

Management of Type 2 Diabetes Mellitus

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December 4, 2003

Objectives

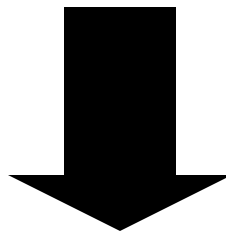
- Overview of Type 2 Diabetes
 - physiology
 - epidemiology
- Review Selected Guidelines
 - screening / diagnosis
 - complications
 - management
- Developments in Pharmacological Care
 - brief medication review

Pathology

Insulin Resistance
[skeletal muscle]
[liver]
genetics / obesity

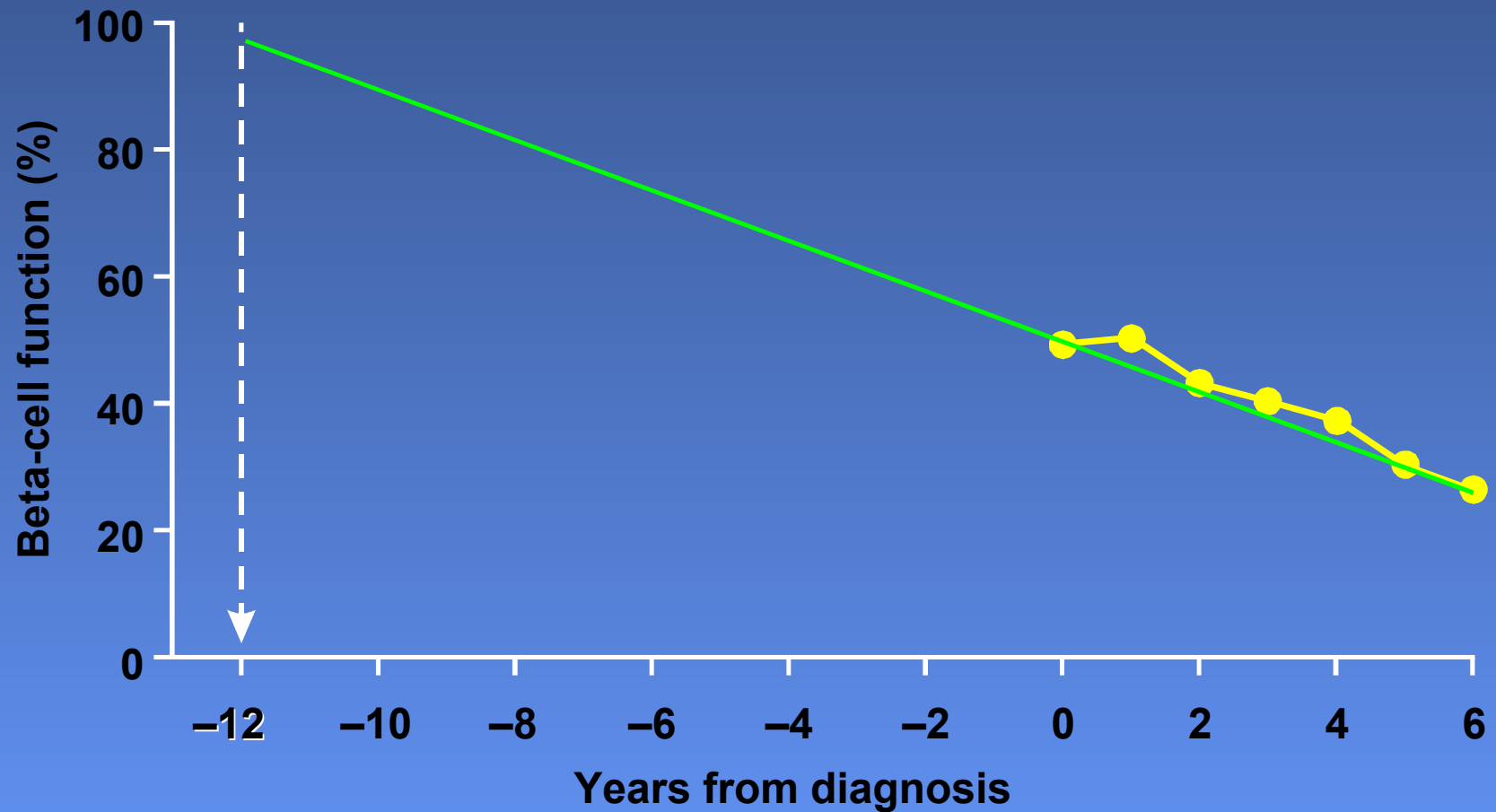


Insulin Loss
[progressive]



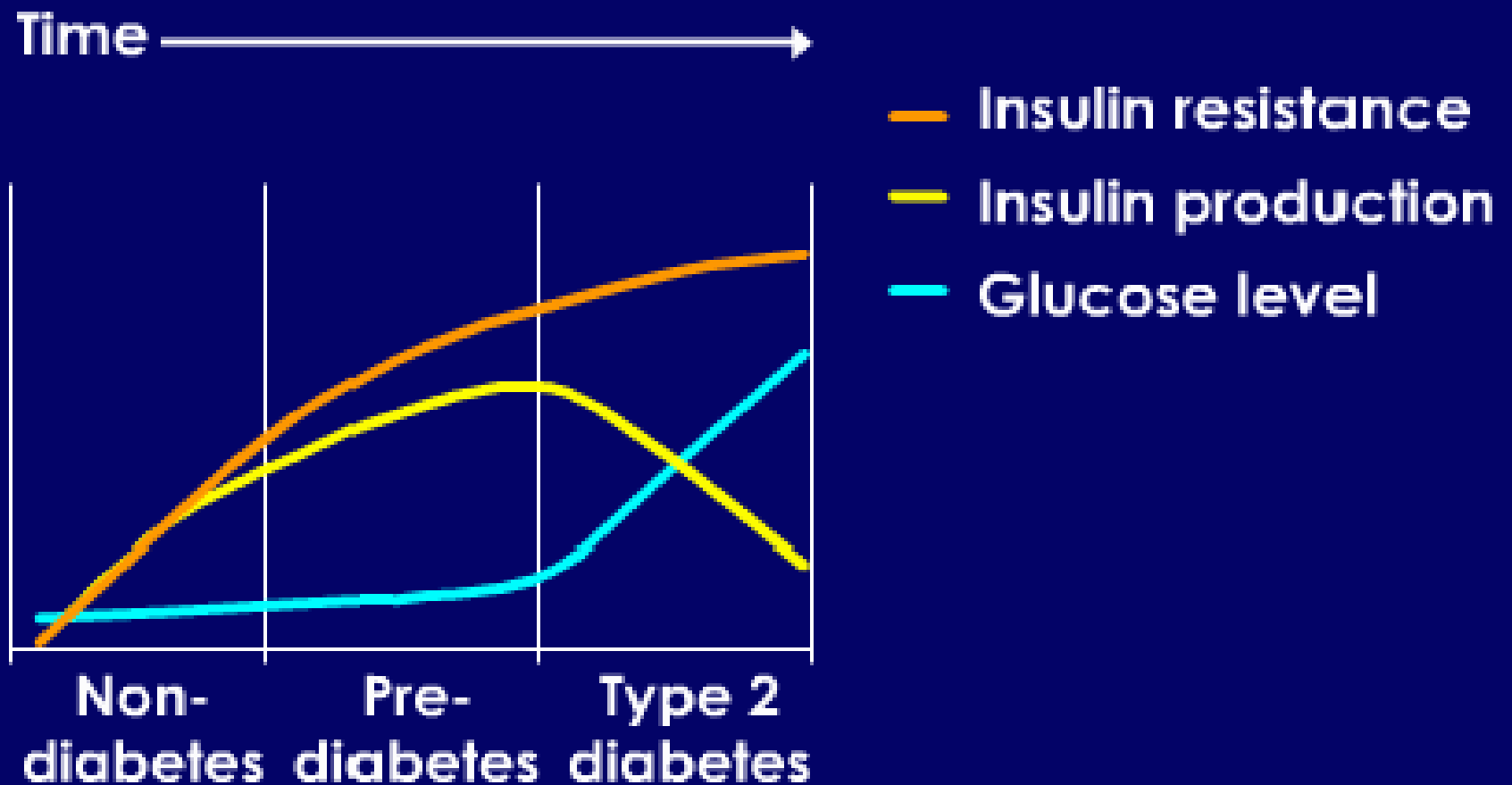
Type 2 diabetes mellitus

Extrapolation of the time to deterioration of beta-cell function



Adapted from UKPDS 16. *Diabetes* 1995;44:1249-58

Insulin resistance: an underlying problem



Pathology of Type 2 DM: 5 stages









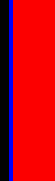
Stages ->	1	2	3	4	5
	NGT	IPG	DM	DM	DM
Hgb A1C (%)	<5.5	6.1	7.5	10	>10
FPG (mmol)	6.1	6.9	8.9	13.3	>13.3
insulin resistance	mod	mod	mod	mod	severe
insulin levels	+++	++	+/-	-	---
treatment	----- diet and exercise -----				
	stages 3-4-5 insulin sensitizer(s)				
	stage 4 secretagogue stage 5 insulin				

Natural History of Type 2 Diabetes

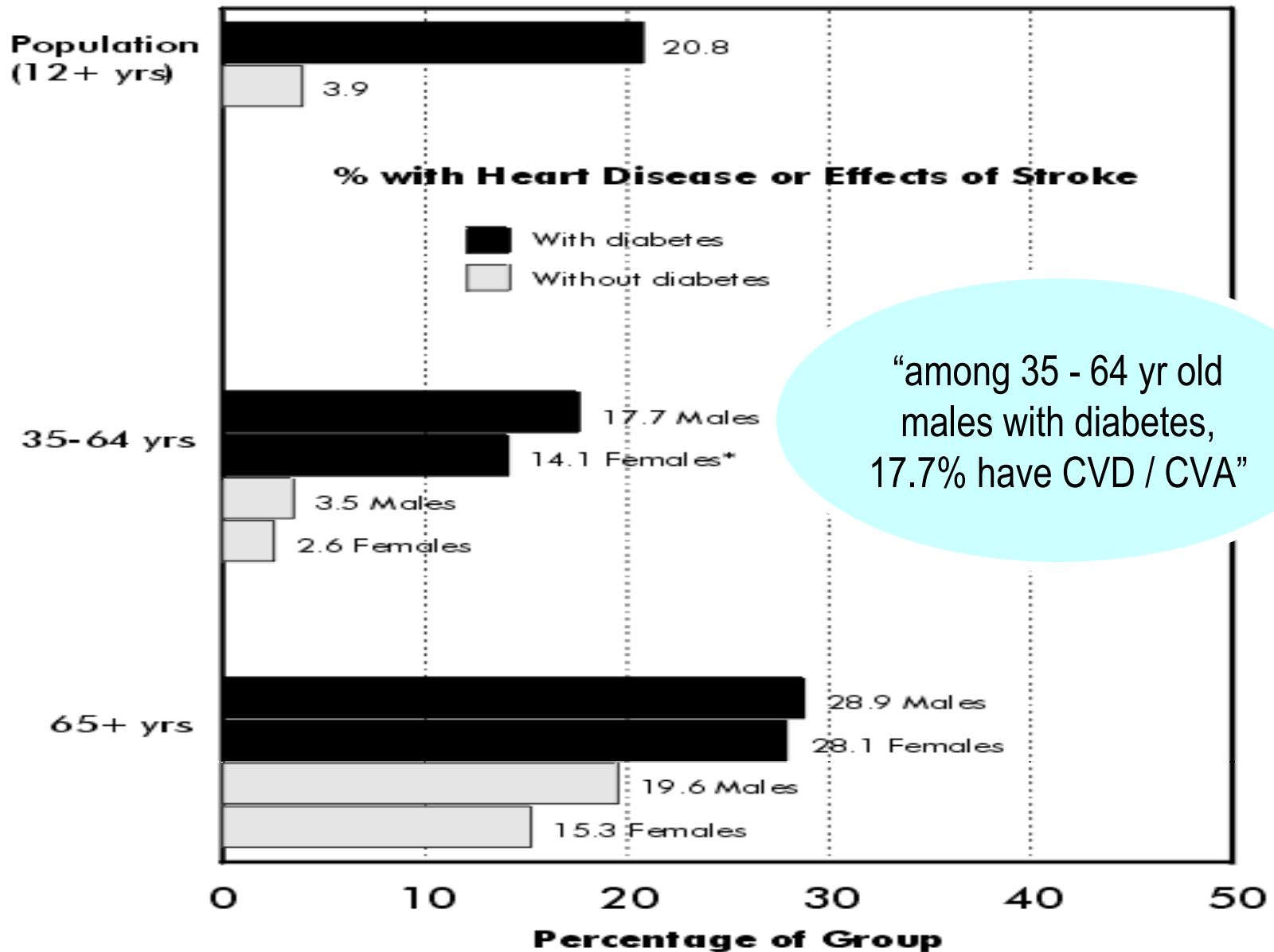
Genes + Ethnicity + Lifestyle Factors (diet, exercise)

Abdominal Obesity \Rightarrow IGT \Rightarrow T2DM

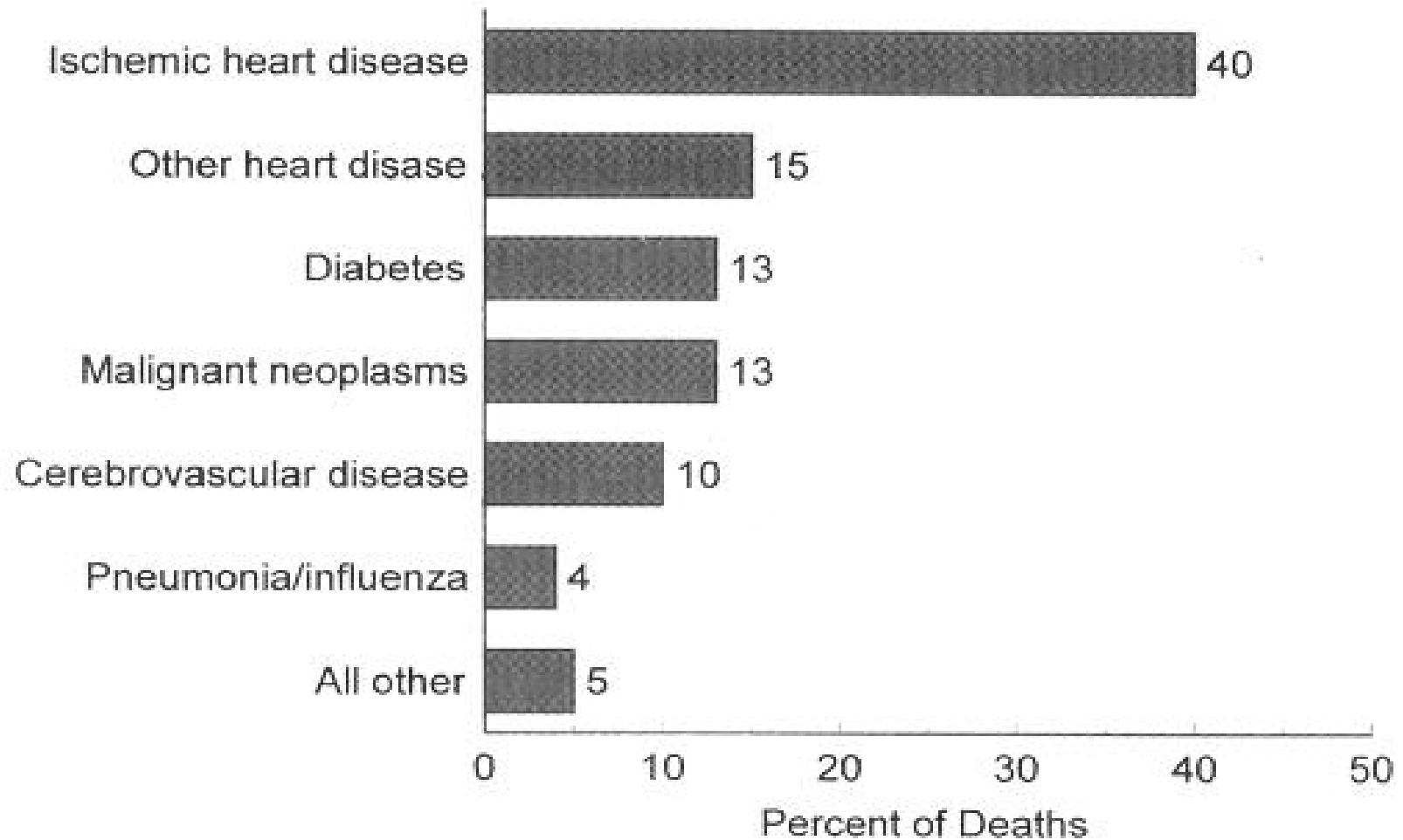
Insulin Resistance + β -Cell Failure

Metabolic Syndrome	 NEFA, Triglycerides  HDL  Small dense LDL
	 BP, PAI-1, Blood viscosity, Platelet aggregation, Uric acid, Microalbuminuria, BPH, Fatty liver
Low-grade chronic inflammation	Activated macrophages  Cytokine production (TNF α , IL-6, IL-1 β) Acute phase proteins
CV morbidity & mortality	 Endothelium function Arterial elasticity  Atherosclerosis Cardiac vulnerability
Complications	Neuropathy Nephropathy  Retinopathy NASH  Blindness, Amputations, Renal failure, Death

