Dichiarazione di Conflitto di Interessi

Honorarium as a speaker in Scientific Events

Sigma-Tau	Lilly/Boheringer Ingelheim	Abbott
AstraZeneca BMS	Takeda	Janssen
Eli-Lilly	Sanofi-Aventis	Menarini Diag
MSD	Novo Nordisk	Roche Diag
Novartis	Servier	Bayer

Grant support

Novo Nordisk (Investigator-Initiated-Study Grant)

Kellogg (Investigator-Initiated-Study Grant)

AstraZeneca, Lilly, Sanofi, Novo Nordisk, Sigma-Tau, Menarini (Travel grants)

Scientific advisory boards

AstraZeneca, Lilly, Sanofi, Takeda, NovoNordisk

Lettura critica di un articolo Scientifico

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Evaluation of RCT

CONSORT
CONsolidated Standards Of Reporting Trials

1) Designed for authors and editors: 'how to report a RCT'

2) Extremely useful for readers

IT'S A CHECKLIST OF ITEMS TO INCLUDE WHEN REPORTING A RANDOMIZED TRIAL

Lo studio ADOPT

ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

Steven E. Kahn, M.B., Ch.B., Steven M. Haffner, M.D., Mark A. Heise, Ph.D., William H. Herman, M.D., M.P.H., Rury R. Holman, F.R.C.P., Nigel P. Jones, M.A., Barbara G. Kravitz, M.S., John M. Lachin, Sc.D., M. Colleen O'Neill, B.Sc., Bernard Zinman, M.D., F.R.C.P.C., and Giancarlo Viberti, M.D., F.R.C.P., for the ADOPT Study Group *

N Engl J Med 2006;355:2427-43.

Item 1
il titolo e l'abstract

ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

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Aspetti metodologici

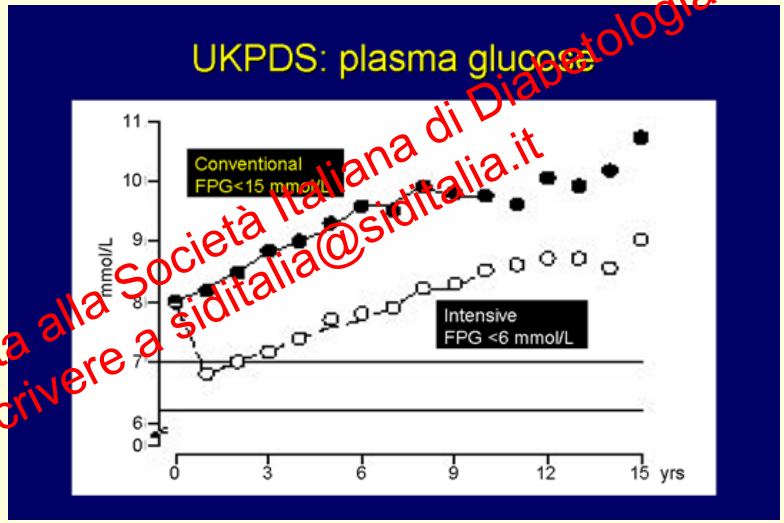
METHODS

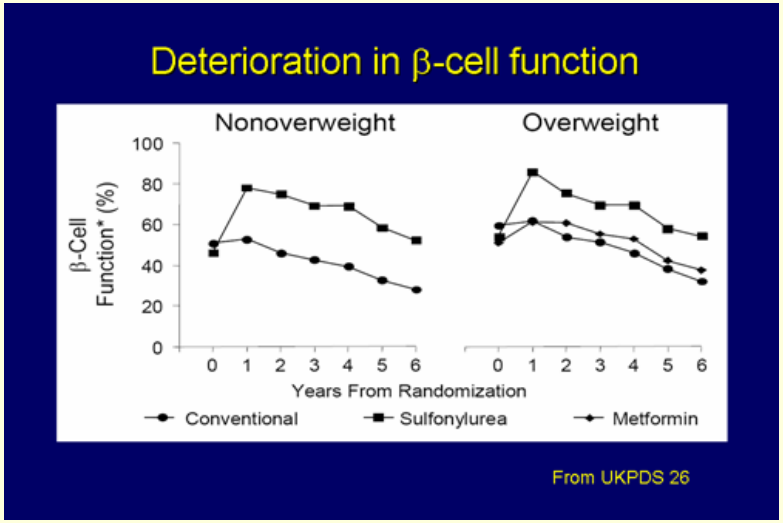
We evaluated rosiglitazone, metformin, and glyburide as initial treatment for recently diagnosed type 2 diabetes in a double-blind, randomized, controlled clinical trial involving 4360 patients. The patients were treated for a median of 4.0 years. The primary outcome was the time to monotherapy failure, which was defined as a confirmed level of fasting plasma glucose of more than 180 mg per deciliter (10.0 mmol per liter), for rosiglitazone, as compared with metformin or glyburide. Prespecified secondary outcomes were levels of fasting plasma glucose and glycated hemoglobin, insulin sensitivity, and β-cell function.

Item 2: il background scientifico è ben descritto ?

