

*Società Italiana Gerontologia e Geriatria*  
*53° Congresso Nazionale*

***Gabriele Perriello***

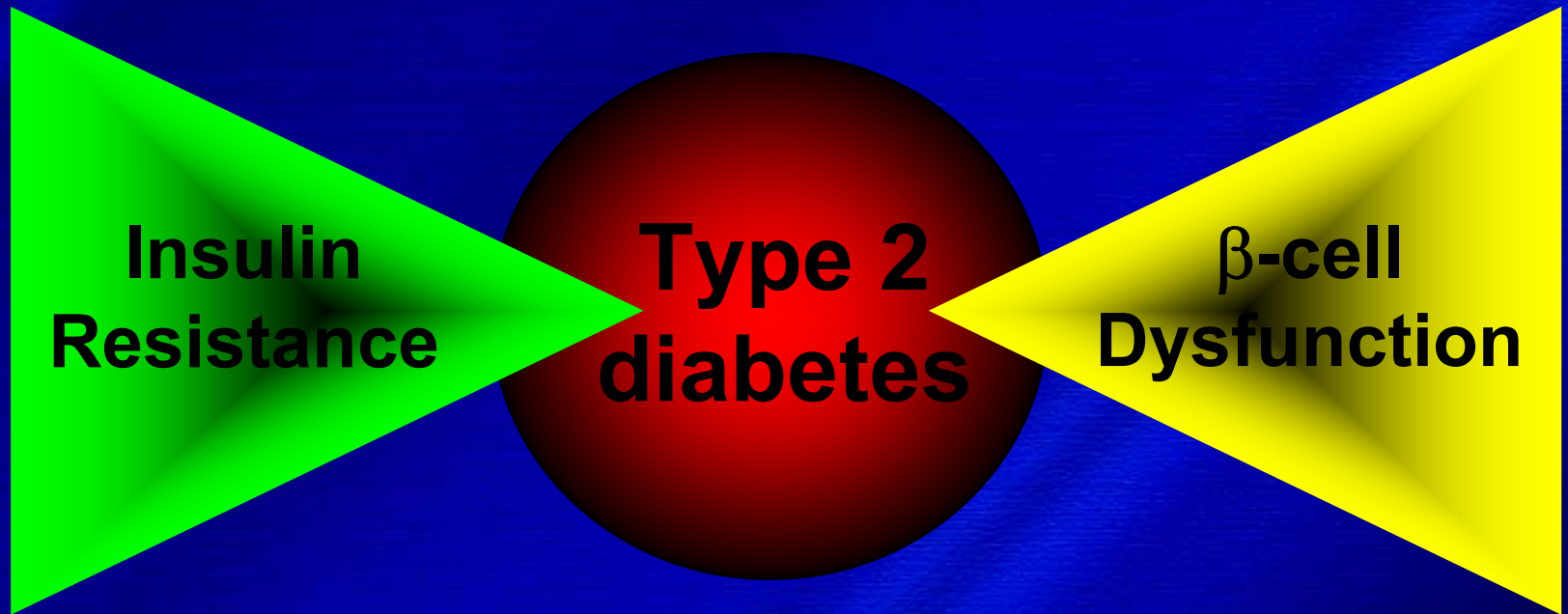
*Dipartimento di Medicina Interna*  
*Università di Perugia*

# **Terapia Orale del Diabete tipo 2: nuove evidenze scientifiche**



Firenze, 27 novembre 2008

# Eterogeneity of T2DM



# Clinical and Functional Heterogeneity of Elderly T2DM

1. Older individuals may have developed diabetes years earlier and may have significant complications
2. Newly diagnosed may have had years of undiagnosed diabetes with resultant complications or may have few complications from the disease
3. Older adults with diabetes may be frail and have other underlying chronic conditions, substantial diabetes-related comorbidity, or limited physical or cognitive functioning
4. Older individuals with diabetes have little comorbidity and are active
5. Life expectancies are highly variable for this population, but often longer than clinicians realize

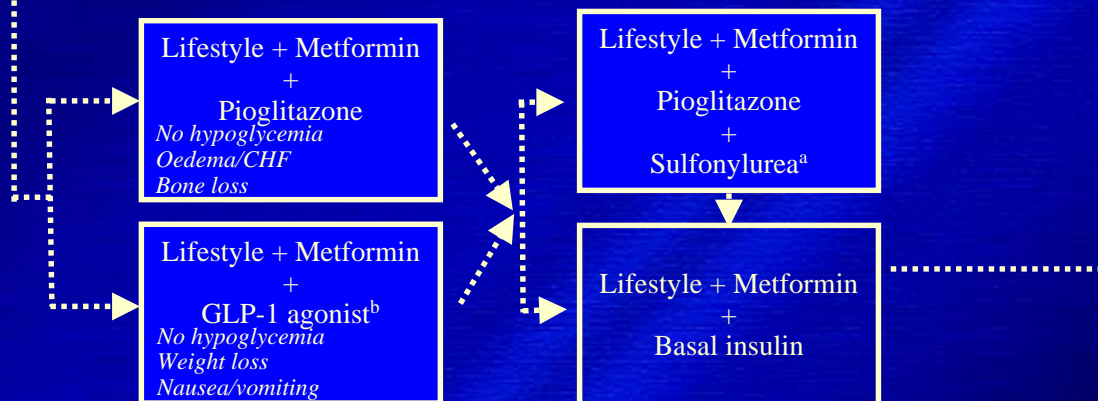
# Algorithm for the metabolic management of type 2 diabetes

## ADA/EASD Consensus Statement

### Tier 1: Well-validated core therapies



### Tier 2: Less well-validated therapies



<sup>a</sup>Other than glibenclamide or chlorpropamide

<sup>b</sup>Insufficient clinical use to be confident regarding safety



# Factors influencing targets and OHA choice

Life expectancy <5 yrs  
Functional and cognitive impairment  
Life-limiting comorbidities  
Polytherapy  
Diabetic complications

