IMET 2000 PAL

International Medical Education Trust – Palestine

Diabetes Mellitus in Clinical Practice

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Definition of Diabetes

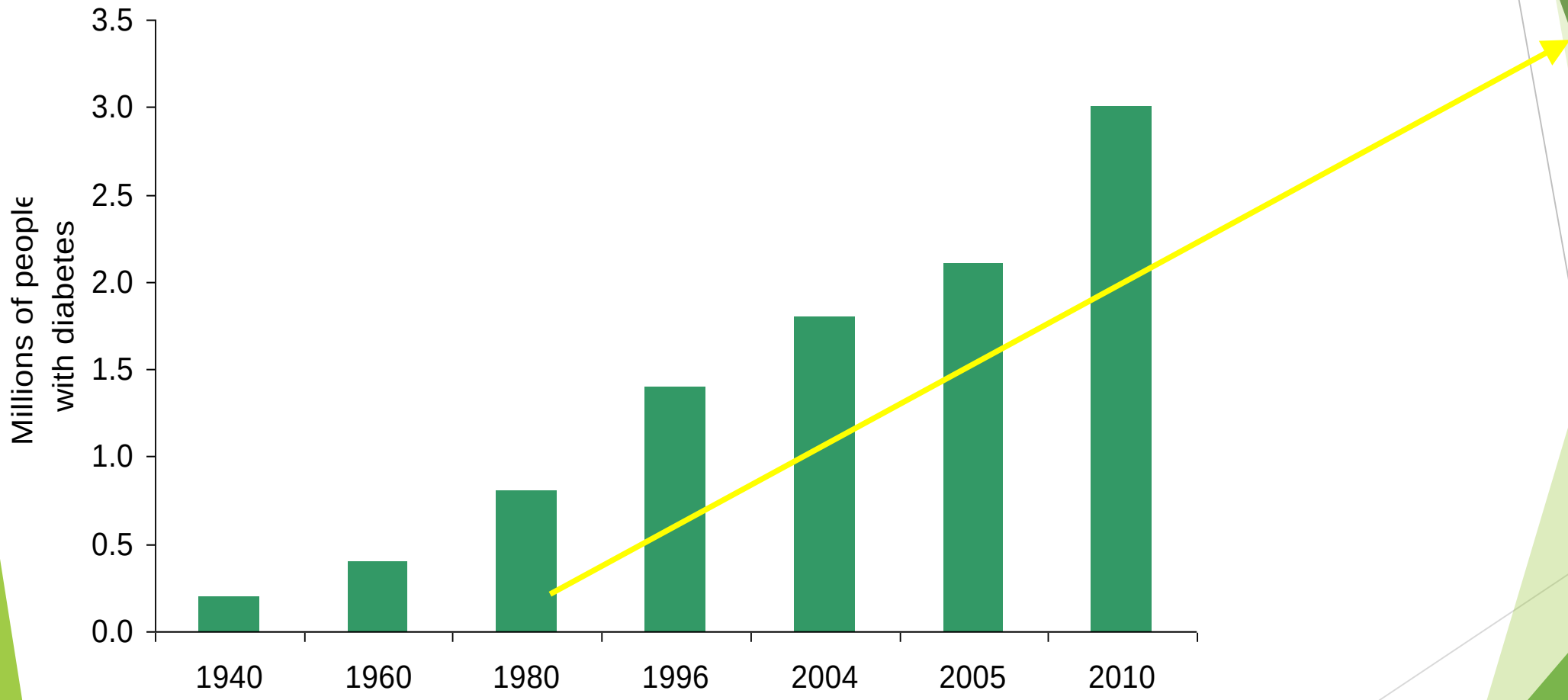
- It is a group of **metabolic diseases** characterized by hyperglycemia resulting from defects of insulin secretion and/or increased cellular resistance to insulin.

- **Chronic hyperglycemia** and other metabolic disturbances of DM lead to long-term tissue and organ damage as well as dysfunction.

Type 2 diabetes
the modern epidemic

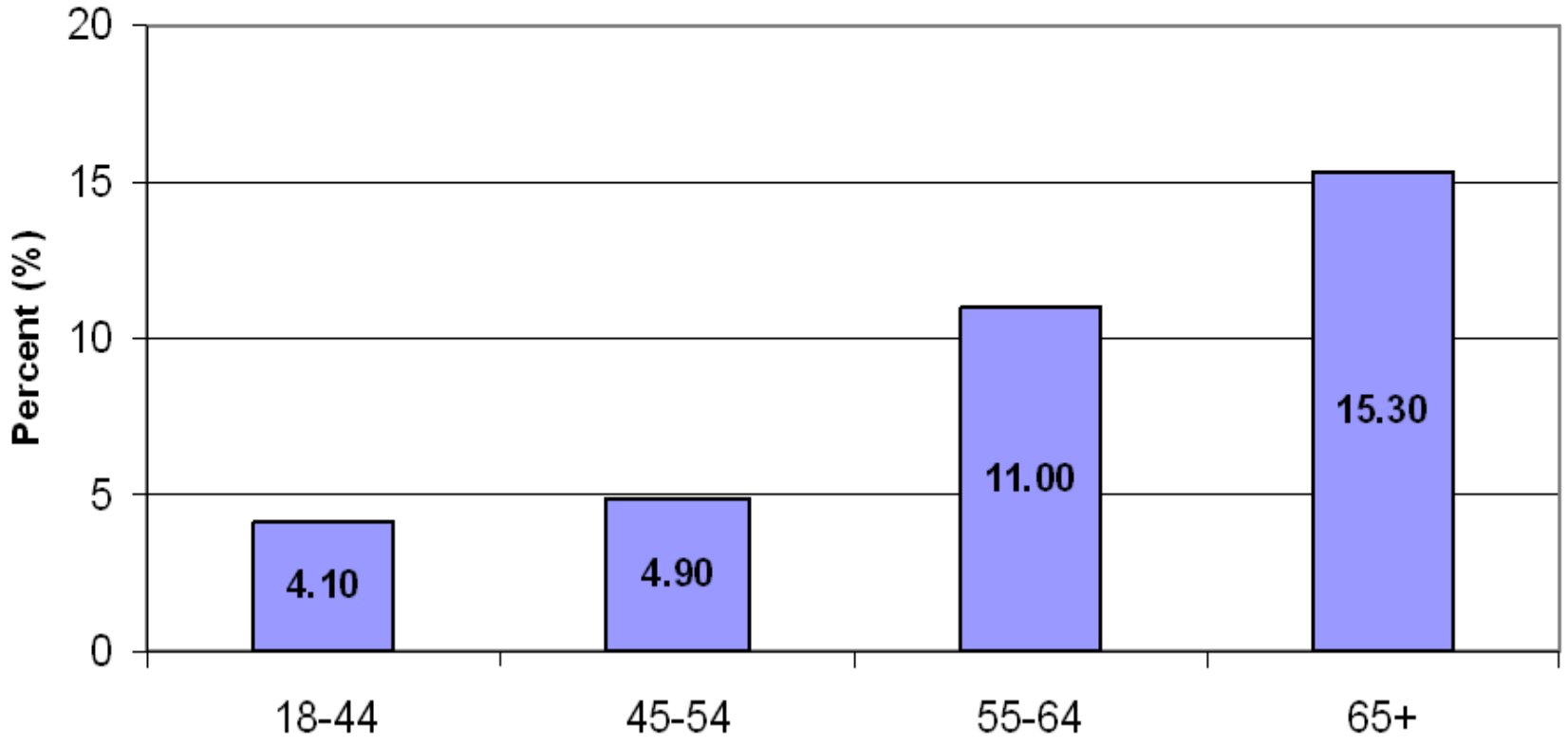
- Type 2 diabetes is a major clinical and public health problem.
- It is estimated that in the year 2000, 171 million people worldwide had type 2 diabetes
- **In Palestine**, the prevalence of diabetes between 9 – 13% of the population.

Diabetes in the UK is increasing



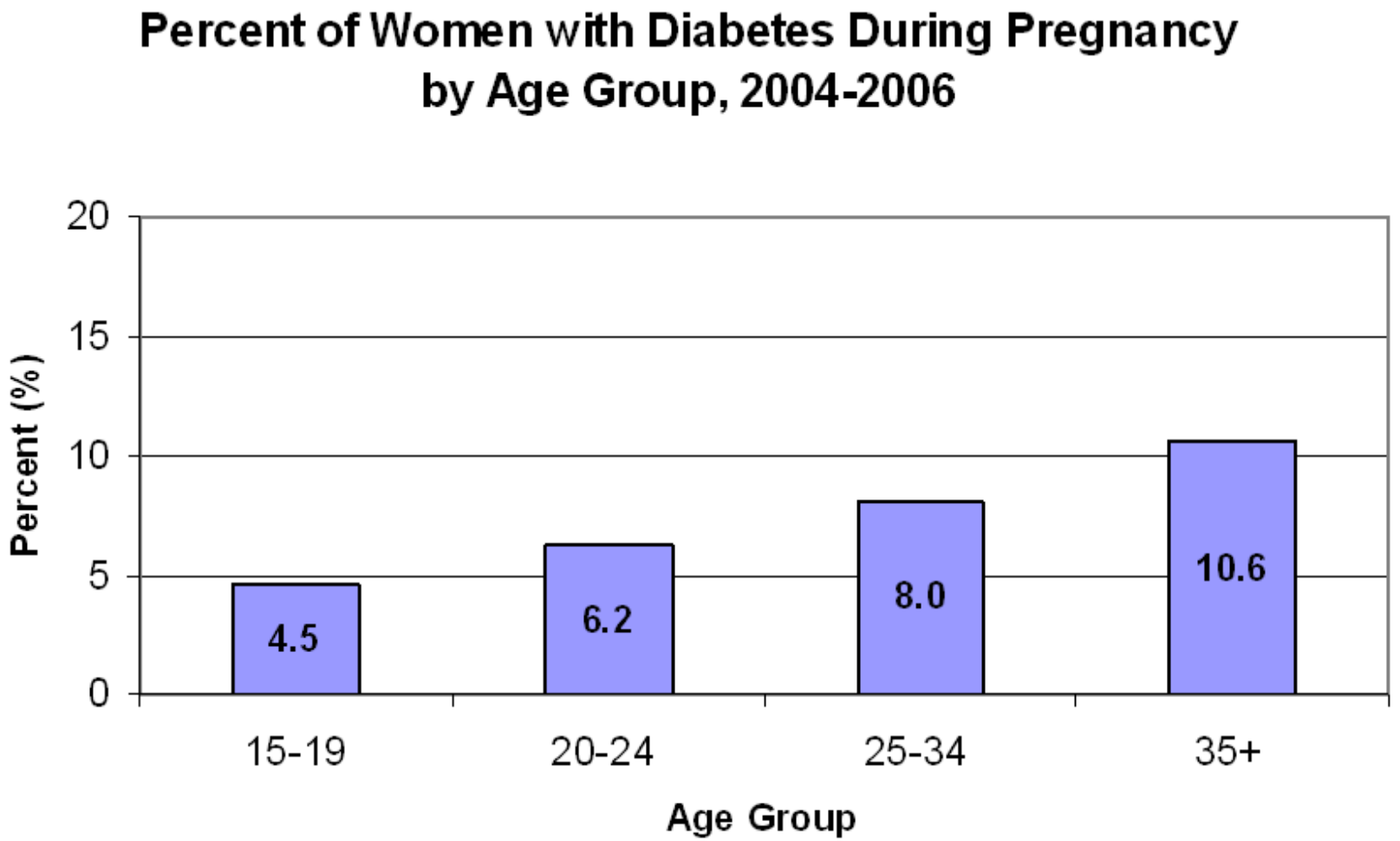
Prevalence: Age

Prevalence of Persons with Diabetes Aged 18 Years and Older by Age Group, 2007



Source: Behavioral Risk Factor Surveillance System, Health Statistics Section, CDPHE

