Targeting the Underlying Pathophysiology of Type 2 Diabetes
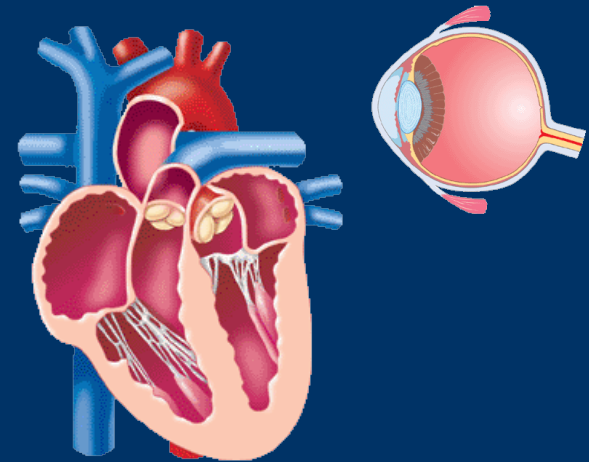
Aim

Provide practical guidance on improving diabetes care through highlighting the need to:

- understand that insulin resistance and β-cell dysfunction are core defects of type 2 diabetes

- address the underlying pathophysiology

Type 2 diabetes

- Characterized by chronic hyperglycemia

- Associated with microvascular and macrovascular complications

- Generally arises from a combination of insulin resistance and β-cell dysfunction

Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Department of Noncommunicable Disease Surveillance, World Health Organization, Geneva 1999. Available at: http://www.diabetes.org.uk/infocentre/carerec/diagnosi.doc

What is insulin resistance?

- Major defect in individuals with type 2 diabetes[1]

- Reduced biological response to insulin[1–3]

- Strong predictor of type 2 diabetes[4]
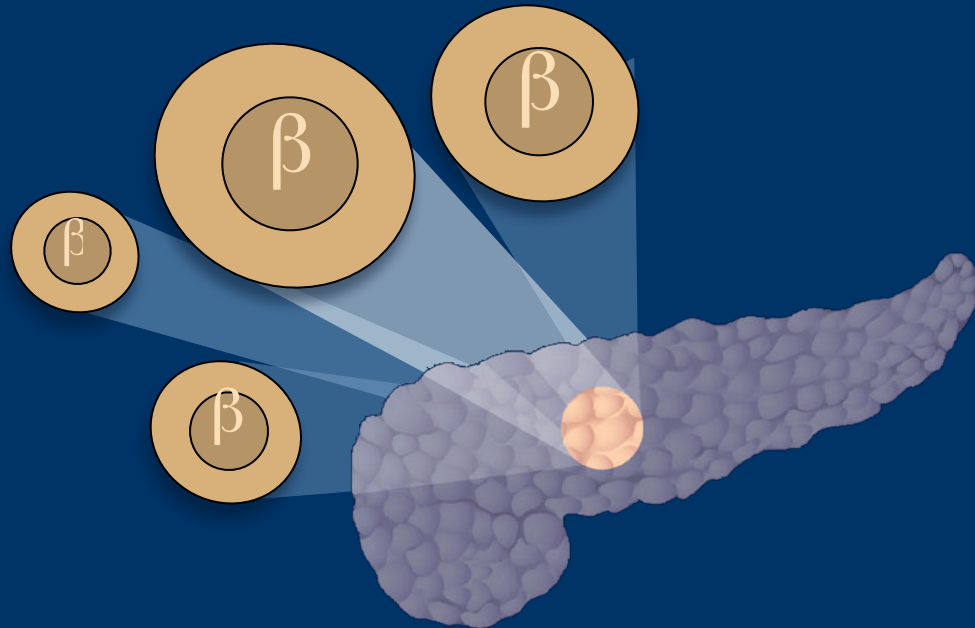
- Closely associated with obesity[5]
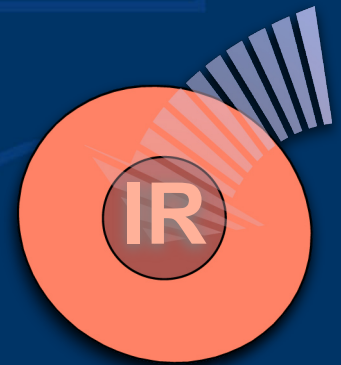
[1]American Diabetes Association. *Diabetes Care* 1998; 21:310–314.
[2]Beck-Nielsen H & Groop LC. *J Clin Invest* 1994; 94:1714–1721. [3]Bloomgarden ZT. *Clin Ther* 1998; 20:216–231.
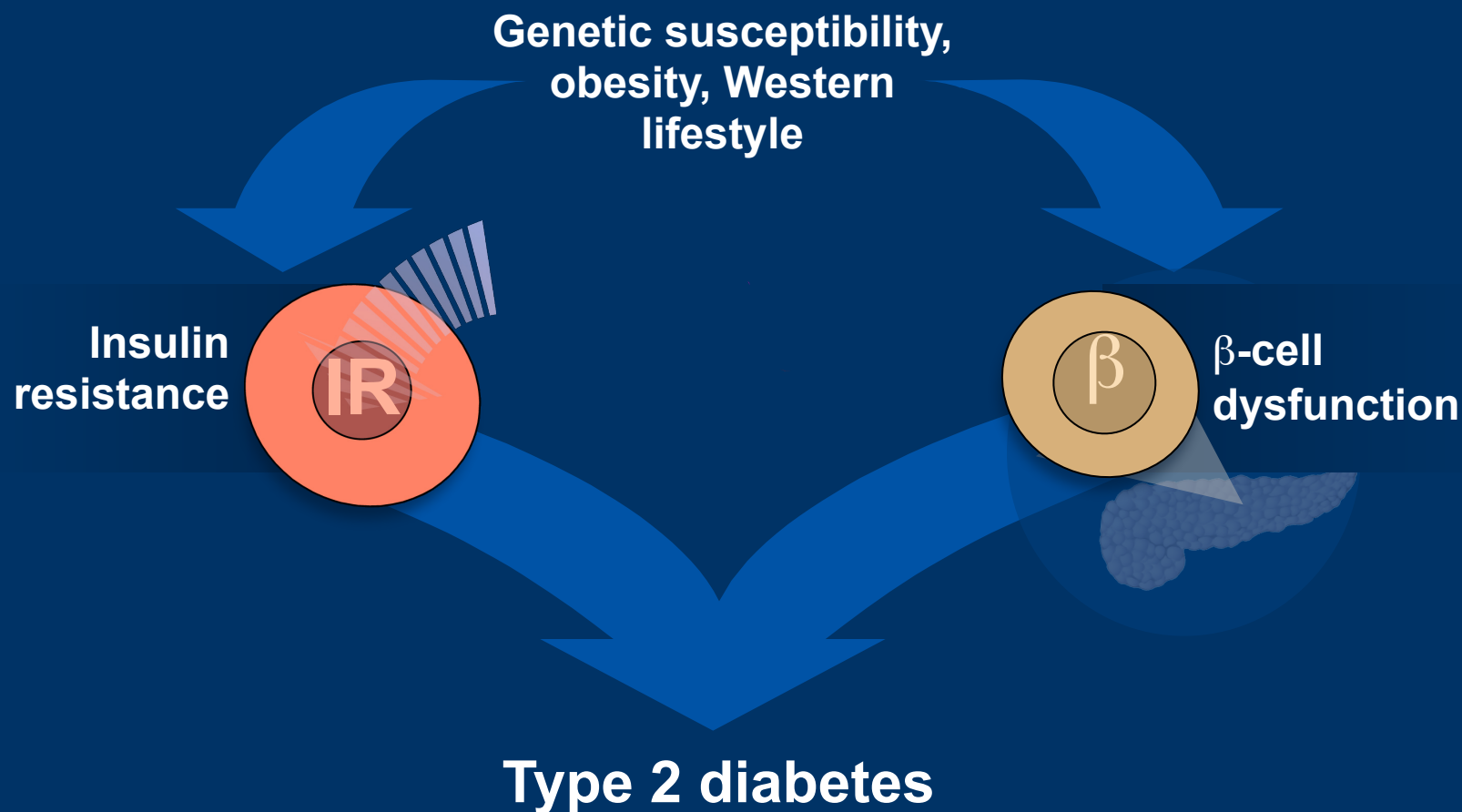[4]Haffner SM, *et al. Circulation* 2000; 101:975–980. [5]Boden G. *Diabetes* 1997; 46:3–10.

What is β-cell dysfunction?

