

**Caso clinico :  
Gestione personalizzata del paziente  
con diabete**

**La riduzione del rischio cardiovascolare  
principale obiettivo della terapia**

**Discussant :Prof. Ivana Zavaroni**

*Ferrara, 22 Novembre 2013*

# Diabete mellito di tipo 2

## Complicanze, mortalità e morbidità



Retinopatia

2° causa di cecità  
in Italia

30%



Nefropatia

1° causa di dialisi  
in Italia

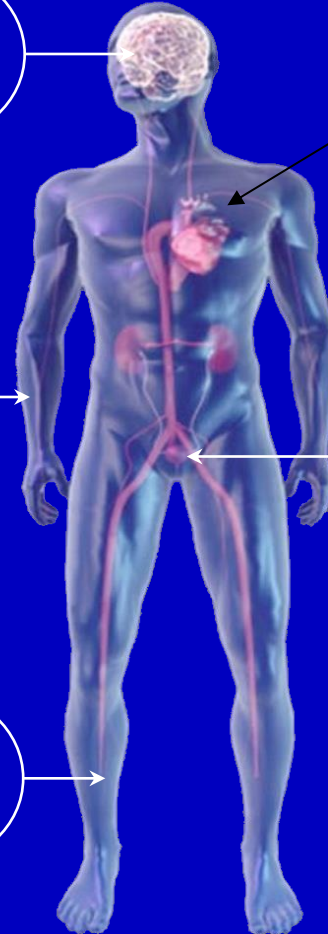
20%



Neuropatia

2° causa di  
amputazione degli  
arti inferiori in  
Italia

15%



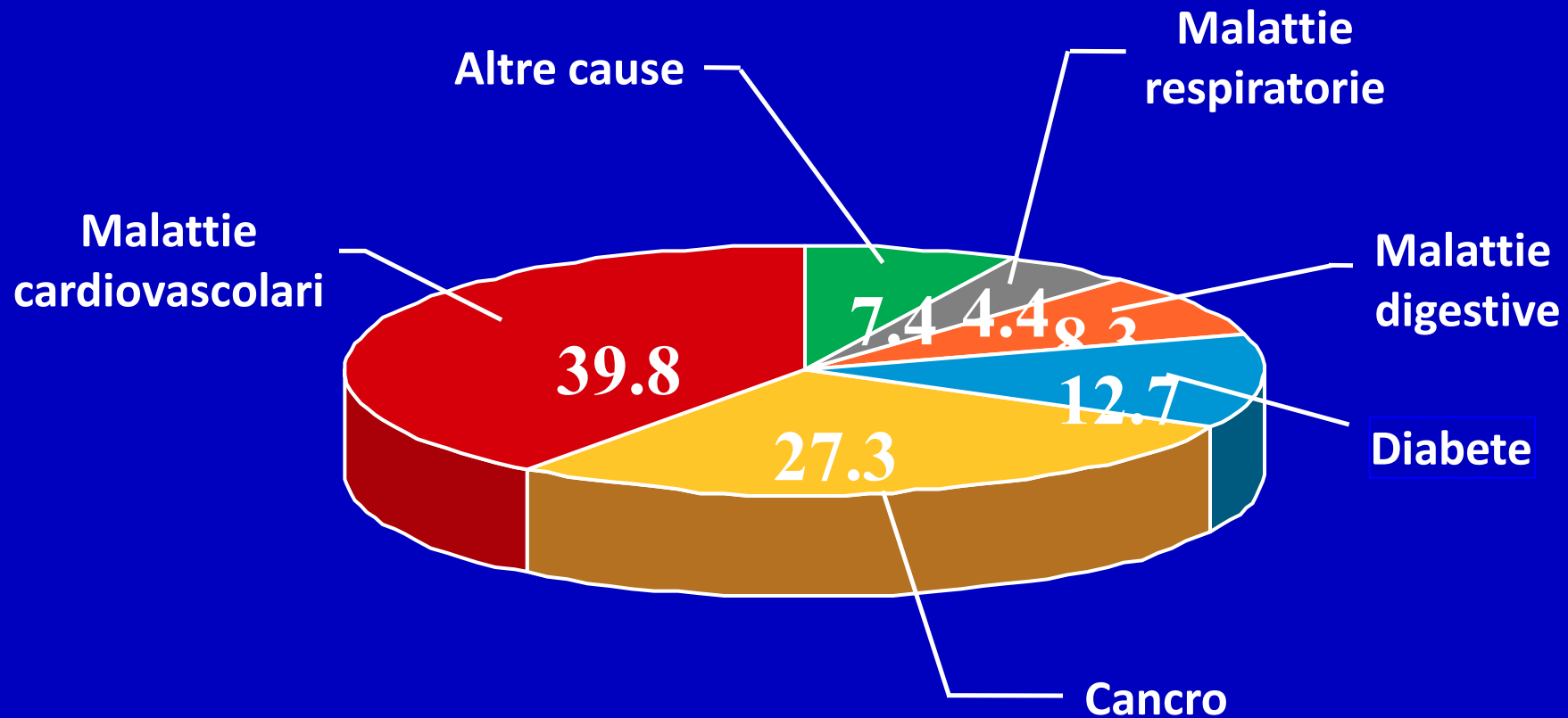
Circa il 75% dei pazienti  
con diabete mellito di  
tipo 2 ha un evento  
cardiovascolare

30%

Disfunzione  
Erettile

# CAUSE DI MORTE NEL DIABETE DI TIPO 2

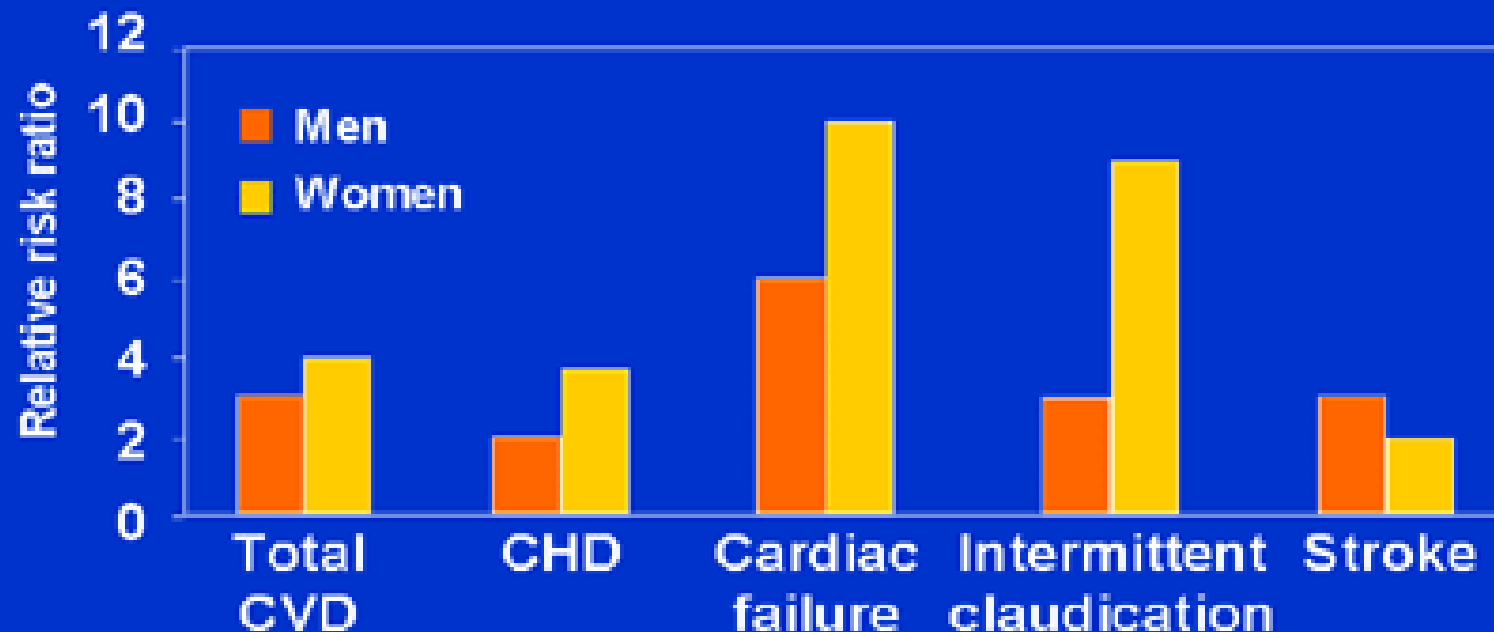
## The Verona Diabetes Study



N = 7148; follow-up = 10 aa (1986-1995)

# Framingham Heart Study 30-year follow-up

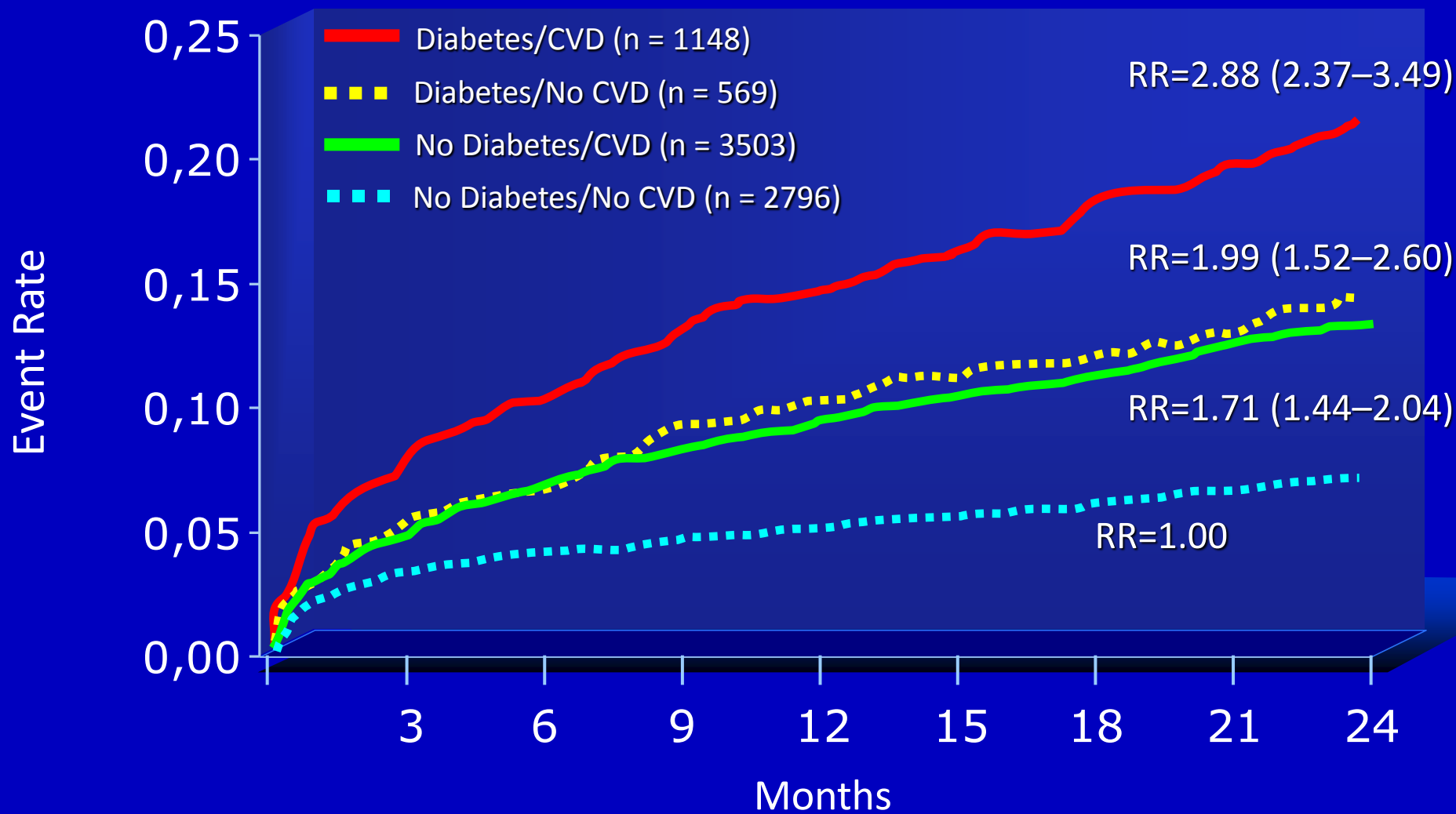
CVD events in patients with diabetes (ages 35–64)



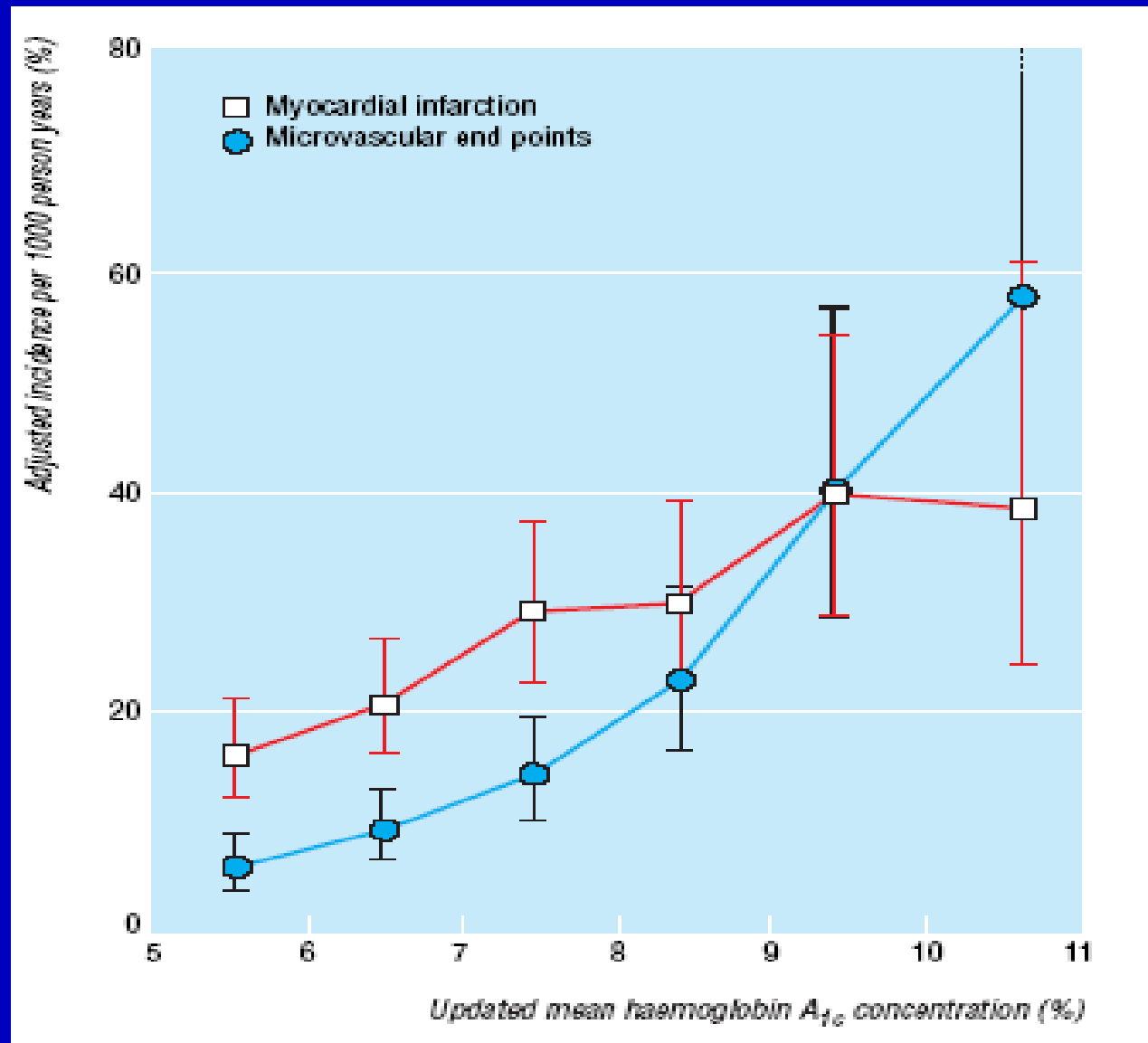
$P < 0.001$

Wilson PWF, Kannel WB. In: Hyperglycemia, Diabetes and Vascular Disease. Ruderman N, et al. eds. Oxford;1992.

# OASIS Study: Total Mortality



# L' emoglobina glicata è un fattore di rischio per IMA

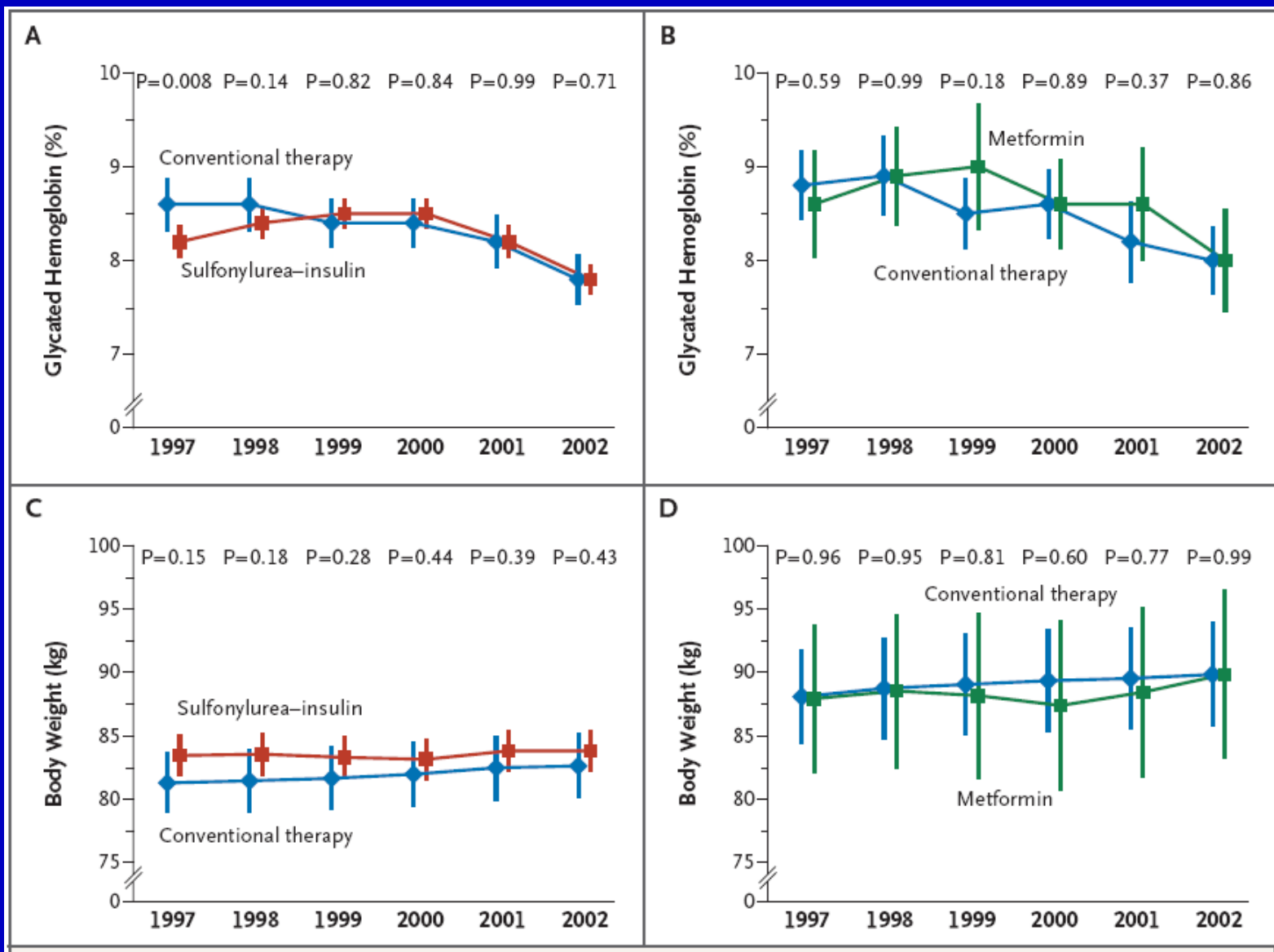


## STUDIO UKPDS

Trattamento ipoglicemizzante intensivo vs convenzionale

<b>END POINT CLINICO</b> a 10 anni	<b>RIDUZIONE DEL RISCHIO</b> <b>RELATIVO</b>	<b>p</b>
<b>Mortalità complessiva</b>	<b>6 %</b>	<b>0,44</b>
<b>Mortalità da cause connesse al diabete</b>	<b>10 %</b>	<b>0,34</b>
<b>Ogni evento connesso al diabete</b>	<b>12 %</b>	<b>0,029</b>
<b>Complicanze microvascolari</b>	<b>25 %</b>	<b>0,0099</b>
<b>Infarto miocardico</b>	<b>18 %</b>	<b>0,052</b>

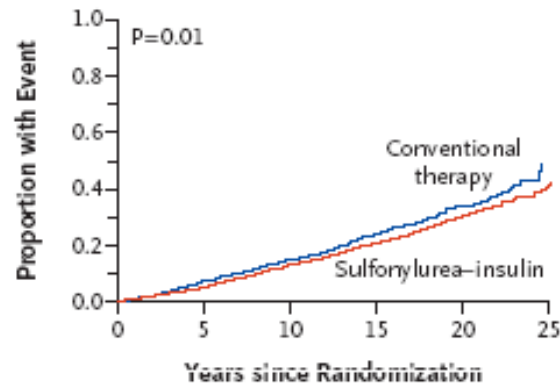
# UKPDS: risultati di follow-up a 10 anni





# UKPDS: risultati di follow-up a 10 anni

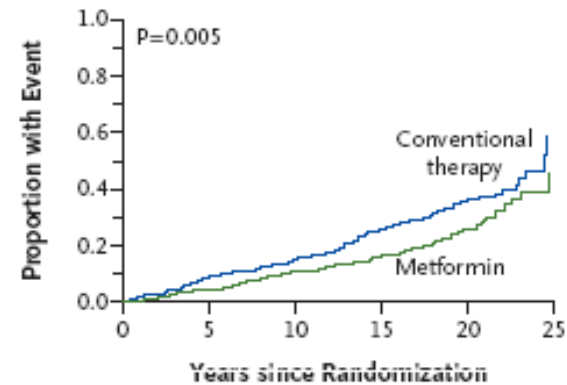
**C Myocardial Infarction**



**No. at Risk**

Conventional therapy	1138	1013	857	578	221	20
Sulfonylurea-insulin	2729	2488	2097	1459	577	66

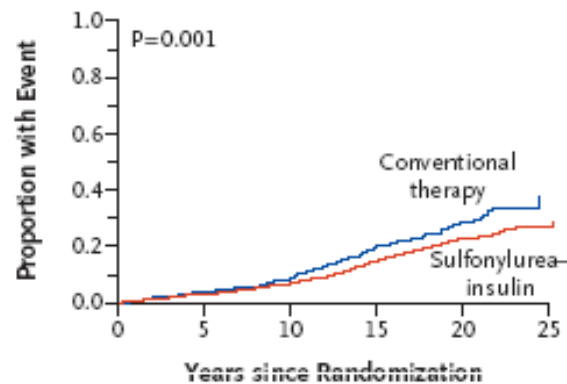
**D Myocardial Infarction**



**No. at Risk**

Conventional therapy	411	360	311	213	95	4
Metformin	342	317	274	214	106	16

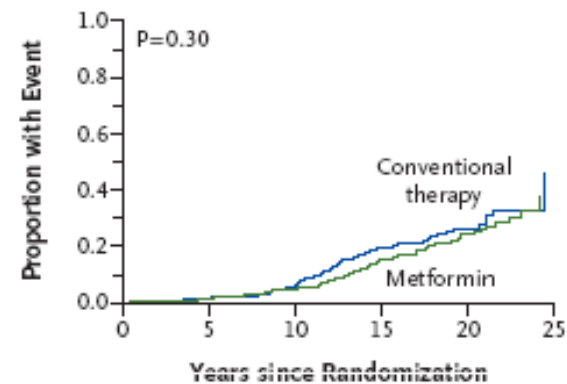
**E Microvascular Disease**



**No. at Risk**

Conventional therapy	1138	1018	844	508	172	13
Sulfonylurea-insulin	2729	2465	2076	1368	488	53

**F Microvascular Disease**



**No. at Risk**

Conventional therapy	411	377	316	186	72	2
Metformin	342	319	278	197	92	16

# Intervento glicemico intensivo

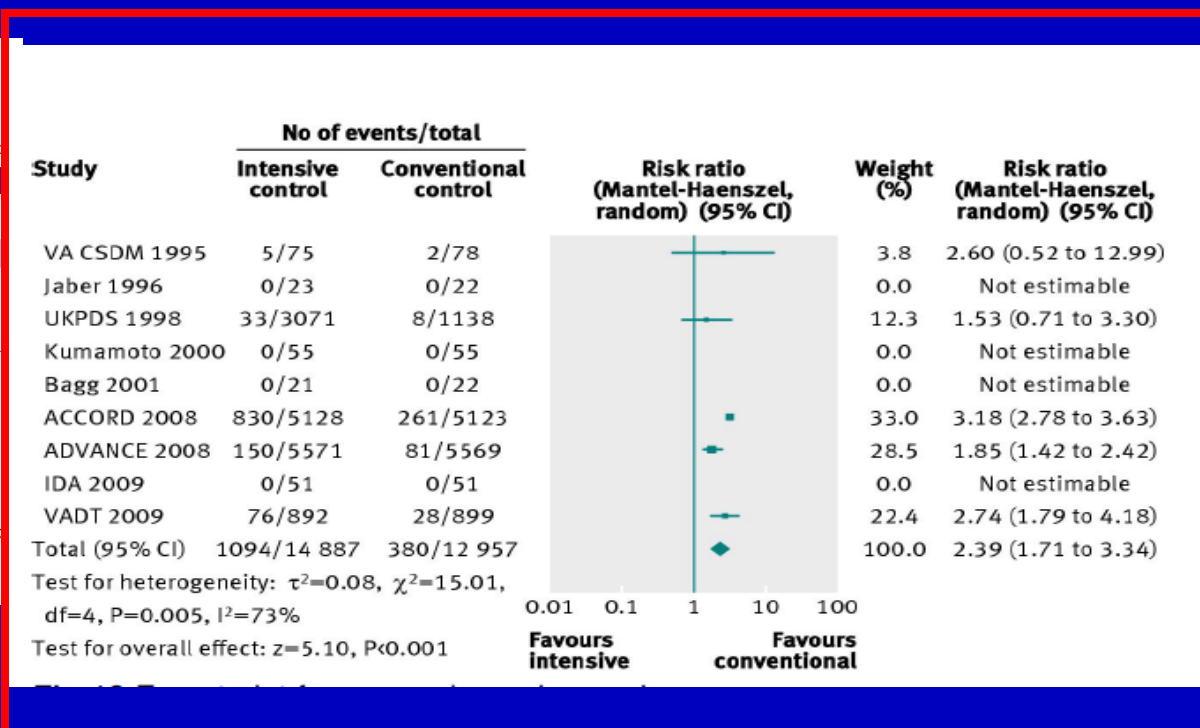
- L'inizio precoce dell'intervento glicemico intensivo si associa ad una significativa riduzione degli eventi cardiovascolari (e non solo della microangiopatia)
- L'effetto appare essere ritardato nell'insorgenza (al contrario di quanto accade per la microangiopatia) e persistente nel tempo
- L'effetto persiste anche se l'intervento diviene progressivamente meno efficace (memoria metabolica)

RESEARCH

**Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials**

OPEN ACCESS

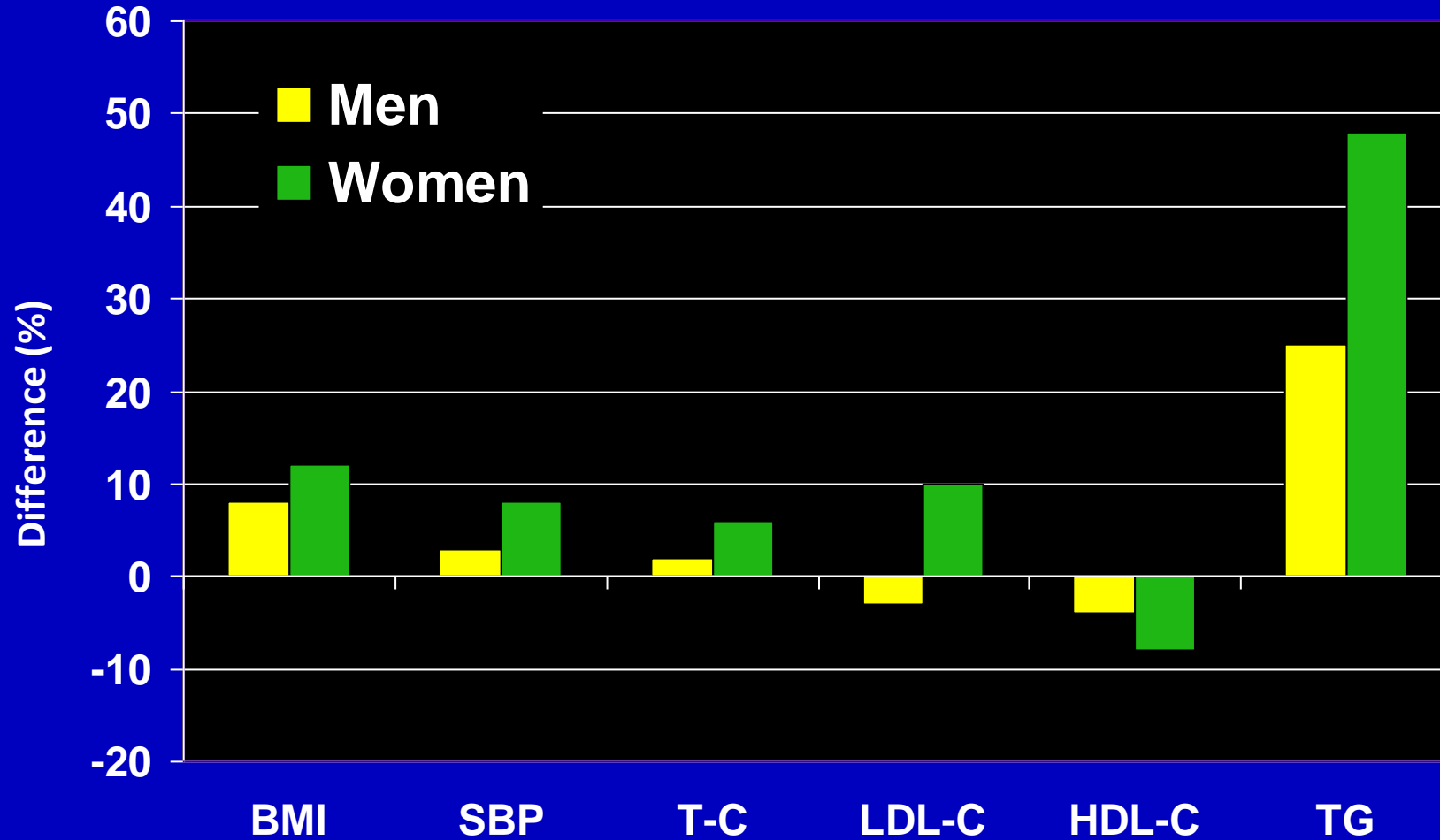
Bianca Hemmingsen *PhD student*<sup>1</sup>, Soren S Lund *physician*<sup>2</sup>, Christian Gluud *chief physician and head of department*<sup>1</sup>, Allan Vaag *professor*<sup>3</sup>, Thomas Almdal *chief physician and head of department*<sup>2</sup>, Christina Hemmingsen *research assistant*<sup>1</sup>, Jørn Wetterslev *chief physician*<sup>1</sup>



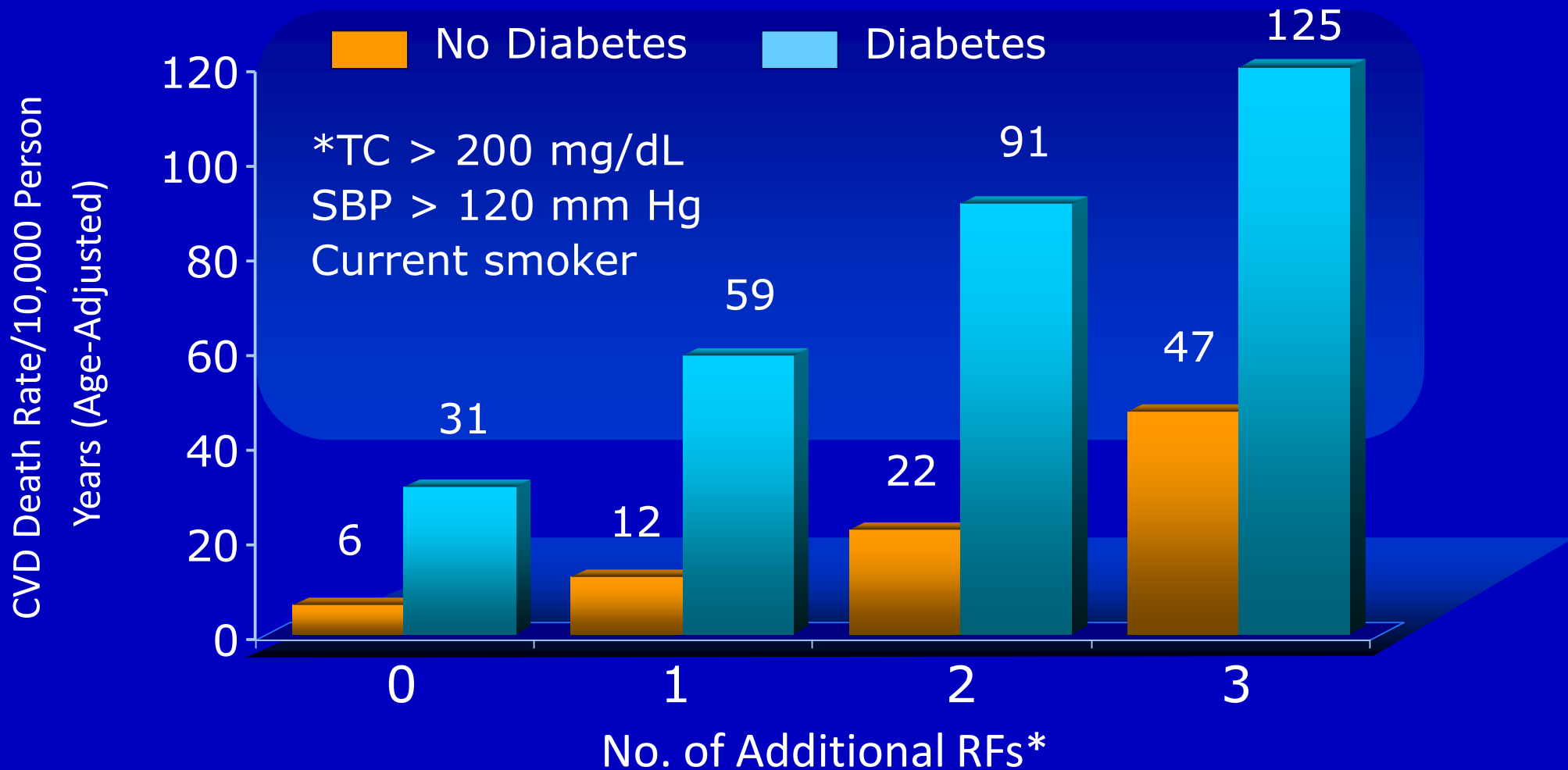
**Conclusion** Intensive glycaemic control does not seem to reduce all cause mortality in patients with type 2 diabetes. Data available from randomised clinical trials remain insufficient to prove or refute a relative risk reduction for cardiovascular mortality, non-fatal myocardial infarction, composite microvascular complications, or retinopathy at a magnitude of 10%. Intensive glycaemic control increases the relative risk of severe hypoglycaemia by 30%.