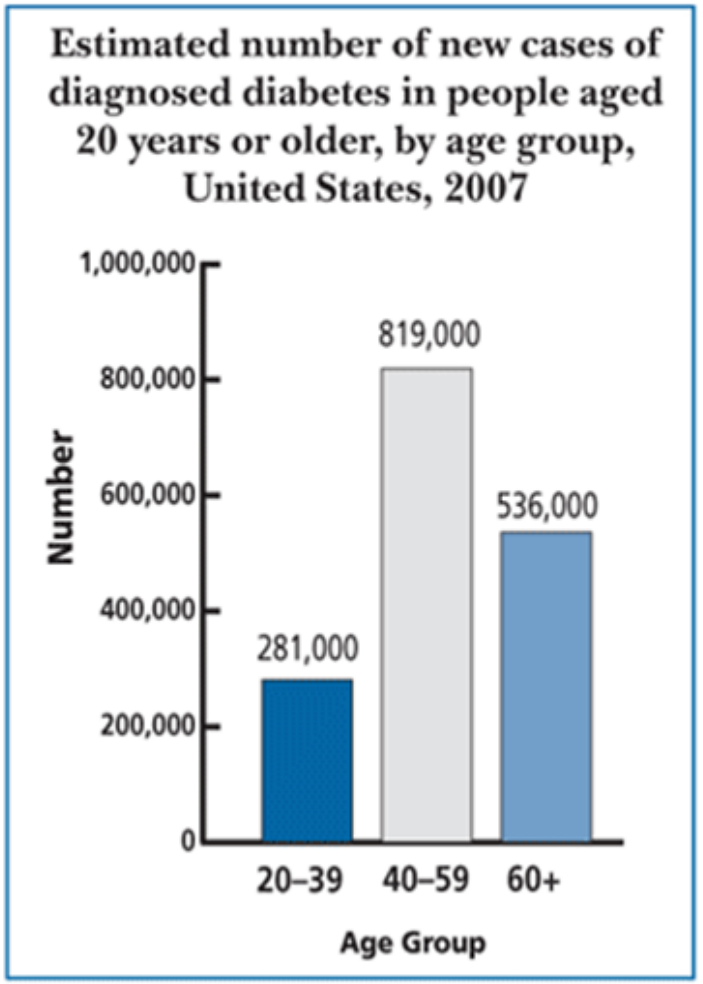
Pregnancy & Diabetes



Source: PRAMS, Health Statistics Section, CDPHE

Adult Incidence of Diabetes in US

Annual Newly Diagnosed Cases



Source: SEARCH for Diabetes in Youth Study.

Liese et al. *Pediatrics*. 2006;188:1510-1518.

How we

Diagnose Diabetes?

Criteria for the diagnosis of DM

1. Symptoms of diabetes plus **random plasma glucose** concentration >200 mg/dL.
2. **Fasting plasma glucose** >126 mg/dL. (Fasting for at least 8 h.)

Criteria for the diagnosis of DM

3. **Two-hour plasma glucose** >200 mg/dL during an **OGTT** (75 g).
4. **HbA1c > 6.5%** *(ADA in 2010)*

Diagnosing Diabetes Using A1C

- Diabetes diagnosed when A1C ≥6.5%
  - **Confirm with a repeat A1C test**
  - **Not necessary to confirm in symptomatic persons with PG >200 mg/dL**
- If A1C testing not possible, use previous tests
- **Can not be used during pregnancy** because of changes in red cell turnover

July 2009, International Committee, American Diabetes Association & International Diabetes Federation

Diagnosing Diabetes Using A1C

- A1C ≥6.0% should receive preventive interventions (pre-diabetes)

- A1C: reliable measure of chronic glucose levels; values vary less than FPG and testing more convenient for patients (can be done any time of day)

July 2009, International Committee, American Diabetes Association & International Diabetes Federation

Justifications for the new recommendations

- Ease of testing- non fasting, one time
- Reproducibility
- Reliability
- **Less variable than FBG that has 6-10% intra-individual variability and the 2h PG that has variability up to 15%**
  - Diabetes Care

Who should be screened for diabetes

- All individuals >45 years
  - If normal, repeat every 3 years
- Consider testing at a younger age or more frequently for high-risk individuals

HIGH-RISK Individuals

- **Obese** (BMI >27 kg/m²)
- Having a **first-degree relative** with DM
- High-risk **ethnic population**

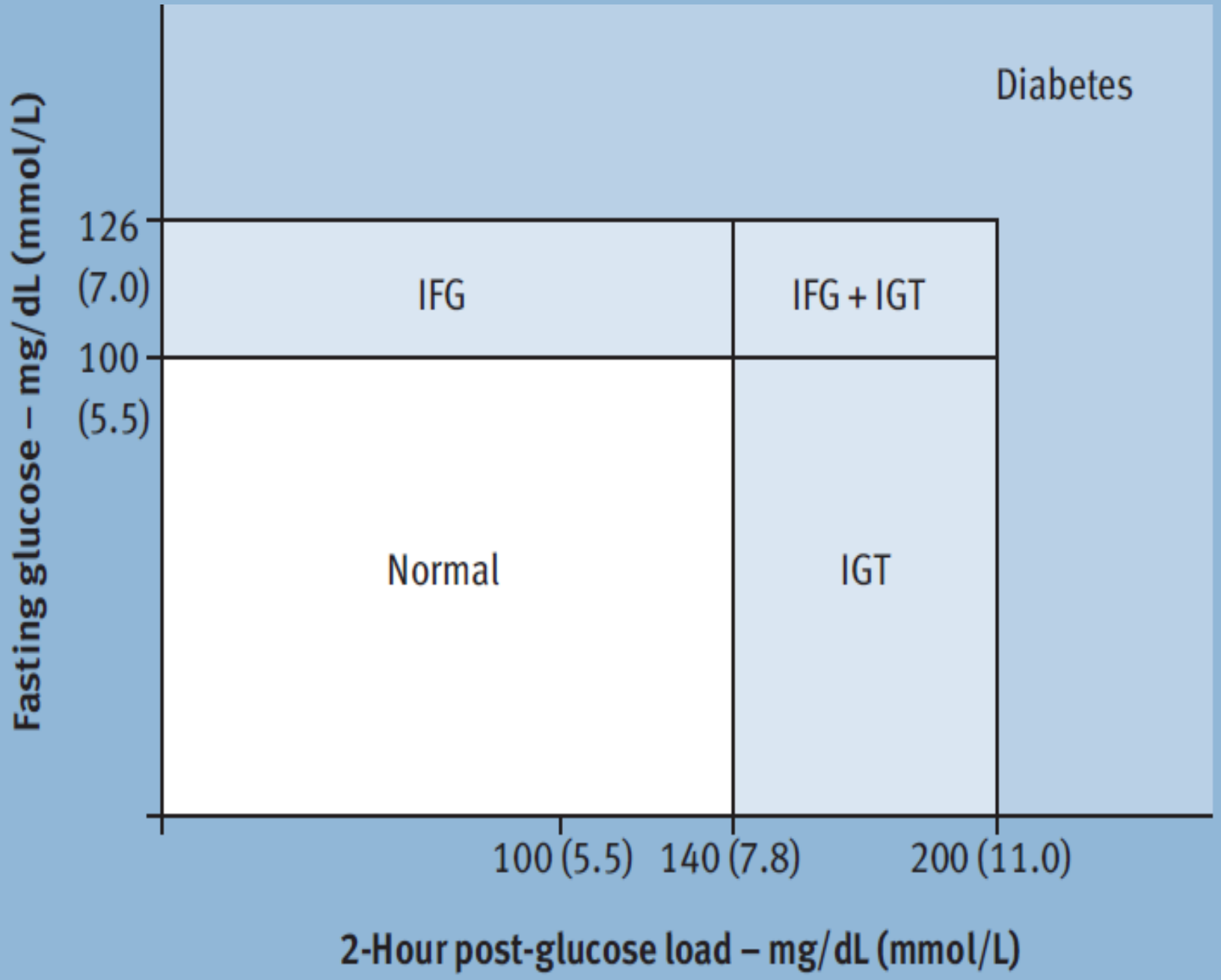
HIGH-RISK Individuals

- Delivered a **baby weighing >4 kg** or **gestational DM**
- **Hypertensive** (>140/90 mmHg)
- Having **HDL-C <35** mg/dL and/or a **Triglyceride >250** mg/dL
- **IGT** or **IFG** on previous testing

In clinical settings . . .

- The **FPG** is preferred over the OGTT due to:
  - Ease of administration
  - Convenience, patient acceptability
  - Lower cost

Summary of diagnostic criteria for diabetes



Can we prevent or delay the onset of Diabetes?

Pre-diabetes

- "Impaired glucose tolerance"
- Nearly 1 in 5 people have pre-diabetes
- 70% Increased risk of developing diabetes during your lifetime

Risk of Doing

NOTHING

Complications

Complications

Complications

Summary of major diabetes prevention studies

Study	Intervention	Relative risk reduction (%)
Finnish DPS	Diet and exercise	58
Diabetes Prevention Program	Diet and exercise	58
	Metformin	31 (53% if obese)
STOP-NIDDM	Acarbose	36
TRIPOD	Troglitazone	56
DREAM	Rosiglitazone	60
	Ramipril	NS

Who should start the prevention

Individuals with impaired fasting glucose and impaired glucose tolerance and any of the following:

- <60 years of age
- BMI >35 kg/m^2
- Family history of diabetes in first-degree relatives
- Elevated triglycerides
- Reduced HDL cholesterol
- Hypertension
- Hemoglobin A1C >6.0%

