



**Celerion's Symposia Series:
Bridging the Gap from Phase I to
Proof-of-Concept**

San Francisco, CA

Tue 8th, Apr 2014



Diabetes and Drug Development

Helmut Steinberg MD

Professor of Medicine, University of Tennessee
Health Science Center (UTHSC), Department of
Medicine, Division of Endocrinology

Diabetes and Drug Development

- Considerations about a complex chronic disease
 - Epidemiology
 - Physiology/Pathophysiology
 - Regulatory

Framework for Evaluating Investments in New Drugs

Dimension	Examples of types of drugs	Possible influences
Development cost	Niche drugs vs. drugs for common chronic diseases	Regulatory policy or new business model
Selling cost of drug	Specialist vs. GP	Regulatory policy or new business model
Differentiation from existing drugs	Short survival vs. chronic	Only influenced via investment in basic scientific research
Incidence and prevalence of treated condition	Rare vs. common chronic	Only influenced via investment in basic scientific research

* Drugs are most favorable for investment when they have low development and selling costs, are highly differentiated from available treatments, and target conditions with a high incidence and prevalence.

Definition of Diabetes

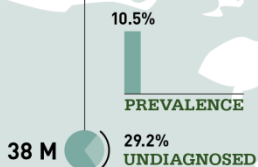
- Fasting Blood Glucose ≥ 126 mg/dL
- 2 hour post OGTT ≥ 200 mg/dL
- Casual Blood Glucose ≥ 200 mg/dL and Symptoms of Hyperglycemia
- HbA1c $\geq 6.5\%$

Epidemiology

- Based on the IDF Diabetes Atlas 5th Edition 2012 Update - New estimates for 2012 of diabetes prevalence, mortality, and healthcare expenditures

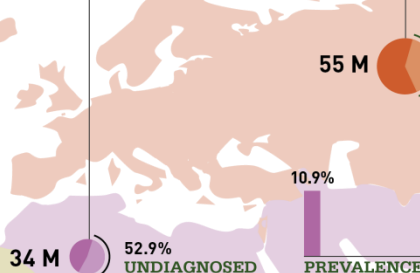
NORTH AMERICA AND CARIBBEAN

More healthcare dollars were spent on diabetes in this region than any other
1 in 10 adults in this region has diabetes



MIDDLE EAST AND NORTH AFRICA

1 in 9 adults in this region has diabetes
More than half of people with diabetes in this region don't know they have it



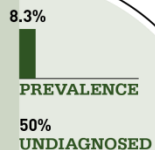
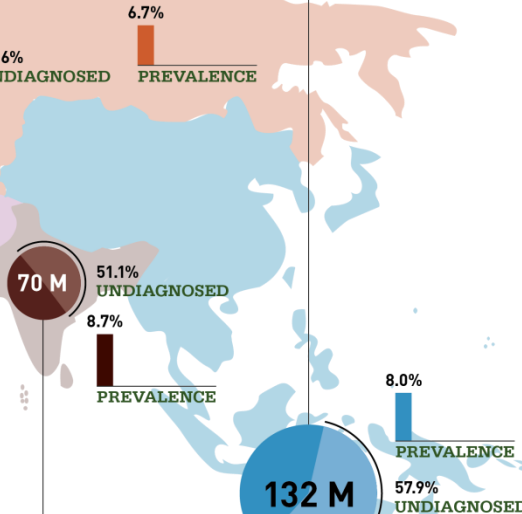
EUROPE

1 out of every 3 dollars spent on diabetes healthcare was spent in this region
21.2 million people in this region have diabetes and don't know it



WESTERN PACIFIC

1 in 3 adults with diabetes lives in this region
6 of the top 10 countries for diabetes prevalence are Pacific Islands



WORLD
371 M
people living with diabetes

26 M



SOUTH AND CENTRAL AMERICA

Only 5% of all healthcare dollars for diabetes were spent in this region
1 in 11 adults in this region has diabetes

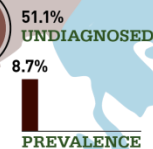
15 M



AFRICA

Over the next 20 years, the number of people with diabetes in the region will almost double
This region has the highest mortality rate due to diabetes

70 M



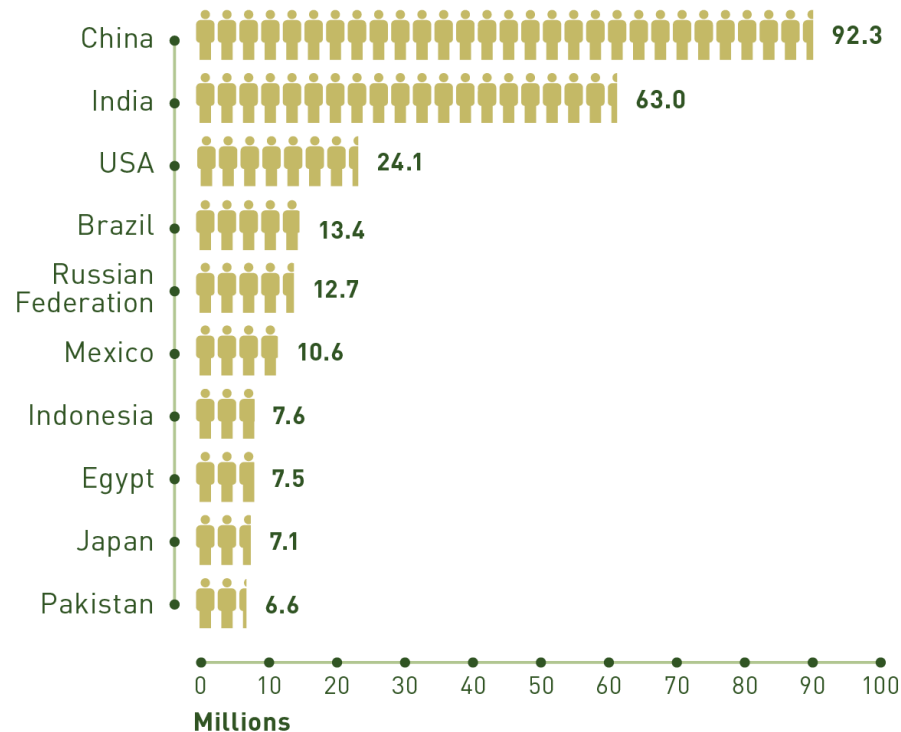
SOUTH-EAST ASIA

1 in 5 of all undiagnosed cases of diabetes is in this region
1 in 4 deaths due to diabetes occurred in this region

*all estimates are presented as comparative rates

More than **371 million** people have diabetes.