# **Rischio cardiovascolare multifattoriale nel paziente diabetico**

# Level of Established Risk Factors of CHD in Type 2 Diabetic Compared with Non-Diabetic Populations



# MRFIT: Diabetes Amplifies Risk from Other Risk Factors



# Stepwise Selection of Risk Factors\* in 2693 White Patients with Type 2 Diabetes with Dependent Variable as Time to First Event: *UKPDS*

Coronary Artery Disease (n=280)

Position in Model	Variable	P Value
First	Low-Density Lipoprotein Cholesterol	<0.0001
Second	High-Density Lipoprotein Cholesterol	0.0001
Third	Hemoglobin A <sub>1c</sub>	0.0022
Fourth	Systolic Blood Pressure	0.0065
Fifth	Smoking	0.056

\*Adjusted for age and sex.

Turner RC et al. *BMJ* 1998;316:823-828.

**L'intervento sui singoli fattori di rischio  
cardiovascolare nei pazienti con  
diabete è efficace**



**Trattare il colesterolo LDL nei diabetici  
previene efficacemente gli eventi  
cardiovascolari**

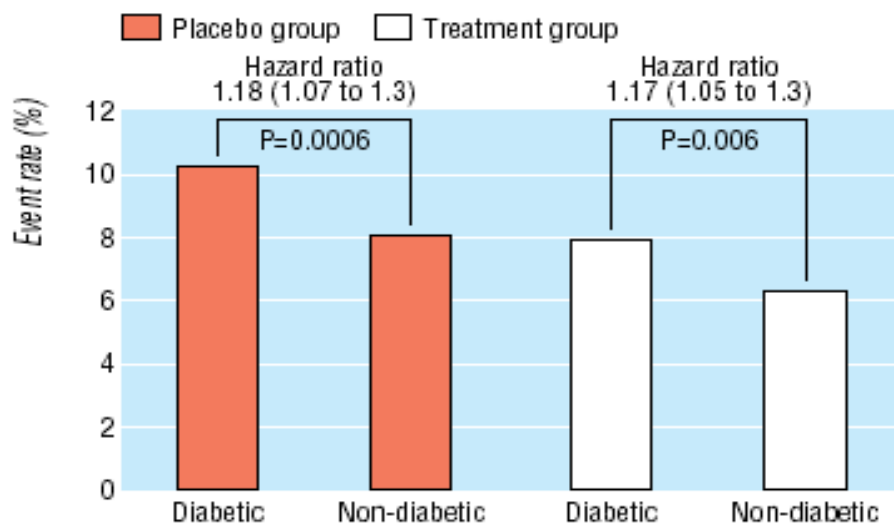
# Meta-analisi di trials con utilizzo di statine nei pazienti diabetici

Trial	Type of prevention	Patients	Drug	No	Mean (range) age	Women (%)	DM (%)	Mean baseline total-C (mmol/l)	Mean follow-up (years)	Primary outcome	Quality appraisal (Jadad scale)
AFCAPS/ TexCAPS <sup>20</sup>	Primary	22% HT; 13% smoking; 35% low HDL-C	Lovastatin 20 mg/day, titrated to 40 mg/day if LDL-C >2.84 mmol/l	6 605	58 (45-73)	15	2.3	5.7	5.2	Fatal or non-fatal MI, unstable angina, or sudden cardiac death	5
ALLHAT-LLA <sup>21</sup>	Primary	HT plus one other CHD risk factor; 13% had CHD	Pravastatin 40 mg/day v usual care rather than placebo	10 355	66 (55-?) (55% ≥65)	49	35	5.8	4.8	All cause mortality	3
HHS <sup>22</sup>	Primary	Primary dyslipidaemia (non-HDL-C >5.2 mmol/l)	Gemfibrozil 600 mg twice a day	4 081	47 (40-55)	0	3.3	6.3*	5.0	CHD death or MI (fatal or non-fatal)	5
ASCOT-LLA <sup>23</sup>	Primary	HT plus three other cardiovascular risk factors	Atorvastatin 10 mg/day	10 305	63 (40-79)	19	24.6	5.5	3.3**	CHD death or non-fatal MI	5
HPS <sup>11,24</sup>	Primary and secondary	65% CHD; 35% CVD, PAD, or DM	Simvastatin 40 mg/day	20 536	64 (40-80)	25	29	5.9	5.0	All cause mortality	5
PROSPER <sup>25</sup>	Primary and secondary	44% vascular disease (CHD, CVD, PAD); 56% HT, DM, or smoking	Pravastatin 40 mg/day	5 804	75 (70-82)	52	10.7	5.7	3.2	CHD death or non-fatal MI or stroke (fatal and non-fatal)	5
4S <sup>26,28</sup>	Secondary	MI (80%) or angina pectoris	Simvastatin 20 mg/day, titrated to 40 mg/day if total cholesterol >5.17 mmol/l	4 444	59 (35-70)	19	10.8	6.8	5.4**	All cause mortality	5
CARE <sup>29,30</sup>	Secondary	MI	Pravastatin 40 mg/day; cholestyramine added if LDL-C >4.53 mmol/l	4 159	59 (21-75)	14	14.1	5.4	5.0**	CHD death or non-fatal MI	4
LIPID <sup>31,32</sup>	Secondary	MI (64%) or unstable angina	Pravastatin 40 mg/day	9 014	62 (31-75)	17	12.1	5.6	6.1	CHD death	5
LIPS <sup>33</sup>	Secondary	Successful PCI	Fluvastatin 40 mg twice a day	1 677	60 (18-80)	16	12	5.2	3.9**	CHD death, non-fatal MI, or reintervention procedure	5
Post-CABC <sup>34,35</sup>	Secondary	Coronary bypass grafts; 49% had MI	LDL-C goal of 1.55-2.20 mmol/l v 3.36-3.62 mmol/l using lovastatin	1 351	62 (21-74)	7.8	8.6	5.9	4.3	Angiographic outcomes	3
VA-HIT <sup>36,37</sup>	Secondary	MI (61%), angina, coronary revascularisation, or angiographic stenosis >50%	Gemfibrozil 600 mg twice a day	2 531	64 (?-74) (77% >60)	0	30	4.5	5.1**	CHD death or non-fatal MI	5

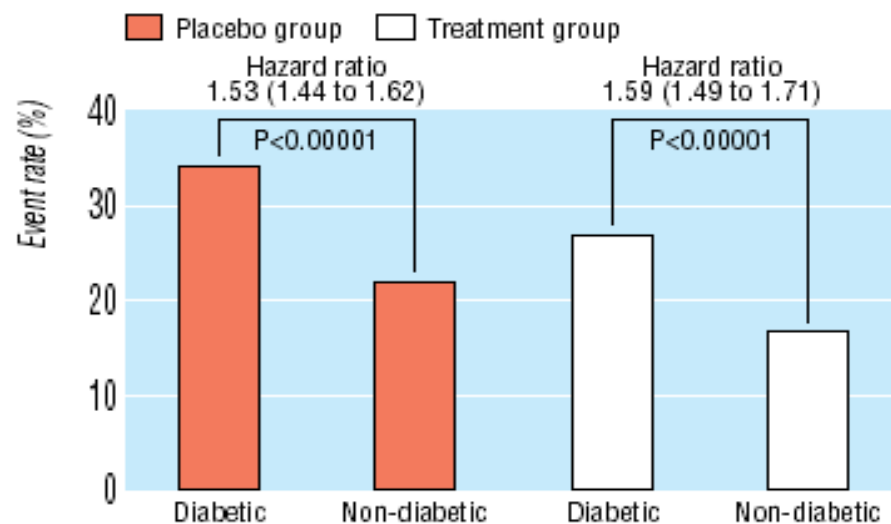
CHD=coronary heart disease; CVD=cerebrovascular disease; DM=diabetes mellitus; HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; total-C=total cholesterol  
MI=myocardial infarction; HT=hypertension; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention.  
\*Non-HDL-C (total cholesterol minus LDL cholesterol).  
\*\*Median.

# Meta-analisi di trials con utilizzo di statine nei pazienti diabetici

## Prevenzione primaria

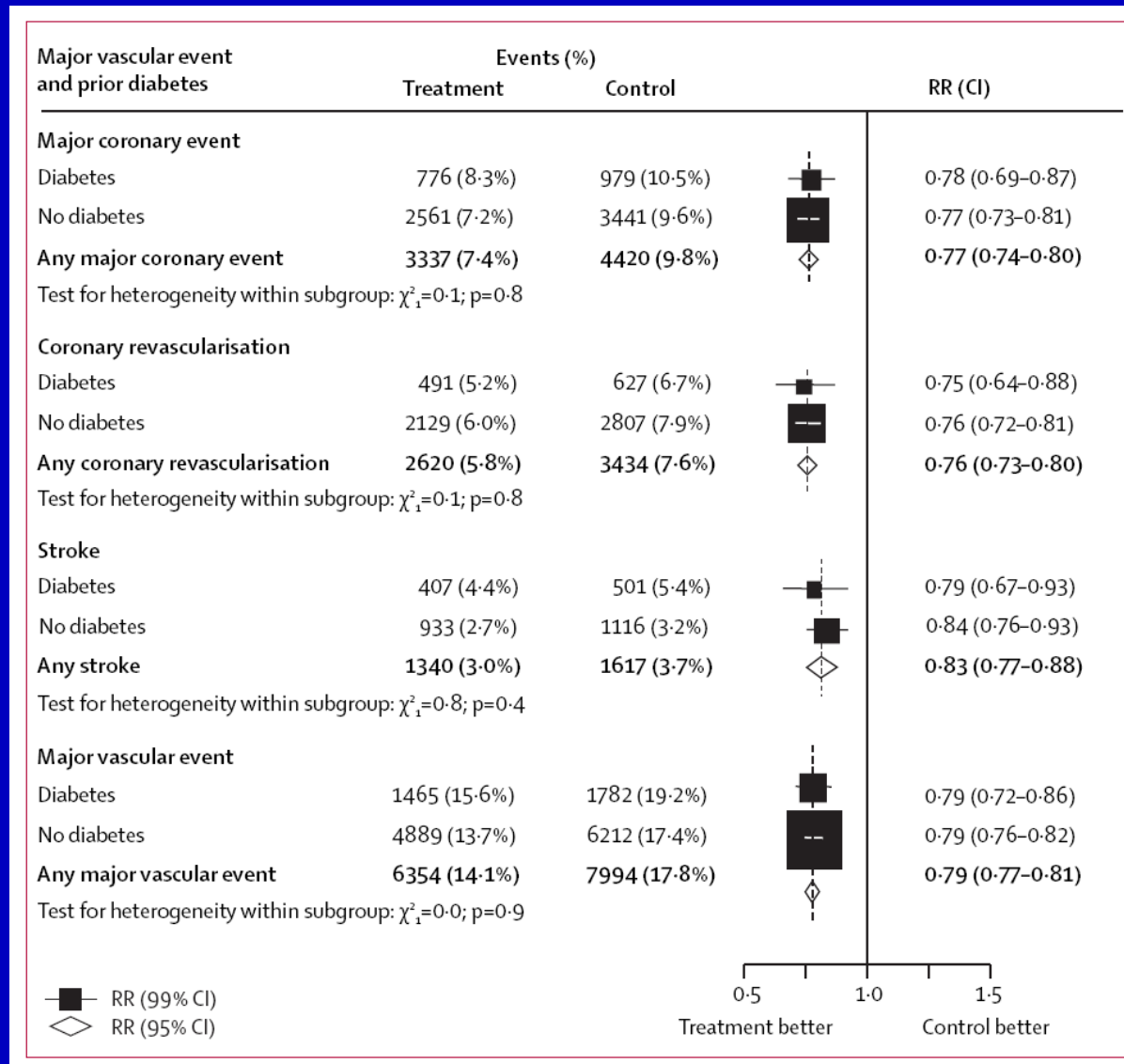


## Prevenzione secondaria



Follow-up medio : 5 anni

# Riduzione proporzionale degli eventi per mmol/L di riduzione di LDL colesterolo nei pazienti diabetici



# Standard di Cura del Diabete Mellito in Italia

## - Confronto tra linee guida internazionali -

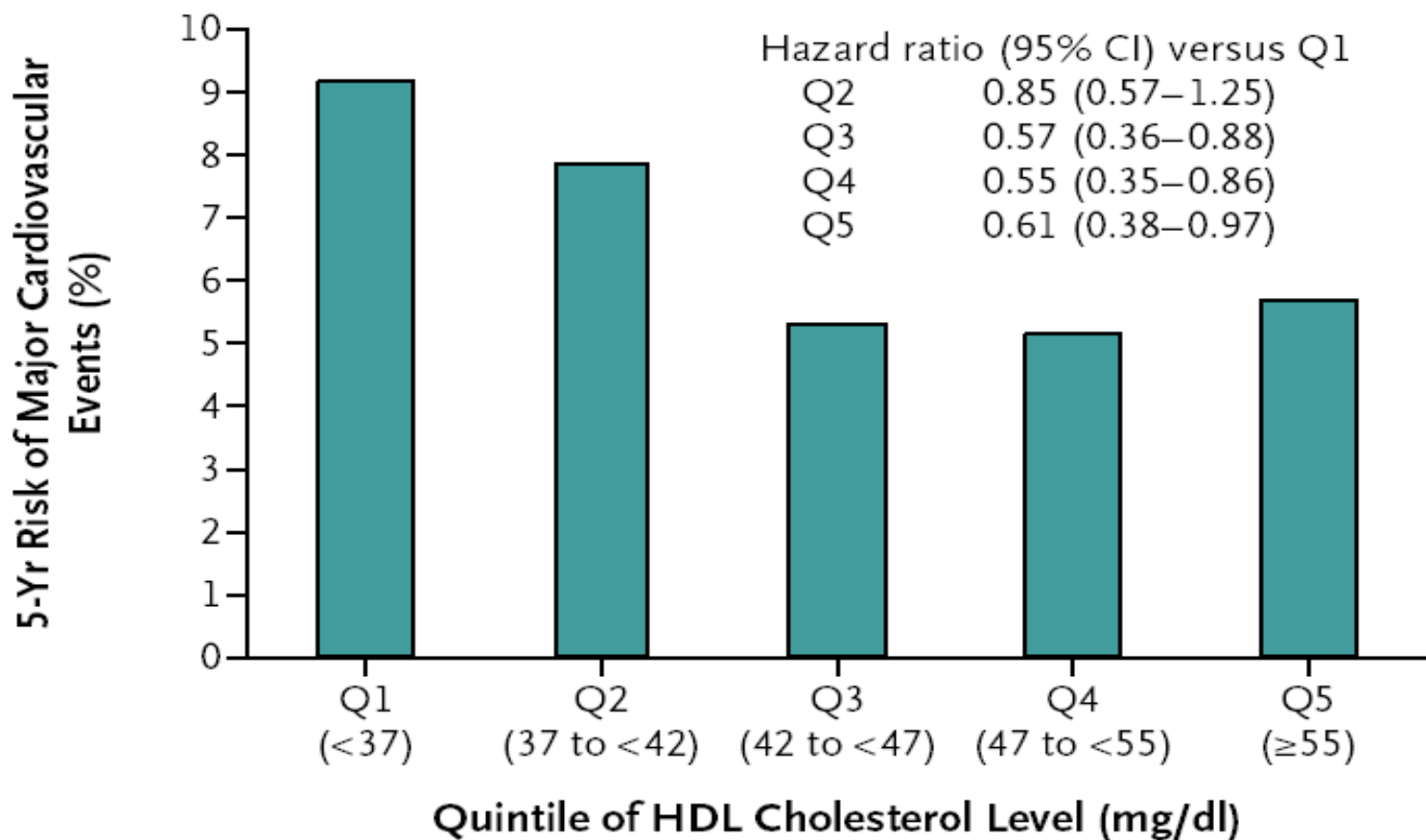
### Obiettivi terapeutici suggeriti

	AMERICAN DIABETES ASSOCIATION	THIRD JOINT TASK FORCE EUROPEA	EASD/ESC GUIDELINES 2007
Colesterolo	<i>normale</i>	<175 mg/dl	<175 mg/dl
Colesterolo LDL	<100 mg/dl In soggetti a rischio particolarmente elevato <70 mg	<100 mg/dl	<97 mg/dl <70 mg/dl in prevenzione secondaria
Colesterolo HDL	>40 mg/dl nel maschio >50 mg/dl nella femmina	>40 mg/dl	>40 mg/dl nel maschio >46 mg/dl nella femmina
Trigliceridi	<150 mg/dl	<150 mg/dl	<150 mg/dl

**Raggiungere il target di LDL  
colesterolo può non essere  
sufficiente:  
il problema del “rischio residuo”**

# Ruolo del colesterolo HDL in pazienti con LDL < 70 mg/dL (studio TNT)

**B**

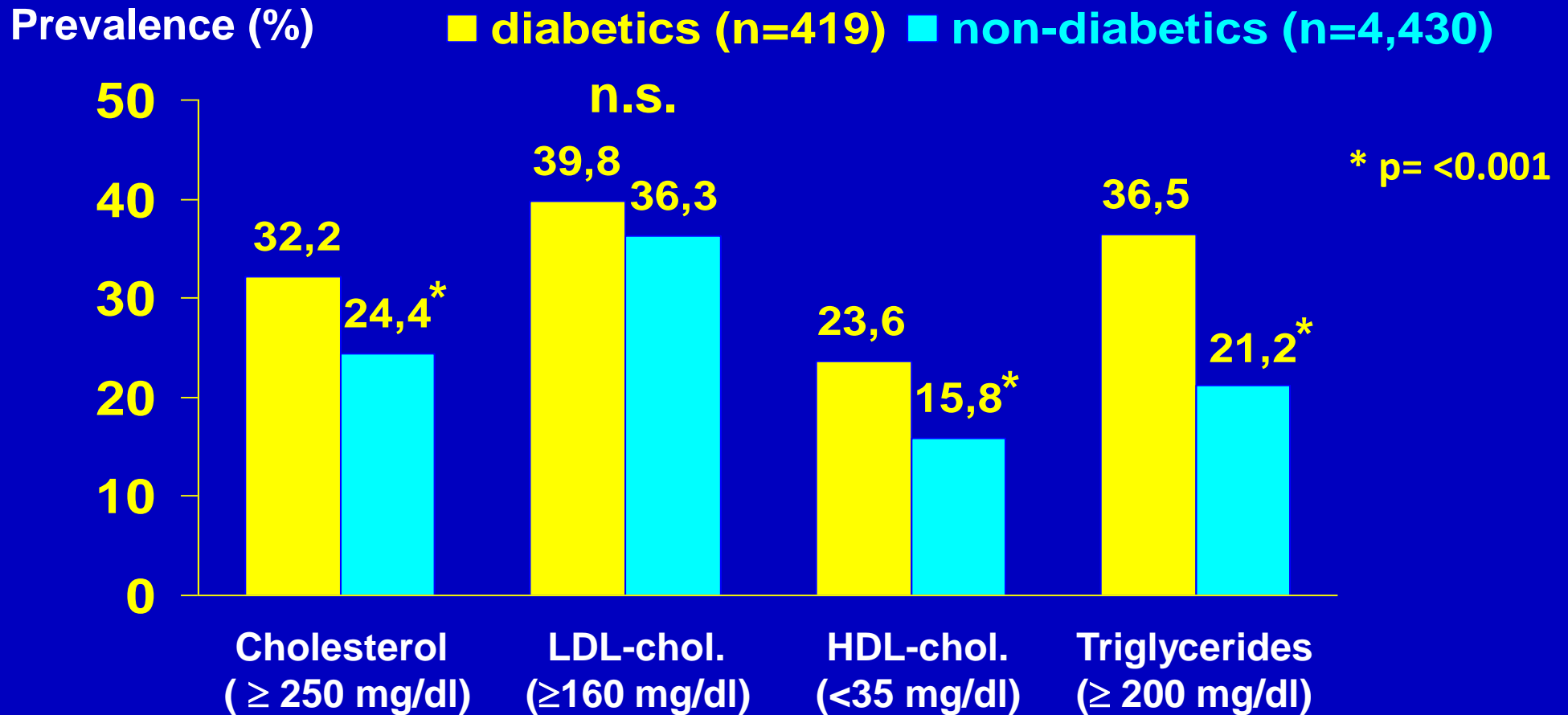


No. of Events	57	50	34	34	35
No. of Patients	473	525	550	569	544

**Evidenze di efficacia dell'intervento  
sulla triade lipidica per la prevenzione  
della malattia cardiovascolare**



# PROCAM (Münster Heart Study): Lipids in Diabetics



# CHD Prevention Trials with Fibrates in Diabetic Subjects: Subgroup Analyses

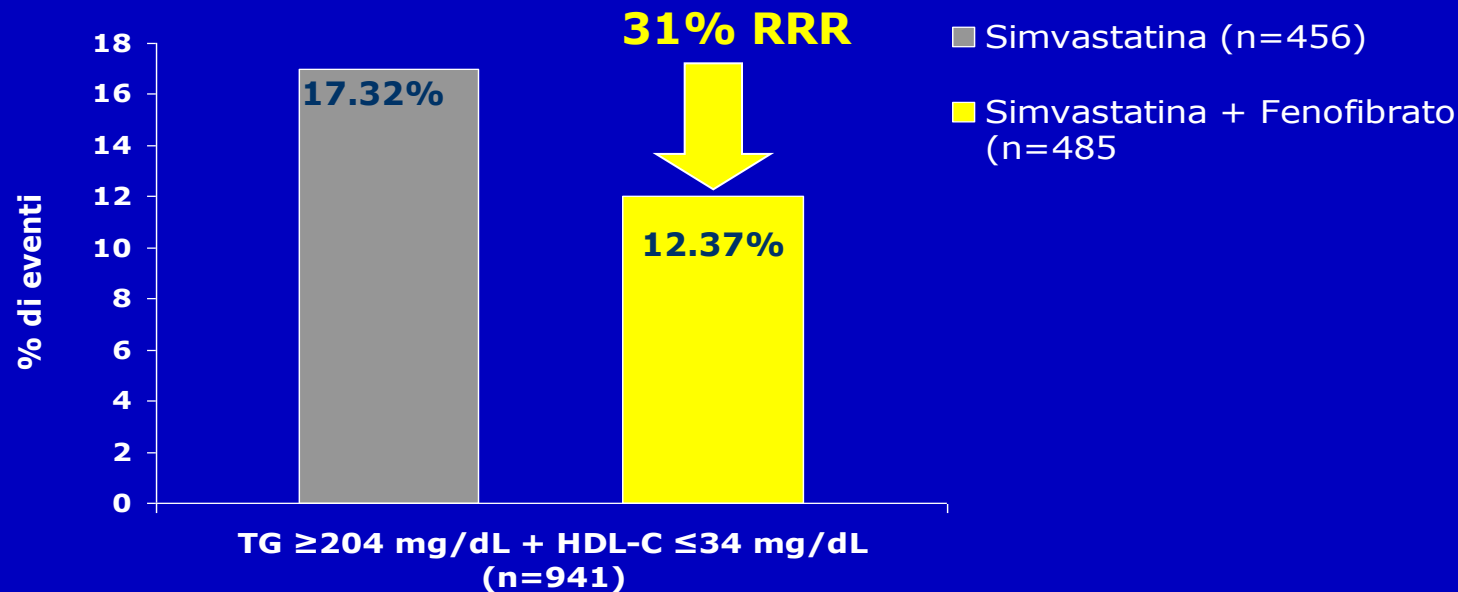
Study	Drug (dose)	No.	Baseline LDL-C, mg/dl (mmol/L)	LDL-C Lowering	CHD Reduction
<b>Primary Prevention</b>					
Helsinki Heart Study	Gemfibrozil (1200 mg/d)	135	203 (5.2)	6%	68% NS
<b>Secondary Prevention</b>					
VA-HIT	Gemfibrozil (1200 mg/d)	627	112* (2.9*)	—	24% P=.05
DAIS	Fenofibrate (200 mg/d)	418	130	6%	23% NS

\*Median value

Koskinen P et al. *Diabetes Care* 1992;15:820-825. | Rubins HB et al. *N Engl J Med* 1999;341:410-418. | DAIS Investigators. *Lancet* 2001;357:905-910.

## Effetto del fenofibrato sugli eventi CV maggiori nei pazienti dislipidemici

- Il trattamento con Fenofibrato è associato ad una riduzione del numero di eventi cardiovascolari maggiori\* nel sottogruppo dei pazienti dislipidemici (TG  $\geq$ 204 mg/dl e HDL-C  $\leq$ 34 mg/dl)



RRR: riduzione del rischio relativo

\*Eventi CV maggiori definiti con morte CV, IMA non fatale, ictus non fatale (endpoint primario)

**Trattare l'ipertensione nei diabetici  
previene efficacemente gli eventi  
cardiovascolari**

**Table 2.** Absolute risk, absolute risk reduction, relative risk reduction and *P*-values for selected endpoints in studies randomising patients to different blood pressure levels or to active or placebo treatment with reference to evaluation of the effect of intensified blood pressure control.

	Number of patients	Follow-up time	Endpoint	Absolute risk Control	Absolute risk Active	Absolute risk reduction	Relative risk reduction*	<i>P</i> -value
<i>UKPDS</i> †	1148	8.4 yr	Any diabetes-related endpoints‡	43.5%	34.2%	9.3%	24%	0.005
			Diabetes-related death§	15.9%	10.8%	5.1%	32%	0.02
			Myocardial infarction	17.7%	14.1%	3.6%	31%	0.13
			Microvascular complications	13.8%	9.0%	4.8%	37%	0.01
<i>HOT</i>								
All patients	18790	3.8 yr	Major cardiovascular event	3.7%	3.6%	0.2%	5%	0.50
Diabetic patients	1501	3.7 yr	Major cardiovascular event	9.0%	4.4%	4.6%	51%	0.005
<i>SHEP</i>								
Non-diabetic patients	4736	4.5 yr	All cause mortality	10.2%	9.0%	1.2%	15%	NS
			Cardiovascular event	17.4%	12.2%	5.2%	24%	<0.05
Diabetic patients	583	4.7 yr	All cause mortality	16.0%	13.8%	2.2%	24%	NS
			Cardiovascular event	27.7%	20.1%	7.6%	34%	<0.05
<i>Syst-Eur</i>								
All patients	4695	2.0 yr	All cause mortality	6.0%	5.1%	0.9%	15%	0.50
			Cardiovascular mortality	3.4%	2.5%	0.9%	26%	0.32
Diabetic patients	492	2.0 yr	All cause mortality	10.8%	6.3%	4.5%	41%	0.09
			Cardiovascular mortality	6.7%	2.0%	4.7%	55%	0.01

\* In case of discrepancy between the calculated relative risk reduction from values given in the table and the value given in the specific study the latter has been used since this value could have been adjusted for covariates.

† Only patients with diabetes have been included in the study.

‡ Sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction.

§ Death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia, and sudden death.

