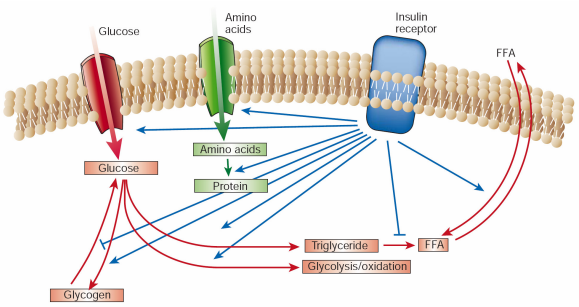
3° Congresso Sezione Regionale Triveneta SIO
"Obesità, Nutrizione e Stili di Vita"
Trento, 31 marzo 2007

Farmaci insulino-sensibilizzanti

Sandro Inchiostro

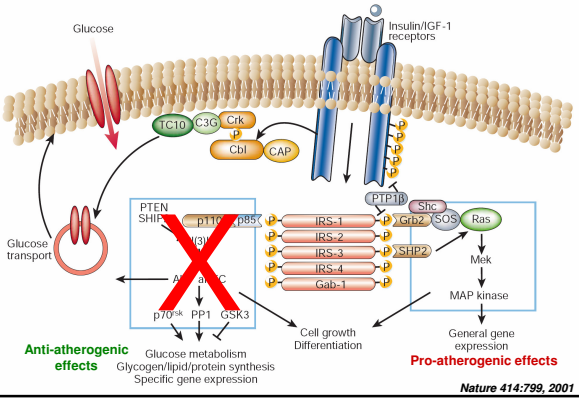
Medicina II e Centro Diabetologico
Dipartimento di Medicina Interna
Ospedale S. Chiara, Trento

Azioni metaboliche dell'insulina



Nature 414:799, 2001

Trasmissione del segnale insulinico ed suoi effetti biologici



Nature 414:799, 2001

Clinical manifestations of insulin resistance

ulin
tance
toxicity
oxicity

Type 2 diabetes and glycemic disorders

Dyslipidemia
- Low HDL
- Small, dense LDL
- Hypertriglyceridemia

Hypertension

Endothelial dysfunction/ inflammation (hsCRP)

Impaired thrombolysis
↑ PAI-1

Atherosclerosis

Courtesy of Selwyn AP, Weissman PN.

La circonferenza dei fianchi ha un effetto *indipendente* ed *opposto* rispetto alla circonferenza della vita sui fattori di rischio CV, sulla morbilità e mortalità CV, ……..

Seidell JC et al: **Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study.**
Am J Clin Nutr 74:315-321, 2001.

Snijder MB et al: **Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study**
International Journal of Obesity 28:402-409, 2004.

Heitmann BL et al.: **Hip circumference and cardiovascular morbidity and mortality in men and women.**
Obesity Research 12: 482-487, 2004.

…… sulla tolleranza glucidica e sul rischio di insorgenza di diabete.

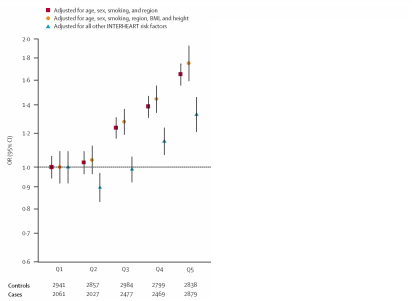
Snijder MB et al: **Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study.**
Am J Clin Nutr 77:1192-1197, 2003.

Snijder MB et al: **Larger thigh and hip circumferences are associated with better glucose tolerance: the Hoorn study**
Obesity Research 11 (1): 104-111, 2003

Snijder MB et al: **Trunk fat and leg fat have independent and opposite Associations with fasting and postload glucose levels**
Diabetes Care 27:37-377, 2004

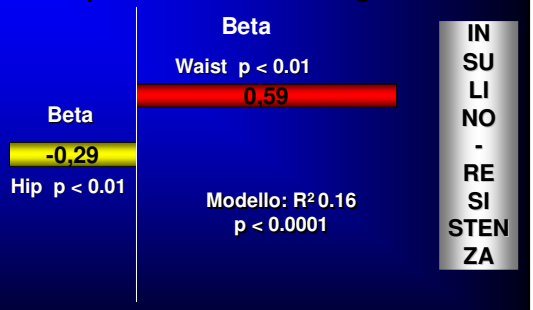
Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study