Positive Lifestyle Changes

Can **Delay** or **Prevent** Type 2 Diabetes

Modest Changes in Diet

Moderate Physical Activity

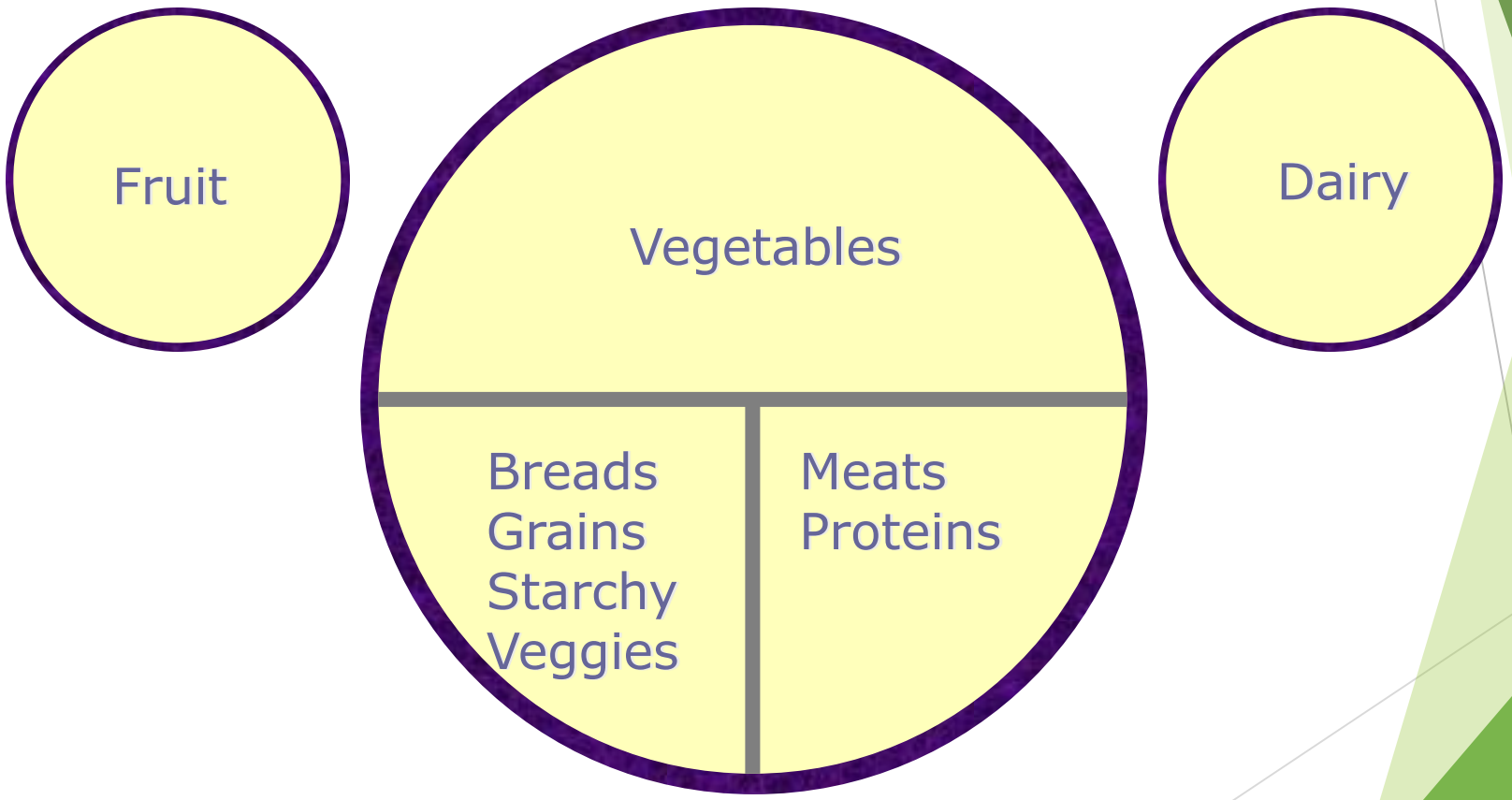
Reach and Maintain a Healthy Weight

These steps can reduce the development of diabetes by 58 % !

Strategies for prevention of type 2 diabetes

1. Weight loss of 5 – 10%
2. Physical activity ~ 30 min/day
3. Metformin [some patients]

The Plate Method



Strategies for prevention of type 2 diabetes (Con…)

- Monitoring for the development of diabetes should be performed every 1–2 years.
- Close attention and treatment for other CVD risk factors.
- Drug therapy should not be routinely used to prevent diabetes.
- However, metformin could be used cautiously in selected patients.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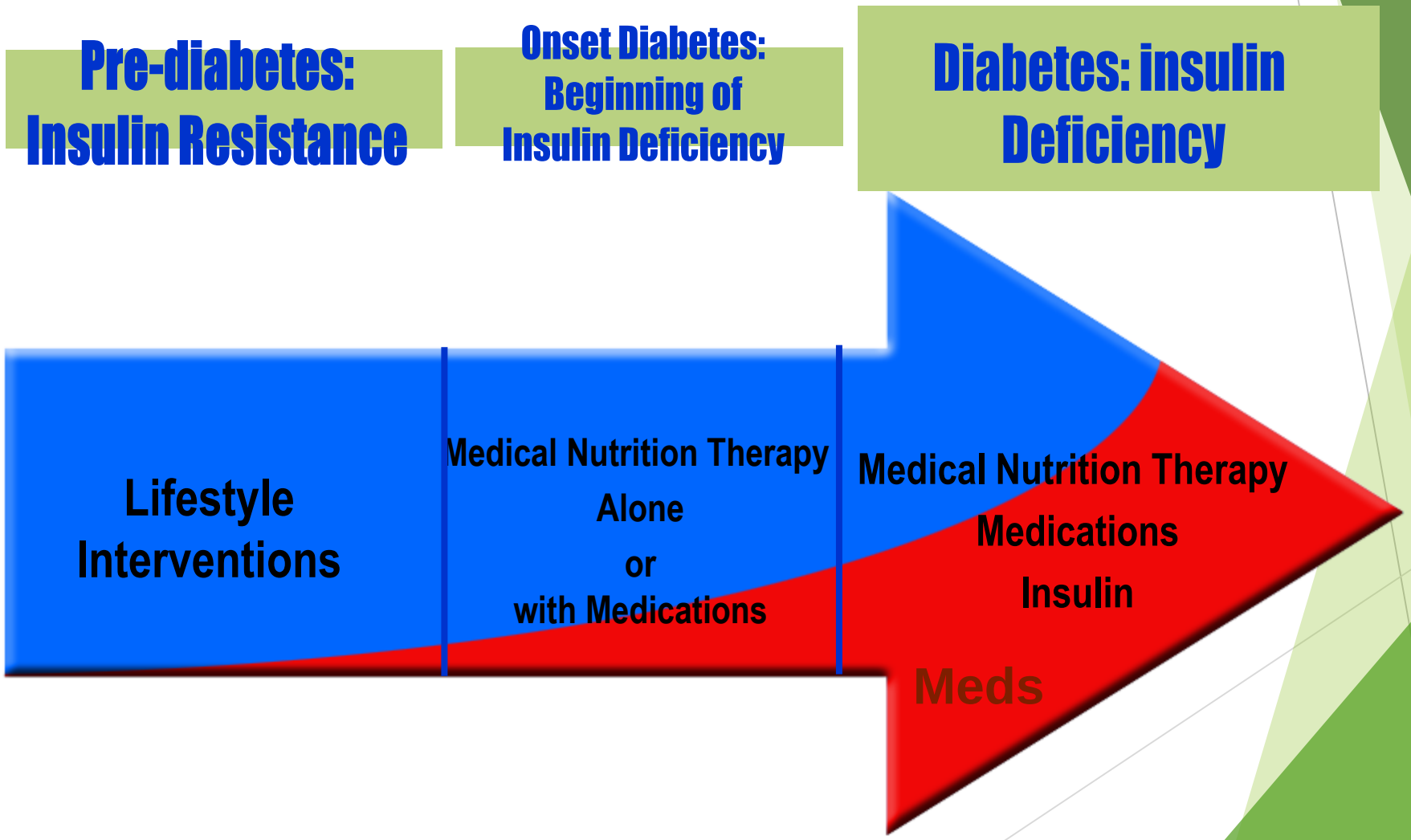
Management of

Diabetes

Type 2 Diabetes:
A Progressive Disease



Goals for Glycemic Control

Hemoglobin A1C	< 7%
Preprandial glucose	90–130 mg/dL (5.0–7.2 mmol/L)
2 h postprandial glucose	< 180 mg/dL (<10 mmol/L)

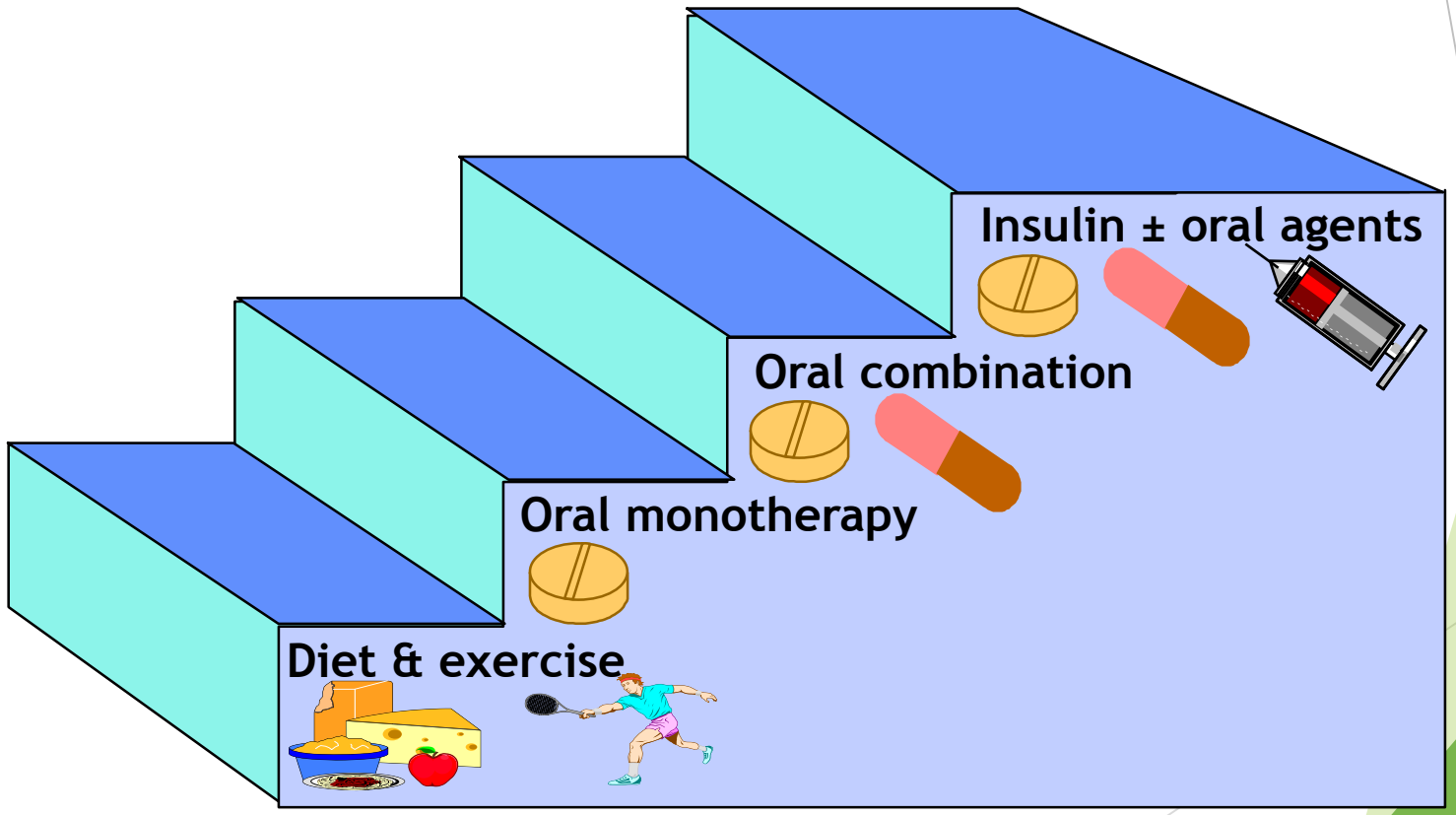
Goals for Lipid Control

Low-density lipoprotein	< 100 mg/dL
Triglycerides	< 150 mg/dL
High-density lipoprotein	> 40 mg/dL (>

Goals for BP Control

< 130/80 mmHg

Stepwise Management of Type 2 Diabetes



How to follow up your diabetic patient?