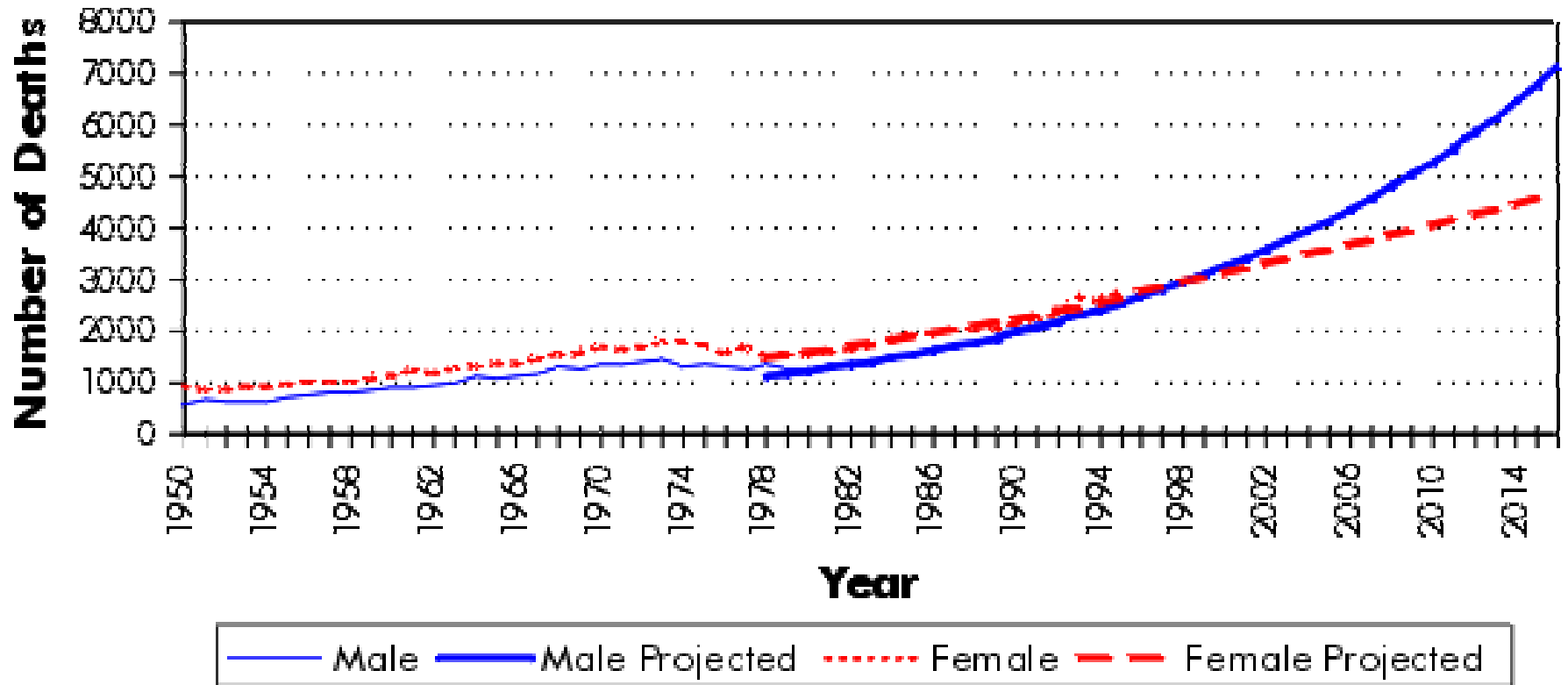
Prevalence of heart disease or stroke, by diabetes status, gender, and age group — Canada excluding Territories, 1996/97



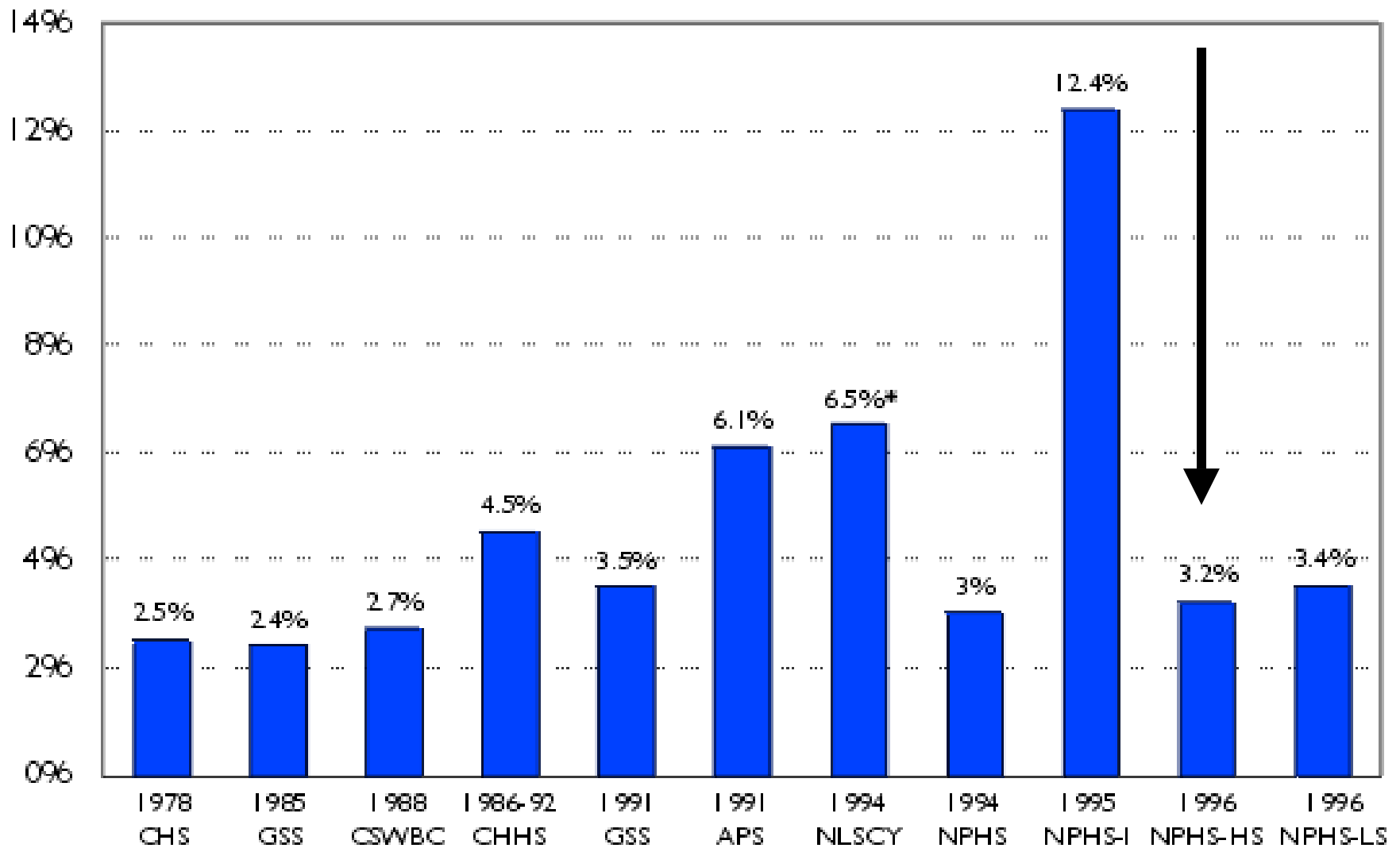
Mortality in Diabetes



Mortality Future Trends - Canada



Prevalence of Diabetes in Canada



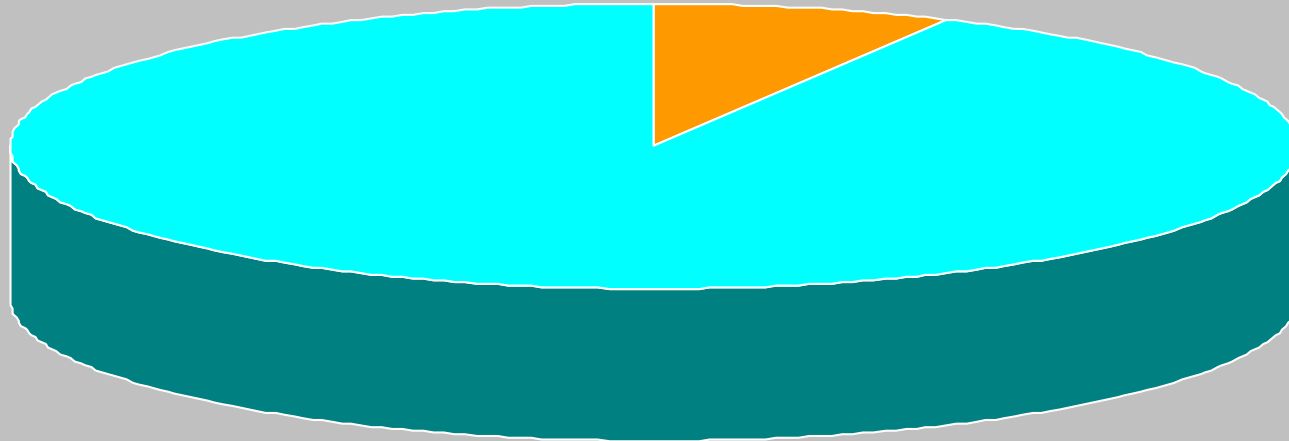
Prevalence of Diabetes in Canada

%	all	12-34	35-64	> 64
Male	3.5	0.5	3.7	12.1
Female	2.9	0.5	2.7	9.1
Both	3.2	0.5	3.2	10.4

- prevalence increases with age
- prevalence higher among males

DM: type 1 and 2

Type 1 diabetes: 5%-10% of all patients with diabetes



Type 2 diabetes: 90%-95% of all patients with diabetes

Gestational DM: Temporary, reported in 6.5% of women with children < 2 yrs

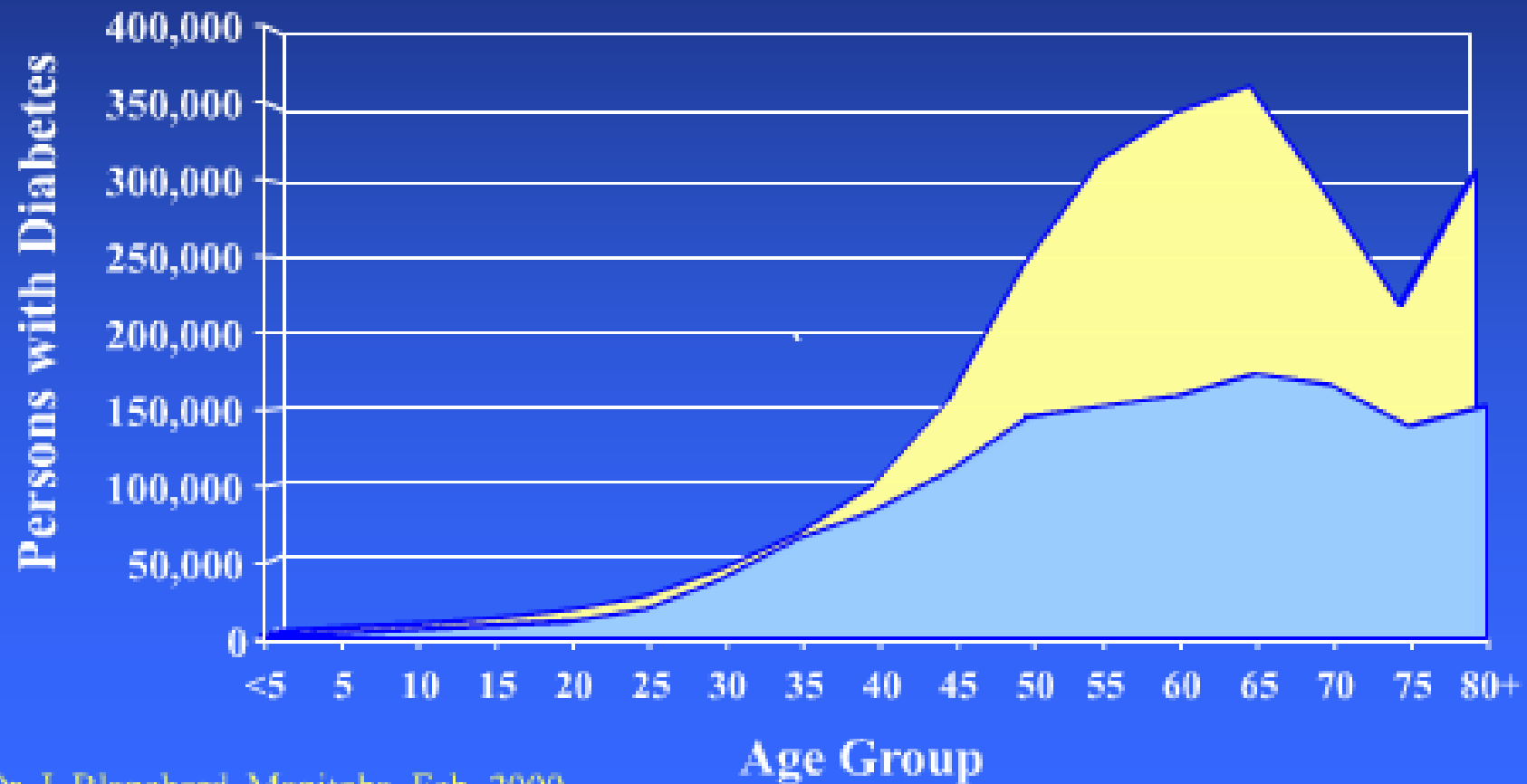
Other types: relatively uncommon, associated with other diseases, drug use

Prevalence of diabetes in Canada

**Prevalence of
diabetes is estimated
to double by 2010**

Canadians Living with Diabetes 2000 and 2016

- 2000 (n=1.4 million)
- 2016 (n=2.5 million)



DM Prevalence: First Nations Adults

First Nations Prevalence

compared to general population...