- Major defect in individuals with type 2 diabetes

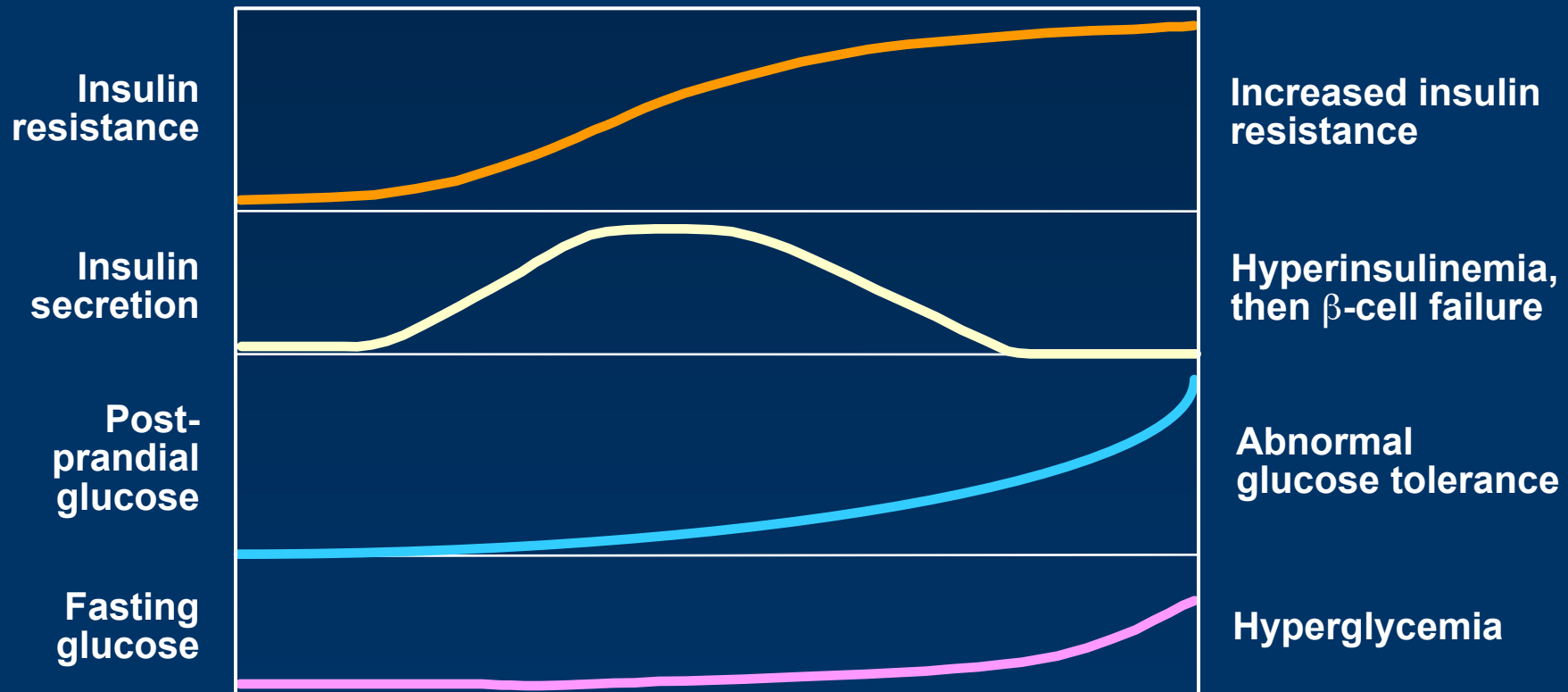- Reduced ability of β-cells to secrete insulin in response to hyperglycemia

DeFronzo RA, *et al. Diabetes Care* 1992; 15:318–354.

Insulin resistance and β-cell dysfunction are core defects of type 2 diabetes

Genetic susceptibility, obesity, Western lifestyle

Insulin resistance

IR

β

β-cell dysfunction

Type 2 diabetes

Rhodes CJ & White MF. *Eur J Clin Invest* 2002; 32 (Suppl. 3):3–13.

How do insulin resistance and β-cell dysfunction combine to cause type 2 diabetes?

Normal ⟶ IGT* ⟶ Type 2 diabetes

Insulin resistance	**Increased insulin resistance**
Insulin secretion	**Hyperinsulinemia, then β-cell failure**
Post-prandial glucose	**Abnormal glucose tolerance**
Fasting glucose	**Hyperglycemia**

*IGT = impaired glucose tolerance

How is insulin resistance measured?
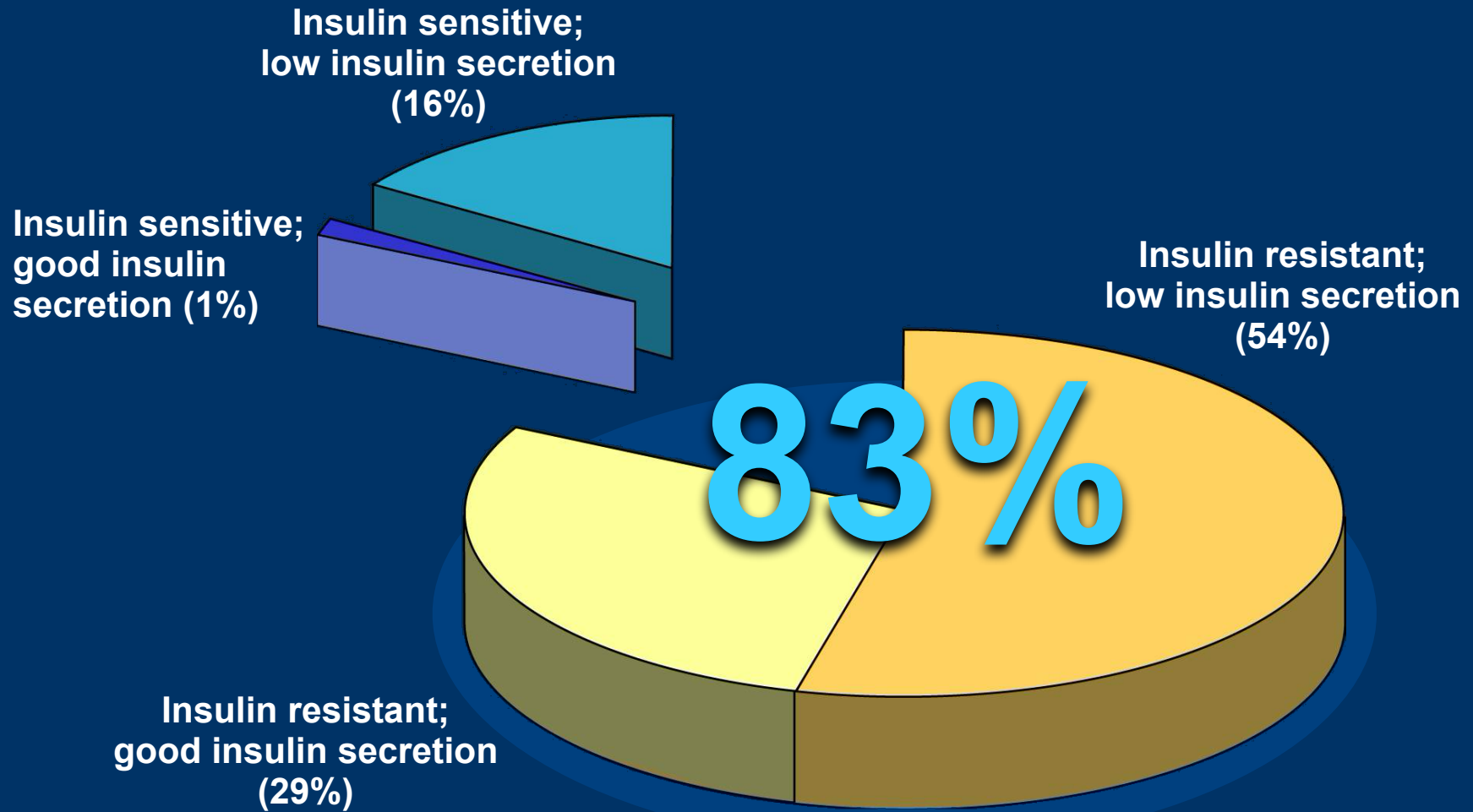
- Several methods exist, including:

    - continuous sampling of insulin/glucose[1]
        - gold standard, but impractical for large-scale use