Salim Yusuf, Steven Hawken, Stephanie Ôunpuu, Leonelo Bautista, Maria Grazia Franzosi, Patrick Commerford, Chim C Lang, Zvonko Rumboldt, Churchill L Onen, Liu Lisheng, Supachai Tanomsup, Paul Wangai Jr, Fahad Razak, Arya M Sharma, Sonia S Anand, on behalf of the INTERHEART Study Investigators*



The Lancet
Vol 366 November 5, 2005

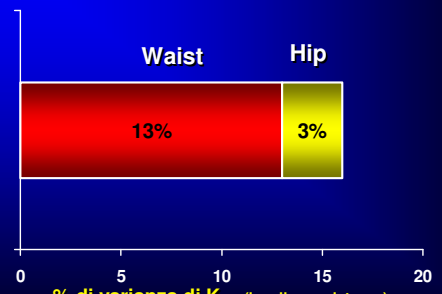
Regressione lineare multipla stepwise (coefficiente β) tra indici di adiposità ed insulino-resistenza in 247 pazienti con DM2 neodiagosticato



Variabili non entrate nel modello: età, sesso, BMI

Citroni N. et al GIDM 25: 7, 2005

Effetto di waist ed hip nello spiegare la varianza dell'insulino-resistenza in 247 pazienti con DM2 neodiagosticato



Citroni N. et al GIDM 25: 7, 2005

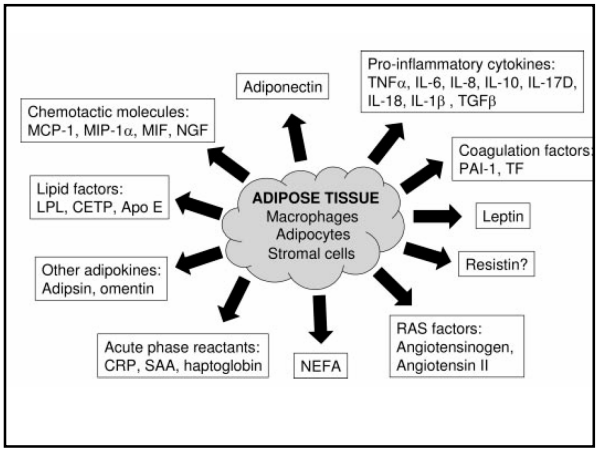
Grasso ectopico e resistenza insulinica

Insuccesso nella differenziazione/divisione delle cellule adipose

Grasso ectopico con adipociti grandi

Insulino resistenza

Heilbronn L et al. Int J Obes Relat Metab Disord 2004;28 Suppl 4:S12-21.



Metformina

Diabetologia (2006) 49: 434–441
DOI 10.1007/s00125-006-0141-7

REVIEW

A. Natali · E. Ferrannini

Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review

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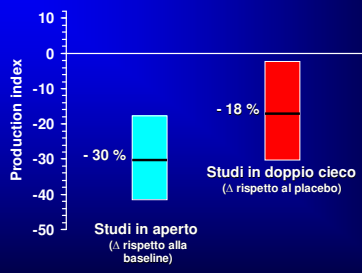
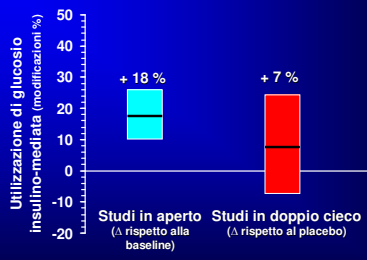


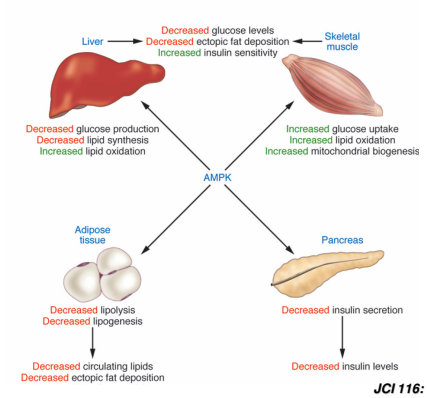
Diabetologia 49: 434, 2006

Modificazione della Sensibilità Insulinica in studi condotti con Metformina in aperto e in doppio cieco



Diabetologia 49: 434, 2006

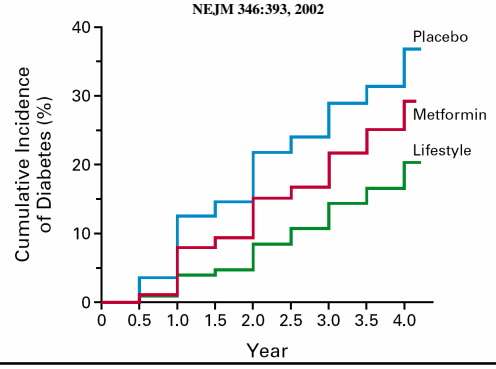
Ruolo dell'AMPK nell'omeostasi del glucosio