HbA1c = 8%

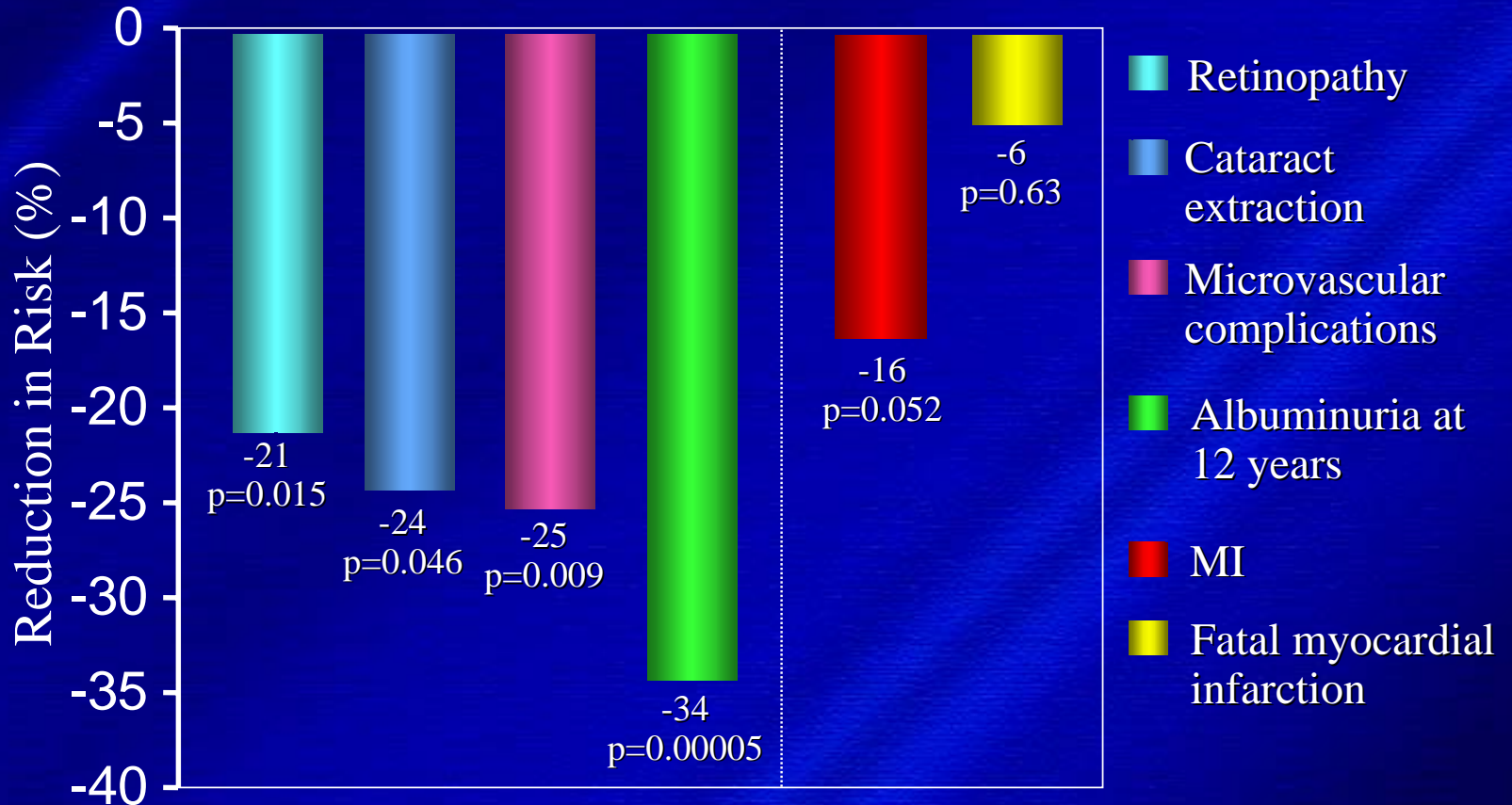
Most OHA contraindicated

Long life expectancy  
Active  
Good functional status  
Otherwise healthy  
Few therapies  
No comorbidities  
No complications

HbA1c < 7%

All OHA recommended

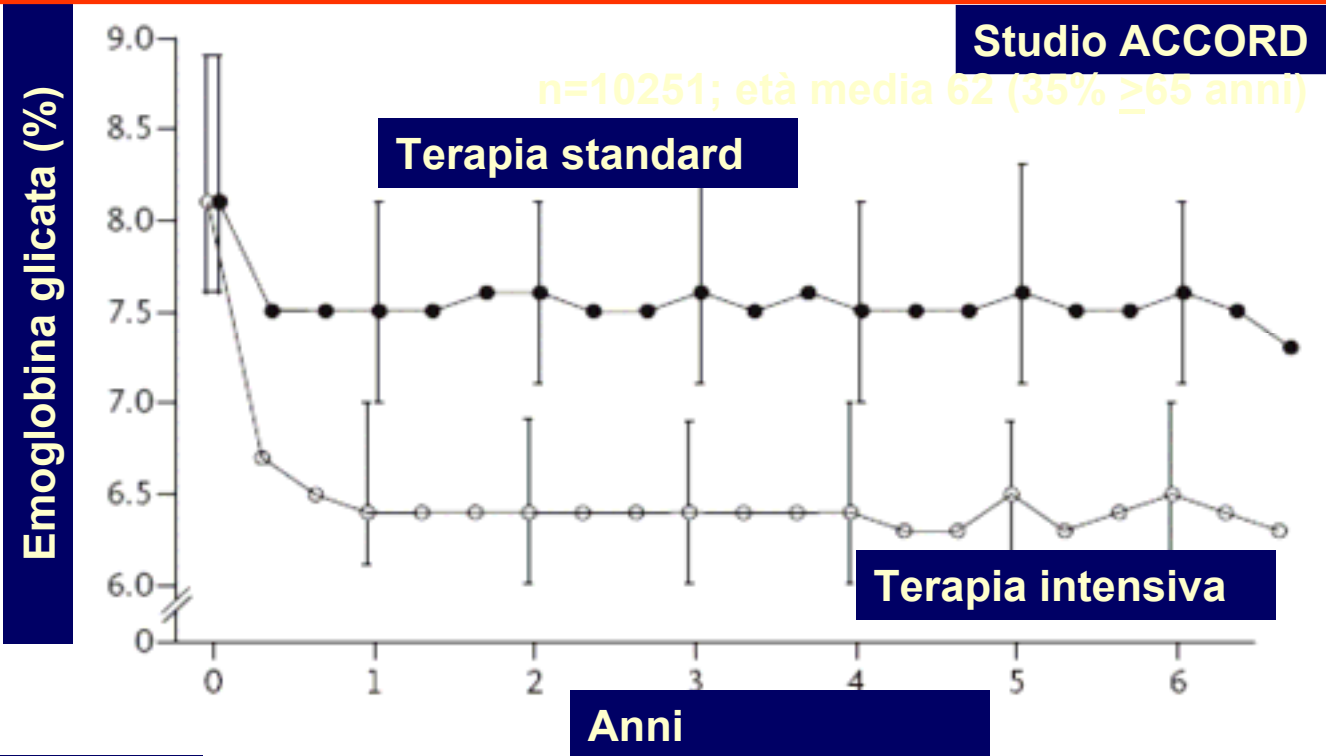
# Lowering HbA1c Reduces Risk of Complications\*



\*Percent risk reduction for  
0.9% decrease in HbA<sub>1c</sub>

UKPDS. Lancet 1998; 352:837

# Livelli mediани di emoglobina glicata



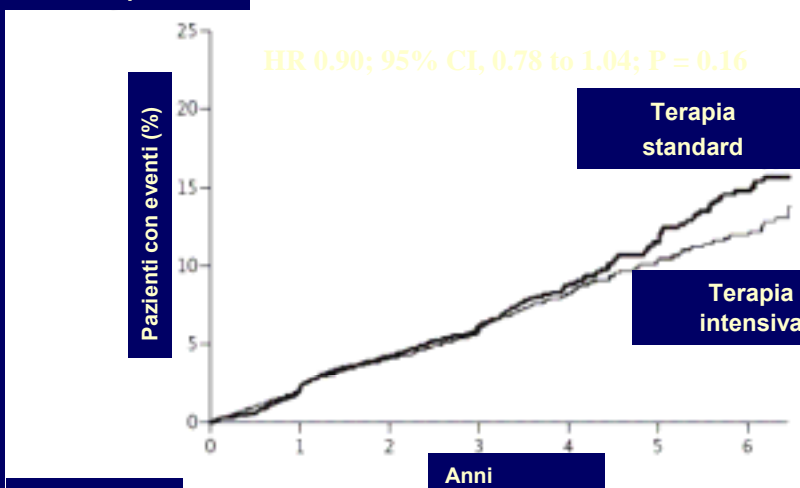
N. a rischio	
Terapia standard	5109    4774    4588    3186    1744    455    436
Terapia intensiva	5119    4768    4585    3165    1706    476    471

# Effetti del controllo intensivo su outcome primario e decesso per qualsiasi causa

Outcome primario: infarto miocardio e ictus non fatali, e morte cardiovascolare

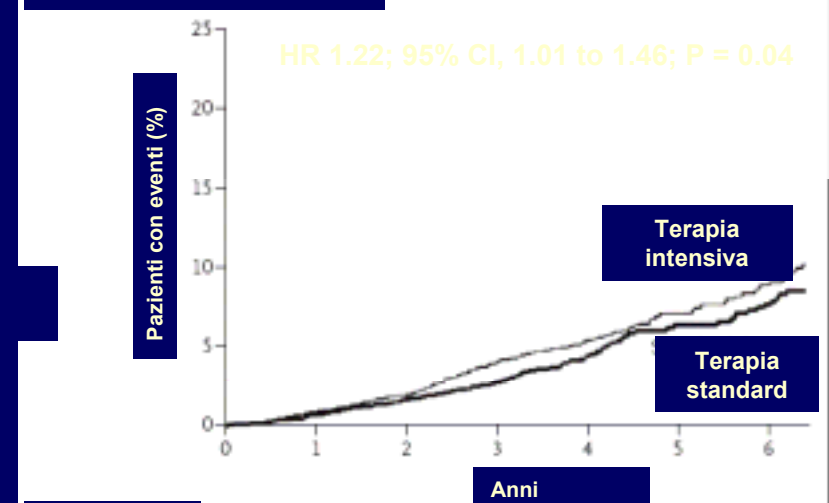
Studio ACCORD

Outcome primario



N. a rischio								
Terapia intensiva	5128	4843	4390	2839	1337	475	448	
Terapia standard	5123	4827	4262	2702	1186	440	395	