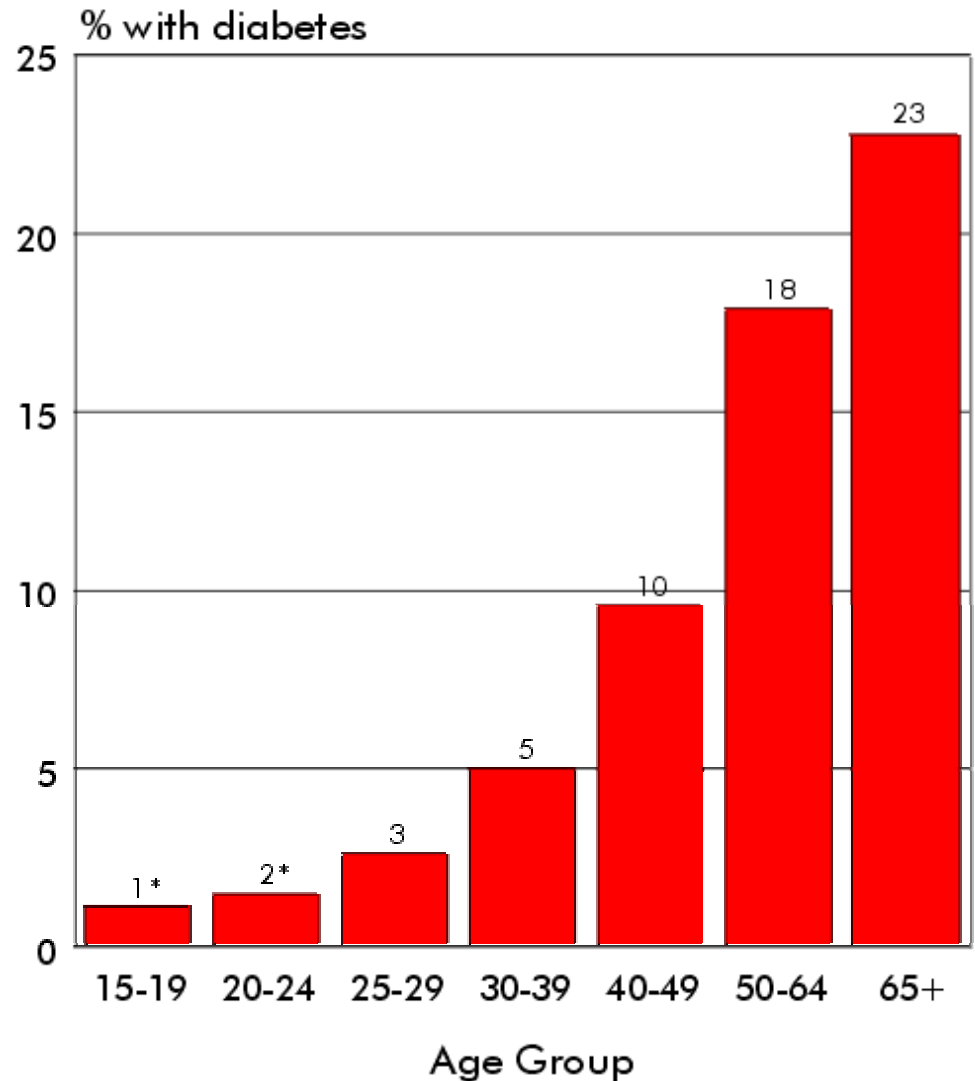
DM: 3x

HTN: 43% vs 10%

CVA: 13% vs 3%

Limb Amputation Rate: 15x

Nephropathy Rate: 12x

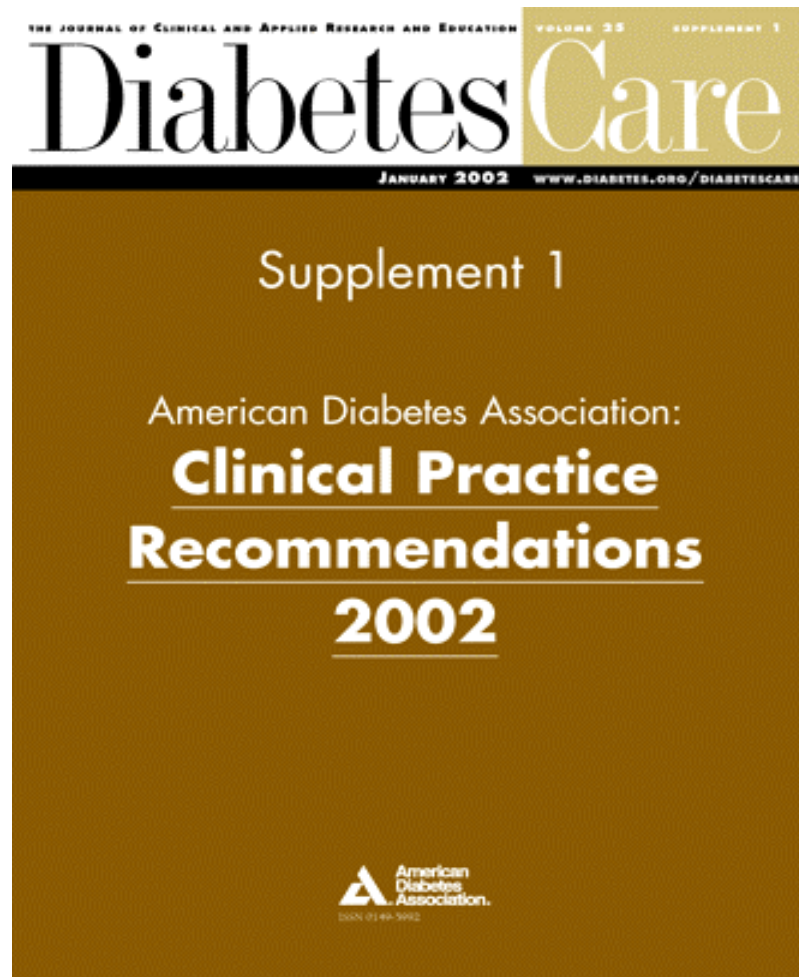


Canadian Diabetes Assn - 1998



www.diabetes.ca

American Diabetes Assn - 2002



www.diabetes.org

Screening for Type 2 DM: ADA ~ CDA

- all: ≥ 45 yr and repeat q 3 yearly if normal
- < 45 yr and/or repeat $< q 3$ yearly if:
 - BMI > 25 kg/m²
 - first-degree relative with diabetes
 - members of a high-risk ethnic population
 - delivered a baby >9 lb or with GDM
 - hypertensive
 - HDL < 0.90 mmol/l
 - triglyceride > 2.82 mmol/l
 - previous IGT or IFG

Diagnosis of diabetes mellitus: CDA = ADA

Symptoms of diabetes plus a casual plasma glucose value ≥ 11.1 mmol/l, or

An 8hr fasting plasma glucose ≥ 7.0 mmol/l, or

Plasma glucose in the 2-h sample of the 75 g OGTT ≥ 11.1 mmol/L

Confirm on another day in the absence of metabolic derangement and unequivocal hyperglycemia.

Monitoring: ADA ~ CDA

Hgb A1C

- q 3 - 4 month on insulin when stable
- q 6 months on diet or OHA when stable

Self Monitoring

- for all on insulin
- for majority on OHA
- helpful on diet only

Preventing Onset of Type 2 Diabetes

- CDA Recommendations 1998
 - weight loss with diet and exercise should be recommended among those at risk
 - no specific drug therapy is recommended

Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

- Objectives

- determine the effect of ramipril on CVD among patients at high risk for, but no history of, LV dysfunction or HF

- Methods

- randomized, 2x2 factorial design n=9297
 - > 55 yrs
 - evidence of vascular disease or diabetes plus one other cardiovascular risk factor
 - were not known to have a low ejection fraction or heart failure

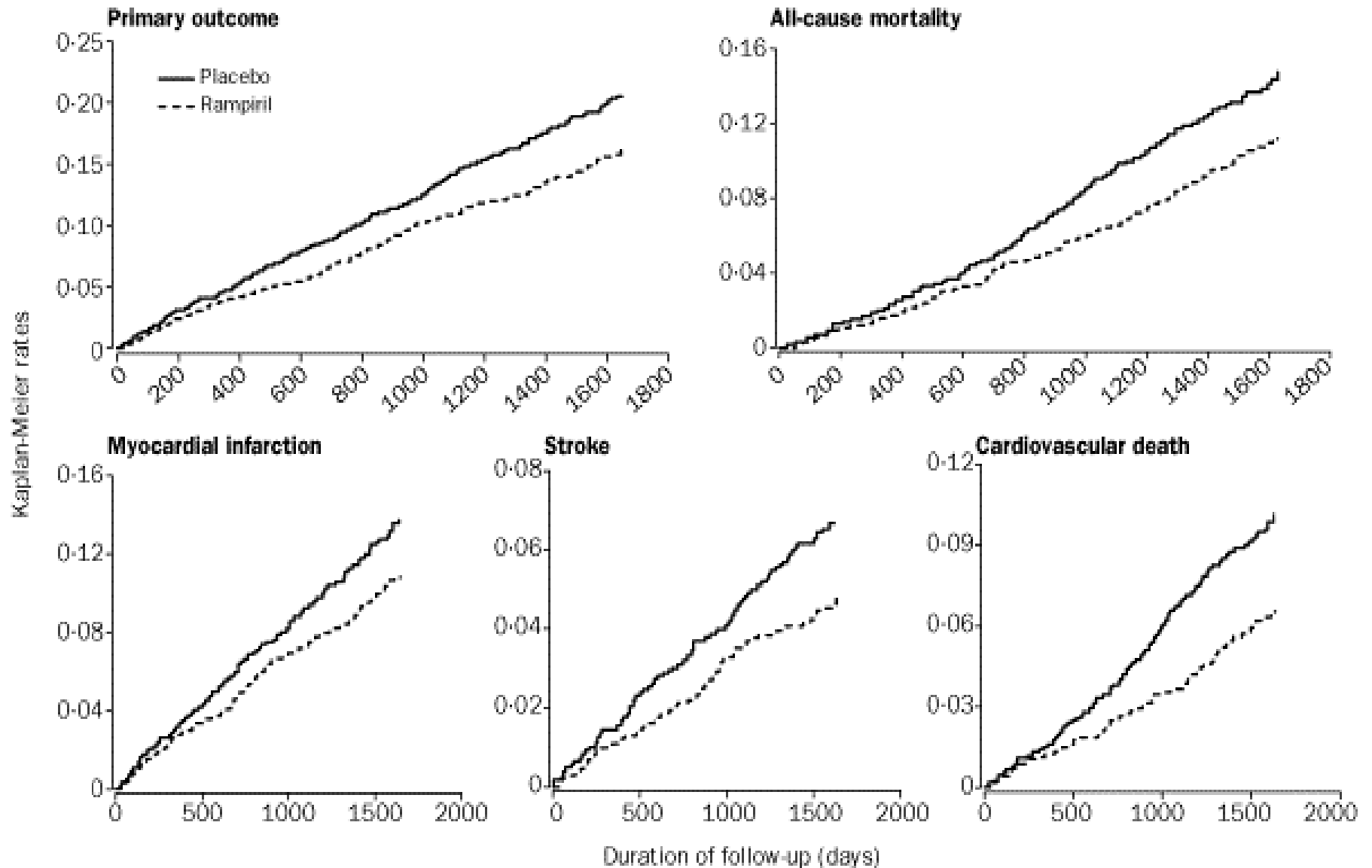
Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

- **Methods**
 - randomized ramipril 10 mg od or placebo
 - vitamin E 400 IU per day or placebo
- **Outcome**
 - composite of MI, CVA or CV death

Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59



Heart Outcomes Prevention Evaluation Trial

Lancet 2000; 355: 253-59

TABLE 4. INCIDENCE OF SECONDARY AND OTHER OUTCOMES.

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	Z STATISTIC	P VALUE†
	no. (%)				
Secondary outcomes‡					
Revascularization	742 (16.0)	852 (18.3)	0.85 (0.77–0.94)	–3.17	0.002
Hospitalization for unstable angina	554 (11.9)	565 (12.1)	0.98 (0.87–1.10)	–0.41	0.68
Complications related to diabetes§¶	299 (6.4)	354 (7.6)	0.84 (0.72–0.98)	–2.16	0.03
Hospitalization for heart failure	141 (3.0)	160 (3.4)	0.88 (0.70–1.10)	–1.16	0.25
Other outcomes					
Heart failure				1.99	<0.001

new diagnosis diabetes 102(3.6%) 155(5.4%) 0.66

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡These events were centrally adjudicated.

§All cases are included, whether or not hospitalization was required.

¶Complications related to diabetes include diabetic nephropathy (defined as urinary albumin excretion of at least 300 mg per day or urinary protein excretion of 500 mg per day), the need for renal dialysis, and the need for laser therapy for diabetic retinopathy.

||The denominator in the ramipril group is the 2837 patients who did not have diabetes at base line. The denominator in the placebo group is the 2883 patients who did not have diabetes at base line.

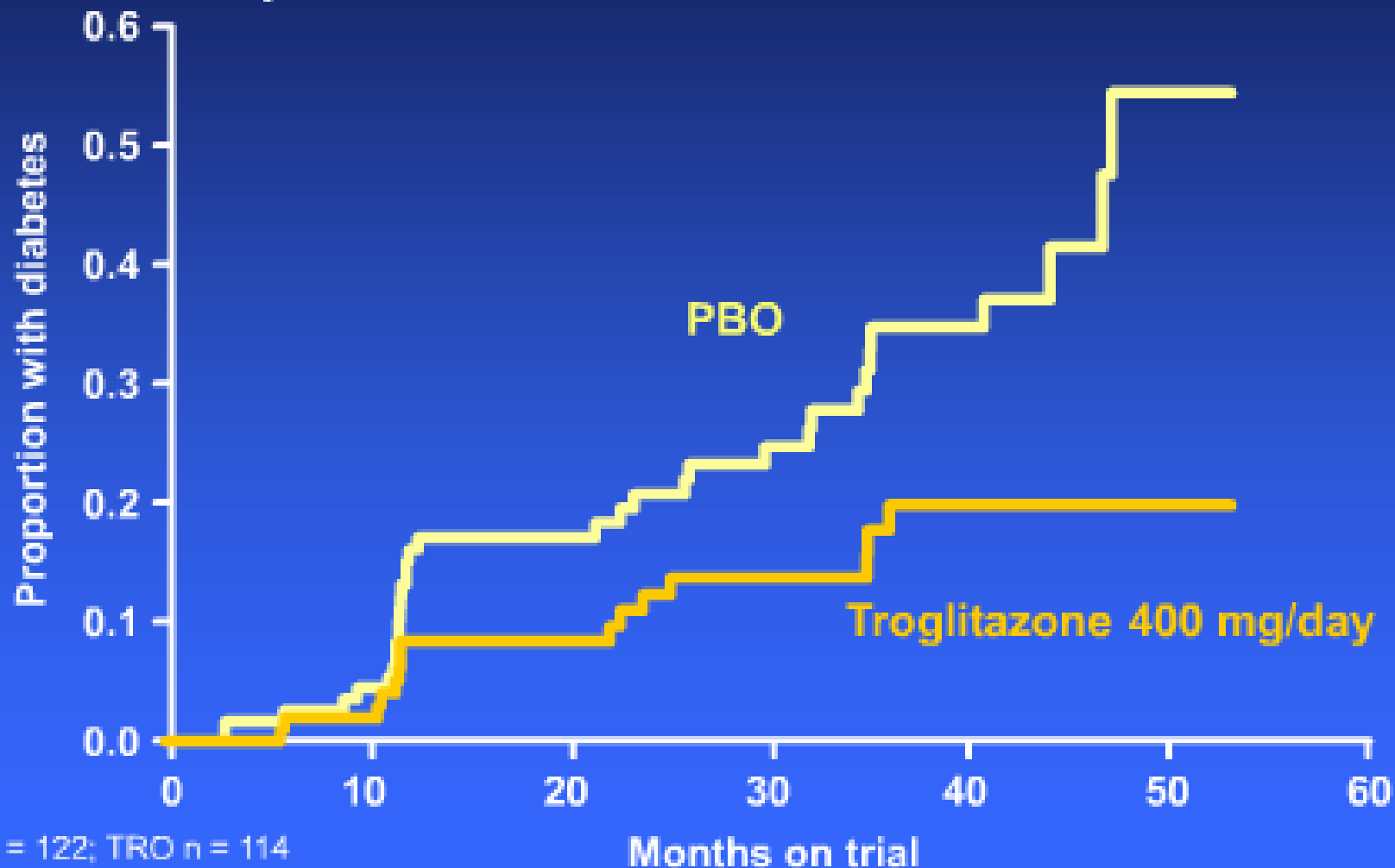
Preventing Onset of Type 2 DM

- Four-year effect of orlistat plus lifestyle changes vs placebo plus lifestyle changes

Variable	Placebo	Orlistat	p
Reduction in body weight	4.1kg	6.9 kg	<0.001
Reduction in LDL cholesterol	5.1%	12.8%	<0.001
Reduction in SBP	3.42 mmHg	4.94 mm Hg	<0.01
Reduction in DBP	1.89 mm Hg	2.58 mm Hg	<0.01
Incidence of type 2 diabetes	9.0%	6.2%	0.0032

TZDs have the potential to prevent progression to type 2 diabetes

TRIPOD Study



PBO n = 122; TRO n = 114

The rate in the troglitazone group was significantly lower than the rate in the PBO group ($P = 0.009$)

Buchanan TA, et al. *Diabetes* 2002; 51:2796–2803.

Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin

Diabetes Prevention Program Research Group

N Engl J Med 346: 393-403, 2002

(7th February)

**3234
subjects
for 2.8 yr**

Placebo: 11.0 cases / 100 person years

Metformin: 7.8 cases / 100 person years

31 % reduction

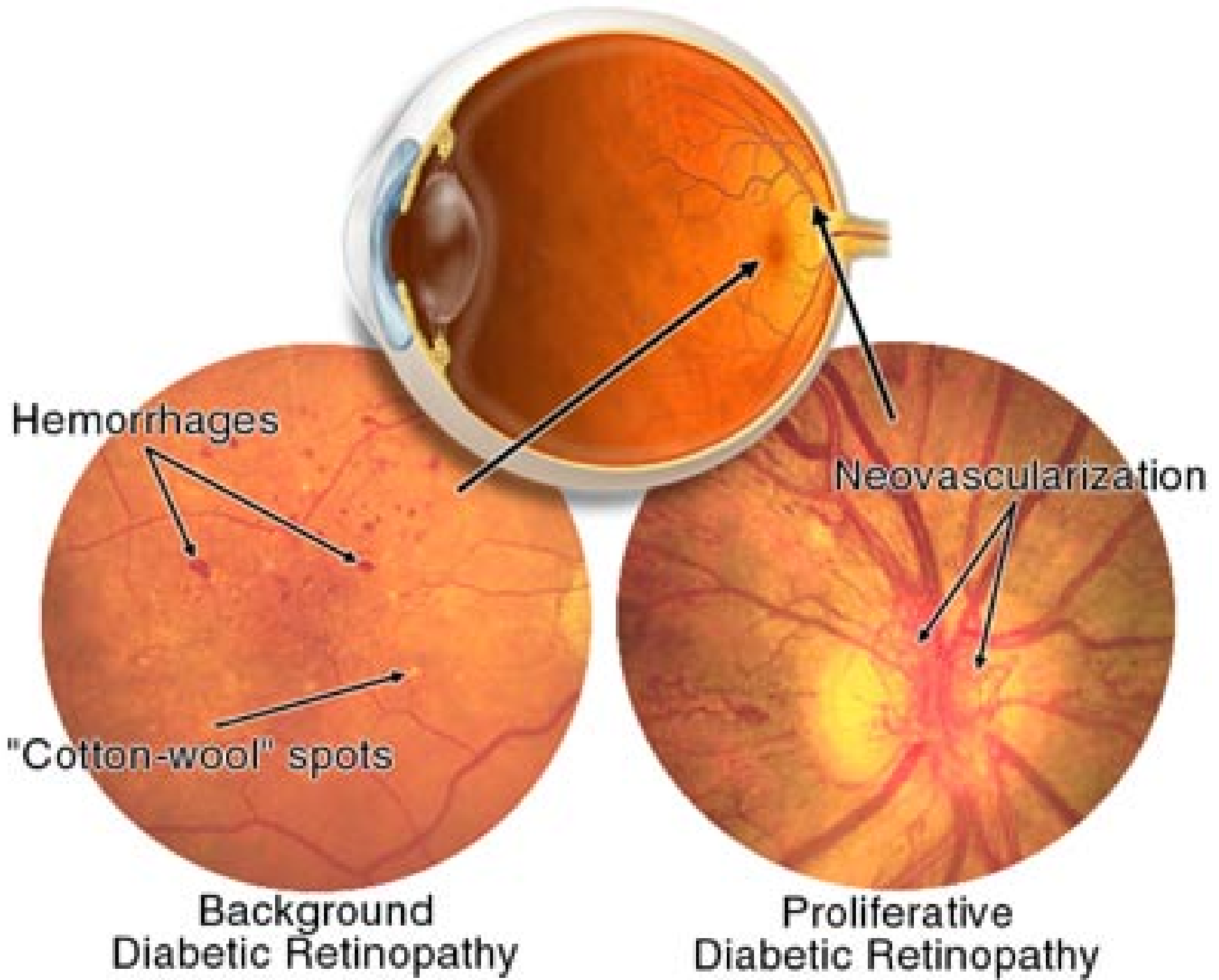
Lifestyle: 4.8 cases / 100 person years

58 % reduction

Retinopathy Screening: Type 2 DM

- First Screen at Diagnosis
 - 21% of Type 2 at diagnosis may have retinopathy
- Subsequent assessments per severity
 - 2 to 4 years if minimal / none







Normal vision



Vision with
diabetic retinopathy

Nephropathy Screening: Type 2 DM

- First Screen at Diagnosis
 - If dipstick is negative or trace....
 - albumin : creatinine on random daytime urine
 - male: > 2.0
 - female: > 2.8
 - confirm with repeat

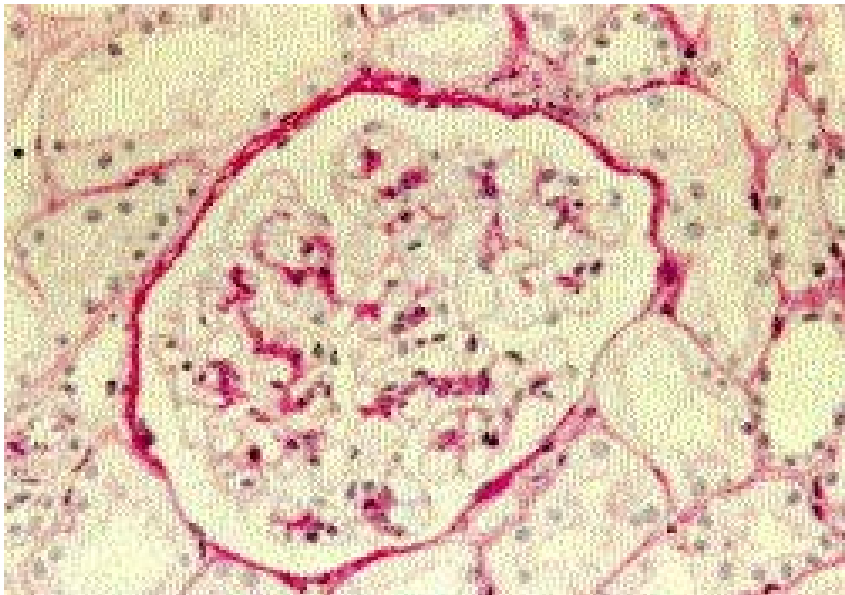
Diabetic Renal Disease

- hyperfiltration (increased GFR)
- microalbuminuria:
 - albumin 30 - 300 mg/day
- nephrotic syndrome
 - protein loss of 3,500 mg / day
 - edema
 - low albumin
 - hyperlipidemia
- renal failure

Diabetic Glomerulosclerosis



Diffuse and nodular diabetic glomerulosclerosis (PAS stain). Note diffuse increase in mesangial matrix and characteristic acellular PAS-positive nodules



Minimal change disease. Thin section of glomerulus stained with PAS. Note thin basement membrane and absence of proliferation.

HOPE: Ramipril - DM

	Ramipril	Placebo	RR	95% CI	P
Microvascular					
Nephropathy	6.5	8.4	0.76	0.60-0.97	0.027
Laser Rx	9.4	10.5	0.88	0.72-1.09	0.24
Dialysis	0.5	0.5	1.2	0.47-3.05	0.70
Any of above	15.1	17.6	0.84	0.71-0.99	0.036
TIAs	4.4	5.9	0.74	0.55-0.99	0.04
Worse Angina	20.1	22.4	0.87	0.76-1.00	0.057

Neuropathy Screening: Type 2 DM

- First Screen at Diagnosis
- Annually thereafter to assess for ulcer risk
 - examine foot
 - 128 Hz tuning fork
 - 10 gram monofilament at great toe

Lipid Screening: Type 2 DM

- First Screen at Diagnosis
- q 1 to 3 years thereafter

Reducing Risk - Lipid Control

- “Patients over the age of 30 who have diabetes are now classified as being at "very high risk" for CAD (CAD risk equivalent).

Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias *CMAJ* 2000;162(10):1441-7

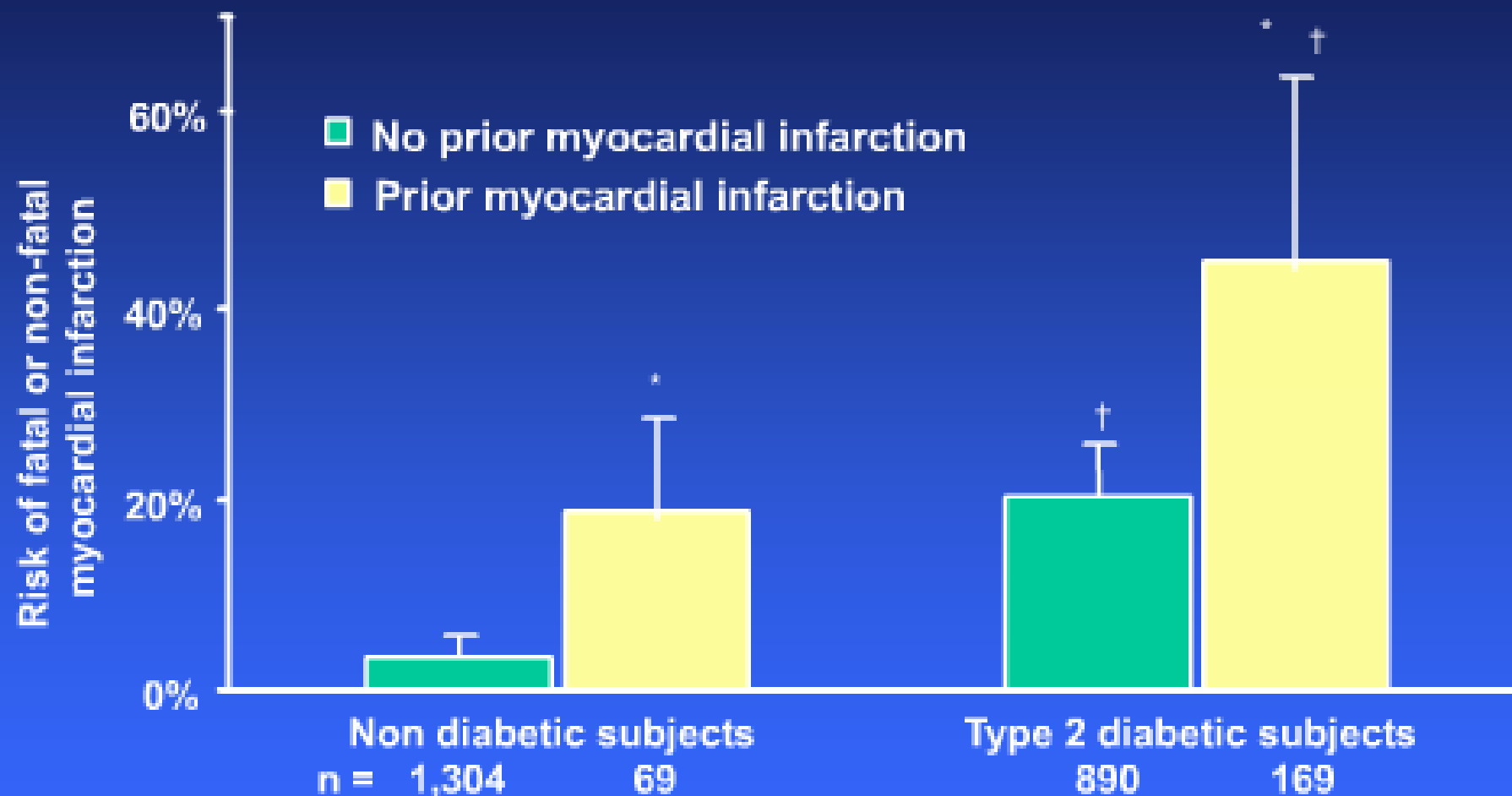
Reducing Risk - Lipid Control

Table 2: Risk categories and target lipid levels

Risk category	Target level	
	LDL-C level, mmol/L	Total cholesterol: HDL-C ratio
High* (10-year risk of coronary artery disease \geq 20%, or history of diabetes mellitus† or any atherosclerotic disease)	< 2.5 <i>and</i>	< 4.0
Moderate (10-year risk 11%–19%)	< 3.5 <i>and</i>	< 5.0
Low‡ (10-year risk \leq 10%)	< 4.5 <i>and</i>	< 6.0

Canadian Working Group Guidelines for the management of dyslipidemia - CMAJ 2003

Risk of myocardial infarction is increased in type 2 diabetes



Seven-year incidence in a Finnish-based cohort

* $P < 0.001$ vs no prior MI

† $P < 0.001$ vs no diabetes

Adapted from Haffner SM. *New Engl J Med* 1998; 339:229-234.

Threshold for Initiation of Treatment and Target Values (Can HTN Society)

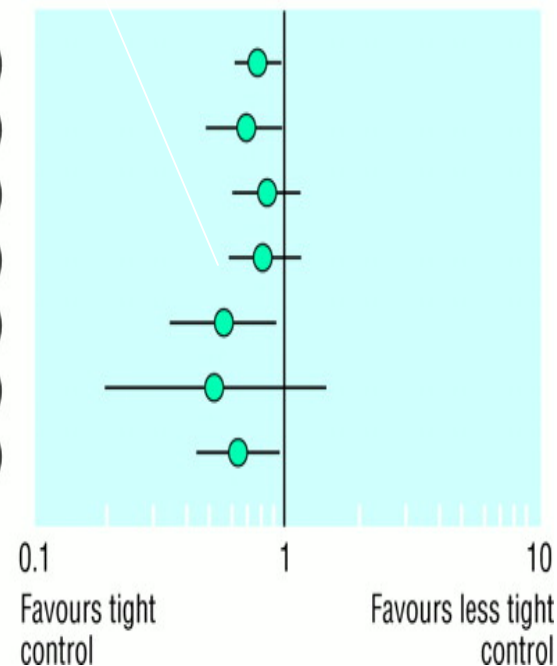
Condition	Initiation	Target
	SBP / DBP mmHg	SBP / DBP mmHg
Diastolic \pm systolic hypertension	$\geq 140/90$	$<140/90$
Isolated systolic hypertension	SBP >160	<140
Home BP measurement (no diabetes, renal disease or proteinuria)	$\geq 135/85$	$<135/85$
Diabetes	$\geq 130/80$	$<130/80$
Renal disease	$\geq 130/80$	$<130/80$
Proteinuria >1 g/day	$\geq 125/75$	$<125/75$

Reducing Risk - BP Control

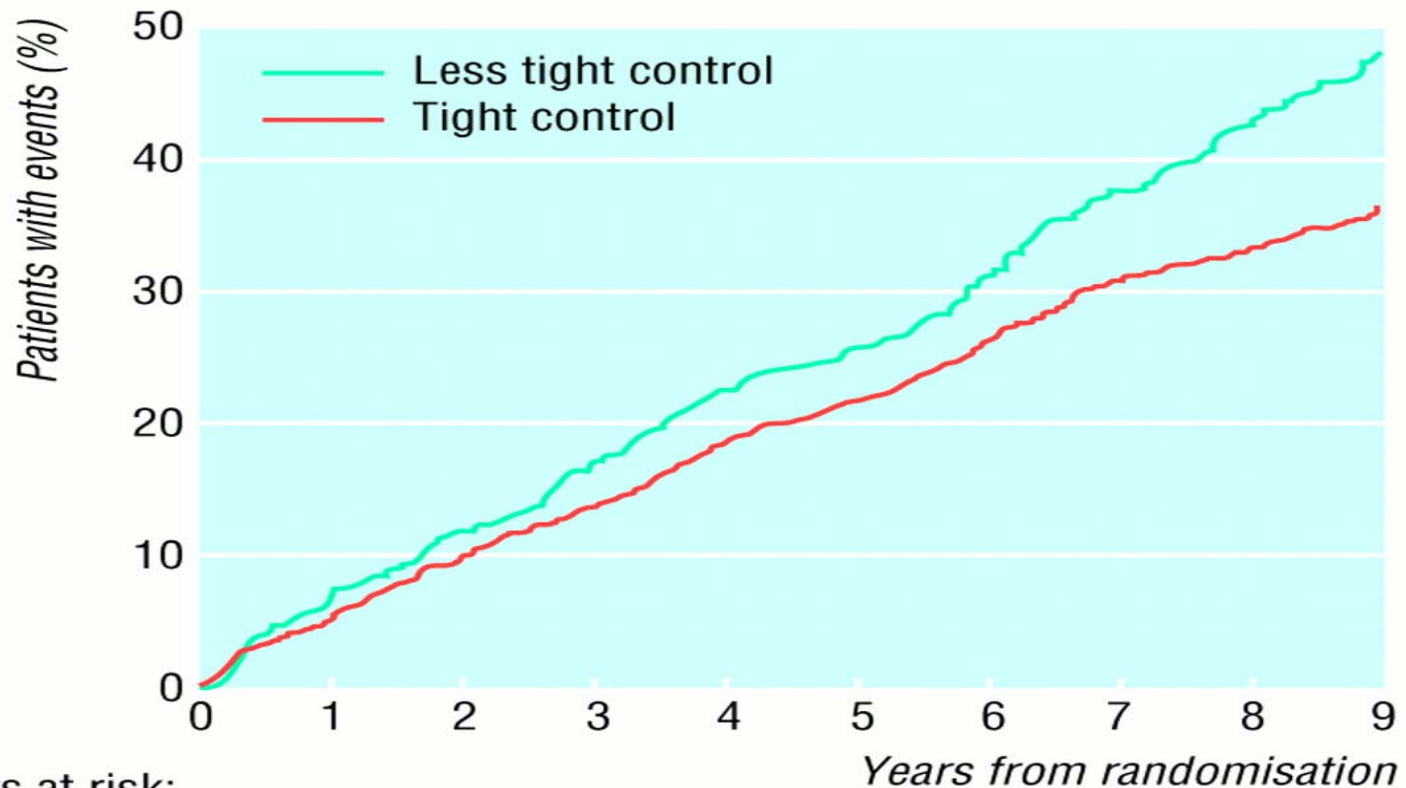
- UK Prospective Diabetes Study
 - aggressive treatment of even mild-to-moderate hypertension is beneficial
 - continued reduction of blood pressure into the normal range resulted in fewer complications
 - BP should be kept below 130/85 mmHg