    - single measure of insulin/glucose[2]
        - simple estimate from fasting insulin and glucose
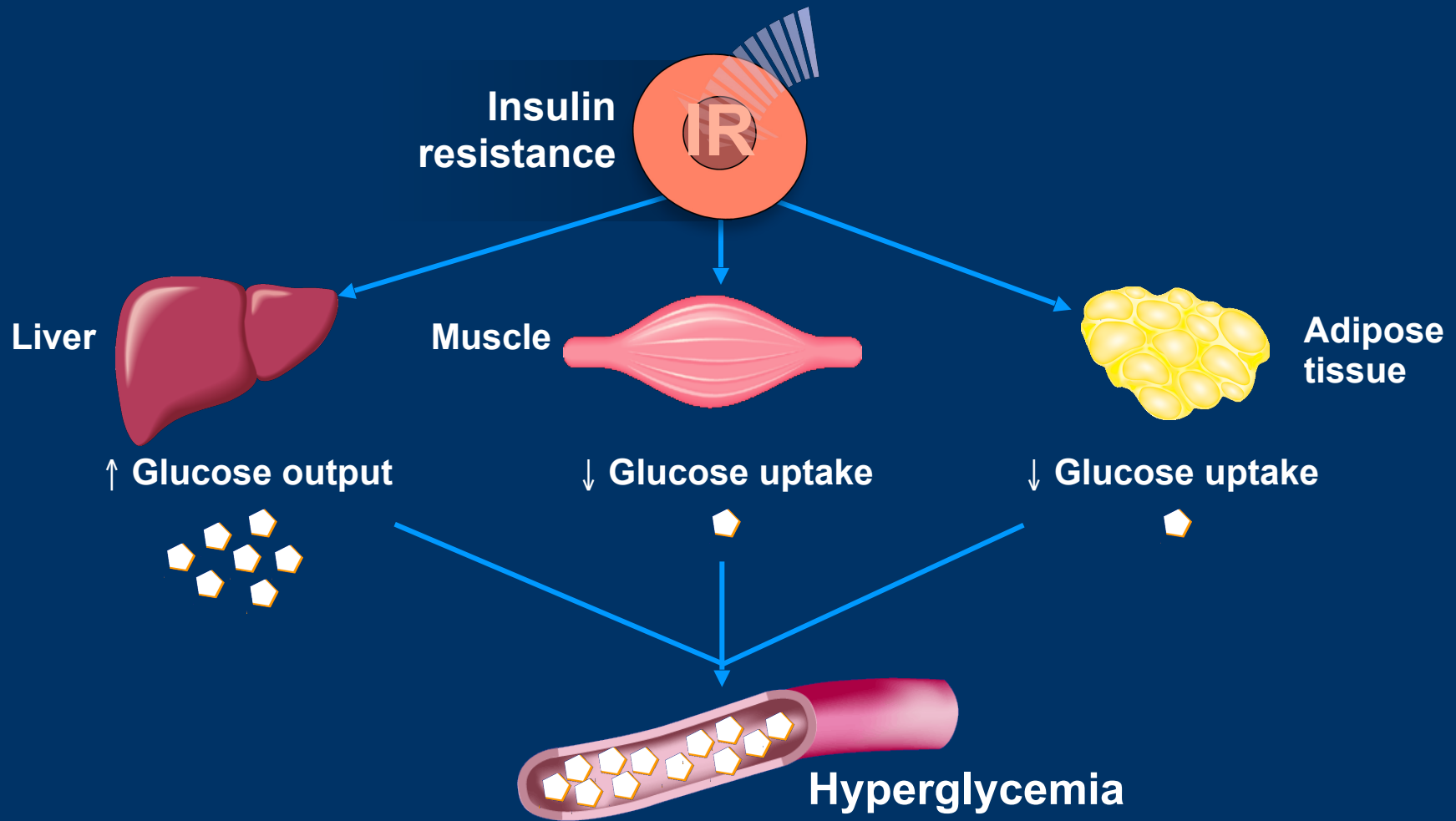   - useful for assessment on a larger scale
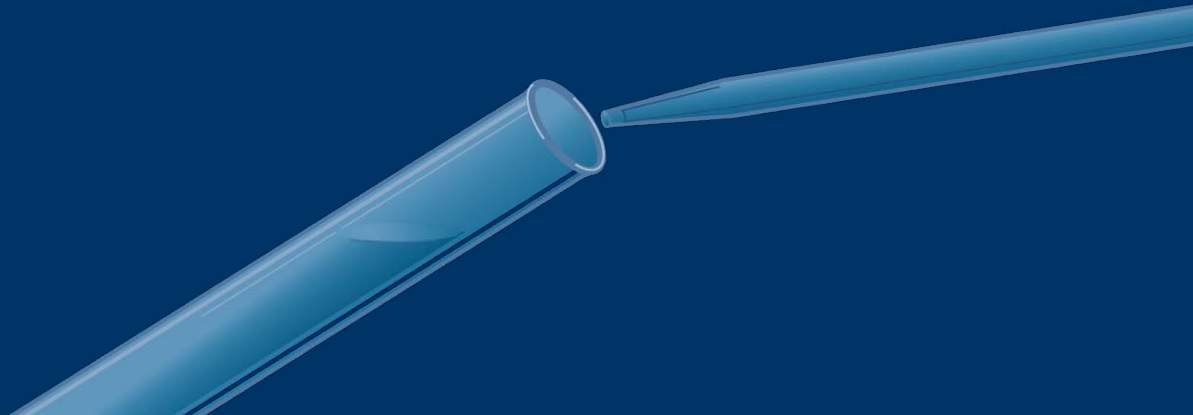
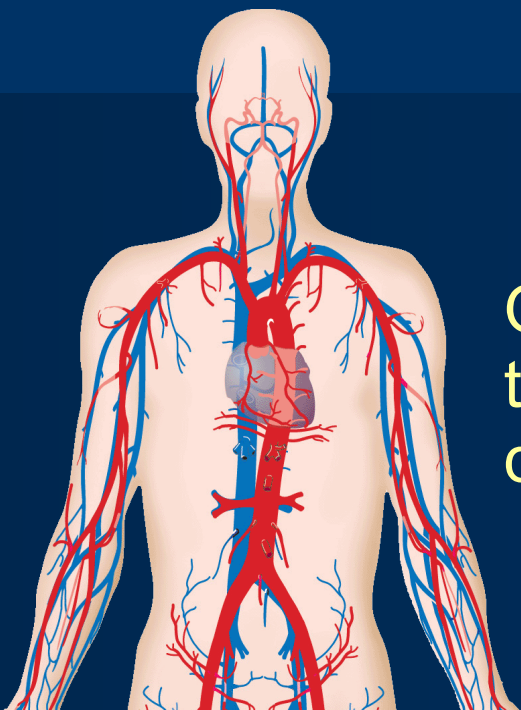[1]Bergman RN, *et al*. *Eur J Clin Invest* 2002; 32 (Suppl. 3):35–45.
[2]Matthews DR, *et al*. *Diabetologia* 1985; 28:412–419.

More than 80% of patients progressing to type 2 diabetes are insulin resistant

Insulin sensitive; low insulin secretion (16%)

Insulin sensitive; good insulin secretion (1%)

Insulin resistant; low insulin secretion (54%)

Insulin resistant; good insulin secretion (29%)

83%

Insulin resistance – reduced response to circulating insulin

Insulin resistance

IR

Liver — ↑ Glucose output

Muscle — ↓ Glucose uptake

Adipose tissue — ↓ Glucose uptake

Hyperglycemia

Overall, 75% of patients with
type 2 diabetes die from cardiovascular
disease

Gray RP & Yudkin JS. Cardiovascular disease in diabetes mellitus. In *Textbook of Diabetes* 2nd Edition, 1997. Blackwell Sciences.

Insulin resistance is as strong a risk factor for cardiovascular disease as smoking

Bonora E, *et al. Diabetes Care* 2002; 25:1135–1141.
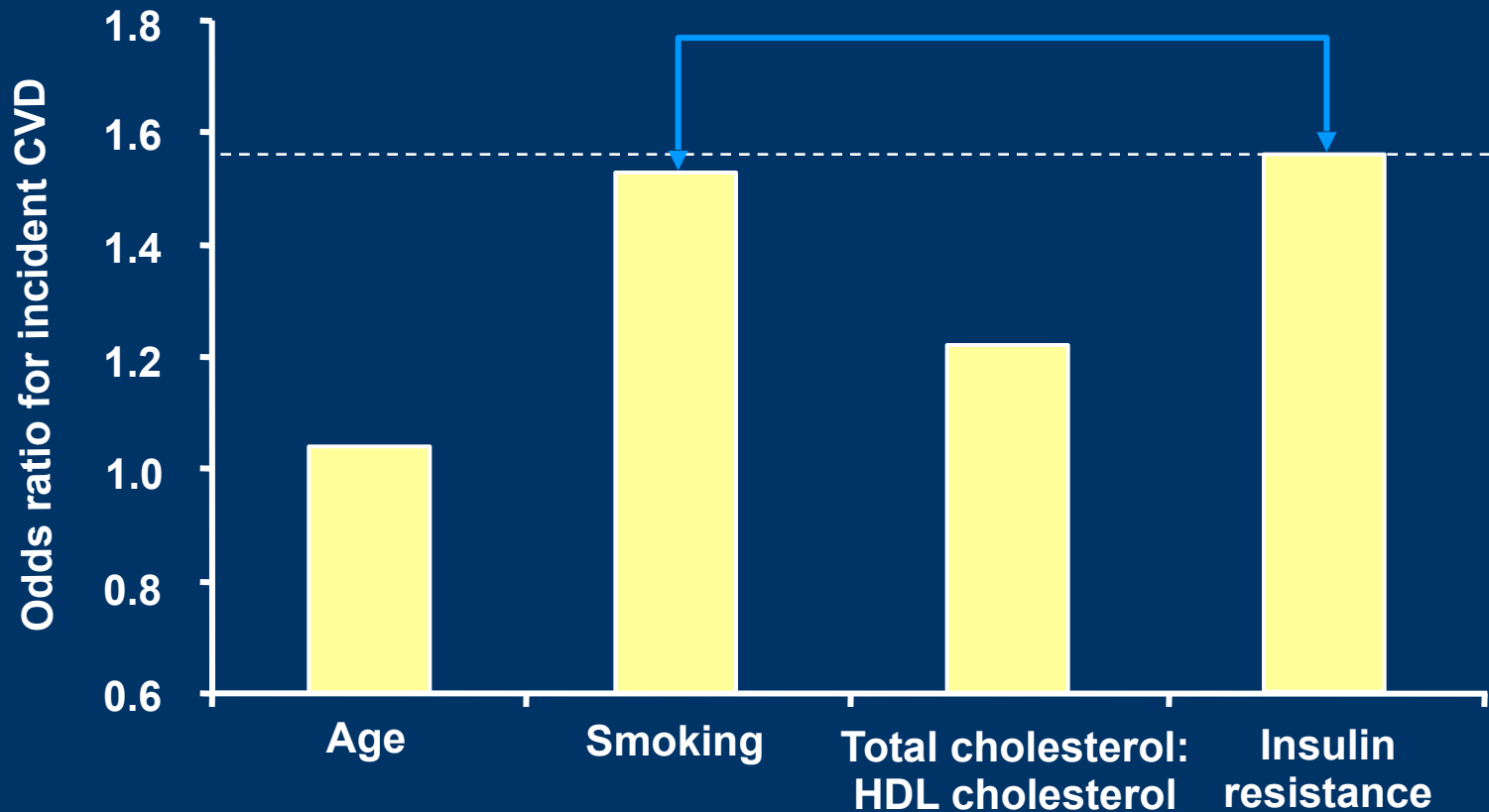
Insulin resistance is closely linked to cardiovascular disease