Problema clinico

THE ATTAINMENT AND MAINTENANCE of near-normal glycemia reduces the risk of long-term complications of diabetes.[1-3] Despite lifestyle and pharmacologic interventions, glucose levels increase over time in type 2 diabetes, probably as a consequence of declining β-cell function.[4] The progressive nature of type 2 diabetes makes it difficult to maintain target levels of glycated hemoglobin with traditional glucose-lowering agents[5,6] and generally necessitates the escalation of drug doses and the use of combination therapies or insulin.[7]





Item 3a: criteri inclusione ed esclusione

PATIENTS

Eligible patients were between the ages of 30 and 75 years, with fasting plasma glucose levels ranging from 126 to 180 mg per deciliter (7.0 to 10.0 mmol per liter), while their only treatment was lifestyle management.[13] Exclusion criteria included clinically significant hepatic disease, renal impairment, a history of lactic acidosis, unstable or severe angina, known congestive heart failure (CHF, New York Heart Association class I, II, III, or IV), or uncontrolled hypertension.[13]

Item 3a: criteri inclusione ed esclusione con caratteristiche della popolazione selezionata

Table 1. Baseline Characteristics of the Patients.*

Variable	Rosiglitazone (N=1456)	Metformin (N=1454)	Glyburide (N=1441)
Demographic characteristics			
Age — yr	56.3±10.0	57.9±9.9	56.4±10.2
Male sex — no. (%)	811 (55.7)	864 (59.4)	836 (58.0)
Race or ethnic background — no. (%)†			
White	1270 (87.2)	1295 (89.1)	1282 (89.0)
Black	61 (4.2)	54 (3.7)	61 (4.2)
Asian	39 (2.7)	35 (2.4)	32 (2.2)
Hispanic	76 (5.2)	55 (3.8)	61 (4.2)
Other	10 (0.7)	15 (1.0)	5 (0.3)
Region — no. (%)			
North America	758 (52.1)	758 (52.1)	738 (52.2)
Europe	698 (47.9)	696 (47.9)	683 (47.4)
Time since diagnosis of diabetes — no. (%)			
<1 yr	650 (44.6)	673 (46.3)	637 (44.2)
1–2 yr	759 (52.1)	724 (49.8)	751 (52.1)
>2 yr	47 (3.2)	57 (3.9)	53 (3.7)
Anthropometric characteristics			
Weight — kg	91.5±19.7	91.6±18.7	92.0±20.0
Body-mass index‡	32.2±6.7	32.1±6.1	32.2±6.3
Waist circumference — cm	105.3±14.6	105.6±14.3	105.6±15.1
Hip circumference — cm	111.4±14.1	111.2±13.4	111.8±14.2
Waist-to-hip ratio	0.95±0.09	0.95±0.10	0.94±0.09
Blood pressure			
Systolic — mm Hg	133±16	133±15	133±15
Diastolic — mm Hg	80±9	80±9	79±9
Antihypertensive therapy — no. (%)	744 (51.1)	737 (50.7)	753 (52.3)

Table 1. (Continued.)

Variable	Rosiglitazone (N=1456)	Metformin (N=1454)	Glyburide (N=1441)
Metabolic characteristics			
Fasting plasma glucose — mg/dl	151.5±25.4	151.3±25.6	152.4±27.3
Glycated hemoglobin — %	7.36±0.93	7.36±0.93	7.35±0.92
Fasting insulin — pmol/liter	149.9±108.2	151.8±111.6	150.4±113.1
Insulin sensitivity — %‖			
Median	33.8	33.3	33.1
Interquartile range	22.7–48.6	22.6–47.4	22.5–49.2
β-cell function — %‖			
Median	68.0	69.5	67.9
Interquartile range	51.4–87.8	52.0–90.2	52.8–87.7
GAD positive — no. (%)¶	55 (4.0)	70 (5.1)	50 (3.6)
Lipids			
Total cholesterol — mg/dl			
Median	205	204	202
Interquartile range	177–231	177–231	177–230
LDL cholesterol — mg/dl‖			
Median	121	120	119
Interquartile range	98–144	96–143	98–144
HDL cholesterol — mg/dl			
Median	46.9	46.5	47.3
Interquartile range	39.0–54.6	39.6–55.0	39.0–55.4
Triglycerides — mg/dl			
Median	163	165	156
Interquartile range	116–230	112–233	112–222
Lipid-lowering therapy — no. (%)	378 (26.0)	377 (25.9)	370 (25.7)

Item 3b: setting and location

drugs (Fig. 1). Investigators at 488 centers in the United States, Canada, and 15 European countries

participated in the study. Randomization was performed centrally and was concealed and stratified according to the sex of the patients in blocks of six.

Item 4: descrizione dell'intervento

In a double-blind regimen, patients received initial daily doses of 4 mg of rosiglitazone, 500 mg of metformin, or 2.5 mg of glyburide. All drugs were prepared in identical capsules to make them indistinguishable. For each drug, the dose was increased according to the protocol to the maximum daily effective dose (4 mg of rosiglitazone twice daily, 1 g of metformin twice daily, and 7.5 mg of glyburide twice daily). A dose increase was required at each visit if the fasting plasma glucose level was 140 mg per deciliter or more; a dose reduction was permitted if adverse events occurred.

Item 5: lo scopo delle studio è chiaro ?

Our study, called A Diabetes Outcome Progression Trial (ADOPT), was a multicenter, randomized, double-blind, controlled clinical trial designed to evaluate the durability of glycemic control in patients receiving monotherapy with a thiazolidinedione, rosiglitazone (Avandia, GlaxoSmithKline); a biguanide, metformin (Glucophage, Bristol-Myers Squibb); or a sulfonylurea, glyburide (Micronase, Pfizer). All the patients in the study had not received previous pharmacologic treatment for type 2 diabetes that had been recently diagnosed (i.e., within 3 years). The primary out-

Item 5: L'ipotesi di lavoro è ben posta ?

Ipotesi fisio-patologica

Plausibile ?

Thiazolidinediones reduce insulin resistance by sensitizing muscle, liver, and adipose tissue to insulin[8] and delay progression to type 2 diabetes in patients with glucose intolerance.[9-11] Small clinical studies have suggested that thiazolidinediones preserve β-cell function.[9,12] Thus, they may be of benefit as initial treatment of type 2 diabetes.