Assessment guidelines

EVERY VISIT

- Blood pressure
- Weight
- Visual foot examination

QUARTERLY

- Hemoglobin A1C

BIANNUAL

- Dental examination

Assessment guidelines

ANNUALLY

- **Albumin/creatinine ratio** (unless proteinuria is documented)
- Pedal **pulses** and **neurologic** examination
- **Eye** examination (by ophthalmologist)
- Blood **lipids**

Correlation of A1C with Average Glucose

	Mean plasma glucose
A1C (%)	mg/dl
6	126
7	154
8	183
9	212
10	240
11	269
12	298

Diabetes Care 32(Suppl 1):S19, 2009

Glycemic Control

- **Each 1% reduction in mean HbA1c was associated with:**
  - 21% for deaths related to diabetes
  - 14% for myocardial infarction
  - 37% for microvascular complications

- **Stratton IM, Adler AI, Neil HA, et al *BMJ* 2000 Aug 12;321(7258):405-12**

Non-insulin agents in the management of type 2 diabetes

Effectiveness of agents on A1C levels

Class (example)	Approximate A1C reduction (%)
Biguanides (metformin)	0.9–2.5
Sulfonylureas (glipizide, glyburide, glimiperide, others)	1.1–3.0
Glinides (repaglinide, nateglindide)	1.0–1.5
Thiazolidinediones (pioglitazone, rosiglitazone)	1.5–1.6
α-Glucosidase inhibitors (acarbose, miglitol)	0.6–1.3
Gliptins (sitagliptin)	0.8
GLP-1 analogs (exenetide)	0.8–0.9
Amylin analogs (pramlintide)	0.4–0.6

Potential treatment algorithm for patients with diabetes

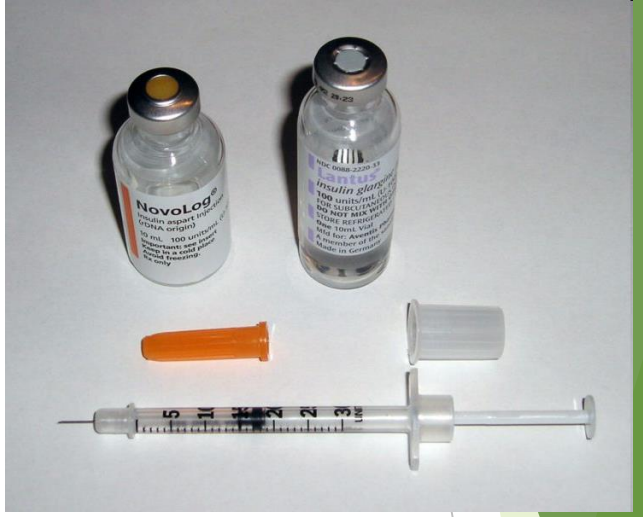
Therapy	Advantages	Disadvantages
Initial therapy		
Recommended		
Decrease body weight and increase physical activity	Improves CVD risk factors	Difficult to achieve and maintain
AND		
Metformin (Choose if no contraindications)	No hypoglycemia Weight loss/neutral Inexpensive	GI side effects

Potential treatment algorithm for patients with diabetes

Therapy	Advantages	Disadvantages
Alternative to metformin		
Insulin (Choose if very hyperglycemic, ketotic, thin and/or losing weight)	Most effective Relatively inexpensive	Injections Monitoring Hypoglycemia Weight gain

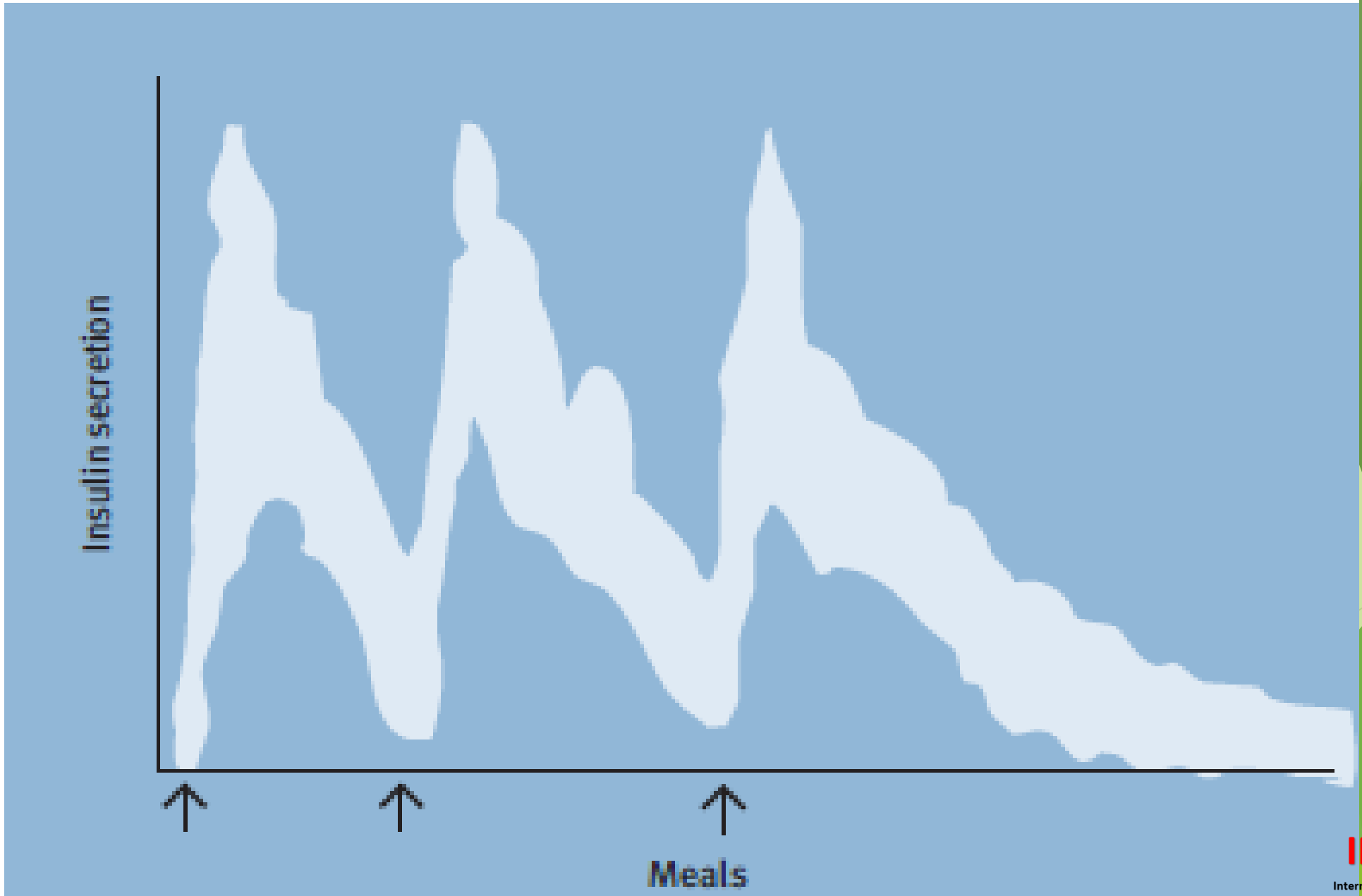
Potential treatment algorithm for patients with diabetes

Second agent (in addition to intial therapy)		
Recommended		
Sulfonylurea	Inexpensive	Hypoglycemia Weight gain
OR		
GLP-1 analog	No hypoglycemia Weight loss	Injections GI side effects Expensive
OR		
Gliptin	No hypoglycemia	Limited long-term data Expensive
OR		
Thiazolidinedione	No hypoglycemia	Weight gain CHF Increased fracture risk Possible increased CVD risk Expensive

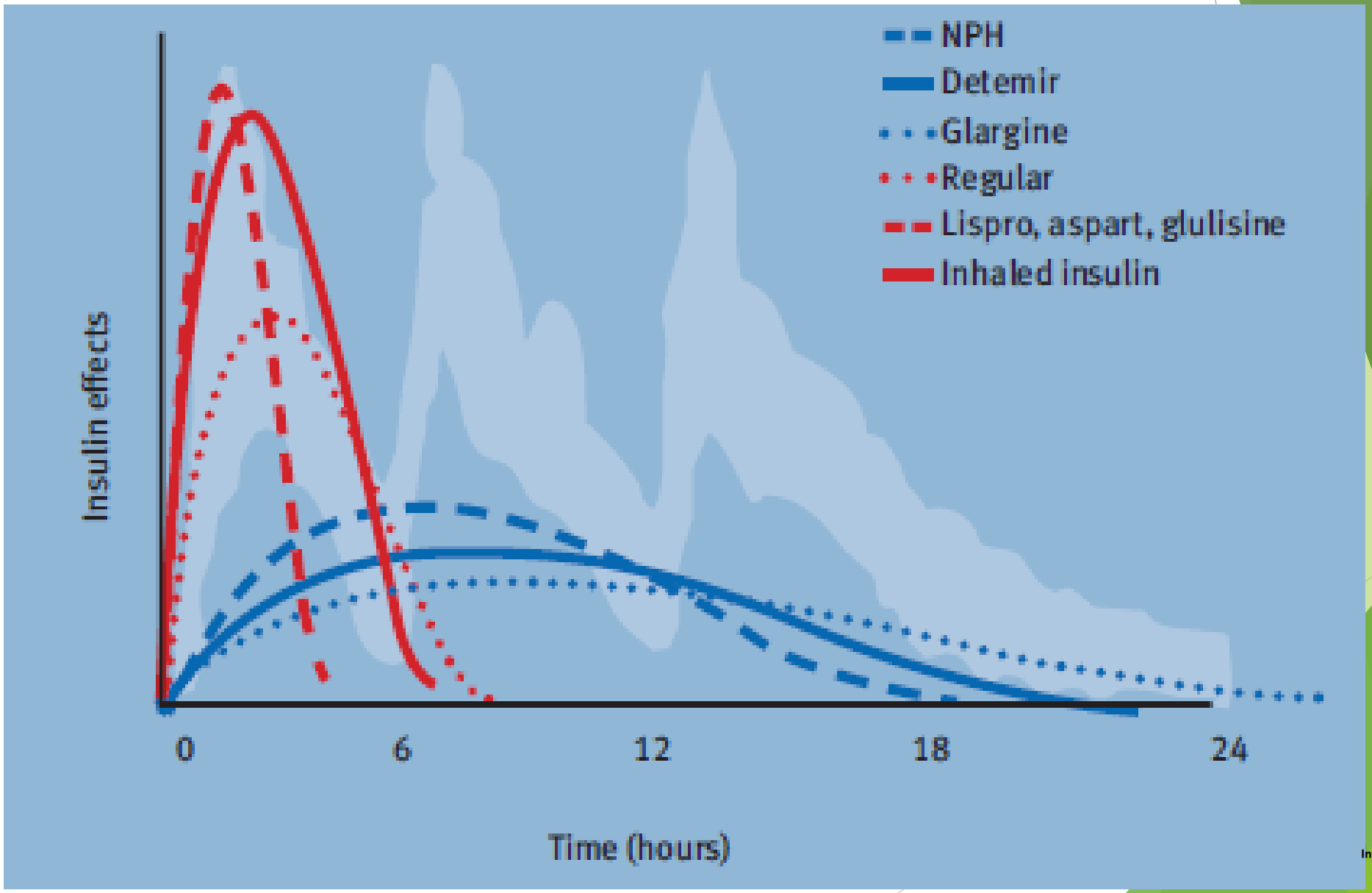


in the Management of Type 2 Diabetes

Figure 4.1 Normal insulin secretion and action



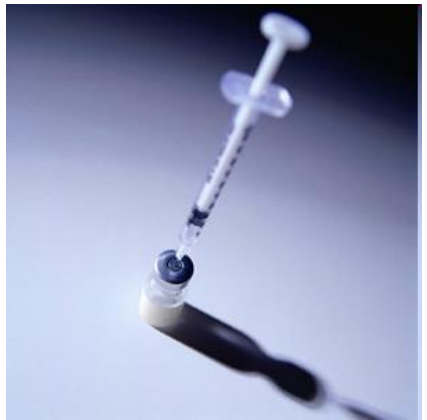
Profiles of available insulins



Approximate duration of action of insulin preparations

Insulin	Onset of action	Peak action	Effective duration
Rapid-acting			
Insulin aspart	5–15 min	30–90 min	<5 h
Insulin lispro	5–15 min	30–90 min	<5 h
Insulin glulisine	5–15 min	30–90 min	<5 h
Insulin inhalation powder	5–15 min	30–90 min	5–8 h
Short-acting			
Regular insulin	30–60 min	2–3 h	5–8 h
Intermediate-acting			
NPH insulin	2–4 h	4–10 h	10–16 h
Long-acting			
Insulin glargine	2–4 h	None	20–24 h
Insulin detemir	3–8 h	None	6–23 h

