



*Dipartimento di Geriatria e
Malattie del Metabolismo
Seconda Università Napoli*



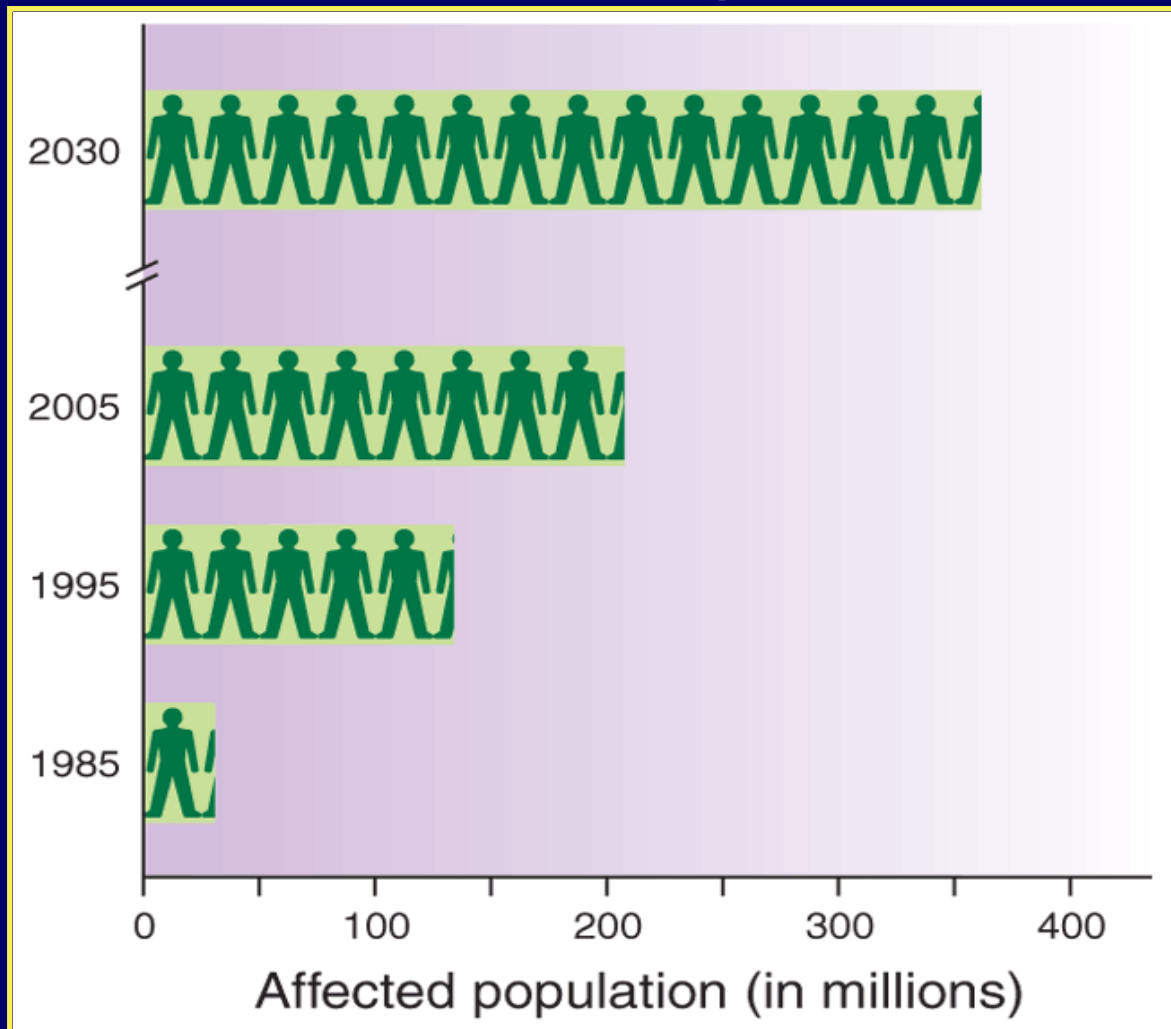
*Sviluppo dei farmaci ipoglicemizzanti:
metformina, acarbose, agonisti
PPAR- γ*

Raffaele Marfella

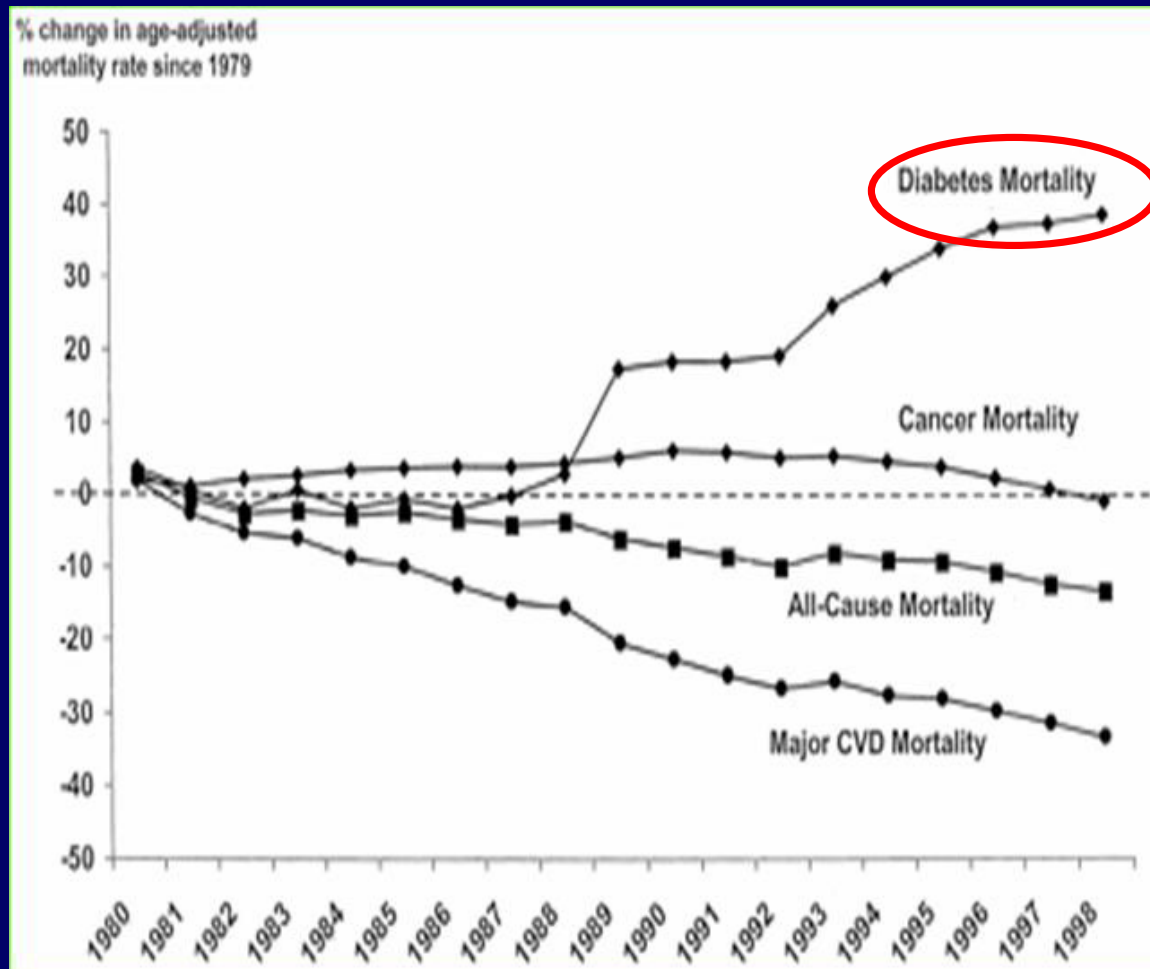


52° Congresso Nazionale SIGG
Firenze, 28 novembre - 2 dicembre 2007

La prevalenza del diabete mellito nel mondo aumenterà del 60% passando dal 4 al 6,4% nei prossimi 20 anni



Diabete e cause di morte



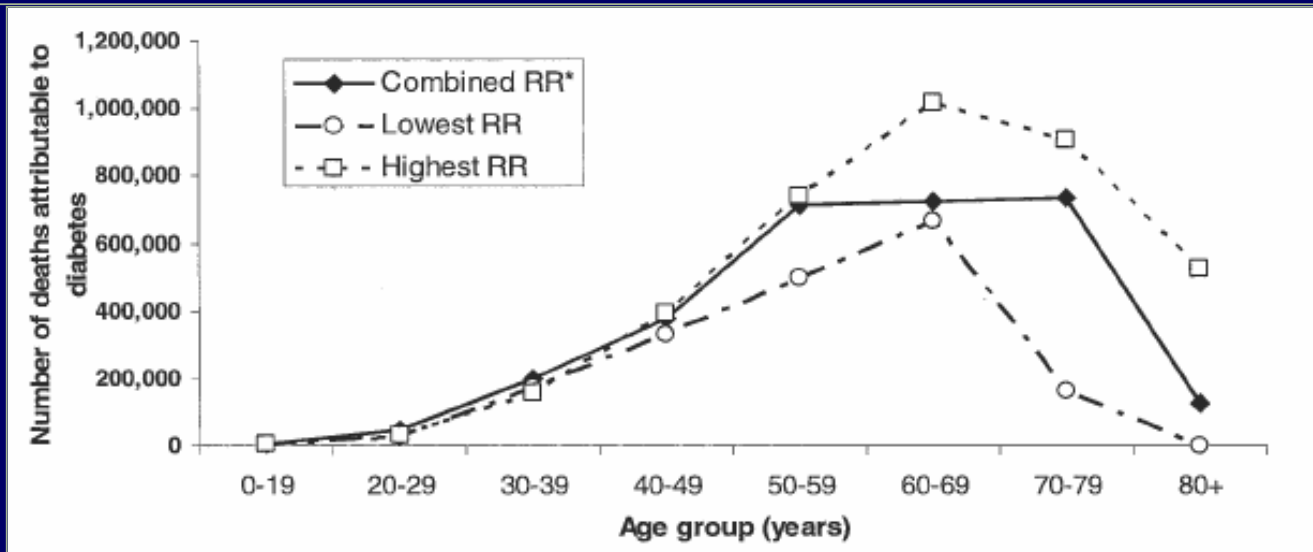
The Burden of Mortality Attributable to Diabetes

Realistic estimates for the year 2000

Grega Rosic, MD¹
 Nicola Uzzau, MD, MPH¹
 Peter H. Bennett, MD, FRCP²
 Colin Mathew, MD, PhD²

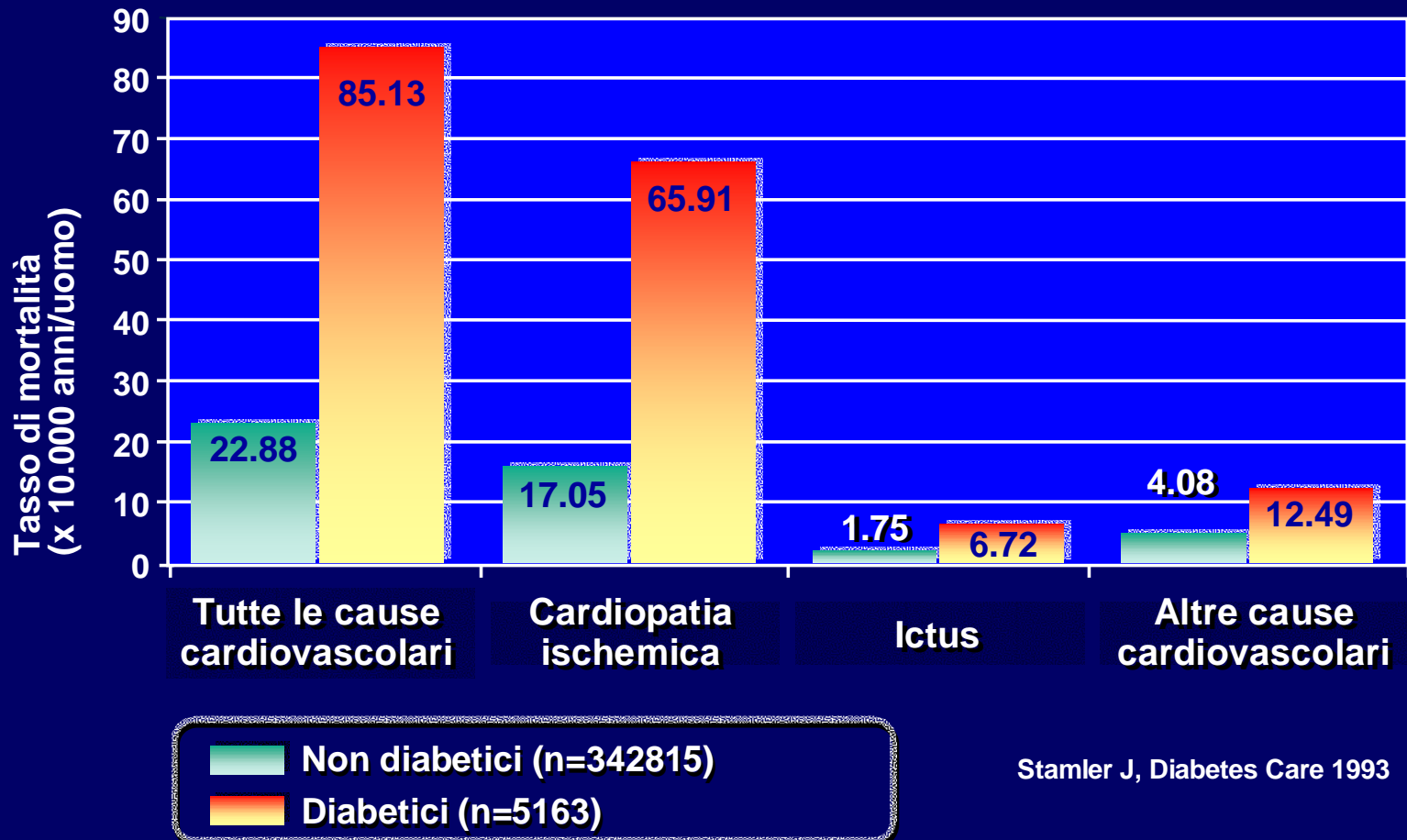
Javier Tusell-Luque, MD, PhD^{3,4,5,6}
 Sanyam Malhotra, MD⁷
 Vincent Conroy, MD, FRCP⁷
 Hilary Keith, MD, DSc¹

The excess global mortality attributable to diabetes in the year 2000 was estimated to be 2.9 million deaths, equivalent to 5.2% of all deaths.



