Diabetes: Update 2008

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Diabetes: Update 2008

1. Current ADA Recommendations
2. Changes in approaches to Type 1 and Type 2 Diabetes
3. Current demographics of diabetes and projections for the future

ADA Goals for Glycemic Control in Type 2 Diabetes

	Goal
A1C (%)	<7*
Preprandial plasma glucose	90–130 mg/dL
Peak postprandial plasma glucose†	<180 mg/dL
Blood pressure	<130/<80 mm Hg

*Using DCCT-based assay, goal referenced to a range of 4%–6%, which equals no diabetes. For the individual patient, A1C goal is as close to normal (<6%) as possible without hypoglycemia.
†Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

ADA. *Diabetes Care*. 2006;29(suppl 1):S4-S42.

Criteria for the diagnosis of diabetes mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dl (any time of day without regard to time since last meal) (sx. PUPD, unexplained wt. loss)

2. FPG ≥ 126 mg/dl (7.0 mmol/l) Fasting is defined as no caloric intake for at least 8 h.

3. 2-h postload glucose ≥ 200 mg/dl (75 g of anhydrous glucose dissolved in water)

ADA Clinical Practice Recommendations

Screening Criteria for diabetes mellitus

- Age > 45, repeat every 3 years
- Obesity: > 120% IBW or BMI > 27
- Family history (first degree relative with DM)
- Habitual physical inactivity
- High risk ethnic group (e.g. AA and Hispanic-A, Native-A, Asian-A, Pacific Islanders)
- Previous identified IFG or IGT
- Hypertension (>140/90)
- HDL cholesterol < 35 mg/dl &/or TG>250)
- PCOS
- History of vascular disease

ADA Clinical Practice Recommendations

Using biochemical markers for diagnosis

Type 1 DM

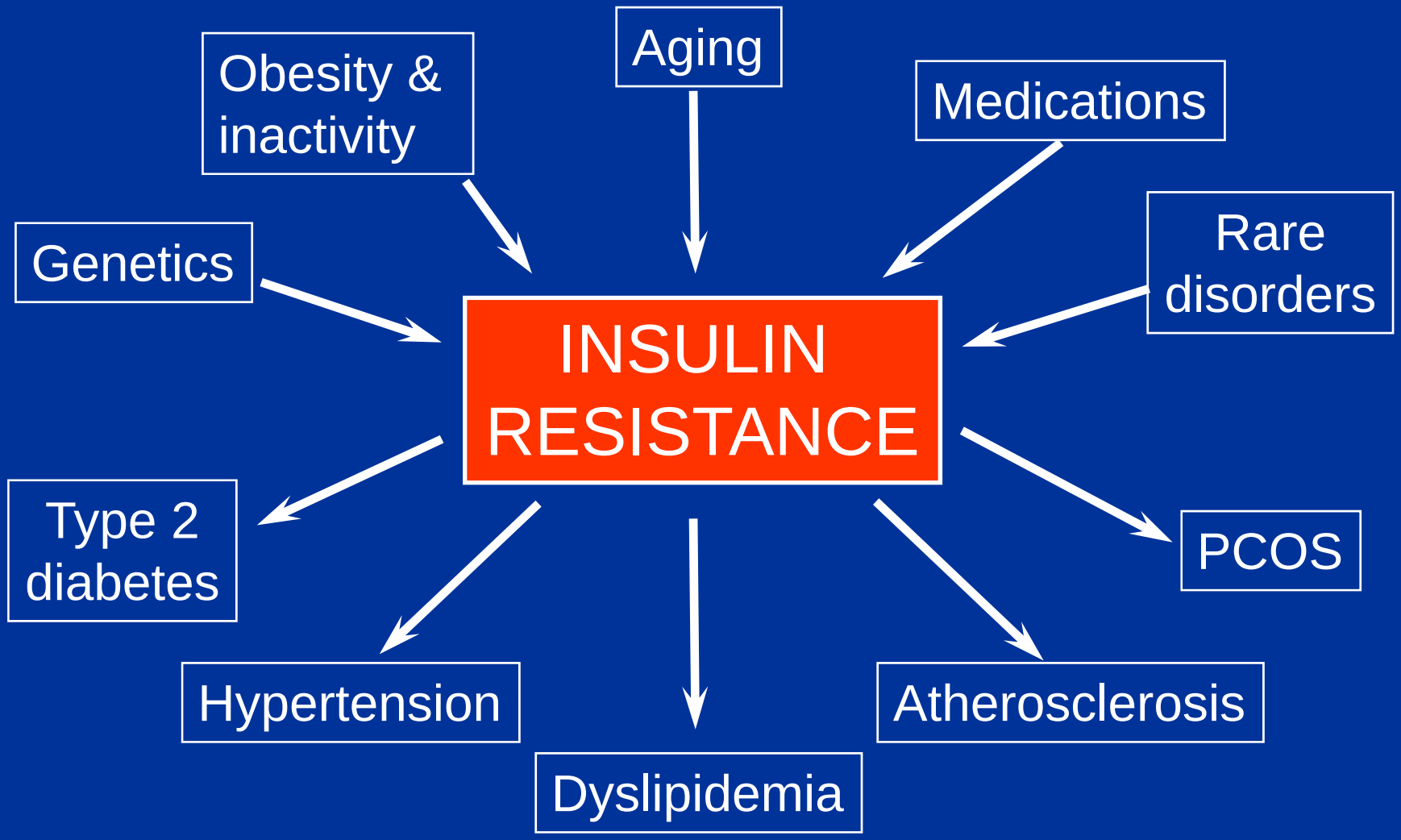
1. Anti-GAD anti-bodies are usually positive
2. C-peptide levels are usually <0.5