Insulin resistance

IR

Present in **> 80%** of people with type 2 diabetes[1]

Approximately **doubles** the risk of a cardiac event[2]

Implicated in almost **half** of CHD events in individuals with type 2 diabetes[2]
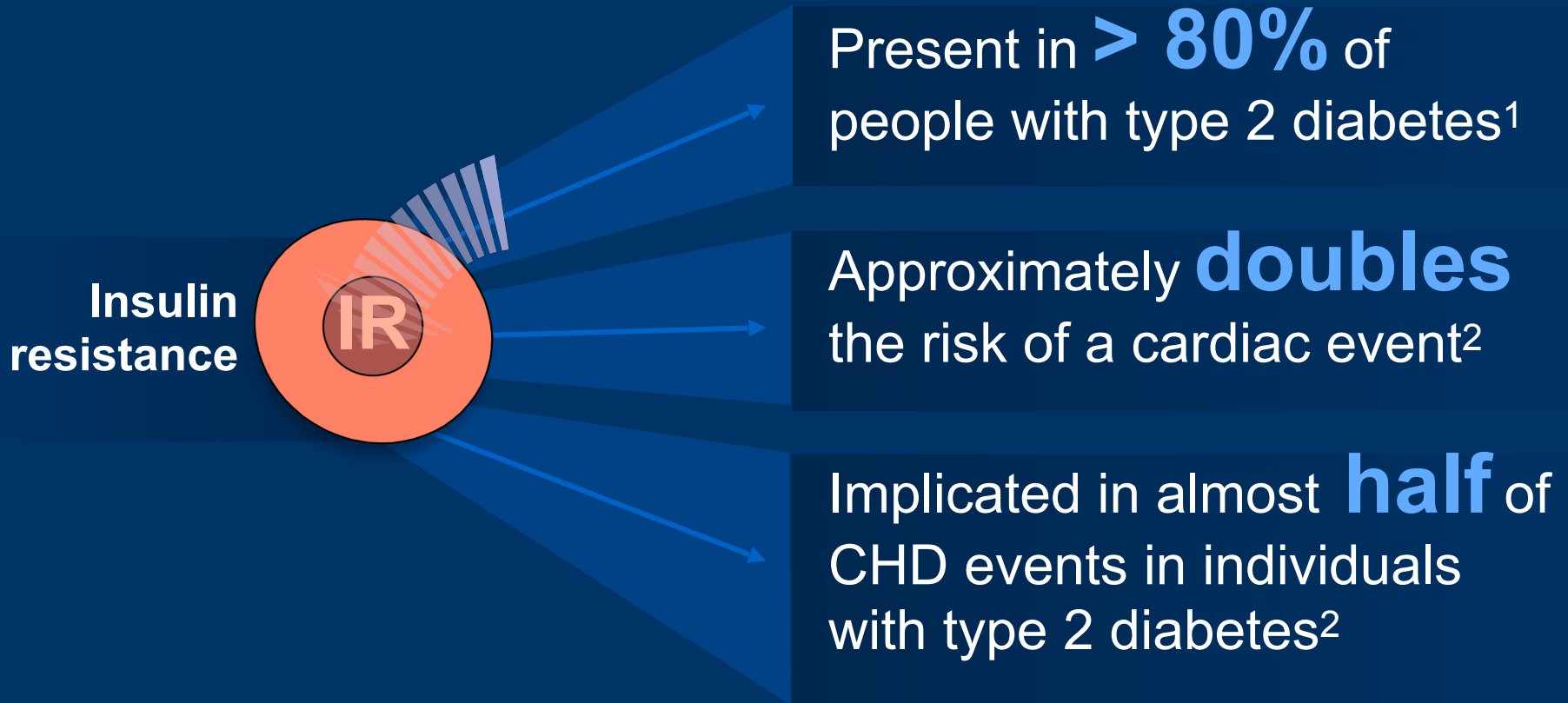
[1]Haffner SM, *et al. Circulation* 2000; 101:975–980.
[2]Strutton D, *et al. Am J Man Care* 2001; 7:765–773.