TOP 10 COUNTRIES/TERRITORIES FOR PEOPLE WITH DIABETES (20-79 YEARS)



The number of people with diabetes is **increasing** in every country.

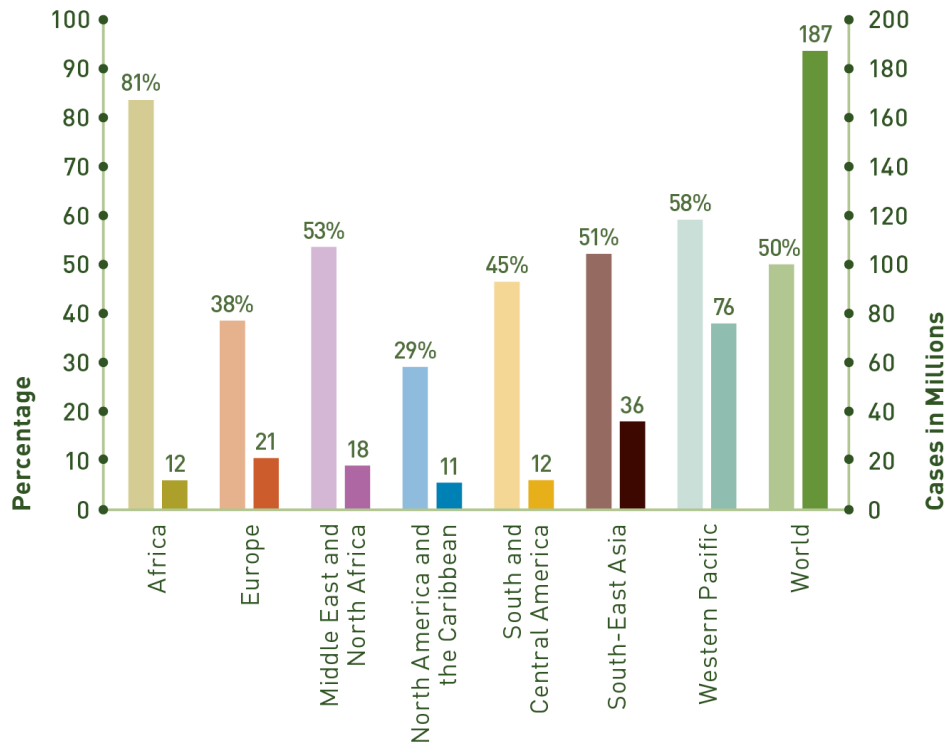
TOP 10 COUNTRIES/TERRITORIES FOR PREVALENCE* (%) OF DIABETES (20-79 YEARS)

COUNTRY /TERRITORY	PREVALENCE (%)
1 Federated States of Micronesia	37.2
2 Nauru	30.1
3 Marshall Islands	27.1
4 Kiribati	25.5
5 Tuvalu	24.8
6 Kuwait	23.9
7 Saudi Arabia	23.4
8 Qatar	23.3
9 Bahrain	22.4
10 Vanuatu	22.0

*comparative prevalence

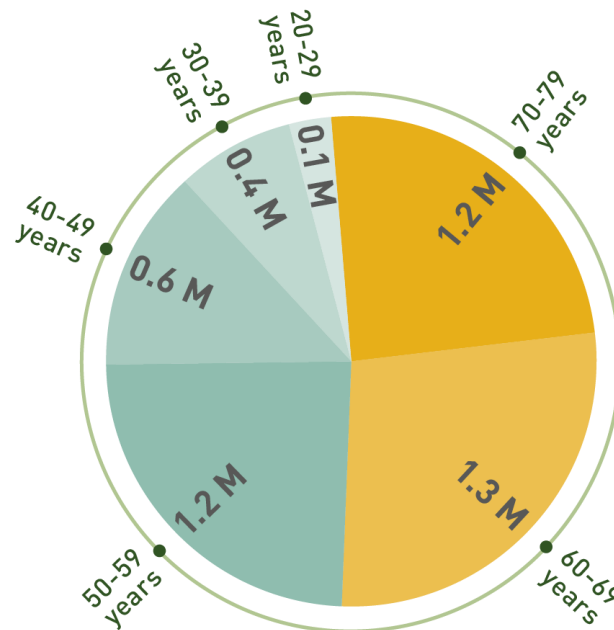
Half of people with diabetes don't know they have it.

