Diabetes for GP CME 2009

The good, the bad and the ugly

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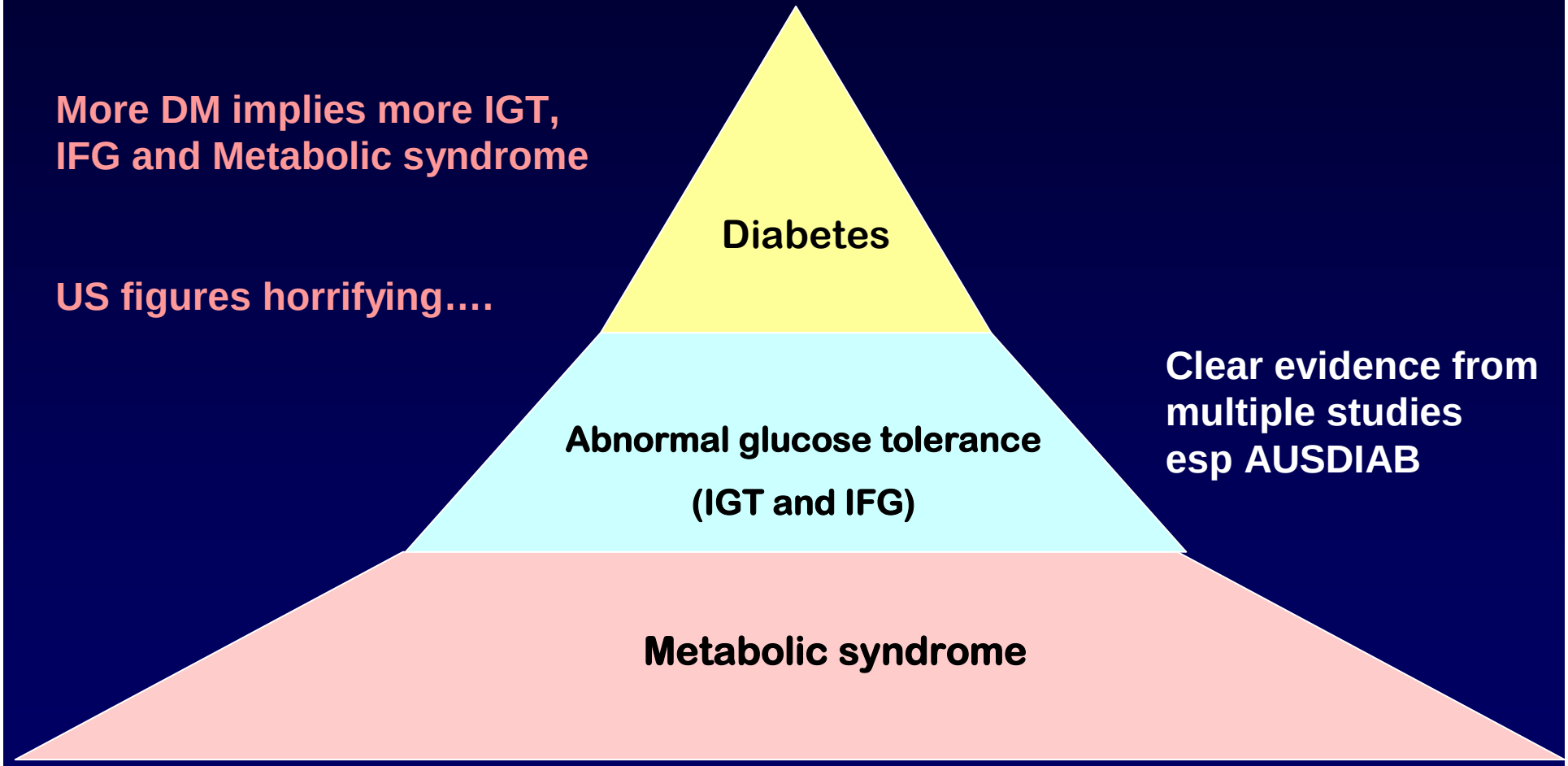
Some of the areas to cover

- New NZ data on epidemiology
- New trials: ACCORD, ADOPT, ADVANCE, VA...
- New targets: HbA1c
- New treatments and old : metformin and incretins
- New toxicities and concerns, need for CV studies
- New NZ renal data from ANZDATA
- New risk issues

The pyramid (or iceberg) of metabolic syndrome ca 2009

More DM implies more IGT, IFG and Metabolic syndrome

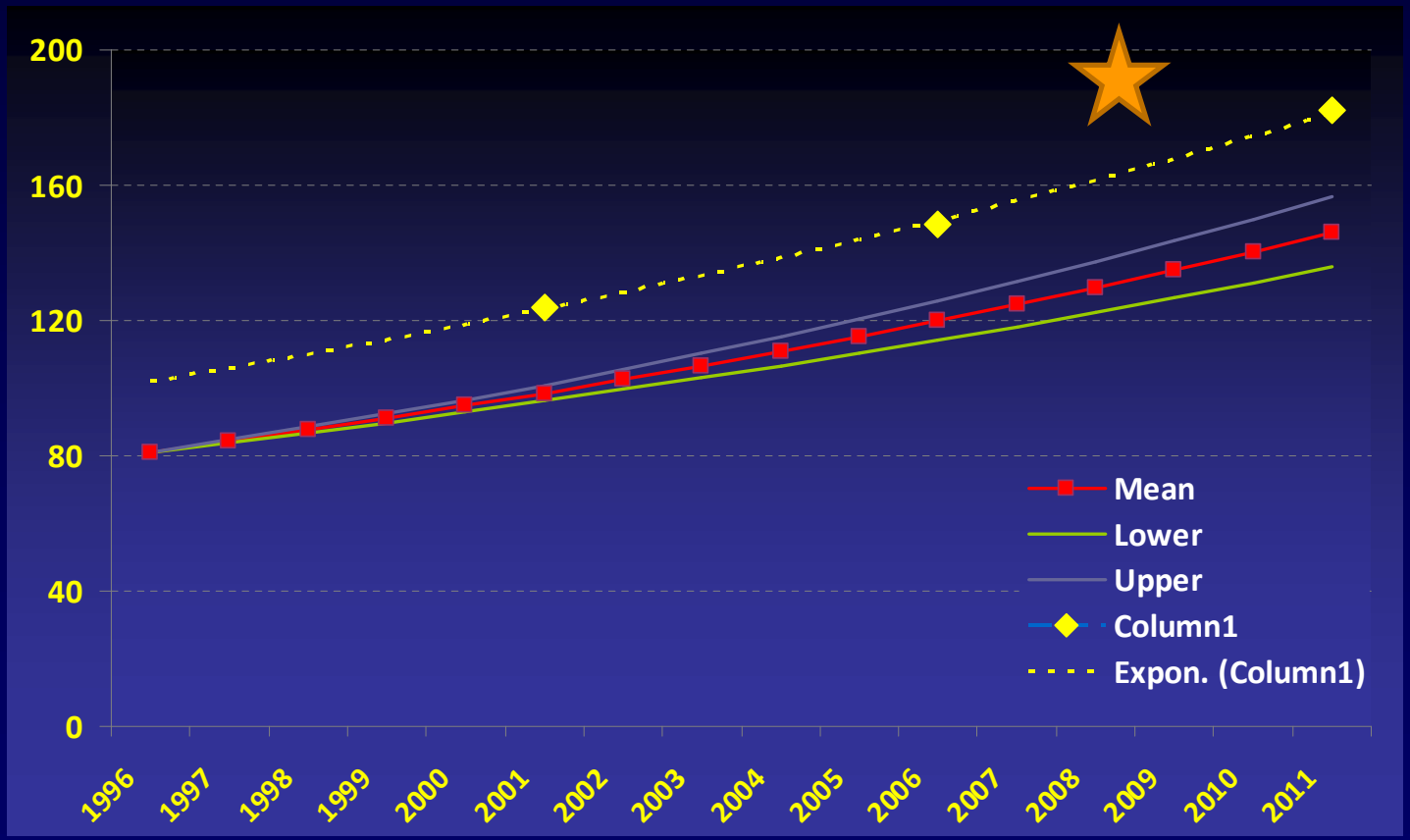
US figures horrifying….



Clear evidence from multiple studies esp AUSDIAB

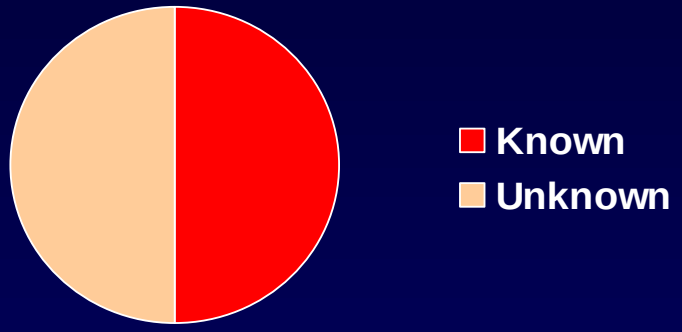
Models and Forecasts 2002 and 2006/7

NZ Prevalence 1996-2011 (all in 1000s)

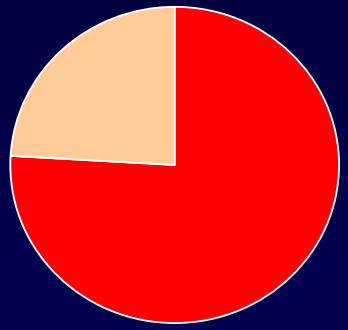


Diagnosed and undiagnosed diabetes in NZ

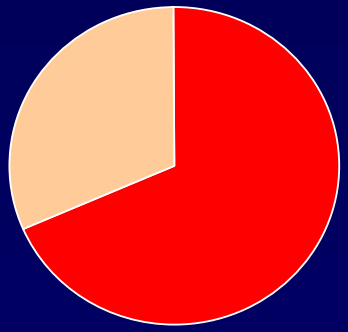
"Tradition"



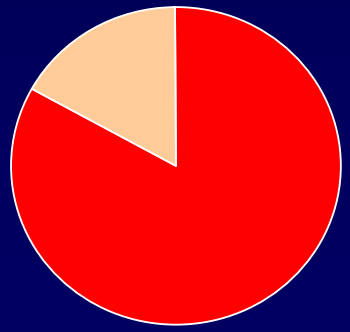
"Maori 2003"



"European 2003"



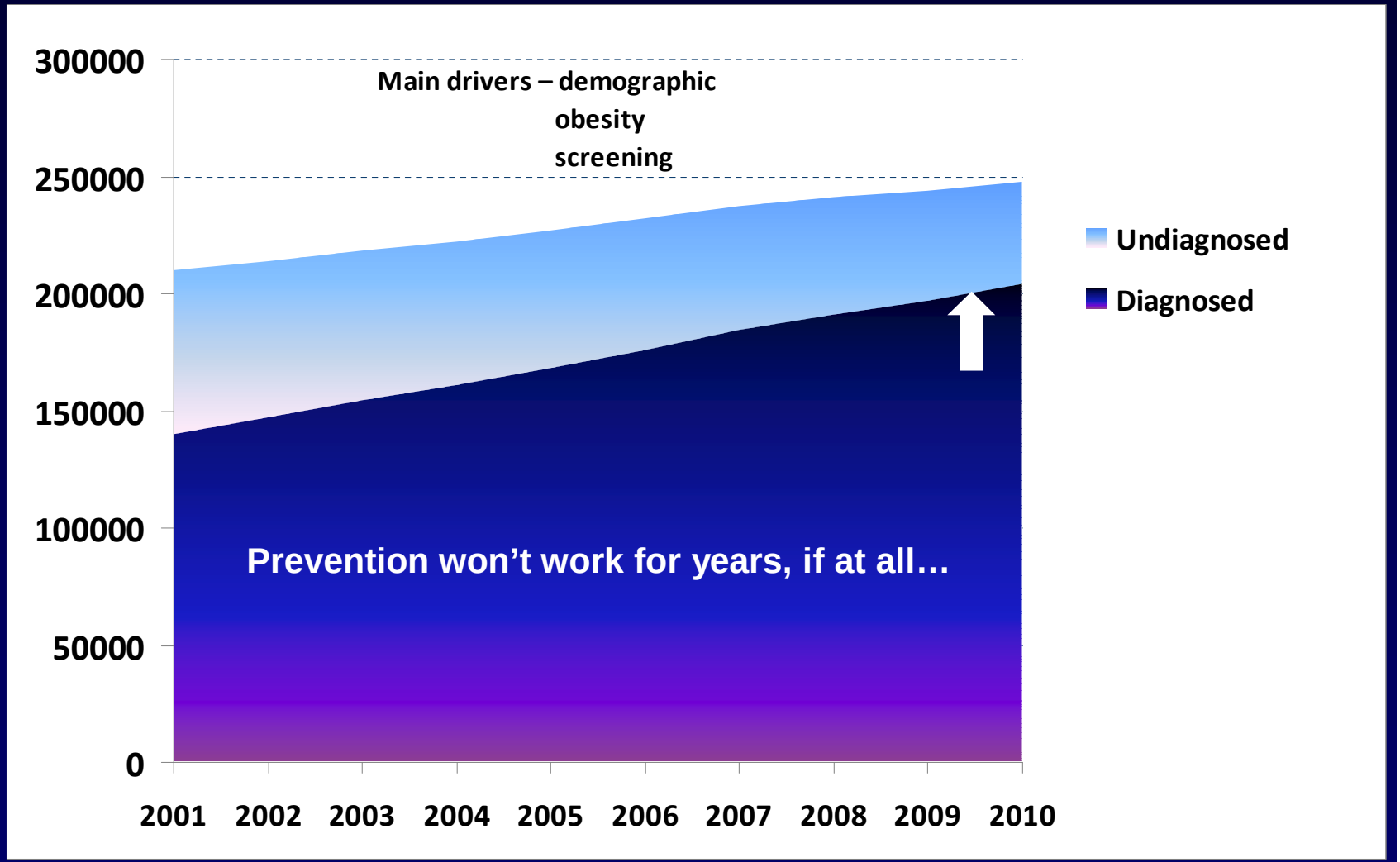
"Pacific 2003"



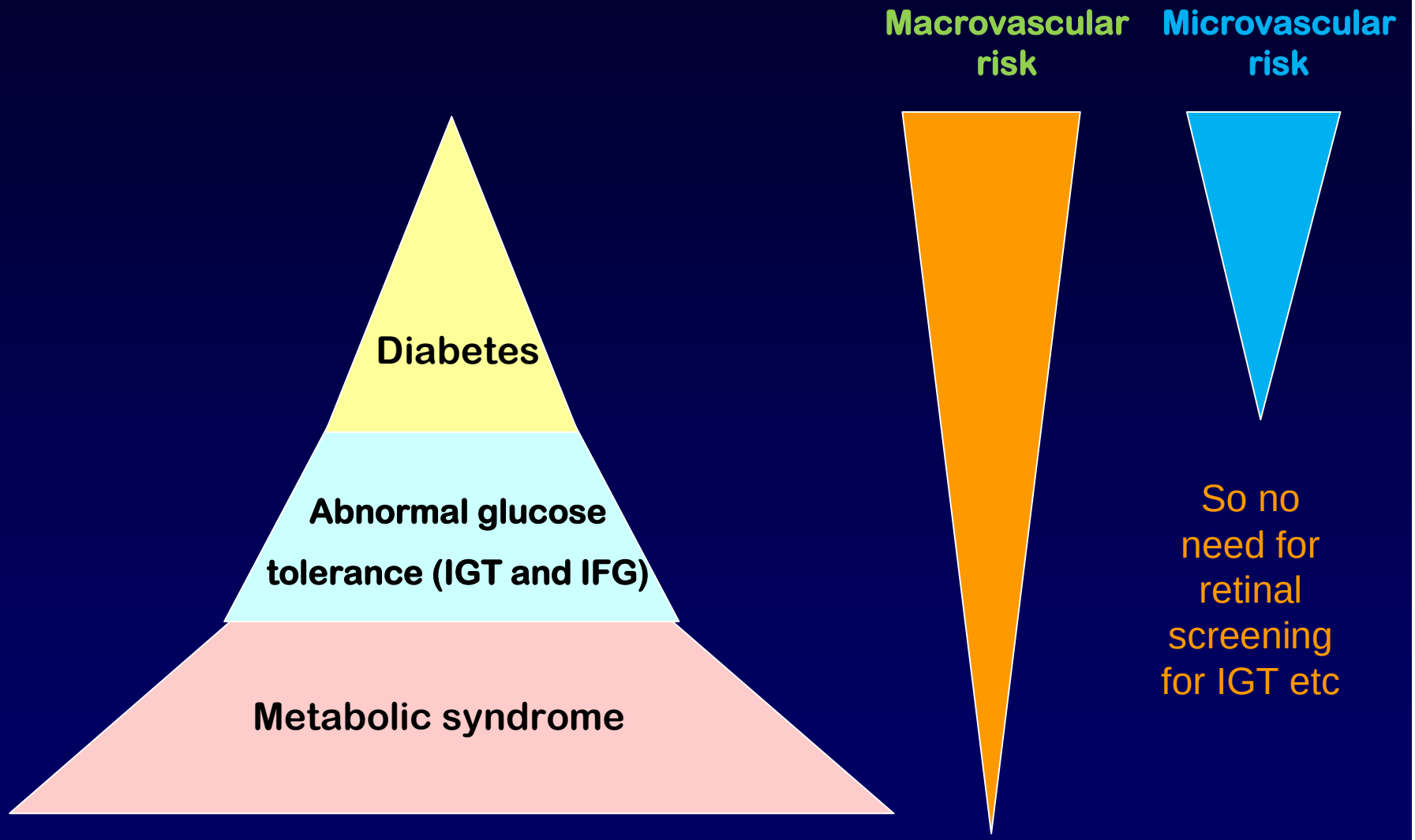
Recent data from Sundborn et al, NZMJ 2007

What's possibly happening mid 2009?