## STUDIO HOT

Diabetici con PAD  $\leq$  80 mmHg vs PAD  $\leq$  90 mmHg

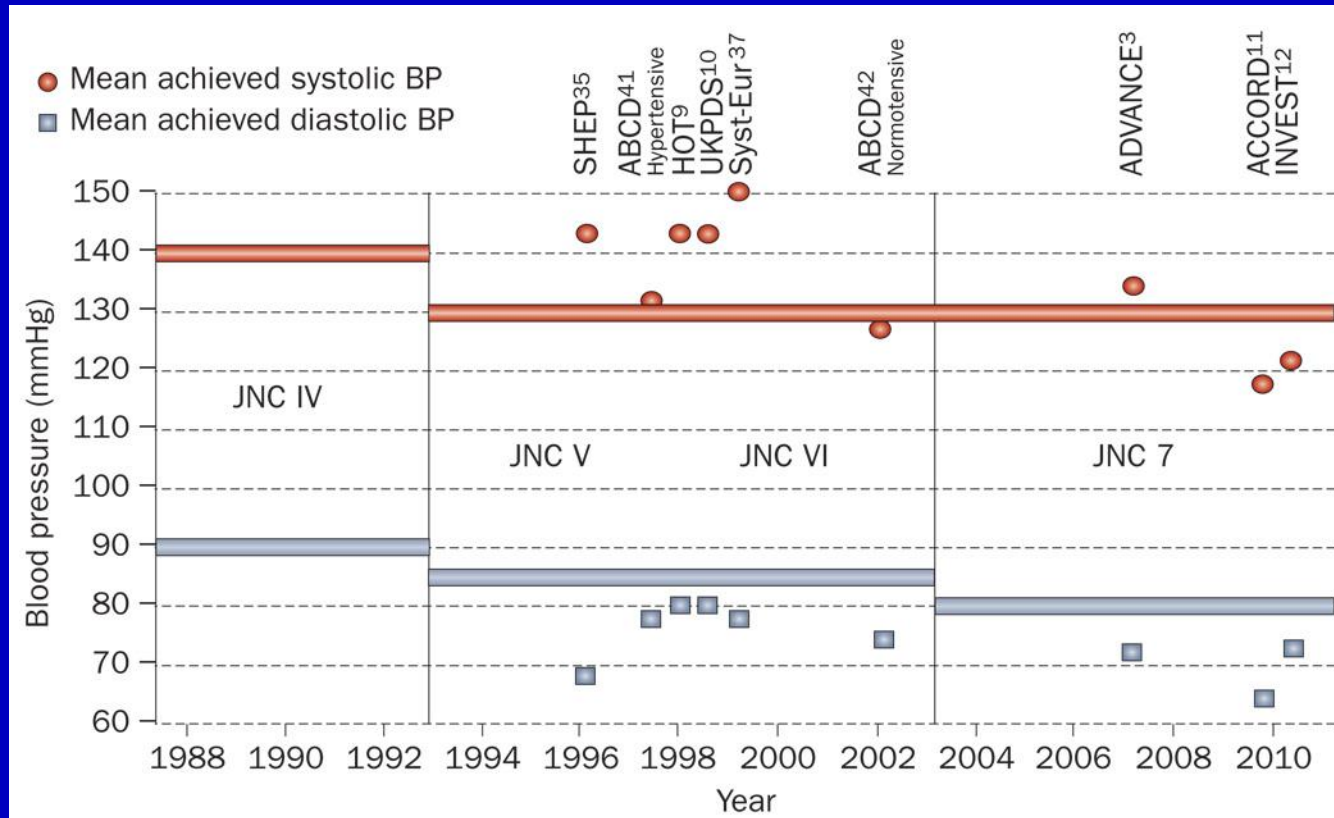
<b>END POINT CLINICO</b> a 10 anni	<b>RIDUZIONE DEL RISCHIO</b> <b>RELATIVO</b>	<b>p</b>
Mortalità complessiva	43,4 %	0,068
Mortalità cardiovascolare	66,7 %	0,016
Eventi cardiovascolari maggiori	51,2 %	0,005
Infarto miocardico (solo 14 vs 7 casi)	50,7 %	0,11
Ictus (solo 17 vs 12 casi)	29,7 %	0,34

## STUDIO UKPDS

Controllo pressorio stretto (PA a fine follow-up 144/82)  
vs meno stretto (PA a fine follow-up 154/87)

<b>END POINT CLINICO</b> a 10 anni	<b>RIDUZIONE DEL RISCHIO</b> <b>RELATIVO</b>	<b>p</b>
<b>Mortalità complessiva</b>	<b>17,6 %</b>	<b>0,17</b>
<b>Mortalità da cause connesse al diabete</b>	<b>32,5 %</b>	<b>0,019</b>
<b>Ogni evento connesso al diabete</b>	<b>24,5 %</b>	<b>0,0046</b>
<b>Infarto miocardico</b>	<b>20,8 %</b>	<b>0,13</b>
<b>Ictus</b>	<b>44 %</b>	<b>0,013</b>
<b>Vasculopatia periferica</b>	<b>48,1 %</b>	<b>0,17</b>
<b>Complicanze microvascolari</b>	<b>37,5 %</b>	<b>0,0092</b>

# Blood pressure lowering in patients with diabetes—one level might not fit all



Nat Rev Cardiol. 2011 January; 8(1): 42–49.



**Trattare i pazienti diabetici con  
antiaggreganti  
riduce gli eventi cardiovascolari**

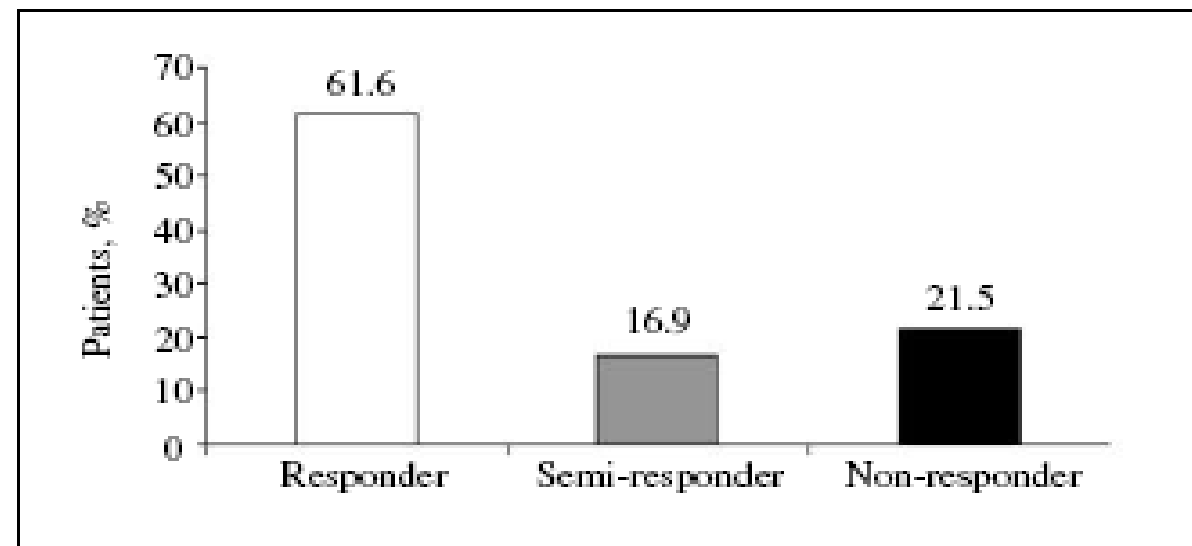
**Table 4.** Absolute risk, absolute risk reduction, relative risk reduction and *P*-values for selected endpoints in studies comparing acetylsalicylic acid and placebo

	Number of patients	Follow-up time	Endpoint	Absolute risk Control	Absolute risk Active	Absolute risk reduction	Relative risk reduction*	<i>P</i> -value
<i>HOT</i>								
All patients	18790	3.8 yr	Major cardiovascular events	3.9%	3.4%	0.5%	15%	0.03
		3.8 yr	Myocardial infarction	1.4%	0.9%	0.5%	36%	0.002
<i>Primary Prevention Project</i>								
All patients	4495	3.6 yr	Major cardiovascular events	8.2%	6.3%	1.9%	23%	<0.05
<i>US Physicians' Health Study</i>								
All patients	22071	5.2 yr	Myocardial infarction	2.3%	1.3%	1.0%	44%	<0.001
Diabetes patients	533	–	Myocardial infarction	10.1%	4.0%	6.1%	61%	0.006
<i>ETDRS</i>								
All patients	3711	5 yr	Myocardial infarction	12.3%	9.1%	3.2%	17%	<0.05
Type 2 diabetes	1152	5 yr	Myocardial infarction	8.1%	6.0%	2.1%	17%	NS

\* In case of discrepancy between the calculated relative risk reduction from values given in the table and the value given in the specific study the latter has been used since this value could have been adjusted for covariates.

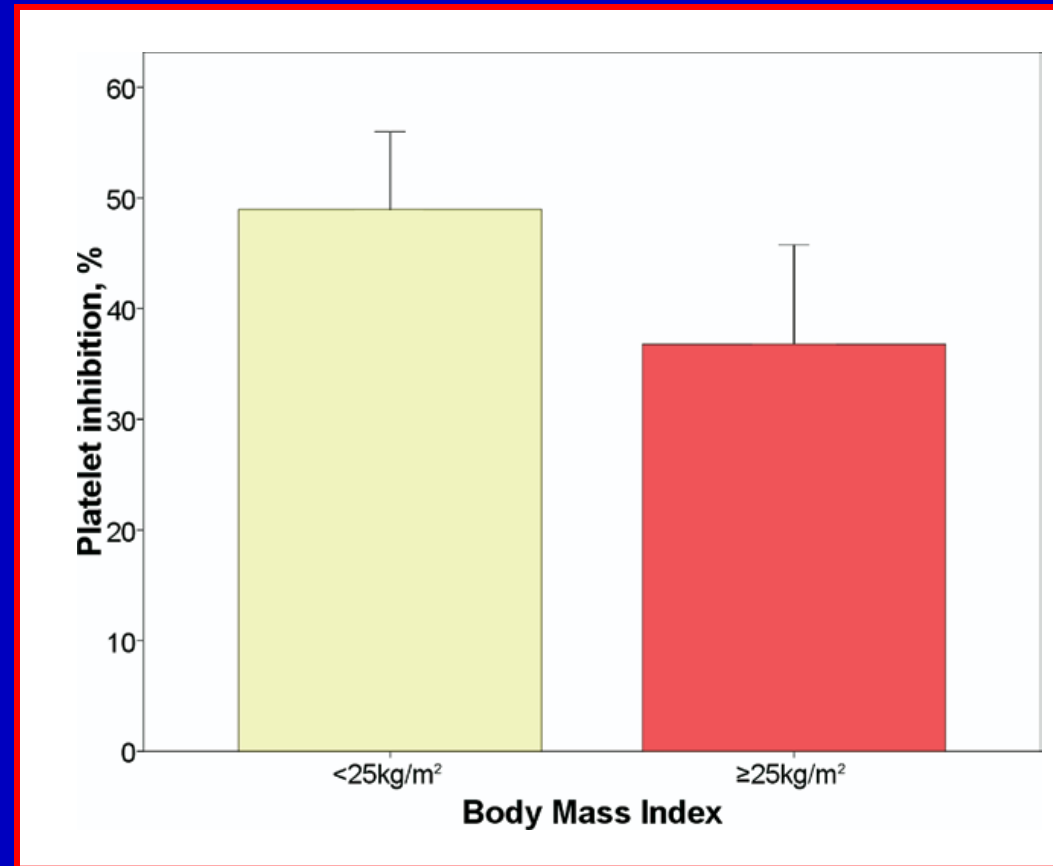
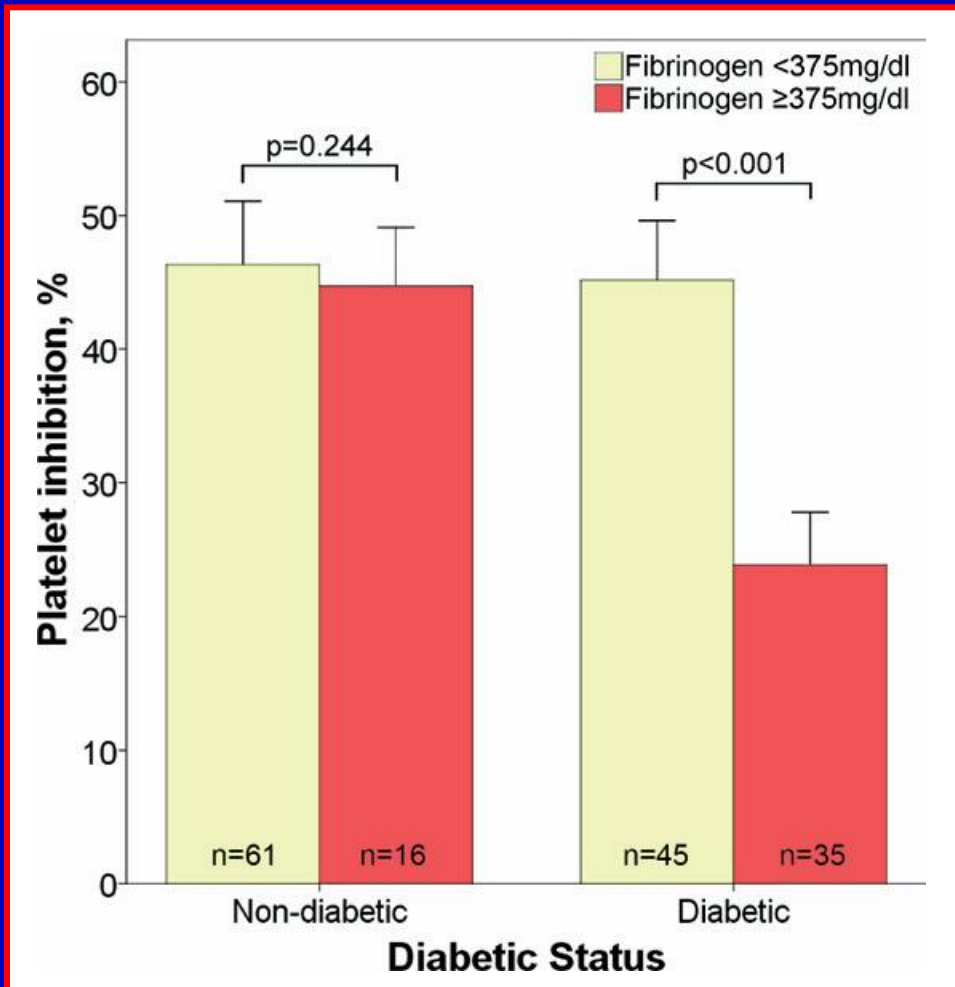
– Indicates that follow-up time for the diabetic subpopulation has not been given or cannot be estimated from information available.

## Prevalenza di aspirino-resistenza tra i pazienti affetti da diabete mellito di tipo 2



Fateh-Moghadam et al., *Acta Diabetol.* 2005;42:99-103.

# Decreased response to Clopidrogrel in myocardial infarction patients with type 2 diabetes



L'impiego dell'aspirina nel diabete deve essere attuato in conformità a quanto raccomandato dalle Linee-Guida Internazionali.

Il **problema** di una eventuale minore risposta al farmaco nei pazienti diabetici rispetto alla popolazione non diabetica

(**"aspirino-resistenza"**) è tuttora oggetto di studio:

esso peraltro **non giustifica atteggiamenti di rinuncia** nei confronti della prescrizione del farmaco nell'ambito di una strategia preventiva multifattoriale

**Correggere il sovrappeso nei diabetici  
riduce gli eventi cardiovascolari**

## **PERDITA INTENZIONALE DI PESO**

in soggetti diabetici sovrappeso con un follow-up di 12 anni

( Dati aggiustati per età, sesso, peso iniziale, razza, fumo, alcolici, attività fisica, anamnesi patologica )

<b>END POINT CLINICO</b>	<b>RIDUZIONE DEL R.R.</b>	<b>p</b>
<b>Mortalità cardiovascolare e da diabete</b>	<b>28 %</b>	<b>&lt; 0,05</b>
<b>Mortalità totale</b>	<b>25 %</b>	<b>&lt; 0,05</b>

# **Intervento multifattoriale : evidenze epidemiologiche**



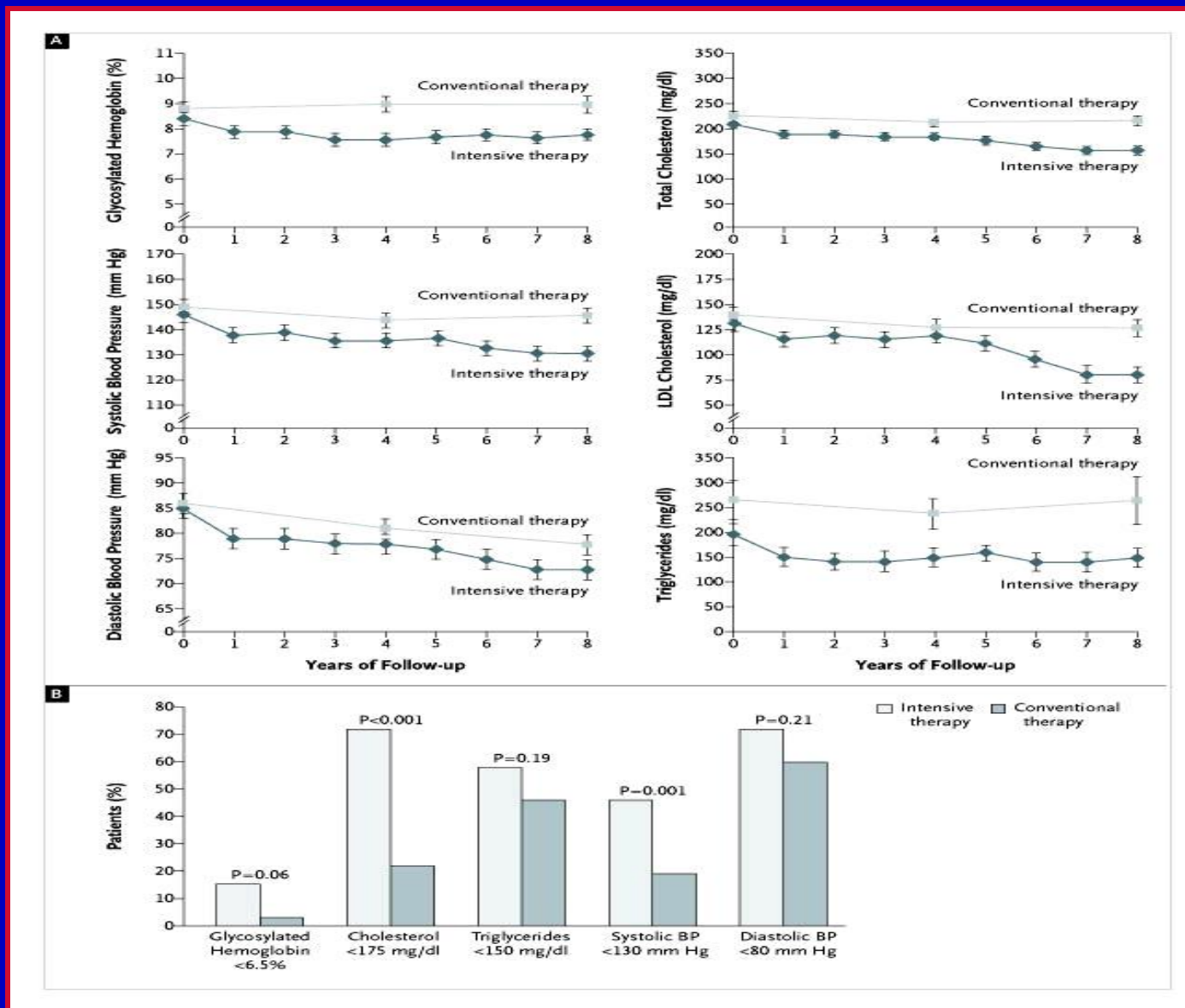
# THE STENO TYPE TWO STUDY

- Studio di intervento a gruppi randomizzati e paralleli in aperto
- Pazienti diabetici tipo 2 con microalbuminuria
- 80 pazienti assegnati a trattamento standard
  - Secondo raccomandazioni della Danish Medical Association
- 80 pazienti assegnati a trattamento intensivo con approccio “stepwise”, comprendente:
  - Modificazione stile di vita
  - Terapia farmacologica a step

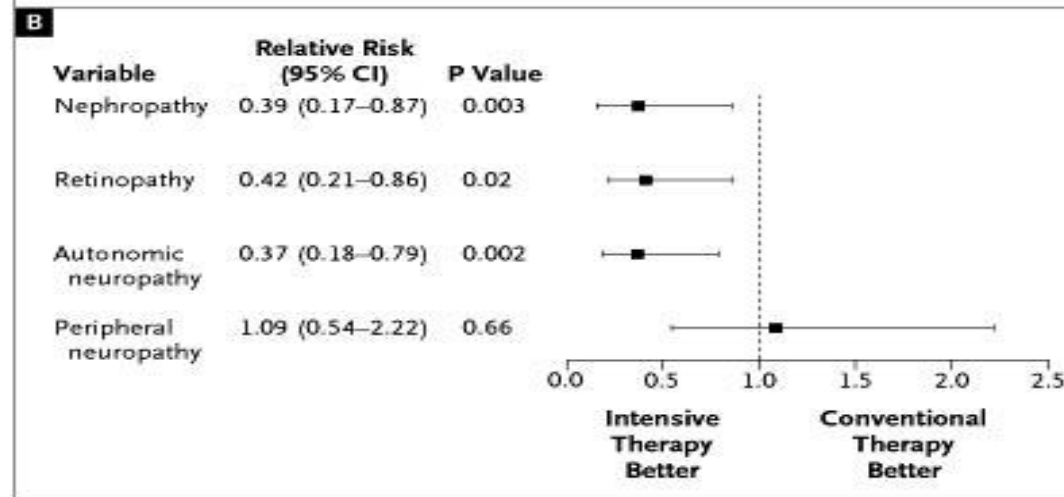
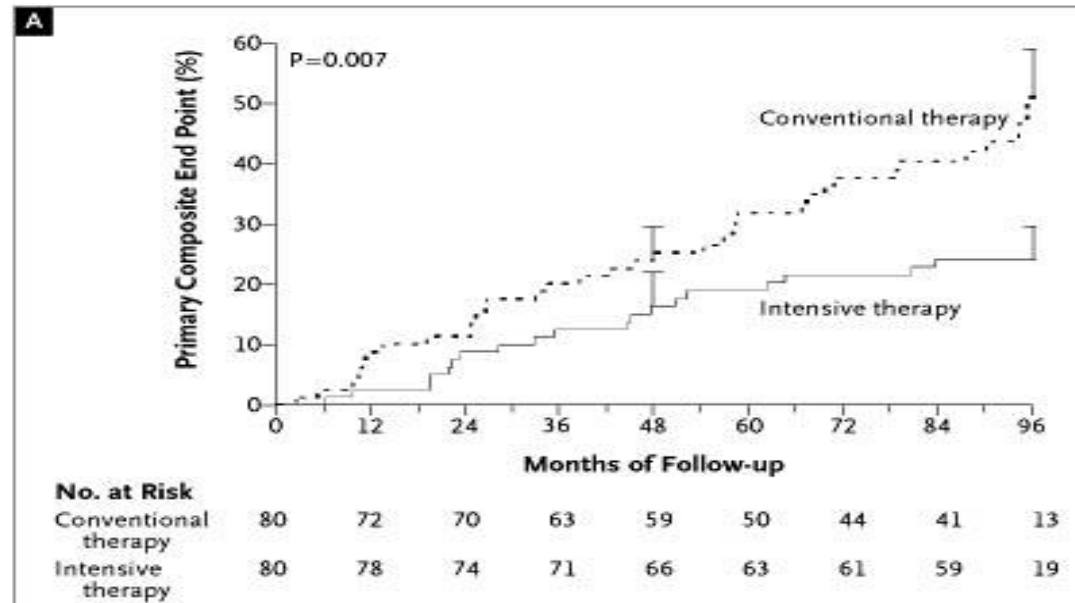
## GOALS

- PAS < 140 mmHg
- PAD < 85 mmHg
- HbA1c < 6,5 %
- TG < 150 mg/dL
- COL. < 190 mg/dL
- HDL > 42 mg/dL
- ACE-inibitore (indip. da PA)
- ASPIRINA

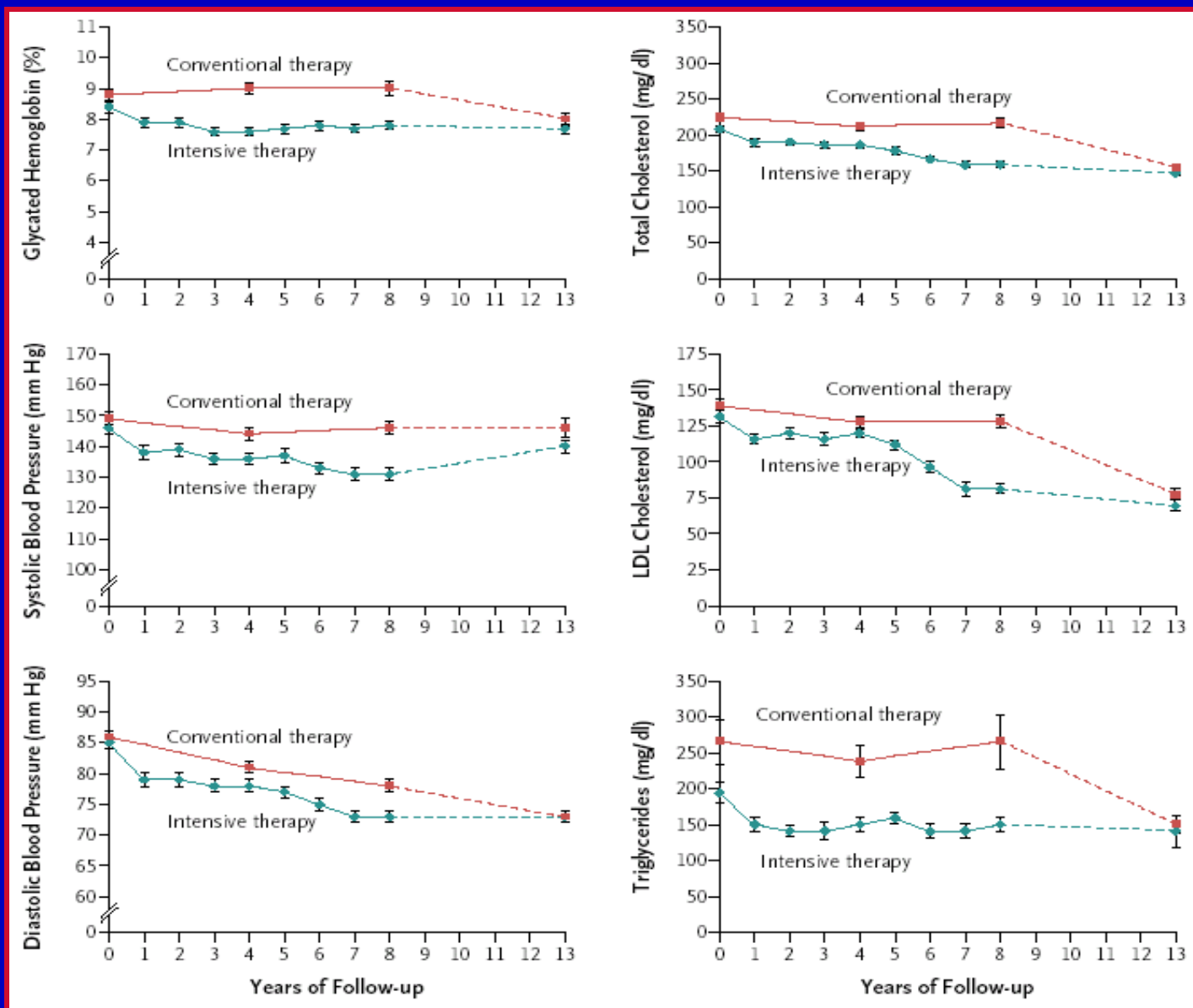
# Changes in selected risk factors during the study: 8 years follow up



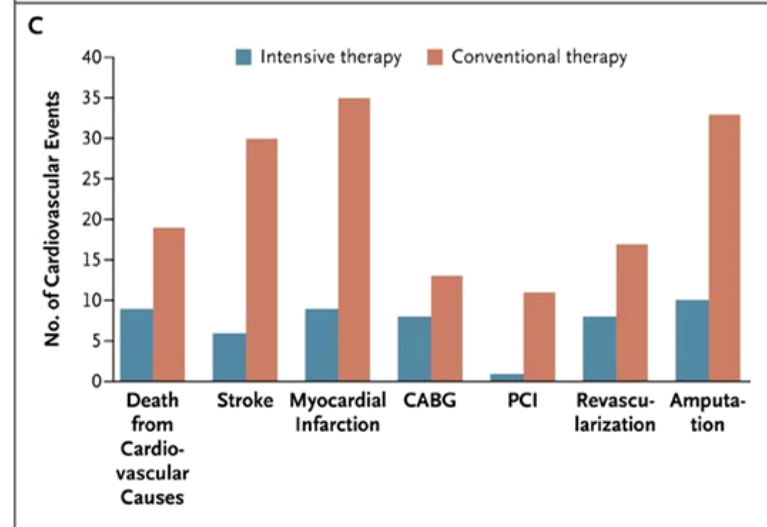
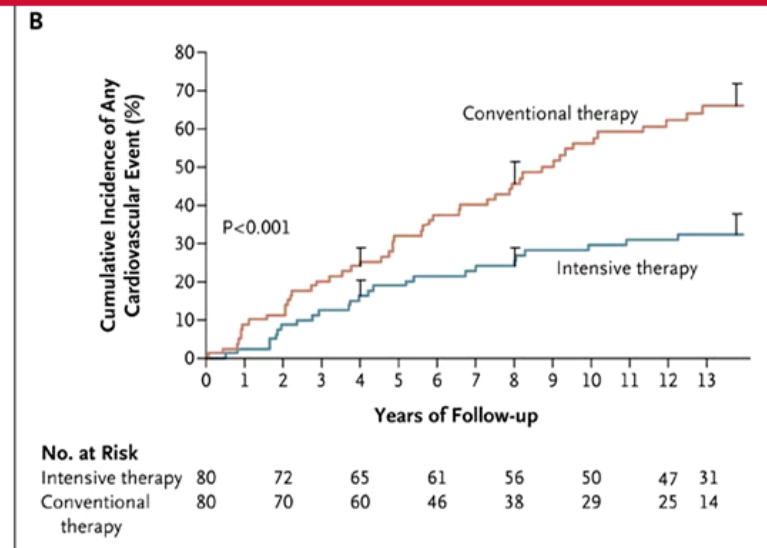
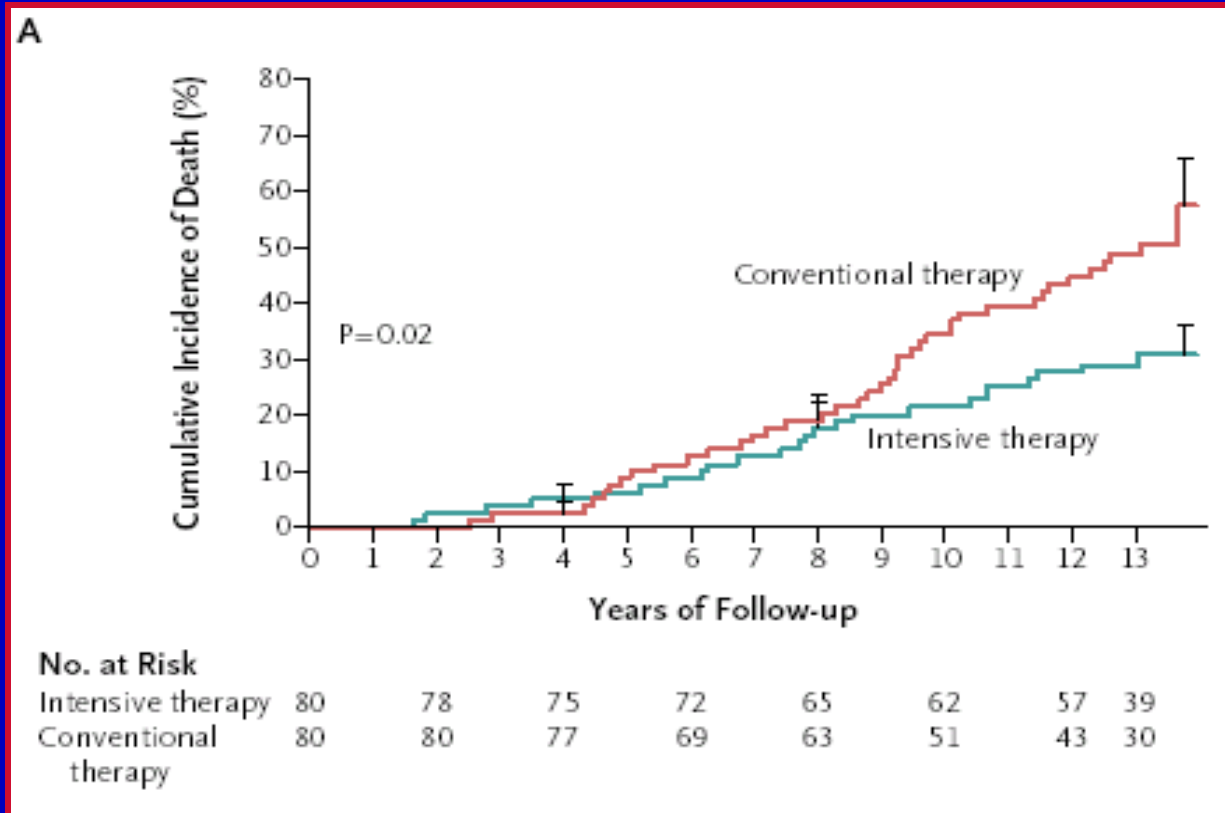
# Incidence of cardiovascular events and mortality : 8 years follow up