Combination between Insulin and other antihyperglycemics



Insulin initiation and titration algorithm

Start with 10 IU/day bedtime basal insulin* and adjust weekly	
Mean of self-monitored FPG values from preceding 2 days	Increase of insulin dosage (IU/day)
≥180 mg/dL (10 mmol/L)	8
140–180 mg/dL (7.8–10.0 mmol/L)	6
120–140 mg/dL (6.7–7.8 mmol/L)	4
100–120 mg/dL (5.6–6.7 mmol/L)	2

Potential strategy for insulin initiation and advancement

1 Start 10 units NPH, glargine or detemir at bedtime*

2 Continue metformin. Stop all other antihyperglycemic medications.

3 Have patient check daily FBG

4 Increase insulin doses according to Figure 4.4

5 If A1C meets goal (usually <7%), continue with single daily injection of insulin

Potential strategy for insulin initiation and advancement

6 If A1C is above goal, and FBG has been 100–120 mg/dL for at least 2 months, have patient check BG before breakfast, lunch, dinner, and bedtime

Initiate 1–3 additional insulin injections per day, according to the following:

- if pre-lunch BG is above 180 mg/dL (10 mmol/L), add pre-breakfast insulin aspart, lispro or glulisine
- if pre-dinner BG is above 180 mg/dL (10 mmol/L), add pre-lunch insulin aspart, lispro or glulisine
- if pre-bedtime BG is above 180 mg/dL (10 mmol/L), add pre-dinner insulin aspart, lispro or glulisine

Conclusions

- **Many, if not most, patients with type 2 diabetes will eventually require insulin to achieve their glycemic goals.**
- Insulin should be offered to patients as a safe and effective treatment option, not as a punishment

Conclusions

- Insulin doses must be **adjusted frequently** until the patient achieves the desired target.
- Treatment is initiated with a **single bedtime injection of basal insulin** and the dose is titrated until the fasting glucose is normal.

Conclusions

- If the fasting glucose normalizes but the A1C remains elevated, additional injections, typically given as **pre-meal doses** of rapid-acting insulin, may be required.

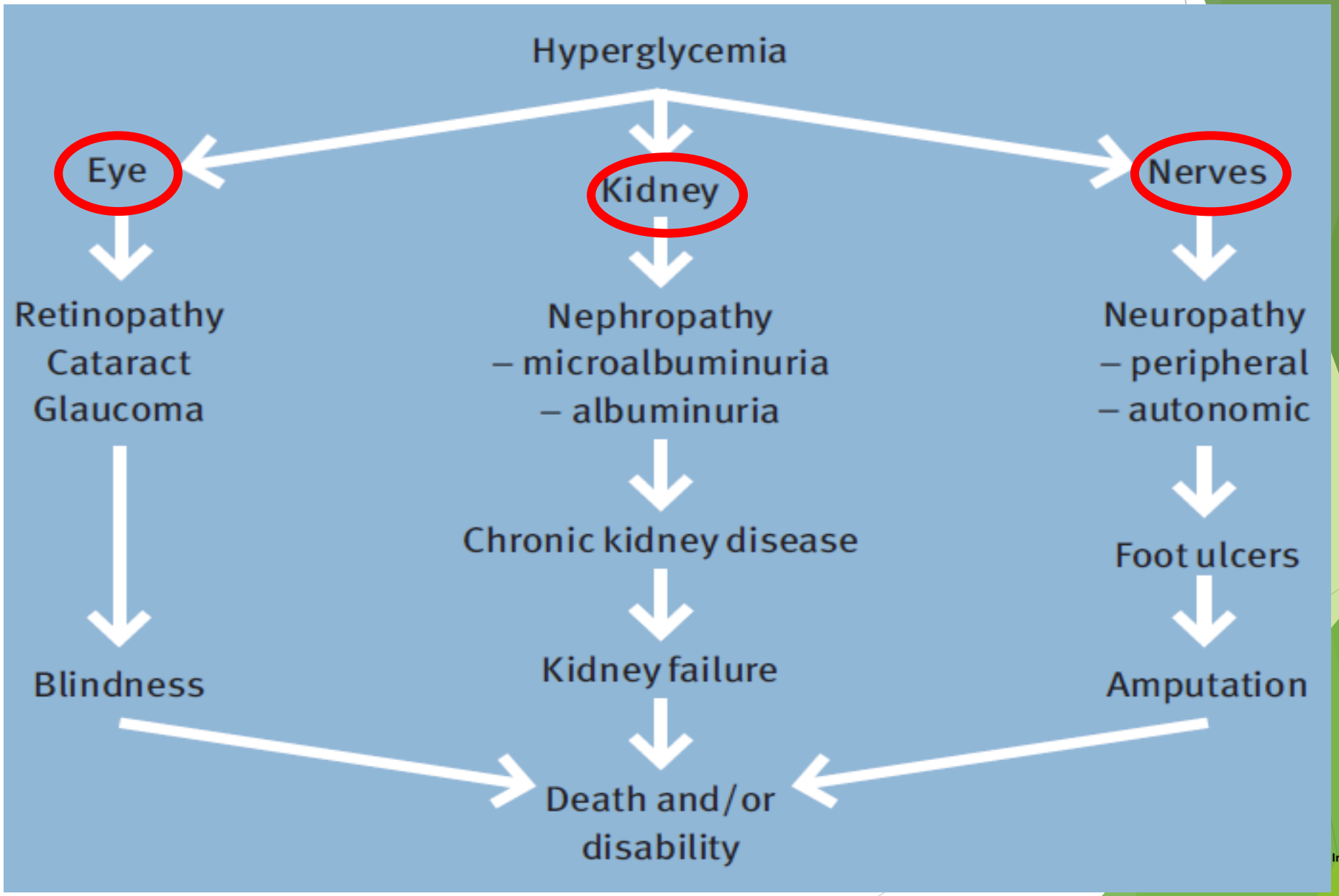
- Patients with long-standing diabetes and non-obese, frequently may require multiple daily insulin injections.

Take Home Points

- When Oral Agents Fail, Add Basal Insulin While Continuing Orals
- Titrate Basal Insulin *Rapidly* To Normalize FBS
- When FBS Normal But A1C Elevated, Add Mealtime Bolus Insulin One Meal At A Time & Withdraw Sulfonylurea when All Meals Covered
- Don't Forget The ABC's

Complications of Diabetes

Biology of microvascular complications of diabetes



Lowering A1C reduces complications in type 1 and type 2 diabetes

	DCCT	Kumamoto	UKPDS
A1C reduction	9% to 7%	9% to 7%	8% to 7%
Retinopathy ↓	76%	69%	17–21%
Neuropathy ↓	50%	Significantly improved	–
Macrovascular disease ↓	41%	–	16%

Risk reduction with treatment of diabetes

	Microvascular events	Macrovascular events
Blood pressure treatment	20–40%	20–50%
Lipid treatment	–	25–55%
Glucose treatment	12–35%*	10–20%*

Diabetic Nephropathy

- Optimize glucose control
- Optimize blood pressure control
- Limit protein intake
- Test for microalbuminuria
- Measure serum creatinine annually
- Treat with either ACE inhibitors or ARBs

Definitions of abnormalities in albumin excretion

Category	
Normal	<30
Microalbuminuria	30–299
Macroalbuminuria (clinical)	≥300

Monitoring and Preventing Hypertension

- BP should be measured at every routine diabetes visit.
- Patients with diabetes should be treated to a SBP <130/80 mmHg.
- Multiple drug therapy is generally required to achieve targets.

Monitoring and Preventing Hypertension

- Initial drug therapy for raised BP should be with **ACE inhibitors or ARBs**

- All patients with diabetes and hypertension should be treated with a regimen that includes either an **ACE inhibitor or an ARB**.

Monitoring Lipid Levels

- In adults, test for lipid disorders at least annually and more often if needed to achieve goals.
- Lifestyle modification including reduction of saturated fat and cholesterol intake, weight loss, and increased physical activity.
- In individuals without overt CVD, the primary goal is an LDL <100 mg/ dL. In those with overt CVD, the goal is <70 mg/dL.

Monitoring Lipid Levels

- For those over the age of 40 years, **statin** therapy to achieve an LDL reduction of 30–40% regardless of baseline LDL levels.
- Lower **LDL cholesterol** to <100 mg/dL
- Lower **triglycerides** to <150 mg/dL
- Raise **HDL cholesterol** to >40 mg/dL.
- In women, an HDL goal should be >50 mg/dL.

Additional approaches to decrease CVD events

Antiplatelet agents

Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes with a history of CVD.

Use aspirin therapy (75–162 mg/day) as a primary prevention strategy

Combination therapy using other antiplatelet agents such as clopidogrel in addition to aspirin should be used in patients with severe and progressive CVD.

Smoking cessation

Advise all patients not to smoke.

Include smoking cessation counseling and other forms of treatment as a routine component of diabetes care.

