

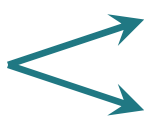
# **Definition and Classification**

## **of Diabetes and Pre-diabetic glucometabolic disturbances**

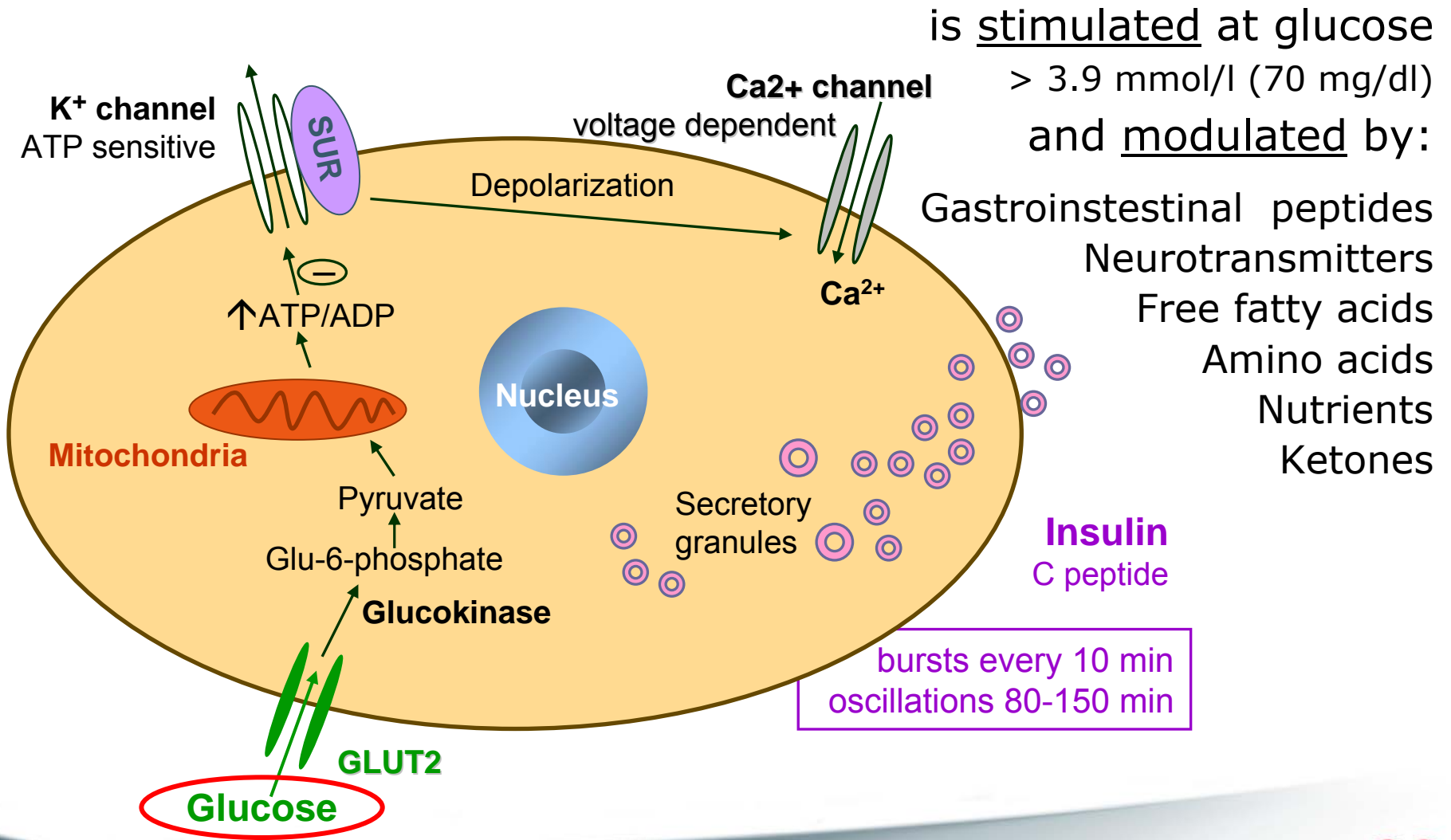
# Diabetes mellitus

is a common name for metabolic disorders of multiple aetiology characterized by chronic hyperglycaemia

Chronic Hyperglycaemia results from

- defects in insulin secretion
- impaired insulin action 
  - diminished glucose utilization*
  - increased glucose production*
- or combination of both

# Insulin production and secretion → $\beta$ -cell

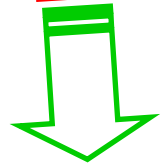


# Insulin action ⇌ Glucose production

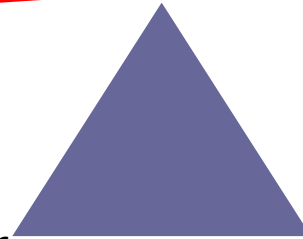
Insulin action →  
Glucose utilization

↑ Glucose production  
Insulin resistance

GLUCOSE HOMEOSTASIS



activation of GLUT4 transporter  
enabling glucose uptake,  
↑ glucose metabolism and  
↑ synthesis of glycogen, protein  
and lipogenesis  
cell growth and differentiation