JCI 116: 1776, 2006

Riduzione dell'incidenza di diabete di tipo 2 con interventi sullo stile di vita o con metformina

Diabetes Prevention Program Research Group
NEJM 346:393, 2002



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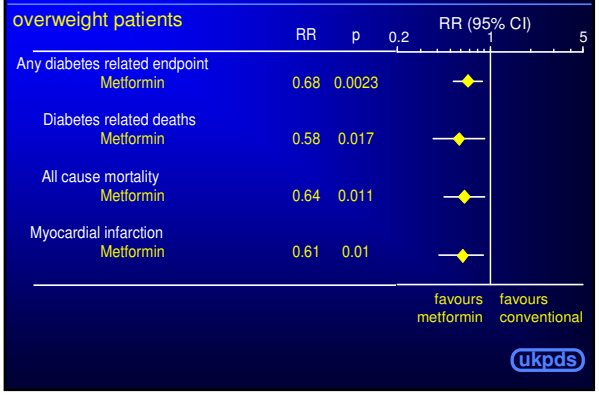
Inzucchi SE, JAMA 2002

Metformin Comparisons



Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

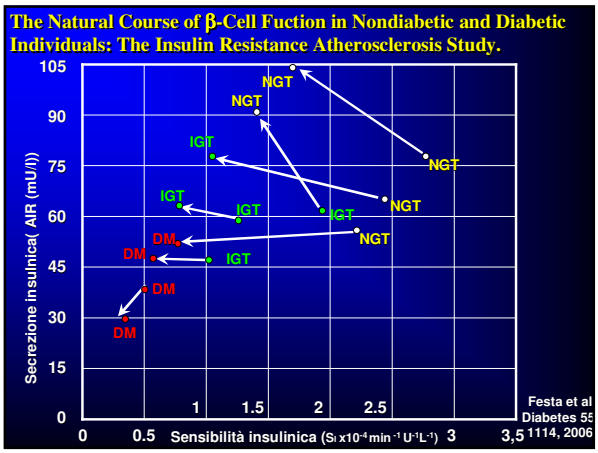
A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

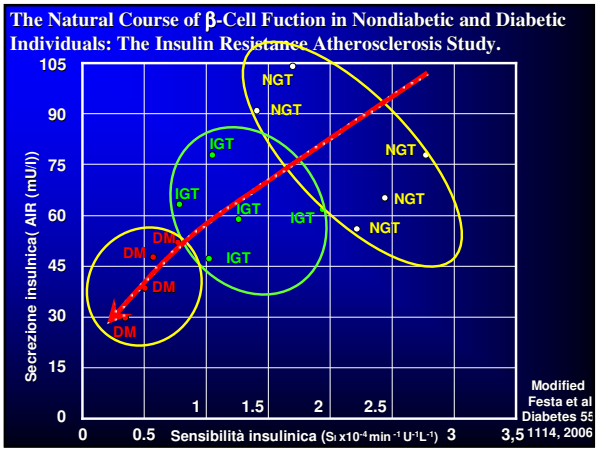
Interventions	Expected decrease in A1C (%)	Advantages	Disadvantages
Step 1: initial			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in 1st year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: additional therapy			
Insulin	1.5–2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycemia, weight gain
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycemia*
TZDs	0.5–1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Other drugs			
α-Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5†	Short duration	Three times/day dosing, expensive
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience

*Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (e.g. chlorpropamide, glyburide [glibenclamide], and sustained-release glipizide) are more likely to cause hypoglycemia than glipizide, glimepiride, and gliclazide. †Repaglinide is more effective at lowering A1C than nateglinide.