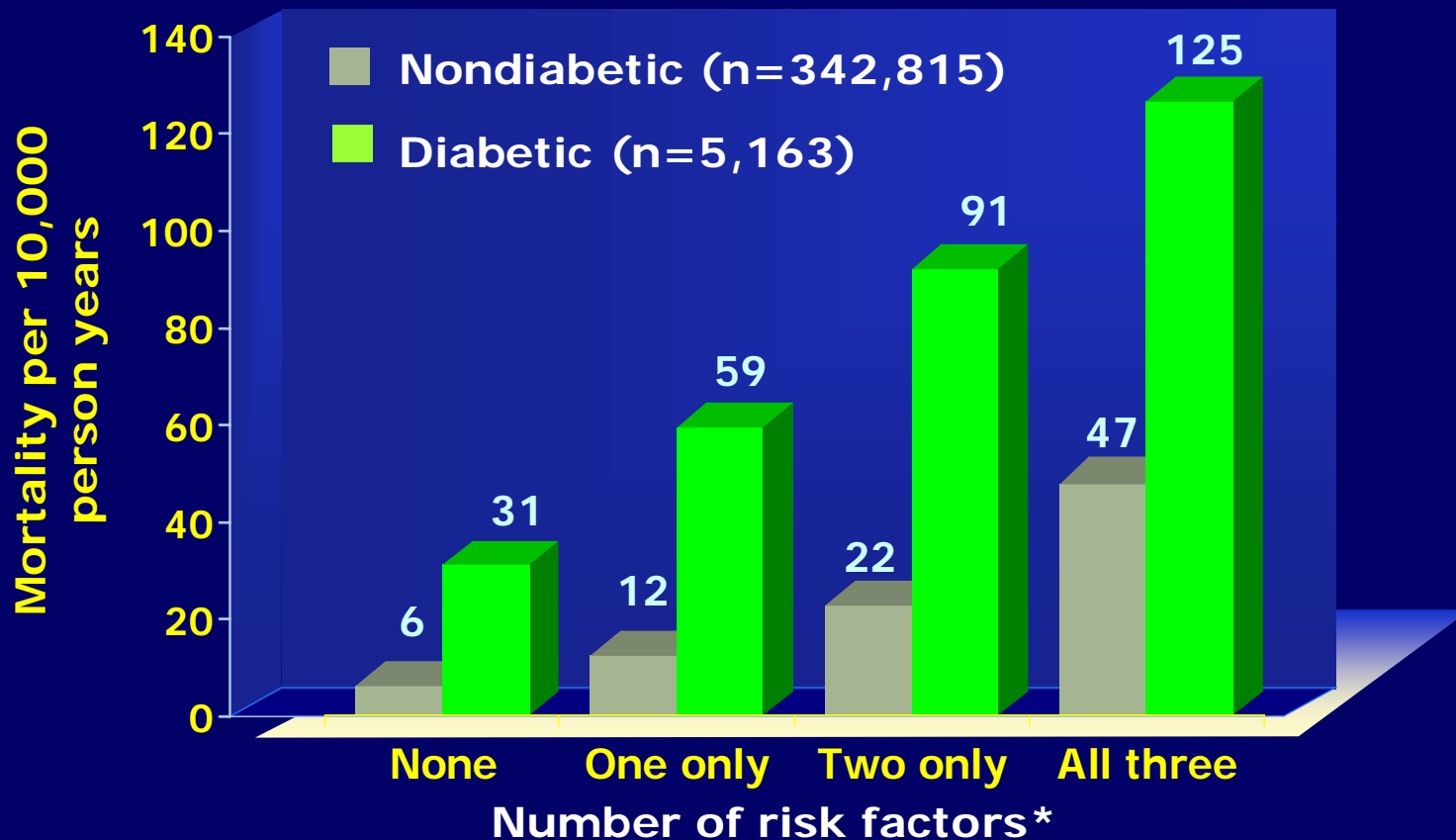
STUDIO MRFIT

Tasso di mortalità da causa cardiovascolare in pazienti di sesso maschile non diabetici e con diabete noto al momento dell'arruolamento





Impact of Diabetes on Cardiovascular Mortality in MRFIT

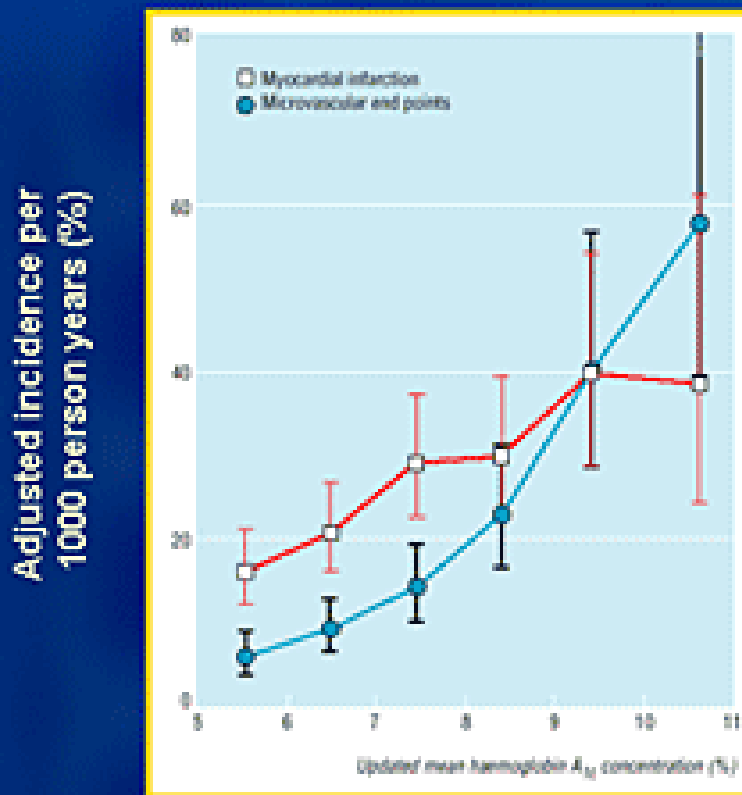


MRFIT=Multiple Risk Factor Intervention Trial

*Risk factors analyzed: smoking, hypercholesterolemia, and hypertension.

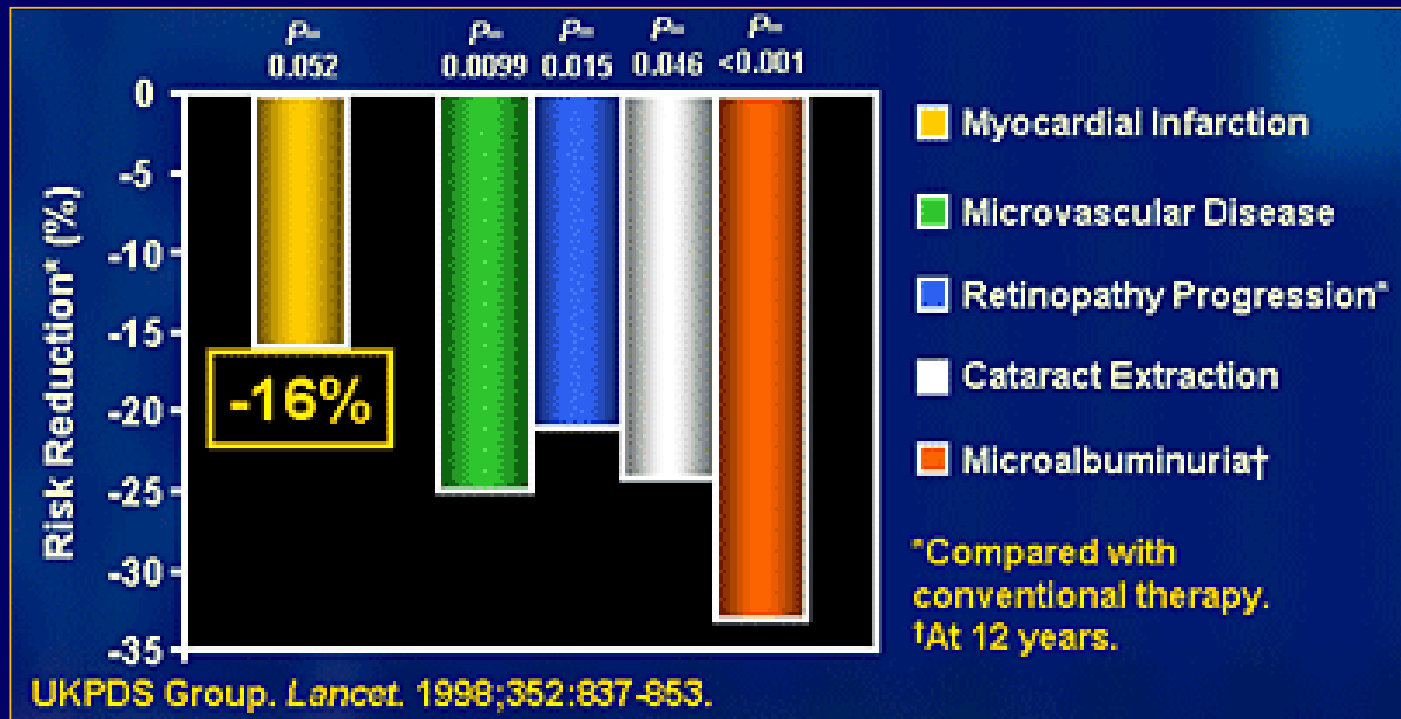
Per each 1% increment in HbA_{1c}, there was an 10% increase in the risk of coronary heart disease

UKPDS: A1C and Diabetic Complications



Incidence rates and 95% confidence intervals for **myocardial infarction** and microvascular complications by category of updated mean haemoglobin A1C concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years.

Per each 1% decrement in HbA_{1c}, there was an 16% decrease in the risk of coronary heart disease



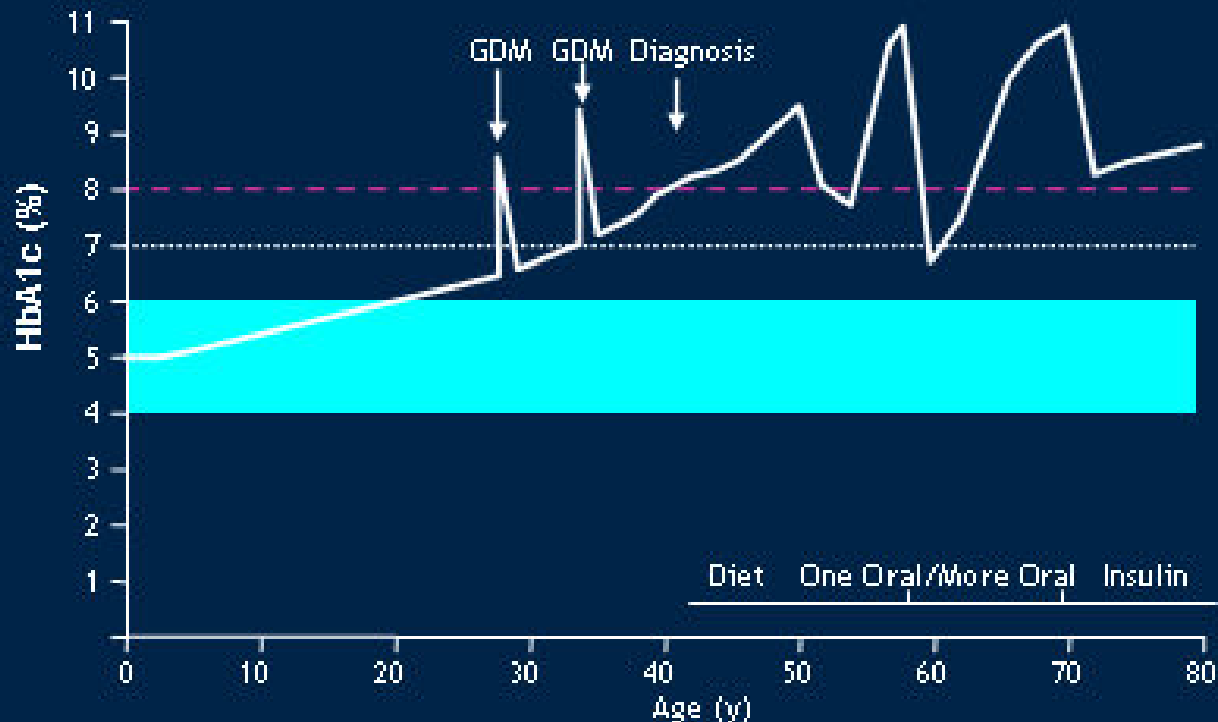
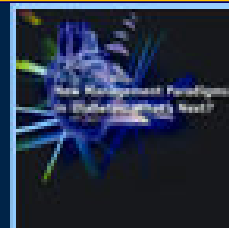
Glycemic goals of therapy to reduce cardiovascular events

Goal	ADA	ACE	Verbal Target
Premeal plasma glucose (mg/dl)	90- 130	<110	~100
2-h postprandial plasma glucose	<180*	<140	<200
A1C	<7%**	<6.5%	As low as possible w/o unacceptable AE

Diabetes Care. 28:s4-36, 2005.

<http://www.ace.com/pub/press/releases/diabetescnsensuswhitepaper.php>

NIDDM: Current Natural History



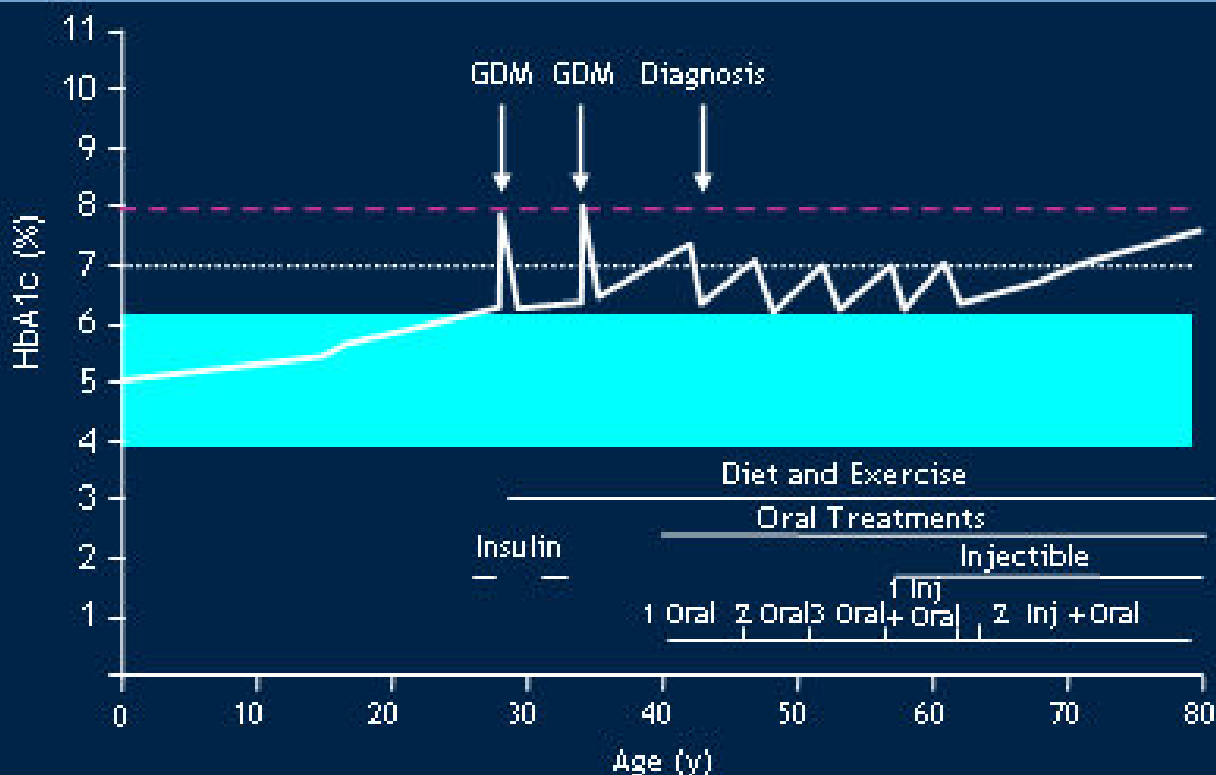
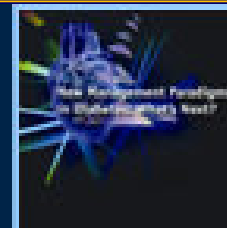
NIDDM = non-insulin-dependent diabetes; GDM = gestational diabetes mellitus.

Rodriguez WC. *Ann J Med.* 2004;116:35-95. [Evidence Level C]

Reasons for not achieving goals?

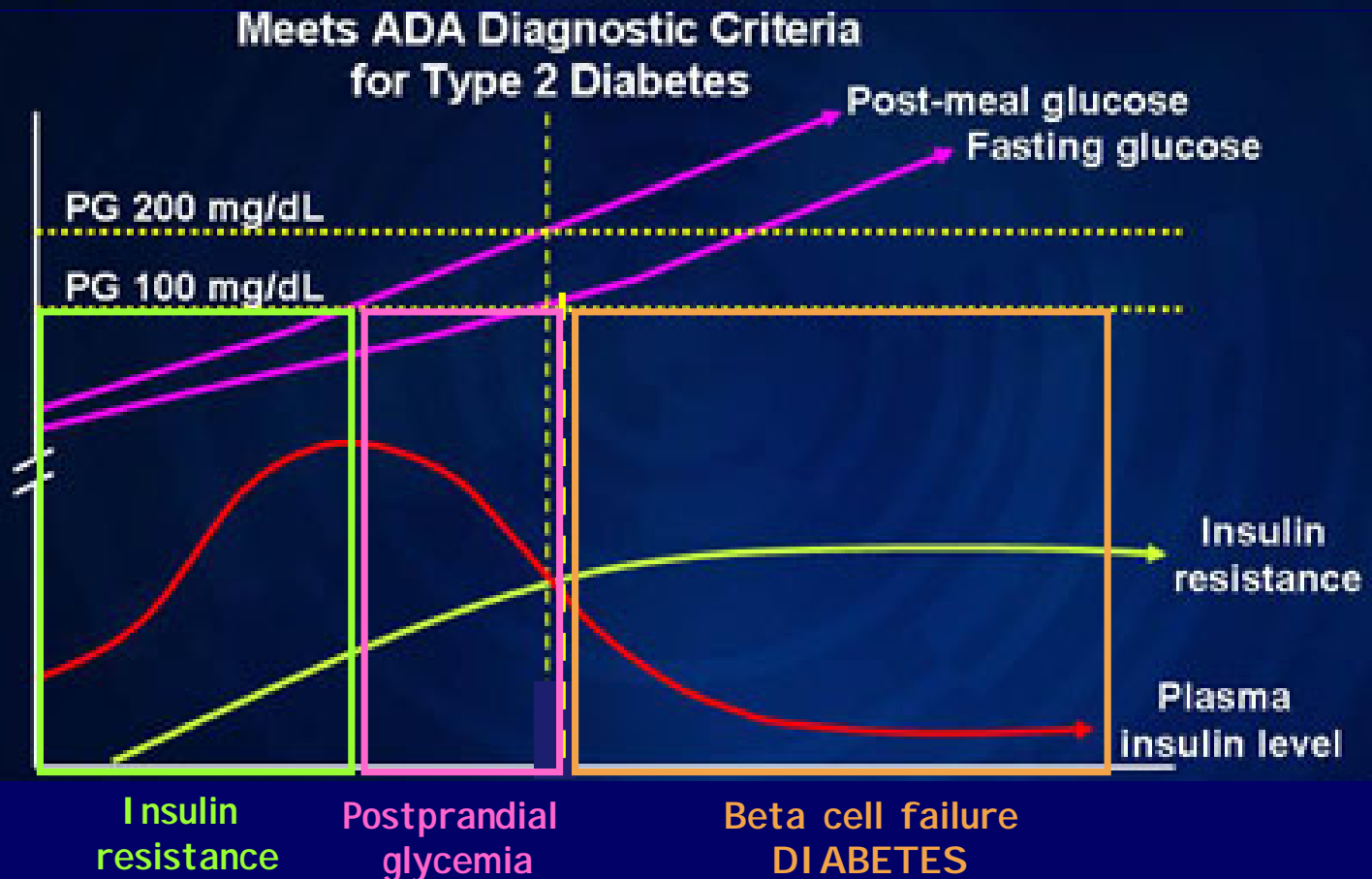
- Failure to understand progression of disease
- Lack of understanding of efficacy/time activity profiles of currently available agents:
“Clinical Inertia”