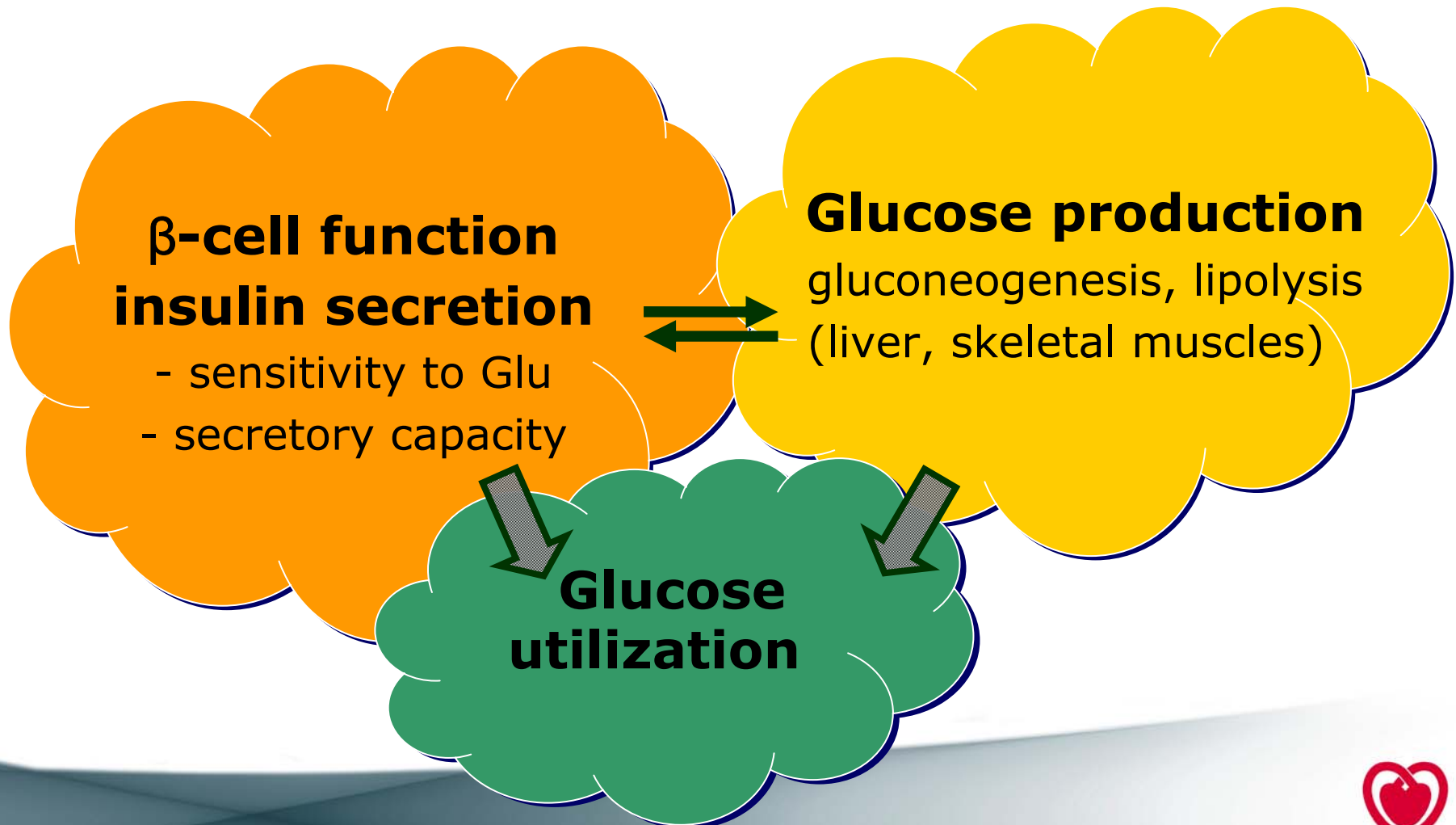


## Glucose production

↑ hepatic gluconeogenesis  
↑ glycogenolysis  
↑ glycaemia  
↓ glucose utilization  
↑ Insulin demand  
insulin resistance



# Glucose homeostasis - key factors



# Diabetes mellitus – chronic Hyperglycaemia

- ♥ Is associated with disturbances of carbohydrate, fat and protein metabolism
- ♥ Hyperglycaemia leads to development of specific microvascular complications and long-term organ damage due to microvascular disease:
  - retinopathy
  - nephropathy
  - neuropathy

# Classification of diabetes mellitus

1. Aetiological types of glycaemic disorders
2. Clinical stages of hyperglycaemia

classification criteria defined by WHO (A+B) and ADA (A) by means of blood glucose measurements:

- A. fasting plasma glucose (FPG)
- B. 120 minutes after a glucose load (2h-PG) following a standardized oral glucose tolerance test (OGTT)

OGTT is performed in the morning after 8-14 h fast. Blood is sampled before and after intake of 75 g glucose dissolved in 250-300 mL water within 5 minutes.

# Aetiological classification of diabetes (1)

**Diabetes type 1** –  $\beta$ -cell destruction

**1A** Autoimmune

**1B** Idiopathic

**Diabetes type 2** – combination of both insulin resistance and  $\beta$ -cell dysfunction

**Other specific types** *following slides...*

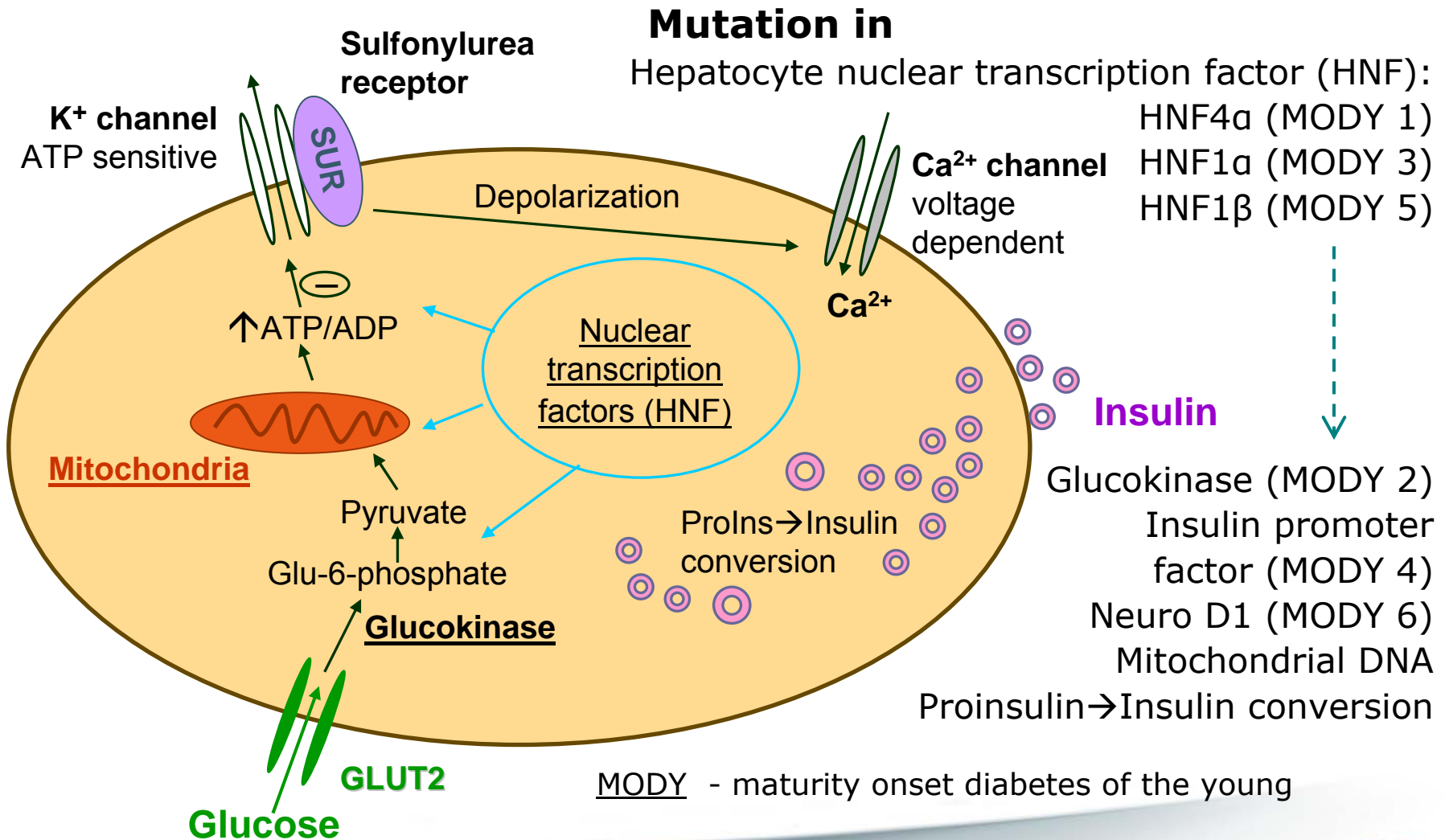
**Gestational diabetes** – any glucose perturbation beginning during pregnancy and disappearing after delivery