# Changes in selected risk factors during the study (13 years of follow-up)



# Incidenza di mortalità , di mortalità cardiovascolare e di eventi cardiovascolari durante il periodo di studio (13.3 yrs follow-up)



# Messaggio chiave

**-Un intervento intensivo multifattoriale con approccio «treat to target» in pazienti diabetici tipo 2 è fattibile ed è efficace nel prevenire la malattia cardiovascolare**

**-un intervento educativo e di supporto motivazionale sono essenziali per ottenere la compliance del paziente all' intervento intensivo.**

**-L' intervento con più farmaci richiede una elevata consapevolezza del paziente sui benefici della terapia per garantirne la compliance**

**-L' intervento intensivo multifattoriale precoce mantiene l' efficacia dell' intervento a lungo termine nella prevenzione della malattia cardiovascolare nonostante si riduca nel tempo la differenza dei fattori di rischio.**

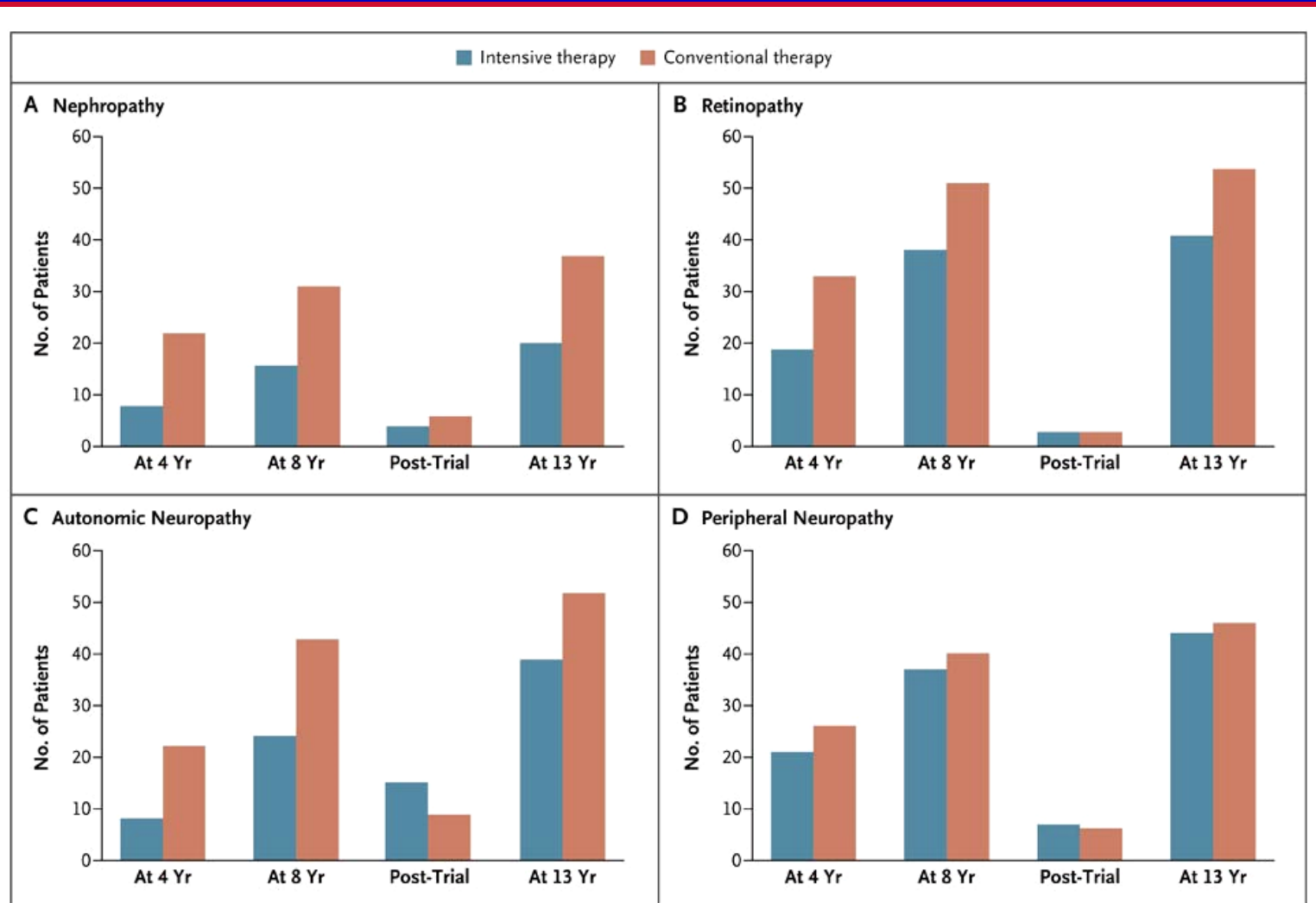
# Multifactorial Intervention in type 2 Diabetes – Italy : MIND:IT



Studio di intervento multicentrico randomizzato che confronta la usual-care con un intervento multifattoriale intensivo “treat-to-target” (Intensive Care) per la prevenzione primaria cardiovascolare

9 centri – 1461 diabetici tipo 2 (759 M / 702 F, età  $61 \pm 5$  anni) follow up 5 anni.

# Progressione delle complicanze microangiopatiche (13 anni di follow-up)





**OBIETTIVI DELL'INTERVENTO MULTIFATTORIALE PER LA PREVENZIONE  
DEL RISCHIO CARDIOVASCOLARE  
NEL PAZIENTE DIABETICO  
Linee guida SID(2001)**

- BMI < 25 kg/m<sup>2</sup> o calo ponderale del 5-10%
- HBA1c < 7.0 %
- LDL Colesterolo < 100 mg/dL
- TG <150 mg/dL e HDL >40 (M) o 50 (F) mg/dL
- Pressione arteriosa < 130 / 80 mmHg
- Terapia antiaggregante
- Abolizione del fumo di sigaretta

# OBIETTIVI

## 1) Fase Trasversale

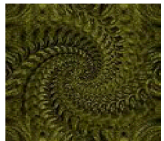
Valutare in che misura sono applicate nella pratica clinica le raccomandazioni per la prevenzione cardiovascolare

## 2) Fase di Intervento

Valutare se, nella realtà dell'assistenza diabetologica italiana, un intervento intensivo multifattoriale, sia:

- fattibile
- efficace nel raggiungimento degli obiettivi indicati dalle raccomandazioni
- efficace nel ridurre l'incidenza di eventi cardiovascolari
- vantaggioso per rapporto costi/benefici

## 3) Costituzione di una banca biologica



**BARI**  
**LA SPEZIA**  
**MASSA CARRARA**  
**PAVIA**  
**PIACENZA**  
**PISA**  
**PERUGIA**  
**ROMA**  
**TORINO**





**Pazienti in follow-up  
e stima dati mancanti**

## Pazienti in follow-up a Maggio 2007

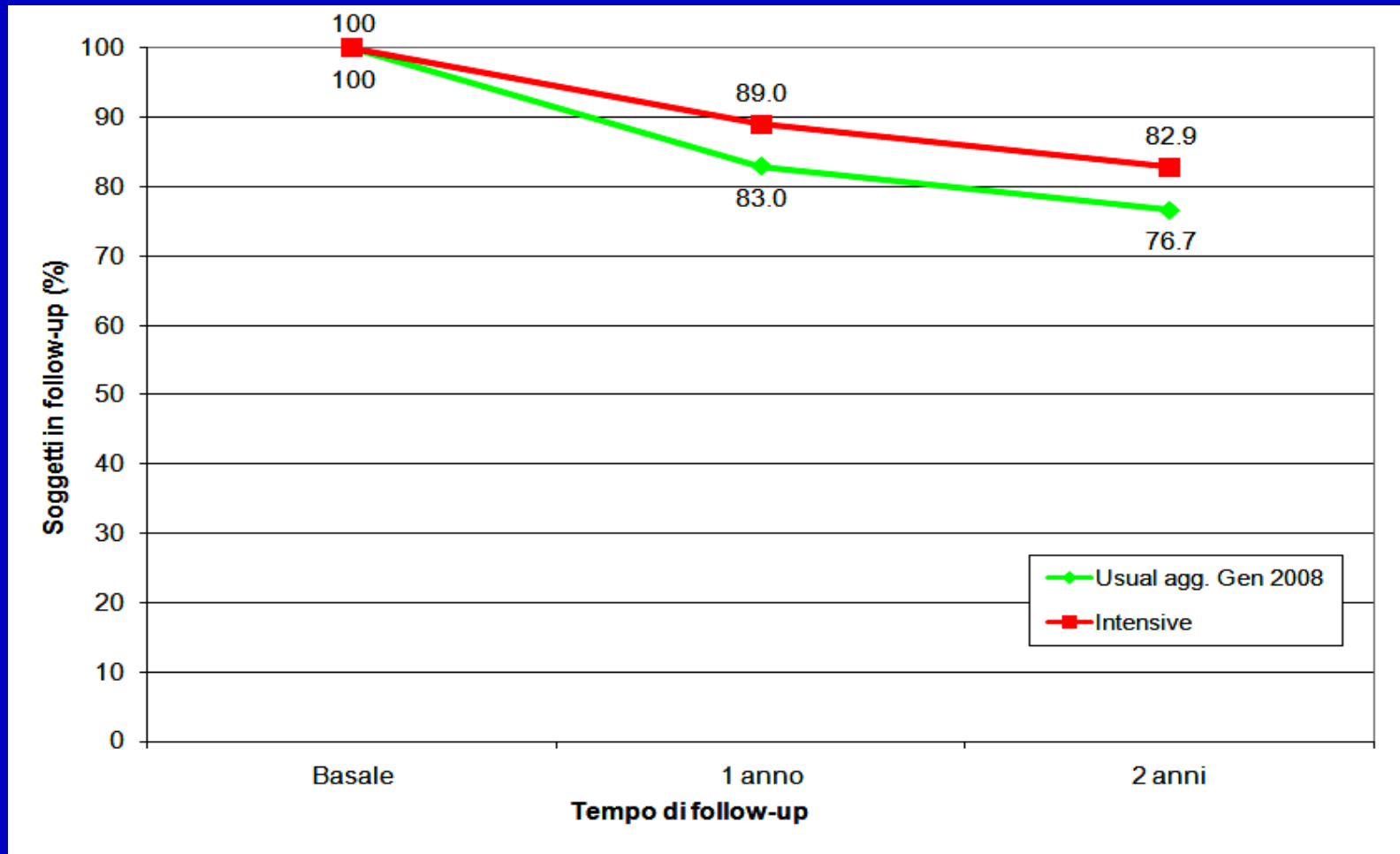
(su questi dati sono stati elaborati tabelle e grafici di follow-up a 2 anni)

Gruppo	Centro	Visite		
		Basale	1 anno	2 anni
Usual	Bari	155	128	73
	Carrara	125	106	108
	La Spezia	199	107	136
	Piacenza	200	187	173
	Pisa	200	174	93
	Roma	124	113	103
Intensive	Pavia	130	124	116
	Perugia	149	125	114
	Torino	179	159	150
Totali	USUAL	996	808	680
	INTENSIVE	455	405	377
	TOTALE	1461	1223	1066

## Pazienti in follow-up (dati aggiornati)

Gruppo	Centro	Visite		
		Basale	1 anno	2 anni
Usual	Bari	155	132	104
	Carrara	125	106	108
	La Spezia	199	107	136
	Piacenza	200	187	173
	Pisa	200	182	140
	Roma	124	113	103
Intensive	Pavia	130	124	116
	Perugia	149	125	114
	Torino	179	159	150
Totali	USUAL	996	827	764
	INTENSIVE	455	405	377
	TOTALE	1461	1232	1141

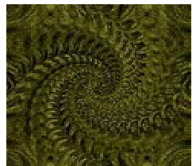
## Percentuale di pazienti in follow-up (basato sui dati aggiornati)





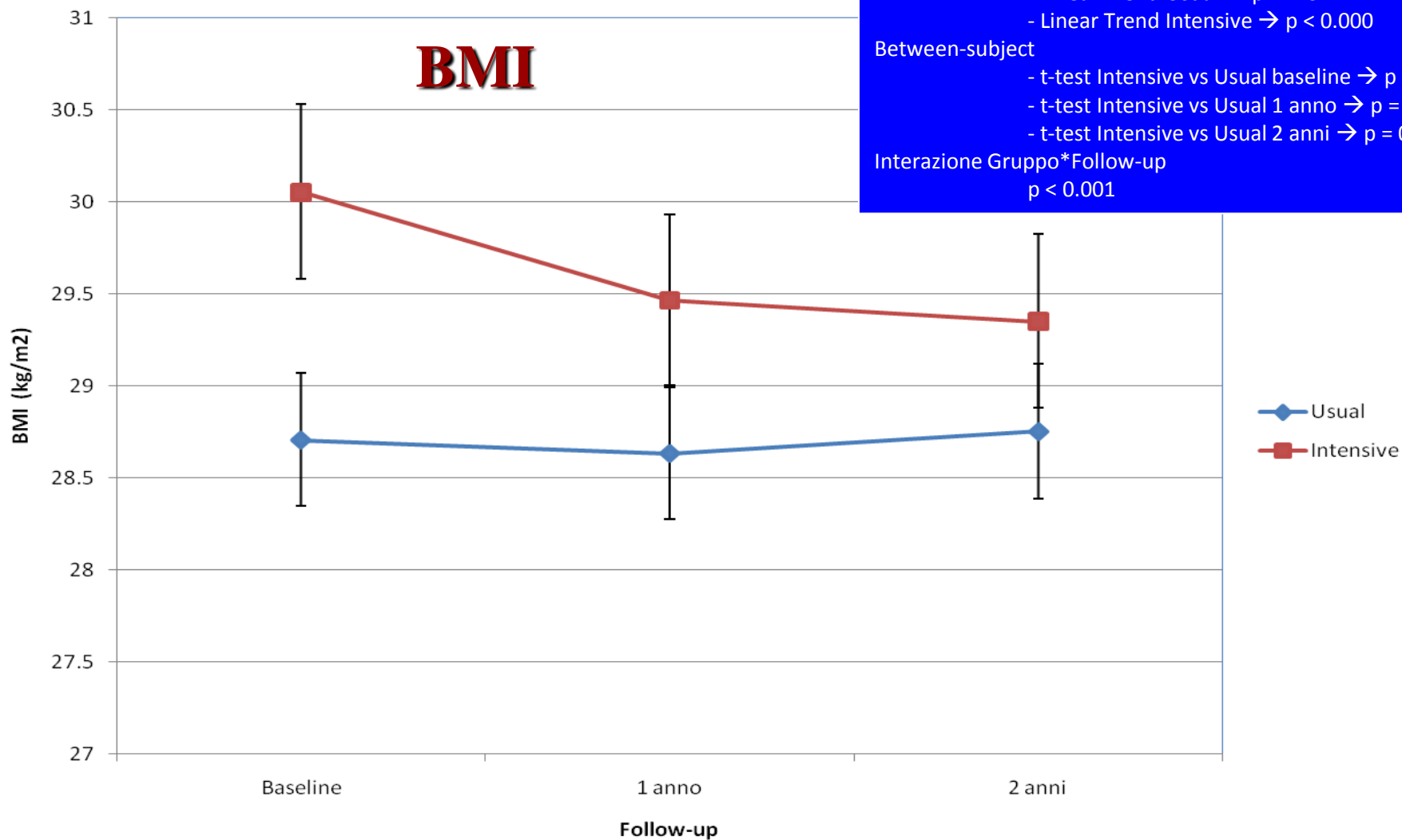
## **Follow-up parametri metabolici**





## Studio MIND-IT -Follow-Up a 2 anni-

# BMI



### ANOVA per misure ripetute

#### Within-subject

- Linear Trend Usual → p = N.S.
- Linear Trend Intensive → p < 0.000

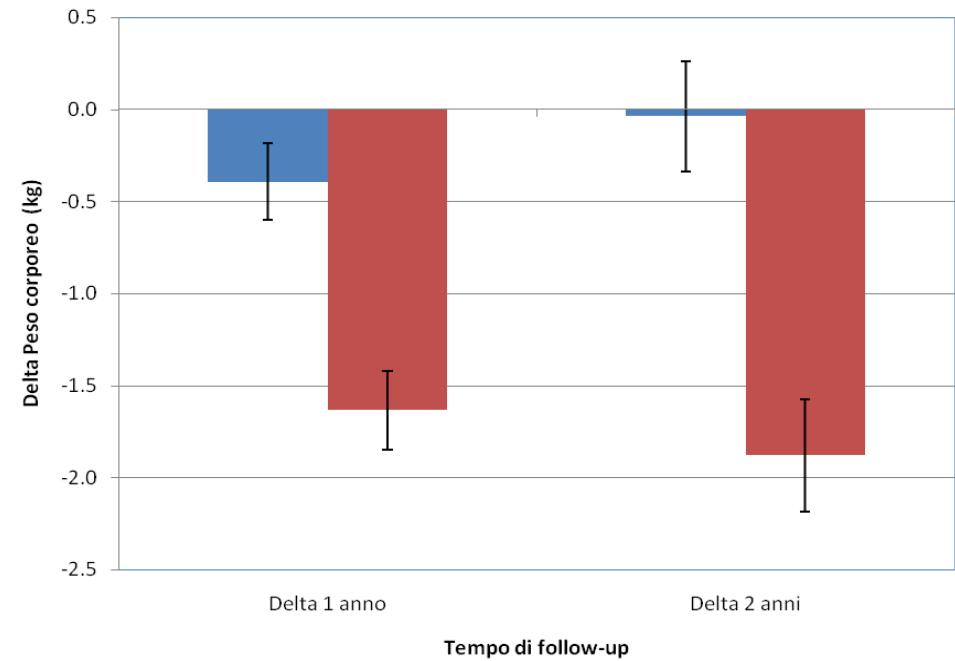
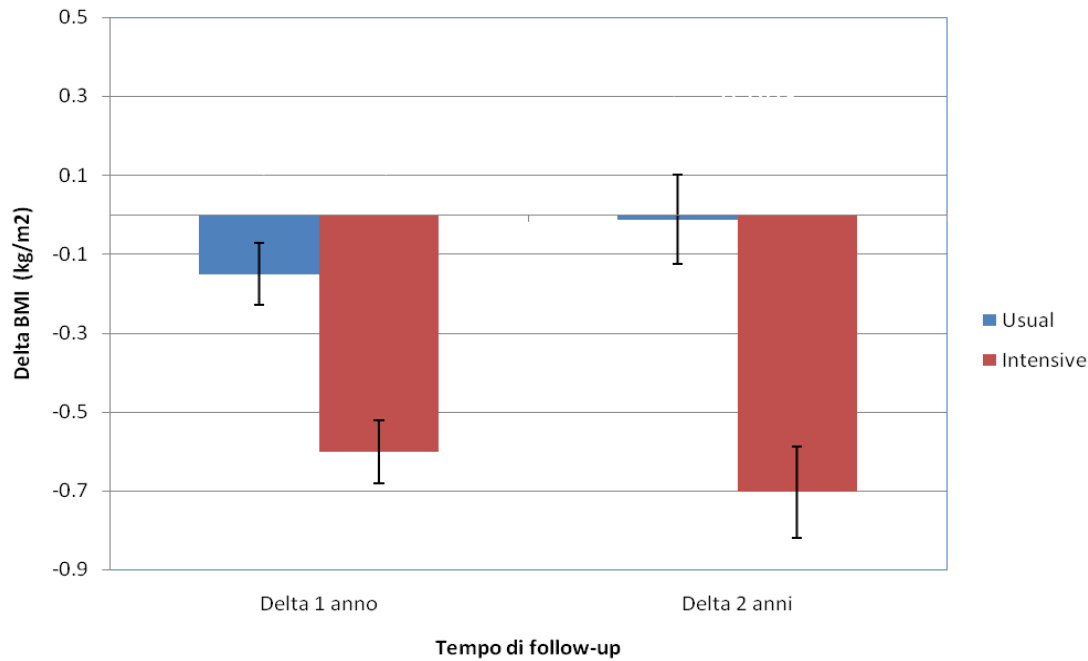
#### Between-subject

- t-test Intensive vs Usual baseline → p < 0.001
- t-test Intensive vs Usual 1 anno → p = 0.007
- t-test Intensive vs Usual 2 anni → p = 0.014

Interazione Gruppo\*Follow-up  
p < 0.001



## Variazione di BMI e peso durante follow-up



# Pressione Sistolica

## ANOVA per misure ripetute

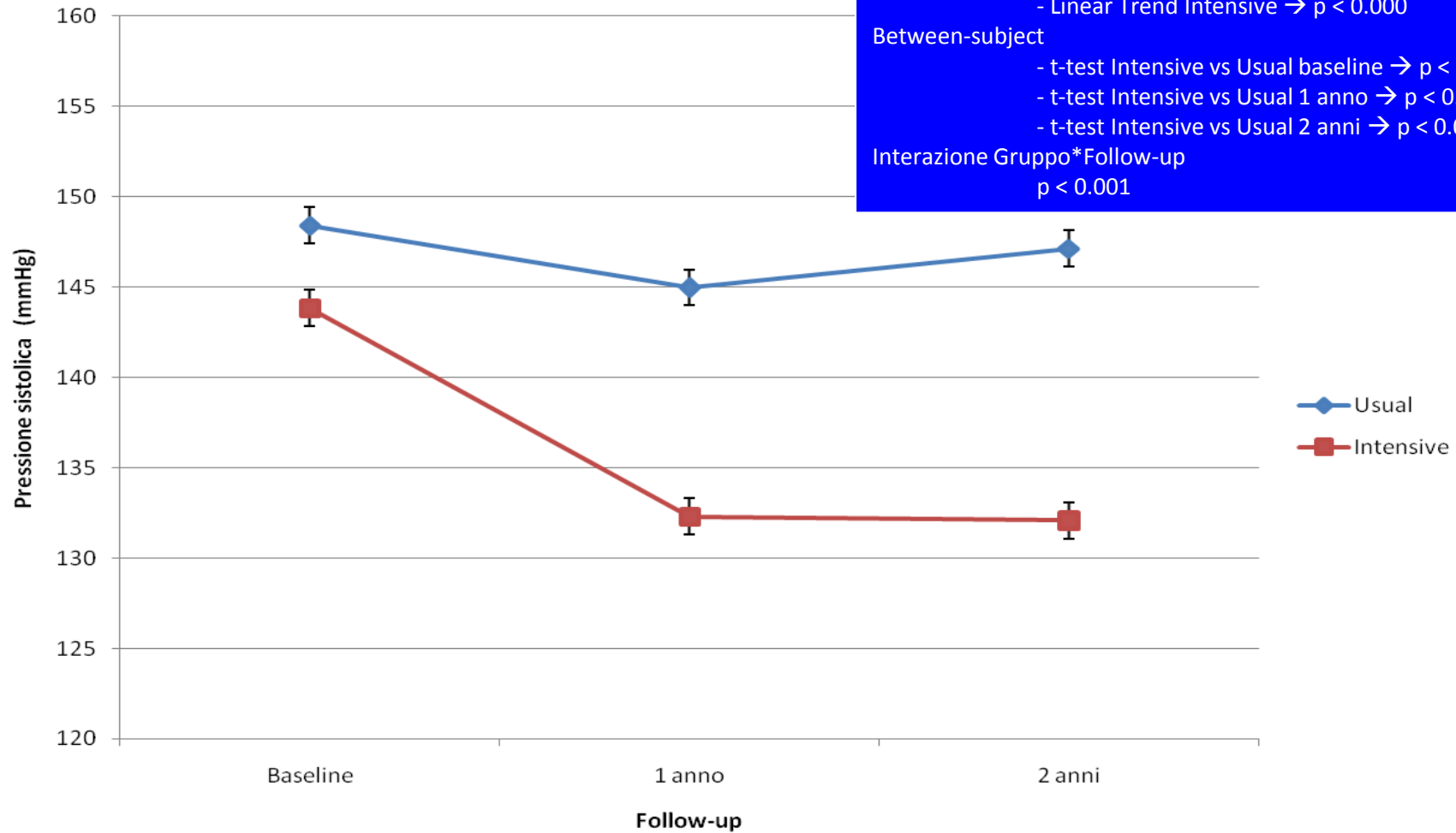
### Within-subject

- Linear Trend Usual  $\rightarrow p < 0.005$
- Linear Trend Intensive  $\rightarrow p < 0.000$

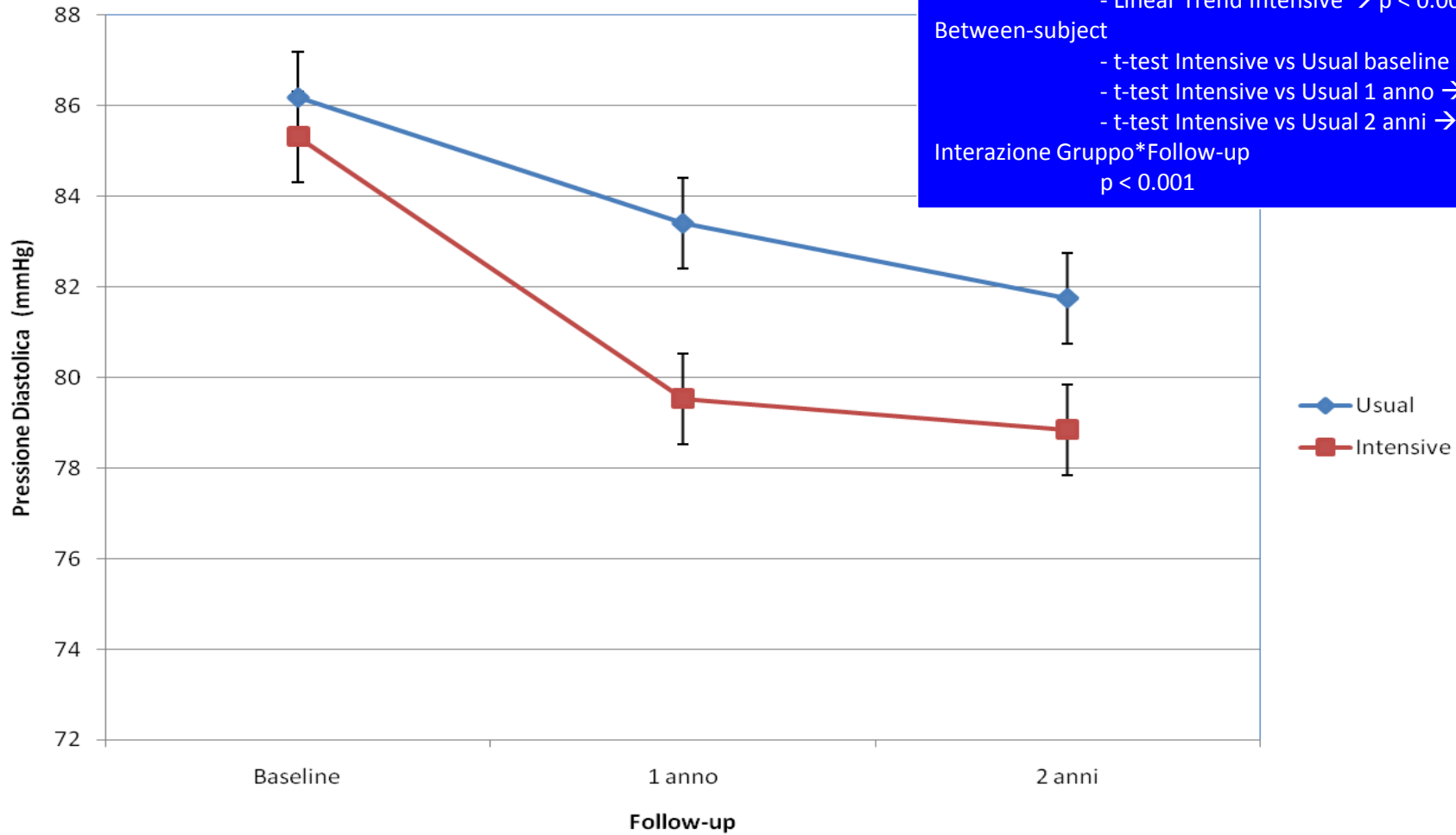
### Between-subject

- t-test Intensive vs Usual baseline  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 1 anno  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 2 anni  $\rightarrow p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$



# Pressione Diastolica



## ANOVA per misure ripetute

### Within-subject

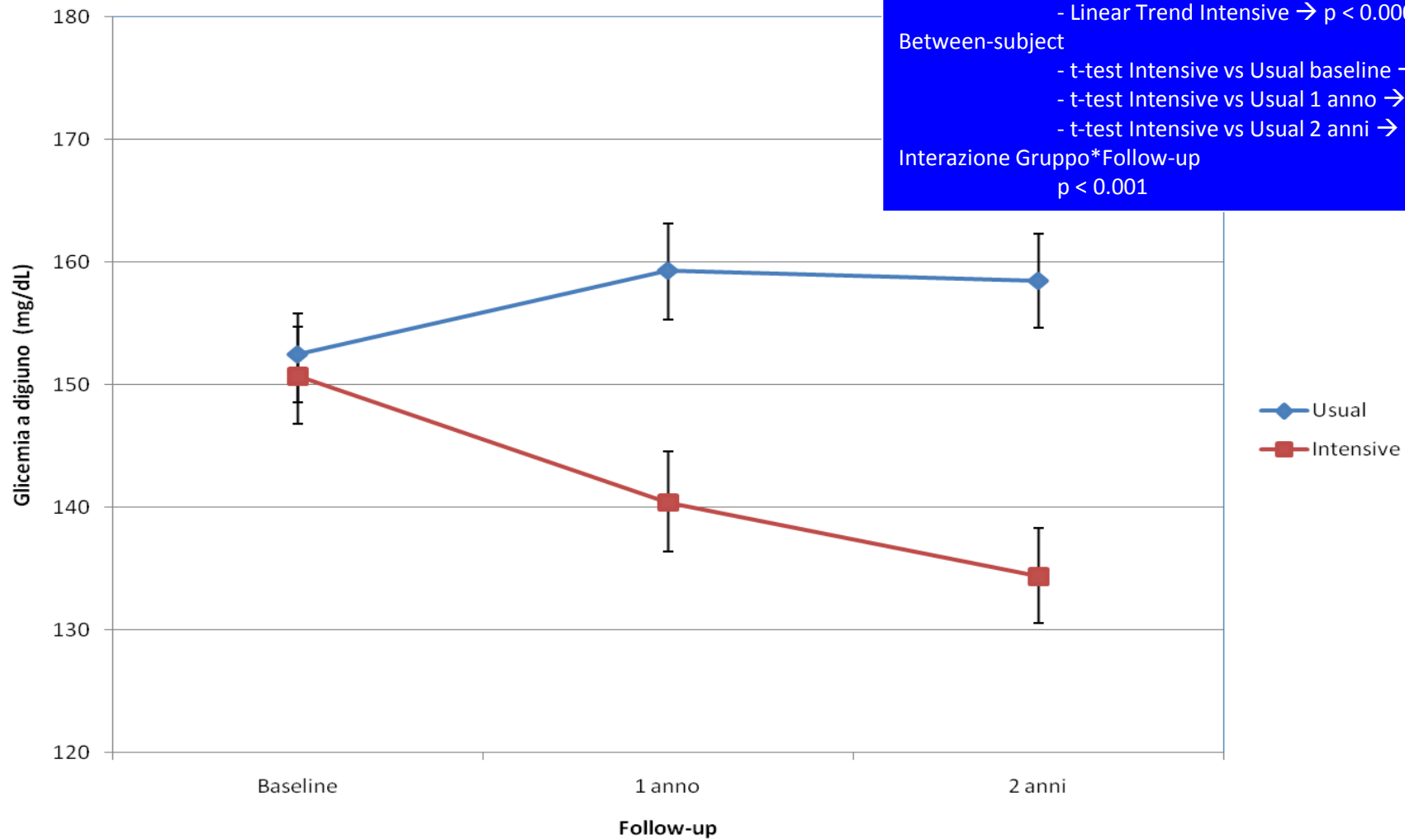
- Linear Trend Usual  $\rightarrow p < 0.000$
- Linear Trend Intensive  $\rightarrow p < 0.000$

