

# Epidemiology of Diabetes & Insulin Resistance

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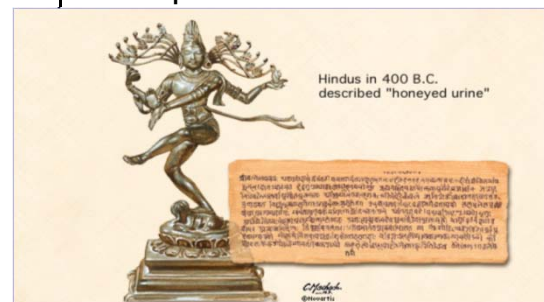
## Structure of Session

- **What is diabetes?**
  - Definition and classification
  - Prevalence
  - Cost of diabetes
  - Risk factors
  - Diabetes and Obesity
  - Diabetes and Hypertension
- **Insulin Resistance and Metabolic syndrome**
  - Definitions
- **Diabetes and Cardiovascular Disease**
  - Role of Diabetes in cardiovascular morbidity and mortality
- **Primary prevention of diabetes: evidence so far**

## Take home message

- Diabetes is a common disease, with rapidly increasing prevalence.
- Insulin resistance is a fundamental unifying basis of diabetes, obesity and the metabolic syndrome.
- Diabetes and impaired glucose regulation are associated with a considerable cardiovascular morbidity and mortality, and reduction in life-span by 8 to 10 years.
- Diabetes is a preventable disease in the majority of cases.

## Diabetes, an old disease but new epidemic



## What Is Diabetes?

- **Definition:** Diabetes Mellitus is a group of metabolic diseases characterised by *hyperglycaemia* resulting from defects in insulin secretion, insulin action, or both.

## Types of Diabetes

- **Type 1 Diabetes**
  - Low or absent circulating insulin, onset in youth, associated with HLA, and GAD and IC antibodies are usually present at diagnosis.
- **Type 2 Diabetes**
  - Insulin levels are variable; characterised by **Insulin Resistance** and hyperinsulinemia. **Obesity** and age related.
- **Gestational Diabetes**
  - Glucose intolerance, with onset or recognition during pregnancy. It is a risk factor for Type 2 Diabetes.
- **Other types of Diabetes**
  - Hormonal causes, pancreatic disease, drug induced, genetic disorders

## Diabetes Mellitus: diagnosis criteria

Plasma glucose levels\* (mmol/l):

	FPG	OGTT(2hr)
Diabetes	$\geq 7.0$ mmol/l	or $\geq 11.1$ mmol/l
Impaired fasting glucose	$> 6.0$ & $< 7.0$ mmol/l	
Impaired glucose tolerance		$\geq 7.8$ & $< 11.1$ mmol/l

FPG = Fasting plasma glucose  
OGTT = Oral glucose tolerance test at 2 hours (75 g glucose)

\* At least 2 readings on separate days, except when associated with classical symptoms like polyuria, polydipsia, thirst etc, when one reading is sufficient.

WHO 1999, and IDF/WHO 2006

## Diabetes Mellitus: diagnosis criteria

Recent changes: new criteria

Diabetes: **HbA1c  $\geq 6.5\%$ \***

ADA in 2010 added 3<sup>rd</sup> criteria for diagnosing diabetes

In 2011, the WHO, IDF and Diabetes UK endorsed the use of HbA1c in diagnosis of diabetes, provided a few conditions are met.

## Use of HbA1c in diagnosis of diabetes: WHO recommendations

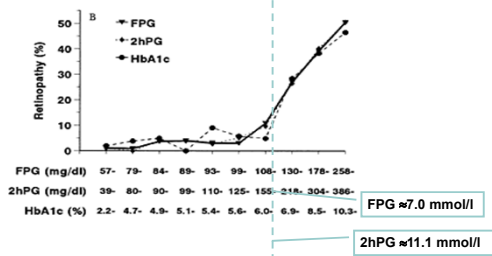
“HbA1c  $> 6.5\%$  can be used as a diagnostic test for diabetes, provided that **stringent quality assurance tests** are in place and **assays are standardised** to criteria aligned to the international reference values, and there are **no conditions present** which preclude its accurate measurement.”