Item 6: End-point primario

The primary outcome was the time from randomization to treatment failure, which was defined as confirmed hyperglycemia (fasting plasma glucose level, >180 mg per deciliter) on consecutive testing after at least 6 weeks of treatment at the maximum-dictated or maximum-tolerated dose of the study drug. An independent adjudication committee, whose members were unaware of assignments to treatment groups, used prespecified

Item 6: End-points secondari

Prespecified secondary outcomes included the time from randomization to a confirmed fasting plasma glucose level of more than 140 mg per deciliter after at least 6 weeks of treatment at the maximum-tolerated dose of a study drug (for patients who entered the study with a fasting plasma glucose level of 140 mg per deciliter or less). Other prespecified outcomes were levels of fasting plasma glucose and glycated hemoglobin, weight, and measures of insulin sensitivity and β-cell function,[16] as determined by homeostasis model assessment (HOMA 2) with the use of the HOMA Calculator (www.dtu.ox.ac.uk).

Item 6: End-point primario

As part of its mandate, the ADOPT Steering Committee periodically monitored the overall hazard rate of monotherapy failure in the combined cohort, masked to treatment group differences. During a September, 2003 data review, the Steering Committee was concerned by the high incidence of initial fasting plasma glucose values >180 mg/dl that were not subsequently followed by repeat testing due to withdrawal from the study, and the high incidence of withdrawals due to insufficient therapeutic effect. As a result, the protocol was amended to establish an independent adjudication committee to review all such cases and to determine whether each represented a primary outcome.

Comitato (di 3 esperti) di aggiudicazione dell'end-point primario. **Key message molti paz si ritiravano all'inizio per insufficiente effetto terapeutico**

Item 7a: sample size

We originally calculated that we would need to enroll 3600 patients to provide the study with a power of 90% to detect a 30% reduction in the risk of treatment failure for rosiglitazone, as compared with metformin and glyburide, at a significance level of P=0.05 (two-sided, adjusted for two comparisons), assuming an event rate of 0.072 per year for metformin or glyburide and a rate of loss to follow-up of 0.064 per year in each group. The protocol was amended in March 2002 to increase the number of patients to 4182 and in February 2004, to extend the follow-up period beyond 4 years, in order to compensate for an overall rate of withdrawal that was greater than anticipated and an overall rate of primary outcome events that was lower than anticipated. The revised power estimate was 83%, assuming a rate of loss to follow-up of 0.128 per year and a hazard rate for treatment failure of 0.035 per year.

Item 7b: interim analysis

STUDY OVERSIGHT

The study protocol was approved by the institutional review board at each center, and all patients provided written informed consent. An independent data safety and monitoring board met twice a year to review unblinded safety data prepared by an independent statistical analysis group at the University of Wisconsin-Madison.

Study design, implementation, and analysis were performed under the supervision of the steering committee, which was composed of seven members from academic institutions and two from the sponsor, GlaxoSmithKline. The sponsor housed all blinded data during the treatment phase of the study and performed data analyses according to a prespecified plan developed with the academic biostatistician and approved by the steering committee. Independent academic statisticians confirmed key efficacy and safety results (see the Supplementary Appendix). Steering committee members, who had access to all data analyses and wrote the manuscript, attest to the veracity and completeness of the data. The decision to publish was made by the committee's academic members, with no restrictions imposed by the sponsor.

Item 8:

Method to generate the random allocation (unpredictability)

Details of any restriction

Item 9: Method to implement the generation of the random allocation

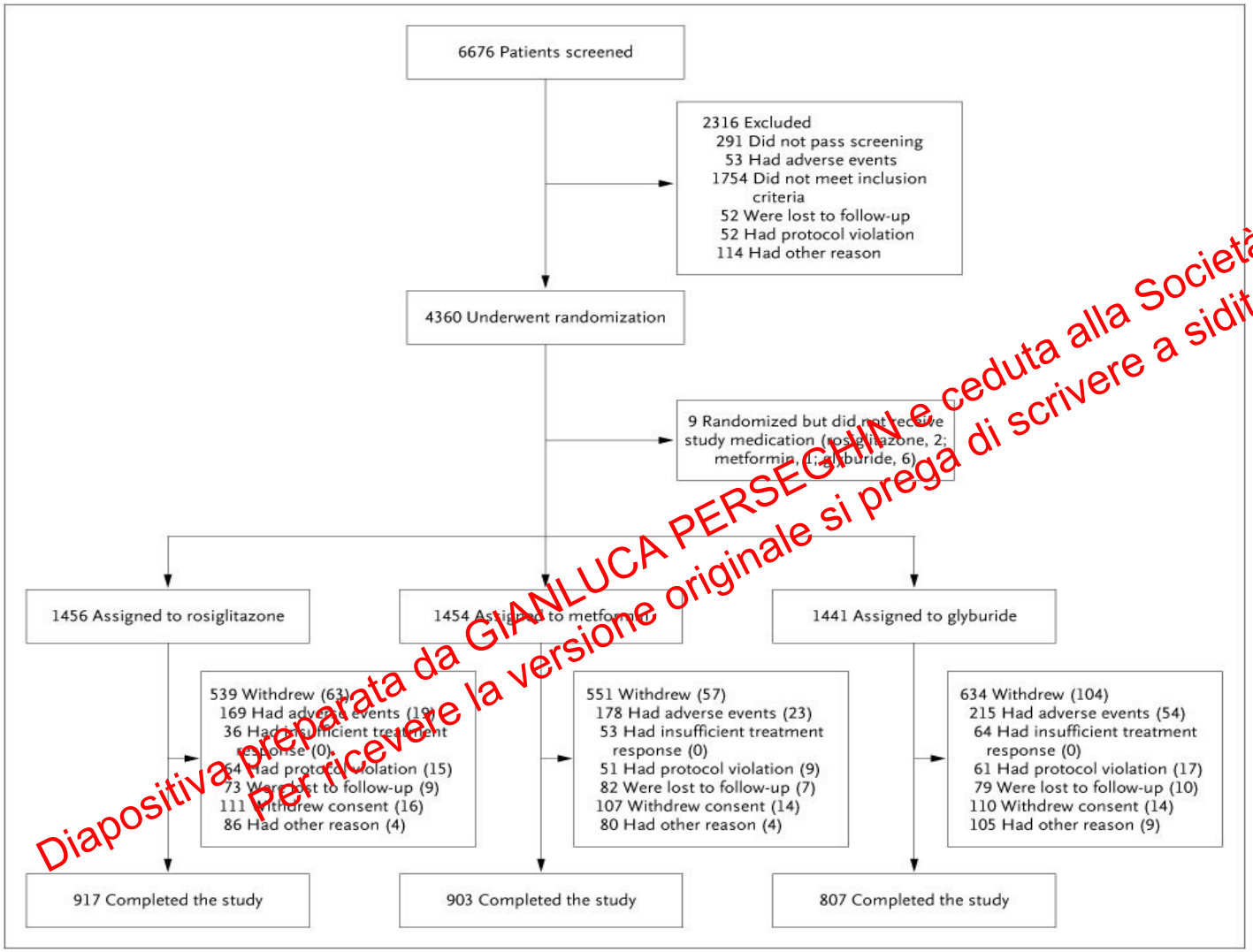
Item 10: Who generated the allocation sequence, who enrolled participants and who assigned participants