### Between-subject

- t-test Intensive vs Usual baseline  $\rightarrow p = 0.012$
- t-test Intensive vs Usual 1 anno  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 2 anni  $\rightarrow p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$

# Glicemia a digiuno



**ANOVA per misure ripetute**

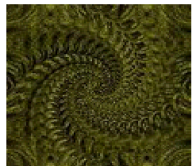
Within-subject

- Linear Trend Usual  $\rightarrow p < 0.005$
- Linear Trend Intensive  $\rightarrow p < 0.000$

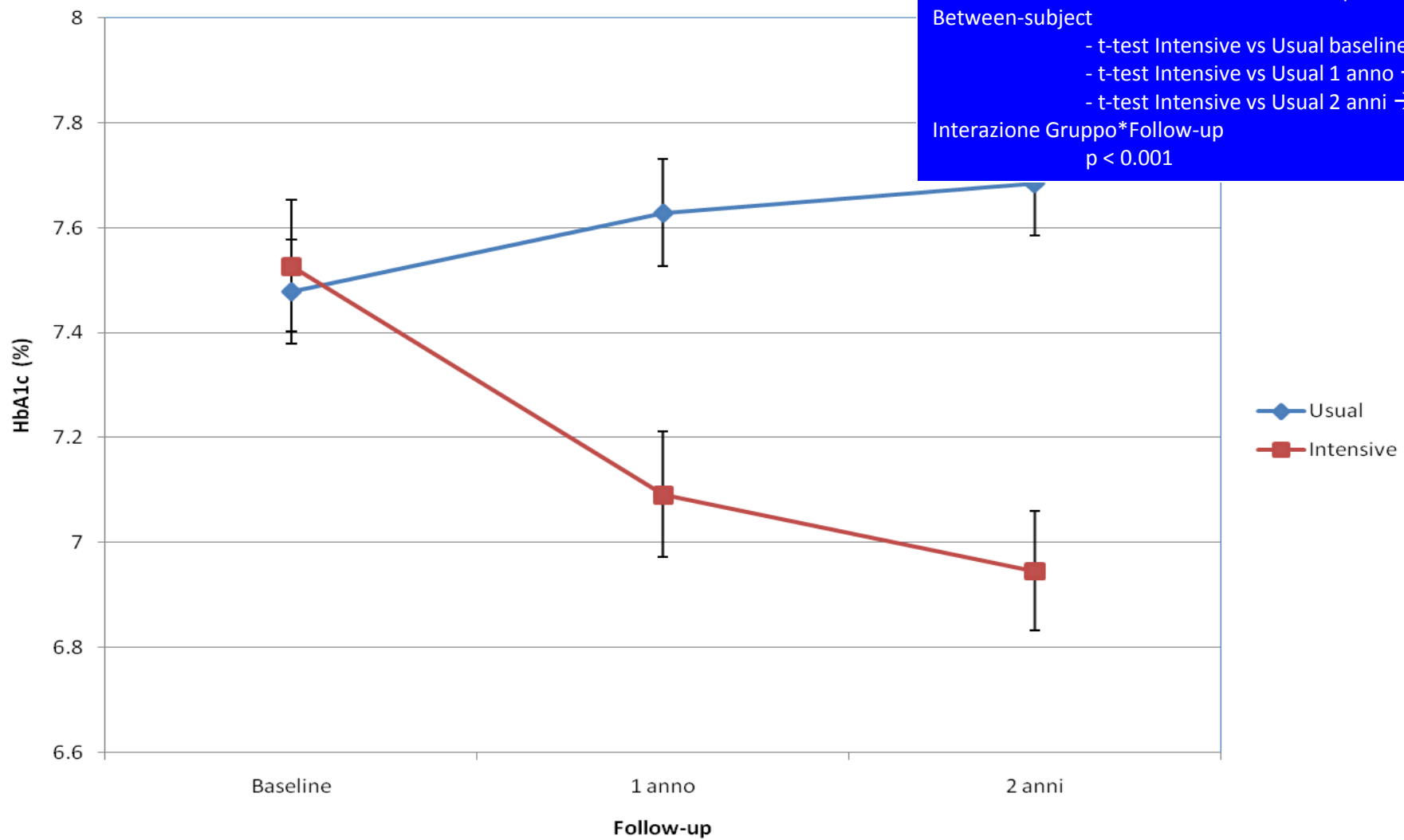
Between-subject

- t-test Intensive vs Usual baseline  $\rightarrow p = \text{NS}$
- t-test Intensive vs Usual 1 anno  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 2 anni  $\rightarrow p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$



## HbA1c



ANOVA per misure ripetute

Within-subject

- Linear Trend Usual →  $p < 0.000$
- Linear Trend Intensive →  $p < 0.000$

Between-subject

- t-test Intensive vs Usual baseline →  $p = \text{NS}$
- t-test Intensive vs Usual 1 anno →  $p < 0.001$
- t-test Intensive vs Usual 2 anni →  $p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$

# Colesterolo LDL

## ANOVA per misure ripetute

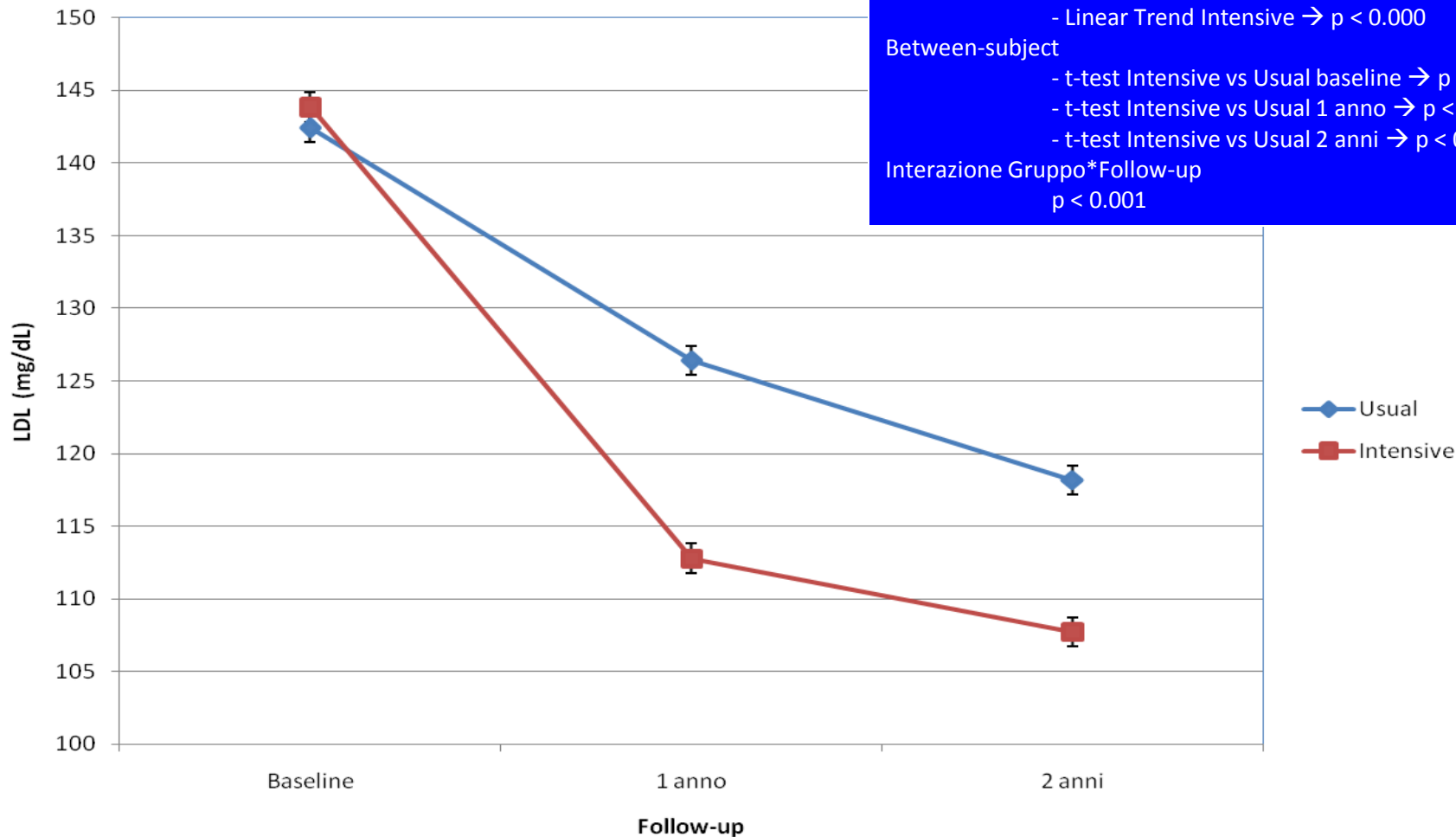
### Within-subject

- Linear Trend Usual  $\rightarrow p < 0.000$
- Linear Trend Intensive  $\rightarrow p < 0.000$

### Between-subject

- t-test Intensive vs Usual baseline  $\rightarrow p = \text{NS}$
- t-test Intensive vs Usual 1 anno  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 2 anni  $\rightarrow p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$



# Trigliceridi

## ANOVA per misure ripetute

### Within-subject

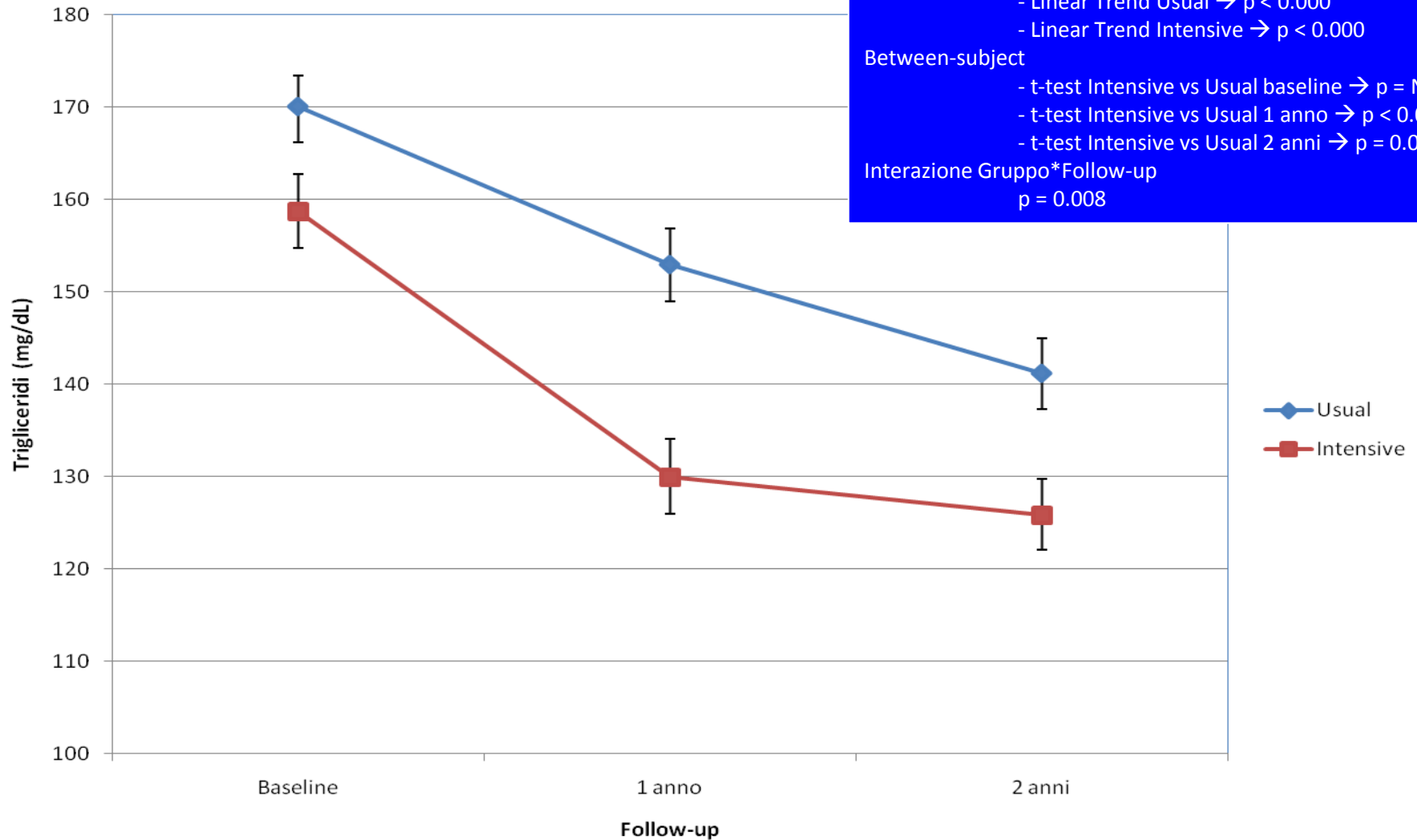
- Linear Trend Usual  $\rightarrow p < 0.000$
- Linear Trend Intensive  $\rightarrow p < 0.000$

### Between-subject

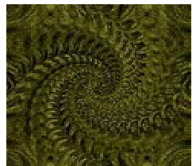
- t-test Intensive vs Usual baseline  $\rightarrow p = \text{NS}$
- t-test Intensive vs Usual 1 anno  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 2 anni  $\rightarrow p = 0.001$

### Interazione Gruppo\*Follow-up

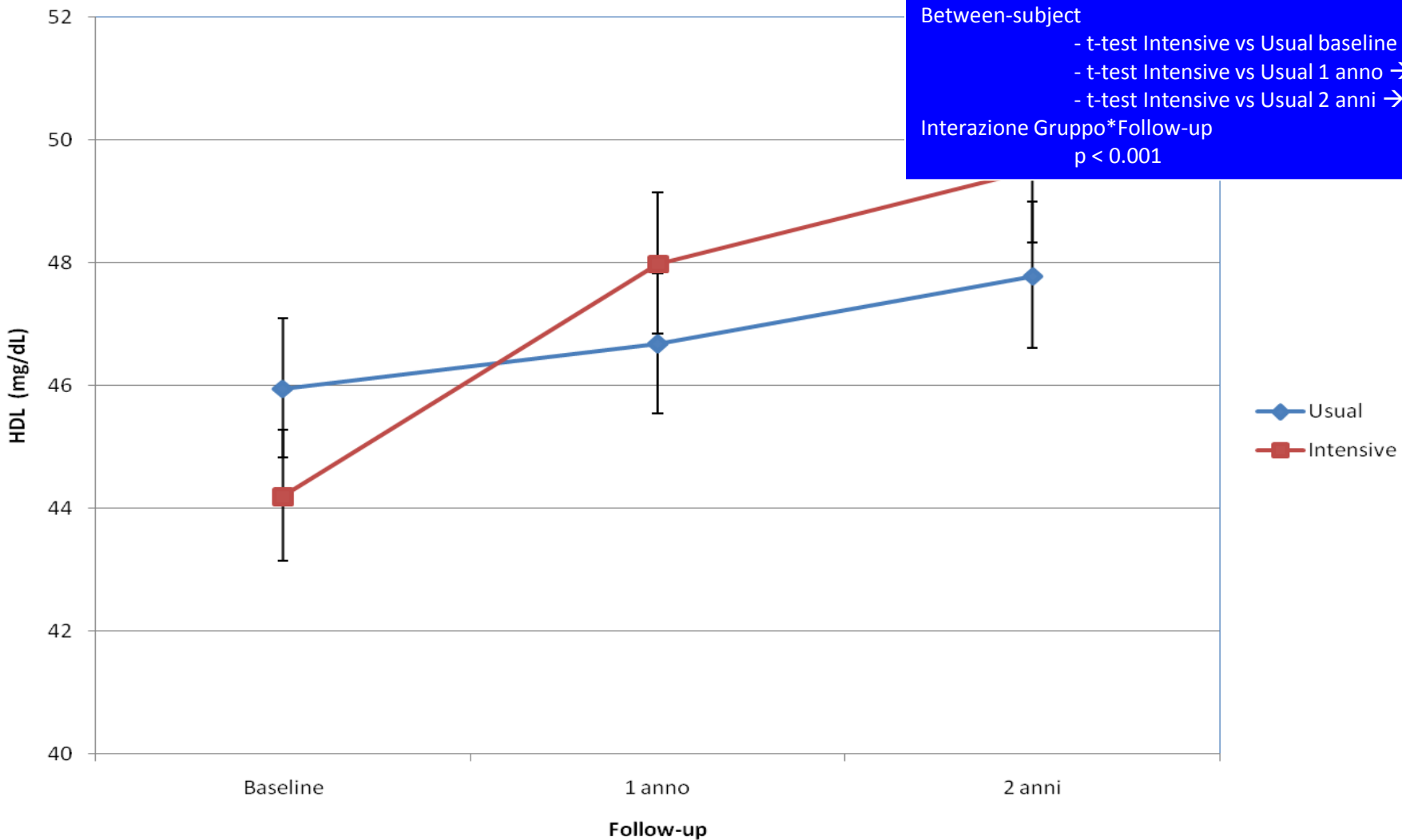
$p = 0.008$







# Colesterolo HDL



## ANOVA per misure ripetute

### Within-subject

- Linear Trend Usual  $\rightarrow p < 0.000$
- Linear Trend Intensive  $\rightarrow p < 0.000$

### Between-subject

- t-test Intensive vs Usual baseline  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 1 anno  $\rightarrow p = \text{NS}$
- t-test Intensive vs Usual 2 anni  $\rightarrow p = 0.020$