Insulin resistance is linked to a range of cardiovascular risk factors

Insulin resistance **IR**

Hyperglycemia

Dyslipidemia

Hypertension

Damage to blood vessels

Clotting abnormalities

Inflammation

Atherosclerosis

Zimmet P. *Trends Cardiovasc Med* 2002; 12:354–362.
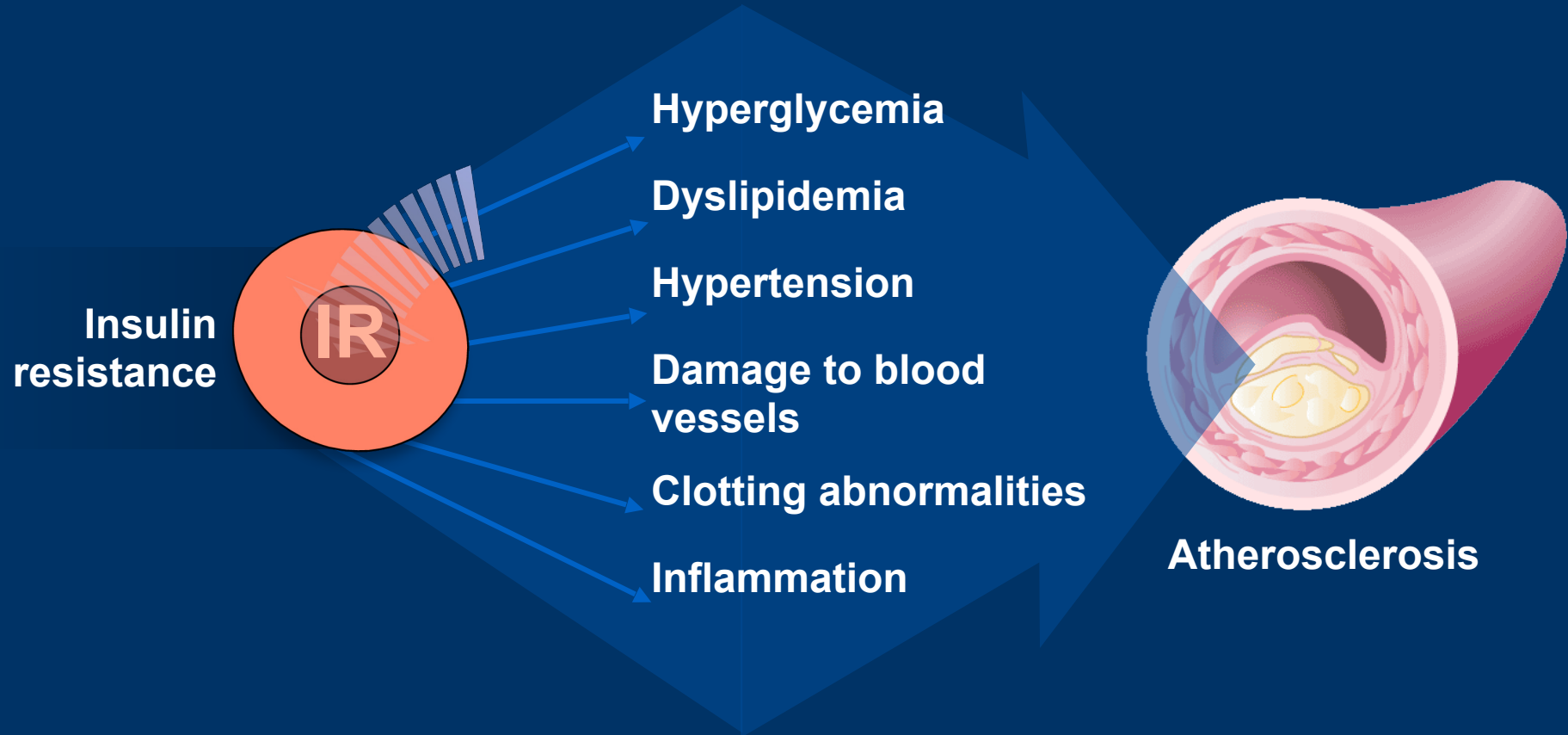
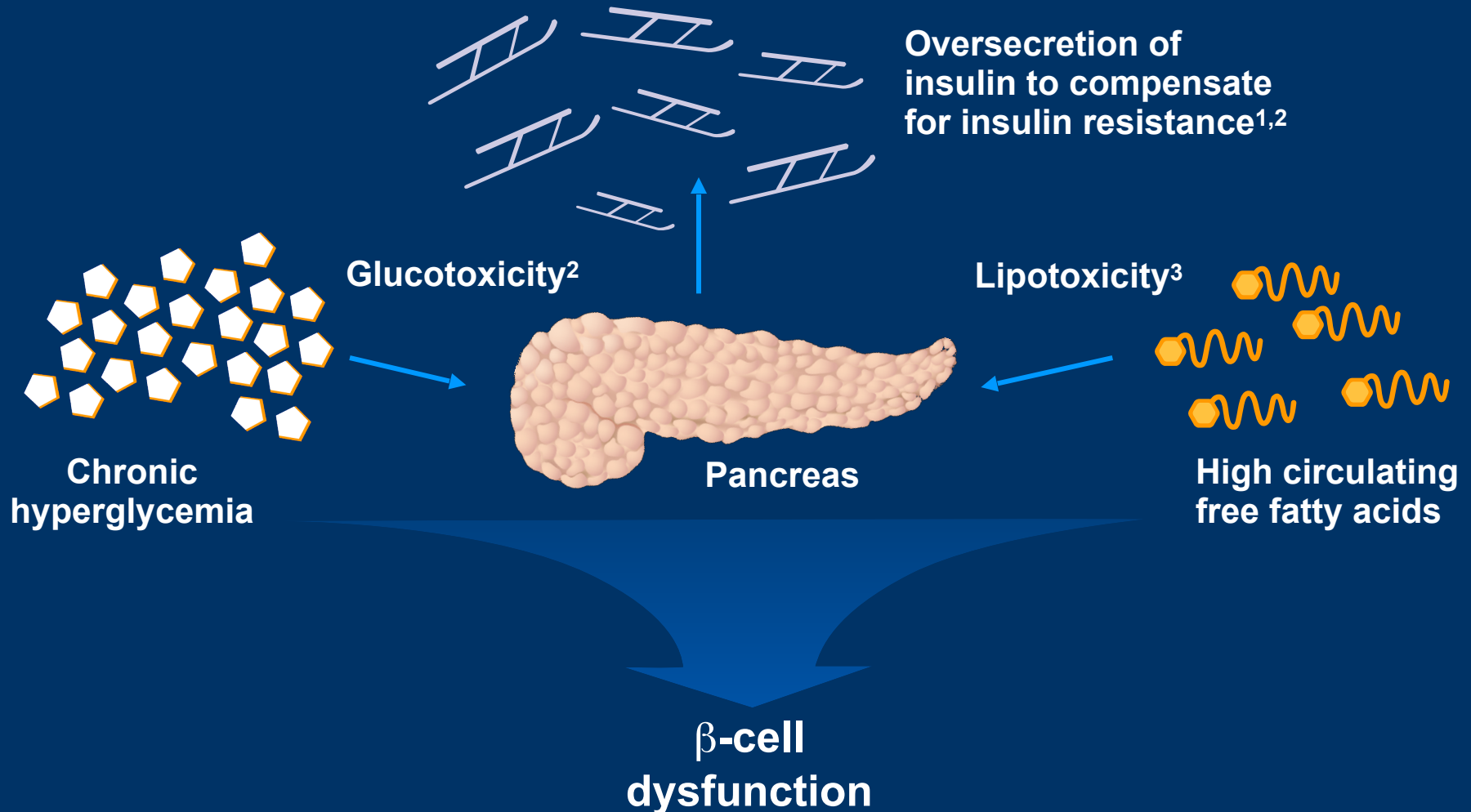~90% of people with type 2 diabetes are overweight or obese

How is β-cell function measured?

- β-cell function is difficult to measure and most methods are impractical for large-scale use[1]

- Homeostasis model assessment (HOMA) provides a simple estimate of β-cell function[2]

- Proinsulin:insulin ratio is sometimes used as a marker of β-cell dysfunction[1]

[1]Matthews DR, *et al. Diabetologia* 1985; 28:412–419.

Why does the β-cell fail?

Oversecretion of insulin to compensate for insulin resistance[1,2]

Glucotoxicity[2]

Lipotoxicity[3]