NIDDM: Possible Natural History

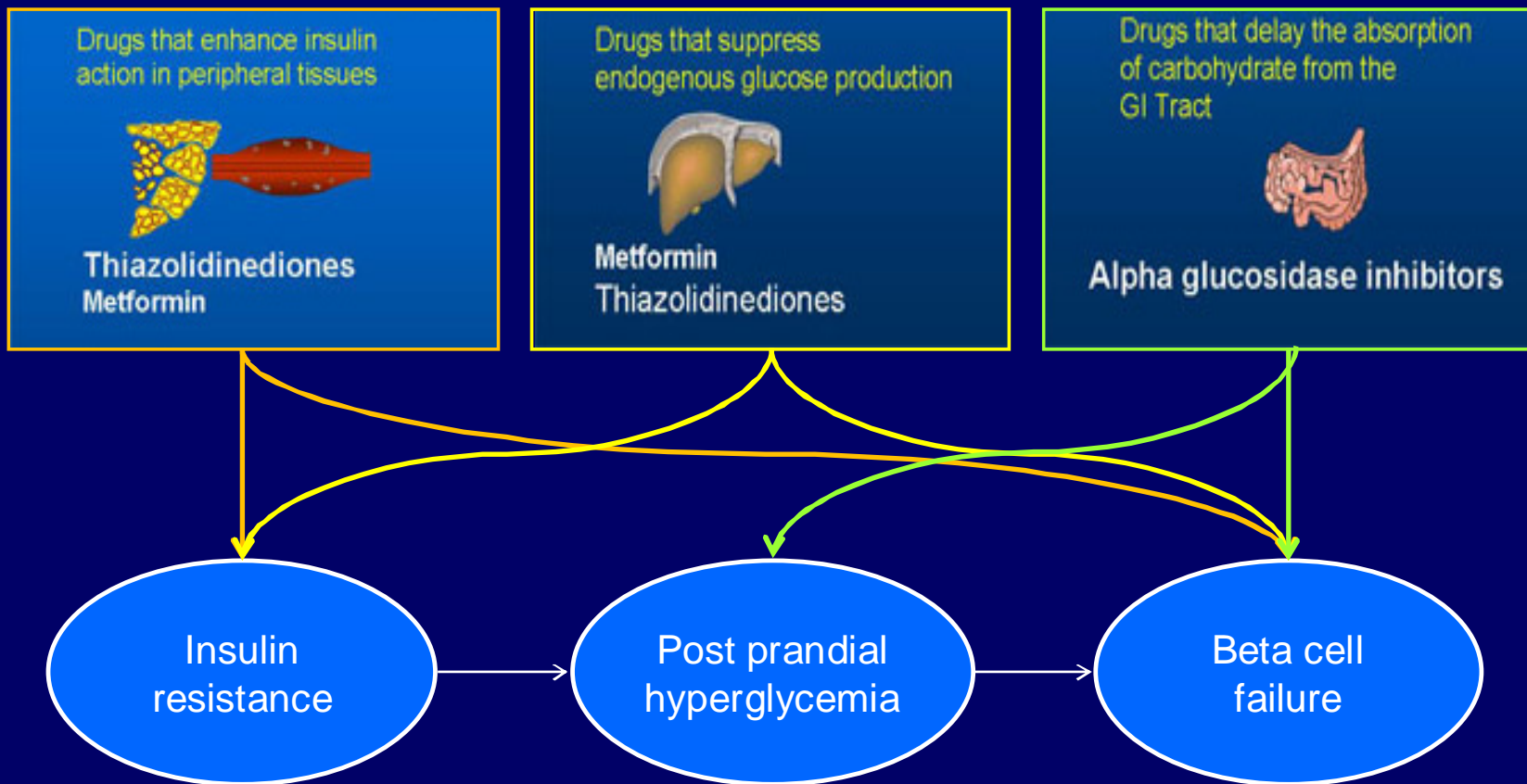


Wade WC. *Am J Med.* 2004;116:35-95. [Evidence Level C]

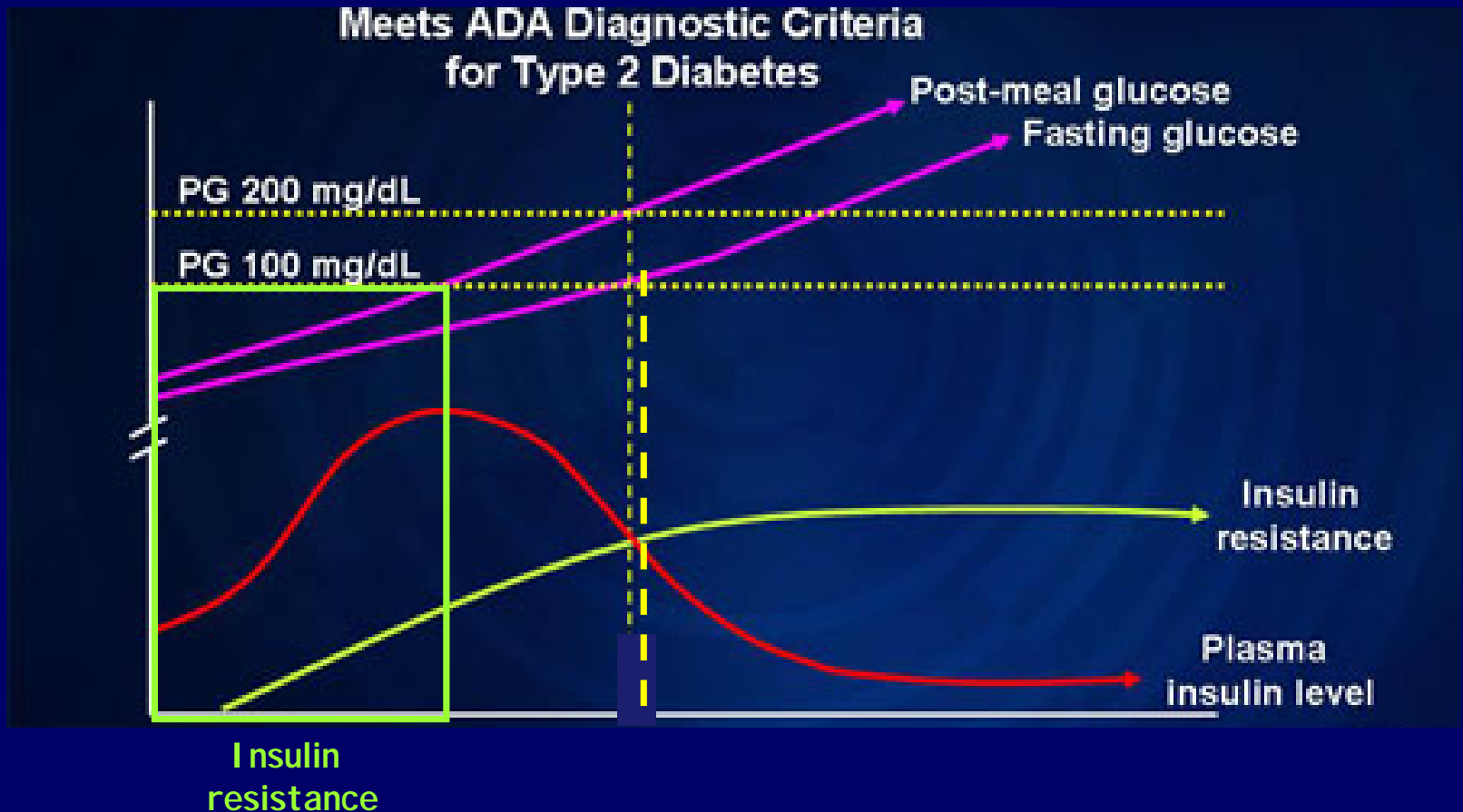
Natural Development of Type 2 Diabetes and CV Risk



Drugs that may influence the natural history of diabetes

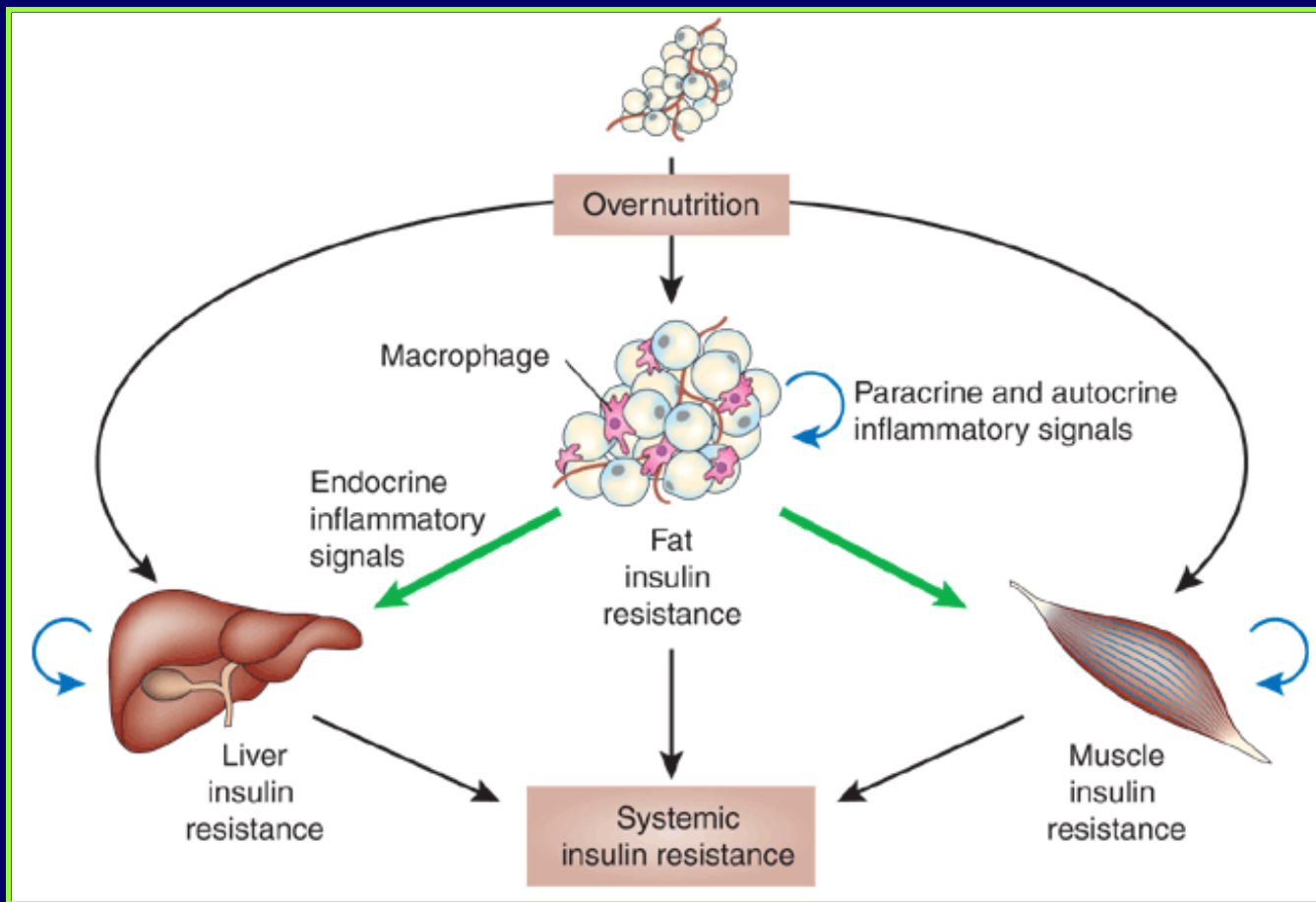


FROM OVERFEEDING TO INSULIN RESISTANCE: effects of PPAR-gamma Agonist and Metformin



Stressed out about obesity and insulin resistance

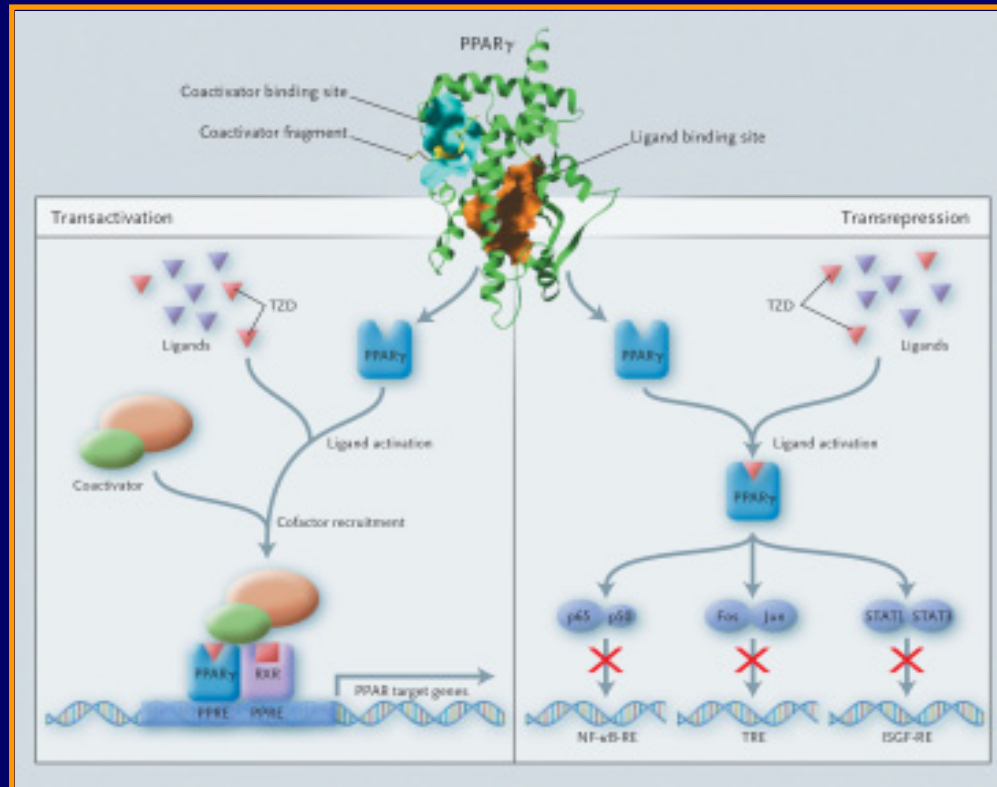
Carl de Luca, Jerrold M Olefsky





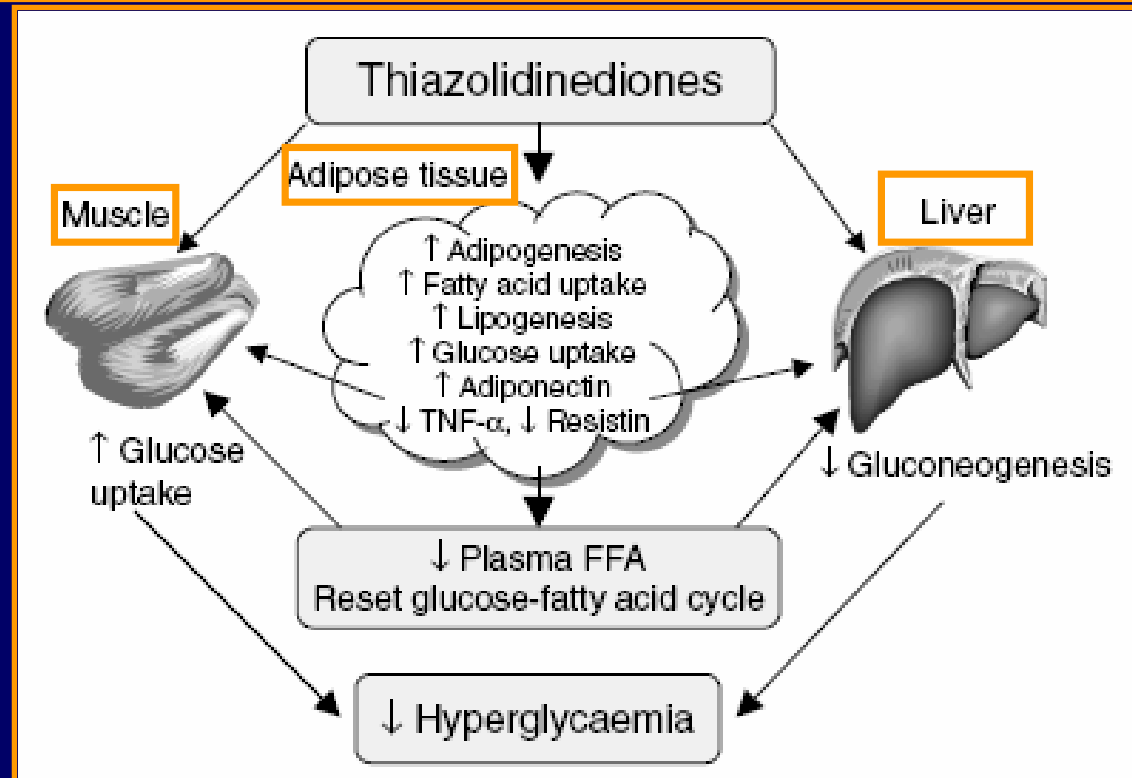
Thiazolidinediones

Hannele Yki-Järvinen, M.D., F.R.C.P.