Ignore exact numbers



The ‘pyramid’ or ‘iceberg’ of metabolic syndrome and vascular risk



Controversies in Screening & Diagnosis

After selection by clinical risk scores what is best test?

- **Casual plasma glucose**
  - **Variable;**
  - **Poor sensitivity;**
- **Fasting plasma glucose**
  - **Reliable;**
  - **Misses IGT;**
  - **Inconvenient;**
- **Glucose Tolerance Test**
- **HbA1c**
  - **As good as Fasting plasma glucose (FPG)?**
    - As screen?
    - As diagnosis?

HbA1c – things likely to change

Assuming a standardised assay – may be reported in mmol/L:

1. **A rise in cardiovascular events occurs with rising HbA1c well below the diabetic range**
   - ***Approximately 10% ↑ risk for 1% HbA1c rise***

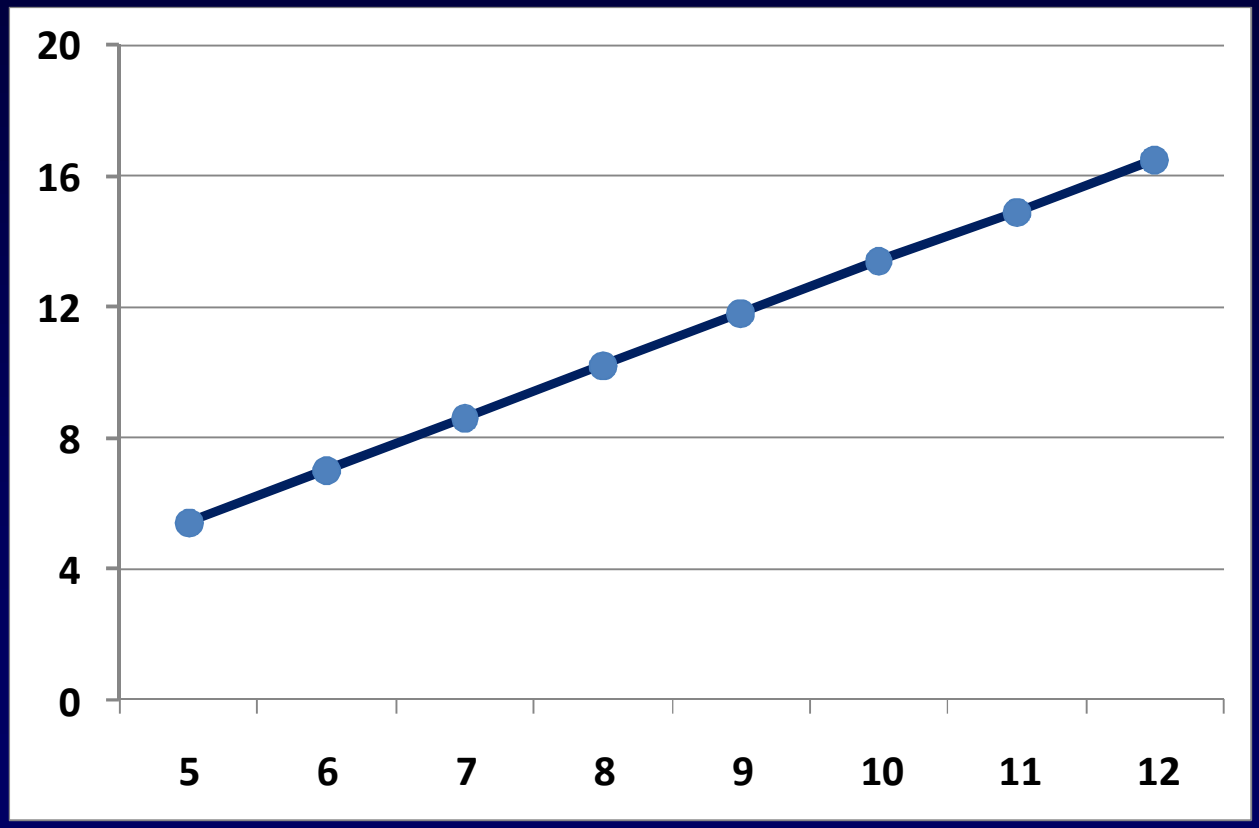
2. **If aim of screening is to identify people at high risk of vascular disease could HbA1c be added to CV risk tables?**

3. **Proposal (*JCEM July 2008*)**
   - ***HbA1c > 6.0% - re-screen with FPG or OGTT***
   - ***HbA1c ≥ 6.5% - confirm possible diagnosis of diabetes with fasting/random glucose***

4. **Average Blood Glucose (eAG) for communication**

Relationship of HbA1c with estimated average glucose

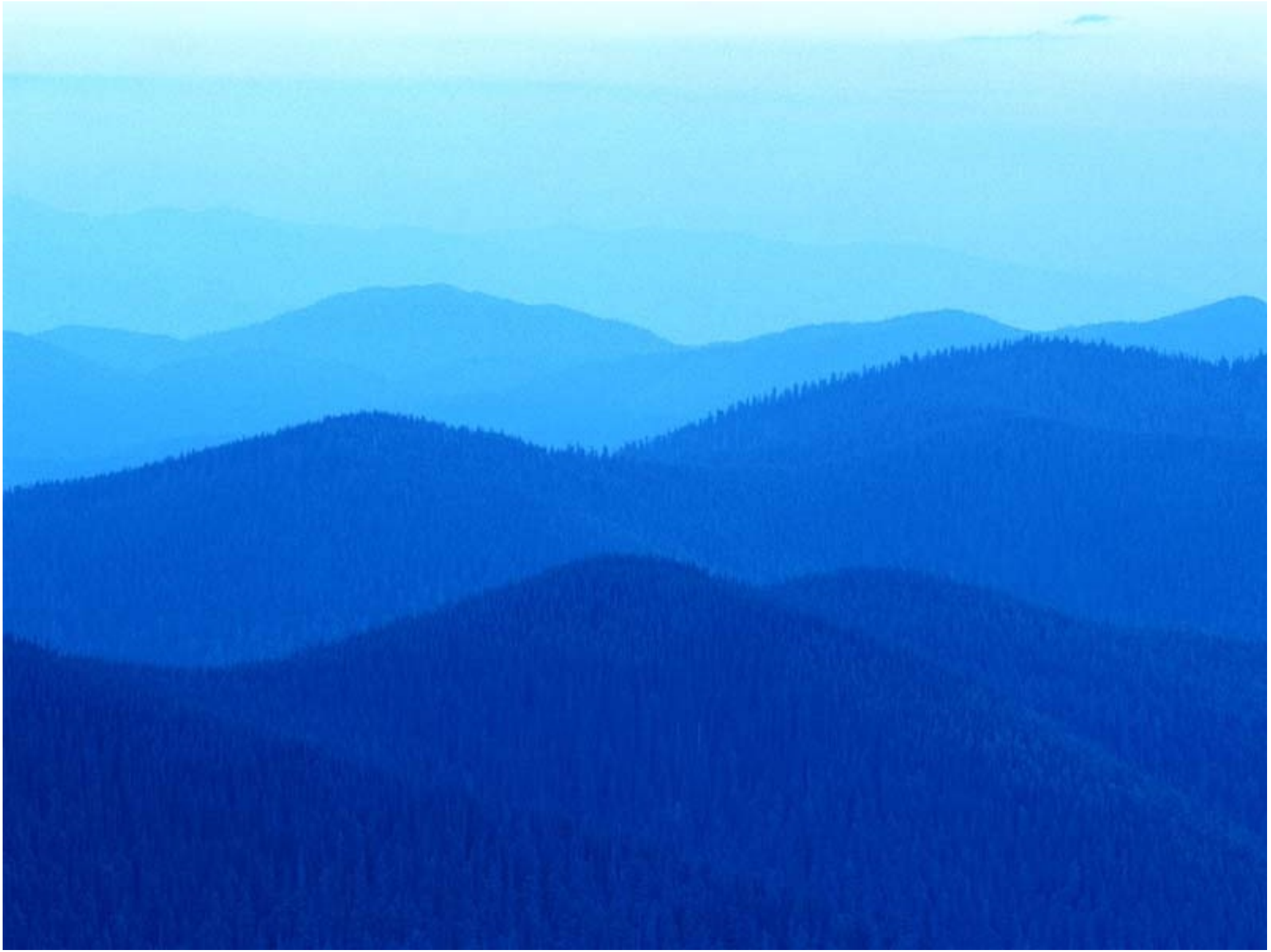
We may be moving to reporting estimated average glucose



Who to risk assess NZGG 2003

Possible changes for 2010 ? Or even more aggressive?

	Men	Women
Asymptomatic people, without other known risk factors	Age 45	Age 55
Māori, Pacific people and people from the Indian sub-continent	Age 35 ? Now 30	Age 45 ? Now 40
Those with at higher risk of CVD or developing diabetes	Age 35 ? Now 30	Age 45 ? Now 40
People with diabetes or IGT or IGF or ?? MetS	At diagnosis	



HbA1c and vascular events

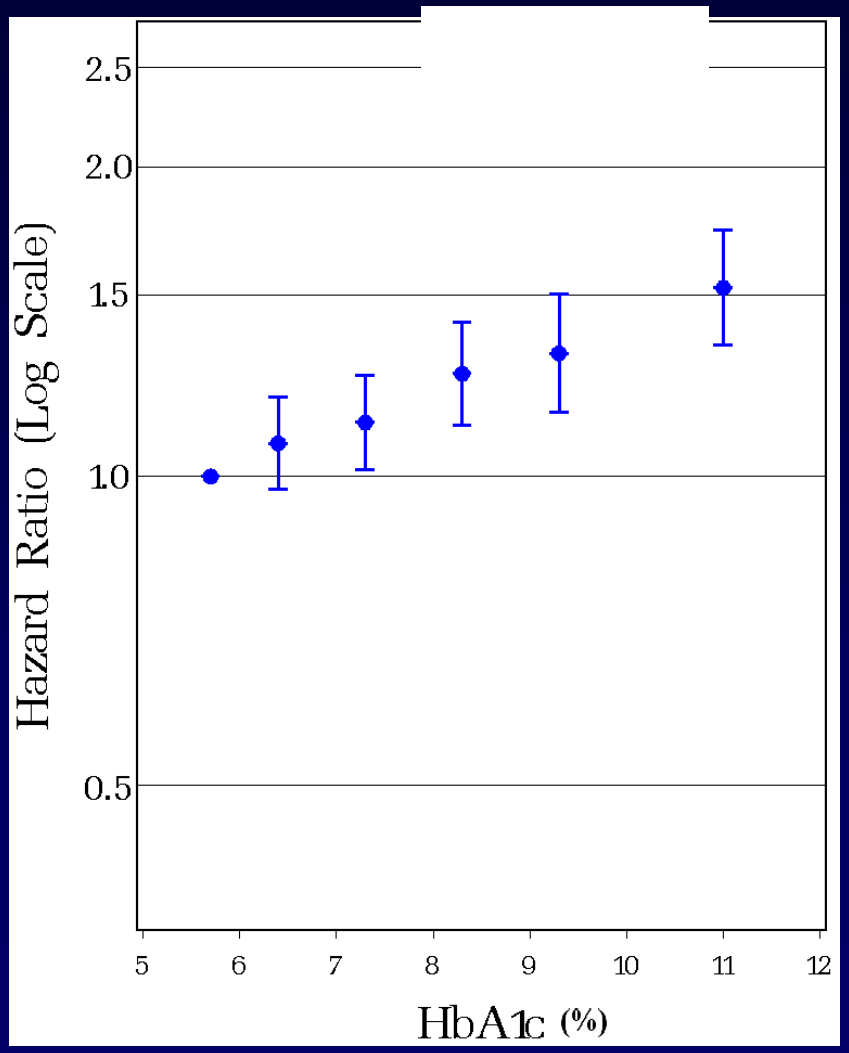
- **There is strong evidence regarding the relationship between HbA1c and microvascular events e.g. DCCT, Kumamoto, UKPDS.**

But

- **What about <u>macrovascular</u> events in Type 2 Diabetes?**
  - In UKPDS HbA1c 7.9 → 7.1% resulted in 18% ↓ in events (NS)
  - Meta-analysis suggests 16% increase in CV events per 1% ↑ HbA1c
  - Local actual "Get Checked' data shows 8% increase

Adjusted hazard ratios of association between HbA1c and risk of first CVD event *(95% CIs)*

Elley et al, 2008 I n press



8% increase in CV event rate per 1% increase in HbA1c

(Previous estimate around 15%)

From NZ "Get Checked" data

Many/most patients on cardio-protective medication

Effect present in both sexes

(not significantly different)

Targets for HbA1c in 2009 ?

What are your targets for:

1. **A 66-year old overweight but asymptomatic Caucasian man with newly-diagnosed type 2 diabetes on screening? HbA1c 8% two months later on lifestyle measures alone.**

2. **A 47-year old Maori woman, diabetic for 9 years, with HbA1c 9%, ACR 34.8 and previous marked hypos on insulin. Not optimal adherence.**

Targets for HbA1c in 2009 ?

≤ 7% ? ADA, NZGG

≤ 6.5% ? EASD, AACE??

Does one size fit all? ?