Please note : A value HbA1c of less than 6.5% does not exclude diabetes diagnosed using recommended glucose tests

## Glucose and HbA1c measurement in diagnosis of diabetes

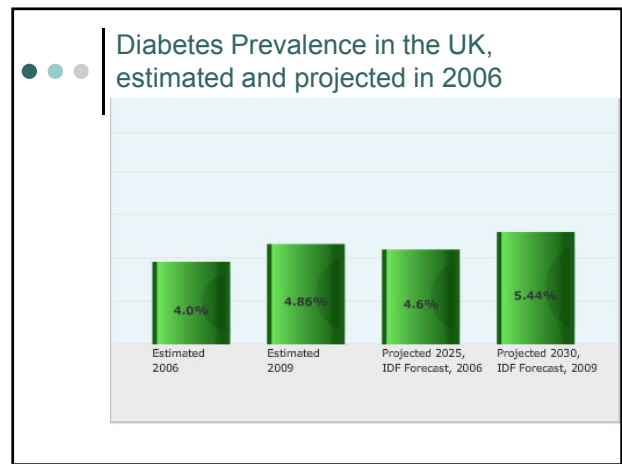
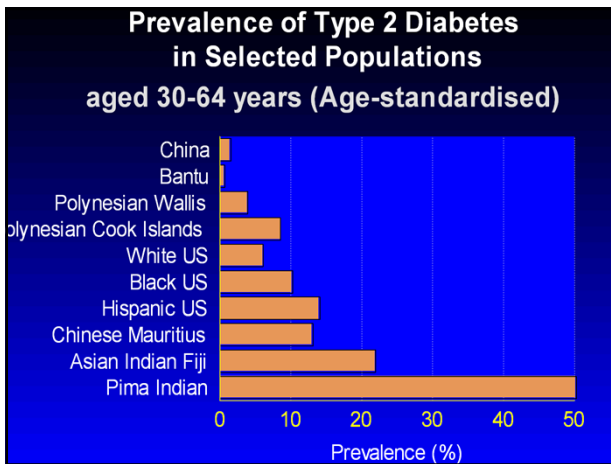
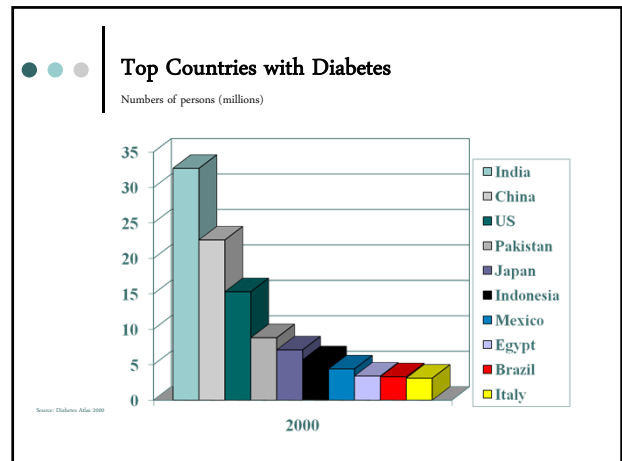
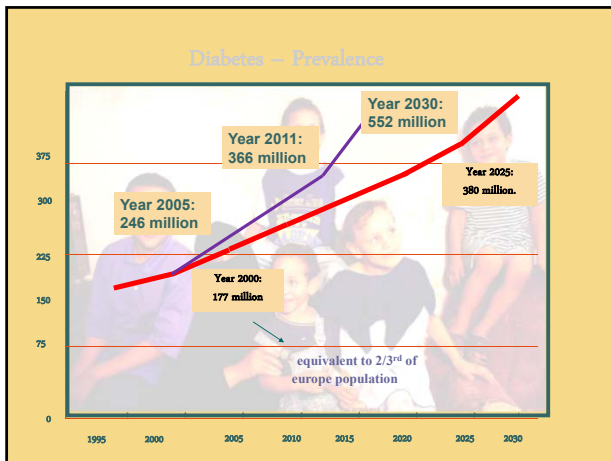
	Glucose	HbA1c
Patient preparation prior to collection of blood	Stringent requirements if measured for diagnostic purposes.	None.
Measurement	Widely available	Not readily available world-wide
Standardization	Standardized to reference method procedures.	Standardized to reference method procedures.
Routine calibration	Adequate.	Adequate.
Interferences: illness	Severe illness may increase glucose concentration.	Severe illness may shorten red-cell life and artifactually reduce HbA1c values.
Haemoglobinopathies	Little problem unless the patient is ill.	May interfere with measurement in some assays.
Haemoglobinopathy traits	No problems.	Most assays are not affected.
Affordability	Affordable in most low and middle income country settings.	Unaffordable in most low and middle-income country settings.

## Why FPG of 7 mmol/l cut-off?



Incidence of retinopathy in a population survey by deciles of glycaemia

## Diabetes- “The Epidemic”



### Diabetes Prevalence in the UK, estimation and projections in 2011

**2011 estimations:**

- 2.90 million people with diagnosed diabetes, and 0.85 million with undiagnosed diabetes in the UK
- Prevalence: overall 4.5%, with 5.5% in England and 5.0% in Wales.