Item 11: Blindness to assignement

Item 12: Stat Methods for primary outcome (and additional analysis)

The primary comparisons were rosiglitazone versus metformin and rosiglitazone versus glyburide. A secondary analysis compared metformin and glyburide. The percent reduction in risk was computed as 100 × (1−the hazard ratio), with the hazard ratio estimated from the Cox proportional-hazards model. The cumulative incidence was estimated with the Kaplan–Meier method and with Gray's method, which adjusts for deaths.[17] Two-sided nominal P values are reported for all comparisons. The Hochberg method was used to determine statistical significance at the 0.05 level, adjusted for two comparisions.[17] Other details about the statistical methods used in the study are available in the Supplementary Appendix.

Item 13: flow of participants



Kahn SE et al. N Engl J Med 2006;355:2427-2443

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Item 14: Dates defining the periods of recruitment and follow-up

The ADOPT protocol, methods, and baseline characteristics of the cohort have been described previously.[13,14] Between April 2000 and June 2002, 4360 patients who had not received previous pharmacologic treatment for recently diagnosed type 2 diabetes were randomly assigned to receive double-blind monotherapy with one of the three study

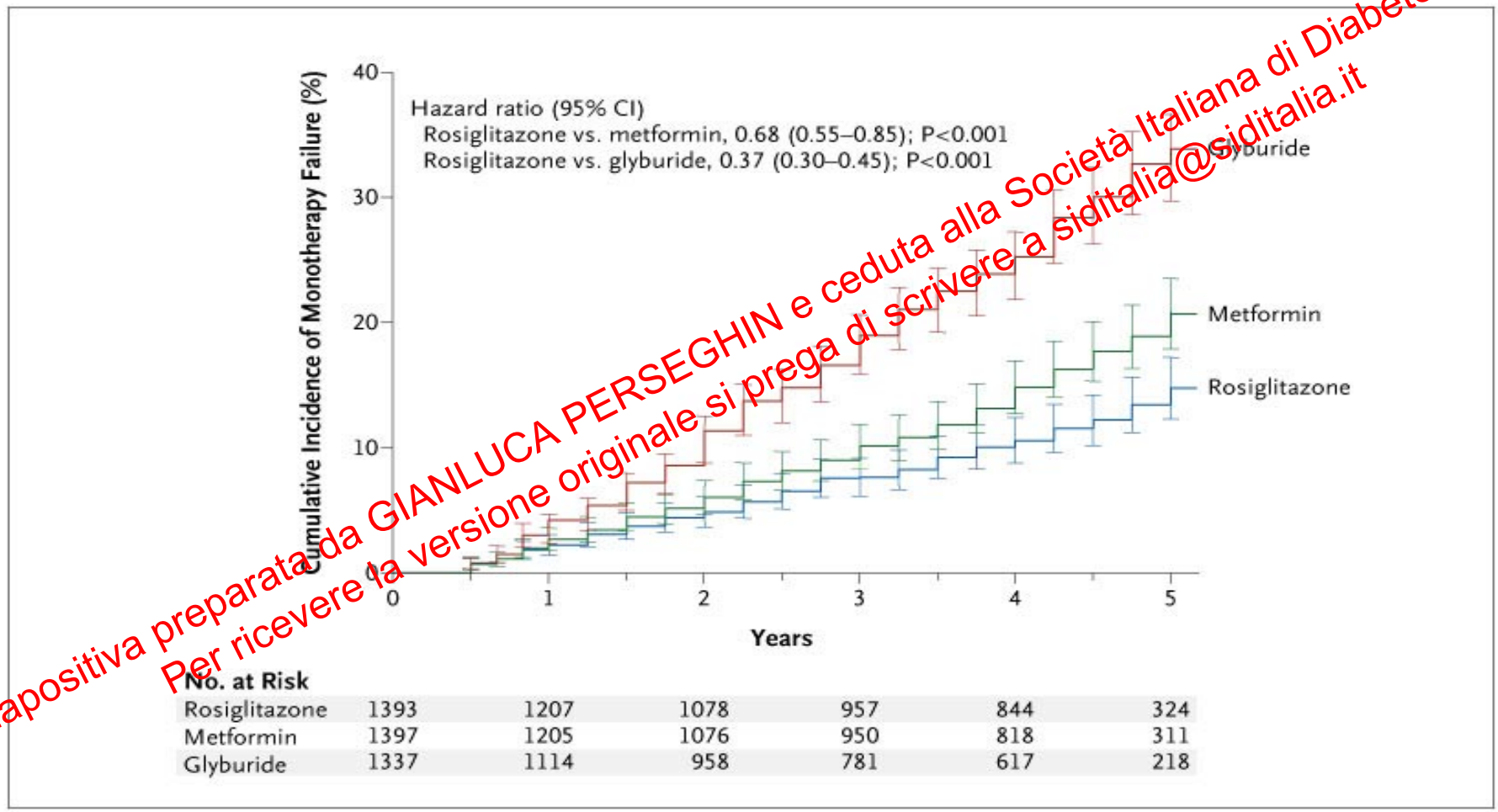
per liter). Patients were followed until the termination of the study in June 2006, with a median treatment duration of 4.0 years (maximum, 6.0).

