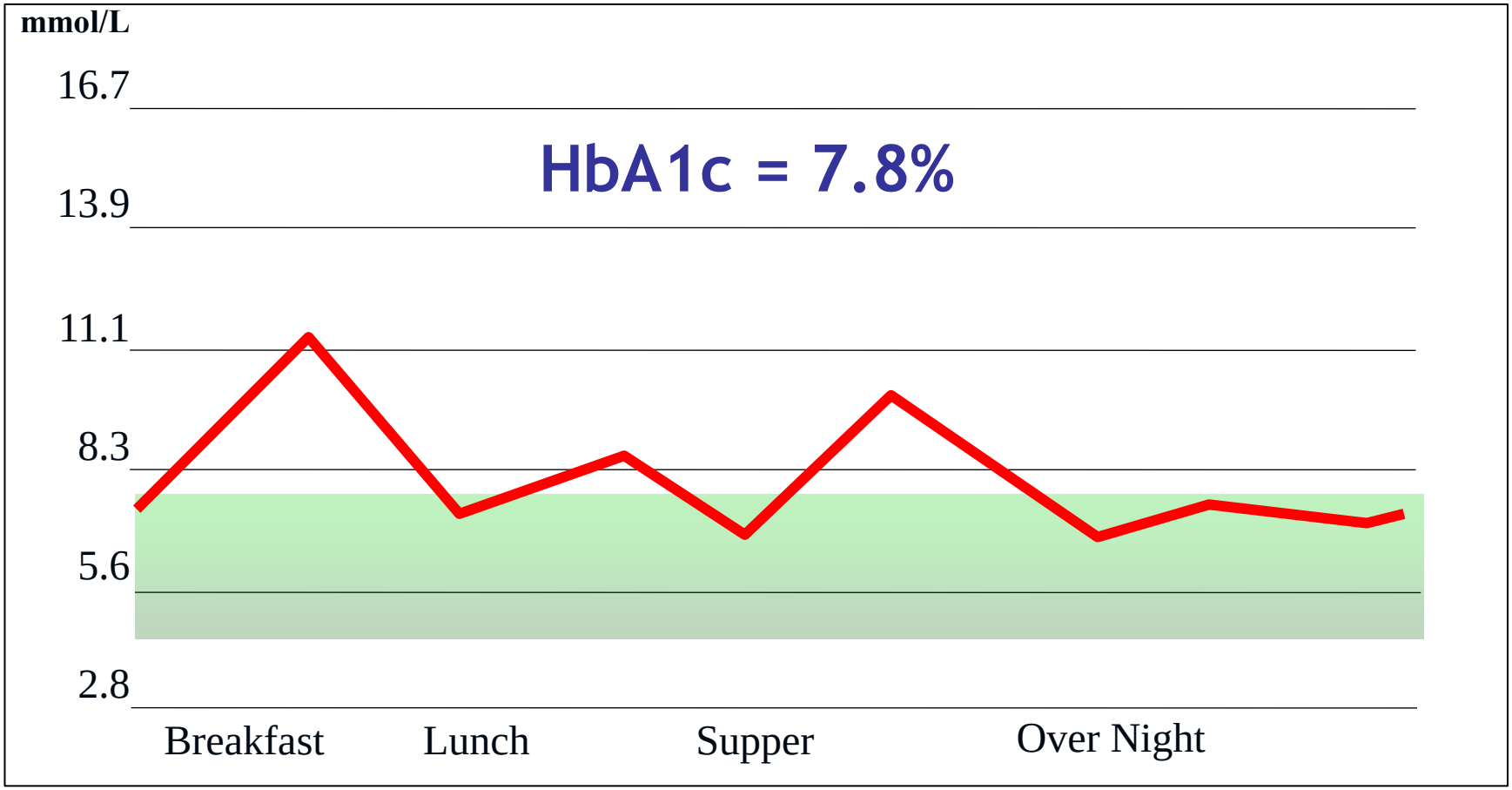
DECODE Study Group. *Lancet.* 1999;354:617-621.