Around 6- 7% ? But not if CVD or very high risk

Hypo risk may be more important than we think

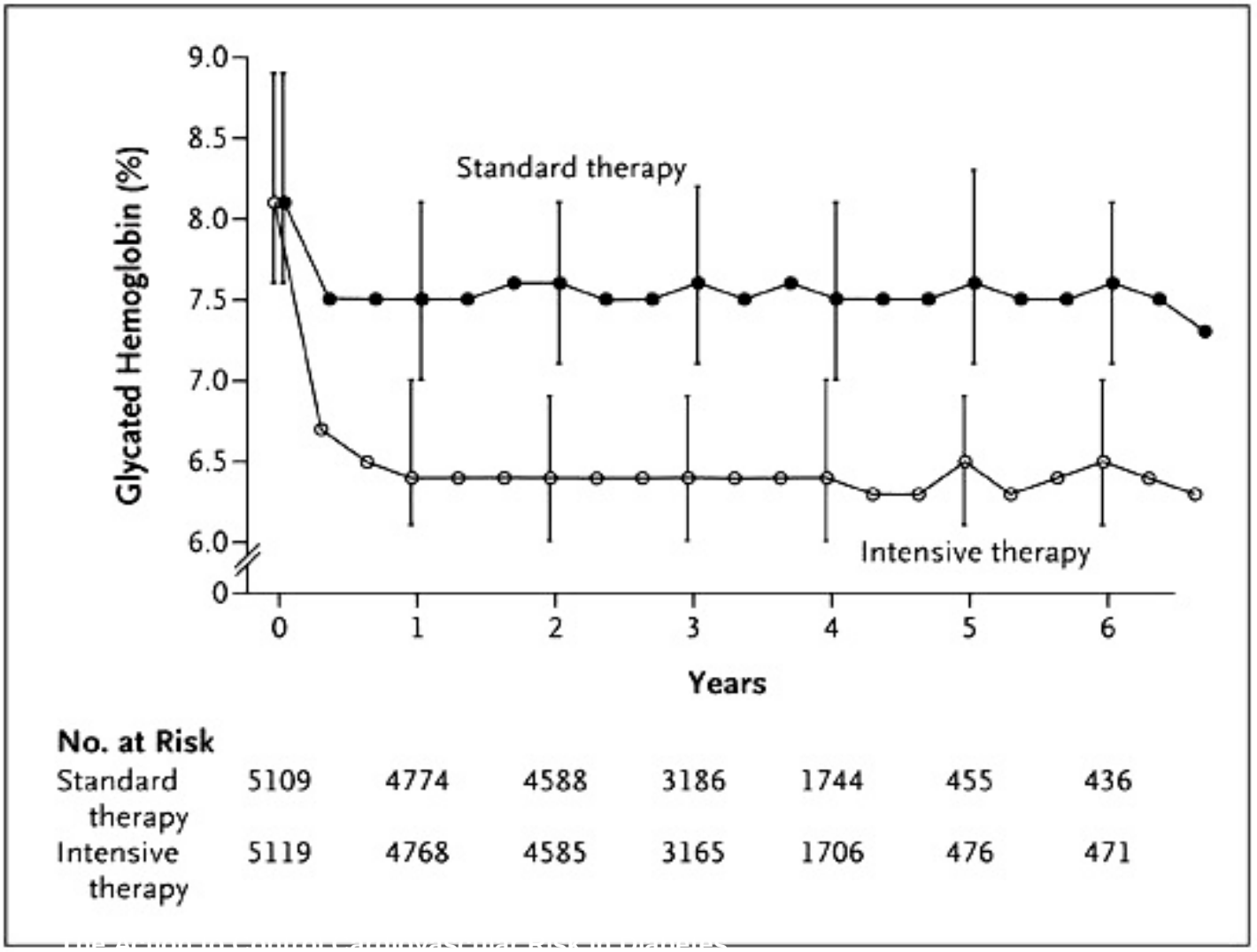
ACCORD Study *(NEJM June 2008)*

T2 Diabetes aged > 40 years + C/V risk or CV Disease
10,000 patients

Baseline:

- **Aged** — **62 years**
- **BMI** — **32**
- **BP** — **136/75**
- **HbA1c** — **8.3% (10 year duration)**
- **Previous C/V event** — **35%**
- **High use of statin, ACE-I, aspirin**

ACCORD results June 2008



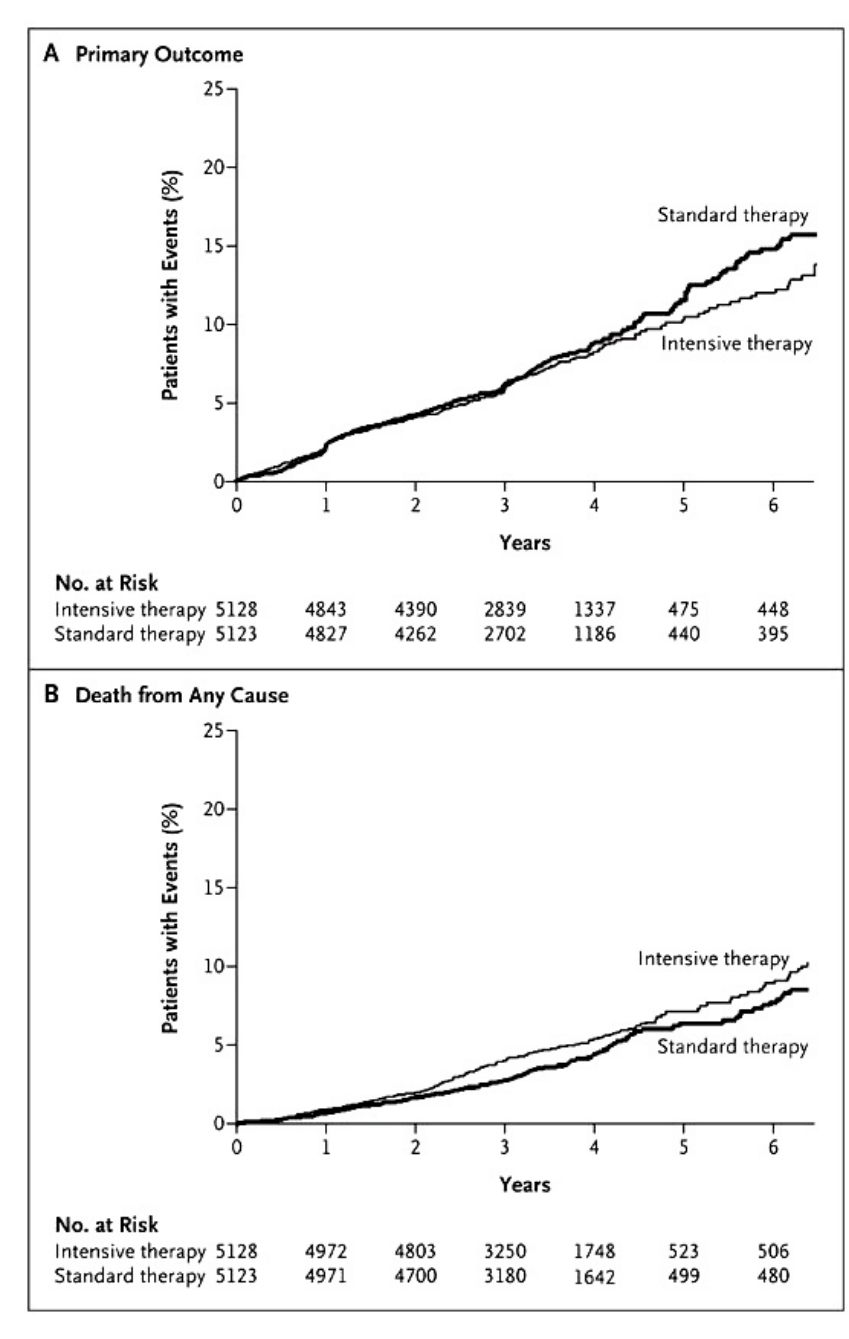
No. at Risk

Standard therapy	5109	4774	4588	3186	1744	455	436
Intensive therapy	5119	4768	4585	3165	1706	476	471

The NEW ENGLAND JOURNAL of MEDICINE

ACCORD results

June 2008



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ACCORD Study *(NEJM June 2008)*

Results: *(prematurely stopped after 3.5 years)*

	Intensive	*Standard*
HbA1c	6.4%	7.5%
Insulin Use	77%	55%
TZD Use	92%	58%
Hypos (needing assistance)	16%	5%
Non Fatal MI/CVA or CV Death	n = 352	n = 372
Total Mortality	257	203
Fatal MI	19	13
Fatal CHF	23	16
Unexpected Death	86	67

Effect apparently not attributable to any single/combo drugs…

ADVANCE Study *(NEJM June 2008)*

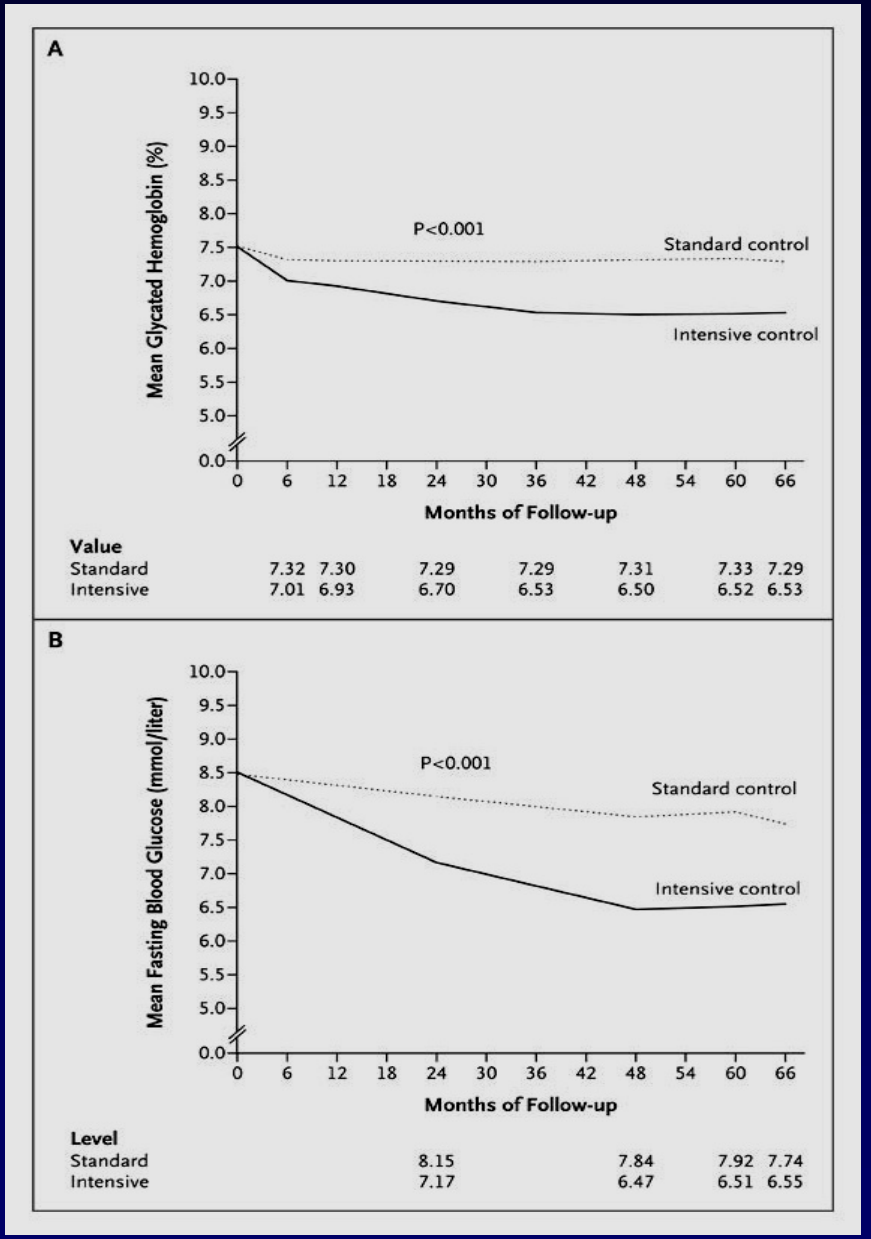
T2 Diabetes aged > 55 years + 1 risk factor
11,000 patients

Baseline:

➢ Aged	66 years
➢ BMI	28
➢ Mean HbA1c	7.5% (8 year duration)
➢ Previous macrovascular event	35%
➢ Microalbuminuria	27%
➢ Statin use	28%

ADVANCE results

June 2008



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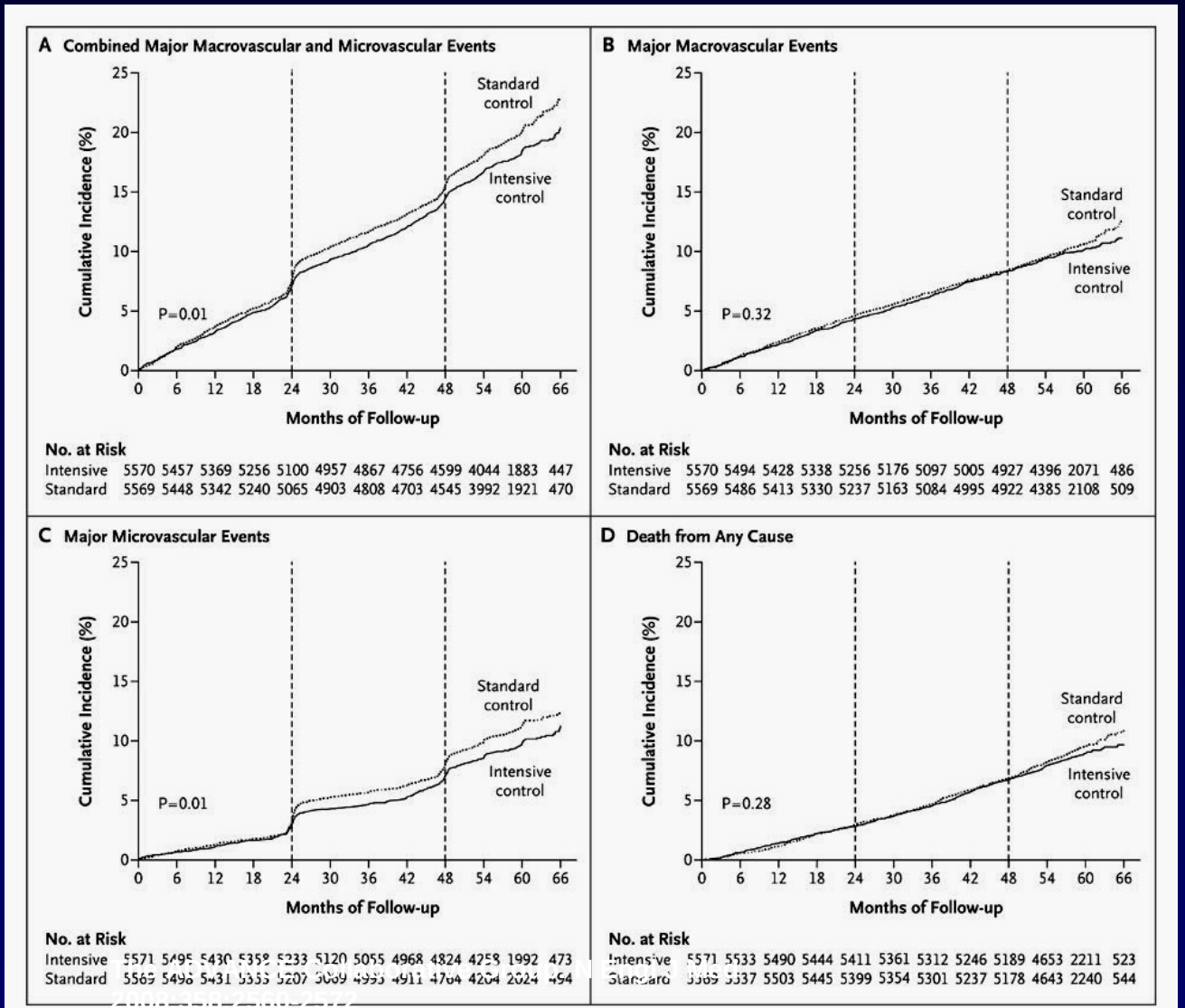
ADVANCE results June 2008

The NEW ENGLAND JOURNAL of MEDICINE



ADVANCE Study *(NEJM June 2008)*

Results: (after 5 years)

	Intensive	*Standard*
HbA1c	6.5% (80% < 7%)	7.3% (50% < 7%)
Insulin Use	40%	24%
TZD Use	17%	11%
Sulphonylurea	92%	58%
Metformin	74%	67%
Statin	45%	47%
CV Death	n = 253	n = 289
Major CV event	n = 557	n= 590
Coronary events	560	572
✳New or worsening nephropathy	230	292

ADVANCE Study *(NEJM June 2008)*

- **Suggests the current target of 7% and not lower is reasonable for those with:**

  8 - 10 years T2DM

  and/or established CV disease

As long as BP/Lipids controlled + aspirin

This was less well done than in ACCORD and higher mortality in ADVANCE

Targets for HbA1c in 2009 ?

What are your targets for:

1. **A 66-year old overweight but asymptomatic Caucasian man with newly-diagnosed type 2 diabetes on screening? HbA1c 8% two months later on lifestyle measures alone.**

2. **A 47-year old Maori woman, diabetic for 9 years, with HbA1c 9%, ACR 34.8 and previous marked hypos on insulin. Not optimal adherence.**

There will always be a need for drug therapy

"Welcome to the Diabetic Hotline! If you need a new excuse for cheating on your diet, press 1. If you need a new excuse for skipping your workout, press 2..."

Diabetes drugs – old and new - and HbA1c reductions

adapted from NEJM review Nathan, 2007

Insulin	Hypo	1922	>2.5%
Inhaled insulin		2006-08	1.5%
Sulphonylureas	Hypo	1946	1.5%
Phenformin		1957-?	1.5%
Metformin		1960s	1.5%
Alpha-glucosidase inhibs (acarbose)		1995	0.7%
Glinides e.g. repaglinide	Hypo	1997	1.2%
Troglitazone		1997-00	1 %
Rosiglitazone		1999	1 %
Pioglitazone		1999	1 %
GLP analogues		2005	1 %
Amylin analogues		2005	1 %
DPP-4 inhibitors		2006	1 %
Diet and exercise (UKPDS)		????	≥ 2%

Type 2 DM – Which Drug is Best to Start?