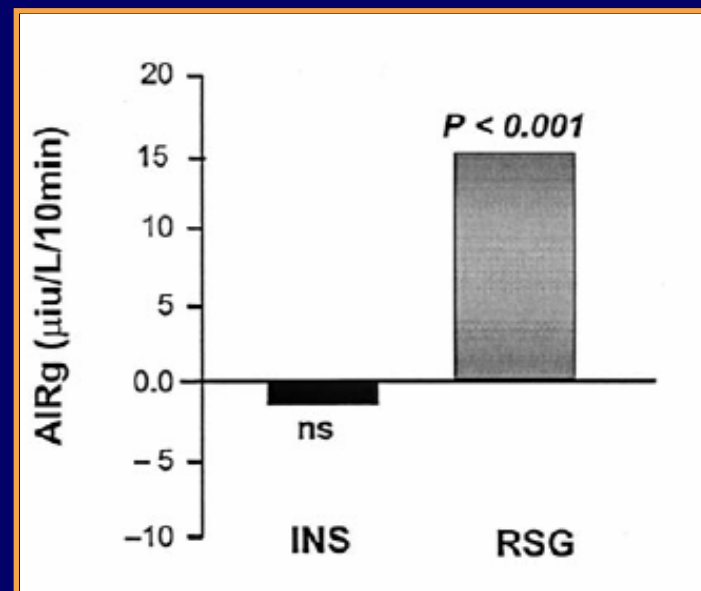
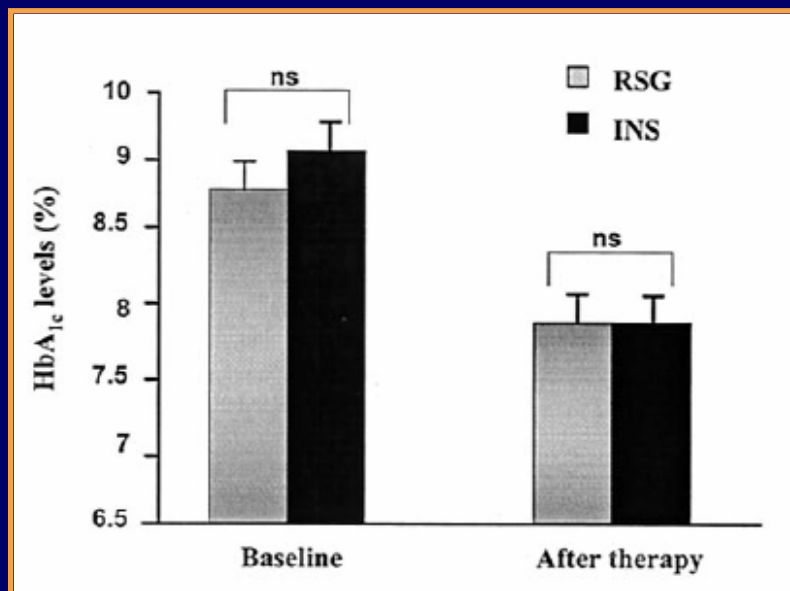
Treating insulin resistance in type 2 diabetes with metformin and thiazolidinediones

C. J. Bailey



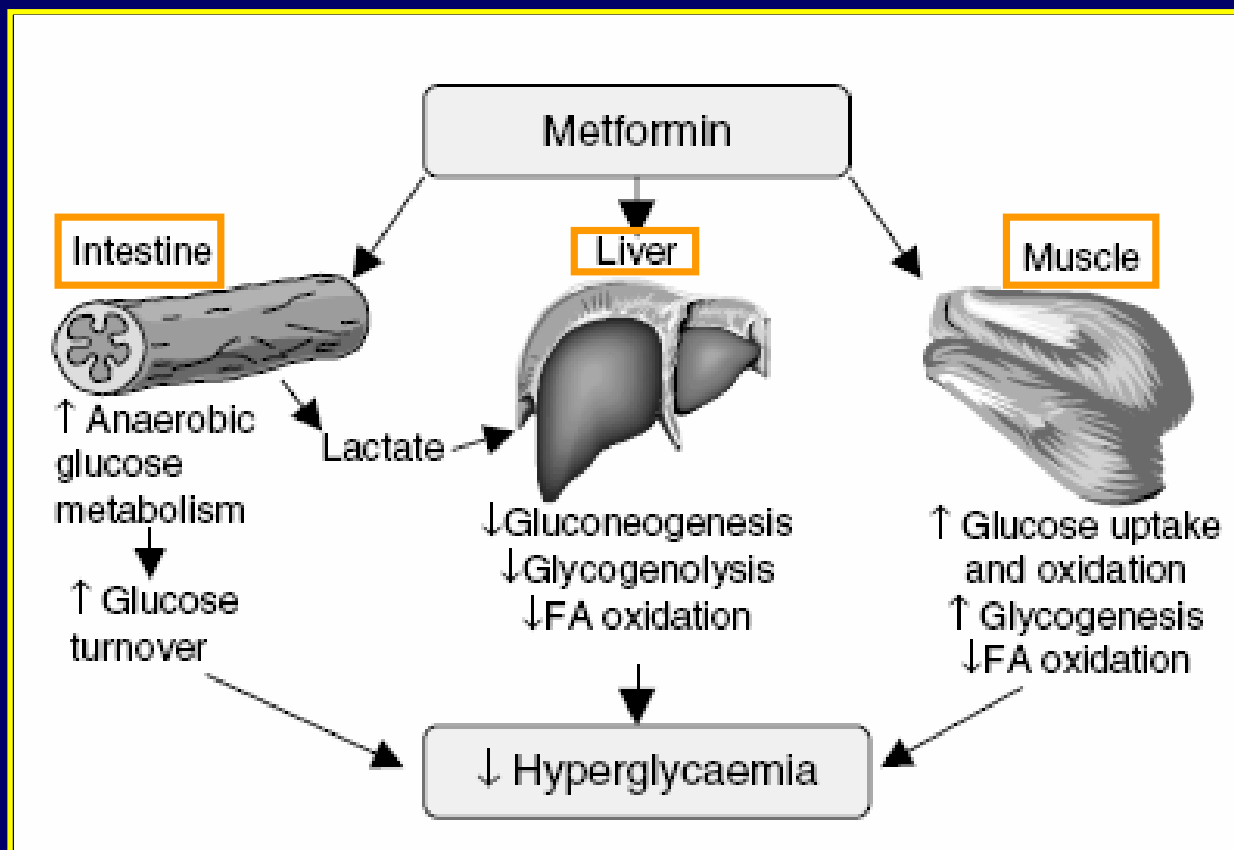
Effect of Rosiglitazone Versus Insulin on the Pancreatic β -Cell Function of Subjects With Type 2 Diabetes

FERNANDO OVALLE, MD, FACE
DAVID S.H. BELL, MB, FACE



Treating insulin resistance in type 2 diabetes with metformin and thiazolidinediones

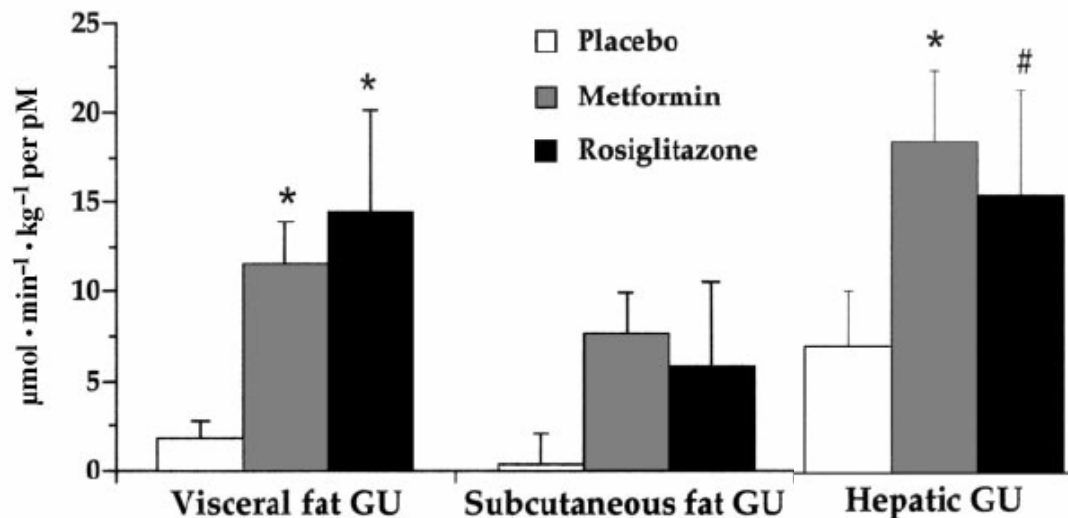
C. J. Bailey



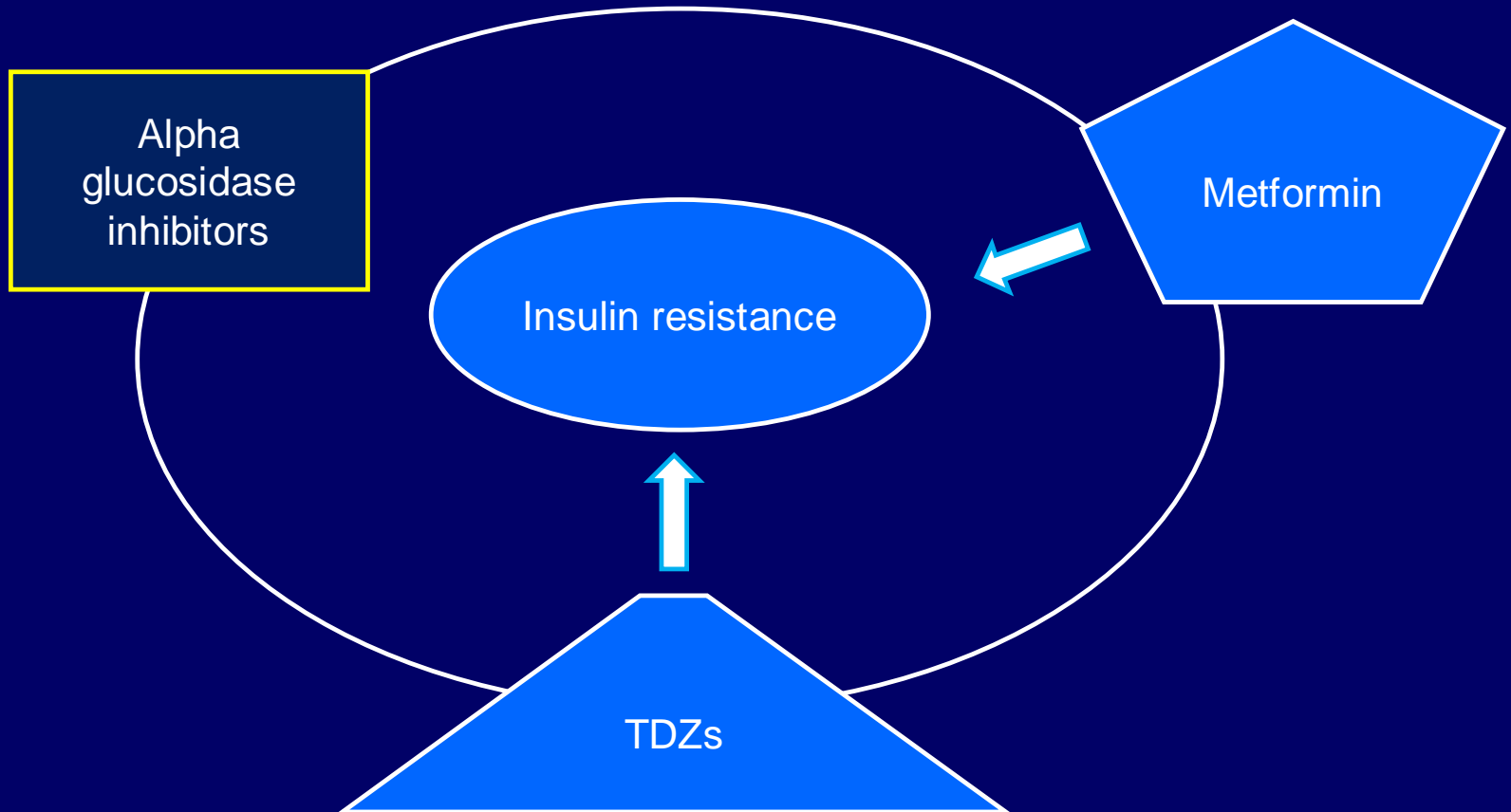
Effects of Metformin and Rosiglitazone Monotherapy on Insulin-Mediated Hepatic Glucose Uptake and Their Relation to Visceral Fat in Type 2 Diabetes

PATRICIA IOZZO, MD^{1,2}
KIRSTI HALLSTEN, MD¹
YESA OIKONEN, MSc¹
KIRSI A. VIRTANEN, MD¹
RIITTA PAREKOLA, MD³
JUKKA KEMPPAINEN, MD¹

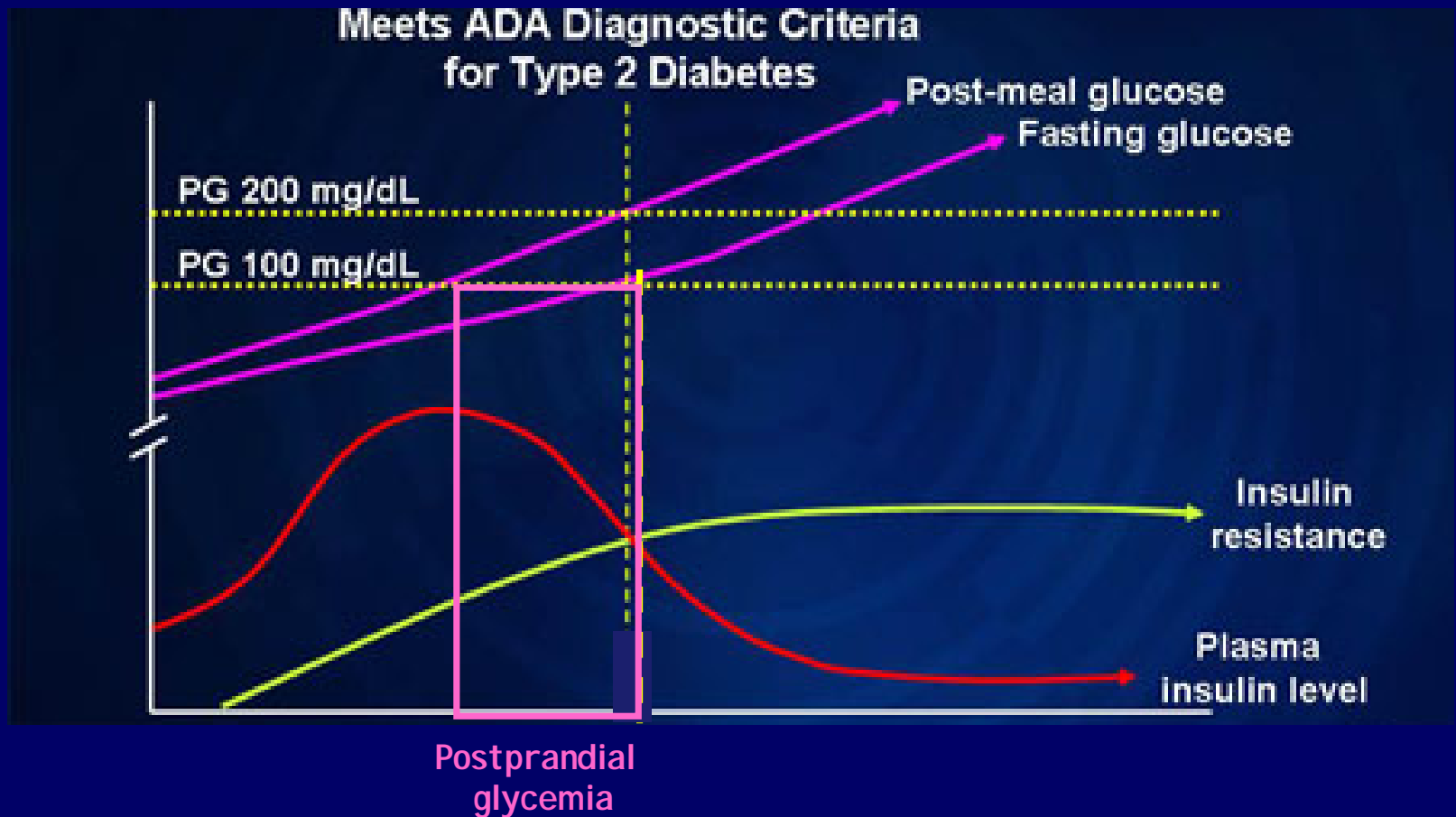
OLOF SOLIN, PhD¹
FREDRIK LONNQVIST, MD⁴
ELE FERRANNINI, MD^{2,5}
JUHANI KNUUTI, MD¹
PIRJO NUUTILA, MD^{1,6}