Chronic hyperglycemia

Pancreas

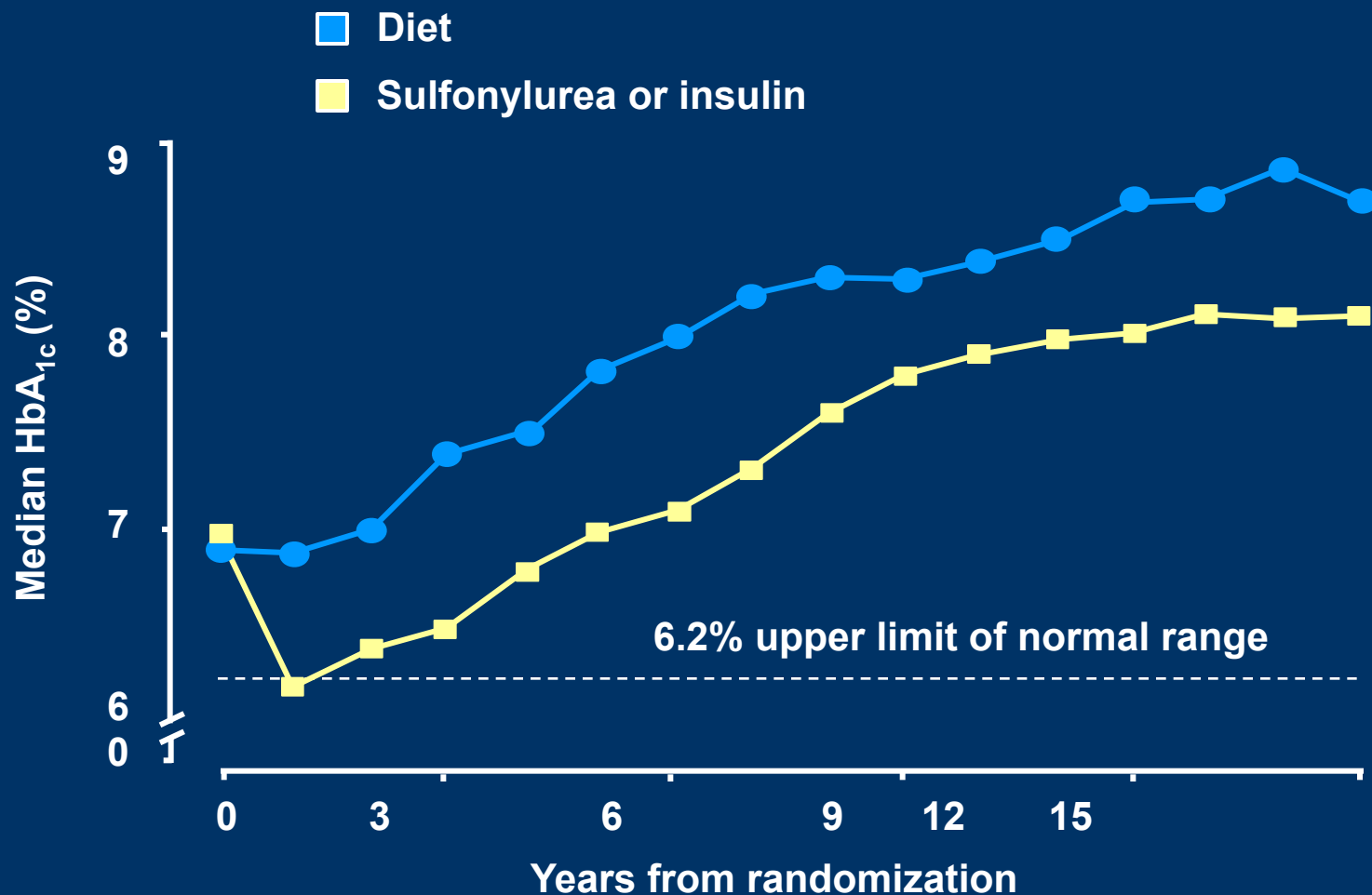High circulating free fatty acids

β-cell dysfunction

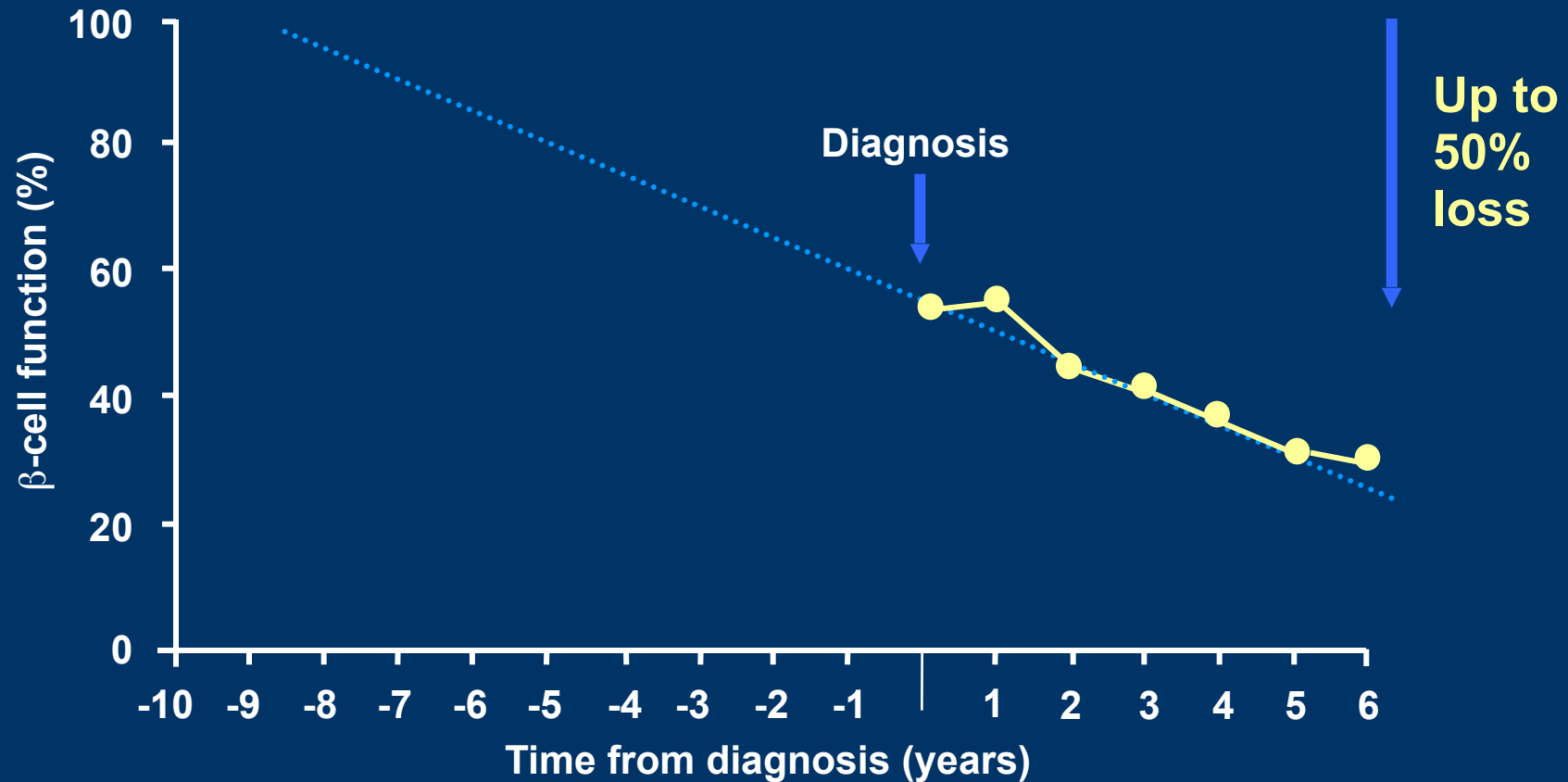[1]Boden G & Shulman GI. *Eur J Clin Invest* 2002; 32:14–23.
[2]Kaiser N, *et al. J Pediatr Endocrinol Metab* 2003; 16:5–22.
[3]Finegood DT & Topp B. *Diabetes Obes Metab* 2001; 3 (Suppl. 1):S20–S27.

Glycemic control declines over time

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:837–853.

Loss of β-cell function occurs before diagnosis

Holman RR. *Diabetes Res Clin Prac* 1998; 40 (Suppl.):S21–S25.

Oral antidiabetic agents – do they target insulin resistance and
β-cell dysfunction?

Barriers to achieving good glycemic control

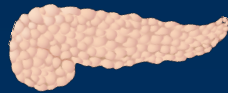Inadequate targeting of underlying pathophysiology

Primary sites of action of oral antidiabetic agents

α-glucosidase inhibitors

Sulfonylureas/ meglitinides

Biguanides

Thiazolidinediones

↓ **Carbohydrate breakdown/ absorption**

↑ **Insulin secretion**

↓ **Glucose output**
↓ **Insulin resistance**

↓ **Insulin resistance**

Kobayashi M. *Diabetes Obes Metab* 1999; 1 (Suppl. 1):S32–S40.
Nattrass M & Bailey CJ. *Baillieres Best Pract Res Clin Endocrinol Metab* 1999; 13:309–329.
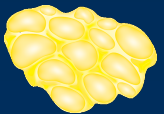
The dual action of thiazolidinediones reduces HbA$_{1c}$