Type 2 DM

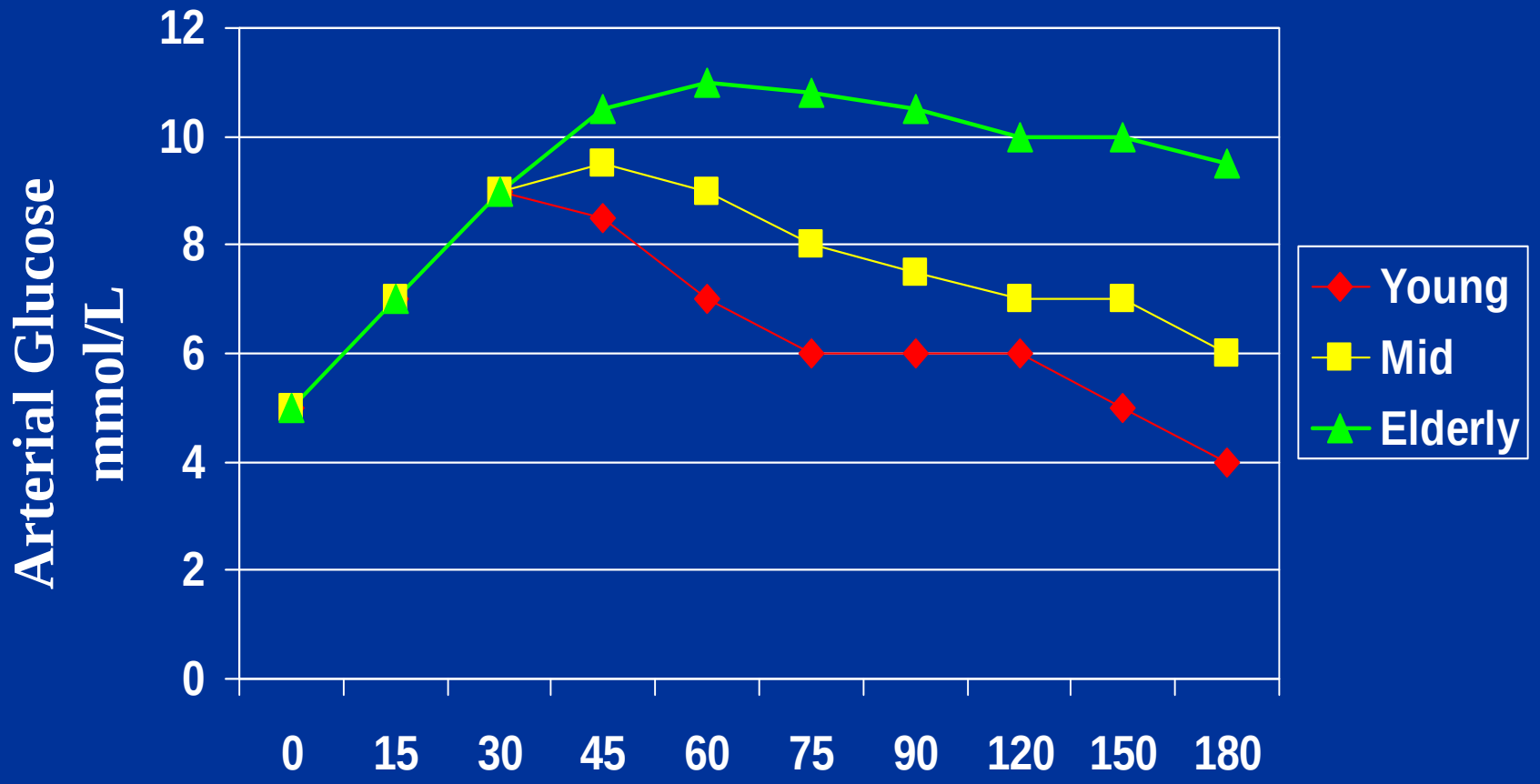
1. Anti-GAD anti-bodies are usually negative
2. C-peptide levels are usually normal or elevated

C-peptide low in advanced diabetes but not as low as in Type 1 DM

Causes and associated conditions of insulin resistance



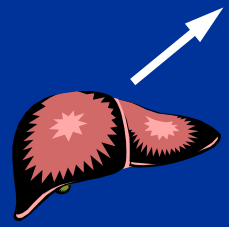
Influence of age on oral glucose tolerance

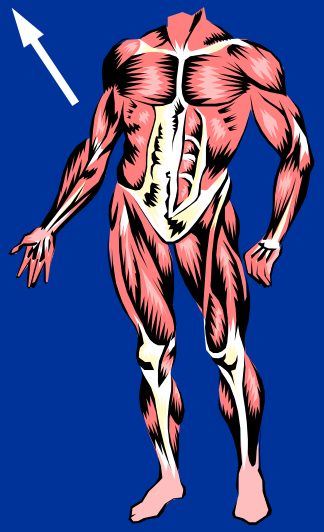


JCEM 1982; 55:840

Metabolic sequence in developing Type 2 Diabetes

Peripheral Insulin Resistance





Hyper-insulinemia

β cell hypertrophy & hyperplasia

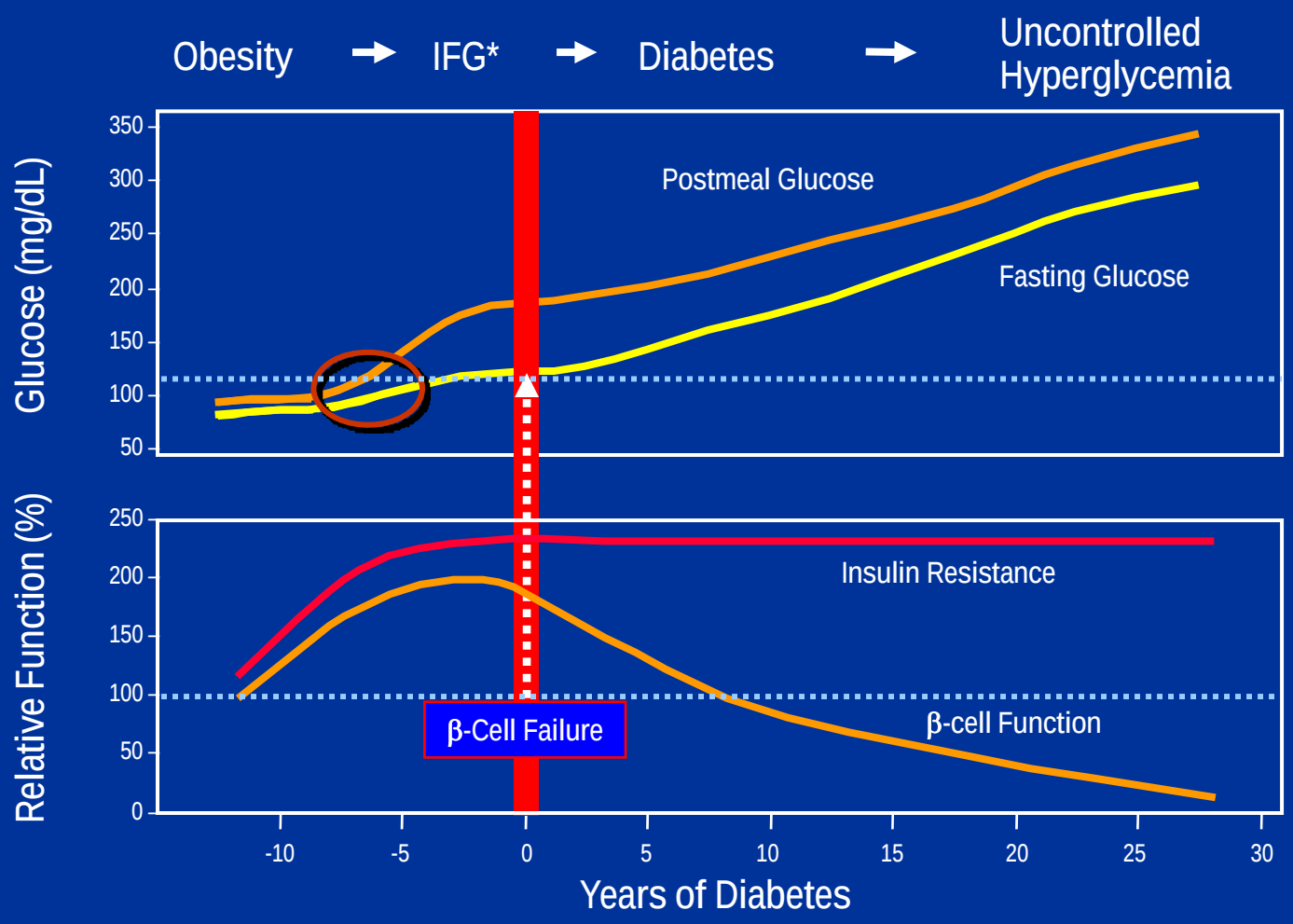
Impaired Glucose Tolerance

Hyperglycemia

Early Diabetes: Partial β cell failure

Late Diabetes: Total β cell failure

Natural History of Type 2 Diabetes



*IFG=impaired fasting glucose.