DIABETES CARE, VOLUME 29, NUMBER 8, AUGUST 2006

Tiazolidinedioni


The Natural Course of β-Cell Fuction in Nondiabetic and Diabetic Individuals: The Insulin Resistance Atherosclerosis Study.
Secrezione insulinica(AIR (mU/l))
Sensibilità insulinica (Si x10-4 min-1 U-1L-1)
Festa et al Diabetes 55 1114, 2006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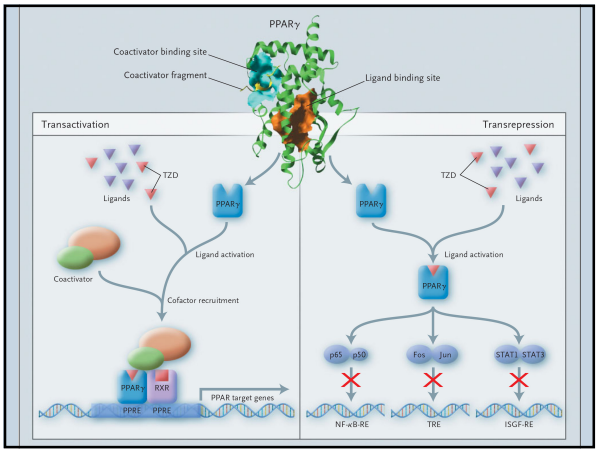
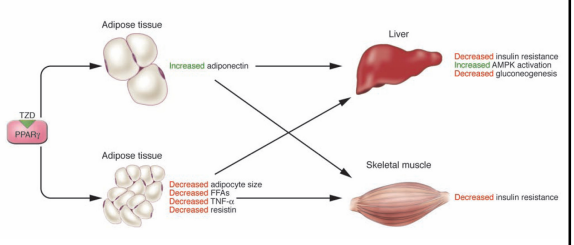
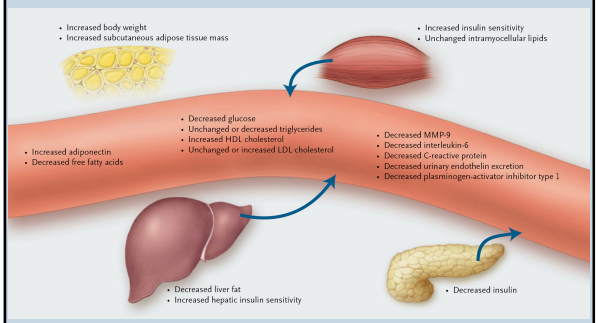

PPARγ
Coactivator binding site
Coactivator fragment
Ligand binding site
Transactivation
Transrepression
TZD
Ligands
Ligand activation
Coactivator
Cofactor recruitment
RXR
PPRE
PPAR target genes
p65
p50
Fos
Jun
STAT1
STAT3
NF-κB-RE
TRE
ISGF-RE

Azioni cellulari e metaboliche dei Glitazoni

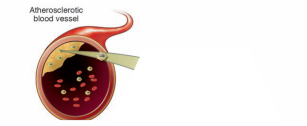


JCI 116: 1784, 2006

Effetti dei glitazoni in vivo nell'uomo

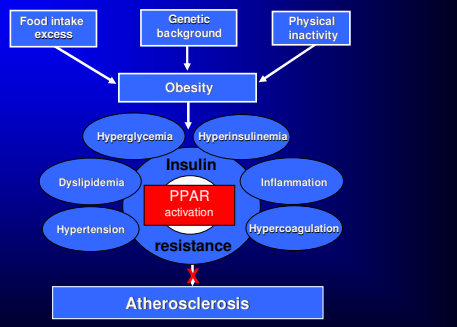


NEJM 351: 1106, 2004



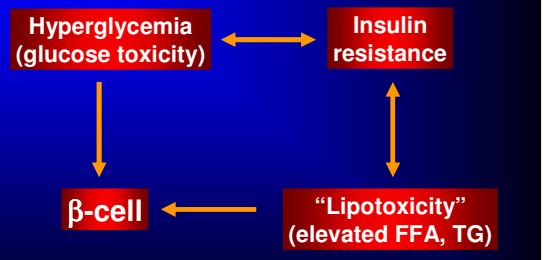
JCI 114: 1538,2004

Potential role of PPAR activation in CV risk reduction



Adapted from Tenenbaum A et al. *Intl J Cardiol.* 2004;97:167-72.

Factors that may drive the progressive decline of β-cell function



Adapted from Kahn SE. *J Clin Endocrinol Metab.* 2001;86:4047-58.
Adapted from Ludwig DS. *JAMA.* 2002;287:2414-23.