# Aetiological classification of diabetes (2)

## Other specific types:

- A. Genetic defects of  $\beta$ -cell function
- B. Genetic defects in insulin action
- C. Diseases of exocrine pancreas
- D. Endocrinopathies: acromegaly, Cushing's S., pheochromocytoma, etc
- E. Drug- or chemical- induced: steroids, beta blockers, thiazides, phenytoin, anti-depressive drugs, nikotin acid,  $\alpha$ -interferon, etc
- F. Infections: congenital rubella, cytomegalovirus, coxackie,
- G. Uncommon forms of immune-mediated diabetes:  
"stiff man" Syndrome, anti-insulin receptor antibodies,
- H. Genetic syndromes (S) associated with diabetes:  
Down's S., Turner's porphyria, S., Friedreich ataxia, myotonic dystrophy, Klinefelter's S., Wolfram's S., etc

# Other specific types A) Genetic defects of $\beta$ -cell function:



# The most common types of diabetes

## Diabetes type 1

- absolute insulin deficiency following almost complete  $\beta$ -cell destruction,
- occurs usually in children and younger adults,
- commonly associated with rapid symptoms aggravation but may in some cases progress slowly (LADA).

## Diabetes type 2 characterised by:

- a triad: Impaired insulin secretion, Excessive hepatic glucose production and Peripheral insulin resistance,
- relative insulin deficiency,
- the most common form: **80-90%** of all people with DM
- prevalence increasing with age, symptomatic for years
- **50%** of people with diabetes type 2 are undiagnosed.

# Diagnosis of diabetes mellitus

## Can be established based on:

- ♥ Symptoms: polyuria, polydypsia and weight loss, (glukosuria, ketones, infection) with random plasma glucose  $\geq 11.1$  mmol/L (200 mg/dL)
- ♥ Presence of specific diabetic complications – retinopathy (cutpoints on glucose values)
- ♥ Glucometabolic classification by means of updated criteria issued by WHO and ADA

# Glucometabolic classification criteria

Glucometabolic category	Source	Classification criteria (mmol/L)
<b>Normal</b> glucose regulation (NGR)	WHO	FPG < 6.1 and 2-h PG < 7.8
	ADA 1997	FPG < 6.1
	ADA 2003	FPG < 5.6
<b>Impaired</b> fasting glucose (IFG)	WHO	FPG ≥ 6.1 and <7.0 and 2-h PG < 7.8
	ADA 1997	FPG ≥ 6.1 and FPG < 7.0
	ADA 2003	FPG ≥ 5.6 and FPG < 7.0
glucose tolerance (IGT)	WHO	FPG < 7.0 and 2-h PG ≥ 7.8 and <11.1
glucose homeostasis (IGH)	WHO	IFG or IGT
<b>Diabetes Mellitus</b> (DM)	WHO	FPG ≥ 7.0 or 2-h PG ≥ 11.1
	ADA 1997	FPG ≥ 7.0 or 2-h PG ≥ 11.1
	ADA 2003	FPG ≥ 7.0 or 2-h PG ≥ 11.1

FPG fasting plasma glucose,  
2-h PG two hours post load plasma glucose

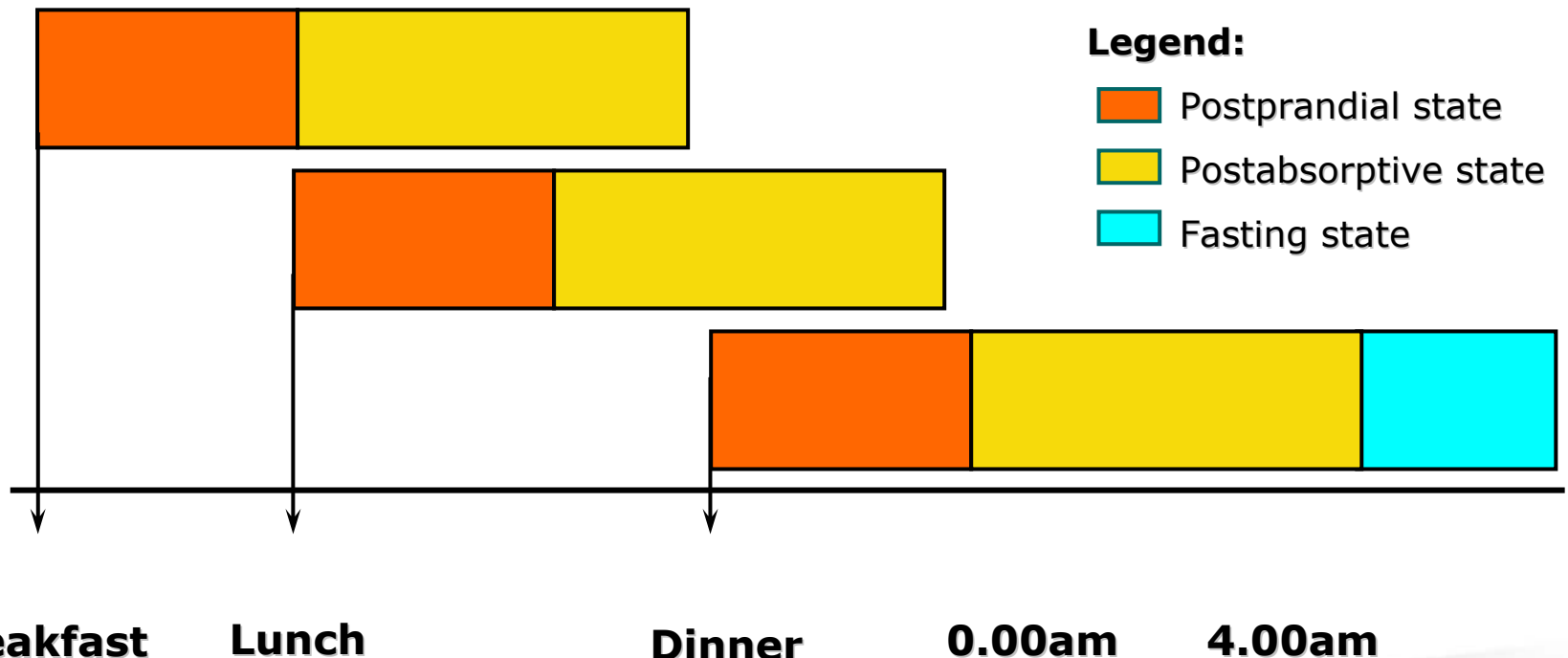
# Glucometabolic classification criteria