Reducing Risk - BP Control

Clinical end point	Patients with aggregate end points		Absolute risk (events per 1000 patient years)		P value	Relative risk for tight control (95% CI)
	Tight control	Less tight control	Tight control	Less tight control		
	(n=758)	(n=390)	control	control		
Any diabetes related end point	259	170	50.9	67.4	0.0046	0.76 (0.62 to 0.92)
Deaths related to diabetes	82	62	13.7	20.3	0.019	0.68 (0.49 to 0.94)
All cause mortality	134	83	22.4	27.2	0.17	0.82 (0.63 to 1.08)
Myocardial infarction	107	69	18.6	23.5	0.13	0.79 (0.59 to 1.07)
Stroke	38	34	6.5	11.6	0.013	0.56 (0.35 to 0.89)
Peripheral vascular disease	8	8	1.4	2.7	0.17	0.51 (0.19 to 1.37)
Microvascular disease	68	54	12.0	19.2	0.0092	0.63 (0.44 to 0.89)



Reducing Risk - BP Control



No of patients at risk:

Less tight control	390	321	247	106
Tight control	758	640	494	235

Reduction in risk with tight control 24% (95% CI 8% to 38%)(P = 0.0046)

Tight: <150/85 mmHg

Less Tight: <180/105 mmHg

Diabetic Management: Glycemia

	ideal	optimal	suboptimal	inadequate
HbA1C%	4 - 6	< 7.0	7.0 - 8.4	> 8.4 %
fasting or pre-meal	3.8 - 6.1	4 - 7	7.1 - 10	>10 mmol
1 - 2 hour post-meal	4.4 - 7.0	5.0 - 11	11.1 - 14	>14 mmol

Stepped Approach to Type 2 DM

advance
q 2 - 4 months
if target not met

Insulin 1-4/day

qhs Insulin +/- Oral Agents

Oral Combination Therapy

Oral Agent Monotherapy

Non-pharmacological Therapy

Non-pharmacological Therapy

Lifestyle Modifications

nutrition / exercise / no smoking

Education

self-care / monitoring

Oral Agent Monotherapy (post CDA)

Sulfonylureas

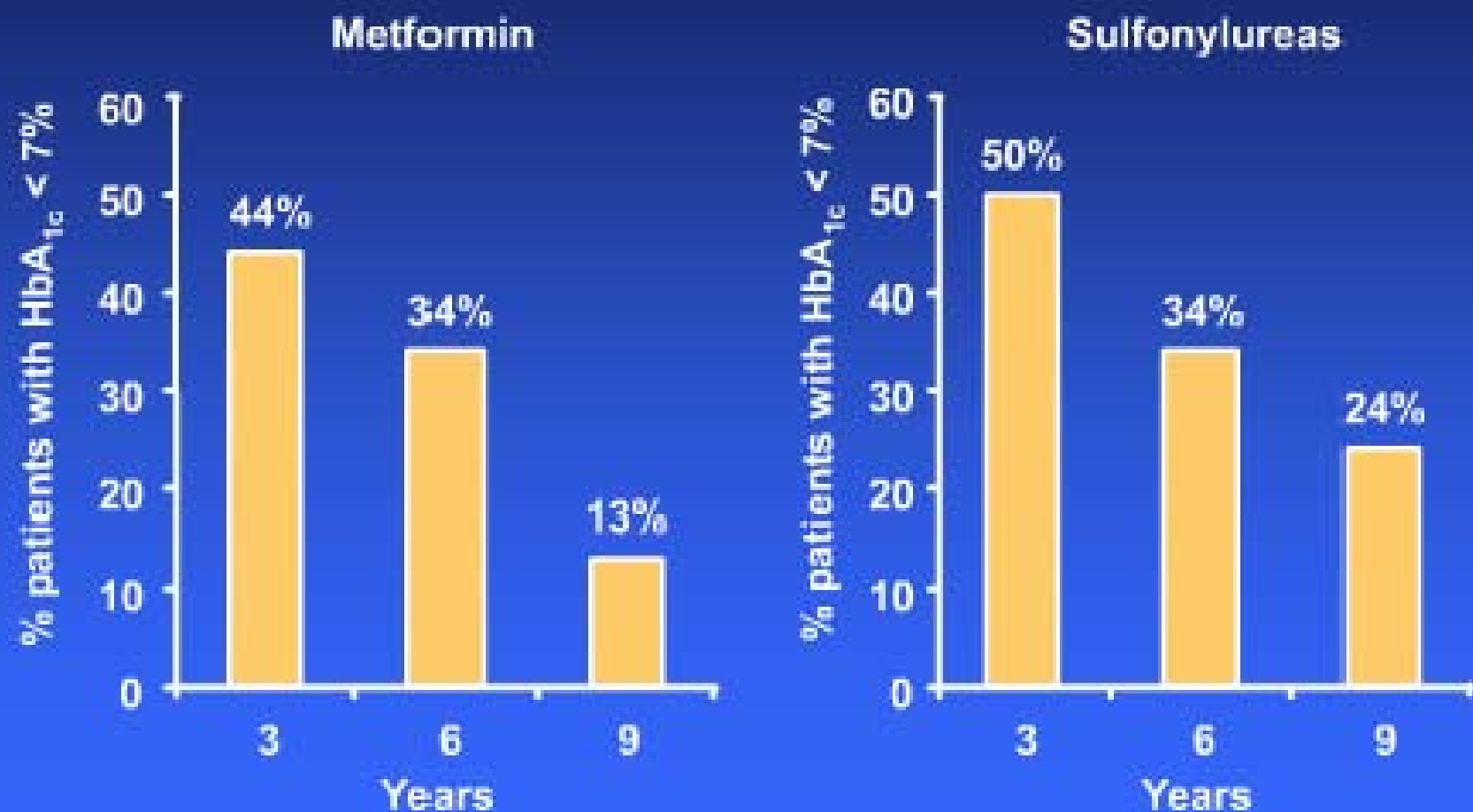
α -glucosidase
inhibitors

Meglitinides

Thiazolidine-
diones

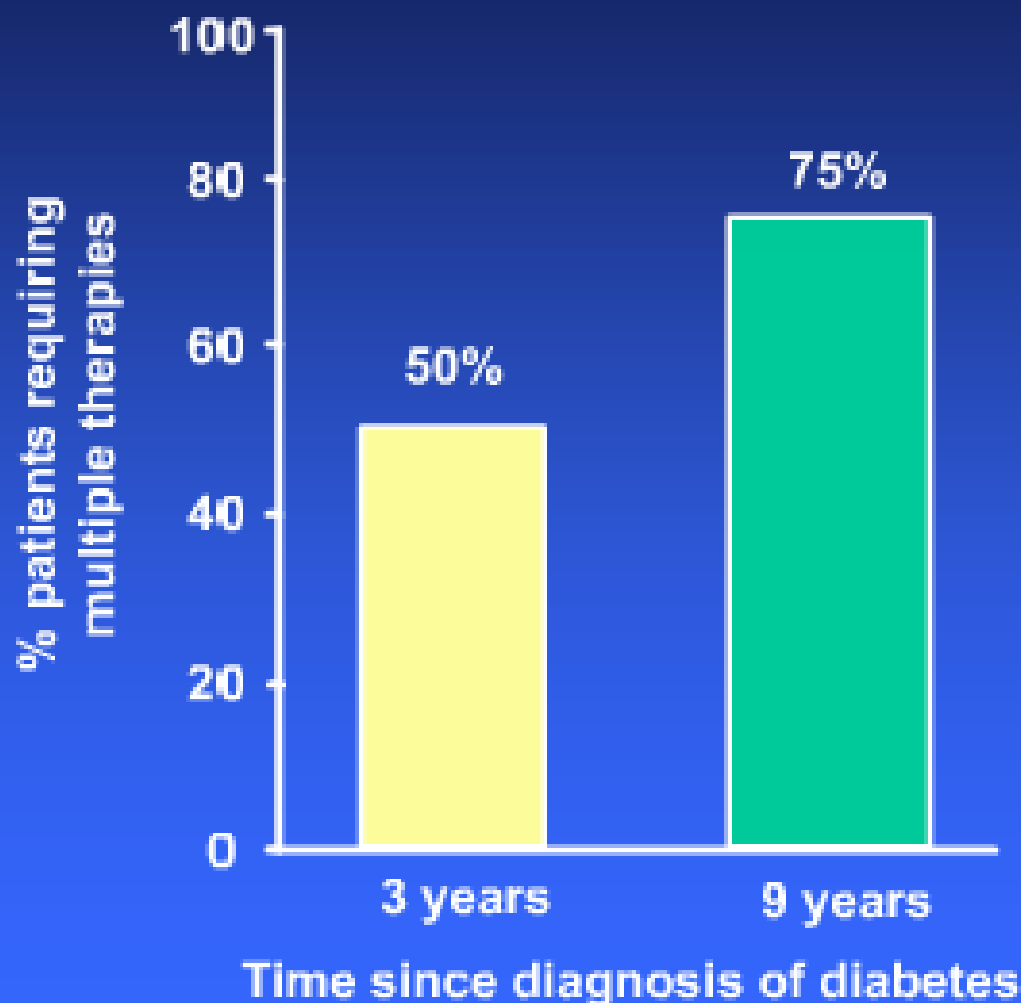
Biguanides

UKPDS demonstrated that glycemic control declines over time with metformin or sulfonylureas



Adapted from Turner RC, et al. *JAMA* 1999; 281:2005-2012.

Loss of glycemic control leads to the need for combination therapy



Adapted from Turner RC, *et al.* *JAMA* 1999; 281:2005–2012.

Oral Combination Therapies (post CDA)

Sulfonylureas



α -glucosidase inhibitors

Sulfonylureas



Biguanides

Sulfonylureas



Thiazolidinediones

Oral Combination Therapies (post CDA)