**Projections for 2030:**

- Total number of patients with diabetes will be around 5 million.

### Diabetes Epidemic: Reasons

- Increasing lifespan
- Urbanisation: change in lifestyle
- Obesity epidemic

## Urbanisation

For example in India

- 1970- Agrarian society, more than 80% in rural area

↓  
Industrialisation  
↓

- 2003 :-73% live in rural area

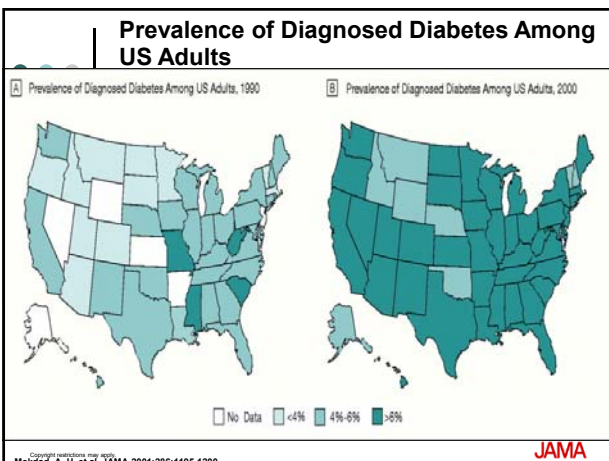
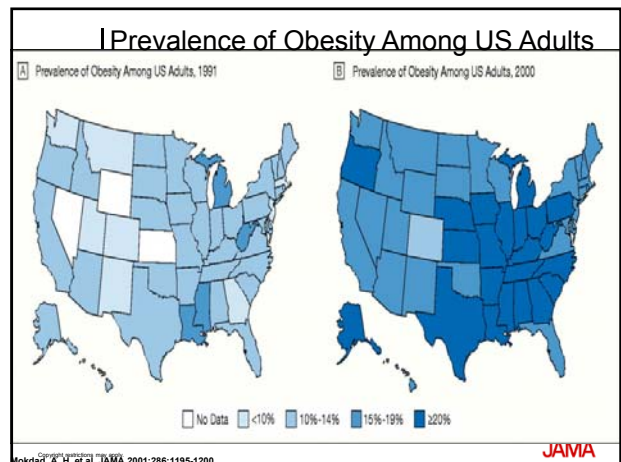
## Diabetes prevalence in Southern India

Rural	2.4 %
Peri-urban	5.9 %
Urban	11.6 %

Ramachandran et al, Diab Res Clin Prac 1997;44 : 207-213

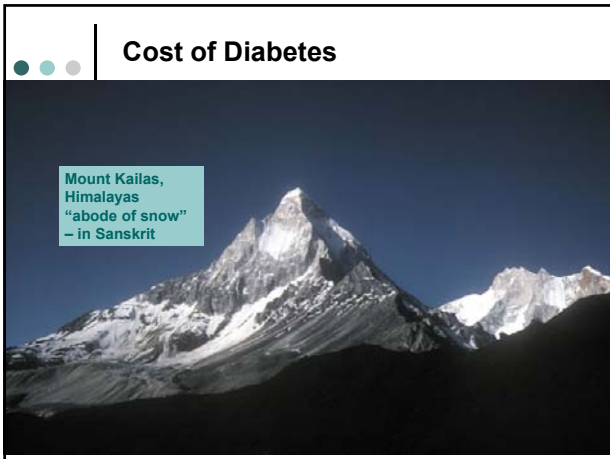
## Rising prevalence of Obesity

- Obesity worldwide prevalence**
  - 1995-200 million
  - 2000-300 million
- Developed world**
  - US – prevalence estimates**
    - 1994:22.9%
    - 1999: 30.5%
    - 2008: 40%
  - UK: similar rates, tripling of prevalence between 1980 - 1997**



“58% of Diabetes Cases Globally Can Be Attributed to Body Mass Index Above 21 Kg/m<sup>2</sup>”