UNDIAGNOSED PERCENTAGE AND UNDIAGNOSED CASES OF DIABETES (20-79 YEARS) BY REGION



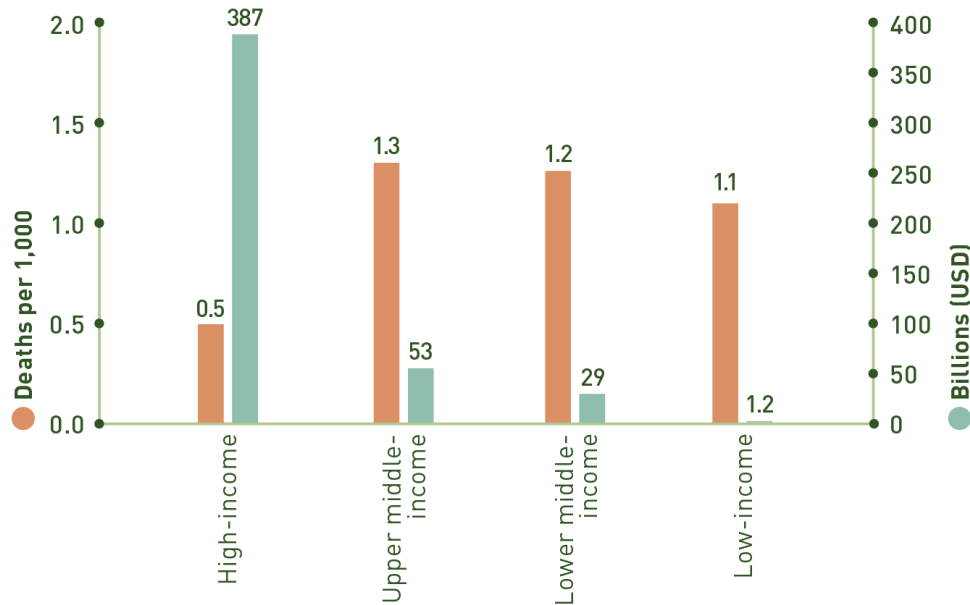
Half of people who die from diabetes are **under the age of 60.**

DEATHS ATTRIBUTABLE TO DIABETES BY AGE (20-79 YEARS)



4.8 million people died and 471 billion USD were spent due to diabetes in 2012.

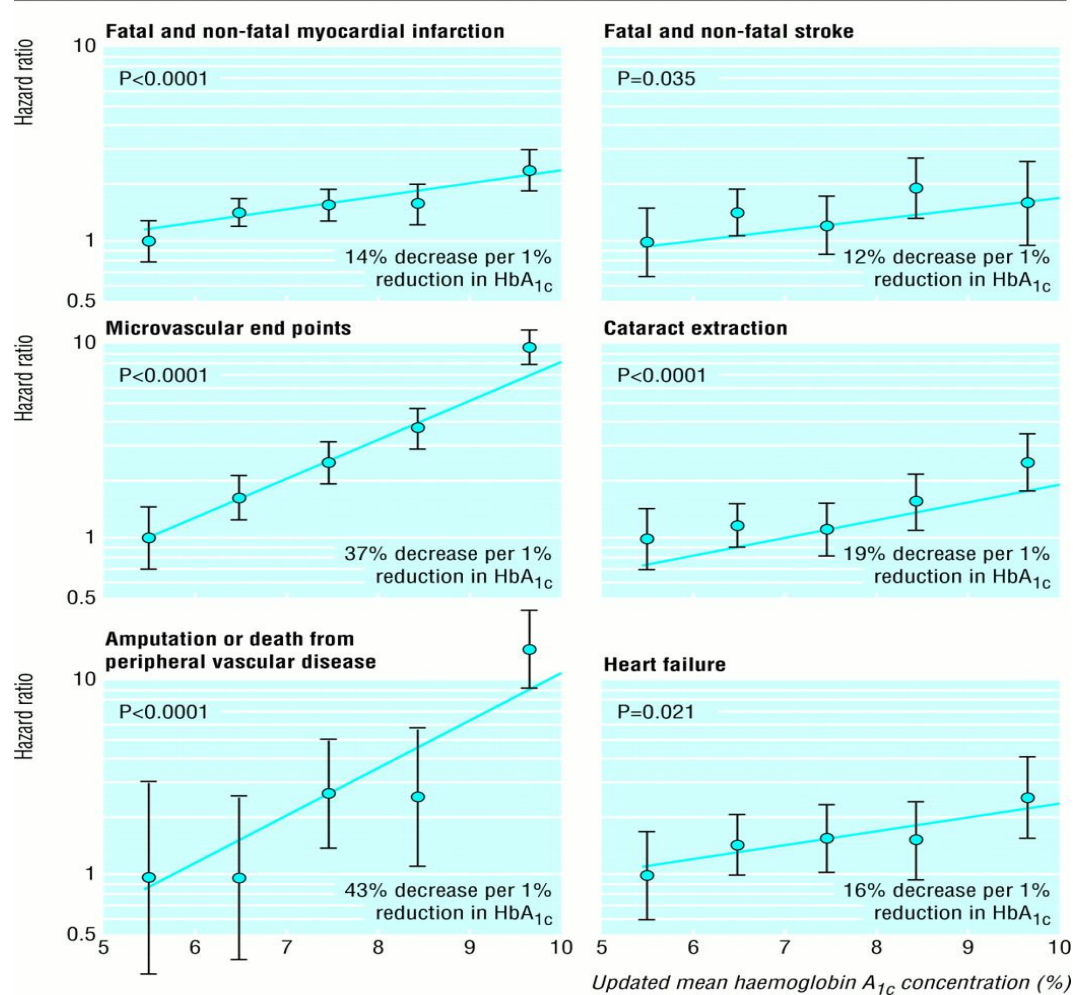
HEALTHCARE EXPENDITURES AND DEATHS PER 1,000 DUE TO DIABETES BY INCOME GROUP