Biguinide



Meglitinide

Biguinide



Thiazolidine-
diones

Biguinide



α -glucosidase
inhibitors

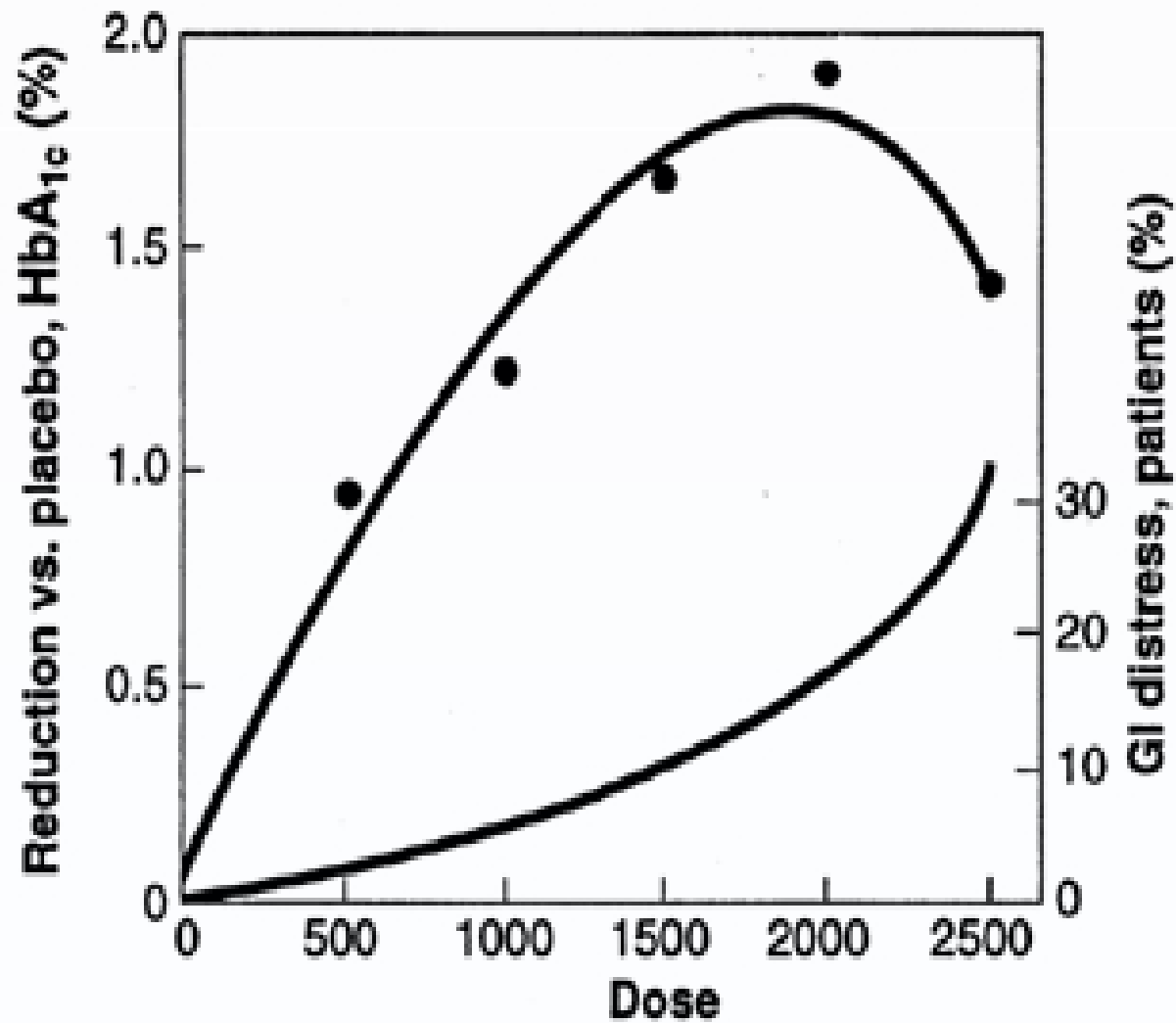
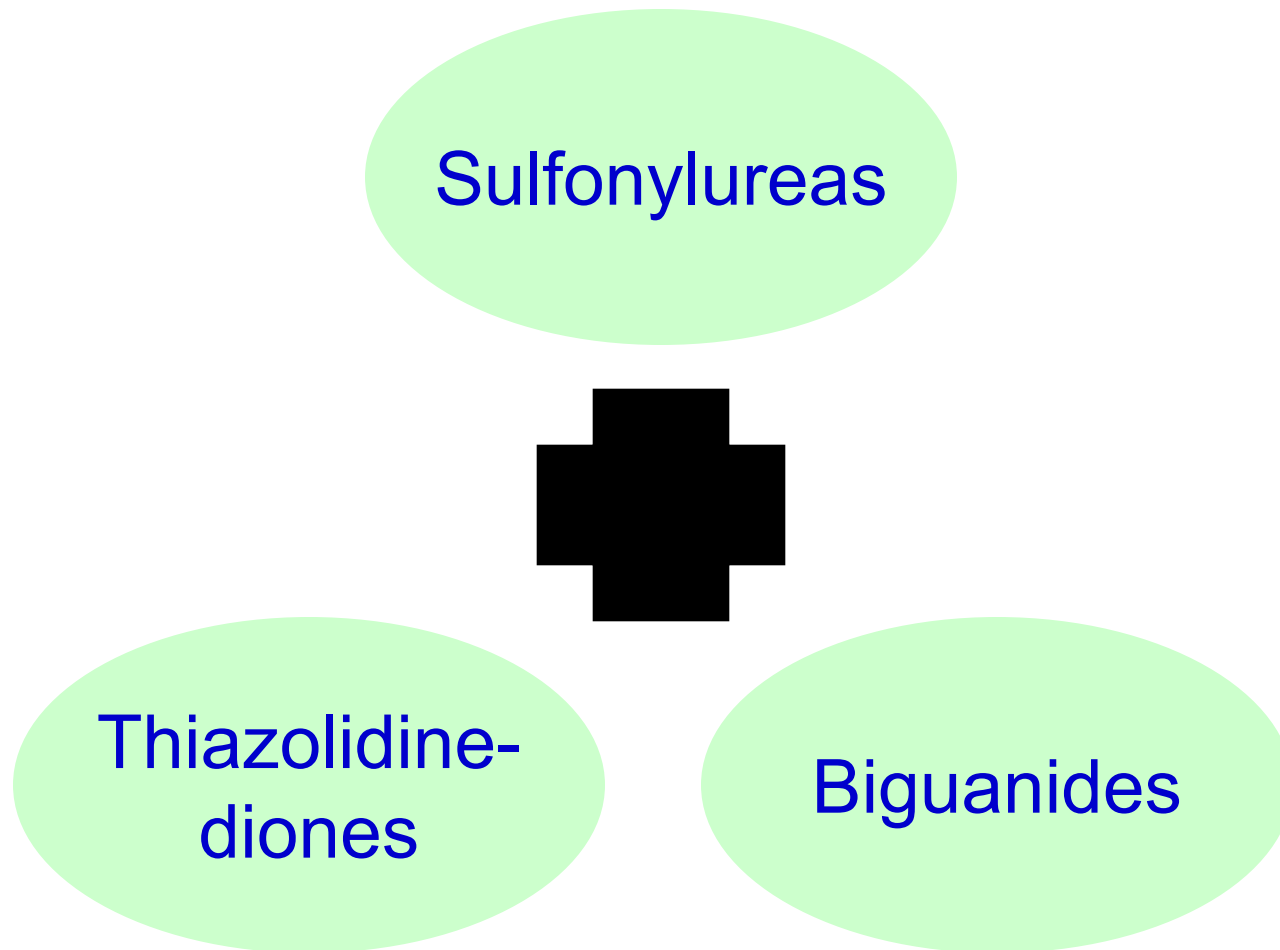
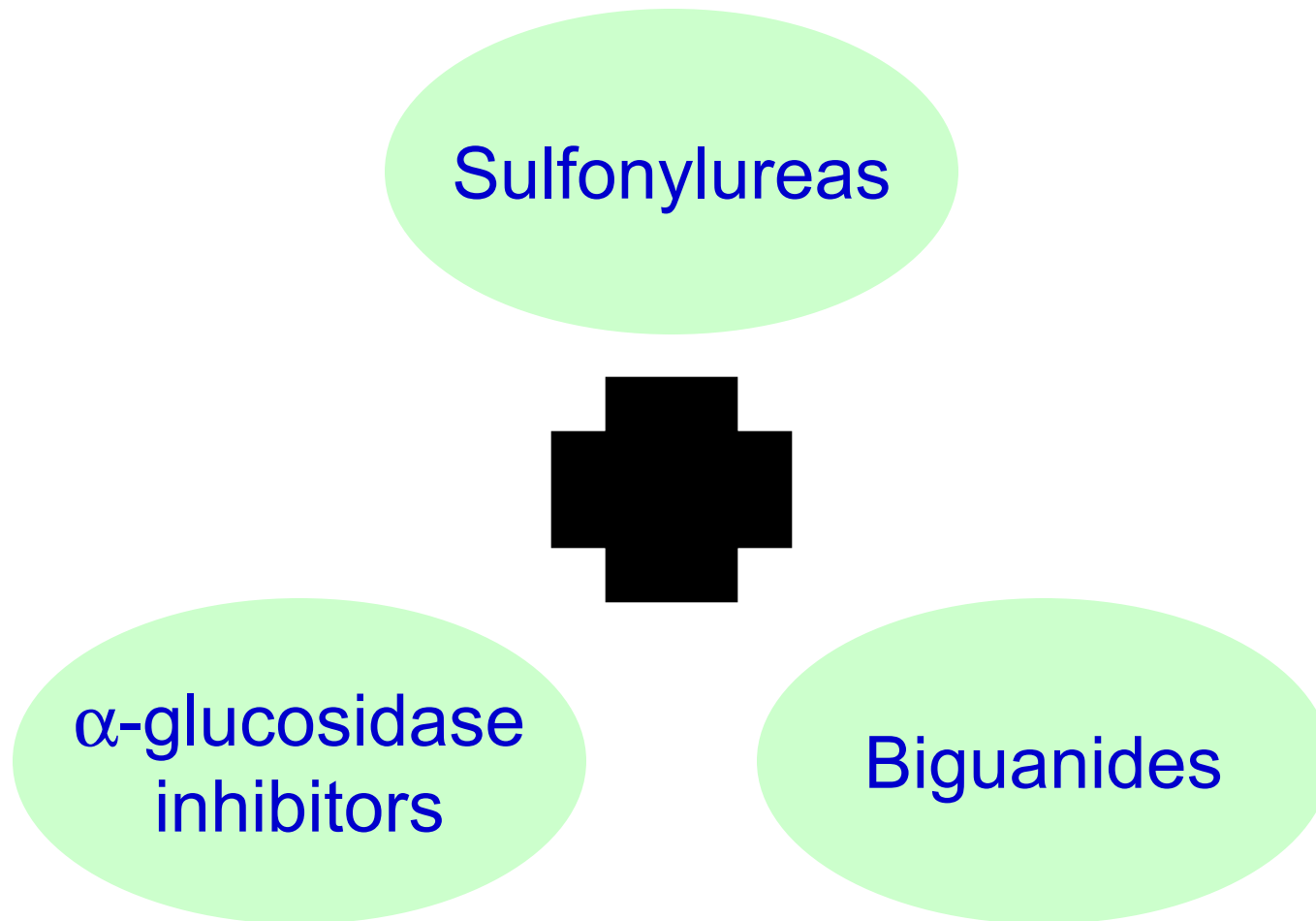


Figure 4. Metformin dose-response curve, showing the sharp decline in the drug's ability to reduce hemoglobin A_{1c} (HbA_{1c}) levels as the dose is raised above approximately 2,000 mg. Note also the steeper increase in gastrointestinal (GI) side effects at the higher doses. (Adapted with permission from *Am J Med.*²³)

Oral Combination Therapies (post CDA)



Oral Combination Therapies (post CDA)



qhs Insulin +/- Oral Agents

Intermediate Acting Insulin
as add-on to OHA regimen

1 - 4 Insulin Injections / day

Insulin Therapy Alone

or

Insulin + metformin

or

Insulin + thiozolidinedione

or

Insulin + acarbose

or

Insulin + glimipiride

New Diabetic Medications

- **Thiazolidinediones**
 - Rosiglitazone (Avandia)
 - Piaglitazone (Actos)
- Meglitinides
 - Repaglinide (Gluconorm)
 - Nateglinide (Starlix)
- Sulfonylurea
 - glimepiride (Amaryl)

Thiozolidinediones

actos[®]
pioglitazone HCl

Avandia[®]
rosiglitazone maleate

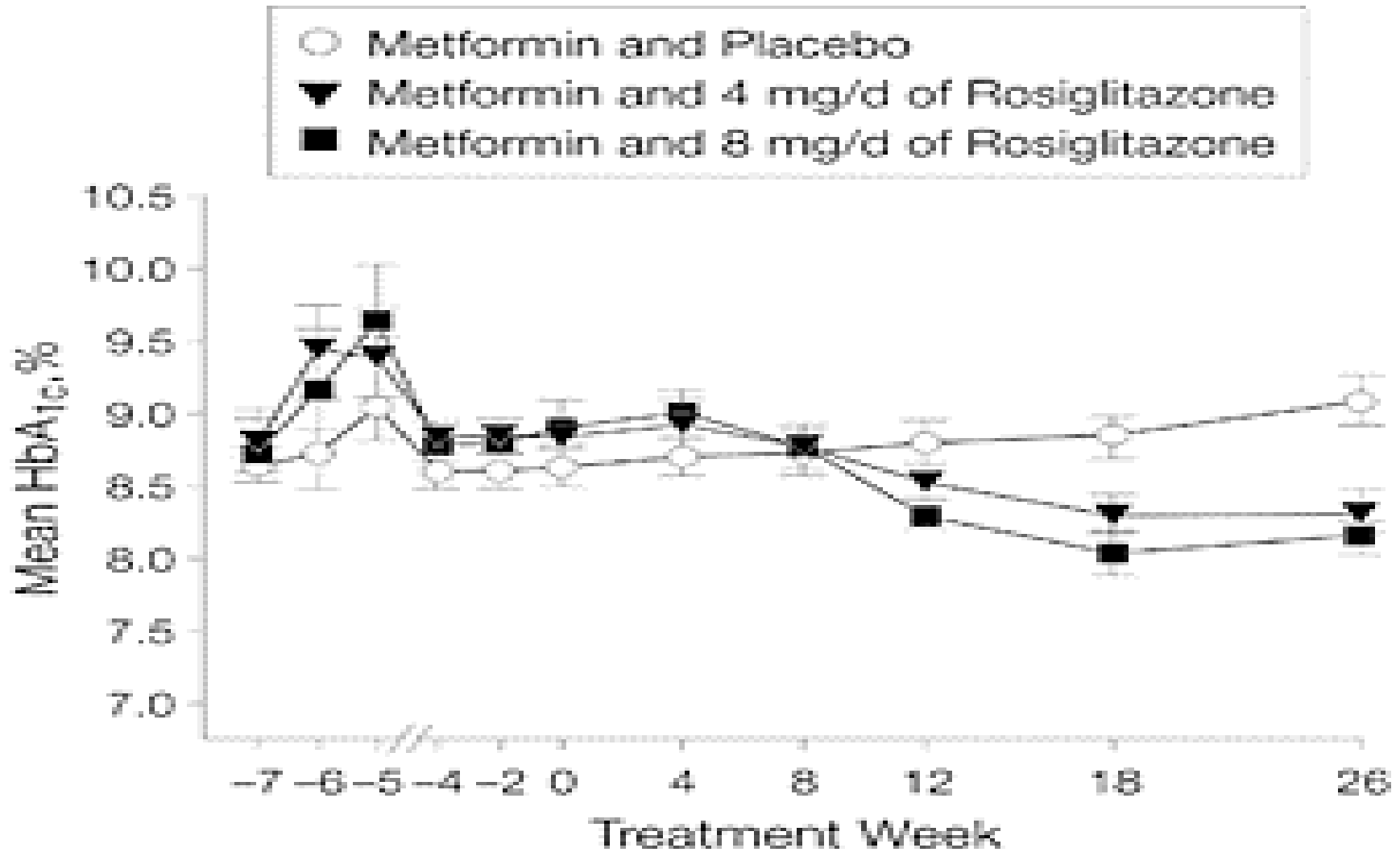
Thiozolidinediones

- Mechanism of Action
 - potent / highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR γ)
 - PPAR receptors
 - found in adipose tissue, skeletal muscle, and liver
 - activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism

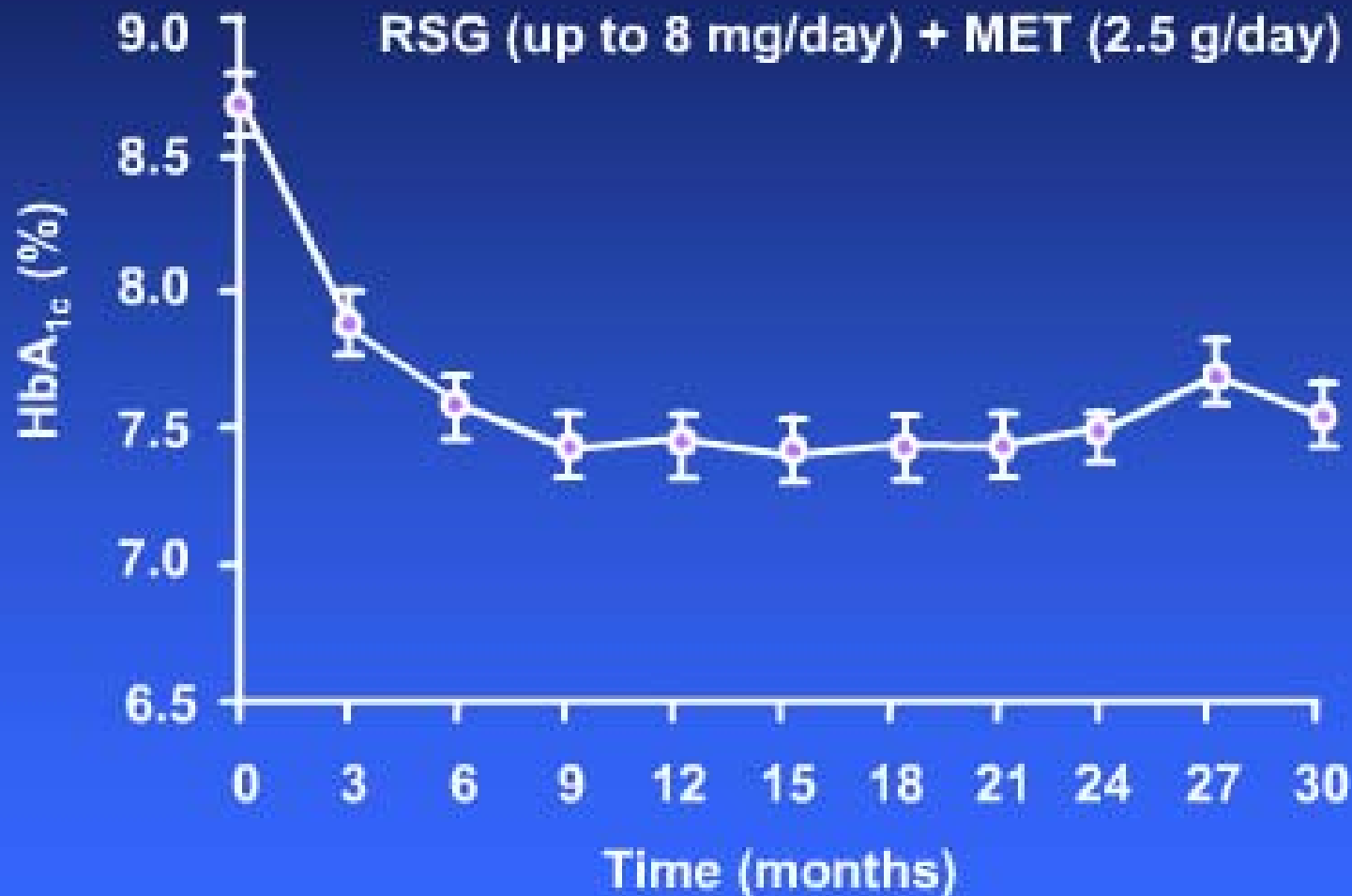
Thiazolidinediones - Summary

- Mechanism of Action
 - enhance insulin sensitivity in muscle & adipose
 - inhibiting hepatic glucose production
 - improves insulin resistance
 - no effect on insulin secretion
 - no hypoglycemia if monotherapy
- Efficacy
 - reduces Hgb A1C 0.5 - 1.5%
 - expect ~ 2 weeks to start, max effect 6 - 8 weeks