Item 15: Baseline demographic and clinical features of each group
Item 16: Number of participants in each group

Table 1. Baseline Characteristics of the Patients.*

Variable	Rosiglitazone (N=1456)	Metformin (N=1454)	Glyburide (N=1441)
Demographic characteristics			
Age — yr	56.3±10.0	57.9±9.9	56.4±10.2
Male sex — no. (%)	811 (55.7)	864 (59.4)	836 (58.0)
Race or ethnic background — no. (%)†			
White	1270 (87.2)	1295 (89.1)	1282 (89.0)
Black	61 (4.2)	54 (3.7)	61 (4.2)
Asian	39 (2.7)	35 (2.4)	32 (2.2)
Hispanic	76 (5.2)	55 (3.8)	61 (4.2)
Other	10 (0.7)	15 (1.0)	5 (0.3)

Item 17: summary of results by each single end-point Kaplan-Meier Estimates of the Cumulative Incidence of Monotherapy Failure at 5 Years



No. at Risk						
Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

Kahn SE et al. N Engl J Med 2006;355:2427-2443

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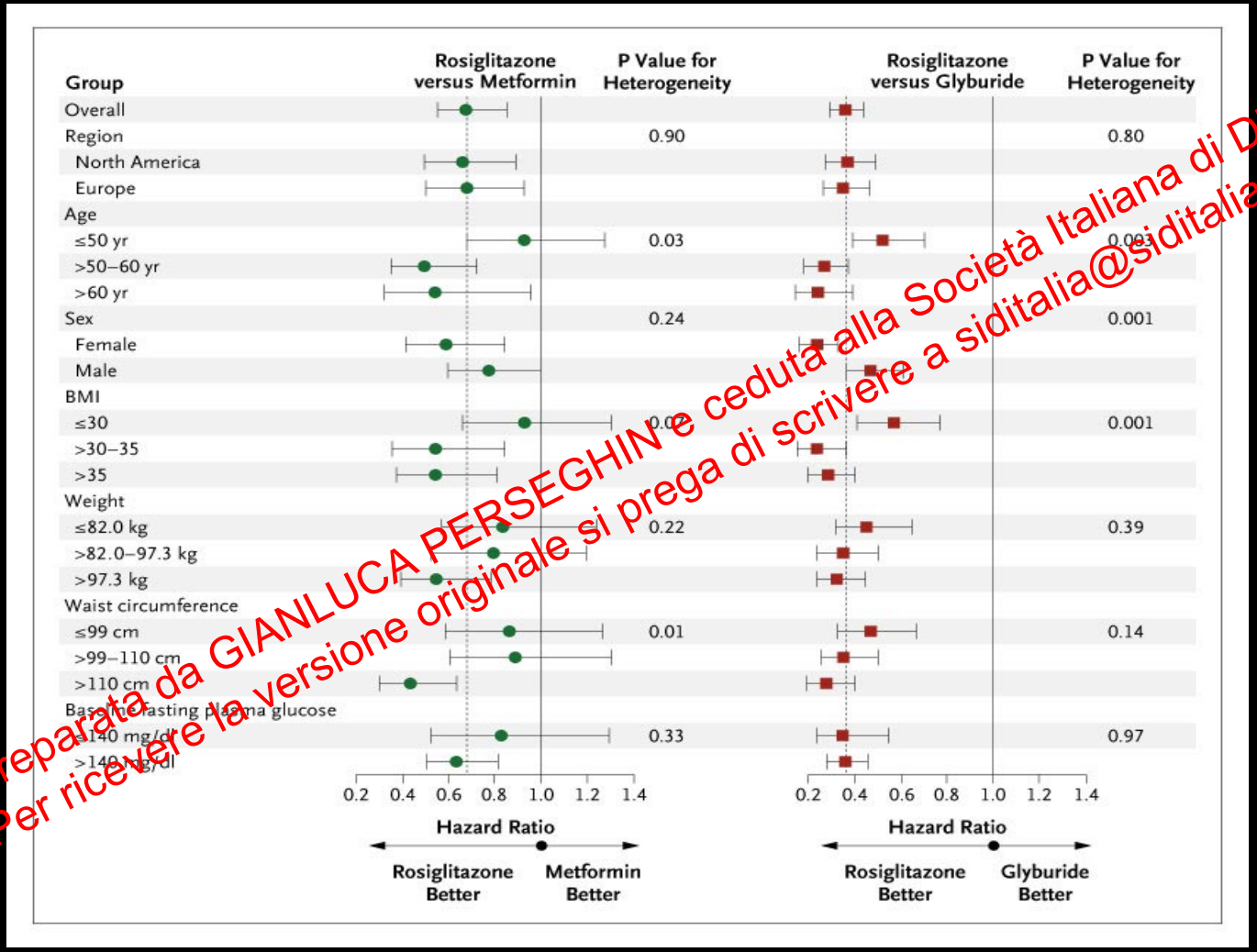
Hazard Ratio for Monotherapy Failure in the Rosiglitazone Group, as Compared with the Metformin and Glyburide Groups in Key Subgroups