Insulin resistance — IR

β

β-cell function

+

HbA$_{1c}$

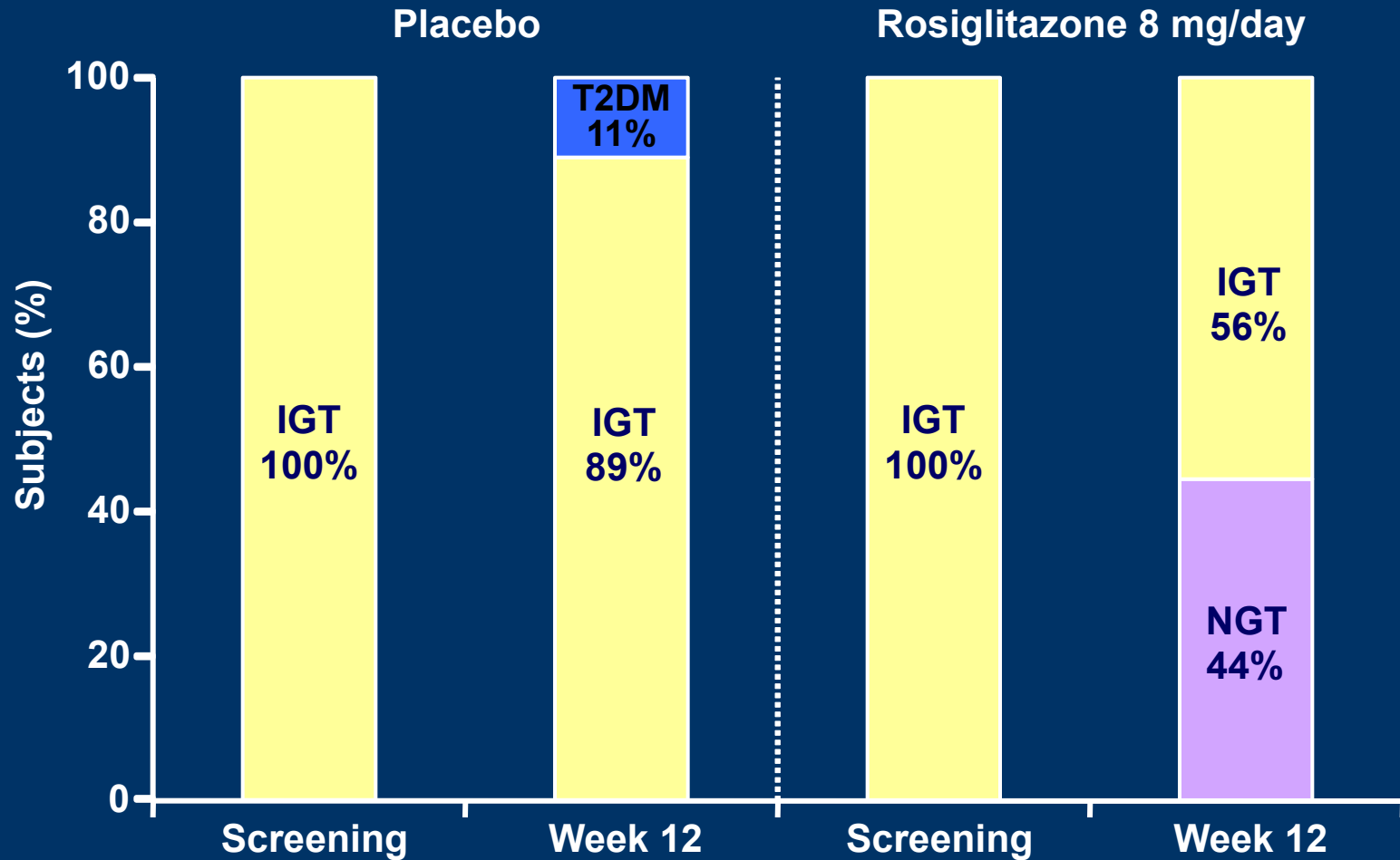Lebovitz HE, *et al. J Clin Endocrinol Metab* 2001; 86:280–288.
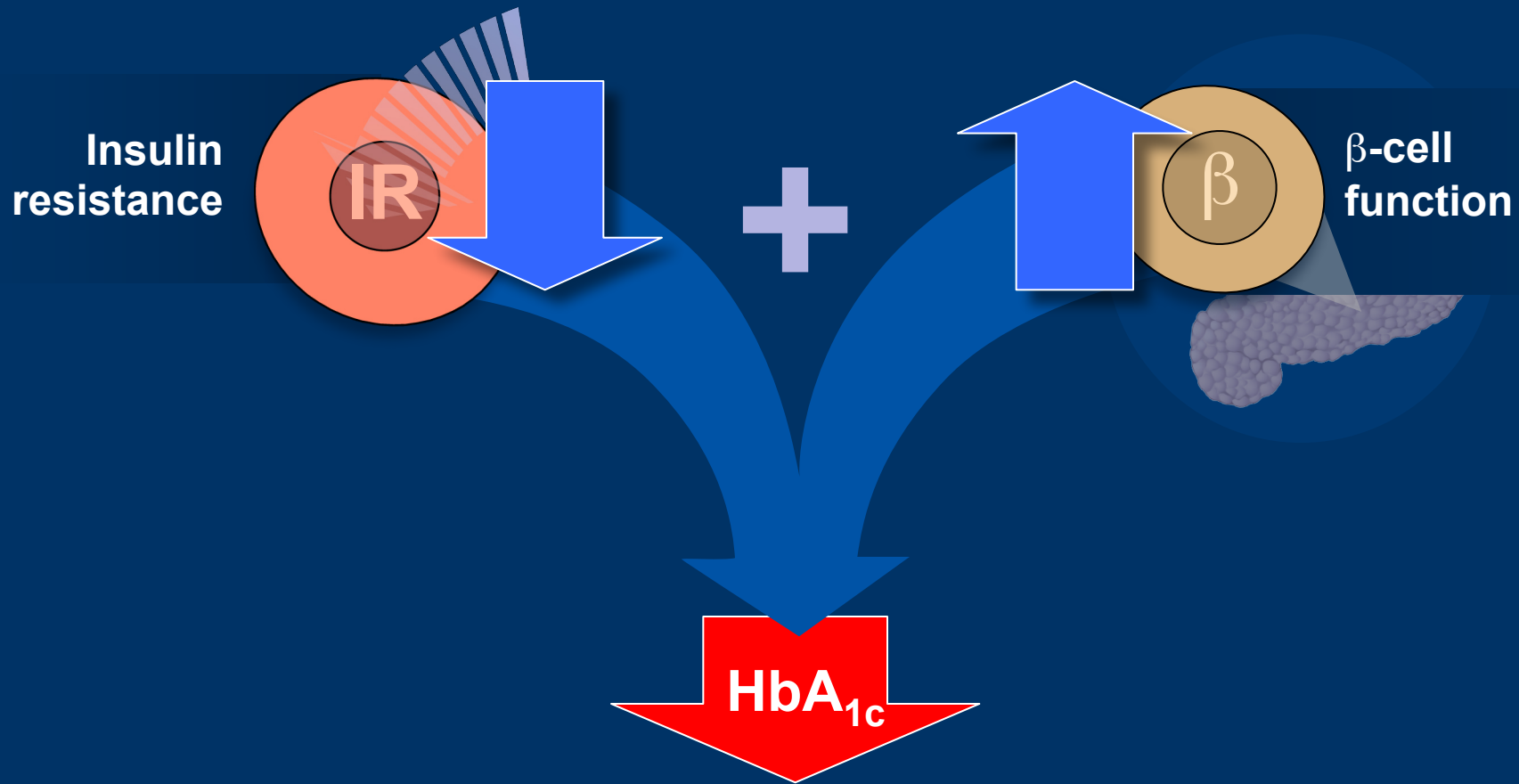
Potential to prevent progression to type 2 diabetes in at-risk women