To normalise BG both FPG & PPG need to be controlled

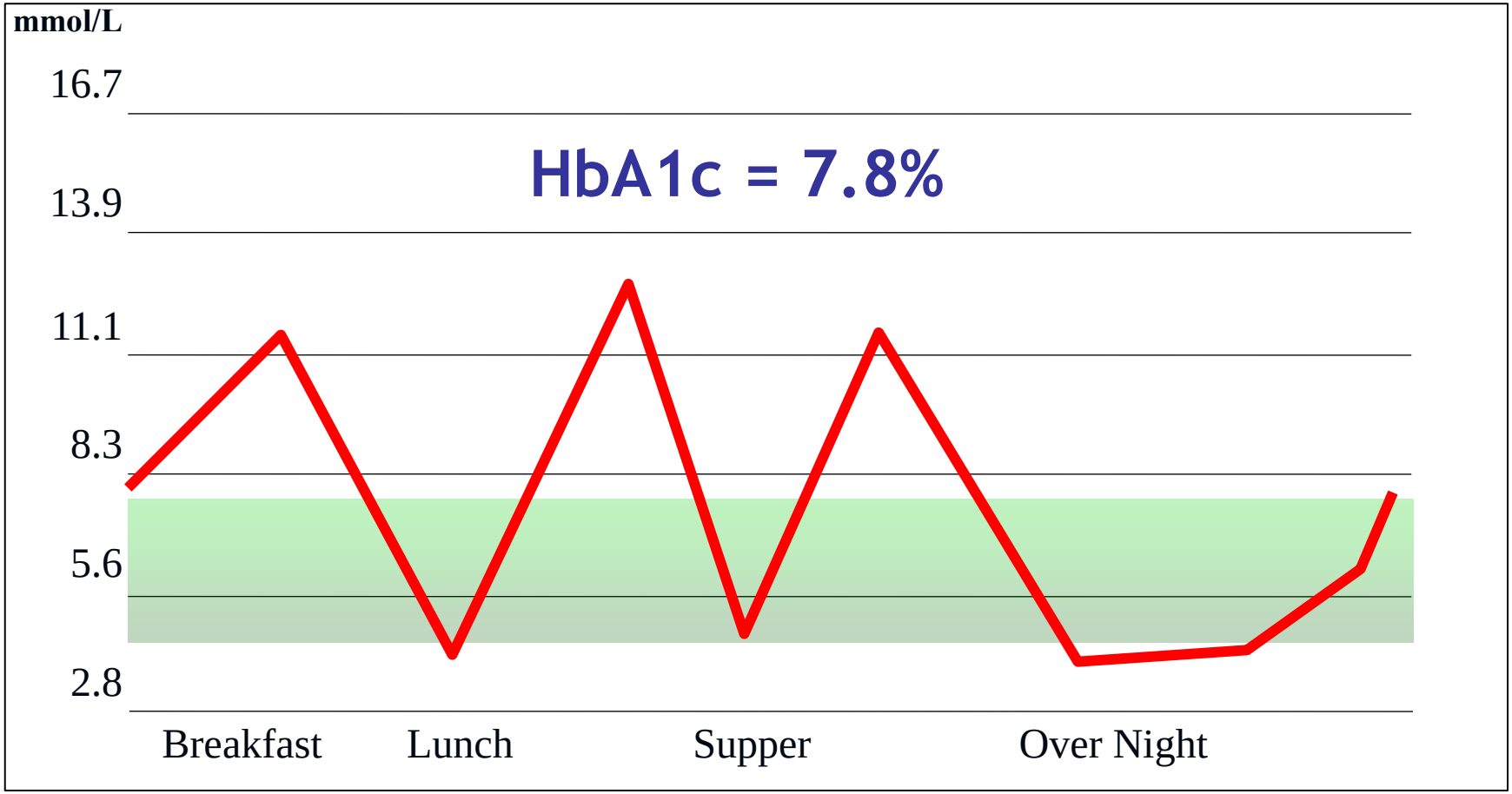


Adapted from Monnier L *et al. Diabetes Care* 2003;26:881–5

HbA1c's are not created equal



HbA1c's are not created equal



Example of someone on too much long/intermediate acting insulin & not enough prandial insulin who will need to snack in between meals & at bedtime to avoid hypoglycaemia.