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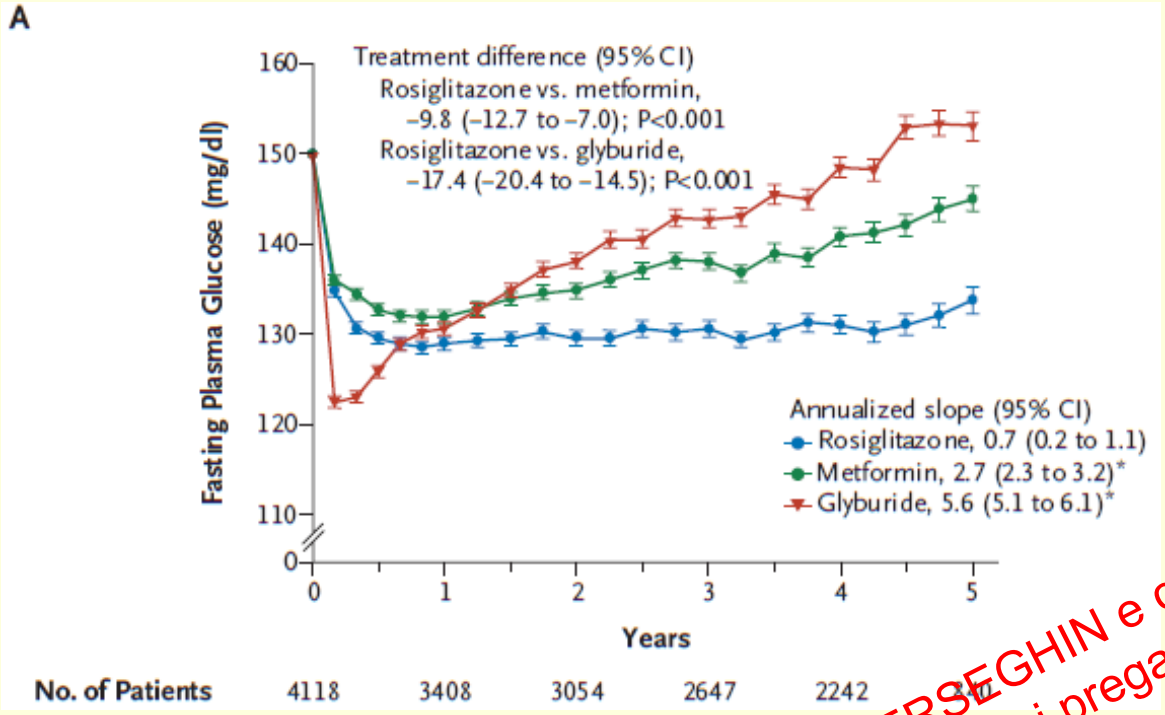