The Action to Control CardiOvascular Risk in Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

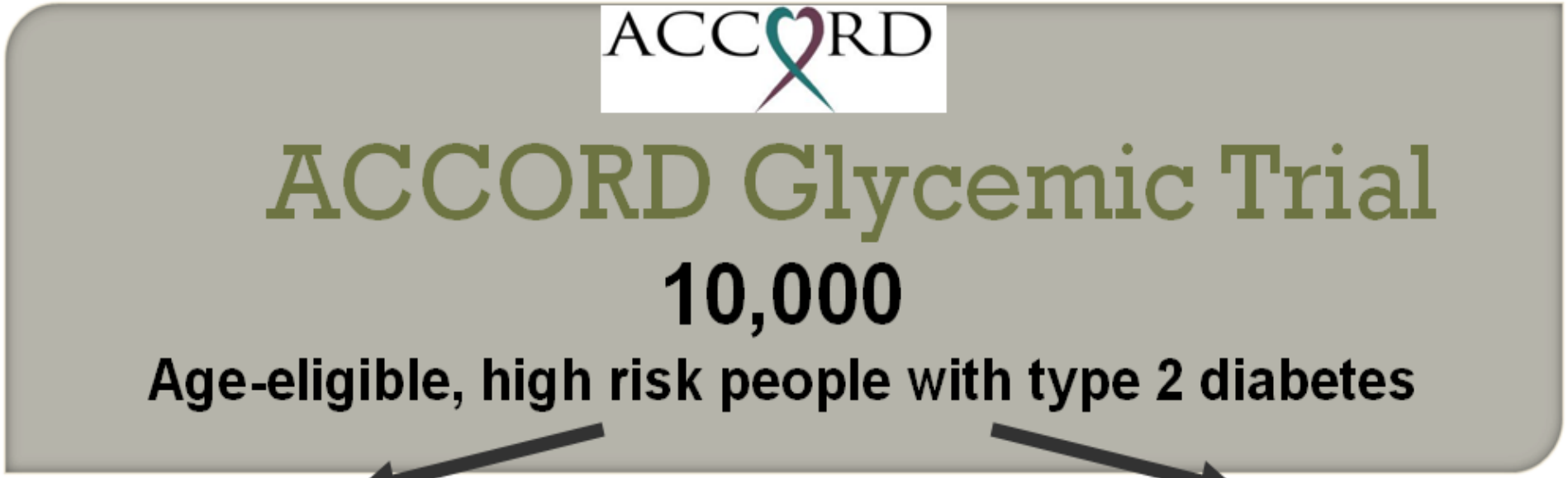
ESTABLISHED IN 1812 JUNE 12, 2008 VOL. 358 NO. 24

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

STUDY HYPOTHESIS:

A therapeutic strategy that targets HbA1c < 6.0% reduces the rate of CVD events more than a strategy that targets HbA1c 7.0% to 7.9%



5,000 to Intensive Group
(A1c Target < 6.0%)

5,000 to Standard Group
(A1c Target 7.0 -7.9%)

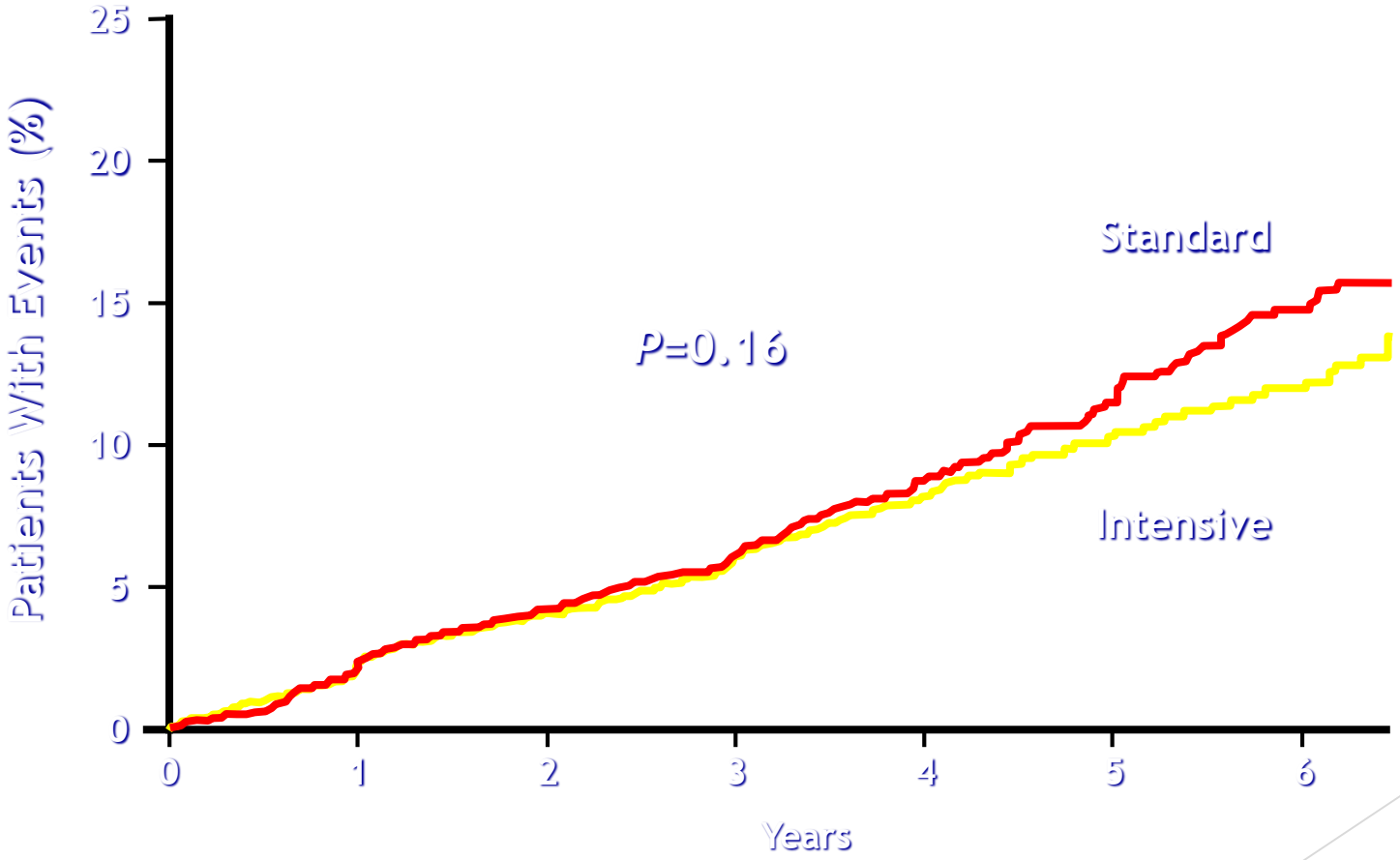
Treated and followed
for > 4 years (mean 5.5 yrs)

MAJOR CVD EVENTS

ACCORD

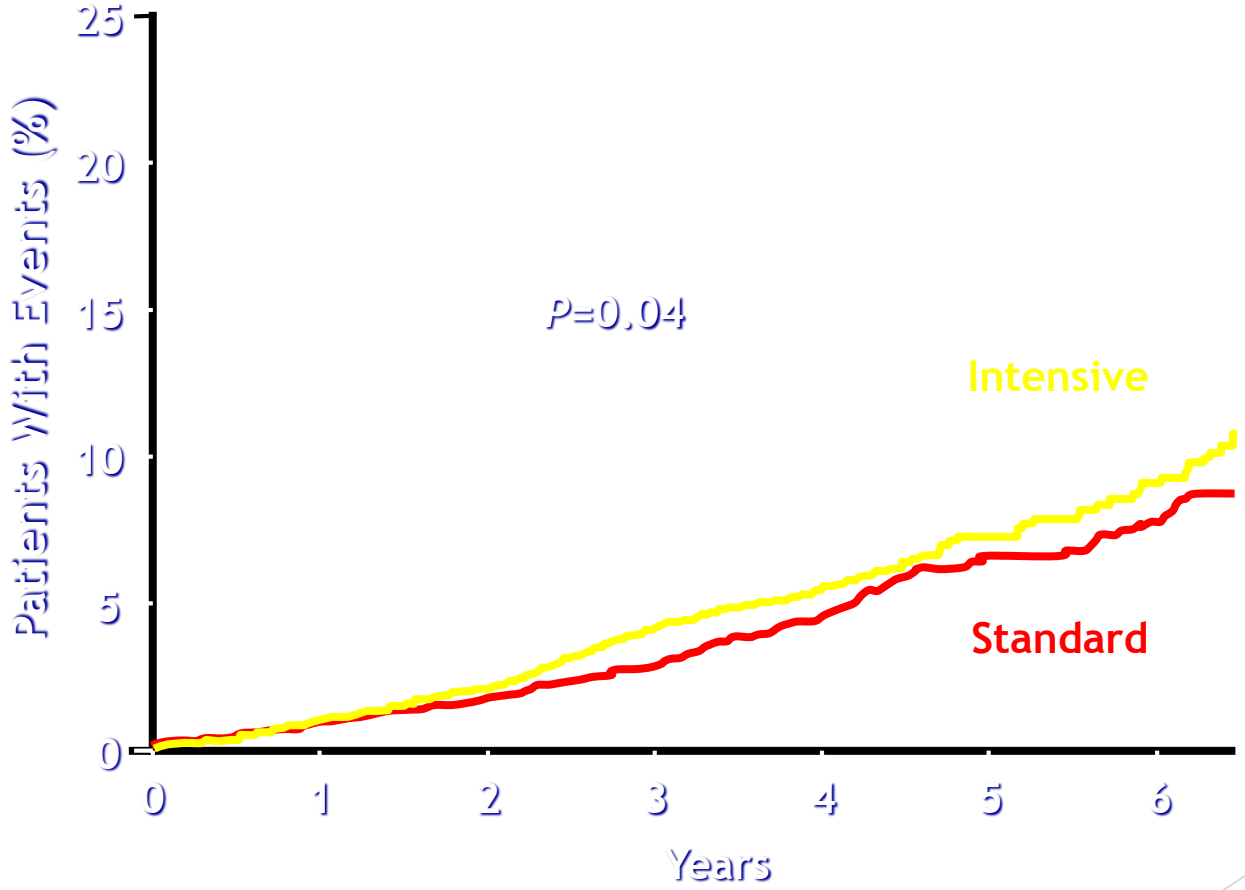
- **257 Deaths** In Intensive Arm
- **203 Deaths** In Conventional Arm
- Not Due To Hypoglycemia
- Not Due To Medication

ACCORD: Primary Outcome



The ACCORD Study Group. N Engl J Med. 2008;358:2545-2559.

ACCORD: All-Cause Mortality



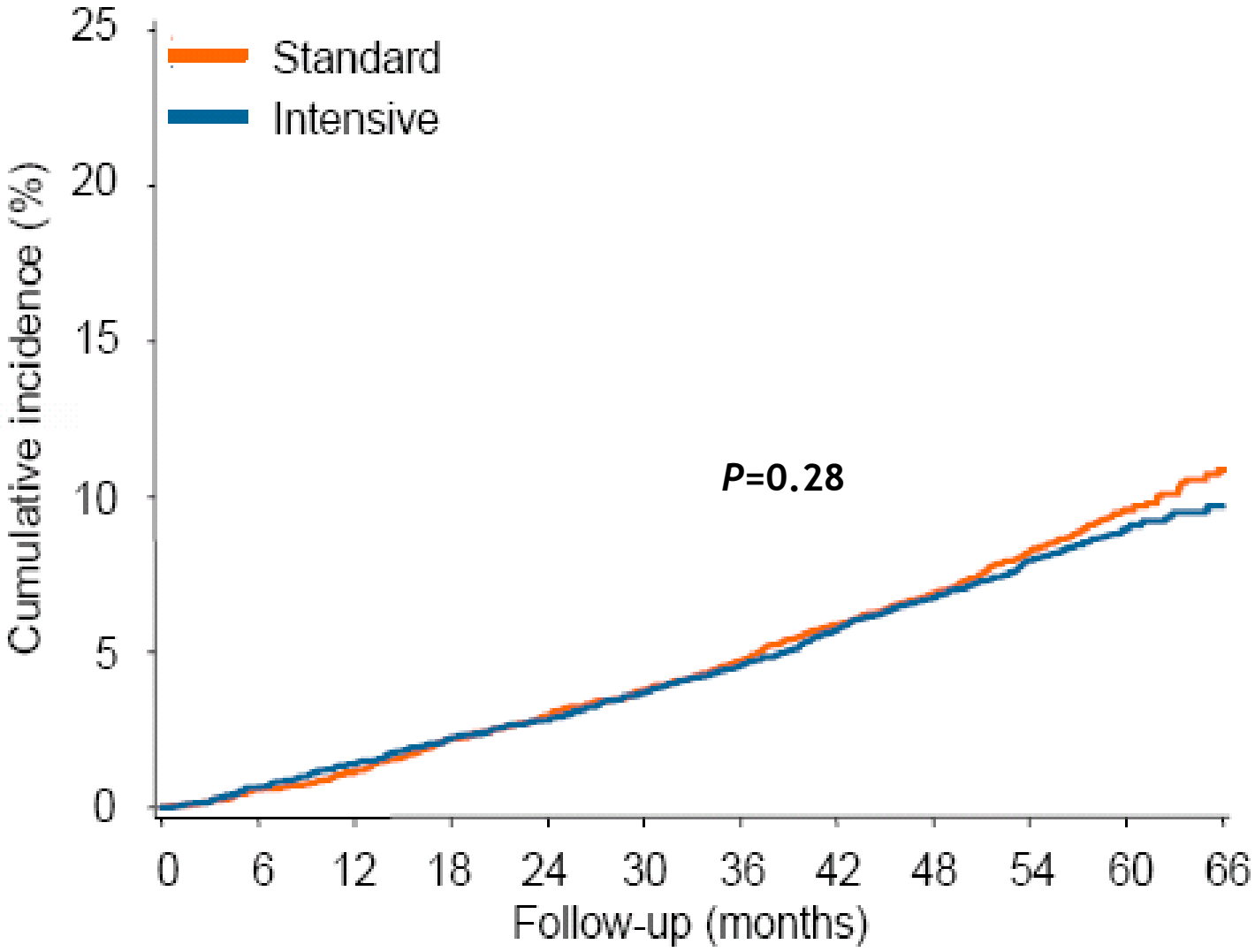
The ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559.