Self Monitoring of Blood Glucose (SMBG)

- HBA1c only provides information on average blood sugar.
- It will not tell you the range of blood sugars.
- SMBG is essential in treatment of DM.
  - Analogy: It is hard to drive safely if you can't see where you are going.

SMBG

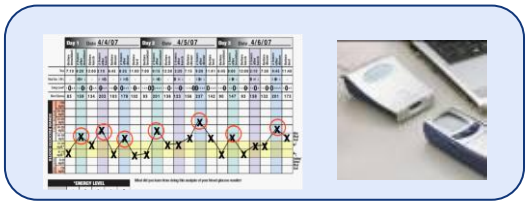
- On lifestyle alone/Metformin
  - Useful intermittently to establish effect of food/exercise on glucose (consecutive measurements are most helpful)
    - Allows direct feedback to the patients & contributes to patient knowledge
    - Hopefully helps modify behaviour (if patients are educated)
  - Useful to examine pattern of glucose elevation to help assess adequacy of Rx (ex: 2-3 days of 6 X day testing just prior to seeing physician)
- Type 2 DM on oral hypoglycaemic agents or insulin
  - As above, plus
  - Monitoring for hypoglycaemia (recommend a day of 6X day testing after commencing Rx or dose change).

Glucose Focused Testing Examples

Actionable information for informed decision-making

Pattern Testing …

Multi-point BG profiles for a specific duration to use pattern analysis to identify problem areas for remediation.

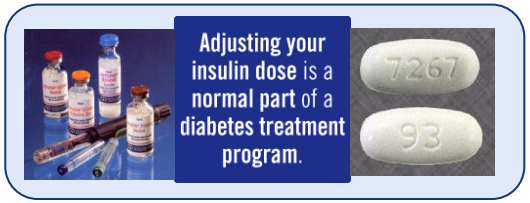


Paired Testing …

Testing to explore cause and effect BG variance related to life events or activities, such as food, lifestyle, and current medication. Supports patient self-learning and engagement.

Adjustment Testing …

BG testing to support activities to determine dose adjustment.




I BEAT
ANOREXIA
Bud Light

ADA & EASD Consensus Statement (2006 & revised in 2009)

- Management of hyperglycaemia in DM2 Algorithm.
- Goal HBA1c is < 7.0 (IDF rec. < 6.5)
- Basis for anti-hyperglycaemic agent choice:
  - Effectiveness in lowering glucose
  - Effectiveness in decreasing complications
  - Safety profile
  - Ease of use & expense.