ADOPT Study 2006: ***(NEJM December 2006)***

- **4360 patients given either Rosiglitazone, Metformin or Glyburide as monotherapy.**

At 4 yrs	**HbA1c < 7%**	**HbA1c maintained < 7%**
Rosi	40%	60 mths
Met	36%	45 mths
Gly	26%	33 mths

But only 60% completed study.

ADOPT - Adverse Events

		Rosi	Metf	Glyburide
CV Events	n=	62	58	41
CHF		1.5% (22)	1.3% (19)	0.6% (9)
Oedema		14%	7.2%	8.5%
Hypos (Self reported)		9.2%	11.6%	38.9%
GI Events		23%	38%	22%
Weight gain		+ 4.8 kg	- 2.9 kg	+ 1.6 kg
Fractures		6.3% (92)	4.1% (59)	3.4% (49)
Costs		↑	-	-

Metformin

Pros:

- Many years of experience
- Reduces insulin resistance
- Weight neutral
- No hypoglycaemia
- Reduces risk of CV events (stroke esp. plus MI in obese subset in UKPDS)
- Cost is low

Cons:

- G.I. intolerance in 5 - 20%
- But lactic acidosis is rare

N.B. ? Cautious reduction in dose when eGFR 40ml/min STOP once eGFR 30-35 ml/min

- Mild ↓ in B_{12} levels

Slow release and combos available elsewhere, but not in NZ
Better tolerability and fewer tablets

Sulphonylurea as Monotherapy

Sulphonylurea:

- **OK if BMI < 25 (consider LADA)**
- **OK if BMI > 25 and Metformin cannot be used.**

Pros:

- Promotes insulin release
- Generally well tolerated
- Variable in renal impairment
- Low cost

Cons:

- Hypoglycaemia
- Can be severe
- Weight gain
- Earlier ß Cell failure?
- Avoid in elderly/frail

(“ADOPT” Study 2006)

Glitazones

Pioglitazone (Actos); Rosiglitazone (Avandia)

- **Insulin sensitizers.**
- **Only Actos currently funded in N.Z. No longer specialist only approval.**
- **Take ages e.g. months to work, but not always**

Monotherapy

- Met. Intol

and

- BMI >33 or S.U. intol

Dual Therapy

- With Met or SU

- **May use with insulin if > 1.5u/kg but best avoided here.**
  - **Best left to specialists as higher risk of HF**

Glitazones

Pros:

- Good insulin sensitisers
- Equipotent with other oral agents. Additive effect on HbA1c
- Actos has benefit of ↓ Triglyceride and ↑ HDL
- ↓ CRP and may ↓ BP.
- May preserve ß cell function longer than other oral agents. (ADOPT Study)
- Reduces fat in liver

Cons:

- Weight gain – common.
- Oedema – ankle 2-5%.
- Heart failure in 2-3% – not cardio-depressant but contraindicated in heart failure.
- Cost high – CV outcomes still unclear.
- No long term reduction in C/V events proven.
- Rosi – relation to MI currently questioned but no signal from large RECORD study yet. (Meta analysis by Nissen et al NEJM 2007).
- Increase in non-vertebral # in women - recently demonstrated (2 - 2.5 x risk ↑).

Pioglitazone (Actos) - how to use

- Start at 15mg, ↑ to 30mg soon– max dose 45mg but often needed in large patients!.
- Watch for early weight gain, SOB, ankle swelling.
- May not have any clinical effect for 4-6 weeks and maximal effect at 6-8 months.... or more
- Patient may give up if not educated well about slow action
- Not always easy to decide who will respond best, but usually the most insulin resistant (truncally obese).

Acarbose

Pros

- α-glucosidase inhibitor – slows CHO breakdown
- Post-prandial ↓ in glucose
- ↓ in HbA1c by ca 0.5%
- Reduction in CV mortality when used for IGT (STOP NIDDM)
- Useful if significant CHO in diet?
- Start 25mg pre-dinner and build to 50-100mg t.d.s.

Cons

- Significant GI. side effects.
- Specialist approval to start.

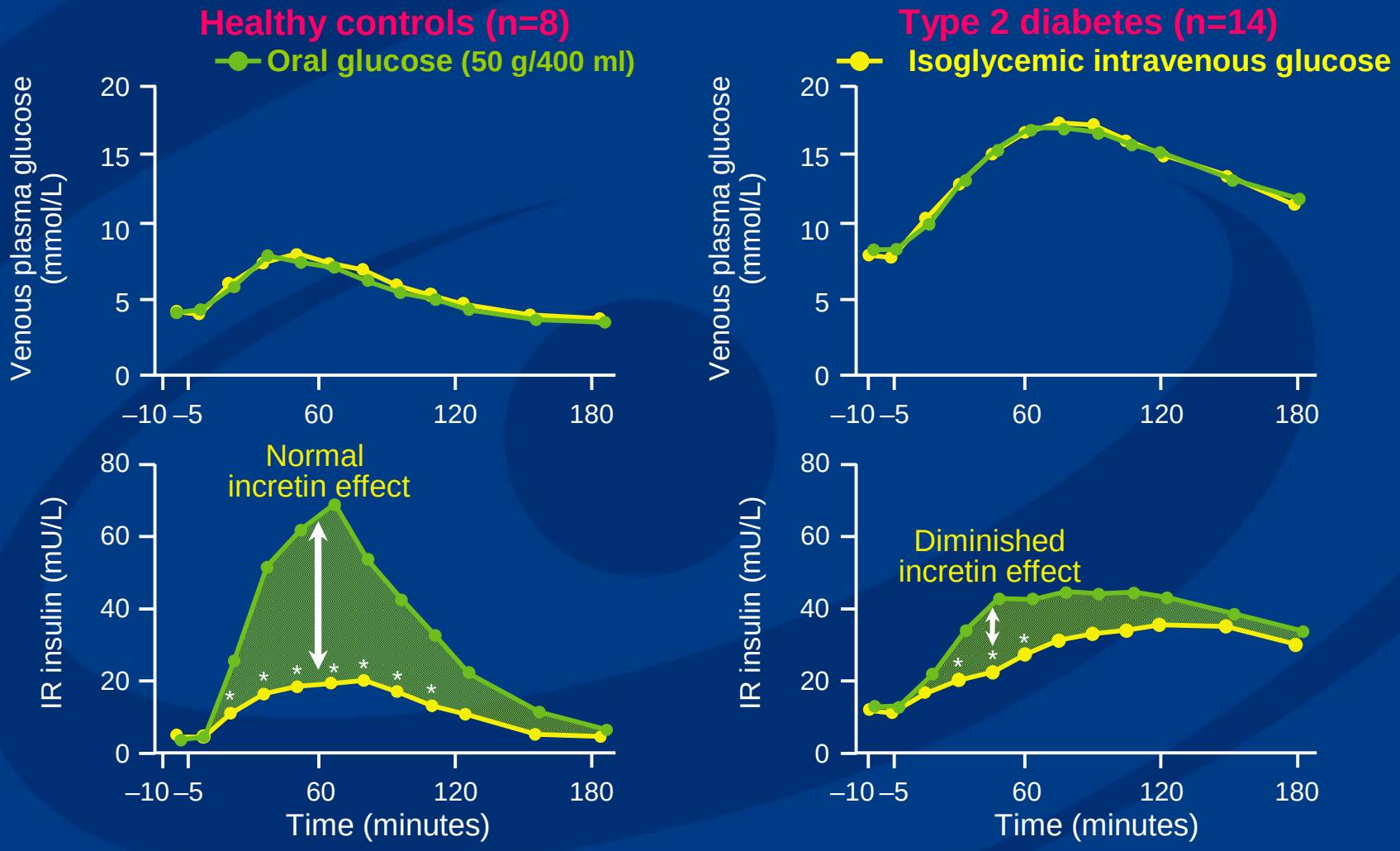
What are Incretins?

- Incretins are gut hormones that help the body response to elevated glucose
- Incretins (GLP-1 and GIP) are naturally occurring hormones released in response to meals. GLP-1 analogues are now available e.g. exenatide.
- When glucose levels are elevated, GLP-1 and GIP signal ß cells to increase insulin release and GLP-1 signals α-cells to suppress glucagon release
- The physiologic activity of incretins is limited by the enzyme dipeptidyl peptidase 4 (DPP-4), which rapidly degrades incretins after their release. DPP-4 inhibitors are now available e.g. Sitagliptin.

Gila Monster

World's largest lizard holds key to diabetes treatment in its mouth

Incretin Effect After Oral vs IV Glucose is diminished in Type 2 Diabetes

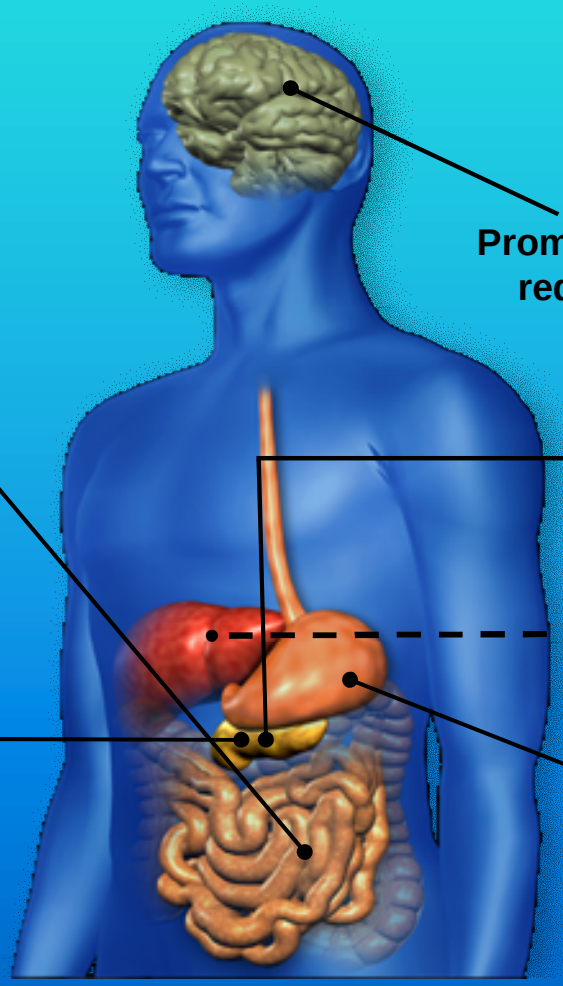


*p≤0.05 vs. respective value after oral load, IR=immunoreactive

Adapted from Nauck M et al *Diabetologia* 1986;29:46–52.

GLP-1 Effects in Humans

Understanding the Glucoregulatory Role of Incretins



GLP-1 secreted upon the ingestion of food

↓ Beta-cell workload

Promotes satiety and reduces appetite

↑ Beta-cell response

Alpha cells:
↓ Postprandial glucagon secretion

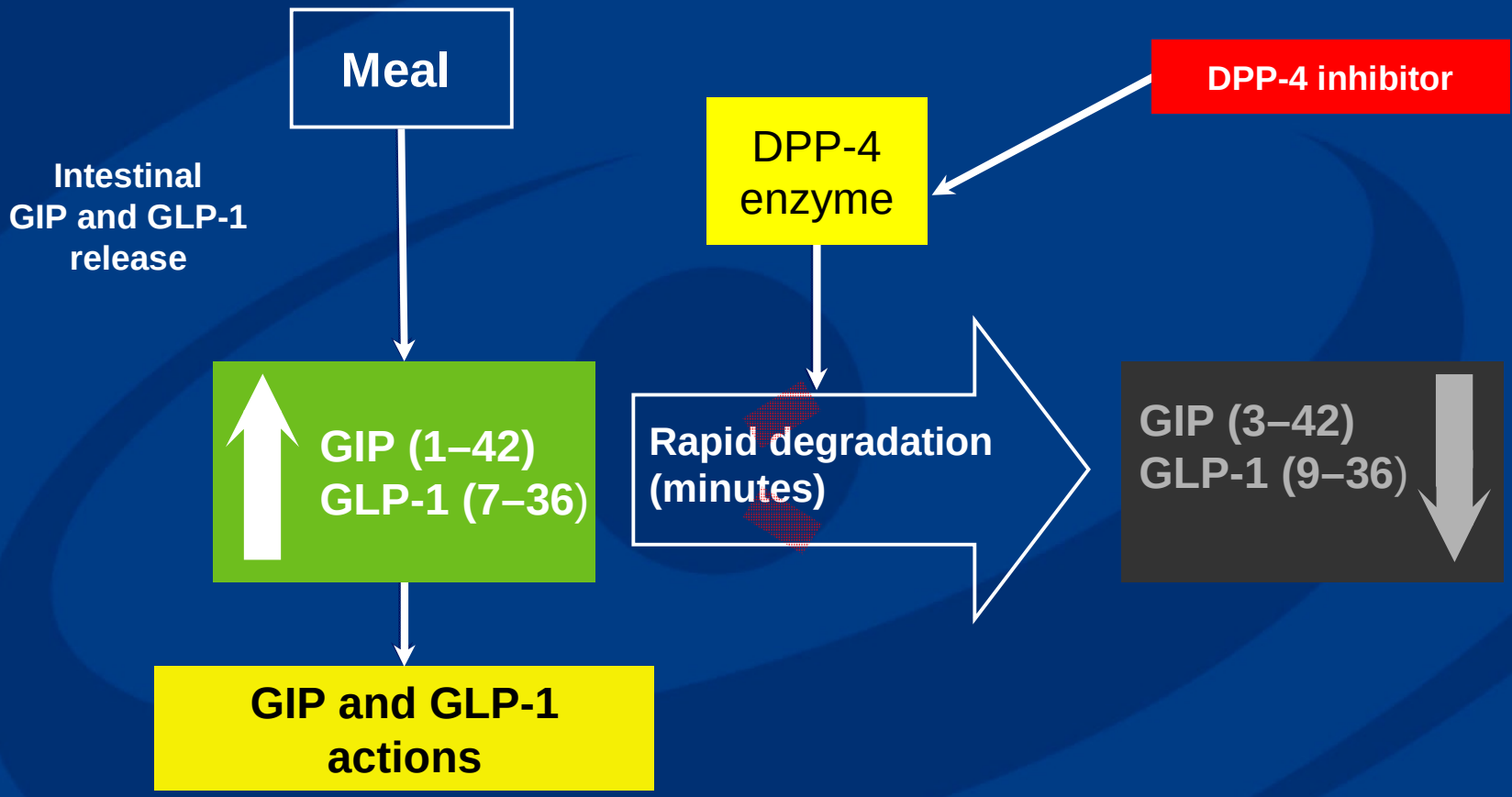
Liver:
↓ Glucagon reduces hepatic glucose output

Beta cells:
Enhances glucose-dependent insulin secretion

Stomach:
Helps regulate gastric emptying

Adapted from Flint A, et al. *J Clin Invest*. 1998;101:515-520.; Adapted from Larsson H, et al. *Acta Physiol Scand*. 1997;160:413-422.; Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553.; Adapted from Drucker DJ. *Diabetes.* 1998;47:159-169.

In Vitro and *In Vivo* DPP-4 Inhibition Increases Levels of Biologically Active Incretins GLP-1 and GIP



Adapted from Deacon CF et al *Diabetes* 1995;44:1126–1131; Kieffer TJ et al *Endocrinology* 1995;136:3585–3596; Ahrén B *Curr Diab Rep* 2003;3:365–372; Deacon CF et al *J Clin Endocrinol Metab* 1995;80:952–957; Weber AE *J Med Chem* 2004;47:4135–4141.