Glucometabolic category	Source	Classification criteria (mg/dL)
<b>Normal</b> glucose regulation (NGR)	WHO	FPG < 110 and 2-h PG < 140
	ADA 1997	FPG < 110
	ADA 2003	FPG < 100
<b>Impaired</b> fasting glucose (IFG)	WHO	FPG ≥ 110 and <126 and 2-h PG < 140
	ADA 1997	FPG ≥ 110 and FPG < 126
	ADA 2003	FPG ≥ 100 and FPG < 126
glucose tolerance (IGT)	WHO	FPG < 126 and 2-h PG ≥ 140 and < 200
glucose homeostasis (IGH)	WHO	IFG or IGT
<b>Diabetes Mellitus</b> (DM)	WHO	FPG ≥ 126 or 2-h PG ≥ 200
	ADA 1997	FPG ≥ 126 or 2-h PG ≥ 200
	ADA 2003	FPG ≥ 126 or 2-h PG ≥ 200

FPG fasting plasma glucose,  
2-h PG two hours post load plasma glucose

# Identifying hyperglycaemia – why measuring FPG is not good enough?

Most of our lives are spent in the postprandial state



*Monnier L. Eur J Clin Invest 2000; 30 (Suppl 2): 3*

# Diabetes mellitus - complications

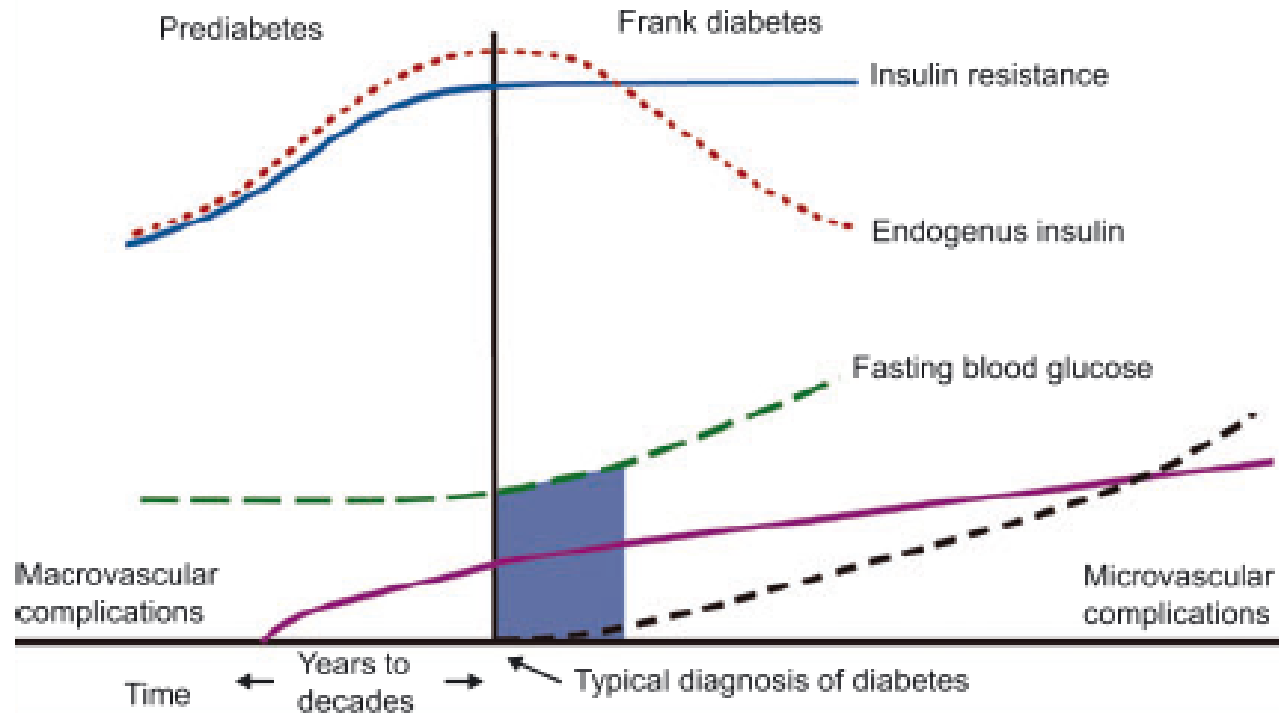
- ♥ The prevalence of retinopathy starts to increase steeply at certain glucose values, which were primarily used as cutpoints for diabetes.

FPG > 6.4 mmol/L (116 mg/dL), 2h-PG >10.3 (185), HbA1c of 6.0%

- ♥ The vast majority of patients with diabetes suffer and die from macrovascular complications:

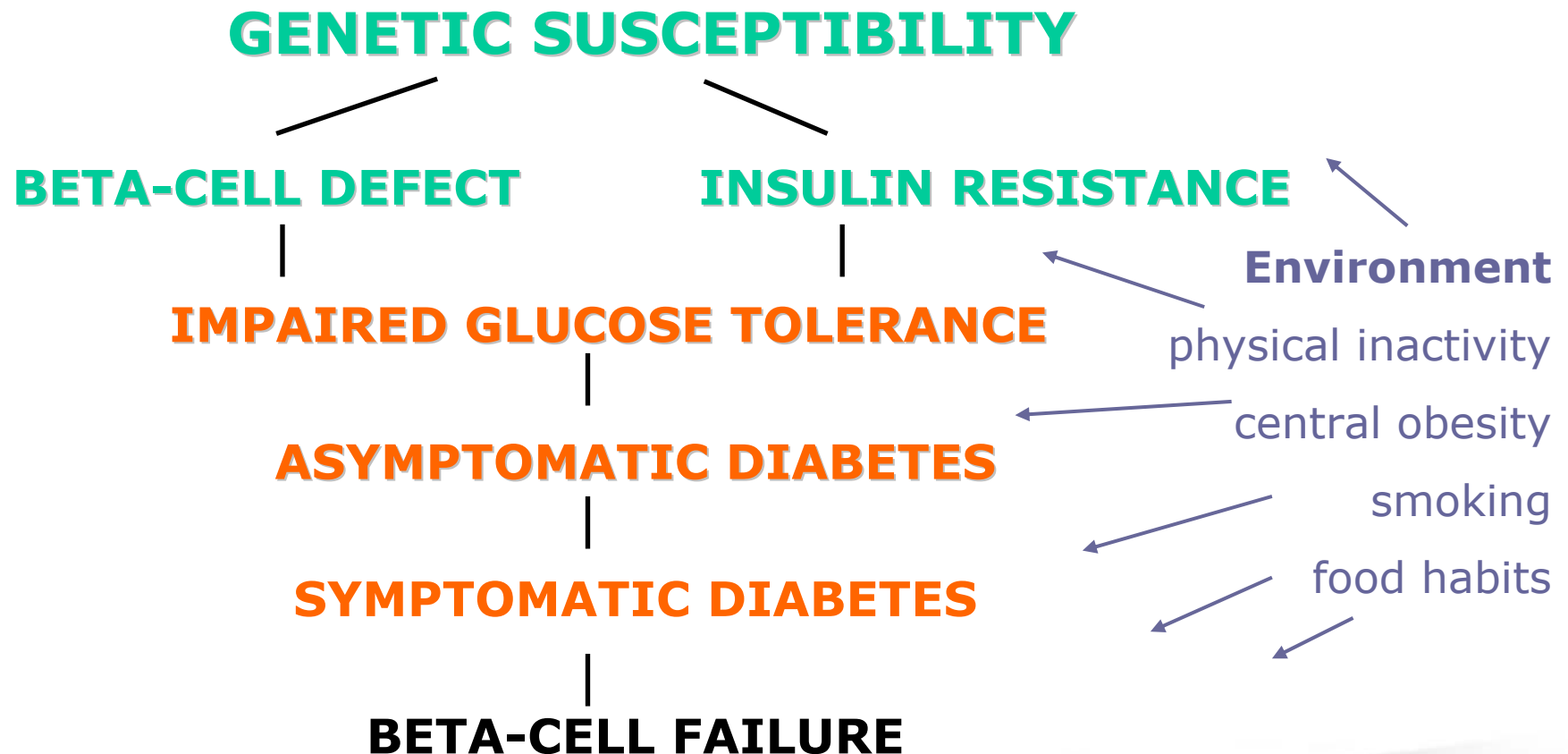
- cardiovascular,
- cerebrovascular and/or
- peripheral artery disease