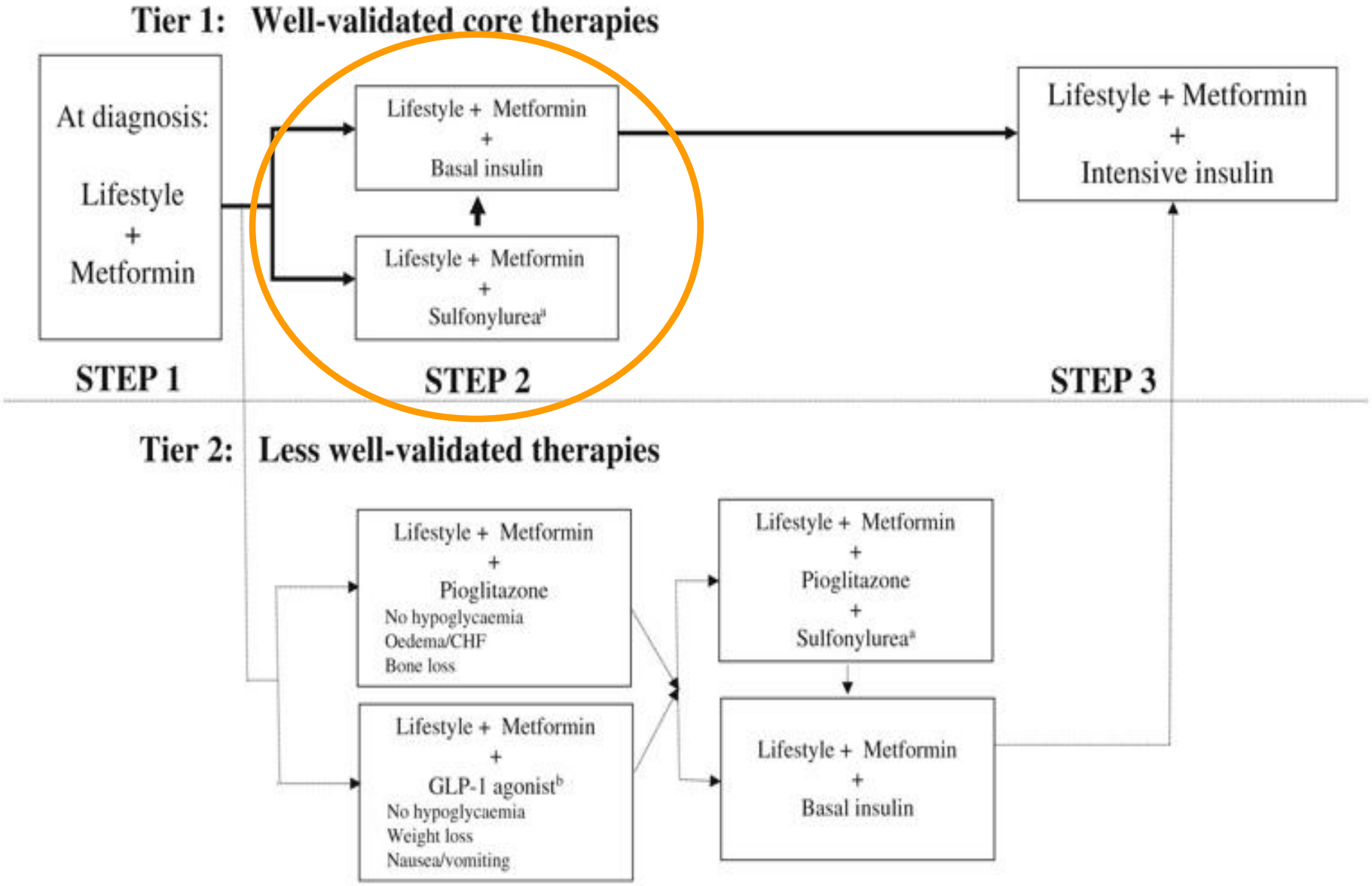


Fig. 2 Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle interventions at every visit. Check HbA_{1c} every 3 months until HbA_{1c} is <7%, and then at least every 6 months. The interventions should be changed if HbA_{1c} is ≥7%. [a]Sulfonylureas other than glybenclamide (glyburide) or chlorpropamide. [b]Insufficient clinical use to be confident regarding safety. See text box: Titration of metformin. See Fig. 1 for initiation and adjustment of insulin. CHF, congestive heart failure

Diabetalogia. 2009. 52:17-30

Treatment Targets

HBA1c	< 7.0 (< 6.5 if it can be done safely)
Pre-meal BS	≤ 6.0
2 hr pp BS	≤ 8.0
LDL	< 2.5
	< 2.0 (current NZ CV guidelines)
	< 1.8 for those with pre-existing CVD
BP	< 130/80 (if no renal impairment)
	< 125/75-80 (with renal impairment)

"Clinical inertia is due to at least three problems:

1. **overestimation of care provided**
2. **use of "soft" reasons to avoid intensification of therapy**
3. **lack of education, training, and practice organization aimed at achieving therapeutic goals**

Physicians will need to build into their practice a system of reminders and performance feedback to ensure necessary care."

★ Work to meet Targets

Phillips et al, Annals of Internal Medicine, 2001

Key Points

- Diabetes is a major health problem with multiple complications (esp. Maori/Pacific and Asian populations)

- Set the patient up realistically for the future
  - DM is a disease of insulin deficiency (& resistance in DM2) that naturally progresses with time

- Education on lifestyle/meds & their effects on BSLs so that glucose readings are interpretable to the patient.

- Don't delay in advancing treatment to reach glucose targets (to get rid of highs & lows)
  - Metformin
  - SU or Insulin

- Reach non-glycaemic targets
  - BP & Lipids
  - ASA & Smoking Cessation

Early insulin can never be too early!

EARLY INSULIN SAVES HEALTH; SAVES WEALTH

Fight clinical inertia