Incretin Drugs available in U.S. and Europe and now NZ

But not funded

Exenatide (Exendin), LA prep and others in hand

- Binds to GLP receptor.
- Injected b.d. – often some nausea initially.
- **Weight loss of 4-5kg.**
- HbA1c ↓ by 0.8 - 0.9%, possibly more with newer agents
- No hypos.
- Not funded – ideal after 2 oral agents instead of insulin?
- Perhaps available in daily and once weekly injections soon

Incretin Drugs available in U.S. and Europe and now NZ

But not funded

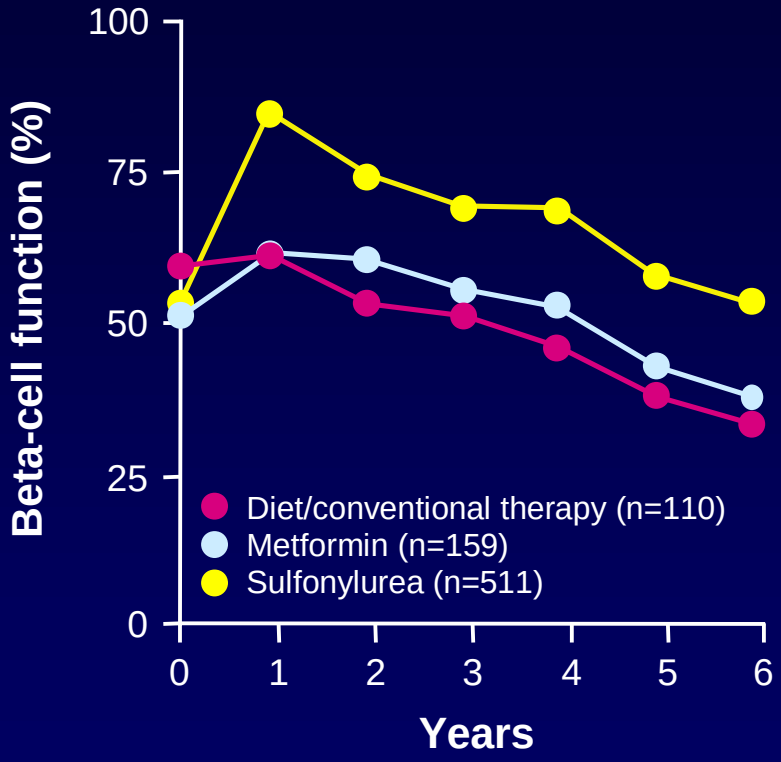
DPP – IV Inhibitors, e.g. Sitagliptin

- ↑ GLP by inhibiting breakdown
- Oral medication
- HbA1c ↓ by 0.6 - 0.9%
- No hypos
- Weight neutral
- Not funded
- Works well with Metformin
- Perhaps ideal for elderly or in those where hypoglycaemia likely e.g. renal impairment

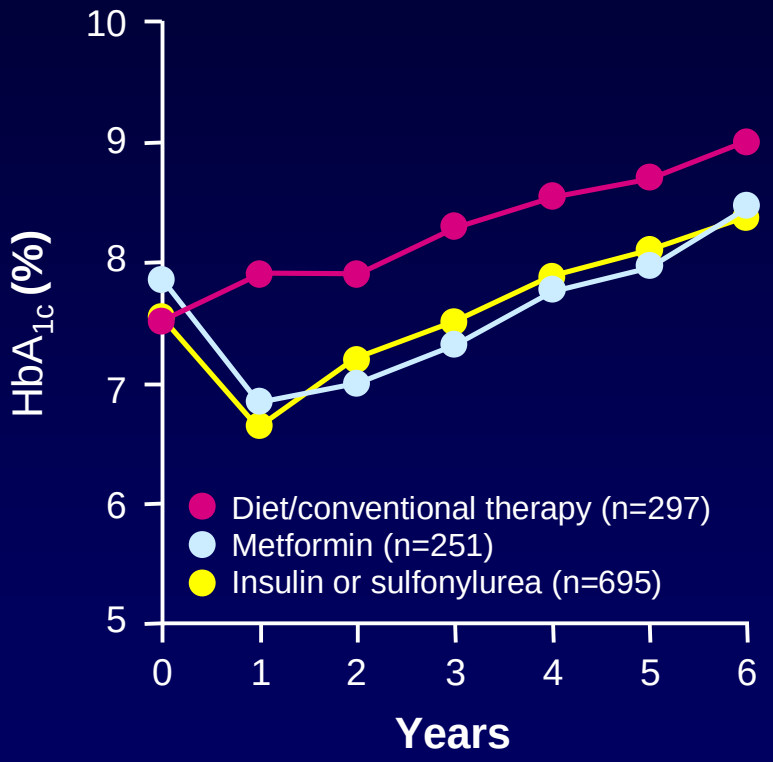
Poor control in type 2 diabetes

- If patient has poor control and many of the following then they are VERY likely to have ß–cell failure:
  - Longer duration of diabetes e.g. > 7 years
  - Initial high HbA1c at presentation
  - Very high HbA1c > 9-10%
  - Have needed progressive increases in oral medication over the years
  - Are losing weight
- Poor diet, limited exercise and /or poor compliance are also possible or likely but
  - Unlikely to be the whole explanation

Declining Beta-Cell Function Associated with Increasing Hyperglycemia UKPDS 16



Beta-cell function assessed by HOMA



HbA_{1c} results shown from obese patients

UKPDS=United Kingdom Prospective Diabetes Study; HbA_{1c}=glycosylated hemoglobin

Adapted from UKPDS Group *Diabetes* 1995;44:1249–1258.

So why don’t we use insulin earlier?

- Better glycaemic control.
- Reduces lipotoxcity (↓ NEFA, ↓ TG).
- Conserves B cell function.
- Improves endothelial function.

Clinical Inertia in T2DM Management in Auckland

Choe & Cutfield 2008

Study of 2240 patients in 1° care in S.W. Auckland in 2004-2006 on 2 oral agents:

- 954 (42.6%) of these had HbA1c ≥ 8%

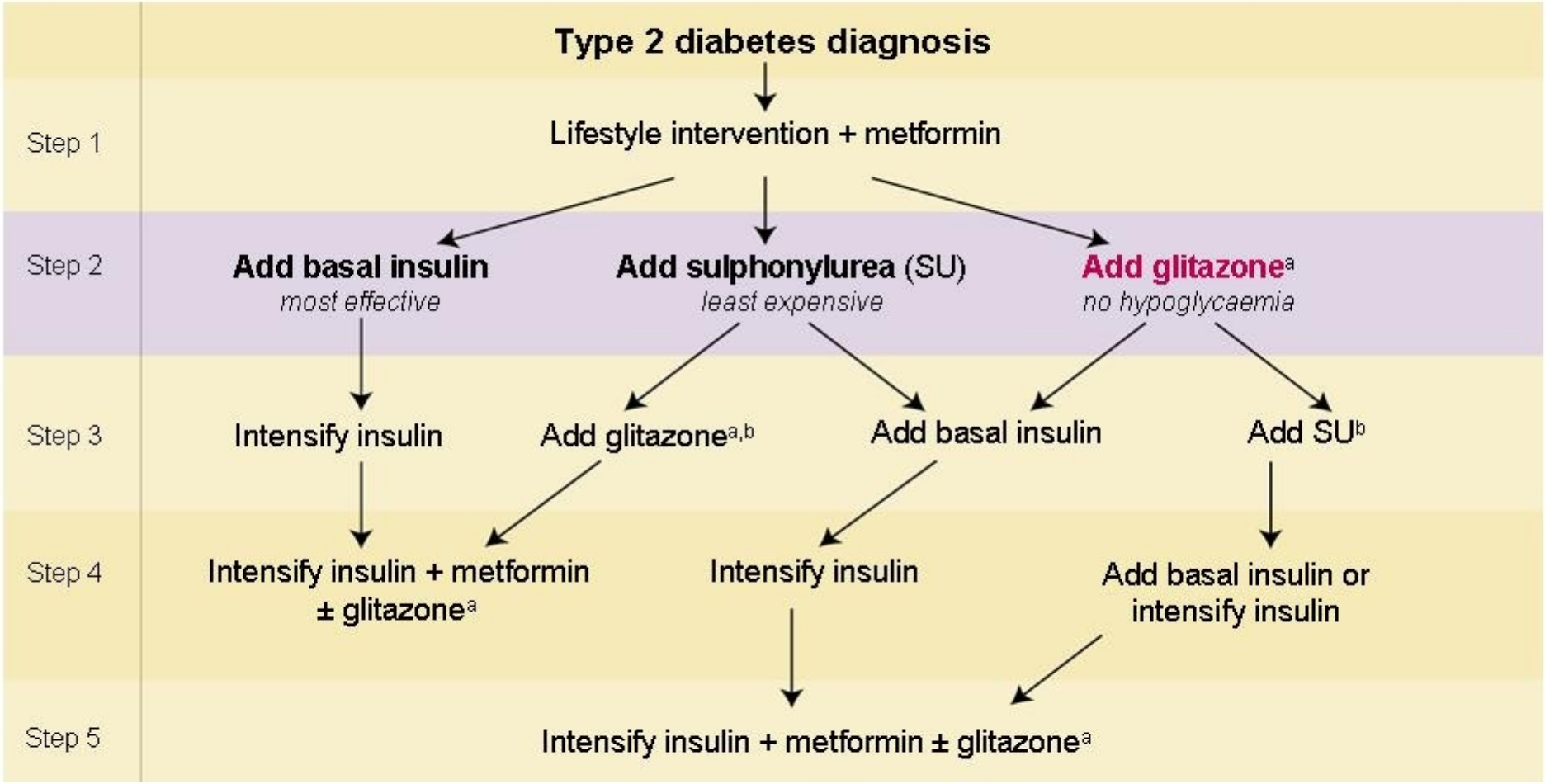
Nearly 2 year s later:

- 451 out of 605 patients with second HbA1c ≥ 8 were still not on insulin

Overcoming Barriers

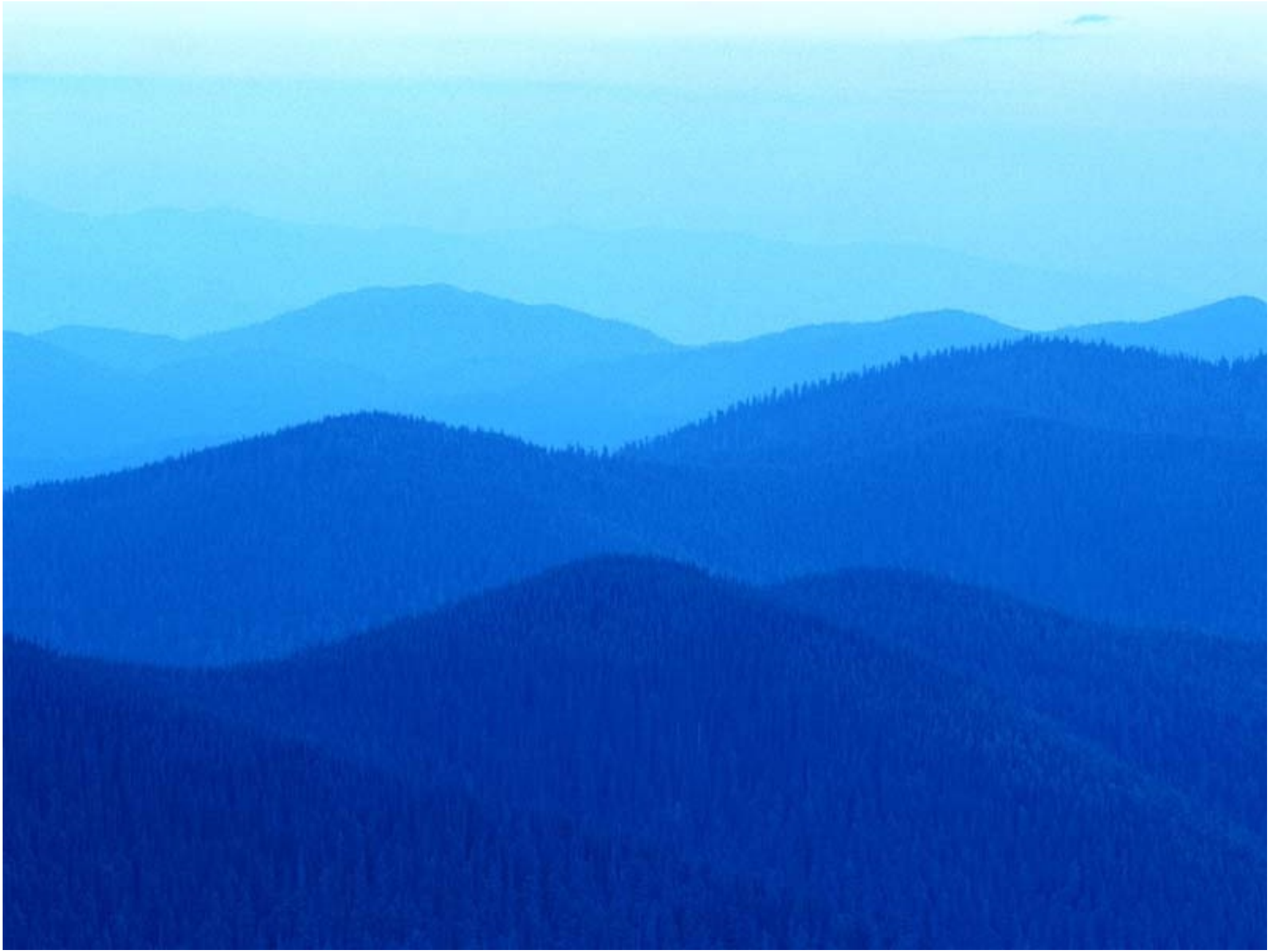
- Introduce concept of insulin early, not as threat.
- Pain – Demonstrate how to inject early with appropriate education; usually painless.
- Inconvenience – keep regimen simple e.g. Nocturnal NPH by pen.
- Quality of Life – Does not reduce / May increase.
- Hypos – minimal.
- Weight gain – use with Metformin / Review food plan.
- Cultural issues – involve family, friends, church leaders.
- CHANGE ATTITUDES of Health Professionals.

Achieving Glycaemic Goals
2008 ADA/EASD Consensus Treatment Algorithm



Check HbA1c every 3 months. If HbA1c >7%, consider next step therapy until HbA1c<7%. Then check HbA1c at least every 6 months. **a**. Associated with increased risk of fluid retention, CHF, and fractures. Rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of myocardial infarction. **b**. Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and lower expense.

Adapted from Nathan DM, Buse JB, Davidson MB, et al. *Diabetes Care*. Jan 2008;31(1):173-175.



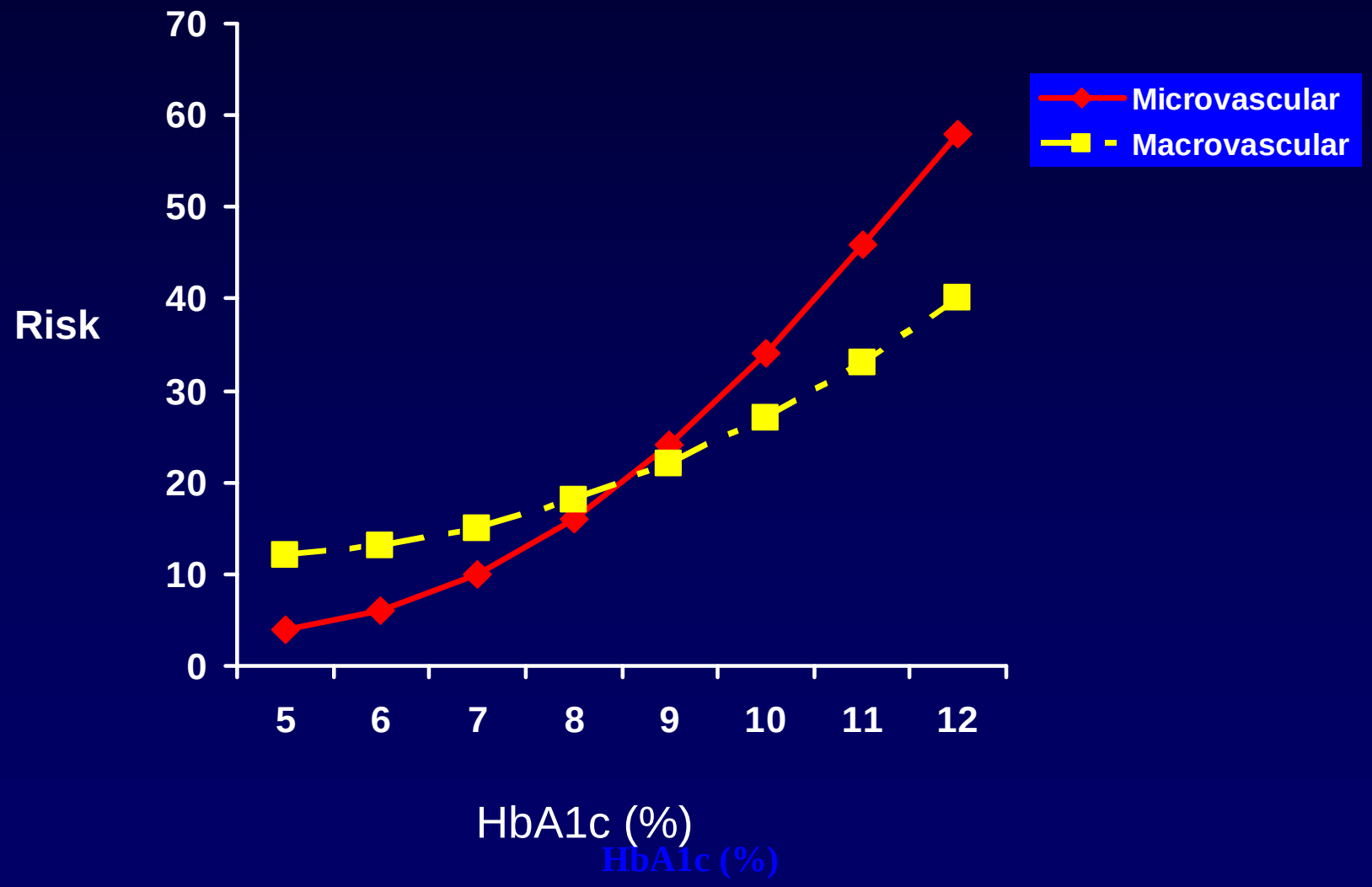
Cardiovascular risk in diabetes

Basically same as anyone else BUT

- **Current equations, even NZGG, don't adequately allow for:**
  - **Ethnicity (also deprivation) – Maori + 30%, East Asian -20%**
  - **Microalbuminuria**
  - **Macroalbuminuria**
  - **Poor glycaemic control**
- **Newer data show significant and major effect of:**
  - **Reduced renal function, even marginal, as eGFR**
  - **Lesser effect of glycaemic control (if on CV Rx)**
- **Increasing evidence of increasing benefit from**
  - **Duration of anti-risk treatment**

Microvascular and macrovascular risk vs HbA1c

UKPDS data – type 2



Attack the Risk Factors and overall risk - but which drugs?