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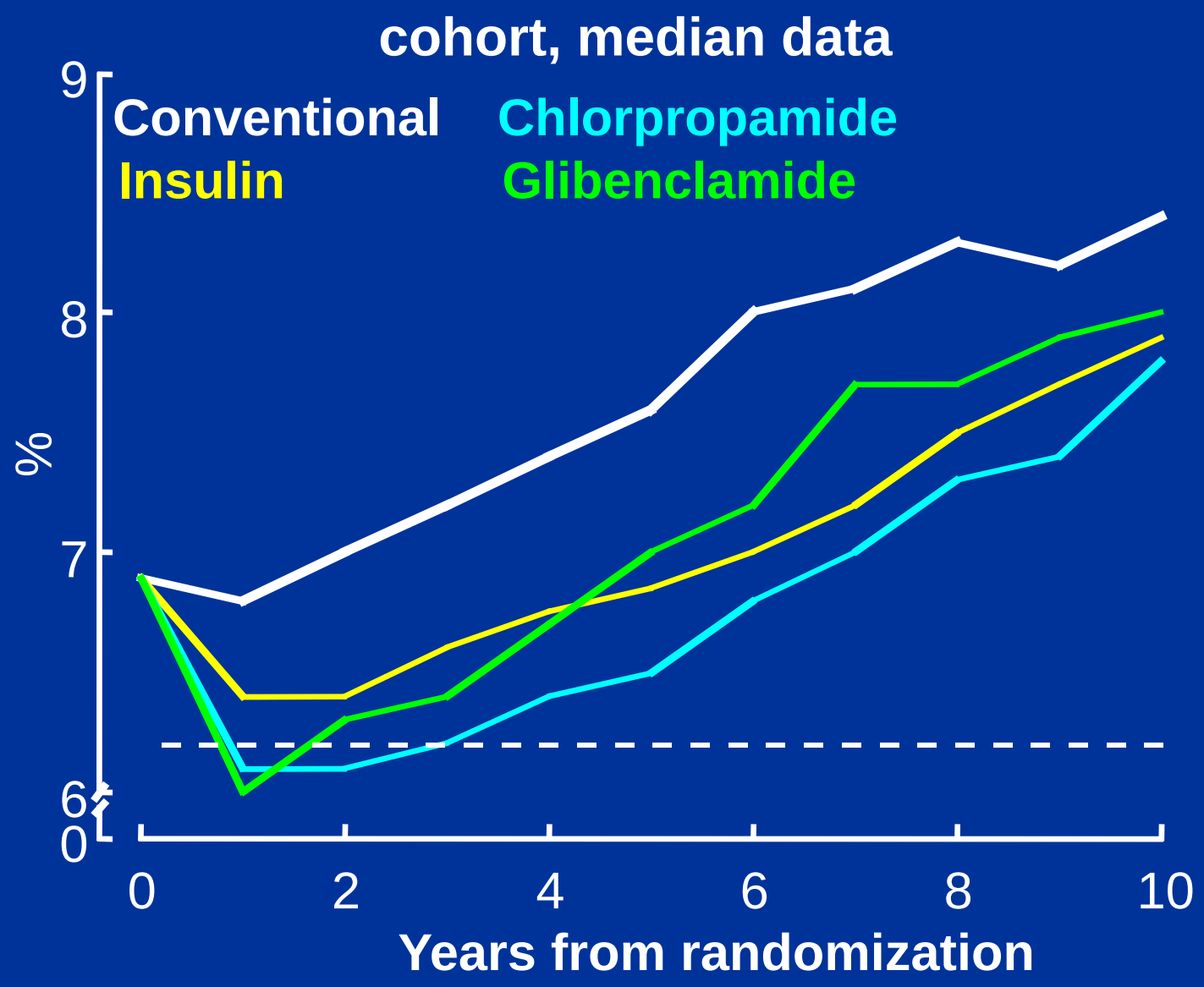
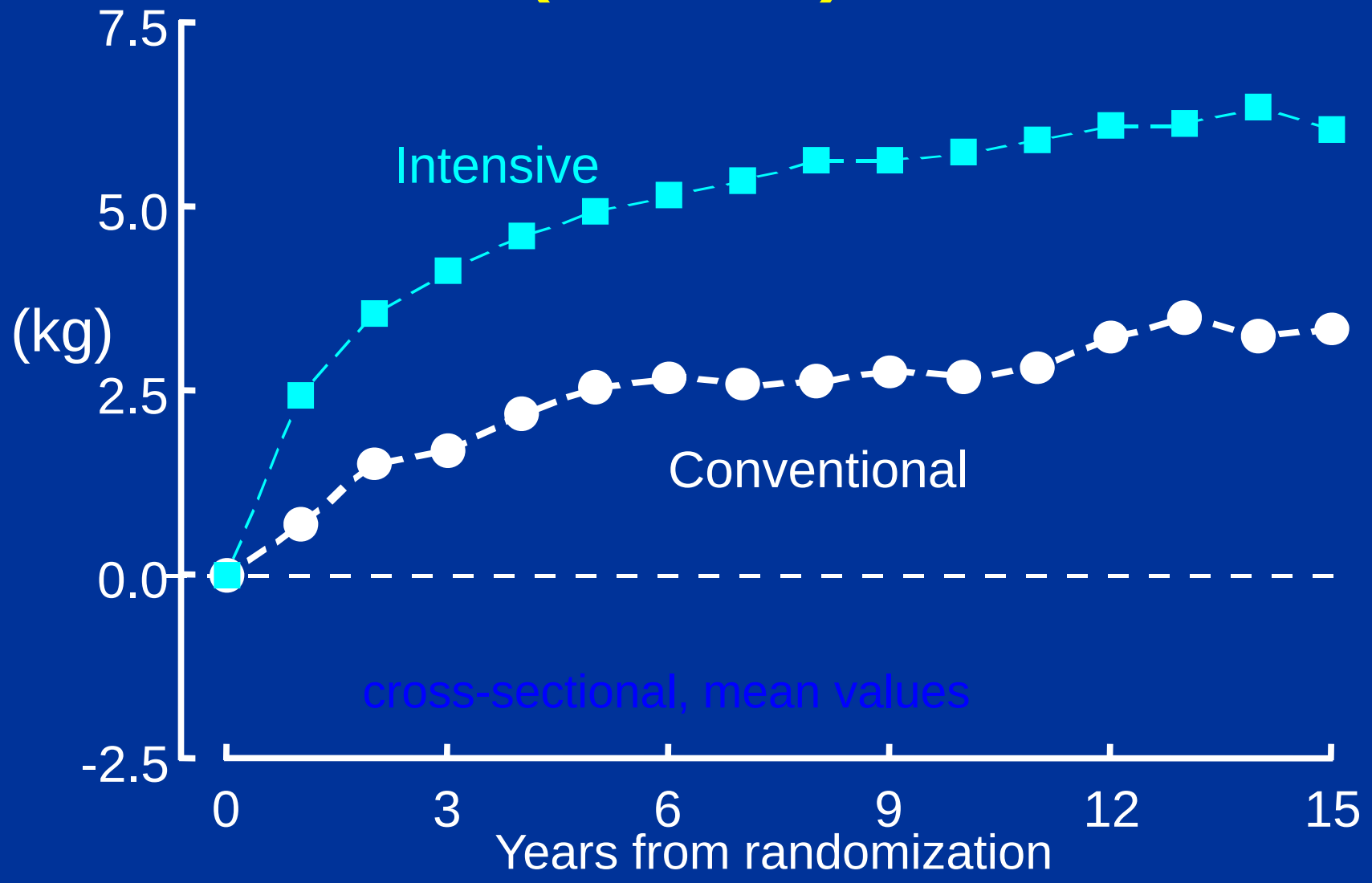
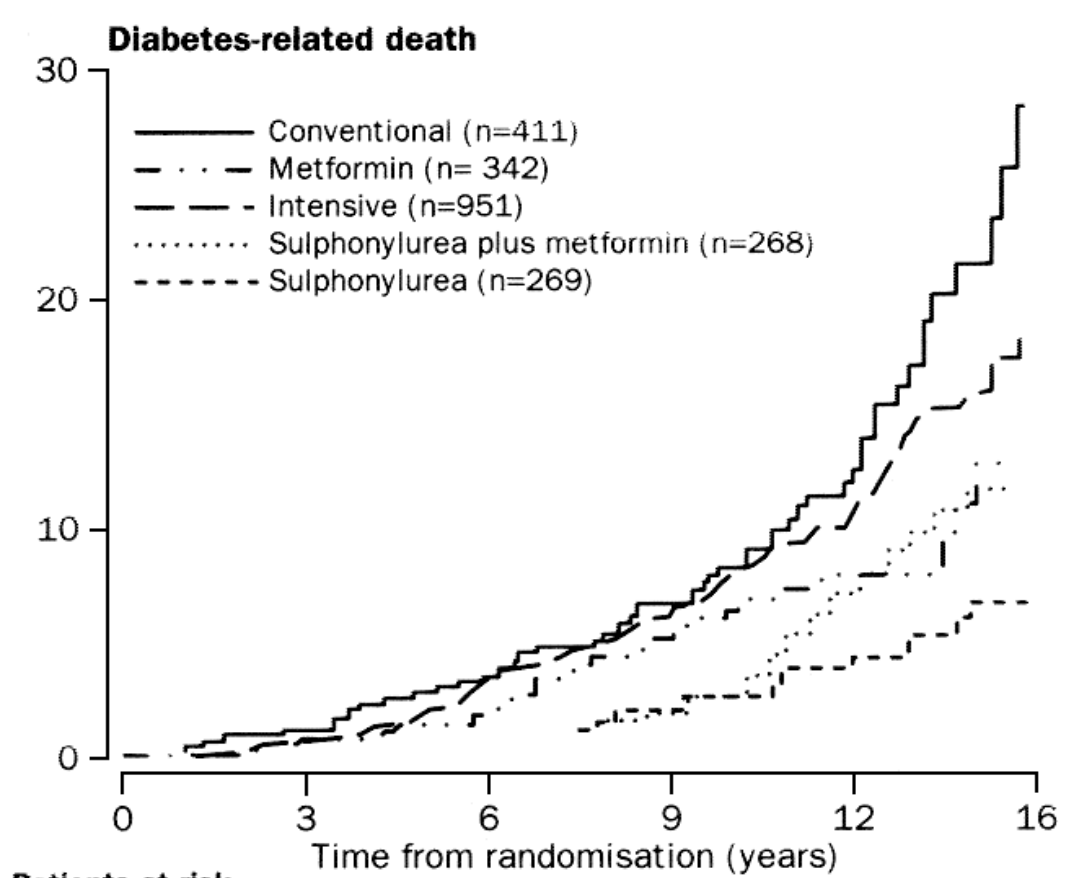
UKPDS: HbA_{1c}