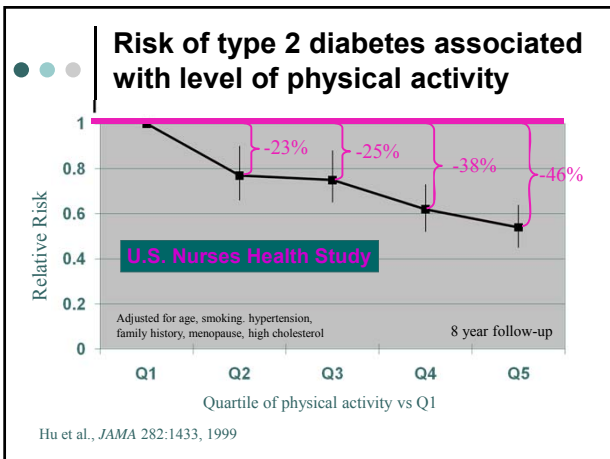
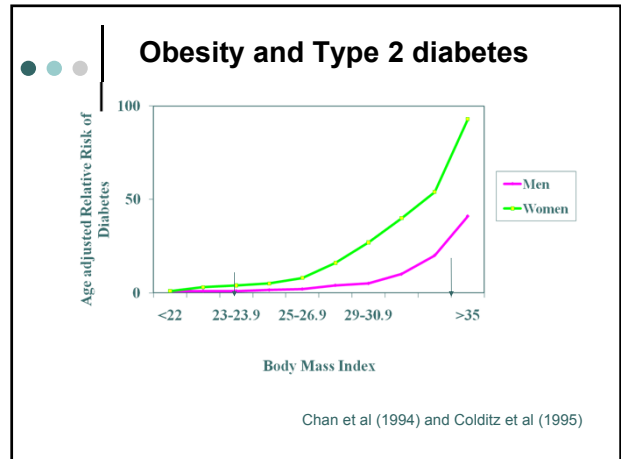
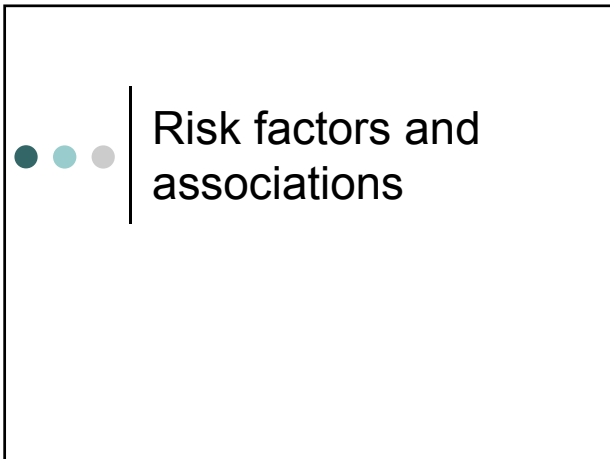
Source: IDF Press Release August 25, 2003



## Costs

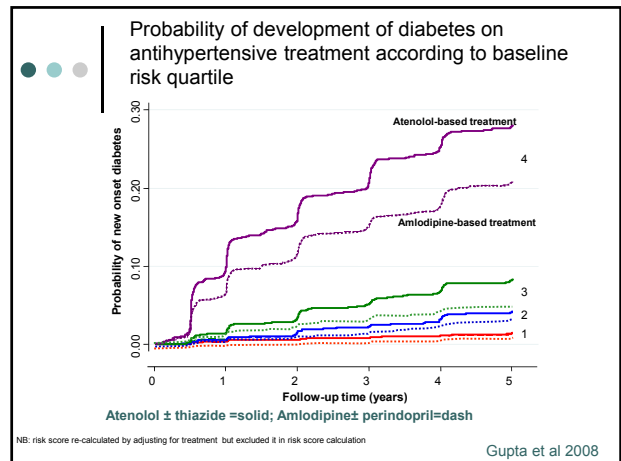
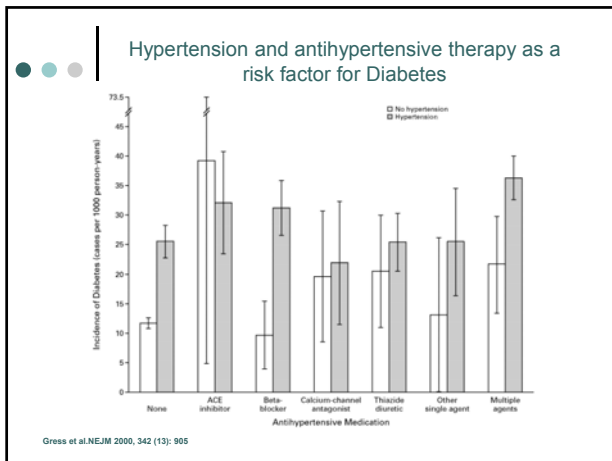
- Worldwide: It is estimated that the total costs of diabetes care in 2010 was about \$376 billion, with about 12% of total health expenditure spent globally on diabetes, and its related complications.
- Cost is mainly due to vascular complications and hospitalisation.