### Interazione Gruppo\*Follow-up

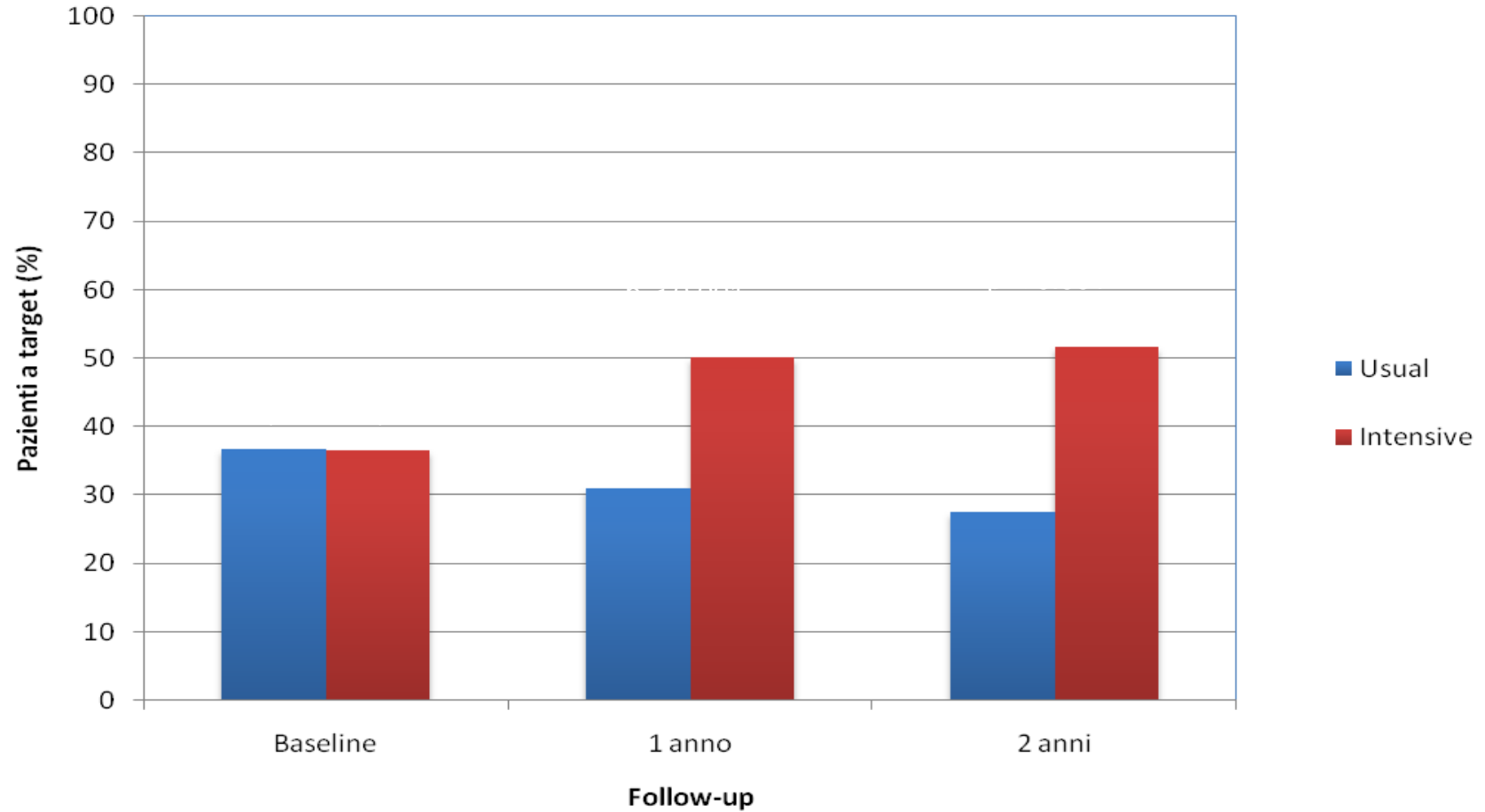
$p < 0.001$



## **Raggiungimento dei target**

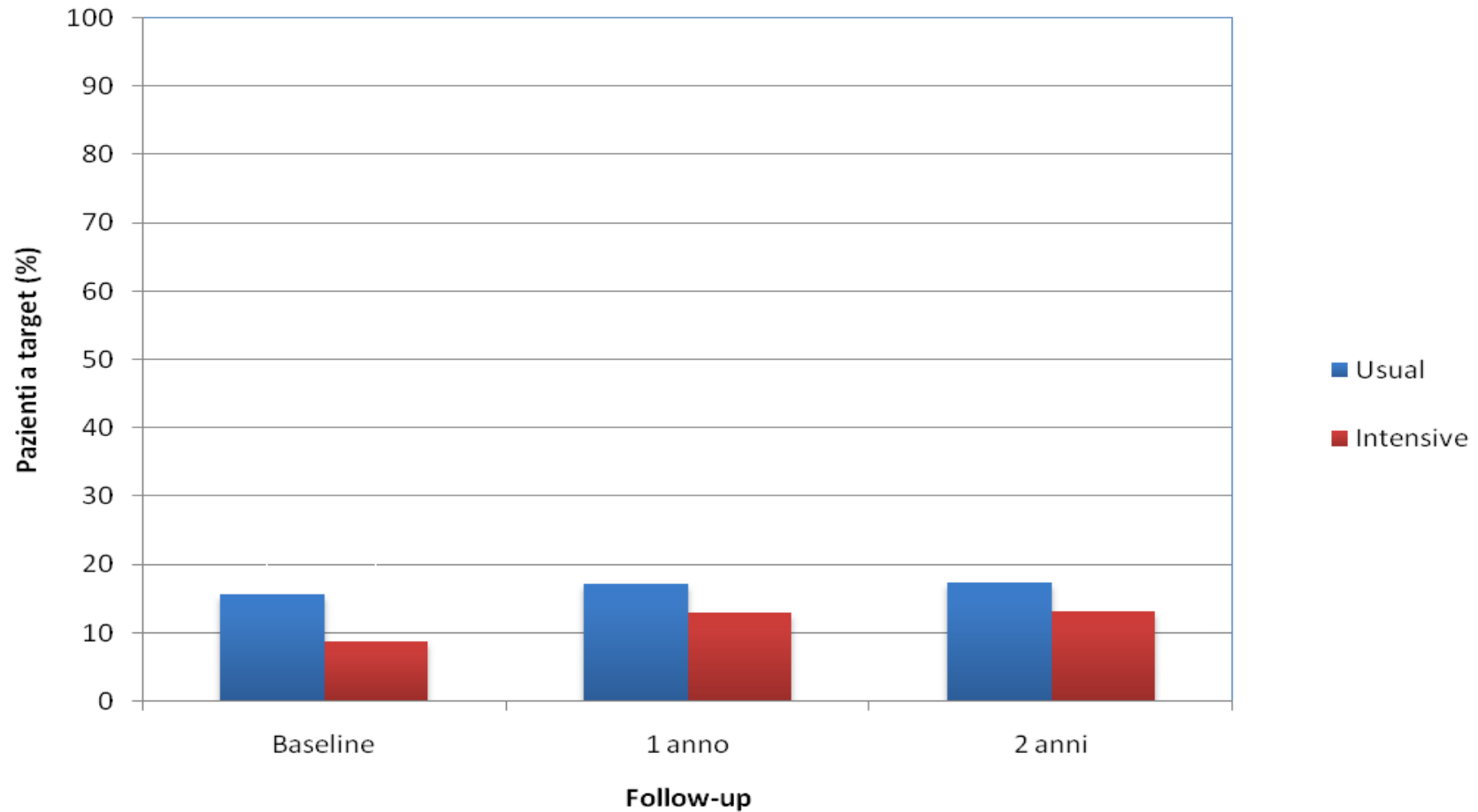


# HbA1c < 7 %



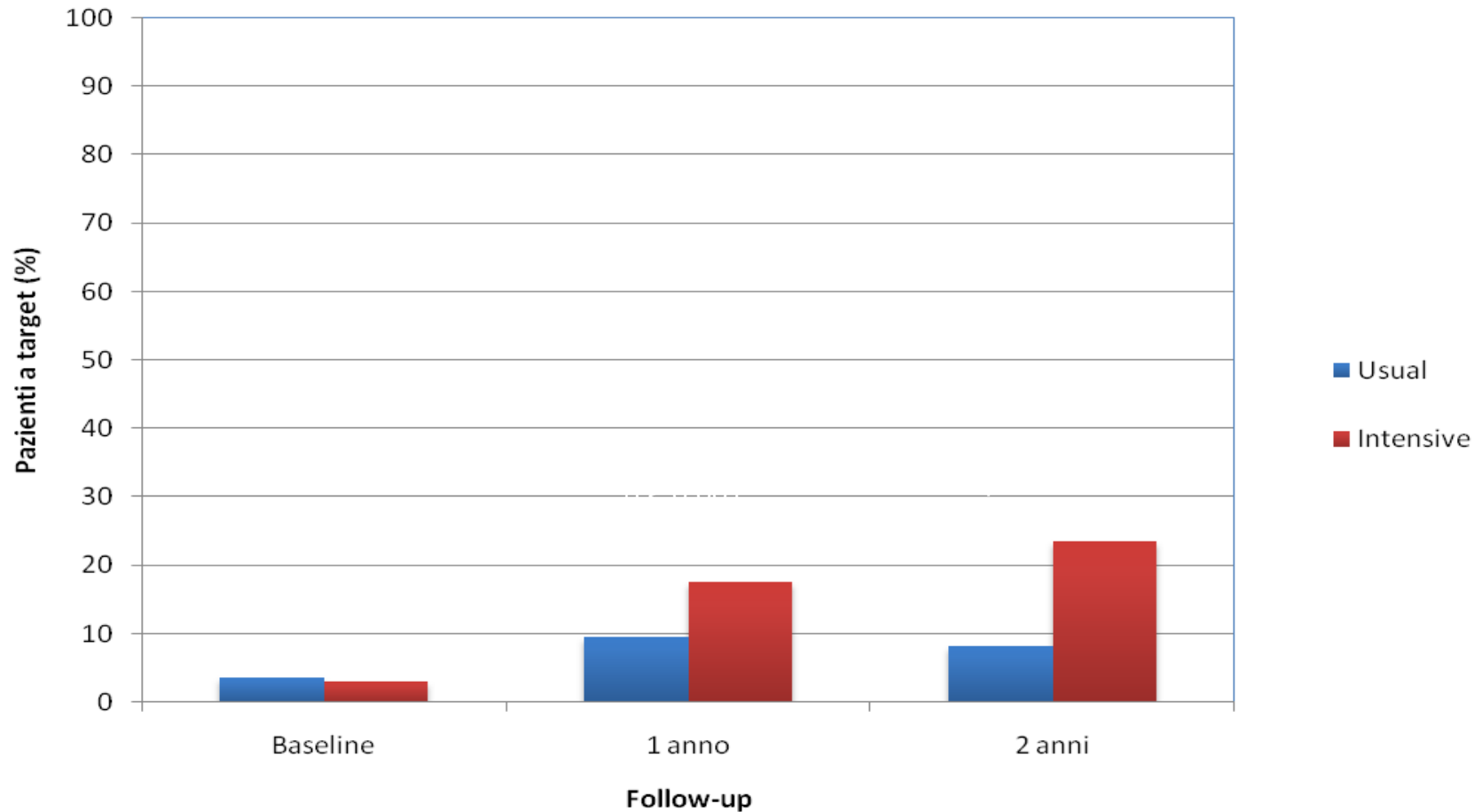


# BMI < 25 kg/m<sup>2</sup>



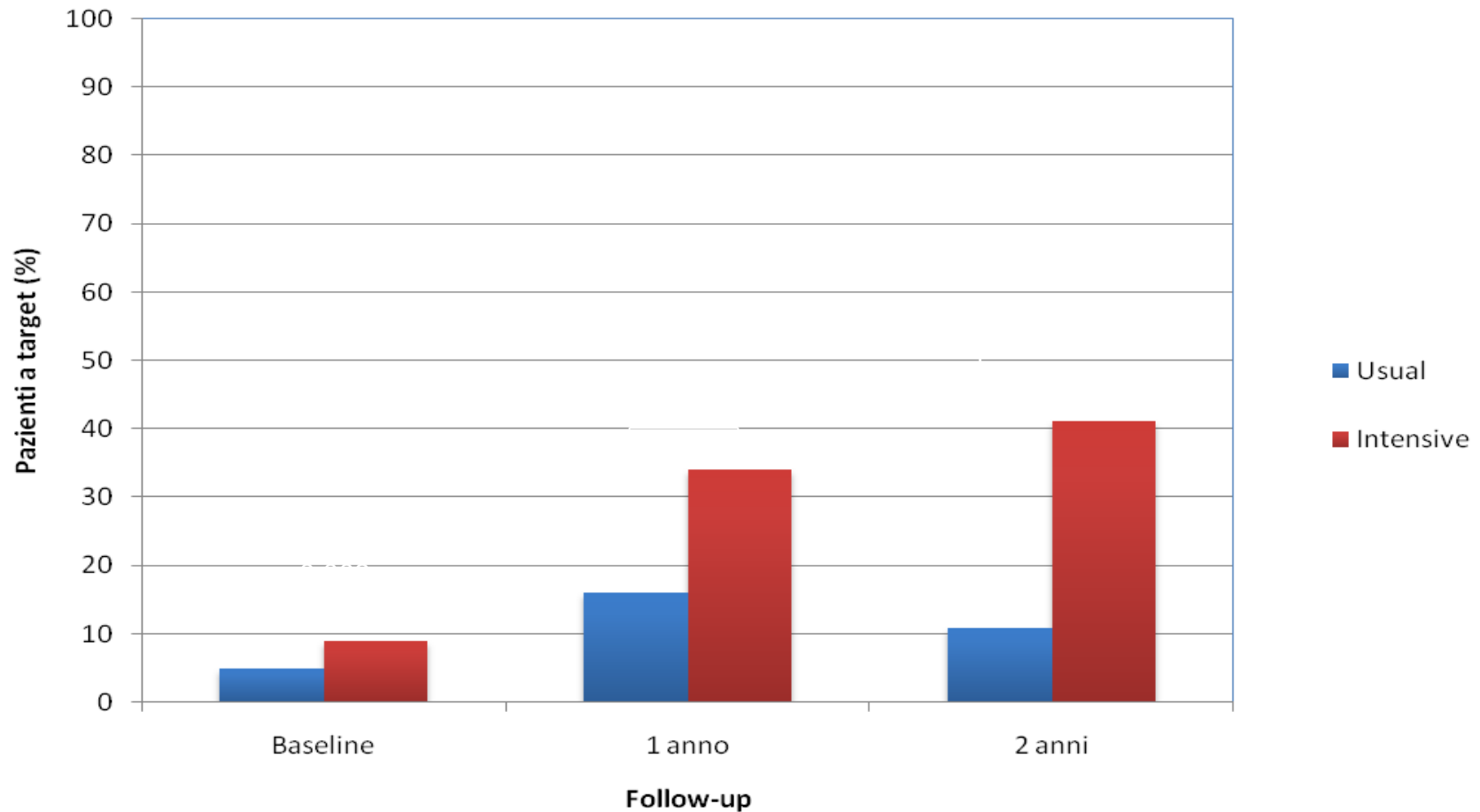


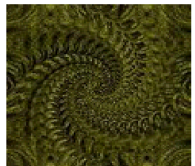
## Pressione arteriosa < 130/80 mmHg



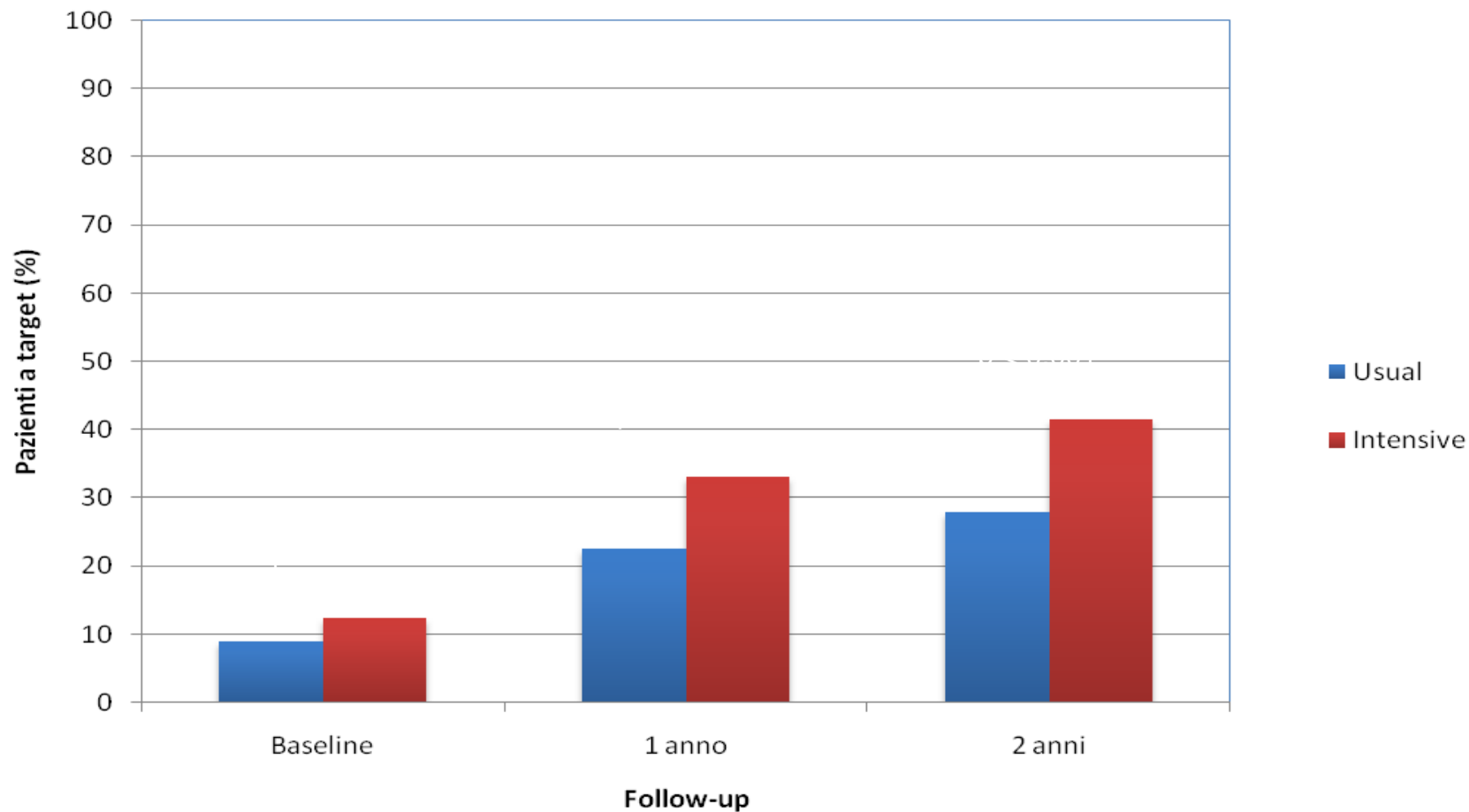


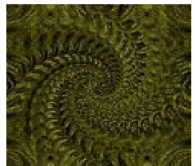
## Pressione sistolica < 130 mmHg



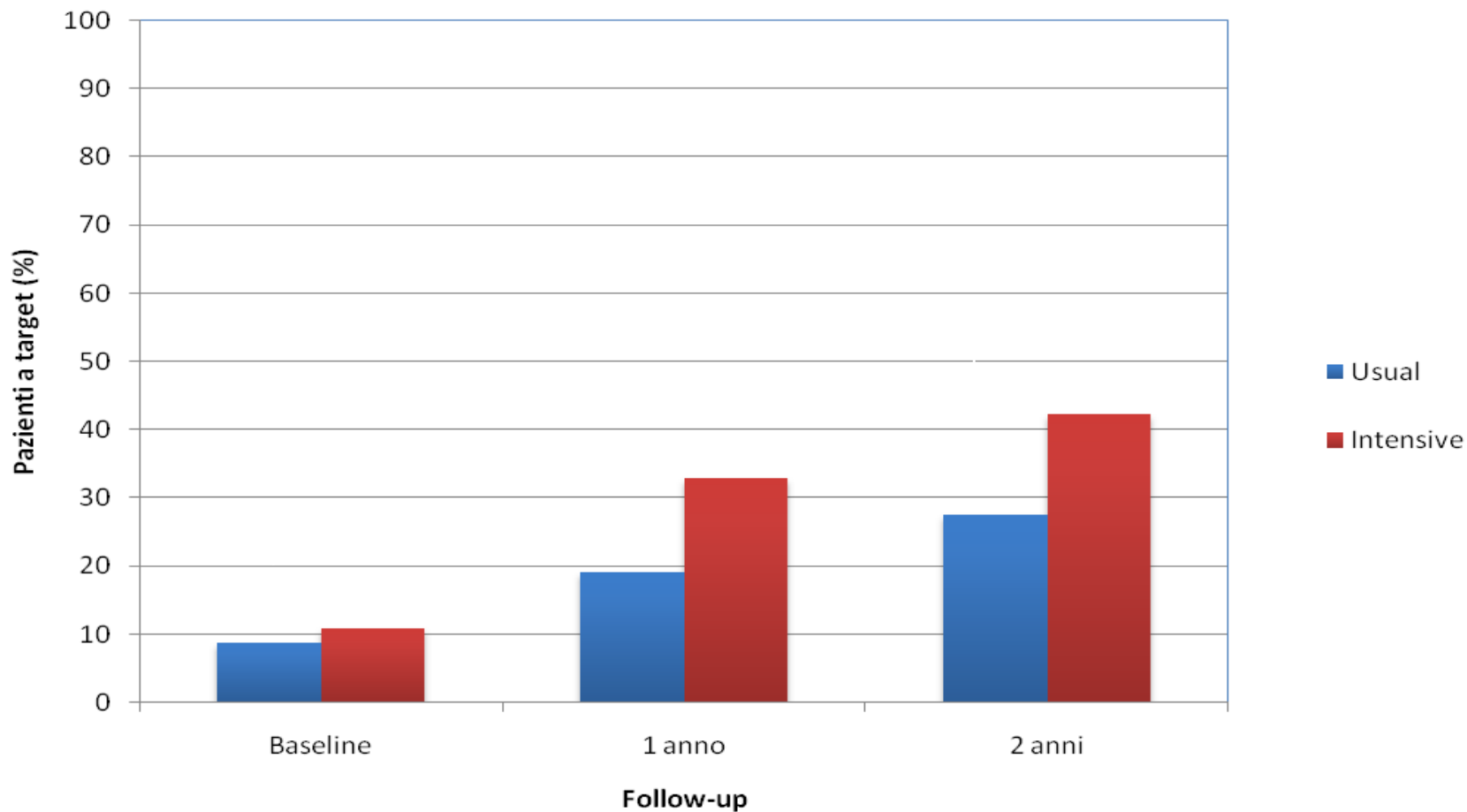


## Pressione diastolica < 80 mmHg

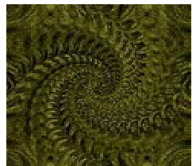




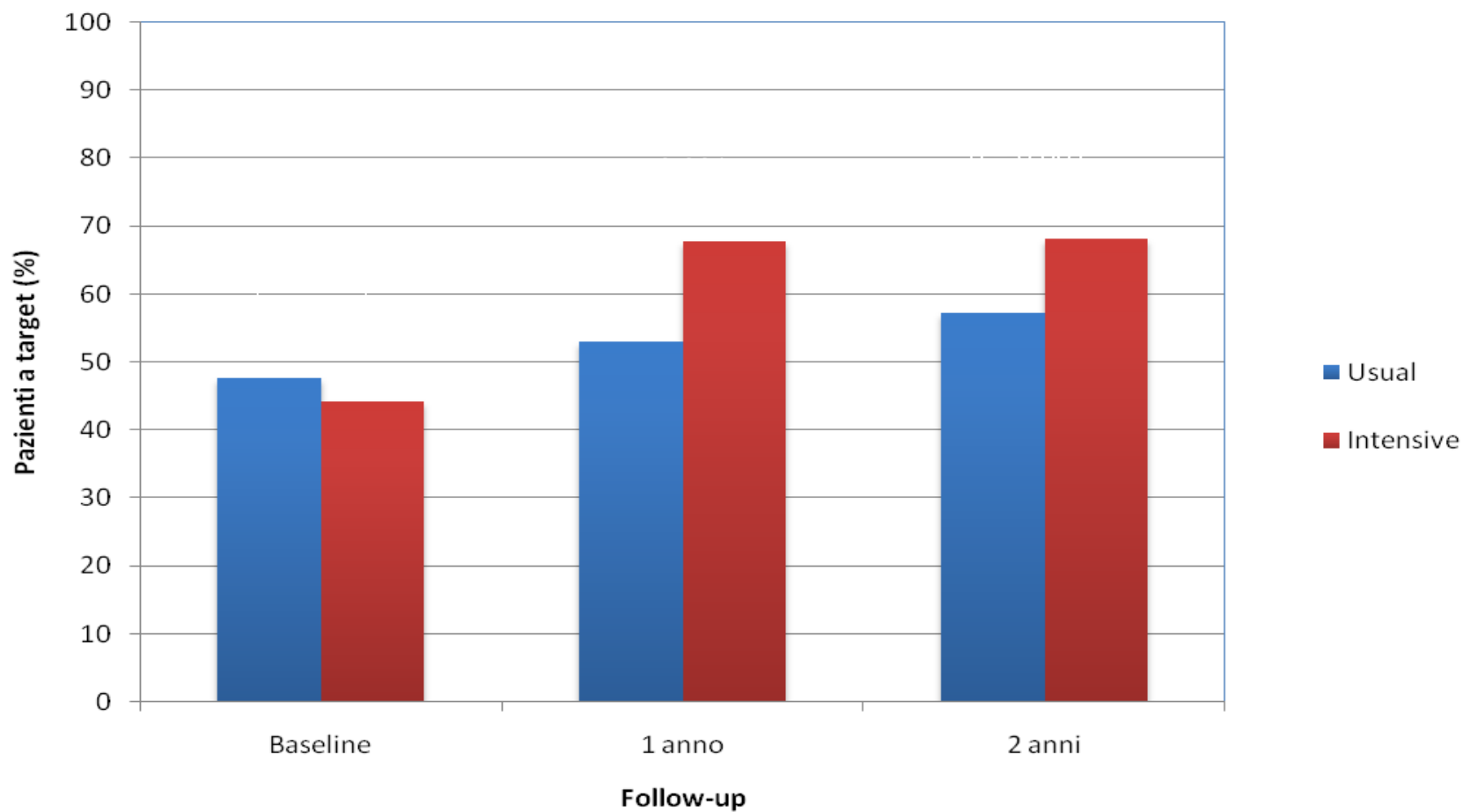
## Colesterolo LDL < 100 mg/dL





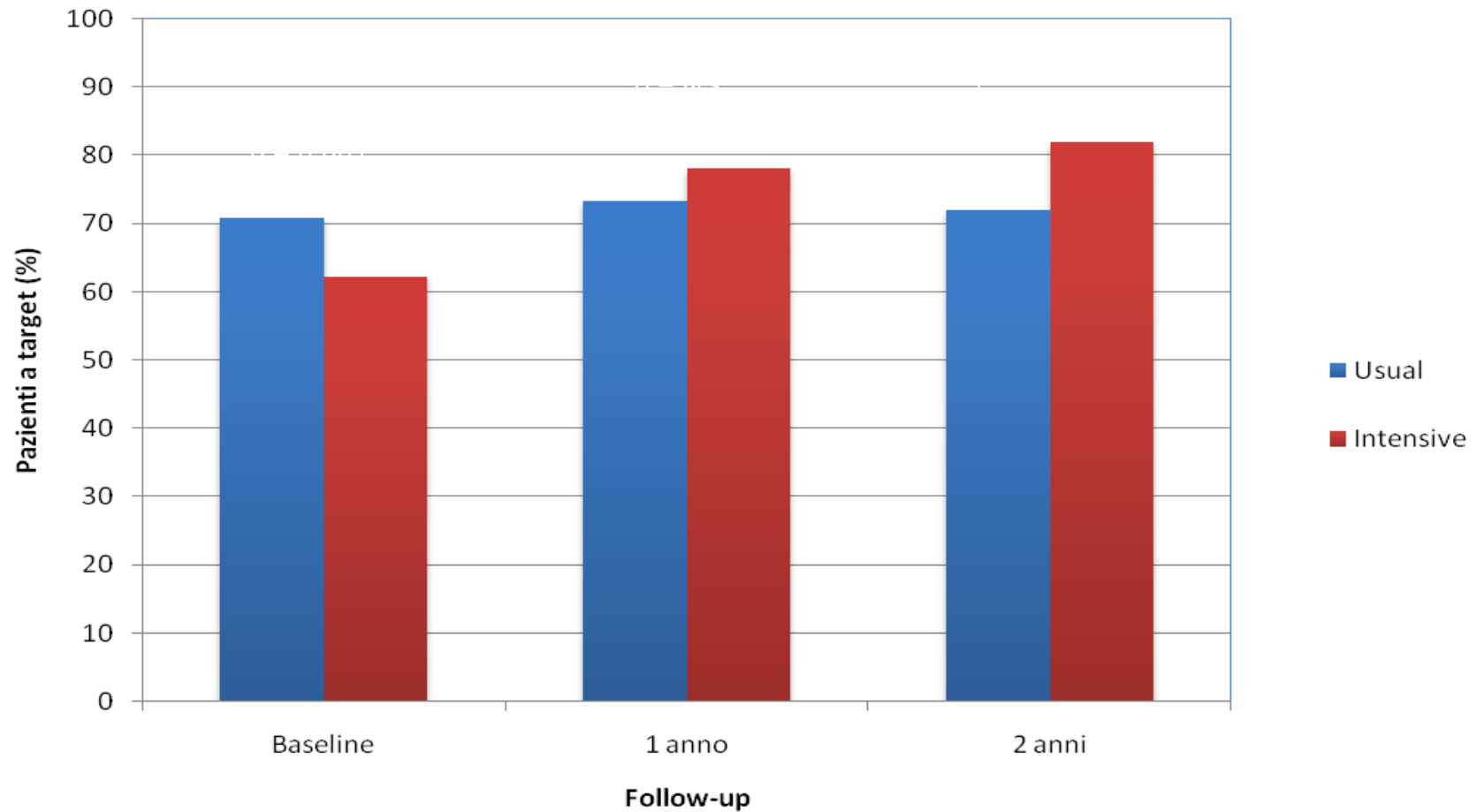


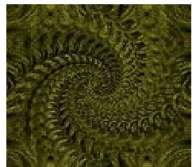
# Trigliceridi < 150 mg/dL





## Colesterolo HDL > 40 mg/dL





## **CONCLUSIONI-i**

- ❖ Il controllo abituale dei fattori di rischio cardiovascolare nel diabete di tipo 2 è insufficiente
- ❖ Una strategia di intervento intensivo multifattoriale permette di ottenere un significativo miglioramento dei fattori di rischio cardiovascolare
- ❖ L'intervento sullo stile di vita permette di migliorare il compenso glicemico e metabolico senza incrementare il peso corporeo
- ❖ Il peggioramento del compenso glicemico non è una evoluzione obbligata nel diabete di tipo 2

## **CONCLUSIONI-ii**

- ❖ **Gli effetti del trattamento intensivo sui fattori di rischio cardiovascolare si mantengono nel tempo**
- ❖ **Nonostante il trattamento intensivo, il raggiungimento degli obiettivi terapeutici -se pur significativamente migliorato- non è ancora ottimale**
- ❖ **Evidenza di inerzia al “treat to target”**
- ❖ **La prosecuzione dello Studio MIND-IT permetterà di evidenziare se il contemporaneo miglioramento di tutti i fattori di rischio cardiovascolare considerati si traduce in una riduzione degli eventi cardiovascolari, come atteso in base alle premesse dello studio.**

# **L' educazione terapeutica nella cura del diabete**

# Multifactorial Intervention in type 2 Diabetes – Italy : MIND:IT



Studio di intervento multicentrico randomizzato che confronta la usual-care con un intervento multifattoriale intensivo “treat-to-target” (Intensive Care) per la prevenzione primaria cardiovascolare

9 centri – 1461 diabetici tipo 2 (759 M / 702 F, età  $61 \pm 5$  anni) follow up 5 anni.

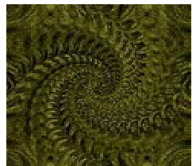
## SCOPO DELLO STUDIO

- Valutare fattibilità ed efficacia di un intervento multifattoriale di prevenzione primaria degli eventi CV nel diabete di Tipo 2, disegnato secondo le Linee Guida elaborate dal GDS SID Diabete ed Aterosclerosi confrontato con la gestione usual care

## Strategie di intervento. OBIETTIVI

- ✓ Sospensione del fumo
- ✓ Riduzione del peso >5% nei soggetti in sovrappeso
  
- ✓ **Intervento di educazione terapeutica:**
- ✓ **Intervento dietetico:**
- ✓ **Grassi saturi <10%**
- ✓ **Fibre >15g/1000 cal**
- ✓ **Esercizio fisico: dispendio calorico 200-300cal /die**
  
- ✓ HbA1c <7%,
- ✓ LDL colesterolo < 100 mg/dl, Trigliceridi <150 mg/dl, HDL colesterolo >40 mg/dl negli uomini, >45 mg/dl nelle donne;
- ✓ Pressione arteriosa <130/80 mm Hg
- ✓ Terapia antiaggregante



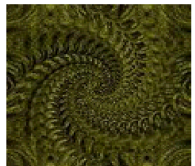


## METODOLOGIA DELLO STUDIO

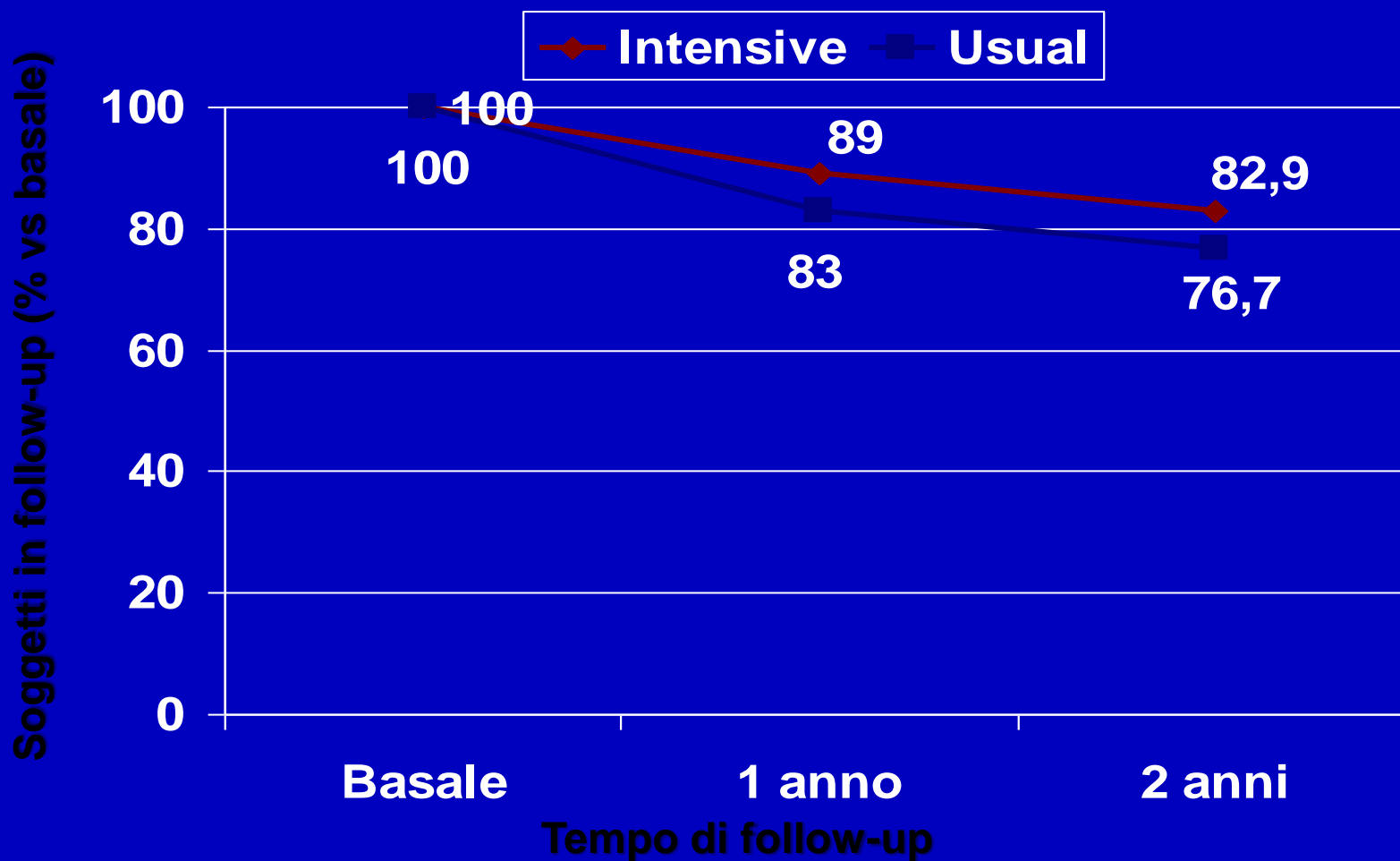
- ❖ Intervento Stile di vita
- ❖ Predisposizione di manuali operativi (procedure, intervento per la sospensione del fumo, per la dieta e per l'attività fisica)
- ❖ Incontri di training per i Centri intensive ,per uniformare gli interventi sullo stile di vita e sulla prescrizione di farmaci
- ❖ Incontri con dietista e training attività fisica : all' inizio e dopo 1 mese, ogni 3 mesi per valutazione diario alimentare e diario attività fisica

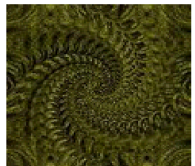


## Risultati al follow-up



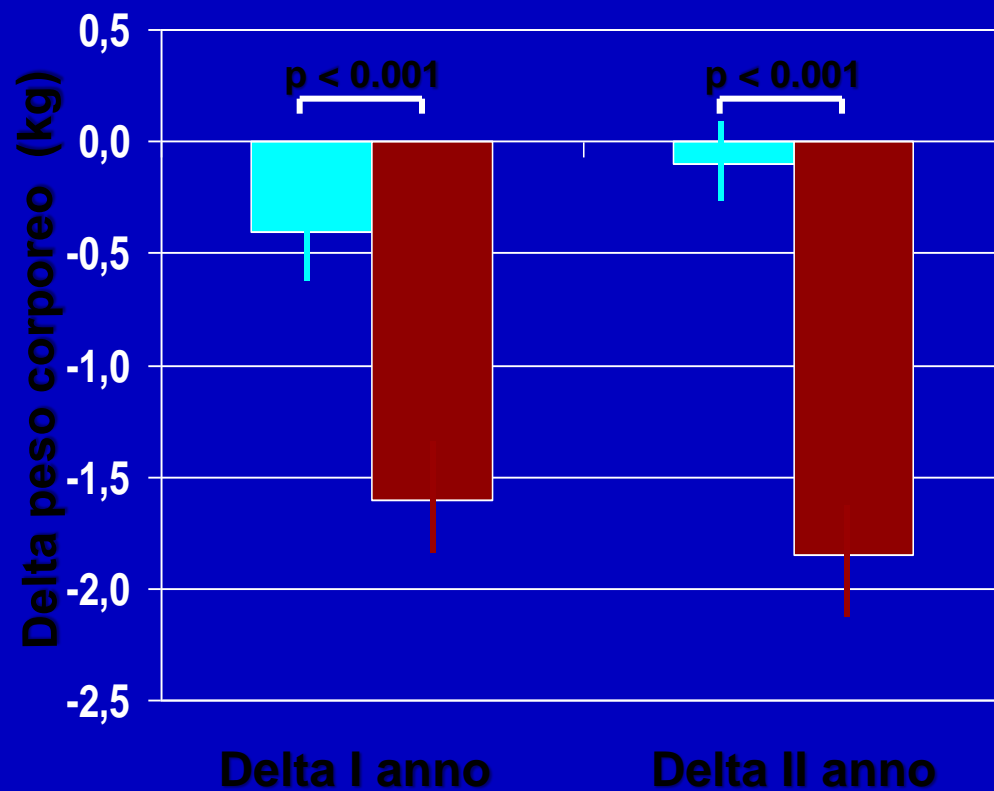
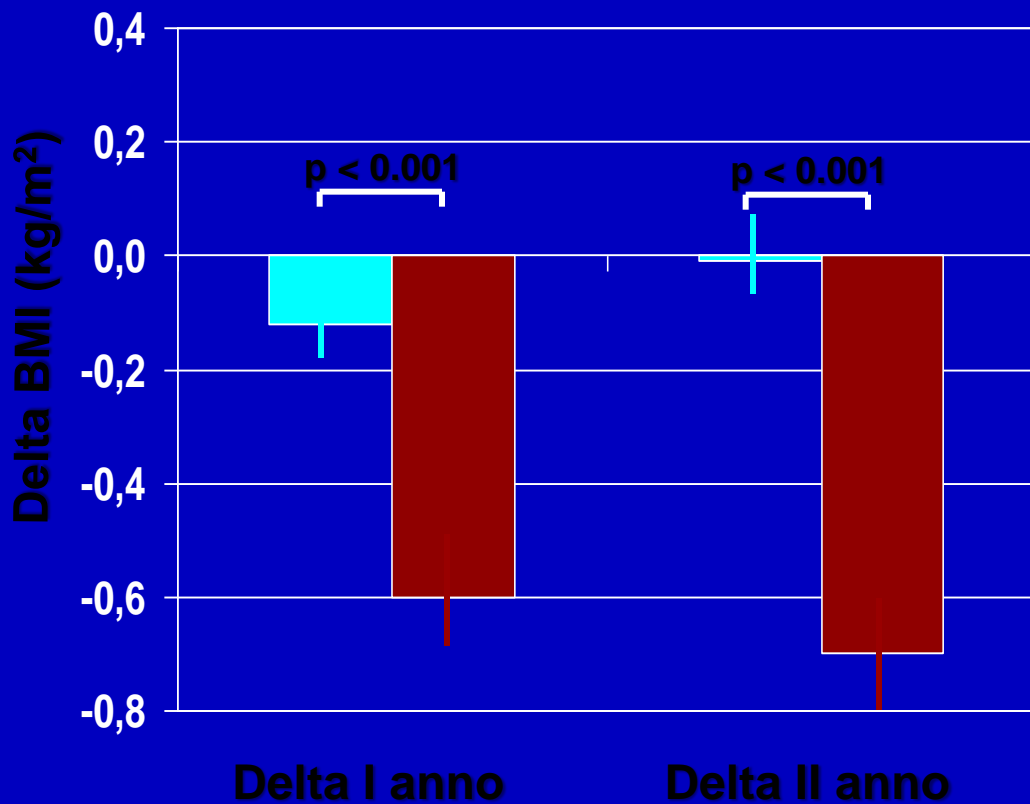
## Percentuale di pazienti in follow-up