ADVANCE

Action In Diabetes And Vascular Disease:
Preterax And Diamicron MR Controlled Evaluation

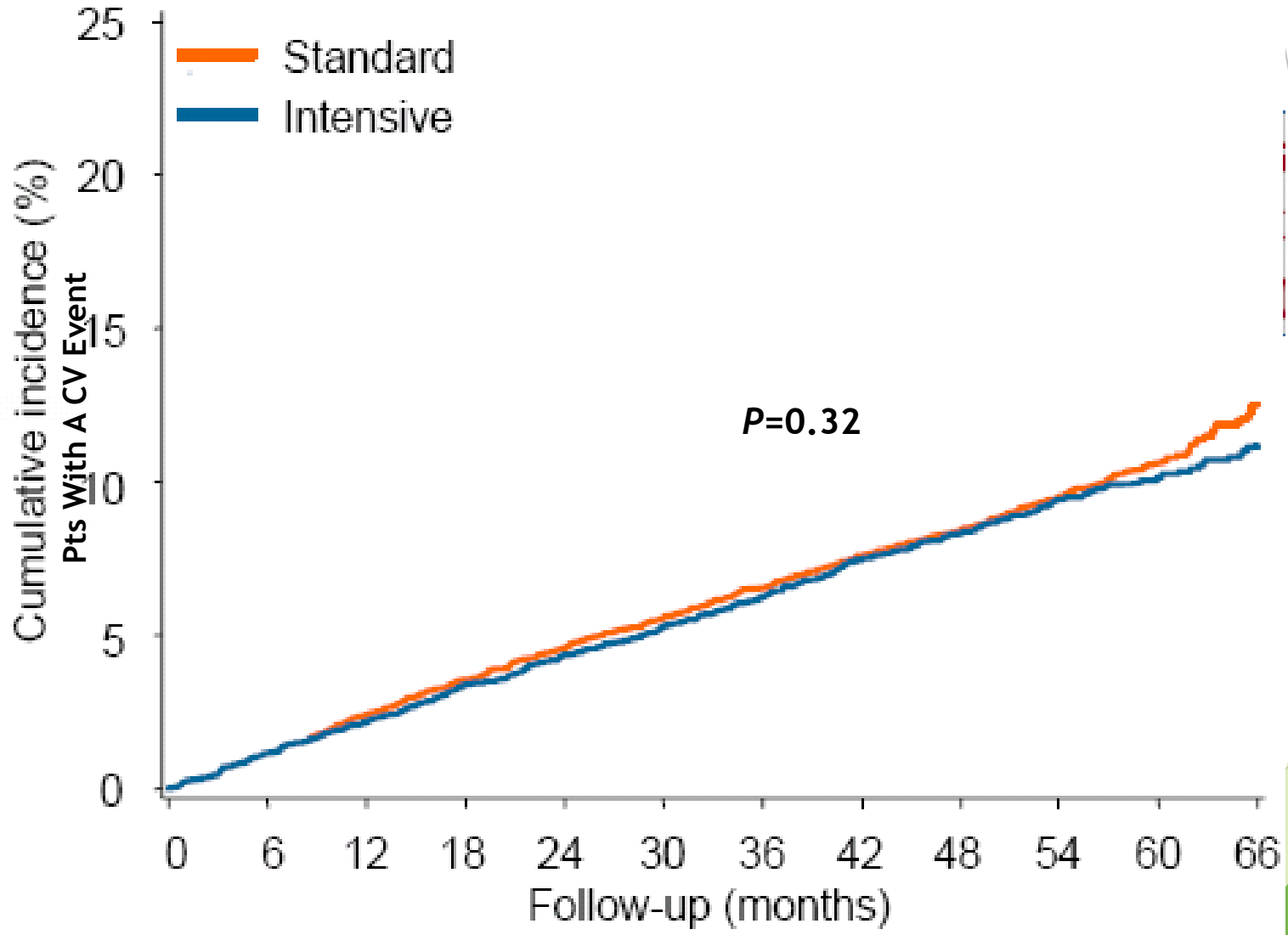
- 11,140 Patients, Age ~66, With Type 2 DM, And High CV Risk
- Intensive (*A1c 6.4%*) vs Conventional (*A1c 7%*)
- *No Excess Mortality In Intensive Group*

ADVANCE: All-Cause Mortality



Advance Collaborative Group. *New Engl. J. Med.* 2008;358:2572.

ADVANCE: Macrovascular Events

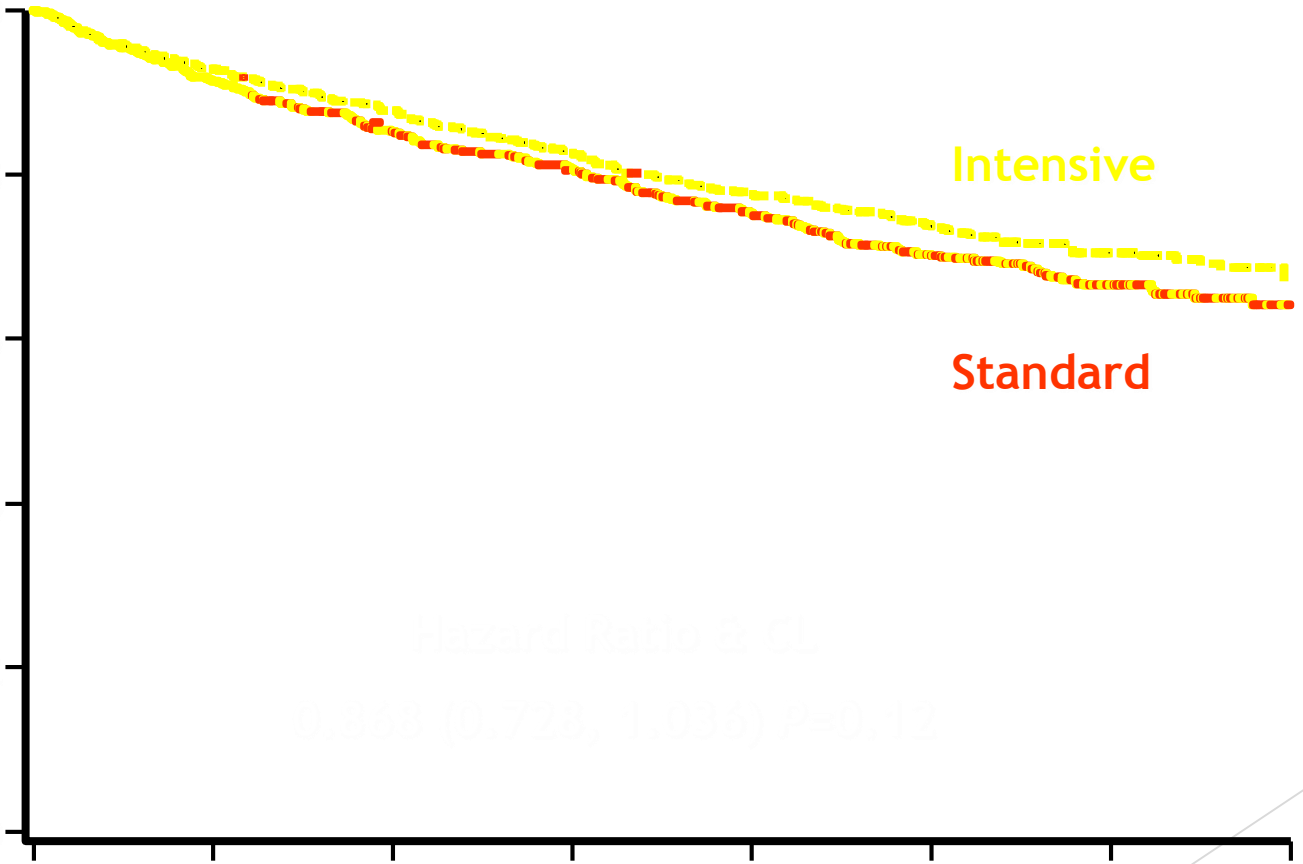


Advance Collaborative Group. New Engl. J. Med. 2008;358:2572.