Category	Percentage
Hospitalisation	55%
Other drugs	21%
Ambulatory	15%
Antidiabetic drugs	7%

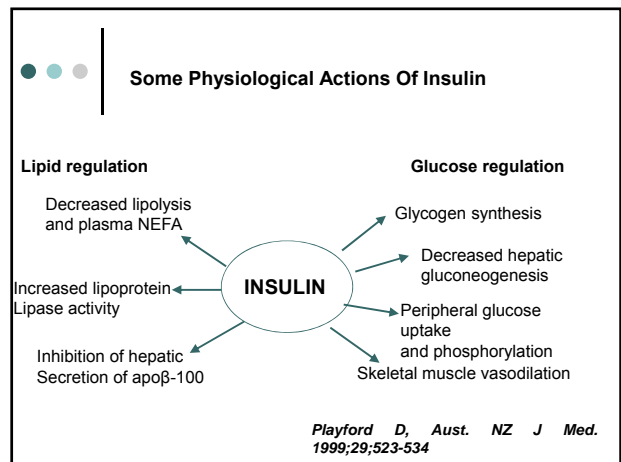


## Hypertension and Diabetes

- Hypertension and diabetes are common co-morbid conditions, and their relationship is complex.
- Hypertension is an independent risk factor for diabetes development, and increases risk by 2-3 times.
- Recent studies have shown that antihypertensive drugs - particularly beta-blockers and diuretics - variably potentiate this enhanced risk.

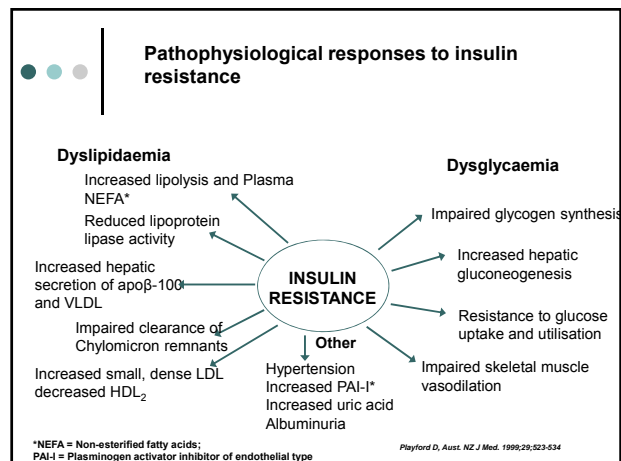


## Insulin Resistance and Metabolic Syndrome



### Hyperglycaemia and insulin response

- Pancreatic beta cells increase insulin secretion to maintain normoglycaemia.
- Hyperinsulinaemia commonly observed in insulin resistant states.
- Eventual beta cell exhaustion occurs, so that normoglycaemia cannot be maintained, and type 2 diabetes develops.



## Metabolic syndrome definitions

### Modified NCEP-ATP III definition

Any 3 or more of the following criteria:

1. Waist circumference >102 men & >88 cm in women
2. Serum triglycerides 1.7mmol/l
3. Blood pressure >130/85
4. HDL cholesterol <1.0 mmol/l men and <1.3 mmol/l women
5. Serum glucose 5.6 mmol/l

**16 potential defining combinations!**

JAMA 2001; 285: 2486  
Circulation 2004; 109: 433

### WHO definition

Insulin resistance (clamp studies) or diabetes & at least 2 of the following criteria:

1. Waist-hip ratio >0.90 men or >0.85 women
2. Serum triglycerides 1.7 mmol/l or HDL cholesterol <0.9 men & <1.0 mmol/l women
3. Blood pressure 140/90 mm of Hg
4. Urinary albumin excretion >20 µg/min or albumin-creatinine ratio >30 mg/g

WHO Geneva 1999

## IDF 2005 worldwide metabolic syndrome definition

- Essential criteria: **Central obesity**
  - Waist circumference  $\geq 94$  cm for men and  $\geq 80$  cm for women (Europid values)
- Plus  $\geq 2$  of the following:
  - TG level  $\geq 150$  mg/dL (1.7 mmol/L) or treatment for hypertriglyceridemia
  - HDL-C  $< 40$  mg/dL (1.03 mmol/L) in males and  $< 50$  mg/dL (1.29 mmol/L) in females or treatment for reduced HDL-C
  - Systolic BP  $\geq 130$  mmHg or diastolic BP  $\geq 85$  mmHg or treatment for hypertension
  - Fasting plasma glucose  $\geq 100$  mg/dL (5.6 mmol/L) or Type 2 diabetes

[http://www.idf.org/webdata/docs/IDF\\_Metasyndrome\\_definition.pdf](http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf)  
Alberti KGMM et al. Lancet 2005; 366: 1059