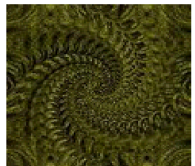




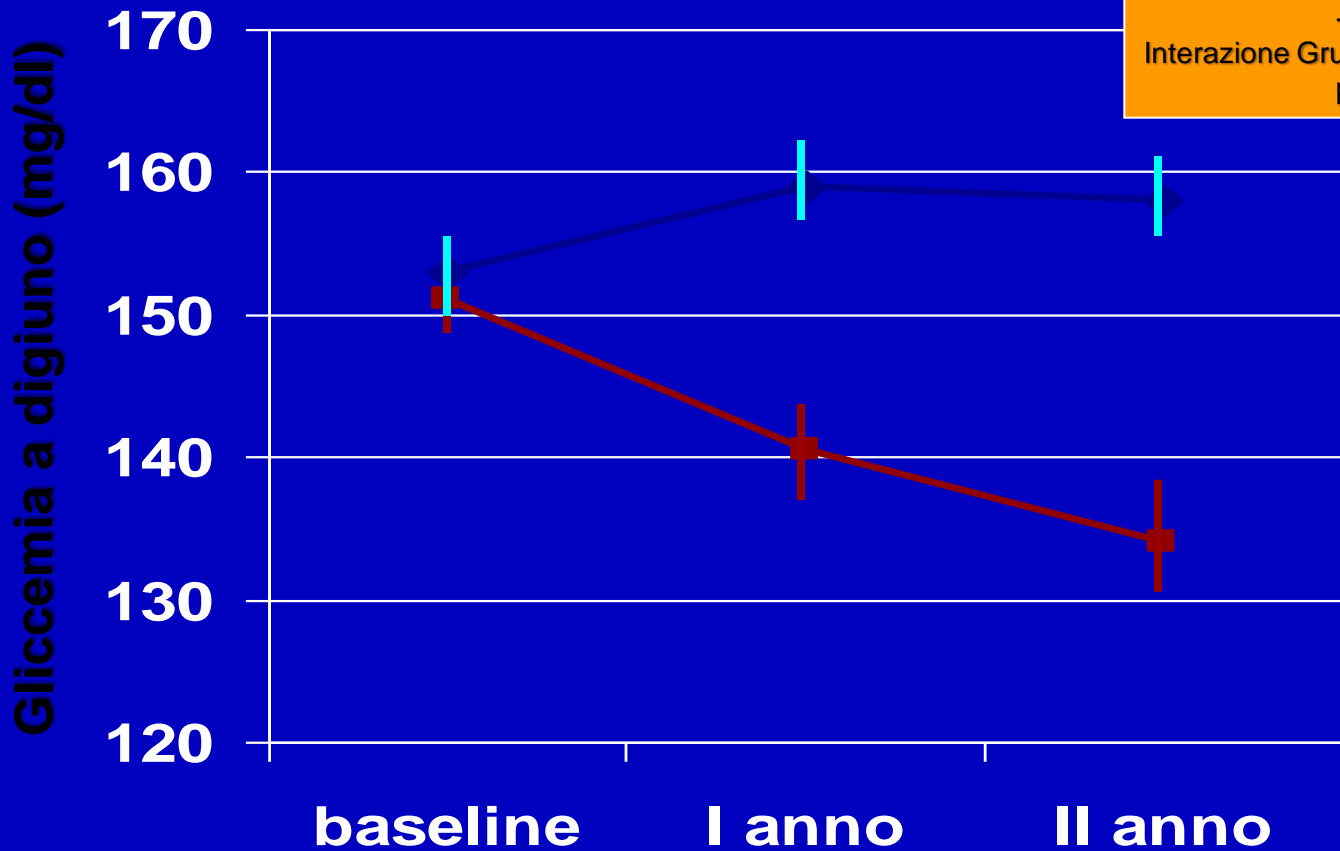
## Variazione di BMI e peso durante il follow-up

Usual Intensive





# Glicemia a digiuno



**ANOVA per misure ripetute**

Within-subject

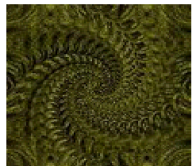
- Linear Trend Usual →  $p < 0.005$
- Linear Trend Intensive →  $p < 0.000$

Between-subject

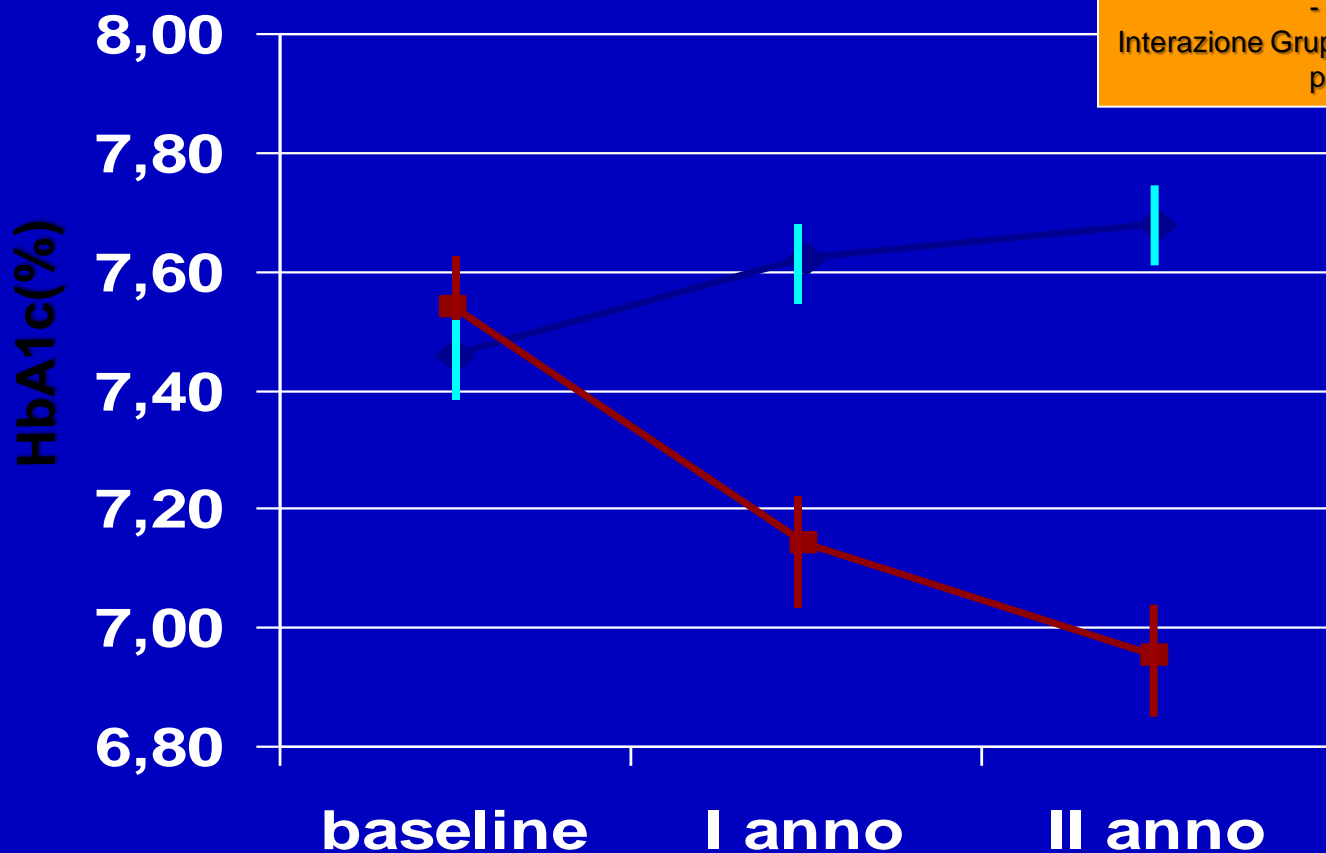
- t-test Intensive vs Usual baseline →  $p = \text{NS}$
- t-test Intensive vs Usual 1 anno →  $p < 0.001$
- t-test Intensive vs Usual 2 anni →  $p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$

◆ Usual  
■ Intensive



# HbA1c



**ANOVA per misure ripetute**

Within-subject

- Linear Trend Usual →  $p < 0.000$
- Linear Trend Intensive →  $p < 0.000$

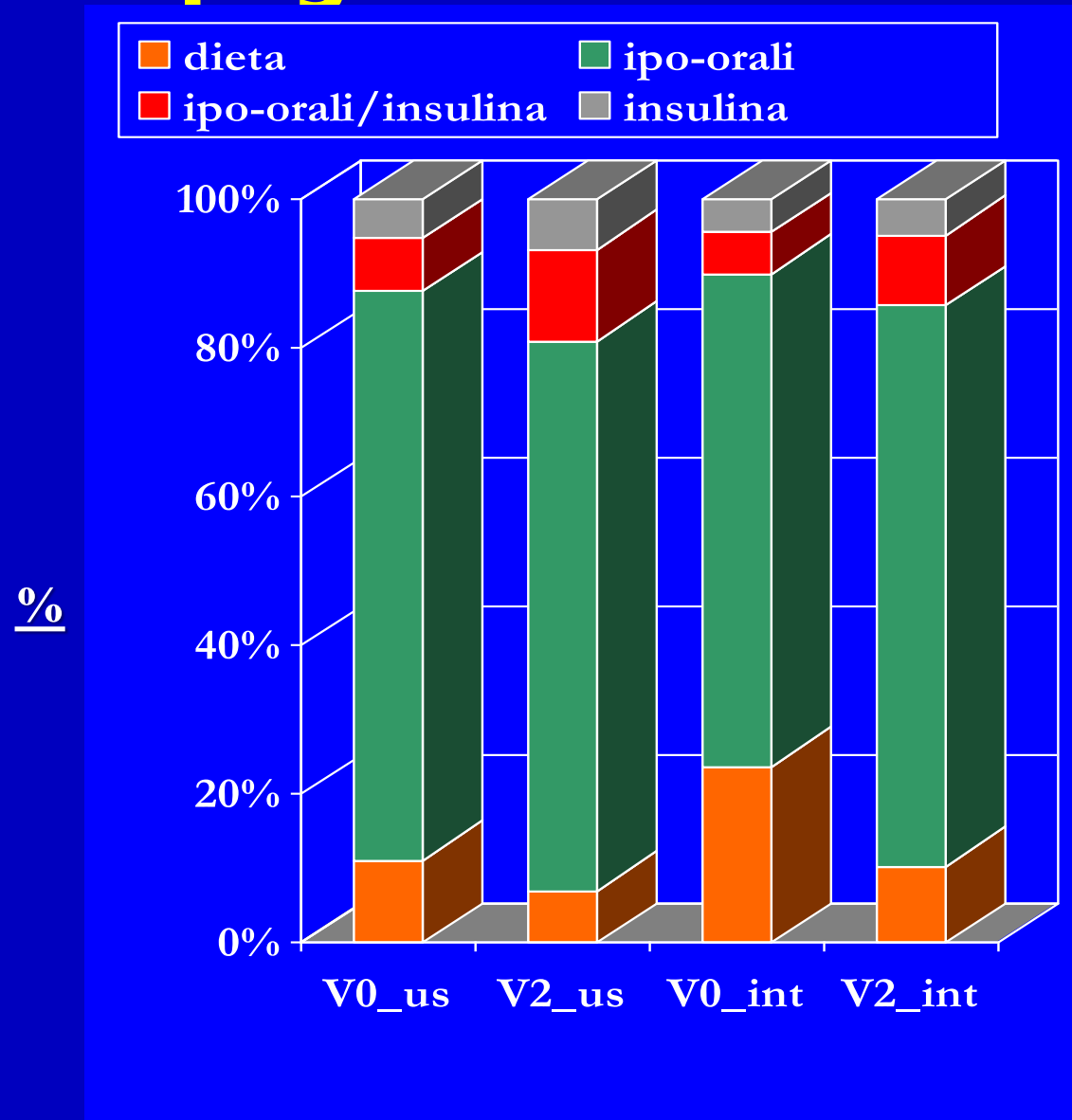
Between-subject

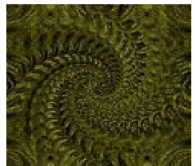
- t-test Intensive vs Usual baseline →  $p = \text{NS}$
- t-test Intensive vs Usual 1 anno →  $p < 0.001$
- t-test Intensive vs Usual 2 anni →  $p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$

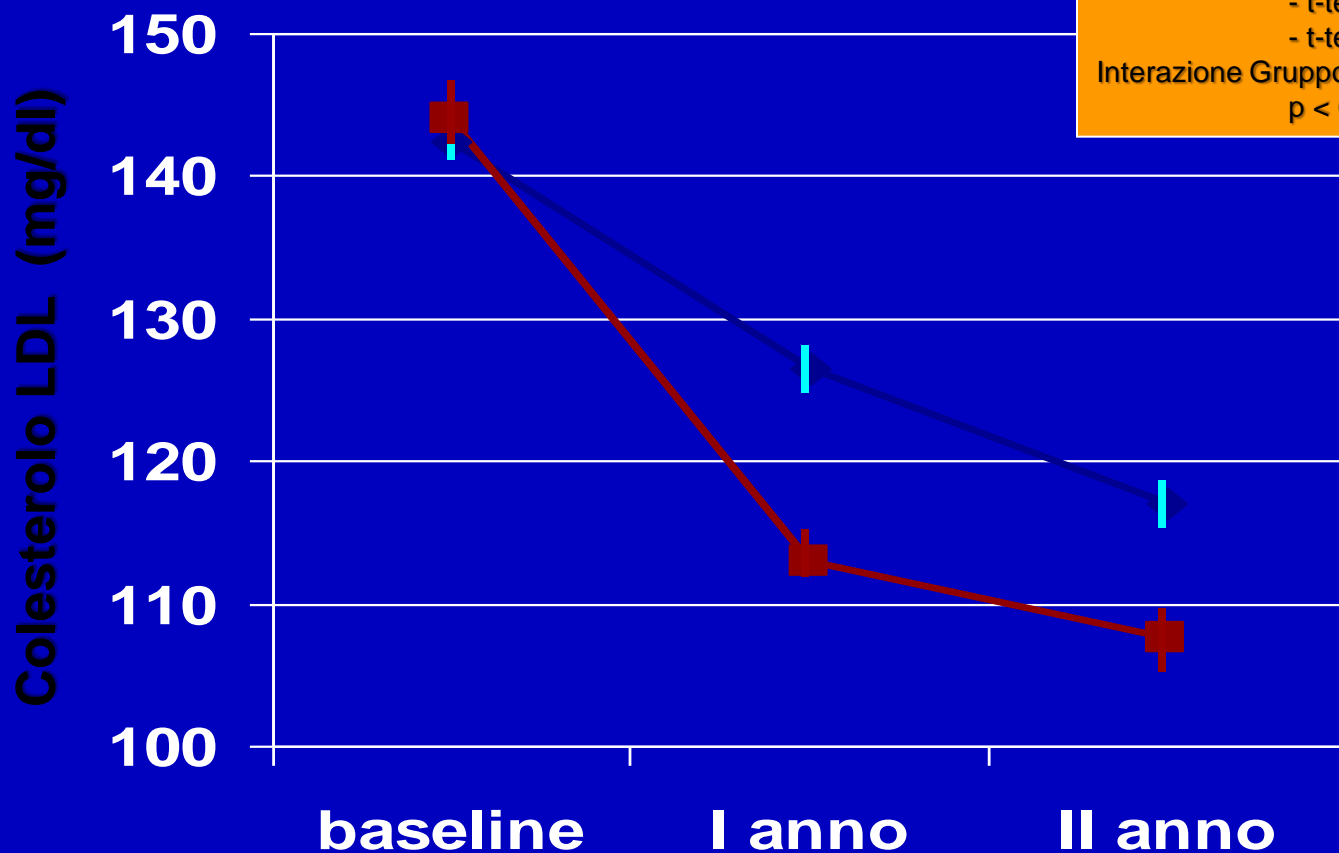
◆ Usual  
■ Intensive

# Terapia farmacologica ipoglicemizzante





## Colesterolo LDL



### ANOVA per misure ripetute

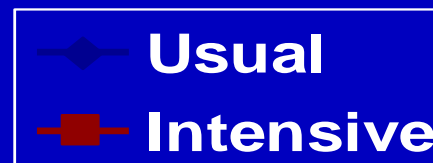
#### Within-subject

- Linear Trend Usual  $\rightarrow p < 0.000$
- Linear Trend Intensive  $\rightarrow p < 0.000$

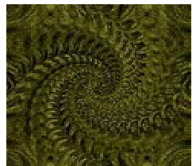
#### Between-subject

- t-test Intensive vs Usual baseline  $\rightarrow p = \text{NS}$
- t-test Intensive vs Usual 1 anno  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 2 anni  $\rightarrow p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$







# Trigliceridi

**ANOVA per misure ripetute**

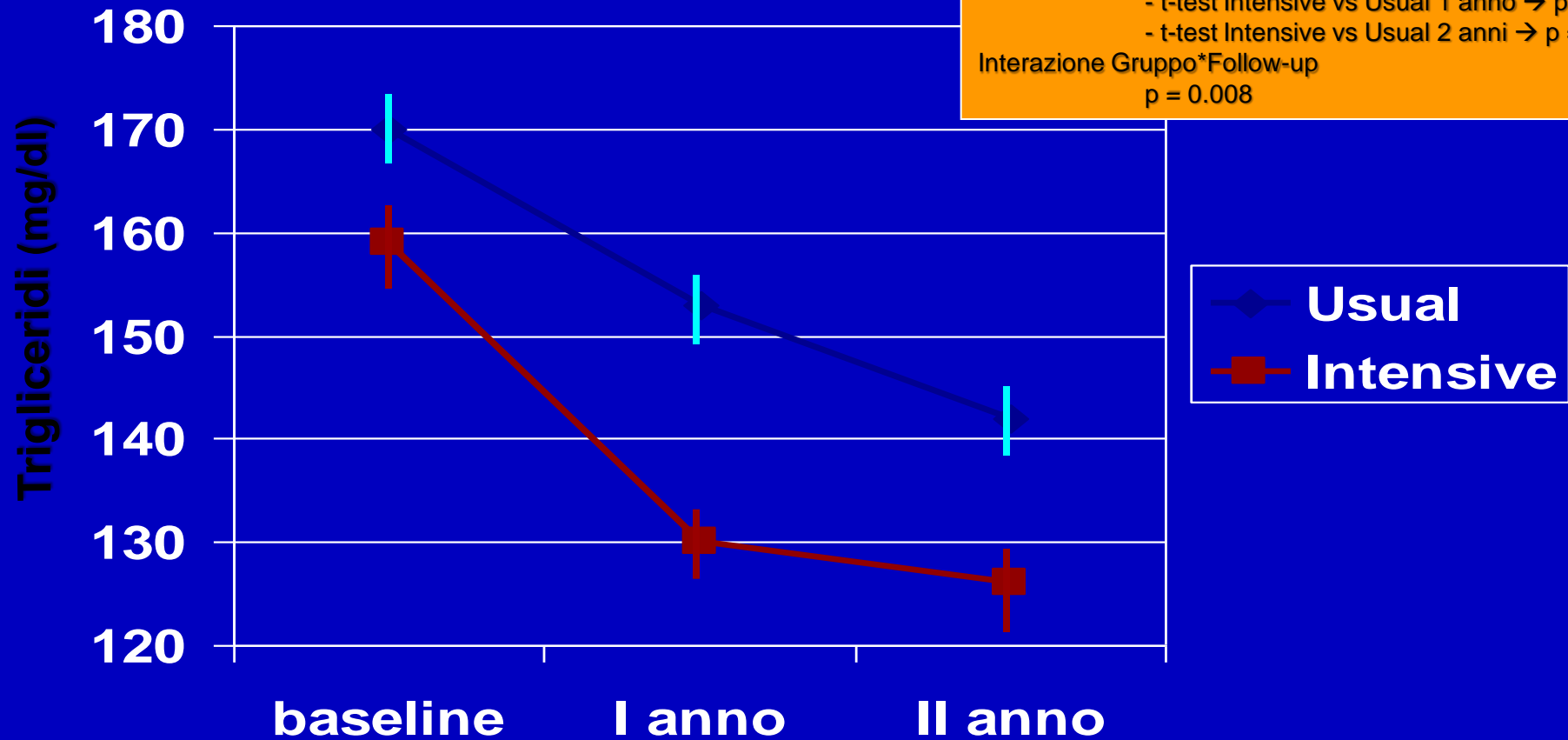
Within-subject

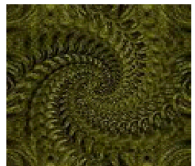
- Linear Trend Usual →  $p < 0.000$
- Linear Trend Intensive →  $p < 0.000$

Between-subject

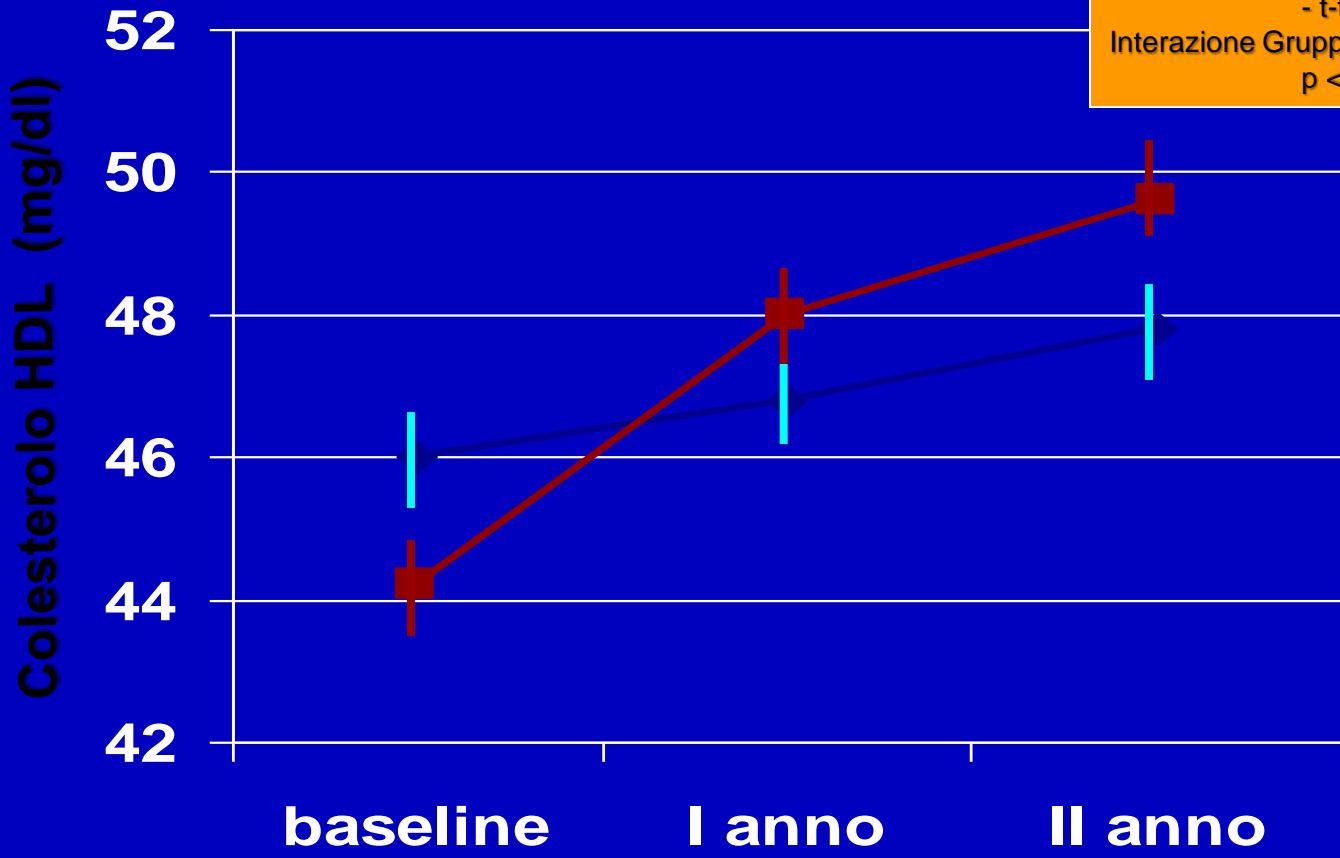
- t-test Intensive vs Usual baseline →  $p = \text{NS}$
- t-test Intensive vs Usual 1 anno →  $p < 0.001$
- t-test Intensive vs Usual 2 anni →  $p = 0.001$

Interazione Gruppo\*Follow-up  
 $p = 0.008$





# Colesterolo HDL



**ANOVA per misure ripetute**

Within-subject

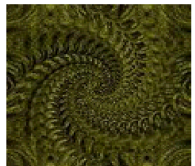
- Linear Trend Usual →  $p < 0.000$
- Linear Trend Intensive →  $p < 0.000$

Between-subject

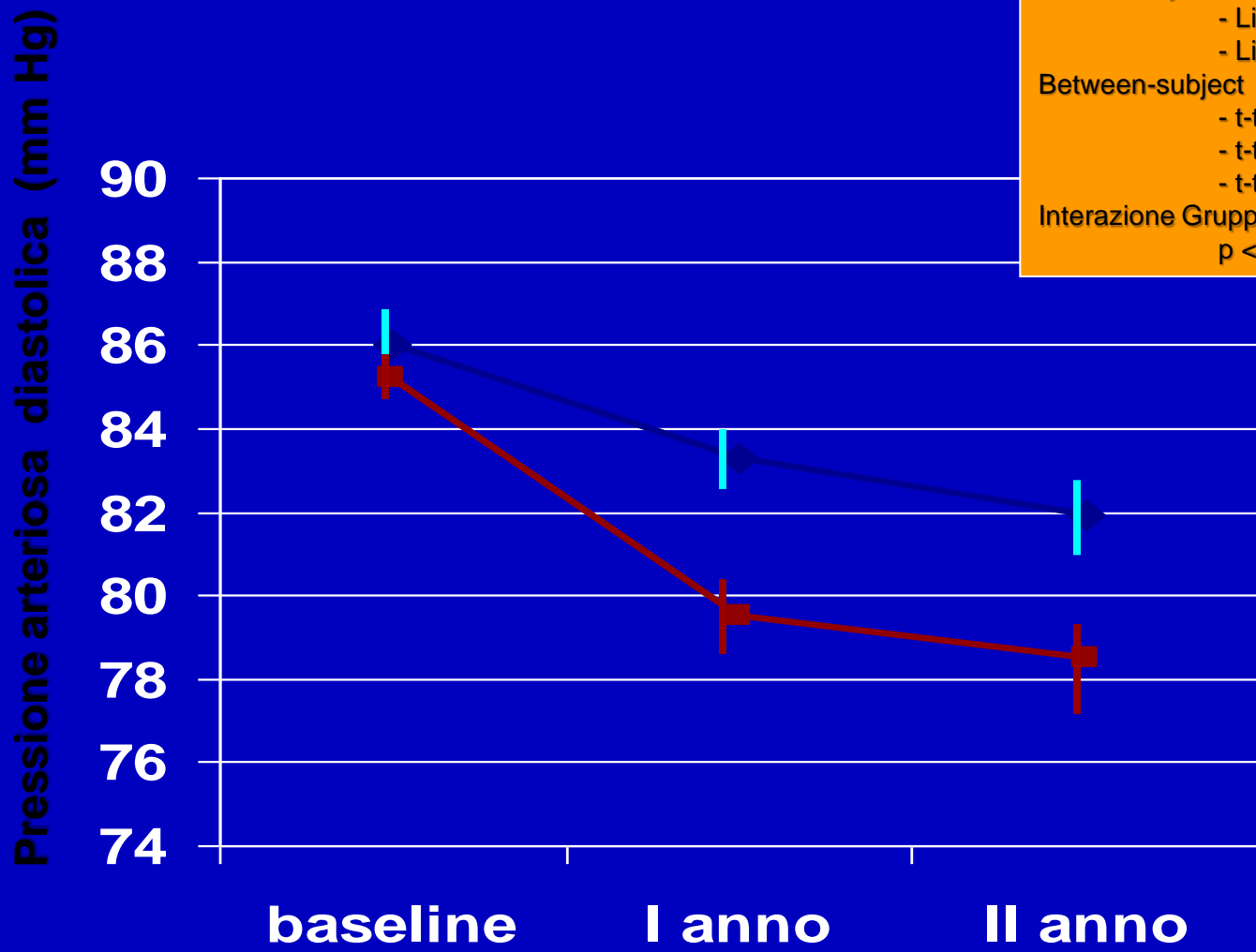
- t-test Intensive vs Usual baseline →  $p < 0.001$
- t-test Intensive vs Usual 1 anno →  $p = \text{NS}$
- t-test Intensive vs Usual 2 anni →  $p = 0.020$

Interazione Gruppo\*Follow-up  
 $p < 0.001$

◆ Usual  
■ Intensive



# Pressione Arteriosa Diastolica



**ANOVA per misure ripetute**

Within-subject

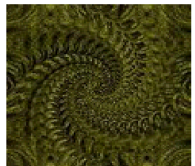
- Linear Trend Usual →  $p < 0.000$
- Linear Trend Intensive →  $p < 0.000$

Between-subject

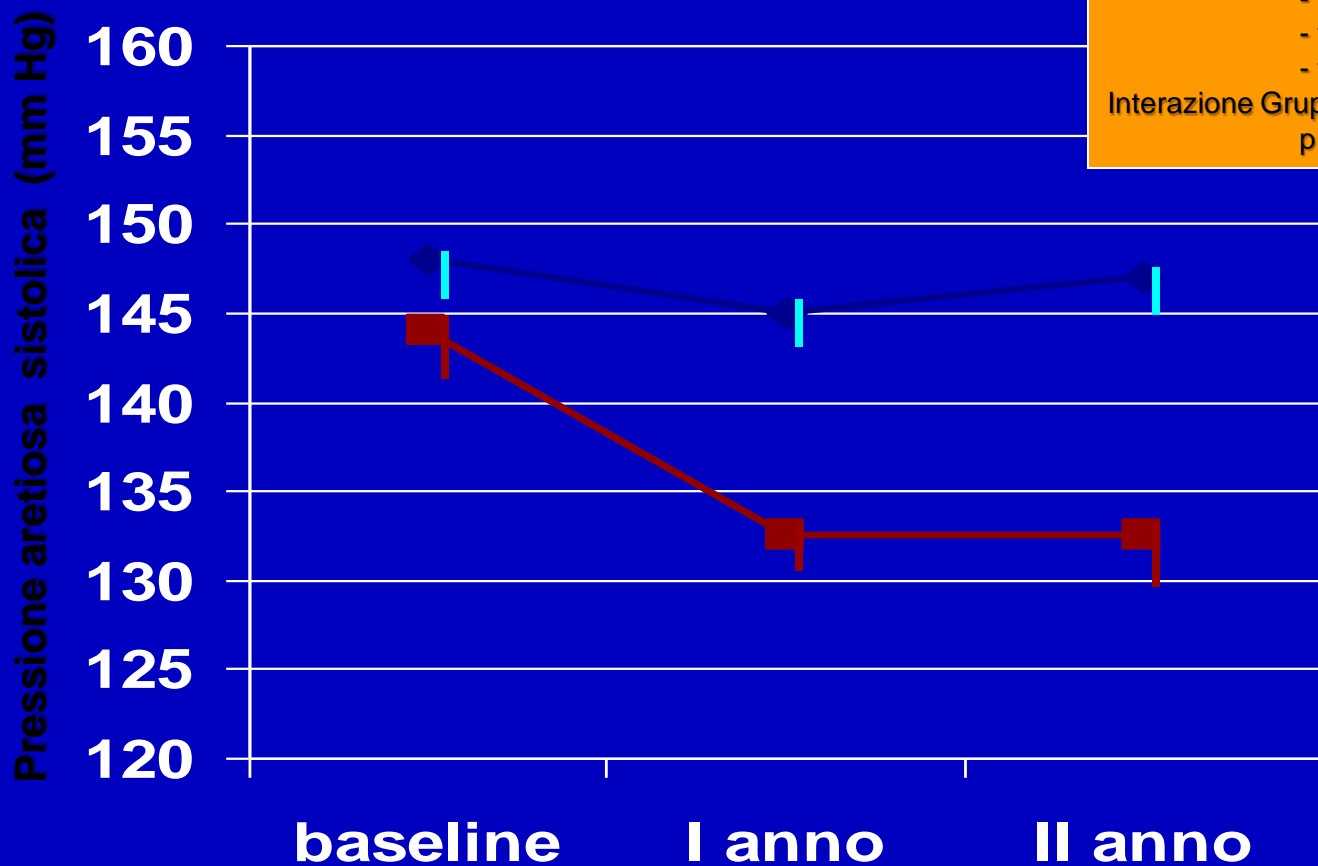
- t-test Intensive vs Usual baseline →  $p = 0.012$
- t-test Intensive vs Usual 1 anno →  $p < 0.001$
- t-test Intensive vs Usual 2 anni →  $p < 0.001$

Interazione Gruppo\*Follow-up  
 $p < 0.001$

◆ Usual  
■ Intensive



# Pressione Arteriosa Sistolica



## ANOVA per misure ripetute

Within-subject

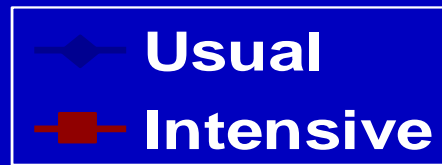
- Linear Trend Usual  $\rightarrow p < 0.005$
- Linear Trend Intensive  $\rightarrow p < 0.000$