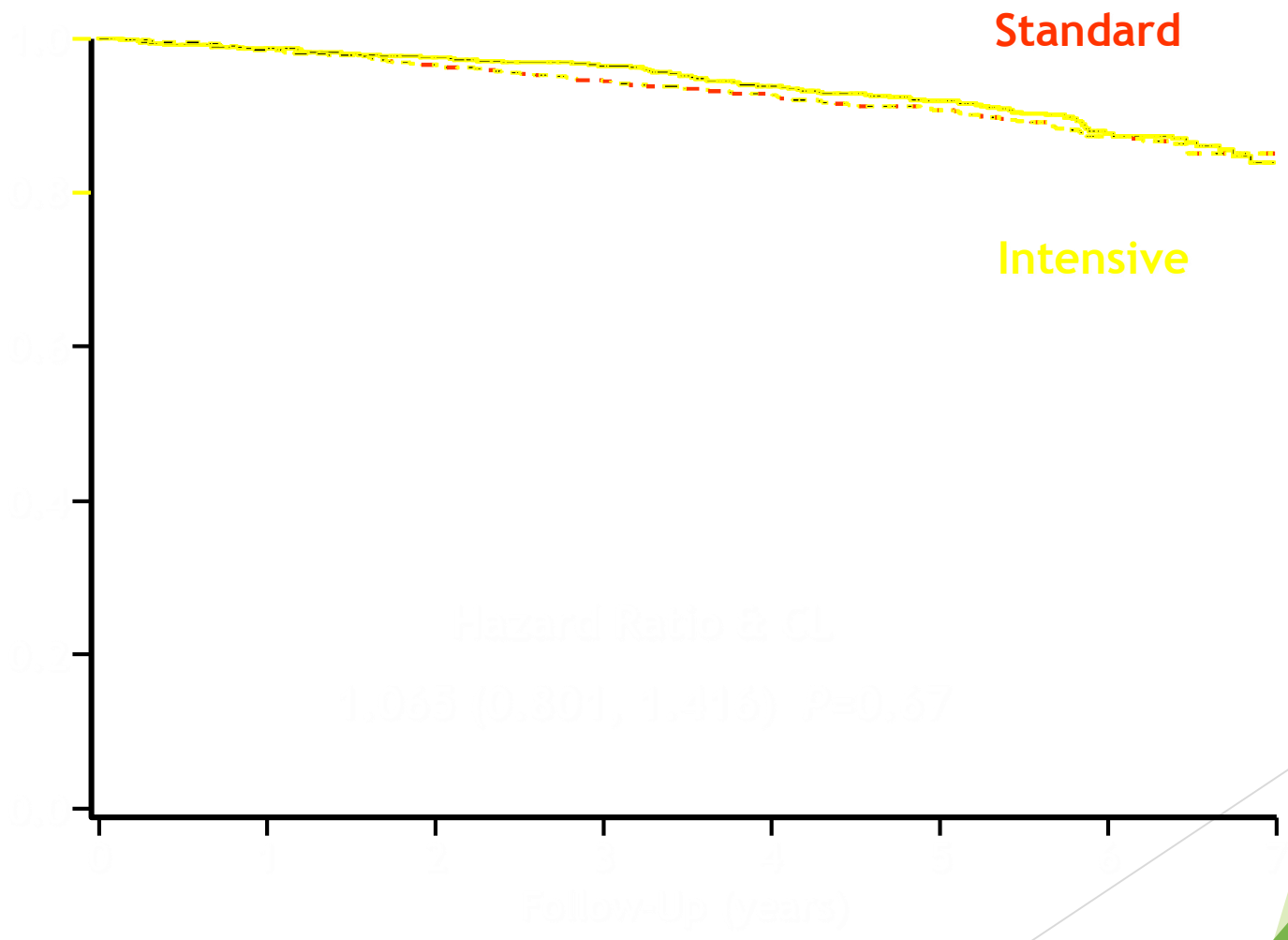
VADT
Veterans Affairs Diabetes Trial

- Glycemic Control And CV Events
- Somewhat Less Intense Glycemic Separation *(6.9% vs 8.4%)*
- Optimal CV Risk Factor Control
- Completed May And Presented At The ADA June, 2008
- *No Excess Mortality In Intensive Group*

VADT : Primary Outcome



VADT: Total Mortality



Duckworth WC. ADA 68th Scientific Sessions; June 8, 2008; San Francisco, CA.

VA Diabetes Trial
End of Trial Median Values

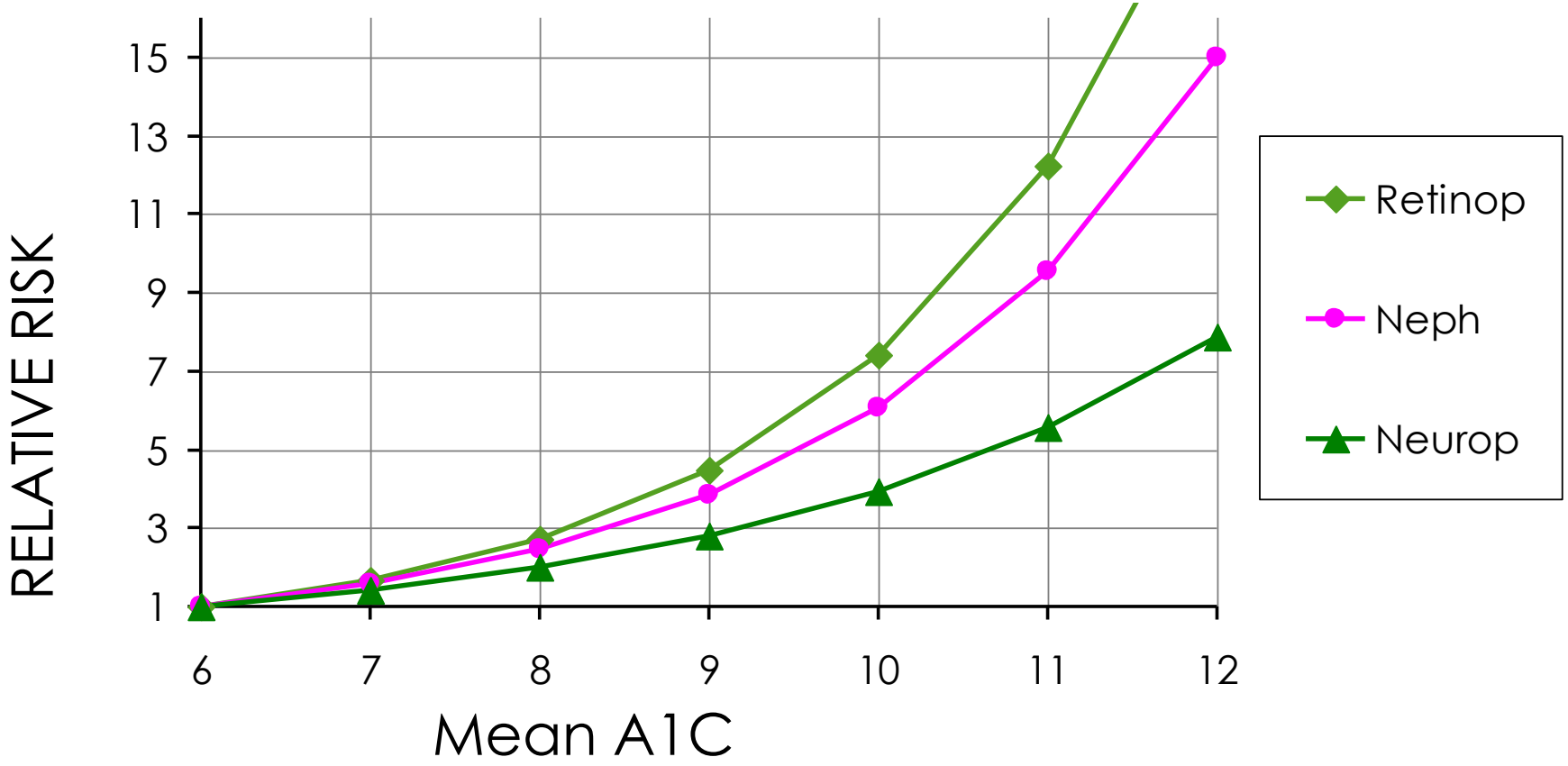
	BP	LDL
VADT	127/69	72
ADVANCE	137/74	102

Conclusions

- The Overall Effect Of Glycemic Target On Macrovascular Events, If Any, Is Small
- Extremely Tight Glycemic Control In Very High Risk Patients Is Not Benign
- Lipid And BP Control, Smoking Cessation And Anti-platelet Therapy Remain Most Important For Reducing CVD Risk In Diabetes

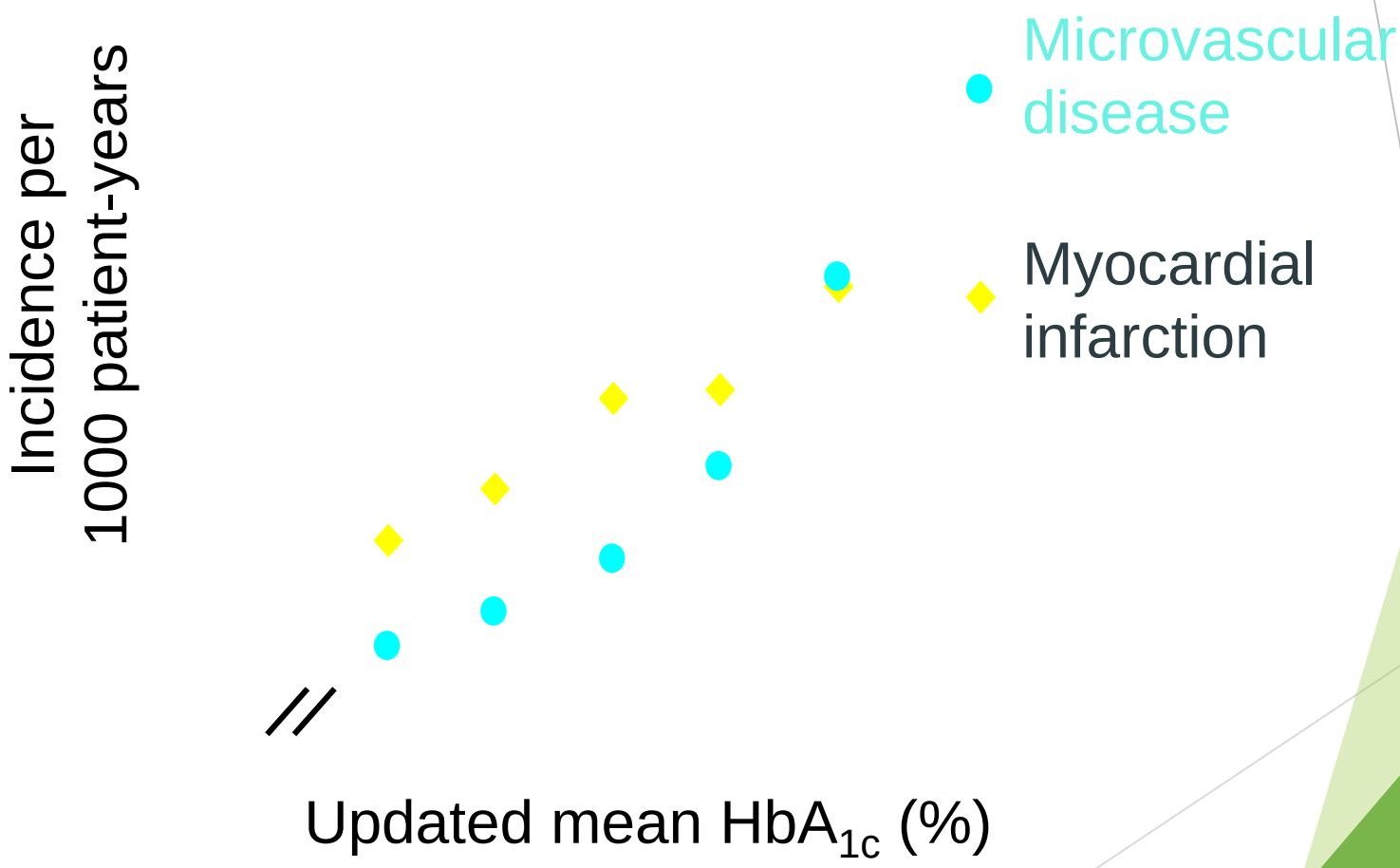
A1c As Close to Normal
<u>Without Hypoglycemia</u>
And Goals Need to Be Individualized!

Relative Risk of Progression of Diabetic Complications



DCCT Research Group, *N Engl J Med* 1993, 329:977-986.

Glycemic control and complications
UKPDS study



UKPDS 35. BMJ 2000; 321: 405-12

The patients agenda may not be yours ! ! ! !

So remember…

- Type 2 diabetes is largely asymptomatic and the treatments are inconvenient, impose on daily life and employment
- The patient's agenda may be very different from yours
- Lifestyle change is the most important but the most difficult to achieve
- In insulin-treated patients, hypoglycaemia is a major risk, especially in the young and elderly.

Summary

- Most patients with type 2 diabetes still die of cardiovascular disease regardless of their blood glucose control.

- Patients with highest HbA1c have most to gain from any improvement in blood glucose control