## Diabetes- A Dangerous Disease

## Diabetes Care: The Problems

**Retinopathy**  
Common cause of blindness in people of working age in West



**Nephropathy**  
20% of all ESRD



**Erectile Dysfunction**  
May affect up to 50%



**Macrovascular**  
2-4 x increased risk of CVD, 75% have hypertension



**Foot Problems**  
15% develop foot ulcers; 5-15% need amputation

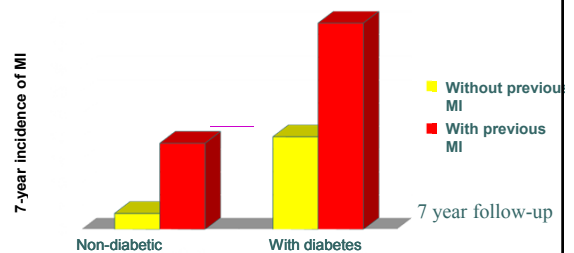


## Deaths attributable to diabetes



## Mortality in Diabetes

Diabetic patients without previous MI have as high a risk of MI as non-diabetic patients with previous MI

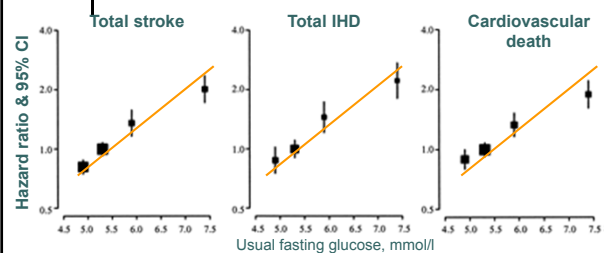


New England Journal of Medicine 1998;339:229-234.

## Diabetes and vascular disease

- Relative risk of cardiovascular disease in diabetes is 2-5 times in non-diabetic population.
- 80% of people with type 2 diabetes die of a cardiovascular cause.
- Up to 40% of acute cardiac admissions may have diabetes.
- Most common cause of non-traumatic lower limb amputations.

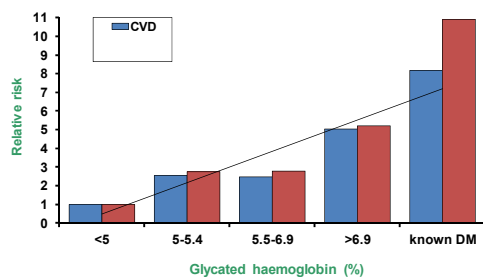
## Usual fasting glucose & risk of CV end points



237,468 participants (14,282 Chinese); ~1.2 million person-years follow-up  
1,661 strokes & 816 IHD events  
Each 1 mmol/l ↓fasting glucose associated with ~20% ↓risk of CVD death

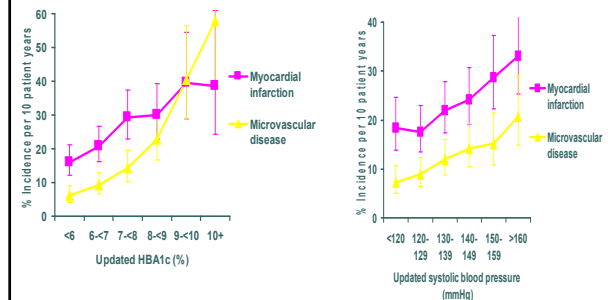
Asia Pacific Cohort Studies Collaboration. Diabetes Care 2004; 27: 2836

## Age adjusted relative risk of CVD and MI by baseline glycated haemoglobin status



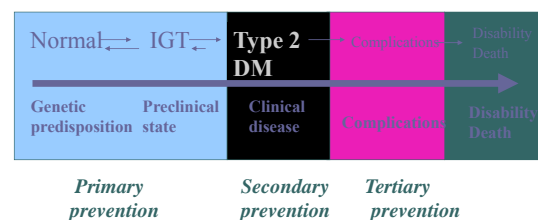
Khaw KT et al. BMJ 01;322:1-6

## Glycaemic and BP control in diabetic patient and risk for vascular complications



## Primary Prevention of Diabetes Mellitus

## Stages in the natural history of Type 2 diabetes





## Secondary prevention: Is it good enough?

### Points to Ponder

- Only partially successful in preventing complications.
- Costly in itself. Needs considerable resources.
- Rising prevalence of diabetes will eventually offset the gains made in cardiovascular disease prevention.
- 25-50% of patients may have some evidence of complications at the time of diagnosis of diabetes.

## Primary prevention of diabetes: The evidence so far

## Finish Diabetes Prevention Study

522 – IGT people, Aged 40-65 years

- Average Age 55 yrs
- Average BMI 31

Tuomilehto et al, NEJM, May 2001

## Finish Diabetes Prevention Study

- Diet and exercise intervention
- Goals
  - **5% weight loss**
  - Total fat intake < 30%
  - Saturated fat intake <10%
  - Fibre intake of >15gm per 1000 kcal per day
  - Moderate exercise for 30 mins every day
- Seven intervention sessions in first year, one 3-monthly session with dietician thereafter throughout the 4 years of study

## Finish Diabetes Prevention Study- Results

- 11% vs 23% cumulative risk of developing diabetes in the intervention and control group respectively
- Risk of developing diabetes reduced by 58% after 4 years.