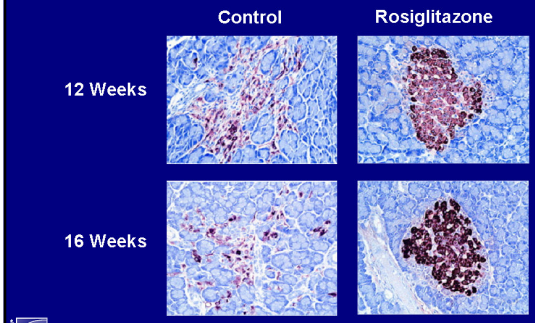
Nature Medicine - **13**, 340 - 347 (2007)
Published online: 18 February 2007; | doi:10.1038/nm1546

β-cell ABCA1 influences insulin secretion, glucose homeostasis and response to thiazolidinedione treatment

Liam R Brunham[1], Janine K Kruit[1], Terry D Pape[1], Jenelle M Timmins[2], Anne Q Reuwer[1], Zainisha Vasanji[3], Brad J Marsh[4], Brian Rodrigues[5], James D Johnson[6], John S Parks[2], C Bruce Verchere[3] & Michael R Hayden[1]

Type 2 diabetes is characterized by both peripheral insulin resistance and reduced insulin secretion by β-cells. The reasons for β-cell dysfunction in this disease are incompletely understood but may include the accumulation of toxic lipids within this cell type. We examined the role of Abca1, a cellular cholesterol transporter, in cholesterol homeostasis and insulin secretion in β-cells. Mice with specific inactivation of *Abca1* in β-cells had markedly impaired glucose tolerance and defective insulin secretion but normal insulin sensitivity. Islets isolated from these mice showed altered cholesterol homeostasis and impaired insulin secretion *in vitro*. We found that rosiglitazone, an activator of the peroxisome proliferator–activated receptor-γ, which upregulates *Abca1* in β-cells, requires β-cell Abca1 for its beneficial effects on glucose tolerance. These experiments establish a new role for Abca1 in β-cell cholesterol homeostasis and insulin secretion, and suggest that cholesterol accumulation may contribute to β-cell dysfunction in type 2 diabetes.

PPARγ Ligand May Prevent Loss of β-Cell Mass



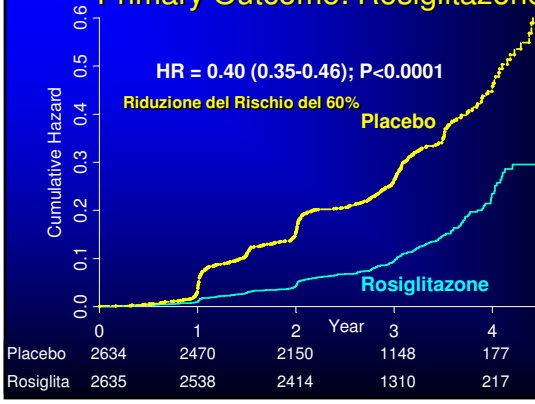
Finegood D et al. *Diabetes*. 2001;50:1021-1029.

The *DREAM* Trial

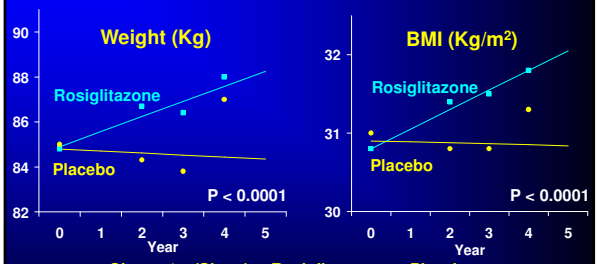
Aims:	Does ramipril 15 mg/d prevent diabetes?
	Does rosiglitazone 8 mg/d prevent diabetes?
Design:	2 X 2 factorial, double-blind RCT
Sample:	Age 30+; IGT (FPG <7 & 2 hr 7.8-11) &/or IFG (FPG 6.1-6.9)
Pts:	5269 in 191 sites, 21 countries, & F/U 3 yrs
Outcome:	Incident DM (confirmed FPG ≥ 7 or 2 hr ≥ 11.1; or MD diagnosis) or death*

*because undiagnosed diabetes may be more frequent in those who die than in those who do not

Primary Outcome: Rosiglitazone

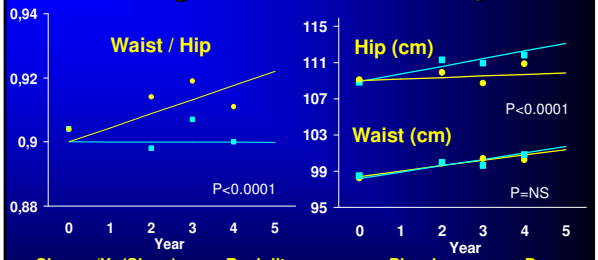


Rosiglitazone & Weight, BMI



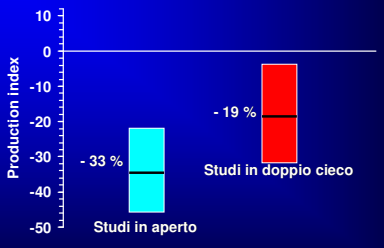
Change/yr (Slope)	Rosiglitazone	Placebo
Weight (kg)	0.67(2.77)	-0.09 (2.41)
BMI (kg/m²)	0.25 (1.01)	-0.01 (0.84)