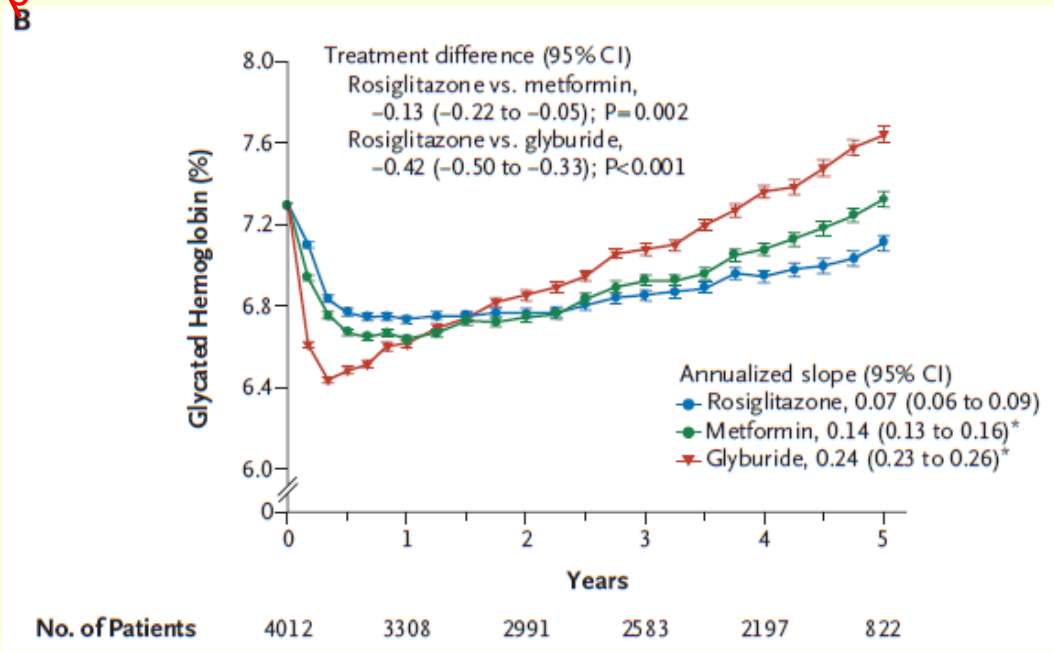
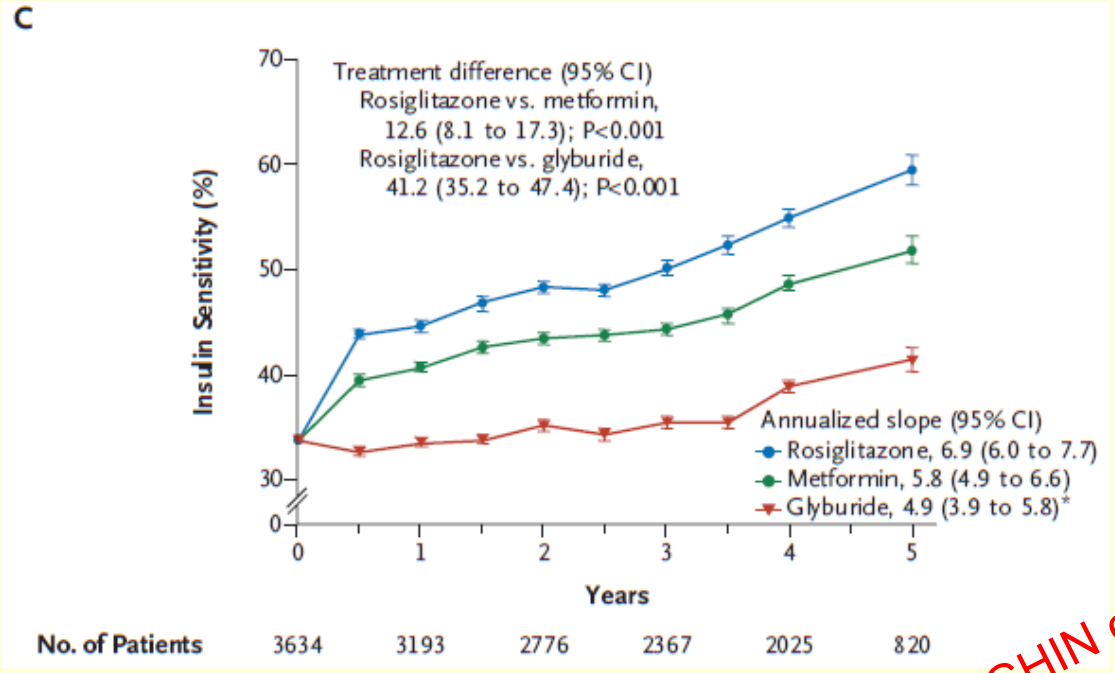
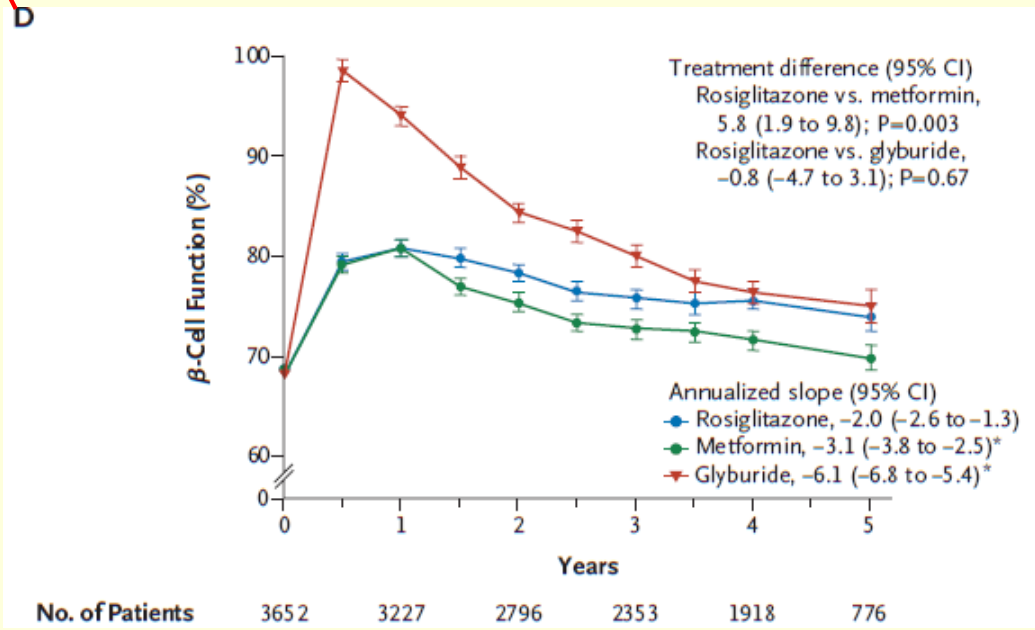