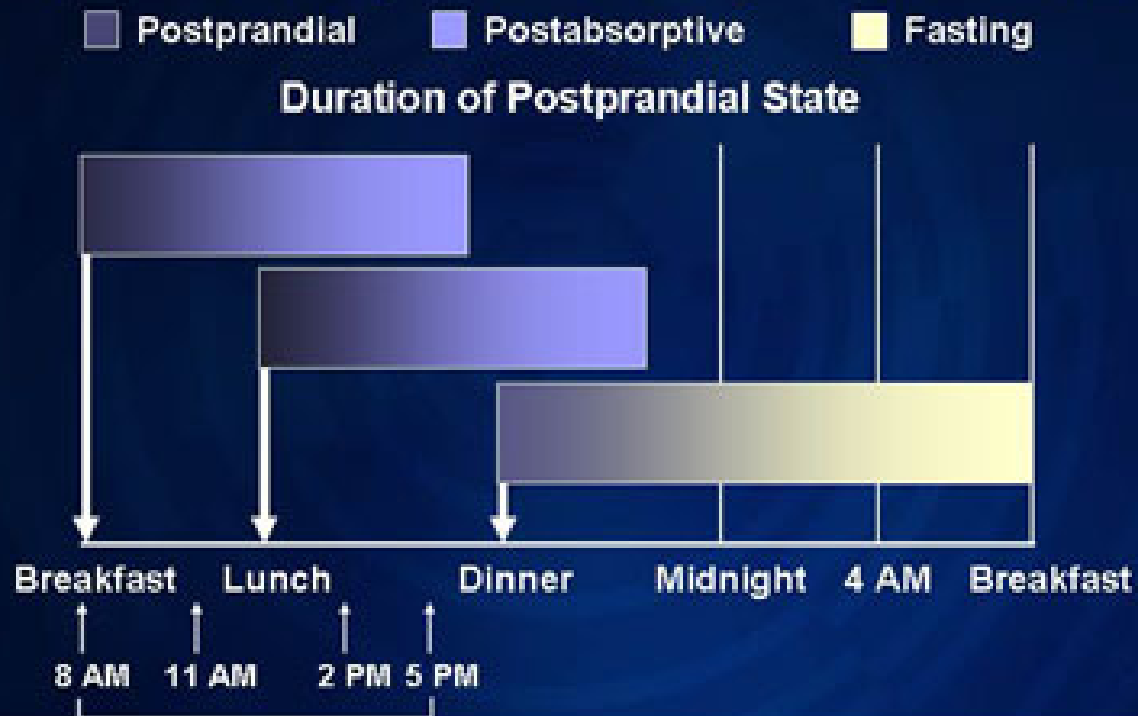
Pharmacotherapy tailored for the multiple defects of type 2 diabetes



FROM INSULIN RESISTANCE TO POSTPRANDIAL HYPERGLYCEMIA: EFFECTS OF ACARBOSE



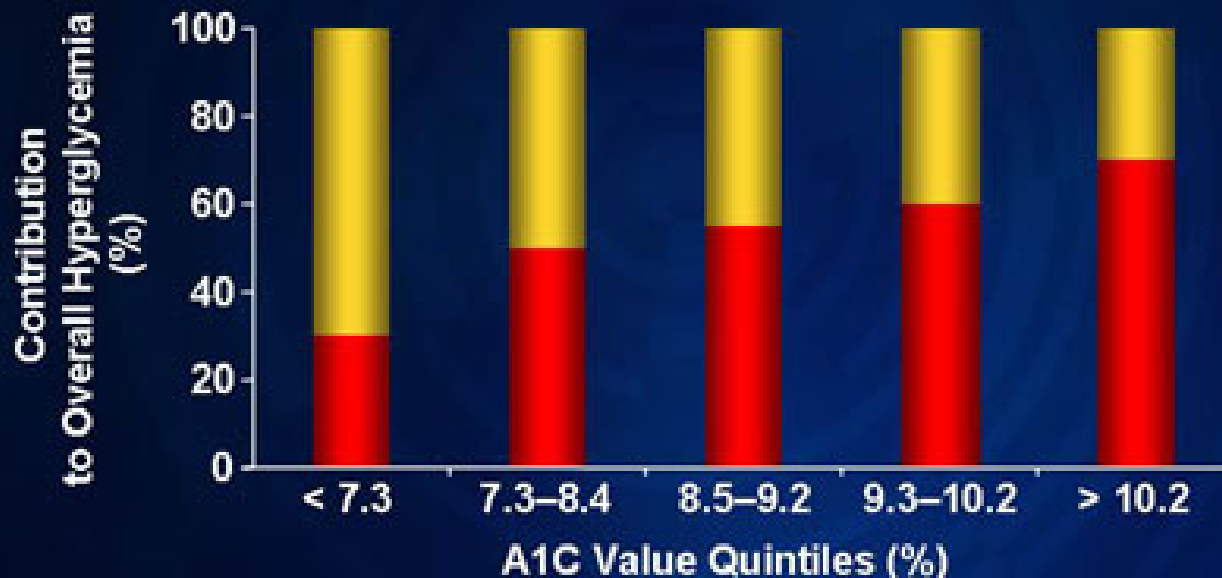
The Post-Prandial State: Patients With Type 2 Diabetes May Spend 12 Hours Per Day in the Postprandial State



Adapted from Monnier L. *Eur J Clin Invest.* 2000;30(suppl 2):3-11.

Contribution of Postprandial Glucose Is Greater as A1C Level Improves

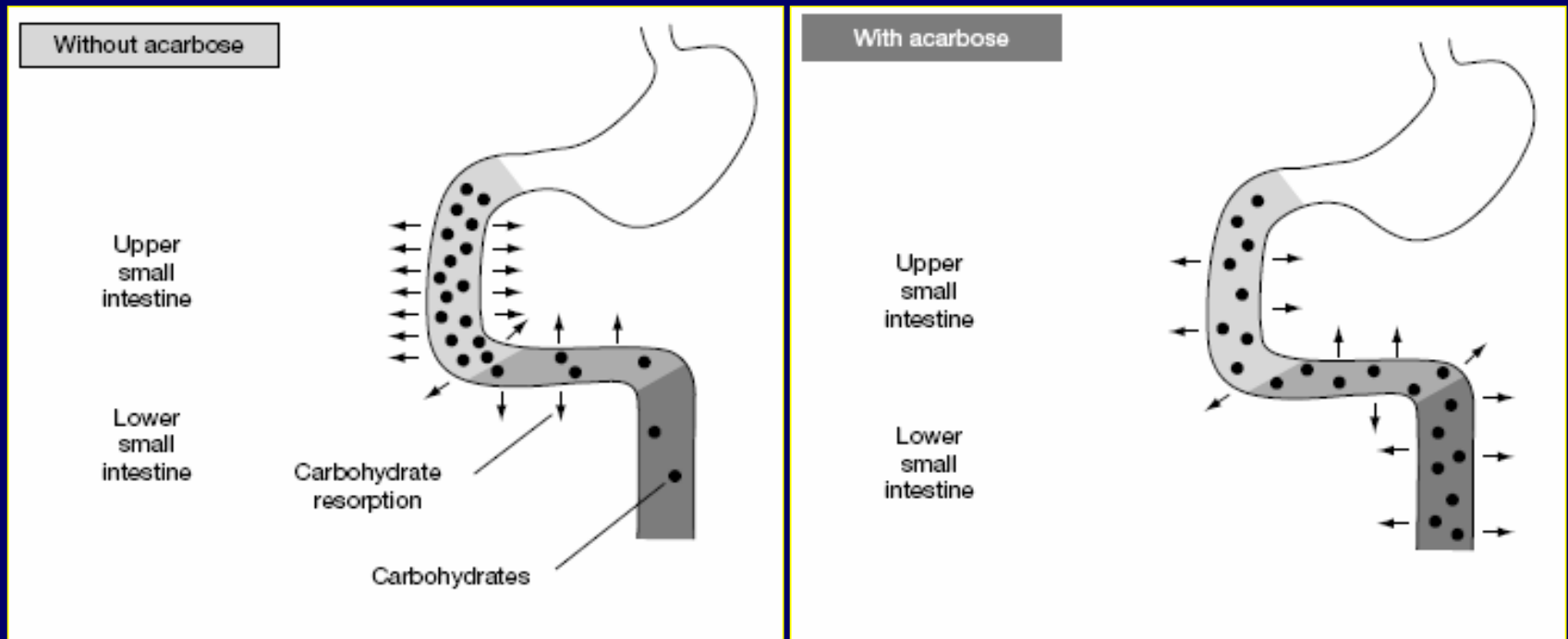
PPG Becomes More Important to Control in Patients With Type 2 Diabetes as A1C Level Improves



Monnier L, et al. *Diabetes Care*. 2003;26:881-885.

Cardiovascular benefits and safety profile of acarbose therapy in prediabetes and established type 2 diabetes