Troglitazone reduced progression to type 2 diabetes by > 50%
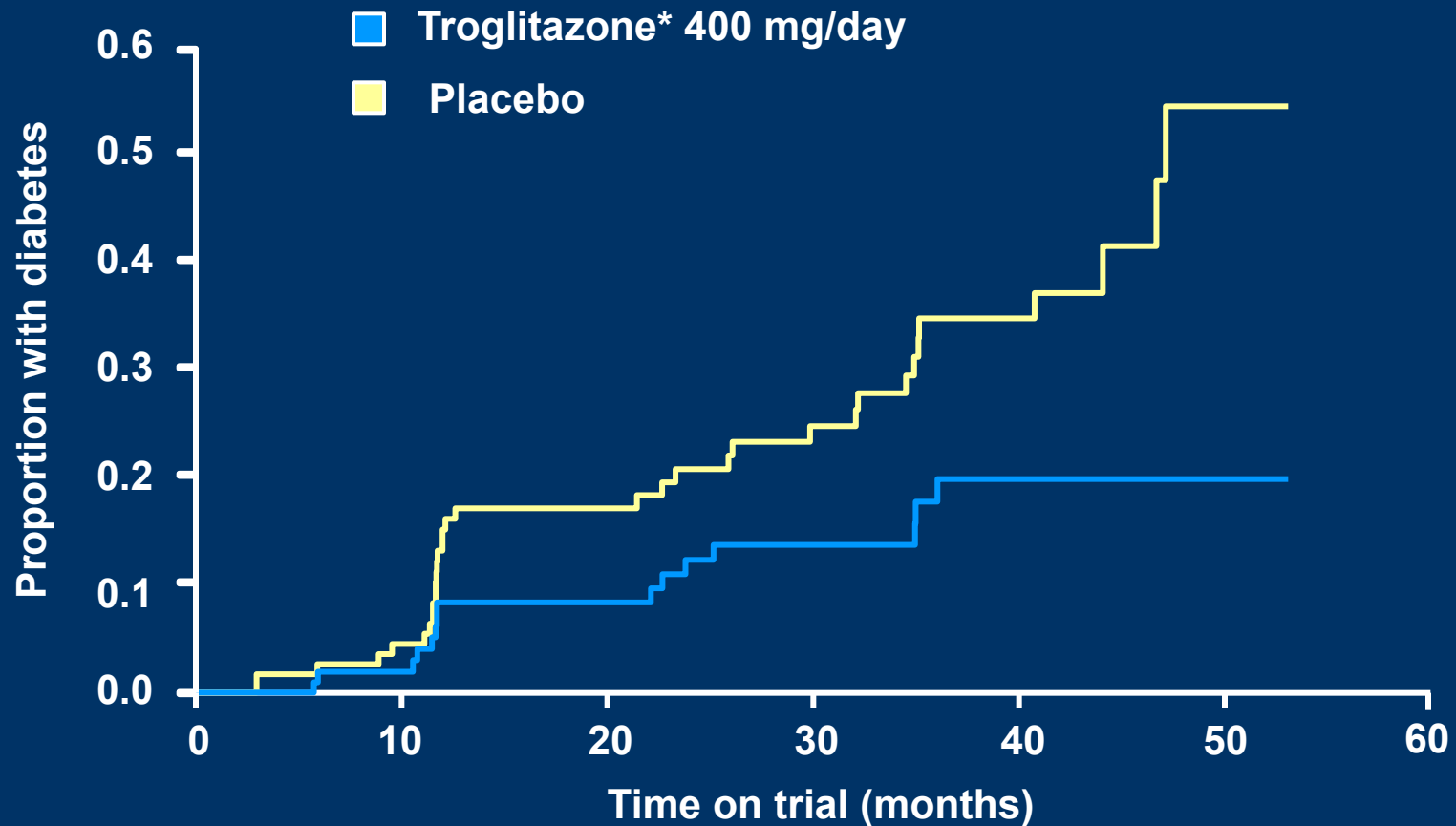
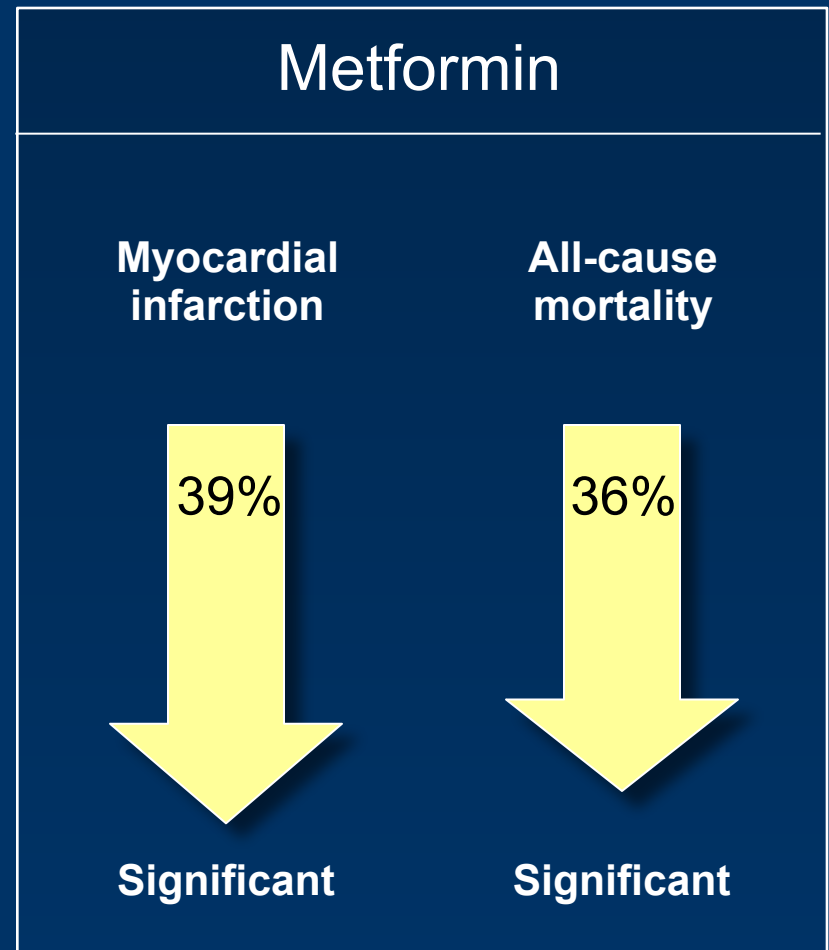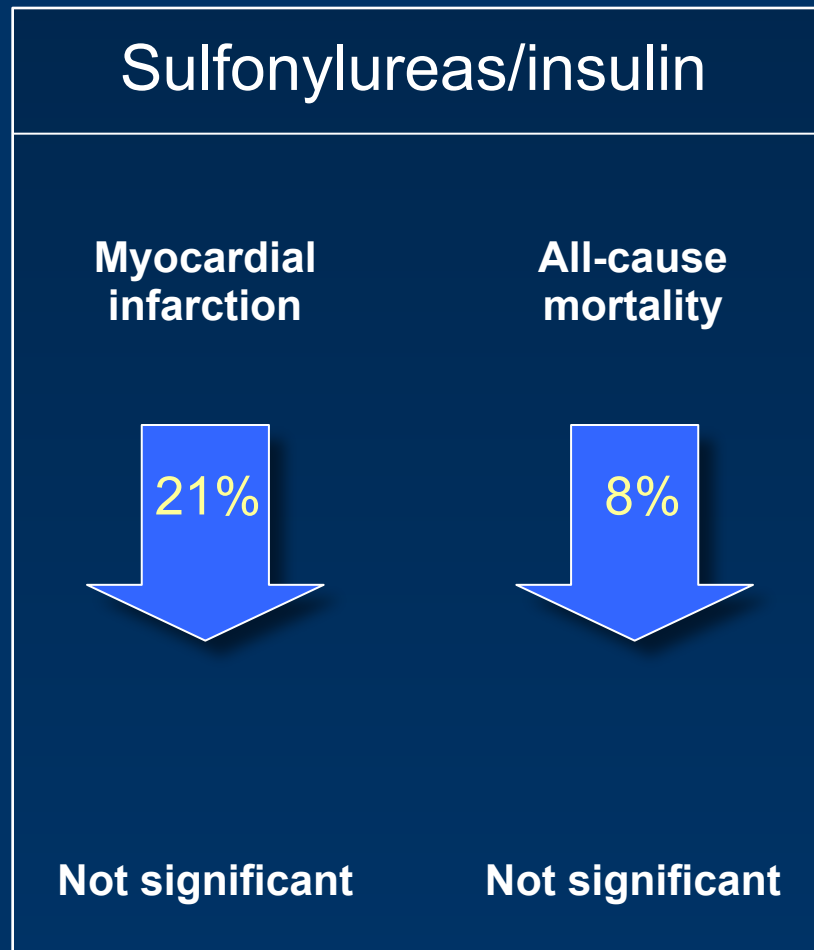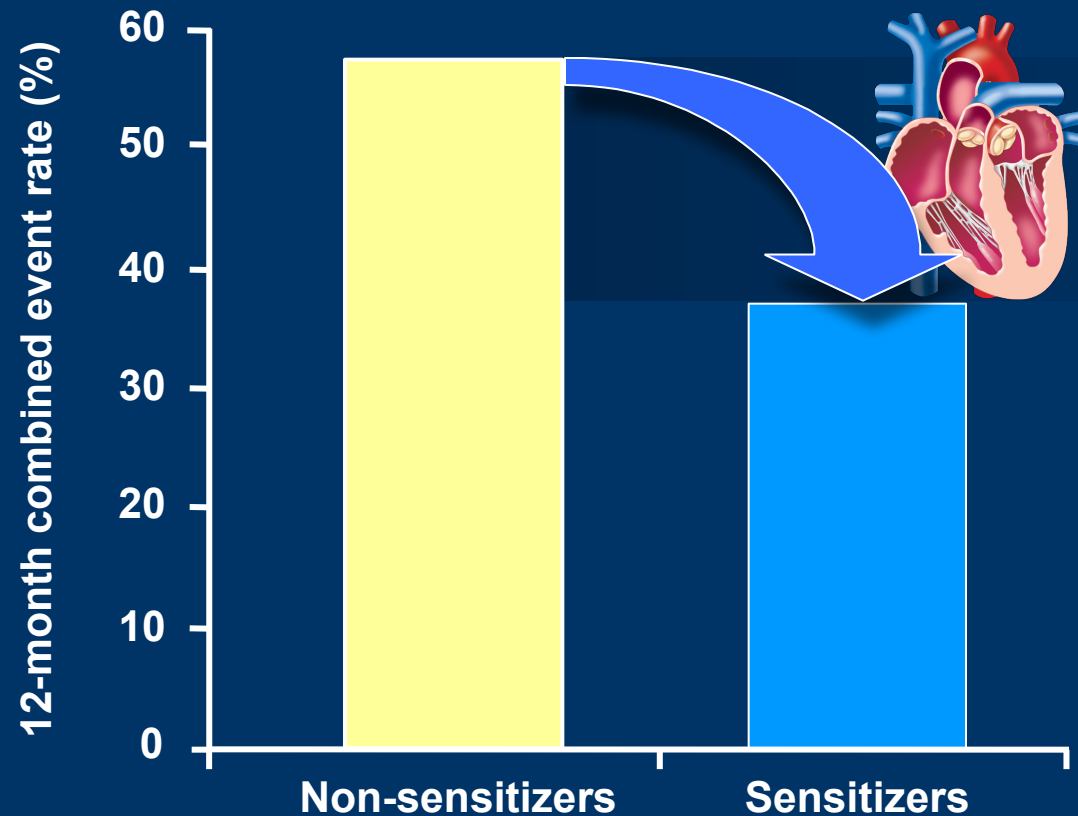*Troglitazone is no longer available

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

Can thiazolidinediones delay progression from IGT to T2DM?

Bennett SM, *et al. Diabet Med* 2004; 21:415–422.

Does decreasing insulin resistance decrease macrovascular complications?

Sulfonylureas/insulin		Metformin	
Myocardial infarction	**All-cause mortality**	**Myocardial infarction**	**All-cause mortality**
21%	8%	39%	36%
Not significant	**Not significant**	**Significant**	**Significant**

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352:854–865.

Insulin sensitizers reduce cardiovascular events in type 2 diabetes

Kao JA, *et al. J Am Coll Cardiol* 2004; 43:37A.

How can diabetes care and outcomes be improved?

SLOW

Disease Progression

The Global Partnership recommends:

Address the underlying pathophysiology, including treatment of insulin resistance

Improved Patient Outcomes

Insulin resistance ⬇

Beta cell function ⬆

Del Prato S, *et al. Int J Clin Pract* 2005; 59:1345–1355.