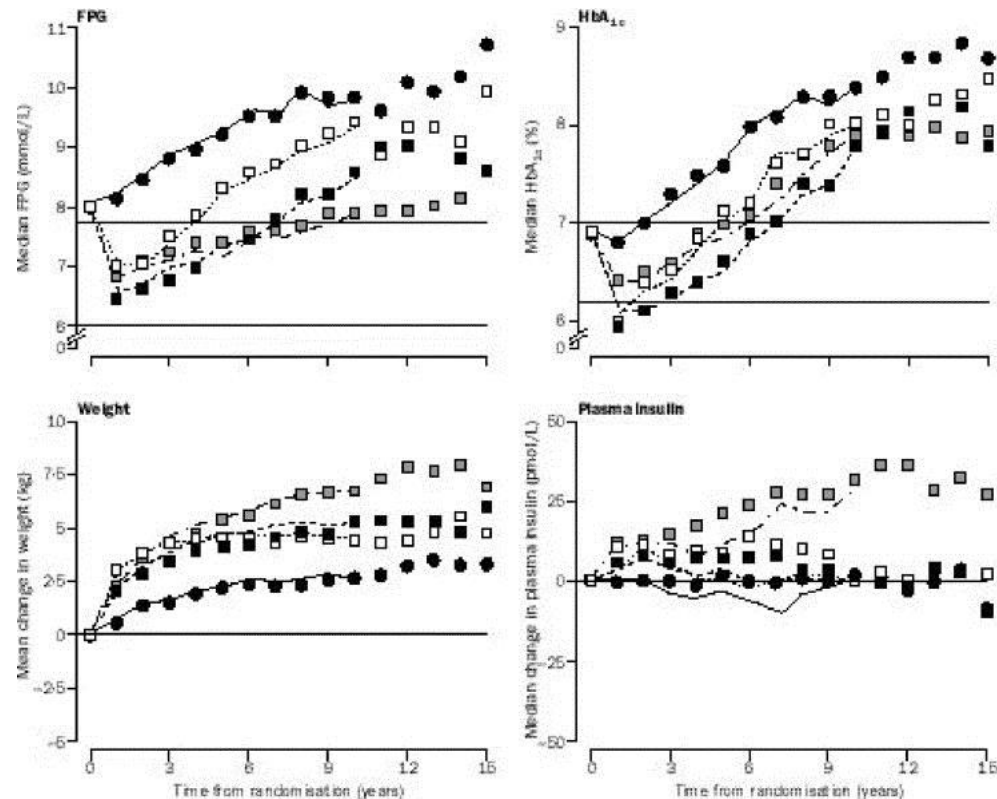
Pathophysiology

- Impact of dysglycemia on complications
- Some known contributors to diabetes
- Genes and clinical factors in diabetes prediction

Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A1c concentration and myocardial infarction, stroke, microvascular end points, cataract extraction, lower extremity amputation or fatal peripheral vascular disease, and heart failure.



UKPDS Cross-sectional and 10-year cohort data for FPG, HbA_{1c}, weight, and fasting plasma insulin in patients on chlorpropamide, glibenclamide, or insulin, or conventional treatment