cohort, median data
Conventional
Insulin
Chlorpropamide
Glibenclamide
%
9
8
7
6
0
0
2
4
6
8
10
Years from randomization

Change in Body Weight (UKPDS)



Conventional therapy had the highest overall death endpoint

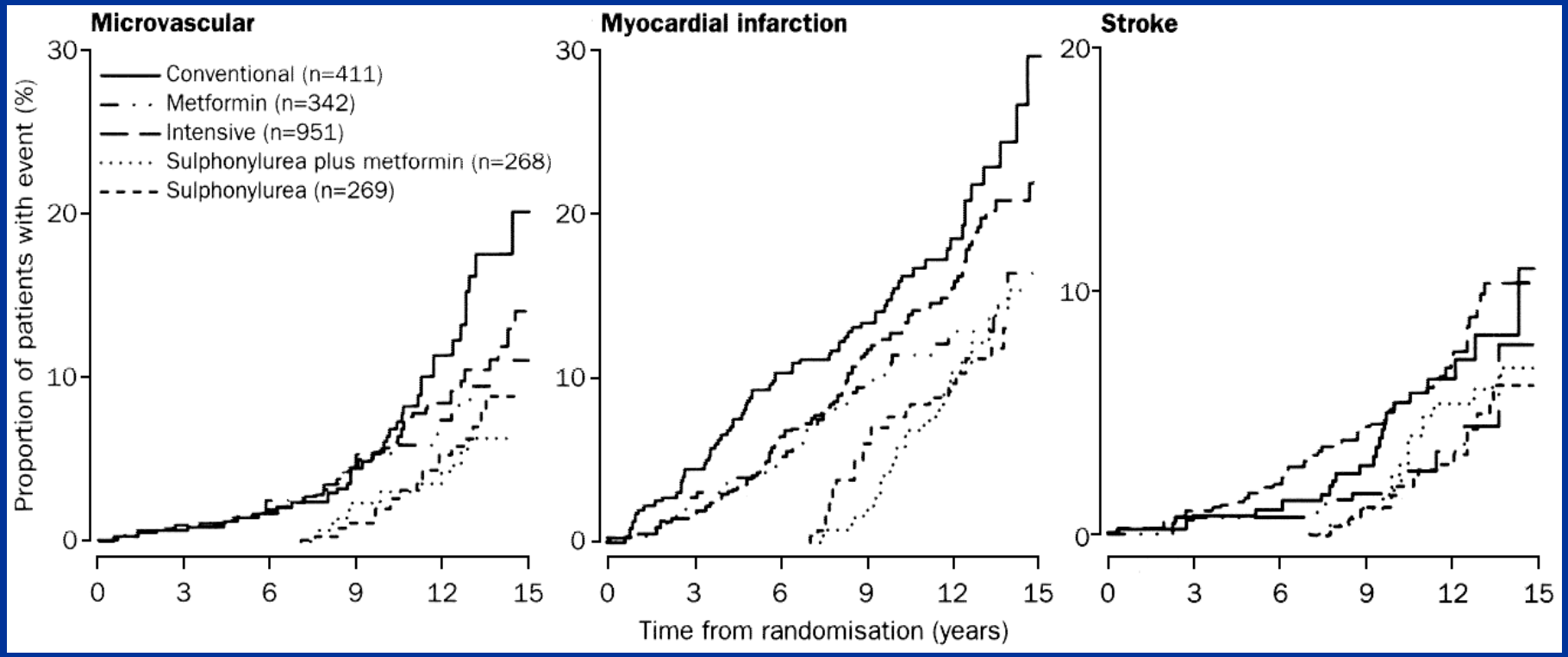


Patients at risk

Conventional	404	378	304	132	23
Metformin	339	321	267	123	28
Intensive	930	870	701	319	61