BP:

- ACE inhibitor / A2 antagonist – but NOT both
- Thiazide
- Ca^{2t} antagonists
- B-Blocker

Lipids:

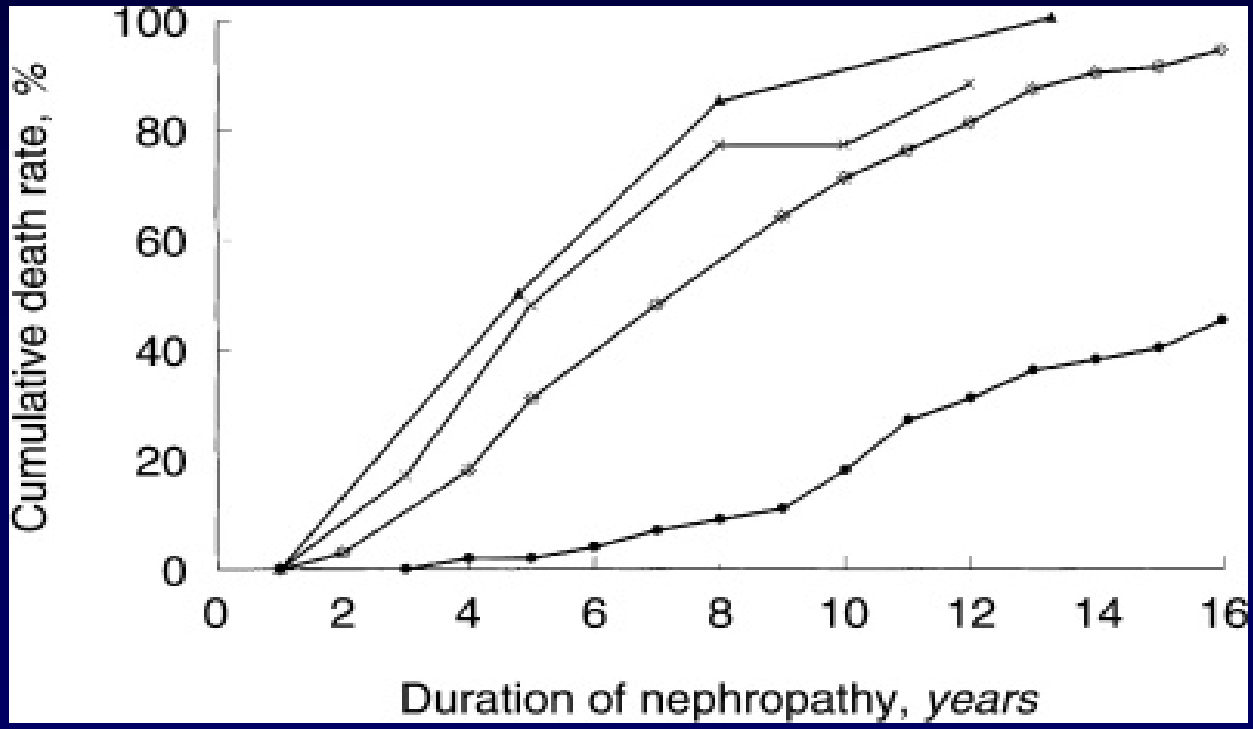
- STATIN for most
- Fibrate if TG > 3.0 +(-) STATIN
- Ezetemibe to ↓ LDL if target not reached but.....

Aspirin:

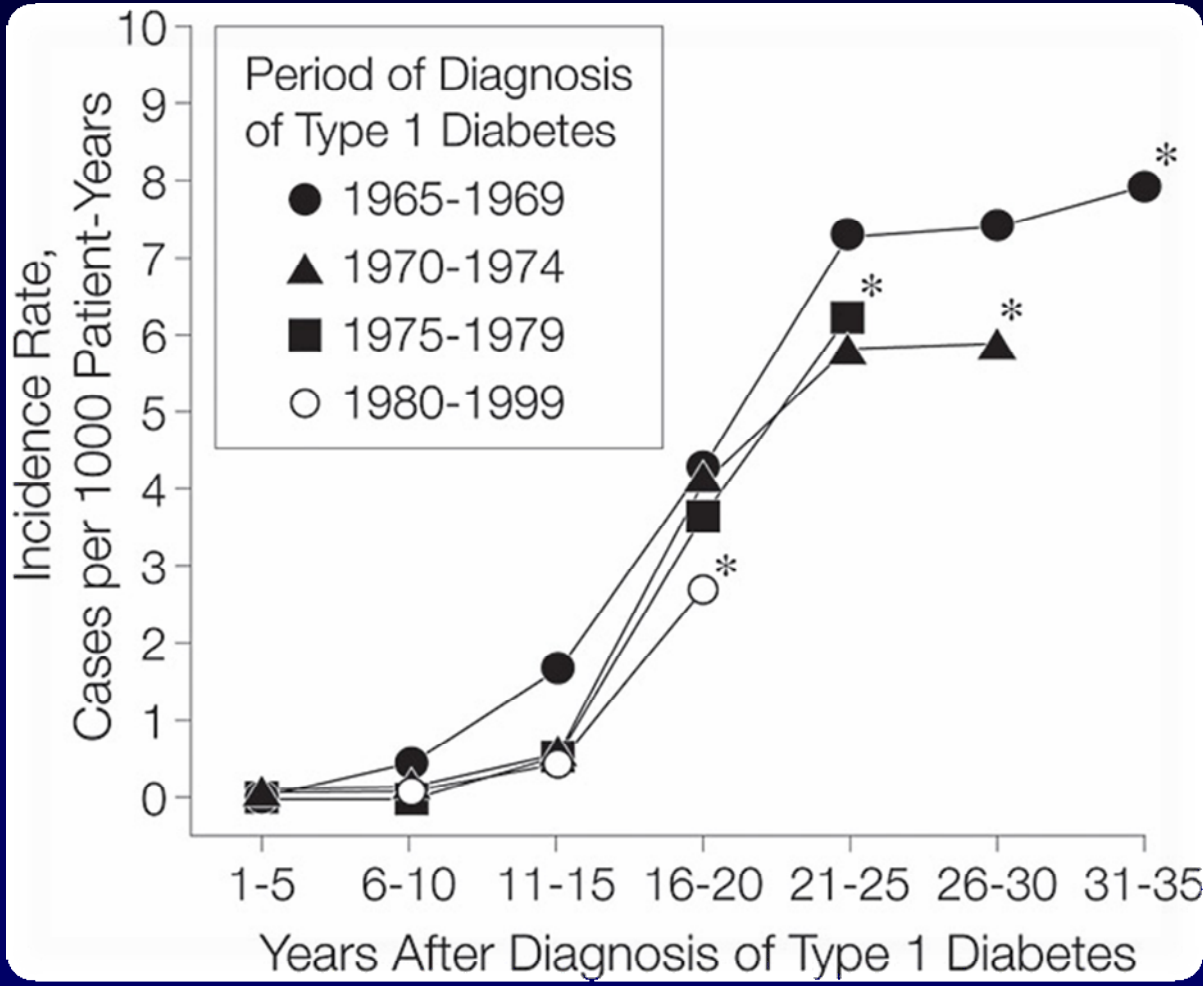
If C.V. risk > 15% at 5 years
or DM with 1 risk factor
or DM > 10 years duration
or > 50 years age.

But new data…..

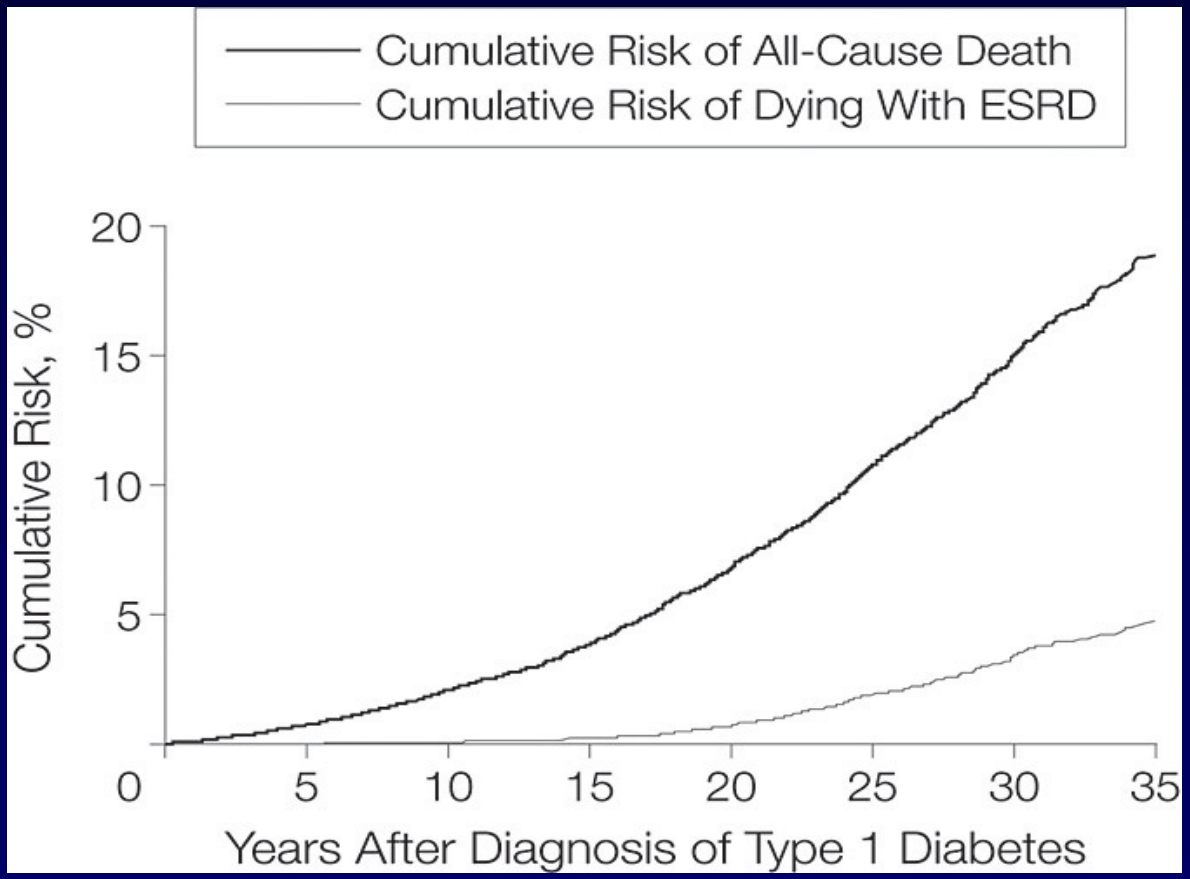
Previous prognosis of diabetic nephropathy
from type 1 cohorts