NNT = 8

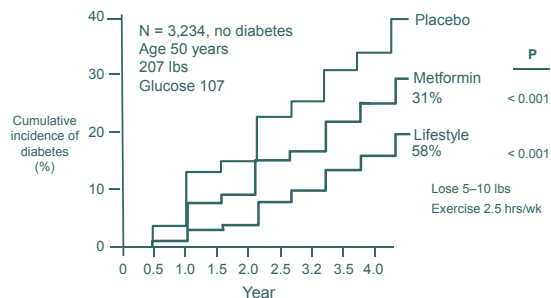
## Diabetes Prevention Programme (DPP)

- 27 centres
- 3,234 participants
- ≥ 25 years
- BMI ≥ 24 (22 for American Indian)
- IGT
- 45%- Ethnic minority population
  - American Indian, African American, Hispanic American, Asian American, pacific islanders

## Diabetes Prevention Program

- Study Population
  - Average Age -51 Years, Av. BMI -34 Kg/m<sup>2</sup>
- RCT
- Intervention :
  - Lifestyle intervention
    - Goals: Weight reduction ≥ 7%
      - Low fat diet
      - Exercise for 150 minutes per week
  - OR
    - Metformin 850mg BD
- Trial stopped 1 year early, after 2.8 years of median follow-up.

## Diabetes Prevention Program: Impact of Lifestyle Intervention or Metformin



## Studies using oral hypoglycaemic agents for primary prevention of diabetes

Study	Type	Number of subjects	Intervention	Effect on Diabetes incidence/progression
DPP	RCT	2155	Metformin	Reduction in incidence
FHS	RCT	188	Gliclazide	No benefit
TRIPOD	RCT	266 (Hispanic women)	Troglitazone	Decrease incidence from 45% to 20%
STOP-NIDDM	RCT	1429	Acarbose	25% decrease in progression to Diabetes

## Other trials with diabetes prevention as a secondary/tertiary objective

Study	Type	Number of subjects	Intervention	Effect on Diabetes incidence/progression
XENDOS	RCT	3305	Orlistat	Decreased incidence (9% to 6%)
HOPE	RCT	5720	Ramipril vs Placebo	34 % risk reduction
LIFE	RCT	9000	Losartan vs Atenolol	25% risk reduction with losartan
WOSCOPS	RCT -	6447	Pravastatin	significantly lower incidence
ASCOT-BPLA	RCT	14120	Amlodipine ± Perindopril	34% risk reduction with CCB±ACE inhibitor

## The DREAM Trial

**Aims:** Does ramipril 15 mg/d prevent diabetes?  
Does rosiglitazone 8 mg/d prevent diabetes?

**Design:** 2 X 2 factorial, double-blind RCT

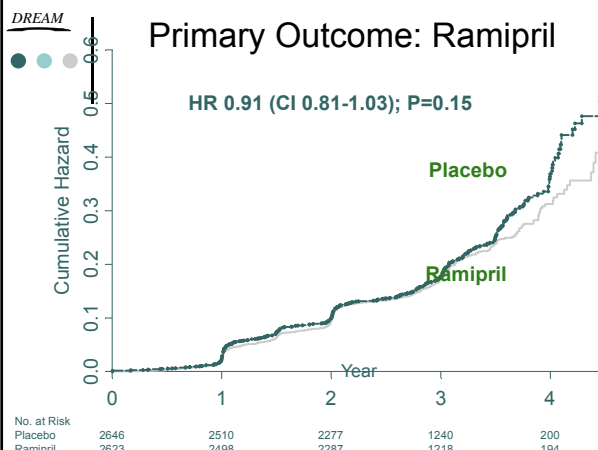
**Sample:** Age 30+; IGT (FPG <7 & 2 hr 7.8-11) &/or IFG (FPG 6.1-6.9)

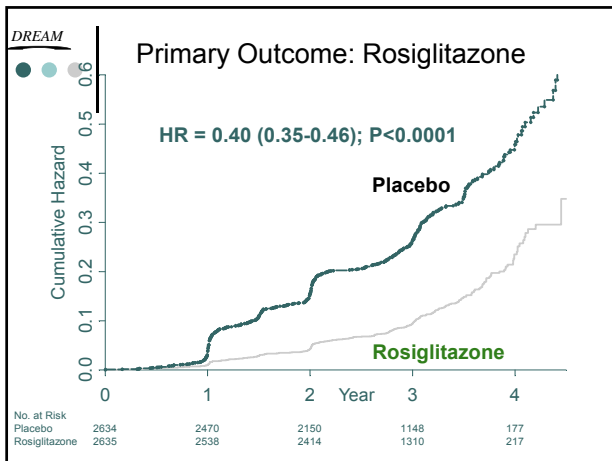
**Patients:** 5269 in 191 sites, 21 countries, & F/U 3 yrs