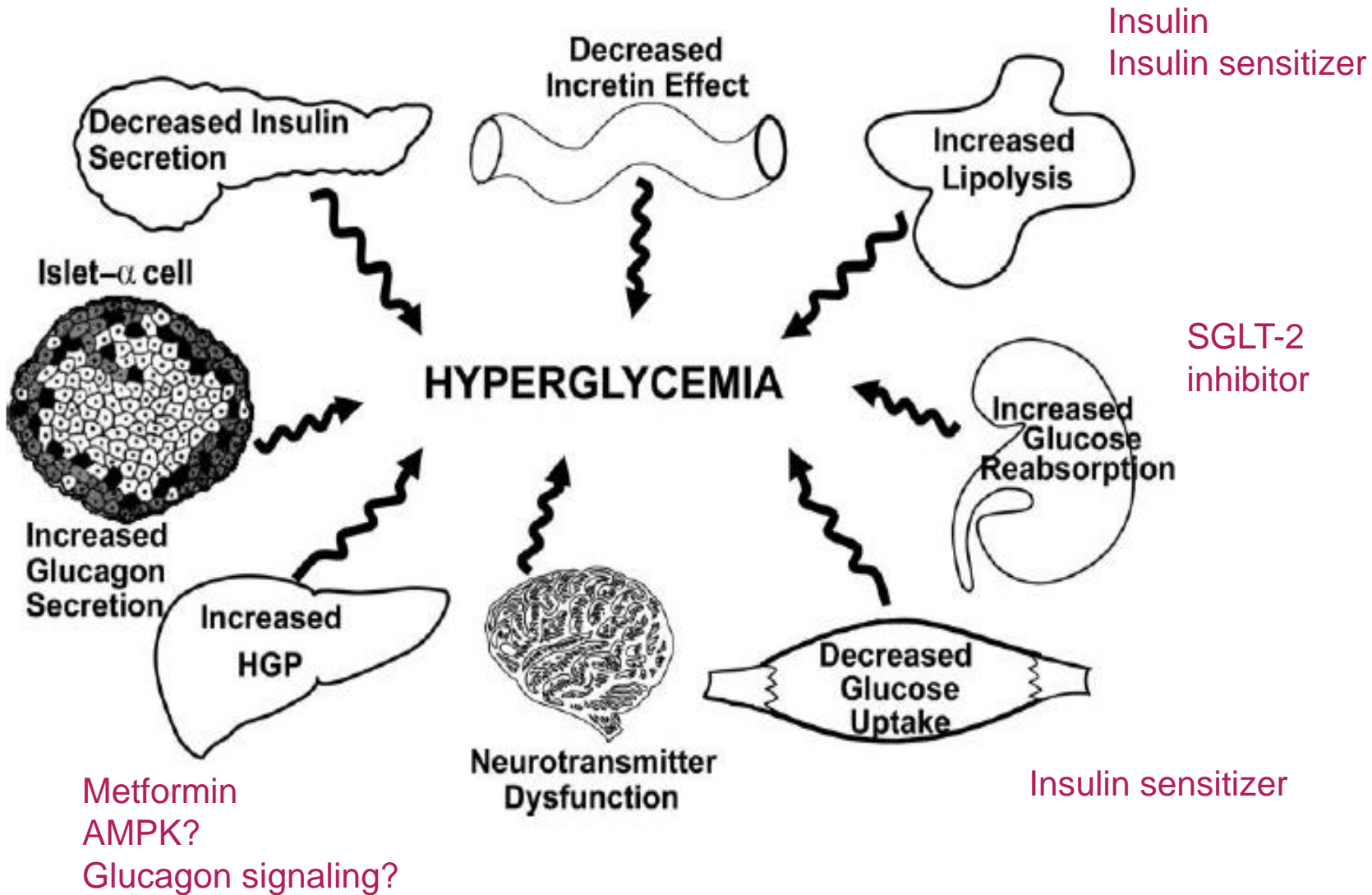
Patients followed for 10 years



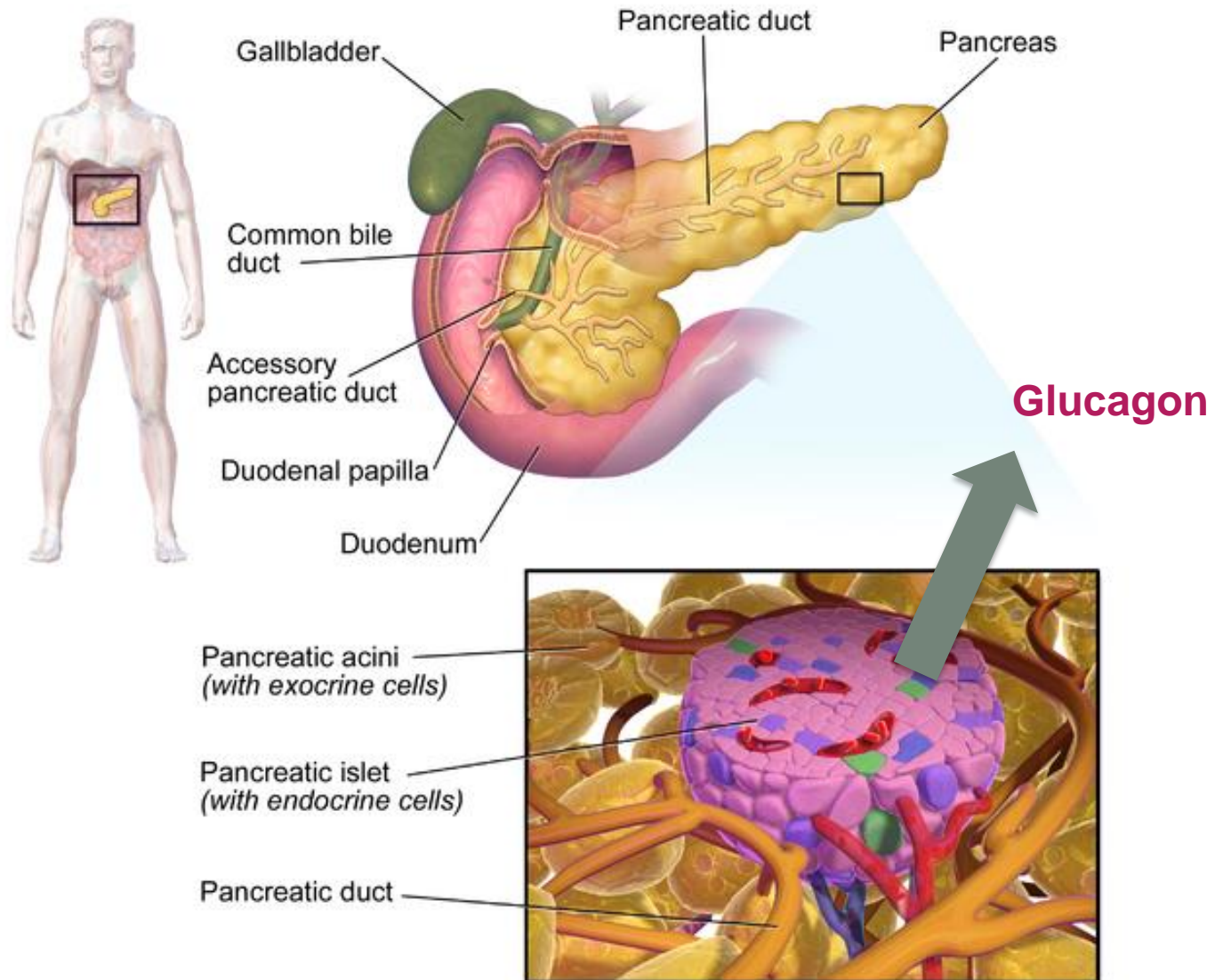
All patients assigned to regimen



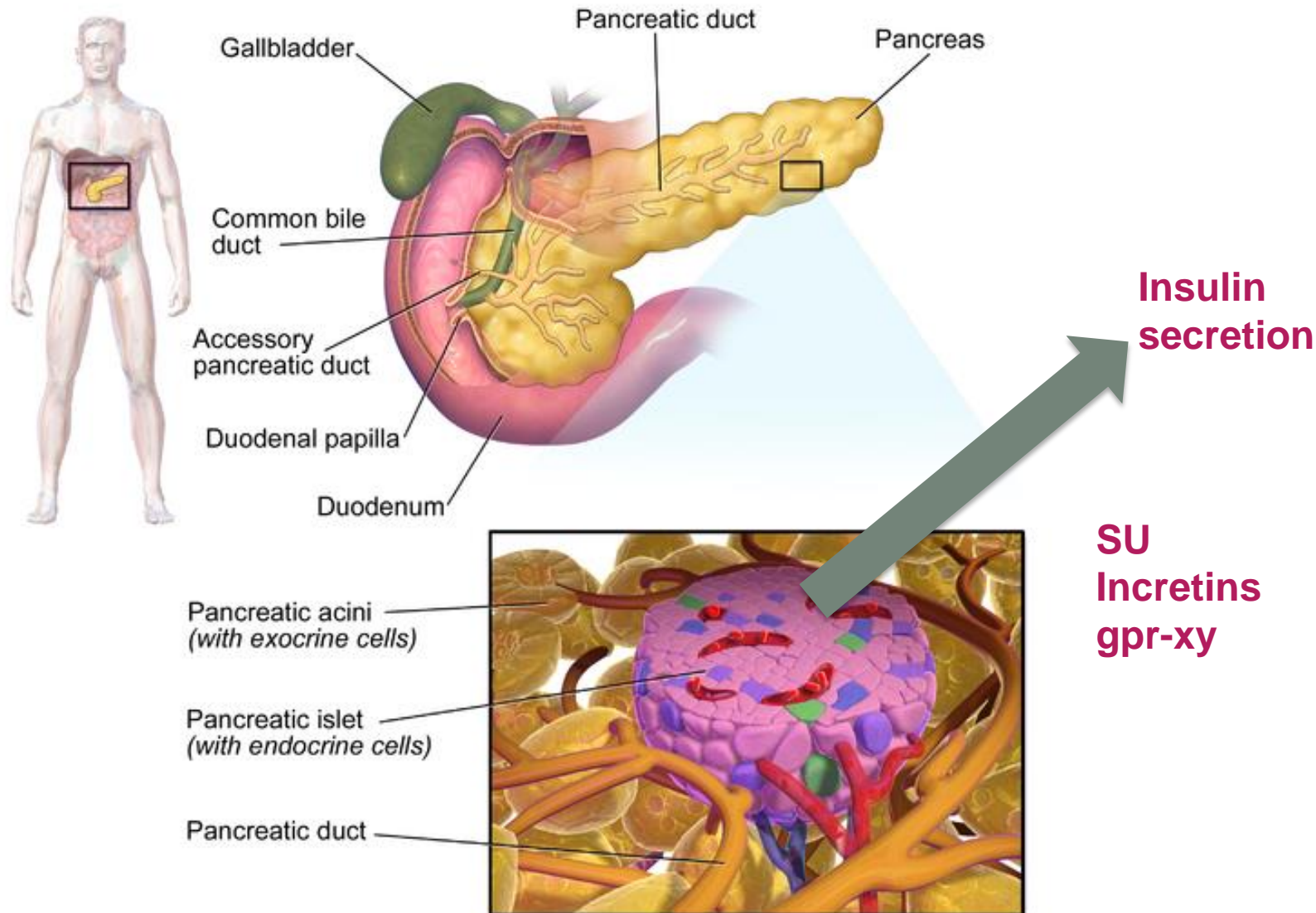
The Ominous Octet



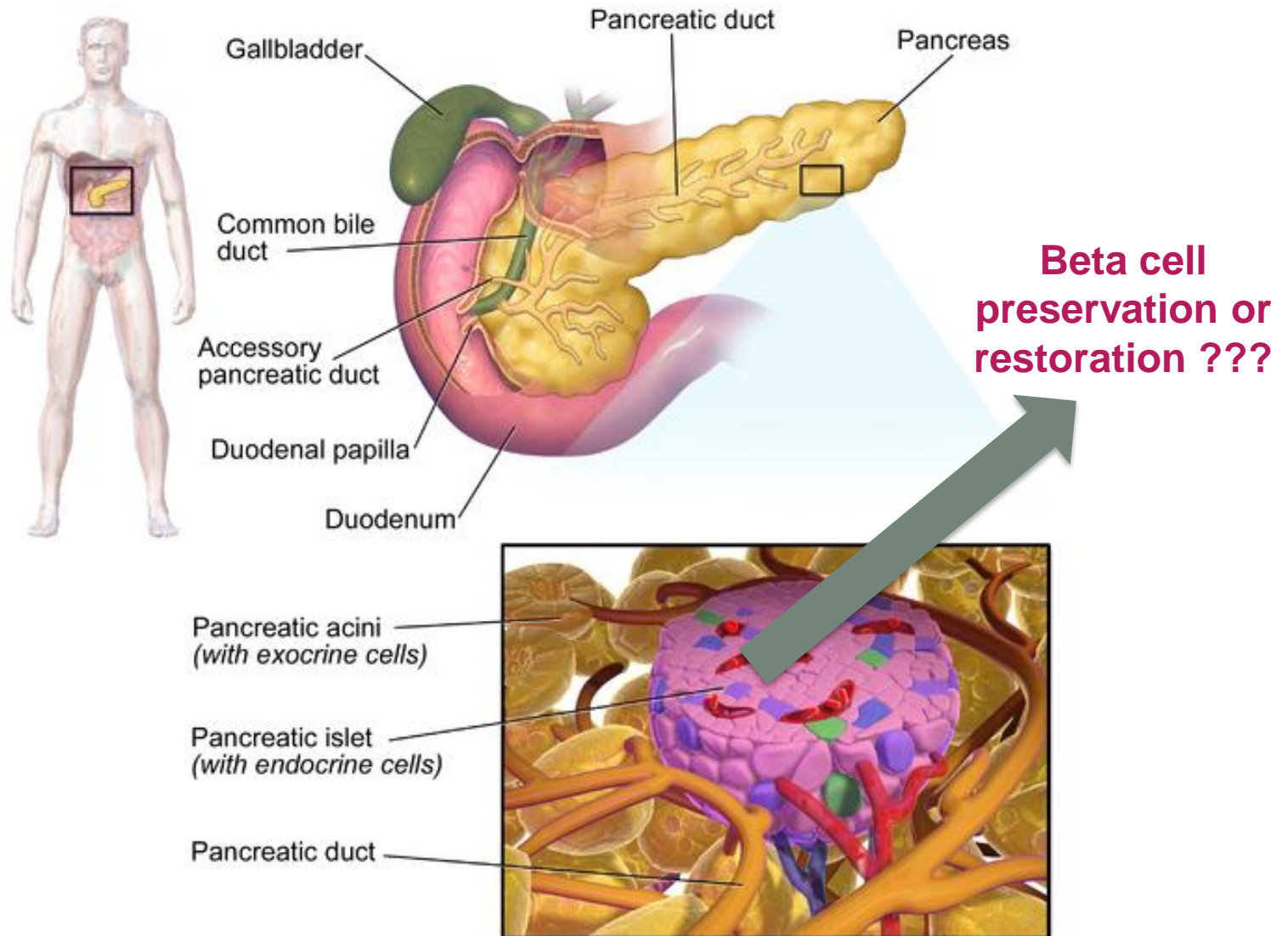
Pancreatic Tissue



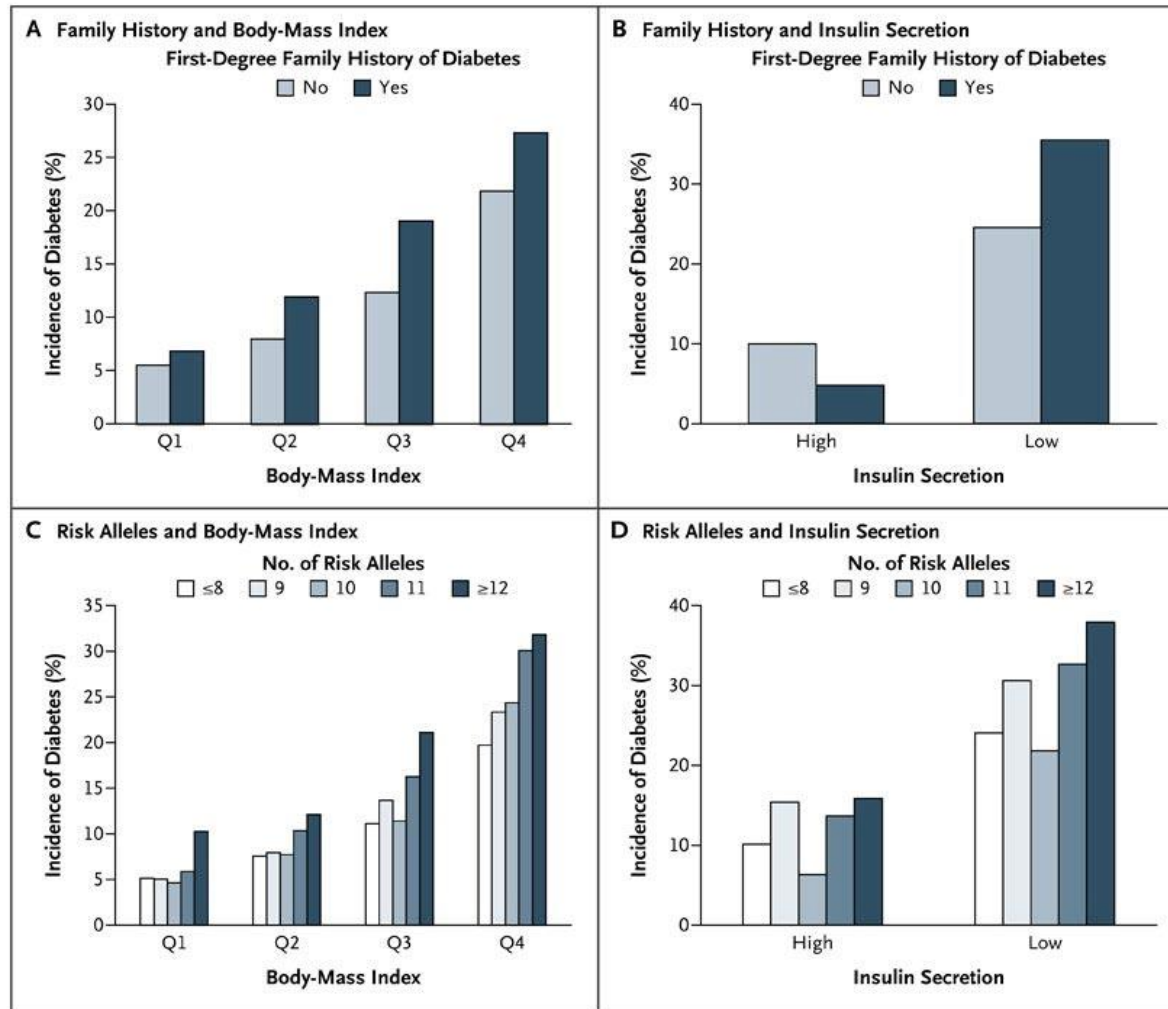
Pancreatic Tissue



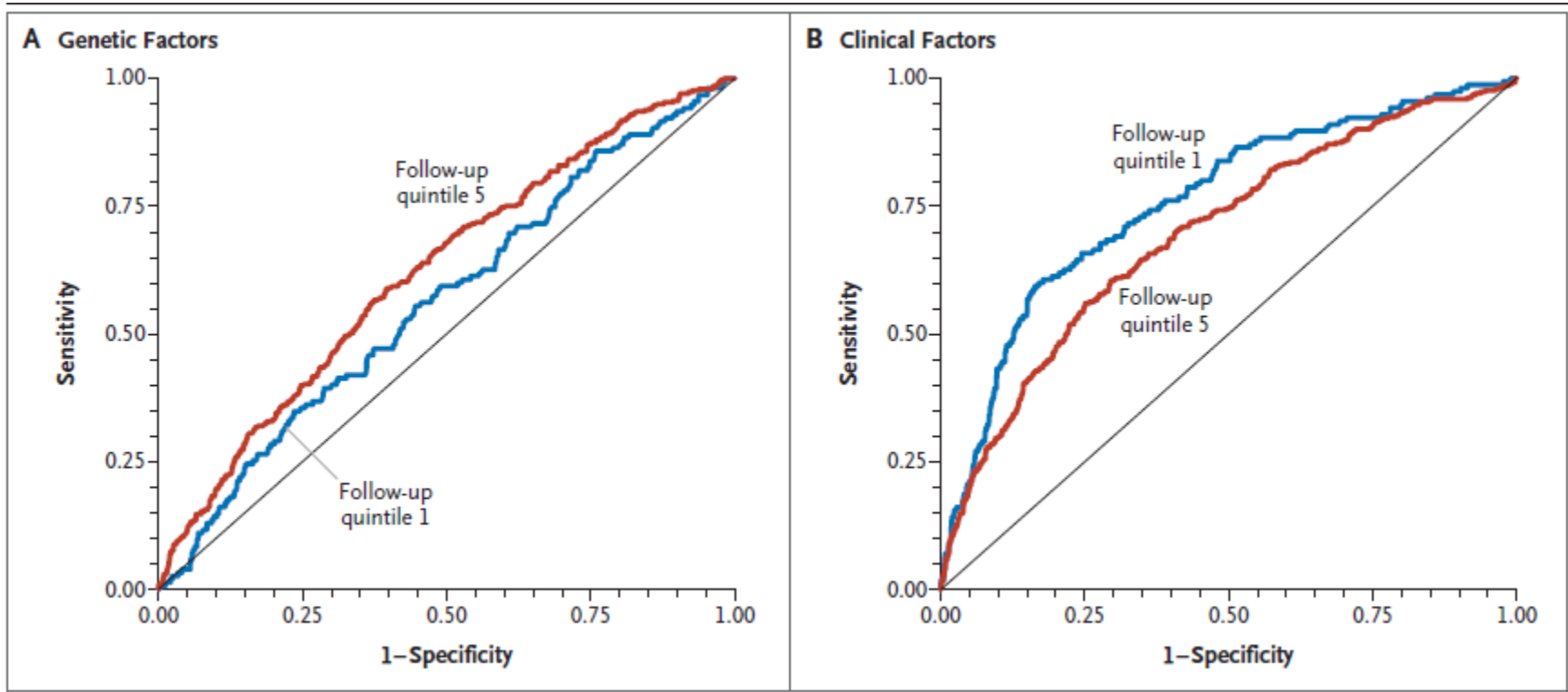
Pancreatic Tissue



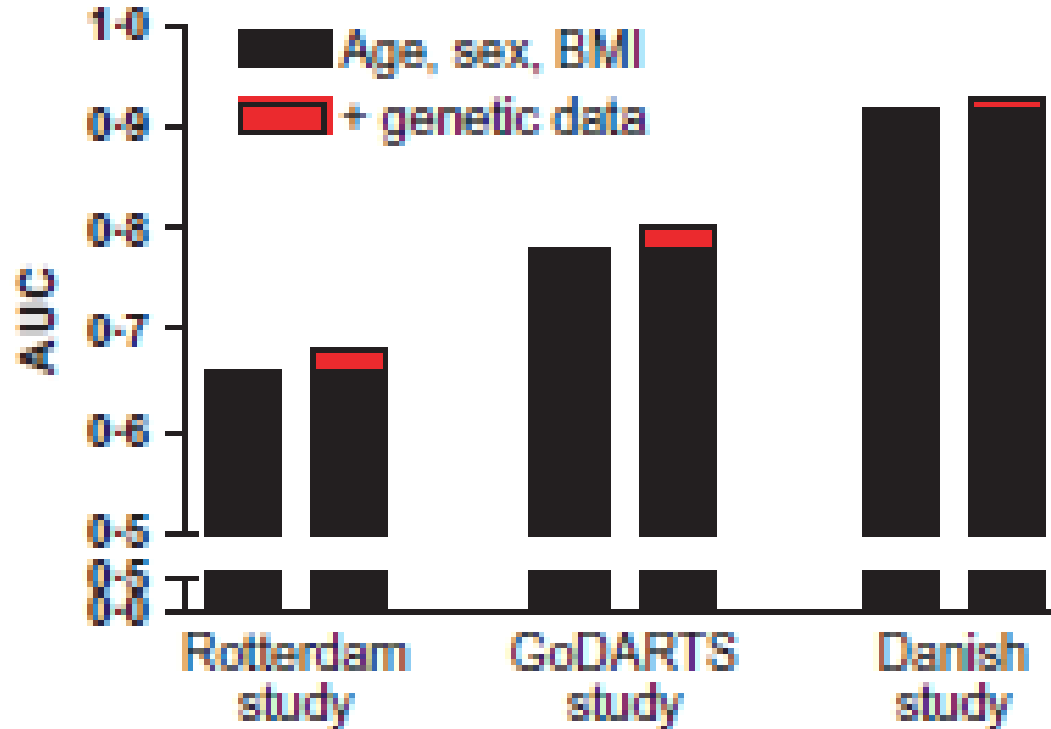