Type 1 diabetes and nephropathy incidence

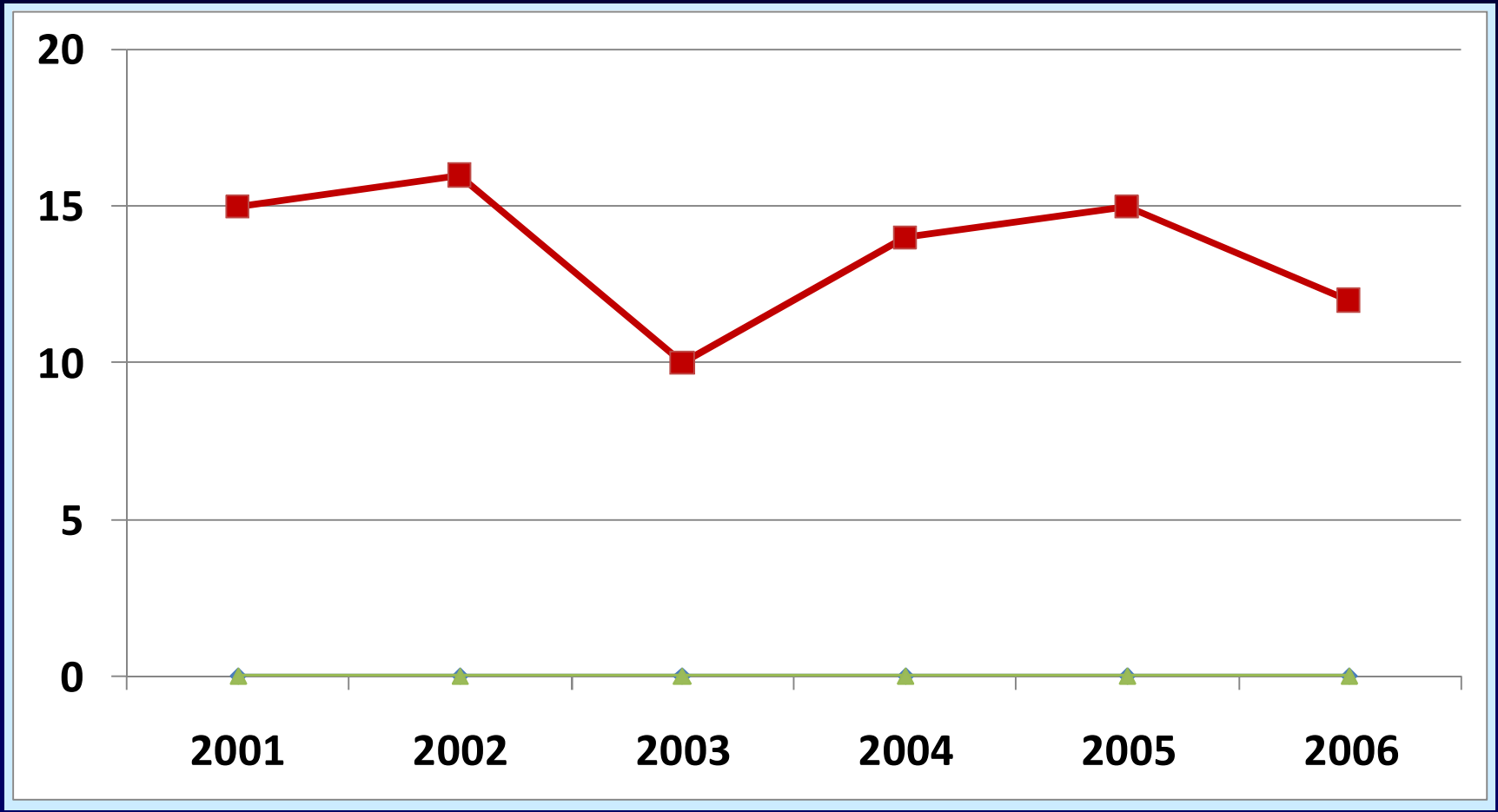


Type 1 DM and risk of death from ESRD



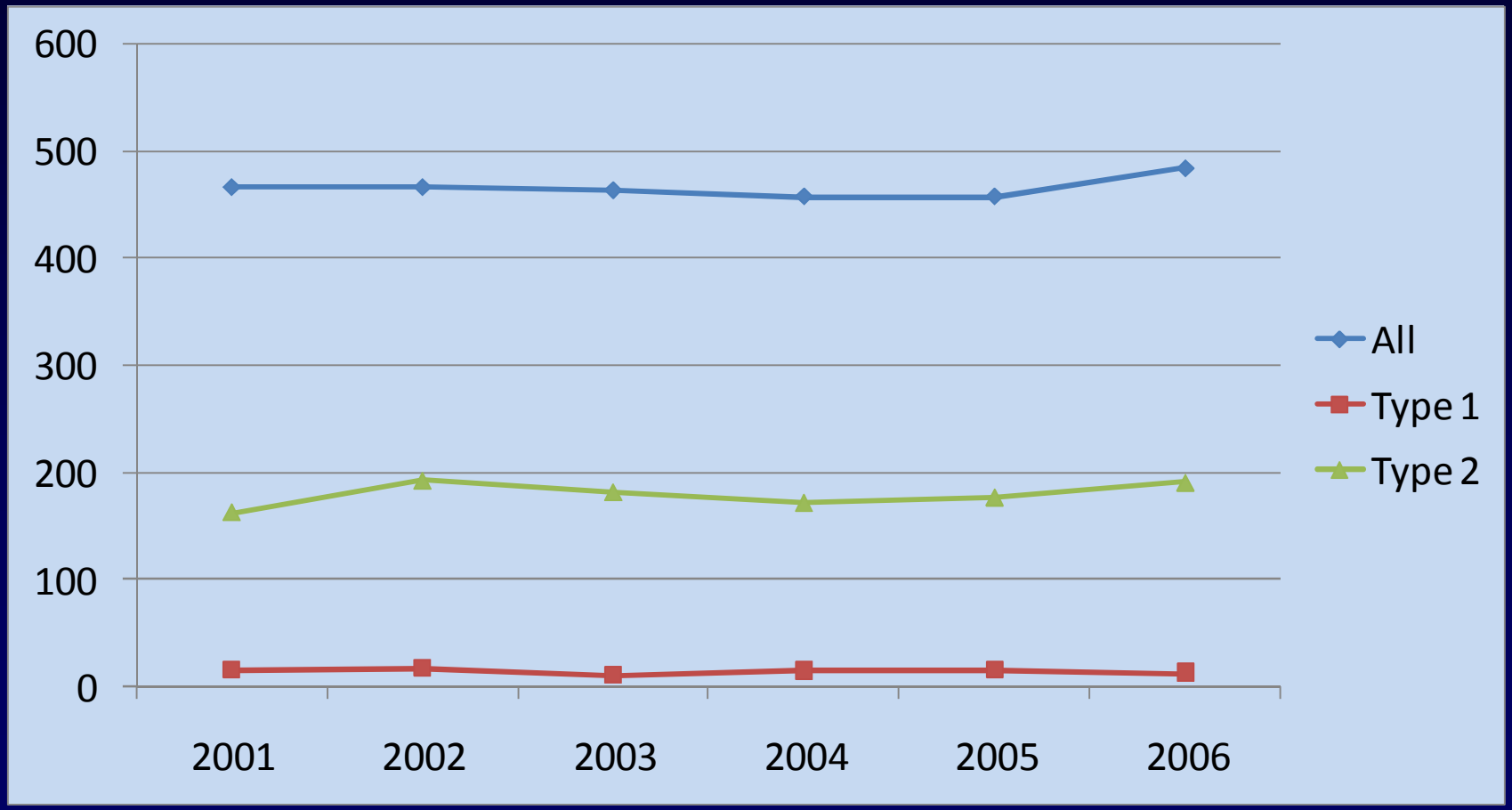
New type 1 DM RRT patients New Zealand 2001-06

ANZDATA



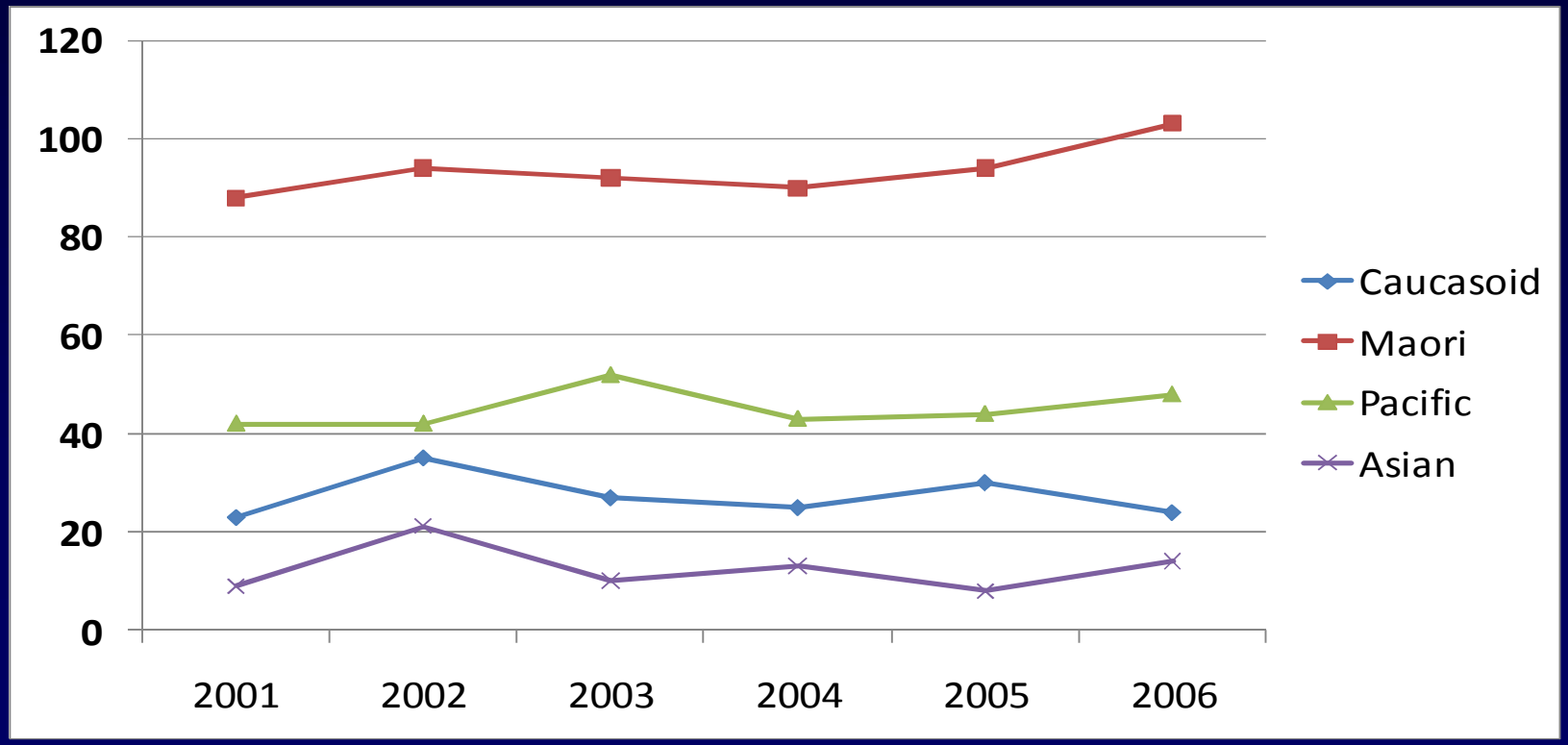
New RRT patients New Zealand 2001-06

ANZDATA – uncorrected numbers



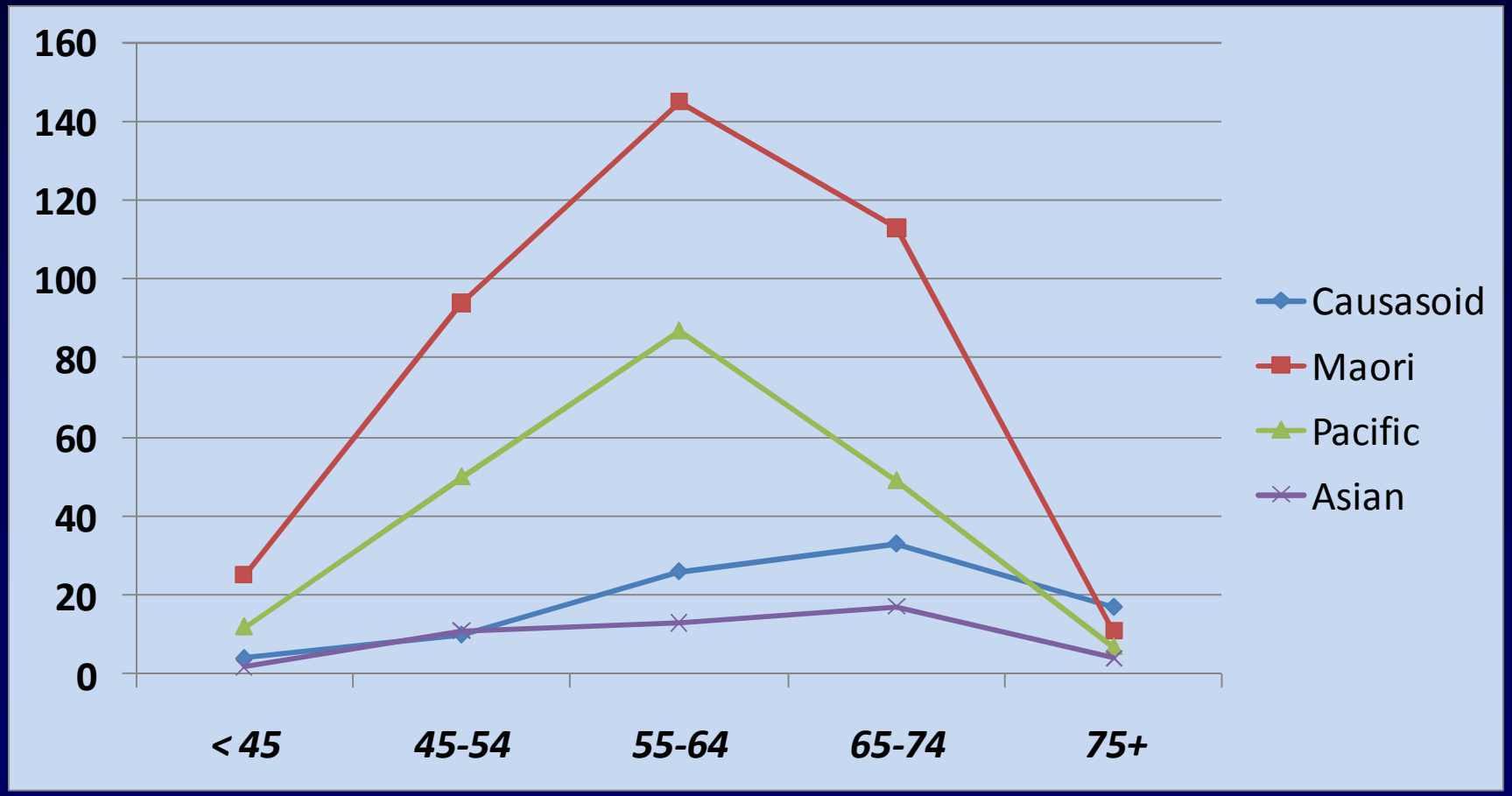
New RRT NZ by ethnicity 2001-06

ANZDATA – uncorrected numbers

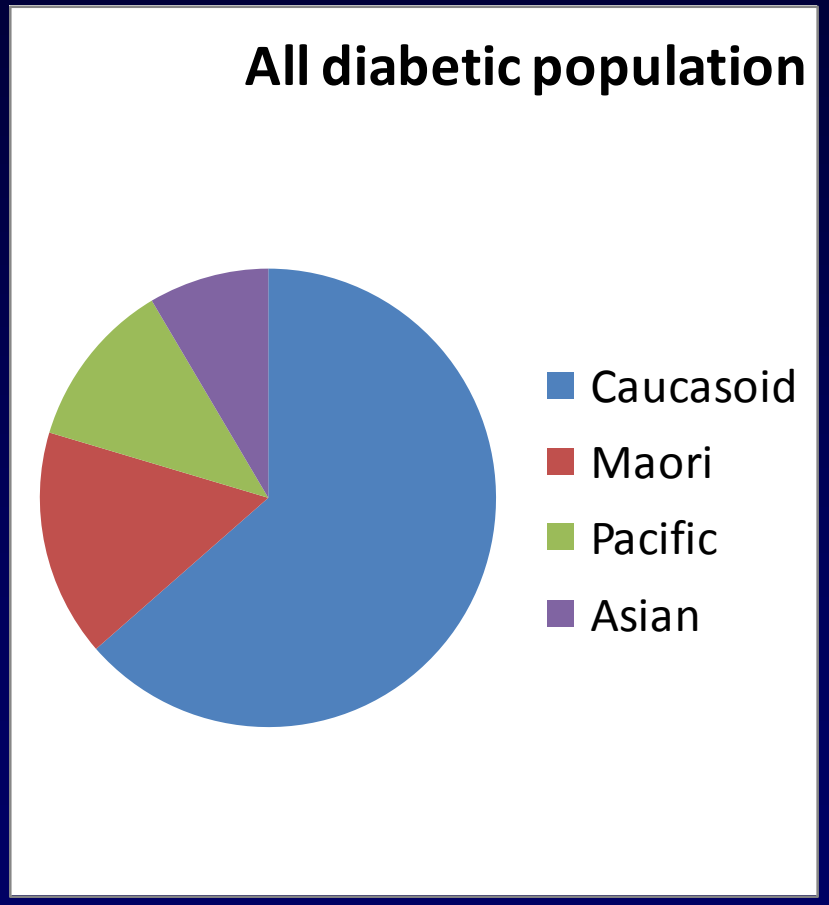


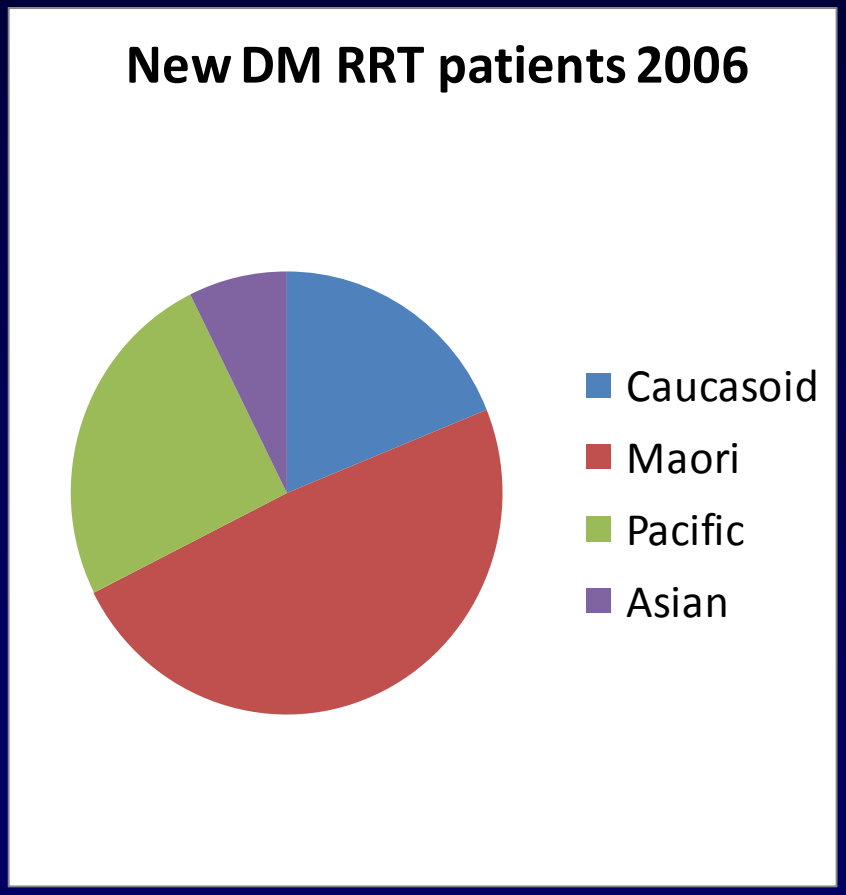
NZ diabetes on dialysis (end 2006) by age