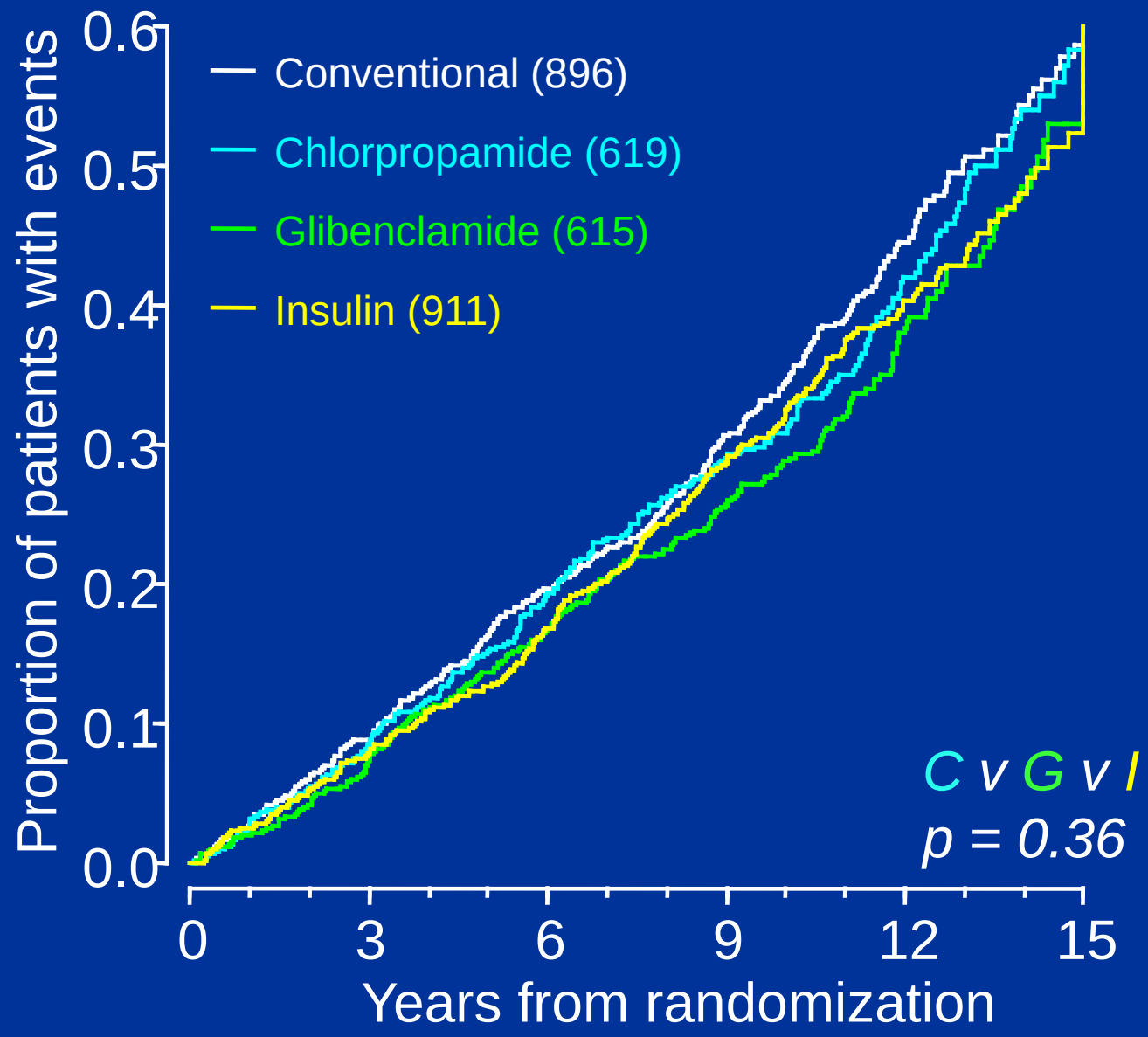
Lancet, 1998, 353, Sept. 12.

Conventional therapy resulted in overall higher micro- & macro-vascular events



Lancet, 1998, 353, Sept. 12.

Any diabetes-related endpoints: UKPDS



Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA_{1c} by 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of

12%	for any diabetes related endpoint	p=0.029
25%	for microvascular endpoints	p=0.0099
16%	for myocardial infarction	p=0.052
24%	for cataract extraction	p=0.046
21%	for retinopathy at twelve years	p=0.015
33%	for albuminuria at twelve years	p=0.00005

Lancet, 1998, 353, Sept. 12.

Pharmacotherapy for DM

Insulin secretagogues

- Sulfonylureas (SURs)
- Glinides

Biguanides

- Metformin

Thiazoladinediones (TZDs)

- Pioglitazone & Rosiglitazone

Incretins and Incretin mimetics

- Exenatide
- Sitagliptin

Glucosidase inhibitors

- Acarbose & Miglitol

Insulin and insulin analogs

Pharmacotherapy for DM

Insulin secretagogues

Sulfonylureas

glyburide (Micronase, Diabeta)

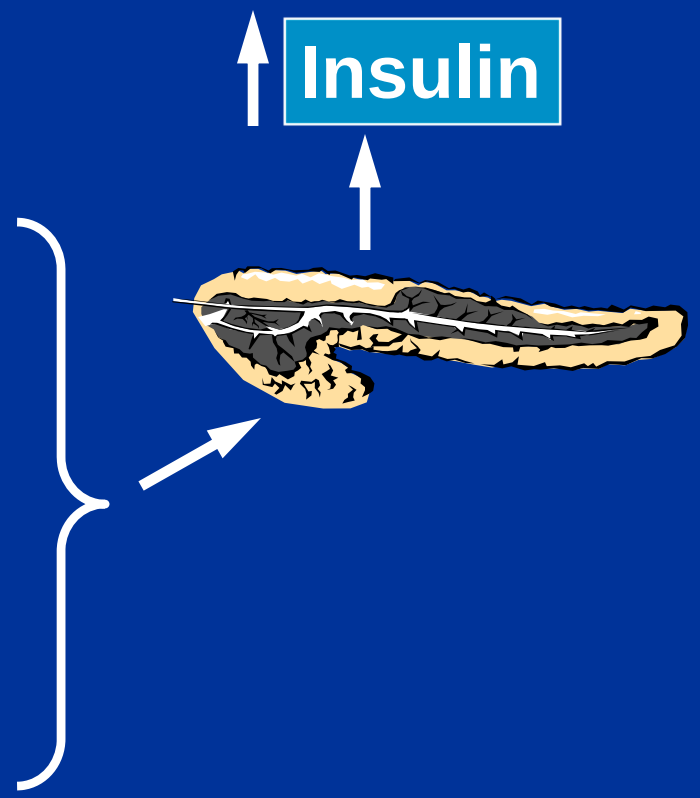
glipizide (Glucotrol [XL])

glimepiride (Amaryl)