Decesso per qualsiasi causa

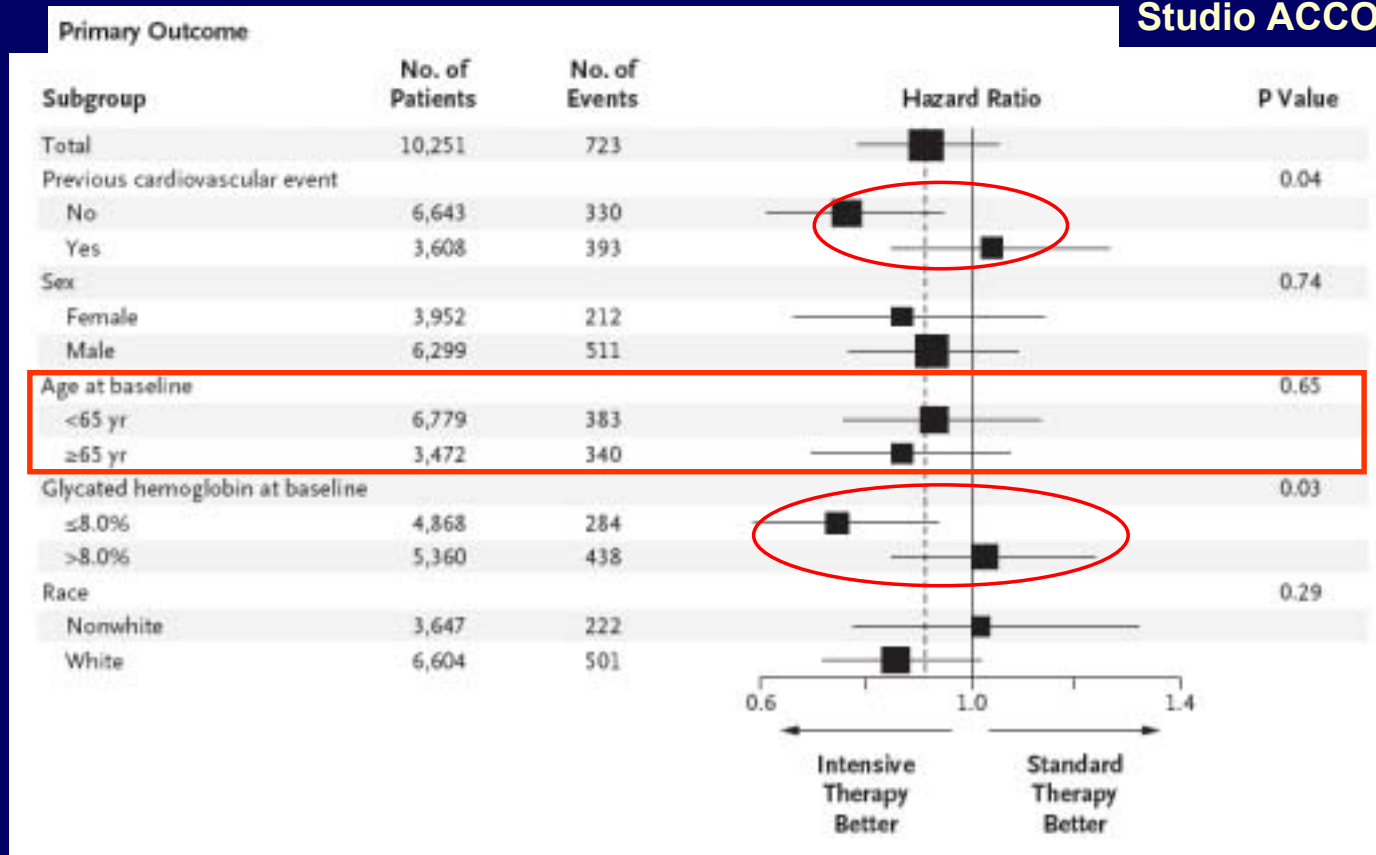


N. a rischio								
Terapia intensiva	5128	4972	4803	3250	1748	523	506	
Terapia standard	5123	4971	4700	3180	1642	499	480	



# Effetti del controllo intensivo in gruppi di pazienti pre-selezionati

Studio ACCORD



***“..Intensive blood glucose control may be better at protecting people who have lower cardiovascular risk and/or start off with better diabetes control”***

# Hypoglycemic efficacy of available oral agents for T2DM

Oral agent	HbA1c change
Metformin	1.62 (0.8-3.0)
Sulfonylureas	1.65 (0.9-2.5)
Glinides	1.30 (0.6-1.9)
Thiazolidinediones	1.3 (1.1-1.6)
Acarbose	0.8 (0.4-1.3)

# Metformin vs other OHAs

<i>Aggregate Endpoint</i>	<i>p</i>
<b>Any diabetes related endpoint</b>	<b>0.0034</b>
Diabetes related deaths	0.11
<b>All cause mortality</b>	<b>0.021</b>
Myocardial infarction	0.12
<b>Stroke</b>	<b>0.032</b>
Peripheral vascular disease	0.62
Microvascular	0.39

# Contraindications to metformin therapy

- **Reduced metformin clearance**
  - renal impairment (creatinine  $\geq 1.5$  mg/dl in men;  $\geq 1.4$  mg/dl in women)
- **Increased lactate production**
  - Respiratory insufficiency
  - Cardiovascular insufficiency
- **Reduced lactate uptake**
  - Liver failure
  - Alcoholism
- **Critical limb ischemia**
- **Severe acute illness**