Markolf Hanefeld

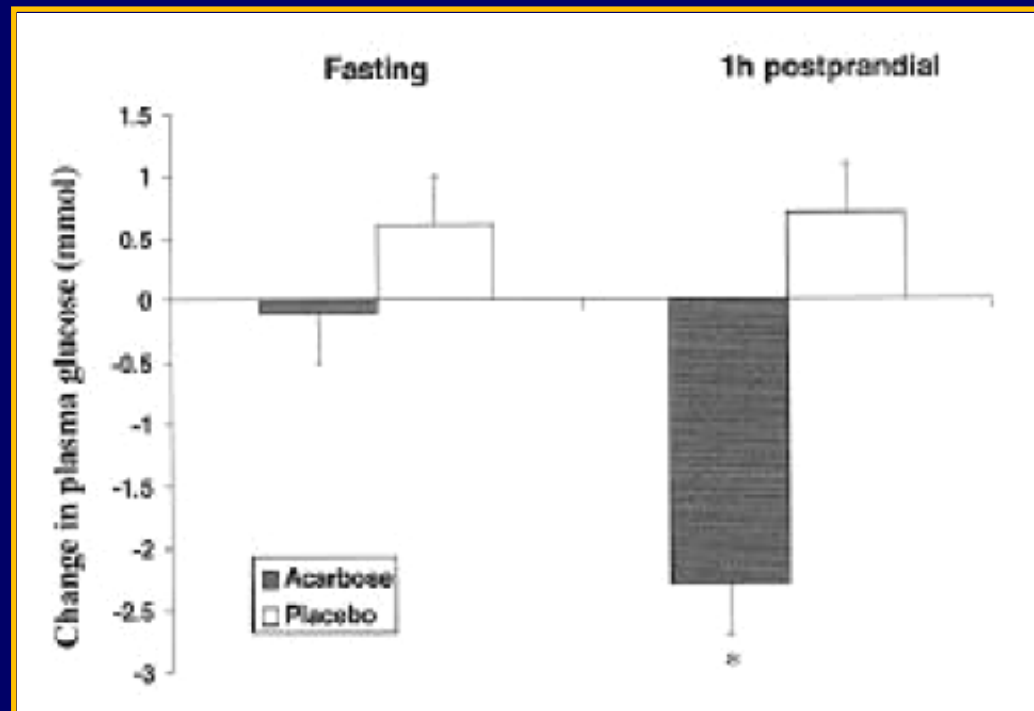


Acarbose in NIDDM Patients With Poor Control on Conventional Oral Agents

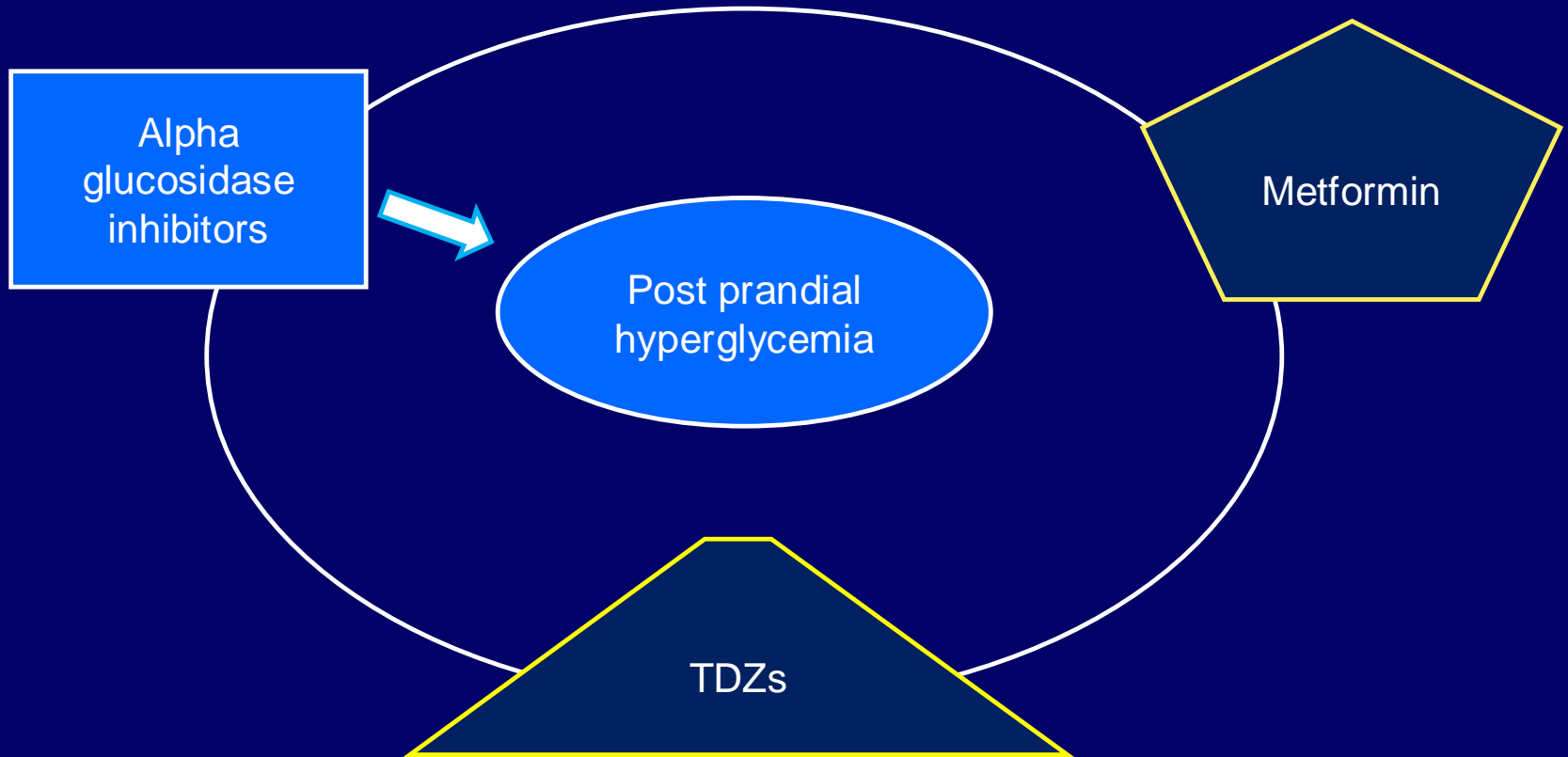
A 24-week placebo-controlled study

KAREN S.L. LAM, MD
S.C. TIU, MBBS
M.W. TSANG, MBBS

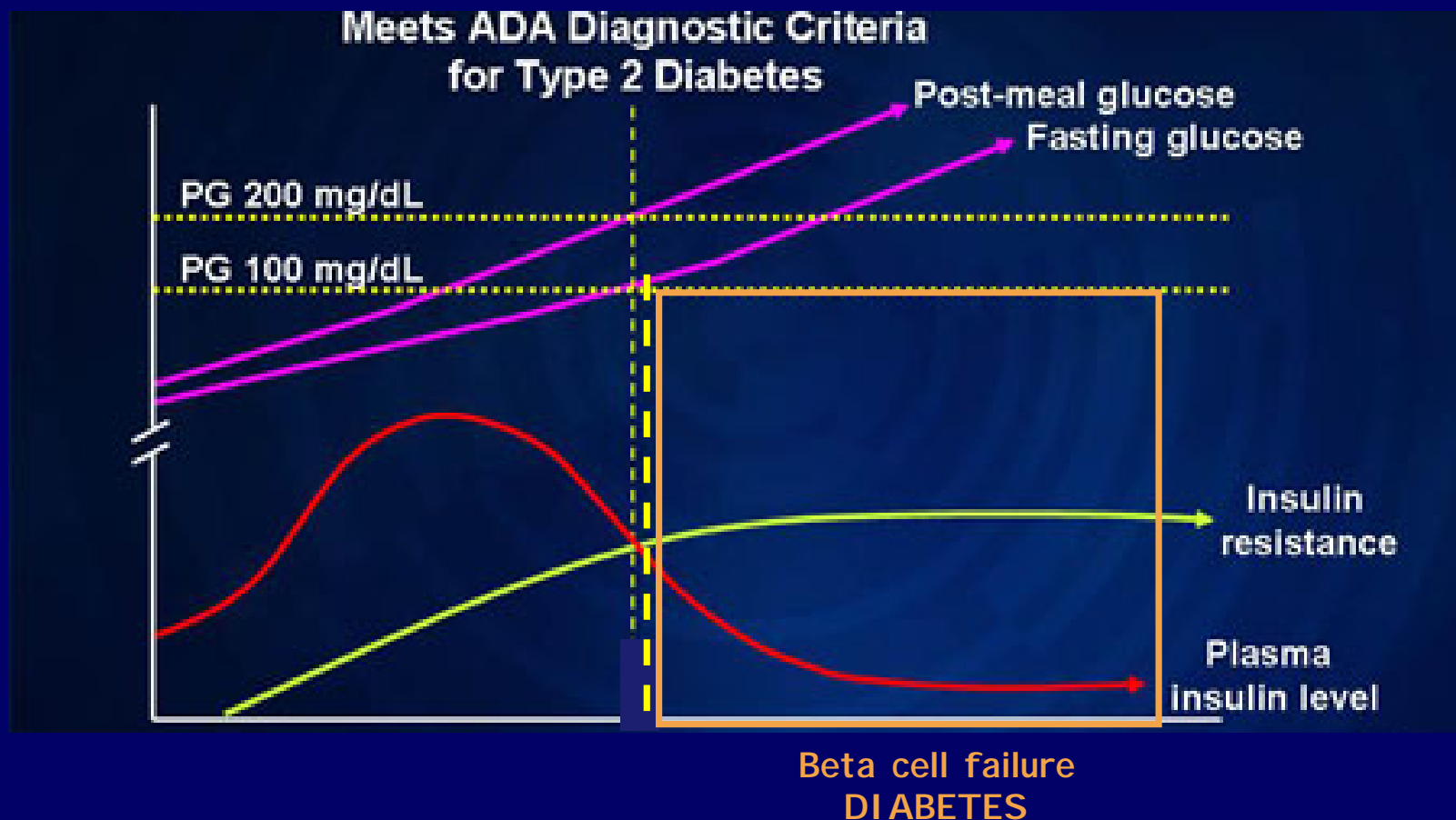
T.P. IP, MBBS
SIDNEY C.F. TAM, MBBS



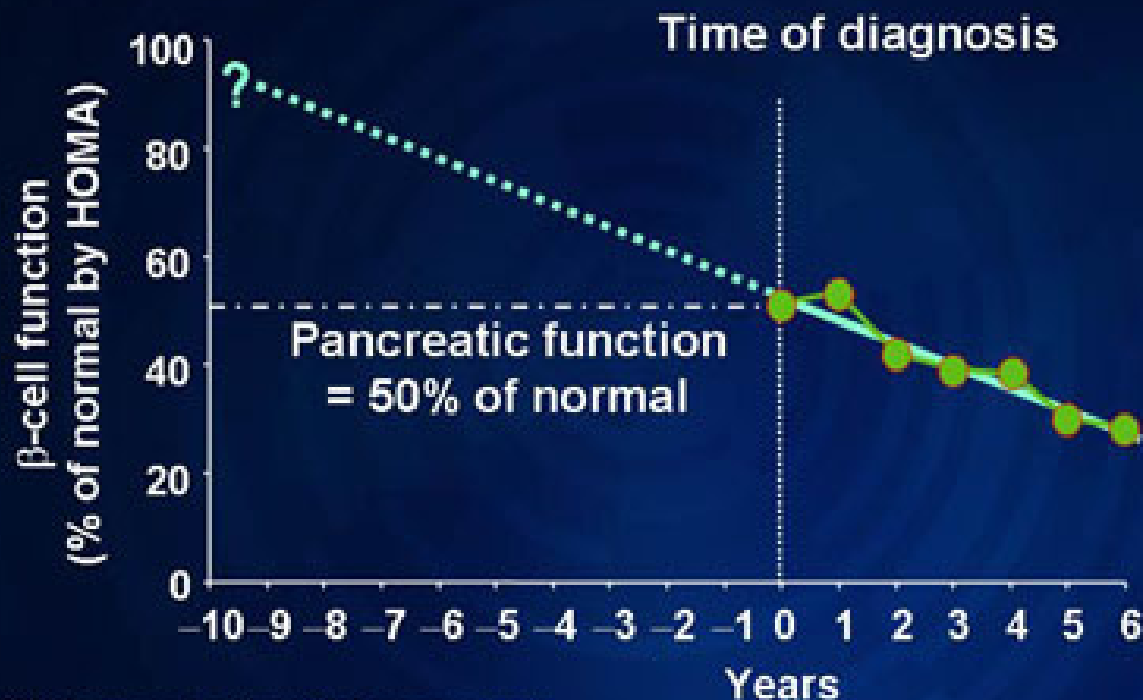
Pharmacotherapy tailored for the multiple defects of type 2 diabetes



FROM POSTPRANDIAL HYPERGLYCEMIA TO BETA-CELL FAILURE: Effects of PPAR-gamma AGONIST, Metformin and Acarbose



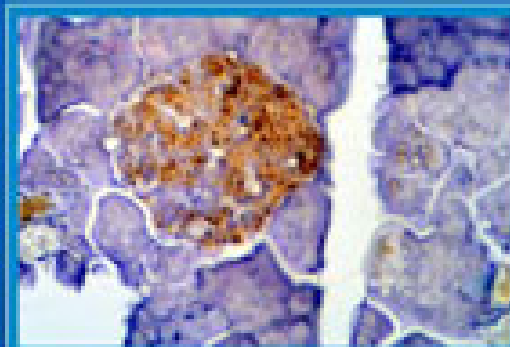
β -Cell Function in Type 2 Diabetes



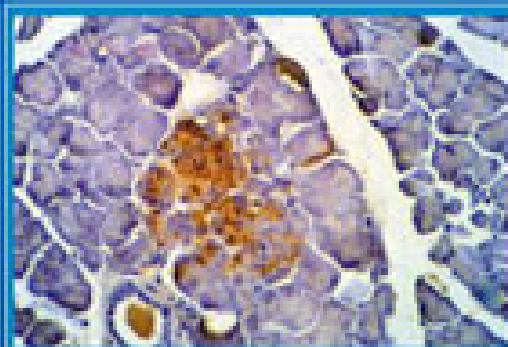
HOMA=homeostasis model assessment

Adapted from Holman RR. *Diab Res Clin Pract.* 1998;40(suppl):S21-S25; UKPDS. *Diabetes.* 1995;44: 1249-1258.

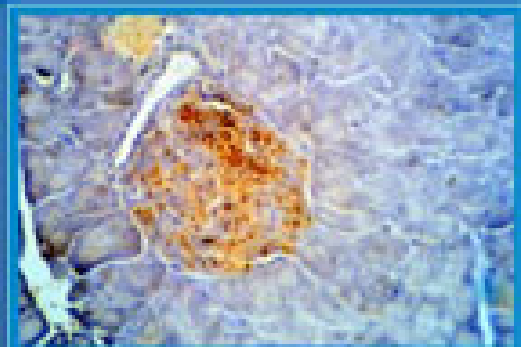
Rosiglitazone Restores β -Cell Insulin Content in Pancreatic Islets of db/db Mice



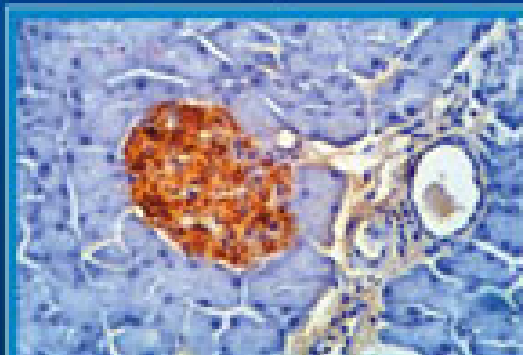
db/db



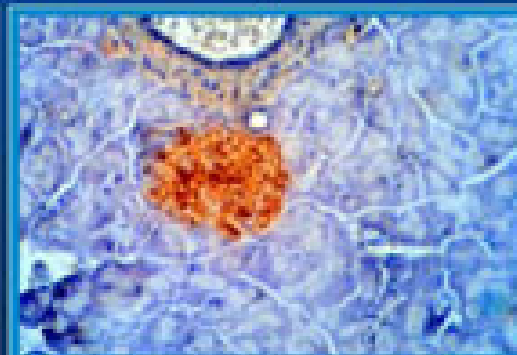
Glyburide



Metformin



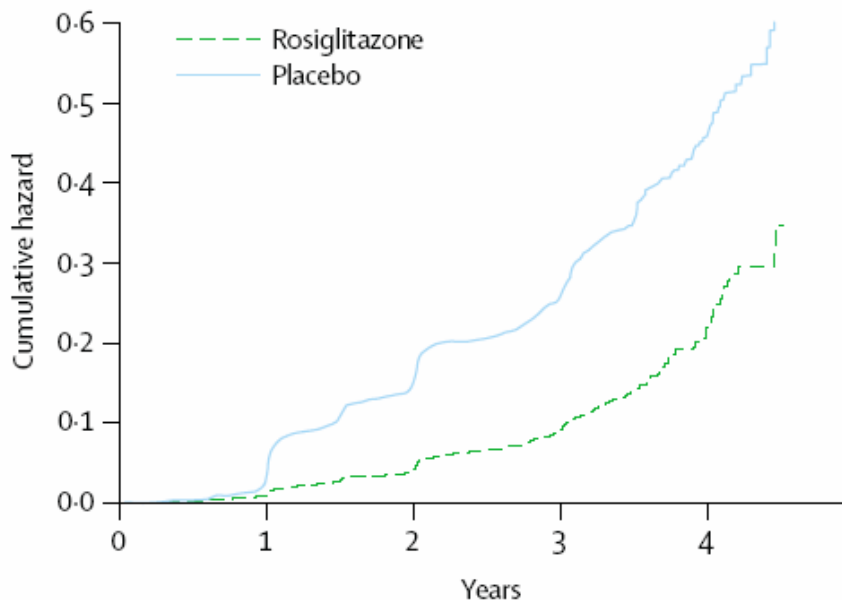
Rosiglitazone



Lean control

Lister CA et al. *Diabetologia*. 1999;42(suppl 1):A150. Abstract 556.

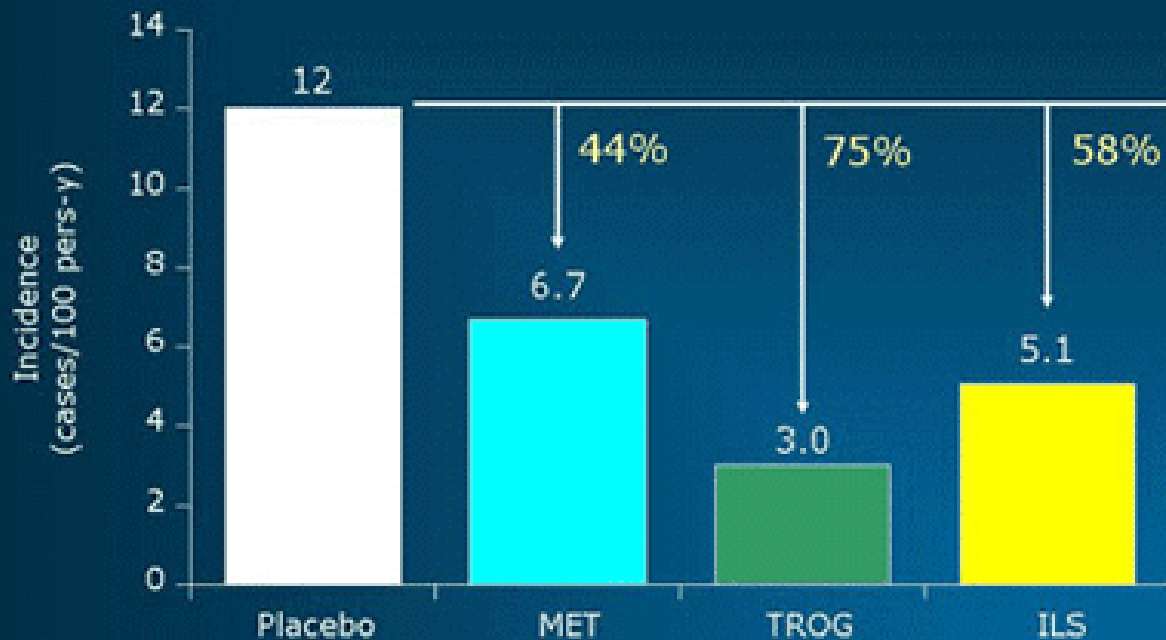
Dream Primary Outcome: Development of Type 2 Diabetes



Number at risk

Placebo	2634	2470	2150	1148	177
Rosiglitazone	2635	2538	2414	1310	217

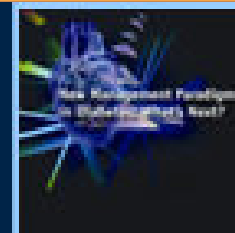
DPP: Diabetes Incidences Rates



MET=metformin, TROG=troglitazone, ILS=intensive lifestyle.
TROG=0.9 yr (range 0.5-1.5 yr).

Diabetes Prevention Program Research Group. *Diabetes*. 2005;54:1150-1156.