# Development of complications in relation to hyperglycaemia (pre-diabetes, diabetes)

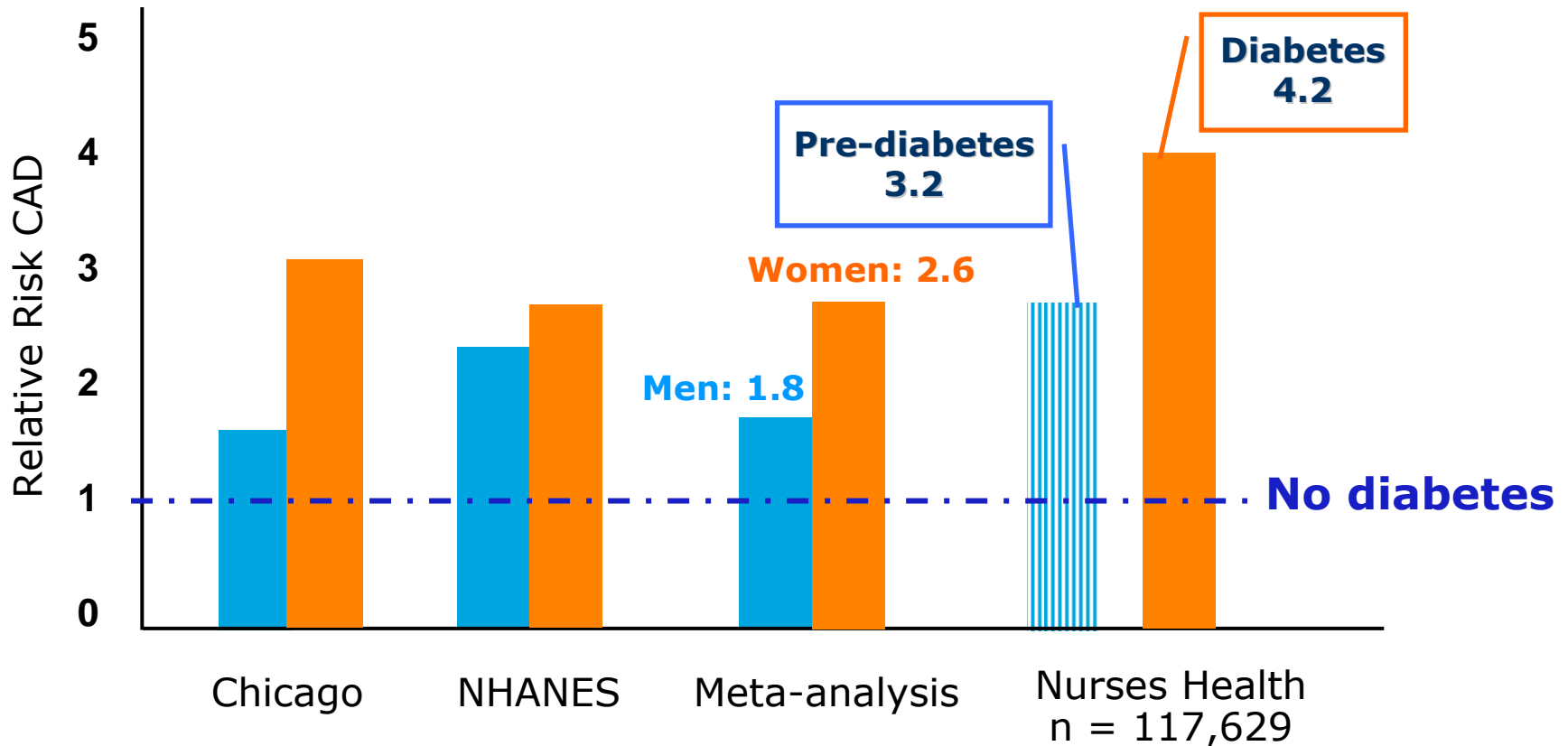


(Laakso et al. Europ Heart J 2003; 5 (suppl): B5-13)