Significant Benefit



Rosiglitazone added to metformin: long-term effect on HbA_{1c}

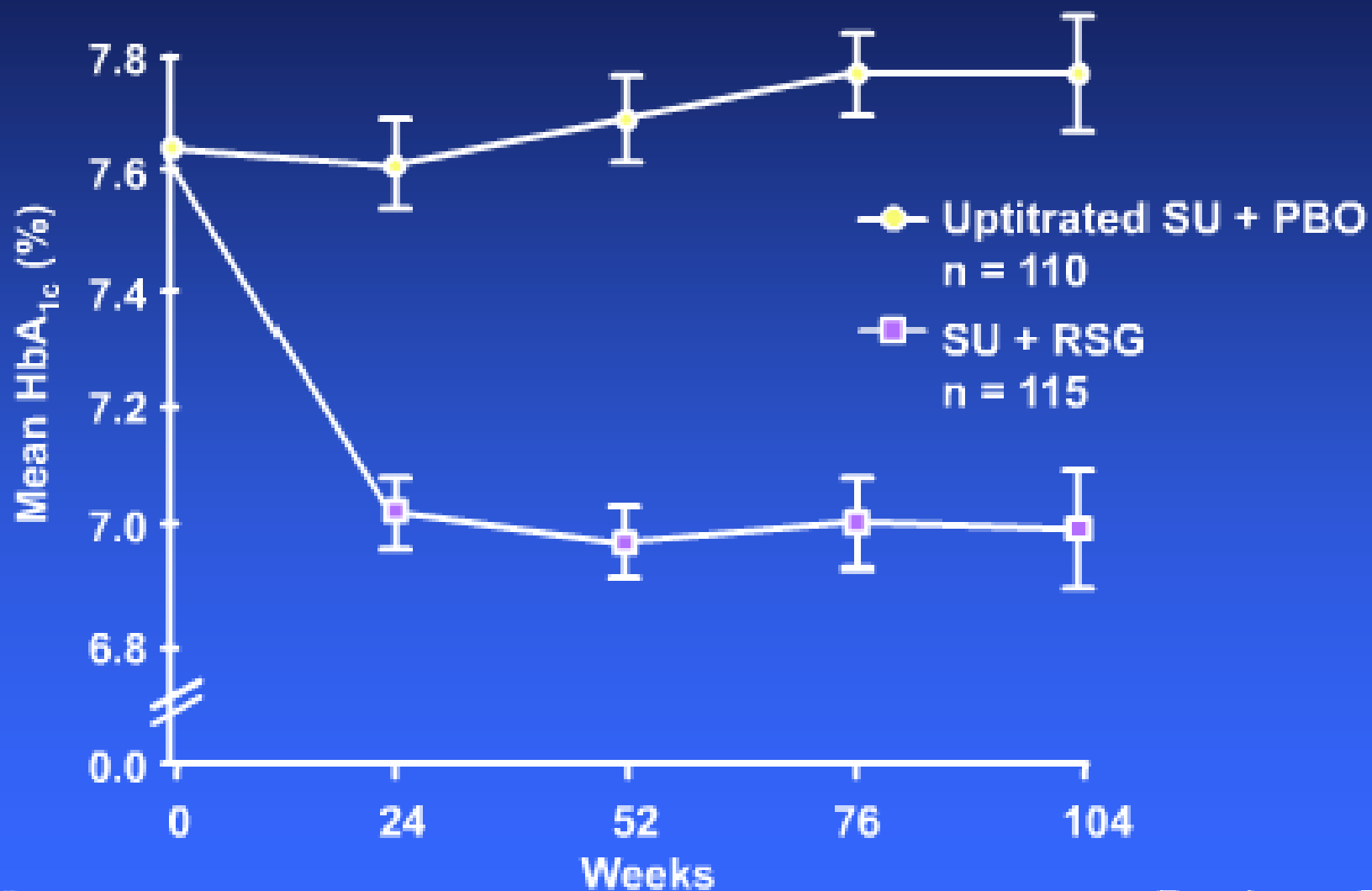


Open-label extension;
30-month completer population (n = 222)

Error bars = SEM

Adapted from Jariwala S, et al. *Diabetes UK* 2003. Abstract/Poster 277.

Rosiglitazone added to SU compared with uptitration of SU over 2 years (RESULT study) – glycemic control



ITT population
On therapy values

Error bars = SE

Rosenstock J, et al. *Diabetes Metab*2003; 29:4S247–4S248. Poster 2278: presented at IDF.

Thiazolidinediones - Summary

- Safety
 - safe in patients with impaired renal function
 - caution in patients with hepatic dysfunction
 - fluid retention
 - reduces plasma OCP levels (birth control)
- Cautions
 - not for those with liver enzymes > 2.5 ULN
 - not for Class 3 or 4 Heart Failure
 - not for Type 1 DM

Thiozolidinediones

Supplied / Doses

Avandia[®]
rosiglitazone maleate

4, 8 mg tablets

4 to 8 mg po od (4 mg po bid)

actos[®]
pioglitazone HCl

15, 30, 45 mg tablets

15 - 45 mg po od

Thiozolidinediones

- monotherapy
- with metformin
- with sulfonylurea
- with insulin
- with acarbose

- ** variable approval from FDA

Thiozolidinediones

- Adverse Effects
 - liver
 - edema
 - anemia (1%)

Rosiglitazone and Liver Dysfunction

- Conclusion:
 - No evidence of hepatotoxic effects was observed in patients taking rosiglitazone as monotherapy or combination therapy for 5,508 person-years.
- Methods:
 - meta-analysis of 22 trials
 - 30-80 yrs
 - DM2

Rosiglitazone and Liver Dysfunction

- Results:

- at baseline 5.6% had ALT 1.0 - 2.5 X ULN

- on therapy 83% had improvement of ALT

- ALT > 3X ULN

- rosiglitazone-treated 0.32%
- placebo-treated 0.17%
- sulfonylurea, metformin, or insulin-treated 0.40%.

- No cases of liver failure

- Lebovitz HE - Diabetes Care - 01-May-2002; 25(5): 815-21

Pioglitazone vs Rosiglitazone

- Methods:
 - 186 on troglitzone were randomized to either PIO or ROSI after 2 week washout.
- Results:
 - baseline same, 4 months later....
 - no change in HbA(1c)
 - both groups gained 2.0 kg
 - significant improvements (-20 mg/dl (total) in lipid profile noted in PIO group ($P < 0.01$), none were detected with conversion to ROSI

Pioglitazone vs Rosiglitazone

- Conclusion:
 - Differing effects on lipid profile were apparent after random conversion from TROGLITAZONE to either PIOGLITAZONE or ROSIGLITAZONE, despite similar weight increase and glycemic control. The clinical significance of these differences remains to be determined, and further comparative research is warranted.

- Khan MA - Diabetes Care - 01-Apr-2002; 25(4): 708-11

New Diabetic Medications

- Thiazolidinediones
 - Rosiglitazone (Avandia)
 - Piaglitazone (Actos)
- **Meglitinides**
 - Repaglinide (Gluconorm)
 - Nateglinide (Starlix)
- Sulfonylurea
 - glimepiride (Amaryl)

Meglitinides

GlucNorm[®]



Meglitinides

- Mechanism of Action
 - stimulating insulin secretion from the pancreas
 - dependent upon functioning beta-cells
 - uses different binding site on sulfonylurea receptor
 - quick onset and short duration of action
 - C_{max} and $T_{max} < 1$ hour
 - Onset of action 15 - 30 minutes

Meglitinides

- Efficacy
 - 0.5 to 2.0% reduction in HgbA1C
- Safety / Cautions
 - no dose change in renal failure (including dialysis)
 - probably safe in hepatic dysfunction but not studied
 - risk of hypoglycemia
 - adverse events similar to placebo except hypoglycemia
 - drug increases when used with OCP (repag only)

Meglitinides

- monotherapy
 - with metformin
 - with thiozolidinedione*
-
- didn't see formal indication

Meglitinides

Supplied / Dosing

GlucNorm[®]

0.5, 1.0, 2.0 mg tablets

0.5 - 4 mg with each meal

max 16 mg / day

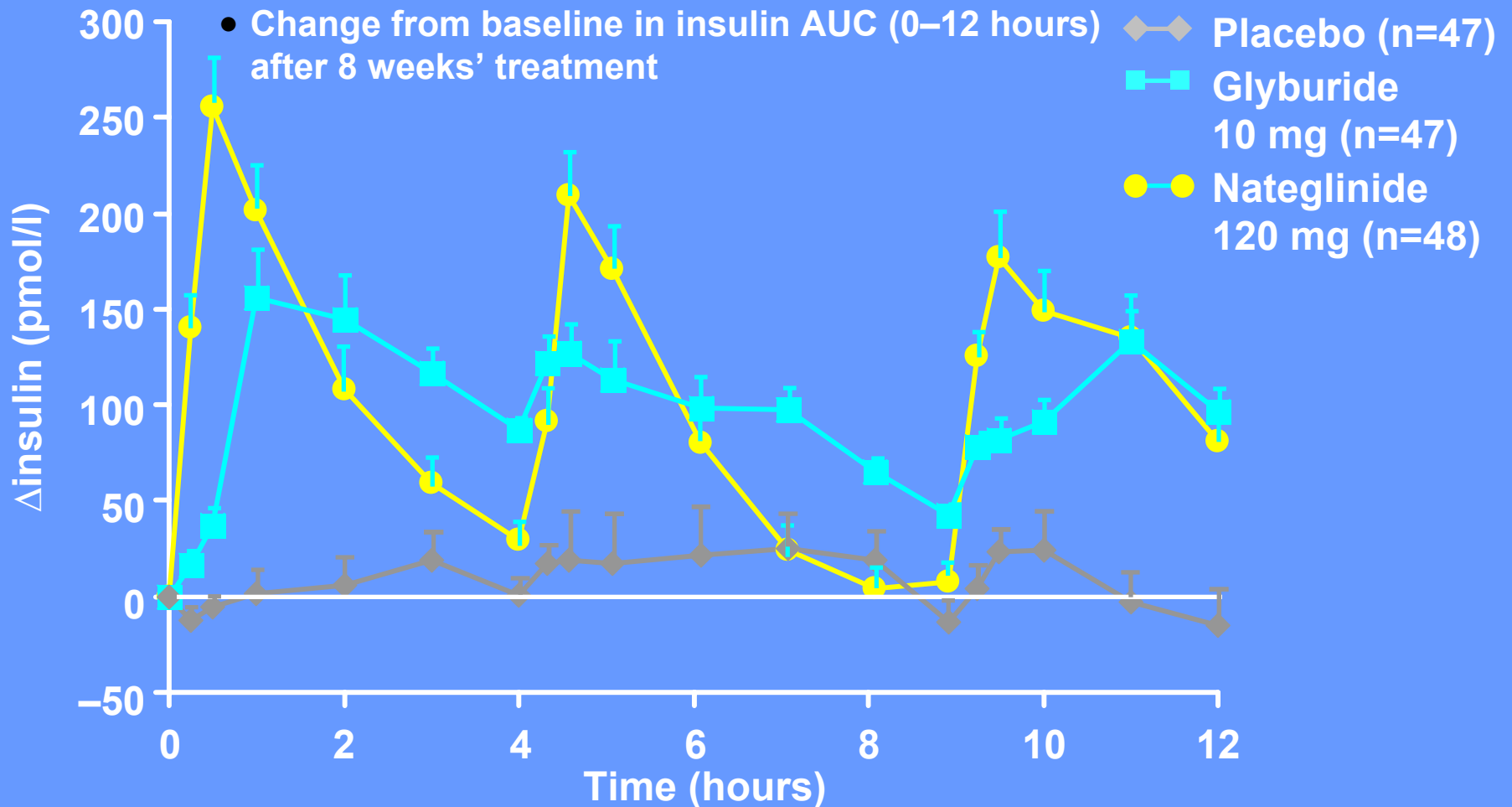


60, 120 mg tablets

120 mg po tid-meals

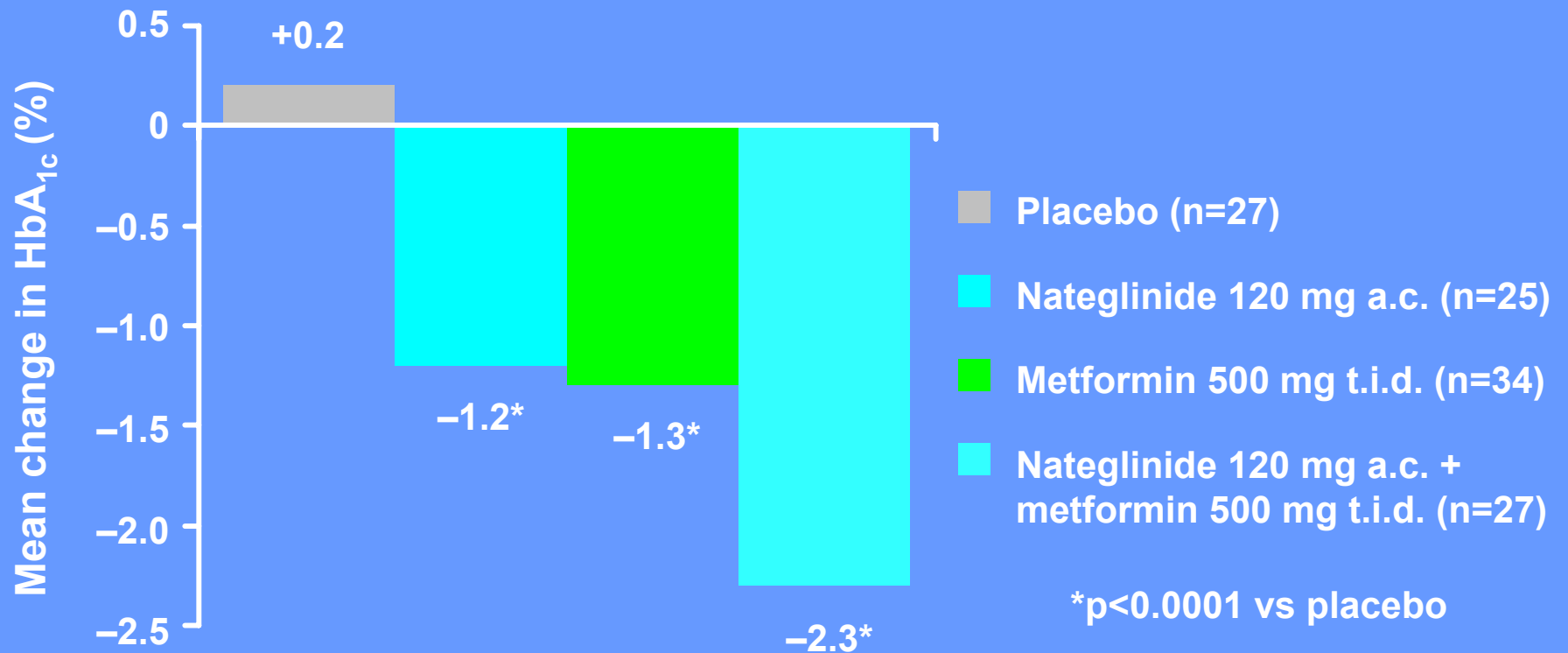
(start lower if near target)

Comparison between nateglinide and glyburide of the potentiation of insulin secretion from placebo



Incremental insulin AUC: glyburide 2-fold >nateglinide ($p < 0.05$); nateglinide and glyburide >placebo ($p < 0.05$)
Hollander P et al. *Diabetes Care* (in press)

Change in HbA_{1c} in type 2 diabetes patients with baseline HbA_{1c} ≥9.5%



Nateglinide is associated with minimal weight gain, alone or in combination with metformin

	Change from baseline in weight (kg)
Placebo (n=160)	-0.4
Nateglinide 120 mg a.c. (n=169)	+0.9*
Metformin 500 mg t.i.d. (n=169)	-0.1
Nateglinide 120 mg a.c. + metformin 500 mg t.i.d. (n=160)	+0.2