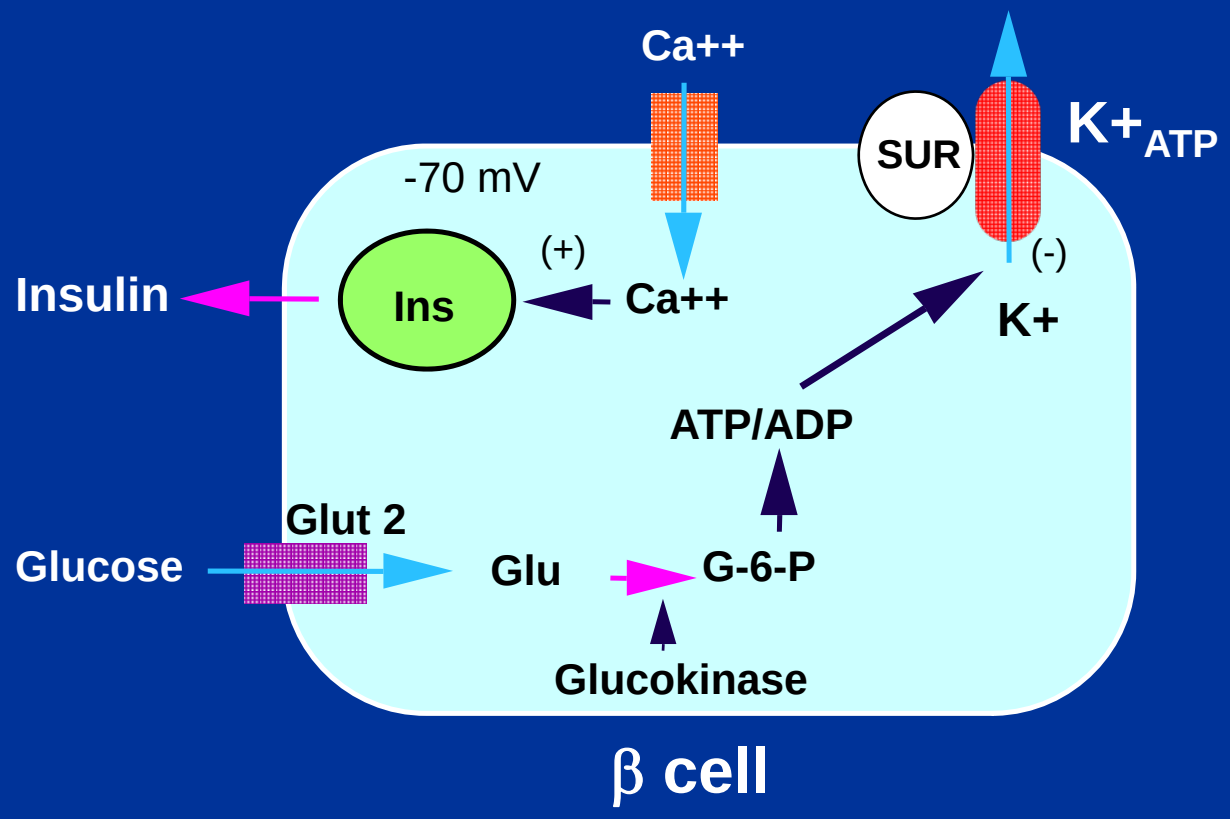
Meglitinides

repaglenide (Prandin),

netaglenide (Starlix)



Regulation of insulin secretion from the islet β-cell



Sulfonylureas

- Common choice as monotherapy
  - Low cost and high efficacy
- Increase dose at intervals of 2 weeks based on glucose levels
  - (e.g. Glipizide 2.5 mg qd to 20 mg bid)

  or Glucotrol XL (2.5 to 10 qd)
- Do not combine two sulfonylureas
- More effective during the first 10 years of diabetes
- Combination therapy with metformin, acarbose, insulin, and rosiglitazone effective
- Short-term treatment with insulin may be needed
  - May be able to wean off insulin

Sulfonylureas

- **Disadvantages**
  - **risk of hypoglycemia especially with chlorpropamide**
  - **hyperinsulinemia and weight gain (less than TZDs)**
  - **30% long-term failure rate (stress, infection, failure of lifestyle change, inadequate dose, non-compliance)**
- **Contraindications**
  - **Type 1 diabetes, pregnancy, sulfa allergy**
- **Use with caution**
  - **hepatic disease, renal disease, Type 2 diabetes with ketosis**

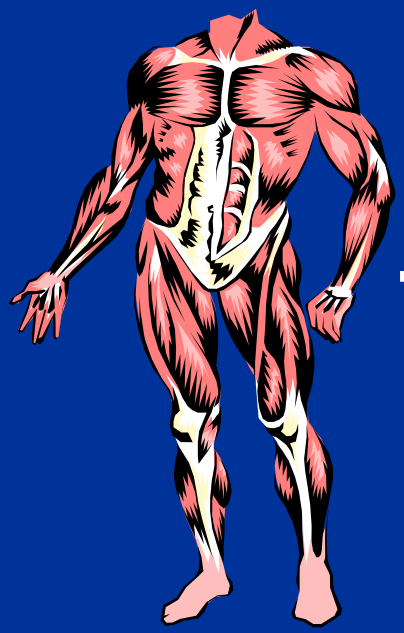
Properties of Repaglinide and Prandin

- acts as an insulin secretagogue
- acts primarily on ATP K+ channel
- the SUR is part of the complex
- requires glucose for its action, thus theoretical reduction in hypoglycemia
- similar efficacy profile as the other SUR
  - 0.5 mg tid to max of 15 mg/d (Prandin)
  - 60 to 120 mg tid (Starlix)

Pharmacotherapy for DM: Biguanides

Biguanides
[Metformin (Glucophage)]

↓ **Hepatic Glucose Output**



↑ **Muscle Glucose Uptake**

↓ **Intestinal Glucose Absorption**

Pharmacodynamic properties of Metformin

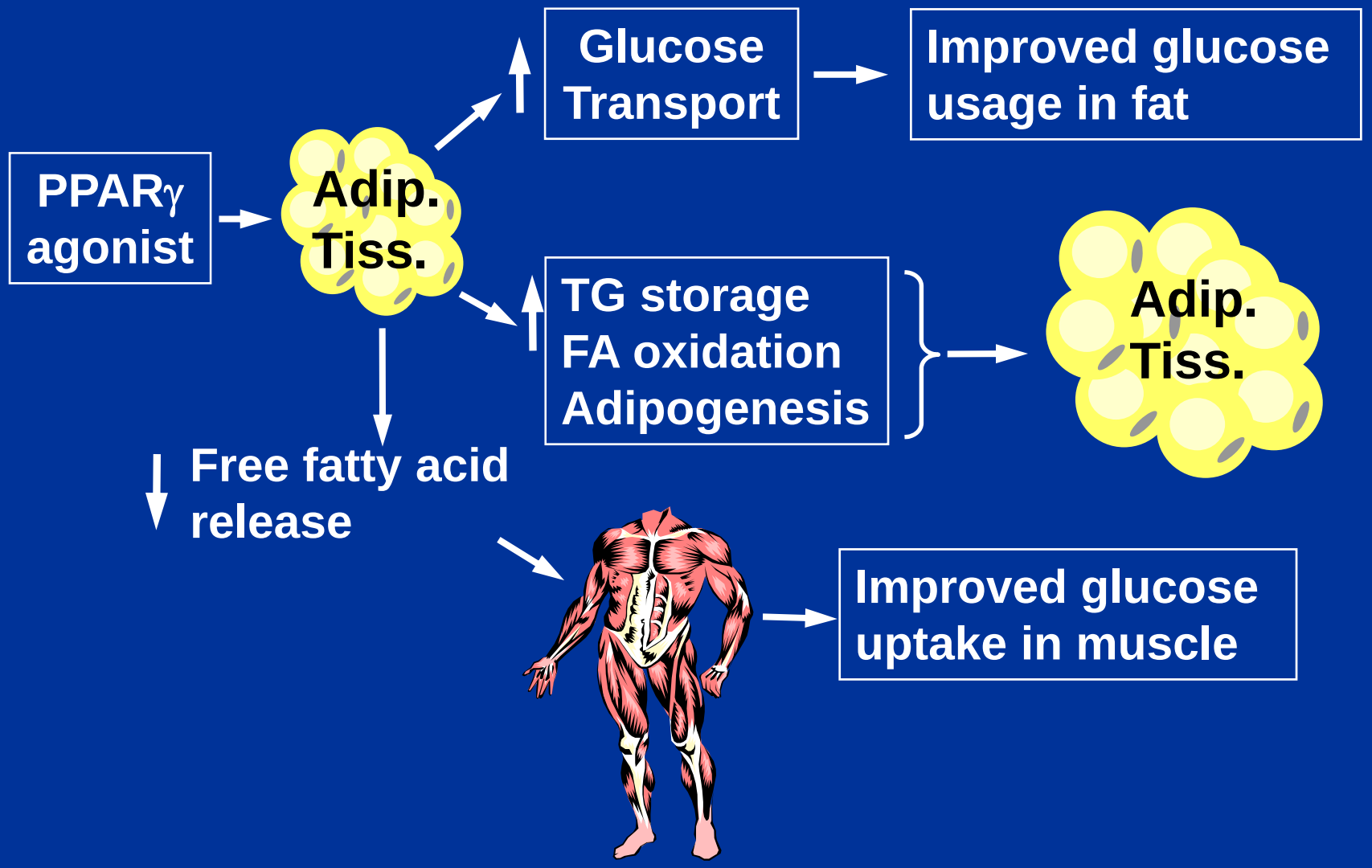
- **Reduces hepatic glucose output, with some increase in insulin sensitivity**
- **Effective as monotherapy or added to another drug**
  - **Popular combination with SUR (e.g. Glucovance-metformin + glyburide)**
- **Weight gain and hyperinsulinemia less common than with SUR**
- **Does not produce hypoglycemia if used as a single drug**
- **Effective with insulin and sulfonylurea, but may increase risk of hypoglycemia**
- **Gastrointestinal symptoms common**
  - **diarrhea most common, usually self limited**
  - **important to titrate dose slowly and give with food**
  - **4% discontinue use with long-term treatment**