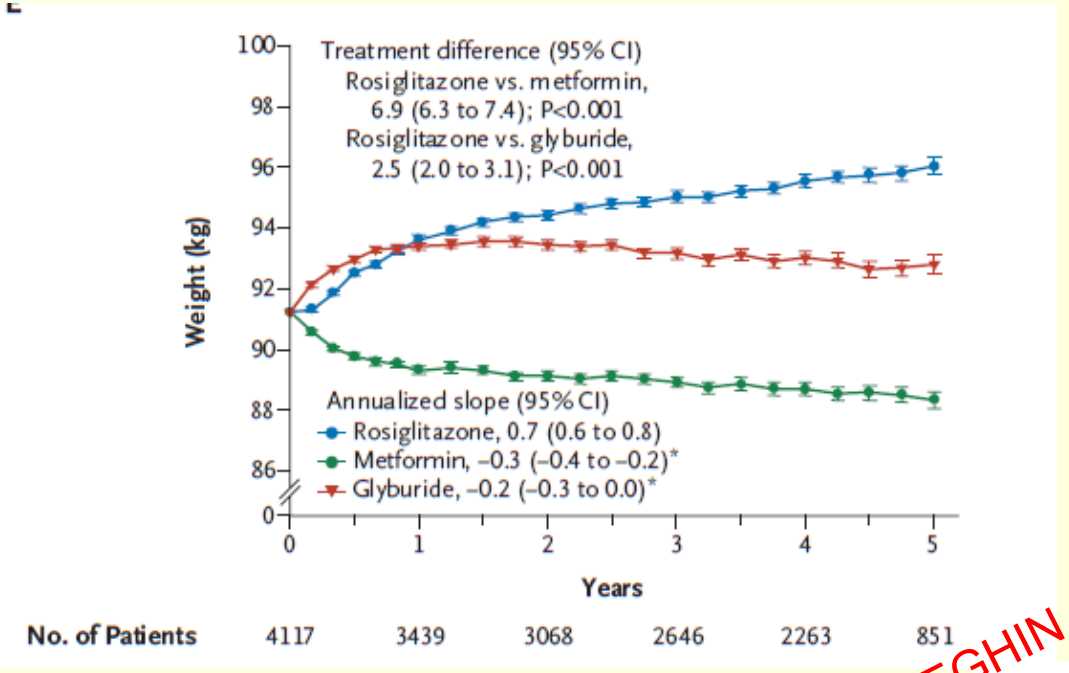


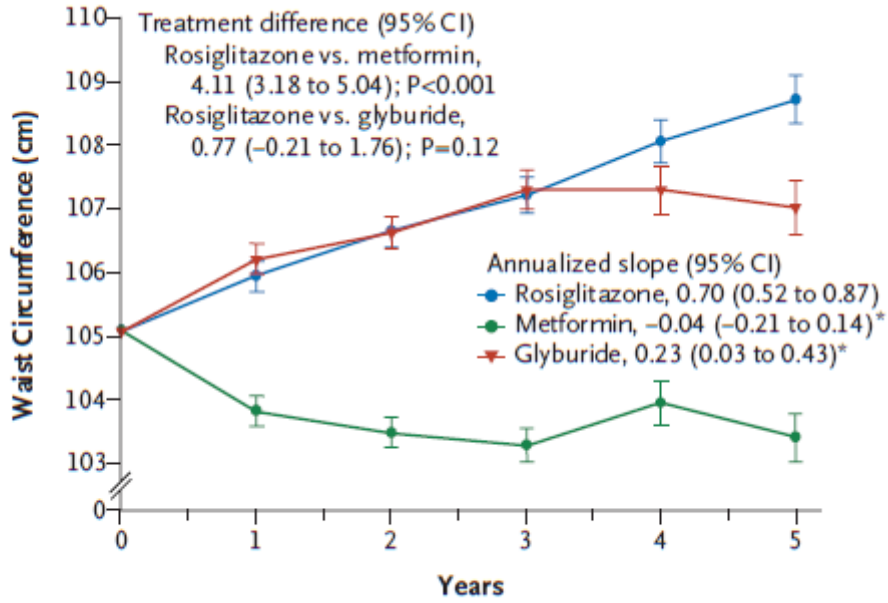
Item 17: summary of results by each single end-point





Item 17: summary of results by each single end-point





Item 17: summary of results by each single end-point

Item 18: additional findings
Item 19: All important adverse events or side effects in each group (expected or unexpected)

Table 2. Adverse Events, Laboratory Assessment, Concomitant Use of Cardiovascular Drugs, Hospitalization, and Death.*

Variable	Rosiglitazone (N=1456)		Metformin (N=1454)		Glyburide (N=1441)	
	Serious Events	Total Events	Serious Events	Total Events	Serious Events	Total Events
Adverse events — no. of patients (%)						
Total events	346 (23.8)	1338 (91.9)	331 (22.8)	1341 (92.2)	308 (21.4)	1321 (91.7)
Cardiovascular disease	49 (3.4)	62 (4.3)	46 (3.2)	53 (3.6)	26 (1.8)†	41 (2.8)
Myocardial infarction						
Fatal	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)	3 (0.2)
Nonfatal	22 (1.5)	25 (1.7)	18 (1.2)	21 (1.4)	11 (0.8)	15 (1.0)
Congestive heart failure (investigator-reported)	12 (0.8)	22 (1.5)	12 (0.8)	19 (1.3)	3 (0.2)†	9 (0.6)†
Stroke	13 (0.9)	16 (1.1)	17 (1.2)	19 (1.3)	12 (0.8)	17 (1.2)
Peripheral vascular disease	7 (0.5)	36 (2.5)	6 (0.4)	27 (1.9)	4 (0.3)	31 (2.2)
Gastrointestinal events	8 (0.5)	335 (23.0)	7 (0.5)	557 (38.3)‡	3 (0.2)	316 (21.9)
Nausea	2 (0.1)	112 (7.7)	0	170 (11.7)‡	0	99 (6.9)
Vomiting	0	58 (4.0)	1 (0.1)	84 (5.8)†	0	45 (3.1)
Diarrhea	1 (0.1)	129 (8.9)	1 (0.1)	345 (23.7)‡	0	142 (9.9)
Abdominal discomfort	5 (0.3)	161 (11.1)	6 (0.4)	224 (15.4)‡	3 (0.2)	163 (11.3)
Hypoglycemia§	1 (0.1)	142 (9.8)	1 (0.1)	168 (11.6)	8 (0.6)†	557 (38.7)‡
Weight gain	3 (0.2)	100 (6.9)	0	18 (1.2)‡	0	47 (3.3)‡
Edema	2 (0.1)	205 (14.1)	0	104 (7.2)‡	2 (0.1)	123 (8.5)‡

	Rosiglitazone	Metformin	Glyburide
	number of patients (percent)		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

* P<0.01 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).
† P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

Item 20: Interpretation of the results based on the hypothesis, sources of imprecision and bias and taking into account the danger with multiplicity of analyses

1) Brief synopsis of key findings
2) Possible mechanistic explanation
3) Limitations (high drop out rate)
4) Implications (clinical implication)

Item 21: Generalizability (external validity) of the trial findings

Item 22: General interpretation in the context of current evidence

In conclusion

ADOPT: studio storico che influenza tutt'ora le linee guida in riferimento al farmaco di prima scelta nel paziente con primo riscontro di diabete o naïve alla terapia farmacologica

Robusto nell'ipotesi

Un altro esempio di come le cose non siano andate come ci si aspettasse