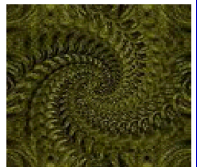
Between-subject

- t-test Intensive vs Usual baseline  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 1 anno  $\rightarrow p < 0.001$
- t-test Intensive vs Usual 2 anni  $\rightarrow p < 0.001$

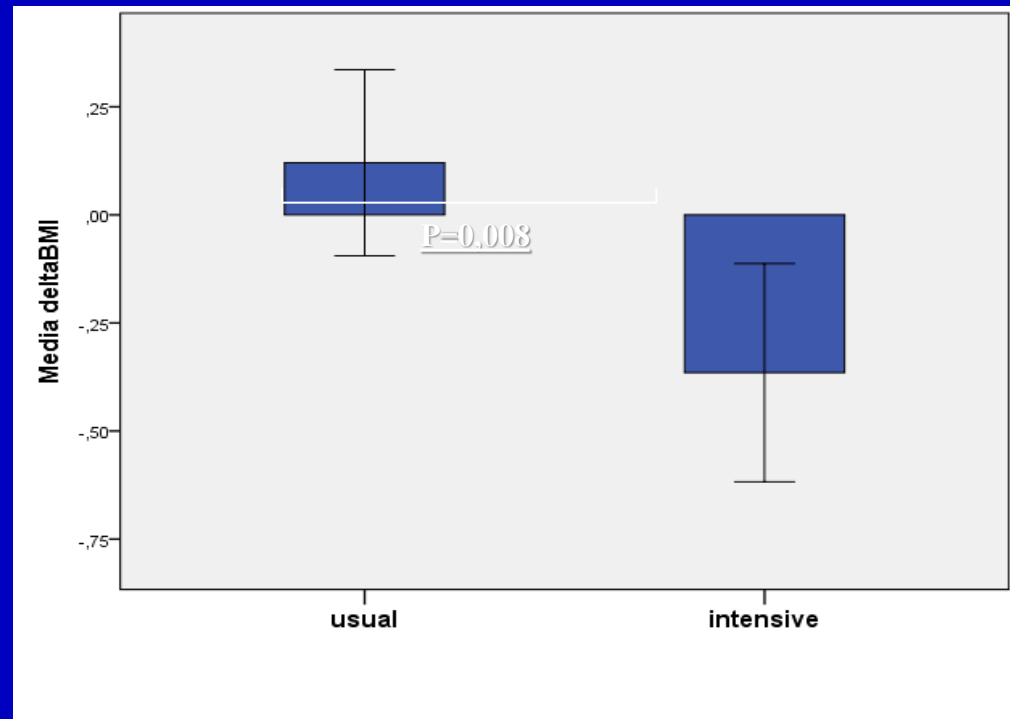
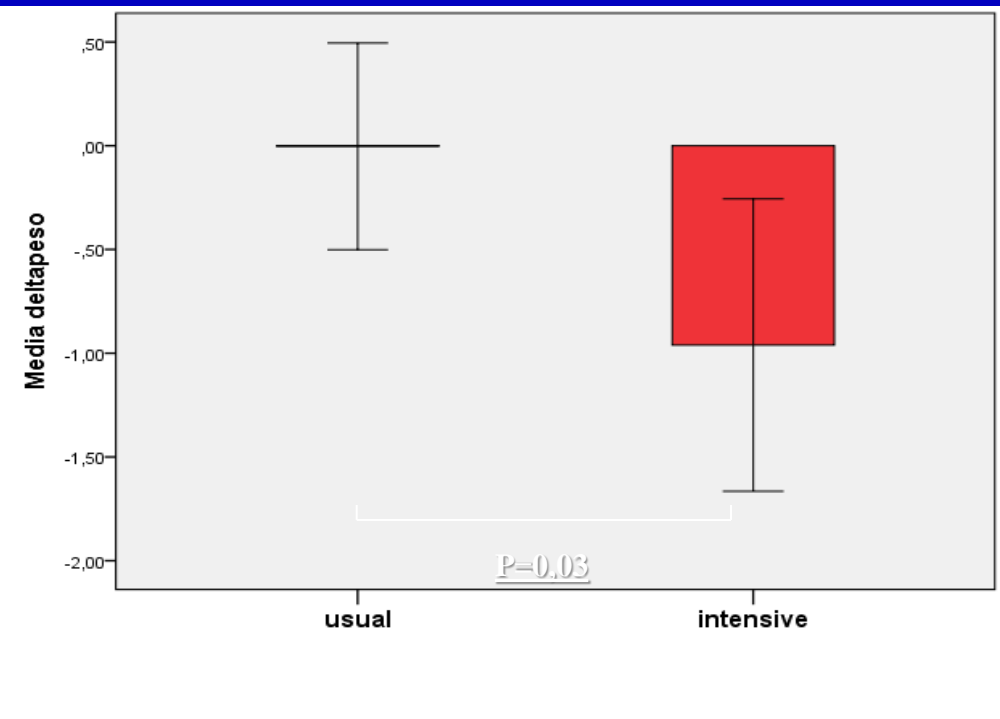
Interazione Gruppo\*Follow-up

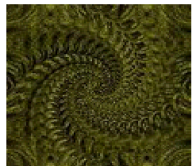
$p < 0.001$





# Variazione di peso e BMI e a 5 anni di follow up ( n . 11

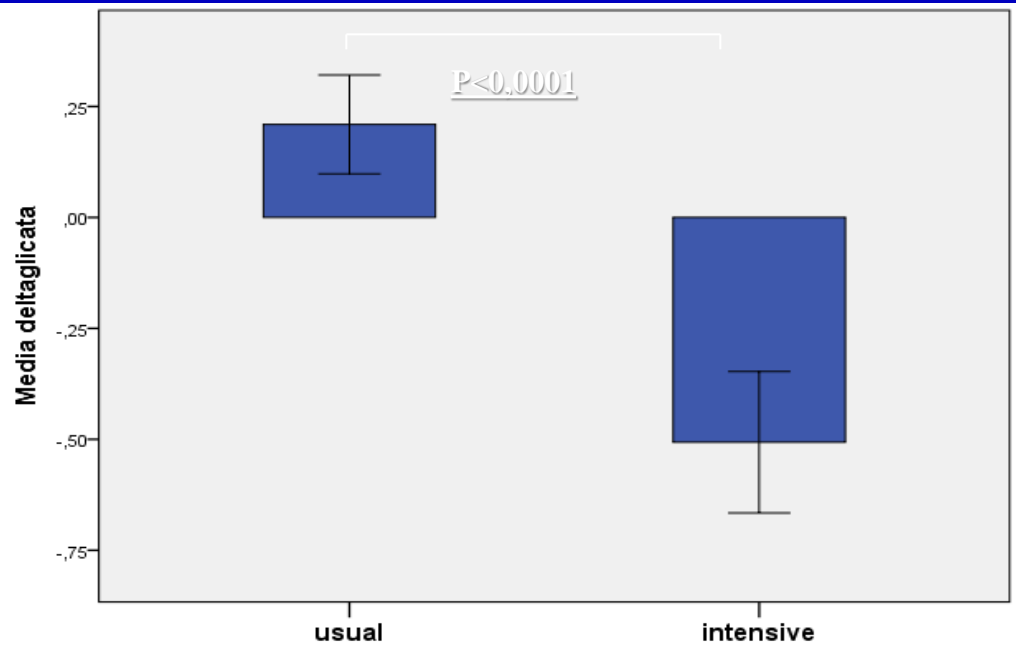
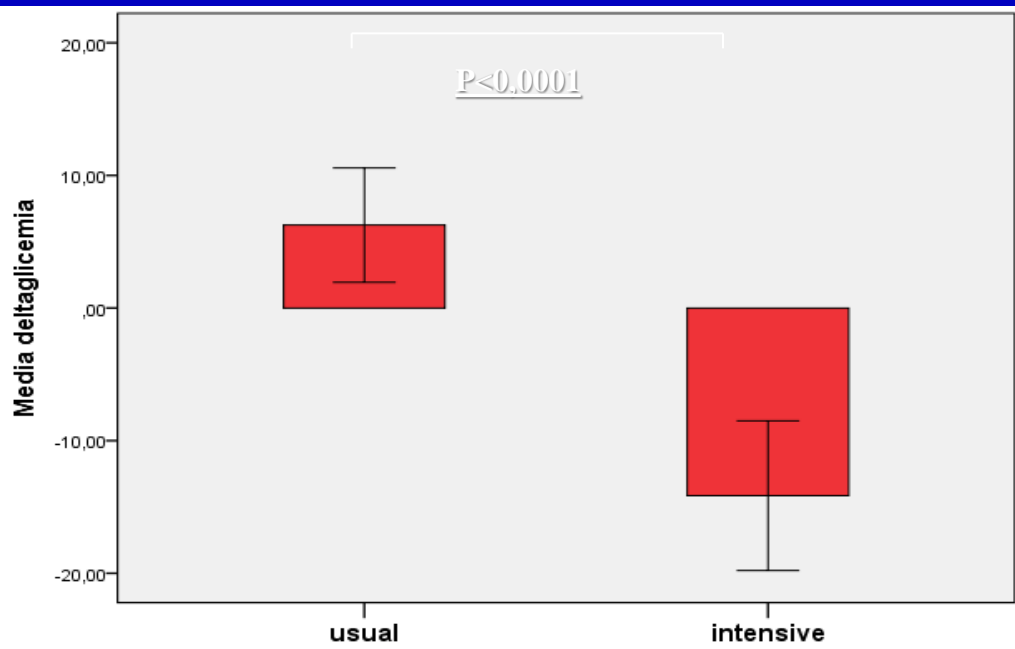


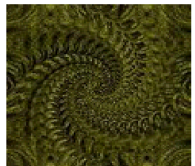


# Variazione di peso e glicemia e emoglobina glicata e a 5 anni

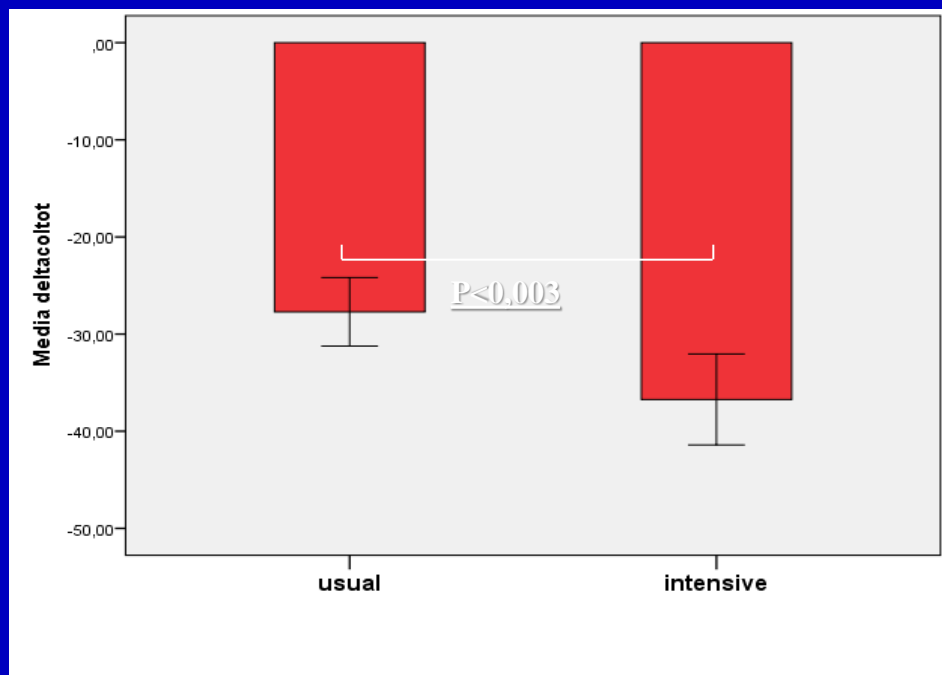
## Glicemia a digiuno

## HbA1c

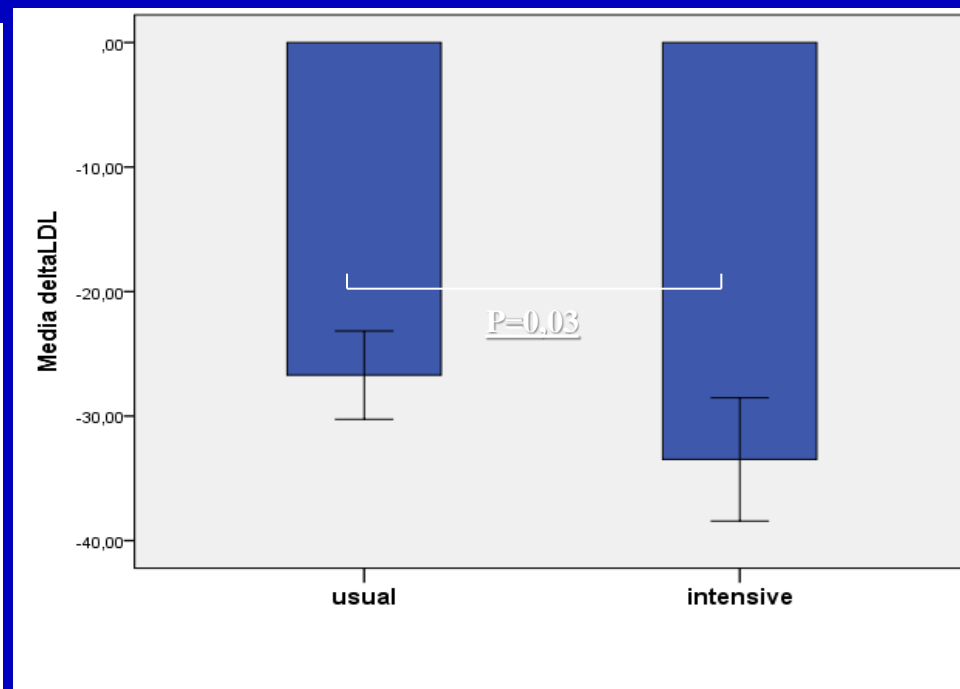




## HDL



## LDL



Variazioni di colesterolo totale colesterolo LDL a 5 anni di FU  
n=1117



## Incidenza di eventi CVD maggiori a 5 anni di follow up

	Eventi CV	RR	p
Usual	110/942	1,946 (1,270-2,979)	0,001
Intensive	24/400	0,940 (0,908-0,972)	
tot	134/1342		



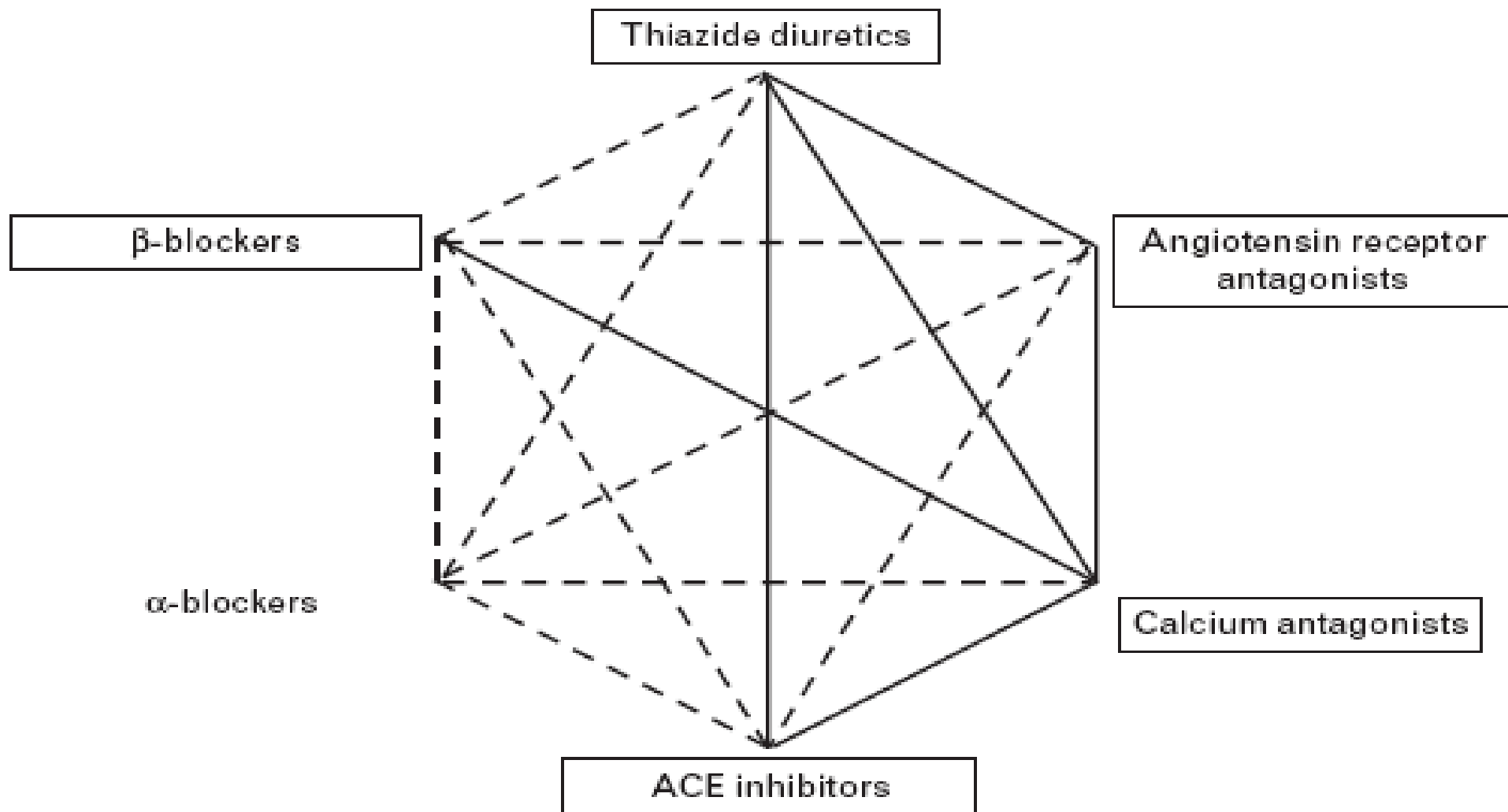
# ESC/EASD guidelines 2007

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
In patients with diabetes and hypertension, the recommended target for blood pressure control is <130/80 mm Hg	I	B
The cardiovascular risk in patients with diabetes and hypertension is substantially enhanced. The risk can be effectively reduced by blood pressure-lowering treatment	I	A
The diabetic patient usually requires a combination of several anti-hypertensive drugs for satisfactory blood pressure control	I	A
The diabetic patient should be prescribed a renin-angiotensin-system inhibitor as part of the blood pressure-lowering treatment	I	A
Screening for microalbuminuria and adequate blood pressure-lowering therapy including the use of ACE-inhibitors and angiotensin receptor II blockers improves micro- and macrovascular morbidity in type 1 and type 2 diabetes	I	A

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

# The ESC-ESH guidelines 2007: possible therapeutic associations



# NICE 2008

- **HPT: BP $\geq$ 130/80 mmHg in 2 misure**
- **Target: BP<140/80 mmHg in generale, <130/80 mmHg in pazienti con micro- o macro- albuminuria, eGFR<60 mg/min/1.73m<sup>2</sup>, retinopatia, precedente TIA/Stroke**
- **Target ideale: La minore PA tollerata**
- **Trattamento farmacologico per BP $\geq$ 140/90 mmHg in generale,  $\geq$ 130/80 mmHg in pazienti con micro- o macro- albuminuria, eGFR<60 mg/min/1.73m<sup>2</sup>, retinopatia, precedente TIA/Stroke dopo implementazione del TLS**
- **Farmaci utilizzabili: ACE-I, ARB, CCA, tiazidici, risparmiatori di K, Alfa-B, Beta-B**
- **Plausibili anche 5 farmaci**
- **ARBs meno efficaci che in non DM per prevenire stroke, ma più efficaci per HF**
- **CCB meno efficaci per prevenire HF di D/BB**
- **Trattamento di prima linea: ACE-I +/- CCB o tiazidico a bassa dose**
- **Trattamento di seconda linea: ARB +/- CCB o tiazidico a bassa dose**
- **Intensificare trattamento ogni 1-2 mesi fino a target**

# ADVANCE trial

- **Enrolled patients: 11.140 T2DM**
- **215 centers in 20 countries worldwide**
- **5 years follow-up**
- **Double-blind randomization to a fixed combination of perindopril and indapamide or matching placebo, and in the other arm of the study to either standard glucose control or intensive glucose control, defined as the use of modified-release gliclazide plus any additional drugs to achieve a HbA1c level of 6.5% or less.**
- **Primary end points: composites of major macrovascular events (nonfatal MI, nonfatal stroke, or CV death) and major microvascular events (new or worsening nephropathy or retinopathy) assessed both together and individually**

## **Dietary intervention and exercise**

The aim was to reduce fat intake to <30% and saturated fatty acids to <10% of total daily energy intake and to increase the daily intake of vegetables, fruits, walnuts, almonds, and seafood. The reduction of daily energy intake was not a goal.

- Exercise: light to moderate leisure time exercise of any type for at least 30 min 3–5 times a week.

## **Hyperglycemia**

Target: HbA<sub>1c</sub> <6.5%

- Oral antidiabetic drugs (OAD) were introduced if HbA<sub>1c</sub> was >6.5% after 3 months of dietary intervention. Overweight and obese patients were started on metformin to maximum of 2 x 1,000 mg. If contraindicated or in lean patients, a sulfonylurea (gliclazide) was prescribed.

- Combination of the two drugs was considered when HbA<sub>1c</sub> target was not met.

- NPH at bedtime was added when HbA<sub>1c</sub> was >7.0% despite maximal dose of both OADs. At the start of insulin treatment, obese patients stopped the sulfonylurea and the lean patients stopped metformin.

- If the daily insulin dose exceeded 80 IU, or if no decrease of HbA<sub>1c</sub> was observed, patients were switched to regimens (two to four daily injections) with fast-acting and NPH insulin.

## **Hypertension**

Target: <140/85 mmHg (study years 1993–1999); <130/80 mmHg (2000–2001)

- ACE inhibitor as initial treatment. If side effects, angiotensin II receptor antagonists were used.
- If target not achieved, combination with any of the following antihypertensive drugs was prescribed: thiazides, calcium antagonists, and  $\beta$ -blockers.

## **Microalbuminuria**

- As all patients had microalbuminuria, ACE inhibitors were prescribed irrespective of blood pressure values.

## **Dyslipidemia**

Targets: total cholesterol <190 mg/dl (1993–1999) and <175 mg/dl (2000–2001); triglycerides <150 mg/dl

- Treatment: atorvastatin for raised isolated fasting cholesterol or combined dyslipidemia; fibrates in isolated fasting hypertriglyceridemia (>350 mg/dl)

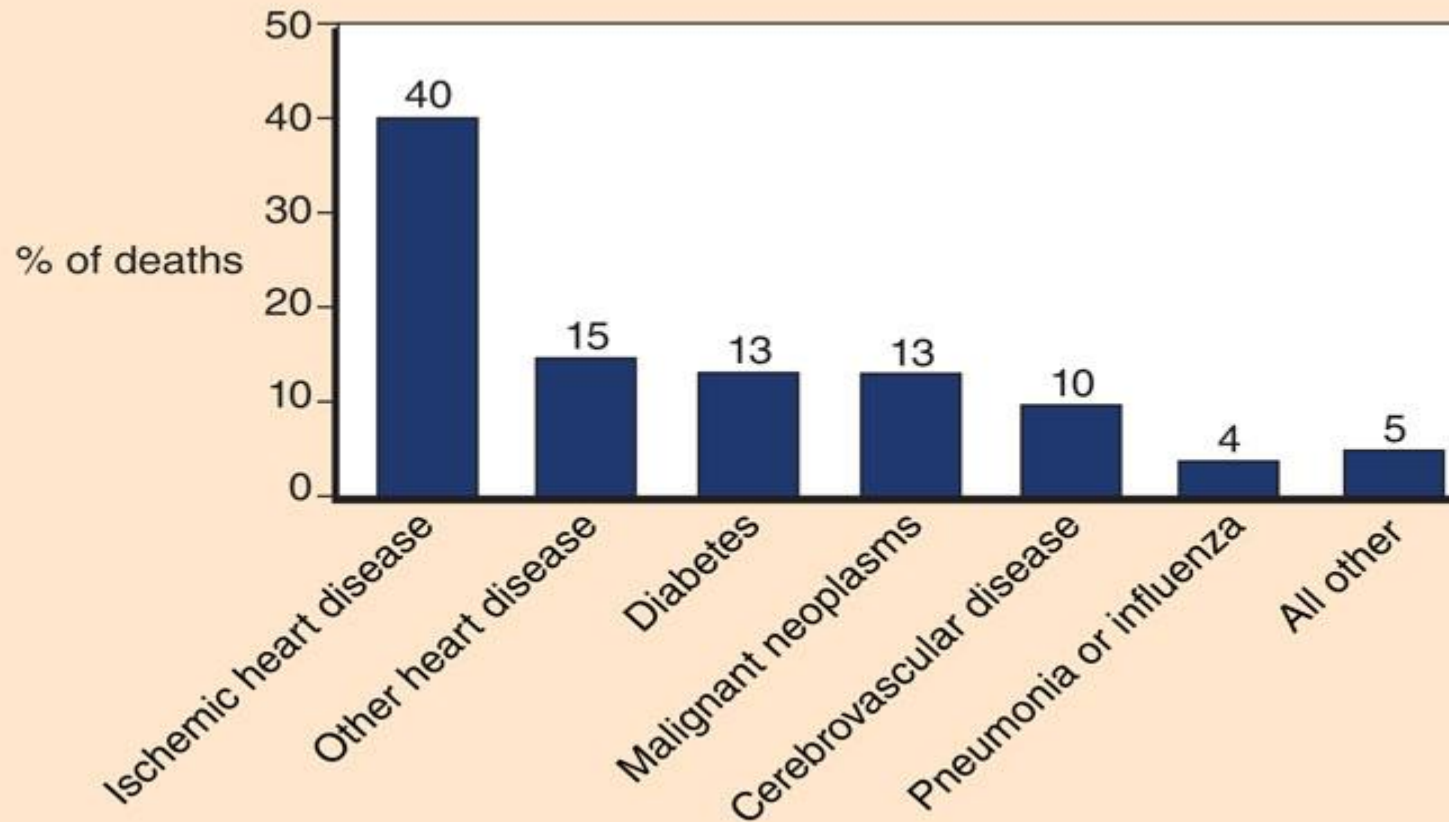
## **Smoking**

Patients and their spouses were invited to smoking cessation courses.

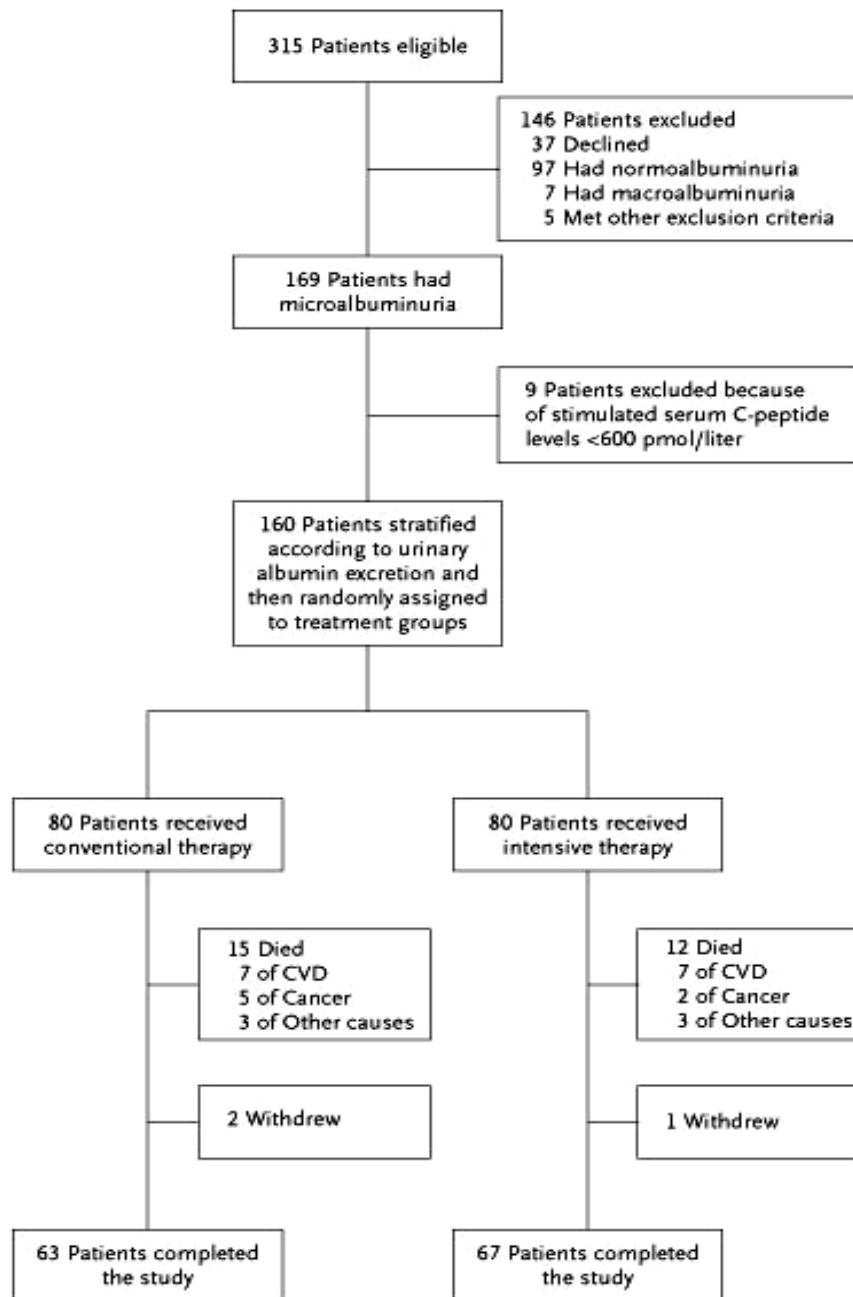
## **Aspirin**

Aspirin 150 mg/daily was given to all patients with known ischemia and/or PAD

# Most common causes of death in individuals with diabetes



Geiss LS *et al.* In: Diabetes in America. 2nd edn. NDD Group, eds. NIH, NIDDKD, Bethesda, MD; 1995.





# VA-HIT: Relative Risk (RR) of Nonfatal Myocardial Infarction or Coronary Disease (CAD) Death predicted by On-Trial Concentrations of Lipids

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	Multivariate Model	
	RR (95% CI)	p Value
HDL (5 mg/dl)	0.89 (0.81-0.98)	0.02
Triglycerides (50 mg/dl)	1.03 (0.95-1.11)	0.48
LDL-C (25 mg/dl)	1.09 (0.98-1.21)	0.13

Calculated from Cox proportional hazards models with treatment as covariate and adjustments made for the coronary disease risk factors of age, smoking, hypertension, diabetes, and body mass index .

# Reduction in Nonfatal Myocardial infarction or Coronary Disease (CAD) Death in Patients with Diabetes Mellitus and CAD in VA-HIT Intervention Trial and the Statin Trial

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		<u>CAD Events</u>				
		Placebo	Drug	Relative RR	Absolute RR	NNT to
Trial	n	%	%	(95% CI)	(%)	Prevent 1 event
4S	483	37.5	23.5	42 (59 to 20)	14.0	7 (1/0.14)
CARE/LIPID	1368	22.1	18.6	17 (35 to 5)	3.5	29 (1/0.035)
VA-HIT	769	29.4	21.2	31 (48 to 8)	8.2	12 (1/0.082)

# Rischio residuo

**I fibrati possono aggiungere un beneficio alle statine ?**

**Potrebbero ridurre il rischio residuo in pazienti diabetici con dislipidemia e già in trattamento con statine ?**

**Rappresenta un approccio “safe” perseguibile nella maggior parte dei pazienti ?**

**Una risposta dovrebbe essere ottenuta dallo studio Accord  
(statine + fenofibrato)**