# Il trattamento del diabete nell'anziano

## Quadro sinottico

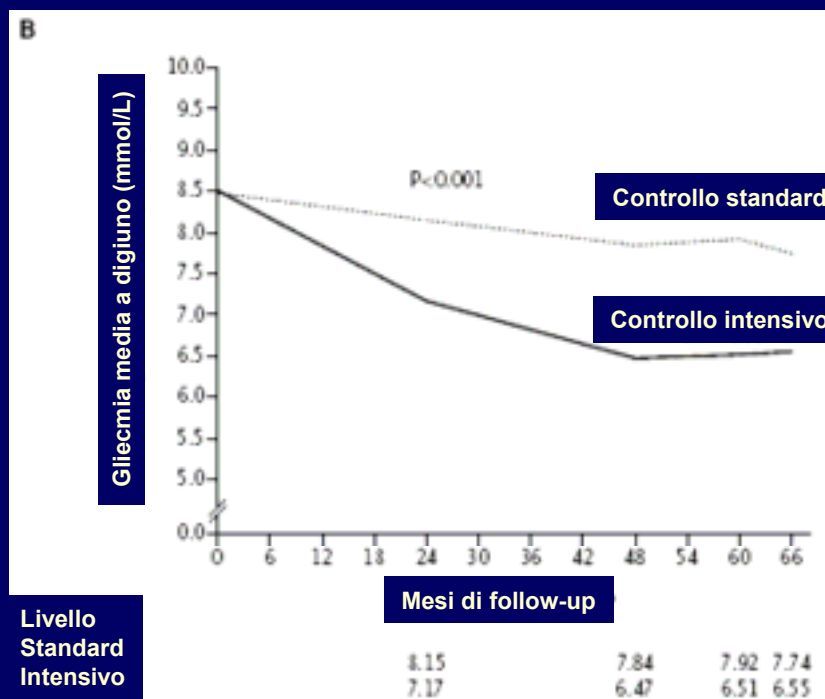
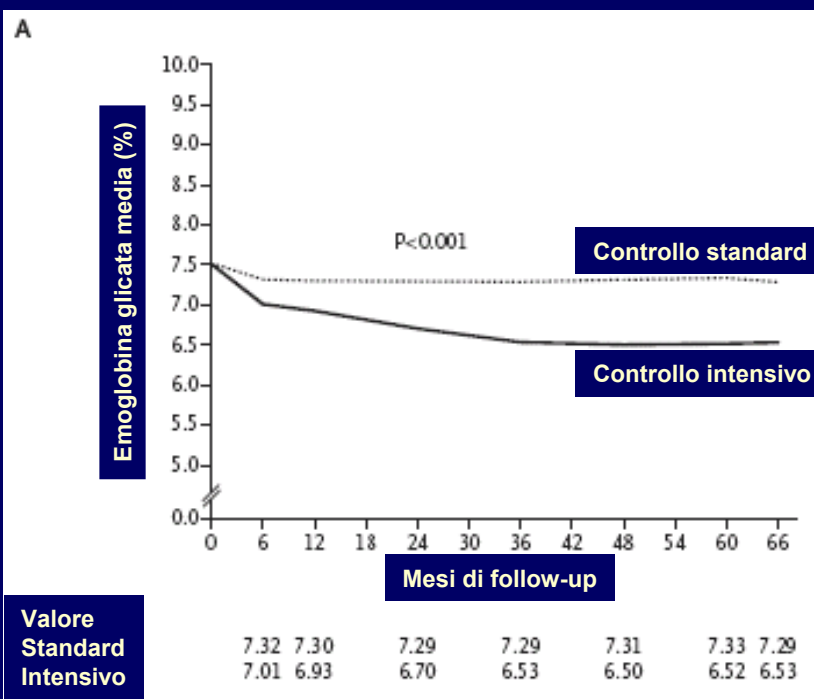
- La terapia va intrapresa solo quando la dieta, l'esercizio fisico e l'eliminazione di eventuali farmaci ad azione diabetogena non abbiano raggiunto gli obiettivi prefissati.
- È opportuno iniziare con sulfoniluree a piccolo dosaggio ed a breve emivita, tenendo presenti assorbimento, emivita e funzionalità renale.
  - Nessuna esitazione nel passaggio alla terapia insulinica nei casi in cui questa sia indicata.
  - Terapia insulinica in due o tre somministrazioni.
  - Trattamento tempestivo e intensivo delle patologie concomitanti o delle complicanze, specie l'ipertensione, con il ricorso anche a più farmaci.

# Controllo della glicemia al basale e durante il follow-up in base alla strategia impiegata

Studio ADVANCE

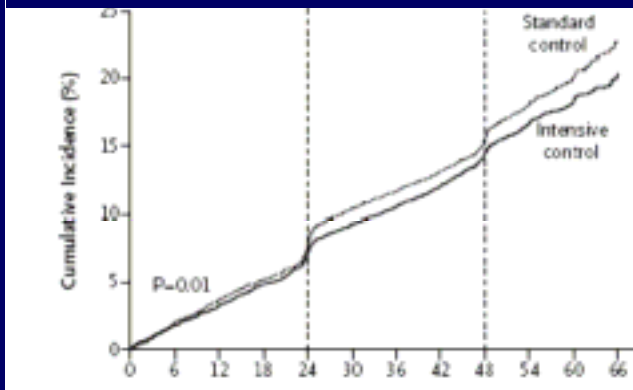
N=11140; età media= 66 anni

Valori considerati: emoglobina glicata media (A) e glicemia media a digiuno (B)

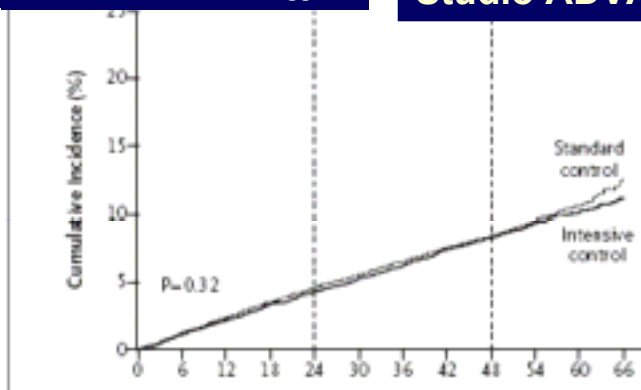


# Incidenza cumulativa di eventi in base alla strategia di controllo glicemico

Eventi macrovascolari e microvascolari maggiori combinati



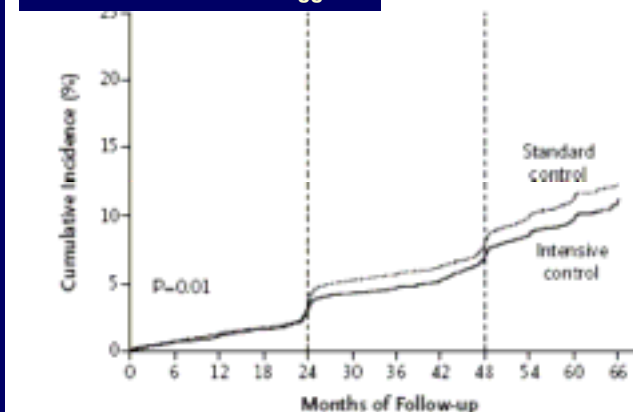
Eventi macrovascolari maggiori



Studio ADVANCE

Severe hypoglycemia was more common in the intensive-control group (2.7%, vs. 1.5%; hazard ratio, 1.86; 95% CI, 1.42 to 2.40;  $P < 0.001$ )

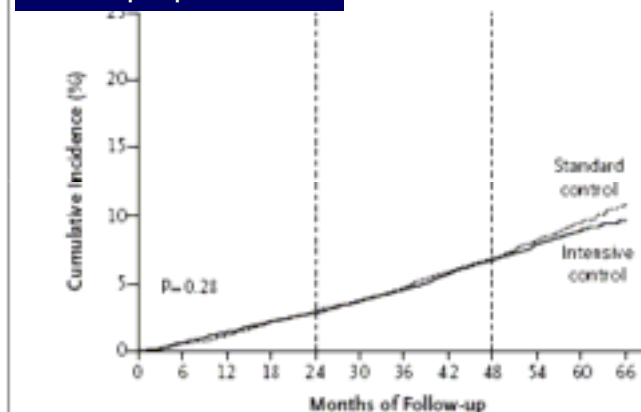
Eventi microvascolari maggiori



No. at Risk

Intensive	5571	5495	5430	5358	5233	5120	5055	4968	4824	4258	1992	473
Standard	5569	5498	5431	5353	5207	5069	4995	4911	4764	4204	2024	494

Decesso per qualsiasi causa



No. at Risk

Intensive	5571	5533	5490	5444	5411	5361	5312	5246	5189	4653	2211	523
Standard	5569	5537	5503	5445	5399	5354	5301	5237	5178	4643	2240	544

# **Reasons for increased rate of hypoglycemia in elderly diabetics**

- 1. Decrease in hepatic oxidative enzyme activity**
- 2. Age-related decline in renal function**
- 3. Less protective hormonal CR function**
- 4. Loss of symptom recognition (hypoglycemia unawareness)**
- 5. Inadequate education regarding signs and symptoms of hypoglycemia**



# Asse Incretine: siti per intervento terapeutico

Incretino-mimetici  
• Exenatide

Analoghi GLP-1  
• Liraglutide

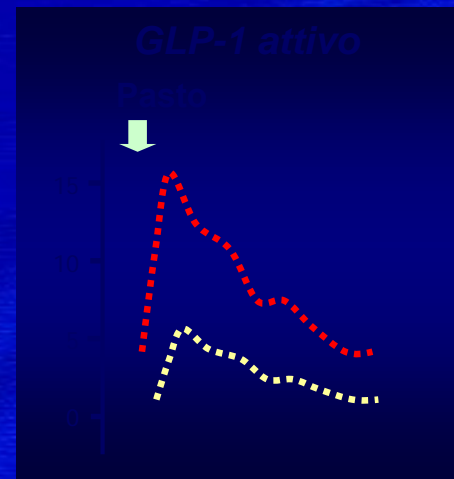
Inibitori DPP-4  
• Sitagliptin  
• Vildagliptin