# Stages in the natural history of type 2 diabetes



# Impact of diabetes and pre-diabetes for cardiovascular disease

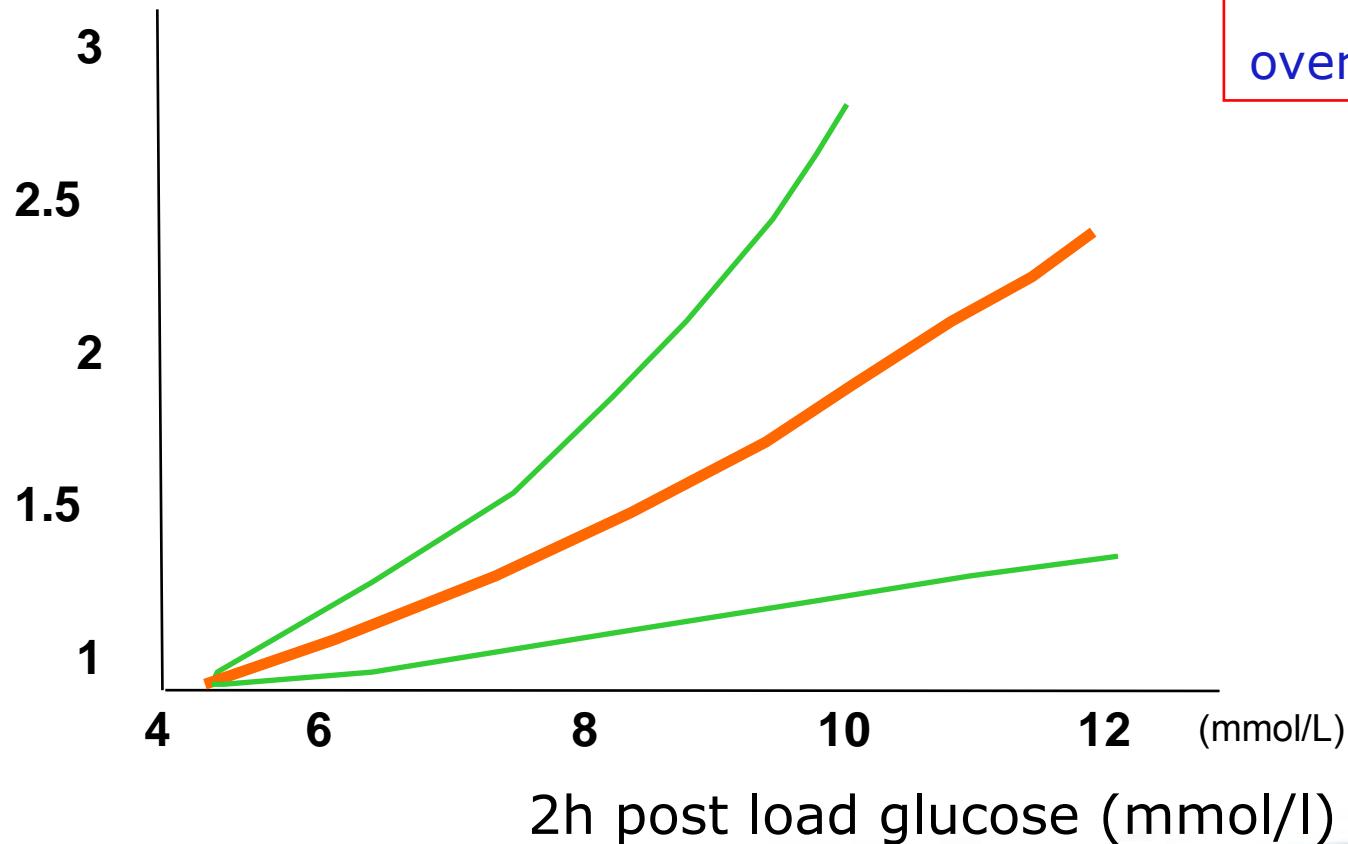


Lee WL et al. 2002; Hu et al. 2002

# Blood glucose - a continuous risk factor for cardiovascular disease

Relative Risk

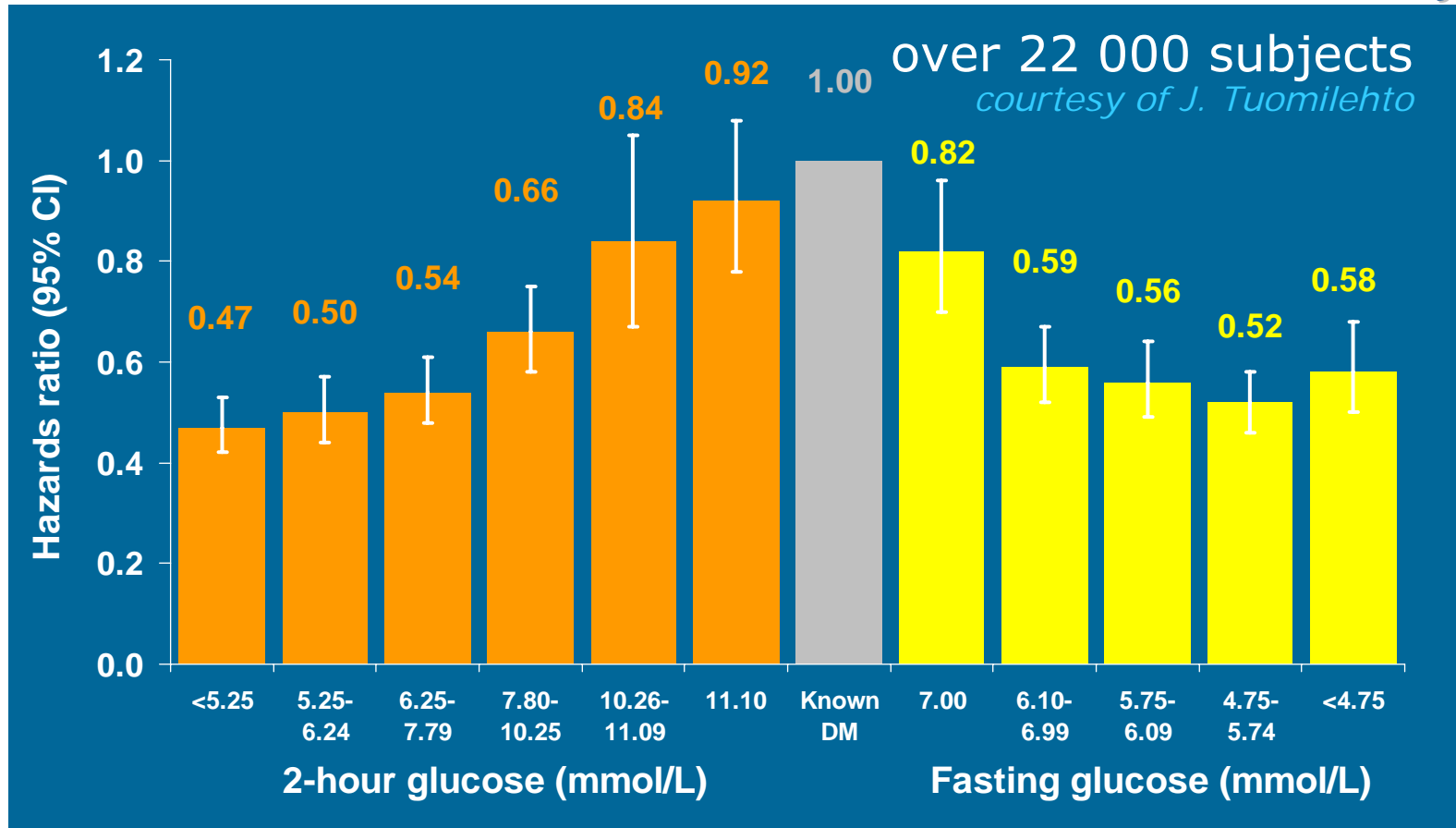
meta-analysis  
over 12 studies



*Coutinho et al. Diab Care 1999;22:659*

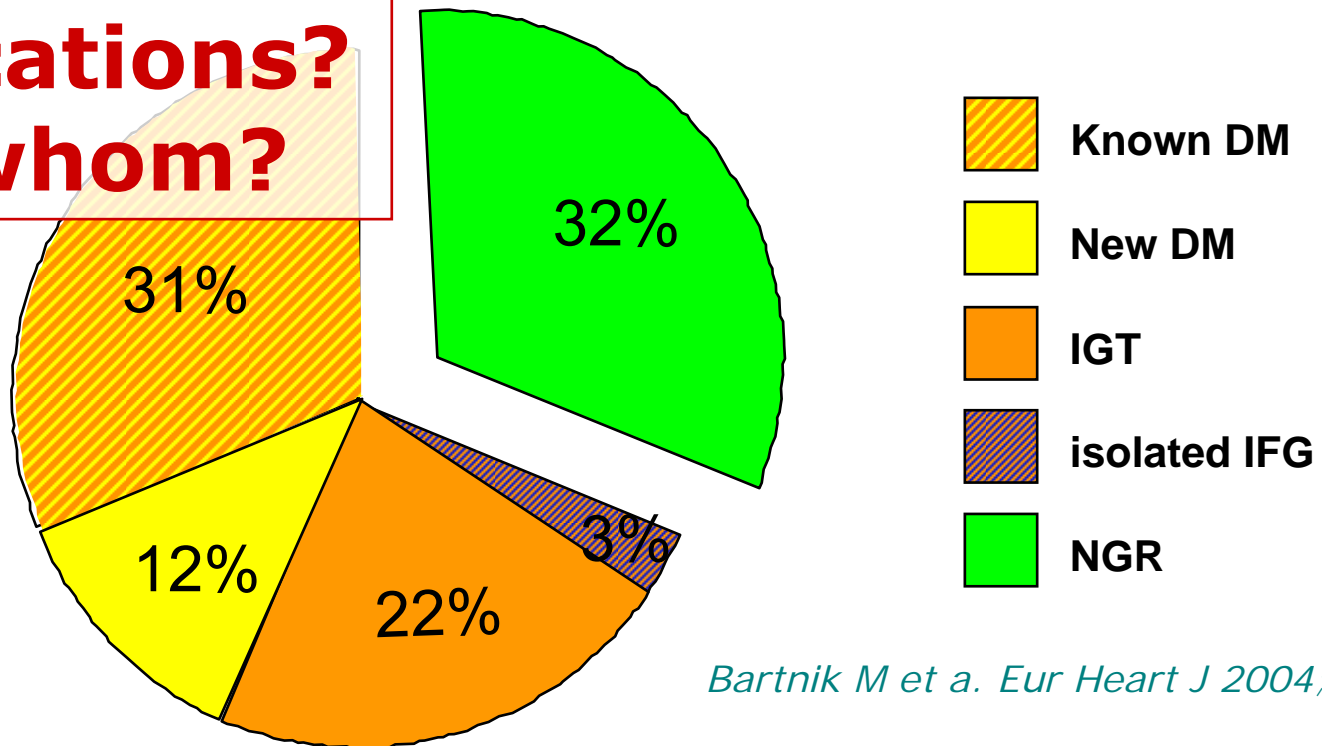
# All-cause mortality in asymptomatic people with elevated 2-hour PG compared to patients treated for diabetes