ANZDATA – uncorrected numbers



Comparison of ethnicities

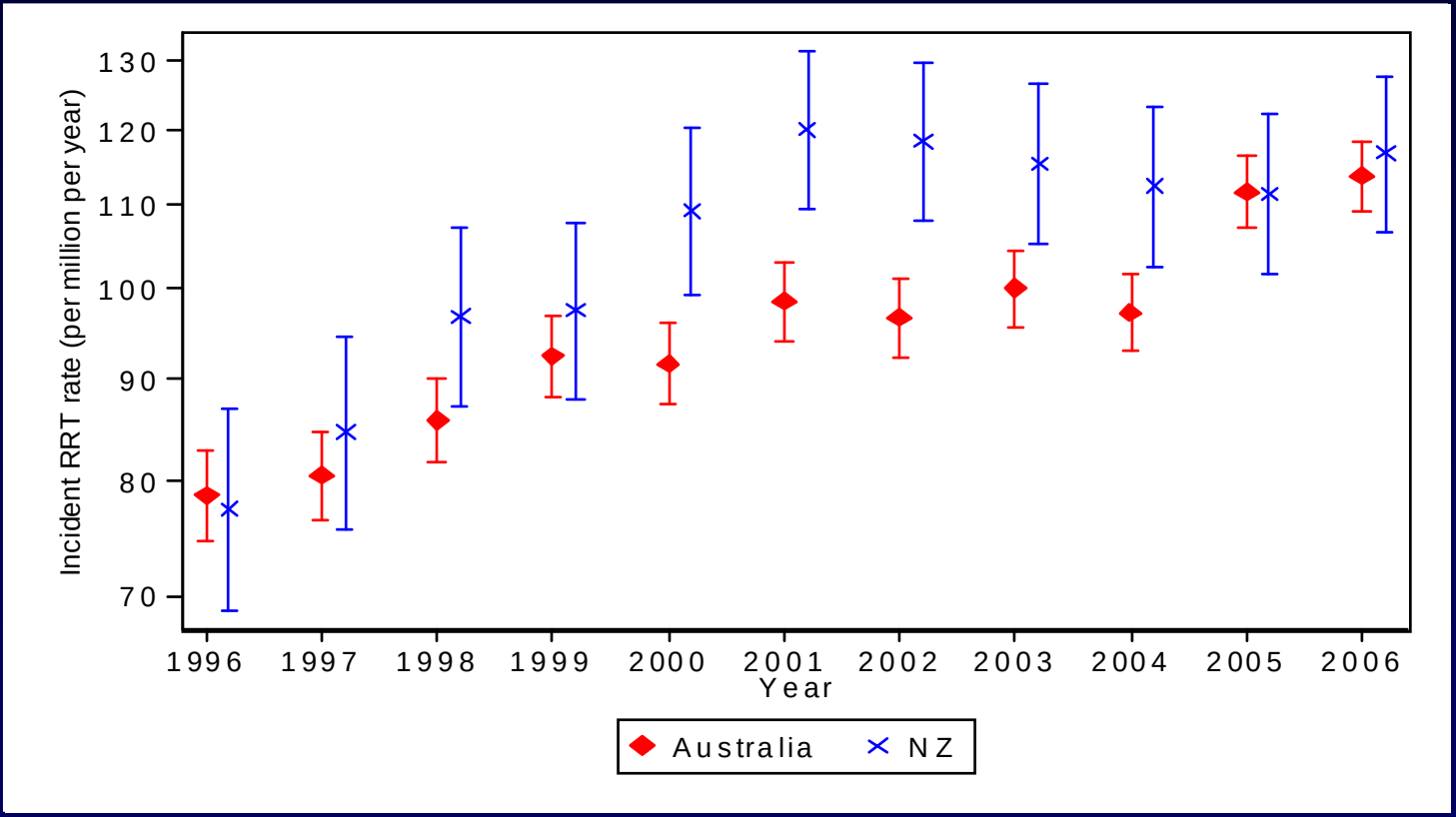




New Patient ESRF Rates: ANZDATA 1996-2006

Diabetes consistently 40-45% of NZ new RRT

Uncorrected for diabetes prevalence

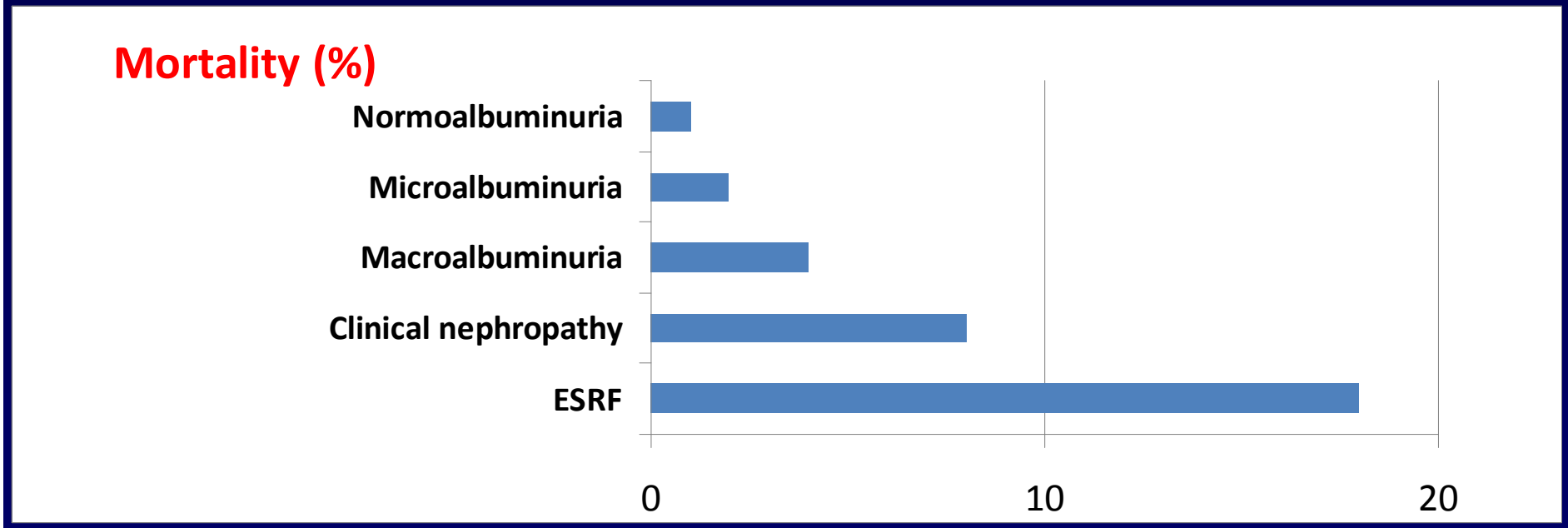


Is that a plateau or not? 2007 data now shows no sig rise

Given rising prevalence are we winning ?

Albuminuria – mortality rates (UKPDS data)

- Microalbuminuria predates proteinuria
- May predate renal impairment
- Also very powerful CV risk factor, tho' so is renal function alone (eGFR)



Original Article

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes

Peter Gæde, M.D., D.M.Sc., Henrik Lund-Andersen, M.D., D.M.Sc., Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

N Engl J Med
Volume 358(6):580-591
February 7, 2008

Intensified Multifactorial Intervention

Steno 2 Study *(NEJM 2008)*

- **160 patients with type 2 diabetes and microalbuminuria**
- **Intensive group treat to target for first 8 years, then all intensive**
- **All offered aspirin/ACE inhibitor (85-90%), + statin intensive**

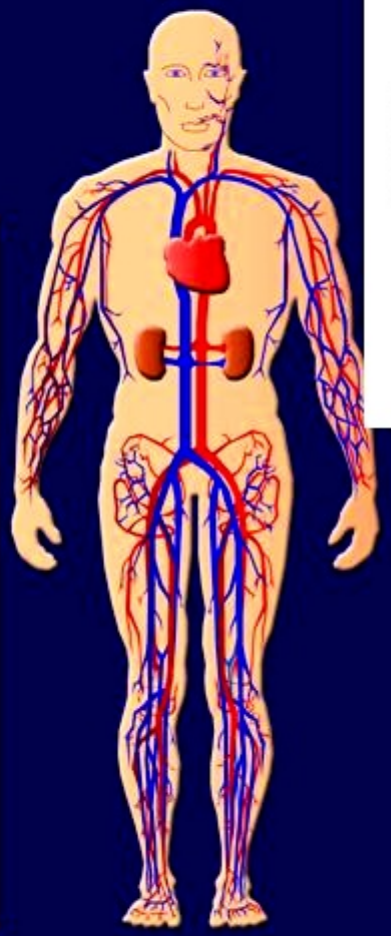
		Intensive		Conventional	
	Baseline	At 7 yrs	13 yrs	7 yrs	13 yrs
BP	146/85	131/73	140/74	146/78	146/73
LDL	3.4	2.0	1.8	3.2	1.9
Smoking	40%	31%	22%	27%	18%
HbA1c	8.4	7.9%	7.7%	9.0%	8.0%

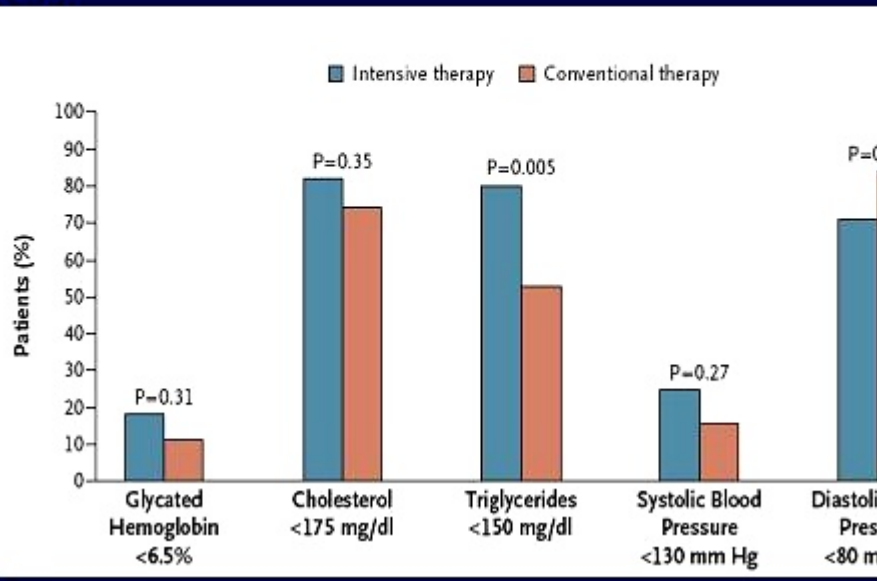
Macro and microvascular complications
Lesson from the STENO 2 Study
13.3 yrs Follow-up

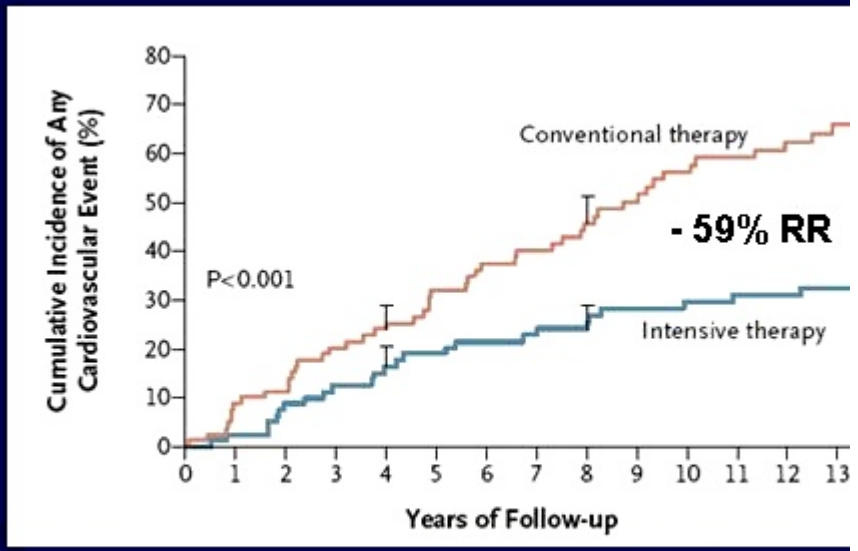
Micro Complications

Despite an intensive treatment with OAD, antiHT, LLA + diet and lifestyle program, after a mean follow-up of 13.3 years still*:

- **32%** with **CVD events**
- **51%**: progression of **retinopathy**
- **25%**: development of **nephropathy**
- **50%**: progression of peripheral **neuropathy**



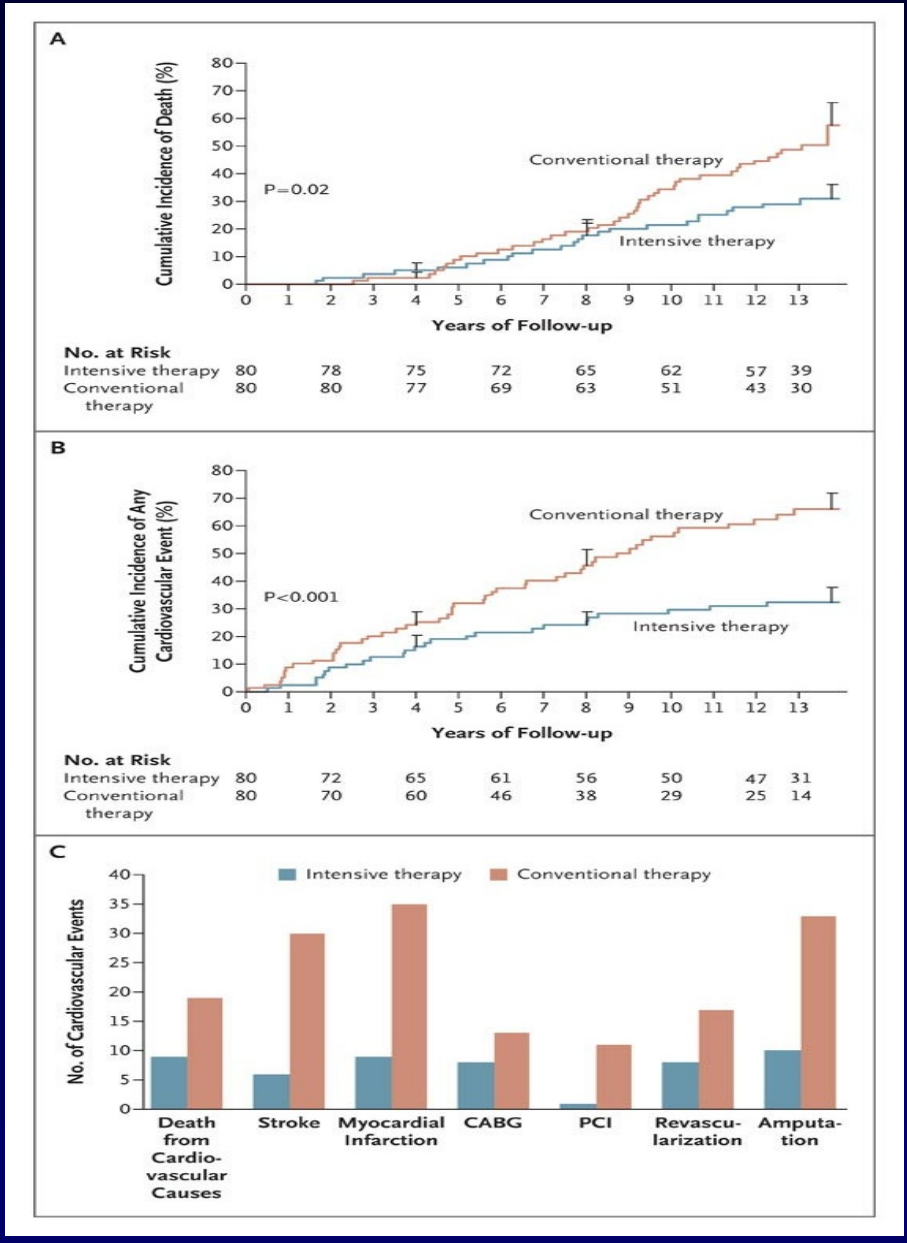




eno2 study Gaede P et al. N Engl J Med 2008 (Feb 7);358:580-91

Cumulative incidence of death: RR -46%
Death from CV causes: RR -57

Kaplan-Meier Estimates of the Risk of Death from Any Cause and from Cardiovascular Causes and the Number of Cardiovascular Events, According to Treatment Group



Gaede P et al. N Engl J Med 2008;358:580-591

The NEW ENGLAND JOURNAL of MEDICINE

Some brief issues on risk

- Several studies fail to confirm efficacy of ASP in type 2 DM with no CV event e.g. primary prevention ineffective?
- In contrast STATINS are beneficial, though absolute risk reduction dependent on absolute risk (20% reduction of 5% is not a lot)
- Overall CV event rates in all T2DM recent studies have been well below predictions e.g. FIELD, CARDS, POPADAD……
- May be benefit of METFORMIN separate from BG lowering effect. Should almost everyone have METF?
- Fenofibrate may have some specific actions on eye disease and on amputation
- May be long lag period before maximal benefit from intervention


My thanks to Dr Rick Cutfield and Prof Tim Cundy for slides
Thank you for your interest and attention