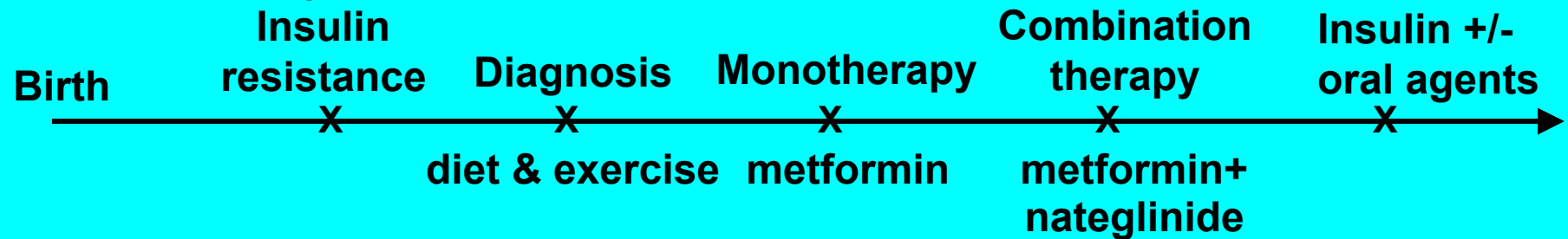
*p=0.0005 vs baseline

Horton ES et al. *Diabetes Care* 2000;23:1660-5

Nateglinide: How it fits in the treatment algorithm

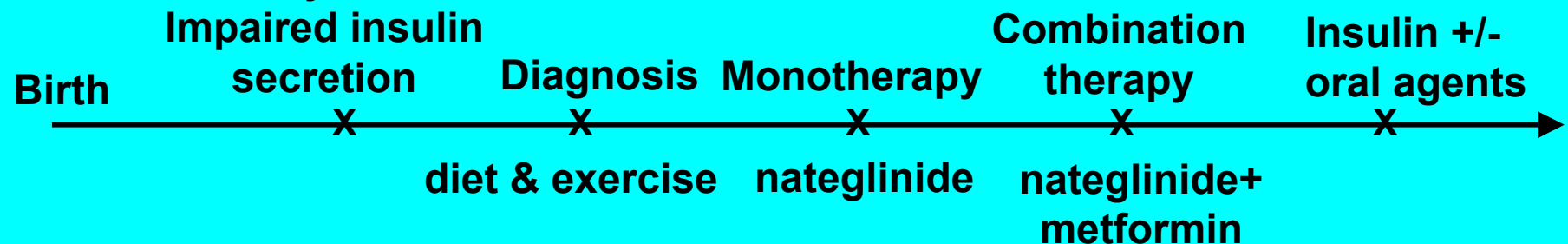
Obese Patients ~ 80% of type 2 diabetes

Primary defect:



Lean Patients ~ 20% of type 2 diabetes

Primary defect:



New Diabetic Medications

- Thiazolidinediones
 - Rosiglitazone (Avandia)
 - Piaglitazone (Actos)
- Meglitinides
 - Repaglinide (Gluconorm)
 - Nateglinide (Starlix)
- **Sulfonylurea**
 - **glimepiride (Amaryl)**

New Sulfonylurea



Amaryl (glimepiride)

- Mechanism of Action
 - sulfonylurea oral hypoglycemic agent
 - stimulates insulin release
 - increased sensitivity of peripheral tissues to insulin

Amaryl (glimepiride)

- Efficacy
 - once daily dosing
 - reduces HgbA1C ~ 1.0%
 - glycemic control with lower plasma insulin concentrations
- Safety / Cautions
 - low frequency of hypoglycemia
 - can be used in renal failure
 - no data in hepatic dysfunction
 - no significant drug interactions

A placebo controlled randomized study of glimepiride in patients with Type 2 diabetes mellitus for whom diet therapy is unsuccessful. J Clin Pharm 1998;38:636-41

- Objective

- determine the effects of glimepiride on glycemic control among Type 2 diabetics who failed diet

- Methods

- placebo controlled randomized clinical trial

- dose titrated glimepiride vs placebo

- 10 weeks adjustment + 12 weeks maintenance

A placebo controlled randomized study of glimepiride in patients with Type 2 diabetes mellitus for whom diet therapy is unsuccessful. J Clin Pharm 1998;38:636-41

- Results

- 123 glimepiride

- 126 placebo

- mean age 52 yrs

- duration of diabetes 3.1 yr

- baseline Hgb A1C 9.1 glimepiride / 8.9 placebo

A placebo controlled randomized study of glimepiride in patients with Type 2 diabetes mellitus for whom diet therapy is unsuccessful. J Clin Pharm 1998;38:636-41

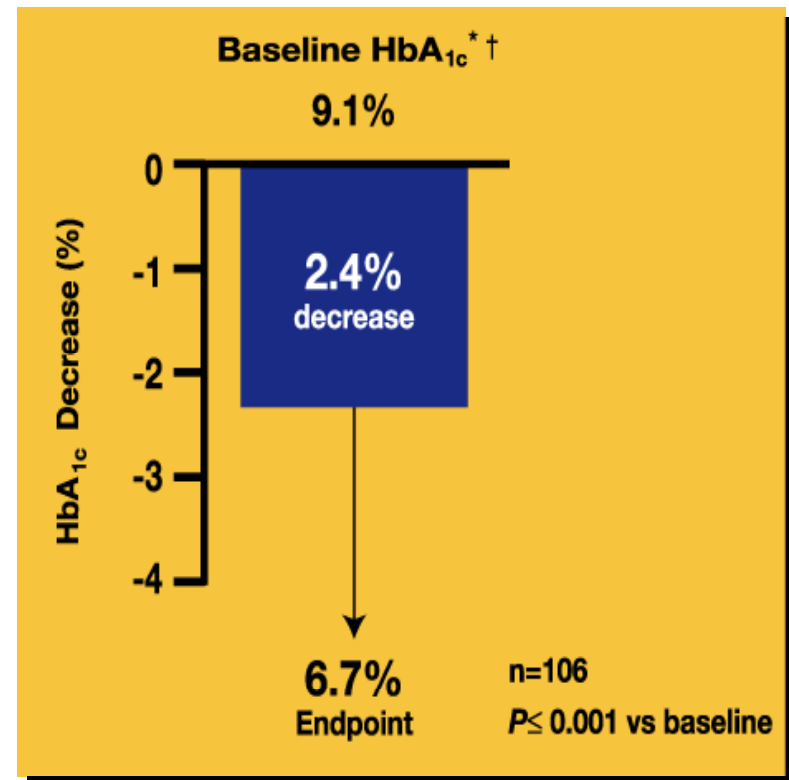
Hgb A1C (22 wk)

glimepiride: -2.4%

placebo: -1.0%

net: -1.4%*

*p <0.001



A placebo controlled randomized study of glimepiride in patients with Type 2 diabetes mellitus for whom diet therapy is unsuccessful. J Clin Pharm 1998;38:636-41

- Frequency of patients with Hgb A1C < 7.2% after 22 weeks

glimepiride 69%

placebo 32%

Glimepiride Adverse Effects ($\geq 1\%$)

Effect	Glimepiride	Placebo
Dizziness	1.7%	0.3%
Asthenia	1.6%	1.0%
Headache	1.5%	1.4%
Nausea	1.1%	0%

Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study.

Horm Met Res 1996;28:428-9

- Objective
 - determine the effect of glimepiride on frequency of hypoglycemia in comparison to glyburide
- Methods
 - 1 year randomized double blinded clinical trial
 - type 2 DM
 - 30 - 80 years
 - no hepatic or renal disease

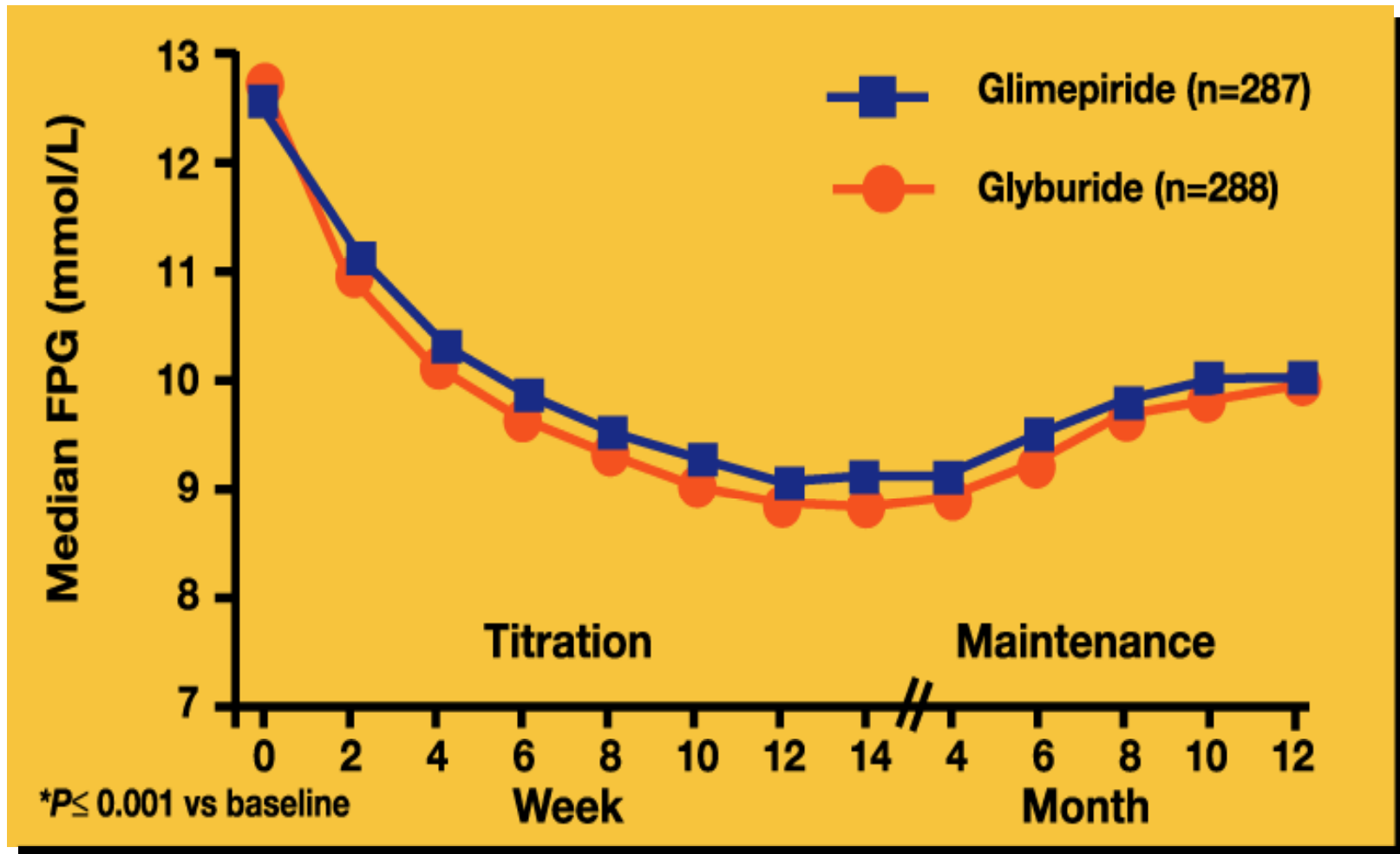
Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study.

Horm Met Res 1996;28:428-9

- **Outcomes - Baseline Data**
 - glimepiride 289 / glyburide 288 subjects
 - median duration of dm = 5.6 years
 - mean age 60 yrs
 - 60% males
 - Hgb A1C 8.5%

Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study.

Horm Met Res 1996;28:428-9



Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study

Horm Met Res 1996;28:428-9

Symptomatic Hypoglycemia

1 month

glimepiride	1.7% (5/289)	
glyburide	5.0% (16/288)	p=0.014

12 months

glimepiride	11.8% (34/289)	
glyburide	16.7% (48/288)	p=0.069

UKPDS- insulin 34% (historical control)

3 Indications

- **Monotherapy (diet and exercise)**
- **Combination with Metformin**
- **Combination with Insulin**

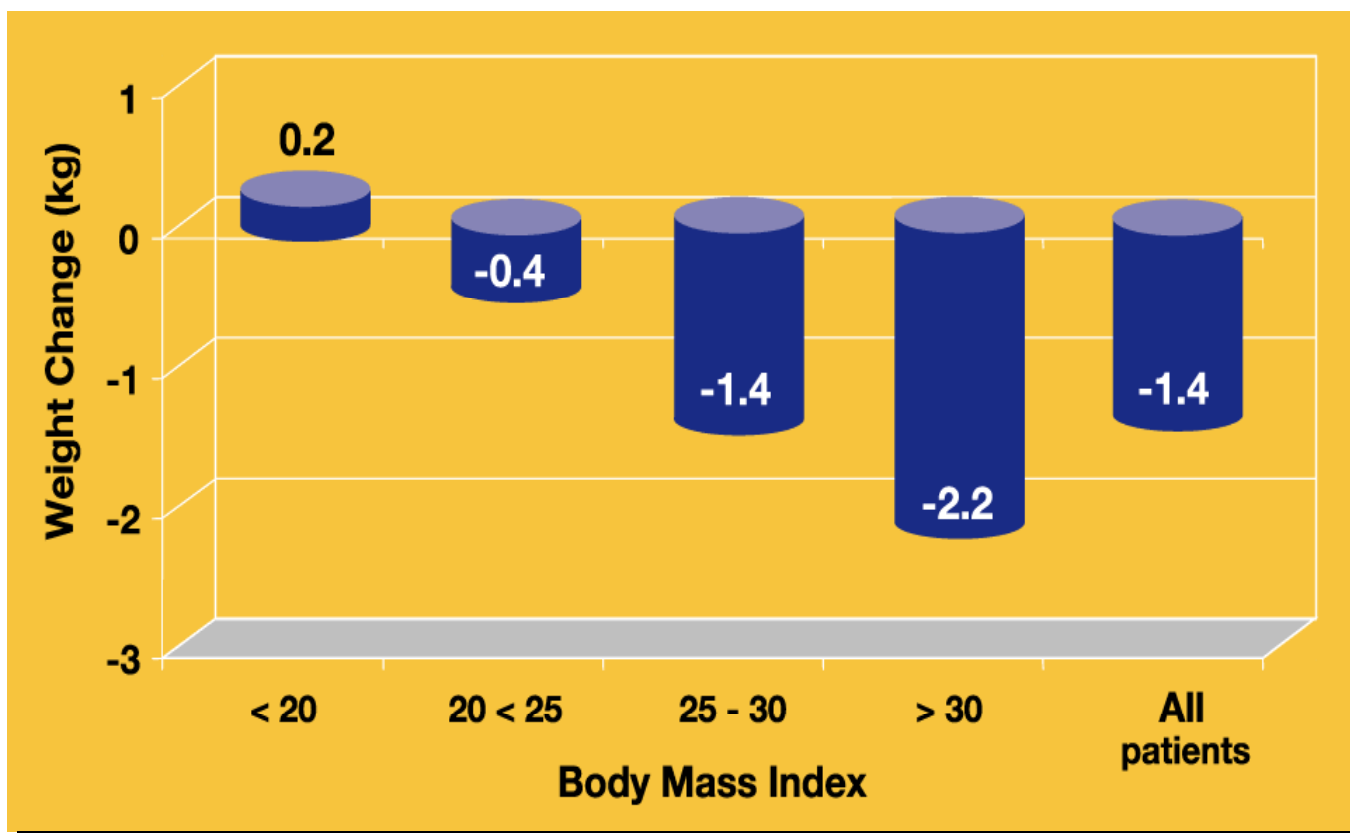
Glimepiride Combination with Insulin

- **Glimepiride reduced the mean daily insulin requirements by 38% ($P < 0.001$)**
- **Fewer Glimepiride patients required doses >100 U/day**

Glimepiride + Insulin	Placebo + Insulin
48.5 U	77.9 U
6.0%	14.0%

Neutral Effect on Weight

Large-scale (>22,000 patients) Post-Marketing Surveillance Study (Germany):
- Change in body weight (kg) after 2 months of Glimepiride treatment



Glimepiride: Dosage and Administration



- Usual Starting dose 1 mg od
- Usual Maintenance dose 1 to 4 mg od
- Maximum dose 8 mg od
- Combination with metformin 1 to 8 mg qd
- Combination with insulin 8 mg qd

New Diabetic Medications

- Thiazolidinediones
 - Rosiglitazone (Avandia)
 - Piaglitazone (Actos)
- Meglitinides
 - Repaglinide (Gluconorm)
 - Nateglinide (Starlix)
- Sulfonylurea
 - glimepiride (Amaryl)

Do you need them?

- Thiozolidinediones
 - novel mechanism
 - renal patients
 - sustainability
- Meglitinides
 - dosing flexibility
 - renal patients
- Glimipiride
 - lower hypoglycemia
 - lower plasma insulin
 - renal and hepatic patients

Summary

- Take home points
 - increasing prevalence of Type 2 DM
 - multistage disease
 - think about co-morbidities
 - management will change with natural history
 - management depends on stage of disease