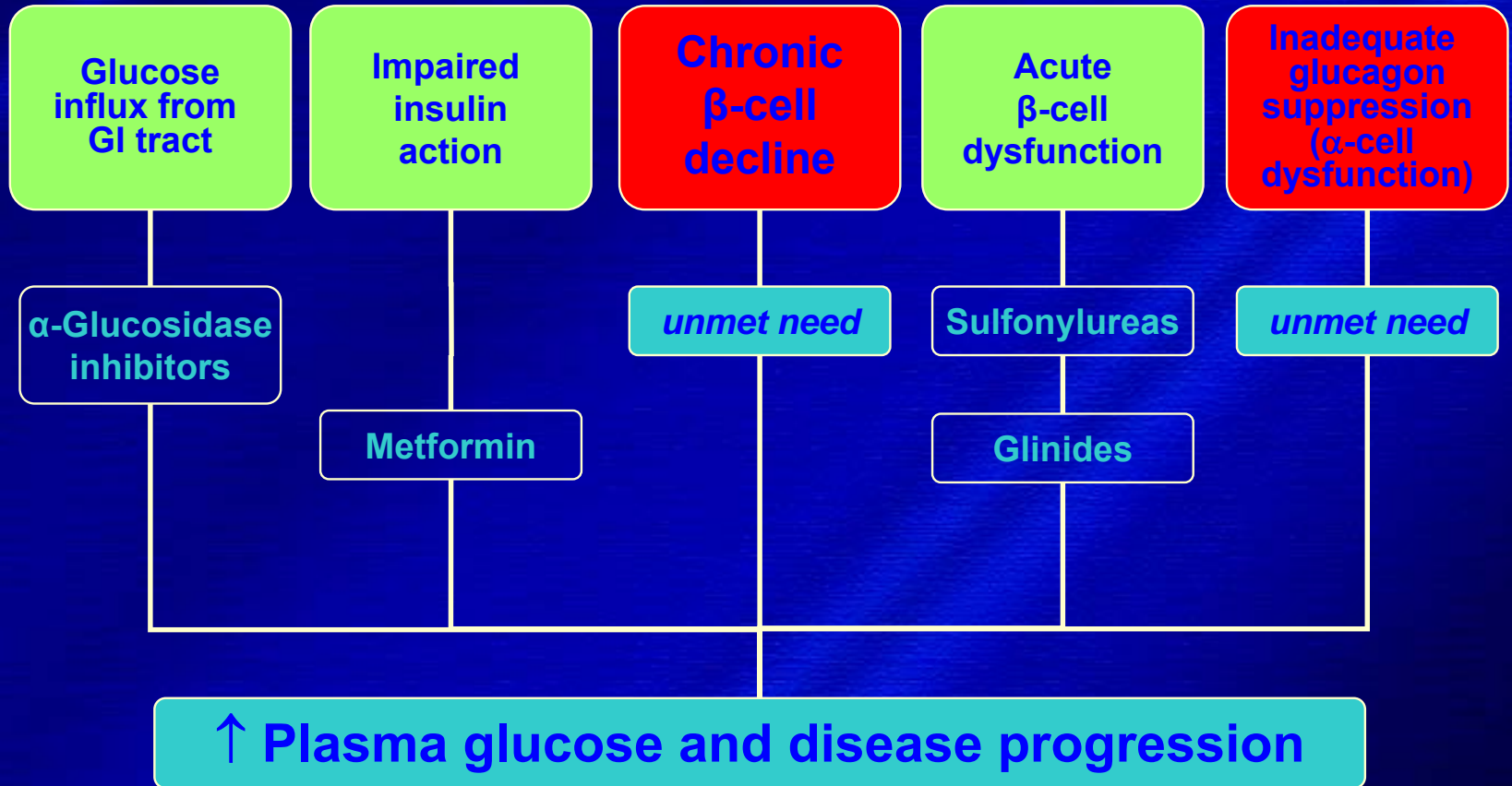
Incretine:  
• GLP-1 intatto  
• GIP intatto