Cautions Using Metformin

Minimize risk of lactic acidosis

- small risk of lactic acidosis (9 per 100,000 person years)
- avoid use in alcoholics, binge drinkers
- avoid use in congestive heart failure, renal insufficiency (Cr>1.5), and liver failure
- discontinue during intercurrent illness or surgery (risk of decreased renal blood flow)
- discontinue use before radiographic studies using contrast agents (risk of renal dysfunction secondary to dye study)

Mechanism of action of Thiazolidinediones: PPARγ agonist



Thiazolidinediones (TZDs)

Rosiglitazone (Avandia) 4 mg bid in single or divided doses
--do not use if hx of CAD
Pioglitazone (Actos) 15 to 45 mg/d in single or divided doses

Effective as monotherapy and with insulin, sulfonylureas and/or metformin
--use with caution in CHF and peripheral edema

Rare LFT abnormalities

Does not cause hypoglycemia as monotherapy
(may increase hypoglycemia risk of other agents such as insulin, sulfonylureas)

Pharmacotherapy: Acarbose & Miglitol

- **Inhibits intestinal disaccharidase, delaying glucose absorption**
- **Reduces postprandial glucose and insulin response**
- **Most useful with high carbohydrate diet**
- **Effective with diet, sulfonylurea, metformin, and insulin**
- **Does not cause hypoglycemia**

Pharmacotherapy: Acarbose & Miglitol

Gastrointestinal side effects

- **flatulence, diarrhea, nausea/vomiting**

Hepatic dysfunction

- **elevated aminotransferases**
- **hyperbilirubinemia rare**
- **follow liver function tests every 3 months for the first year**
- **use <u>miglitol</u> instead**

Incretin Mimetics

Exenatide (Byetta)

Analog of GLP-1, a glucoincretin

Mechanism of Action:

- increases insulin secretion
- decreases glucagon secretion
- delays gastric emptying
- promotes satiety and weight loss
- increases beta cell mass

Lowers FBS 10-20 mg/dl, A1c 1%

Incretin Mimetics

Pros: no hypoglycemia, weight loss

Cons: GI intolerance, requires injection and refrigeration

Newer agents in development

- liraglutide (acylated GLP-1 analogue)
- exenatide-LAR
- vildagliptin, sitagliptin (DPP-IV inhibitors; orally active, but weight neutral)

Sitagliptin (Januvia)

Mechanism

--DPP-IV inhibitors; orally active, but weight neutral

--can be used with other oral agents

(combined with metformin in Janumet)

The most common side effects of JANUVIA include:

Upper respiratory infection

Stuffy or runny nose and sore throat

Headache

Stomach discomfort and diarrhea

Combination Drugs

SU + metformin (Glucovance, Metaglip)

SU + TZD (Avandaryl)

Metformin + TZD (Avandamet and Actoplusmet)

Sitagliptin + metformin (Janumet)

Lower A1c 2 – 4 %

Pros: cost savings, convenience, improved adherence

Cons: limited flexibility

Pramlintide

Pramlintide (Symlin); a synthetic amylin analogue (amylin or islet amyloid polypeptide is co-secreted with insulin)

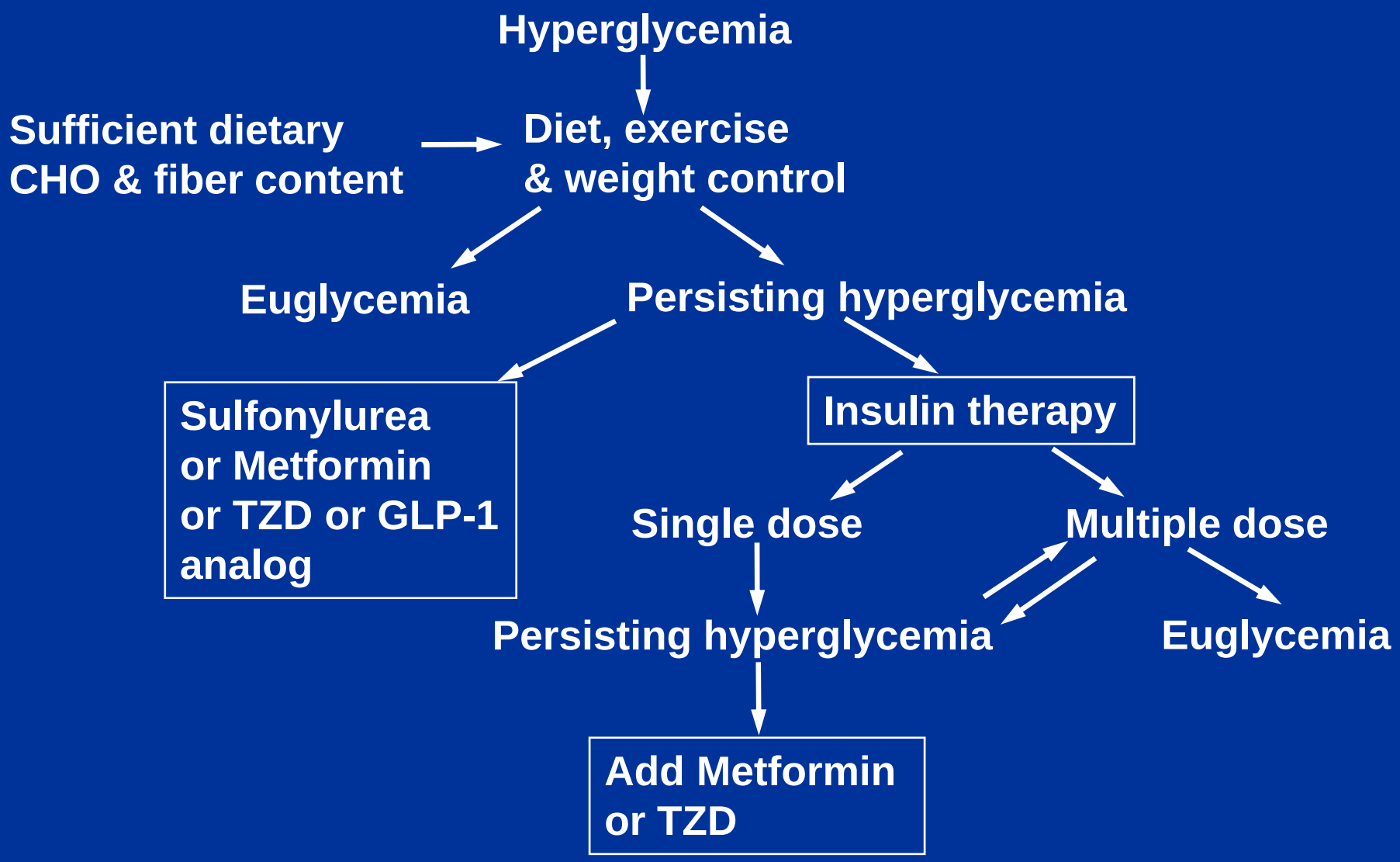
Mechanism of Action:

- inhibits glucagon secretion
- slows gastic emptying
- promotes satiety and weight loss

Pros: lowers PPG, lowers A1c 0.5 % and promotes weight loss

Cons: GI intolerance, hypoglycemia, another injection, and cost

Treatment algorithm



Indications for Insulin Therapy in Type 2 Diabetes

- FPG > 200 mg/dl (11.1 mmol/l)
- FPG > 140 mg/dl (7 mmol/l) despite maximal doses of oral agents
- Decompensation: infection, surgery, injury, uncontrolled weight loss
- Pregnancy
- Allergy to oral agents

Practical approach to Dosing insulin

0.1 to 0.5 U/kg/day in single or divided doses

or

Body Weight (lbs)/10 (e.g. 220#/10=22 U/d)

or

FBS/18

Insulin and Insulin Analogs

Glargine (Lantus) and Detemir (Levemir) Insulin

- “Peakless” basal insulin
- Can be used alone or in combination with short or ultra-short acting insulins
- Can not be mixed with other insulins

Lispro (Humulog) and Aspart (Novolog) Insulin

- Ultra-short acting insulins
- Can be given with the meal
- Available in 70/30 or 75/25 for bid or tid dosing

Inhaled Insulin

Exubera (inhaled powdered insulin)

Pros: kinetics similar to rapid acting injectable insulin analogs, does not require injection

Cons: inhaler device, contraindicated in smokers and patients with lung disease, limited ability to titrate dose, and cost

What should we be doing to manage diabetes

1. Maintaining glycemic goals with diet, exercise, & pharmacotherapy
2. Maintenance of BP (optimal 130/80)
3. Monitor renal function for micro-albuminuria and begin ACE inhibitors
4. Monitoring and treatment of hyperlipidemia (LDL<100)
5. Bi-annual eye exams (dilated)
6. Annual examination of the feet for signs of PVD and/or neuropathy
   -more frequent if the above are present and appropriate referral to foot specialist

Current Demographics of Diabetes and Projections for the Future

Number of Americans with Diabetes: 18.2 million people
Percent of American Population: 6.3% of the population
Total Diagnosed: 13 million people
Total Undiagnosed: 5.2 million people

Under 20 Years of Age

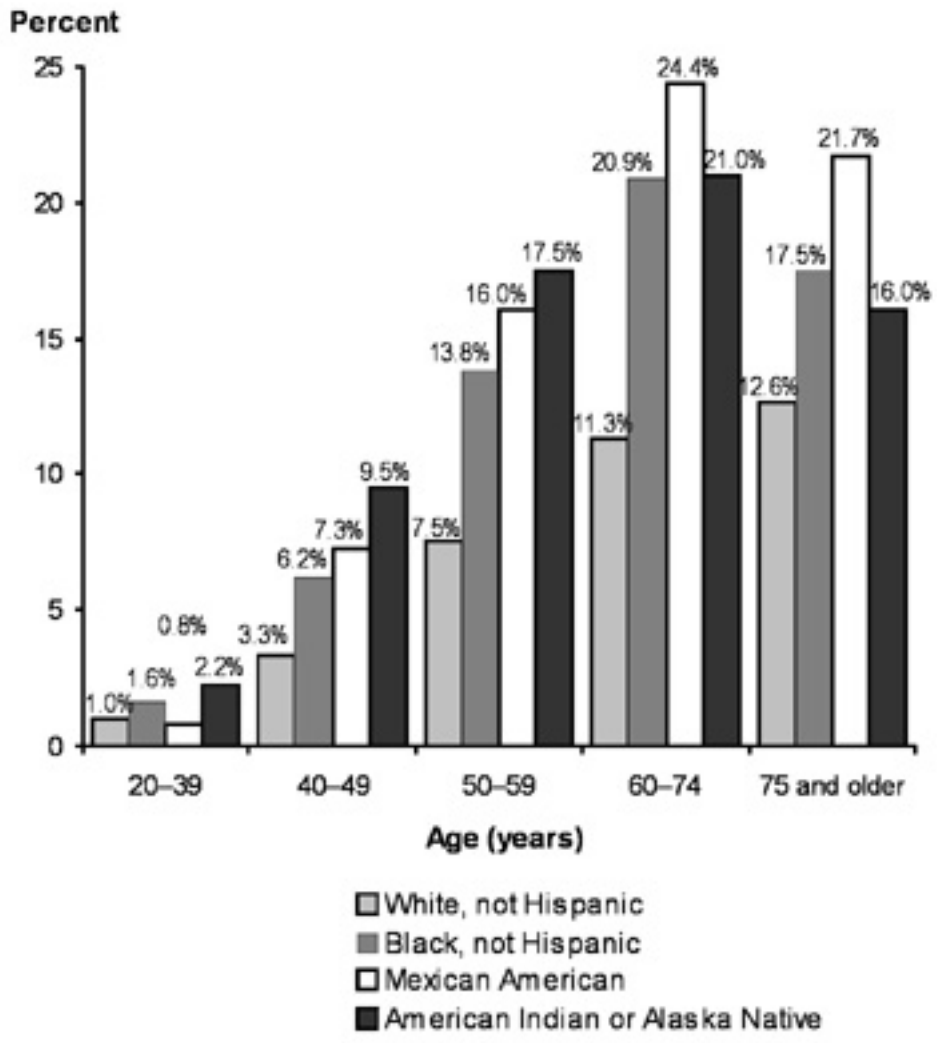
Number of Americans with Diabetes: 210,000 people
Percent of Age Group: 0.26%
Frequency of Occurrence: one in every 400 to 500 children and adolescents has type 1 diabetes

Over 20 Years of Age

Age 20 years or older: 18 million (8.7% of age group)
Age 60 years or older: 8.6 million (18.3% of age group)
Men: 8.7 million (8.7% of age group/gender)
Women: 9.3 million (8.7% of age group/gender)

Proportion of the Population With Diabetes

(Persons aged 20 years and older by age group and race/ethnicity, United States, 1988–94)



Sources: Harris, M.; Flegal, K., Cowie, C.; et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: The Third National Health and Nutrition Examination Survey, 1998–1994. *Diabetes Care* 21(4):518–524, 1998. Indian Health Service, national outpatient database.

Future directions

1. Diabetes prevention strategies
2. Improved pharmacotherapy
3. Improvement in co-morbidity therapies.

The End