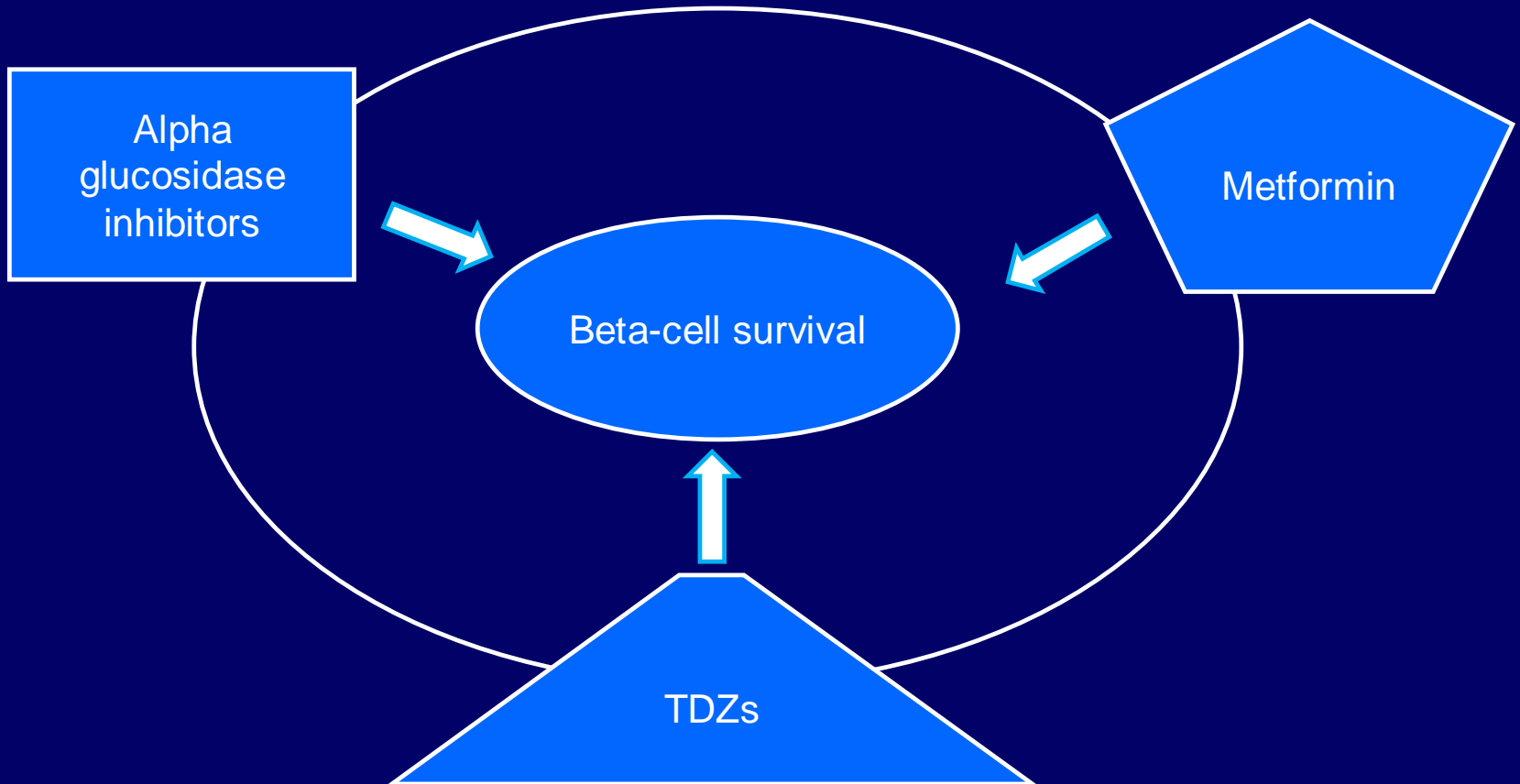
Prevention of T2DM: Medication



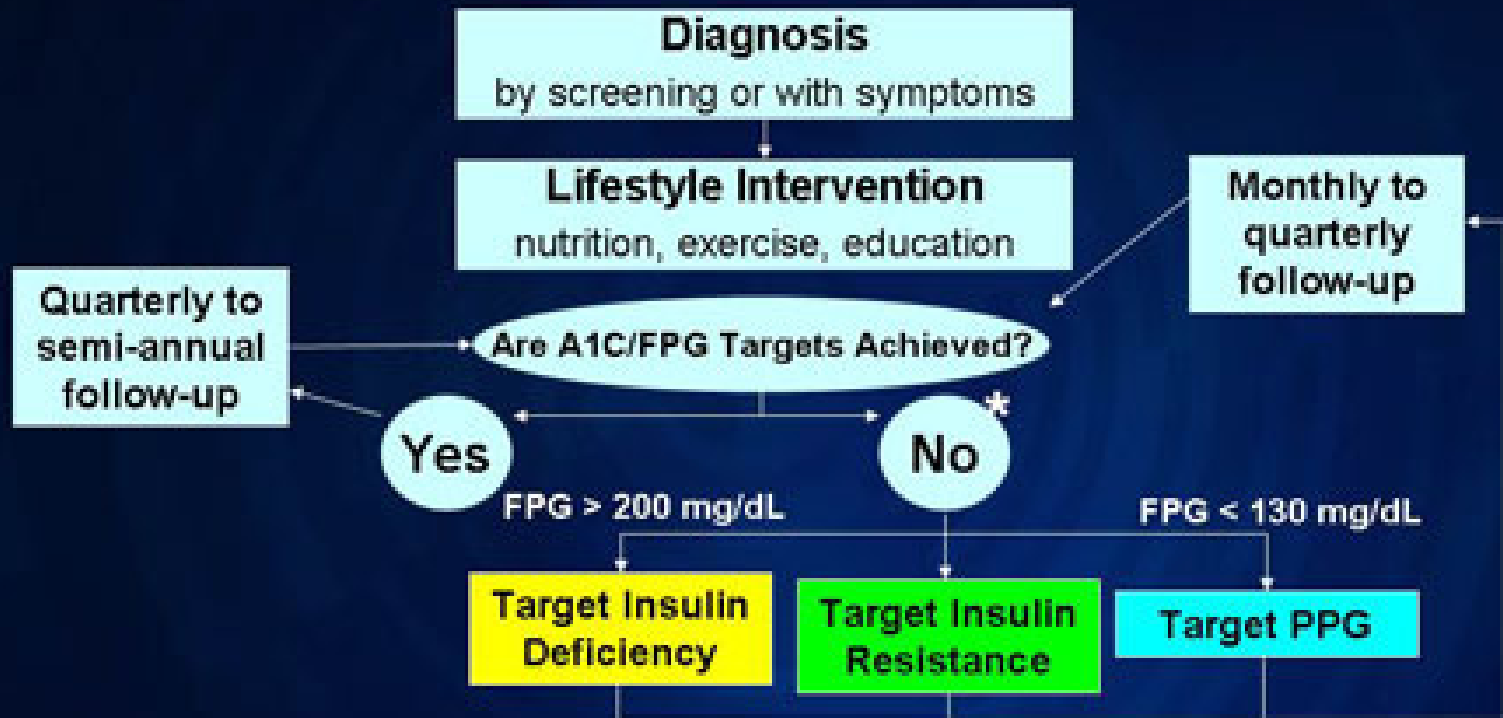
Study	Subjects	N	Intervention	Duration (y)	RRR (%)
DPP ¹	IGT	3324	Metformin	3	-31
TRIPOD ²	Prior GDM	235	Troglitazone	3	-56
PIPOD ³	Prior TRIPOD	89	Pioglitazone	3	N/A
STOP-NIDDM ⁴	IGT	1429	Acarbose	3	-36
DREAM ⁵	IGT	5269	Rosiglitazone	3	-60

1. Knowler WC, et al. *N Engl J Med*. 2002;346:393-403 [Evidence Level A]; 2. Buchanan TA, et al. *Diabetes*. 2002;51:2796-2803 [Evidence Level A]; 3. Wang AH, et al. *Diabetes*. 2006;55:517-522 [Evidence Level A]; 4. Chaffetz JL, et al. *JAMA*. 2003;290:496-494 [Evidence Level A]; 5. The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. *Lancet*. 2006;368:1096-1105. [Evidence Level A]

Pharmacotherapy tailored for the multiple defects of type 2 diabetes



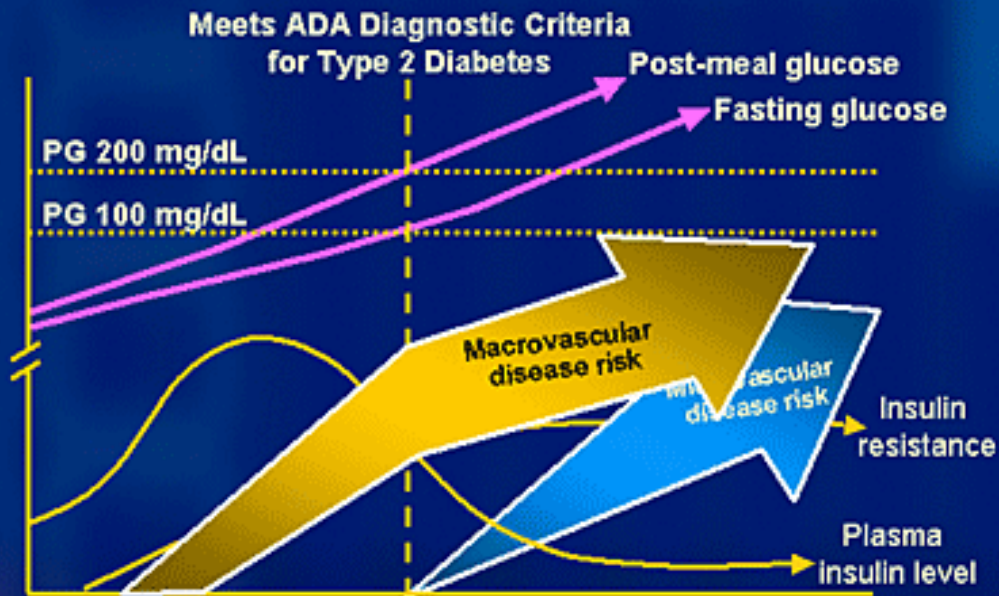
Treatment Algorithm - Glucose



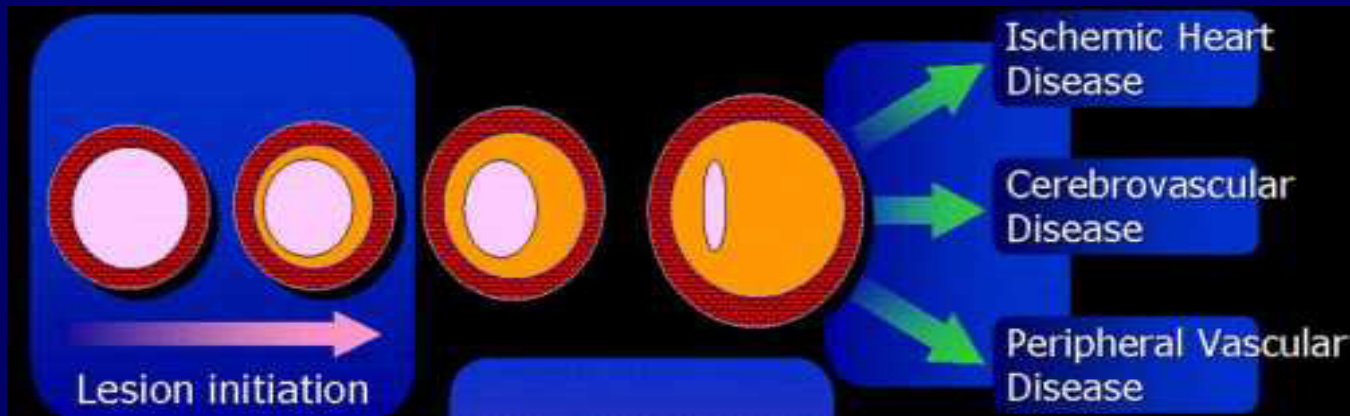
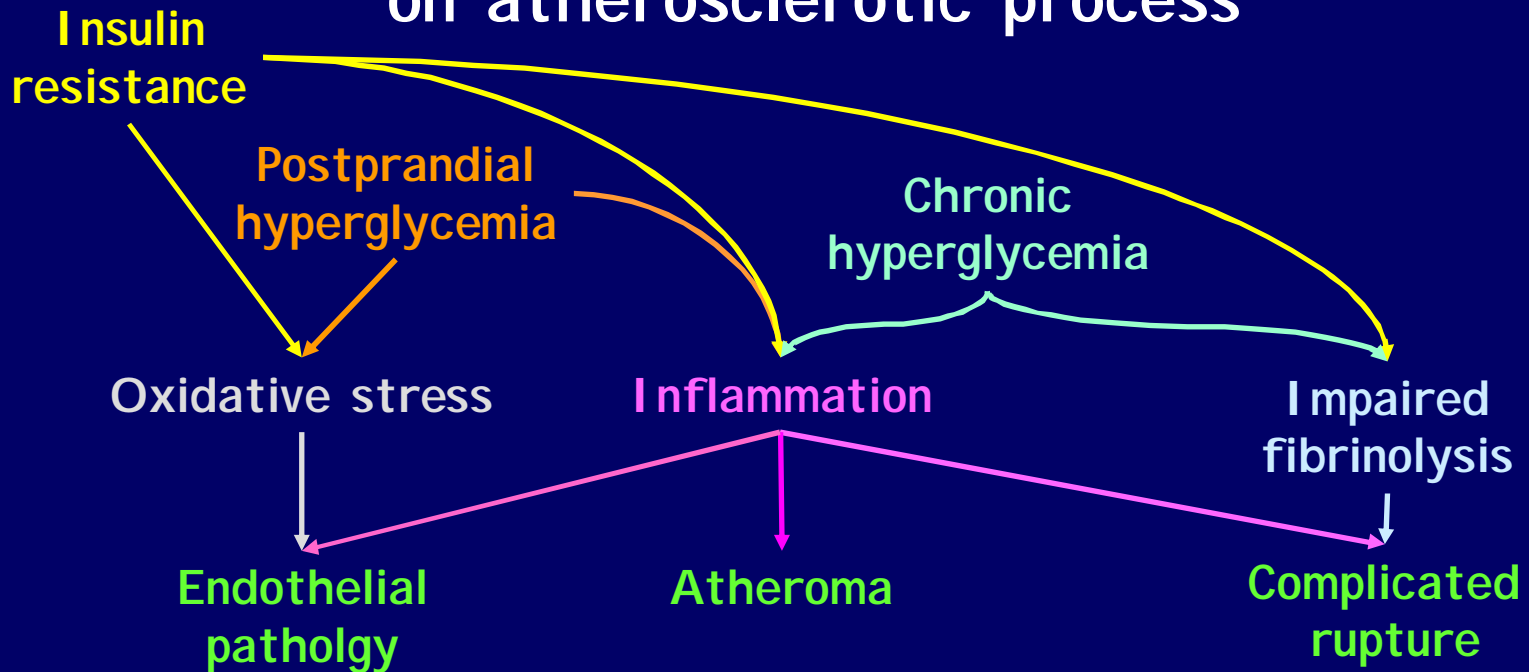
*Keep adding agents until target is reached. Self-titration at home when possible.

FROM DIABETES TO CARDIOVASCULAR EVENT: effects of PPAR-gamma Agonist, Metformin and Acarbose on CVD Risk Factors

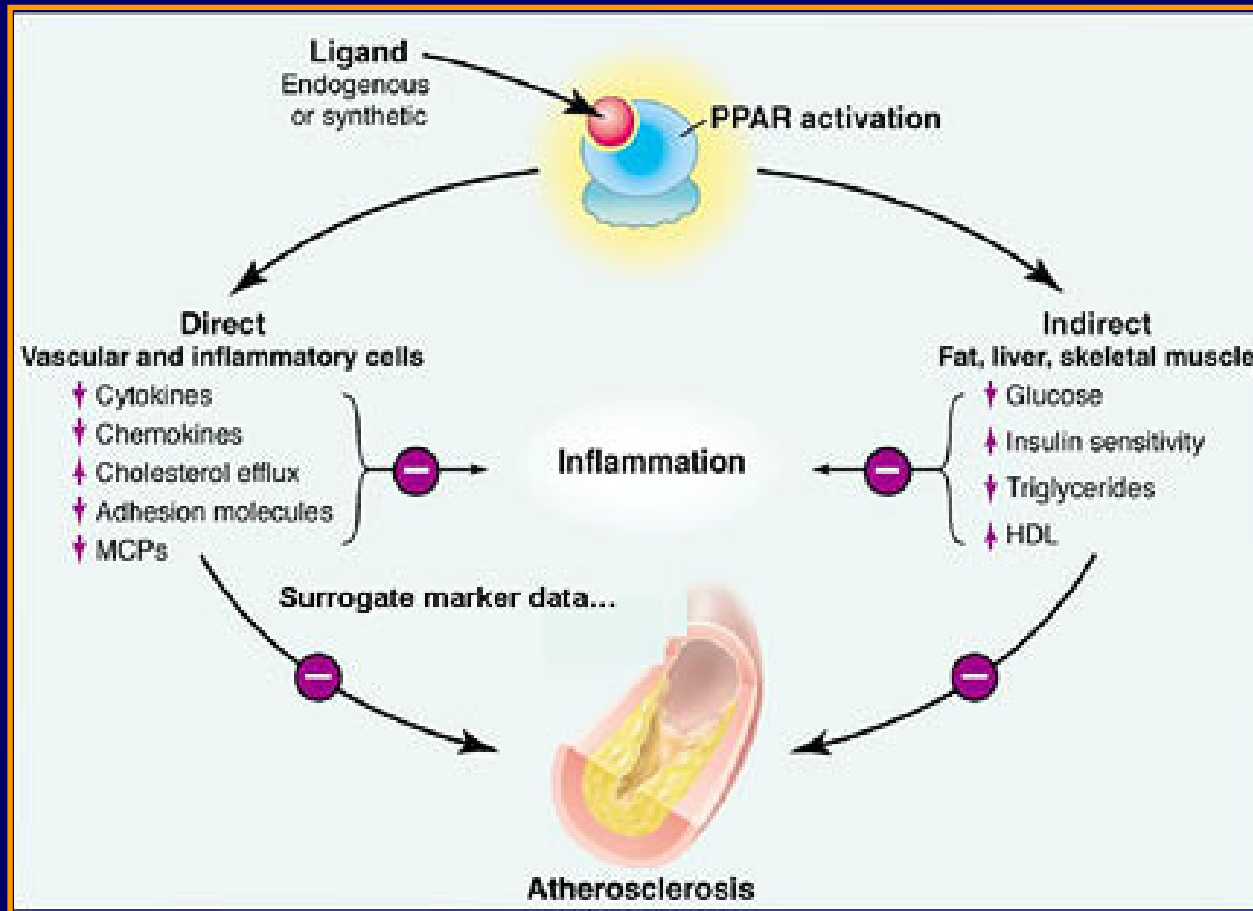
Natural Development of Type 2 Diabetes and CV Risk