DECODE study



# The prevalence of hyperglycaemia (DM or IGH) estimated in patients with coronary artery disease

**implications?  
for whom?**

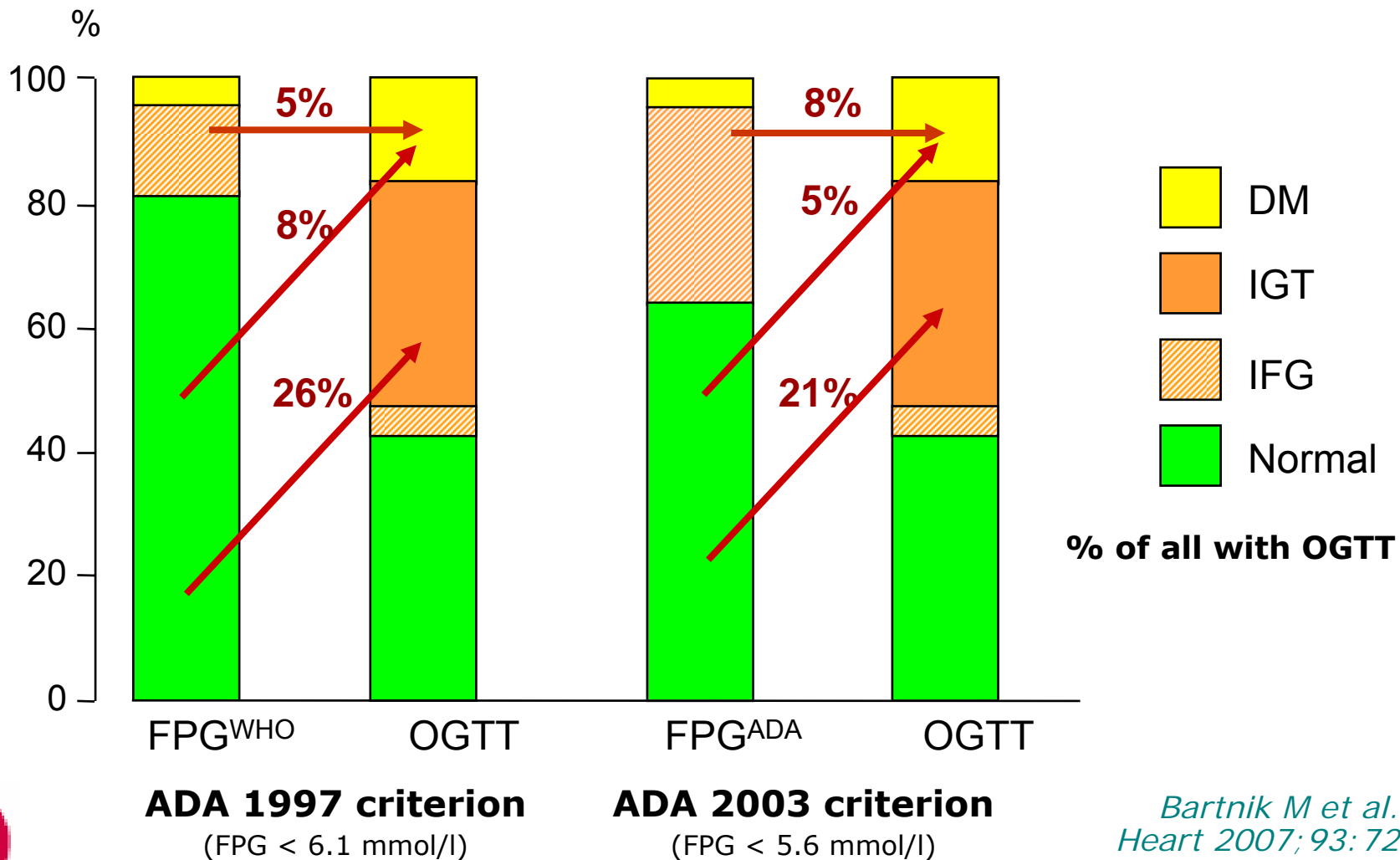


*Bartnik M et al. Eur Heart J 2004; 25:1880*

**Collaboration across speciality borders**

***Euro Heart Survey on Diabetes and the Heart***

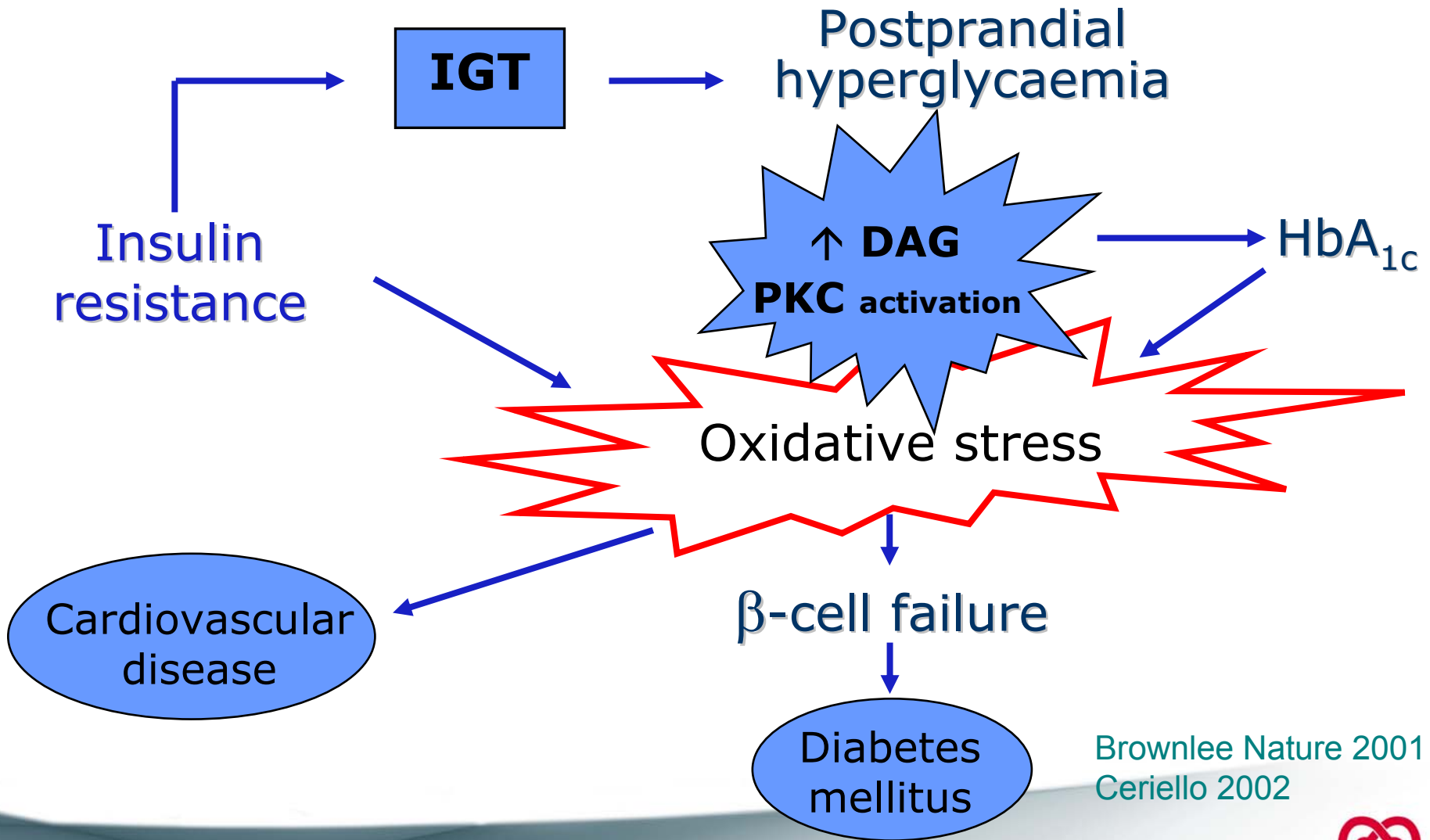
# Glucometabolic characterisation FPG versus OGTT in patients with CAD



# Recommendation regarding Diagnosis and Classification of diabetes and pre-diabetic states

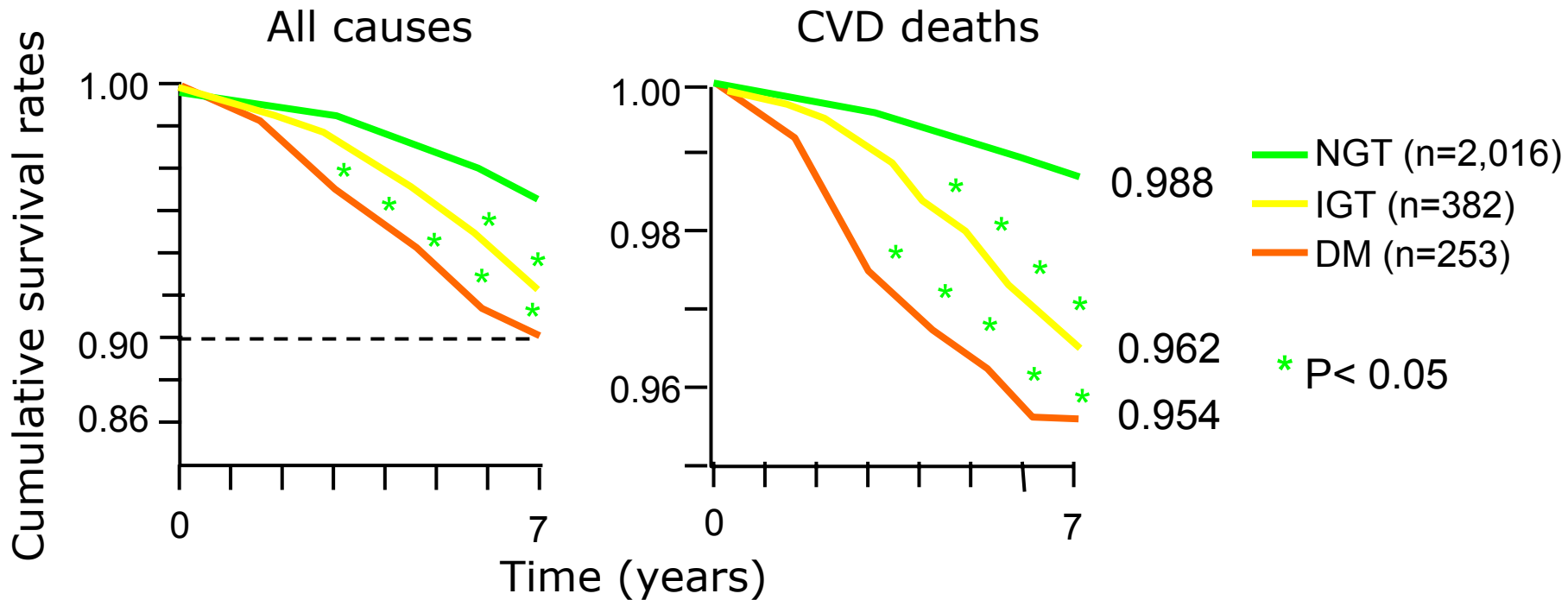
- ♥ Definition and diagnostic classification should be based on the level of subsequent risk of cardiovascular complications.
- ♥ Asymptomatic type 2 diabetes and early stages of hyperglycaemia are best identified by an OGTT - oral glucose tolerance test including both fasting and 2h-post load glucose values.

# Linking hyperglycaemia to macrovascular disease



Brownlee Nature 2001  
Ceriello 2002

# Impaired glucose tolerance (from IGT to overt DM) is a risk factor for death from cardiovascular diseases (CVD)



Tominaga M, et al. *Diabetes Care* 1999;22:920-924.