**Outcome:** Incident DM (confirmed FPG ≥ 7 or 2hr ≥ 11.1; or MD diagnosis) or death\*

\*because undiagnosed diabetes may be more frequent in those who die than in those who do not

## Primary Outcome: Ramipril





### Conclusions of the DREAM Trial

- Rosiglitazone has a substantial benefit on prevention of diabetes & regression to normoglycaemia.
- Ramipril has a modest benefit on regression to normoglycaemia.

**Update 2010: Rosiglitazone has been withdrawn from the market, as it is proven to increase the risk of CV events.**

### NAVIGATOR Trial

- 9,306 IGT patients with FPG between 5.3 to 7 mmol/L and either presence of one cardiovascular risk factor (if age >55 years) or established CVD (if age < 55 years)
- 2X2 factorial design randomised trial.
- Assigned either Nateglinide 60 mg three times a day before meals or placebo, and Valsartan 160 mg once a day or a placebo
- Median follow-up: 5 years
- All subjects participated in a lifestyle modification program

**NAVIGATOR**

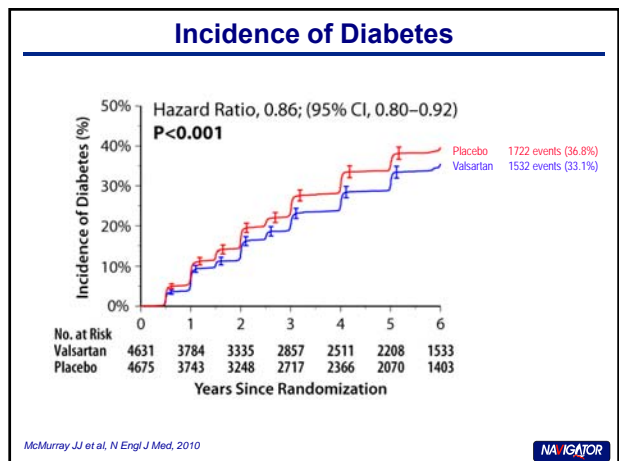
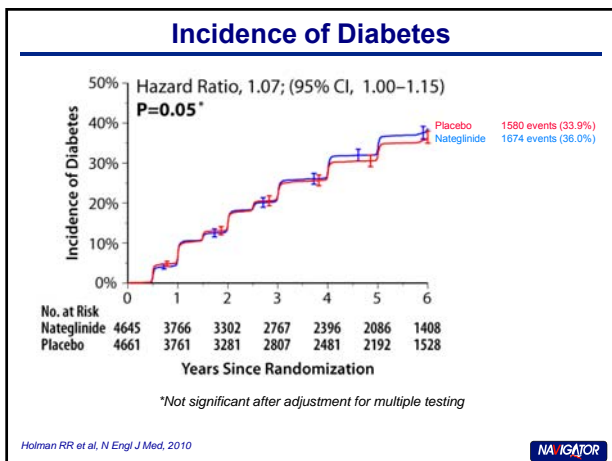
### NAVIGATOR 2 × 2 Factorial Design

		Valsartan Comparison		Nateglinide Comparison
		Valsartan/Nateglinide (n=2316)	Nateglinide/Placebo (n=2329)	
Valsartan Comparison		Valsartan/Placebo (n=2315)	Placebo/Placebo (n=2346)	

Outcomes evaluated:

1. Development of new-onset diabetes
2. Cardiovascular outcomes ( composite of several CHD and stroke outcomes)
3. Composite of new-onset diabetes and extended cardiovascular outcomes.

**NAVIGATOR**





## Lifestyle or Medication?

### Summary of current literature

- Life style modifications appear to be more efficacious.
- All drugs cause some degree of adverse effects.
- Life style modifications have beneficial effect on other disease e.g. CVD morbidity/mortality.
- Prescribing early- long duration of drug therapy, drugs have not been shown to have everlasting effect.



## Summary of session

- Diabetes is a common but serious disease, incidence and prevalence of whom is rapidly increasing in conjunction with obesity
- Insulin resistance, is a fundamental unifying basis of Diabetes, Obesity and Metabolic syndrome.
- Diabetes, impaired glucose regulation and metabolic syndrome are associated with considerably higher risk of cardiovascular morbidity and mortality
- Diabetes is a preventable disease