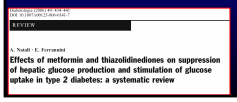
Rosiglitazone & Waist, Hip



Change/Yr (Slope)	Rosiglitazone	Placebo	P
Waist / Hip	-0.00002 (0.03)	0.004 (0.04)	<0.0001
Waist	0.70 (3.49)	0.60 (3.91)	0.4
Hip	0.84 (3.46)	0.17 (3.01)	<0.0001

Production index (produzione epatica di glucosio x insulinemia basale) in studi condotti con Glitazoni in aperto e in doppio cieco nel DM tipo 2





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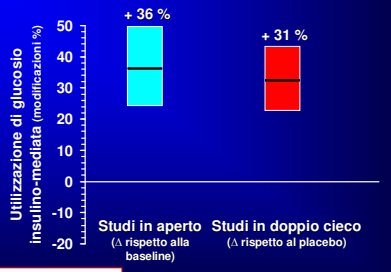

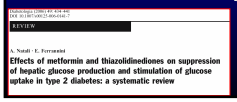
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Inzucchi SE, JAMA 2002

ADOPT Objective

Compare the durability of glycaemic control using rosiglitazone versus metformin or glyburide as initial monotherapy in patients with recently diagnosed type 2 diabetes mellitus

ADOPT

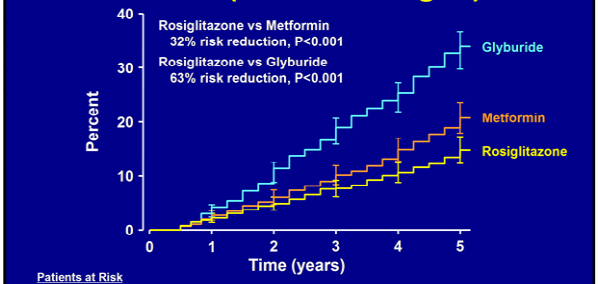
Baseline Characteristics

	Rosiglitazone (N = 1456)	Metformin (N = 1454)	Glyburide (N = 1441)
Age, yr	56.3 ± 10.0	57.9 ± 9.9	56.4 ± 10.2
Male	56%	59%	58%
Caucasian	87%	89%	89%
North America	52%	52%	53%
Europe	48%	48%	47%

P>0.05 for all comparisons

ADOPT

Cumulative Incidence of Monotherapy Failure (FPG >180 mg/dl)

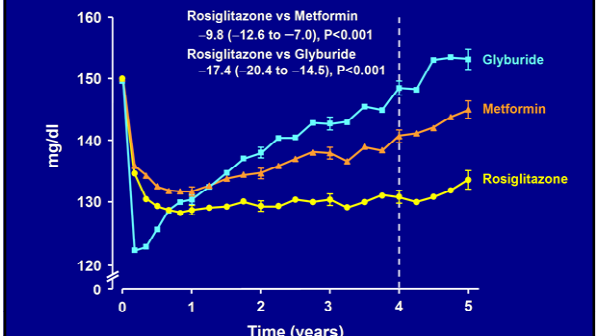


Patients at Risk

Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

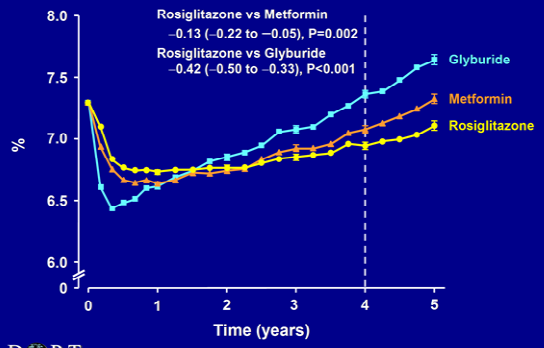
ADOPT

Fasting Plasma Glucose Over Time



ADOPT

HbA1c Over Time



ADOPT

Summary of Glycaemic Efficacy

Initial treatment of type 2 diabetes with rosiglitazone slowed progression of hyperglycaemia compared to metformin or glyburide as assessed by:

- FPG >180 mg/dl
- FPG >140 mg/dl
- Mean HbA1c >7%

ADOPT

Adverse Events

- Rosiglitazone was associated with weight gain and oedema, and in women, fractures
- Metformin was associated with adverse gastrointestinal events
- Glyburide was associated with hypoglycaemia and weight gain
- Rosiglitazone and metformin had a similar risk of cardiovascular events. Glyburide had a lower risk of cardiovascular events than rosiglitazone

ADOPT

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Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycemia*
TZDs	0.5–1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Other drugs			
α-Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5†	Short duration	Three times/day dosing, expensive
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience

*Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (e.g. chlorpropamide, glyburide [glibenclamide], and sustained-release glipizide) are more likely to cause hypoglycemia than glipizide, glimepiride, and gliclazide. †Repaglinide is more effective at lowering A1C than nateglinide.

DIABETES CARE, VOLUME 29, NUMBER 8, AUGUST 2006

TIAZOLIDINEDIONI

Pioglitazone	**Dose: 15-45 mg/die, 1 somministrazione/die, anche in presenza di IRC (fino a GFR di 4 ml/m),**
Rosiglitazone	**Dose: 4-8 mg/die, 1-2 somministrazioni/die, anche in presenza di IRC (fino a GFR di 30 ml/m)**

Controindicazioni

- transaminasi > 2.5 la norma
- Insufficienza epatica
- Insufficienza cardiaca (classe NYHA I-IV)

TIAZOLIDINEDIONI

Effetti collaterali comuni

- Anemia
- Aumento del peso
- Edema
- Disturbi visivi (pioglitazone)
- Infezioni del tratto respiratorio superiore (pioglitazone)
- Ipoestesia (pioglitazone)
- Ipercolesterolemia (rosiglitazone)

Insulin Sensitizers: Surrogate and Clinical End-Point Beyond Glycemic Control

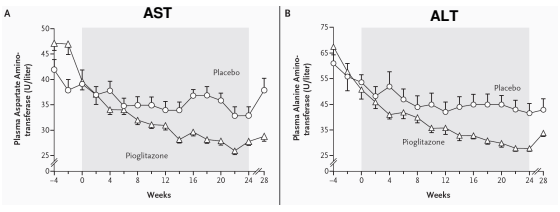
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

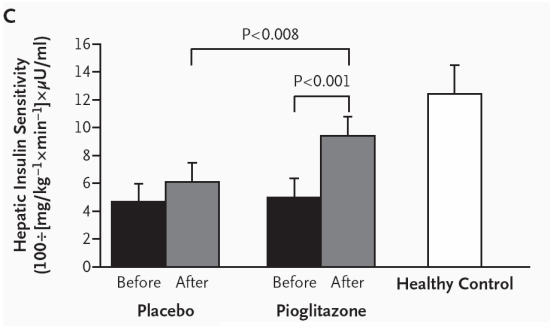
A Placebo-Controlled Trial of Pioglitazone in Subjects with Nonalcoholic Steatohepatitis

Renata Belfort, M.D., Stephen A. Harrison, M.D., Kenneth Brown, M.D., Celia Darland, R.D., Joan Finch, R.N., Jean Hardies, Ph.D., Bogdan Balas, M.D., Amalia Gastaldelli, Ph.D., Fermin Tio, M.D., Joseph Pulcini, M.D., Rachele Berria, M.D., Jennie Z. Ma, Ph.D., Sunil Dwivedi, M.D., Russell Havranek, M.D., Chris Fincke, M.D., Ralph DeFronzo, M.D., George A. Bannayan, M.D., Steven Schenker, M.D., and Kenneth Cusi, M.D.

N ENGL J MED 355;22 WWW.NEJM.ORG NOVEMBER 30, 2006



Sensibilità insulinica epatica: effetto del pioglitazone



N ENGL J MED 355;22 WWW.NEJM.ORG NOVEMBER 30, 2006

Effect of Pioglitazone Compared With Glimepiride on Carotid Intima-Media Thickness in Type 2 Diabetes

A Randomized Trial

Theodore Mazzone, MD
Peter M. Meyer, PhD
Steven B. Feinstein, MD
Michael H. Davidson, MD
George T. Kondos, MD
Ralph B. D'Agostino, Sr, PhD
Alfonso Perez, MD
Jean-Claude Provost, MD
Steven M. Haffner, MD