DPP-4  
 $t_{1/2} \sim 1 \text{ min}$

GLP-1 inattivato  
GIP inattivato

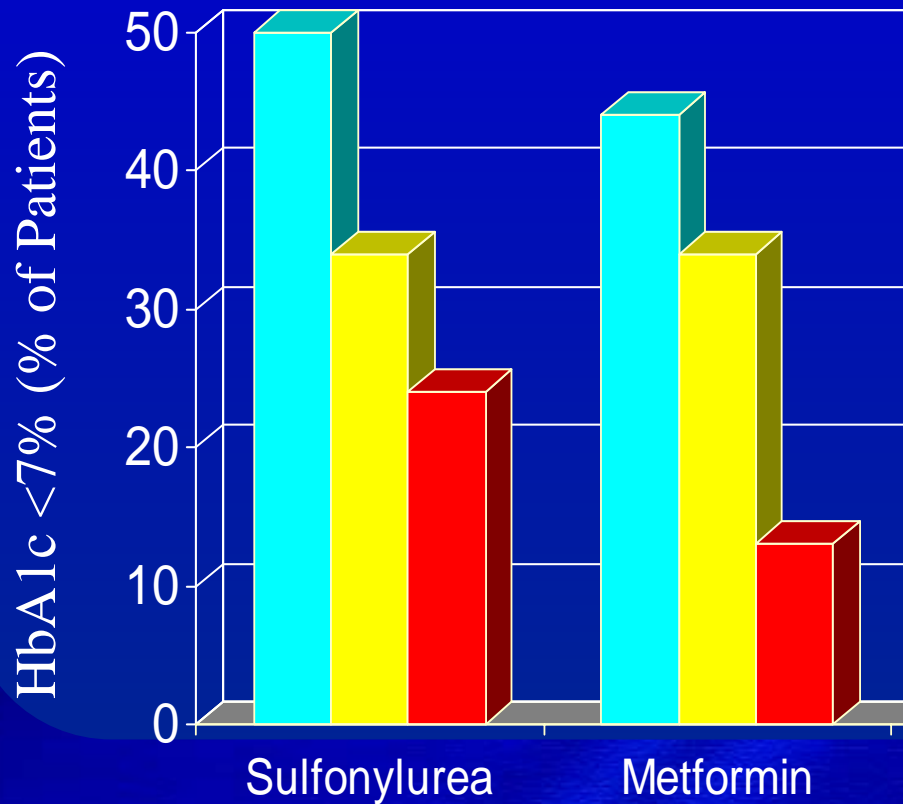


# Current Oral Therapies Do Not Address the Multiple Defects in Type 2 Diabetes



# Proportions of patients achieved control targets

■ 3 Years ■ 6 Years ■ 9 Years

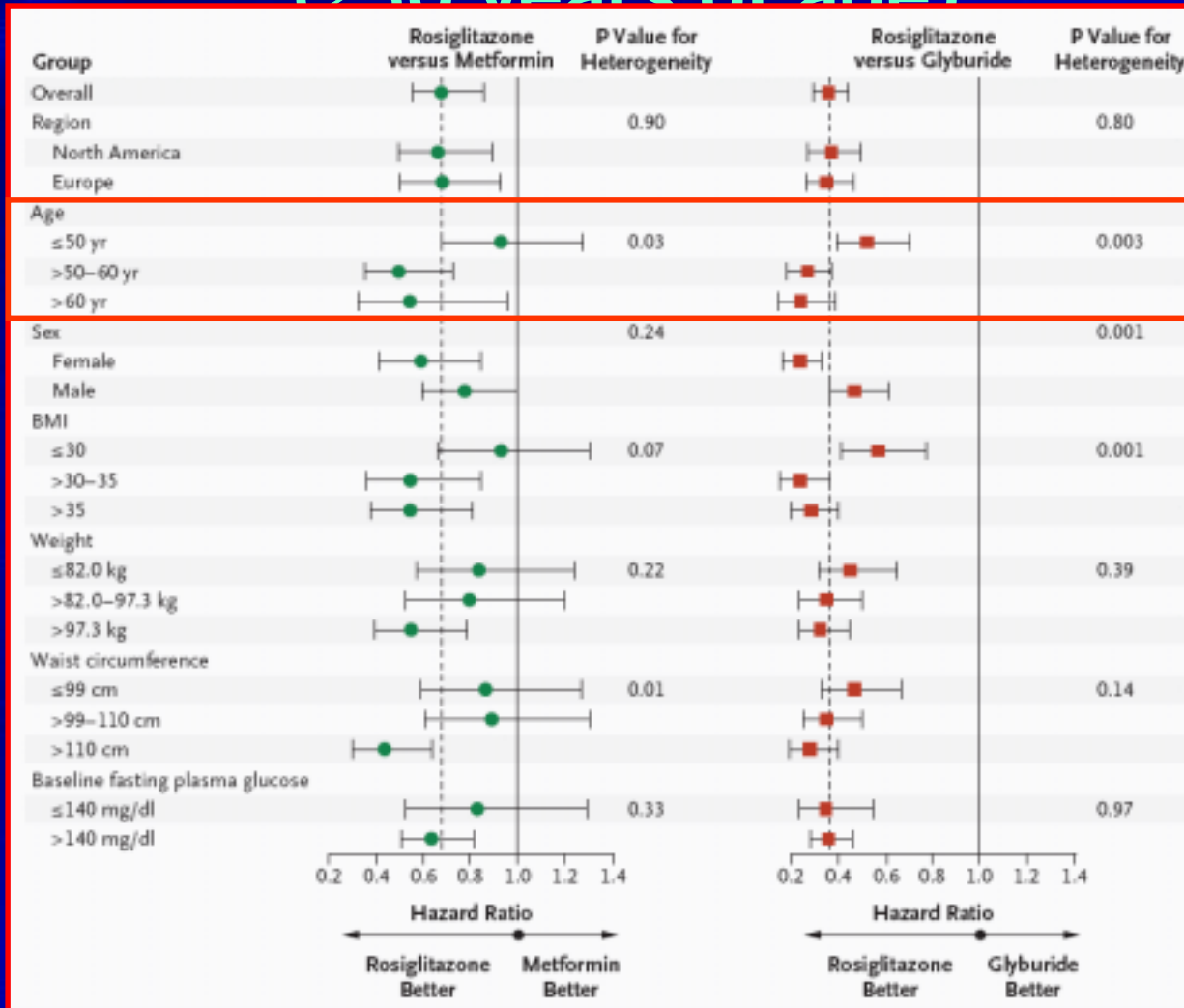


4 Years

ADOPT, *NEJM* 2006;355:2427-43

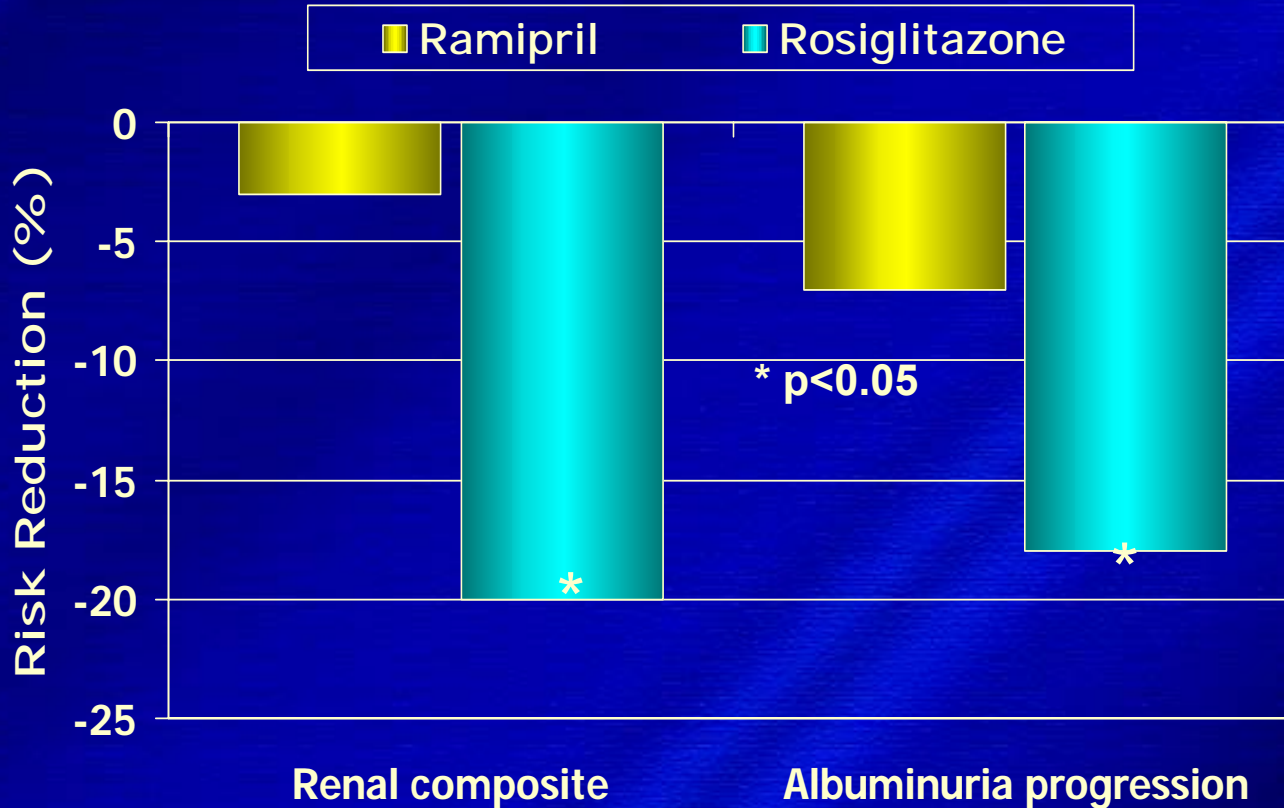
UKPDS, *JAMA* 1999;281:2005-12

# Effect was greater with rosiglitazone than with SU or metformin among older patients (>50 years of age)



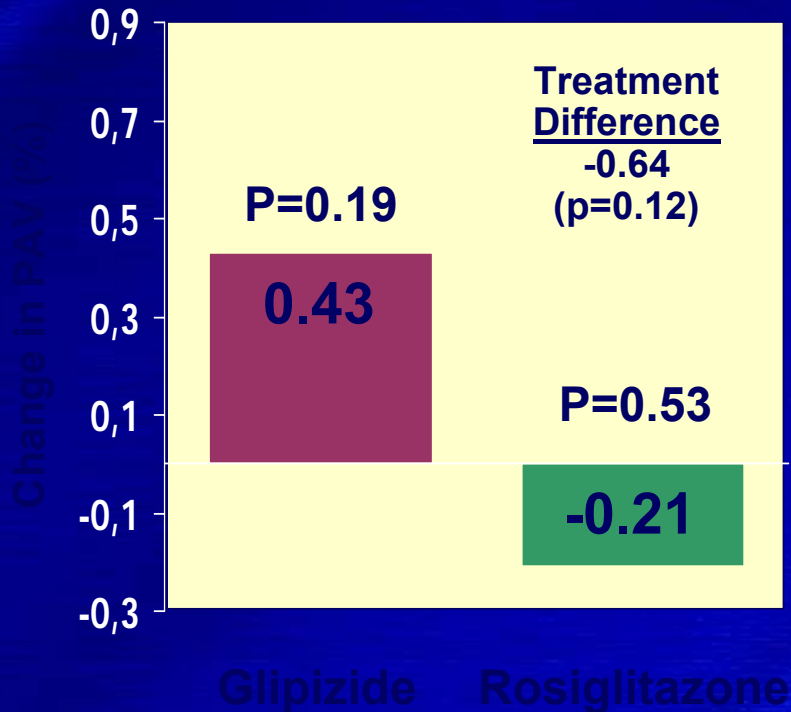


# Effects of rosiglitazone on renal outcomes in patients with IGT

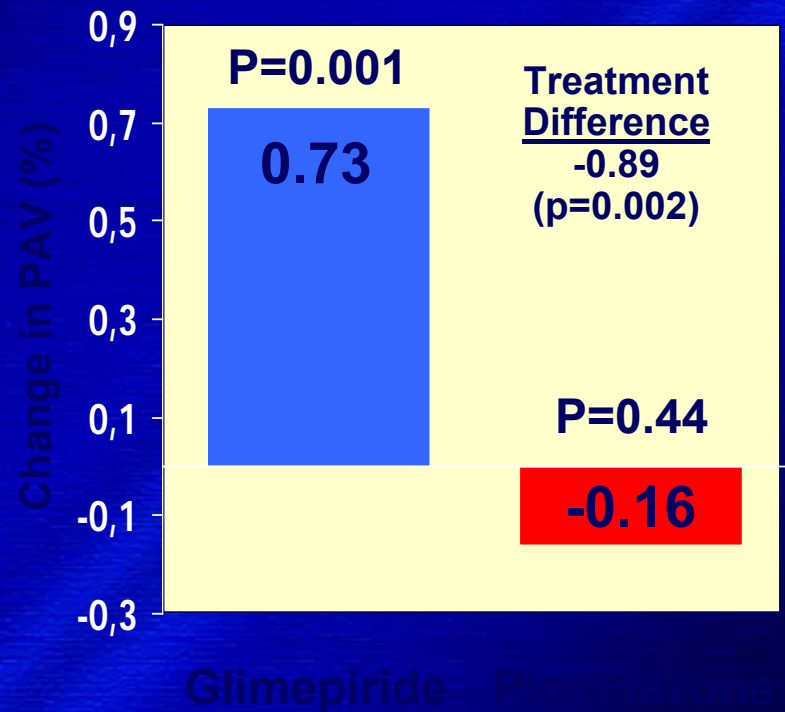


# Effect of rosiglitazone or pioglitazone on atherosclerosis

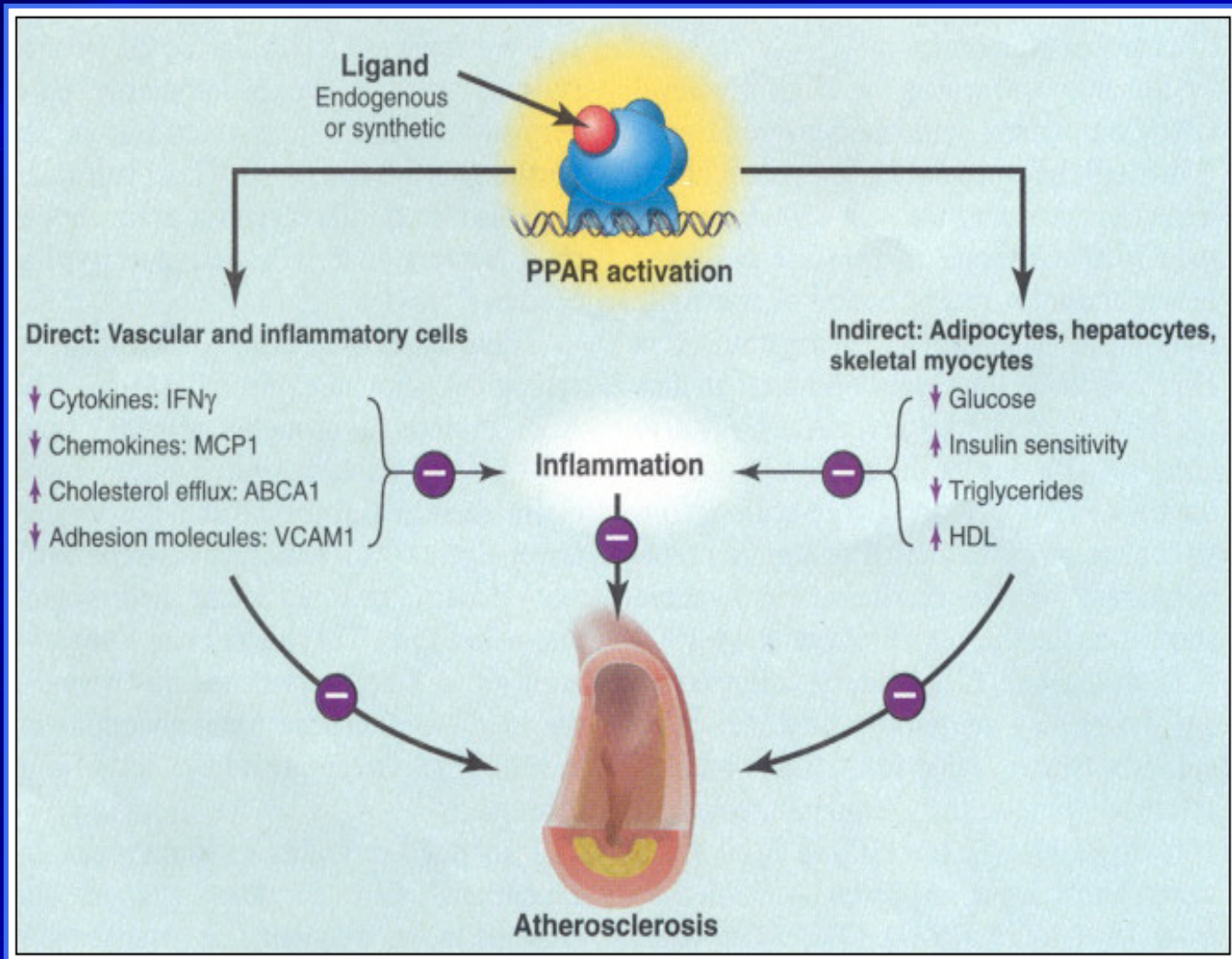
## APPROACH



## PERISCOPE



# Pleiotropic effects of TZDs

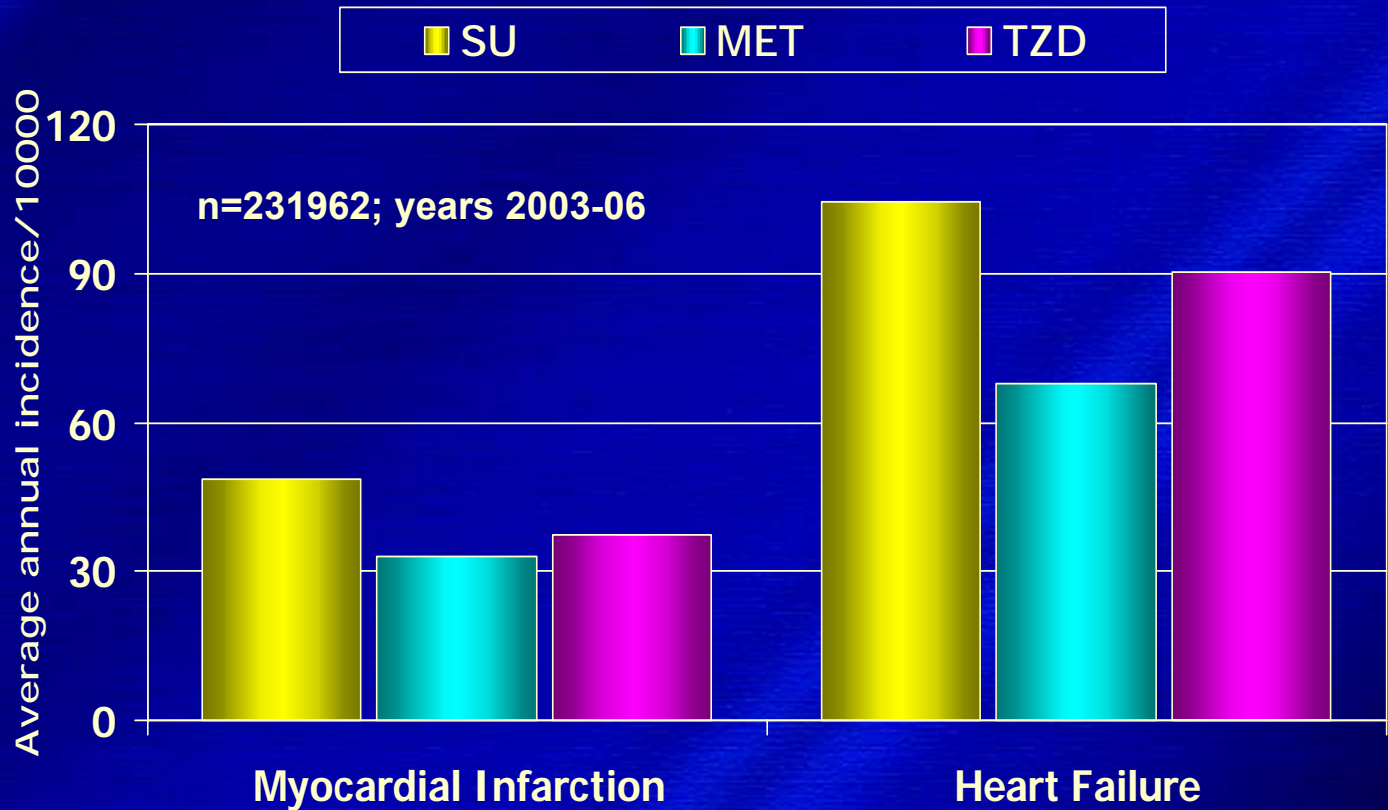


# Cardiovascular risk related to TZD therapy in T2DM

<b>Study</b>	<b>N°</b>	<b>CV event</b>	<b>OR (95% CI)</b>