Effects of diabetes on atherosclerotic process



Anti-atherosclerotic effects of PPAR-gamma agonist





Original Article

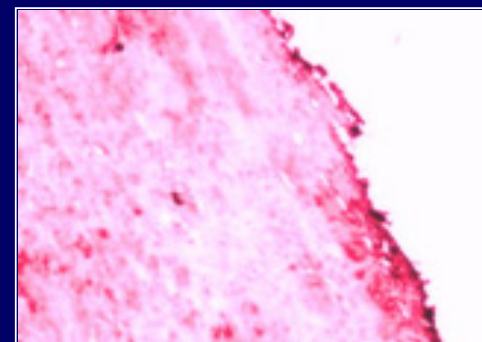
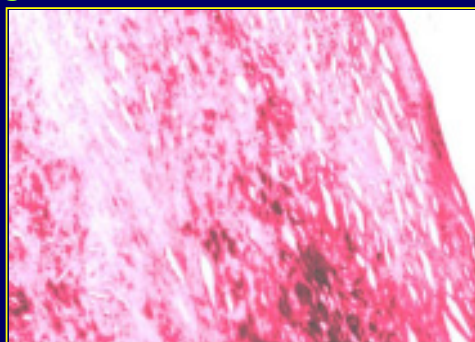
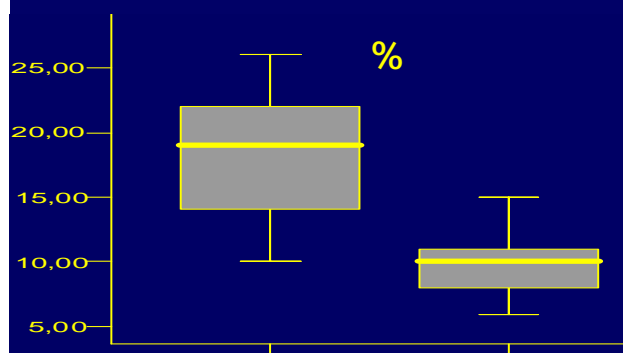
The Ubiquitin-Proteasome System and Inflammatory Activity in Diabetic Atherosclerotic Plaques

Effects of Rosiglitazone Treatment

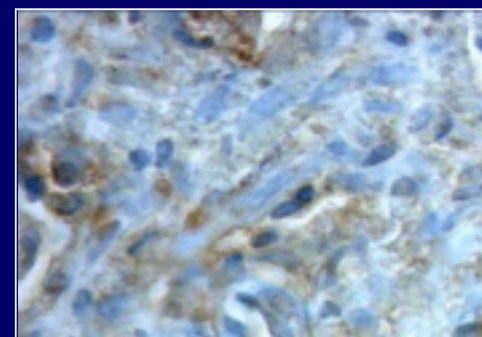
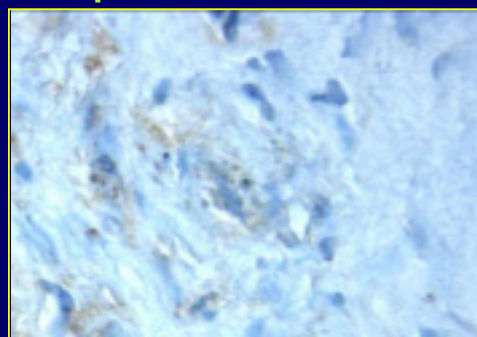
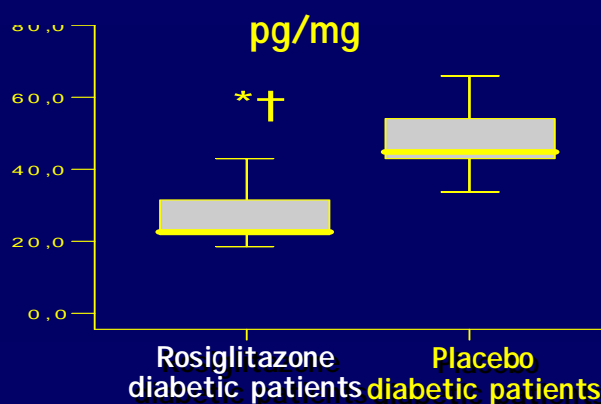
Raffaele Marfella,^{1,2} Michele D'Amico,^{2,3} Katherine Esposito,^{1,2} Alfonso Baldi,⁴ Clara Di Filippo,^{2,3} Mario Siniscalchi,¹ Ferdinando Carlo Sasso,¹ Michele Portoghese,⁵ Francesca Cirillo,⁶ Federico Cacciapuoti,¹ Ornella Carbonara,¹ Basilio Crescenzi,⁹ Feliciano Baldi,⁴ Antonio Ceriello,^{7,8} Giovanni Francesco Nicoletti,⁸ Francesco D'Andrea,⁸ Mario Verza,¹ Ludovico Coppola,¹ Francesco Rossi,^{2,3} and Dario Giugliano^{1,2}

DIABETES, VOL. 55, MARCH 2006

Collagen content



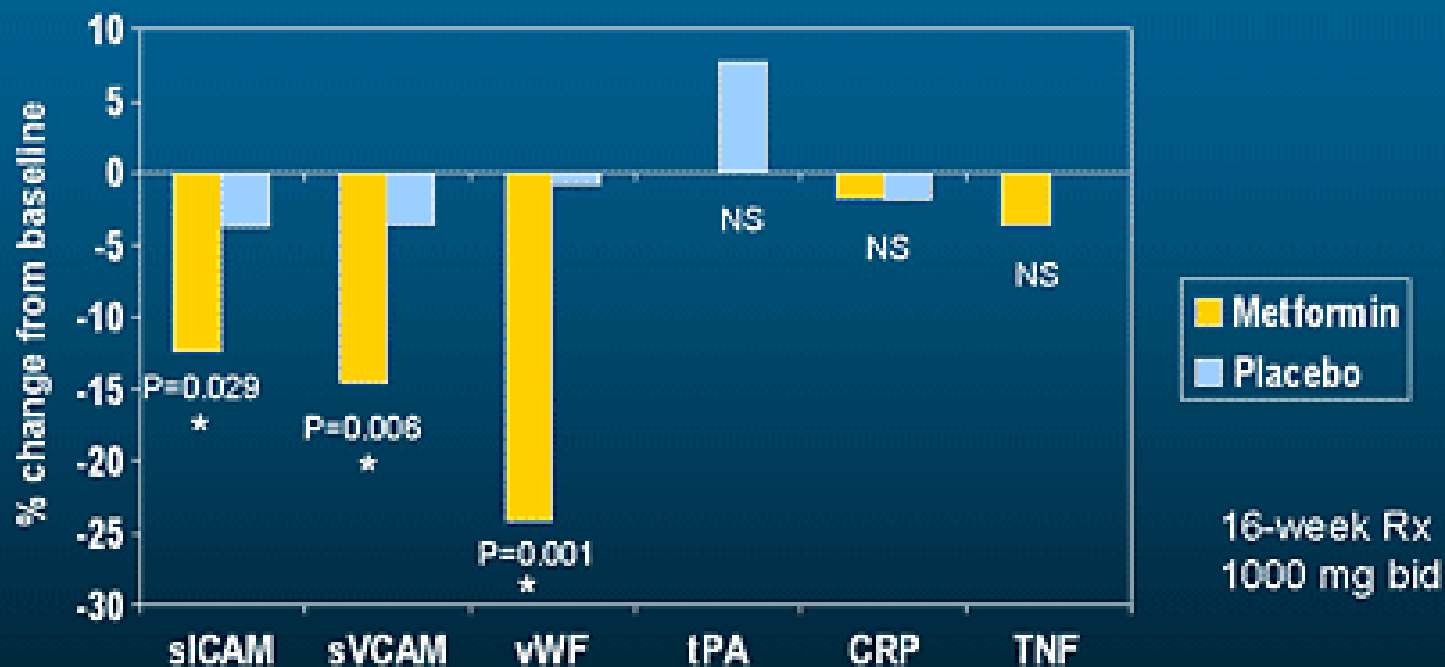
TNF-alpha



Rosiglitazone
diabetic patients

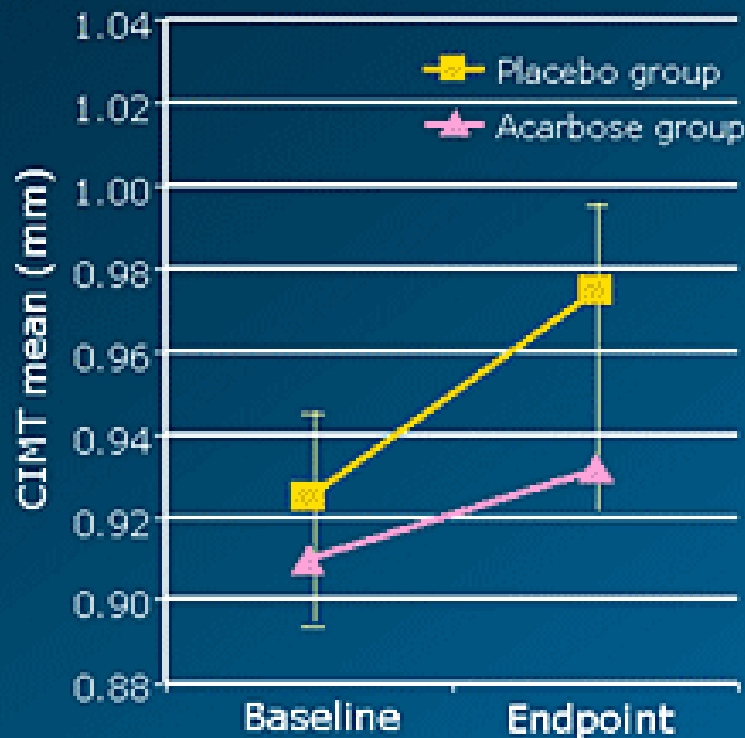
Placebo
diabetic patients

Effect of Metformin on Some Markers of Endothelial Activation and Inflammation in Hispanic Subjects with IGT



* Effect after controlling for changes in weight, HOMA, lipids, BP and glucose

Acarbose Slows Progression of Carotid IMT

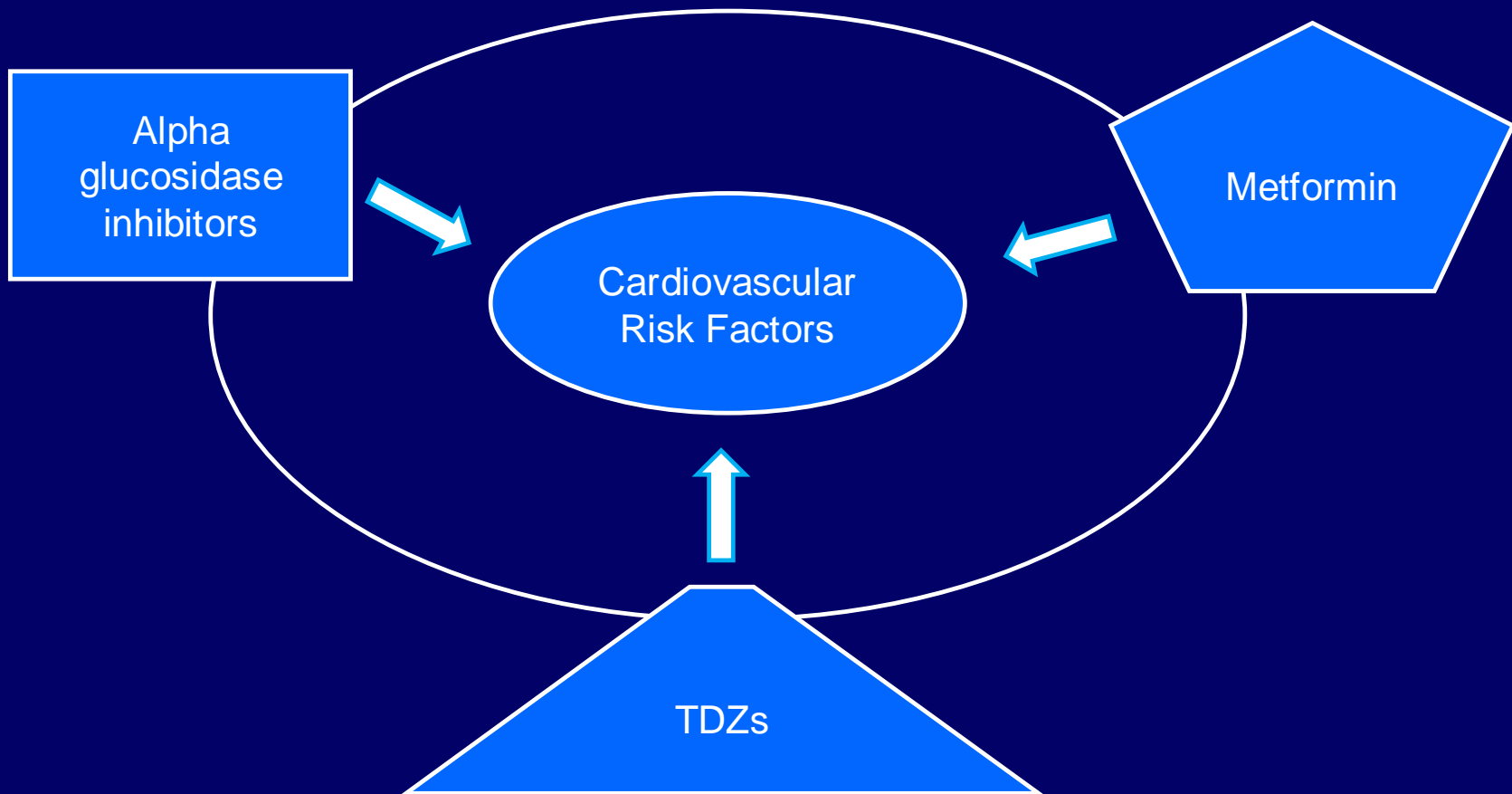


Acarbose was independently related to the change in CIMT

- Not FPG
- Not 2-hour PPG
- Not A1C
- Not TC, LDL, HDL, \pm TG
- Not sys BP

CIMT, carotid intima-media thickness
Hanefeld M et al. *Stroke*. 2004;35:1073-1078.

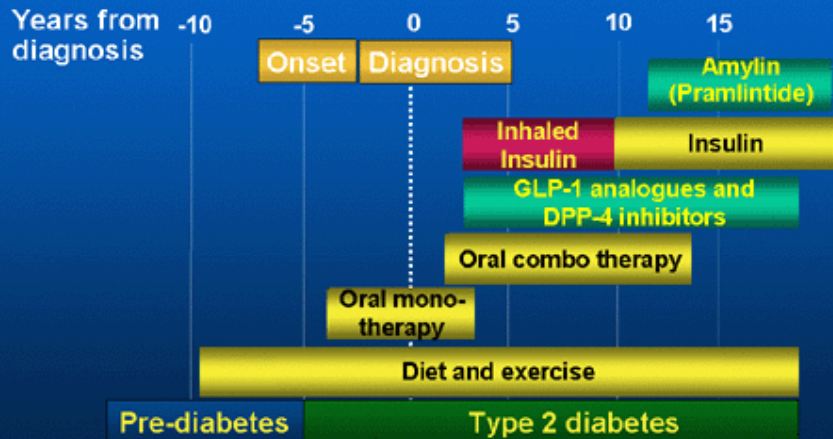
Pharmacotherapy tailored for the multiple defects of type 2 diabetes



Using Pharmacotherapy Wisely in Type 2 Diabetes

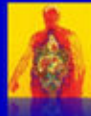
- ▶ Select medication based on understanding of pathophysiology
- ▶ Target both beta cell dysfunction and insulin resistance
- ▶ Stage of the disease will determine initial choice
- ▶ Treat to goal
- ▶ Consider nonglycemic effects of drugs

Type 2 Diabetes Predicted Treatment Paradigm

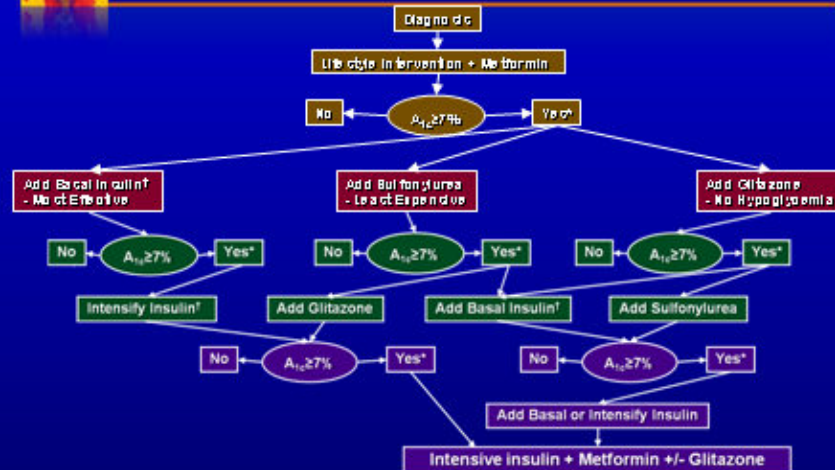


← Pathogenesis treatment

Treat earlier →



ADA/EASD Consensus Algorithm for Type 2 DM An Evolving Position Statement...!



*Check HbA_{1c} every 3 months and adjust HbA_{1c} < 7%

*Although oral agents can be used, insulin therapy is preferred based on efficacy and expense

Nathan D, et al. *Diabetologia*. 2006;49:1711-1721.



The NEW ENGLAND JOURNAL of MEDICINE

Facing the Diabetes Epidemic — Mandatory Reporting of Glycosylated Hemoglobin Values

Robert Steinbrook, M.D.

Perspective
FEBRUARY 9, 2006

Only 37% of adults 20 years of age or older have values <7% of glycosylated hemoglobin