Nongenetic and Genetic Risk Factors for Type 2 Diabetes in the Malmö Study



Receiver/Operator Curves for Genetic and Clinical Factors



Improvement of diabetes risk score with genetic markers for genes associated with T2DM



Regulatory

- FDA Guidance for Industry:
 - Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes – 2008
 - Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention - 2008

Regulatory

- Preclinical Development
 - Target identification
 - Cell studies, target engagement, signaling
 - Animal studies (efficacy and safety)
 - Toxicology studies
 - FDA consultation
- Clinical Development
 - Phase I – FIM, PK, PoC

Regulatory cont.

- Clinical Development \$\$\$\$\$\$\$\$\$\$\$\$\$\$
 - Phase II
 - Phase III
 - ~2500 exposed subjects at filing
 - 1300-1500 with 12 month data
 - 300-500 with \geq 18 month data
durability, comparator
 - Phase IV - Pediatric development program
 - Safety monitoring

Regulatory

- Clinical Development
 - Phase I
 - FIM, PK, Proof of Concept (PD)...
 - Phase II
 - Dose finding (focusing)
 - Phase III
 - Efficacy and safety
 - CV safety

Summary

- Diabetes is a complex and chronically progressive disease with increasing world-wide prevalence
- There is a need for additional diabetes drugs
- Many potential targets exist to improve glycemic control and prevent diabetic complications
- Development of new drugs is challenging and expensive

Questions?