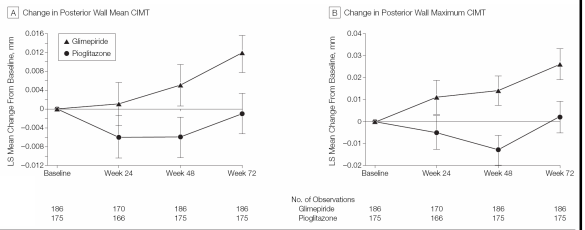
Context Carotid artery intima-media thickness (CIMT) is a marker of coronary atherosclerosis and independently predicts cardiovascular events, which are increased in type 2 diabetes mellitus (DM). While studies of relatively short duration have suggested that thiazolidinediones such as pioglitazone might reduce progression of CIMT in persons with diabetes, the results of longer studies have been less clear.

Objective To evaluate the effect of pioglitazone vs glimepiride on changes in CIMT of the common carotid artery in patients with type 2 DM.

Design, Setting, and Participants Randomized, double-blind, comparator-controlled, multicenter trial in patients with type 2 DM conducted at 28 clinical sites in the multiracial/ethnic Chicago metropolitan area between October 2003 and May 2006. The treatment period was 72 weeks (1-week follow-up). CIMT images were captured by a single ultrasonographer at 1 center and read by a single treatment-blinded reader

JAMA 296:2572, 2006

Modificazioni dello spessore medio-intimale medio e massimo della carotide comune nel corso dello studio CHICAGO: Pioglitazone Vs Glimepiride



JAMA 296:2572, 2006

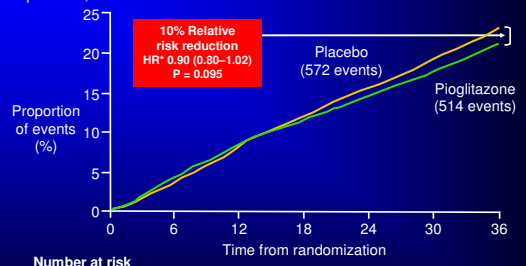
PROactive: Study design

Objective:	Assess the effects of pioglitazone on reducing macrovascular events in type 2 diabetes
Design:	Randomized double-blind, controlled outcome
Population:	N = 5238 with type 2 diabetes and history of macrovascular disease
Treatment:	Pioglitazone (up to 45 mg) or placebo
Primary outcome:	Composite of all-cause mortality, MI, ACS, coronary or peripheral revascularization, amputation, stroke
Secondary outcomes:	Individual components of primary outcome, CV mortality
Follow-up:	4 years

Charbonnel B et al. *Diabetes Care.* 2004;27:1647-53.
Dormandy JA et al. *Lancet.* 2005;366:1279-89.

PROactive: Reduction in primary outcome

All-cause mortality, MI, ACS, coronary or peripheral revascularization, amputation, stroke



Number at risk

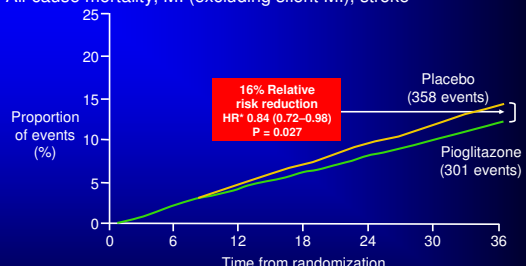
Pioglitazone	2488	2373	2302	2218	2146	348
Placebo	2530	2413	2317	2215	2122	345

*Unadjusted

Dormandy JA et al. *Lancet.* 2005;366:1279-89.

PROactive: Reduction in secondary outcome

All-cause mortality, MI (excluding silent MI), stroke



Number at risk

Pioglitazone	2536	2487	2435	2381	2336	396
Placebo	2566	2504	2442	2371	2315	390

*Unadjusted

Dormandy JA et al. *Lancet.* 2005;366:1279-89.

Tiazolidinedioni: *pros*

- Rallentano la progressione da alterata omeostasi glucidica a DM 2
- Mantengono un buon controllo glicemico nel DM 2, in monoterapia, più a lungo di metformina e glibenclamide
- Migliorano la steato-epatite non alcolica
- Riducono la progressione dell'aterosclerosi subclinica
- Riducono l'incidenza di morte, IMA non fatale e stroke nel DM2 ad elevatissimo rischio CV

Tiazolidinedioni: *cons*

- Aumento del rischio di scompenso cardiaco
- Aumento del peso corporeo
- Aumento del rischio di fratture nelle donne
- Costo terapia superiore a metformina e secretagoghi