Nissen and Wolski <i>NEJM 356:2457, 2007</i>	42 (27847)	AMI CV death	1.43* (1.03-1.98) 1.64 (0.98-2.74)
Home et al. <i>NEJM 357:28, 2007</i>	- (4447)	AMI CHF CV death	1.16 (0.75-1.81) <b>2.24* (1.27-3.97)</b> 0.97 (0.73-1.29)
Diamond et al. <i>Ann Int Med; 147:578, 2007</i>	42 (27847)	AMI CV death	1.26 (0.99-1.69) 1.17 (0.77-1.77)
Singh et al. <i>JAMA 298:1189, 2007</i>	4 (14291)	AMI CHF CV death	1.42* (1.06-1.91) <b>2.09* (1.52-2.88)</b> 0.90 (0.63-1.26)
Lincoff et al. <i>JAMA 298:1180, 2007</i>	19 (16390)	MACE CHF	0.82* (0.72-0.94) <b>1.41* (1.14-1.76)</b>
Lago et al. <i>Lancet 370:1129, 2007</i>	7 (20191)	CHF CV death	<b>1.72* (1.21-2.42)</b> 0.93 (0.67-1.29)



# CV outcomes (MI and HF) according to OHA in patients with type 2 diabetes

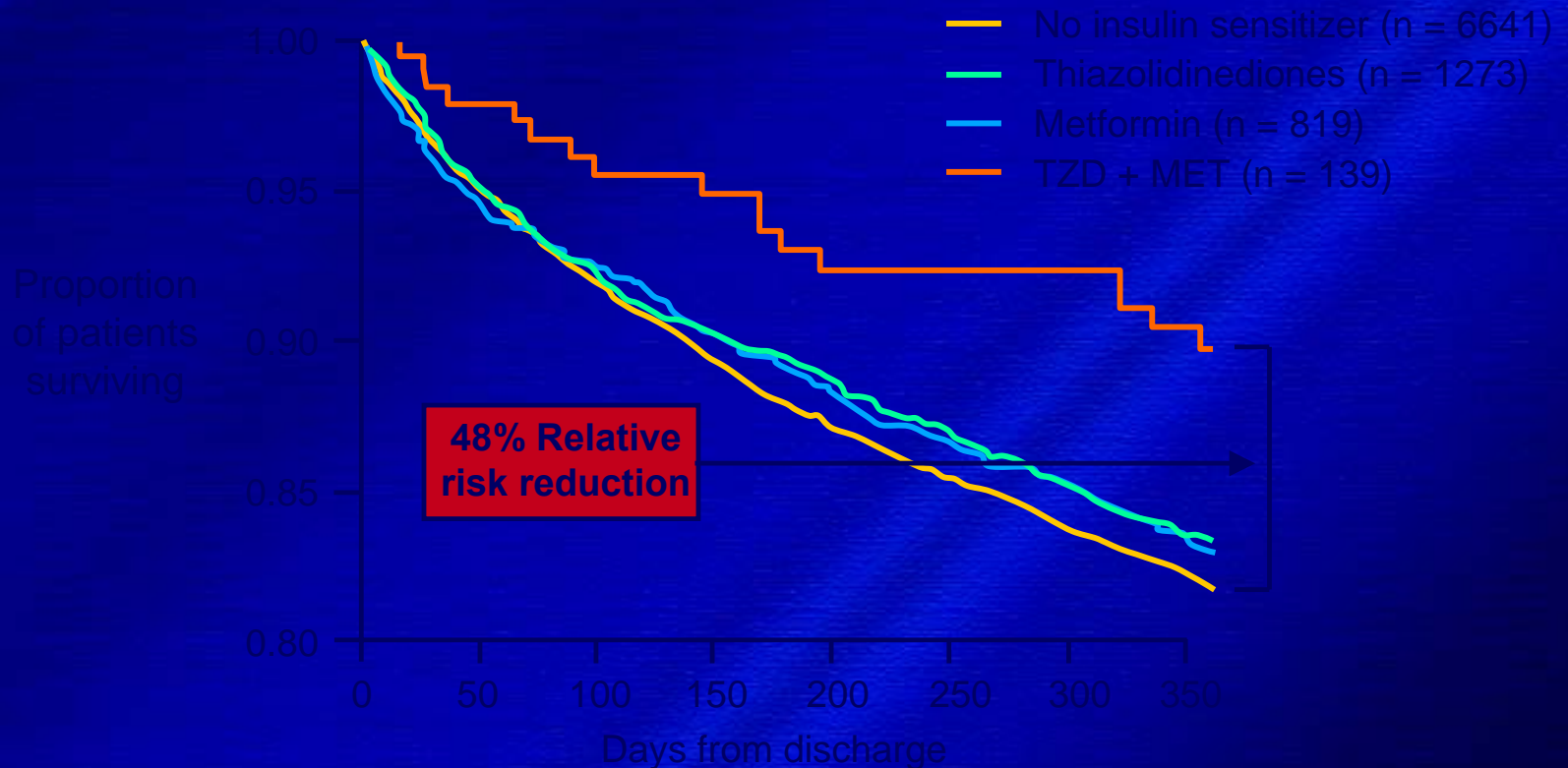




# Mortality after Acute Myocardial Infarction

National Heart Care Project

8872 acute MI patients, mean age 76.4 years, discharged on glucose-lowering medication



# Rosiglitazone and cardiovascular mortality in large RCT trials

In the **ACCORD** study [n=10251; mean age 62 yrs (35%  $\geq$ 65 anni)] extensive use of rosiglitazone (92% in the intensive and 52% in the standard group) did not explain increased mortality rates in the intensive group.

In the **VADT** study (n=1791; mean age 62 yrs) treatment with rosiglitazone in older adults did not lead to increased risk of cardiovascular outcomes.

# Primary aims for the care of the older adult with diabetes

1. Elimination of symptoms of uncontrolled hyperglycemia and avoiding treatment related hypoglycemia
2. Individualization of care, taking into account the patient's longevity, personalized glucose goals, financial resources, and life situation
3. Attention to nonglycemic risk factors that contribute to cardiovascular mortality, namely blood pressure, dyslipidemia, tobacco use, and physical inactivity

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**Grazie per  
la vostra attenzione**



Firenze, 27 novembre 2008